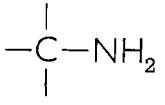
THE CHEMISTRY OF FUNCTIONAL GROUPS

A series of advanced treatises under the general editorship of Professor Saul Patai

The chemistry of alkenes (published)
The chemistry of the carbonyl group (published)
The chemistry of the ether linkage (published)
The chemistry of the amino group (published)



The chemistry of **the amino group**

Edited by

SAUL PATAI
The Hebrew University
Jerusalem, Israel

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Foreword

The principles governing the plan and pattern of the present volume have been summarized in the Preface to the series 'The Chemistry of the Functional Groups'.

Out of the originally planned contents, three chapters failed to materialize. These should have been chapters on the 'Photochemistry of the Amino Group', on the 'Syntheses and Uses of Isotopically Labelled Amines' and on 'Enamines'.

Jerusalem, September 1967 SAUL PATAI

The Chemistry of the Functional Groups
Preface to the series

The series 'The Chemistry of the Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group, but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between the chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of

cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasimonographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance, and mass spectra; a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases, certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally

planned parts of a volume, it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of an additional part, this will be done as soon as possible.

It is hoped that future volumes in the series 'The Chemistry of the Functional Groups' will include the topics listed below:

The Chemistry of the Alkenes (*published*)
The Chemistry of the Carbonyl Group (*published*)
The Chemistry of the Ether Linkage (*published*)
The Chemistry of the Amino Group (*published*)
The Chemistry of the Nitro Group (*in press*)
The Chemistry of Carboxylic Acids and Esters (*in press*)
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group (*in preparation*)
The Chemistry of the Carboxamido Group (*in preparation*)
The Chemistry of the Carbon–Halogen Bond
The Chemistry of the Hydroxyl Group (*in preparation*)
The Chemistry of the Carbon–Carbon Triple Bond
The Chemistry of the Azido Group
The Chemistry of Imidoates and Amidines
The Chemistry of the Thiol Group
The Chemistry of the Hydrazo, Azo and Azoxy Groups
The Chemistry of Carbonyl Halides
The Chemistry of the SO, SO_2, —SO_2H and —SO_3H Groups
The Chemistry of the —OCN, —NCO and —SCN Groups
The Chemistry of the —PO_3H_2 and Related Groups

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr. Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Jerusalem helped me in the solution of various major and minor matters and my

thanks are due especially to Prof. Y. Liwschitz, Dr. Z. Rappoport and Dr. J. Zabicky. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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CHAPTER 1

General and theoretical

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I. THE NATURE OF THE CHEMICAL BOND AND THE MAIN METHODS OF CALCULATING MOLECULAR WAVE FUNCTIONS

A. Some Aspects of Molecular Structure

In order to help the readers who are not specialized in the field of quantum chemistry we will summarize in this first section some important results on the nature of the chemical bond and the main ideas which form the basis of the usual methods of calculating electronic wave functions[1].

It will be convenient to introduce the subject by the analysis of the electronic structure of an atom. Let us take, as an example, a helium atom in its first excited state (which is a triplet state). In the old

theory of Bohr this state would correspond to one K electron in a certain circular orbit and one L electron in another one. From the wave-mechanical point of view the electronic structure of the atom appears to be rather different.

First of all, since no experiments have as yet been devised to determine the trajectories of electrons in atoms and molecules, it is assumed that such trajectories (if they exist) cannot be known. The wave mechanics can only give us a procedure to calculate *the probability* of finding an electron at a certain instant in such and such a small volume of an atom or molecule.

However, the main forces which from the wave-mechanical viewpoint are responsible for the 'motion' of electrons and nuclei, remain essentially the same as in classical mechanics; these forces are the coulombic interactions (repulsive between electrons or between nuclei, attractive between an electron and a nucleus). The Coulomb attraction that the nucleus of an atom exerts on the electrons holds them in a very small region of space, despite the repulsive forces between the electrons. Likewise, the repulsion between the nuclei of a molecule is compensated for by the attraction of electrons for the nuclei. But furthermore, we must take into account the spin of the electrons. Let us recall that this kinetic moment is quantized, in such a way, that if its projection along a given axis is measured, only one of the two values $\pm \frac{1}{2}h/2\pi$ (where h is Planck's constant) can be found.

Obviously it is more difficult to obtain a simple geometrical picture of an atom in the framework of the wave mechanics than with the theory of Bohr.

However, such a picture is very useful, especially for chemists who like to use intuitive concepts. This is why the notion of 'loge'[2] has been introduced into the wave mechanics.

Let us go back to our helium atom in its first excited state. Let us consider a sphere of radius r (this value being completely arbitrary) with its center at the nucleus. With the help of wave mechanics it is possible to calculate the probability P of finding one electron, and one only, in this sphere. When r is very small this probability is also very small because the sphere is generally empty. When r is very large, P again will be very small because now the sphere will generally contain the two electrons (and not one only). Thus, intuitively, we must anticipate that P will possess a maximum for at least one value of r. The curve[3] of Figure 1 shows that this is true. The maximum is large as it corresponds to $P = 0.93$. The corresponding radius is $1{\cdot}7\ a_0$. ($a_0 = 0.529$Å being the atomic unit of length.) We shall say

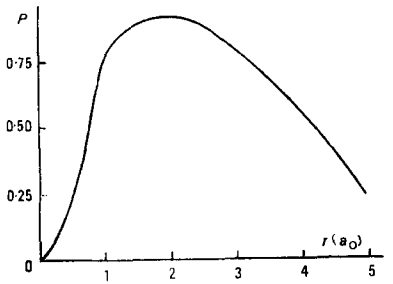


FIGURE 1. The probability P as a function of r.

that the best division of the atomic space into spherical loges is obtained when $r = 1{\cdot}7\ a_0$ and that there is a probability of 93 per cent of finding one electron, and only one, in this sphere (the other one being outside). Therefore Figure 2 symbolizes the most probable organization of the electrons of helium in its first excited state. We are thus quite naturally led to associate the sphere of radius $1{\cdot}7\ a_0$ with the K shell and the rest of the space with the L shell.

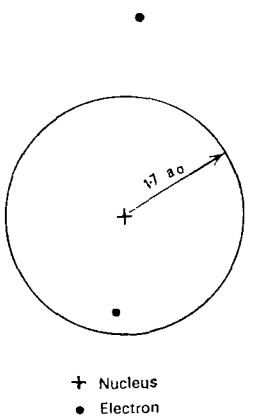


FIGURE 2. The best decomposition in loges for the helium atom (first excited state).

It is important to point out that the K and L shells are associated with some portion of space, but not with a particular electron. It would not be convenient to speak of a K electron or an L electron from the wave-mechanical point of view, since we know that the various electrons of a system are assumed to be undistinguishable.

These results can be extended. The space associated with an atom can be cut up into spherical rings, all concentric with the nucleus, one built on the other in such a way that there is a high probability of finding in each ring a certain number of electrons[4]. For example, in the fluoride ion F^- (ground state) there is an 81 per cent probability of finding two electrons of opposite spin in a sphere with the center at the nucleus and with radius $r = 0{\cdot}35\ a_0$, the other 8 electrons being outside. The sphere corresponds to the K loge, the remaining part of the space corresponding to the L loge (Figure 3).

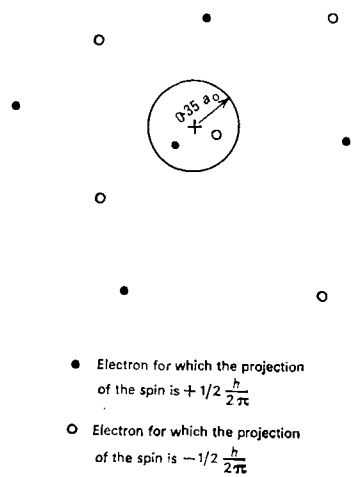


FIGURE 3. The best decomposition in loges for the fluorine negative ion.

If the volume of a given loge is divided by the number of electrons which it usually contains, a certain volume v is obtained which gives an idea of the space associated with one electron in the loge. Moreover, we can evaluate the average value p of the electronic potential which is exerted in the loge. Odiot and Daudel[5] observed that for all atoms and all shells the following relation applies:

$$p^{\frac{4}{3}}v = \text{constant}$$

A kind of Boyle–Mariotte law exists between the 'electronic pressure' p and the volume v associated with one electron in an atomic loge.

Another important feature arises from the Pauli principle or in other words from the symmetry of the electronic wave functions. In wave mechanics the probability dP of finding an electron in a volume dv surrounding a point M is written as:

$$dP = |\psi_{(M)}|^2\, dv$$

where $\psi_{(M)}$ is the de Broglie wave function which satisfies the Schrödinger equation. For a system of electrons this writing is generalized and

$$dP_{12} = |\psi(M_1, \omega_1, M_2, \omega_2)|^2\, dv_1\, dv_2$$

represents the probability of finding electron 1 with a projection of the spin equal to ω_1 in a volume dv_1 surrounding the point M_1, and electron 2 with a projection of the spin ω_2 in a volume dv_2 at point M_2. As a consequence of the indistinguishability of electrons it is easy to show that ψ must be symmetric or antisymmetric with respect to a permutation of the electronic coordinates. That is to say:

$$\psi(M_1, \omega_1, M_2, \omega_2) = \pm\psi(M_2, \omega_2, M_1, \omega_1)$$

The *Pauli principle* consists of selecting the sign minus. We are led to the very important relation:

$$\psi(M_1, \omega_1, M_2, \omega_2) = -\psi(M_2, \omega_2, M_1, \omega_1) \qquad (1)$$

Let us calculate the probability of finding the two electrons in the same volume dv at point M with the same projection of the spin ω. This probability will be:

$$dP = |\psi(M, \omega, M, \omega)|^2\, dv\, dv$$

but the relation (1) becomes:

$$\psi(M, \omega, M, \omega) = -\psi(M, \omega, M, \omega)$$

which obviously shows that:

$$\psi(M, \omega, M, \omega) = 0$$

Therefore the probability of finding two electrons with the same projection of the spin in the same small volume is zero. In other words two electrons with the same projection of the spin (or, in short, 'with the same spin') do not like to occupy the same small volume of the space. Obviously this is also true for two electrons of opposite spin as there is always the Coulomb repulsion, but when the spins are the same a stricter repulsion is added to this Coulomb repulsion. This is why two electrons with opposite spins are sometimes said to be coupled. This does not mean that they like to occupy the same small volume of space. The interaction between them remains a strong repulsion but the repulsion is less severe than when they have the same spin. In conclusion it may be said that two electrons with opposite spin can be found in a smaller portion of space than two electrons possessing the same spin.

Another way of picturing this phenomenon is to compute the most probable configuration of the electrons of various atoms. The most probable configuration of an atom is the set of electronic coordinates which corresponds to the highest maximum of the modulus of the wave function. Figure 4 represents the most probable configuration of

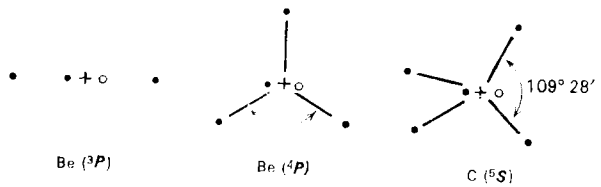


FIGURE 4. The most probable electronic configuration of small atoms.

some small atoms, computed by Linnet and Poe[6]. For beryllium in its ^3P state, the most probable configuration corresponds to two electrons of opposite spins at the nucleus and two electrons of the same spin at 2·7 a_0 from the nucleus; the angle formed by these two electrons and the nucleus is therefore 180°. In the case of boron in its ^4P state, two electrons of opposite spins are found at the nucleus and three electrons with the same spin are found 2·45 a_0 from the nucleus at the vertices of an equilateral triangle. In the case of carbon (^5S) four electrons possessing the same spin are found at the vertices of a regular tetrahedron. It is observed, as expected, that in the same loge, the electrons possessing the same spin tend to form the largest possible angles with the nucleus.

The notion of loge is also helpful in describing the electronic structure of molecules. In a good division of a molecule into loges, some loges usually appear which were also representative of the free atoms before bonding. Such loges are said to be *loges of the cores* while the others can be called *loges of the bonds*. As an example let us take the case of the lithium molecule Li_2. Figure 5 represents a good division

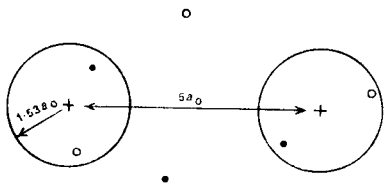


FIGURE 5. A good decomposition in loges for the lithium molecule.

of this molecule[3] into loges. In the two spherical loges which look like the K loges of the lithium atoms there is a probability of 0·96 of finding two electrons (and two only) with opposite spins. Therefore the distribution of the electrons symbolized by Figure 5 has a very high probability. The region of space outside of the two spheres where there is also a high probability of finding a pair of electrons, can be considered as the loge corresponding to a two-electron bond.

Another useful notion which gives information on the nature of the chemical bond is the *density difference function* given by the equation:

$$\delta(M) = \rho(M) - \rho^f(M)$$

where $\rho(M)$ is the actual electronic density at a given point M of a molecule, and $\rho^f(M)$ is the electronic density which would occur at this point if the density in the molecule were the simple sum of the density in the free atoms. Therefore, at any point where $\delta(M)$ is positive, an increase of electronic density results from the binding. On the other hand, in any region where $\delta(M)$ is negative, the binding has led to a decrease in the electronic density. Figure 6 shows the variation of $\delta(M)$ along the line of the nuclei of the hydrogen molecule H_2[7]. It is seen that between the nuclei $\delta(M)$ is positive. In agreement with chemical intuition the chemical binding produces an increase in the electronic density in this region.

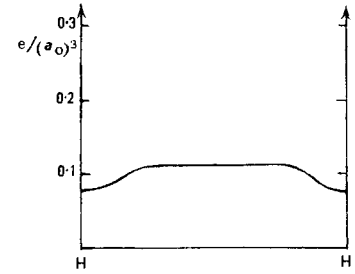


FIGURE 6. The density difference function in the hydrogen molecule.

If we consider now a molecule like O_2 we are led to a rather different conclusion. Figure 7 corresponds to that case[8]. There is no increase of electronic density between the nuclei but an annular region centered on the axis of the molecule where $\delta(M)$ is positive. The fact that there is no increase of electronic density along the nuclear axis is probably due to the presence of four electrons (two of each spin) in this vicinity. The strong repulsion between electrons possessing the same spin tends

to place them outside the small space surrounding the bond axis. Therefore we can say that between the cores of small atoms near the bond axis there is only room for two electrons with opposite spins.

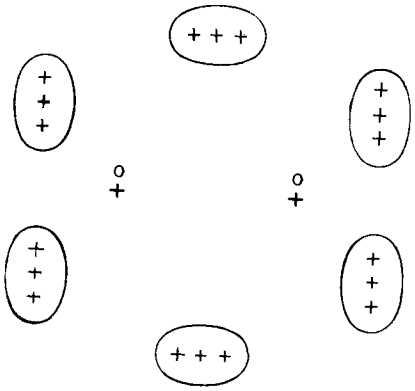


FIGURE 7. The density difference function in the oxygen molecule.

This is the reason why a molecule in which the number of electrons of the loges of the bonds is twice the number of adjacent atomic cores usually contains two-electron bonds. Let us consider methane. This molecule contains ten electrons. In a good division into loges two will be associated with the K loge of the carbon atom in such a way that eight electrons remain in the binding region. As there are four pairs of neighboring cores we expect the formation of four C-H loges associated with the two electrons which are very often near the bond axis (Figure 8). Four electrons possessing a projection of the spin $+\frac{1}{2}h/2\pi$

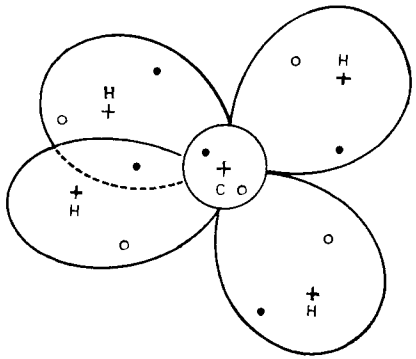


FIGURE 8. Methane.

will very often be in the binding region surrounding the carbon core. They will tend to form angles of 109° 28′ with the carbon nucleus. The same will be true for the four electrons of spin $-\frac{1}{2}h/2\pi$. As in the vicinity of each C—H axis there is very often one electron of positive spin (and also one of negative spin) we must expect that the angle between the C—H axes will also be 109° 28′. This explains why methane is a tetrahedral molecule.

Now let us consider the molecule NH_3 (the simplest amine!). It also contains ten electrons and two will be associated with the K loge of the nitrogen atom and eight electrons will remain in the binding region. As the total projection of the spin of such a molecule is zero this region will often contain four electrons with positive spin and four with negative spin. In the case of CH_4, the electrons possessing the same spin tended to form tetrahedral angles but as in NH_3 there are only three pairs of neighboring cores, six electrons only will be used to form three N—H bonds, while two electrons will remain as a lone pair (Figure 9). However, the angle between the N—H bonds will again be of the order of 109°, explaining why NH_3 is pyramidal. Obviously the lone pair can be considered as 'a potential bond'. If a proton is added to the system, the NH_4^+ ion is obtained (Figure 9) where the four N—H bonds produce a structure very similar to that of methane.

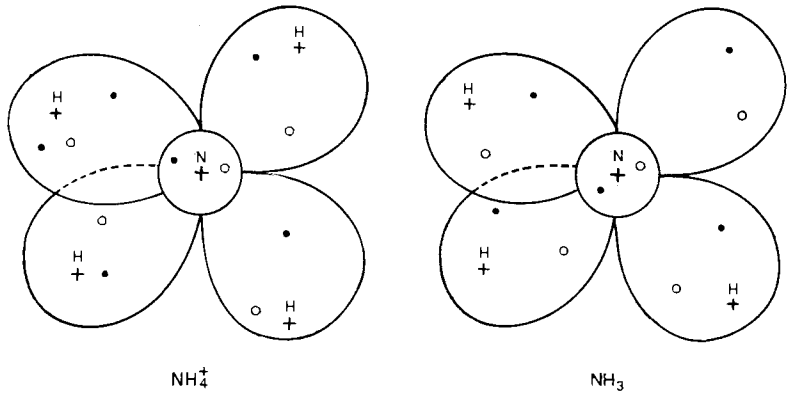


FIGURE 9. Ammoniac and ammonium ion.

When, as in CH_4, NH_3, NH_4^+, it is possible to find, between two neighboring cores, a good loge associated with a certain number n of electrons possessing a given organization of spin, it can be said that an n-electron localized bond between these cores has been defined.

But it is easy to see that in certain cases it is not possible to localize, between only two cores, a region where there is a high probability of finding n electrons with a precise organization of spins. This is the case with diborane B_2H_6. This molecule contains 16 electrons. Four of them can be associated with the two K loges of boron. Twelve electrons remain for binding purposes. Diborane consists of eight pairs of neighboring cores. Therefore it is not possible to associate a two-electron localized bond with each pair of neighboring cores. From the experimental viewpoint the four outer B—H bonds have the same behavior as normal localized two-electron bonds. Then, we are led to try a division into loges similar to the one described in Figure 10a,

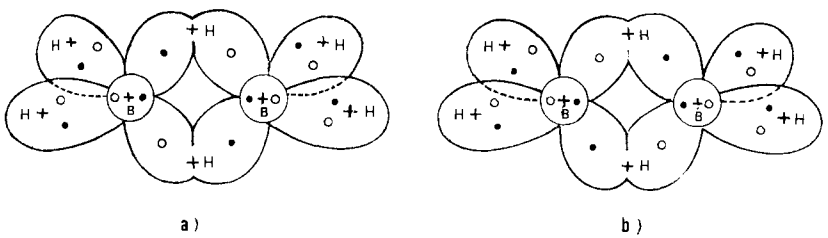


FIGURE 10. Decompositions in loges of diborane.

since only four electrons remain for the four central pairs of neighboring cores. But obviously, Figure 10b corresponds to another situation, which for symmetry reasons possesses the same probability as the one shown in Figure 10a. Therefore the probability of the electronic configuration being symbolized by one of these two figures cannot be higher than $\frac{1}{2}$ which does not correspond to a good division into loges.

If now, the space of the central B—H is divided between two three-center loges, as in Figure 11, this difficulty disappears. There are no

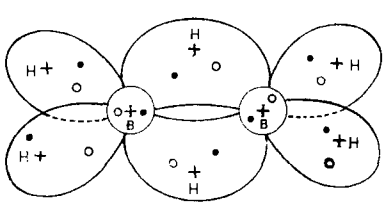


FIGURE 11. Another decomposition in loges of diborane.

a priori reasons to exclude the possibility of finding such good loges. As they are now extended over more than two cores we shall say that they correspond to delocalized bonds; more precisely to two-electron

bonds delocalized over three centers. In conclusion, when it is not possible to find a good loge between two cores the loge will be extended over a greater number of cores and an n-electron bond delocalized over p centers will be considered.

B. The Main Methods of Calculating Electronic Molecular Wave Functions[9]

Assuming that the Born–Oppenheimer approximation is convenient, the main ideas forming the basis of the principal methods of calculating electronic molecular wave functions will now be summarized.

In the approximation the calculation of this function is done as if the nuclei were fixed. To obtain the space part Φ of the wave function we are led to solve a Schrödinger equation

$$\mathbf{H}\Phi = W\Phi$$

where $\mathbf{H}$ is the non-relativistic Hamiltonian and W the energy of an electronic state of the molecule. The total electronic wave function Ψ is obtained by multiplication of Φ by a convenient spin function σ and after transformation of the product $\Phi\sigma$ in order to obey the Pauli principle, we can write

$$\Psi = A\Phi\sigma \tag{2}$$

if A represents the convenient antisymmetrisor.

As it is not possible to solve the Schrödinger equation (except for very simple molecules) it is customary to use approximate solutions. An important starting point to find such solutions lies in the independent electron model. In this model the repulsion between the electrons is neglected. The corresponding part of the Hamiltonian $\mathbf{H}$ vanishes and only a certain part $\mathbf{H}^0$ remains. Thus, one must solve the equation

$$\mathbf{H}^0\Phi^0 = W^0\Phi^0 \tag{3}$$

It is easy to show that

$$\Phi^0 = \varphi_1(M_1)\varphi_2(M_2)\ldots\varphi_n(M_n) \tag{4}$$

is a solution of equation (3) if n electrons are involved in the problem, and if the various φ_i obey the equation

$$h\varphi_i = \varepsilon_i\varphi_i \tag{5}$$

where h is the Hamiltonian corresponding to the motion of one electron

in the field of the nuclei of the molecule under consideration. If this solution is taken

$$W^0 = \varepsilon_1 + \varepsilon_2 + \cdots \varepsilon_n + \cdots \quad (6)$$

The functions φ_i are called molecular orbitals. Obviously the discussion applies to the case of one atom (which may be considered to be a monoatomic molecule), and then the φ_i are atomic orbitals. The relation (6) shows that the energy associated with a given state of the independent-electron model is the sum of the energies ε_i associated with the various orbitals introduced in the wave function Φ^0.

If now we consider the total wave function obtained from equation (2) we have

$$\Psi^0 = A\Phi^0\sigma \quad (7)$$

and it is readily seen that this function is a linear combination of Slater determinants. For this reason it is not possible to introduce in Φ^0 a given orbital more than twice (one with the α spin function corresponding to the positive projection of the spin and one with the β spin function corresponding to the negative projection), otherwise the determinants will vanish.

But the solutions of the independent model are very far from exact solutions because the repulsion between the electrons is far from being negligible. For this reason this interaction must be taken into account at least in part. To do so the general form of equation (7) can be kept, that is to say it is assumed that Φ^0 is a product of monoelectronic functions φ, but that these φ do not obey equation (5) and must be chosen by a variational procedure. The functions φ obtained in this way are again called molecular orbitals. This is the essence of the *self-consistent field method.* In fact it is very tedious to solve the exact equation corresponding to the self-consistent field method. A new approximation is usually made; it is assumed that a molecular orbital can be expanded as a linear combination of the atomic orbitals associated with the atoms constituting the molecule: this is the LCAO approximation.

Some aspects of the calculation of wave functions in this framework will be demonstrated, using the simplest amine, NH_3, as an example. The ammonia molecule has been studied by several authors[10] using the self-consistent field method with the LCAO approximation. Kaplan's results will be analyzed. Figure 12 shows how the axes are chosen. The three hydrogen nuclei $H_{(1)}$, $H_{(2)}$ and $H_{(3)}$ lie in the plane xOy, $H_{(1)}$ being on Ox. The nitrogen nucleus is on the z axis. First of all, the most important atomic orbitals must be listed. As the

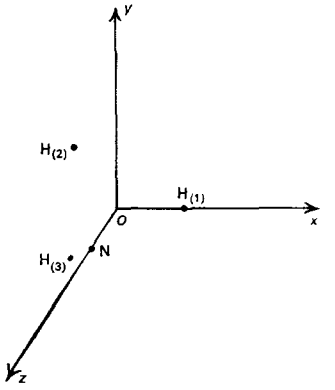


FIGURE 12. Coordinate axis for NH_3.

ground-state wave function must be computed, only those atomic orbitals which are usually used in the representation of the ground states of the free atoms will be considered. These are:

— the $1s$ orbital corresponding to the K shell for each hydrogen atom (Let a, b and c be the $1s$ orbitals of $H_{(1)}$, $H_{(2)}$ and $H_{(3)}$ respectively)
— the $1s$ orbital corresponding to the K shell of the nitrogen atom
— and the $2s$, $2p_x$, $2p_y$ and $2p_z$ orbitals associated with the L shell of the same atom.

TABLE 1. Ammonia molecular orbitals.

$$\varepsilon_1 = -15{\cdot}5682$$
$$\varphi_1 = 1{\cdot}001(1s) - 0{\cdot}0033(2s) - 0{\cdot}0020(2p_z) - 0{\cdot}0013(h_0)$$
$$\varepsilon_2 = -1{\cdot}1482$$
$$\varphi_2 = 0{\cdot}0286(1s) + 0{\cdot}7591(2s) + 0{\cdot}1616(2p_z) - 0{\cdot}2711(h_0)$$
$$\varepsilon_3 = \varepsilon_4 = -0{\cdot}6625$$
$$\varphi_3 = 0{\cdot}6195(2p_x) + 0{\cdot}4860(h_x)$$
$$\varphi_4 = 0{\cdot}6195(2p_y) + 0{\cdot}4860(h_y)$$
$$\varepsilon_5 = -0{\cdot}4646$$
$$\varphi_5 = 0{\cdot}0257(1s) - 0{\cdot}4418(2s) + 0{\cdot}8956(2p_z) - 0{\cdot}2582(h_0)$$

with,

$$h_0 = n_0(a + b + c)$$
$$h_x = n_x(a - \tfrac{1}{2}(b + c))$$
$$h_y = n_y(b - c)$$

n_0, n_x, n_y being normalization coefficients.

Following the LCAO approximation each molecular orbital φ_i is expanded as a linear combination of these various atomic orbitals

$$\varphi_i = k_1 a + k_2 b + k_3 c + k_4 1s + k_5 2p_x + k_6 2p_y + k_7 2p_z + k_8 2s$$

where the k's are numerical coefficients that must be computed in such a way that the total energy associated with the wave function is a minimum, since we are concerned with the ground state.

Thus a mathematical problem must be solved which leads to Roothaan's equations. In the case of ammonia these equations have been solved by Kaplan who obtained the following results. Table 1 contains the explicit form of the molecular orbitals obtained with the values of the associated energies ε_i (in atomic units).

The corresponding function Φ is

$$\Phi = \varphi_1(M_1)\varphi_1(M_2)\varphi_2(M_3)\varphi_2(M_4)\varphi_3(M_5)\varphi_3(M_6)\varphi_4(M_7)\varphi_4(M_8)\varphi_5(M_9)\varphi_5(M_{10})$$

and the total electronic wave function

$$\Psi = A\Phi\sigma$$

can be written as

$$\Psi = \det \varphi_1(M_1)\overline{\varphi_1(M_2)}\varphi_2(M_3)\overline{\varphi_2(M_4)}\varphi_3(M_5)\overline{\varphi_3(M_6)}\varphi_4(M_7)\overline{\varphi_4(M_8)}\varphi_5(M_9)\overline{\varphi_5(M_{10})}$$

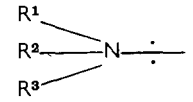
where 'det' means the Slater determinant built by permutation of the coordinates in the product of orbitals; a molecular orbital with a bar, e.g. $\bar{\varphi}$, being associated with a β spin function and an orbital without a bar being associated with an α spin function. The total energy corresponding to this wave function is $-56{\cdot}266$ a.u. There is a fair agreement with the experimental value of $-56{\cdot}596$, the error being smaller than one per cent. It is interesting to note that this energy is not the sum of the energies associated with the molecular orbitals introduced in the wave function. Such a relation only applies in the framework of the independent-electron model and disappears when the repulsion between electrons is taken into account.

Other properties can be computed from the wave function but as is well known the precision is not as good as in the case of the total energy. If the first ionization energy is calculated using Koopman's approximation, that is to say if it is taken as equal to $-\varepsilon_5$ a value of about 14 ev is obtained. Experiment gives 11 ev. Furthermore the wave function Ψ corresponds to a dipole moment of 1·82 D, the experimental value being 1·46.

II. SOME ASPECTS OF THE PROPERTIES OF AMINES IN THEIR GROUND STATE

A. A Theoretical Discussion of some Physical Properties of Aliphatic Amines in their Ground State

The general formula of aliphatic amines can be written as



where R^1, R^2 and R^3 are hydrogen atoms or alkyl groups. As has been stated the ammonia molecule NH_3 can be considered as the simplest aliphatic amine. In fact many aliphatic amines possess the most important properties of ammonia. They all contain a lone pair of electrons on the nitrogen atom and three two-electron localized bonds starting from this atom. Therefore, as in the case of NH_3, four pairs of electrons are found surrounding the nitrogen core. For this reason it must be expected that the $\widehat{RNR}$ angles will be about 109° except when steric hindrance or geometrical strain appears.

For example, in trimethylamine the $\widehat{CNC}$ angle is 108° 40′ ± 1°[11]. Table 2 contains other geometrical data concerning this molecule.

TABLE 2. Valence angles and interatomic distances in trimethylamine.

$\widehat{CNC}$ angle	108·7° ± 1°[11]	or	108 ± 4°[12]
C–N distance	1·472 ± 0·008 Å[11]	or	1·47 ± 0·002 Å[12]
$\widehat{HCH}$ angle	108·5 ± 1·5°[11]		
C–H distance	1·090 Å[11]		

The electronic structure of the N—H bond in ammonia has been carefully investigated by Tavard[13] from the theoretical viewpoint. Since the electronic structure of the N—H bond in aliphatic amines is probably very similar, the main results obtained by Tavard will be reported. He calculated the electronic density in NH_3 using a very elaborate electronic wave function obtained by Moccia[14]. Figure 13 shows lines corresponding to various values of the density difference function $\delta(M)$. From this figure it appears that during the formation of the chemical bond there is some electron transfer from the hydrogen to the nitrogen (as δ is negative near the hydrogen and positive near the nitrogen in the vicinity of the bond axis). This transfer is in good agreement with chemical intuition as nitrogen is considered to be more

electronegative than hydrogen. Furthermore, Figure 13 shows a region in which δ is positive and which forms an angle of about 109° with the bond axis. This result is consistent with the idea of the localization of a lone pair near this region.

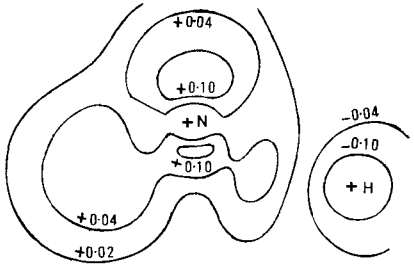


FIGURE 13. Density difference function in NH_3.

Electron diffraction experiments[15] confirmed this effect of the binding on the distribution of electron density in ammonia. Figure 14, reproduced from the paper of Iijima and coworkers[15], shows the variation of density as a function of the diffraction angle. Curve a corresponds to theoretical calculations for which it is assumed that

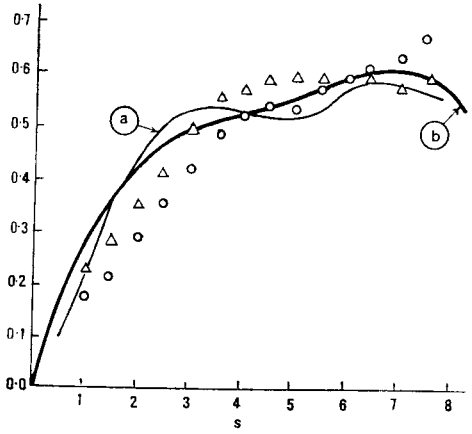


FIGURE 14. Intensity scattered as a function of the diffraction angle.

the electron density at a given point of the molecule is the sum of the electron densities of the free atoms, curve b is calculated from the actual density in the molecule when the Moccia electron wave function is used and finally the points Δ and O correspond to the experimental

results. First of all, it can be seen that there is a significant difference between curve a and curve b for the small angles. This difference is a theoretical measurement of the effect of the binding on the electron density (as is the δ function). The agreement observed between curve b and the experimental results inspires confidence in this measurement.

The N—H stretching vibration corresponds to an infrared band between 3500 and 3400 cm^{-1} in the spectra of secondary aliphatic amines taken in dilute solution in carbon tetrachloride to avoid molecular association[16]. Under these conditions primary aliphatic amines show two bands near 3500 and 3400 cm^{-1} (asymmetrical and symmetrical vibrations)[16]. Among the vibration frequencies associated with ammonia two harmonic frequencies are found in approximately the same region (3506 and 3577 cm^{-1})[17]. Therefore we can anticipate that the main force constant K_{RR} will be of the same order of magnitude for NH_3, as well as for secondary and primary amines. This fact supports the hypothesis that the electronic structure of the N—H bonds would not be very different in all these molecules.

The force constant K_{RR} of ammonia has been evaluated as 7·17 from the infrared spectrum. Allavena calculated the same constant[18] (with the help of an electronic wave function similar to Moccia's function, but a little less precise) and obtained a value of 9. The agreement between experiment and theory is not very satisfactory and could certainly be improved if Moccia's function itself were used.

The first ionization energy of aliphatic amines, as in the case of NH_3, is essentially the production of an electron hole in the lone-pair region. It must therefore be expected that the first ionization energy is of the same order of magnitude in all this set of molecules. This is found to be the case since in ammonia the first ionization energy has been evaluated as 10·5[19] or 11[20] ev, the corresponding energy being estimated as 9 ev in trimethylamine[21].

The electric dipole moment of aliphatic amines also contains a contribution from the lone pair, but as the various bonds also contribute, the resulting value varies in a more significant manner in going from one molecule to another. For example, it is evaluated as 1·46 D in the case of ammonia, while values between 0·61[22] and 0·86 D[23] can be found in the literature for the dipole moment of trimethylamine.

B. Physical Properties of Aromatic Amines in their Ground State

Very little precise information is known about the geometry of aromatic amines. Some problems remain even in the case of the simplest aromatic amine, aniline. The main part of the molecule is certainly

planar and the nitrogen is certainly in the plane of the aromatic ring. Figure 15 shows for example, the values of valence angles and interatomic distances in a parent compound[24]. It is seen that the geometrical organization of the aromatic ring is very similar to that of

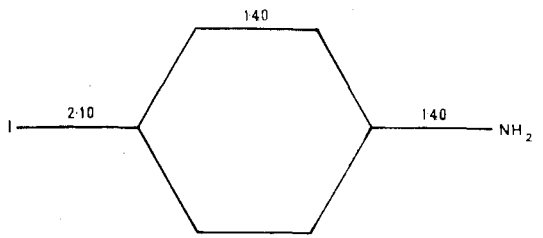


FIGURE 15. Interatomic distances in *para*-iodoaniline.

benzene, but the position of the two hydrogen atoms of the NH_2 group is not yet known exactly. Van Meerssche and Leroy[25] studied the geometrical structure of 2-bromo-4′-dimethylamino-2-cyanostilbene by x-ray diffraction. Figure 16 shows the results concerned with the part of the molecule which contains the amino group. The authors claim that the dimethylamino group and the neighboring aromatic ring are coplanar. Furthermore, it is seen that again the geometry of the aromatic ring does not differ greatly from that of benzene. It should be noted that the length of the C—N bond connecting the amino group and the ring is only 1·34 Å. (The length of a normal C—N simple bond is 1·47 Å.)

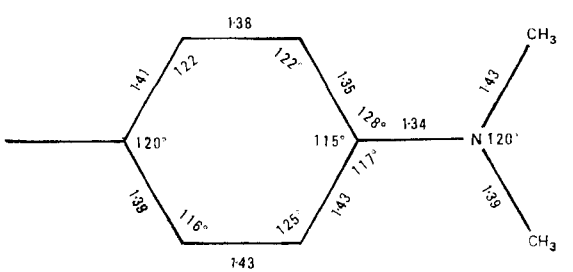


FIGURE 16. Geometry of a part of 2-bromo-4′-dimethylamino-2-cyanostilbene.

On the other hand, in their recent book Higasi and coworkers[26] remark that if the group NH_2 were in the plane of the ring, *p*-diaminobenzene should be non-polar like *p*-dichlorobenzene. This is not so, as the former has a large dipole moment of 1·5 D[27]. An explanation of this

apparent discrepancy may lie in the fact that the amino group and the ring would not be coplanar in the gaseous or liquid phase, but would be so in the crystal used to observe the x-ray pattern.

No precise detailed experimental study of the electronic distribution in aromatic amines seems to be available. The only way to obtain such information is from theory. Let us consider the case of aniline. As this molecule contains a ring similar to that in benzene, data known about the latter will first be recalled. The total number of electrons is 42. If 12 electrons are accounted for as being associated with the six *K* loges corresponding to the carbon cores, 30 electrons remain to be associated with the loges of the bonds. The benzene molecule contains 12 pairs of neighboring cores. The number of electrons is therefore higher than twice the number of the pairs of neighboring cores. If two electrons are associated with each pair of neighboring cores, six additional electrons must still be accounted for. As the C—H bonds appear to be normal simple bonds a convenient division into loges will contain a two-electron localized bond associated with each C—H bond. The six remaining electrons have to be associated with the central hexagon. Figure 17a shows a possible division into loges but Figure 17b represents another one which for symmetry reasons has the same probability.

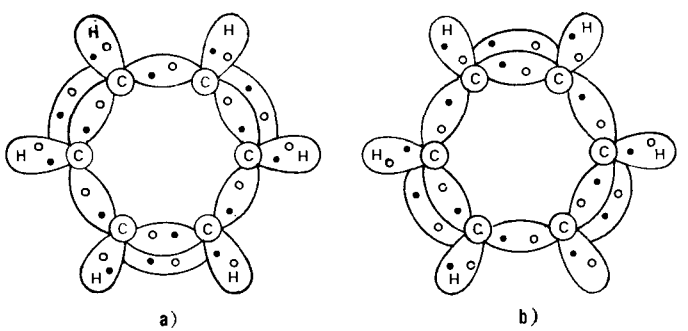


FIGURE 17. Decompositions in loges of benzene.

Therefore this probability will be at best equal to 0·5. This value does not correspond to a good division into loges. Figures 18a and 18b correspond to other divisions, which are poor for the same reasons. Thus the division shown in Figure 19 is usually adopted, in which there is a six-electron bond delocalized over the six carbon cores.

To calculate a corresponding electronic wave function the LCAO approximation must be introduced. In this approximation the molecular orbitals will be expanded on the atomic orbitals associated with

the free atoms, that is to say a $1s$ orbital for each hydrogen atom (let us call them $h_1, h_2, \ldots, h_6$ respectively) and for each carbon atom the orbitals $1s$, $2s$, $2p_x$, $2p_y$, $2p_z$. Obviously the carbon $1s$ orbitals can be associated with the carbon K loges.

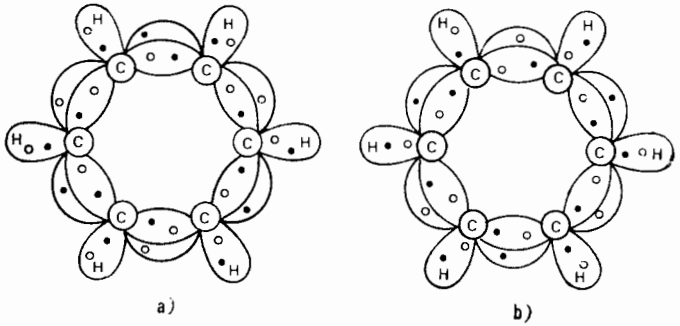


FIGURE 18. Other decompositions in loges of benzene.

To represent a two-electron localized bond a function must be built with important values in the corresponding loges. As the nuclei about a carbon atom ($C_{(1)}$ for example) make angles with it of approximately 120° the following three hybrid orbitals must be considered for this atom

$$tr_1 = \frac{1}{\sqrt{3}} 2s_1 + \frac{\sqrt{2}}{\sqrt{3}} 2p_{1x}$$

$$tr_1' = \frac{1}{\sqrt{3}} 2s_1 - \frac{1}{\sqrt{6}} 2p_{1x} + \frac{1}{\sqrt{2}} 2p_{1y}$$

$$tr_1'' = \frac{1}{\sqrt{3}} s_1 - \frac{1}{\sqrt{6}} 2p_{1x} - \frac{1}{\sqrt{2}} 2p_{1y}$$

the Ox axis being along the corresponding $C_{(1)}$—$H_{(1)}$ bond and the Oy axis in the plane of the ring, because the hybrid tr_1 points in the direction of the hydrogen atom, tr_1' and tr_1'' point respectively in the directions of the neighboring carbon atoms as seen in Figure 20. These hybrid orbitals are called *trigonal orbitals*. Therefore, associated with the $C_{(1)}$—$H_{(1)}$ bond is the bond orbital

$$ah_1 + btr_1$$

and with the localized $C_{(1)}$—$C_{(2)}$ bond, the bond orbital

$$ctr_1' + dtr_2''$$

and so on.

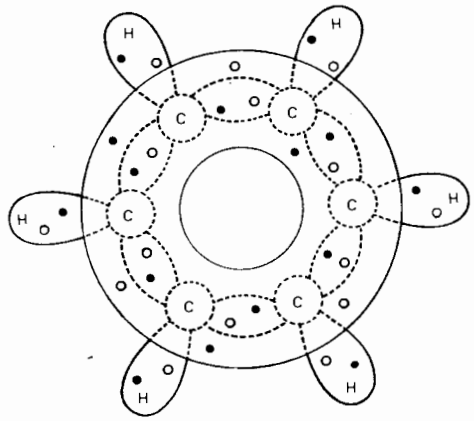


FIGURE 19. A better decomposition in loges of benzene.

Of all atomic orbitals only the $2p_z$'s remain unused. It is natural to associate them with the delocalized bond and to consider the molecular orbitals

$$\pi_i = s_{1i}2p_{1z} + s_{2i}2p_{2z} + \cdots + s_{6i}2p_{6z}$$

where the s_i's are unknown coefficients.

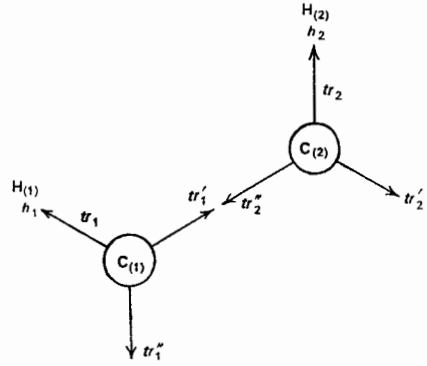


FIGURE 20. Hybridization in benzene.

As six electrons must be associated with the delocalized bonds at least three π orbitals will have to be introduced. To compute the coefficients s_i it is necessary to introduce additional approximations such as the Hückel[28] or the Pariser and Parr[29] approximation. Details

of these approximations can be found elsewhere[1]. Table 3 contains the π orbitals obtained and the associated energies when the Hückel approximation is used[30].

The square of an s_i coefficient before a certain $2p_z$ is considered to be the electronic charge introduced by the π orbital in the corresponding carbon atom. It is seen, for example, that the orbital π_1 introduces a charge equal to $(0{\cdot}408)^2$ on each carbon atom. As each of the three π orbitals must be used twice for the description of the ground state of benzene (as there are six electrons associated with the delocalized bond) the total electronic charge introduced in carbon 1 by the delocalized bond is

$$q_1 = 2(0{\cdot}408)^2 + 2(0{\cdot}577)^2 = 1$$

The same result is obtained for the other carbon atoms.

On the other hand, the quantity $s_{2i}s_{3i}$ is considered to be the contribution of the orbital π_i to the bond order[31] introduced between carbon 2 and carbon 3 by the delocalized bond. Then the bond order between carbon 1 and carbon 2 due to the presence of the delocalized bond is

$$p_{23} = 2(0{\cdot}408)^2 + 2(0{\cdot}500)^2 - 2(0{\cdot}288)^2 = 0{\cdot}666$$

The same bond order is obtained for the other pairs of adjacent carbon atoms.

Let us consider now the case of aniline. The orbitals $1s_N$, $2s_N$, $2p_{Nx}$, $2p_{Ny}$, $2p_{Nz}$ will have to be introduced to take account of the nitrogen atom in place of the orbital h_1, and the $1s$ orbitals associated with the hydrogen $H_{(7)}$ and $H_{(8)}$ belonging to the amino group must be considered. Let us call h_7 and h_8 these orbitals. Let us assume that aniline is a completely planar molecule. The $1s_N$ orbital will be associated with the nitrogen K loge. The $2s_N$, $2p_{Nx}$ and $2p_{Ny}$ orbitals will be combined in such a way as to produce three trigonal orbitals tr_N, tr'_N and tr''_N which will be used to represent the various two-electron localized bonds $C_{(1)}$—N, N—$H_{(7)}$ and N—$H_{(8)}$ (Figure 21). The

TABLE 3. Benzene molecular orbitals.

$$\varepsilon_1 = 2\beta$$
$$\pi_1 = 0{\cdot}408(2p_{1z} + 2p_{2z} + 2p_{3z} + 2p_{4z} + 2p_{5z} + 2p_{6z})$$
$$\varepsilon_2 = \beta$$
$$\pi_2 = 0{\cdot}500(2p_{2z} + 2p_{3z} - 2p_{5z} - 2p_{6z})$$
$$\varepsilon_3 = \beta$$
$$\pi_3 = 0{\cdot}577(2p_{1z} - 2p_{4z}) + 0{\cdot}288(2p_{2z} - 2p_{3z} - 2p_{5z} + 2p_{6z})$$

delocalized bond can therefore be extended over the nitrogen atom as the $2p_{Nz}$ orbital is not yet used. The π orbitals become

$$\pi_i = s_{1i}2p_{1z} + s_{2i}2p_{2z} + s_{3i}2p_{3z} + s_{4i}2p_{4z} + s_{5i}2p_{5z} + s_{6i}2p_{6z} + s_{Ni}2p_{Nz}$$

A simple calculation shows that the nitrogen atom introduces two electrons into the delocalized bond. Therefore to describe the ground state of aniline four different π orbitals must be considered, each of them being used twice.

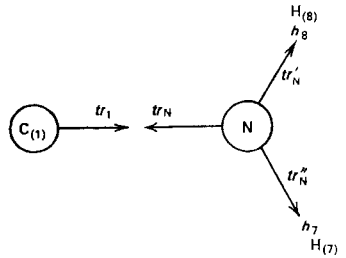


FIGURE 21. Hybridization in aniline.

Obviously, as in the case of benzene, additional approximations are necessary in calculating the coefficients s. But contrary to the case of benzene, the values of these coefficients depend on the values chosen for the parameters which characterize the atoms and the bonds. The parameters under consideration are therefore very often chosen in order to obtain a good agreement between experiment and calculation for certain properties of the molecule. In the present case, it is believed that the error introduced by assuming that aniline is completely planar is probably reduced by using this empirical choice of parameters.

A recent study of aniline using the Hückel method has been made by Fischer-Hjalmars[32]. The same author also used the more sophisticated Pariser and Parr approximation. Figure 22 represents the corresponding molecular diagrams showing the distribution of bond orders and atomic charges associated with the delocalized bonds. The presence of a bond order of the order of 0·3 along the C—N bond explains why it is shorter than a normal C—N two-electron bond. From the diagram showing the distribution of the electronic charge it is seen that in the delocalized bond there is a charge transfer of about 0·07 electrons from the nitrogen atom to the ring. The main result of this transfer is the presence of an excess of electrons at the *ortho* and *para* positions which therefore become negative.

It must also be pointed out that the charge is more negative in the *ortho* than in the *para* position when the Pariser and Parr method is used. This result seems in agreement with recent measurements of these charges based on n.m.r. experiments[33]. Finally, the contribution

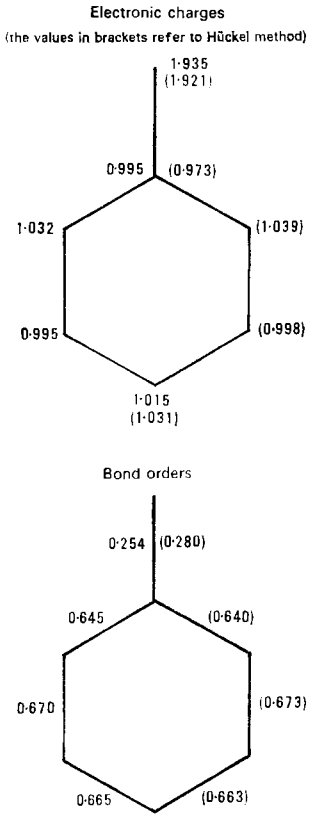


FIGURE 22. Molecular diagrams of aniline.

of the delocalized bond to the dipole moment of aniline is calculated as 1·2 D by the Hückel method and as 0·78 D by the Pariser and Parr method. The corresponding experimental estimation is 0·7 D[34].

C. Chemical Properties of Amines in their Ground State

The basic behavior of amines is certainly one of their most important chemical properties. If B denotes the neutral molecule the corresponding equilibrium constant can be written as:

$$B + H^+ \underset{K}{\rightleftharpoons} BH^+$$

and the equilibrium constant K is a measure of the basic strength of the amine.

Let us consider the equilibrium

$$A + B \underset{K}{\rightleftharpoons} C + D.$$

It is well known that K can be expressed as

$$K = \frac{f_A f_B}{f_C f_D} e^{-\Delta\varepsilon/\chi T}$$

if the concentrations are small. In this expression the f's denote the various partition functions associated with the distribution of the various chemical species on the various translational, rotational and vibrational levels at the temperature T, and $\Delta\varepsilon$ represents the difference between the sum of the ground-state energies of molecules C and D and the sum of the ground-state energies of molecules A and B. Finally χ denotes the Boltzmann constant. Therefore

$$\Delta\varepsilon = \varepsilon_{0C} + \varepsilon_{0D} - (\varepsilon_{0A} + \varepsilon_{0B})$$

Now for a large molecule a ground-state energy ε_{0i} may be divided into various parts:

(a) the vibrational energy ε_v corresponding to the zero point energy,
(b) the energy ε_l associated with the localized bonds and the atomic cores,
(c) the energy ε_d associated with the delocalized bonds taking account of the interaction of these bonds with the cores and the localized bonds,
(d) the energy ε_{nb} associated with the interaction between non-bonded atoms, including the steric effect.

Therefore with obvious notations $\Delta\varepsilon$ can be written as

$$\Delta\varepsilon = \Delta\varepsilon_v + \Delta\varepsilon_l + \Delta\varepsilon_d + \Delta\varepsilon_{nb}$$

which leads to

$$K = \frac{f_A f_B}{f_C f_D} e^{-(\Delta\varepsilon_v + \Delta\varepsilon_l + \Delta\varepsilon_d + \Delta\varepsilon_{nb})/\chi T}$$

But in many cases the reaction takes place in a solvent and then it is necessary to take into account the solvent effect. A simple way to do that, is to introduce a term $\Delta\varepsilon_s$ into $\Delta\varepsilon$ representing the difference between the solvation energies of the final products and the solvation

energies of the initial products. But, as the solvation energy of a molecule depends on the temperature, we shall write this term as

$$\Delta\varepsilon_s(\mathrm{T})$$

Furthermore, an index s will be put on each partition function to recall that the solvent effect can affect greatly this function. (Very often, for example, the free rotation of molecules becomes impossible and is replaced by oscillation.) Finally the expression

$$K = \frac{f_A^s f_B^s}{f_C^s f_D^s} e^{-[\Delta\varepsilon_v + \Delta\varepsilon_l + \Delta\varepsilon_d + \Delta\varepsilon_{nb} + \Delta\varepsilon_s(\mathrm{T})]/\chi\mathrm{T}} \quad (8)$$

is obtained, which shows that an equilibrium constant depends on six terms:

(a) the vibrational energy change $\Delta\varepsilon_v$
(b) the localized bond energy change $\Delta\varepsilon_l$
(c) the delocalized bond energy change $\Delta\varepsilon_d$
(d) the non-bonded atoms energy change $\Delta\varepsilon_{nb}$
(e) the solvation energy change $\Delta\varepsilon_s(\mathrm{T})$
(f) the ratio

$$f = \frac{f_A^s f_B^s}{f_C^s f_D^s}$$

of the partition functions.

To show how it is possible to use equation (8) in studying the basic strengths of amino compounds one should try to understand which are the main factors responsible for the change in base strength of the amino group from one amino acid to another. For such substances two different pK values must be considered; pK_1 corresponds to the equilibrium between

$$H_3N^+—CRR'—CO_2H \text{ and } H_3N^+—CRR'—CO_2^-;$$

and pK_2 is associated with the equilibrium between

$$H_3N^+—CRR'—CO_2^- \text{ and } H_2N—CRR'—CO_2^-.$$

Therefore the problem is the study of pK_2. Let us consider two amino acids with K_2 and K_2' as the corresponding equilibrium constants.

Taking account of equation (8)

$$\frac{K_2'}{K_2} = \frac{f'}{f} e^{-[\Delta\Delta\varepsilon_v + \Delta\Delta\varepsilon_l + \Delta\Delta\varepsilon_d + \Delta\Delta\varepsilon_{nb} + \Delta\Delta\varepsilon_s(\mathrm{T})]/\chi\mathrm{T}} \quad (9)$$

In this equation

$$\Delta\Delta\varepsilon_l = \Delta\varepsilon_l' - \Delta\varepsilon_l$$

The theoretical prediction of the variation of the pK in the set of molecules under consideration requires the calculation of f'/f and of the five $\Delta\Delta\varepsilon$ terms which appears in the exponent.

This calculation has been made by Del Ré, Pullman and Yonezawa[35]. They assumed that the ratio f'/f does not differ significantly from one and that $\Delta\Delta\varepsilon_v$ is negligible.

Obviously $\Delta\Delta\varepsilon_l$ is a very important term because during the protonation of the amino group a new N—H bond appears and it is necessary to compute the energy of this new bond. For this calculation the Del Ré method[36] is used. In this method an orbital is associated with each bond and by the LCAO approximation this bond orbital is taken as a linear combination of the two convenient hybrids associated with the two atoms constituting the bond.

The $\Delta\Delta\varepsilon_d$ terms are calculated using the Hückel approximation and as all these approximations do not take account explicitly of the electrostatic interaction occurring between the atomic charges Q, an additional term

$$\underset{\mu<\nu}{\Delta\varepsilon} \frac{Q_\mu Q_\nu}{r_{\mu\nu}}$$

is calculated in which $r_{\mu\nu}$ is the interatomic distance between atom μ and atom ν. This term contains the main part of $\Delta\varepsilon_{nb}$ when no steric hindrance occurs. Furthermore estimation of the $\Delta\varepsilon_s(\mathrm{T})$ terms has shown that $\Delta\Delta\varepsilon_s(\mathrm{T})$ is negligible, and by plotting the experimental pK as a function of

$$\Delta\varepsilon_l + \Delta\varepsilon_d + \underset{\mu<\nu}{\Delta\varepsilon} \frac{Q_\mu Q_\nu}{r_{\mu\nu}}$$

a rather satisfactory relationship was observed between the pK's and the considered term[35].

Another theoretical discussion of the pK of amino compounds is given in the case of amino derivatives of molecules like pyridine, quinoline, isoquinoline and acridine. There is experimental evidence to show that with such molecules protonation occurs at the nitrogen belonging to the aromatic rings. Therefore the pK is not related to the protonation of the amino group. However, its study is extremely interesting because it permits a measurement of the perturbation brought to the heteroatom by the amino group. It was seen in Figure 21, that *the amino group is able to increase significantly* the electronic charge of certain atoms of the aromatic ring. It must be expected, therefore, that this group is able to increase the ease of protonation of the

heteroatom and therefore to increase the pK_a of molecules like pyridine, quinoline and so on. This is exactly what experiment has shown.

Effectively the pK_a of pyridine at 20°c in water solution is 5·23[37] and the pK_a of *p*-aminopyridine is 9·17[37]. Therefore the dissociation constant of the positive ion is reduced by a factor of 10,000 as a result of the presence of an amino group, that is to say the amino derivative is much more basic than the pyridine itself.

Many authors[38] have discussed the role of $\Delta\varepsilon_d$ in the determination of the pK of such compounds. The importance of $\Delta\varepsilon_d$ is obvious, since during protonation the proton is directly bonded to the nitrogen heteroatom which belongs to the delocalized bond. The change in energy of the delocalized bond which results from this binding can be estimated by various methods. Figure 23 shows the results obtained[39] when the pK_a is plotted as a function of $\Delta\varepsilon_d$ calculated by

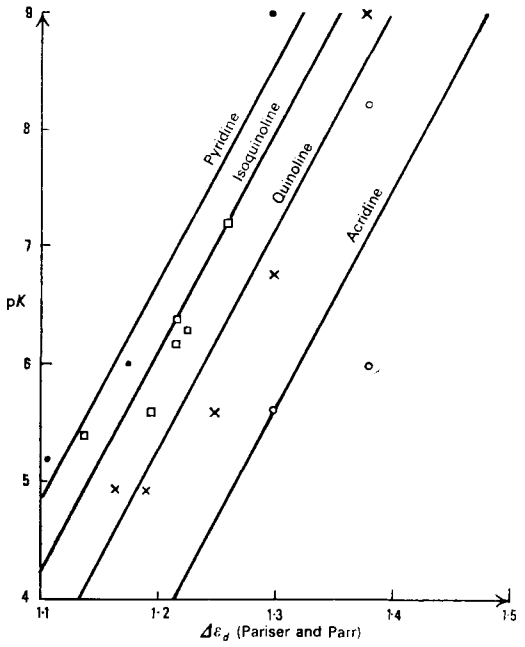


FIGURE 23. The pK as a function of $\Delta\varepsilon_d$.

the Pariser and Parr method. It is seen that the points corresponding to a set of compounds derived from a given skeleton (pyridine, isoquinoline, quinoline or acridine) lie along a straight line.

The role of the solvent effect has been discussed by Chalvet, Daudel and Peradejordi[39, 40].

The solvation energy of a molecule can be divided into three parts: the cavitation energy ε_{sc} associated with the hole that the molecule creates in the solvent, the orientation term ε_{so} due to the fact that the molecule modifies the average orientations of neighboring molecules of the solvent and the interaction energy ε_{si} due to the intermolecular forces which appear between the solvated molecule and the solvent. With obvious notations we can write

$$\Delta\varepsilon_s = \Delta\varepsilon_{sc} + \Delta\varepsilon_{so} + \Delta\varepsilon_{si}$$

In the present case we can assume that $\Delta\varepsilon_{si}$ is the most important term because during the protonation we are going from a neutral molecule to a positive ion, therefore we must expect a rather large $\Delta\varepsilon_{si}$ term. The discussion will be focused on the estimation of $\Delta\varepsilon_{si}$. This term itself can be divided into three parts. Let us call $\Delta\varepsilon_{sia}$ the part corresponding to the anisotropic interaction like those due to the formation of hydrogen bonds between the solvated molecule and the solvent molecules. In our case this term is certainly important because a hydrogen bond can appear between the heteroatom of a molecule like pyridine and the water molecules.

But as $\Delta\varepsilon_{sia}$ represents the corresponding change of energy between the neutral and the protonated molecule, it can be assumed that this term will have about the same value for all the set of molecules under consideration, in such a way that the $\Delta\Delta\varepsilon_{sia}$ terms which appear in equation (9) will vanish in the first approximation.

The part $\Delta\varepsilon_{sid}$ due to dispersion forces will in this case be of small importance in comparison with the part $\Delta\varepsilon_{sii}$ associated with the isotropic interaction between electric charges and dipole moments. In conclusion, to estimate $\Delta\Delta\varepsilon_s$, account need only be taken of the $\Delta\Delta\varepsilon_{sii}$ term.

The term $\Delta\varepsilon_{sii}$ can be estimated from the formula[41]

$$\Delta\varepsilon_{sii} = -\Delta\Sigma \frac{Q_i Q_j}{2r_{ij}} \left(1 - \frac{1}{D}\right) \qquad (10)$$

where the Q_i's are the apparent charges of each atom, and where r_{ij} denotes the distance between the atom i and the atom j except when i and j are identical. In the latter case r_{ii} represents a certain empirical effective radius. Finally D is the effective dielectric constant of the solvent.

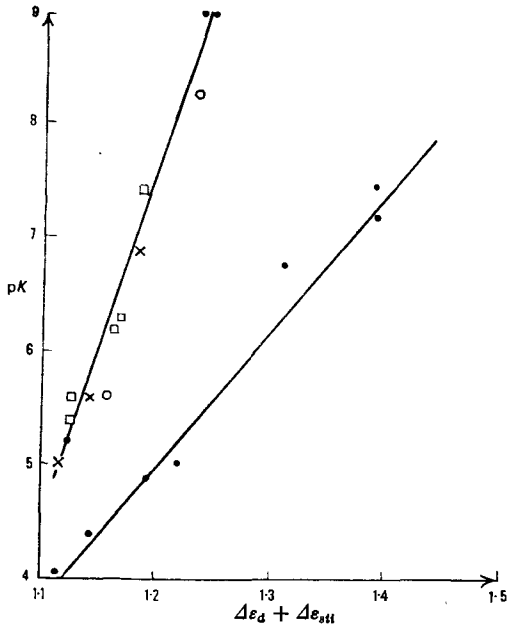


FIGURE 24. The pK as a function of $\Delta\varepsilon_d + \Delta\varepsilon_{stl}$.

Figure 24 shows what happens when the pK_a of the amino derivatives under consideration is plotted as a function of $\Delta\varepsilon_d + \Delta\varepsilon_{stl}$, this last term being derived from equation (10). Twelve points corresponding to all families of compounds are now found along the same straight line with a deviation of no more than 0·3 units of pK. The introduction of $\Delta\varepsilon_{stl}$ destroys the segregation of the various families. The precision is very satisfactory as the theory predicts the constant with an uncertainty of a factor of only 2 and there is a factor of 10,000 between the highest and the lowest values of K.

Also shown in Figure 24 are various points which lie near another straight line; they correspond to molecules containing an amino group in an *ortho* or *peri* position to the nitrogen heteroatom. In this case a special $\Delta\varepsilon_{nb}$ term appears mainly due to the interaction between the lone pair of the heteroatom and the amino group.

In conclusion, Figure 24 clearly shows the importance of $\Delta\varepsilon_d$, $\Delta\varepsilon_s(T)$ and $\Delta\varepsilon_{nb}$ in the determination of the pK of the molecules under consideration.

The basic properties of amines are also seen in other reactions. For example, amines are able to act as proton acceptors in the presence

of proton donors in such a way that association compounds are formed. There is an obvious analogy between the acid–base equilibrium

$$B + H^+ \underset{K}{\rightleftharpoons} BH^+$$

and the association equilibrium

$$B + HR \underset{K'}{\rightleftharpoons} B\cdot HR$$

where HR denotes the proton donor and K' the association constant. It is, therefore, interesting to compare the pK and the association constant.

With obvious notations one can write

$$K = \frac{f_{BH^+}}{f_B f_{H^+}} e^{-[\Delta\varepsilon_v + \Delta\varepsilon_i + \Delta\varepsilon_d + \Delta\varepsilon_{nb} + \Delta\varepsilon_s(T)]/\chi^T}$$

$$K' = \frac{f_{B\cdot HR}}{f_B f_{HR}} e^{-[\Delta\varepsilon'_v + \Delta\varepsilon'_i + \Delta\varepsilon'_d + \Delta\varepsilon'_{nb} + \Delta\varepsilon'_s(T)]/\chi^T}$$

Association constants are usually measured in a non-polar solvent like carbon tetrachloride. The solvent effect represented by $\Delta\varepsilon'_s(T)$ is still further reduced.

Furthermore, the interatomic distance between the amino nitrogen and the proton is greater in the association complex B·HR than in the positive ion BH^+. Therefore we must expect that the effect of the electronic structure of amines will be less apparent in K' than it is in K.

Finally we can expect that K' will vary more slightly with the electronic structure than K. However there is a chance that K and K' run parallel. The following table taken from Bonnet's thesis[42] shows such an example

TABLE 4. Comparison of the pK and of values of K' at 25°c (in n-heptane).

	$10^6\,K$		$10^{10}\,K$	*p*-Cresol 0·65	Phenol 1·06	Naphthol 1·40
Triethylamine	435	$K' =$		55	86	117
Dibutylamine	1282			83	128	162

Such a parallel disappears if the pK depends strongly on the solvent effect and, as has been said, the association constants are measured in such conditions that this effect is usually very small.

III. SOME ASPECTS OF THE PROPERTIES OF AMINES IN THEIR ELECTRONICALLY EXCITED STATES

A. Electronic Spectra of Amines

The electronic spectrum of aniline has been analyzed, using wave-mechanical methods, by various authors[32, 43]. The self-consistent field method which has been presented in section I and used in section II to describe the ground state of this molecule can also be used to represent its electronically excited states. For practical reasons it is necessary to introduce the LCAO approximation and either the Hückel or the Pariser and Parr method is used. Furthermore, the 'virtual orbitals' approximation is added. Let us consider the eigenfunctions π_i of the self-consistent field operator h^{SCF} corresponding to the ground state of aniline in the LCAO approximation. They obey the equation

$$h^{SCF}\pi_i = \varepsilon_i\pi_i$$

Obviously the molecular orbitals π_i^0 which are used to represent the ground state are solutions of this equation. But there are also other functions π_i^u which obey the equation. They are called virtual orbitals for the ground state. It is possible to show that if in the total wave function of the ground state one (or more) orbital π_i^0 is replaced by one (or more) virtual orbital, a convenient approximate wave function is obtained which represents an electronically excited state of the molecule.

In Table 5 some of the values obtained by Fischer–Hjalmars using this procedure are compared with experimental results.

TABLE 5. Electronic excitation energies of aniline (in ev).

Theoretical	Experimental[44]
4·83	4·32
5·29	5·31
7·03	6·32

Taking account of the various approximations introduced into the calculation, the agreement is satisfactory. Other authors obtained analogous results. For example, Bloor and coworkers[43e] are led to the conclusion that by adjusting the core integral empirically, or by using a variable electronegativity approach, it is possible to obtain agreement between experiment for the first two electronic transitions in the

vapor state, the change in ionization potential relative to benzene and the electron density *para* to the amino group.

Mataga[43d] performed an analogous analysis of the spectra of isomeric phenylenediamines, of *s*-triaminobenzene and of several amino-substituted nitrogen heterocycles such as 4-aminopyridine, 1,4-diaminotetrazine and melamine.

B. Base Strength of Aromatic Amines in their Electronically Excited States

Coulson and Jacobs[45] had studied, theoretically, charge migration in aniline under the effect of irradiation. They observed that the π electronic charge of nitrogen is smaller in the first excited state than in the ground state, that is to say, it should be less basic. Förster[46] has effectively observed that if a base, such as 3-aminopyrene (which from the theoretical viewpoint must have a similar behavior) is irradiated, the excited molecules have acidic properties. To show this fact Förster studied the absorption and fluorescence spectra as a function of the pH of a solution of 3-aminopyrene. The absorption spectrum gives information about the ground state of the molecule. On the other hand, the fluorescence spectrum depends on the excited states of the same molecule. It is found that up to pH $\sim$ 2, the absorption spectra are those of the $ArNH_3^+$ ions, whereas the fluorescence spectra correspond to $ArNH_2$. It appears that as predicted by the theory, the molecules in their excited states have less tendency to add a proton than the ground-state molecules. Furthermore, near pH 12 some new bands appear in the fluorescence spectra which can be attributed to the $ArNH^-$ ions. This attractive result shows that the excited molecules $ArNH_2^*$ are able to react as an acid

$$ArNH_2^* \rightleftharpoons ArNH^- + H^+$$

The phenomenon has been analyzed in more detail by Sandorfy[47] who calculated the distribution of the electronic charges, taking account of both the π and the σ orbitals. He found that the nitrogen which is negative in the ground state becomes positive in the first electronically excited state, which completely explains why the molecule becomes an acid.

Other amines have been studied from the same viewpoint. For example it has been possible to measure the pK of β-naphthylamine in various states. A value of 4·1 is found for the ground state, whereas a value of -2 is obtained for the first singlet state and a value of 3·3 for the first triplet state[48].

To explain the difference between the first excited singlet and triplet levels Murrell[49] pointed out that the energy of the direct donor–acceptor charge-transfer configuration lies at a higher energy than any of the actual states considered. Therefore is it normal that the actual charge transfer is greater for the excited singlet state than for the triplet, as the energy of the former is nearer the energy of the charge-transfer configuration than is the energy of the triplet state.

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CHAPTER 2

The introduction of the amino group

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I. INTRODUCTION

For the purposes of discussion, the term amino group is taken to include not only the primary amino group (—NH_2) but also substituted-amino groups bearing one or more aliphatic or aromatic groups

on the nitrogen atom. This chapter is concerned with methods of synthesis of aliphatic, aromatic and mixed aliphatic–aromatic amines, including primary, secondary and tertiary amines, and related quaternary compounds. Other classes of nitrogen compounds which contain an amino group, e.g. amides, are considered only in relation to preparative routes to amines.

The preparation of amines by methods involving substitution, addition and exchange reactions are discussed in sections II to VI, and reductive procedures are considered separately in section VII; molecular rearrangements are not considered as such, but are mentioned where appropriate in the text. Steric factors influence many amine syntheses, but these are considered principally in section IV, as much of the relevant information has come from studies of aminolysis of halides and related compounds.

II. INTRODUCTION OF AMINO GROUPS BY REPLACEMENT OF HYDROGEN

A. Direct Amination of Aromatic Compounds in the Presence of Lewis Acids

Examples of the amination of aromatic compounds by various electrophilic species, derived from hydroxylamine[1], and from hydrogen azide[2], have been known for some time. Aromatic compounds which have been aminated in this way range from benzene and alkylbenzenes to substances such as anthraquinone[3]. Recently, some of these reactions have been systematically examined, and the principal mechanistic features elucidated, mainly by Kovacic and coworkers.

Direct amination of toluene can be effected with hydroxylamine-*O*-sulphonic acid[4], alkylhydroxylamines[5] and hydroxylammonium salts[6] in the presence of aluminium chloride (at least two moles per mole of aminating agent), and with hydrogen azide in the presence of aluminium chloride or sulphuric acid[7]. These reactions lead to the corresponding toluidines. Thus toluene and hydroxylamine-*O*-sulphonic acid give mixed toluidines (50% yield) of the following composition:

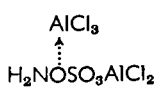
o-toluidine (51%),
m-toluidine (13%),
p-toluidine (36%).

The preponderance of *ortho* and *para* isomers indicates attack by an active, if somewhat unselective, electrophilic species. In fact, the

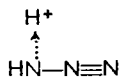
Selectivity Factor, S_f, for this reaction, calculated according to equation (1)[8] is 0·74, and similar values were calculated for the other

$$S_f = \log\left(\frac{2 \times \%\ para}{\%\ meta}\right) \quad (1)$$

aminations examined. Comparison of these values of S_f for the amination reactions with those for other electrophilic substitutions led to the view that the aminating agent is likely to be the protonated or Lewis acid-complexed nitrogen compound rather than the NH_2^+ cation, and this view is reinforced when the results of competitive aminations of toluene and benzene are compared with those of other substitution reactions. Likely electrophiles in the hydroxylamine-*O*-sulphonic acid/aluminium chloride and hydrogen azide/sulphuric acid aminating systems are **1** and **2**:

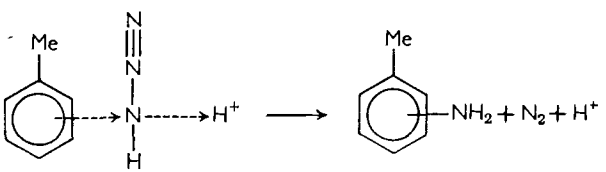


(1)



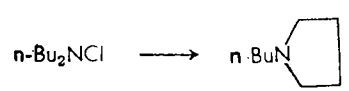
(2)

and the amination of toluene by hydrogen azide may be represented schematically by reaction (2).



(2)

Dialkylamino groups may, in principle, be introduced into aromatic rings using the dialkylchloroamine and concentrated sulphuric acid[9], except in those cases where the chloroamine undergoes preferential ring closure (Hofmann–Loffler reaction[10]) (reaction 3). However,

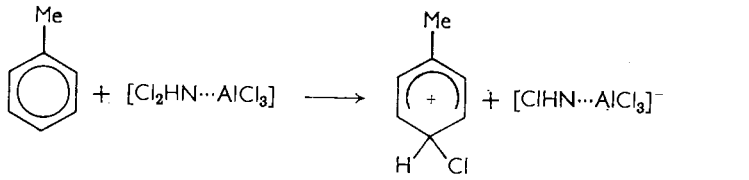


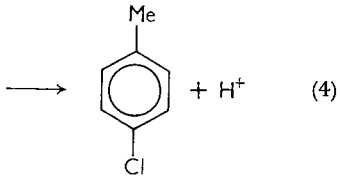
(3)

these reactions are unselective and appear to be of preparative value only in a limited number of cases, for example benzene → *N*-phenylpiperidine.

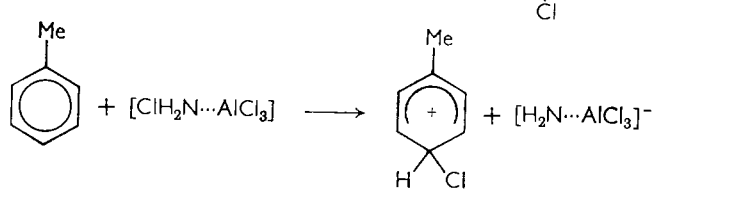
By contrast, reaction of toluene with dichloroamine or trichloroamine in the presence of aluminium chloride gives *m*-toluidine[11], and the same unusual *meta*-amination pattern was subsequently observed

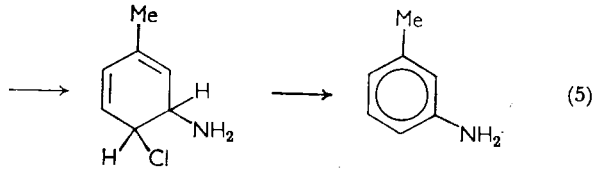
when the reaction was extended to include other alkylbenzenes[12]. Other products (from toluene) are *o*- and *p*-chlorotoluenes, and small amounts of *m*-chlorotoluene, 2-chloro-5-methylaniline and 4-chloro-3-methylaniline. The absence of substantial amounts of the last two compounds has been taken to indicate that *N*-chloro-*m*-toluidine is not an intermediate in the formation of *m*-toluidine, and after consideration of various possibilities, a σ-substitution mechanism has been advanced to explain the observed orientation. This involves the formation of a chloroarenonium ion, followed by addition of a nucleophilic nitrogen species, and subsequent aromatisation through loss of hydrogen chloride. The nature of the nucleophile is not certain, but it is not considered to be trichloroamine[12,13]. The overall result may be illustrated by reactions such as (4) and (5); these also account satisfactorily for the orientation of the chlorotoluenes produced.





(4)





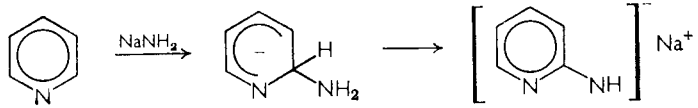
(5)

In spite of the unattractive properties of trichloroamine, this procedure may be of value for the preparation of certain *m*-alkylanilines;

the amination reactions based on hydroxylamine-*O*-sulphonic acid, hydrogen azide, etc., seem to offer little in comparison with other routes to the corresponding amines.

B. The Chichibabin and Related Reactions

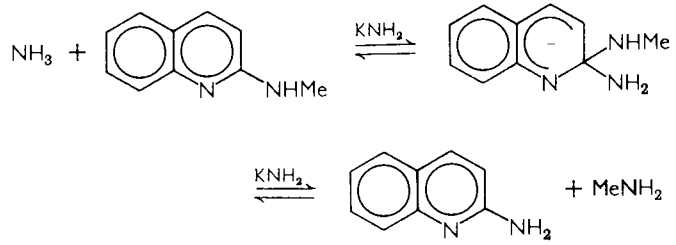
Direct amination by amide ion is possible with aromatic molecules which are susceptible to nucleophilic attack. This group includes many heterocyclic compounds, particularly derivatives of pyridine, quinoline and related ring systems[14], and also a number of benzenoid compounds containing appropriate electron-attracting substituents. These reactions may be conducted at elevated temperatures in dimethylaniline or a hydrocarbon for example, or at lower temperatures in liquid ammonia. In the pyridine series, it is the electron-deficient α-position which is preferentially aminated, though γ-substitution may occur if no α-site is available (reaction 6). The second stage



(6)

involves dehydrogenation, and ammonium and potassium nitrates have been used as additives on a number of occasions.

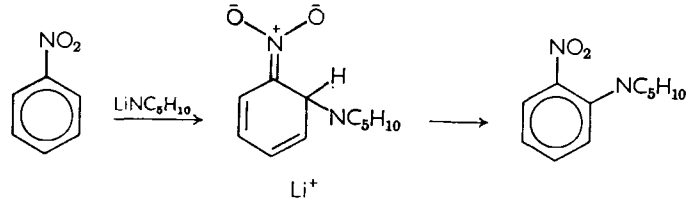
In some cases, conducting this type of reaction in the presence of a primary alkylamine (rather than dimethylaniline) allows effective introduction of the alkylamino group[15]. There are grounds for believing that the amino group is introduced and then displaced to a greater or lesser extent, by the alkylamino group; indeed, equilibration of 2-methylaminoquinoline and 2-aminoquinoline by means of potassamide in liquid ammonia has been demonstrated in separate experiments[16] (reaction 7).



(7)

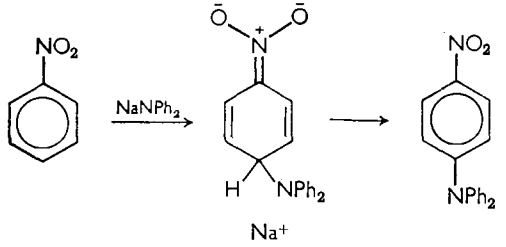
Nitrobenzene may undergo nucleophilic substitution at the *ortho* and *para* positions, but it is desirable to employ nitrobenzene in excess

as some is destroyed by reduction. Thus *N-o*-nitrophenylpiperidine is formed from nitrobenzene and lithium piperidide (reaction 8)[17],



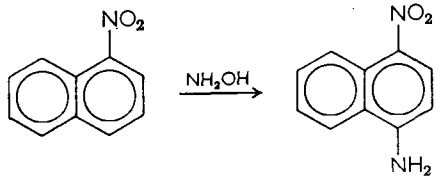
(8)

whilst nitrobenzene and sodium diphenylamide give 4-nitrotriphenylamine (reaction 9)[18].



(9)

Hydroxylamine has also been employed for direct amination of a few nitro compounds (reaction 10)[19,20].



(10)

C. Photoamination of Cyclohexane

Direct photoamination of cyclohexane with hydrazine in *t*-butanol solution has recently been demonstrated, the most favourable yield of cyclohexylamine being 45%. Cyclohexanol occurs as a by-product, but its yield may be reduced by excluding oxygen[21]. Other by-products include bicyclohexyl and cyclohexylhydrazine, but the latter is not apparently an intermediate in the formation of cyclohexylamine[22].

A radical process is favoured for this reaction, with N—N bond fission as the important initiating step (reactions 11–14).

$$NH_2NH_2 \xrightarrow{h\nu} NH_2NH_2^* \longrightarrow 2\,NH_2^{\cdot} \quad (11)$$

$$NH_2^{\cdot} + C_6H_{12} \longrightarrow NH_3 + C_6H_{11}^{\cdot} \quad (12)$$

$$C_6H_{11}^{\cdot} + NH_2^{\cdot} \longrightarrow C_6H_{11}NH_2 \quad (13)$$

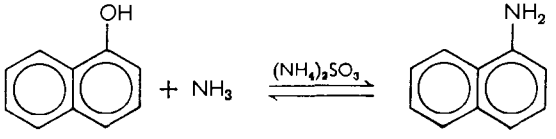
$$2\,C_6H_{11}^{\cdot} \longrightarrow C_{12}H_{22} \quad (14)$$

III. INTRODUCTION OF AMINO GROUPS BY REPLACEMENT OF HYDROXYL

For most laboratory purposes, the important reactions under this heading are the Bucherer Reaction, chiefly useful in the naphthalene series, and the Ritter Reaction, which will be considered in sections IV.B and VI.B.

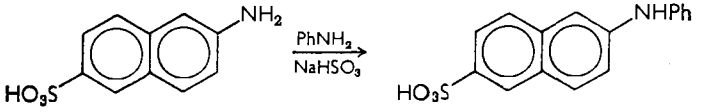
The Bucherer Reaction

Naphthols and the corresponding naphthylamines are interconvertible in aqueous media containing sulphite or bisulphite ion at elevated temperatures[23]. Thus naphthols may be converted to naphthylamines by reaction with ammonia and ammonium sulphite in aqueous solution, usually in the temperature range 90–150°; the corresponding dinaphthylamine is sometimes obtained as a by-product (reaction 15). Monoalkylamines and dialkylamines similarly



(15)

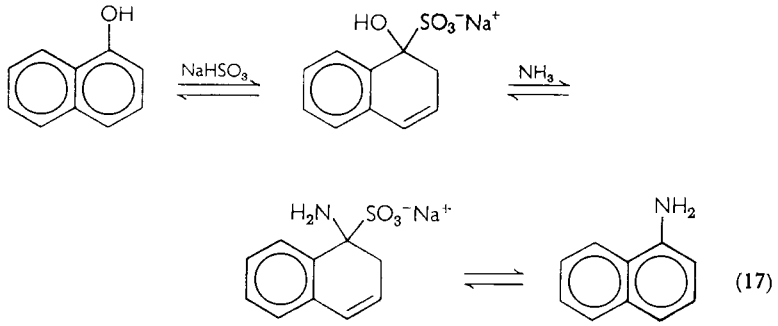
give the alkylamino- and dialkylaminonaphthalenes, though higher temperatures are normally required. Naphthols also react with arylamines to give the arylaminonaphthalene, 1-naphthols reacting less readily than 2-naphthols. Similar cases have also been noted with arylamines (reaction 16).



(16)

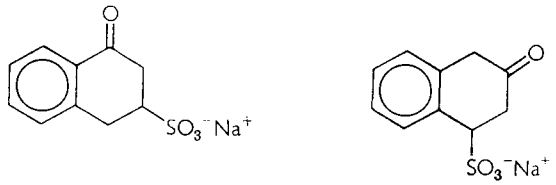
Bisulphite addition compounds of naphthols have been isolated in a number of cases, and for a considerable time these were formulated as

derivatives of the ketonic form of the naphthol. Until recently, the generally accepted reaction scheme was (17) with the naphthol possibly reacting in the keto form. This overall equilibrium picture



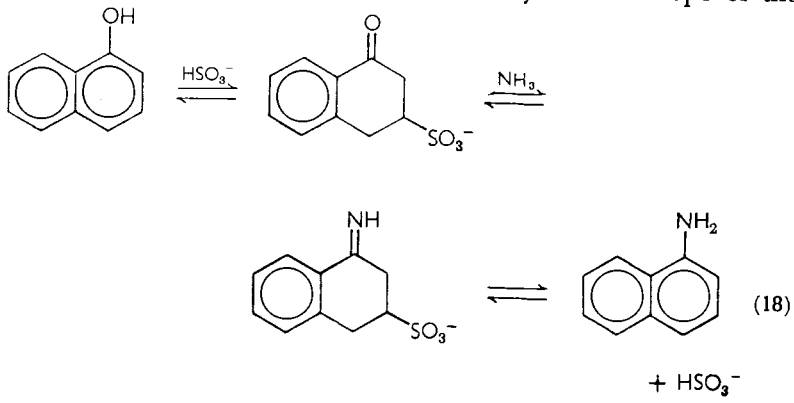
(17)

was consistent with the results of a systematic kinetic study of the reaction conducted with a number of naphthol and naphthylamine sulphonic acids and reported in 1946[24].



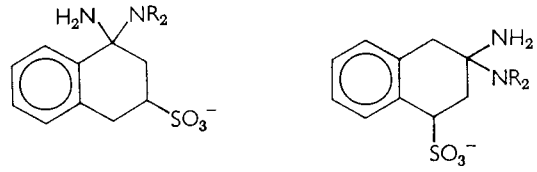
(3) (4)

The structures of the intermediate addition compounds have been reconsidered in the light of their physical and chemical properties, and the compounds from 1- and 2-naphthols are now formulated as tetral-1-one-3-sulphonates (**3**) and tetral-2-one-4-sulphonates (**4**) respectively[25,26]. Discussion of this evidence is beyond the scope of the



(18)

present chapter but it is interesting to note that a new synthesis of 1-naphthol-3-sulphonic acids has emerged from this work. The scheme for the interconversion of naphthols and naphthylamines may be summarised by reaction (18), with the possibility of ketimine and enamine intermediates, except in the special case of reactions involving dialkylamines, when only an enamine intermediate is possible. Amine exchange reactions of 1- and 2-naphthylamines with an amine R_2NH are likely to involve further intermediates of types **5** and **6** respectively, formed by addition of the amine R_2NH to the intermediate ketimine or enamine.



(5) (6)

IV. INTRODUCTION OF AMINO GROUPS BY REPLACEMENT OF HALOGEN, AND RELATED REACTIONS

A. The Alkylation of Ammonia and Amines

The preparation of amines and quaternary ammonium salts through displacement of halide ion from alkyl halides by ammonia or amines is commonly referred to as alkylation of ammonia (or amines); alkyl esters of other strong acids have also been used in similar alkylation procedures. Equations (19) to (22) represent in simple terms the sequence of reactions which may occur in the interaction of ammonia or an amine with an alkyl halide.

$$NH_3 + RX \longrightarrow \overset{+}{N}H_3R \quad X^- \tag{19}$$

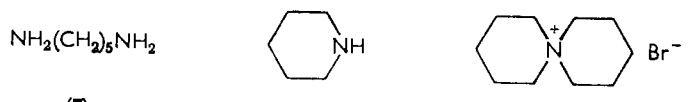
$$NH_2R + RX \longrightarrow \overset{+}{N}H_2R_2 \quad X^- \tag{20}$$

$$NHR_2 + RX \longrightarrow \overset{+}{N}HR_3 \quad X^- \tag{21}$$

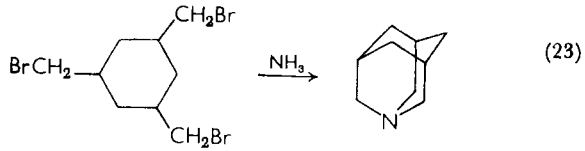
$$NR_3 + RX \longrightarrow \overset{+}{N}R_4 \quad X^- \tag{22}$$

In principle, these reactions lead to a wide range of amines and quaternary salts, containing identical or differing R groups. Internal alkylation is also possible in appropriate cases. Thus ammonia and 1,5-dibromopentane react to give the amines (**7**) and (**8**), and the

quaternary salt (**9**)[27]; ammonolysis of **10** similarly gives the symmetrical, high-melting 1-aza-adamantane (**11**) (reaction 23)[28].

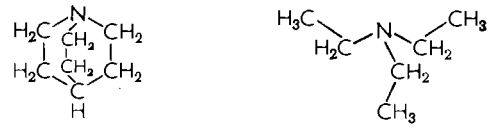


(7) (8) (9)



(10) (11) (23)

Studies of the mechanism of a number of these reactions, and particularly of the quaternisation reaction (22) (commonly known as the Menschutkin reaction), have been reviewed elsewhere[29] and only certain points are relevant here. The reactions generally exhibit the normal characteristics of S_N2 reactions with regard to kinetics, solvent polarity and structural requirements of the alkyl halide. The basic strength of the amine may provide a rough guide to its reactivity, the more strongly basic amines being frequently the most nucleophilic. Weakly basic amines such as diphenylamine can be methylated directly[30] (even to the quaternary stage under forcing conditions[31]), but in preparative work it is not uncommon to enhance nucleophilicity by conversion to an alkali-metal or Grignard derivative prior to alkylation[32]. However, steric factors are also important in relation to the nucleophilicity of amines. These may be illustrated by the relative rates of reaction of the comparably strong bases, quinuclidine and triethylamine, with methyl, ethyl and isopropyl iodides in nitrobenzene[33]. At 25°, the ratio (k_Q/k_T) of the specific rate constants for quinuclidine (**12**) (k_Q) and triethylamine (**13**) (k_T) have been determined as 57, 254 and 705 for methyl, ethyl and isopropyl iodides

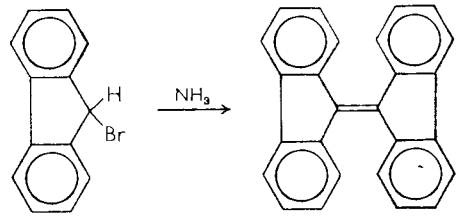


(12) (13)

respectively; for both bases, the rates decrease in the expected order MeI > EtI > i-PrI. These results indicate not only that the steric

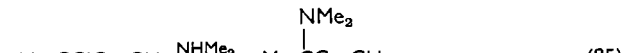
requirements of quinuclidine are lower than those of triethylamine, but also that this difference in steric requirement becomes more important as the steric requirements of the alkyl halide increase. Similar effects have been observed in the reaction of pyridine and monoalkylpyridines with the same alkyl iodides[34]. Again the reaction rates drop sharply in the order MeI > EtI > i-PrI for each amine, but whereas (relative to pyridine) 3- or 4-alkyl substitution leads to slight increases in rate, 2-alkyl substitution results in decreases which become very pronounced in the case of 2-*t*-butylpyridine. These steric factors are of considerable importance in amine alkylations.

Limitations are also imposed by the nature of the alkyl group in the alkyl halide. Broadly speaking, the alkyl halides which react with ammonia (or amines) to give amines and quaternary ammonium salts are those which are susceptible to substitution by the S_N2 mechanism. Amines preparable by this route are consequently those in which primary or secondary alkyl groups are attached to the nitrogen atom. Attempts at alkylation of ammonia and amines using tertiary alkyl halides are normally frustrated by the occurrence of alternative elimination reactions and such problems are also apparent with other halides in which structural features favour alternative reactions (reaction 24)[35]. An important group of tertiary halides which may be



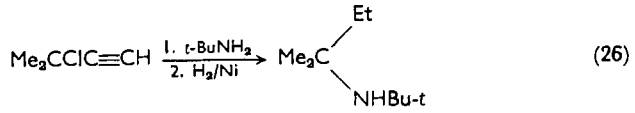
(24)

used for the alkylation of ammonia and amines are the tertiary propargylic halides (reaction 25)[36]. The ethynyl group may be reduced



(25)

to a vinyl or ethyl group and, since the steric requirements of the ethynyl group are small, a large variety of sterically hindered amines have become available, e.g. reactions (26) and (27)[37]. These reactions



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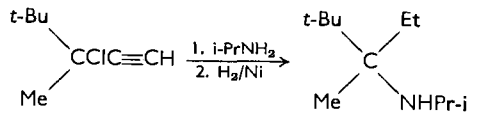
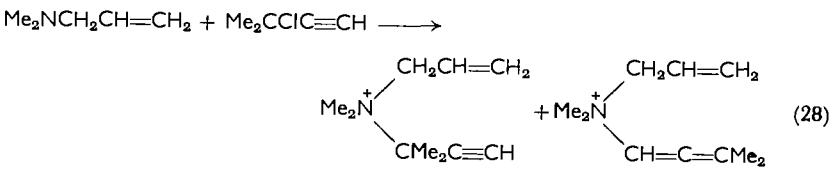


(27)

are relatively free from complications, although quaternisation of tertiary amines with tertiary propargylic halides may lead to the propargylic and the isomeric allenic quaternary salts (reaction 28), and may involve some destruction of the propargylic halide through dehydrohalogenation[38]. Allylic halides react with ammonia and



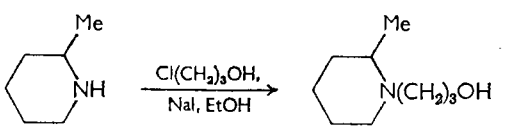
(28)

with amines to give allylic amines and quaternary salts which may contain the original or the rearranged allylic group (reaction 29)[39].

$$MeCH{=}CHCH_2Cl \xrightarrow{NHEt_2} MeCH{=}CHCH_2NEt_2 \xleftarrow{NHEt_2} MeCHClCH{=}CH_2 \quad (29)$$

Primary allylic halides generally give normal products, whilst secondary allylic halides frequently give rearranged products, or mixtures of normal and rearranged products. A general discussion of the factors relevant to reactions of allylic compounds with nucleophiles, including amines, has been given in the first volume of this series[40].

Amongst the alkyl halides, the order of ease of replacement of halogen is I > Br > Cl. This may be turned to advantage, even when the iodo compound is not readily available, by conducting the reaction of amine with alkyl halide in the presence of iodide ion, so as to generate the organic iodide *in situ* by halogen exchange. The preparation of 3-(2-methylpiperid-1-yl)propanol[41] is illustrative



(30)

(reaction 30). Whilst alkyl halides probably represent the most general type of alkylating agent for amines, various other esters have been used (particularly for the transfer of small alkyl groups) and in many cases offer practical advantages. Amongst sulphur esters, these include alkyl sulphates, and alkylbenzene- and toluene-*p*-sulphonates[42], methyl trifluoromethanesulphonate[43] and methyl sulphite[44].

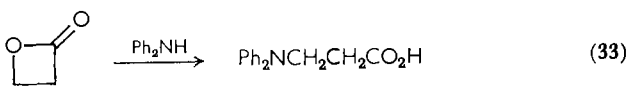
Interestingly, use of methyl sulphite leads to the methanesulphonate of the methylated amine. A recently reported method, considered to be suitable for alcohols capable of yielding fairly stable carbonium ions, involves thermolysis of the corresponding dimethylsulphamate, followed by hydrolysis (reaction 31). The method may prove a useful

$$ROH \longrightarrow ROSO_2NMe \xrightarrow{\Delta} \bar{S}O_3{-}\overset{+}{N}RMe_2 \xrightarrow{H^+} NRMe_2 \quad (31)$$

supplement to the S_N2 alkylation procedures[45]. Amines have also been alkylated by the use of alkyl phosphates[46], and in a few cases by preparation and decomposition of alkyl phosphoramidates (reaction 32)[47]. Alkyl nitrates are effective alkylating agents for aliphatic

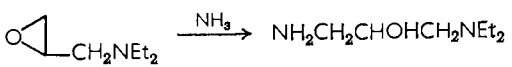
$$(EtO)_2PONHPh \xrightarrow{\Delta} PhNEt_2 \quad (32)$$

amines, though complications arise with aromatic amines[48]. Alkylation of amines is also possible with certain types of carboxylic esters[49], and under appropriate conditions propiolactone can be used to introduce β-carboxyethyl groups (reaction 33)[50]. Epoxides are suitable



(33)

for β-hydroxyalkylation of amines (reaction 34)[51]; this type of reaction is very general. being useful for the introduction of amino groups in the glycerol and sugar series[52,53].



It will be appreciated that many of these alkylation reactions (19) to (22) can be made reasonably selective, for example (20) to the virtual exclusion of (21) and (22), by appropriate choice of nucleophile and alkylating agent. This selectivity is not likely to occur, however, in the corresponding reactions of ammonia and unhindered primary and secondary n-alkylamines with primary alkylating agents (except in favourable cases where the desired product separates from the reaction), where mixtures of amines are to be expected. The problems attending separation of such mixtures are discussed below.

In the quaternisation reaction (22), or any sequence ending in quaternisation, separation of the ionic quaternary salt from unreacted amine(s) presents few problems as reaction is normally conducted

under conditions in which step (22) is effectively irreversible. It is well to remember, however, that quaternary ammonium ions are susceptible to nucleophilic displacement reactions[31]. Ethanolamine has been shown to dealkylate tetraalkylammonium and aryltrialkylammonium salts[54] at about 154° according to reaction (35). In

$$HOCH_2CH_2NH_2 + R_3\overset{+}{N}Ar \longrightarrow HOCH_2CH_2\overset{+}{N}H_2R + R_2NAr \qquad (35)$$

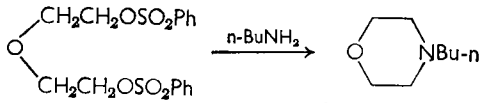
reactions involving a tertiary amine and a derived quaternary ammonium ion, such reaction may lead to redistribution of alkyl groups between the amine and the ion[55]. This has been demonstrated for benzyldimethylamine and the benzyltrimethylammonium ion, and for related pairs (reactions 36 and 37). The evolution of trimethyl-

$$PhCH_2NMe_2 + PhCH_2\overset{+}{N}Me_3 \longrightarrow (PhCH_2)_2\overset{+}{N}Me_2 + NMe_3 \qquad (36)$$

$$(PhCH_2)_2\overset{+}{N}Me_2 + PhCH_2NMe_2 \longrightarrow (PhCH_2)_2NMe + PhCH_2\overset{+}{N}Me_3 \qquad (37)$$

amine allows disproportionation of benzyldimethylamine to proceed in the presence of a catalytic amount of the quarternary salt. It is clearly desirable to avoid use of high temperatures for prolonged periods in these reactions.

The preparation of tertiary amines from alkyl halides and a secondary amine, or a primary amine in which both *N*-hydrogen atoms are to be replaced by identical alkyl groups, can be carried out with favourable yields in many cases, as evidenced by preparations of diethyl-n-hexadecylamine (from diethylamine) and of dimethyl-n-docosylamine (from dimethylamine)[56]. Alkyl sulphonates have similarly been used, and the reaction extended to the preparation of cyclic tertiary amines from primary amines and appropriate terminal disulphonates (reaction 38)[57]. Satisfactory conditions have been reported

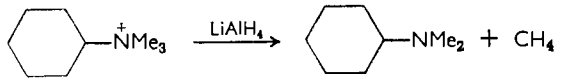


(38)

for dimethylation of primary aromatic amines using methyl sulphate[58] and for di-n-alkylation[46a] using n-alkyl phosphates; aniline and isopropyl phosphate, however, give *N*-isopropylaniline, indicating the different steric requirements of the reactants.

The isolation of tertiary amines from alkylation reactions is normally straightforward; except in special cases[59], unwanted primary and secondary amines can usually be removed from the basic fraction by conversion to non-basic carboxamides (cf. ref. 46a) or sulphonamides

(cf. ref. 28). If quaternisation has occurred, the desired tertiary amine may still be obtainable if the unwanted group can be removed reductively by use of lithium aluminium hydride (reaction 39)[60], or sodium and liquid ammonia[61]. With allyl or benzyl trialkylammonium



(39)

salts, the allyl or benzyl group is removed more readily than a methyl group. It may be noted in passing that there is a tendency to solvolytic cleavage of an allyl group in certain tertiary amine hydrochlorides, and appropriate precautions should be taken during purification (reaction 40)[62]. (The other product of solvolysis was not identified, but is

$$\text{i-Bu}\overset{+}{N}H(CH_2CH{=}CH_2)_2\ Cl^- \xrightarrow{EtOH} \text{i-Bu}\overset{+}{N}H_2CH_2CH{=}CH_2\ Cl^- \qquad (40)$$

presumably allyl ethyl ether.)

The preparation of dialkylamines from ammonia or primary amines can be realised where steric factors militate against tertiary amine formation. Thus monoalkylation of *t*-butylamine with some alkyl halides and epoxides has been accomplished (reaction 41)[63].

$$t\text{-BuNH}_2 + PhCH_2Cl \longrightarrow t\text{-BuNHCH}_2Ph \qquad (41)$$

More generally, ammonolysis or aminolysis of alkyl halides, and particularly primary alkyl halides, is likely to give rise to mixtures of the primary, secondary and tertiary amines (reactions 19, 20 and 21). The proportions of the three possible amines in such a mixture may be varied by alterations in the relative proportions of the reactants. Where, for example, the primary amine is the desired product, the use of liquid ammonia[27] (to ensure high concentration of ammonia), and also of sodamide (one mole per mole of alkyl halide) in liquid ammonia[64] have been recommended, though some dehydrohalogenation of the alkyl halide may occur when sodamide is used (reaction 42).

$$n\text{-}C_6H_{13}Br \longrightarrow \underset{(74\%)}{n\text{-}C_6H_{13}NH_2} + \underset{(5\%)}{n\text{-BuCH}{=}CH_2} \qquad (42)$$

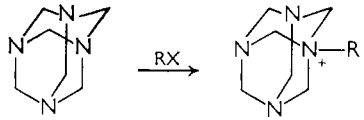
In the reaction of ammonia with the alkyl halide, secondary and tertiary amine formation become more important as the concentration of ammonia is reduced. In favourable cases, e.g. the mono-, di- and trioctylamines from ammonolysis of n-octyl chloride[65], the amines may be separable by distillation. In other cases, chemical methods

may be employed. Treatment of such a mixture of amines with benzenesulphonyl chloride (Hinsberg's method) gives an 'alkali-soluble' amide (from the primary amine) and an 'alkali-insoluble' amide (from the secondary amine); again, phthalic or 3-nitrophthalic anhydride converts the primary and secondary amines into the phthalamic acids, but only the acid from the primary amine can be dehydrated to the corresponding phthalimide[66]. Both of these separation methods allow direct recovery of the tertiary amine from the unreacted amine fraction. Recovery of primary and secondary amines from these derivatives is considered below. Another method, suitable for separation of secondary amines, involves formation of the *N*-nitroso compound and subsequent regeneration[67].

B. The Use of Blocking Groups for Control of Alkylation

The difficulties associated with direct alkylation of ammonia and amines have led to the development of indirect alkylation procedures designed specifically for the preparation of primary and secondary amines. These depend on the blocking of the required number of sites in the ammonia molecule so as to limit the extent of the alkylation reaction, and fall into two categories depending on whether or not the alkylation step involves the formation of a quaternary ammonium ion.

The Délepine method[68], for primary amines, is based on the quaternisation of hexamine with an alkyl halide; the resulting hexaminium salt is then decomposed with ethanolic hydrochloric acid to give the desired amine, ammonia and the carbon fragments of the ring as diethylformal (reaction 43).



(43)

Primary amines are also available through the Ritter reaction in which an organic nitrile provides the blocked nitrogen atom. Though relatively poor nucleophiles, nitriles are able to capture carbonium ions; the resulting nitrilium ion reacts with water to give the amide, which can then be hydrolysed to the amine. A number of alkyl and aralkyl halides capable of yielding carbonium ions have been shown to react with nitriles in the presence of aluminium chloride[69], silver sulphate[70] or particularly antimony pentachloride (reaction 44)[71].

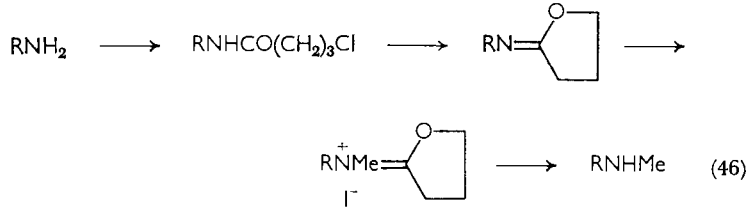
$$RCN + R^1Cl \xrightarrow{SbCl_5} [RC{\equiv}N{-}R^1]^+SbCl_6^- \xrightarrow{H_2O} RCONHR^1 \qquad (44)$$

For preparative purposes, Ritter's original procedure of generating the carbonium ion from the alcohol (or olefin) and sulphuric acid is preferred; under these conditions, hydrogen cyanide, produced *in situ* from sodium cyanide, can replace the nitrile[72]. Secondary and tertiary alcohols can be used[73], and the reaction, providing essentially for substitution by the S_N1 mechanism, is a valuable addition to the methods already discussed. It must be borne in mind, however, that under certain conditions carbonium ion rearrangement is possible, and has indeed been observed in some applications of this reaction[74].

For preparations of secondary amines by way of quaternisation reactions, it is necessary to employ a blocking group for two of the nitrogen valencies. Benzylidene derivatives of primary amines fulfil this function, and quaternisation of such compounds, followed by hydrolysis, gives benzaldehyde and the desired secondary amine (reaction 45)[75]. Incorporation of the primary amine into an imidate

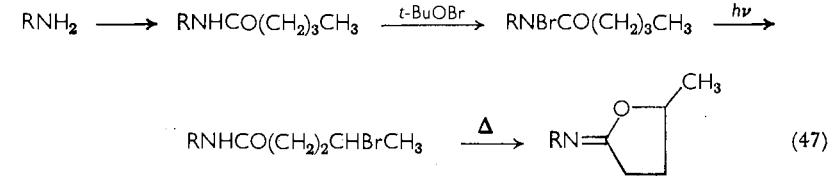
$$PhCH{=}NR \xrightarrow{MeI} [PhCH{=}NMeR]^+I^- \longrightarrow PhCHO + RNHMe \qquad (45)$$

provides a new and interesting variant of this method, and has been employed for monomethylation of the N_α atom of tryptophan. The primary amine is condensed with γ-chlorobutyroyl chloride in pyridine, and the resulting amide cyclised to the iminolactone with silver fluoroborate. Methylation with methyl iodide, followed by hydrolysis, provides the secondary amine (reaction 46)[76]. Another route to this



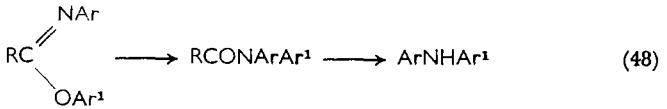
(46)

type of iminolactone (and, by implication, to secondary amines) which would appear to be particularly suitable where R is a tertiary alkyl group, is exemplified by reaction (47)[77]. It may be noted in



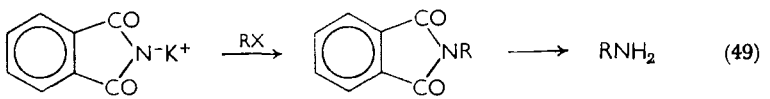
(47)

passing that, in the aromatic series, rearrangement of imidates provides a useful source of diarylamines (Chapman rearrangement) (reaction 48)[78].



(48)

A somewhat different approach to the synthesis of primary and secondary amines is involved in the use of blocking groups that so reduce the nucleophilicity of ammonia or a primary amine that alkylation does not proceed to the quaternary stage. For the conversion of ammonia to primary amines, these conditions are met in the Gabriel synthesis in which the nucleophile is the anion of phthalimide and the product the *N*-alkylphthalimide. Alkyl halides containing a variety of other substituents, e.g. —CN, —COR, —COOR, —OR, in the alkyl chain undergo this reaction, and the method has enjoyed considerable popularity[79]; alkyl toluene-*p*-sulphonates[80] and epoxides[81] can also be used as alkylating agents. The alkylamine can be obtained from the alkylphthalimide by hydrolysis or by the milder hydrazinolysis procedure (reaction 49)[82]. In a recent improvement, the use of dimethylformamide as solvent is recommended for the alkylation reaction[83].



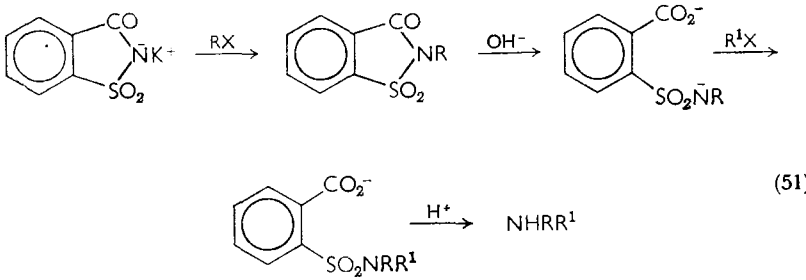
(49)

A similar conception underlies the Hinsberg synthesis of secondary amines in which the anion of a sulphonamide is alkylated[84], and the amine obtained by hydrolysis (reaction 50). Mono- and dialkylation

$$[PhSO_2NR^1]^-K^+ \longrightarrow PhSO_2NRR^1 \longrightarrow NHRR^1 \qquad (50)$$

of toluene-*p*-sulphonamide, for example, provide routes to primary and symmetrically substituted secondary amines[85], and mixed aliphatic–aromatic amines are obtainable by use of sulphonanilides[86]. An interesting synthesis of secondary amines, embodying features of both the Gabriel and Hinsberg reactions, employs saccharin in a two-stage alkylation (reaction 51)[87]. The Hinsberg method has not attracted wide popularity because of the difficulty of liberating the amine, and similar objections have attended the use of sulphonyl groups for protecting amino groups. Hydrolysis by moderately concentrated mineral acids at elevated temperatures is frequently

undesirable, and other acidic procedures have been recommended for sensitive molecules[88]. A number of reductive methods (zinc and hydrochloric acid, sodium and isoamyl alcohol) have been reported for splitting sulphonamides[89], and sodium and liquid ammonia has been successfully used for this purpose in syntheses of oxytocin and related compounds[90].



(51)

Alkylation of cyanamide (anion), followed by hydrolysis, has been used for the preparation of some symmetrically substituted secondary amines (reaction 52)[91]. It is clear from alkaloid studies that reduction

$$(N{-}CN)^{2-}\,2\,Na^+ \xrightarrow{RX} R_2NCN \longrightarrow R_2NH \qquad (52)$$

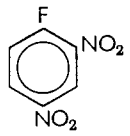
with lithium aluminium hydride may be used as an alternative to the hydrolysis stage[92].

A method which is suitable for the preparation of allylic amines involves the allylation of thiocyanate ion to give the allyl thiocyanate followed by rearrangement (by the S_Ni mechanism in many cases) to the isothiocyanate, and subsequent hydrolysis[40].

C. Nucleophilic Aromatic Substitution by Ammonia and Amines; the Bimolecular Mechanism[93]

Aryl halides are relatively insensitive to nucleophilic substitution, i.e. replacement of halogen as halide ion, by ammonia and amines. However, susceptibility of the halogen atom to displacement (or of other groups displaceable as anions) increases as the *ortho* and *para* positions become progressively substituted by electron-attracting groups, nitro groups being particularly effective. The reactivity of the halogen atoms in 2,4-dinitrofluorobenzene (**14**)[94] and in 4,4′-difluoro-3,3′-dinitrodiphenylsulphone (**15**)[95] are cases in point. These examples illustrate an important difference between alkyl halides and activated aryl halides towards nucleophilic substitution, namely the generally high susceptibility of fluorine to displacement in the aromatic series;

this indicates the relative importance of the bond-making step in these reactions.



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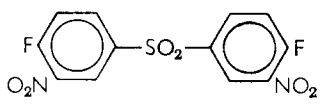
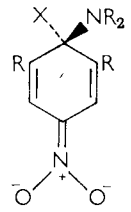


(15)

Nucleophilic aromatic substitution has been the subject of considerable investigation[93] and of some controversy[96]. Certain features are particularly relevant to the practical problem of introducing amino groups. The formation of the transition state or intermediate complex in these reactions involves approach of the amine from within a plane perpendicular to that of the aromatic ring, with the valencies of the carbon atom $C_{(1)}$ which bears the displaceable substituent becoming approximately tetrahedral. When the nucleophile is an unhindered amine, relatively little steric hindrance to this approach is offered by 2- and 6-substituents in the aromatic ring unless these are especially bulky, e.g. *t*-butyl, but as the steric requirements of the amine increase, even 2- and 6-methyl groups may exert detectable interference (cf. **16** below for the case where the activating



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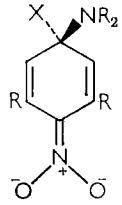
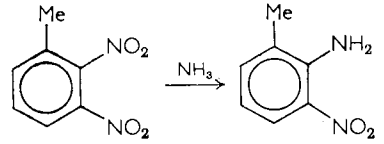


(17)

substituent is a 4-nitro group). It will be noted that for effective activation at $C_{(1)}$ by a 4-nitro group the latter should ideally be coplanar with the ring and this may be rendered difficult by the presence of alkyl groups at $C_{(3)}$ and $C_{(5)}$ (cf. **17**); 3- or 5-substitution does in fact markedly reduce ease of replacement at $C_{(1)}$[93,97]. This second effect is often product-determining in reactions of amines with alkyldinitrobenzenes (reaction 53)[98], but is not observed with such activating substituents as the cyano group where the question of coplanarity with the ring does not arise[99]. In a number of cases, competitive displacement of substituents has been noted, as for example in reaction (54)[100].



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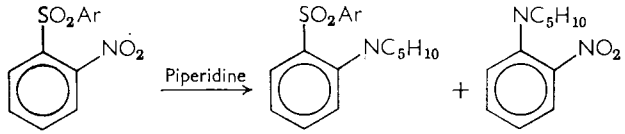
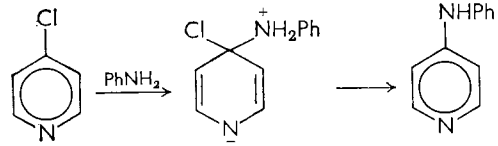


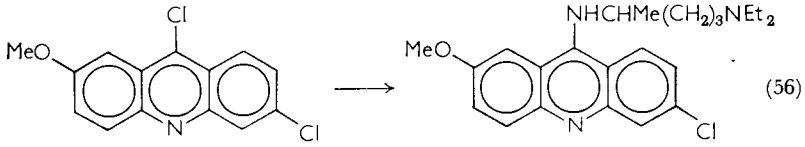
(54)

Almost comparable with the activating influence of a nitro group is that of the ring nitrogen atom in pyridine, and many examples of the introduction of amino groups by nucleophilic displacement of halogen atoms from the α- and γ-positions are known (reaction 55)[101]. Cor-



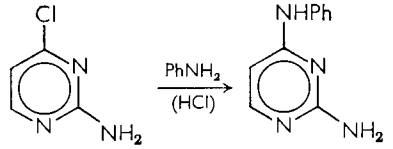
(55)

responding positions, i.e. α- or γ- with respect to the ring nitrogen atom, in related ring systems are similarly activated[102]. The synthesis of atebrine (reaction 56)[103a] is illustrative, and numerous potential antimalarial drugs have been similarly prepared from substituted 4-chloroquinolines[103b]. Site activation is likely to be increased by



(56)

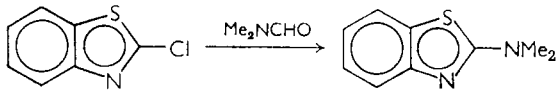
protonation or quaternisation of the ring nitrogen, and acidic catalysis has been noted in a number of cases (reaction 57)[93,104].



(57)

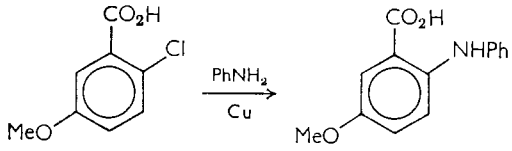
In the reactions discussed in this subsection, the displacing nucleophile has been ammonia or an amine. A number of cases have been reported, however, in which a dimethylamino group has been introduced by use of dimethylformamide; these include displacement of

halogen from halogenonitrobenzenes[105a] and heterocyclic chloro compounds (reaction 58)[105b]. Urea has also been used for the preparation of aromatic primary amines such as 2,4-dinitroaniline from the corresponding chloro compounds[106].



(58)

Amines can often be induced to react with aromatic halides, in which activating influences of the type discussed above are absent, by employing the device of catalysis by copper and various copper compounds (reactions 59 and 60). Diarylamines (from aromatic amines[107a]) and mixed aliphatic–aromatic amines (from aliphatic amines[107b]) are obtainable in this way. These induced reactions have



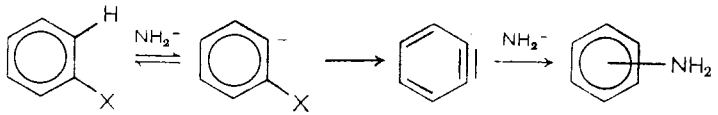
(59)

$$PhCl + MeNH_2 \xrightarrow{Cu_2Cl_2} PhNHMe \qquad (60)$$

been presented as nucleophilic substitutions of copper-complexed aryl halides in which the halogen has acquired positive character by coordination[93a].

D. The Route to Aromatic Amines via Aryne Intermediates

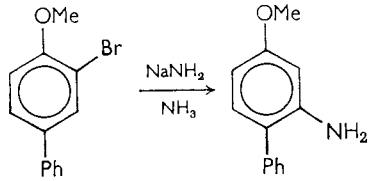
Many cases are known of the reaction of non-activated aryl halides, possessing at least one free *ortho* position, with metallic amides by an elimination–addition, i.e. aryne[108] or heteroaryne[109], mechanism. With the halogenobenzenes, the observed order of reactivity is Br > I > Cl ≫ F. The rates of the steps **18** → **19** and **19** → **20** are expected to decrease in the orders F > Cl > Br > I and I > Br > Cl > F respectively. The stepwise sequence **18** → **19** → **20** thus becomes effectively synchronous, i.e. **18** → **20**, when the rate of the second step



(18) (19) (20)

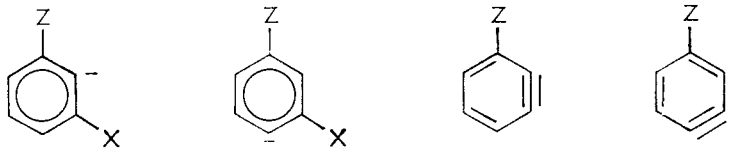
sufficiently exceeds the rate of the first, and this change occurs between chlorobenzene and bromobenzene[110].

With substituted halogenobenzenes, the amide ion might be expected to add preferentially to one or other end of the 'triple bond' and so lead to rearranged amines or mixtures of amines. The occurrence of such cine substitution has obvious attractions for the synthetic chemist in providing useful routes to various amines which might otherwise be difficult to obtain. An example is provided by the synthesis of 2-amino-4-methoxybiphenyl from 3-bromo-4-methoxybiphenyl (reaction 61)[111]. A similar rearrangement is exploited in a recent synthesis of the aporphine alkaloid, laureline[112].



(61)

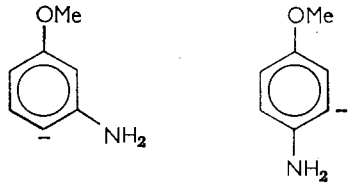
The factors underlying the orientation pattern observed with substituted halogenobenzenes have been generalised by Roberts and coworkers[113]. In the stages leading to the aryne, *ortho*- and *para*-substituted aryl halides give the 3- and 4-substituted benzynes, (**20a**) and (**20b**) respectively. Where the synchronous mechanism, **18** → **20**, applies, *meta*-substituted halides are expected to give preferentially the benzyne formed by removal of the more acidic of the hydrogen atoms *ortho* to halogen; for example, *m*-bromobenzotrifluoride gives 3-trifluoromethylbenzyne. Where the stepwise mechanism, **18** → **19** → **20**, applies, loss of halide ion from the two possible aryl anions (**19a**) and (**19b**) becomes a contributory and possibly determining factor, as in the formation of 3,4-pyridyne from 3-halogenopyridines[109].



(19a) (19b) (20a) (20b)

The preferred site of addition of amide ion to substituted benzynes is considered to be that giving the aryl anion which is most stabilised by the inductive effect of the substituent. With 3-substituted benzynes, amide ion would thus be expected to add preferentially to the *meta*

position if Z is electron attracting, and to the *ortho* position (neglecting steric effects) if Z is electron releasing. Similarly, 4-substituted benzynes would be expected to give 4- and 3-substituted anilines respectively depending on whether Z is electron attracting or releasing. However, inductive effects are weaker with 4- than with 3-substituted benzynes, and conjugative effects may become relatively important; for example, approximately equal amounts of *m*- (**21a**) and *p*-anisidine (**21b**) are formed from *p*-bromoanisole and sodamide. These con-



(21a) **(21b)**

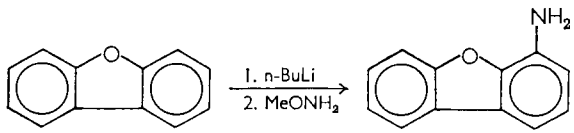
siderations have been generally used for predicting and rationalising product orientation in additions of amide ion (and of alkylamide ions) to arynes[114], though the possible involvement of conjugative effects in the corresponding additions to 3-substituted benzynes has also been recently discussed[115].

V. PREPARATIONS OF AMINES INVOLVING THE USE OF GRIGNARD REAGENTS

A number of amine syntheses take advantage of the nucleophilic character of the alkyl (or aryl) group in a Grignard reagent. Thus direct amination of Grignard reagents (preferably those derived from alkyl chlorides or bromides rather than iodides) by methoxyamine leads to primary amines (reaction 62)[116,117]. In a similar way,

$$t\text{-BuMgCl} + NH_2OMe \longrightarrow t\text{-BuNH}_2 \qquad (62)$$

various aromatic compounds have been metalated using n-butyllithium and the resulting aryllithium aminated with methoxyamine (reaction 63)[118].

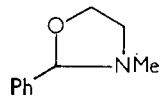


(63)

A number of α-dialkylaminoalkyl compounds, such as ethers and cyanides, react with Grignard reagents and so provide useful supplementary routes to tertiary amines. Dialkylaminomethyl ethers, prepared from the dialkylamine, formaldehyde and n-butanol, for example, react as in (64)[119]. Corresponding compounds, available

$$R_2NCH_2OBu\text{-}n + R^1MgX \longrightarrow R_2NCH_2R^1 \qquad (64)$$

from cyclic secondary amines such as morpholine[120], or from aromatic aldehydes[121], react in the same way. The amino–ether grouping may also be incorporated in a cyclic structure, in which case the reaction gives rise to a hydroxy amine (reaction 65)[122].

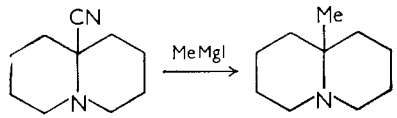


$$\xrightarrow{MeCH{=}CHMgBr} MeCH{=}CHCHPhNMeCH_2CH_2OH \qquad (65)$$

α-Dialkylaminoalkyl cyanides react in a similar way to yield tertiary amines[123], although various complications have been observed[124,125]. The reaction has, however, continued to find application and has been used for the synthesis of triisopropylamine (reaction 66)[126]. Incidental examples of the reaction are also provided by

$$i\text{-Pr}_2NCHMeCN \xrightarrow{MeMgCl} i\text{-Pr}_3N \qquad (66)$$

displacement of angular cyano groups in the quinolizidine and octahydropyrrocoline series (reaction 67)[127].



(67)

A few tertiary amines have been prepared from *N*,*N*-dialkylformamides by reaction with an excess of Grignard reagent, though yields are frequently not high (reaction 68)[128].

$$(i\text{-Pr})_2NCHO \xrightarrow[n\text{-BuMgBr}]{\text{Excess}} (i\text{-Pr})_2NCH(n\text{-Bu})_2 \qquad (68)$$

VI. INTRODUCTION OF AMINO GROUPS BY ADDITION TO CARBON–CARBON DOUBLE BONDS

A. Nucleophilic Addition of Ammonia and Amines to Carbon–Carbon Double Bonds

Olefins are normally susceptible to attack by electrophiles rather than nucleophiles, and the addition of ammonia or amino compounds to carbon–carbon double bonds is only expected to occur readily in

cases where the double bond bears one or more electron-attracting substituents. Typical activating substituents[129] are —CN, —COOR, —COR, —NO_2, —SO_2R. The general mechanistic features of this type of reaction have been discussed in an earlier volume of this series[130], and only problems pertinent to amination reactions will be discussed here.

These addition reactions may be typified by equation (69) where Y

$$R_2NH + CH_2{=}CHY \longrightarrow R_2NCH_2CH_2Y \qquad (69)$$

is an activating substituent. Reaction often occurs at normal or elevated temperatures without added catalysts, though catalysis is desirable and often necessary for efficient reaction between aromatic amines and, α,β-unsaturated esters and nitriles, for example. Typical catalysts are acetic acid[131], and various metallic compounds such as stannic chloride[132] or cupric acetate[133]. Catalysis by bases (sodium ethoxide, benzyltrimethylammonium hydroxide) is also employed, particularly in reactions of amines with α,β-unsaturated nitriles[131,134].

In addition reactions involving ammonia, it is sometimes difficult to obtain solely the desired product. The problem is well illustrated by McElvain and Stork's synthesis of guvacine[135], by way of the ammonia–ethyl acrylate reaction, which proceeds by reactions (70), (71) and (72). The optimum yield of the secondary amine, required for

$$NH_3 \underset{}{\overset{CH_2=CHCO_2Et}{\rightleftharpoons}} NH_2CH_2CH_2CO_2Et \qquad (70)$$

$$NH_2CH_2CH_2CO_2Et \overset{CH_2=CHCO_2Et}{\rightleftharpoons} NH(CH_2CH_2CO_2Et)_2 \qquad (71)$$

$$NH(CH_2CH_2CO_2Et)_2 \overset{CH_2=CHCO_2Et}{\rightleftharpoons} N(CH_2CH_2CO_2Et)_3 \qquad (72)$$

benzoylation, was about 44% (obtained using a 5:1 molar ratio of ammonia to ethyl acrylate), but the tertiary amine was formed in comparable amount (47%). The reversibility of the individual steps, however, allowed conversion of the tertiary amino compound to *N,N*-di(β-carbethoxyethyl)benzamide by thermal decomposition in the presence of benzoyl chloride.

Ammonia and acrylonitrile react similarly to give the corresponding primary, secondary and, to a lesser extent, tertiary amine[131]. Methylamine and ethyl acrylate give a mixture of the corresponding secondary and tertiary amines[136], or almost exclusively the tertiary amine[137], according to conditions. Methylamine and acrylonitrile, however, give mainly the corresponding secondary or tertiary amine[131], again depending on conditions. In this situation, it is customary to control the reaction as far as possible by adjusting the temperature and

proportions of the reactants. With aromatic amines[138] and higher primary n-alkylamines the problems of selective reaction become less acute and it is usually possible to obtain principally the secondary or tertiary amino compound as desired[136,139].

Secondary amines react with acrylonitrile and with ethyl acrylate to give the tertiary amino compounds. Piperidine, morpholine and to a lesser extent diethylamine react readily enough but the rates of these reactions drop with increasing size and branching of alkyl groups, and may fail with highly branched alkyl amines where branching occurs near the nitrogen atom[103b,140]. These are reactions in which base catalysis is frequently employed[131]. Appropriate acidic conditions (with copper catalysis) have been used for the reaction of diphenylamine with acrylonitrile[141].

Attachment of an alkyl group to the double bond, either α- or β- to the activating substituent, may result in a decrease in reactivity of the unsaturated compound, but also in greater selectivity of reaction. Thus methylamine and methyl methacrylate interact to give the corresponding secondary amino compound (1:1 adduct) in very good yield (reaction 73)[142]. Esters of crotonic acid and its homologues

$$MeNH_2 + CH_2{=}CMeCO_2Me \longrightarrow MeNHCH_2CHMeCO_2Me \qquad (73)$$

give similar 1:1 adducts with ammonia, and primary and secondary amines (reaction 74)[143]. Interestingly, ammonia and ethyl γ-tri-

$$EtCH{=}CHCO_2Et + NHMe_2 \longrightarrow EtCH(NMe_2)CH_2CO_2Et \qquad (74)$$

fluorocrotonate give β-amino-γ,γ,γ-trifluorobutyramide, the inductive effect of one —CF_3 group being insufficient to reverse the direction of addition (reaction 75)[144a]; two β-CF_3 groups are however effective in this respect (reaction 76)[144b]. Esters of cinnamic acid react slug-

$$CF_3CH{=}CHCO_2Et + NH_3 \longrightarrow CF_3CH(NH_2)CH_2CONH_2 \qquad (75)$$

$$(CF_3)_2C{=}CHCO_2H + NH_3 \longrightarrow (CF_3)_2CHCH(NH_2)CO_2H \qquad (76)$$

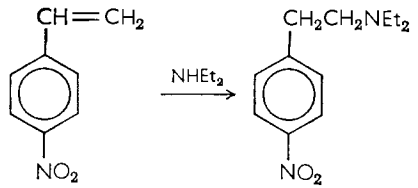
gishly with amines to give indifferent yields of the corresponding β-amino-β-phenylpropionic esters[145].

Ammonia and amines add readily to the double bond in α,β-unsaturated ketones (reaction 77)[146] and nitro compounds (reaction 78)[147], catalysis being usually unnecessary even for aromatic amines.

$$PhCH{=}CHCOMe \xrightarrow{Piperidine} PhCHCH_2COMe \quad (NC_5H_{10}) \qquad (77)$$

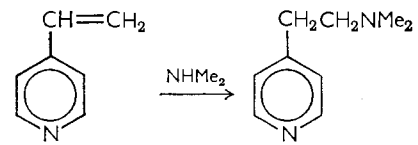
$$PhCH{=}CHNO_2 \xrightarrow{PhNH_2} PhCHCH_2NO_2 \quad (NHPh) \qquad (78)$$

The activating effect of a nitro group is even sufficient to promote amine addition when transmitted through a benzene ring. Thus primary and secondary amines add to *o*- and *p*-nitrostyrenes to give 1:1 adducts (reaction 79)[148], though yields decrease with increasing size of alkyl groups in the amine. Similar considerations apply to the



(79)

direct addition of amines to α- and γ-vinylpyridines (reaction 80)[149a,b].



(80)

Styrene itself can be aminated in the presence of sodium, but the reaction here probably involves addition of the highly nucleophilic amide ion[129,150].

A few instances have been noted of allylic compounds bearing an electron-attracting substituent undergoing addition reactions with amines. These cases appear to involve shift of the double bond from the β,γ- to the α,β-position prior to reaction. For example, benzyl allyl sulphone and piperidine react to give benzyl β-piperidinopropyl sulphone (reaction 81)[151]. Allyl cyanide similarly reacts with am-

$$PhCH_2SO_2CH_2CH{=}CH_2 \longrightarrow PhCH_2SO_2CH_2CH(CH_3)NC_5H_{10} \qquad (81)$$

monia and amines at elevated temperatures to give adducts derived from crotononitrile (reaction 82)[152].

$$CH_2{=}CHCH_2CN \xrightarrow{NHEt_2} CH_3CH(NEt_2)CH_2CN \qquad (82)$$

Transamination reactions are occasionally used as an adjunct to the addition reactions described in this section. Aniline and β-diethylaminopropionitrile (as hydrochloride) undergo amine exchange at 140–150° to give β-anilinopropionitrile (reaction 83)[153]. These

$$PhNH_2 + Et_2\overset{+}{N}HCH_2CH_2CN \longrightarrow PhNHCH_2CH_2CN + Et_2\overset{+}{N}H_2 \qquad (83)$$

reactions may proceed in some cases by an elimination–addition mechanism, i.e. via acrylonitrile, but Cymerman–Craig and co-

workers have adduced evidence for a substitution mechanism[154]. In another context, the β-cyanoethyl group may be seen as a potential blocking group for —NH_2 as in recently reported syntheses of glycylglycine and other simple peptides[155]; removal of the blocking group may be effected using 10% ammonium hydroxide (reaction 84).

$$RN(CH_2CH_2CN)_2 \xrightarrow[\text{reflux}]{10\%\ NH_4OH} RNH_2 \qquad (84)$$

B. Routes to Amines Involving Electrophilic Additions to Carbon–Carbon Double Bonds

A number of routes to amino compounds take advantage of the normal susceptibility of olefins to attack by electrophiles. In general these reactions do not lead directly to amines, but rather to compounds which can be transformed to amines by subsequent reactions. A notable exception is provided by the reaction of dialkylchloroamines with terminal olefins in acidic media (reaction 85)[156]. The

$$Et_2NCl + CH_2{=}CHR \xrightarrow{H^+} Et_2NCH_2CHClR \qquad (85)$$

process involves addition of an aminium ion-radical, e.g. $(^{\cdot}NHEt_2)^+$ to the double bond followed by chain transfer. With the higher dialkylchloroamines, pyrrolidine formation (cf. section II.A) takes precedence over addition to the olefin (though not in the case of butadiene). Chlorination of the olefin is another possible complicating reaction. Nonetheless, yields of the 1:1 adduct are of the order 30–60% where the reaction is applicable.

α-Piperidyl radicals, generated from piperidine and benzoyl peroxide, also add to terminal olefins to give the alkylpiperidine[157], whilst addition of nitrogen dioxide to olefins gives products which are reducible to amino compounds[158].

Further examples of the Ritter reaction[72,73] (cf. section IV.B) are provided by the many substituted olefins that may be protonated to give carbonium ions which can be intercepted by hydrogen cyanide or organic nitriles; cyanogen chloride can also be used as intercepting species[159], but offers no advantages. Mixtures of the two possible amides, and hence amines, are to be expected from non-terminal alkenes and from such olefinic compounds as oleic acid[160].

Olefins may also be converted to amines with yields of up to 60%, by hydroboration and subsequent reaction of the organoborane with chloroamine in alkaline solution or preferably with hydroxylamine-*O*-sulphonic acid in diglyme (reaction 86)[161]. The reaction is applicable

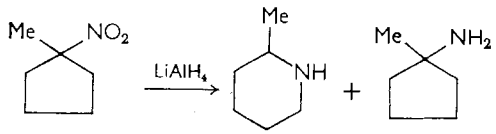
$$RCH{=}CH_2 \xrightarrow{B_2H_6} RCH_2CH_2{-}B\!\!\diagup\!\!\diagdown \longrightarrow RCH_2CH_2NH_2 \qquad (86)$$

to hindered olefins and is stereospecific, the boron being replaced by the NH_2 group with retention of configuration.

VII. REDUCTIVE METHODS FOR THE PREPARATION OF AMINES

A comprehensive review is available covering a large number of known reductive methods for the production of amines[162]. In principle, compounds containing an alkyl or aryl group linked to a nitrogen functional group at a higher oxidation level than —NH_2, or those containing an amino group directly linked to a carbon atom at a higher oxidation level than alkyl, or again compounds containing carbon–nitrogen multiple bonds, may all be reducible to amines.

Within the first group, reduction of nitro compounds is by far the most important, though principally in the aromatic series. Aliphatic nitro compounds may be reduced to the corresponding primary amines by catalytic hydrogenation[162-164] or by chemical means. Favoured chemical methods include reduction by iron and hydrochloric acid (with optional catalysis by ferric chloride[163]) or by lithium aluminium hydride[165]. With the latter reagent, ring enlargement has been noted with some tertiary cyclic nitroalkanes (reaction 87)[166]. Lithium aluminium hydride has also been extensively



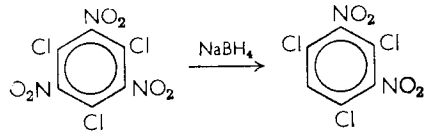
used for the reduction of β-nitrostyrenes to the important β-phenylethylamines (reaction 88)[165]. The utility of these reductions is limited

$$ArCH{=}CHNO_2 \xrightarrow{LiAlH_4} ArCH_2CH_2NH_2 \qquad (88)$$

by the availability of the nitro compounds, and many applications depend on the use of condensation reactions involving simple nitroalkanes to provide the required nitro compound[167].

Aromatic nitro compounds are a much more accessible class of substances, and a wide choice of methods exists for their reduction to amines. The choice of reducing agents includes (i) a variety of metals, usually employed in acidic or faintly acidic media, (ii) metallic compounds involving a low valency state of the metal, stannous chloride being frequently used and (iii) anionic sulphur compounds such as ammonium and sodium sulphides and polysulphides, and

sodium hydrosulphite[162]. Catalytic hydrogenation is also widely employed[162]. Lithium aluminium hydride reduces simple aromatic nitro compounds to the azo compound[165]; sodium borohydride does not affect nitro groups except in special cases where a nitro group is displaced or eliminated as nitrite ion (reaction 89)[168]. A number of

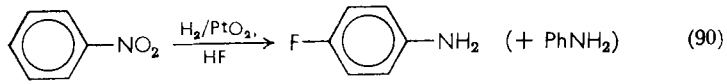


(89)

reductive procedures involving hydrogen transfer in the presence of palladium catalysts are known; hydrazine[169], and sodium borohydride in neutral or acidified solutions[170] have been used for this purpose.

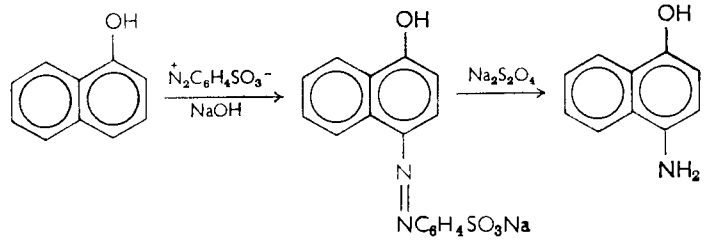
A number of these methods of reduction are pleasingly selective and may be employed with molecules containing other potentially reducible groups; amongst the selective reagents are ferrous hydroxide and, particularly for the partial reduction of polynitro compounds, sodium and ammonium sulphides[162].

The substitution of a chlorine atom in the aromatic ring has been noted during some reductions in which concentrated hydrochloric acid is used; this presumably occurs by conversion of the intermediate arylhydroxylamine to the *N*-chloroamine and thence by rearrangement to the chloroaniline. A recent preparation of *p*-fluoroaniline exploits this type of substitution (reaction 90)[171].



(90)

With aromatic compounds which are very reactive towards electrophiles, it may be preferable to introduce a nitroso or arylazo group rather than a nitro group; reduction to the amine can be effected in a number of ways (reaction 91)[162,172].



(91)

The reduction of hydrazine derivatives has not been widely exploited for the preparation of amines, but might be useful in certain cases. Benzhydrazide can be alkylated on the terminal nitrogen atom; hydrogenolysis then gives the amine (reaction 92)[173].

$$PhCONHNRR^1 \longrightarrow PhCO\overset{-}{N}\overset{+}{N}RR^1Me \longrightarrow PhCONH_2 + NRR^1Me \quad (92)$$

More widely used as a source of aliphatic and alicyclic amines is the reduction of azides (reaction 93), many of which are available by

$$RN_3 + H_2 \longrightarrow RNH_2 + N_2 \quad (93)$$

stereospecific S_N2 azidolysis of various alkyl halides and toluene-*p*-sulphonates. The reduction may be carried out catalytically under very mild conditions[162], or by use of lithium aluminium hydride[174] or diborane[175].

The principal compounds in the second group, i.e. those containing an amino group linked to a carbon atom at a higher oxidation level than alkyl, are the carboxylic amides. These are reducible by lithium aluminium hydride to the corresponding amine; primary, secondary and tertiary amides give respectively the primary, secondary and tertiary amines[165]. This method of reduction allows indirect introduction of bridging amino groups in certain cyclic systems[176]. There is evidence that the reduction of primary amides involves the corresponding nitrile as an intermediate in at least some cases[177]. Amides, especially tertiary amides, can also be reduced to the amine by means of diborane (reaction 94)[178].

$$RCONR_2 \longrightarrow RCH_2NR_2 \quad (94)$$

Compounds containing carbon–nitrogen multiple bonds are also potential sources of amines; these compounds include imines (Schiff's bases), oximes, hydrazones, azines and nitriles.

Imines can be reduced to amines by catalytic hydrogenation, or by reduction with lithium aluminium hydride, sodium borohydride or amine–borane complexes[179]. For many purposes, it is not necessary to prepare the imine as the desired amine can, at least in principle, be obtained by catalytic reduction of a mixture of the corresponding carbonyl compound and precursoral amine (reaction 95)[180]. The

$$R_2C{=}O + R^1NH_2 \rightleftharpoons R_2C(OH)NHR^1 \rightleftharpoons R_2C{=}NR^1 \longrightarrow R_2CHNHR^1 \quad (95)$$

amine R^1NH_2 can even be replaced by compounds, e.g. nitro compounds, which are reducible to the amine under the reaction conditions[180,181]. This reaction is termed reductive alkylation and suffers

from the drawback that the amine formed may also condense with the carbonyl compound and so undergo further reductive alkylation. In practical applications of this method, undesired reactions of this type can often be minimised by suitably adjusting the concentrations of the carbonyl compound and the starting amine. A recent variant involves the reduction of a mixture of the carbonyl compound and the amine salt by sodium borohydride in aqueous solution[182].

Reductive alkylation of amines by carbonyl compounds can also be effected by procedures in which formic acid and its derivatives provide the reducing system[183]. The particular combination of formaldehyde and formic acid (Clarke–Eschweiler method) provides for the methylation of amines, usually to the tertiary stage (cf. ref. 60)[183]; the Délepine method (cf. section IV.B) can be modified to give alkyldimethylamines by use of formic acid[184]. These reactions are considered to involve decarboxylation of the intermediate aminocarbinyl formate (reaction 96)[185].

$$R_2C{=}O \rightleftharpoons R_2C(NHR^1)OH \longrightarrow R_2C(NHR^1)OCH{=}O \longrightarrow R_2CHNHR^1 + CO_2 \quad (96)$$

Oximes, hydrazones and azines are obtainable from carbonyl compounds and can be reduced to primary amines (sometimes accompanied by secondary amines) in various ways (reaction 97)[162,186].

$$RCH{=}NOH \longrightarrow RCH_2NH_2 \quad (97)$$

Rearrangements have been noted in the reduction of some oximes with lithium aluminium hydride[187].

The catalytic reduction of nitriles is also frequently employed as a route to primary amines (reaction 98)[162,188]. This involves an imine

$$RC{\equiv}N \longrightarrow RCH_2NH_2 \quad (98)$$

as an intermediate stage and may, as in the reductive alkylation procedures, lead to the primary amine together with appreciable amounts of the secondary amine. For the preparation of primary amines, it has become common practice to conduct hydrogenation in the presence of an excess of ammonia, or alternatively in the presence of acetic anhydride, when the primary amide is produced. Lithium aluminium hydride is also widely used for the reduction of nitriles[165].

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CHAPTER 3

Detection, determination, and characterisation of amines

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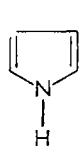
I. INTRODUCTION

The wide distribution of amines in nature, their importance in industry as raw materials, intermediates, and finished products, and their use in the laboratory causes continuous interest in the analytical problems connected with them. These will be focussed at two levels in the present chapter; at the purely functional level attention will be paid to the nitrogen atom and its immediate vicinity, and at the molecular level the interactions between the amino group and the rest of the molecule will be considered. The alternative approach, centered on the discussion of the available methods, techniques, and instrumentation, is essential when one has to carry out an actual analysis, and constitutes the main part of the literature on the subject, in books and treatises on general analysis, organic analysis, and organic chemistry, as well as in original papers and reviews. Some outstanding titles are listed in references 1 to 16.

(1)

(2)

This chapter will deal with compounds in which structures **1** or **2** appear at least once, where the nitrogen atoms are singly bonded to carbon or hydrogen atoms, and furthermore, when these carbon atoms are linked to hydrogen or carbon atoms. Thus structures such as pyrrole (**3**), morpholine (**4**), and their salts will be considered, whereas pyridine (**5**) and 1-aminoethanol will be excluded, in spite of the fact that many of the methods applied in analysing the former compounds are useful for the latter too.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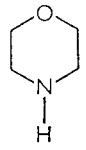
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(5)

II. FEATURES OF THE GROUP

The amino group is endowed with a set of physical and chemical properties which depend mainly on the possession of certain structural elements. These do by no means belong to amines exclusively, but they may be used for the partial or total solution of many analytical problems.

A. The Nitrogen Atom

1. Pyrolyses and other chemical methods

On strong heating, many nitrogen-containing organic compounds yield hydrogen cyanide and a few yield cyanogen. Ammonia is evolved from compounds such as urea, guanidine, and some of their derivatives. Trimethylamine is released by compounds such as choline and betaine[9]. If the pyrolysis is carried out in the presence of calcium oxide the evolution of ammonia can be detected easily[9,17].

The reductive pyrolysis of organic compounds in the presence of metals leads to the formation of the metal cyanide, which can be detected as Prussian blue ($Fe_4[Fe(CN)_6]_3$) or by the copper(II) acetate–benzidine test[18]. Several metals and salts have been recommended for the fusion of the organic compound, e.g. potassium[19,20], sodium[21,22], magnesium mixed with potassium carbonate[23], zinc mixed with potassium carbonate[24], and a mixture of dextrose with sodium carbonate[25]. When the compound contains sulphur the metal thiocyanate is also produced, which can be detected by ferric chloride[26,27].

Another type of reductive process is the combustion in hydrogen atmosphere in the presence of a nickel catalyst, where at temperatures over 1000° nitrogen is converted into ammonia and subsequently determined[28–30]. A similar method adapted for ultramicroanalysis has been proposed[31].

Nitrogen and hydrogen can be determined simultaneously by burning in dry carbon dioxide in the presence of a copper–copper oxide–silver catalyst, when water and nitrogen are liberated and subsequently determined[32].

A very sensitive test for nitrogen consists of heating the sample in admixture with manganese dioxide or other oxidants such as lead dioxide, red lead oxide (Pb_3O_4), cobalt(III) oxide, nickel(III) oxide, or manganese(III) oxide. Nitrous acid is evolved and can be detected by the Griess reaction[9,33].

Many determinations of nitrogen based on oxidative pyrolyses of organic samples are variations, adaptations, and refinements of the original Dumas method[34], consisting of burning the organic compound in oxygen. Adaptations suited to ultramicroanalysis (nitrogen content of the order of 1 μg) have been reported[35,36]. The Dumas method has been amply reviewed[15,30,37,38].

The Kjeldahl method[39,40] converts the bonded nitrogen into ammonium bisulphate which is then determined as ammonia. Many variations have been introduced in order to refine the method or adapt it to diverse types of organic materials. It was originally devised to determine the nitrogen of amino or amido groups and it cannot be used for other functions without due precautions or previous treatment of the sample, and in certain cases it fails to render quantitative results, for example when applied to compounds with partial structure C—N—N—C, probably because elementary nitrogen is lost. Ultramicro scale determinations have been carried out by this method[41,42]. Ample reviews and discussions can be found elsewhere[15,30,43,44].

Various classes of nitrogen-containing organic compounds were found to give colour reactions with *p*-dimethylaminobenzaldehyde in the presence of sulphuric acid in toluene solution[45].

2. Nitrogen by mass spectrometry

High-resolution mass spectrometers are capable of recording *m/e* values down to several decimal places, and the intensity of the peaks with an accuracy of fractions of 1%. This allows one to carry out elegant, though by no means straightforward, determinations of the elementary analysis and molecular weight of organic compounds.

The *m/e* value of the molecular ion—the ion resulting from losing one electron of the original molecule—is equal to the molecular mass M of the compound. It can be computed from equation (1), where n_i is the number of atoms of the nuclide with mass number i present in the molecule, and d_i is the difference between the atomic mass of the nuclide and its mass number. The fractional part of M can be calculated from equation (2), where I is an arbitrarily large positive integer. By finding the values of n_i which best fit equations (1) and (2), the elementary analysis, and therefore the nitrogen content of the compound, have in fact been determined. This can be accomplished by trial and error or by computer. In Table 1 the isotopes most frequently encountered in organic compounds are listed.

$$M = \sum_i n_i(i + d_i) \tag{1}$$

$$\text{Fractional part of } M = \text{Fractional part of } \left[I + \sum_i n_i d_i\right] \tag{2}$$

An alternative approach correlates the natural abundance of the isotopes (see Table 1) with the relative intensities of the peaks at M, $M + 1$, $M + 2$, etc. In order to illustrate the method consider a molecule with n carbon atoms with molecular ion of mass M. The intensity of the peak at $M + 1$ will be close to $(n \times 1{\cdot}1)\%$ of the

TABLE 1. Naturally occurring isotopes frequently encountered in organic compounds[a].

Element	Mass number[b]	Atomic mass[c]	Difference[d]	Natural abundance (%)
Hydrogen	1	1·007825	0·007825	99·985
	2	2·01410	0·01410	0·015
Carbon	12	12·00000	0·00000	98·89
	13	13·00335	0·00335	1·11
Nitrogen	14	14·00307	0·00307	99·63
	15	15·00011	0·00011	0·37
Oxygen	16	15·99491	−0·00509	99·759
	17	16·99914	−0·00086	0·037
	18	17·99916	−0·00084	0·204
Fluorine	19	18·99840	−0·00160	100
Phosphorus	31	30·97376	−0·02624	100
Sulphur	32	31·97207	−0·02793	95·0
	33	32·97146	−0·02854	0·76
	34	33·96786	−0·03214	4·22
	36	35·96709	−0·03291	0·014
Chlorine	35	34·96885	−0·03115	75·53
	37	36·96590	−0·03410	24·47
Bromine	79	78·9183	−0·0817	50·54
	81	80·9163	−0·0837	49·46
Iodine	127	126·9044	−0·0956	100

[a] From reference 46.
[b] i in equation (1).
[c] Based on the arbitrarily assigned atomic mass of 12·00000 to the nuclide $^{12}_{6}C$, in the physical scale.
[d] d_i in equation (1).

intensity of the peak at M, because for every carbon atom in the molecule there is a probability of 1·1% of it being ^{13}C. The contribution of ^{2}H to the $M + 1$ peak is much smaller because of the low natural abundance of this isotope, however ^{15}N and other nuclides may have a noticeable effect, especially when more than one atom of these elements is present in the molecule. For compounds of high molecular weight, containing many carbon atoms, statistical considerations have to be made in order to calculate the M to $M + 1$ intensity ratio. The $M + 2$ peak can be used in the same way relative to the $M + 1$ peak. By comparing the calculated and experimental values of these ratios the elementary composition of the molecular ion can be found.

The amino group is a source of instability in the molecular ion which may cause its rearrangement before reaching the collector of the mass spectrometer. If such rearrangements involve splitting of all

the molecular ions into two particles neither the molecular weight nor the elementary analysis will be accessible by mass spectrometry. This splitting will occur less frequently in cyclic compounds, where the bond rearrangements will not cause fragmentation of the molecule.

The molecular ions of amines frequently abstract a hydrogen atom from a neutral species thus acquiring stability. This will make the molecular peak appear at $M + 1$. Such processes can be detected by studying the relative intensities of many peaks in the spectrum, as the relative intensities of peaks resulting from hydrogen abstraction will be pressure-dependent, as their corresponding ions result from bimolecular processes[47–51].

The application of mass spectrometry in the determination of molecular weights has been reviewed[47, 48, 52–54] and tables for the elementary analysis of compounds containing C, H, N, and O, according to both mass spectrometry methods previously described, have been compiled[55].

3. Nuclear activation

Activation analysis is a method that in some cases allows one to determine small amounts of nitrogen, of the order of 1 μg or less. It consists of irradiating the sample in a suitable generator of particles or rays, most frequently in a nuclear reactor, and measuring the decay of the new radioactive nuclides produced. The radioactivity A induced in such a manner can be calculated from equation (3), where N is the number of target atoms, σ the cross section of the reaction, Φ the irradiation flux, t the irradiation time, and λ the decay constant of the new nuclide[56].

$$A = N\sigma\Phi(1 - e^{-\lambda t}) \qquad (3)$$

In a nuclear activation reaction the following factors have to be considered besides the variables of equation (3): threshold energy, mode of decay of the product, interference by other elements present in the sample yielding the same products as the element investigated, or products with overlapping decay spectra, etc. For example in the determination of compound **6** the $^{14}N(n, 2n)^{13}N$ reaction was used[57].

$O{=}P(CH_2CH_2NH_2)_3$
(6)

This is a 'fast neutrons' reaction, with threshold energy of 10·5 MeV, and is applicable only if sufficient high-energy neutrons are available. The other two neutron reactions which could be possibly used,

namely $^{14}N(n,p)^{14}C$ and $^{15}N(n,\gamma)^{16}N$, are not very useful in this case because of their low yields: with the former ^{14}C has a very low decay constant λ, resulting in a low saturation factor, which is the expression enclosed in brackets in equation (3), whereas with the latter reaction the natural abundance (see Table 1) which is directly related to N, and the thermal neutron cross section σ of ^{15}N, are small[58]*.

In Table 2 nuclear reactions are listed in which nitrogen is converted into a radioactive nuclide.

TABLE 2. Nuclear activation reactions of nitrogen.

Reaction[a,b,c]	Half-life of product[d]	Possible interferences[a,b,c]
$^{14}N(n,p)^{14}C$	5770 years	$^{17}O(n,\alpha)^{14}C$ and $^{13}C(n,\gamma)^{14}C$
$^{14}N(n,2n)^{13}N$	10·0 min	$^{13}C(p,n)^{13}N$ and $^{16}O(p,\alpha)^{13}N$
$^{14}N(\gamma,n)^{13}N$	10·0 min	$^{13}C(p,n)^{13}N$ and $^{16}O(p,\alpha)^{13}N$
$^{14}N(d,n)^{15}O$	2·03 min	$^{16}O(d,dn)^{15}O$, $^{14}N(p,\gamma)^{15}O$, and $^{15}N(p,n)^{15}O$
$^{14}N(p,\gamma)^{15}O$	2·03 min	$^{16}O(p,pn)^{15}O$
$^{15}N(p,n)^{15}O$	2·03 min	$^{16}O(p,pn)^{15}O$
$^{14}N(p,\alpha)^{11}C$	20·5 min	
$^{15}N(n,\gamma)^{16}N$	7·35 sec	

[a] From references 58 and 59.
[b] In a reaction X(a, b)Y, nuclide X irradiated with a releases b yielding nuclide Y.
[c] n–neutron, p–proton, γ–γ-ray, d–deuterium nucleus, α–α-particle.
[d] From reference 46.

B. The Free Electron Pair

The fact that in amines the nitrogen atom has two free electrons readily available for reaction is the basis of a large number of detection and determination methods. Furthermore, in many cases in which the products are apparently the result of a reaction with N—H groups, the presence of the free electron pair is essential for the reaction to take place. The latter cases however will be treated in section II.C together with other properties of the N—H moiety.

Table 3 summarises the various ways in which the free electron pair (p electrons) of amines can react with other compounds or func-

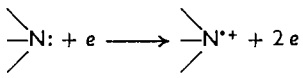
* The nuclides ^{2}H, ^{12}C, ^{13}C, ^{14}N, ^{15}N, ^{16}O, ^{17}O, and ^{18}O can be determined after proton or deuteron activation, in gaseous samples, at pressures of a few mm Hg, by neutron time of flight spectroscopy[610]. In the case of nitogen the reactions are $^{14}N(d,n)$ ^{15}O and $^{15}N(p,n)^{15}O$.

tions. Types 1 and 2 of this table can be considered to differ from one another in the degree of coordination of the p electrons with a proton, types 2 to 7 are distinguished by the nature of the electron acceptor, and type 8 is a contribution (hypothetical or actual) to the structure of amines where the amino group is attached to an unsaturated system. It should be noticed that the molecule tends to be planar at the nitrogen site in type 8, in contrast with the nearly tetrahedral geometry in the remaining seven types.

TABLE 3. Coordination of the p electrons of amines.

Type of coordination	Section in which considered
1. Hydrogen bonding	II.E, IV.C.4
2. Ammonium salts of protonic acids	II.B.1
3. Ammonium compounds with Lewis acids	II.B.2, IV.C.4
4. Complexes with metallic ions	II.B.3, IV.C.2
5. Quaternary ammonium compounds	II.B.4, III
6. Amine oxides	
7. Complexes with π acids	II.B.1.b
8. Electron transfers in unsaturated molecules	IV.B

A further way in which the free electrons may react is by losing only one of them, thus yielding a radical–cation, for example by electron impact in a mass spectrometer, where reaction (4) probably takes place (see also sections II.A.2 and IV.A.2).



(4)

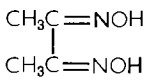
1. Reaction with protonic acids

a. Basicity tests. Amines are weak bases capable of reacting with acids. Several methods of detecting this reaction have been proposed. The simplest is the solubility test of a sample in dilute mineral acid, used in qualitative organic analysis[8,16]. In another test the sample is dissolved in hydrochloric acid, evaporated to dryness, the residue redissolved, and the solution tested for chloride with silver nitrate[9]. Some basicity tests make use of equilibria involving the formation of coloured precipitates, such as the complex of dimethylglyoxime (**7**) with nickel(II) ions[60], or 8-hydroxyquinoline (**8**) with zinc ions[61]. If in equations (5) and (6) the concentration of protons is adjusted to a value at which the solubility product of the metal complex is nearly

reached, then the addition of a base will lower the proton concentration and enhance the complex concentration thus causing its precipitation.

$$Ni^{2+} + 2\,XH \rightleftharpoons NiX_2 + 2\,H^+ \quad (XH = \mathbf{7}) \qquad (5)$$

$$Zn^{2+} + 2\,XH \rightleftharpoons ZnX_2 + 2\,H^+ \quad (XH = \mathbf{8}) \qquad (6)$$



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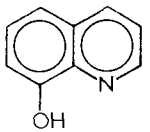


(8)

Many aliphatic amines have pK_a values in the range of 9 to 11, and aromatic ones in the range of 4 to 5. Accordingly, an aqueous solution buffered at pH 5·5 will dissolve alkylamines but not arylamines[62].

b. Precipitation of salts. Amines are lipophilic substances, especially when no acidic groups are present in the same molecule, and therefore they will dissolve in organic solvents such as chloroform, ether, benzene, etc., whereas their water solubility is small, except for a few with low molecular weight[63]. On the other hand, ammonium salts are lipophobic owing to their ionic character. These properties can be applied to the separation of amines from other organic materials dissolved in solvents of low polarity. Precipitation by acids from these solutions, according to equation (7), has been applied qualitatively and quantitatively. The extraction of ion pairs by organic solvents is sometimes possible owing to the hydrophobic character of the radicals attached to the ammonium moiety[64].

$$R^1R^2R^3N + HX \rightleftharpoons R^1R^2R^3NH^+X^- \qquad (7)$$

(R^1, R^2, R^3 = H, alkyl, aryl)

A great variety of salts derived from amines have been used for analytical purposes, a partial list of which appears in Table 4. It should be noticed that the nitro compounds listed in this table are both protonic and π acids, and therefore their derivatives may be ammonium salts, or under certain circumstances π complexes. With the commercial availability of reagent **18**, the preparation of tetraphenylborates has become an important method for the determination of organic bases[95].

c. Aqueous titrations. Amines in aqueous solution interact with water yielding two formal species: a hydrate in which water is hydrogen bonded to the nitrogen atom, and an ammonium ion. The former can

TABLE 4. Salts derived from amines and used for analysis[a].

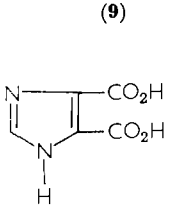
Halides[65]
Perchlorates[65]
Antimony(III) iodide complexes (**9**, **10**, M = Sb)[66,67]
Bismuth(III) iodide complexes (**9**, **10**, M = Bi)[68,69]
Chloroaurates[65]
Metaphosphates[70]
Phosphomolybdates[71]
Phosphotungstates[71,72]
Silicotungstates[71,73–76]
Fluorosilicates[77]
Reinecke salts (**11**)[78,79]
Chloroplatinates[65,79]
Oxalates[65]
Imidazole-4,5-dicarboxylates (**12**)[80]
3,5-Dinitrobenzoates[81]
2,4-Dinitrobenzoates[82]
3,5-Dinitro-*o*-toluates[83]
3,5-Dinitro-*p*-toluates[84]
Picrates (**13**)[65,79,85,86]
Picrolonates (**14**)[79,87–89]
Flavianates (**15**)[90]
Styphnates (**16**)[79,91]
2-Nitro-1,3-diketohydrindene salts (**17**)[92]
Tetraphenylborates (**18**)[79,93–97]

[a] Formulae **11** to **18** belong to the reagents.

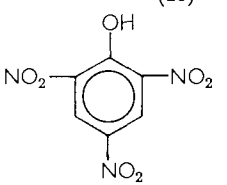
$Amine.MI_3.HI$ (**9**)

$2\,Amine.MI_3.HI$ (**10**)

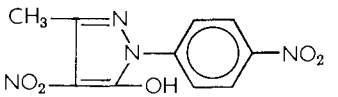
$NH_4[Cr(NH_3)_2(SCN)_4]$ (**11**)



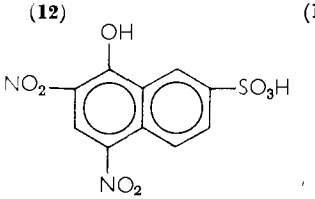
(**12**)



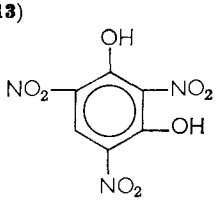
(**13**)



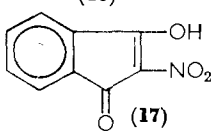
(**14**)



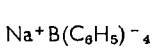
(**15**)



(**16**)

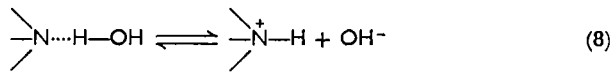


(**17**)



(**18**)

be considered as the most abundant species when amines are dissolved in water[98–100], whereas the latter is the result of the acid–base dissociation of the former according to equation (8).

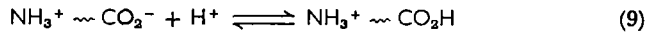


(8)

The equilibrium favours the undissociated form on the left hand side of equation (8), but it can be displaced to the right by addition of a strong acid which will react with the hydroxide ions. Titrations with standard mineral acids can be carried out easily in aqueous solution when the amine has $pK_a \geq 9$, while for lower values it is difficult to distinguish the end-point. By adding neutral salts to the solution, the potentiometric break is enhanced, allowing better detection of the end-point[101,102].

The low solubility of most amines in water is usually corrected by adding organic solvents such as ethanol, methanol, or dioxane. Another potential source of error arises from the possibility of association in solution, for example if the ammonium ion and a neutral amine molecule become associated the potentiometric break will be produced before the equivalent amount of acid has been added, as was found to be the case with aminophenols[103].

Amino acids in the zwitterion form[104,105] can be titrated with mineral acids only if the acid moiety is a weak acid such as a carboxyl group, as in equation (9), which is a special case of titration of ammonium salts of weak acids.



(9)

Aqueous titrations of amines are amply discussed elsewhere[14,15,37].

d. Nonaqueous titrations. Three main purposes may be served by carrying out titrations in nonaqueous solvents: increased solubility, change of the pH scale, and resolution of mixtures. The prediction of a potentiometric titration curve in an arbitrary solvent is a difficult task, in which many factors intervene, such as dielectric constant, definition of acid and base in relation to the solvent, electrodes, actual structure of conjugate acids and bases, etc. Acetic acid, sulphuric acid, acetonitrile, and alcohol–water mixtures have been extensively studied and were reviewed elsewhere[106]. Some solvents will be treated here briefly:

Acetic acid. Bases with $pK_a \geq 2$ can be titrated in anhydrous acetic acid[107], where they show a good potentiometric break. On the other hand, in this solvent bases become distinguishable only if their pK_a values differ widely, and it is therefore not recommended for the determination of mixtures in which concentrations of the various components are required[108]. Standardised perchloric acid in anhydrous acetic acid is the titrant most frequently used. Very weak bases such as diphenylamine were titrated with this solvent–titrant system by differential thermometry[109]. It should be noted that approximately 0·6% of water is contained in a 0·1N perchloric acid solution prepared from commercially available reagents, and if strictly anhydrous conditions are required, it can be removed by treatment with the required amount of acetic anhydride[110].

Acetic anhydride. This is also an excellent solvent for titrating organic bases, giving good end-points when they have $pK_a \geq 0{\cdot}5$[107], although acetylation may occur to some extent in certain cases. Standard perchloric acid[107,111,112] or fluorosulphuric acid[113] in acetic anhydride have been used as titrants. Mixtures of acetic acid with acetic anhydride were also proposed as solvents for the titration of amines[107,114,115].

Acetonitrile is a solvent in which excellent end-points and resolution of mixtures can be attained[14,116,117]. It has, however, the disadvantage of enabling the titration of many amides which may be mixed with amines in the sample. Perchloric acid is usually the titrant. Hydrogen bromide was used for thermometric titrations of amines in this solvent[118].

Nitromethane has properties similar to those of acetonitrile[119–121].

Dioxan gives good end-points. It can be used for titrating bases such as pyridine, but titrations of aniline were not satisfactory in this solvent. The titrant is perchloric acid[122].

Glycols give good resolution in the titration of amines with close pK_a values[123,124].

Many other solvents have been used for the determination of pure and mixed amines. The subject is amply reviewed and discussed elsewhere[14,15,37,125–128].

2. Reaction with Lewis acids

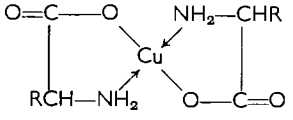
A limited application of Lewis acids has been made in analyses of amines; boron trifluoride[129], titanium tetrachloride, and tin tetrachloride[130] were used to titrate heterocyclic bases in aprotic solvents. Other applications connected with steric effects in amines will be discussed in section IV.C.4.

3. Complexes with metal ions

Amines can coordinate their free electron pair into empty orbitals of some metal ions, much in the same way as ammonia does in inorganic

complexes. This has found some application in the detection and determination of amines although the scope of each reaction is limited by factors such as the type of amine analysed and interferences from other classes of compounds.

Aqueous solutions of copper(II) salts give a green to blue colour or precipitate in the presence of water-soluble amines[16]. In organic solvents, and preferably in the absence of water, aliphatic amines form a complex with excess of copper(II) chloride. Although the structure of this complex is unknown, it has composition $2CuCl_2$.amine, becoming therefore useful for quantitative analysis[131]. Amino acids yield complexes with the same salts, which are stabilised by a chelate structure **19**. After isolation of the complex, it can be analysed for its copper content gravimetrically[132,133] or colourimetrically[133–135].



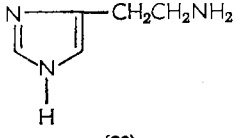
(19)

Ferric complex ions have been used for very sensitive tests of detection and identification of certain classes of amines. Green to blue complexes are formed by the reaction of primary aromatic amines with sodium pentacyanoaquoferriate, as in equation (10)[9,136].

$$Na_2[Fe(CN)_5H_2O] + C_6H_5NH_2 \longrightarrow Na_2[Fe(CN)_5C_6H_5NH_2] + H_2O \quad (10)$$

When a secondary amine is treated with sodium nitroprusside ($Na_2[Fe(CN)_5NO]$) in the presence of acetaldehyde, acetone, pyruvic acid, etc., blue to violet compounds of unknown structure are obtained[9,137,138]. This is the so-called Rimini test[139]. A colourimetric method for determining secondary amines is based on this reaction[140].

In the absence of oxidants, cobalt(II) nitrate in a basic medium yields deeply coloured complexes with certain classes of amines, such as histamine (**20**), which can thus be determined colourimetrically. The formation of such complexes does not seem to depend on the presence of the imidazole (**21**) partial structure, although **21** itself yields a violet precipitate[4,141].



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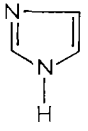


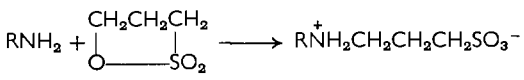
(21)

Copper and cobalt complexes of amino acids have found applications in the solution of stereochemical problems, as mentioned in section IV.C.2.

4. Quaternisation

Amines react with alkyl halides or certain esters attaining a higher degree of alkylation. Primary and secondary amines give, usually, mixtures of amines and ammonium salts while tertiary amines undergo a one-step reaction (equation 11), the product of which is relatively easy to separate and purify. Some reagents which raise the degree of substitution by one only, are treated in section II.C.3, and similarly sultones react according to equation (12), the best results being obtained with primary amines[142].

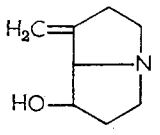
$$R^1R^2R^3N + R^4X \longrightarrow R^1R^2R^3R^4N^+X^- \quad (11)$$



(12)

Quaternisation reactions can be carried out with alkyl halides such as methyl iodide[143,144], and esters of strong acids such as methyl 2,4-dinitrobenzenesulphonate[145], methyl *p*-toluenesulphonate[146], methyl picrate (*O*-methyl derivative of **13**)[147], and methyl sulphate[148]. The reaction can take place with or without solvent and at temperatures ranging from room temperature up to that of reflux[79,143–145]. If the quaternary salt is obtained quantitatively it can be filtered off and weighed, or otherwise determined according to section III.

Some amines in chloroform solution yield the corresponding *N*-(dichloromethyl)ammonium chloride[149]. This reaction may lead to abnormal products, as is the case with **22**, from which **23** is derived[150].



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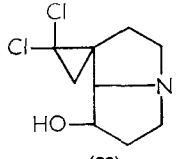
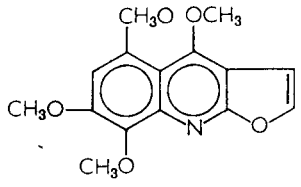


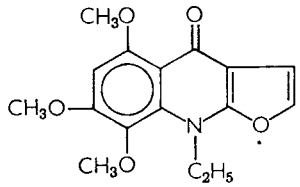
(23)

For heterocyclic bases a method of determination was proposed based on quaternisation with ethyl iodide or methyl sulphate, followed by treatment with basic potassium permanganate. Volatile amines are thus formed which can be collected in standardised mineral acid and back titrated[148].

Certain complex structures yield with alkylating reagents atypical products, for example acronycidine (**24**) on treatment with ethyl iodide yields the *N*-ethyl analogue of isoacronycidine (**25**)[151]. More complex results were reported for the action of the same reagent on the similar compound dictamnine (**34**)[151] (section II.C.2.b).



(**24**)



(**25**)

A method based on quaternisation was proposed for the detection of β-hydroxyethylamines[9,152], which can be possibly extended to other β-substituted ethylamines. It consists of heating the amine with sodium chloroacetate. A betaine is first formed (equation 13), which decomposes on further heating, yielding acetaldehyde (equation 14). The latter can be detected with a morpholine–sodium nitroprusside solution (compare with the Rimini test in section II.B.3).

$$R_2NCH_2CH_2OH + ClCH_2CO_2Na \longrightarrow \begin{matrix} R_2\overset{+}{N}CH_2CH_2OH \\ | \\ CH_2CO_2^- \end{matrix} + NaCl \qquad (13)$$

$$\begin{matrix} R_2\overset{+}{N}CH_2CH_2OH \\ | \\ CH_2CO_2^- \end{matrix} \longrightarrow R_2\overset{+}{N}HCH_2CO_2^- + CH_3CHO \qquad (14)$$

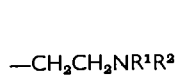
5. Some oxidation methods

Oxidations of amines usually yield degradation products, some of which provide indirect evidence for the presence of different types of amines.

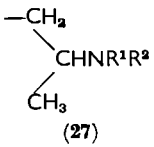
A solution of potassium dichromate in sulphuric acid has been used for the detection of classes of amines according to the colour changes observed[153], and in thin-layer chromatography for the identification of arylamines[154]. Ceric sulphate in sulphuric acid can be used for spotting alkaloids and probably other bases in thin-layer chromatography[155]. A standard solution of ceric sulphate was used for determining *p*-methylaminophenol[156].

Lead dioxide in dilute acetic acid or alcohol reacts with aromatic amines giving characteristic colours[157]. The same oxide dissolved in phosphoric acid can be used for colourimetric determination of aromatic amines[158].

The following oxidants were reported to give colour reactions with aromatic amines, which may be used for identification purposes under controlled conditions: chloric acid[159], ammonium persulphate–silver nitrate[160], benzoyl peroxide[161], and sodium hypochlorite[162]. Amines with partial structures **26** and **27**, where R^1, R^2 = H, alkyl, give the haloform reaction with hypochlorites in basic media[163].



(**26**)



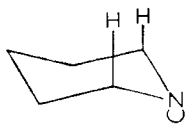
(**27**)

N-Iodosuccinimide with primary and tertiary amines yields stable brown solutions whereas with secondary amines the colour fades in a few minutes; *N*-bromosuccinimide yields orange precipitates with tertiary amines[16,164], and gives colour reactions which may be of aid in the classification of other types of amines[165].

6. Spectral properties of the electron pair

a. Electronic spectrum. The *p* electrons of amines have an absorption band at the fringes of the far ultraviolet region, due to a transition from a *p* orbital to an antibonding σ orbital of nitrogen. Thus trimethylamine[166] and piperidine (**28**)[167] have a band at 200 mμ, ε_{max} 4000. It has been suggested[166] that this band can be used to distinguish primary, secondary, and tertiary amines, but this region is frequently obscured by other chromophores and is therefore rather difficult to interpret in more complicated cases[168]. A band at ~214 mμ, shows that the amino group is not attached to an unsaturated carbon atom, as otherwise the band is displaced towards longer wavelengths[169]. Further spectral properties associated with transitions of the *p* electrons of amines are discussed in section IV, in connection with molecular structure.

b. Vibrational spectrum. Bands in the 2800 cm^{-1} region are associated with the *p* electrons of certain amines, because they disappear on coordination of these electrons[170]. Some of the structures in which these bands arise are the following: *N*-methyl and *N*,*N*-dimethyl (not in *N*-ethyl) with medium to strong bands[171–174], in cyclic compounds when two or more adjacent C—H groups are *trans* to the electron pair as in 10-methyl-*trans*-quinozilidine (**29**), with a group of small bands[175], and in other compounds such as di- and triethylamine, piperidine (**28**), *N*-ethylpiperidine, morpholine (**4**), etc., with a group of small bands[176].



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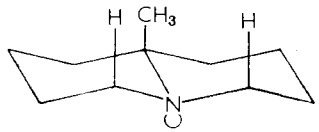


(29)

The *N*-methyl bands may be of aid in the further characterisation of the molecule[172] as they appear at 2810–2820 cm^{-1} in aromatic amines and at 2780–2805 cm^{-1} in aliphatic or alicyclic amines. A dimethylamino group attached to an aromatic system has a band near 2800 cm^{-1}, and when attached to an aliphatic or alicyclic system it has two bands, a strong one at 2765–2775 cm^{-1} and the second one at 2810–2825 cm^{-1}.

C. The N—H Bond

Among the most important reactions of ammonia and of amines are ammonolyses and condensations. Both start with an attack of the *p* electrons on an electrophilic centre, followed by the loss of one or two protons, and other transformations depending on the electrophile. These reactions are the basis of many analytical methods for amines. Other methods are based on the instability of the bond, on its ability to form hydrogen bonds, and on its distinctive vibrational and nuclear magnetic resonance spectra.

I. Active hydrogen

The N—H partial structure confers upon primary and secondary amines a set of properties which can be connected mainly with two phenomena: active hydrogen and hydrogen bonding. Both are interrelated, although the methods of determining the former are usually 'chemical', while the latter is investigated mainly through physical properties as shown in section II.E.

Contrasting with the high thermochemical stability of the N—H bond (bond energies at 0°K, in kcal/mole: C—H 98·2, C—N 78, N—H 92·2[177]) it is most unstable kinetically, and is capable of undergoing extremely fast proton interchange reactions in protonic solvents such as water or alcohols[178], and even in the gas phase this interchange is probably very fast[179].

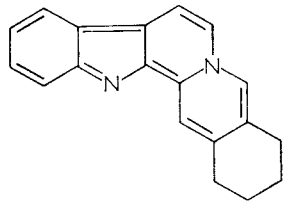
Various methods have been used for detecting and determining active hydrogen in general, and they can be applied with diverse degrees of success to amines.

a. The Zerewitinoff method. This consists of allowing the active hydrogen compound to react with a Grignard reagent (equations 15 and 16) and measuring the evolved hydrocarbon[180–182].

$$RNH_2 + 2\,CH_3MgI \longrightarrow RN(MgI)_2 + 2\,CH_4 \quad (15)$$

$$R_2NH + CH_3MgI \longrightarrow R_2NMgI + CH_4 \quad (16)$$

An interesting example of a positive Zerewitinoff reaction is provided by sempervirine (**30**), in spite of its lack of N—H bonds. It was proposed that the active hydrogen is present in the methylene group marked with (*) in **31**, as **31** is a resonance form of **30**[183].



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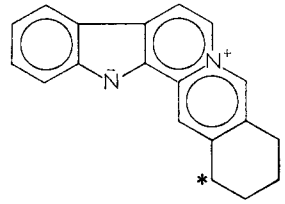


(31)

b. Lithium aluminium hydride. In the presence of active hydrogen compounds (X—H) $LiAlH_4$ decomposes according to equation (17), and the evolved hydrogen is measured[184, 185].

$$X—H + \tfrac{1}{4}\,LiAlH_4 \longrightarrow X—(LiAl)_{1/4} + H_2 \quad (17)$$

c. Isotopic exchange methods. Amines exchange their active hydrogen among themselves and with other active hydrogen compounds, in particular with water. This provides a method for detecting and determining active hydrogen by equilibrating with pure deuterium oxide, and then estimating the amount of O—H bond formed by means of density measurements[186], i.r. spectrophotometry[187], n.m.r. spectroscopy[188], or alternatively, by using tritium-labelled water and measuring the radioactivity of the amine after equilibration[189].

d. N—H and C—H spin–spin coupling. That the amino group is able to exchange protons in aqueous solutions was also shown by nuclear magnetic resonance. In solutions of high pH methylamine shows a singlet corresponding to the three methyl protons, although a triplet could be expected from coupling of these protons with the two on the nitrogen atom. The singlet was interpreted as a result of the rapid exchange of the protons on the amino group, which does not allow their alignment with the external field, and therefore the spin states of the amino protons are averaged to zero. On the other hand, in solutions of low pH, where the methylammonium ion is prevalent, proton

exchange with the solvent occurs at a slow rate and a quartet is observed for the methyl group, resulting from spin–spin coupling with the three ammonium protons[190].

The analysis of active hydrogen is extensively discussed elsewhere[15,180,185,191,192].

2. Acylation

Table 5 summarises some of the derivatives obtained by acylation (equation 18), which have found application in analysis. Acyl derivatives are widely used for identification purposes[8,16].

$$R^1R^2NH + Acyl\text{-}X \longrightarrow R^1R^2N\text{-}Acyl + XH \quad (18)$$

(R^1, R^2 = H, alkyl, aryl; X = halogen, OH, alkoxy, O-acyl, etc.)

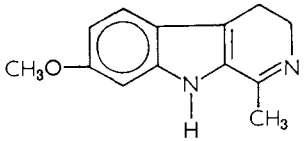
TABLE 5. *N*-Acyl derivatives of primary and secondary amines.

Derivatives	Type of reagent
Acetamides[184,193–204,a]	Anhydride or acyl chloride
Formamides[162,205–207]	Acid or mixed acetic–formic anhydride
Trifluoroacetamides[162,208–210,b]	Anhydride
p-Nitrophenylacetamides[211,212]	Acyl chloride
Benzamides[213–219,a]	Anhydride or acyl chloride
3,5-Dinitrobenzamides[220–222]	Acyl chloride
p-Phenylazobenzamides[223]	Acyl chloride
Phthalimides[224,a,c]	Anhydride
Pyromellitic diimides[225,226,a,c]	Dianhydride
N- and *N,N*-substituted 3-nitrophthalamic acids[227,a]	Anhydride
3-Nitrophthalimides[227,a,c]	Anhydride
N,N-Diphenylureas[228]	Acyl halides
Benzenesulphonamides[229–231,a]	Acyl chloride
p-Toluenesulphonamides[72,232–234]	Acyl chloride
Benzylsulphonamides[233]	Acyl chloride
Methanesulphonamides[235]	Acyl chloride
p-Bromobenzenesulphonamides[236]	Acyl chloride
m-Nitrobenzenesulphonamides[237]	Acyl chloride
Sulphonebisacetamides[238]	Ethyl ester
p-Phenylazobenzenesulphonamides[239]	Acyl chloride
2,4-Dinitrobenzenesulphenamides[240]	Sulphenyl chloride
o-Nitrobenzenesulphenamides[241,242]	Sulphenyl chloride

[a] See text.
[b] Derived from esters of amino acids.
[c] Primary amines only.

a. Acetylation. A great variety of methods for the preparation of acetamides from acetic anhydride have been suggested, both in the absence of catalyst[16] and in the presence of catalysts such as acids[193–195], pyridine[16,196,197], and sodium hydroxide[8].

Although this reaction is of great value in the characterisation of primary and secondary amines, the reagents can cause rearrangements obscuring structural elucidation. Thus for example, harmaline (**32**) undergoes acetylation at $N_{(2)}$ yielding compound **33**[198,199].



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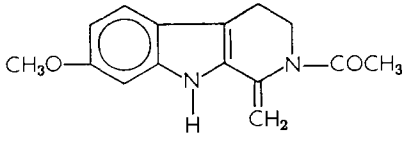


(33)

Acetylation with acetic anhydride in anhydrous pyridine can be used for the determination of primary and secondary amines according to equations (19) and (20).

$$RNH_2 + (CH_3CO)_2O \longrightarrow RNHCOCH_3 + CH_3CO_2H \quad (19)$$

$$R_2NH + (CH_3CO)_2O \longrightarrow R_2NCOCH_3 + CH_3CO_2H \quad (20)$$

The amount of amine reacted is determined by titration of the liberated acid[196] or by the amount of water necessary for hydrolysing the excess acetic anhydride[197].

Acetylation proceeds at different rates for alcohols, phenols, aliphatic amines, and aromatic amines. It is possible therefore to determine the latter in the presence of all the others[200], or sometimes even in alcoholic solution[201]. Similar determinations based on the use of acetyl chloride were proposed[202,203], but the anhydride methods seem to be more advantageous[15].

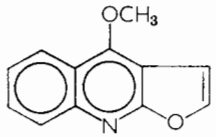
Further discussions of this reaction and lists of acetamides can be found elsewhere[8,10,14–16,37,203,204].

b. Benzoylation. This reaction has found its main application in the characterisation of compounds as 'acylatable'[184], and in the identification of primary and secondary amines.

Benzoylation of certain compounds may yield atypical products, for example dictamnine (**34**) gives no reaction with acetic anhydride but yields *N*-benzoylnordictamnine (**35**) on treatment with benzoyl chloride[213], and myosmine (**36**) yields compound **37** on treatment with benzoic anhydride[214].

Further discussions of benzoylation and lists of benzamides can be found elsewhere[8,10,14–16,204,215–219].

c. Phthaloylations. Phthalic anhydride[224] and pyromellitic anhydride (**38**)[225,226] are reagents for the determination of primary and secondary amines.



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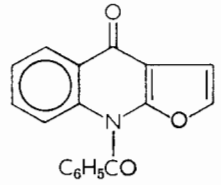

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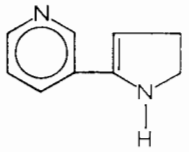

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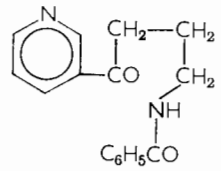

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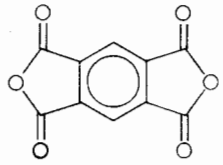
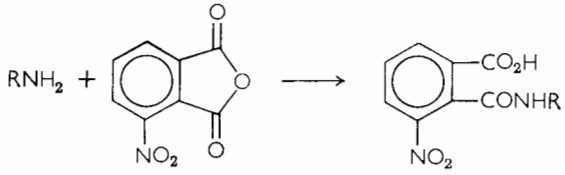


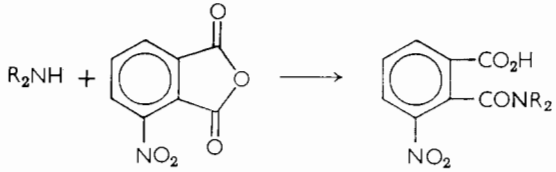
(38)

3-Nitrophthalic anhydride reacts with primary and secondary amines according to equations (21) and (22)[227], on mild heating. On further heating at about 145° dehydration (equation 23) takes place in the case of primary amines, while the phthalamic acids (**40**) derived from secondary amines are stable. Compounds **40** and **41** can be easily distinguished by their chemical properties.



(21)

(39)



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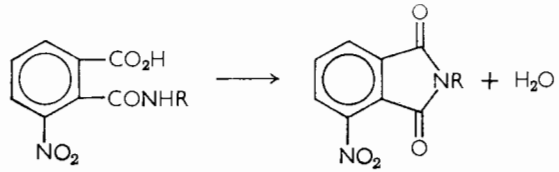
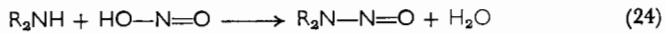


(23)

(41)

d. Sulphonylations. Sulphonyl chlorides (see Table 5) yield, with primary and secondary amines, the corresponding sulphonamides, which can be used for identification purposes. An application of these reactions is the Hinsberg method[229] which is amply discussed elsewhere[8, 16, 204, 230].

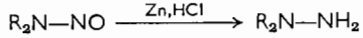
e. Nitrosation of secondary amines. Nitrous acid yields nitrosamines with aromatic and aliphatic secondary amines (equation 24). The mechanism probably involves dinitrogen trioxide as intermediate[243, 244].



(24)

This reaction has been applied in the determination of secondary amines, and their mixtures with other classes of amines. Although the latter react with nitrous acid in a different way (sections II.C.10 and II.F.3) the one-to-one stoichiometry is preserved. The determinations can be carried out by direct titration of the organic sample with standardised sodium nitrite[245], back titration of the excess reagent[246, 247], or by measuring the nitrosamine spectrophotometrically[248, 249].

An indirect method was proposed consisting of hydrogenation of the nitrosamine to a hydrazine and oxidation of the latter (reactions 25 and 26), the nitrogen thus liberated being measured[250].



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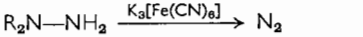
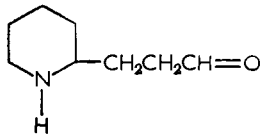


(26)

Again, abnormal behaviour in nitrosation is observed with certain complex molecules. Thus, pelletierine (**42**) fails to undergo *N*-nitrosation, although it yields the corresponding acetamide and benzamide[251], and on the other hand, the tertiary amine codeine (**43**) yields *N*-nitrosonorcodeine by displacement of the *N*-methyl group[252].

Analysis of secondary amines via nitrosation is further discussed elsewhere[14, 15, 37].



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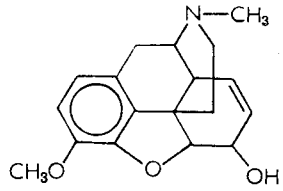


(43)

3. Nitroarylations and nitrobenzylations

Certain aryl and benzyl halides react with primary and secondary amines yielding the corresponding secondary and tertiary amines, in addition to hydrogen halide, much in the same fashion as described in section II.B.4. However, by virtue of the electronegative nature of the reagents, the reaction does not proceed further up to quaternisation as with the previous case, neither does it yield quaternary ammonium compounds with tertiary amines.

Many authors include these reactions among acylations, based on the similarity of the processes and the nomenclature of some reagents, for example from picric acid (**13**) one prepares picryl chloride which yields a picramide according to equation (18).

The reactions of amines with *p*-nitrobenzyl chloride[253], and of amino acids with 5-fluoro-2,4-dinitroaniline[254], were recommended for identification purposes. So was picryl chloride[255], which can be also used in quantitative analysis, by determining the hydrogen chloride released in the reaction[255,256].

2,4-Dinitrophenyl chloride or fluoride with amines give a strong colour which under certain conditions can be tentatively correlated with the type of amine, i.e. yellow for primary amines and orange to brown for other types[9]. The derivative is useful for identification purposes[257].

2,4-Dinitrophenyl fluoride has found wide application in biochemical analysis, in problems related to amino acids, peptides, and proteins, such as the chromatographic separation and identification of amino acids[258,259], and the analysis of end amino acids of peptidic chains, (equations 27 and 28)[260–265]. The same reagent was used for the determination of primary and secondary amines in general[266,267] and of α-amino acids in particular[268,269], by measuring the derivative spectrophotometrically after extraction with a suitable solvent or after chromatographic separation[270]. The spectra of the derivatives present bands at 350 and 390 mμ, providing a way of distinguishing between primary and secondary amines, as the ratio of the extinction

coefficient of the former band to that of the latter varies from 0·4 to 0·8 for primary amines, and from 2·1 to 2·4 for secondary amines[271]. It was pointed out[15] that the ratio is 2·1 to 2·4 for α-amino acids, that is, similar to the case of secondary amines.

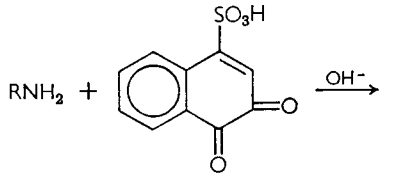
$$2,4\text{-}(NO_2)_2C_6H_3F + NH_2CHRCO\text{-Peptide residue} \xrightarrow[2.\ \text{Acid}]{1.\ \text{Base}} 2,4\text{-}(NO_2)_2C_6H_3NHCHRCO\text{-Peptide residue} \quad (27)$$

$$2,4\text{-}(NO_2)_2C_6H_3NHCHRCO\text{-Peptide residue} \xrightarrow{H_2O(\text{Acid})} 2,4\text{-}(NO_2)_2C_6H_3NHCHRCO_2H + \text{Peptide degradation products} \quad (28)$$

The applications of 2,4-dinitrophenyl fluoride in organic analysis are amply reviewed elsewhere[260,272].

4. The Folin reaction

In this method primary aliphatic and aromatic amines yield coloured products by nucleophilic displacement of the sulphonic group of 1,2-naphthoquinone-4-sulphonic acid (**44**) (equation 29)[273]. This reaction has also been applied in colourimetric determinations[274,275].



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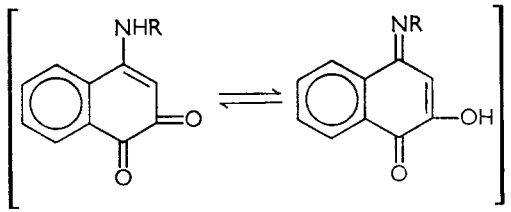


(29)

5. Ureas, thioureas, hydantoins, and thiohydantoins

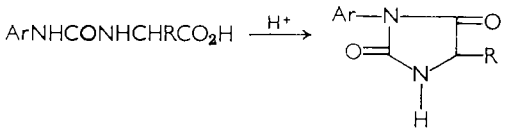
Primary and secondary amines react with aryl isocyanates, as in equations (30) and (31), or with azides of arylcarboxylic acids, after their rearrangement to isocyanates, according to equation (32).

$$ArN{=}C{=}O + NH_2R \longrightarrow ArNHCONHR \quad (30)$$

$$ArN{=}C{=}O + NHR_2 \longrightarrow ArNHCONR_2 \quad (31)$$

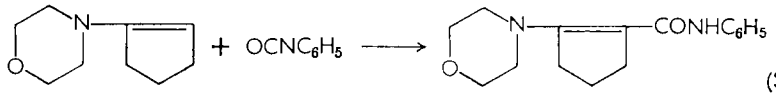
$$ArCON_3 \longrightarrow ArN{=}C{=}O + N_2 \quad (32)$$

When the arylurea derivative of an α-amino acid is treated with acid a hydantoin is formed, according to equation (33), which can be used for detection and identification[276].



(33)

It is sometimes advantageous to use aryl isothiocyanates instead of aryl isocyanates yielding the corresponding thioureas, as these reagents are more resistant to decomposition by water[8]. Both aryl isocyanates and aryl isothiocyanates were found to yield atypical products with certain enamines, as shown for example in (34), where a vinylogue of an arylurea is obtained from an aryl isocyanate[277].



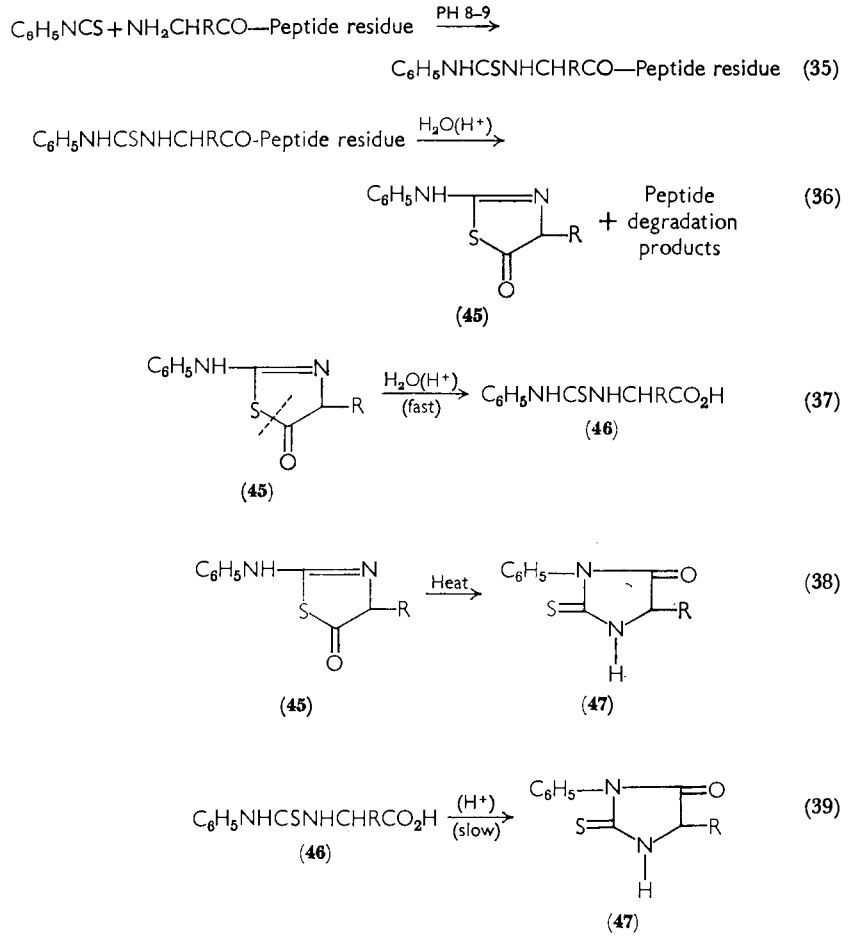
(34)

Table 6 summarises the ureas and thioureas derived from amines and used in analysis.

TABLE 6. Arylureas and arylthioureas derived from primary and secondary amines.

Derivatives	Type of reagent
N,N-Diphenylureas[228]	Carbamoyl chloride
α-Naphthylureas[278]	Isocyanate
β-Naphthylureas[279]	Isocyanate
m-Chlorophenylureas[280]	Isocyanate
p-Chlorophenylureas[281]	Isocyanate
m-Bromophenylureas[280, 282]	Isocyanate or benzazide
p-Bromophenylureas[283, 284]	Isocyanate or benzazide
m-Iodophenylureas[265]	Benzazide
p-Iodophenylureas[266]	Isocyanate
m-Nitrophenylureas[287, 288]	Isocyanate or benzazide
p-Nitrophenylureas[289]	Isocyanate or benzazide
3,5-Dinitrophenylureas[290, 291]	Isocyanate or benzazide
2,6-Dinitro-*p*-tolylureas[292]	Benzazide
Phenylthioureas[293]	Isothiocyanate
α-Naphthylthioureas[294]	Isothiocyanate
β-Naphthylthioureas[293]	Isothiocyanate
p-Biphenylylthioureas[293]	Isothiocyanate
o-Tolylthioureas[293]	Isothiocyanate
p-Chlorophenylthioureas[293]	Isothiocyanate
m-Nitrophenylthioureas[295]	Isothiocyanate

An important application of phenyl isothiocyanates is the analysis of end amino acids in peptides and proteins. This is represented by equations (35) to (39), and involves derivatives of the end amino acids such as thiazolines (**45**), phenylthioureas (**46**), and phenylthiohydantoins (**47**)[296–301].



The applications of phenyl isothiocyanate to biochemical analysis are amply discussed elsewhere[260, 272].

The reaction of amines with phenyl isothiocyanate is of the second order and proceeds at different rates for different amines, thus providing a means of determining the components of a mixture, by following kinetically the decrease of the amine concentration in the

reaction mixture[302,303]. Among aliphatic amines secondary ones react faster than primary ones, but alkylarylamines react slower than primary arylamines. In general aromatic amines react faster than aliphatic amines[302].

6. Reactions with carbon disulphide

Primary and secondary amines yield dithiocarbamic acids with carbon disulphide (equations 40 and 41).

$$RNH_2 + CS_2 \longrightarrow RNHCS_2H \quad (40)$$

$$R_2NH + CS_2 \longrightarrow R_2NCS_2H \quad (41)$$

After discarding the excess reagent, the presence of dithiocarbamic acids can be detected by their catalytic action on the process in equation (42), as the evolution of nitrogen becomes patent, or by a black precipitate obtained on adding silver nitrate solution[9].

$$2\,NaN_3 + I_2 \longrightarrow 2\,NaI + 3\,N_2 \quad (42)$$

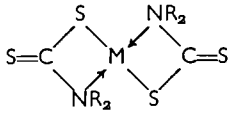
Iodine can be used to oxidise the dithiocarbamic acids to an isothiocyanate and sulphur; the latter is insoluble and therefore detectable by the turbidity it produces (equations 43 and 44)[304]. Alternatively the dithiocarbamic acids can be oxidised with iron(III) chloride or mercury(II) chloride, as in equation (45), and the hydrogen sulphide easily detected[305].

$$2\,RNHCS_2H \xrightarrow{I_2} RNHC(=S)SC(=S)NHR \quad (43)$$

$$RNHC(=S)SC(=S)NHR \xrightarrow[2.\ I_2]{1.\ NaOC_2H_5} 2\,RNCS + 2\,S \quad (44)$$

$$RNHCS_2H \longrightarrow RNCS + H_2S \quad (45)$$

Dithiocarbamic acids with copper(II) salts in the presence of ammonia give coloured complexes (**48a**). If the R groups are sufficiently hydrophobic the complex can be extracted into benzene for better detection[9]. For secondary amines the complex **48a** can be extracted into chloroform and measured spectrophotometrically[306,307]. With nickel(II) salts coloured precipitates (**48b**) can be obtained[9,308].



(**48a**) M = Cu;
(**48b**) M = Ni

Reactions (40) and (41) can be followed by direct titration of the dithiocarbamic acids with alkali[309,310], or by precipitating complex **48b** and determining the nickel in the precipitate[311]. Secondary amines were determined coulometrically as the dithiocarbamate anions react with mercury(II) cations generated at the electrode, as in equation (46)[312].

$$2\,R_2NCS_2^- + Hg^{2+} \longrightarrow (R_2NCS_2)_2Hg \quad (46)$$

The analysis of amines via dithiocarbamic acids is amply discussed elsewhere[14–16,37].

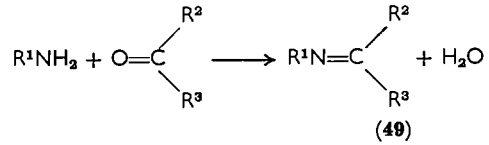
7. Reaction with sulphur trioxide

Aromatic amines can be determined in dioxane solution by adding excess of sulphur trioxide (equation 47), then destroying the excess reagent with water and titrating the sulphuric acid thus produced[313].

$$ArNH_2 + SO_3 \longrightarrow ArNHSO_3H \quad (47)$$

8. Reactions of primary amines with aldehydes and ketones

The general reaction described by equation (48), when carried out with certain reagents and under controlled conditions, provides good methods of detection and determination of primary amines, although some amines of other types may interfere.



(**49**)

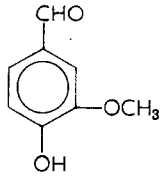
(R^1, R^2, R^3 = H, alkyl, aryl)

a. Benzaldehyde and similar reagents. Primary aliphatic and aromatic amines can be determined with benzaldehyde in nonaqueous solution. Excess of reagent is used and destroyed afterwards with hydrogen cyanide[314] (equation 49), and the water produced according to (48) is measured by the Karl Fischer method[315].

$$C_6H_5CHO + HCN \longrightarrow C_6H_5CH(CN)OH \quad (49)$$

2-Ethylhexaldehyde[119] and vanillin (**50**) react, in a way similar to benzaldehyde, with primary aromatic amines; the Schiff base (**49**) derived from **50** can be determined spectrophotometrically[316]. With salicylaldehyde (**51**) the use of hydrogen cyanide is avoided, and instead the excess reagent is titrated with standardised sodium

methoxide[317], or otherwise the Schiff base is measured spectrophotometrically[318].



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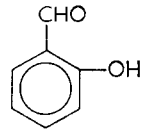

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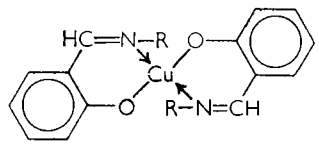
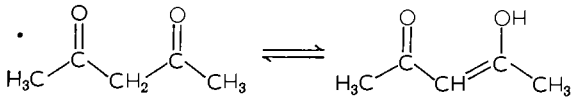


(52)

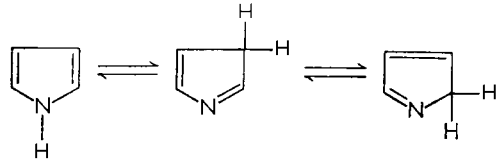
A variation of the salicylaldehyde method, applicable only to primary aliphatic amines with an unbranched α-position, consists of carrying out the reaction in the presence of copper(II) chloride and a base such as triethanolamine, whence complex **52** is formed, which can be extracted and measured spectrophotometrically[310].

2,4-Pentanedione undergoes tautomerisation according to equation (50), and therefore resembles salicylaldehyde in its reactions with primary amines[319,320].



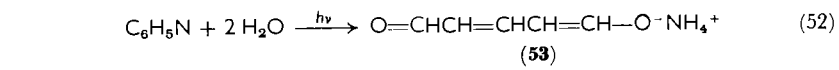
(50)

p-Dimethylaminobenzaldehyde is the reagent used in very sensitive tests for the detection and possibly identification of primary amines as coloured Schiff bases[9,321]. Other amines, notably diphenylamine and pyrrole derivatives in which the NH group and at least one hydrogen atom of the pyrrole ring are preserved, also give colour reactions with this reagent[322,323]. The reaction with the pyrrole derivatives is due to condensation of the aldehyde with a methylene group, produced in the heterocyclic compound by tautomerisation according to equation (51). Condensations with pyrroles and other atypical amines can be avoided when detecting primary amines, by controlling the pH of the solution[9].



(51)

b. Glutaconic aldehyde. This compound yields with primary amines polymethyne dyes[324–326] such as **56**. The reagent is however unstable and has to be prepared not more than a few days before use, either by irradiating aqueous pyridine with ultraviolet light[327] according to equation (52) or by treatment of *N*-(4-pyridyl)pyridinium chloride hydrochloride with alkali[328] according to (53). Products **53** and **54** of these reactions are enolate salts derived from glutaconic aldehyde (**55**), and are able to condense with primary amines in the presence of acid (equation 54)[329].



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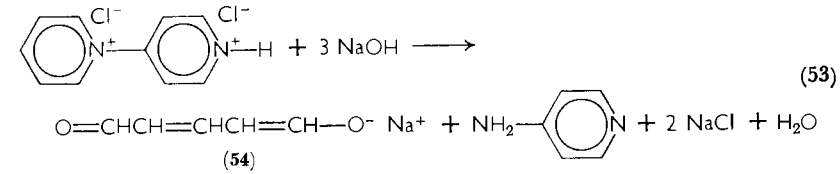

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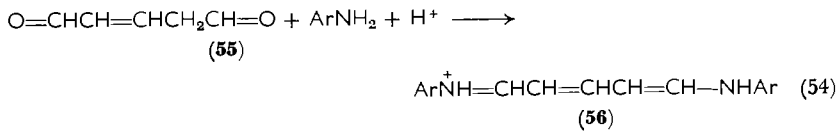


(54)

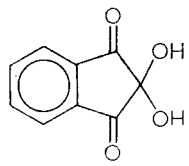
(55)

(56)

Glutaconic aldehyde can react with compounds other than primary amines[325], for example it undergoes condensations at *C*-positions with pyrrole derivatives that tautomerise according to equation (51).

The condensations of amines with aldehydes have been reviewed and discussed elsewhere[9,14–16,37].

9. Reaction of α-amino acids with ninhydrin



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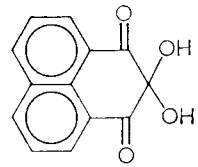
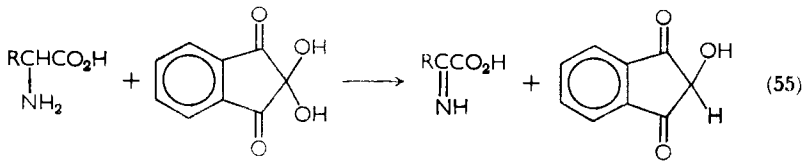


(58)

Ninhydrin (hydrate form, **57**)[330,331] and similar reagents such as perinaphthalenetrione (hydrate form, **58**)[332,333] are capable of oxidising α-amino acids in neutral solution. This provides a very sensitive detection method, as dyes such as **59** are probably produced in a process involving equations (55) to (57) in the case of ninhydrin, and similar ones for the other reagents.



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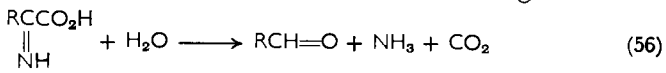

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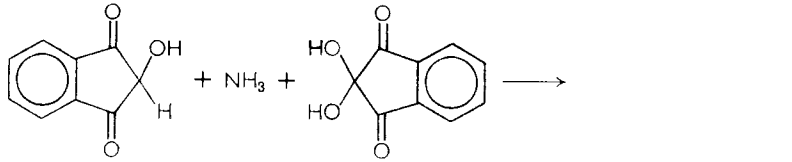

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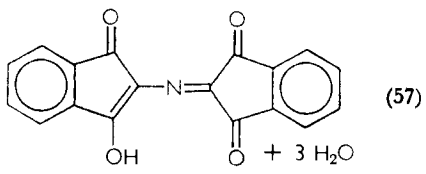


(59)

The colour reaction is transient but it can be fixed with special reagents and applied for detection and identification of individual amino acids, by making use of polychromic methods, especially after a chromatographic separation[334–341].

The determination of amino acids based on the ninhydrin reaction can be carried out in several ways: by spectrophotometry of the coloured solutions[342–345], or spectral reflectance after chromatographic separation of the amino acids and colour development[339,346], by spectrophotometry of ninhydrin–zinc chloride complexes[347], by determining the aldehyde obtained in equation (56), either chemically[342] or by gas chromatography[162], or by determining ammonia, carbon dioxide, or both, produced in equation (56)[348–354].

The ninhydrin reaction has been amply discussed and reviewed elsewhere[9,14–16,133,192,355–359].

10. Diazotisation of primary amines

With nitrous acid, primary amines are diazotised (equation 58), secondary amines undergo *N*-nitrosation (section II.C.2.e), and tertiary aliphatic or alicyclic amines fail to react while tertiary aromatic amines may undergo *C*-nitrosation.

$$R{-}NH_2 + HNO_2 + H^+ \longrightarrow R{-}\overset{+}{N}{\equiv}N + H_2O \qquad (58)$$

(R = alkyl, aryl)

a. The van Slyke method. Primary aliphatic amines, including amino alcohols and amino acids, react with nitrous acid (equation 58), followed immediately by decomposition (equations 59 or 60). The amines are determined by measuring the amount of nitrogen evolved[360,361]. Ammonia reacts as a primary amine, and has to be determined independently when present. Amines of high molecular weight or complex structure fail to give quantitative results[37]. The method has been amply reviewed[14,15,37,356].

$$R{-}\overset{+}{N}{\equiv}N + H_2O \longrightarrow ROH + H^+ + N_2 \qquad (59)$$

$$R{-}\overset{+}{N}{\equiv}N \longrightarrow \text{Olefin} + H^+ + N_2 \qquad (60)$$

b. Aryldiazonium salts. Primary aromatic amines can be detected, after diazotisation and coupling, as deeply coloured azo dyes are produced in the presence of phenols or aromatic amines in solutions of controlled pH[8,14]. Quantitative analyses via diazotisation can be performed in various ways; for example by titrating with standardised sodium nitrite[3,362], or by spectrophotometry of the diazonium salt itself[363] or its coupled product[364].

Several methods have been proposed based on the decomposition of diazonium salts. The volume of nitrogen can be measured after treating aryldiazonium compounds with copper(I) chloride[14], potassium iodide[365], or titanium(III) chloride[366,367]. Otherwise, the excess catalyst can be determined, as in the case of titanium(III) chloride[14], or chromium(II) chloride[368]. The diazonium compound strongly heated with hydriodic acid yields iodine which can be titrated[369].

The differential kinetic method (section II.C.5) is also applicable to mixtures of primary aromatic amines, which after diazotisation can be determined by measuring the first-order rates of evolution of nitrogen, catalysed by copper(I) chloride[370].

These methods are further discussed elsewhere[8,14,15,65].

11. Spectral properties of the N—H bond

a. Vibrational spectrum. Two complementary spectroscopic methods are available, namely infrared and Raman spectroscopy. Unfortunately the latter has not yet acquired the popularity and widespread application of the former. Raman spectra can be used as fingerprints of compounds for identification, and for the detection of functional groups, among which amino groups appear with characteristic bands arising from N—H vibrations. The N—H group of primary and secondary amines has characteristic infrared absorption bands which are summarised in Table 7.

TABLE 7. Absorption bands of N—H in amines[a].

Region[b] (cm^{-1})	Origin of band
1600	Deformation modes
3400	Stretching (fundamental)
5000	Combination of stretching and deformation modes
6700	Stretching (1st overtone)
10000	Stretching (2nd overtone)

[a] Data from references 170, 371, and 372.
[b] The influence of hydrogen bonding is not included.

Considerable discussion notwithstanding, the absorption band in the 1600 cm^{-1} region has been assigned to N—H deformation modes[371]. For primary amines a medium to strong band appears almost always at 1590–1650 cm^{-1}; in aromatic amines this can be confused with a band from an aromatic ring vibration near 1600 cm^{-1}. In the case of secondary amines this band is much weaker.

The most useful region for analytical purposes is that of the fundamental stretching modes. In the absence of association, primary amines present two bands, which for aromatic amines appear at about 3400 and 3500 cm^{-1}, while in the case of aliphatic amines they appear at frequencies, lower by about 100 cm^{-1}. The lower frequency band is assigned to the symmetric and the higher to the asymmetric stretching mode, both being of medium strength[373–378]. This pair of bands can be identified more easily if the correlation in equation (61) is used[377]. Secondary amines show, in the absence of association phenomena, a single band in the 3300–3500 cm^{-1} region[379–384]. The intensities in the fundamental stretching region are much higher for aromatic and some heterocyclic primary and secondary amines than for aliphatic amines, and the former can be determined in this region[372, 385, 386].

$$\nu_{sym} = 0.876\nu_{asym} + 345.5 \qquad (61)$$

Primary amines have absorption bands in the 5000 cm^{-1} region, probably arising from the additive combination of bending and stretching modes[387]. For aromatic amines it appears at 5050–5100 cm^{-1} and has been proposed for the characterisation and determination of these compounds[388, 389]. The absorptions of aliphatic amines are of about half the intensity of those of aromatic amines, appearing at somewhat lower frequencies, and it has been suggested that they too can be used for quantitative analysis[372].

Primary aromatic amines have two bands assigned to the first overtone of the stretching mode, the symmetric one appearing at about 6700 cm^{-1} and the asymmetric one at about 6900 cm^{-1}, the former being some six times more intense than the latter[389]. Secondary aromatic amines have only one band in this region, near the site of the symmetric band of primary aromatic amines but of about half the intensity[372, 388, 390]. Primary and secondary aliphatic amines absorb at about 6500 cm^{-1}, which is out of the range of the aromatic ones[390], and allows the determination of mixtures of both classes[388]. It has been suggested that this and the combination region are better than the fundamental region for the determination of aliphatic amines, owing to the wider choice of solvents that can be used for this purpose[372].

Finally, in the second overtone region only very weak bands can be observed for aromatic amines, the most outstanding being the symmetric band at about 9800 cm^{-1}, of limited analytical value[389].

It has been pointed out that a possible way of distinguishing between primary, secondary, and tertiary amines is by treatment with acid and looking for the bands arising from the ammonium salt, as these are distinctive for each ammonium type[170, 176]. The problem of distinguishing between OH and NH groups in the fundamental stretching region was also considered[391]. A comparison of absorption bands and intensities of functions containing N—H bonds can be found elsewhere[392].

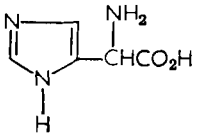
b. Nuclear magnetic resonance spectrum. The resonance bands due to NH groups are summarised in Table 8. The main factors affecting the location and shape of the N—H bands are hydrogen bonding[393, 394], the quadrupole moment of ^{14}N, and the fast proton exchange occurring in certain solvents[394]. Two main effects stem from the quadrupole moment of ^{14}N, namely a splitting of the band into a triplet, by coupling with the three states of ^{14}N, and the bands becoming broad, even sometimes disappearing[395, 396]. The fast proton exchange occurring in certain solvents tends to sharpen the N—H band (see however reference 397, and also section II.C.1).

TABLE 8. Chemical shifts of NH groups[a].

Type of compound	Chemical shift[b]
Aliphatic and alicyclic amines	2·9–5·0
Aromatic amines	3·6–4·7
Amides	5·0–8·0

[a] Data from reference 393.
[b] In parts per million (p.p.m.) of the δ scale.

The values in Table 8 are only general guides for the assignment of resonance bands, and wide discrepancies have been observed, for example histidine (**60**) dissolved in trifluoroacetic acid presents a band at $\delta -1$, assigned to the nitrogen-bonded imidazole proton[398].



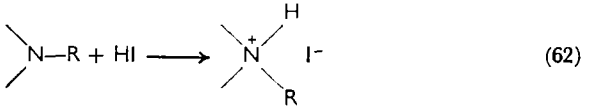
(**60**)

D. The N—C Bond

1. Chemical methods

The N—C bond of amines is very resistant to chemical attack and is usually cleaved only under drastic conditions.

a. The Herzig–Meyer method[399–402]. When an amine and hydriodic acid are heated strongly, dealkylation occurs (equations 62 and 63).



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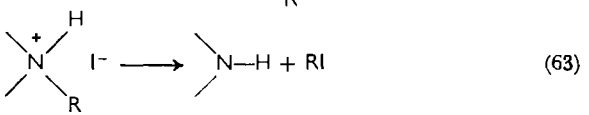


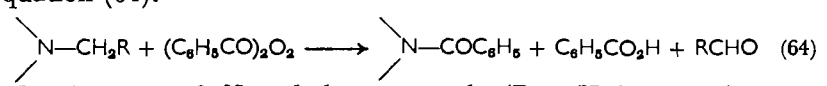
(63)

The alkyl iodide can be determined by gravimetry, iodometry, or gas chromatography, and identified by the latter method or by preparing derivatives recommended for alkyl halides[2,10,16].

Alkoxy groups undergo dealkylation more readily than amines, and in the presence of the former, after addition of the hydriodic acid the sample should be subjected first to distillation at 150°, in order to determine the alkoxy groups, and then to pyrolysis at 360°, where the Herzig–Meyer method is operative[403].

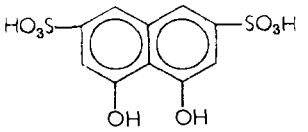
The method is further discussed elsewhere[15,356,404].

b. Fusion with benzoyl peroxide[9]. On melting an amine with benzoyl peroxide, the *N*-alkyl substituents become oxidised according to equation (64).



(64)

In the case of *N*-methyl compounds (R = H in equation 64) formaldehyde is liberated, which gives a violet colour with a chromotropic acid (**61**)–sulphuric acid solution[405]. When R = CH_3 or a

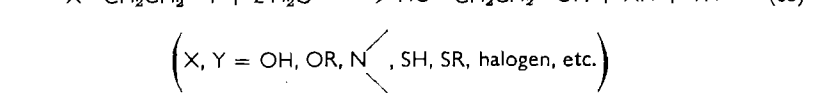


(**61**)

somewhat higher homologue, the aldehyde produced can be detected by the colour it produces with a solution of sodium nitroprusside and morpholine, which is similar to the Rimini test described in section II.B.3.

Compounds containing alkoxy or propenyl groups interfere with this method, as they too yield aldehydes on fusion with benzoyl peroxide.

c. β-Substituted ethylamines[9]. The process in equations (65) and (66) takes place when compounds of general structure X—CH_2CH_2—Y are fused with moist zinc chloride[406]. The acetaldehyde of equation (66) can be detected by the sodium nitroprusside–morpholine reagent.



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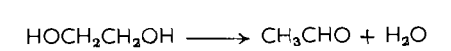
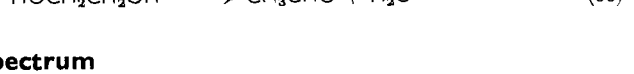




(66)

2. Vibrational spectrum

Table 9 summarises the regions in which bands assigned to C—N vibrations appear. In the case of aliphatic amines[407] the band is difficult to locate both because of its low intensity and the fact that it appears in a region where other bands also usually do[371]. The bands of aromatic amines[407,408] can be used for confirmation of proposed structures, although the possibility of confusion with bands belonging to other groups should be born in mind.

TABLE 9. Absorption bands of C—N stretching vibrations[a].

Type of compound	Region (cm^{-1})	Intensity
Aliphatic amines	1020–1220	Weak to medium
Aromatic amines		
Primary	1250–1340	Strong
Secondary	1280–1350	Strong
Tertiary	1310–1360	Strong

[a] Data from references 170 and 371.

E. Hydrogen Bonding in Amines

In sections II.A to II.D the main features of the amino group were examined from the point of view of organic qualitative and quantitative analysis. Section IV will deal with some of the structural problems posed by amines. It is convenient to bridge these two aspects of analysis with a brief examination of hydrogen bonding in the amino group, which has a deep influence on a wide range of physical and chemical properties used in the elucidation of molecular structure. The importance of hydrogen bonding can be more fully appreciated by considering Table 10, in which nearly all these properties are listed.

TABLE 10. Influence of hydrogen bonding on the properties of a system[a].

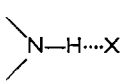
Property	Intramolecular hydrogen bond	Intermolecular hydrogen bond
Structure of compound	Usually found in *ortho*, *cis*, *peri*, diequatorial, and equatorial-axial positions	Usually found in *meta*, *para*, *trans*, and diaxial positions
Geometry of bond	Usually bent	Usually straight
Molecular weight	Normal	Increased
Density		Increased
Molecular volume	Decreased	Decreased
Molecular refraction	Increased	
Viscosity	Decreased	Increased
Self diffusion		Decreased
Parachor	Decreased	Decreased
Surface tension	Decreased	Increased
2nd Virial coefficient (Berthelot equation)	Normal	Absolute value increased
Vapour pressure	Normal	Decreased
Boiling point	Normal	Increased
Melting point	Normal	Increased
Solvent power	Normal	Increased if solute becomes hydrogen bonded to solvent
Thermal conductivity	Normal	Increased
Acoustic conductivity	Normal	Increased
Electric conductivity	Normal	Increased if hydrogen-bonded network is formed
Dielectric constant	Normal for solids and variable according to molecular shape for liquids	Increased for solids and variable according to molecular shape for liquids
Dipole moment	Lower than calculated for structure. Concentration independent	Higher than calculated for structure. Increases with concentration

TABLE 10—(*Cont.*).

Property	Intramolecular hydrogen bond	Intramolecular hydrogen bond
Reaction rate	Often influenced	Often influenced
Reaction mechanism	Often influenced	Often influenced
Optical rotation	Can be large if spiro structures are formed	Usually none
Electronic absorption bands	Shifted	Shifted
Phototropy	Often presented	Seldom presented
Vibrational spectrum		
Stretching frequencies (ν_s)	Shifted down	Shifted down
Bending frequencies (ν_b)	Shifted up	Shifted up
Concentration dependence of ν_s and ν_b	None	Present
Size of $\Delta\nu_s$	Determined by functional groups and size of ring formed	Determined by functional groups
Effect of phase change on $\Delta\nu_s$	Small	Large
Intensity of stretching band	Somewhat increased	Very much increased
Half-width of stretching band	Somewhat increased	Very much increased
Nuclear magnetic resonance		
Chemical shifts	Shifts to lower field	Shifts to lower field
Concentration dependence of chemical shifts	Small	Large

[a] From G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond*, W. H. Freeman and Company, San Francisco, 1960.

Amino groups are capable of becoming associated among themselves or with other functions by two types of hydrogen bonding, formally represented as **62** and **63**. In the former the amine acts as a weak protonic acid, and must therefore be primary or secondary (or an ammonium compound other than quaternary). On the other hand, in **63** it acts as a weak base, sharing its p electrons, and can be any type of amine (but not an ammonium compound).



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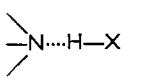


(63)

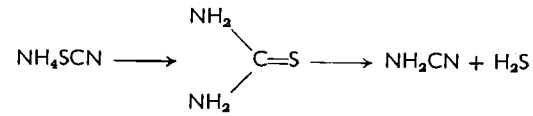
Hydrogen bonds of types **62** and **63** are relatively weak and therefore amenable to investigation by i.r. spectroscopy[179,384,409-412]. Special attention should be paid to the stretching frequencies of the N—H and X—H bonds, the shape and intensity of the absorption bands, and the effect of temperature, concentration, and deuterium exchange.

F. Miscellaneous Chemical Properties

1. Preliminary tests for detection and classification

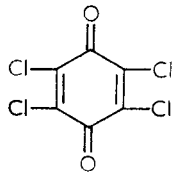
A great number of methods have been proposed hitherto in order to ascertain whether a nitrogen-containing compound is an amine or not. It is possible to use some of these tests to classify amines into aromatic, aliphatic, primary, secondary, or tertiary. As the chemical process involved in most of them is vaguely known, results should be taken only as a helpful guide. Such tests include many of the oxidations described in section II.B.5 and the ones listed below.

a. Potassium thiocyanate test. Salts of amines (not quaternary ammonium compounds) yield hydrogen sulphide on heating at 200–250° with potassium thiocyanate[413]. Compounds which liberate water on heating also give a positive test. The process is probably similar to the ammonium thiocyanate rearrangement (equation 67)[414,415].



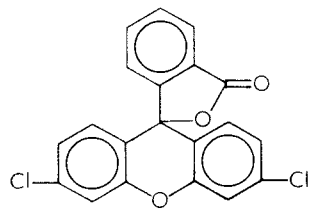
(67)

b. Chloranil test. Chloranil (**64**) yields coloured products in the presence of amines. Amino acids do not react, but some amides such as anilides do. Aliphatic amines react more readily than aromatic amines, and the colour may be used for classification as follows[416,417]: red—primary, violet—secondary, and emerald—tertiary. This reaction can be used for chromatographic development[418].



(64)

c. Reaction with triphenylmethyl dyes. All amines yield on melting with a mixture of 'fluorescein chloride' (**65**) and anhydrous zinc chloride, red water-soluble dyes of structure **66**. Their fluorescence under u.v. illumination may be used to classify amines as follows: yellow-green fluorescence shows the presence of an NH—alkyl partial structure in **66**, orange fluorescence shows the $N(alkyl)_2$ partial structure, and if an *N*-aryl group is present in **66** no fluorescence is observed[419,420]. Pyrroles, indoles, and carbazoles give blue fluorescence[9].



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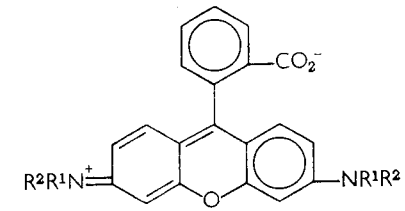
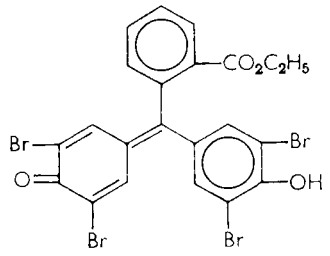


(66)

Bromophthalein magenta E (**67**) yields coloured derivatives with aliphatic amines in anhydrous solutions. The colour can be correlated with structure as follows: purple (λ_{max} 530–540 mμ)—primary, blue (λ_{max} 570–580 mμ)—secondary, and red (λ_{max} 520–530 mμ)—tertiary[421].

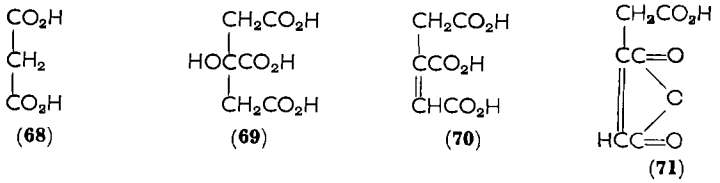


(67)

d. Lignin test. The lignin present in newsprint reacts swiftly at room temperature with primary and secondary arylamines, in the presence of strong acid, yielding yellow to orange spots. Aliphatic and alicyclic primary and secondary amines give the reaction on heating. Tertiary amines, amino acids, and amides do not react[16].

e. o-Diacetylbenzene test. Primary amines, aliphatic and aromatic, undergo colour reactions with this compound. Secondary and tertiary amines, and some primary amines such as glucosamine give negative results[422].

f. Reaction with polycarboxylic acids. Tertiary amines yield red to blue coloured solutions when heated briefly with malonic (**68**), citric (**69**), or aconitic acid (**70**), in acetic anhydride solution[423]. Aconitic anhydride (**71**) can also be used for this test[417].



(**68**) (**69**) (**70**) (**71**)

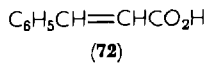
TABLE 11. Reagents for development of amines in thin-layer chromatography[a].

Reagent	Amine for which reagent is recommended
Bismuth(III) iodide/acetic acid (Dragendorff reagent)	Alkaloids
Cerium(IV) sulphate/sulphuric acid	Alkaloids
Chloranil (**64**)	Aliphatic amines
Chloroplatinic acid/potassium iodide	Alkaloids, *N*-heterocyclic compounds
Chromic acid/sulphuric acid	Aromatic amines
Cinnamic acid (**72**)/hydrochloric acid	Indole derivatives
p-Dimethylaminobenzaldehyde/hydrochloric acid	Indole derivatives, ergot alkaloids
p-Dimethylaminobenzaldehyde-2,4-pentanedione	Aminosaccharides
Formaldehyde/hydrochloric acid (Prochazka reagent)	Indole derivatives
Glucose/phosphoric acid	Aromatic amines
Iodine solution	General reagent for organic compounds
Malonic acid (**68**)/salicylaldehyde (**51**)	Amines, *N*-heterocyclic compounds
Mercury(II) iodide/sodium hydroxide (Nessler reagent)	Alkaloids
4-Methylumbeliferone (**73**)	*N*-heterocyclic compounds
Ninhydrin (hydrate form, **57**)	Amino acids, amines
Ninhydrin/copper(II) nitrate (polychromatic reagent)	Amino acids
Nitric acid	Alkaloids, amines
Potassium iodate	Sympaticomimetic amines[b]
Sodium 1,2-naphthoquinone-4-sulphonate (Folin reagent, sodium salt of **44**)	Amino acids
Sodium nitroprusside/acetaldehyde (Rimini test)	Secondary aliphatic and alicyclic amines
Sulphuric acid (charring reagent)	Alkaloids, amines
Vanillin (**50**)	Amino acids, amines

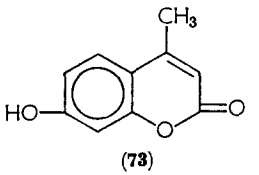
[a] Data from references 16, 424, and 425.
[b] E.g. (phenylethyl)amine and derivatives.

2. Development of chromatograms

In Table 11 a list is given of the most usual developing reagents recommended for amines in thin-layer chromatography, many of which can be used for the same purposes also in column and paper chromatography.



(**72**)



(**73**)

3. Ring substitution in aromatic amines

Aromatic amines are usually very reactive towards electrophilic reagents yielding derivatives substituted at carbon atoms. Reactions such as nitration[8] and bromination[8,14–16,37] can be applied to the amine as such, or to the amine previously protected at the nitrogen site. Although the derivatives from these reactions are useful for identification and possibly quantitative purposes, the site and stoichiometry of the substitution are specific for every system, and no generalisation can be made. Aryldiazonium salts undergo coupling reactions with aromatic amines to yield azo dyes, which can be used for detection and determination. In Table 12 some of the aryldiazonium salts used in analysis are listed.

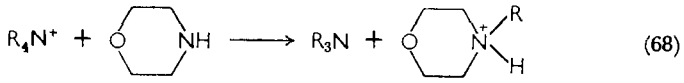
TABLE 12. Diazonium salts for coupling with aromatic amines.

p-Acetylbenzenediazonium chloride[4]
p-Aminobenzenediazonium chloride[4]
p-Arsonobenzenediazonium chloride[426]
Benzenediazonium salts[427]
2-Carboxy-4-nitrobenzenediazonium resinesulphonate[426]
2,5-Dichlorobenzenediazonium resinesulphonate[426]
m-Nitrobenzenediazonium chloride[14]
p-Nitrobenzenediazonium resinesulphonate[426]
p-Nitrobenzenediazonium salts[4,427]
p-Nitrobenzenediazonium tetrafluoroborate[418,428]
p-Phenylazobenzenediazonium tetrafluoroborate[429]
p-Sulphobenzenediazonium salts[4,427,430]
p-Toluenediazonium chloride[14]

III. QUATERNARY AMMONIUM COMPOUNDS

The analytical methods based on chemical reactions of compounds with structure **2**, in which the nitrogen atom is bonded to four carbon atoms, can be grouped into two classes, namely methods preserving the cationic part of the molecule, and methods in which this part is destroyed.

The latter class is rather limited as it involves, usually, drastic treatment of the sample. Quaternary ammonium compounds treated with morpholine yield tertiary amines (equation 68) which can be fractionally distilled and determined[431]. Simple quaternary ammonium compounds can be determined by repeatedly heating with sodium hydroxide and collecting the liberated tertiary amines, for example tetramethylammonium salts yield trimethylamine by this method[432].



(68)

In the most important methods the ammonium ion is not destroyed. Quantitative analyses can be carried out by determining either the cation or the anion, whereas in detection or identification problems, of course, the cation has to be traced.

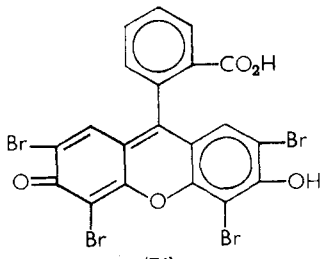
Quaternary ammonium hydroxides are strong bases, comparable with alkali hydroxides, and therefore can be easily titrated with standardised mineral acid. This affords a method of determining quaternary salts, by using ion exchangers and titrating the resulting hydroxide[433,434]. Ammonium salts other than quaternary will yield weak bases distinct from the strong quaternary ones. The converse ion exchange can be also carried out, thus alkaloid salts were converted into magnesium salts, and the metal cation determined[435].

Salts of weak acids such as carboxylates[436], picrates[437], or carbonates[438] can be titrated with mineral acids. Ammonium halides can be converted into acetates by treatment with mercury(II) acetate in glacial acetic acid, and determined by subsequent titration with perchloric acid[439,440]. Salts of strong acids, such as sulphates and halides, can be determined by measuring the anion[441], or alternatively the quaternary cation can react to form complexes which precipitate, or remain in aqueous solution, or have to be extracted into organic solvents. These complexes can be measured directly, or indirectly by measuring the excess reagent. In Table 13 appears a list of reagents used for the determination of quaternary ammonium compounds by complex formation.

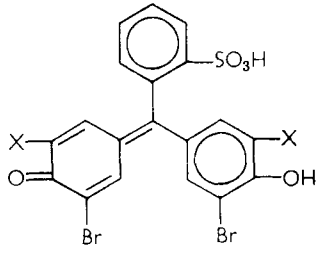
TABLE 13. Reagents for the determination of quaternary ammonium compounds.

Reinecke salt (**11**)[3,442]
Phosphotungstic acid[443]
Potassium dichromate[444]
Picric acid (**13**)[445,446]
Dipicrylamine[447–449]
Potassium iodide[450]
Potassium cadmium iodide ($CdI_2.2\,KI$)[451]
Sodium tetraphenylborate (**18**)[95,452,453]
Alipal CO-436[14,a]
Igepon T-77[14,b]
Sodium lauryl sulphate[454,455]
Sodium dodecyl sulphate[456]
Sodium sulphosuccinate[457]
Eosin A (**74**)[458,c]
Bromophenol blue (**75**)[453,459–463,c]
Bromothymol blue (**76**)[449,461,462,c]
Bromocresol purple (**77**)[464,c]
Chloranil (**64**)[465,c]
Aconitic anhydride (**71**)[465,c]

[a] Trade name for ammonium nonyl phenoxy polyethoxy sulphate of mol. wt. 504.
[b] Trade name for oleyl methyl tauride.
[c] Can be used in colour reactions for detection.



(**74**)



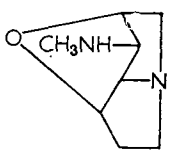
(**75**) X = Br (**76**) X = i-Pr (**77**) X = CH_3

IV. ELUCIDATION OF STRUCTURES

The chemist confronted with the problem of assigning a structural formula to a compound has a great variety of methods to aid him in his pursuit. His choice will usually depend on the amount of background information available, the relation between the amount of work to be invested to the amount of information expected, and the adaptability of the method to the particular problem. Thus for example, if he has to find the structure of a crystalline organic solid, and assuming that all the requirements are met, a single method that

could solve the problem completely is x-ray diffraction. This however will probably be his last resource, as the method requires specialised training and can be extremely time consuming and expensive. Usually information is obtained from elementary analysis and physical properties such as melting point, boiling point, pK_a, etc., and from i.r., u.v., n.m.r., and mass spectra. The compound is subjected to chemical reactions and the above proceedings repeated with the derivatives. At progressive stages it is possible to propose more and more detailed structures, until finally the elucidation is complete or no further advancement can be expected. It may then be necessary to resort to crystallographic methods for confirmation or completion of the solution of the problem. To round up the case a total or partial synthesis of the compound may be attempted, assuming that the structure of the starting material, intermediates, and products is unambiguously known.

For example, the elucidation of the structure of festucine (**78**) went through the following steps[466]: elementary analysis and mass spectroscopy showed formula $C_8H_{14}N_2O$ and molecular weight 154; n.m.r. indicated the presence of one *N*-methyl group, the two nitrogen atoms were shown to be basic by preparing the dihydrochloride, pK_a values 2·5–3·0 and 8·25; the alkaloid underwent monoacetylation and mononitrosation, and the acetyl derivative was an *N*,*N*-disubstituted acetamide as shown from its i.r. spectrum; the oxygen atom was considered to be etheric since no carbonyl or hydroxyl stretching bands were observed; after strong heating with concentrated hydrochloric acid festucine yielded a compound of formula $C_8H_{15}ClN_2O$, which showed a hydroxyl stretching band (and was diacetylated with acetyl chloride but only monoacetylated with acetic anhydride, pointing to a secondary alcohol structure) and from which festucine could be regenerated on treatment with base; and the dihydrochloride of festucine did not undergo hydrogenation, pointing to a saturated structure. From its physical and chemical properties, analogous to those of other known bases, it was concluded that festucine was a cyclic ether with pyrrolizidine skeleton, and the definitive structure **78** was assigned after carrying out an x-ray diffraction study[467].



(**78**)

In the following sections an outline will be presented of the solution of some important structural problems in which the properties of the amino group are taken into account. It should be pointed out that the methods mentioned below, especially those based on spectroscopy and crystallography, are capable of yielding much more detailed information than that stemming from the interactions of the amino group with the rest of the molecule alone, but the discussion of such applications lies beyond the scope of the present chapter.

A. *Saturated Vicinity of the Nitrogen Atom*

It was shown in section II.D.1 that chemical methods for the analysis of groups attached to the nitrogen atom require drastic treatment. On the other hand i.r., n.m.r., and mass spectroscopy afford excellent methods for such studies. In sections II.B.6.b, II.C.11.a, and II.D.2 certain structural features of saturated amines yielding absorption bands in the infrared region were mentioned already, and no further treatment of i.r. spectroscopy will be made here.

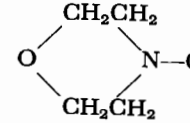
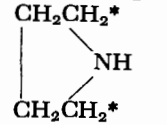
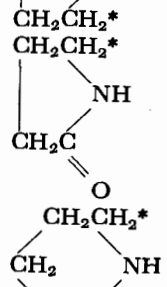
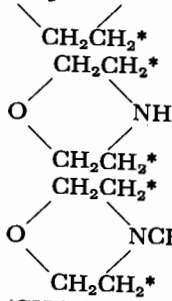
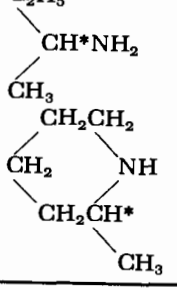
1. Nuclear magnetic resonance spectrum

N-Methyl groups show a band at about δ 2·15 p.p.m.; this is shifted to higher fields when —CH_2—, —CHR—, or —CRR^1— groups are interposed between the nitrogen atom and the methyl group, making the chemical shift almost indistinguishable from a hydrocarbon methyl group. In some cases it may be helpful to locate the band of the interposed methylene or methyne group at lower field (see below), and observe the splitting into a quartet for the free amine and a more complicated pattern when the amine is converted into an ammonium salt (see section II.C.1). The methyl bands of aryl-N—CH_3 and acyl-N—CH_3 systems[468] are shifted towards lower fields, which is of great aid in the assignment of structures.

Protons of *N*-methylene and *N*-methyne groups give rise to bands at slightly lower fields than those of *N*-methyl groups, and they too become shifted to lower fields by *N*-acetylation.

Examples illustrating the chemical shifts of various saturated groups attached to the amino group are given in Table 14. The bands arising from N—H groups were treated in section II.C.11.b. Detailed discussions on this method can be found elsewhere[393, 469–472].

TABLE 14. Nuclear magnetic resonance bands of alkyl groups in amines[a]. (Groups containing the relevant protons are indicated by *).

Structure	Chemical shift[b]
$CH_3{*}NR^1R^2$ (R^1, R^2 = H, alkyl)	~2·15
$(CH_3)_2{*}NCH_2C_6H_5$	2·17
	2·20
$CH_3{*}CH_2NR^1R^2$ (R^1, R^2 = H, alkyl)	~0·95
$CH_3{*}CH_2CH_2CH_2NR^1R^2$	~0·93
$(CH_3)_2{*}CHNH_2$	1·01
$(CH_3)_3{*}CNH_2$	1·15
$(CH_3)_2{*}NC_6H_5$	2·90
$(CH_3)_2{*}NC_6H_4CHO$-*p*	3·05
$Alkyl{-}CH_2{*}NH_2$	2·42–2·63
	2·74
	3·40
	2·69
	2·83
	2·28
$(CH_3)_2CH{*}NH_2$	2·87
	2·78
	2·57 ± 0·10

[a] Data from references 468–470.
[b] In parts per million (p.p.m.) of the δ scale; δ 0·00 for tetramethylsilane.

2. Mass spectrum

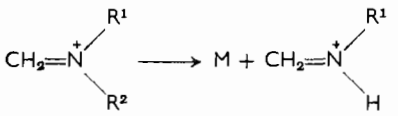
Mass spectroscopy provides a powerful means for the elucidation of the structure of alkylamines. The radical-ions derived from these compounds tend to become stabilised by undergoing scission of α,β-carbon–carbon bonds, as in equation (69).

$$[R^3{-}CH_2{-}NR^1R^2]^{\cdot+} \longrightarrow R^{3\cdot} + [CH_2{=}\overset{+}{N}R^1R^2 \longleftrightarrow \overset{+}{C}H_2{-}NR^1R^2] \quad (69)$$

(79)

(R^1, R^2, R^3 = H, alkyl)

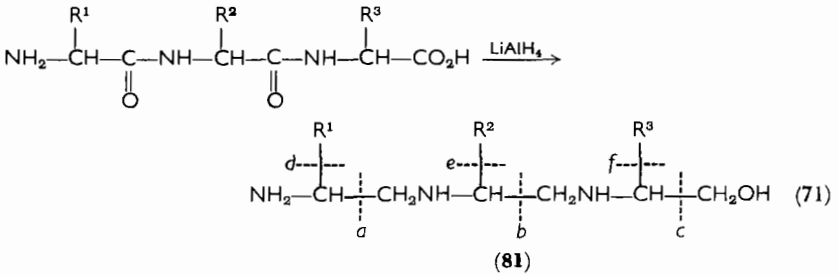
Cation **79** is capable of undergoing further cleavage if R^1 or R^2 have a hydrogen atom in the α-, β-, γ-, or δ-positions, according to equation (70), where M represents a neutral molecule derived from R^2 by scission and loss of one hydrogen atom[473–476]. The same process of course can take place on cation **80**.



(70)

(79) (80)

Cleavage according to equation (69) has been applied in the study of amino acid sequences in oligopeptides, by reducing the peptide to an amino alcohol (**81**) (equation 71) and determining its mass spectrum.



(71)

(81)

In **81** scissions at bonds *a*, *b*, or *c*, yield two different ions, as two heteroatoms can be responsible for the scission. If the reduction is also carried out with lithium aluminium deuteride ($LiAlD_4$), the assignment of the peaks in the mass spectrum will be more facile, as a displacement of +2 mass units will be observed for every reduced carbonyl group included in the ion, for example in **81** the molecular ion and the ions resulting from scissions at *d*, *e*, or *f* will be displaced by +6 mass units, the ion on the left of a scission at *b* will be displaced by +2 units, and that on the right side by +4 units[50, 52].

B. Unsaturated Vicinity of the Nitrogen Atom

1. Ultraviolet spectrum

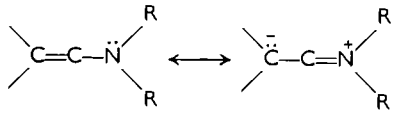
The amino group, when attached to an unsaturated system, shifts the absorption bands in the ultraviolet and visible regions towards longer wavelengths (see Table 15) and enhances their intensity.

TABLE 15. Bathochromic shifts due to an $-NR_2$ (R = H, alkyl) group attached to an unsaturated system[a].

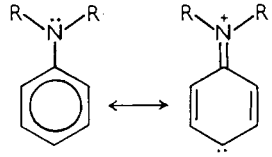
System	Shift (mμ)
$C{=}C{-}NR_2$	40
$C{=}C{-}C{=}C{-}NR_2$	65
$C_6H_5{-}C{=}C{-}NR_2$	58
$O{=}C{-}C{=}C{-}NR_2$	95
$HO_2C{-}C{=}C{-}NR_2$	80
$C_6H_5{-}NR_2$	51 and 43

[a] Data from references 477–479.

The main absorption bands of unsaturated amines are associated with electronic shifts such as those depicted in equations (72) and (73).

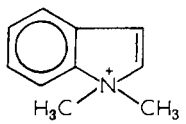


(72)

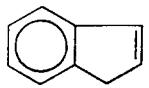


(73)

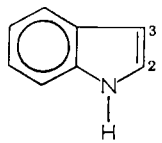
When the *p* electrons of the amino group are coordinated, as occurs in ammonium compounds, the spectra resemble those of the hydrocarbon skeleton, for example the spectrum of the anilinium ion is similar to that of benzene, and differs much from that of aniline[480,481], and that of the *N,N*-dimethylindolium ion (**82**) is similar to that of styrene and indene (**83**) but not to that of indole (**84**) as shown in Table 16[482].



(**82**)



(**83**)

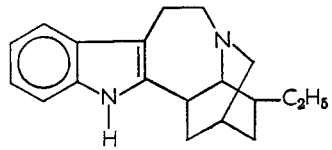


(**84**)

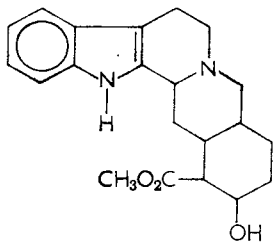
TABLE 16. Ultraviolet spectra of some amines.

Compound	λ_{max} (mμ)	ε_{max}
Indole (**84**)[487]	218	27500
	271	6170
	278	6000
	287	4570
2,3-Dimethylindole (cf. **84**)[487]	228	30200
	283	7080
	290	6300
Ibogamine (**85**)[485]	230	33100
	285	7260
Alloyohimbine (**86**)[486]	225	32900
	290	5540
Ajmalicine (**87**)[486]	226	44400
	291	6760
N-Methyl-$\Delta^{8\text{-}9}$-octahydroisoquinolin-7-one (**90**)[496]	222	5100
3-(Dimethylaminomethyl)cyclohex-2-en-1-one (**91**)[496]	225	5950
4-(2-Dimethylaminoethyl)cyclohex-2-en-1-one (**92**)[496]	224	4150
4-(Dimethylaminomethyl)cyclohex-2-en-1-one (**93**)[496]	225	6140
$\Delta^{1\text{-}9}$-Octahydronaphthalene-2-one (**94**)[496]	241	10000

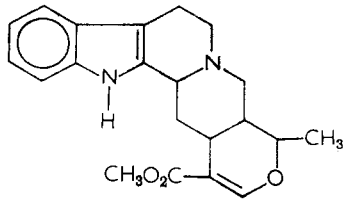
The absorption spectrum of a compound can be associated with a partial structure of the molecule (sometimes the whole molecule), and it can be expected that all molecules embodying that part as their only chromophore will have the same spectrum. This principle has been applied in the elucidation of structures of natural products[483,484]. Thus for example, it was found that the indole alkaloids have two absorption bands, at about 225 mμ, $\varepsilon_{max} \sim 25000$, and at 270–290 mμ, $\varepsilon_{max} \sim 6000$, as in ibogamine (**85**)[485], alloyohimbine (**86**)[486], and ajmalicine (**87**)[486], shown in Table 16. The enhanced absorption of **87** at 226 mμ is due to superimposition of the absorption of the acrylic system also present in the molecule. Some care has to be taken when deciding which is the chromophore responsible for the absorption spectrum of a compound. Thus 2,3-dimethylindole (cf. **84**)[487] is a better choice than indole (**84**)[487] itself, as a model for the spectra of alkaloids **85**, **86**, and **87**, as shown in Table 16.



(**85**)



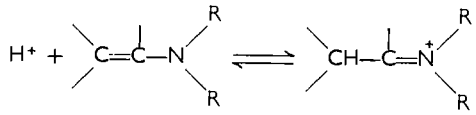
(86)



(87)

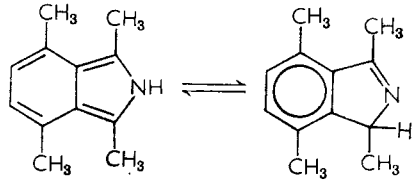
Amino groups attached to vinyl systems can undergo tautomerisation as in equation (74), or take part in processes as in equation (75).

(74)



(75)

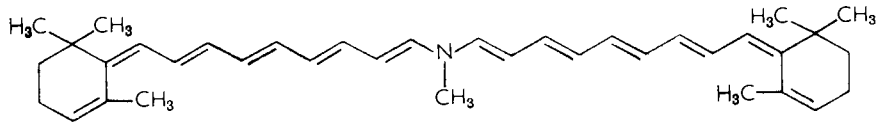
Equations (51) and (76) are examples of tautomerisation equilibria. In the former the *N*-protonated form is predominant, while in the latter it is the *C*-protonated form[488].



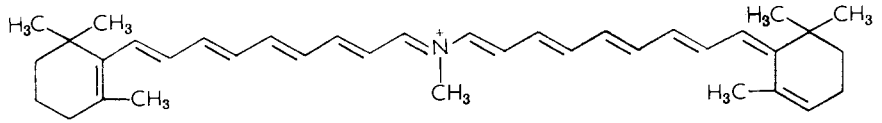
(76)

Reaction (74) is the main reason for the instability of vinylamines, as it facilitates solvolysis in the azomethine form. It has been studied by following the changes in the spectrum of the system[489,490].

Usually an unsaturated amine will change its absorption spectrum on passing from a basic or neutral solution to an acid solution. This is due either to the conversion of the amine into an ammonium salt or to the occurrence of a process similar to equation (75). The former cause allows one to determine pK_a values from spectrophotometric data[479]. An example of the latter cause is found among retinenes: compound **88** has λ_{max} 365 mμ in alkaline solution, and acquires structure **89** in acid solution with λ_{max} 440 mμ[491,492].



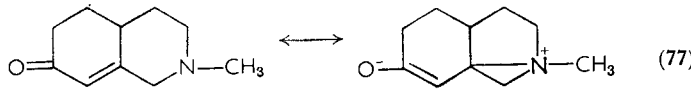
(88)



(89)

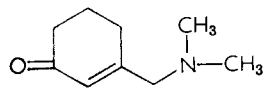
It should be pointed out that the process suggested by equation (75) has been recently subjected to criticism and revision[490,493–495].

The *p* electrons of amines can also influence the spectrum of a distant chromophore. In Table 16 the absorption bands of some compounds (**90–93**) are shown in which 'long range conjugation' (equation 77) possibly takes place, resulting in a displacement towards lower wavelength and smaller ε_{max} values as compared with the model compound **94**[496].

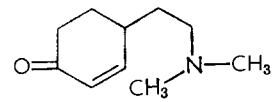


(77)

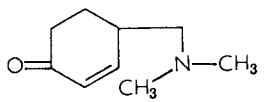
(90)



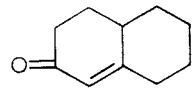
(91)



(92)



(93)



(94)

Fuller discussions on the applications of u.v. spectroscopy in structural elucidation can be found elsewhere[168,479,483,484].

2. Basicity of unsaturated amines

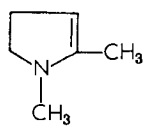
Aromatic amines are less basic than aliphatic ones owing to the delocalisation of the *p* electrons in the resonance hybrid (e.g. equation 73) and to the higher $-I$ effect of unsaturated structures, for example

aniline and cyclohexylamine have pK_a values of 4·58 and 10·64 respectively[497].

Vinylamines (Table 17) capable of reacting according to equation (75) are more basic than their saturated counterparts[498], e.g. compound **95** as compared with **96**[499]. On the other hand, unsaturated amines prevented by their structures from undergoing protonation according to equation (75), will be less basic than their saturated counterparts, owing to the $-I$ effect exerted by the double bond, for example compounds **97–100** of the quinuclidine series[500, 501], and neostrychnine (**101**) as compared with dihydrostrychnine (**101** without the isolated double bond)[502].

TABLE 17. Basicity of unsaturated amines and their saturated counterparts.

Unsaturated amines	←pK_a	pK_a→	Saturated amines
N,2-Dimethyl-Δ^2-pyrroline (**95**)[499]	11·94	10·26	*N*,2-Dimethylpyrrolidine (**96**)[499]
Δ^2-Dehydroquinuclidine (**97**)[500, 501]	9.82	10.95	Quinuclidine (**98**)[500, 501]
Methyl Δ^2-dehydroquinuclidine-3-carboxylate (**99**)[500, 501]	7.17	9.40	Methyl quinuclidine-3-carboxylate (**100**)[500, 501]
Neostrychnine (**101**)[502]	3·8	7·45	Dihydrostrychnine (cf. **101**)[502]
Strychnine (**108**)[502]	7·4		
Retronecine (**102**)[503]	8·94	10·22	Platinecine (**103**)[503]
Deoxyretronecine (**104**)[503]	9·55	10·91	Retronecanol (**105**)[503]
Heliotridine (**106**)[503]	10·60	11·48	Heliotridane (**107**)[503]



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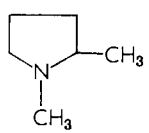

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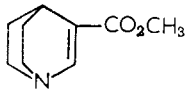

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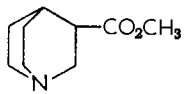

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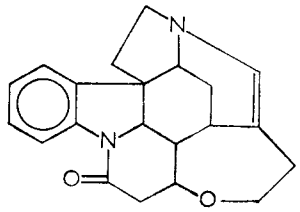
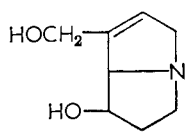


(101)

The comparison between pK_a values of unsaturated and saturated amines may be of aid in placing the unsaturation. Thus the senecio alkaloids **102**, **104**, and **106** were correctly assumed to be allylamines because their pK_a values are lower than those of the saturated alkaloids **103**, **105**, and **107** (Table 17). The vinylamine structure was discarded in these, as basicities higher than those of the corresponding saturated compounds would be expected[503]. The opposite should be true in the case of neostrychnine (**101**), a vinylamine unable to react according to equation (75), and therefore less basic than strychnine (**108**), an allylamine in which the $-I$ effect of the unsaturation on the amino group is weakened by distance (Table 17)[502].



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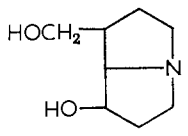

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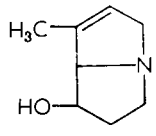

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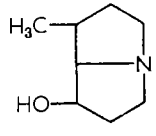

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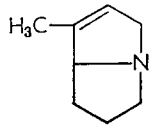

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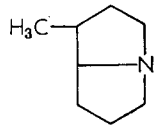

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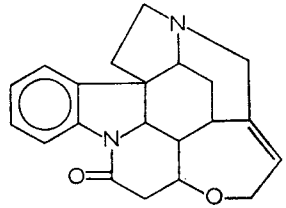


(108)

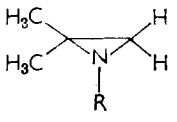
C. Stereochemical Aspects of Amines

1. Asymmetric nitrogen atom

A nitrogen atom can become a centre of asymmetry in compounds such as ammonium salts. The resolution into two optical isomers of benzylmethylphenylpropylammonium salts[504], and other similar compounds[505, 506], was accomplished at the turn of the century, by precipitation of diasteroisomeric salts. A study on aziridinium salts was carried out recently[507].

The nitrogen atom of amines is an asymmetric centre, at least in theory, if three different groups are attached to it, owing to the non-planarity of the group. The fact that such amines cannot be resolved, is attributed to the mobility of the p electrons at the heteroatom[508, 509]. More recently it was shown that in certain cases, such as the aziridines

109 and **110**, the inversion at the nitrogen atom is sufficiently slow near room temperature to show two distinct *C*-methyl bands in the n.m.r. spectra, which should coincide were that inversion much faster[510,511], as is the case with larger heterocycles[510]. This however is still far from actual resolution into optical isomers. In fact, the asymmetric nitrogen has to be held in a rigid structure in order to avoid inversion. In such cases the asymmetric nitrogen is usually accompanied by asymmetric centres at carbon atoms, for example compounds **101–108** and **120–127**. To the author's knowledge, amines with asymmetric centres exclusively at nitrogen atoms have not yet been resolved, although racemic mixtures of compounds such as **111** are known[512]. Tröger's base (**112**) was actually resolved[513], but this example departs slightly from the restricted definition of amines given in section I.



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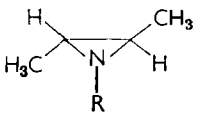

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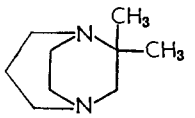
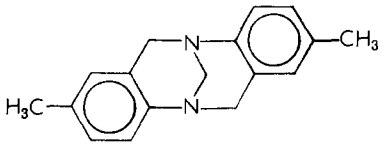


(**111**)

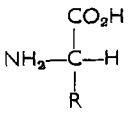


(**112**)

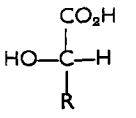
2. α-Amino acids

Among amines where the amino group is attached to an asymmetric centre α-amino acids and peptides are by far the most widely investigated class from the point of view of stereochemistry. The main results will be presented here, and more detailed discussions can be found elsewhere[514–517]. It was found that most α-amino acids derived from peptidic and proteinic materials belong to the L series, that is they have absolute configuration **113**, related to L(+)-lactic acid (**114**), when **113** and **114** are drawn according to the Fischer–Klyne convention[518]. Evidence for these assignments came from optical rotation studies in series of derivatives of hydroxy acids and amino acids[519,520], α-azido- and α-halogenopropionic acid derivatives[521], which can be

correlated with the derivatives of lactic acid and alanine[522,523], and D-2-glucosaminic acid as compared with D-amino acids[524–529].

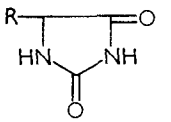


(**113**)



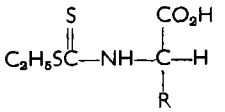
(**114**)

It was shown that the optical rotation changes observed on treating neutral natural amino acids with acid or by converting them into hydantoins (**115**), were of the same sign and about the same magnitude for almost all the cases studied. This was interpreted as being due to all these compounds having a unique configuration[524–531]. Assignments of configuration based exclusively on optical rotatory evidence have led in some cases to the wrong conclusions[532]. It is fortunate therefore that the configurations proposed above were confirmed by several independent methods, including x-ray diffraction[515].



(**115**)

More recently, widespread use has been made of optical rotatory dispersion as a means for studying configurations. α-Amino acids were investigated as such[533–535] or as derivatives, notably alkyl dithiocarbamates (**116**)[536,537], copper(II) complexes[538,539], and cobalt(III) complexes[540]. From these studies useful though not always straightforward correlations have been obtained, between the shape and location of the dispersion curves and the configuration of the compounds.

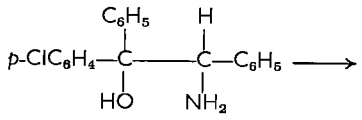


(**116**)

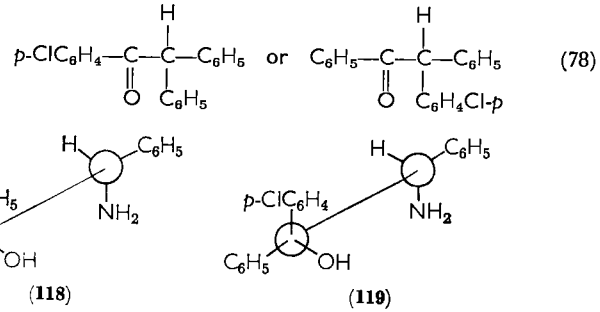
Rotatory-dispersion curves of polypeptides ideally depend almost exclusively on the conformation of the peptide-links backbone, and not on the amino acid composition[541], although in special cases the contribution of individual amino acids may be important[542–544].

3. Examples of configuration assignment

Certain reactions take place under strict steric requirements as is the case of the pinacol-type rearrangement shown in equation (78). Compound **117** has two asymmetric carbon atoms and therefore four diasteroisomers. With racemate α (**118**) the phenyl group migrates, and with racemate β (**119**), the *p*-chlorophenyl group. The conformations shown in **118** and **119** are the less strained, where the smallest group H is staggered between the two bulky aromatic substituents. The relative positions of the groups depicted in **118** and **119** are preserved in the transition state, thus determining the nature of the rearranged product, and from the latter the geometry of the amino alcohol can be deduced[545–547]. The same could be found from kinetic data, as the migration aptitude of a phenyl group is larger than that of a *p*-chlorophenyl group[548]. Similar studies were carried out also with diasteroisomeric 2-amino-1,2-diphenylethanol[549].



(**117**)



(78)

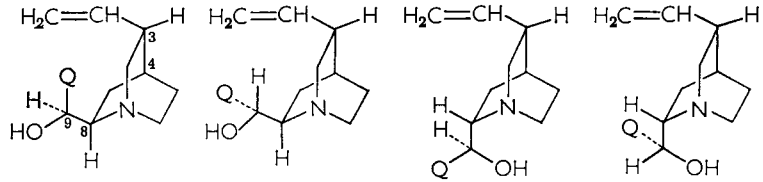
(**118**) (**119**)

Evidence gathered from chemical reactions, optical rotation, and basicity, as well as conformational considerations were applied in order to assign the configurations of the two families of cinchona alkaloids listed in Table 18[550–552]. The main steps of the elucidation were the following: the configuration at $C_{(3)}$ and $C_{(4)}$ (cf. **120**) is the same for the eight alkaloids; the decreasing order of optical rotations in the two series was taken as a guide-line for proposing parallel configurations at $C_{(8)}$ and $C_{(9)}$ (cf. **120**); the highest positive optical rotation and the negative one in each series were considered to have opposite configurations at both $C_{(8)}$ and $C_{(9)}$; quinidine and cinchonine were known to yield a cyclic ether by reaction of the hydroxy

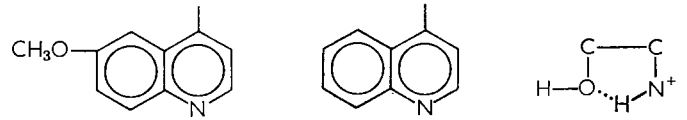
TABLE 18. Physical properties of cinchona alkaloids[a].

Compound	$[\alpha]_D$	pK_a
Quinidine (**120**)	+254°	7·95
*Epi*quinidine (**122**)	+102°	8·32
*Epi*quinine (**124**)	+43°	8·44
Quinine (**126**)	−158°	7·73
Cinchonine (**121**)	+224°	
*Epi*cinchonine (**123**)	+120°	
*Epi*cinchonidine (**125**)	+63°	
Cinchonidine (**127**)	−111°	

[a] Data on optical rotation from reference 551, and on basicity from references 550 and 552.



(**120**) Q = **128** (**122**) Q = **128** (**124**) Q = **128** (**126**) Q = **128**
(**121**) Q = **129** (**123**) Q = **129** (**125**) Q = **129** (**127**) Q = **129**



(**128**) (**129**) (**130**)

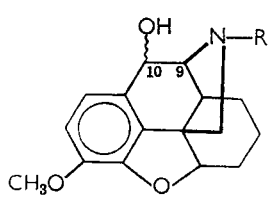
and vinyl groups; an alkaloid could be converted into the *epi* form and vice versa by oxidation of the alcohol followed by reduction; the fact that in a pair, alkaloid-*epi*alkaloid, the latter is the more basic was attributed to the stabilisation of the ammonium cation by hydrogen bonding, as the conformation attained on forming the hydrogen-bonded structure **130** is sterically less hindered in the *epi* forms.

The configurations of four 10-hydroxydihydrodesoxycodeines (**131**) appear in Table 19. The assignments were made by taking into account the stabilisation of the ammonium ion by hydrogen bonding[553], by acquiring a structure such as **130**. Lysergic acid (pK_a 7·8) and isolysergic acid (pK_a 8·4) are two isomers of structure **132**. They were respectively assigned configurations where the carboxyl group could not and could establish hydrogen bonding with the ammonium cation on forming the salt[554–556].

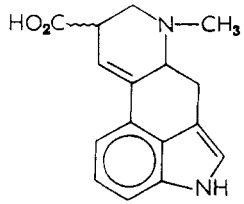
TABLE 19. Configuration of 10-hydroxydihydrodesoxycodeines (**131**)[a].

R	pK_a	Assignment[b]
H	8·72	*trans*
H	9·17	*cis*
CH_3	7·71	*trans*
CH_3	9·41	*cis*

[a] Data from reference 553.
[b] $C_{(10)}$—OH relative to $C_{(9)}$—NR.



(**131**)

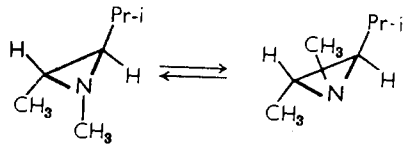


(**132**)

4. Conformations, steric hindrance, and other stereochemical problems

The preferential conformations of a compound can be deduced in certain cases by considering the bulkiness of the groups present in the molecule, as was done above with the amino alcohols (**118**) and (**119**), and the alkaloids (**120–127**). In other instances more indirect considerations have to be made. For the needs of the present section, the changes in configuration resulting from inversion of *p* electrons at nitrogen atoms will be regarded as changes in conformation.

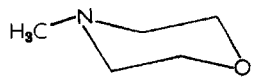
The equilibrium of conformers of *trans*-*N*,2-dimethyl-3-isopropylaziridine, shown in equation (79), was found by n.m.r. spectroscopy to favour the left hand side by a ratio of about 4 to 1, at temperatures from −55·5 to 9°. The method could not be applied at somewhat higher temperatures[557].



(79)

N.m.r. was also used to show that at low temperatures there is considerable freezing of ring conformation in *N*-methylmorpholine

(**133**) and *N*,*N*′-dimethylpiperazine (**134**) as compared with morpholine and cyclohexane[558].



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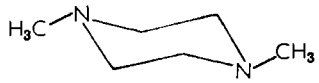
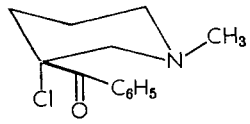


(**134**)

From optical rotatory dispersion studies, 3-benzoyl-3-chloro-*N*-methylpiperidine was shown to have conformation **135**, with the carbonyl group pointing away from the amino function, in neutral solution, and conformation **136**, with the carbonyl and ammonium moieties pointing towards each other, in acid solution[559].



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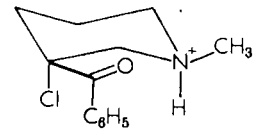
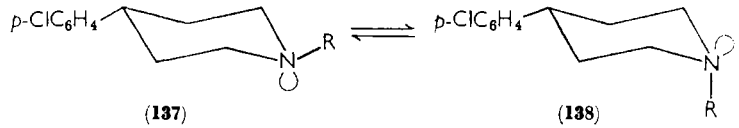


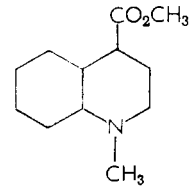
(**136**)

The preferential conformation of a substituent at the nitrogen atom of piperidine seems to depend on its size and the state of solvation of the *p* electrons[560]. Thus it was found that the steric requirements of the unsolvated pair are less than those of a proton or a methyl group[561,562], for example in equation (80) equilibrium favours form **137** over **138** at room temperature in benzene solution (~88% for R = H, and ~94% for R = CH_3), as was shown by dipole-moment measurements[561]. On the other hand, the solvated electron pair has larger steric requirements than an *N*-hydrogen, as shown for example from the kinetics of equilibration of epimers of methyl *N*-methyldecahydroquinoline-4-carboxylate (**139**)[563]. Results from the n.m.r. spectroscopy of piperidine and *N*-methylpiperidine in methanol (a



(80)

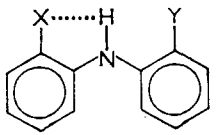
(**137**) (**138**)



(**139**)

strongly solvating solvent), also support these hypotheses on the steric requirements of the *p* electrons of amines[564].

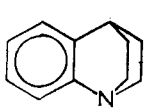
Conformations of *o,o'*-disubstituted diphenylamines could be determined from i.r. spectra by studying the hydrogen bonding established between the N—H group and X or Y, as shown in **140**, in a manner similar to the one applied for *o,o'*-disubstituted diazoaminobenzenes[565].



(140)

In contrast with the tetrahedral disposition of bonds and electron pair at the nitrogen atom in the examples discussed above, it was shown from rotational spectra that pyrrole (**3**) is a planar structure[566]. The degree of planarity at the nitrogen atom varies according to the substituents attached to it. From its rotational spectrum aniline was shown to be non-planar at the nitrogen atom[567], nevertheless arylamines are more planar at that site than alkylamines, owing to the contributions of planar forms to the resonance hybrid (e.g. equation 73). The degree of planarity at the nitrogen atom can be changed by steric hindrance, as can be deduced from the u.v. spectra of substituted *N,N*-dimethylanilines[568,569], their basicity[497], and their dipole moments[570]. Thus methyl groups in the *ortho* positions will hinder the dimethylamino group from attaining coplanarity with the ring, resulting in u.v. spectra that are intermediate between that of dimethylaniline and that of benzene. The *p* electrons by participating less in *p*-π conjugation, will tend to adopt the tetrahedral geometry of ammonia, resulting in their increased availability (basicity) and a lowered dipole moment.

Benzoquinuclidine (**141**) is a case where owing to the rigidity of the structure and to the *p* electrons being held at a right angle with the π system, no *p*-π conjugation occurs, and therefore the main effect of the benzene ring is a negative inductive effect resulting in a basicity higher than that of *N,N*-dimethylaniline but still lower than that of quinuclidine, as shown in Table 20[571,572].

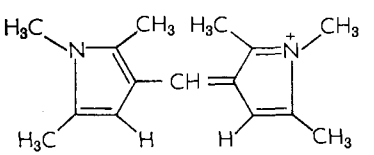


(141)

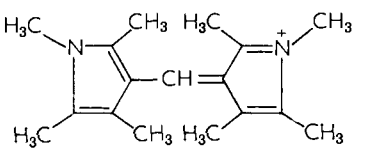
TABLE 20. Basicity of some amines.

Compound	pK_a
N,N-Dimethylaniline[497]	5·06
Benzoquinuclidine (**141**)[571,572]	7·79
Quinuclidine (**98**)[571,572]	10·65
Ammonia[576]	9·25
Methylamine[575]	10·63
Dimethylamine[575]	10·78
Trimethylamine[575]	9·80

Steric hindrance to coplanarity, may also shift u.v. absorption bands to longer wavelengths (Brunings–Corwin effect)[573], for example in dyes such as **142** (λ_{max} 446 mμ) as compared with **143** (λ_{max} 479 mμ). It was suggested that the resonance energy was more affected by steric hindrance in the ground state than in the electronically excited state, in compounds of this type, yielding E_1–E_0 values for the transition which are smaller, and therefore corresponding to a longer λ_{max}, in the case of **143**[574].



(142)



(143)

The basicity of an amine can be considered as the result of electronic and steric effects acting on the functional nitrogen atom. The increasing pK_a values observed on progressively methylating ammonia stop at dimethylamine and drop for trimethylamine[575,576] (Table 20). The increase in pK_a parallels the increasing inductive effect by methyl groups, and the decrease observed for trimethylamine was attributed to steric effects[577–579]. More recent evidence from hydrogen bonding of ammonia and the three methylated amines with methanol in the gas phase, shows strict inductive order for the series[179].

Steric hindrance by substituents at the nitrogen atom of amines has been determined by preparing certain Lewis salts and measuring their dissociation constants and heats of formation. Quinuclidine (**98**) was found to yield the most stable adduct with trimethylboron[580], while the adduct in the case of triethylamine is unstable[581]. These results show that the approach to the nitrogen atom is hindered to a certain extent by the ethyl groups, which are free to rotate and flip

around the nitrogen atom, while in quinuclidine these movements are absent, leaving free the approach to the *p* electrons[580].

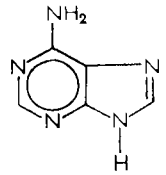
An important consequence of the formation of a hydrogen bond A—H···B is the shortening of the interatomic distance A–B, as compared with the sum of the van der Waals radii of A and B. This has to be considered when studying the stereochemistry of amines and ammonium compounds, especially in the solid phase, as very significant distortions and steric effects may result. Table 21 summarises hydrogen bonds involving nitrogen atoms, and their lengths are compared with the van der Waals distances. The contraction taking place on hydrogen-bond formation is the more noteworthy as the van der Waals radius of hydrogen is not taken into account for this comparison.

TABLE 21. Hydrogen-bond lengths and van der Waals distances in crystalline compounds[a].

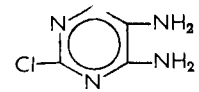
A—H···B	A—H type	A–B distance (Å)	van der Waals A–B distance (Å)[b]
O—H···N	All O—H	2·80 ± 0·09[c]	3·05
N^+—H···O	Ammonium	2·88 ± 0·13[d]	3·05
N—H···O	Amide	2·93 ± 0·10[e]	3·05
N—H···O	Amine	3·04 ± 0·13[f]	3·05
N—H···N	All N—H	3·10 ± 0·13[g]	3·30
N^+—H···F^-	NH_4F	2·69	3·00
N—H···F	$NH_3.BF_3$	3·01 ± 0·3	3·00
N^+—H···Cl^-	$NH_2(CH_2)_6NH_2.2$ HCl	3·01, 3·07	3·45
N—H···Cl^-	Adenine (**144**).HCl.$\frac{1}{2}$ H_2O	3·11, 3·21	3·45
N—H···Cl	4,5-Diamino-2-chloropyrimidine (**145**)	3·51, 3·52	3·45
N^+—H···Br^-	$NH_2(CH_2)_{10}CO_2H.HBr.\frac{1}{2}$ H_2O	3·30, 3·44	3·60
N—H···I^-	Cleavamine methiodide (**146**)[582]	3·4	3·80

[a] From G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond*, W. H. Freeman and Company, San Francisco, 1960.
[b] Estimated from 1·65 Å proposed by Pimentel and McClellan for the van der Waals radius of nitrogen[100], and those given by Pauling for the other atoms[99].
[c] Average of 21 data.
[d] Average of 41 data.
[e] Average of 35 data.
[f] Average of 30 data.
[g] Average of 37 data.

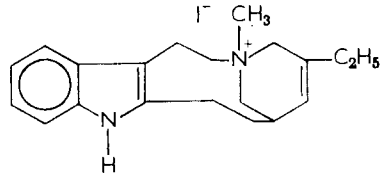
In spite of the A–B contraction, the A—H bond undergoes elongation in these cases. The location of the hydrogen atom participating in a hydrogen bond has been accomplished by several methods, for



(144)



(145)



(146)

example x-ray diffraction which although rather ineffective for this purpose owing to the low scattering amplitudes of hydrogen atoms, yielded in some instances reliable results, e.g. for compound **145**[583]. Electron diffraction was also used for the same purpose[584,585]. The neutron scattering amplitude of hydrogen is comparable with that of carbon or oxygen, allowing therefore the localisation of hydrogen atoms by neutron diffraction. Furthermore, by this method hydrogen and deuterium atoms can be distinguished, thus adding to its usefulness[100]. Finally, N—H distances have been calculated for amines, ammonium compounds, and other functions, based on the band widths measured by n.m.r. spectroscopy[586–593].

D. *Multifunctional Amines*

The presence of additional functional groups in an amine can of course be detected by spectroscopic and chemical methods specially devised for these groups. Functional groups affect strongly the properties of the amino group if they are near the nitrogen atom, but their influence decreases steeply with distance. For example the pK_a values of the senecio alkaloids **102–107** in Table 18 illustrate the effect of the electronegativity of hydroxyl groups, as these lower the pK_a of the compound. Extensive studies have been carried out to establish the influence of substituents on the basicity of amines of structure $X—(CH_2)_n—NH_2$. It was shown that the pK_a value is strongly affected for functional groups X, compared with X = H, when $n = 0, 1$, only slightly for n = 2, and remains practically unaffected for $n \geq 3$. Some of the groups studied were hydrogen[594–596],

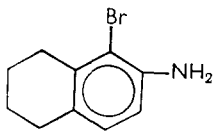
carboxylic acid and ester[597], sulphonic acid[598], phosphonic acid[599], phenyl[600], etc.

An early and extremely important application of basicity studies was made when glycine, and by analogy other natural amino acids, was established as a zwitterion. The dissociation of the conjugate acid of this compound could take place according to equations (81) or (82). The former is similar to the dissociation of the conjugate acid of methylamine (pK_a 10·6) which has been modified by an α-carboxy group, while equation (82) resembles the dissociation of acetic acid (pK_a 4·8) modified by an α-ammonium group. The pK_a value of glycine being 2·3, points to the latter possibility as the correct one[104,105].

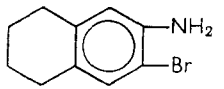
$$NH_3^+CH_2CO_2H \rightleftharpoons NH_2CH_2CO_2H + H^+ \quad (81)$$

$$NH_3^+CH_2CO_2H \rightleftharpoons NH_3^+CH_2CO_2^- + H^+ \quad (82)$$

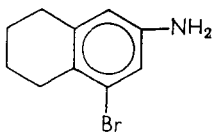
The effect on the basicity of aniline (pK_a 4·58[497]) has been studied for a wide list of substituents in the *ortho*, *meta*, and *para* positions. It was found that the pK_a value of a substituted aniline can be estimated from that of aniline by the use of additive terms depending only on the nature and position of the substituent[552]. Thus the calculated and experimental values of polysubstituted anilines showed good agreement for a wide range of substituents and substitution patterns[601–604], thus providing a method for structural assignment based on a fundamental property of the amino group. For example, on bromination of 6-acetylamino-1,2,3,4-tetrahydronaphthalene followed by hydrolysis of the acetyl group, two monobromo compounds with pK_a 3·05 were obtained. They were assigned structures **147** and **148**, while structure **149** was discarded, as the calculated values, based on aniline and assuming that the tetramethylene chain acts as two methyl groups, are 3·18 for **147** and **148**, and 4·09 for **149**[601,602]. Fuller discussions of substituent effects in amines can be found elsewhere[552,605].



(147)



(148)



(149)

Correlations between chemical shifts of *N*-protons in substituted anilines[606–608], and methyl protons of substituted *N,N*-dimethyl-

anilines[609] have been found, which may be of aid in the assignment of substitution sites of similar compounds.

V. DEDICATION AND ACKNOWLEDGMENT

The author wishes to dedicate this chapter to Dr. José Herrán in recognition of many years of guidance, and to acknowledge the invaluable assistance of his wife in the preparation of the manuscript.

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CHAPTER 4

Basicity and complex formation

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I. INTRODUCTION

Owing to the presence of a lone pair of electrons on the nitrogen atom, all amines can potentially act as bases, accepting protons from Lowry–Brönsted acids. In the case of normal acids in aprotic solvents

this results in the formation of substituted ammonium ions, probably with hydrogen bonds between the proton and the anion, but with some weak proton donors such as alcohols it may lead only to the production of hydrogen bonded complexes (equations 1 and 2).

$$AH + NH_2R \rightleftharpoons A^-...H\overset{+}{N}H_2R \quad (1)$$

$$AH + NH_2R \rightleftharpoons AH...NH_2R \quad (2)$$

The reaction in a so-called 'ionising' solvent, however, is very different. It is generally written formally as in equation (3)

$$SH^+ + RNH_2 \rightleftharpoons S + RNH_3^+ \quad (3)$$

where S represents a solvent molecule, but this is an over-simplified representation of a chemical reaction in which solvent participation is both fundamental and complex. Thus change of solvent is tantamount to a change of reaction under study.

The lone pair of electrons can be broadly described as occupying an sp^3 hybrid orbital of the nitrogen atom, but the precise character of this orbital depends upon the groups linked to the nitrogen atom. Thus the energy of the N—H bond produced, and the thermodynamic stability of the positive ion, depend on the nature of these groups. As a result of this and other factors the strengths of amines as bases vary considerably.

In aqueous solution the strength of a base B can be defined in terms of the equilibrium constant K_b of the reaction (4).

$$B + H_2O \rightleftharpoons BH^+ + OH^- \quad (4)$$

$$K_b = \frac{c_{BH^+} \cdot c_{OH^-}}{c_B} \cdot \frac{f_{BH^+} \cdot f_{OH^-}}{f_B} \quad (5)$$

At low concentrations the activity coefficient term f_B can be taken as unity, and $f_{BH^+} = f_{OH^-} = f_\pm$, so

$$K_b = \frac{c_{BH^+} \cdot c_{OH^-}}{c_B} \cdot f_\pm^2 \quad (6)$$

For convenience in expression, and by analogy with the pH and pK_a scales, K_b may be written in terms of its negative logarithm, i.e. $pK_b = -\log_{10} K_b$.

The alternative and more usual scheme, however, is to describe the strength of a base in terms of the dissociation constant K_a of its conjugate positive ion, i.e. the constant of reaction (7).

$$BH^+ + H_2O \rightleftharpoons B + H_3O^+ \quad (7)$$

$$K_a = \frac{c_B \cdot c_{H_3O^+}}{c_{BH^+}} \cdot \frac{f_B \cdot f_{H_3O^+}}{f_{BH^+}} \quad (8)$$

Having activity coefficient terms for univalent ions in both the numerator and denominator, at low concentrations this reduces to equation (9).

$$K_a = c_B \cdot c_{H_3O^+} / c_{BH^+} \quad (9)$$

The product K_aK_b is given by equation (10).

$$K_aK_b = \frac{c_B \cdot c_{H_3O^+}}{c_{BH^+}} \cdot \frac{c_{BH^+} \cdot c_{OH^-}}{c_B} \cdot f_\pm^2 = c_{H_3O} \cdot c_{OH^-} \cdot f_\pm^2 = K_w \quad (10)$$

Since at 25°c the value of K_w, the ionic activity product of water, is about 10^{-14}g. ion^2/litre^2, it follows that $pK_a + pK_b = -\log K_w = 14$. The lower the value of pK_b and hence the higher the value of pK_a the stronger is the base.

The values of pK_a for bases can be determined by essentially the same methods as are used for acids. These have been listed, and the pK_a values for a large number of amines tabulated, by Perrin[1].

II. FACTORS DETERMINING THE STRENGTHS OF AMINES AS BASES

A. Thermodynamic Considerations

The standard free-energy change ΔG° attending the dissociation of an aminium ion is given by

$$-\Delta G^\circ = RT \ln K_a \quad (11)$$

so it follows that

$$pK_a = \Delta G^\circ / 2{\cdot}303\ RT \quad (12)$$

where the standard states are those of unit activity for the amine, its cation, and the solvated proton and the pure state for the solvent. The pK_a value, therefore, is determined by the temperature and by the free-energy difference between the (imaginary) states of the system when the solution contains (*a*) the amine at unit activity, H_3O^+ ions at unit activity, and solvent, and (*b*) the aminium ions at unit activity and solvent. Again since

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (13)$$

this free-energy difference depends upon the enthalpies and entropies of the two states of the system. Any factors which can modify these

properties in either state will therefore influence the base strength of an amine.

The dissociation of a molecular acid HA is accompanied by net generation of charges, and hence there are very large net hydrational changes. The increased order in the system which this brings about leads to large changes in the entropy of the system. Also, because the extent of this ordering is temperature dependent, it leads to large changes in the heat capacity. Typically for the dissociation of a molecular acid in water (equation 14)

$$HA + H_2O = H_3O^+ + A^- \qquad (14)$$

ΔS° is about -20 cal/deg/mole and ΔC_p° is about -40 cal/deg/mole. The dissociation of an amine cation, on the other hand, is isoelectric, so ΔS° and ΔC_p° may be zero or have low values, positive or negative.

The analysis of the factors determining the value of pK_a is complicated by the fact that ΔG°, ΔH°, and ΔS° all vary with the temperature:

$$d\Delta G^\circ/dT = -\Delta S^\circ, \quad d\Delta H^\circ/dT = \Delta C_p^\circ, \quad d\Delta S^\circ/dT = \Delta C_p^\circ/T.$$

Even ΔC_p° is temperature variant. Since ΔG° is essentially the quantity measured, it follows that the precision with which ΔH°, ΔS°, and ΔC_p° can be determined decreases with the increase in the number of differentials upon which they depend. Thus even if ΔG° can be determined to $\pm 0{\cdot}5$ cal/mole, the error in ΔH° may be ± 20 cal/mole and in ΔS° $\pm 0{\cdot}1$ cal/deg/mole, whilst the error in ΔC_p° will be even greater. Present accuracy does not permit the temperature dependence of ΔC_p° to be determined. The apparent alternative route of measuring ΔH° directly by heat of neutralization measurements is not useful, as it is as yet impossible to achieve the accuracy required with solutions sufficiently dilute for the purpose.

Meaningful values of the thermodynamic quantities at a particular temperature T can only be determined, therefore, by precision measurements over a range of graduated temperatures on either side of T. Then if ΔC_p° can be regarded as effectively constant over the temperature range used,

$$\Delta H_T^\circ = \Delta H_0^\circ + T\Delta C_p^\circ \qquad (15)$$

$$\Delta S_T^\circ = \Delta S_0^\circ + \Delta C_p^\circ \ln T \qquad (16)$$

Introducing these values into equation (13) gives

$$\Delta G_T^\circ = \Delta H_0^\circ + T\Delta C_p^\circ - T(\Delta S_0^\circ + \Delta C_p^\circ \ln T) \qquad (17)$$

and

$$pK_a = \frac{\Delta G_T^\circ}{2{\cdot}303\,RT} = \frac{\Delta H_0^\circ}{2{\cdot}303\,RT} + \frac{\Delta C_p^\circ}{R}\log T - \frac{\Delta S_0^\circ - C_p^\circ}{2{\cdot}303\,RT} \qquad (18)$$

or

$$pK_a = A/T + (\Delta C_p^\circ/R)\log T + B \qquad (19)$$

where $A = -\Delta H_0^\circ/2{\cdot}303\,R$ and $B = -(\Delta S_0^\circ - \Delta C_p^\circ)/2{\cdot}303\,R$. The results of measurements at different ionic strengths are extrapolated to zero ionic strength so as to obtain the value of pK_a at each temperature. The resulting data are then analysed using equation (19) and the best values of A, $\Delta C_p^\circ/R$, and B deduced. Thence the values of ΔH_T°, ΔS_T°, and ΔC_p° are derived[2].

Unfortunately only a few amines have been studied with such precision. A number of authors, however, have deduced approximate values of ΔS° and ΔH° from measurements at two temperatures by using the relationship $(d\Delta G^\circ/dT) = -\Delta S^\circ$, the value of ΔH° being obtained by application of equation (13). The values so obtained are very useful for comparative purposes, but their limitations must be realised when interpreting small differences.

The comparison of data for different amines is made more complicated by the fact that they often refer to measurements with different solvents or solvent mixtures and at different temperatures. The effects of these factors on pK_a will therefore be considered first.

B. The Nature of the Solvent

In general the net effects of the presence of any solute species in a solution should be assessed in terms both of solute–solvent interactions and of the influence of the solute on solvent–solvent interactions, which in water are particularly strong and specialised[3]. For ionic species close-range nearest-neighbour interactions with solvent molecules are strong. This interaction depends on the charge type and effective size of the ion, the factors which determine the intensity of its field, and also on its chemical nature. It may involve orbital overlap, an interaction akin to hydrogen bonding, or intense charge–dipole interaction. For aminium ions or amine molecules in aqueous solution hydrogen-bonding interactions undoubtedly occur with nearest-neighbour water molecules. Whatever type of interaction is involved in this primary hydration 'shell' it is sterically limited in extent but gives rise to a substantial loss of enthalpy (since attractive forces are satisfied), entropy (through loss of freedom of the solvent molecules), and usually, of heat

capacity (through loss of freedom and through the fact that freedom tends to be regained with rise of temperature)[3].

The orderliness of arrangement can be regarded as transmitted outwards from the primary zone, so that there is 'correlation' between the first and second shells. The field of the ion is still strong, and highly polarised water molecules in the first shell readily form hydrogen bonds with others further from the ion. Proceeding outwards, however, the influence of the ion must decline and restriction of freedom of the solvent molecules decreases until orientational rather than translational freedom is lost. As a result, the secondary hydration zone is less well defined than the primary zone, but it contributes to the loss of entropy and of enthalpy. Its effect on heat capacity is probably composite. Since weak restriction of freedom will undergo release with increase of temperature there may be a positive contribution.

The order generated in this way locally around an ion does not fit particularly well into the peculiar orderliness of the structure of the water. It is primarily centro-symmetrical, whereas the water structure is not, and the result of conflict between the incompatible ordering influences seems to be a zone of disorder which makes a substantial positive contribution to the entropy. This is the reason why Frank and Evans[4] found that ions in aqueous solution have 'too much' entropy.

Non-polar solutes have the effect of promoting the ordered arrangement of water molecules about themselves, lowering both the enthalpy and entropy. Thus methane is only very slightly soluble in water because of the very large entropy loss which dissolution involves. This effect is common not only to all non-polar solutes but also to non-polar parts of bifunctional solute molecules with hydrophilic groups. It is called 'hydrophobic hydration'[4] because it involves no specific solute–solvent interactions, but is the effect of an inert body on solvent–solvent interactions in its vicinity. It is the cause of the apparently ice-like structure which seems to exist at the interface between water and gas or water and a hydrocarbon.

This hydrophobic hydration gives a very large contribution to the heat capacity, apparently because it 'melts' with rise of temperature. Since it conflicts with the centro-symmetrical association it is probably weakened or destroyed by the field of a charge on an adjacent part of the molecule. As a result it is more important for the neutral amine molecule than for its conjugate cation, and so it should lead to a negative contribution to ΔS° and a positive contribution to ΔC_p°, as

well as making ΔH° less positive. It may be noted that it is a general phenomenon that the factors which lead to a decrease in ΔH° also decrease ΔS°, and hence there is a partial compensation in the values of ΔG° and hence of pK_a.

These effects have been discussed in detail by Ives and Marsden[3], upon whose views the majority of this section has been based. They will be referred to again later in the discussion of various groups of amines.

In general, the apparent basic character of an amine is influenced by the base strength of the solvent, the greater its proton affinity the lower the pK_a value. In addition, however, it depends upon the relative extents to which the solvation of the amine molecule and the H_3O^+ ion on the one hand, and the amine cation on the other, affect the entropy and enthalpy of the system. There is no simple formula, therefore, relating the relative strengths in one solvent to those of the same amines in another solvent, and it is not surprising that the basic strengths of amines in anisole and chlorobenzene solutions, compared by measuring their equilibria with the indicators 2,6-dinitrophenol and bromophenol blue, do not parallel completely their strengths in water[5]. On the other hand, they show a much closer relationship with the catalytic constants for the decomposition of nitramide in anisole[6]. Similar behaviour has been observed with various bases in isoamyl alcohol[7].

The basic strengths of many amines have been measured in mixed solvents, particularly in mixtures of water with an alcohol. In such media a certain degree of solvent sorting occurs, with the result that the solvation layers around the various species tend to differ in composition from the bulk of the solution, thereby confusing the position still further. In spite of these complications, however, the pK_a values for different amines in these hydroxylic media differ numerically from, but are closely parallel with, their values in water. The parallelism arises doubtless because of the variation of ΔH°, which depends predominantly on the relative proton affinities of the base and solvent. The actual numerical values, however, have not quite the same significance as for aqueous solutions, since the relationship $pK_a + pK_b = 14$ no longer holds.

C. Temperature

Since $\Delta G^\circ = 2{\cdot}303\ RT\ pK_a$ it follows that $(d\Delta G^\circ/dT) = -\Delta S^\circ = 2{\cdot}303R\ pK_a + 2{\cdot}303\ RT(d(pK_a)/dT)$ and hence

$$-\frac{(pdK_a)}{dT} = \frac{\Delta S^\circ}{2{\cdot}303RT} + \frac{pK_a}{T} \qquad (20)$$

Thus (dpK_a/dT) is negative so long as $-\Delta S°$ is less than 4·576 pK_a. As $\Delta S°$ never has such high negative values the temperature coefficient of pK_a is always negative.

Perrin[8] has pointed out that the temperature variation of the pK_a values of univalent organic cations can be represented satisfactorily by the function

$$-\frac{d(pK_a)}{dT} = \frac{pK_a - 0{\cdot}9}{T} \pm 0{\cdot}004 \qquad (21)$$

and for bivalent cations by

$$-\frac{d(pK_a)}{dT} = \frac{pK_a}{T} \qquad (22)$$

These corrections tacitly assume that for univalent cations $\Delta S°$ is about −4·1 cal/deg/mole, whilst for divalent cations it is zero. Since for many amines $\Delta S°$ has relatively low values no great error is introduced by employing these relations, provided that the temperature range over which correction is made is relatively small.

D. Structural Features

The nature of the remainder of the molecule to which the amino group is linked affects the relative energies of the amine and its cation. Factors which decrease the free energy of the cation more than that of the amine tend to stabilize the former and hence to increase pK_a, whilst if the base is stabilized to a greater extent than the ion the pK_a value is reduced. The formation of the amine cation requires the donation of the lone pair on the nitrogen atom to a proton, so any factor which tends to increase the electron density or availability at the nitrogen atom will increase its proton affinity, that is will increase the strength of the base, whilst any factor which tends to decrease this electron density has the reverse effect. The modifications to the base strength produced by various groupings in the molecule are generally classified under three headings.

1. Inductive (polar) effects

When a hydrogen atom linked to a carbon atom in an amine molecule is replaced by a halogen atom or a nitro group, or by any other group attracting electrons, a dipole is set up with its negative end directed away from the carbon atom. This exerts a $-I$ inductive effect, that is electron density is drawn away from the carbon atom making it more electronegative. It therefore tends to draw electron density away from its neighbouring atoms, and eventually this leads to a decrease in the electron density on the nitrogen atom. The new dipole also exerts a direct field effect, tending to polarise the orbitals of all the other electrons in the molecule. The result of these effects is a reduction of the base strength of the amine.

A methyl group, having a weak dipole in the reverse sense, with its positive end away from the carbon atom, should have a slight tendency to exert a $+I$ effect, with resulting increase of base strength.

These inductive effects fall off very rapidly with distance, particularly in saturated compounds, so it is with substituents relatively near to the amine group that they are most marked. When the substituent is linked to an aromatic ring or other conjugated system with a highly polarizable π-electron system, however, these inductive effects extend over much further distances.

2. Mesomeric (resonance) effects

When the amino group is linked directly to a conjugated system the lone-pair electrons tend to become delocalized and to participate in the conjugated system. This reduces their availability for accepting a proton and hence lowers the base strength. If another group is now introduced into the system in such a position that its mesomeric effect can interact with that of the amino group there is a further effect. A nitro group or other group with a $-M$ effect will withdraw electron density from the conjugated system by the mesomeric mechanism and so effectively increase the $+M$ mesomeric effect of the amino group and decrease the base strength still further. On the contrary, a halogen atom, a hydroxyl group, or any other group with a $+M$ effect donates electron density to the system, opposing the mesomeric effect of the amino group and so increasing the base strength.

Since in general the inductive and mesomeric effects of different substituents present in the molecule are roughly additive, attempts have been made to correlate the pK_a values of aromatic amines with the Hammett σ functions of the substituents[9] and those of aliphatic amines with the corresponding Taft σ^* functions[10]. These relationships and their applications have been fully reviewed by Clark and Perrin[11].

3. Steric effects

When bulky groups are present in close proximity to an amino group, steric effects are to be expected. If they are present, for instance in an aromatic amine, in positions where they tend to prevent the

amino group from assuming the conformation most favourable for mesomerism, they should increase the basic strength of the amine relative to that of the corresponding compound in which obstructing groups are absent. Such behaviour is observed with *ortho*-substituted *N,N*-dialkylanilines. In some other cases, however, the presence of such bulky groups tends to decrease the basicity of the amine. Although this general behaviour has been known for some time, the mechanism through which the effect is exerted has been the subject of considerable controversy. Brown and Cahn[12] suggested that the $-NH_3^+$ group in the cation is appreciably larger than the $-NH_2$ group of the free amine and is comparable in size with a methyl group. On this basis the presence of other large groups in the vicinity may cause steric interference which increases the potential energy of the cation relative to that of the free base. This would be unfavourable to cation formation and so would lower the strength of the base.

This theory, however, has not received universal acceptance. For one thing it is by no means certain that the anilinium ion has greater spatial requirements than the free amine, in fact the reverse seems more likely to be true. Although the ammonium ion is tetrahedrally symmetrical, the HN̂H bond angle in ammonia is smaller than the tetrahedral angle. This suggests that the lone-pair electrons exert a greater repulsive force on the hydrogen atoms than does one bound hydrogen atom on another. The relatively small HÔH bond angle ($104\frac{1}{2}°$) in the water molecule and the structures of some of the interhalogen compounds also suggest that a lone pair has considerable spatial requirement. It seems much more likely that in the majority of cases the reason for decreased base strength is to be sought in solvation phenomena, as discussed in section II.B, rather than in actual physical interference of the groups.

As in some instances more than one mechanism may be acting, these effects will be discussed in conjunction with the classes of compounds in which they arise, particularly the alkylamines, *ortho*-substituted anilines and *N,N*-dialkylanilines, and polynuclear aromatic amines.

III. ALIPHATIC AMINES

A. The Methylamines

The basic strength of methylamine is appreciably greater than that of ammonia. This is sometimes attributed to the $+I$ inductive effect of the methyl group, leading to an increased electron availability at the nitrogen atom[13]. It would perhaps be better to regard this as a

mutual polarisation of the methyl and amino groups. At the same time it is of importance to note, as will be discussed later, that the difference in $\Delta G°$ and hence in pK_a arises more from the difference between the entropy changes associated with the dissociation of the ions than from the difference between the enthalpy changes.

The substitution of a second hydrogen atom of the ammonia molecule by a methyl group to give dimethylamine leads to only a small further increase in base strength, whilst the substitution of the third hydrogen atom leads to a considerable decrease, trimethylamine being only slightly stronger as a base than ammonia.

This peculiar order of base strengths was attributed by Brown and his coworkers to what they call 'B-strain'[14,15]. This they define as the strain introduced into a molecule as a result of changes in the normal bond angles of an atom brought about by the steric requirements of bulky groups attached to that atom. Thus they suggested that in trimethylamine the three methyl groups are crowded around the small nitrogen atom, and that their steric requirements are met by a spreading of the CN̂C bond angles to a value greater than the tetrahedral angle. On this view the addition of a proton to the lone pair, which would tend to reduce the bond angle to the tetrahedral value, is resisted by the molecule. Very similar ideas have been expressed by Fyfe[16]. These views, however, seem to be inconsistent with the observations of Lide and Mann[17], who have deduced from the microwave absorption spectrum that the CN̂C bond angle in trimethylamine is $108·7 \pm 1°$.

The apparent anomaly is clarified to a considerable extent, however, by reference to the precision measurements of Everett and Wynne-Jones on ammonia[18,19], methylamine, dimethylamine, and trimethylamine[2], which covered a wide range of temperatures and of ionic strengths. These permitted the evaluation of $\Delta C_p°$, $\Delta S°$, $\Delta G°$, and $\Delta H°$ for the dissociation of each of the cations. The final results for 25° and zero ionic strength are included in Table 1.

For the dissociation of the ammonium ion $\Delta S°$ is small and $\Delta C_p°$ is zero. Unlike methane, which is repelled from water due to the large negative ΔS value involved, the ammonium ion must be very strongly attracted by water. As a result there is only a very small decrease in entropy on dissociation corresponding with the slight changes in the orderliness of arrangement attending the replacement of the NH_4^+ ion by an H_3O^+ ion and a water molecule by an ammonia molecule. The equilibrium is determined principally, therefore, by $\Delta H°$, which in turn depends mainly on the relative base strengths of ammonia and water.

TABLE 1. Thermodynamic functions for the dissociation of amine cations in aqueous solution at 25°C.

Amine	ΔC_p° (cal/deg/mole)	ΔS° (cal/deg/mole)	ΔG (kcal/mole)	ΔH° (kcal/mole)	pK_a
Ammonia[18,19]	0·0	−0·60	12·608	12·425	9·24
Methylamine[21]	+7·5	−4·7	14·484	13·088	10·63
Dimethylamine[21]	+19·9	−9·5	14·687	11·859	10·78
Trimethylamine[21]	+41·0	−15·2	13·358	8·815	9·80
Ethylamine[22,16]	—	−3·1	14·504	13·58	10·61
	—	−11·4	14·55	11·15	10·67
Diethylamine[22,16]	—	−7·2	14·916	12·77	10·94
	—	−15·7	14·97	10·3	10·98
Triethylamine[16]	—	−16·3	14·55	9·7	10·67
n-Propylamine[22]	—	−1·7	14·36	13·85	10·53
n-Butylamine[22]	—	−1·3	14·45	14·07	10·60
Ammonia in 60% MeOH[23]	0·0	+2·65	11·77	12·56	8·64
Methylamine in 60% MeOH[23]	−12	−1·73	13·306	12·79	9·76
[a]Dimethylamine in 60% MeOH[23]	0	−4·6	13·41	12·03	
[a]Trimethylamine in 60% MeOH[23]	Positive	−6·6	11·93	9·97	

[a] Data for ionic strength 0·10.

As the hydrogen atoms of the ammonia molecule are successively replaced by methyl groups the value of ΔS° changes systematically to more negative values. Trotman–Dickenson[20] explained this as arising from the progressive decrease in the number of hydrogen atoms on the amine cation available for hydrogen bonding to solvent molecules, thus decreasing the constraint produced in the solvent through this cause. At the same time ΔC_p° acquires a progressively larger positive value, this being associated with a large decrease in ΔH°. For the change from ammonia to methylamine the entropy effect predominates and leads to a large increase in ΔG° and hence in pK_a, but for the subsequent changes from methylamine to dimethylamine and from dimethylamine to trimethylamine almost similar increases occur in $-\Delta S^\circ$, but with each step ΔC_p° shows increasing increments, with associated decreases in ΔH°. The result is that a maximum value of ΔG° is reached at dimethylamine.

In addition to the effect produced by the reduction of the number of hydrogen bonds to the cation, and the further ordered structure

produced near the aminium group, the successive additions of methyl groups would be expected to yield increasing areas of surface over which hydrophobic hydration can occur in the neutral amine molecule, and to reduce slightly the hydrogen bonding of its amino group. It is difficult to assess the area over which hydrophobic hydration can occur but it is not unreasonable to suppose that this may be very much greater over the almost complete hemisphere formed by three methyl groups than over the smaller surfaces presented by two or one methyl groups. Being close to the centre of positive charge this hydration atmosphere will be almost wholly dispersed in the cation, so the heat capacity of the system in the dissociated state will be higher than that for the cation–solvent system, since it contains a term representing the heat required to disperse this solvent layer. This has a corresponding effect on the enthalpy of the amine–solvent system, since a considerable amount of heat would be required to bring the solvent atmosphere around the methyl groups isothermally to the more random state which exists around these groups in the cation. These effects and theories regarding hydrophobic hydration are discussed fully by Ives and Marsden[3].

It is interesting to note that the effects become modified in aqueous methanol solution, where for ammonia ΔS° becomes positive, possibly through the ammonium ion exerting a greater sorting effect in its hydrogen bonding than does the hydroxonium ion. Although ΔC_p° has the rather unexpected value of −12 cal/deg/mole for methylamine, it is very low for the other amines, indicating that no phenomenon analogous to hydrophobic hydration occurs to an appreciable extent in this solvent mixture. The changes in ΔS°, therefore, may reflect the decrease in the number of hydrogen atoms in the cation available for hydrogen-bond formation. The ΔG° values for dimethylamine and triethylamine must be lower at zero ionic strength than at $I = 0{\cdot}10$, so the net result is that in this medium methylamine seems to be the strongest of the bases.

B. Higher Alkylamines

Lengthening of the alkyl chain makes only relatively slight differences to the pK_a values of primary amines (Table 2). After a very small increase in ethylamine they remain almost constant up to n-decylamine, after which there seems to be a slight decrease. Chain branching also produces very little effect. Amongst secondary amines (Table 3) there is evidence of the values rising to a maximum at di-n-butylamine, after which they assume an almost constant value.

TABLE 2. pK_a Values of primary alkylamines in aqueous solution at 25°C.

Amine	pK_a
Ammonia	9·24[24,19], 9·25[25]
Methylamine	10·62[26], 10·63[21], 10·64[25]
Ethylamine	10·64[22], 10·67[18]
n-Propylamine	10·53[22], 10·69[27]
n-Butylamine	10·60[22], 10·61[28,29], 10·66[30]
n-Pentylamine	10·63[29], 10·61[31]
n-Hexylamine	10·64[29]
n-Heptylamine	10·66[29]
n-Octylamine	10·65[29], 10·57[31]
n-Nonylamine	10·64[29]
n-Decylamine	10·64[29]
n-Undecylamine	10·63[29]
n-Dodecylamine	10·63[29]
n-Tridecylamine	10·63[29]
n-Tetradecylamine	10·62[29]
n-Pentadecylamine	10·61[29]
n-Hexadecylamine	10·61[29]
n-Heptadecylamine–n-Docosylamine	10·60[29]
i-Propylamine	10·63[28]
i-Butylamine	10·43[29]
t-Butylamine	10·68[31]
i-Pentylamine	10·60[29], 10·64[28]
t-Pentylamine	10·72[31]
Methyl(diethylmethyl)amine	10·63[31]
Triethylmethylamine	10·59[31]

TABLE 3. pK_a Values of secondary alkylamines in aqueous solution at 25°C.

Amine	pK_a
Dimethylamine	10·73[25], 10·77[32], 10·78[21], 10·81[33]
Diethylamine	10·94[22], 10·98[28,16], 11·04[33]
Di-n-propylamine	11·00[31]
Di-n-butylamine	11·25[31], 11·31[28]
Di-n-pentylamine	11·18[28]
Di-n-hexylamine	11·01[29]
Di-n-octylamine	11·01[29]
Di-n-dodecylamine–Di-n-octadecylamine	11·00[29]
Di-i-propylamine	11·05[28]
Di-i-butylamine	10·50[34], 10·82[28]
Di-*s*-butylamine	11·01[34]
Di-i-pentylamine	11·00[28]
N-Methyl-2-aminoheptane	10·82[31]

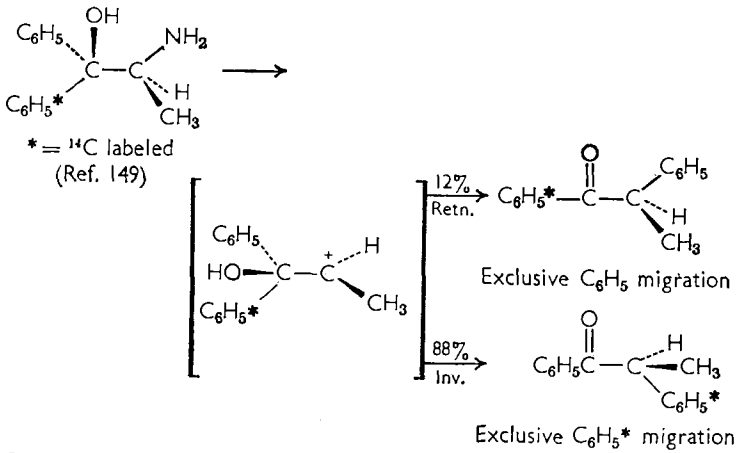
The effect of chain length is more pronounced in the tertiary alkylamines (Table 4), where triethylamine is much more basic than trimethylamine, whilst *N,N*-dimethylethylamine and *N,N*-diethylmethylamine lie intermediately. There are some anomalies amongst the data for the higher members of this series, and further measurements on them would be of interest.

TABLE 4. pK_a Values of tertiary alkylamines in aqueous solution at 25°C.

Amine	pK_a
Trimethylamine	9·74[25], 9·75[36], 9·76[35], 9·80[21,32], 9·81[33]
Triethylamine	10·65[35], 10·67[16], 10·71[32]
Tri-n-propylamine	10·65[28]
Tri-n-butylamine	9·93[28], 10·87[37]
N,N-Dimethylethylamine	9·99[35]
N,N-Diethylmethylamine	10·29[35]
N,N-Dimethyl-n-propylamine	9·99[35]
N,N-Dimethyl-n-butylamine	10·02[35]
N,N-Dimethyl-i-propylamine	10·30[35]
N,N-Dimethyl-i-butylamine	9·91[35]
N,N-Dimethyl-*s*-butylamine	10·40[35]
N,N-Dimethyl-*t*-butylamine	10·52[35]

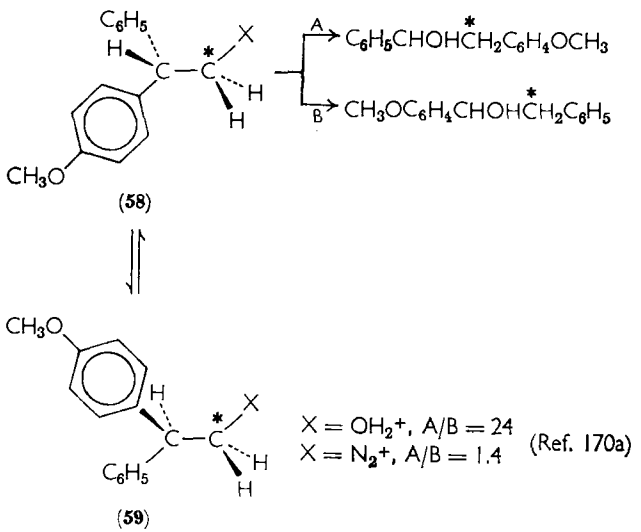
Studies of the entropy changes attending the dissociation of the cations of these amines have led to somewhat conflicting results (Table 1). From measurements at only two temperatures Evans and Hamann[22] found the value of $-\Delta S°$ decreased systematically from methylamine to n-butylamine, this being accompanied by a progressive increase in $\Delta H°$. They also found $-\Delta S°$ for the dissociation of the diethylammonium ion to be less than for the dimethylammonium ion. Fyfe[16], on the other hand, inferred from measurements at four temperatures that the values of $-\Delta S°$ for the ethylammonium, diethylammonium, and triethylammonium ions were all much higher than for the corresponding methylammonium ions.

The difference between these two series of amines is likely to arise principally from the hydrophobic hydration effects. If Evans and Hamann's results are correct they suggest that in ethylamine the extent of hydrophobic hydration may not be much greater than in methylamine, or may persist in part in the cations, since the β-carbon atom is an appreciable distance from the charge centre near the nitrogen atom. Fyfe's measurements, on the contrary, suggest that this hydrophobic hydration atmosphere is dispersed in the cation. Further measurements on these compounds are obviously required.



(157)

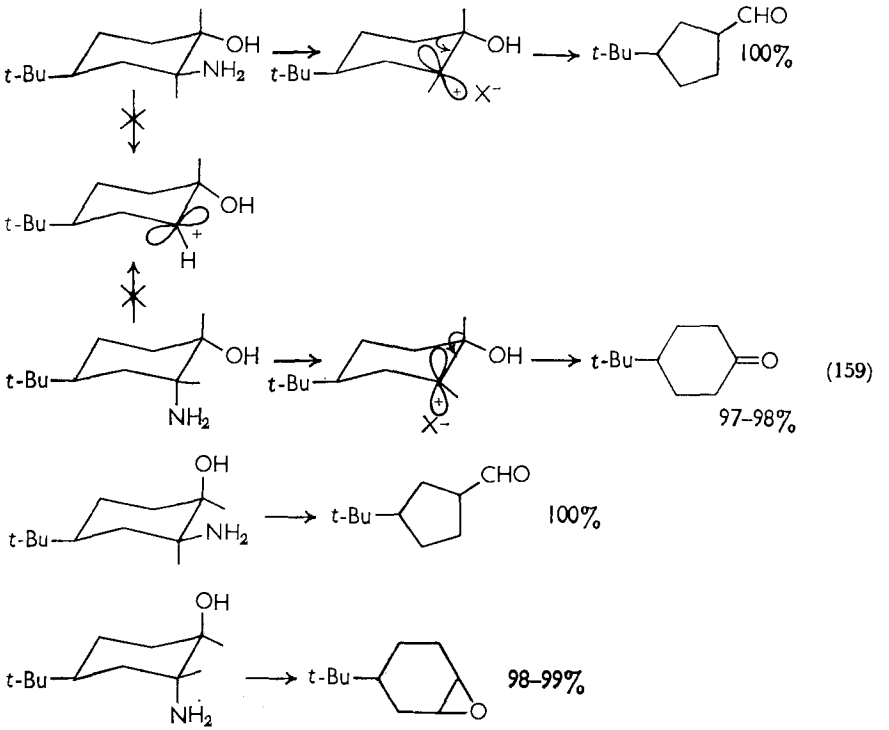
of phenyl groups (equation 142)[170a], and the ground-state control of the group that migrates[171,190]. For the reaction in which water is the leaving group (equation 158), the migration ratio of anisyl to phenyl



is 24, indicating participation by the aromatic rings in the transition state. For the reaction in which nitrogen is the leaving group, the ratio is 1·4, indicating a very low degree of participation in the transition state for the loss of nitrogen. The low ratio is consistent with the view that the transition-state energy is low. Under these conditions, the migration ratio is determined largely by the distribution of isomers in the ground state[171,190]; in the example of equation (158), with

$X = N_2^+$, conformations **58** and **59** should be approximately equally populated.

The highly stereospecific reactions of cyclohexylamines (e.g. equation 159)[191], are accounted for by the maintenance of gross stereochemistry by the counter ion (similar to the interpretation given in section (3)—path (a); see section (1)). By this means, the *trans*-coplanar arrangement of groups favorable for rearrangement on stereoelectronic grounds[192] is obtained.



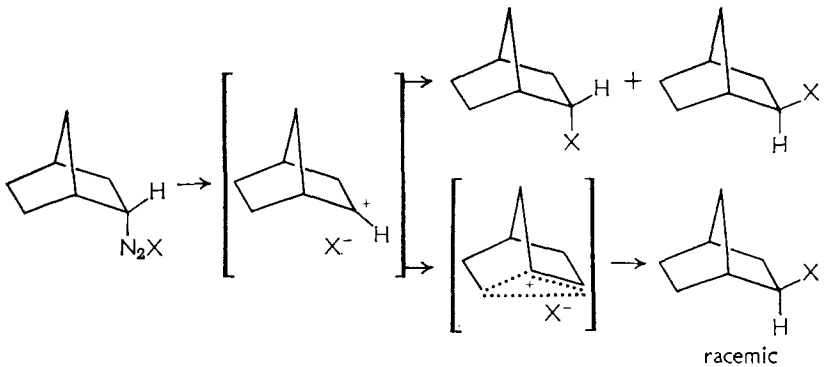
(159)

(5) *The nitrous acid deamination in acetic acid*

On the average, it appears that in the deamination of secondary carbinamines in acetic acid, the substitution products are formed by paths (d), (e), (f) and (g) (equation 146). Note that both axial and equatorial amines yield alcohols with overall retention of configuration (Table 12).

The deamination of *endo*-norbornylamine yields 87% norbornyl acetates (~99% *exo*), 10% norbornanols (98% *exo*) and 2% of the norbornyl nitrates[174]. The *exo* acetate was 89% racemic; this fact

and the large *exo/endo* ratio indicates the involvement of the bridged ion (or of rapidly equilibrating ions) (equation 160)[193]. We have

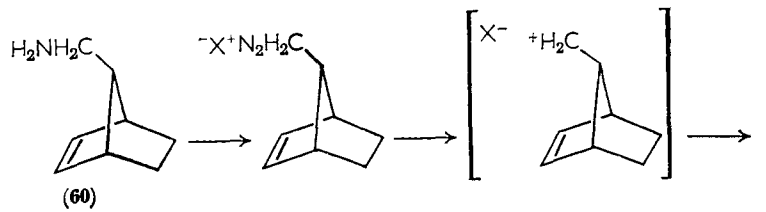


(160)

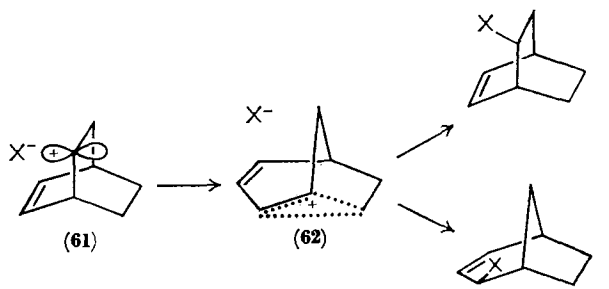
found that the decomposition of ethyl *N-endo*-norbornyl-*N*-nitrocarbamate (X in equation (160) = $^{-}OCO_2C_2H_5$) in acetic acid yields the carbonates with an *exo/endo* ratio of 50–100. Since every other nitrosoamide decomposition we have carried out in acetic acid has proceeded with overall retention of configuration (Table 6), we conclude that some special event must occur in the norbornylamine case to block retention of configuration; the formation of the bridged ion appears to be a logical possibility for this event. Since we have shown that the path to retention is extremely fast, equivalent to rotation times of the ^{18}O-labeled carboxylate ion (section a (3)), we conclude that bridged-ion formation is extremely rapid, and that time scales of the order of molecular rotation times are involved. Thus if equilibrating ions are involved, the rate of equilibration is so fast that the value of drawing a distinction becomes doubtful.

Rearrangement products are often formed stereospecifically in the nitrous acid deamination. Berson and coworkers have recently published an elegant series of papers on such rearrangements[194], of which one example is shown by equations (161) and (162)[195a]. Although isomeric amines (**60**) and (**63**) could in principle yield a common classical 2,2,2-bicyclooctenyl cation, different sets of products were in fact obtained. The results (equations 161 and 162) can be accounted for by the counter-ion hypothesis. Following the loss of nitrogen, the counter ions, by virtue of their positions and weak bonding (section (1)), maintain a difference between species **61** and **64**; in the transition states for rearrangement, the interaction with a neighboring carbon occurs on the opposite side of the electron-deficient carbon relative to the anion (see also sections (3) path (a) and (4)). Skeletal re-

arrangements can be fast relative to reactions between ions (norbornylamine and nitrosoamide results and also equation 159), and most of the product probably comes from bridged ions **62** and **65**. The deamination of **60** also led to the formation of a fair amount (~30%) of the product set obtained from amine **63**, this crossover probably occurs on the way to **61** by a process related to the intramolecular inversion observed in simpler systems (path g).

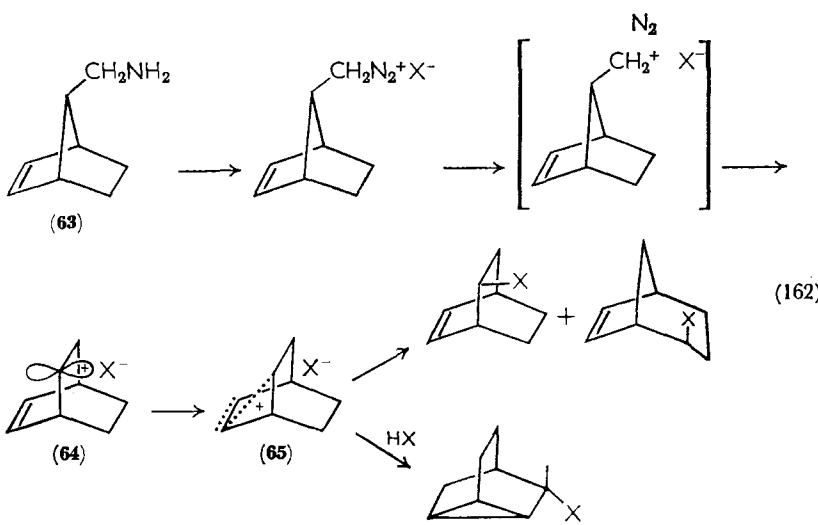


(**60**)



(**61**) (**62**)

(161)



(**63**) (**64**) (**65**)

(162)

Berson and Gajewski[195a] have given an explanation of their experimental results in which the products of the reaction are determined by the formation of the 'deformationally isomeric' ions **66** and **67**. As an alternative, they propose that the different results in the two systems may be 'attributed to transitory differences in the local environment of the cations rather than to two structurally different cations', an explanation that encompasses the counter-ion mechanism given above. The reader is referred to the original work for details.

(66) (67)

(6) *The nitrous acid deamination in water*

The relationship of the nitrous acid and nitrosoamide methods of deamination is more tenuous in water since only one example of the nitrosoamide decomposition in aqueous media has been reported. The decomposition of *N*-nitroso-*N*-n-propylbenzamide in dimethylformamide–water (60/40 by vol) yielded a propyl benzoate fraction containing 9% of the isopropyl isomer and a propanol fraction containing 33% of isopropyl alcohol[141a]. The nitrous acid deamination of n-propylamine under the same conditions yielded an alcohol fraction containing 31% of isopropyl alcohol[141a]. The similarity in the isomer contents of the alcohol portions suggests that common intermediates were involved. The less extensive isomerization of the benzoates may be a reflection of the shorter lifetime of the propyl cations trapped by negatively charged counter ions compared to those trapped by neutral solvent molecules; on the other hand, the role of diazopropane must be determined before definitive conclusions are possible.

The deamination in water–acetic acid mixtures, lean in water, is very similar to that in glacial acetic acid (section 5) and Table 13). In the deamination of *trans-trans*-2-decalylamine (axial amino group)[160] (Table 13), the decalol is formed with overall retention of configuration up to a solvent composition of 75 mole % water–25 mole % acetic acid; presumably the retention path ((d), equation 146) is one of the chief reaction modes operating. The decalyl acetates (the 'solvolysis' products) are formed with overall inversion of configuration in all the solvent mixtures and the proportion of inversion increases with water

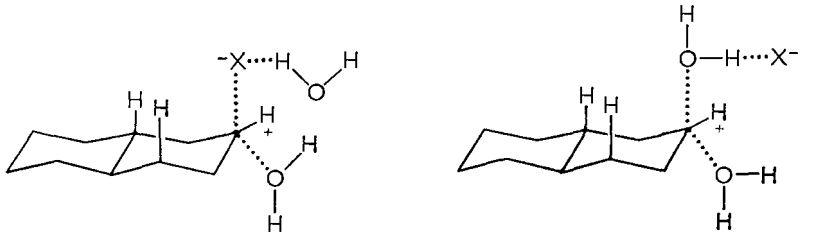
TABLE 13. Deamination of the 9,10-*trans*-2-decalylamines.

Mole % acetic acid (+ water)	100	75	50	25	3·4
A. *trans-trans*[a]-2-Decalylamine		Yields of products			
trans-2-Decalyl acetate	32	29	25	17	7
cis-2-Decalyl acetate	39	35	29	24	26
trans-2-Decalol	27	31	33	32	16
cis-2-Decalol	2	5	13	27	51
B. *trans-cis*[a]-2-Decalylamine					
trans-2-Decalyl acetate	18	15	11	6	3
cis-2-Decalyl acetate	55	48	46	37	26
trans-2-Decalol	1	3	3	4	3
cis-2-Decalol	26	36	40	53	68

[a] Refers to the hydrogen atom in the 2-position.

content. Note that the solvolysis product from nitrosoamide reactions in acetic acid is always formed with more inversion of configuration than the intramolecular product (Table 7). In these cases, the net extra inversion is probably the result of capture of the cation by the solvent cage with predominant, but not complete, inversion of configuration (path (f)).

In the water-rich 3·4 mole % acetic acid mixture, (1) the alcohol is formed with net inversion, (2) 77% of the substitution products are formed with inversion of configuration and (3) most of the product (67%) is now alcohol. In highly polar media, the force between the cation and counter ion (or solvated counter ion) may be so weakened, that collapse to the counter-ion product (paths (d) and (g)) is not inevitable and reactions with molecules of the solvent cage can lead to 'cooler' solvated ion pairs **68** and solvent-separated ion pairs **69** of



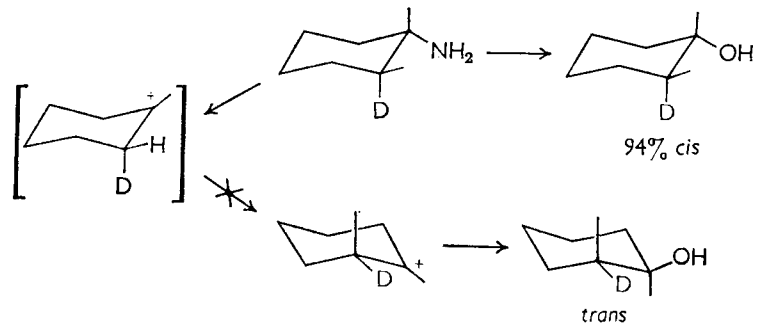
(68) (69)

the type proposed for solvolytic reactions[195b]. Under these circumstances, the competition between inversion and retention modes of decomposition will lead to a dominance of inversion, since nonbonded interactions of the solvent with the axial hydrogens at positions

3 and 5 and the ring itself will raise the energy of bonding from the axial direction over that from the equatorial direction[182].

The deamination of *trans-cis*-2-decalylamine[173] (equatorial amino group) leads to approximately the same ratio of acetate to alcohol as observed in the axial case (Table 13). Over the entire range of water concentrations, in contrast, both the acetate and alcohol are formed with overall retention of configuration—with the proportion of alcohol increasing with the water content of the medium. Presumably in water-lean mixtures, paths (d), (e), (f) and (g) are dominant, and in water-rich mixtures, the mechanism outlined in the axial case is operating, except that the 3,5-axial interactions now lead to overall retention of configuration. It appears that as the solvent becomes richer in water, the alcohol distributions for the *trans* and *cis* amines are approaching a common value, suggesting that a common intermediate is formed which is sufficiently long lived to reach an equilibrium distribution of the solvating molecules.

The substitution reaction is still a fast process in water since it has been found in the deamination of a monocyclic carbinamine that substitution is faster than chair–chair interconversions. It was shown that the deamination of *cis*-2-deuterocyclohexylamine yielded over 94% of *cis*-2-deuterocyclohexanol (equation 163)[196].

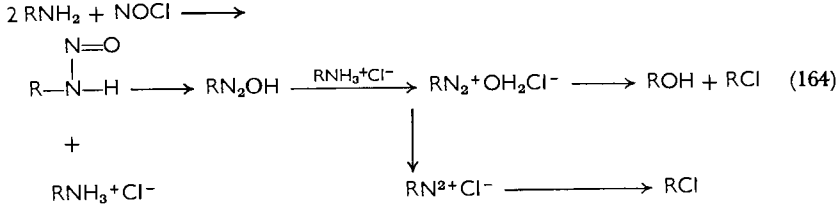


(163)

The examples of Table 13 illustrate a general rule that has been outlined before; namely that in nitrous acid deaminations in *water*, equatorial amines yield alcohols with retention and axial amines yield alcohols with predominant inversion of configuration[181,182]. The interpretation of this rule by Dauben and coworkers[182] is related to that outlined above. Recent work indicates that equatorial amines also yield some alcohol with *inversion* of configuration[131,180], but the rule still holds for the *predominant* mode of decomposition (e → e; a → e).

(7) *Related methods*

Nitrosyl chloride has occasionally been used in the deamination of aliphatic amines[197]; the chloride is often a chief product of the reaction, although alcohols have also been isolated (equation 164). The formation of the nitrosoamine has been demonstrated in the deamination of methylamine at low temperatures[159].



(164)

The reaction of nitrosyl chloride with n-butylamine in methylene dichloride yields n-butyl chloride free of isomers[198] and the reaction with 1-phenylethylamine in dioxane yields 1-phenylethyl chloride with overall retention of configuration[199]. These results are similar to those obtained in the nitrosoamide decomposition in non-polar solvents, and a similarity in mechanisms seems certain. The reaction of nitrosyl chloride with various amines at −75° in methylene dichloride was shown to yield both the alcohol and the chloride (Table 14). 1-Phenylethylamine yielded a larger fraction of alcohol than did

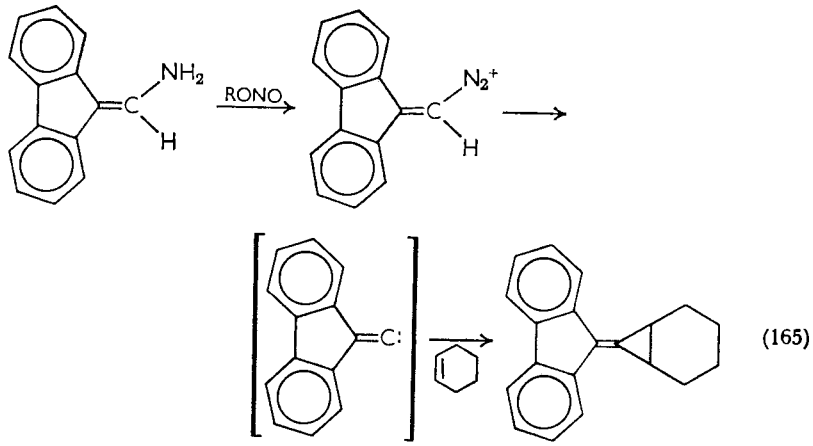
Table 14. Products from the reaction of aliphatic amines with nitrosyl chloride at −75°[200].

Amines (RNH_2)	Products (%)		
R	ROH	RCl	Olefins
n-Butyl	7	42	
1-Phenylethyl	20	30	
t-Butyl	—	—	64

butylamine; possibly with a decrease in the lifetime of the diazonium hydroxide (**50**, **51**; equation 146), the exchange reaction (path (e)) has less of a chance to compete with the intramolecular modes of decomposition (paths (d) and (g)). Under the conditions of the experiment, a number of side-reactions are occurring since only about one-third of the theoretical amount of nitrogen is evolved at −75°, with another third being obtained in warming the reaction

mixture to room temperature. An intractable mixture of nitrogen-containing compounds is also obtained*, presumably formed in part via symmetrical triazenes (RN=N—NHR).

The deamination of aliphatic amines is occasionally effected through reaction of the amine with an alkyl nitrite in a non-polar solvent[188,201,202]. Primary carbinamines apparently react in this system via diazoalkanes[188b] (see section (3), path (b)). Triazenes (RN_2NHR) and free radicals are also possible intermediates that must be considered for deaminations in non-polar solvents. The reaction of amines with nitrosonium salts in aromatic solvents is probably a closely related process[203]. Through the use of alkyl nitrites in non-polar solvents, it has been shown recently that certain vinyl amines yield products that probably stem from carbene intermediates (equation 165)[202].

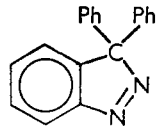


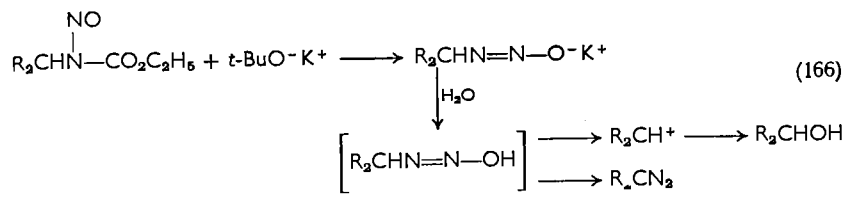
(165)

Lastly, an interesting method of deamination under basic conditions has been reported recently by Moss[204] (equation 166).

* Preliminary evidence indicates the following structures for compounds obtained from n-butylamine and tritylamine:

$C_4H_9N(NO)CH(C_3H_7)N(NO)C_4H_9$, $Ph_3CNHCPh_3$,

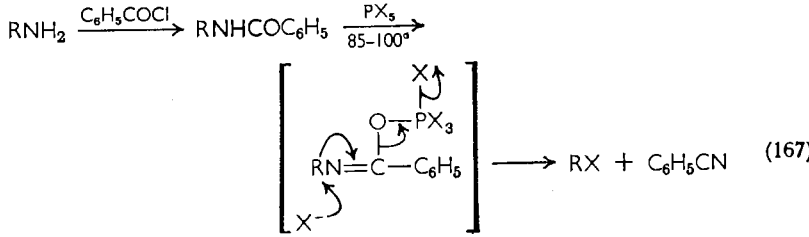




(166)

2. Reactions in which nitrogen is not the leaving group

a. *Von Braun reaction of amides.* The replacement of the amino group of primary aliphatic amines by a halogen may be brought about in good yield by the von Braun reaction of the *N*-substituted benzamide derivatives[205,206]. Treatment of the benzamide with phosphorus pentahalide gives the halide and benzonitrile (equation 167). Thionyl chloride has been employed successfully in the place of phosphorus pentahalide[207].



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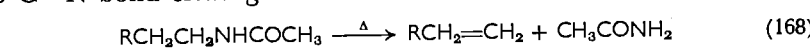
b. *Pyrolysis of amides.* The pyrolysis of *N*-alkylamides can lead to C—N bond cleavage with formation of an alkene and the parent



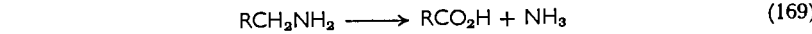
(168)

amide (equation 168)[208]. *N-t*-Alkylamides and *N*-alkylanilides are found to pyrolyze with the same ease as many esters, though in general a higher temperature (> 500°) is required for pyrolysis and low yields (with charring) are obtained. The acid-catalyzed pyrolysis of amides has been observed[209] and *N*-alkyl acetamides form olefins when boiled with 15% hydrochloric acid[210].

c. *Oxidation methods.*

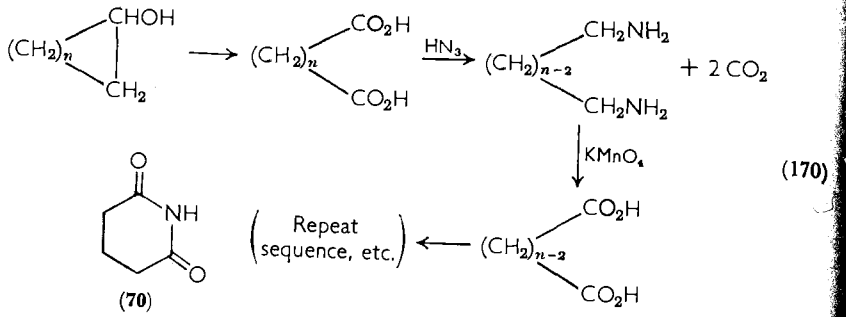
(1) *Oxidation with permanganate*

The oxidation of primary carbinamines with basic potassium permanganate yields the corresponding carboxylic acid (equation 169).



(169)

The reaction has been used in a degradation scheme for the location of ^{14}C in cyclic compounds[211]. At the 1,5-diaminopentane stage, a



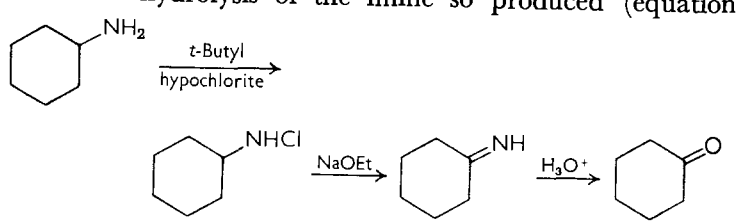
(170)

(70)

neighboring group interaction occurred to give glutarimide (**70**)[211]; hydrolysis in the presence of nitrous acid yielded glutaric acid which was then treated with hydrazoic acid to continue the degradation. A similar scheme has also been used for radioactive 1,3-diaminocyclopentane[140b]. The oxidation of amines with neutral permanganate has been reported recently to give a variety of products[212]; a review of the permanganate oxidation was included in this report[212].

(2) *t-Butyl hypochlorite*

A useful oxidative deamination of aliphatic amines to give the corresponding aldehyde or ketone can be brought about by chlorination of the amine to the *N*-chloroamine followed by dehydrochlorination and hydrolysis of the imine so produced (equation 171).



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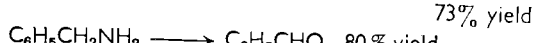
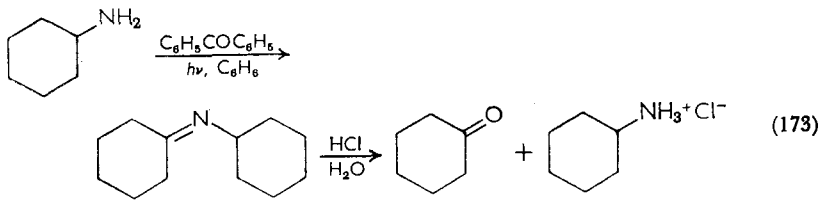


(172)

Hypochlorous acid has been used to effect the chlorination[213], but *t*-butyl hypochlorite has been found to be a more convenient reagent[214].

(3) *Photochemical oxidation*

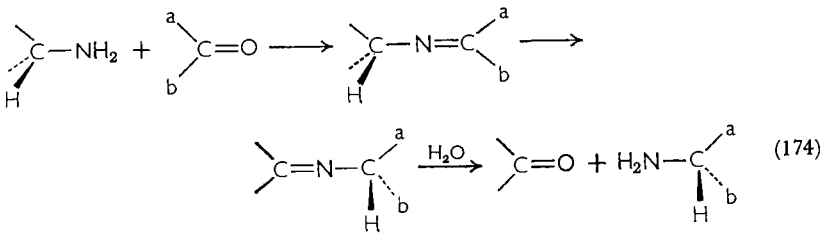
The deamination of cyclohexylamine has been brought about photochemically using benzophenone as sensitizer[215]. Cyclohexanone was produced in 80–90% yields (equation 173). The reaction is also successful with secondary amines.



(173)

(4) *Transamination*

Transamination represents a potentially useful method for the synthesis of amines—and also for the cleavage of C—N bonds with a transfer of asymmetry (equation 174). Snell has reported the synthesis



(174)

of glutamic acid containing an excess of the L isomer from the reaction of ketoglutaric acid with L-alanine, catalyzed by the copper salt of pyridoxal[216]. A discussion of conformational factors in this reaction has appeared recently[217]. The biological applications of transamination are covered in chapter 9 of this volume.

B. Aromatic and Heterocyclic Amines

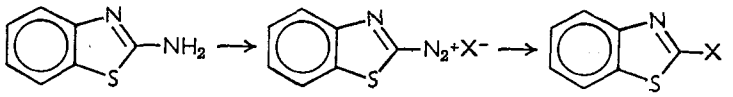
1. Reactions involving diazonium salts

Treatment of a primary amine with aqueous nitrous acid almost invariably gives solutions of more or less stable diazonium salts (equation 175)[218]. The decomposition of the diazonium salt with loss

(175)

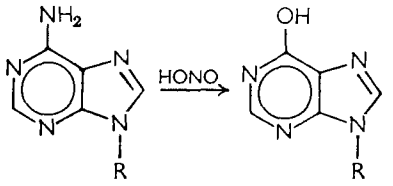
of nitrogen, which can be brought about thermally or catalytically in the presence of cuprous salts or finely divided copper, gives high yields of substituted aromatic derivatives and the reaction has found much use in organic synthesis. This subject will be covered in detail in another volume of this series.

Heterocyclic aromatic amines also react to form diazonium salts (equation 176). With many heterocyclic amines, the substitution



(176)

occurs rapidly and the corresponding hydroxy compound is isolated directly (equation 177). This type of change apparently accounts for

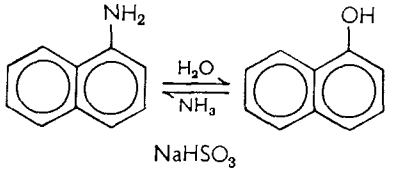


(177)

the ability of nitrous acid to bring about mutations; that is, by its action on DNA[219].

2. The Bucherer reaction

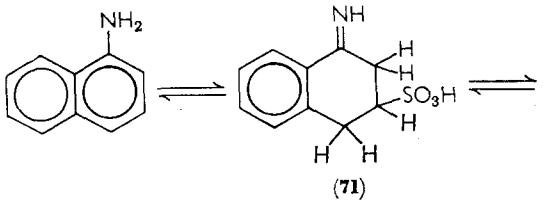
The Bucherer reaction is a useful, though limited, method of deamination[220]. As an example, treatment of naphthylamines with aqueous sodium bisulfite at 160° followed by sodium hydroxide at 100° gives naphthols (equation 178)[220]. The reaction is reversible



(178)

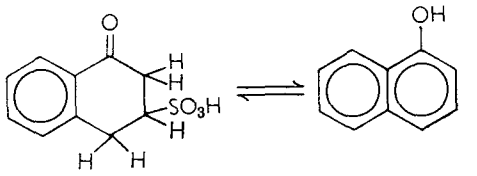
and limited in its application to naphthalene derivatives, resorcinol and compounds of this type. Secondary and tertiary naphthylamines also react to give naphthols.

The mechanism of the reaction has been investigated recently by Seeboth[221] who has isolated 1-tetralone-3-sulfonic acid by the reaction of both 1-naphthylamine and 1-naphthol with excess sodium bisulfite (equation 179); **72** was stable in aqueous media and could be chlorinated or brominated in the 2-position before hydrolysis to the corresponding naphthol; **71** was isolated only from nonaqueous media. Treatment of the 1-tetralone-3-sulfonic acid with arylamines gave good yields of arylnaphthylamines (equation 180). The reaction is



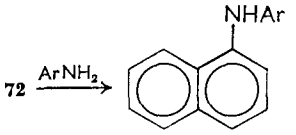
(71)

(179)



(72)

not successful with phenol itself, presumably because of the loss of resonance energy in the addition of bisulfite ion.



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CHAPTER 9

Biological formation and reactions of the amino group

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I. INTRODUCTION

The elements of amino groups obviously originate in the atmosphere but only a few of the simplest, unicellular living organisms are capable of using or fixing atmospheric nitrogen directly as a precursor of amino compounds. Higher plants, as well as those microorganisms which cannot fix atmospheric nitrogen, can use either ammonia or nitrate as a nitrogen source. Animals, which are more complex in structure, function and degree of specialisation, require organic nitrogen compounds, some of which already contain amino groups. The sequence of reactions by which either free or combined nitrogen is converted to naturally occurring amino compounds is not yet

completely worked out, but it is clear that the steps in each sequence are all enzyme catalysed. The ability of different life forms to use free or combined nitrogen is governed, to some extent, by the presence of particular enzymes. Since all enzymes are proteins, and therefore derivatives of the most important naturally occurring amino compounds, the α-L-amino acids, any argument concerned with the purely biological formation of amino compounds is essentially circular. The implication is, then, that at some very early stage, before the evolution of life on this planet, amino acids must have been formed directly from the elements of the atmosphere.

Although Miller[1,2] has shown that the passage of an electric discharge through mixtures of methane, ammonia and water vapour (possible constituents of a primeval atmosphere), results in the production of some α-amino acids, these always occur as racemic mixtures of the L and D forms. In biological systems, both structural and functional proteins are built almost exclusively from L-amino acids. It is clearly easier to construct a well-ordered macromolecule from residues having the same stereochemistry, but the original selection of one-handed residue over the other is as yet unexplained.

Such speculations as to the origin of α-L-amino acids may seem out of place, but they are designed to emphasise the importance of these particular amino compounds in biological systems. Not only must amino acids have been among the earliest formed amino compounds, on the evolutionary scale, since they are the precursors of the natural catalysts of all metabolic processes, but they also appear to be the first-formed products following ingestion of inorganic nitrogen compounds by either plants or microorganisms. All other amino compounds (e.g. purines and pyrimidines, amino sugars, vitamins and chemical transmitters) must, therefore, be derived from amino acids. Although some of the biosynthetic routes are incompletely understood, many are known to involve the transfer of amino groups from either amino acids or from amides of amino acids to receptors such as carbohydrate residues or heterocyclic ring systems.

Between the various life forms now extant, there is a remarkable conservation of so-called fixed nitrogen. Plants, animals and microorganisms enjoy a symbiotic relationship, with microorganisms holding the balance between fixed and atmospheric nitrogen. Apart from the nitrogen-fixing microorganisms, there exist a number of nitrifying bacteria which can convert ammonia, or more importantly organic nitrogen compounds of plant or animal origin, into nitrate. The nitrate may then be assimilated by plants and converted to

organic nitrogen compounds. Of these, certain amino acids, readily synthesised by plants, are necessary in the diet of herbivorous animals while carnivores obtain the same essential amino acids by consuming herbivores. When animals and unconsumed or inedible plants die, the organic amino and nitrogen compounds may be reconverted to nitrate, by nitrifying bacteria, and so the principal cycle of fixed-nitrogen conservation is completed. Alternatively, the nitrogen of nitrate may be returned to the atmosphere by the action of denitrifying bacteria.

Not all animals obtain the essential amino acids from plants. Some (the ruminants) can by-pass the main route by direct assimilation of the amino acids produced by symbiotic bacteria in the gut. These bacteria can break down cellulose, the main structural carbohydrate of plants, and can also synthesise all the amino acids, required for their growth and development, from a simple fixed-nitrogen source. The ruminant obtains its more complex nitrogen requirements by digestion of dead bacteria. (Goats, for example, can survive on a diet of hay and ammonia.) This may appear to be a somewhat one-sided symbiosis, with the bacteria carrying out all the important functions but, in return, the bacteria obtain from the animal a copious supply of carbohydrate and are maintained in a favourable environment with respect to temperature and medium composition.

It is fortunate, not least from the point of view of this chapter, that the fundamental differences in the dietary nitrogen requirements of different forms of life are not followed by an equivalent diversity in the principal routes to amino compounds and their derivatives. Figure 1 shows, in outline, the most important reactions and these are the ones to which the present discussion will be limited. The reactions shown with bold arrows are common to most bacteria and to some cells of multicellular organisms. The reactions shown with light arrows are no less important but they only occur in particular life forms. For example, the decarboxylation of α-L-amino acids to form amines occurs only in bacteria and (to a lesser extent) in plants. Although excess amino acids in animals may be removed by decarboxylation, it is the intestinal bacteria which carry out the reaction and not cells of the animal itself. The production of alkaloids is also marked with a light arrow. Alkaloids, which are formed almost exclusively in plants, with the exception of the poisonous skin secretions of certain toads and salamanders, have profound physiological effects when administered to higher animals, but their function in plants remains quite unknown. Because the function of the product is

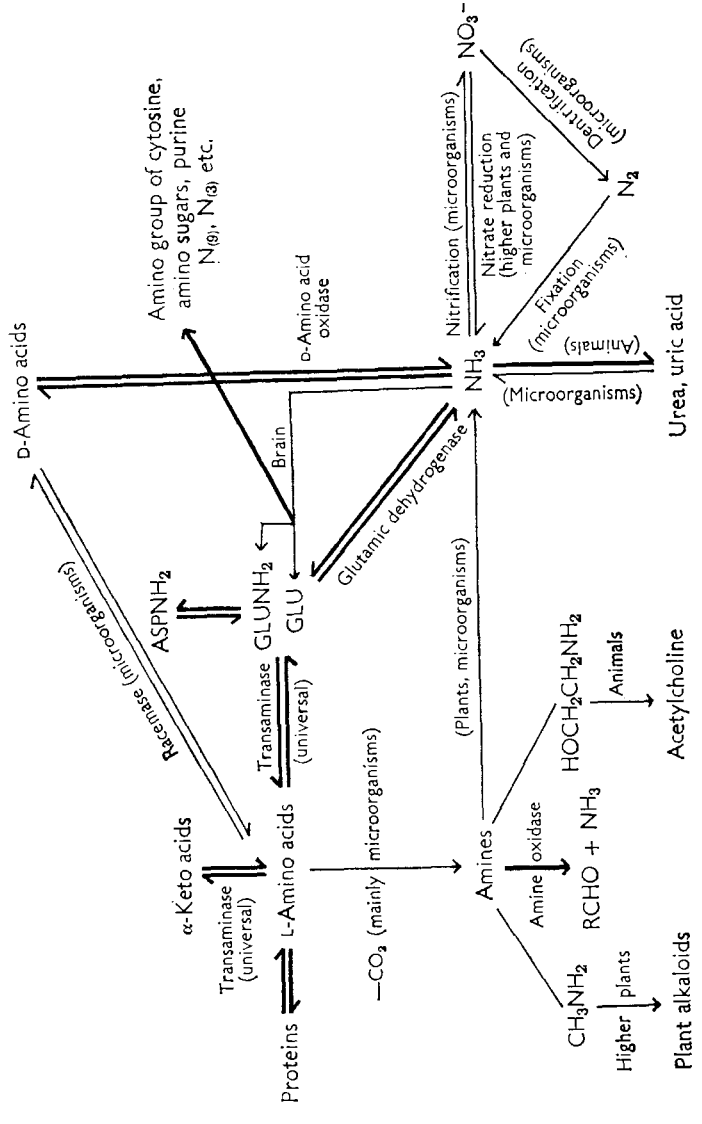


FIGURE 1.

unknown, the formation of plant alkaloids is considered as a *secondary* rather than a *primary* metabolic process.

The first two sections of this chapter are concerned with the general problems involved in elucidating metabolic pathways and with the properties of the necessary catalysts. In later sections, the particular reactions given in Figure 1 are considered separately. The emphasis given in each case reflects more the present state of knowledge of the 'mechanism' of each reaction than the biological importance. Although the formation of proteins from amino acids and of nucleic acids from purine and pyrimidine bases are included in Figure 1, discussion of the biosynthesis of these vital macromolecules is beyond the scope of this chapter.

II. PROPERTIES OF ENZYMES

As stated in the opening paragraph, the basic reason for the profound differences in the nitrogen requirements of different organisms lies in the presence or absence of specific enzymes. Since the great majority of metabolic processes are enzyme catalysed, so each reaction involved in the synthesis and metabolism of amino compounds may be discussed in terms of the properties of individual protein catalysts. In each cell of multicellular organisms and in every unicellular organism, many reactions occur, some only during particular phases of cell development and others throughout the existence of the cell. This fact implies the presence of many different catalysts. Metabolic studies in whole animals, plants and microorganisms, or in tissue slices or homogenates of particular parts of higher organisms, have led to the partial identification of many hundreds of enzymes but relatively few of these have been isolated in forms which satisfy the criteria of purity applied to proteins. (It should be remembered that these criteria are still far less stringent than those applied to conventional organic molecules). However, certain generalisations about some of the properties of enzymes can be made with reasonable safety. For example, all enzymes appear to be proteins (molecular weight, 10^4–10^6) which may or may not require a non-protein adjunct (cofactor) for catalytic activity. The cofactor may be a carbohydrate or polynucleotide fragment, a metal or a relatively small organic molecule. The proteins are all built from some or all of the twenty known, naturally occurring amino acids (Table 1) and therefore the specificity of each enzyme as a catalyst for a particular reaction (or a set of very closely related reactions) must in part be a function of the sequence in which the

TABLE 1. Common α-L-amino acids.

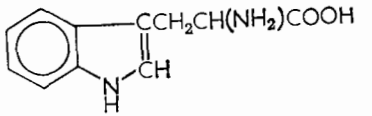
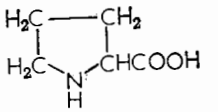
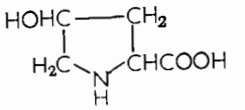
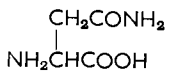
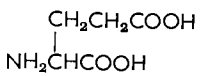
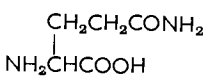
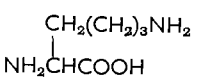
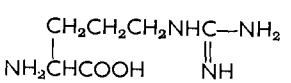
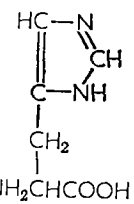
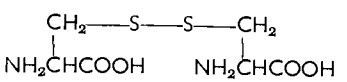
Common name	Chemical structure
Glycine	NH_2CH_2COOH
Alanine	$NH_2CH(CH_3)COOH$
Valine	$CH(CH_3)_2$ $NH_2CHCOOH$
Leucine	$CH_2CH(CH_3)_2$ $NH_2CHCOOH$
Isoleucine	$CH_3CHC_2H_5$ $NH_2CHCOOH$
Serine	CH_2OH $NH_2CHCOOH$
Threonine	$HC(OH)CH_3$ $NH_2CHCOOH$
Methionine	$CH_2CH_2SCH_3$ $NH_2CHCOOH$
Phenylalanine	$CH_2C_6H_5$ $NH_2CHCOOH$
Tyrosine	$CH_2C_6H_4OH\text{-}p$ $NH_2CHCOOH$
Tryptophane	
Proline	
Hydroxyproline	
Aspartic acid	CH_2COOH $NH_2CHCOOH$

TABLE 1. (*continued*)

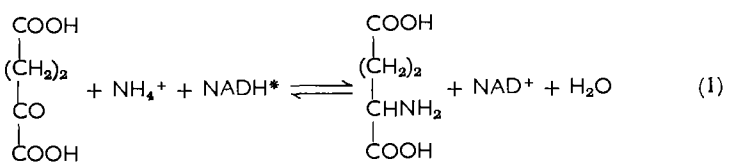
Common name	Chemical structure
Asparagine	
Glutamic acid	
Glutamine	
Lysine	
Arginine	
Histidine	
Cystine	

amino acids are joined. The relative ease with which, for many enzymes, catalytic activity is lost, without any peptide bonds being broken, for example by heating or by change of pH or solvent, suggests that both specificity and activity are functions of the secondary and tertiary structure of the protein, that is, the three-dimensional arrangement of the protein chain or chains.

In spite of the mass of existing literature concerned with the 'mechanisms' of enzyme catalysis (more, perhaps, than in the field of physical organic chemistry), in no single case can an answer be given to the question of how enzymes increase the rates of known chemical reactions by factors which may be as high as 10^8 or 10^9. In one case, the complete three-dimensional structure of a small enzyme (lysozyme (egg-white) mol. wt. ~14,600) is now known, as a result of collaborative efforts of protein chemists and crystallographers. Unfortunately, the chemistry of the substrate of this particular enzyme

(complex polysaccharide molecules containing *N*-acetylglucosamine and *N*-acetylmuramic acid present in some bacterial cell walls—see section V.E) is not well understood, and so even for this enzyme, theories of the mechanism of catalysis, although plausible, are largely speculative[3].

Although it is not known, in detail, how enzymes catalyse metabolic reactions, it is still useful to discuss which enzymes are present in living cells, particularly in relation to cell function and degree of specialisation. It should at once be pointed out that the presence of a particular enzyme in a cell is a necessary but not a sufficient condition for the reaction catalysed by that enzyme to occur. The standard free-energy changes of metabolic processes are all relatively low (about ± 12 kcal/mole), hence the reactant concentrations are as important as the presence of the necessary catalyst in that they determine the direction in which reaction proceeds. An example will serve to illustrate this important factor. It has been emphasised that plant and animal cells do not contain the enzymes, present in some bacteria, which are responsible for converting atmospheric nitrogen to ammonia. Multicellular organisms must be supplied with fixed nitrogen, but the next step in the production of amino compounds from ammonia is most probably that given in equation (1). The reaction is catalysed by an enzyme (glutamic dehydrogenase, see section IV.B) which occurs in bacteria, plants and also animals. (It is not implied that enzymes catalysing the same reaction but present in different species are identical proteins.) In principle, the reaction (equation 1) could be, in all living matter, the first step in the production of amino compounds, as it appears to be in bacteria and probably also in plants.

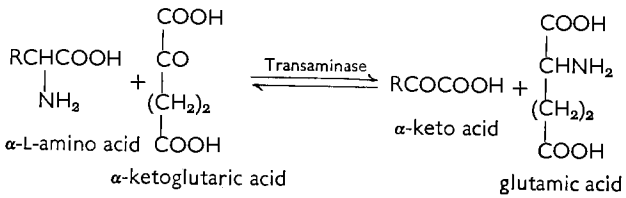


α-ketoglutaric acid glutamic acid (1)

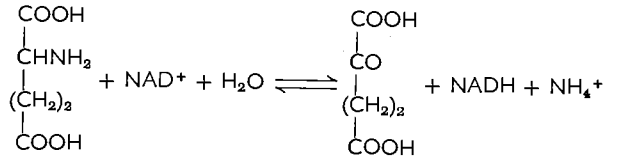
However, it is well known that animals, with the exception of ruminants, cannot survive on ammonia as a source of nitrogen. The reason for this apparent anomaly is that although glutamic dehydrogenase is present in animals (predominantly in the liver), the level of ammonia is too low to drive the reaction to the formation of glutamate.

* See Figure 2a and section IV.A.

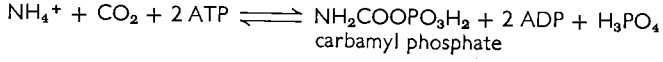
The concentration of ammonium ions is kept at a low level by other enzymes, also active in the liver, notably those concerned with the conversion of free ammonia to the normal waste products (urea or uric acid) and also those concerned with the synthesis of glutamine, subsequently used in a variety of synthetic reactions. Ammonia is toxic in the central nervous system of higher animals and one function of the liver is to keep the concentration in the bloodstream low. It is alleged that the main function of liver glutamic dehydrogenase is in its involvement in the series of reactions by which excess L-amino acids are deaminated. The reactions are summarised in equations (2–5). (See section VI.B). Liver glutamic dehydrogenase is, therefore,



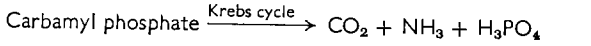
(2)



(3)



(4)



(5)

more concerned with the production of ammonia than of glutamate. The ammonia is fed directly into the cycle of reactions by which excess nitrogen compounds are converted into waste products and so cannot gain access to other parts of the body where it might be toxic. Glutamic dehydrogenase may be involved in a similar series of reactions in plants and bacteria, where the balance between the production of necessary amino acids (reversal of reactions 2 and 3) and the removal of unwanted amino acids (reactions 2–5) is delicate.

It is clear, then, that the earlier statement that dietary nitrogen requirements depend on the presence of particular enzymes is incomplete. It is not possible to deduce, merely from the presence of an enzyme, whether a particular reaction will occur in a given direction. Not only is the location of the enzyme important in multicellular organisms, but also the tolerance of the whole organism for high

concentrations of the appropriate reactants. This is particularly true for those reactions for which the standard free-energy change is low.

III. METHODS OF STUDYING METABOLIC PATHWAYS

The details of the methods used in elucidating metabolic pathways inevitably depend on the particular organisms studied, but the most common approach involves administration of isotopically labelled compounds and detection of the label in metabolic intermediates. Work on whole animals and plants is subject to certain obvious limitations. For example:

(a) A large dilution factor is inevitable since relatively small quantities of labelled compounds are introduced into a large mass of material. In studying the metabolism of amino compounds, this problem is less severe in plants than in animals because the total protein concentration is lower. In animals, proteins are the main structural material whereas plants are built primarily of polysaccharides.

(b) It is difficult to isolate the few possible intermediates from the large number of irrelevant compounds present initially.

(c) Certain intermediates in a reaction sequence may only be present at very low, stationary concentrations. Apart from the problem of identifying such intermediates, there is the additional problem of characterising the enzymes catalysing their interconversion. It is interesting to note that, to date, the best characterised enzymes are those for which at least one substrate is present, *in vivo*, at a significant concentration level, e.g. enzymes of the glycolysis cycle and the Krebs–Henseleit cycle (section VI).

(d) The complex control devices, by means of which life is maintained, may easily be upset. This imposes a limit on the quantity of isotope introduced, the form in which it is administered and the actual method of administration (e.g. by mouth or by injection). Isotope studies on isolated, functional parts of animals or plants (e.g. heart or liver, leaves or seeds) are also subject to these limitations. Indeed, the problem of maintaining an approximation to normal functioning is even more severe in functional parts than in the whole organism. Work on tissue slices or homogenates does not suffer from the same disadvantages but the results obtained are more difficult to interpret unambiguously. In destroying both the inter- and intracellular structure, the distribution of enzymes between and within cells is altered and the spatial arrangement, whereby the product of one enzyme-catalysed reaction passes directly as a substrate for another

reaction, breaks down. Intermediates detected under these conditions may not be formed to any significant extent in whole cells. As pointed out previously, the mere presence of an enzyme in tissue is not indicative of its importance *in vivo*.

Studies of metabolic pathways in microorganisms are not subject to the same limitations as those considered above in relation to plants and animals. There are a number of advantages in working with unicellular organisms. For example:

(a) It is generally easier to keep microorganisms alive under conditions used for the introduction of isotopically labelled compounds.

(b) The dilution of any isotopically labelled compound is less than in multicellular organisms because of the lower mass of material in each microorganism.

(c) The high rate of reproduction, and hence the increased frequency of mutation of microorganisms, permits the culture of mutant strains in which particular metabolic pathways may be blocked. Intermediates present at low stationary concentrations in the wild strain may well accumulate in mutants, and so be more easily identified.

(d) The considerable adaptability shown by many microorganisms, with respect to nutrients in the growth medium, greatly facilitates the production of mutants with desired characteristics. For example, it is possible, in some cases, to produce mutants in which a particular metabolic path is blocked, simply by culturing the organism in the presence of the end-product of that particular path.

Among the disadvantages are:

(a) The difficulty of culturing microorganisms on a large scale.

(b) All the reactions necessary for growth, development and reproduction must occur within each unicellular organism. In multicellular organisms, on the other hand, particular cells are specialised to carry out functions for the organism as a whole and within these specialised cells, the total number of enzyme catalysed reactions may be reduced.

(c) Because of the size of microorganisms, the only feasible method of introducing isotopically labelled compounds is by assimilation. Since transport of material across cell walls is limited to certain chemical compounds, the labelled compounds which can be introduced are similarly limited.

In studying the metabolism of amino compounds, use is commonly made of the stable isotope ^{15}N, the abundance of which may be determined mass spectrometrically. The radioactive isotope of nitrogen, ^{13}N, has too short a half-life (~ 10 min) to be of much value

in this field, though some experiments in the limited field of nitrogen fixation have been reported[4].

IV. FORMATION OF α-L-AMINO ACIDS

There are two main reasons for considering the formation of α-L-amino acids separately from other amino compounds. The first is that the α-L-amino acids are the basic components of enzymes and the second is that those organisms which can use inorganic nitrogen compounds as the sole source of nitrogen appear to form all amino compounds from amino acid precursors. The reactions, included in Figure 1, which are primarily involved in amino acid formation are:

(a) *Ammonia formation*, by nitrogen fixation and nitrate reduction.

(b) *Glutamate formation* by incorporation of ammonia into an existing carbon skeleton (α-ketoglutarate), catalysed by the enzyme glutamic dehydrogenase.

(c) *Transamination* between (i) glutamate and some α-keto acids to form α-L-amino acids with the regeneration of α-ketoglutarate; (ii) aspartate, (formed by (c)(i) from oxaloacetate (or possibly by direct incorporation of ammonia into fumaric acid) and some α-keto acids to form α-L-amino acids with the regeneration of oxaloacetate.

(d) *Miscellaneous* reactions of amino acids formed by reactions (a)–(c).

A. Ammonia Formation

1. Nitrogen fixation

The ability of certain microorganisms to take up and use atmospheric nitrogen was recognised late in the nineteenth century. Since 1890, an increasing number of microorganisms with this ability have been isolated in pure strain and the somewhat surprising fact to emerge is that nitrogen-fixing microorganisms have little else in common. It is conventional to classify microorganisms broadly according to diet, (e.g. autotrophs require only inorganic foodstuffs, heterotrophs require some organic material), energy source (e.g. chemosynthetic microorganisms require a chemical 'energy source', photosynthetic microorganisms can obtain energy directly from sunlight) and type of oxidation reactions (e.g. in anaerobes, oxidation of foodstuffs occurs in the absence of molecular oxygen). Inorganic oxidation–reduction systems such as nitrate–nitrite or sulphate–sulphide, may be involved

$$NO_3^- \rightleftharpoons NO_2^-$$
$$SO_4^{2-} \rightleftharpoons H_2S$$

or, in the case of fermenting microorganisms, carbohydrate products such as pyruvate may undergo the type of reaction

$$2\,CH_3COCOOH \rightleftharpoons CH_3CH(OH)COOH + CH_3COOH + CO_2$$

Aerobic microorganisms use molecular oxygen in the terminal stages of oxidation of foodstuffs.

Nitrogen-fixing microorganisms have representatives in all these classes. For example, among the free living bacteria, *Clostridium pasteurianum* is an anaerobic chemosynthetic heterotroph while *Azotobacter agilis* is an aerobic heterotroph; blue–green algae (nitrogen-fixers which may be found living in symbiosis with higher plants and lichens) and certain photosynthetic bacteria are autotrophs.

There have been a number of claims for nitrogen fixation by higher organisms, including chick embryos[5] and some fungi[6,7] but the most controversial issue is concerned with nitrogen fixation by plants. The requirement of higher plants for an adequate supply of fixed nitrogen (as nitrate or ammonium salts) has been recognised since the late eighteenth century, while crop rotation has been practised since Roman times. In particular, some leguminous plants have a beneficial effect on soil for subsequent crops, the effect being most marked when the plants are turned into the soil as green manure. The possibility that these leguminous plants in some way increased the concentration of fixed nitrogen in the soil led to the proposal that the plants themselves fixed atmospheric nitrogen. The situation was confused by the observation, late in the nineteenth century, that legumes grown in sterile soil do not fix atmospheric nitrogen but examination of the plants grown under sterile and non-sterile conditions showed that only those grown under non-sterile conditions had nodulated roots. Root nodules, characteristic of both legumes and other species capable of fixing nitrogen, were shown to contain microorganisms. These (many bacteria of the species *Rhizobium*, blue–green algae, etc.) live in true symbiosis with the plants, being responsible for fixing atmospheric nitrogen and supplying nitrogenous material to the plant which, in turn, provides the symbiotes with carbohydrate foodstuffs. Isolated bacteria from root nodules cannot themselves fix atmospheric nitrogen.

In the following period of fifty years little progress was made towards elucidating the mechanism of the process. Many attempts were made to obtain cell-free preparations containing the enzymes presumably involved in nitrogen fixation, but these were unsuccessful until 1960. The intracellular organisation of enzyme systems is known to be complex, groups of enzymes involved in sequential reactions

frequently being localised in or on subcellular particles. One would predict that nitrogen fixation would involve a complex series of reactions so it is not surprising that the difficulty experienced in obtaining active, cell-free preparations is associated with the conditions under which the cells are disrupted. Successful methods of cell disruption include sonic, mechanical and enzymic disruption in an atmosphere of hydrogen, but the method of choice depends on the organism studied. Activity is judged by incorporation of $^{15}N^{8}$ or ^{13}N into ammonia and organic nitrogen compounds by the action of the supernatant liquid obtained after high speed centrifugation of the cell extract (25,000–50,000 g), the supernatant liquid having been shown to be cell-free. Knowledge of the mechanism of nitrogen fixation is still in a primitive state but some interesting facts have emerged[9–11]. Firstly, there appears to be a close but non-stoichiometric connection between nitrogen fixation and carbohydrate metabolism. In extracts of *Clostridium pasteurianum*, *Bacillus polymyxa*, *Rhodospirillum rubrum* and *Chromatium* the particular intermediate in carbohydrate metabolism required is pyruvate, believed to be metabolised to acetyl phosphate (equation 6). Working with extracts of *Cl. pasteurianum*, Carnahan and

$$CH_3COCOOH + H_3PO_4 \rightleftharpoons CH_3COOPO_3H_2 + CO_2 + H_2 \qquad (6)$$

coworkers have shown that there is a large molar excess ($\sim$100-fold) of pyruvate metabolised over amount of nitrogen fixed, and also an initial lag period in which nitrogen fixation cannot be detected. Had there been a stoichiometric connection between pyruvate metabolism and nitrogen fixation, the obvious overall reaction would be as shown in equation (7). However, as frequently occurs in biological systems,

$$3\,CH_3COCOOH + 3\,H_3PO_4 + N_2 \rightleftharpoons 3\,CH_3COOPO_3H_2 + 3\,CO_2 + 2\,NH_3 \qquad (7)$$

the connection between the oxidation (of pyruvate) and reduction (of nitrogen) appears to involve an electron-transfer system rather than hydrogen transfer. Since reference will be made, in later sections, to those oxidation–reduction reactions involved in the metabolism of amino compounds, a brief account follows of the currently accepted position with regard to natural redox systems.

The enzymes catalysing reactions involving oxidation and reduction (oxido-reductases) are of two types:

(a) those requiring a readily dissociable, nicotine–adenine nucleotide (NADP) cofactor (Figure 2a, 2b) catalysing reactions of the type

$$MH_2 + NAD^+ \rightleftharpoons M + NADH + H^+ \qquad (8)$$

(MH_2 = reduced metabolite)

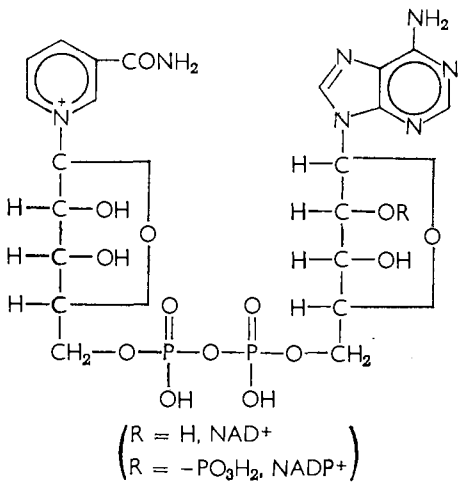


FIGURE 2a. Nicotinamide—adenine nucleotide cofactors (oxidised).

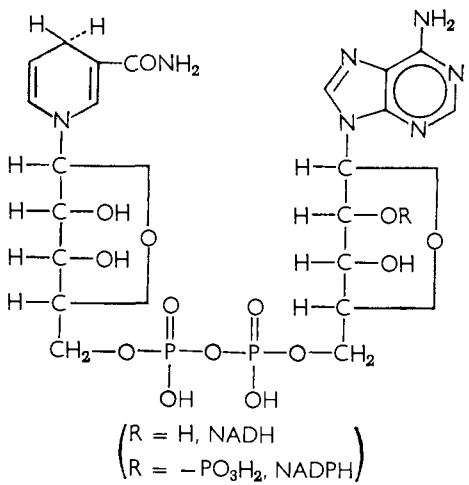


FIGURE 2b. Nicotinamide—adenine nucleotide cofactors (reduced).

(b) those containing a tightly bound flavine cofactor (Figure 2c, 2d) and catalysing reactions of the type

$$MH_2 + FP \rightleftharpoons M + FPH_2 \qquad (9)$$

Reoxidation of the reduced cofactors occurs by one of the reactions shown in Figure 3. The abbreviation 'cyt-system' refers to the complex

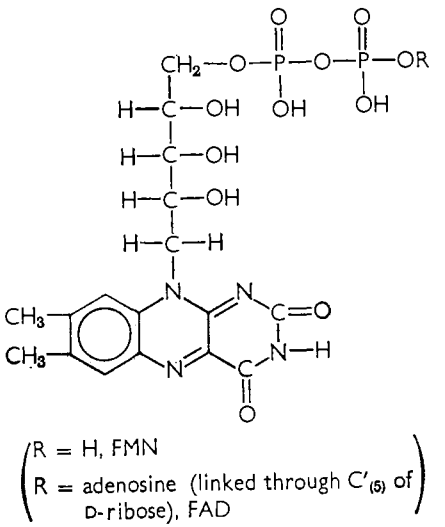


FIGURE 2c. Flavin cofactors (oxidised).

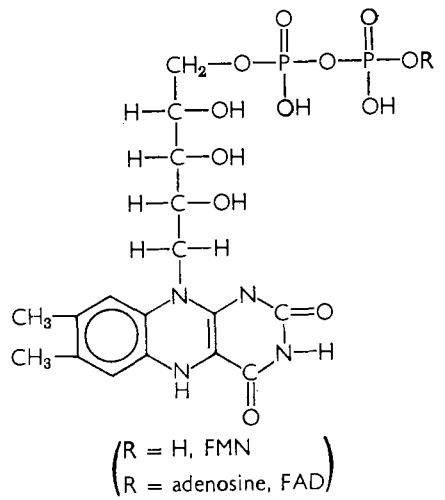


FIGURE 2d. Flavin cofactors (reduced).

arrangement of flavoproteins, a quinone-type derivative and the so-called cytochromes which exist in particular subcellular particles called mitochondria. The cytochromes are protein-bound haem complexes (haem is a porphyrin ring system in which the four pyrrole

ring nitrogens are coordinated to iron). The iron in these haemoproteins undergoes reversible reduction and oxidation as electrons pass from one cytochrome to the next, the ultimate reaction with molecular oxygen, transported to the cells in association with the haemoglobin of blood, is as shown in equation (10).

$$2\ \text{cyt a}_3\ Fe^{2+} + 2\,H^+ + \tfrac{1}{2}\,O_2 \rightleftharpoons 2\ \text{cyt a}_3\ Fe^{3+} + H_2O \qquad (10)$$

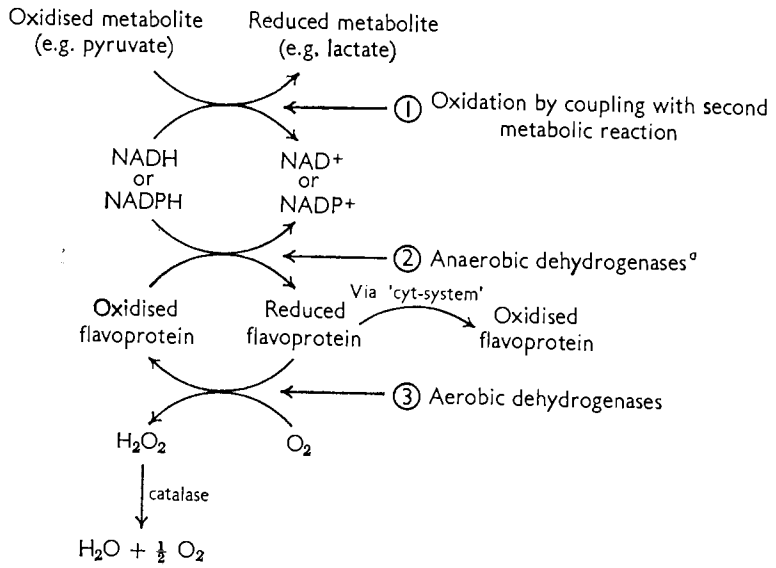


FIGURE 3.

[a] The reduced flavoproteins catalysing reaction ② are always reoxidised by the cytochrome system.

For the particular system involved in nitrogen fixation, an iron-containing protein called *ferredoxin* appears to act as an electron-carrying intermediary between pyruvate metabolism and nitrogen reduction. Ferredoxin was first isolated from *Cl. pasteurianum* in 1962[12]. The iron in ferredoxin is not associated with a porphyrin ring system nor is the protein associated with a flavin entity. The ferredoxin isolated from *Cl. pasteurianum* is a small protein (mol. wt. ~6,000), showing absorption maxima at 280, 300 and 390 mμ when oxidised (brown colour) but only the 280 mμ absorption remains when the protein is reduced. The soluble, nitrogen-fixing system, from *Cl. pasteurianum*, has been fractionated into two parts[13], one called the

hydrogen-donating system (HDS) and the other the nitrogen-activating system (NAS). Both fractions are required for nitrogen fixation. The HDS catalyses the reaction between pyruvate and inorganic phosphate (equation 6) and also the production of molecular hydrogen from hydrogen ions. Both these activities of the HDS fraction are stimulated by ferredoxin. Figure 4 summarises the proposed connection between the nitrogen-activating system and the hydrogen-donating system.

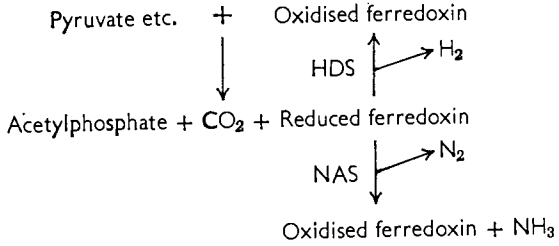


FIGURE 4.

The above account ignores many facets of the problem of nitrogen fixation. For example:

(a) The role of molybdenum, which is known to be an essential trace metal for nitrogen fixation in root nodules[14] and possibly in free living microorganisms[15].

(b) The long-standing argument as to the nature of the 'key-intermediate', that is, the compound immediately preceding incorporation of nitrogen into a carbon compound.

(c) The possibility of a route involving first oxidation and then reduction, for example via nitrous oxide, nitramide or hyponitrous acid to hydroxylamine, and thence to ammonia.

On balance, the evidence so far favours the theory that ammonia is the end-product of nitrogen fixation.

2. Nitrate reduction (in higher plants and some microorganisms)

The biological reduction of nitrate is a stepwise process. The intermediates have not all been characterised but enzymes catalysing some of the postulated steps have been identified in certain higher plants and microorganisms.

a. *Nitrate reductase.* An enzyme catalysing the reduction of nitrate to nitrite has been detected in some moulds[16], bacteria[17], plant leaves and yeasts. In all cases the enzyme activity is associated with a flavoprotein (FP), containing flavine adenine dinucleotide (Figure 2c, 2d) and requires two cofactors, one of which is either NADH or NADPH (Figure 2a, 2b), depending on the source, and the other is a specific metal, molybdenum, known to be essential, in trace amounts, for healthy plant growth. This particular oxidation–reduction system does not come into either of the separate categories given in section IV.A.1 but the possibility still exists that more than one enzyme may be involved. It is interesting, in this context, that removal of the metal, by chelation, inhibits nitrate reduction but not the reduction of the FAD of the enzyme by added NADH or NADPH[18].

b. *Nitrite reductase.* An enzyme catalysing the reduction of nitrite is less well characterised than nitrate reductase, but its presence has been demonstrated in yeasts[19] and plant leaves[19] and some micro-organisms[20]. This enzyme also appears to be a metalloflavoprotein requiring NADH or NADPH, but the heavy metal cofactor has not been positively identified. Likely candidates are iron, copper or manganese. The reduction product is uncertain. The enzyme may well be the same as that designated as hyponitrite reductase, detected in *Neurospora*[21].

c. *Hydroxylamine reductase.* The reduction of hydroxylamine to ammonia is catalysed by another metalloflavoprotein, present in some plant leaves[19], yeasts and microorganisms[20]. The enzyme requires NADH and the metal is most likely to be manganese.

Hydroxylamine is known to be highly toxic to plants so the possibility that it is an obligatory intermediate in nitrate reduction must be considered with caution.* Interest in hydroxylamine arises from the lengthy controversy, briefly mentioned here, concerning the relative merits of hydroxylamine or ammonia as the key intermediate in nitrogen fixation. The toxicity of hydroxylamine may well be due to its action as an enzyme inhibitor. However, in spite of its toxicity, there are still some claims[22] that hydroxylamine may be an intermediate in the formation of amino acids by oxime formation with such carbonyl compounds as glyoxilic acid (formed in photosynthesis), pyruvate, α-ketoglutarate or oxaloacetate (intermediates in carbohydrate metabolism) and subsequent reduction of the oximes to α-amino acids (equation 11). Virtanen and coworkers, the main

$$NH_2OH + RCOCOOH \rightleftharpoons \underset{\displaystyle COOH}{\overset{\displaystyle |}{RC{=}NOH}} \rightleftharpoons \underset{\displaystyle NH_2}{\overset{\displaystyle |}{RCH{-}COOH}} \qquad (11)$$

supporters of hydroxylamine as the key intermediate in nitrogen fixation, originally proposed that the main route to α-amino acids might be through oxime formation; however, this route is now generally believed to be only of minor importance.

The sequence of reactions alleged to occur in nitrate reduction are given in equation (12).

$$HNO_3 \longrightarrow HNO_2 \longrightarrow [HNO] \longrightarrow NH_2OH \longrightarrow NH_3 \qquad (12)$$

3. Nitrification and denitrification

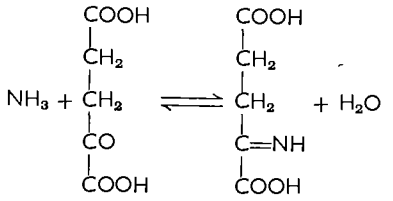
The nitrifying microorganisms, which can convert ammonia and organic amino compounds to nitrate, and the denitrifying micro-organisms which produce elementary nitrogen from nitrate and nitrite, are important in that they control the supply of fixed nitrogen to higher organisms. The mechanisms of the two processes are obscure. It is possible that, at least in *Nitrosomonas*, nitrification may occur by the reverse of the reactions of equation (12). Certainly, enzymes catalysing the production of nitrite from hydroxylamine have been detected[23]. In denitrification, cell-free preparations of *Pseudomonas stutzeri* have been shown to catalyse the reduction of nitrate and nitrite to nitrous and nitric oxides and to gaseous nitrogen. Among the proposed cofactors for the enzymes involved are NAD, NADP, FAD, FMN, iron and copper, but nothing is certain. It is alleged that some of the enzymes contain bound cytochromes, and in this respect, differ from the metalloflavoproteins involved in the reduction of nitrate to ammonia.

B. Glutamic Dehydrogenase

Glutamic dehydrogenase catalyses the formation of glutamate from α-ketoglutarate and ammonia. The cofactor for the enzyme may be NAD (as shown in equation 1), or NADP, depending on the source of the enzyme. In plants and in most animal tissues, the cofactor is NAD while some bacterial and yeast enzymes require NADP. The mammalian liver enzyme works with either cofactor. The equilibrium constant is such that, at the hydrogen ion and substrate concentrations in most regions containing the enzyme, the production of glutamate is favoured. It has been suggested[24] that the reaction may occur in two

* In a sequence of reactions, occurring *in vivo*, if one step is blocked, by addition of a specific inhibitor, the resulting increase in the concentrations of intermediates preceding the block may well prove toxic.

steps, in the first of which an imino acid is formed, and in the second, the imino acid is reduced by the cofactor (equations 13 and 14). The



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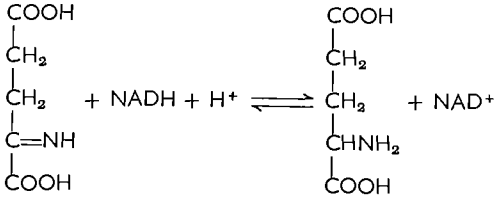


(14)

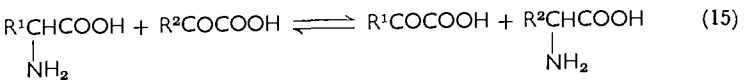
enzyme, which has been crystallised from beef liver, forms active protein aggregates (mol. wt. $\sim 10^6$) which can be dissociated (e.g. by dilution) to give four enzymically active subunits (mol. wt. $\sim 2{\cdot}5 \times 10^5$). The subunits can be further fragmented, by treatment with urea or dodecyl sulphate, to inactive units (mol. wt. $\sim 5 \times 10^4$)[25], suggesting that the enzymically active entities possess a number of polypeptide chains. The original aggregate may be held together by coordination to zinc[26]. The mechanism of catalysis remains obscure.

The biological importance of this enzyme has already been discussed (section II). Its role in producing glutamate, as the first organic amino compound, in bacteria and plants seems reasonably well established. In animals, which do not have the ability to produce all amino compounds from a simple nitrogen source, the enzyme seems to be concerned with the removal of excess amino compounds (equations 2–5) as well as with the production of glutamate for conversion to the acid amide (section V.B) or to take part in transamination reactions to form the non-essential amino compounds. Cellular control of the direction in which reaction occurs may well lie in the ratio of the concentrations of the oxidised and reduced forms of the cofactor. This ratio is not a fixed quantity but depends on the metabolic activity of the cell (NAD and NADP are cofactors for many oxidation–reduction reactions) as well as on the availability of molecular oxygen for the terminal step in respiration, by which the reduced cofactor is reoxidised by the cytochrome system (section IV.A.1).

C. Transamination

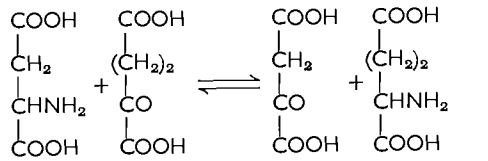
1. General

The enzyme-catalysed, reversible interchange of amino groups between carbon skeletons without the production of ammonia has been recognised since 1937 (equation 15). The actual number of



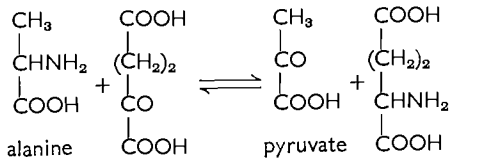
(15)

transaminases and the relevant specificities of these enzymes are still in dispute but indirect evidence suggests that many pairs of α-amino and α-keto acids can take part in transamination reactions. Only two transaminases have been purified to states approaching homogeneity and of these two, (catalysing reactions (16) and (17)) the glutamic–aspartic transaminase has been the subject of most mechanistic studies, partly because one of the substrates (oxaloacetic acid) can be relatively easily estimated. The enzymes catalysing reactions (16)



aspartate α-ketoglutarate oxaloacetate glutamate

(16)



alanine pyruvate

(17)

and (17) do not show absolute specificity for these particular substrates. For example, in equation (16), oxaloacetate can be replaced by α-ketomalonate, aspartate by cysteic acid ($HSO_3CH_2CH(NH_2)COOH$) or glutamate by α-methylglutamate. However, the activities observed with substrates other than the principal ones is too low to account for the production of α-amino acids other than aspartate and alanine by transamination between glutamate and α-keto acids. Indirect evidence for the existence of other transaminases comes from studies of the nutritional requirements of whole animals and mutants of some microorganisms, and from the effects of vitamin B_6 deficiency. The dietary nitrogen requirements of higher animals include certain so-called essential amino acids (listed in Table 2 for man and rat), but

TABLE 2. Essential amino acids.

Arginine[a]	Methionine
Histidine[a]	Phenylalanine
Isoleucine	Threonine
Leucine	Tryptophan
Lysine	Valine

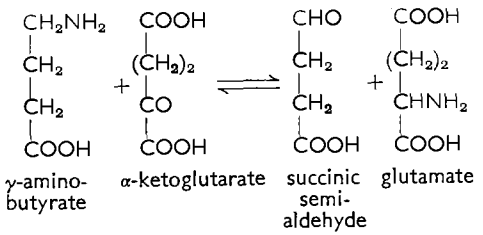
[a] Only in rat.

it has been shown[27] that young rats develop equally well if supplied with the α-keto analogues of at least five of these amino acids (leu, ileu, val, phe and met) together with glutamic acid. Since development of the animal depends on protein biosynthesis which, in turn, depends on the presence simultaneously of all twenty-odd amino acids, the implication is that transamination between glutamate and the dietary α-keto acids must occur rapidly. Organisms requiring certain amino acids do not, then, appear to lack the enzymes catalysing the introduction of the amino group to form these amino acids, but enzymes involved in forming the carbohydrate skeletons into which the amino group is incorporated. The synthesis of particular transaminases can be either induced or repressed in certain microorganisms. For example, if *Escherichia coli* is grown in a medium deficient in valine, the ability of this organism to transaminate between alanine and α-ketoisovalerate increases[28]. If, on the other hand, the growth medium is supplemented with tyrosine, the ability of *E. coli* to form tyrosine and phenylalanine from glutamate and *p*-hydroxyphenylpyruvate or pyruvate, decreases[29].

As will be seen later, enzymes catalysing a number of reactions of α-amino acids, including transamination, require a derivative of vitamin B_6 as cofactor. Vitamin B_6 deficiency in both rats and microorganisms causes, among other things, a decrease in the level of transaminase activity. For example, *Streptococcus faecalis* can grow in the presence of the α-keto acid analogues of normally essential α-amino acids, but when grown in a vitamin B_6 deficient medium, the ability to transaminate between glutamate and α-keto acids is lost. Transaminase activity can be restored by addition of a sufficient quantity of the cofactor.

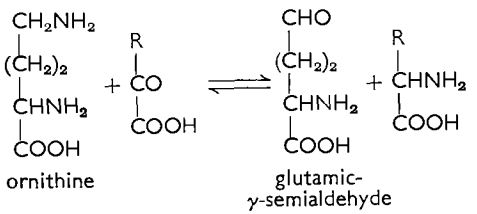
The transamination reaction represented by equation (15) involves the reversible transfer of α-amino groups. Although there are probably more enzymes catalysing this type of reaction, some transaminases catalysing ω-amino group transfer have also been partially identified. For example, the α-ketoglutarate—γ-aminobutyrate transaminase

localised in the mitochondria of the grey matter of brain[30] and also present in some microorganisms[31], catalyses the reaction given in equation (18). Transamination between ornithine and α-keto acids



(18)

(equation 19) has been demonstrated in liver and in *Neurospora crassa*, while an enzyme specific for the reaction between ornithine and α-ketoglutarate has been partially purified from rat liver mitochondria[32]. It may be noted that transamination reactions involving



(19)

glycine may be regarded as both α- and ω-amino group transfers. It is of interest that transamination between glyoxylate and α-amino acids occurs readily, even in the absence of enzyme catalysts[33].

In spite of the failure, to date, to isolate and adequately characterise more than two transaminases, both of which catalyse α-amino group transfer, it is now generally accepted that transamination plays an important part in amino acid metabolism.

2. Mechanism of transamination

The reactions of amino acids, catalysed by enzymes requiring a derivative of vitamin B_6 (Figure 5a) as cofactor, have been the subject of a number of mechanistic studies. Enzymes catalysing decarboxylation, racemisation, dehydration (of serine or threonine) or desulphydration (of cysteine) require pyridoxal-5′-phosphate as cofactor (Figure 5b), and are dealt with in later sections. Enzymes catalysing transamination, on the other hand, require either pyridoxal-5′-phosphate or pyridoxamine-5′-phosphate (Figure 5c). Snell and coworkers[33] showed that the reactions of amino acids normally

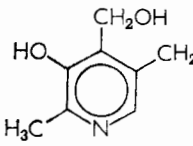


FIGURE 5a. Pyridoxine.

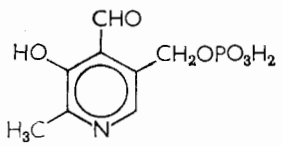


FIGURE 5b. Pyridoxal-5′-phosphate.

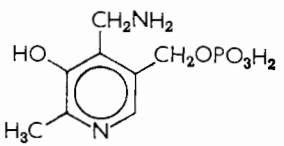


FIGURE 5c. Pyridoxamine-5′-phosphate.

catalysed by pyridoxal phosphate-dependent enzymes occurred in aqueous solutions at 100° in the presence of the non-phosphorylated cofactor and metal ions (e.g. Al^{3+}), the relative extents of decarboxylation, racemisation, transamination etc., depending on pH. The general theory put forward by Snell to account for the reactions occurring in the absence of enzymes is summarised in Figure 6. Metzler[34] later confirmed that imines are formed between pyridoxal and amino acids in aqueous solutions. No detailed analysis of the subsequent reactions of the imines was possible because of the complexity of the product mixture.

It has since been shown[35] that reversible, non-enzymic transamination occurs between pyridoxal and alanine and pyridoxamine and pyruvate in neutral, aqueous solutions, at 25° and in the absence of metal ions. (No evidence has yet been obtained for the presence of metal ions in purified mammalian transaminases.) Under these conditions, no decarboxylation or racemisation of the amino acid could be detected. From the results of kinetic and spectrophotometric studies in this simple model system for transamination it has been shown that imines are formed rapidly and reversibly between the two pairs of reactants and that tautomerisation of the two Schiff's base intermediates is rate limiting in the overall transamination reaction. The reaction scheme is given in Figure 7.

A more complete investigation has recently been made of a model system more relevant to the reaction given in equation (16). (The enzyme catalysing this reaction has proved the most amenable to purification and characterisation). The reactions between pyridoxal-5′-phosphate and glutamate or aspartate and between pyridoxamine-5′-phosphate and oxaloacetate or α-ketoglutarate have been studied individually. Transamination in these systems again occurs by rapid imine formation and slow isomerisation of two imine intermediates. The complete system is best described by the reaction scheme given in Figures 8a and b. Values have been assigned to the six equilibrium

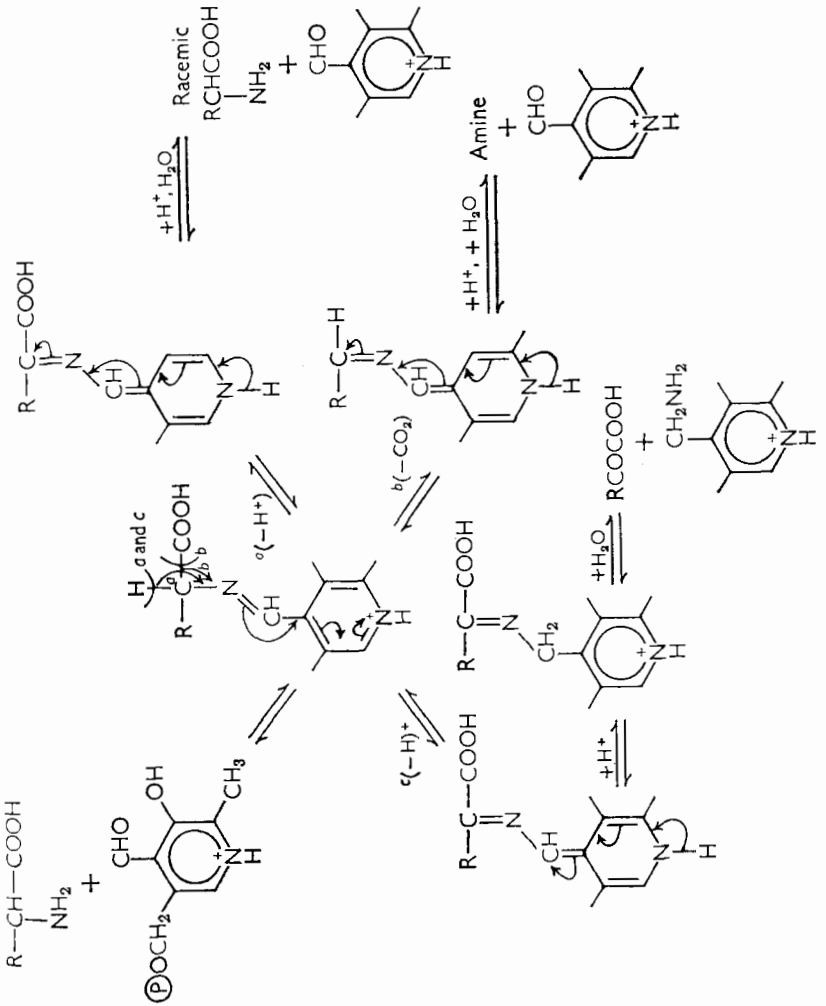


FIGURE 6. Mechanism of reactions catalysed by three pyridoxal phosphate-dependent classes of enzymes.

[a] Racemisation, [b] Decarboxylation, [c] Transamination

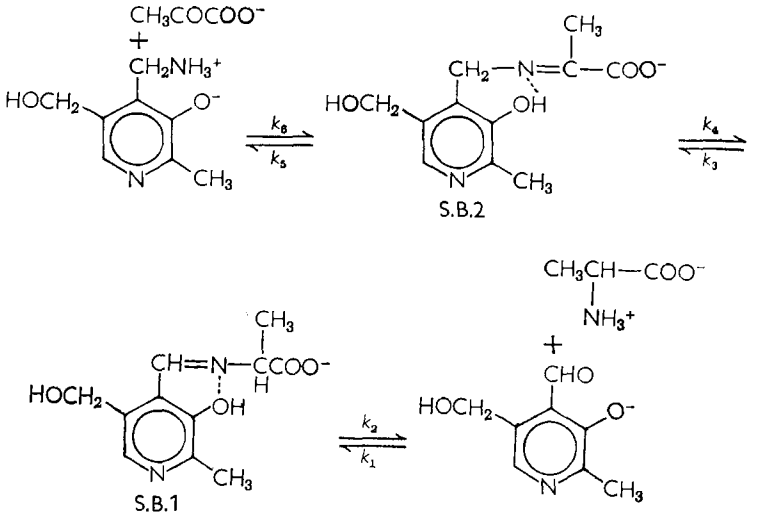


FIGURE 7.

constants associated with this scheme and also to some of the individual rate constants.

Evidence for the view that enzyme-catalysed transamination occurs be a sequence of reactions similar to that given in Figure 8b comes from a number of sources. Using modern methods for protein purification, a number of workers have obtained the soluble glutamic–aspartic transaminase of pig heart muscle in a state of homogeneity with respect to ultracentrifugation and free flow electrophoresis. The enzyme may be purified as the holoenzyme, the cofactor remaining associated with the protein throughout the purification, or as the apoenzyme, the cofactor being removed at an early stage in the purification. The activities of apoenzyme preparations tend to be 30–50% lower than those of holoenzyme preparations, suggesting that the enzyme is less stable in the absence of the cofactor. In order to study the recombination of the apoenzyme and the two forms of the cofactor, it is best to purify the holoenzyme and to remove the cofactor, as the final step, using the mild conditions described by Scardi[37].

There is little certainty about the nature of the link between the apoenzyme and either form of the cofactor. The 5′-phosphate group of the cofactor is probably involved since the non-phosphorylated pyridoxal and pyridoxamine are inactive. The binding is unlikely to be

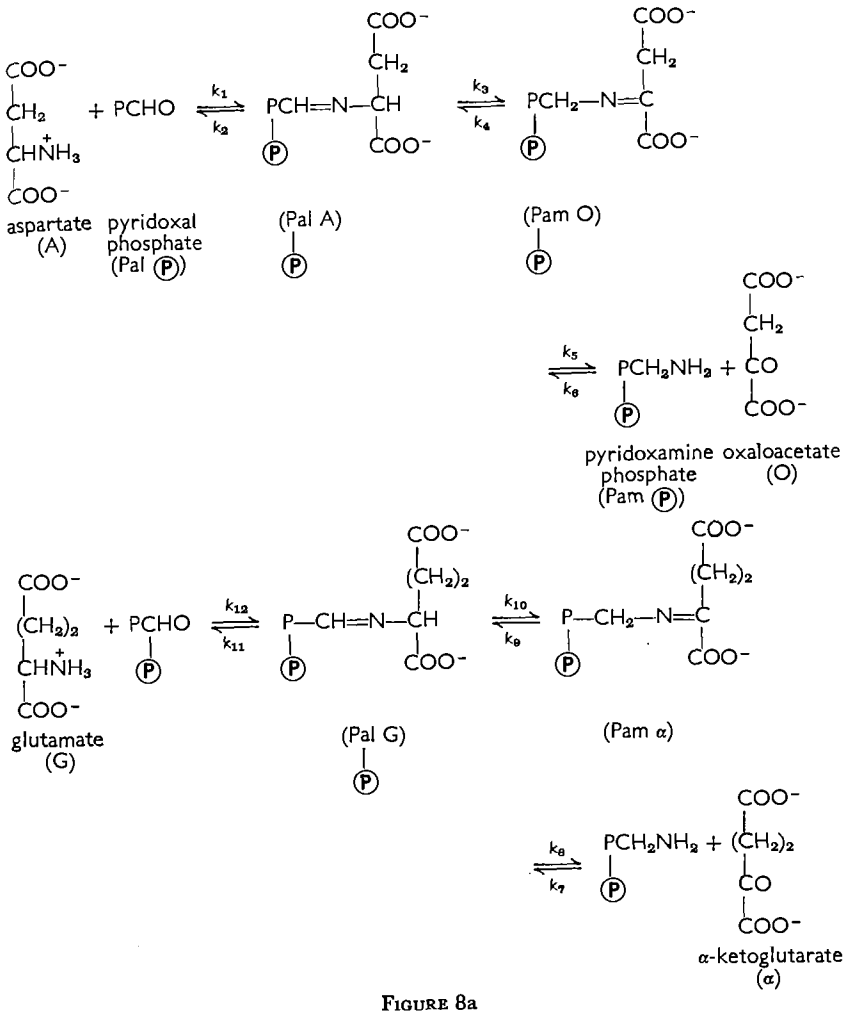


FIGURE 8a

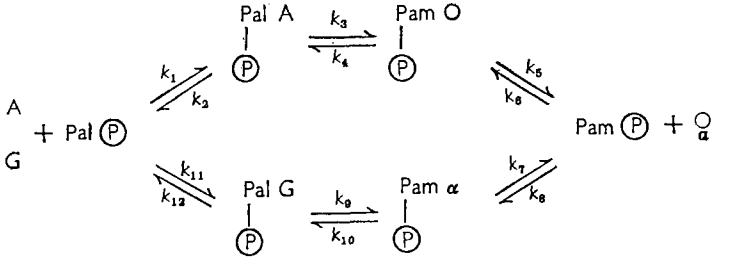
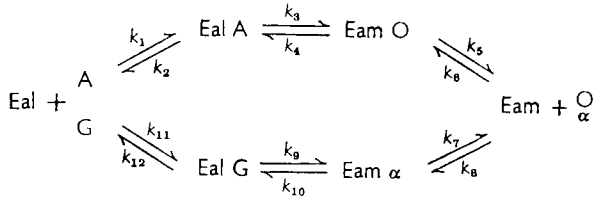


FIGURE 8b.

ionic since recombination of the apoenzyme and cofactors is relatively slow and the kinetics of the recombination are sufficiently complex to suggest that the initial association of protein and cofactor is followed by changes in the tertiary protein structure, to give maximum activity. Reduction of the holoenzyme with lithium borohydride, followed by hydrolysis of the protein and chromatographic analysis of the hydrolysate led to the identification of a lysine-bound pyridinium residue[36]. In consequence, it has been suggested that the aldehyde form of the cofactor is bound to the protein through an azomethine link to the ε-amino group of a lysine residue. If this were true then the first step in transamination would require displacement of the lysine by one of the amino acid substrates. The amine form of the cofactor could not be bound to the apoenzyme in the same way. It is known that the holoenzyme can pick up excess pyridoxal phosphate, with no increase in catalytic activity. This could well be due to non-specific imine formation with ε-amino groups of lysine residues in the protein.

The equal effectiveness of the amine and aldehyde forms of the cofactor, in reactivating the apoenzyme, is consistent with the scheme given in Figure 9. Indirect support for the proposed mechanism comes



E represents the enzyme. al represents the aldehyde form of the cofactor. am represents the amine form of the cofactor

FIGURE 9.

from the technique of Scardi and coworkers[37] for removing the cofactor from the holoenzyme. The method is based on conversion of the holoenzyme to the amine form by treatment with an excess of one of the amino acid substrates. Pyridoxamine-5′-phosphate is more readily lost from the protein than is pyridoxal-5′-phosphate. Interconversion of the amine and aldehyde forms of the holoenzyme in the presence of the appropriate α-keto or α-amino acid substrates has now been demonstrated spectrophotometrically[38, 39]. However, it should be remembered that, in all spectrophotometric studies, the concentrations of holoenzyme required are vastly in excess of the catalytic

quantities used in kinetic studies. Interpretation of data obtained using 10^{-3}M solutions of protein in terms of the mechanism of transamination in the presence of about 10^{-8}M protein solutions should be viewed with caution.

Attempts have been made to estimate the amounts of cofactor present in the catalytically active form of the enzyme. The main problem is that the methods available for such determinations usually require high protein concentrations. For example, in determining the molecular weight of a protein in an analytical ultracentrifuge, 0·3 to 1% protein solutions are required (i.e. 10^{-4}M for an average-sized protein). Many proteins (e.g. insulin and glutamic dehydrogenase) aggregate at this concentration. The literature value[40] for the molecular weight of glutamic–aspartic transaminase (110,000) is in error, the true value being ~80,000[42]. A recent, simple method of molecular weight assessment applicable to globular proteins, involves filtration through a molecular sieve (G-100 sephadex), and has been reviewed recently[41]. The virtue of this technique is that it can be used over a wide range of protein concentrations and so gives information about association phenomena. In the case of transaminase, the molecular weight, estimated by gel filtration, is ~77,000 and shows no variation in the concentration range 10^{-4}–10^{-8}M[42]. Repeated estimations of the amount of cofactor bound in the holoenzyme have given, consistently, one mole per 40,000 g protein[42].

It is well established that the glutamic–aspartic transaminase, while showing no concentration-dependent association phenomena, contains two moles of cofactor per mole of protein, molecular weight ~80,000. This may appear inconsistent with the proposed scheme, in which transamination is regarded as the sum of two independent half-reactions, since the presence of two cofactor molecules might seem to imply that a ternary mechanism (Figure 10) operates, the two half-reactions occurring simultaneously. However, evidence that the true equivalent weight of the transaminase is 40,000 rather than 80,000,

$$E + A \rightleftharpoons EA$$

$$EA + B \rightleftharpoons EAB \rightleftharpoons ECD$$

$$ECD \rightleftharpoons EC + D$$

$$EC \rightleftharpoons E + C$$

Either A and C or B and D are the two amino acid substrates and the two keto acid substrates.

FIGURE 10

has recently been obtained by a method of quantitative estimation of the *N*-terminal amino acid of the protein.

A considerable number of kinetic investigations of the reaction catalysed by pig heart glutamic–aspartic transaminase have been reported, the majority of which are based on ambiguous methods of measurement of reaction rates. Unambiguous assay conditions have now been established[43] and used in a recent and complete investigation[44]. The results are consistent with the binary mechanism (Figure 9) rather than the ternary mechanism (Figure 10). The equilibrium constants associated with all six steps have been evaluated. From conventional studies, for this type of system, of the way in which initial velocities of forward and reverse reactions depend on substrate concentrations, it is normally possible to obtain eight independently variable parameters, each of which is a function of some of the twelve individual rate constants. However, in this particular system, additional information can be obtained from the effects, on measured initial velocities, of deuterium substitution in the α-position of the amino acid substrates. It is possible to predict which of the eight parameters will be affected by deuterium substitution. The scheme in Figure 11

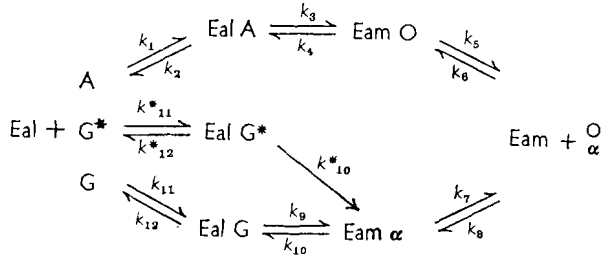


FIGURE 11.

illustrates the situation for transamination between oxaloacetate and α-deuteroglutamate. If, as is known to be the case in the model system, α-deuteration of the amino acids affects only the rate of the slowest steps in transamination, i.e. isomerisation of the Schiff's base intermediates, and not the fast steps, i.e. Schiff's base formation, only parameters containing k_{10} (k_{10}* for α-deuteroglutamate) will be affected in the presence of α-deuteroglutamate (and k_3 in the presence of α-deuteroaspartate). Using the results obtained with normal and α-deutero amino acid substrates, values have been assigned to k_3 and

k_9 (~ 400 sec^{-1}) and k_4 and k_{10} (~ 1000 sec^{-1}). Corresponding values in the model system are $k_3 = 1{\cdot}6 \times 10^{-6}$ sec^{-1}, $k_9 = 1{\cdot}75 \times 10^{-6}$ sec^{-1} and $k_{10} = 0{\cdot}82 \times 10^{-6}$ sec^{-1}. The presence of the enzyme therefore increases the rate of transamination by a factor of 10^8–10^9, which is some 10^3 times higher than the estimated figure quoted by Meister[24] in his recent review.

The above values of certain rate constants are at variance with those quoted by Hammes and Fasella[45]. These workers used the temperature-jump technique to determine the relaxation times associated with intermediates believed to be formed in the course of transamination, but the assignment of the observed phenomena to particular intermediates is somewhat arbitrary. The main source of error in applying this relatively new method to enzyme-catalysed reactions lies in the very high protein concentrations (greater than 10^{-5}M) required. It is quite possible that, under these conditions, enzyme–substrate complexes which do not lie on the normal reaction path may be present in significant amounts.

Enzymes catalysing transamination reactions are clearly of importance in controlling the distribution of amino groups in biological systems. From the mechanistic point of view, transamination is better understood than many other enzyme-catalysed reactions, largely because of the involvement of a well-defined cofactor. If, as seems reasonable, catalysis involves the cofactor directly, it is possible, as here, to design and study model systems from which the enzyme is absent. However, the mechanism of *catalysis* of transamination is as obscure as for other enzyme-catalysed reactions, but at least the magnitude of the problem is now well defined.

3. Formation of individual amino acids

It is clearly not possible to discuss here at any length, the metabolism of individual amino acids. In addition, the details of the biosynthesis and catabolism of amino acids, well reviewed in Volume II of Meister's recent book[46], are concerned more with the formation and breakdown of the carbon skeleton than with the introduction or loss of the amino group. Modifications of some of the twenty amino acids normally found in proteins have been detected in some protein hydrolysates, e.g. iodinated tyrosine, phosphoserine and hydroxylysine. In some cases the modification appears to be made before the amino acid is incorporated into protein (e.g. iodination of tyrosine) while in other cases modification is believed to occur when the amino acid is already present in proteins (e.g. hydroxylation of lysine, and in some cases, of

proline). In addition to these less common amino acid residues in proteins, many non-protein amino acids are known to exist, but the functions of these are, in general, obscure. None of the less common amino acids are considered here but reviews are available[47,48]. The suspected origins of the amino groups of the common α-L-amino acids are summarised in Table 3. Transamination, commonly from glutamate or aspartate, to α-keto acids is the final step in many cases. Apart from reductive aminations of the type discussed in section IV.B, in which ammonia is incorporated into α-keto acids, the main exceptions to terminal transamination are listed below:

TABLE 3. Origins of amino groups of the common α-L-amino acids.

Amino acid	Principal origin of NH_2	Type of reaction
Glutamic acid	NH_4^+	Reductive amination of α-keto acid
Aspartic acid	(a) Glutamate	Transamination
	(b) NH_4^+ ?	Direct amination of fumarate?
Alanine	(a) Glutamate	Transamination
	(b) Aspartate	β-Decarboxylation (bacteria)
	(c) NH_4^+ ?	Reductive amination of pyruvate (bacteria)
Glycine	(a) Glutamate	Transamination
	(b) Serine	Dehydroxymethylation
Serine	(a) Alanine	Transamination
	(b) Glycine	Hydroxymethylation
Cysteine	Serine	(a) Trans-sulphuration from homocysteine
		(b) Direct sulphuration (bacteria)
Methionine	Cysteine	See 3.3 c (iii)
	Homocysteine (NH_2 from asp.)	
Valine	Glutamate?	Transamination
Leucine	Glutamate	Transamination
i-Leucine	Glutamate?	Transamination
Phenylalanine	Glutamate	Transamination
Tyrosine	Glutamate	Transamination
Threonine	Aspartate	Reduction and isomerisation
Histidine	Glutamate	Transamination
Tryptophane	Serine	Conjugation with indole
Arginine		
α-NH_2	Ornithine	Krebs–Hensleit cycle
ω-NH_2	Aspartate, NH_4^+	
Ornithine		
α-NH_2	Glutamate	Reduction of ω-COOH
ω-NH_2	Glutamate	Transamination
	Alanine	
Citrulline		
α-NH_2	Ornithine	
ω-NH_2	NH_3	Krebs–Hensleit cycle
Lysine		
α-NH_2	Aspartate or glutamate	
δ-NH_2	Glutamate	Transamination

(i) The formation of histidine. The α-amino group of histidine is apparently introduced before the carboxylic acid group is formed. The proposed sequence of reactions, deduced from studies of mutants of *Escherichia coli* and *Neurospora crassa*, is illustrated in Figure 12. The enzyme catalysing transamination between glutamate and imidazolylacetol phosphate has been partly purified from *Neurospora crassa*[49] and shown not to be entirely specific for these substrates.

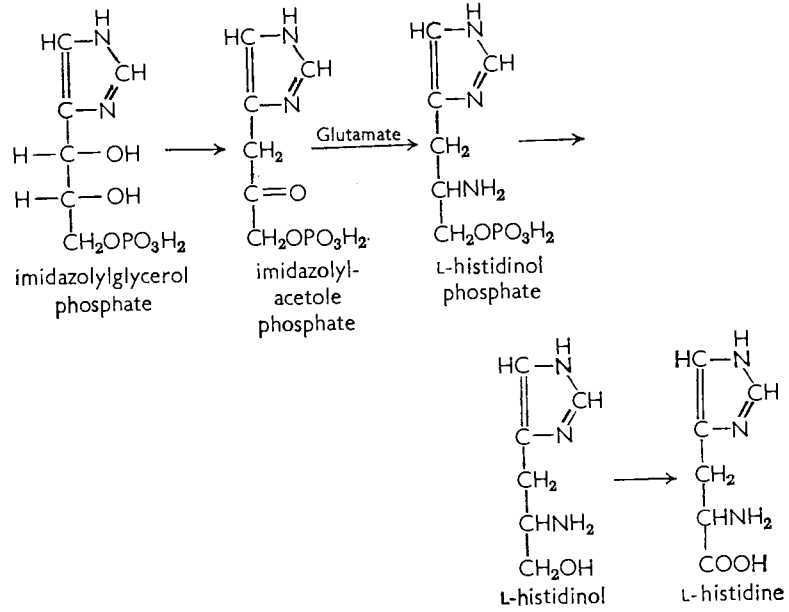
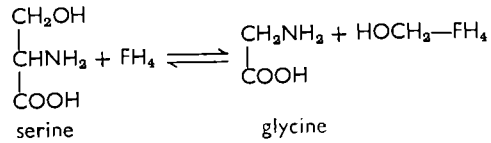


FIGURE 12. Formation of histidine from imidazolylglycerol phosphate.

(ii) Formation of serine and glycine from each other by transhydroxymethylation, mediated by tetrahydrofolic acid (FH_4) (Figure 13). The overall reaction is represented by equation (20).



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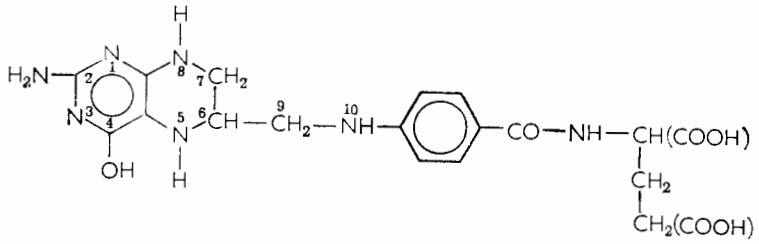


FIGURE 13. Tetrahydrofolic acid (FH_4).

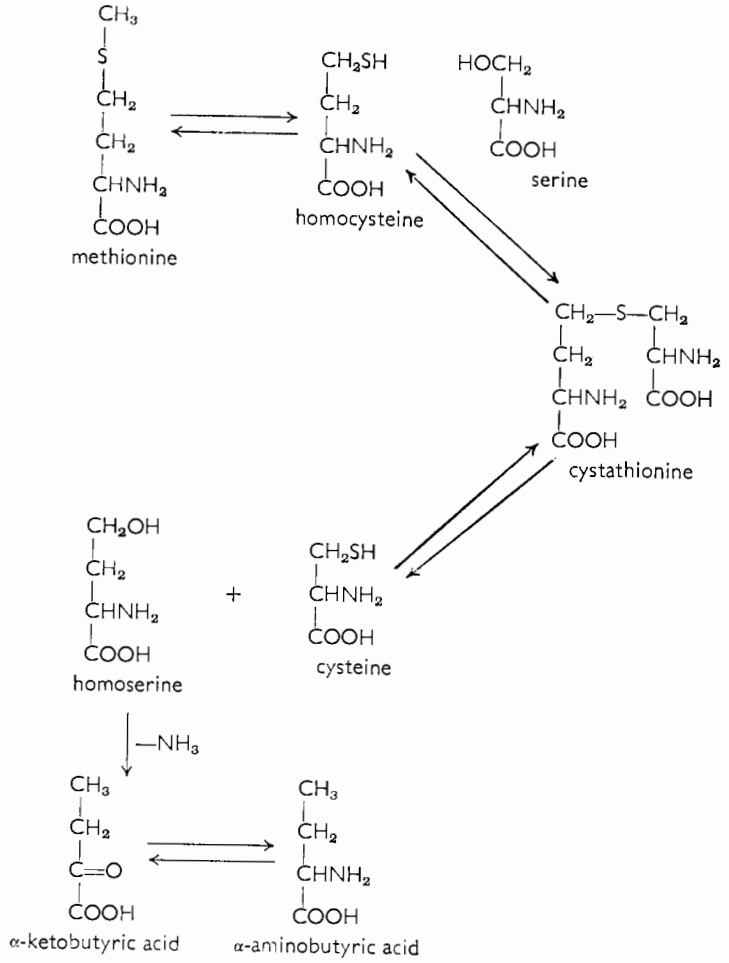
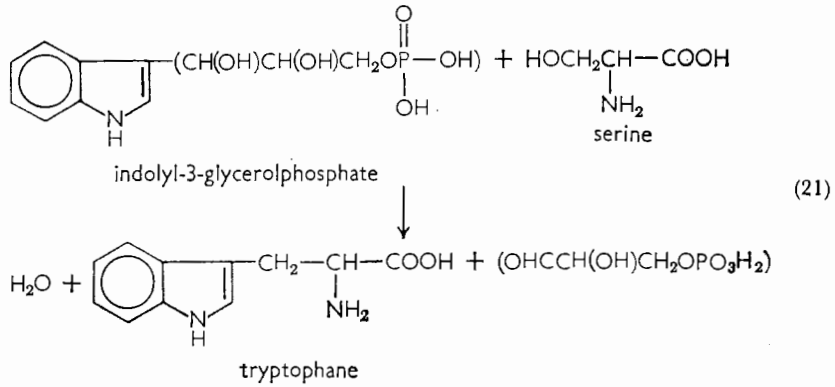


FIGURE 14. Interconversion of cysteine and methionine.

(iii) Formation of the sulphur-containing amino acids, cysteine and methionine, which are interconvertible by the reactions given in Figure 14.

(iv) Formation of tryptophane from serine and indole (or indolyl-3-glycerolphosphate) according to equation (21).



(21)

(v) Formation of threonine from aspartate summarised in Figure 15.

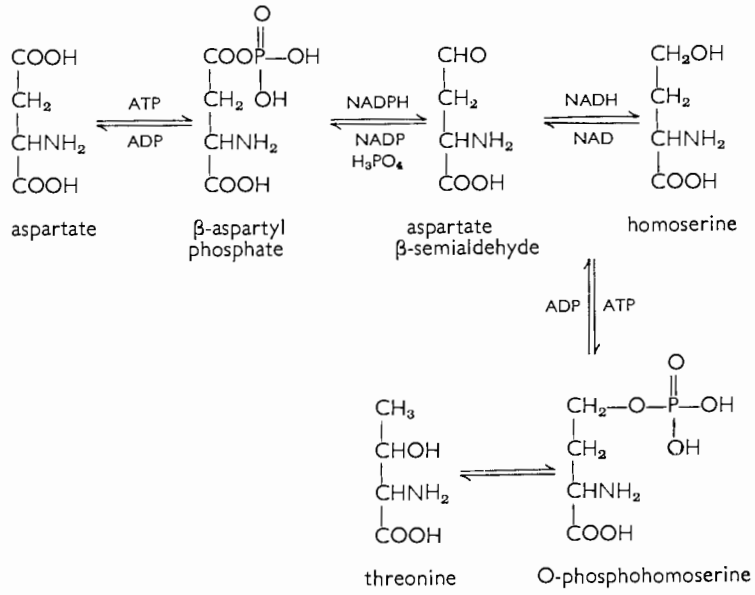


FIGURE 15. Formation of threonine from aspartate.

(iv) Formation of arginine, ornithine and citrulline, all of which are involved in the production of urea, which will be considered in section VI.B.

V. FORMATION OF AMINO COMPOUNDS OTHER THAN α-L-AMINO ACIDS

A. D-Amino Acids

In referring earlier to amino acids of the L configuration as the 'natural' amino acids, no account was taken of the known existence, in biological systems, of D-amino acids. There is no conclusive evidence for the occurrence of D-amino acids in the proteins of plants or higher animals but the possibility of their existence, in trace amounts, is hard to exclude. Total acid hydrolysis of proteins may result in racemisation of the amino acids. Hydrolysis catalysed by enzymes specific for peptide bonds between L-amino acids would be less ambiguous but very much more tedious and so the controversy on this subject remains unresolved[50,51]. It is now well established that peptide-linked, D-amino acids do occur, to a significant extent, in bacteria, particularly in association with the mucopeptide components of bacterial cell walls. In cell-wall hydrolysates of some bacteria 50 to 100% of particular amino acids (e.g. alanine, aspartate, glutamate in some lactic acid bacteria) may be of the D configuration[52]. The presence of the 'unnatural' isomers may well confer a biological advantage since one would predict that microorganisms so endowed would be resistant to attack by plant or mammalian peptidases which are specific for peptide links between L-amino acids. Destruction of bacteria by protease or peptidase action is one method by which bacterial infections are resisted naturally. A modern method of assisting the natural processes is based on the observation that some microorganisms produce antibiotics which are toxic to other microorganisms. Interestingly enough, a number of these antibiotics are polypeptides containing D-amino acids (e.g. Gramicidin-S, Figure 16). The toxicity of these therapeutic agents may be due to interference with cell-wall synthesis in those bacteria normally associated with D-amino acids.

The production of D-amino acids is clearly relevant in the metabolism of microorganisms. In plants and higher animals the main problem is not so much the production of D-amino acids but the removal or utilisation of the 'unnatural' isomers, inevitably present because of the

ubiquity of microorganisms. It is known from nutritional studies that some of the essential L-amino acids can be replaced in the diet by the D-isomers (e.g. methionine and phenylalanine in man[53]) without ill effects, implying that a route exists for inversion of amino acid configuration. (The low concentration of free amino acids, of either configuration, in the waste products of animals also leads to the conclusion that animals have some mechanism for destroying D-amino acids).

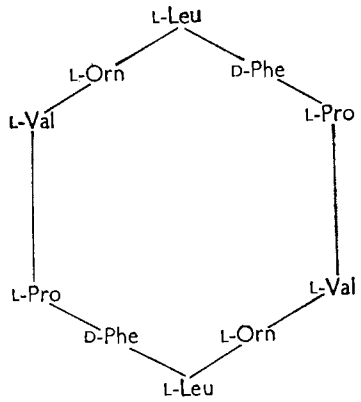


FIGURE 16. Gramicidin—S.

The two types of reaction by which D-amino acids may be formed *in vivo* are dealt with in this section. The mechanisms by which D-amino acids are incorporated into cell-wall mucopeptides and bacterial antibiotics are not well understood but will be mentioned briefly in section V.E.

1. Racemisation

Enzymes catalysing the racemisation of some amino acids have been partly purified only from bacterial sources (e.g. alanine racemase from *Streptococcus faecalis*, methionine racemase from strains of *Pseudomonas*[54]). No direct evidence for their existence in animals is available.

Pyridoxal is known to catalyse racemisation of amino acids in the model systems studied by Snell and coworkers[33] but the evidence for involvement of pyridoxal-5'-phosphate in the enzyme-catalysed reaction is indirect. Nutritional studies on *S. faecalis*[55] have shown that this microorganism has a growth requirement for D-alanine, and that

neither L-alanine nor the α-keto analogue, pyruvate, can replace D-alanine. The vitamin B_6 content of these microorganisms is low. Purified glutamic acid racemase from *Lactobacillus arabinosus*[56] is reported to be inhibited by hydroxylamine, consistent with involvement of an aldehyde group, but there are conflicting reports on activation of the enzyme by added pyridoxal-5′-phosphate[24]. In no case has a racemase been shown, *in vitro*, to require pyridoxal-5′-phosphate as a cofactor.

A possible mechanism of racemisation, in the model system, is included in Figure 6. Some doubt is cast on the exact relevance of this scheme, to the enzyme-catalysed reaction, by recent reports that a reduced flavin cofactor may also be involved[57]. Enzyme-catalysed racemisation is not considered to be of great importance in the metabolism of D-amino acids.

2. D-Amino acid oxidase

Enzymes catalysing the oxidative deamination of D-amino acids are widespread (microorganisms, mammalian liver and kidney etc.). The overall reaction, given in equation (22) is alleged[24] to occur in two

$$RCH(NH_2)COOH + \tfrac{1}{2}O_2 \rightleftharpoons RCOCOOH + NH_3 \qquad (22)$$

steps, through an imine intermediate, but no imine has so far been identified. There is an apparent analogy with the reverse of reductive amination as catalysed by glutamic dehydrogenase (section IV.B) but there is also an important difference. The amino acid oxidases are all flavoproteins, the flavin cofactor being most commonly FAD (Figure 2c and d), and no pyridine nucleotide cofactor is involved. Reoxidation of the reduced flavoprotein (see Figure 3) by molecular oxygen produces hydrogen peroxide which is, in turn, destroyed by the exceptionally efficient enzyme catalase. Equations (23–26) summarise

$$RCH(NH_2)COOH + FAD \rightleftharpoons RC(=NH)COOH + FADH_2 \qquad (23)$$

$$RC(=NH)COOH + H_2O \rightleftharpoons RC(=O)COOH + NH_3 \qquad (24)$$

$$FADH_2 + O_2 \rightleftharpoons FAD + H_2O_2 \qquad (25)$$

$$H_2O_2 \longrightarrow H_2O + \tfrac{1}{2}O_2 \qquad (26)$$

the reactions involved. In the absence of molecular oxygen, that is, under anaerobic conditions, reactions (25) and (26) cannot occur[58]. The reduced flavoprotein resulting by reactions (23) and (24) from one D-amino acid can then be used to catalyse reductive amination of α-keto acids to form other D-amino acids.

There is no certain evidence for the existence of specific D-amino

acid oxidases. The highly purified, crystalline enzyme[58,59] from hog or sheep kidney oxidises most D-amino acids, attacking tyrosine, proline and methionine more rapidly than other substrates[60,61].

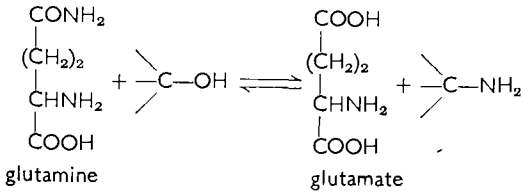
The enzyme forms complexes with benzoic acid, which are more resistant to denaturation than is the native protein. Use is made of this fact in purifying the enzyme. This particular flavoprotein is relatively easily resolved (e.g. by dialysis[62] or dilution[61]) into apoenzyme and FAD. Reported estimates of the size and composition of the active enzyme are at variance, partly because the protein tends to polymerise. The values given by Massey[58] (mol. wt. 182,000, 4 FAD/mole) and by Yagi[63] (mol. wt. 115,000, 2 FAD/mole) are based on ultracentrifuge data and spectrophotometric estimation of FAD concentrations. The apparent discrepancy is discussed by Charlwood[64] in terms of the effects, on sedimentation constants, of changes in shape as well as in size. The most recent value of the minimum molecular weight, quoted by Dixon[61], is 54,000 g/mole FAD. This estimate is based on a polarographic study of the resolution of the holoenzyme on dilution.

Inhibition of the enzyme by reagents combining with sulphydryl groups is consistent with the involvement of a sulphydryl group in the active site of the protein. The rate of inhibition by one of these reagents (*p*-chloromercuribenzoate) has recently been shown[61] to be the same as the rate of loss of FAD from the holoenzyme. The susceptible sulphydryl group may, therefore, be concerned only with binding the cofactor to the protein and not with the mechanism of action of the enzyme. The kinetics of action of the enzyme and inhibition of activity by straight-chain fatty acids has led Dixon[61] to propose that substrates are bound to the holoenzyme by the carboxylic acid group and up to five carbons of the amino acid side-chain. Little can be concluded with safety from spectrophotometric studies because these require very high protein concentrations, (see section IV.C), but some such studies have been reported. The holoenzyme is normally yellow but addition of amino acid substrates, under anaerobic conditions, causes a shift in the absorption maximum, a red-coloured intermediate being formed.

No firm conclusions can be drawn so far concerning the mechanism of action of this enzyme, in spite of its availability in crystalline form and its apparent importance in the metabolism of D-amino acids. The reactions catalysed by D-amino acid oxidase probably account for the production of D-amino acids by microorganisms and also for the removal of D-amino acids from higher animals.

B. L-Amino Acid Amides

This book is not concerned with the behaviour of acid amides but brief mention must be made in this section of two naturally occurring amides of L-amino acids, glutamine and asparagine, both of which occur in proteins. Glutamine is of particular importance because of its involvement in many metabolic processes of the type given in equation (27), where the carbon to which the hydroxyl group is



glutamine glutamate (27)

attached may be part of the ring of a sugar, a purine or a pyrimidine. This is an over-simplification of the situation since a phosphate ester, adenosine triphosphate (ATP, Figure 17) is also commonly involved

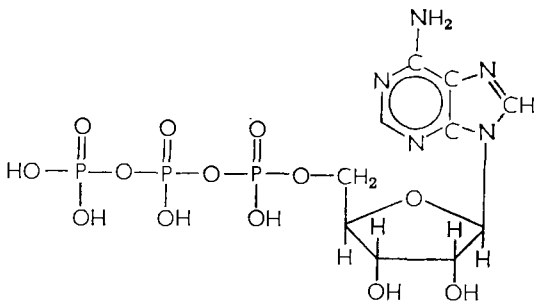
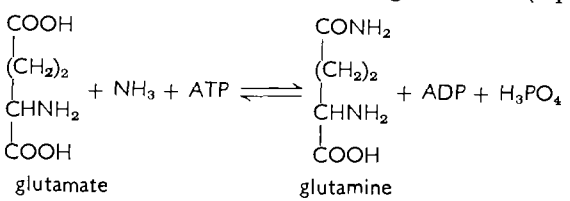


FIGURE 17. Adenosine triphosphate (ATP).

in this type of reaction. The same ester is also involved in the sequence of reactions leading to the formation of glutamine (equation 28).



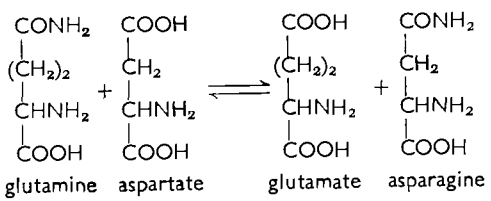
glutamate glutamine (28)

Glutamine synthetase, the enzyme catalysing this reaction, has been purified from sheep brain[65]. The possible mechanism of its action has been reviewed by Meister[24], but none of the intermediate steps,

proposed on the basis of isotope effects, substrate specificity or catalysis of possible intermediate reactions, have been confirmed. The apparent coupling of synthetic reactions with the formation of ADP and inorganic phosphate from ATP has long been recognised and gave rise to the curious myth that 'energy', derived from catabolic reactions, was somehow stored in ATP. Subsequent hydrolysis of ATP was then thought to release the stored 'energy' which could then be used to drive anabolic processes. It is now abundantly clear[66] that the one reaction which must not occur, if there is to be a link between degradative and synthetic processes, is the hydrolysis of ATP. Metabolic reactions involving ATP and other phosphate esters appear now to occur by transphosphorylation, and the coupling of metabolic processes is best discussed in terms of the presence of enzymes catalysing phosphate group transfer reactions. Enzymes catalysing the hydrolytic reactions are localised, within cells, in regions of low metabolic activity (e.g. in association with cell membranes, and the structural protein of muscle). Synthesis of glutamine may well involve the formation of a phosphorylated derivative of glutamate. The failure to identify such an intermediate may be explained if the phosphorylated intermediate is not released from the surface of the enzyme.

The presence of glutamine synthetase in mammalian brain is interesting in view of the account already given (section II) of differences between animals and microorganisms in their tolerance of ammonia. Since ammonia is toxic to higher animals, apparently acting on the central nervous system, the presence of glutamine synthetase in central nervous tissue confers a two-fold advantage. Firstly, given an adequate supply of glutamic acid, ammonia can be converted to and stored as glutamine, which is non-toxic, and secondly, the glutamine so formed can replace ammonia as a source of amino groups.

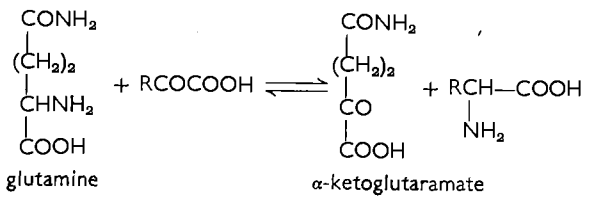
The function of asparagine is obscure. It can be identified in most living tissues and occurs at high concentrations in some higher plants in which it may replace glutamine as a non-toxic source of available nitrogen. Asparagine and glutamine are interconvertible by transamidation (equation 29). Direct formation of asparagine from ammonia



glutamine aspartate glutamate asparagine (29)

and aspartate may occur by a reaction analogous to that given for glutamine (equation 28) but a recent report suggests that the products of ATP cleavage may in this case be AMP and inorganic pyrophosphate[67].

Glutamine (and probably asparagine) can be destroyed by two independent routes. The enzyme catalysing direct deamidation to glutamate is activated by phosphate, suggesting a mechanism related to that of glutamine synthetase. The second path involves transamination (equation 30) and subsequent deamidation (equation 31) of α-ketoglutaramic acid. The two reactions are catalysed by separate enzymes[68].



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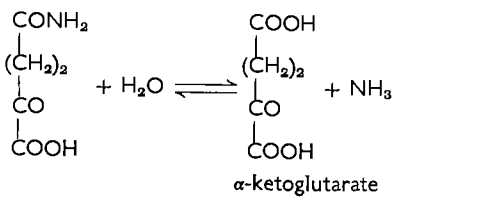


(31)

C. Amines

1. General

The importance of amines in biological systems is undoubted, but they are the hardest to discuss under the heading of this chapter. One reason for this is that different life forms show remarkable differences in relation both to the formation and function of amines. In general, the words 'amine' and 'detoxication' are closely linked in the minds of most biochemists, implying that amines are undesirable metabolites which should be removed forthwith. Putrefaction of organic matter (spoilage of foodstuffs) is largely due to the formation of amines with familiar, offensive smells. The agents primarily responsible for this type of amine formation are microorganisms which contain a range of enzymes catalysing the decarboxylation of amino acids. The toxicity to mammals of amines produced by bacterial decay may be due to effects on blood pressure. Certain amines found normally in mammals

(carried in the blood stream and so classified as *hormones*) are known, among other actions, to affect indirectly the size of certain blood vessels, causing them to constrict (vasopressors) or expand (vasodilators), so increasing or decreasing arterial blood pressure. The specific effects of particular amines depend on the site of action and on the level of concentration so no general statement can be made about their mode of action. In addition, in common with most biological control systems, other factors are involved in the overall control of blood pressure and all the types of control are interdependent.

It appears, from the preceeding paragraph, that in mammals as well as in bacteria there must be a mechanism for the production of at least some amines. The route is now known to be formally the same as that in bacteria, i.e. decarboxylation of amino acids, but a distinction must be made between the bacterial and mammalian enzymes, not only on the grounds of differences in the physiological function of the products, but also because of differences in the substrate specificities of enzymes from the two sources.

Plants can use urea and a variety of relatively simple amines as a source of nitrogen. The first step in the metabolism of amines is probably oxidation to the corresponding aldehyde and ammonia (see section V.A). The amines occurring naturally in plants include methylamine, isoamylamine and other volatile amines, which are found in some flowering species. The route to these amines is not thought to involve decarboxylation of amino acids, but little is yet known with certainty about the metabolism of amines in plants. Glutamic decarboxylase activity has been detected in a wide variety of higher plants, consistent with the widespread distribution of the product of decarboxylation, γ-aminobutyric acid.

2. Mechanism of α-decarboxylation

A number of enzymes catalysing decarboxylation of amino acids, and showing substrate specificity, have been isolated from bacteria and well characterised[69,70]. In all cases, pyridoxal phosphate was found to be a cofactor. The mammalian decarboxylases are less well characterised but in common with the plant glutamic decarboxylase they also require pyridoxal phosphate for activity. The possible mechanism of decarboxylation is illustrated in Figure 18[71]. Data obtained by Mandeles and coworkers[72] on the decarboxylation of α-amino acids in D_2O are consistent with this mechanism, the product amine containing only one deuterium atom attached to the α-carbon of the substrate. An earlier proposal, that loss of hydrogen from the

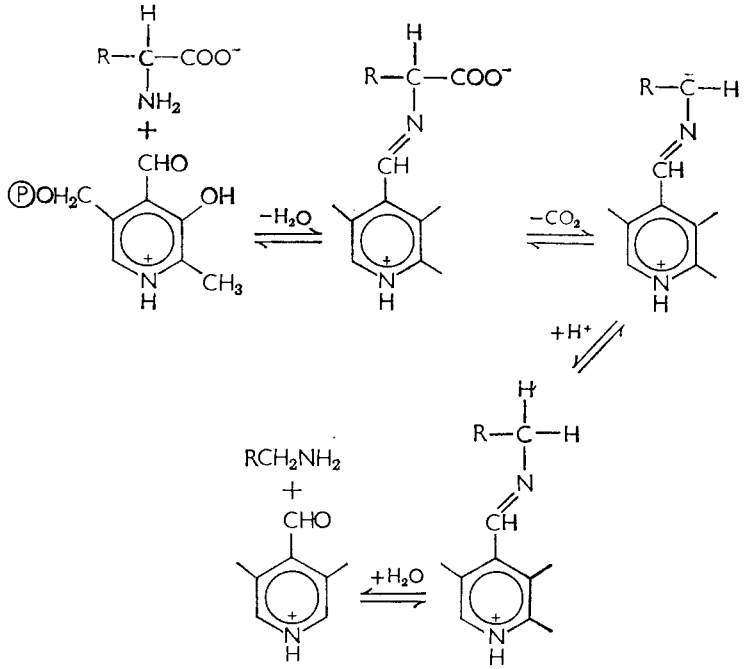
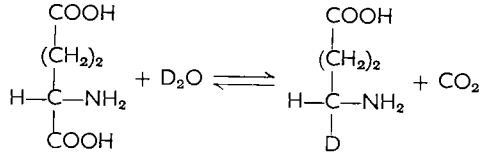


FIGURE 18. Mechanism of α-decarboxylation of amino acids.

α-carbon of the substrate preceeded decarboxylation, is disproved by this experiment, since such a mechanism would require that two deuterium atoms be incorporated into the amine from the solvent. The amine produced by enzyme-catalysed decarboxylation of L-glutamic acid in D_2O is asymmetric about the α-carbon atom (equation 32).



(32)

The enantiomorph of this deuteroamine, prepared by decarboxylation of α-deuteroglutamate in water, does not exchange deuterium with the solvent, under the same conditions. (α-Deuteroglutamate is prepared by enzyme-catalysed racemisation of D- or L-glutamate in deuterium oxide). Additional support for the stereospecificity of enzyme-catalysed decarboxylation of amino acids comes from experiments in which tyrosine was decarboxylated in D_2O to give R-α-

deuterotyramine and α-deuterotyrosine was decarboxylated in H_2O to give S-α-deuterotyramine. The configurations of the products were assigned by comparison of the rates of enzyme-catalysed oxidation (also stereospecific, see section VI.A) of the two isomers with those for oxidation of isomers prepared by unambiguous synthesis[73].

3. Distribution and specificity of α-decarboxylases

Decarboxylases isolated from bacteria act on the amino acids listed in Table 4. Each enzyme appears to be substrate specific and the

TABLE 4. Common amino acids decarboxylated by microorganisms.

Amino acid	Product
Arginine	Agmatine
Aspartic acid	L-Alanine or β-alanine
Cysteic acid	Taurine
Glutamic acid	γ-Aminobutyric acid
Histidine	Histamine
i-Leucine	(2-Methyl)butylamine
Leucine	(3-Methyl)butylamine
Lysine	Cadaverine
Ornithine	Putrescine
Phenylalanine	(2-Phenyl)ethylamine
Tyrosine	Tyramine
Valine	(2-Methyl)propylamine

substrates are in general those found in protein hydrolysates. There is so far no conclusive evidence for decarboxylation of such common amino acids as glycine, serine, alanine, threonine, proline or hydroxyproline, the sulphur-containing acids or the common acid amides.

In animals, decarboxylation of glutamic acid, histidine, tyrosine, phenylalanine and tryptophane and hydroxy derivatives of the aromatic amino acids is reasonably well established. The enzymes catalysing decarboxylation of glutamic acid and of histidine are substrate specific but there is no certain evidence for the existence of specific aromatic amino acid decarboxylases.

a. *Glutamic decarboxylase.* The activity of this enzymye has been demonstrated in the brain[74]. The decarboxylation product (γ-aminobutyric acid) is known to reduce the excitability of nerve cells and has been tentatively identified as the central nervous inhibitor in lobster brain[75], and as the peripheral inhibitor in crustacean muscle.

b. *Histidine decarboxylase.* This catalyses the formation of histamine which is liberated when cells are damaged and which has powerful physiological effects. Although histamine causes contraction of the smooth muscle present in the walls of large blood vessels and one would predict a consequent rise in blood pressure, it also causes dilation of the minute peripheral blood capillaries. The overall affect of administration of histamine is a fall in blood pressure with attendant side effects. The enzyme is present in special components of the blood called mast cells.

c. *The aromatic amino acid decarboxylase.* This catalyses a number of reactions leading to physiologically important amines. Some of these reactions are given in Figures 19a and b. The enzyme has been partly purified from pig kidney[76] and identified in liver[77]. It shows a constant ratio of activities, with respect to decarboxylation of tyrosine, tryptophane and phenylalanine, 3,4-dihydroxyphenylalanine and 5-hydroxytryptophane, up to one hundred-fold purification. Histidine is also decarboxylated by the same enzyme but not as efficiently as by the specific histidine decarboxylase of mast cells.

The specific action of serotonin, the amine produced by decarboxylation of 5-hydroxytryptophane, in stimulating cerebral activity, suggests that a specific decarboxylase for this substrate may be present in brain tissue. The amine itself cannot pass the so-called blood–brain barrier, so must be formed *in situ.* A deficiency of serotonin results in mental depression. The serotonin produced by the kidney decarboxylase and carried in the blood may be concerned with control of blood pressure since it is a powerful vasoconstrictor. The two amines tyramine and tryptamine are both vasopressors.

Norepinephrine, (Figure 19a) and its *N*-methyl derivative epinephrine (adrenalin) are examples of so-called 'chemical transmitters' which are substances released at the end of nerve fibres in response to electrical impulses passing down the fibres. (Electrical impulses, at any rate in the peripheral nervous system, pass down nerves by transverse migration of ions across the nerve membrane.) Their function is to excite neighbouring cells. Where the neighbouring cell is another nerve cell, the junction is called a *synapse*; where the neighbouring cell is a muscle cell, a *neuro-muscular junction* is said to be formed. Norepinephrine and epinephrine are the transmitters at most of the endings of nerve fibres belonging to the sympathetic system affecting smooth and cardiac muscle and glands and, as such, have diverse physiological effects, e.g. increase in rate and force of heart beat, dilation of the bronchi, constriction of peripheral vessels etc. In addition, the same

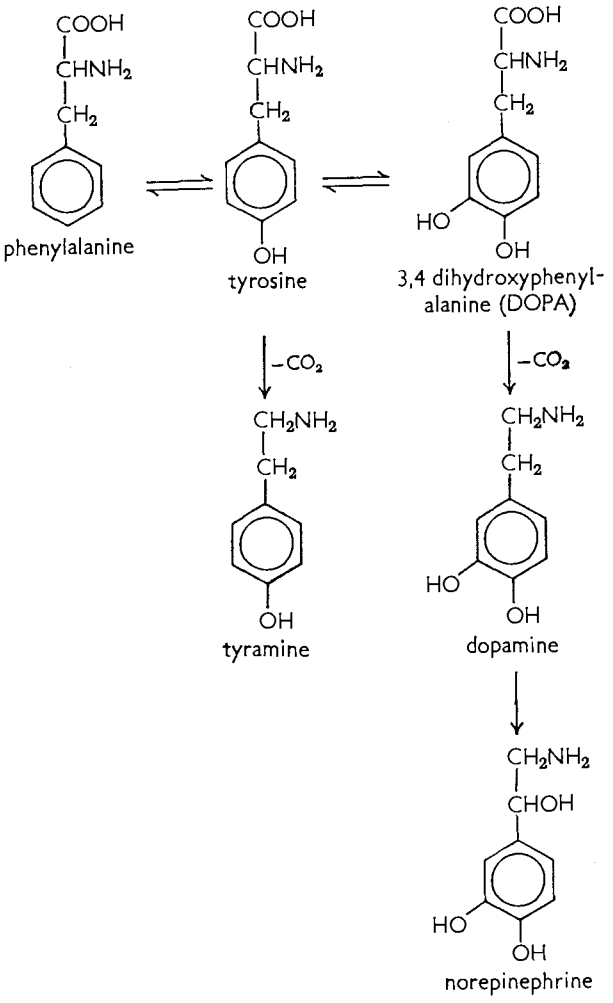


FIGURE 19a.

two substances are produced in the medullary cells of the adrenal glands, again in response to nervous stimulation, and are carried in the blood stream (hence the classification as hormones) to sites at which they reinforce the effect of direct nervous stimulation of effector organs. Epinephrine also affects carbohydrate metabolism in the liver. It is possible that both these substances are also central

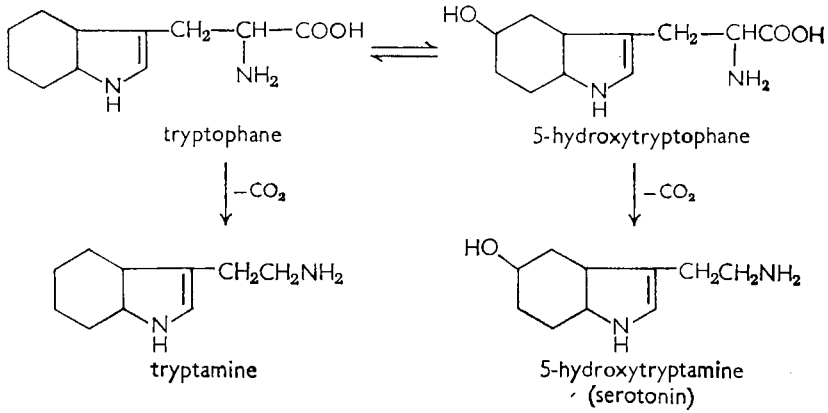


FIGURE 19b.

nervous transmitters but the role of chemical transmitters in the central nervous system is by no means as well elucidated as it is at peripheral junctions.

d. *Decarboxylation of serine.* It was stated at the beginning of this section that there is no conclusive evidence for the existence of a decarboxylase acting on serine. However, the product of decarboxylation of this amino acid, ethanolamine, is well known to occur naturally, in particular in association with phospholipid material. The cephalins are derivatives of phosphatidic acid (Figure 20) in which the phosphate

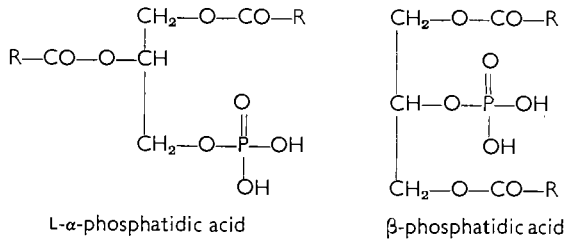


FIGURE 20.

group is esterified with ethanolamine. The lecithins have the same general structure as the cephalins but the phosphate group is esterified with choline in place of ethanolamine. Choline, a quaternary nitrogen

base, is itself derived from ethanolamine, and the acetyl derivative of choline is independently important because it is the chemical transmitter involved in synaptic transmission of nerve impulses in both the sympathetic and parasympathetic systems, and is the post ganglionic transmitter for parasympathetic nerves and for some sympathetic nerves. It is also the transmitter at the neuro-muscular junction of the somatic (voluntary) system. Acetylcholine acts at those junctions outside the central nervous system which do not respond to epinephrine or norepinephrine.

Recent work in the general field of lipid biochemistry has revealed that although the carbon skeleton of serine is extensively used in the biosynthesis of ethanolamine (and hence choline and acetylcholine), decarboxylation of free serine does not occur[78,79], nor is the ethanolamine formed from serine found free. It appears that the hydroxyl group of serine is first esterified with phosphatidic acid by reaction with cytidine diphosphate diglyceride (Figure 21). Phosphatidyl

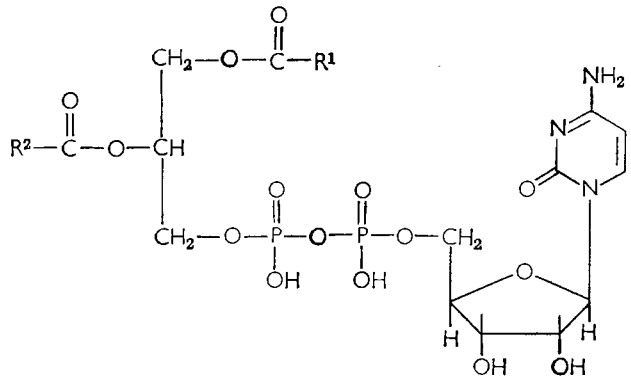


FIGURE 21. Cytidine diphosphate diglyceride.

serine is then decarboxylated[80,81] to phosphatidyl ethanolamine, methylation of which produces phosphatidyl choline (a lecithin) and choline is eventually released by enzyme-catalysed hydrolysis. The reactions are summarised in Figure 22, with the steps involved in reconversion of choline to serine through a betaine which is successively demethylated to glycine and the glycine hydroxymethylated to serine.

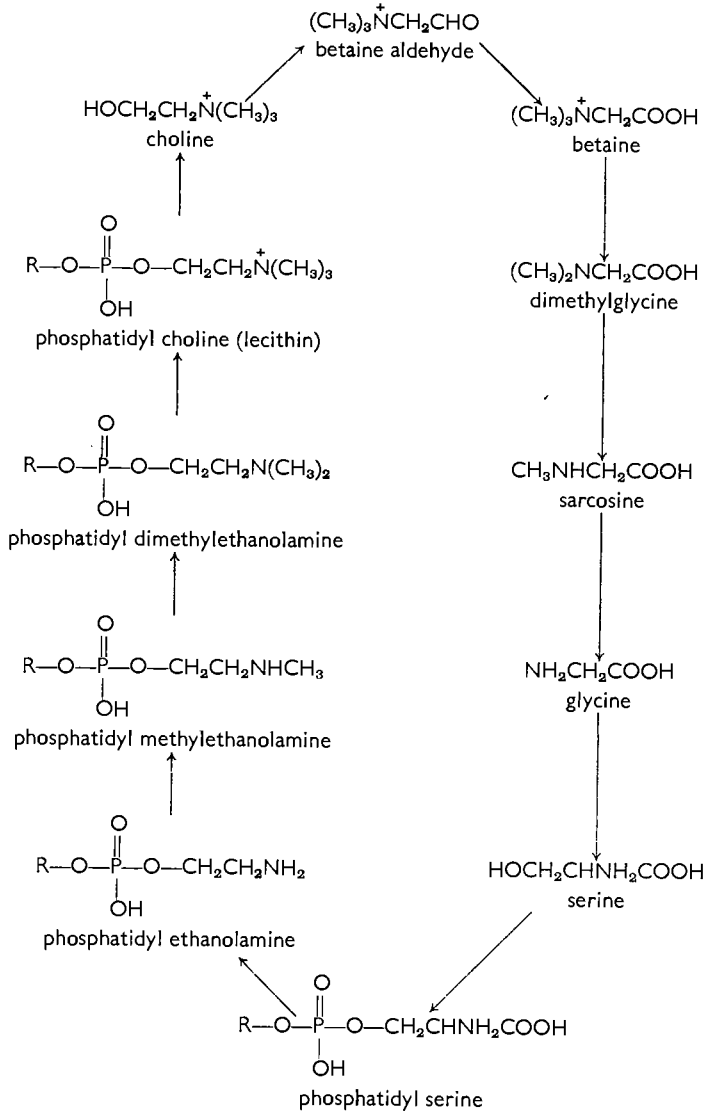


FIGURE 22. Interconversion of serine and choline.

D. Purines and Pyrimidines

1. General

The purine and pyrimidine nucleotides, which are the basic units of the macromolecular nucleic acids, are as important to the functioning of living organisms as are the amino acids. The relevance of these compounds to the present discussion is two-fold. Firstly, three of the five most common nucleotides have amino substituents in the purine or pyrimidine rings (Figure 23), the amino groups coming from the amide group of glutamine or possibly from ammonia, and secondly, the nitrogen atoms of the heterocyclic purine and pyrimidine bases originate variously from aspartate, ammonia (in the form of carbamyl phosphate, see section VI.B) and again the amide group of glutamine. Much information was obtained, in the years 1950–59, concerning the biosynthetic routes to the nucleotides, largely from the results of isotope studies. The fact that purines and pyrimidines are not essential constituents of the diet and, moreover, that dietary purines and pyrimidines are not, in general, incorporated into tissue nucleic acids, suggests immediately that biosynthesis of these compounds may not occur through the free bases. It is now well established that the two types of hetero rings are made at the nucleotide level. Both purine nucleotides originate in inosinic acid, the nucleotide of 6-hydroxypurine, and the pyrimidines originate in uridine-5′-phosphate, a nucleotide of 2,6-dihydroxypyrimidine.

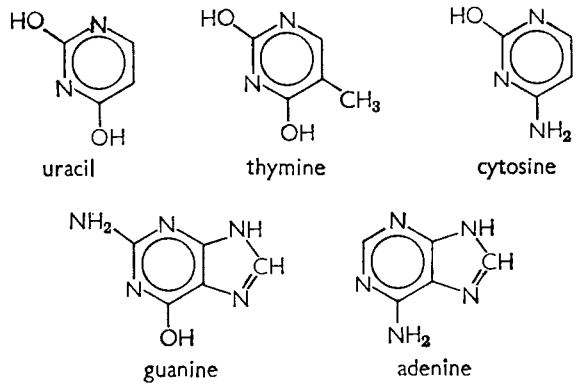
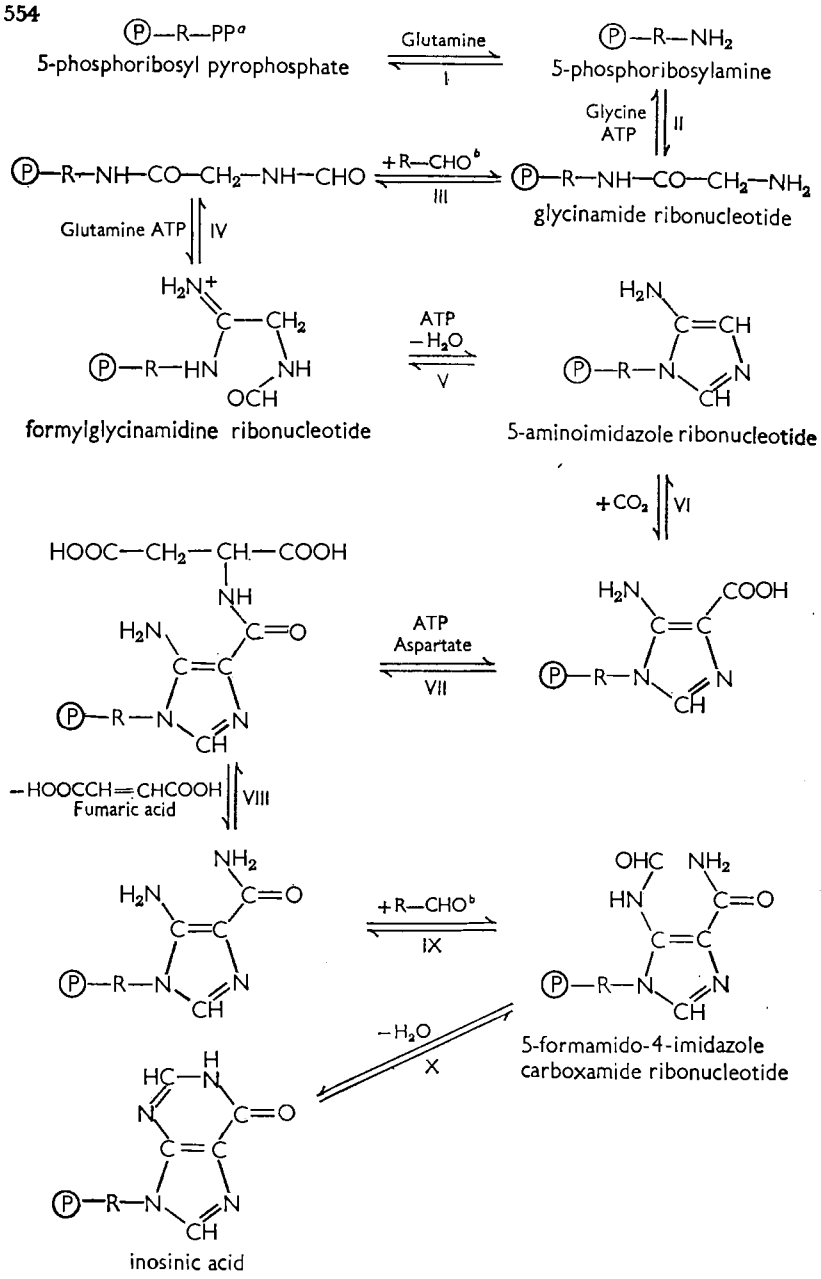


FIGURE 23. Common purine and pyrimidine bases.

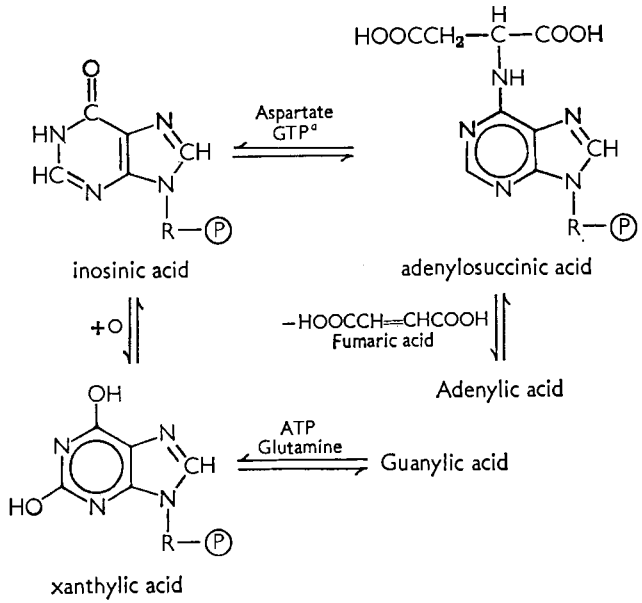
Although the origin of each atom in the two ring systems is now known (Figure 24) the postulated routes are not unequivocally established. This is hardly surprising in view of the number of steps apparently involved and the inherent instability of some of the postulated intermediates. The problem of isolating and characterising the enzymes involved is immense and the frequency with which the



[a] See Figure 25.

[b] C_1 fragment carried on tetrahydrofolic acid (Figure 13) strictly $N_{(5)}N_{(10)}$ methenyl THF (Figure 37), not $N_{(10)}$ formyl THF as is involved at (C).

FIGURE 26a.



[a] Guanosine triphosphate.

FIGURE 26b. Conversion of inosinic acid to adenylic and guanylic acids.

configuration at the $C_{(1)}$ atom, but the ribosylamine intermediate has not been isolated, probably because of its chemical reactivity. Synthetic 5-phosphoribosylamine is converted to the second intermediate (reaction II) in the presence of glycine, ATP and an enzyme isolated from pigeon liver[88]. Enzymes catalysing reactions III, IV and V have been partly purified from liver[89, 90]. Carboxylation of 5-aminoimidazole ribonucleotide (reaction VI) occurs in the presence of high concentrations of bicarbonate buffer. The reaction is strongly inhibited by the product[91]. Reaction VII is blocked in sulphonamide-inhibited cultures of *Eschiarischia coli* and the 5-amino-4-imidazole carboxamide ribonucleotide accumulates under these conditions[92]. The purine-N_3 is introduced by a condensation reaction with aspartate (reaction VII) presumably to form an imine which undergoes prototropic rearrangement to the *N*-succinyl compound shown. The same type of reaction is involved in the conversion of inosinic acid to adenylic acid (see below). Cleavage of the *N*-succinyl compound releasing fumaric acid (reaction VIII) is apparently catalysed by an enzyme (adenylosuccinase) which has been partly purified from yeast[93]. The

enzymes catalysing reactions IX and X have not been separated nor has the formamido intermediate been identified with certainty. However, the synthetic formamido compound is rapidly cyclised to inosinic acid by enzymes present in liver[94].

In the conversion of inosinic acid to adenylic acid (Figure 26b) the amino group is introduced by condensation of the 6-hydroxyl group with aspartate to form adenylosuccinic acid (cf. reactions VII and VIII, Figure 26a). The overall reaction, catalysed by an enzyme isolated from *E. coli*[95] is alleged to involve the purine nucleoside triphosphate GTP. Conversion of inosinic acid to guanylic acid involves first oxidation to xanthilic acid, catalysed by an NAD-dependent dehydrogenase, and then amination of the xanthine base, at the 2-position, by glutamine in the presence of ATP.

E. Amino Sugars

1. General

A number of amino sugars and *N*-acyl derivatives of amino sugars occur widely[96,97] in mucopolysaccharides, e.g. in bacterial cell walls, the skeletal structure of arthropods (chitin), animal cartilage and bone, in bacterial antibiotics[98] and on the exterior of red blood cells where they are concerned with the antigen–antibody reactions, on the basis of which individuals are classified into blood groups. The mucopolysaccharides are crosslinked polymers containing more than one sugar derivative and frequently occurring in association with protein and polypeptide material. Hyaluronic acid, for example, found in skin and bone, is a crosslinked polymer of glucuronic acid and *N*-acetylglucosamine; cartilage contains chondroitin, a polymer of glucuronic acid and *N*-acetylgalactosamine sulphate. Some bacterial cell walls contain crosslinked polymers of *N*-acetylglucosamine, alternate carbohydrate units having a lactyl side-chain substituted on the $C_{(3)}$ of the ring (*N*-acetylmuramic acid), and such cell walls are attacked by the enzyme lysozyme, mentioned in section IV. The lactyl side-chain of *N*-acetylmuramic acid is frequently linked to a peptide chain commonly containing both D- and L-alanine, D-glutamic acid and L-lysine[99] (Figure 27).

A group of compounds, called the sialic acids, are *N*- and *O*-acyl derivatives of neuraminic acid, itself a derivative of D-mannosamine (Figure 28). The sialic[99] acids are widely distributed (e.g. in egg yolk, human semen and in blood serum) both free and bound to the polysaccharide part of most, if not all, mucoproteins. They are closely

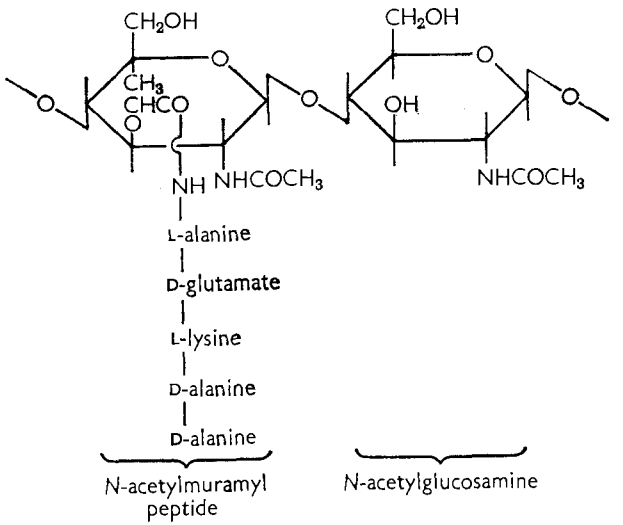


FIGURE 27. Type of polysaccharide structure found in some bacterial cell walls.

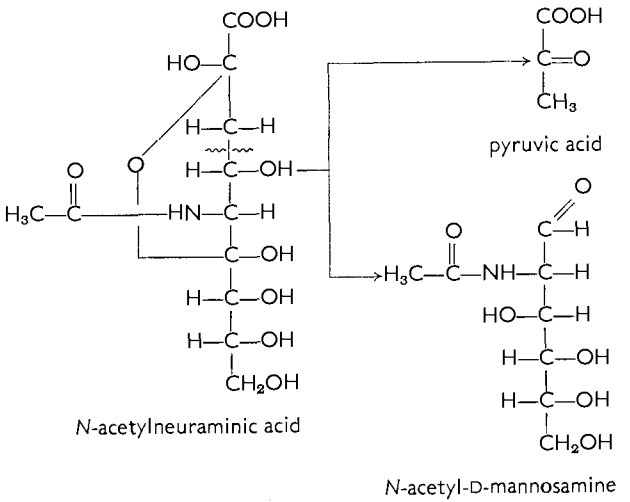


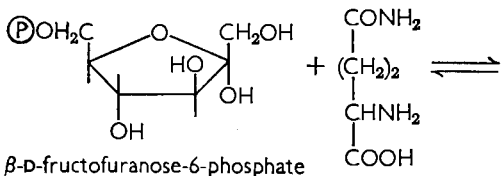
FIGURE 28.

concerned with preventing agglutination of blood cells, (the response to bacterial or virus infection or the introduction of any foreign material which produces an antigen–antibody reaction). There is now evidence that neuraminic acid derivatives also occur in association

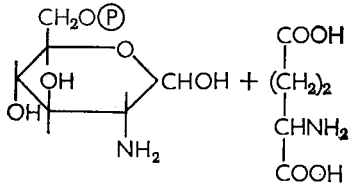
with some enzymes, e.g. placental alkaline phosphatase and prostatic acid phosphatase.

2. Biosynthesis of amino sugars

The most common amino sugars, glucosamine, galactosamine and mannosamine, have a common origin in the hexose-6-phosphate intermediates of the main glycolysis cycle (conversion of glycogen to carbon dioxide and water). The amino group originates from the acid amide group of glutamine. The reaction between fructose-6-phosphate and glutamine (equation 33) is 'unusual' in that it does not involve ATP (see section V.B). Enzymes catalysing this reaction have been



(33)



isolated from *Neurospora crassa*, *E. coli* and rat liver[100]. Earlier reports that glucosamine was formed from glucose in the presence of ATP and glutamine are presumably due to the presence of a phosphohexose isomerase in the crude bacterial extracts used in these experiments. The amino sugar is acetylated in the presence of acetyl coenzyme A (Figure 29), the most common biological acetylating agent.

The reactions by which glucosamine (or *N*-acetylglucosamine) is converted to galactosamine, by inversion at $C_{(4)}$, or mannosamine, by inversion at $C_{(2)}$, are complex. Epimerisation does not occur at the simple hexosamine phosphate level but is preceded by esterification at the $C_{(1)}$ position of the sugar ring by a pyrimidine nucleoside triphosphate (uridine or thymidine triphosphate) to form a nucleoside diphosphoamino (or *N*-acylamino) sugar (Figure 30). Enzymes catalysing epimerisation of uridine (or thymidine) diphosphate esters of glucosamine, to form the nucleoside diphosphate ester of galactosamine, or of *N*-acetylglucosamine, to form the nucleoside diphosphate

esters of *N*-acetylgalactosamine or *N*-acetylmannosamine, have been reported[101–103].

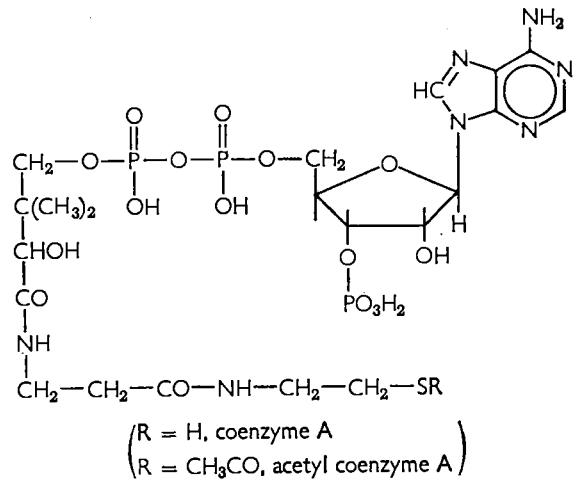


FIGURE 29.

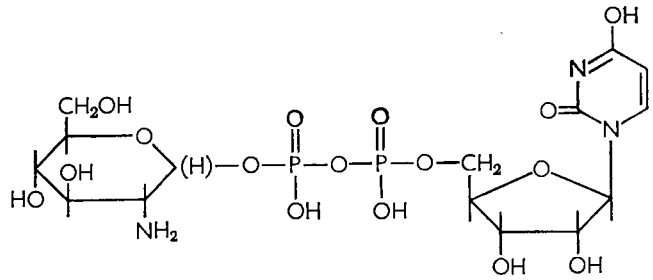


FIGURE 30. Uridine diphosphoglucosamine.

Recent work on the structure and biosynthesis of bacterial cell walls has given some indication of the way in which the crosslinked polysaccharide components are formed. There are several justifications for including here a brief account of work in this field. Firstly, certain antibiotics (e.g. the penicillins, bacitracin A, novabiocin) are known specifically to inhibit bacterial cell-wall synthesis. If, as seems likely, the inhibition is of an enzyme-catalysed reaction, a knowledge of the particular substrates involved might lead to the design of more powerful bactericidal agents. Secondly, the particular type of cell

wall to be described is the substrate for the enzyme lysozyme already discussed in section 2. Thirdly, the enzymes catalysing certain of the steps to be outlined below are of considerable interest from a mechanistic point of view. They show a high degree of substrate specificity and the substrates are chemically more complex than those discussed in previous sections. The mechanisms of catalysis by such enzymes may well be analogous to the hydrolytic reaction catalysed by lysozyme, the protein providing an extensive environment within which correct orientation of the substrates is a stringent prerequisite for reaction to occur.

The cell wall of *Staphylococcus aureus* contains the alternate *N*-acetylglucosamine, *N*-acetylmuramyl peptide structure illustrated in Figure 27.* Studies of the biosynthesis of this type of structure, which are largely due to Strominger and his collaborators[104–106] have given considerable insight into the steps involved. Although *N*-acetylglucosamine is formed as a hexose-6-phosphate, the simple hexosamine derivative is not a substrate for enzymes catalysing cell-wall biosynthesis. The hexose unit is incorporated into polysaccharide from the uridine diphosphate ester of *N*-acetylglucosamine. The nucleoside diphosphate esters of glucosamine or *N*-acetylglucosamine (Figure 30) are formed by reaction between uridine triphosphate and the hexose-1-phosphates which must, in turn, be formed by isomerisation of the hexose-6-phosphates (cf. equations 33 and 34).

$$\text{Hexosamine-1-phosphate} + \text{UTP} \rightleftharpoons \text{Uridine diphosphohexosamine} + \text{Pyrophosphate} \quad (34)$$

The second hexose unit, muramic acid, is apparently formed at the nucleoside diphosphate ester level but the course of this reaction is not well understood. The lactyl side-chain may well be introduced by condensation of uridine diphospho-*N*-acetylglucosamine and phosphoenol pyruvate, liberating inorganic phosphate. The pentapeptide side-chain of the muramyl peptide unit is formed by stepwise addition of the first three amino acids, to uridine diphospho-*N*-acetylmuramic acid, in the presence of ATP and either magnesium or manganese ions, one mole each of ADP and inorganic phosphate being formed for each amino acid added, and final addition of the dipeptide D-alanyl-D-alanine, again in the presence of ATP. The separate enzymes

* The figure illustrates a β 1:4 glycosidic link between successive hexose units but it is possible that β 1:6 links are also present in cell-wall material from different microorganisms.

catalysing each addition have been partly purified[104,105]. Only the completed nucleoside diphospho-*N*-acetylmuramyl pentapeptide acts as a substrate for cell-wall synthesis. Particulate, cell-free preparations from *Staphylococcus aureus* which catalyse a reaction between the nucleoside diphosphate esters of *N*-acetylglucosamine and *N*-acetylmuramyl pentapeptide to form 'cell-wall-like' material have been obtained[106].

The metabolism of *N*-acetylmannosamine and its relation to the formation of the sialic acids (derivatives of neuraminic acid) are not well understood. The subject has been reviewed by Roseman[107].

F. Miscellaneous Amino Compounds and Derivatives

There are a number of amino compounds, of immense biological importance, which cannot be classified with the compounds so far discussed. It is intended, in this section, to discuss the possible origins of some of these compounds and also to give a brief account of the biosynthesis of certain important heterocyclic systems which are derived from the simple amino compounds already discussed.

1. Vitamins[108]

The familiar word vitamin derives from 'vital amine', the term being introduced in 1912 following the recognition that certain diseases could be prevented by addition to the diet of some compounds originally believed to be amines. Later it was revealed that not only are these compounds not all amines but some contain no nitrogen at all, such as the 'fat-soluble' A, D, K and E groups and vitamin C. The water-soluble vitamins (B group), all contain nitrogen, and appear to function, in more or less well-understood ways, as cofactors for enzyme-catalysed metabolic reactions, hence the limitation of the present discussion to members of this group and their derivatives.

a. *Vitamin B_1 (thiamine)*. (Figure 31a). The pyrimidine and thiazole rings of thiamin are formed separately but the origins of the two rings are not yet known. It is presumed that the pyrimidine ring is formed from orotic acid but no information is yet available concerning the introduction of the 4-amino group. Two possible routes to the thiazole ring are given in Figure 31b. The two ring systems are linked by a reaction between the pyrimidine pyrophosphate and the thiazole monophosphate. The product is hydrolysed to free thiamine before conversion to a pyrophosphate, in which form vitamin B_1 is a cofactor for an enzyme catalysing the reversible decarboxylation of pyruvate.

Imine formation between pyruvate and the amino substituent in the pyrimidine ring was at one time suggested as a possible step in decarboxylation but this idea has since been abandoned. The reaction is now believed to involve nucleophilic attack on the carbonyl carbon of pyruvate by an anion formed by loss of a proton from the $C_{(2)}$ position in the thiazole ring. Details of the mechanism need not concern us since no amino group is involved in either the substrate or the cofactor.

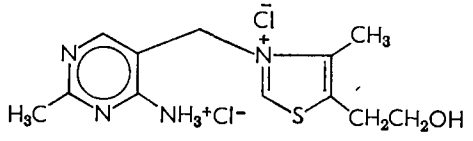


FIGURE 31a. Thiamin.

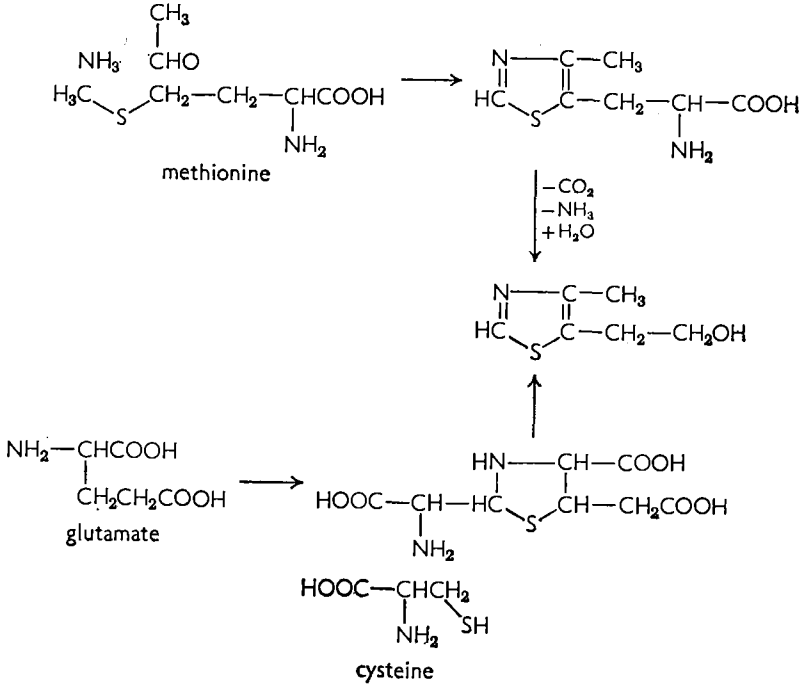


FIGURE 31b.

b. *Vitamin B_2 (riboflavine)*. The two nitrogen-containing rings of the isoalloxazine system of riboflavine (Figure 32) are derived from adenine. The routes to the dimethylbenzo ring and the ribityl sidechain are unknown. The two derivatives of riboflavine (Figure 2c) which occur as the cofactors in flavoprotein enzymes catalysing oxidation–reduction reactions (e.g. amino acid oxidases) act as hydrogen acceptors. The addition of two hydrogen atoms across the conjugated double bonds between $N_{(1)}$ and $N_{(10)}$ gives the reduced flavin ring shown in Figure 2d.

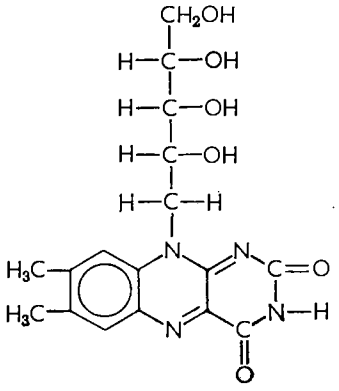


FIGURE 32. Riboflavine.

c. *Vitamin B_6 (pyridoxine)*. (Figure 5a). No information is yet available on the biosynthesis of pyridoxine. The phosphorylated derivatives of pyridoxine (see Figures 5b and c) which act as cofactors for enzymes catalysing certain reactions of α-amino acids, have already been discussed (sections IV.C and V.C).

d. *Vitamin B_{12} (cyanocobalamin)*. The somewhat formidable structure of Vitamin B_{12} is given in Figure 33. The 5:6 dimethylbenzimidazole nucleotide unit is probably joined, through the 1-amino-2-propanol bridge formed by decarboxylation of threonine, to the preformed corrin nucleus. The corrin nucleus is itself a modification of the porphyrin ring system which occurs commonly, for example in haemoglobin, chlorophyll and in the cytochromes. Compounds containing the tetrapyrrole ring system probably have a common origin (see section V.F.2). The acid amide groups in the corrin sidechains may be formed by transamidation between glutamine and the

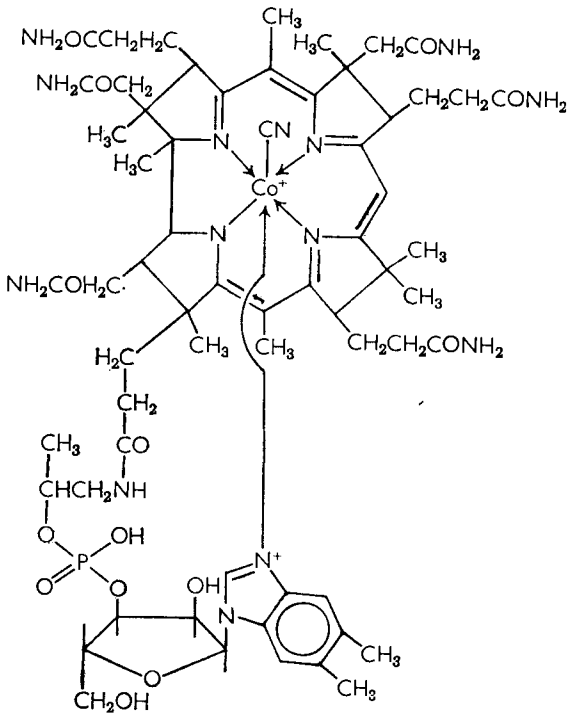


FIGURE 33. Vitamin B_{12}.

acetic acid and propionic acid side-chains which are correctly arranged about the porphyrin rings of uroporphyrin III (Figure 39).

Vitamin B_{12} was first identified as the antipernicious anaemia factor, present in whole liver. Only recently has it been shown that, in common with other members of the B group of vitamins, a derivative of cyanocobalamin (having the cyanide group replaced by adenosine) is a cofactor for certain enzymes, in particular, those catalysing the isomerisation of glutamate to β-methyl aspartate[109] (bacteria) and of the methylmalonyl derivative of coenzyme A (Figure 29) to succinyl CoA[110,111]. It has been suggested that both isomerisations involve cyclic intermediates and that the enzyme–cofactor complexes may stabilise carbanions formed on cleavage of the rings in these intermediates.

e. *Vitamin H (biotin)*. The biosynthetic route to biotin (Figure 34) is unknown, but there is indirect evidence that desthiobiotin is an

intermediate and that the side-chain originates in pimelic acid. Biotin is involved in certain decarboxylation reactions and in the deamination of some amino acids, e.g. aspartate, serine and threonine.

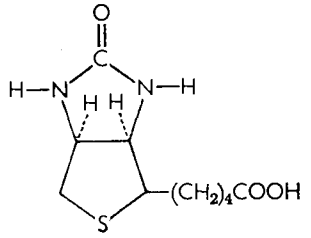


FIGURE 34. Biotin.

f. *Vitamin B_3 (pantothenic acid)*. The precursors of pantothenic acid (Figure 35) are pantoic acid (from α-ketovaleric acid) and β-alanine (a decarboxylation product of aspartate). A bacterial enzyme[112], pantothenic acid synthetase, catalyses the condensation of these two compounds to form pantothenic acid.

Pantothenic acid is a constituent of the CoA molecule (Figure 29), the biosynthesis of which is summarised in Figure 35. Only the sulphydryl group of CoA is known to be directly involved in trans-acetylation reactions. The function of the remainder of the molecule is obscure.

g. *Folic acid*. The structure of folic acid is given in Figure 13. The compound is formed by condensation between *p*-aminobenzoic acid and glutamic acid followed by a second condensation reaction with a substituted pteridine. The pteridine nucleus appears to originate from the purine ring system, probably by a route related to that involved in the formation of the isoalloxazine ring system of riboflavin.

A reduced form of folic acid (tetrahydrofolic acid, FH_4) is active in so-called one-carbon metabolism. A formyl group may be substituted on $N_{(5)}$ or $N_{(10)}$ and the $N_{(5)}$–$N_{(10)}$ methenyl derivative (Figure 36) is also active. Reactions involving the introduction of one-carbon fragments include the conversion of glycine to serine (Section V.C.3), ethanolamine to choline (Section V.C.3) and the introduction of $C_{(8)}$ of the purine nucleus (Section V.D.3).

h. *Nicotinamide*. The route to the precursor of nicotinamide, nicotinic acid, is different in animals and bacteria. In animals (see Figure 37) tryptophane is converted to nicotinic acid by a series of

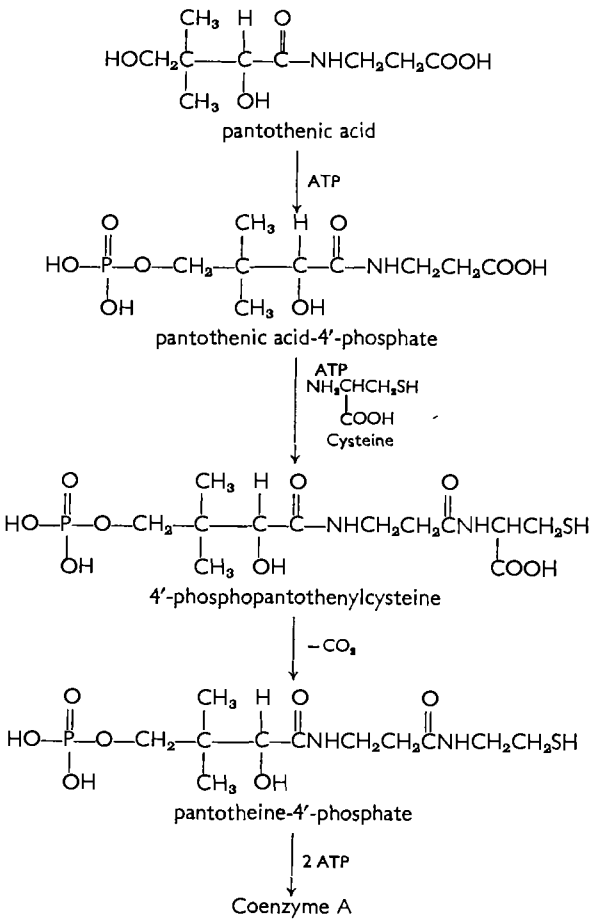


FIGURE 35.

reactions in which first the five-membered ring is opened, the resulting carbon side-chain in the six-membered ring is oxidised and fragmented; the six-membered ring is then opened and reformed to give a quinolinic acid. In bacteria, the carbon skeleton of nicotinic acid is formed from a three-carbon unit (e.g. glycerol) and a four-carbon dicarboxylic acid[113].

The formation of nicotinamide from nicotinic acid occurs at the nucleotide level[114]. Nicotinic acid first reacts with phosphoribosyl pyrophosphate to form nicotinic acid mononucleotide and inorganic pyrophosphate. The mononucleotide then reacts with ATP to form a

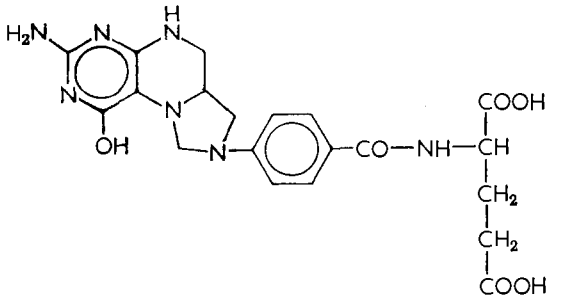


FIGURE 36. $N_{(5)}$, $N_{(10)}$-methyl tetrahydrofolic acid.

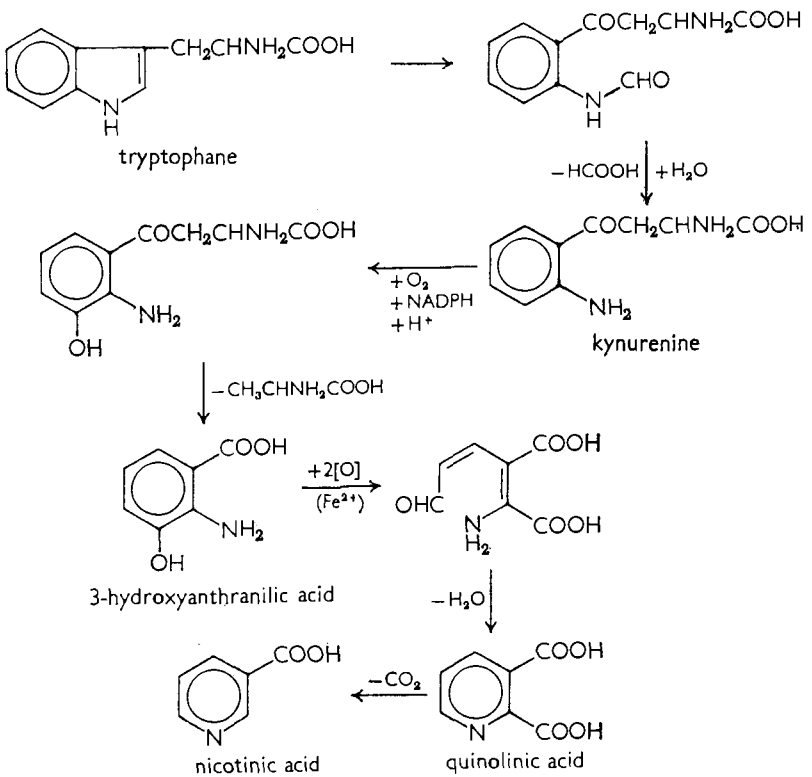


FIGURE 37. Biosynthesis of nicotinic acid (animals).

dinucleotide (and pyrophosphate) and the nicotinic acid–adenine dinucleotide then reacts with glutamine (and ATP) to give nicotinamide–adenine dinucleotide. Nicotinamide–adenine dinucleotides (Figure 2a) are the cofactors for many enzymes.

Addition of hydrogen to the oxidised form of NAD (or NADP) occurs at the 4-position of the pyridine ring (Figure 2b). It is known, from deuterium isotope studies, that the reduction is stereospecific, implying that the link between enzyme protein and cofactor is such that free rotation about the pyridine nitrogen nucleotide bond is prevented. Dehydrogenases can be classified into two groups showing different stereospecificity with respect to reduction of the nicotinamide ring.

2. Pyrrole-containing compounds

A number of biologically important compounds contain substituted pyrroles in cyclic or linear array. With the exception of the corrin nucleus of vitamin B_{12} in which one methylene bridge is missing, the cyclic tetrapyrroles can be regarded as derivatives of the parent porphin, the structure of which is given in Figure 38. The porphyrins

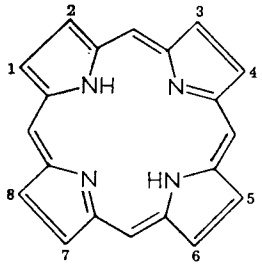


FIGURE 38. Porphin.

are classified in terms of the types of substituents on the pyrrole rings (positions 1 to 8). For example, the coproporphyrins have one methyl and one propionic acid group on each ring; the uroporphyrins (Figure 39) have the methyl groups replaced by acetic acid groups and in protoporphyrins (in haem, and modified in chlorophyll) the groups are variously acetic acid, propionic acid, methyl and vinyl. The linear, bile pigments are breakdown products of porphyrins.

All pyrrole-containing compounds have a common origin, the pyrrole ring itself being formed from glycine and the succinyl derivative of coenzyme A which condense to form α-amino-β-ketoadipic acid. This undergoes α-decarboxylation to form δ-aminolaevulinic acid, two molecules of which condense to give a pyrrole ring which already carries the acetic and propionic acid side-chains found in the uroporphyrins (Figure 39). Subsequent polymerisation of four-substituted pyrroles with the loss of ammonia from the methylamine side-chains gives the reduced precursor of the uroporphyrins. The methyl and vinyl side-chains of copro- and protoporphyrins are formed by decarboxylation of acetic acid side-chains and oxidation and decarboxylation of propionic acid side-chains respectively. The metal ion present in haem compounds and in cytochromes (iron), in chlorophylls (magnesium), and in cyanocobalamine (cobalt), is apparently introduced after the porphyrin (or corrin) nucleus has been formed.

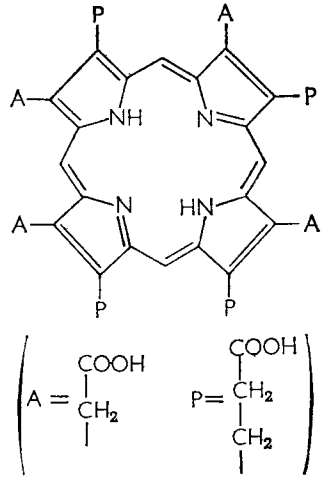


FIGURE 39. Uroporphyrin III.

3. Plant alkaloids

The biosynthesis of plant alkaloids has recently been well reviewed by Bu'Lock[115] and will therefore be considered very briefly. It is not possible to make general statements about the mechanism of biosynthesis of this large and varied class of compounds, partly because of the incomplete state of knowledge of any individual routes. Tracer studies have contributed much information in this field but perhaps more has resulted from hypotheses, based on inductive reasoning, resulting from the observation that certain common units occur within complex organic structures. The alkaloids appear to be derived

largely from only a small number of amino acids. For example, ornithine contributes the C_4N unit to the pyrrolidine alkaloids such as hyoscyamine (Figure 40a) while lysine contributes the C_5N units to the piperidine alkaloids such as lupinine (Figure 40b). Alkaloids such as morphine (Figure 40c) and belladine, contain C_6 C_2 N (phenylethylamine units) derived from the aromatic amino acids, phenylalanine and tyrosine. The fifth amino acid to contribute significantly to alkaloid biosynthesis is tryptophane, from which are derived the so-called indole alkaloids such as strychnine and yohimbine.

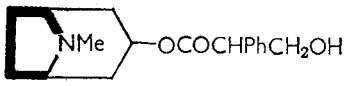


FIGURE 40a. Hyoscyamine.

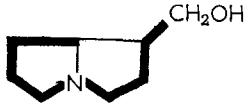


FIGURE 40b. Lupinine.

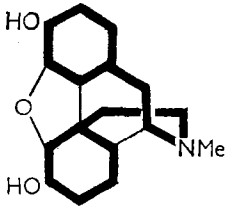


FIGURE 40c. Morphine.

VI. THE FORMATION OF NITROGEN-CONTAINING WASTE PRODUCTS

The reactions of amino compounds, considered so far, have been largely concerned with the production of essential cell constituents from ingested material. The remaining section is concerned with those reactions by which excess amino compounds are converted first to ammonia and then to common excretion products. The division between biosynthetic and degradative reactions is not clear cut as can be seen from the fact that the reaction catalysed by the enzyme glutamic dehydrogenase produces ammonia and has already been discussed in sections II and IV.B. Oxidative deamination of the D-amino acids has also been discussed (section V.A) because the reverse of this reaction appears to be the main route by which D-amino acids are formed in microorganisms but it is also believed to be the

main route by which D-amino acids are broken down in animals. Apart from the routes which have already been discussed, two main types of reaction lead to the production of ammonia.

A. Production of Ammonia

1. L-Amino acid oxidases

The original observation by Krebs[116], that homogenates of mammalian liver and kidney catalysed the oxidation of both D- and L-amino acids, was followed by a number of attempts to purify individual amino acid oxidases. Although a crystalline, non-specific D-amino acid oxidase has been isolated from kidney, the only evidence for the existence, in mammals, of a single enzyme catalysing the oxidative deamination of L-amino acids, comes from an early report by Blanchard and coworkers[117]. This particular flavoprotein, isolated from rat kidney, is odd for two reasons: (a) it shows a higher oxidative activity towards some α-hydroxy acids (e.g. L-lactic acid) than to L-amino acids and (b) the catalytic activity is very low compared with most other enzymes. The amounts of this enzyme in kidney homogenates are certainly too small to account for Krebs' original observations of the oxidation of L-amino acids. It is now generally believed that L-amino acid oxidation by mammalian tissue homogenates is due to the coupling of two enzyme-catalysed reactions, the first a transamination between the L-amino acid substrates and α-ketoglutaric acid and the second, deamination of the resulting glutamic acid, catalysed by glutamic dehydrogenase (Section IV.B). This is probably the principal route, in mammals, to the production of ammonia from excess amino acids.

The highest L-amino acid oxidase activity is found in the venoms of a variety of snakes, the enzyme being present to the extent of up to 3% of dried, whole venom in some species. Crystalline enzymes (both flavoproteins) have been isolated from the venoms of water moccasin[118] (*Ancistrodon piscivorus*) and rattle snake[119] (*Crotalus adamanteus*) and shown to be similar with respect to molecular weight (130,000) and flavin content (2 moles FAD/mole protein). The enzymes are not substrate-specific but are more active with the L-isomers of methionine, leucine, tryptophan, phenylalanine and tyrosine than with other L-amino acids. The reactions catalysed by L-amino acid oxidase are formally the same as those discussed in section V.A (reactions 23–26) but, as is the case for the D-amino acid oxidase, the mechanism of

oxidative deamination remains obscure. The function of large quantities of L-amino acid oxidase in snake venom is quite unknown.

L-Amino acid oxidase activity has been detected in a variety of moulds, yeasts and bacteria, but the enzymes from these sources have not been well characterised. A partly purified enzyme from *Proteus vulgaris*[120] is curious in that it does not apparently produce hydrogen peroxide in the presence of molecular oxygen (equations 22–26) and absence of catalase.

2. Amine oxidases[24]

The enzymes catalysing the oxidation of naturally occurring amines, according to equation (35), found in both plants and animals, were

$$RCH_2NH_2 + O_2 + H_2O \rightleftharpoons RCHO + NH_3 + H_2O \quad (35)$$

originally classed as monoamine oxidases and diamine oxidases. Recent work has shown that, although there are two separate types of enzymes, the difference between them does not lie in the number of amino groups in the substrates. The substrate specificities are, in both cases, more complex. There are two main types of monoamine oxidases, the intracellular, mitochondrial enzyme (present to a significant extent in liver tissue) and the extracellular, soluble enzymes present in the blood serum, particularly that of ruminants. The former are poorly characterised as proteins because of the common problem of solubilising normally particulate enzymes. (A fifty-eight fold purification of the beef mitochondrial enzyme was recently reported[121].) The enzyme acts on simple aliphatic amines (with the exception of methylamine and ethylamine) according to equation (35) and catalyses the oxidation of such physiologically important amines as serotonin, tyramine and norepinephrine (section V.C). It also oxidises secondary and tertiary *N*-methyl derivatives of amines, e.g. epinephrine and *N*,*N*-dimethyltryptamine, producing methylamine and dimethylamine in place of ammonia, and slowly attacks such diamines as cadaverine (formed by decarboxylation of lysine) and some long-chain diamines (C_{14}, C_{16} and C_{18}). Histamine is also oxidised slowly in the presence of the mitochondrial monoamine oxidase. The enzyme is believed to contain functional copper and also, possibly, a flavin cofactor[122]. Final decision on these points must await further purification of the enzyme. The activity of 'monoamine oxidase' is unaffected by reagents known to inhibit pyridoxal phosphate-dependent, enzyme-catalysed reactions.

Soluble amine oxidases have been crystallised from the blood serum of beef[123] and pigs[124]. In both cases the properties of the purified

enzyme were notably different from those of the mitochondrial enzymes, both in regard to substrate specificity and cofactor requirement. The beef plasma enzyme, although classified as a monoamine oxidase, does act on certain diamines, in particular spermine and spermidine, (amines found in seminal fluid and apparently derived from putrescine, the decarboxylation product of ornithine). The oxidation products from spermine and spermidine are a dialdehyde and a monoaldehyde respectively[125] (equations 36 and 37). The en-

$$\underset{\text{spermine}}{NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2} + 2\,O_2 + 2\,H_2O \longrightarrow CHO(CH_2)_2NH(CH_2)_4NH(CH_2)_2CHO + 2\,NH_3 + 2\,H_2O_2 \quad (36)$$

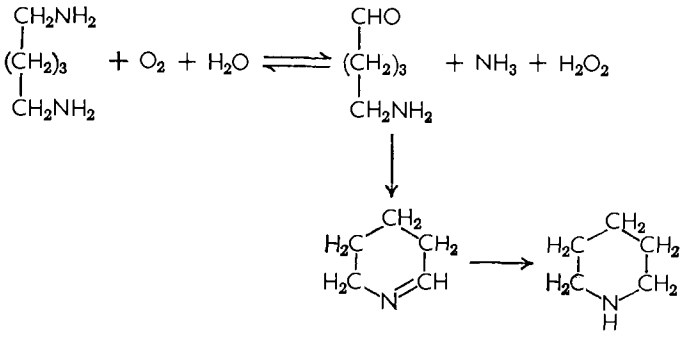
$$\underset{\text{spermidine}}{NH_2(CH_2)_3NH(CH_2)_4NH_2} + O_2 + H_2O \longrightarrow CHO(CH_2)_2NH(CH_2)_4NH_2 + NH_3 + H_2O \quad (37)$$

zyme crystallised from pig plasma has been called 'benzylamine oxidase'[124] in spite of the fact that it acts equally well with mescaline (2,3,4-trimethoxyphenyl ethylamine) and also oxidises histamine (at approximately half the rate). The enzyme from beef plasma acts on the same monoamine substrates. Unlike the mitochondrial enzymes, neither plasma enzyme will oxidise *N*-methyl derivatives of amines and this is consistent with the recent finding that the plasma amine oxidases contain tightly bound pyridoxal-5'-phosphate. (The suggestion that pyridoxal phosphate might be involved in amine oxidation was made as long ago as 1949[126].) It is an unusual finding, in that other pyridoxal phosphate-dependent enzymes catalyse reactions of amino acids, rather than amines.* It is now suggested that the reactions catalysed by plasma amine oxidases occur by Schiff's base formation between primary amino groups in the substrates and the aldehyde group of pyridoxal phosphate. The involvement of a pyridoxal cofactor could explain the known sensitivity of plasma amine oxidases to carbonyl reagents such as cyanide. The plasma oxidase is also believed to contain copper (3 g atoms per mole of protein, mol. wt. ~200,000.) An amine oxidase present in pea seedlings also contains copper[127] and is sensitive to carbonyl reagents, but there is no direct evidence for the presence of bound pyridoxal phosphate.

The enzymic activity originally attributed to a diamine oxidase was first observed in pig kidney and later shown to be fairly widespread in animals, plants and microorganisms. The enzyme catalyses the

* The exception being muscle phosphorylase which contains pyridoxal phosphate, the function of which remains obscure.

oxidation of the diamine decarboxylation products from arginine, (agmatine), lysine, (cadaverine) and ornithine, (putrescine) and the more complex diamines spermine and spermidine. The oxidation products are amine aldehydes which might be expected to cyclise. The amine aldehyde from cadaverine would cyclise to an oxidised precursor of piperidine (equation 38). The enzyme appears to be



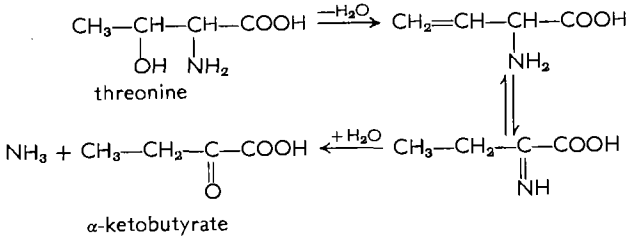
(38)

mitochondrial but is more readily solubilised than the mitochondrial monoamine oxidase. The recent report[128] of a substantial purification (1000-fold) of the enzyme from pig kidney suggests also that the enzyme contains both copper and firmly bound pyridoxal phosphate. There has been some controversy regarding the possible identity of the diamine oxidase with histaminase, the enzyme catalysing the oxidation of histamine to imidazole acetaldehyde[129]. (It should be noted that histamine is not a diamine, a fact which underlines the unsatisfactory nature of the original classification of amine oxidases.) The most recent data[128] shows that the ratio of the activities with respect to diamine substrates and histamine, remains constant throughout the purification of the pig kidney 'diamine oxidase'.

3. Miscellaneous reactions

The production of ammonia by non-oxidative processes is of less general importance. Enzymes catalysing non-oxidative deamination are relatively substrate-specific.

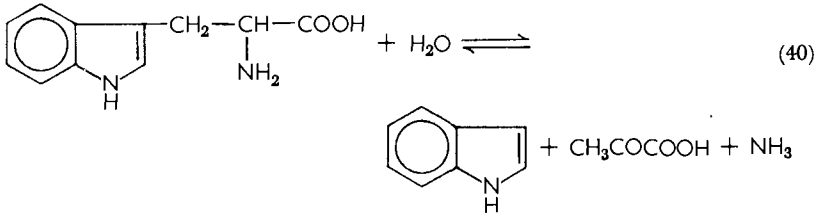
a. *Amino acid dehydrases.* The two hydroxyamino acids, serine and threonine, are both dehydrated and deaminated in the presence of specific dehydrases. It has been suggested[130] that the reaction may involve dehydration, to give α, β- or β,γ-unsaturated amino acids, followed by rearrangement, to the corresponding imino acids, and hydrolysis to an α-keto acid and amonia (equation 39). The dehydrases



(39)

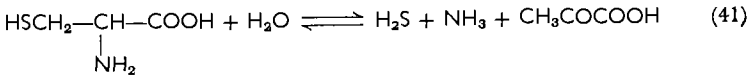
present in *Neurospora crassa*[131], *E. coli*[132] and sheep liver[133] are said to be pyridoxal phosphate dependent. A recent report[134] suggests that the threonine dehydrase of sheep liver may normally be present to variable extents as an inactive complex with serine. Threonine dehydrase activity could be demonstrated after heat treatment to remove serine.

b. *Tryptophanase.* The breakdown of tryptophane to indole, pyruvate and ammonia, is catalysed by a bacterial enzyme which requires pyridoxal phosphate as a cofactor (equation 40).



(40)

c. *Cysteine desulphydrase*[135]. Removal of hydrogen sulphide from cysteine is accompanied by non-oxidative deamination (equation 41). The reaction is analogous to the dehydration and deamination of the hydroxy amino acids and is catalysed by pyridoxal phosphate-dependent enzymes present in some mammalian tissues and some micro-organisms.



(41)

d. *Deamination of purines and pyrimidines.* The amino substituents in the purines, guanine and adenine, and the pyrimidine, cytosine, are not apparently lost by deamination of the free bases. Enzymes catalysing non-oxidative deamination of the corresponding nucleosides have been demonstrated in liver and other tissues, while the enzyme adenylic deaminase, present in muscle, converts the nucleotide adenylic acid to the deaminated analogue, inosinic acid.

B. Formation of Excretory Products

The discussion in this last section is limited to the fate of the ammonia, produced by deamination of amino compounds, in animals. Excretion is a function not normally attributed to plants or to micro-organisms, a fact which may reflect the greater economy of these simpler life forms in regard to the utilisation of ingested nitrogen compounds. In animals, the general efficiency with which ingested nitrogenous materials are used to maintain a healthy state of existence is relatively low. In addition, the turnover of such essential nitrogenous compounds as proteins and nucleic acids is relatively rapid. The main problem is the efficient conversion of excess amino compounds to non-toxic products excreted in the urine. The toxicity of ammonia, particularly in the central nervous system of higher animals, has already been noted and it has long been recognised that the level of free ammonia in the tissues, in blood and in urine, is only significant in certain cases of metabolic disorder.

The principal nitrogenous excretion product is urea in mammals and most aquatic species, and uric acid in birds and reptiles. There are, of course, a number of exceptions to this generalisation. The Dalmation dog, for example, excretes significant quantities of uric acid while spiders excrete guanine in place of uric acid. Other species are known to show different behaviour in the course of their development, e.g. tadpoles and chicken embryos form ammonia, while frogs and hens produce urea and uric acid respectively. Certain lower aquatic species lose ammonia directly, a simple diffusion process replacing the complex excretory systems of higher animals.

The main routes by which surplus amino compounds are converted to urea and uric acid, are considered below.

1. Urea formation

It was suggested, by Krebs and Henseleit[136] more than thirty years ago, that urea is formed (primarily in liver tissue), by a cycle of reactions between the basic amino acids, ornithine, citrulline and arginine. The original scheme, given in Figure 41, is now known to be oversimplified. Other intermediates are involved, and enzymes catalysing the individual steps in the reaction have been purified and partly characterised. The reactions involved are as follows:

(a) Formation of carbamyl phosphate from ammonia, carbon dioxide and adenosine triphosphate (ATP). The reaction is catalysed by carbamyl phosphate synthetase which requires two cofactors, i.e.

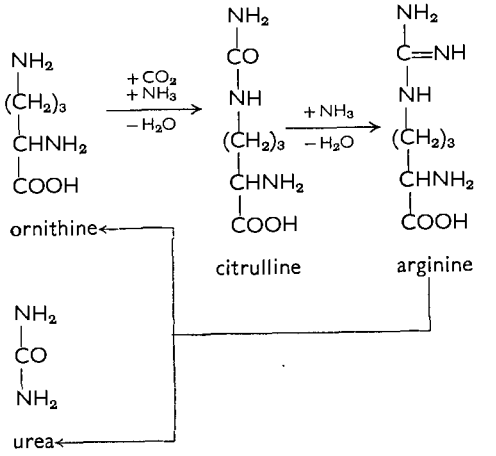
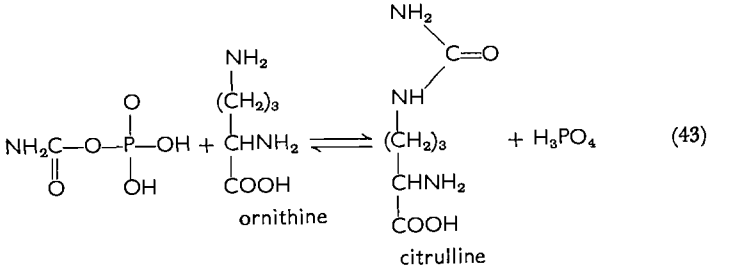


FIGURE 41. Formation of urea.

magnesium ions and an *N*-acyl derivative of glutamate. Two moles of ATP are broken down in the course of the reaction (equation 42). Equilibrium lies towards carbamyl phosphate formation. The mechanism of the reaction is obscure.

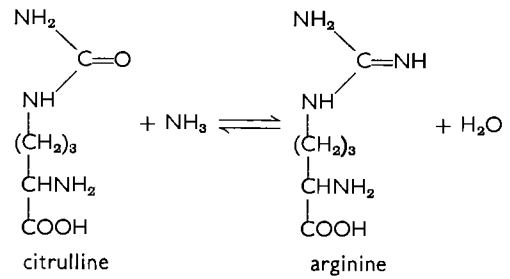
$$CO_2 + NH_3 + 2\,ATP \rightleftharpoons NH_2C(=O)OPO_3H_2 + 2\,ADP + H_3PO_4 \qquad (42)$$

(b) Elimination of inorganic phosphate between carbamyl phosphate and ornithine to give citrulline. The reaction (equation 43) is catalysed by ornithine transcarbamylase which has been purified from liver tissue of rat and ox.



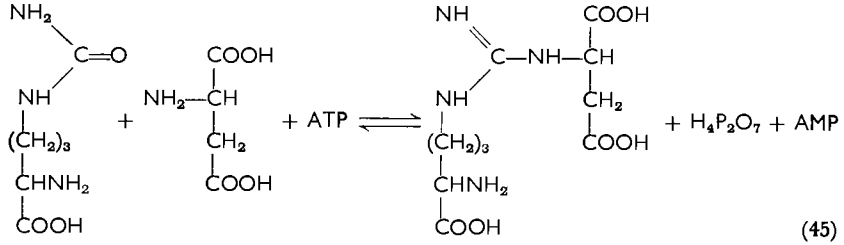
(43)

(c) The formation of arginine from citrulline can be represented formally by equation (44). However, the reaction neither occurs in one step nor involves free ammonia. Ratner[137] and her colleagues have shown that arginine formation requires the presence of both aspartate and ATP and that reaction occurs through the intermediate



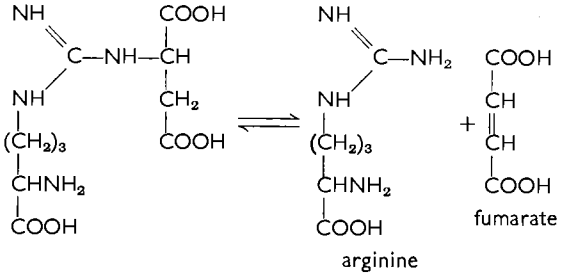
(44)

argininosuccinate, (see also section V.D). The formation of the intermediate involves the production of adenosine monophosphate and inorganic pyrophosphate (equation 45). The enzyme catalysing



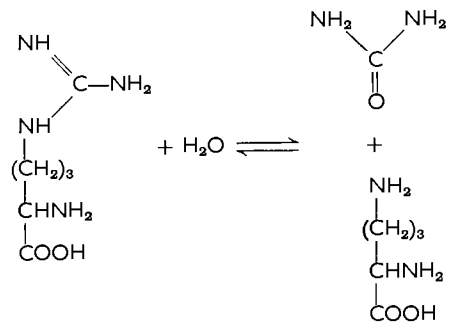
(45)

this reaction (argininosuccinate synthetase) is inhibited by inorganic pyrophosphate. The presence, in liver, of an inorganic pyrophosphatase is presumed to prevent inhibition, under physiological conditions. Cleavage of argininosuccinate to produce arginine and fumaric acid (equation 46) is catalysed by a second enzyme, argininosuccinase.



(46)

(d) Arginine is hydrolysed to produce urea and regenerate ornithine (equation 47). The enzyme catalysing this reaction (arginase) is activated by some divalent metal ions, e.g. Ni^{2+}, Co^{2+}, Mn^{2+}.



(47)

Although the present discussion is limited to reactions catalysed by liver enzymes, it may be noted that analogous enzymic activities have been demonstrated in both plants and microorganisms.

2. Uric acid formation

Although uric acid is known to be the main nitrogenous excretion product in birds and in reptiles, the route by which it is formed from excess amino compounds is not well understood. Uric acid is also the end product of purine breakdown in man and is excreted as such, while in subprimate mammals, the purine ring is further oxidised to produce first, allantoin and, in some species, eventually urea. The interrelationship between these compounds is illustrated in Figure 42.

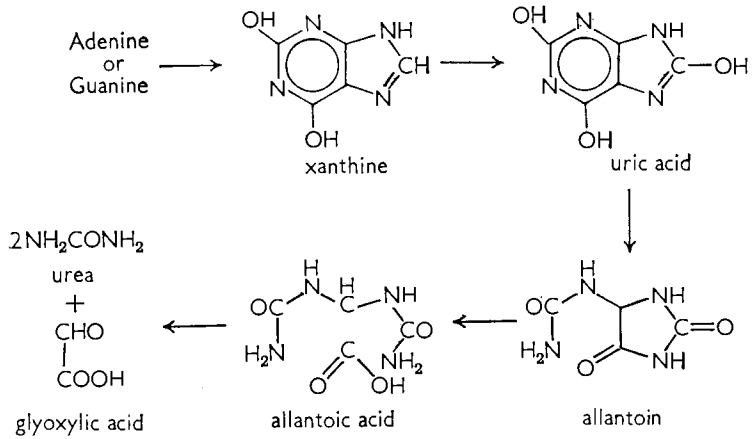


FIGURE 4

VII. GLOSSARY OF ABBREVIATIONS

NAD^+, NADH $NADP^+$, NADPH	Refer to the oxidised and reduced forms of the nicotinamide–adenine dinucleotide cofactors of certain enzymes (see Figures 2a, b).
FP, FPH_2	Refer to flavoprotein enzymes in which the flavin may be flavin mononucleotide (FMN) or flavin-adenine dinucleotide (FAD) (see Figures 2c, d).
Pal, Pam	Refer to the aldehyde and amine derivatives of pyridoxine (vitamin B_6) (see Figures 5a, b, c).
FH_4	Tetrahydrofolic acid (Figure 13).
ATP	Adenosine triphosphate (Figure 17).
GTP	Guanosine triphosphate.
CoA	Coenzyme A (Figure 29).

In Figures 1 and 16, names of amino acids are indicated by the first three letters only. Thus glu represents glutamic acid and phe represents phenylalanine.

The nomenclature used in this chapter for metabolites which contain carboxylic acid groups and for phosphate esters is imprecise since the relevant ionisation states *in vivo* are, in general, ill-defined. α-Keto acids and acidic amino acids are, therefore, referred to as α-ketoglutarate, aspartate etc., but it is not intended to imply that all carboxylic acid groups are necessarily fully ionised under all conditions. In the text, esters of orthosphosphoric acid, orthophosphoric acid itself and pyrophosphoric acid are referred to simply as phosphates (e.g. adenosine triphosphate), inorganic phosphate and inorganic pyrophosphate respectively, whereas in the figures, phosphate groups are generally shown, incorrectly, as being unionised (e.g. as $X—OPO_3H_2$). In no case can the cation associated with an ionised group be specified.

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CHAPTER 10

Rearrangements involving amino groups

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The title reactions can be grouped into several classes depending on the existence, and nature, of intermediates. The following sections summarise the most important examples, but the extent of the literature precludes an exhaustive treatment. Often, especially for minor topics, questions of historicity and priority will be ignored and citation will be made to articles containing discussion of earlier work.

I. REARRANGEMENTS ACCOMPANYING DEAMINATION

A. Ionic Intermediates

In the generally accepted mechanism for deamination of primary alkylamines with nitrosating agents, the transiently formed diazonium ion loses nitrogen, with neither solvent nor neighbouring group assistance to give an unsolvated carbonium ion which is negligibly encumbered by the departing molecule and has no counter ion in the vicinity[1]. This high-energy or 'hot' ion differs from the formally identical but solvated species typically generated in an S_N1 reaction by undergoing a wider spectrum of reactions, some of which, however, are attendant on partial or almost complete solvation[2-7]. Other interpretations require the intervention of diazoalkanes[8] or diazohydroxides[2,9,10], or the direct decomposition at the diazonium ion stage to products[11,12]; but the last two distinctions may be semantic, for the energy profiles for the different mechanisms (exhibiting shallow minima for the various intermediates), must be almost indistinguishable; especially when smoothed out by the thermal energy of the system. Nevertheless, the carbonium ion mechanism is usually considered to accommodate the data most satisfactorily[1].

Much of the evidence for hot ions has been adduced from the study of rearrangements accompanying deamination, and in this review we will assume the existence of such intermediates. Classical ions, which can be represented by one or a series of equilibrating structures in which the charge is largely localised on one carbon and the normal covalencies occur, and also non-classical ions with charge delocalisation and partial bonding are both believed to exist in deamination. The existence of the latter in reactions generally, has been disputed[13], but there is considerable stereochemical evidence, particularly for bridged substrates, that cannot be convincingly interpreted on the classical model[14]; although in many cases a decision as to whether the non-classical species are intermediates or merely transition states is difficult. Unfortunately, kinetic evidence for mesomeric cations, perhaps the best criterion[15], is unavailable because deamination occurs after the rate-determining step of the reaction sequence, but we will follow the literature and often assign non-classical intermediates, on admittedly, minimal evidence, and will represent them using the partial-bond symbolism, despite recent objections to this[16].

Deaminations have usually been conducted in acetous or aqueous media, at 0 to 30°, yielding olefins and either acetates or alcohols respectively. For uniformity, all reactions forming acetates will be referred to alcohol products in the following sections, and the reaction conditions will only be mentioned when mechanistically significant.

B. Acyclic Amines

Deamination of short-chain primary alkylamines with nitrous acid has long been known to give not only an enhanced (25–30%) yield of olefin compared with the analogous S_N1 reactions of halides, but also rearranged products absent from the latter. The proportion of rearranged alcohols falls with increasing homology[17-19] (Table 1) and

Table 1. Rearranged products from nitrous deamination of alkylamines[17-19].

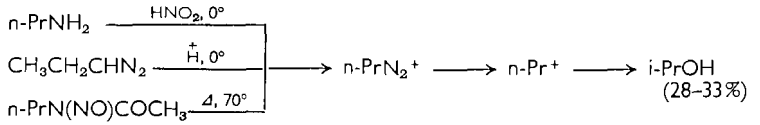
R in RNH_2	n-Pr	n-Bu	i-Bu	n-Oct	n-Non	n-Dec
% Rearranged ROH	58	34	75, 25	5	0	0
Isomer formed	iso	*s*	*t*, *s*	*s*	—	—

(conditions: aqueous or aqueous–acetic acids)

competition of the 1,2-methyl and hydride shifts responsible for the rearrangement with direct S_N1 and $E1$ is very dependent on conditions: e.g. the proportion of rearranged product from n-propylamine

falls from 58% in totally aqueous solvent to 31% in aqueous dimethylformamide[6,7]. Later it was appreciated that the driving force of these Wagner–Meerwein-like isomerisations (which can also involve aryl shifts) was the tendency, usually only capable of fruition in hot ions, of the initially formed ion to rearrange to a more stable secondary or tertiary ion. Thus normal and iso substrates yield secondary and tertiary products respectively, whereas secondary substrates never form normal products[20]. Sometimes the hot-ion model seems inadequate[20]—iso:*s*:*t* product from isobutylamine changes from 10:19:71 in water to 23:21:56 in 7 N aqueous sodium thiocyanate, and the ratio of alkyl thiocyanate and isothiocyanate products also suggests that the anion participates in C–N cleavage to some extent.

Analogous rearrangements accompany related deaminations (reaction 1), in which the similarity of products under comparable conditions suggests a common intermediate[6,7,21,22]; the slight differences being attributable to the (necessarily) different reaction



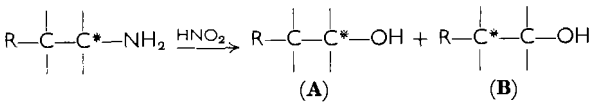
(1)

temperatures. Only about 1% isoalcohol results from decomposition of diazopropane in ethereal acid[6,7], probably owing to the formation of specifically orientated ion pairs in these non-solvating conditions (e.g. $\overset{+}{R}N_2\bar{O}Ac$, when acetic acid was the catalyst) which inhibit rearrangement. In more polar media, ion dissociation simulates the situation in nitrous deamination and permits extensive rearrangement. It is interesting that at the other end of the solvation scale, the nitrous deamination, under completely aqueous conditions, of substrates that initially form stabilised carbonium ions (e.g. *t*-amines) gives little rearrangement[117]. Here the relatively stable ion initially formed may solvate to form a 'cold' ion before rearrangement can occur; or it may orientate an incipient hydroxide ion from the solvent shell to act as a counter ion at the diazonium-forming stage.

The pyrolyses of *N*-nitroso-*N*-acetylamines also probably generate ion pairs in the usual non-polar reaction media, e.g. *p*-cymene, for little rearrangement is reported[23,64]. Diazoalkanes, formed by elimination from diazohydroxides, are unlikely intermediates in nitrous deamination, for neither ethylamine nor isobutylamine gives labelled products when the reaction is conducted in deuterated media: these observations also exclude π-complex intermediates[19,24].

Tracer studies have shown that a proportion of the apparently unrearranged product can result from 1,2-shifts (Table 2). About 90%

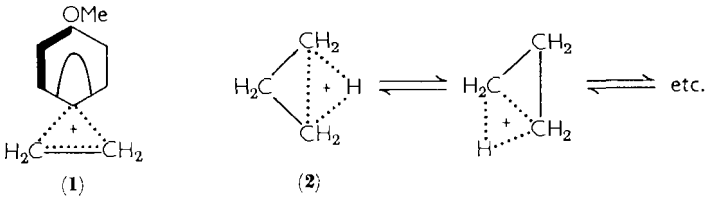
TABLE 2. Rearrangement in deamination of β-substituted ethylamines.



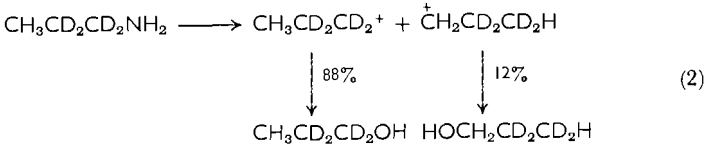
(C* represents ^{14}C)

R	H	Ph	*p*-$MeOC_6H_4$	*p*-$HOCH_2CH_2OC_6H_4$
% B	1·5	27	45	40
References	24	25, 26	25, 26	27

of the *p*-anisyl compound must have reacted through the bridged ion or transition state **1**, whereas such a route was much less favoured for hydrogen migration. Early investigations of n-propylamine[28,29,30]



reported 9% rearrangement of ^{14}C tracer from $C_{(1)}$ exclusively to $C_{(3)}$ and so excluded methyl shifts in favour of 1,3- or successive 1,2-hydride migrations. An n.m.r. study[31] of products from deuterated substrate indicated 1,3-migration (reaction 2) and was considered to



(2)

rule out the intermediacy of equilibrating cyclopropanes (**2**)[32]. The existence of the latter are also inconsistent with the ^{14}C studies, but reinvestigation[33] has led to a reappraisal in that not only a lower proportion (about 4%) of tracer rearrangement, but also nearly equal migration to $C_{(2)}$ and $C_{(3)}$, was demonstrated. These, and concurrent

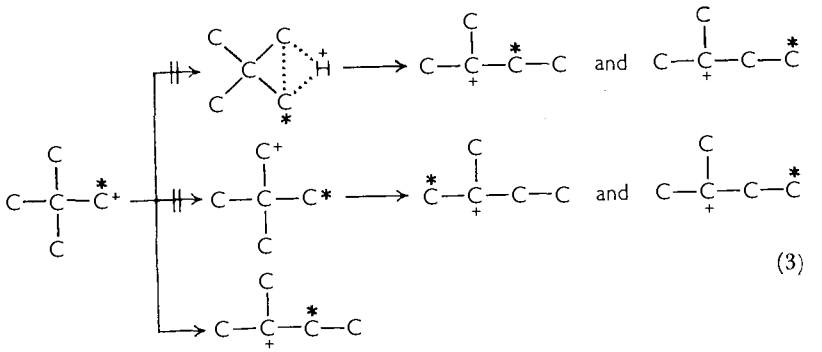
studies on deuterated and tritiated substrates[34], are inconsistent with the 1,3-shift occurring entirely through open classical ions, and favour **2** as specific intermediates (rather than transition states) which can give up to 10% cyclopropane in addition to the usual products[35]. Isolation of cyclopropane-d_2 and -d_3 in comparable amounts from decomposition of γ-trideuterated n-propylamine supports this view[36]. Certain other alkylamines give up to 15% cyclopropanes under conditions not favourable to diazoalkane formation and its subsequent carbenoid decomposition, and presumably in all cases proton loss from bridged ions similar to **2** leads to products, but it is difficult to rationalise the relative ease of cyclisation and 1,2- and 1,3-shifts in these compounds in any convincing manner[37].

Reactions of *neo*-pentyl derivatives, based on a skeleton well known for rearrangement tendencies in S_N1, are summarised in Table 3. As

TABLE 3. Deamination of *neo*-pentyl-like structures.

Compound	% Rearrangement	Migrating group	Reference
$Me_3CCH_2NH_2$ (**3**)	100	Me	38
$Me_3CCHPhNH_2$ (**4**)	0	—	38
$Et_3CCHPhNH_2$ (**5**)	~30	Et	38
$R_2CPhCHPhNH_2$ (**6**)	~50	Ph	38
$(p\text{-}MeOC_6H_4)_3CCH_2NH_2$ (**7**)	17	$p\text{-}MeOC_6H_4$	39
$Ph_3CCH_2NH_2$ (**8**)	28	Ph	39

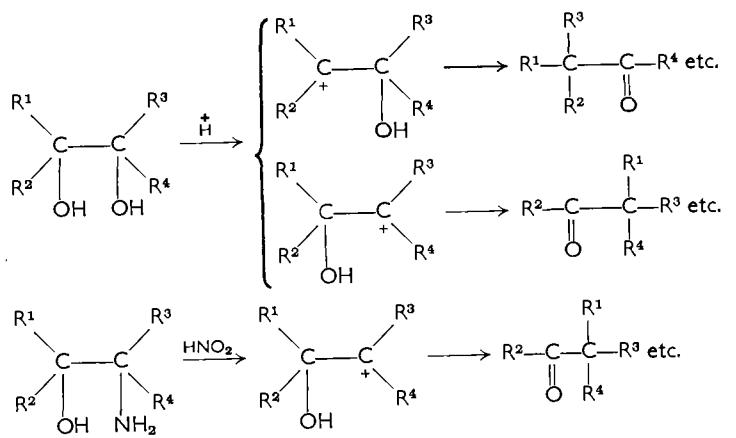
expected, **3** gives products derived from a tertiary ion, but the first-formed ion from **4** is stabilised by the phenyl group. Such a substituent cannot prevent rearrangement when steric congestion at $C_{(2)}$ is relieved in so doing, as in **5**, or when phenyl migration is possible as in **6**. The size and relative order of rearrangement in **7** and **8** is also surprising. ^{14}C Labelling of the 1-position of **3** leads to *t*-pentanol with tracer solely located at $C_{(3)}$[40], indicating a 1,2-methyl shift rather than hydride migration via open ions or protonated cyclopropanes, in contrast with the situation for n-propylamine (reaction 3). Other differences between the two substrates are that **3** yields no cyclopropane, but gives larger quantities of rearranged olefins[41]. Other tracer studies of alkylamines have demonstrated similar skeletal migrations[42, 43].



(3)

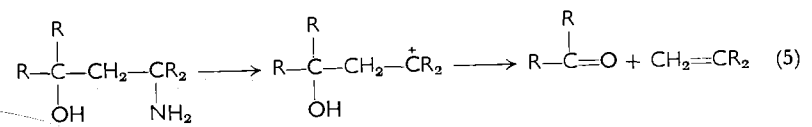
C. Semipinacols

1,2-Aminoalcohols (semipinacols) undergo aryl, alkyl, and hydride shifts on treatment with nitrosating agents, and 1,2-diamines behave analogously[44]. The former class gives similar products to those of the corresponding pinacol rearrangement (reaction 4), but with the



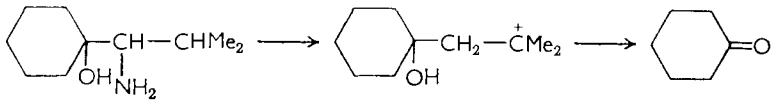
(4)

important modification of hot-ion formation; although the product distribution from particular substrates in the two reactions may be identical if the hot ion can be solvated before it reacts further[45], and here glycols and epoxides may predominate[44]. 1,3-, 1,4-, and some 1,2-aminoalcohols give up to 20% fragmentation (reaction 5), even



(5)

when phenyl migration is occurring at the same time[46]; and such cleavage may follow hydride migration (reaction 6)[47]. Poorly solvating



+ $CH_2{=}CMe_2$ (6)

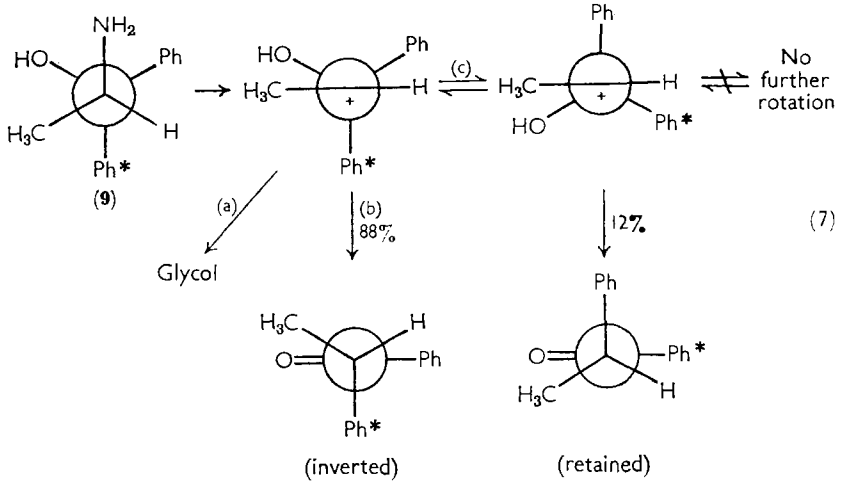
media, e.g. dioxan, inhibit rearrangement, even when phenyl migration is possible[48,49]; presumably ionic aggregation here, occurs even for nitrous deamination (see section I.B), facilitated by the low dielectric constant and the orientating effect on the solvation sheath caused by the neighbouring hydroxyl group.

D. Stereochemistry

The fragmentary data[50] available for normal and semipinacolic deamination was once held to indicate strictly stereospecific migration that was synchronous with, or followed shortly after, C—N fission to give inversion at the terminus. More recent work has modified this conclusion, although the stereochemical consequences at the migrating group and the migration origin have still remained largely unelucidated.

A reexamination of the original data indicates up to 12% retention of configuration accompanying inversion, and a brilliant radio- and stereochemical study with specific ^{14}C labelling showed that the labelled group migrated exclusively with inversion, whereas a second, identical but unlabelled group migrated with retention (reaction 7)[51,52]. These results were convincingly interpreted, as shown, on the basis of classical carbonium ions which rearranged to products before complete rotation around the central C—C bond could be achieved, and non-classical intermediates or rearrangement synchronous with nitrogen loss were excluded. The *anti*-periplanar* relationship between the migrating and leaving groups implied by this scheme is certainly consistent with the last mechanism, but the consensus of opinion, here and in other examples, is that the *anti* relationship enables maximum overlap between the bond electrons of the migrating group and the

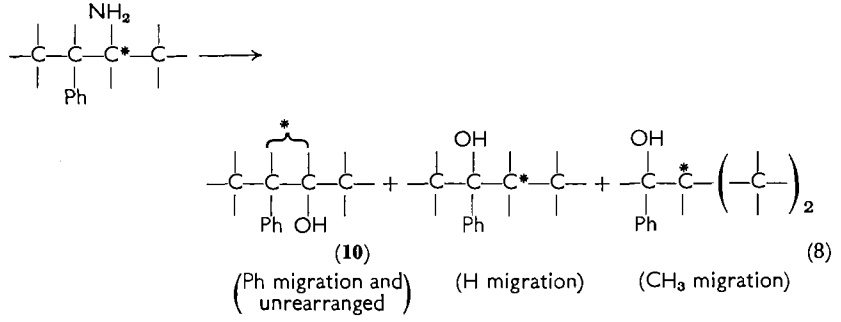
* For the purpose of this review, *anti*-periplanar, *syn*-periplanar, and *syn*-clinal relationships between two bonds linked to adjacent atoms refer to conformations with dihedral angles of 180°, 0 to 15°, and 15 to 90° respectively. For more complete definitions see reference 398.



(7)

freshly formed empty *p* orbital on $C_{(1)}$. Rotation of the ion into other conformations than those shown would have given retention with the labelled phenyl having migrated.

Earlier ^{14}C studies (reaction 8) had demonstrated that the ap-

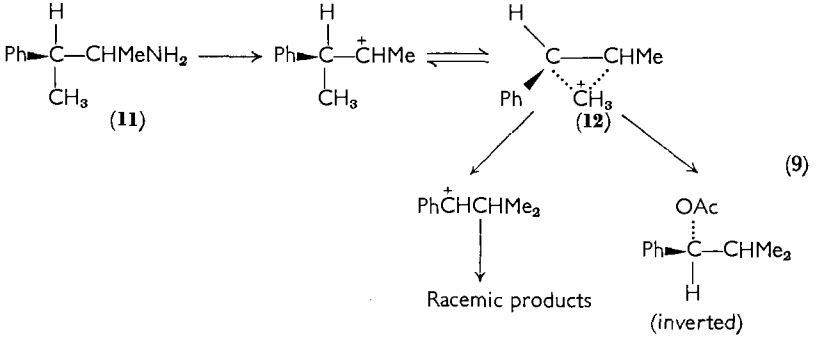


(8)

parently unrearranged product **10** had tracer distributed equally between the two carbons indicated[53], and although this was consistent with phenyl migration through a non-classical intermediate similar to **1**, the initial formation of a classical ion was preferred for such an exothermic process as deamination, with (presumed) lack of neighbouring group participation. Much evidence for non-classical phenonium ions is available in S_N1[54], but stereospecific 'equilibrating' rearrangement of the above type is necessary, although not sufficient, evidence for proving such intermediates in deamination.

Extensive tracer and stereochemical studies on deaminations, or semipinacolic rearrangements, and on thermal decompositions of the *N*-nitroso-*N*-acetyl derivatives, of 1,2-, 2,2-, and 1,2,2-polyarylalkylamines are all consistent with schemes similar to (7), involving classical ions which largely invert their configuration at the terminus owing to: (a) steric shielding of the positive centre and (b) the similar rates of migration and rotation about the central bond[55-58]. The schemes in general, and factor (b) in particular have been criticised[59] as being based on an incorrect ground-state conformation, but computer analysis of the data from several reactions supports the original proposals[60,61], and indicates rate ratios (see reaction 7): $k_c/k_b = 0{\cdot}9$ to $1{\cdot}8$; $k_a/k_b = 1{\cdot}1$ to $2{\cdot}3$. As the energy barrier[62] for step (c) is about 0·006 to 1·15 kcal/mole, the rate of migration can be readily estimated.

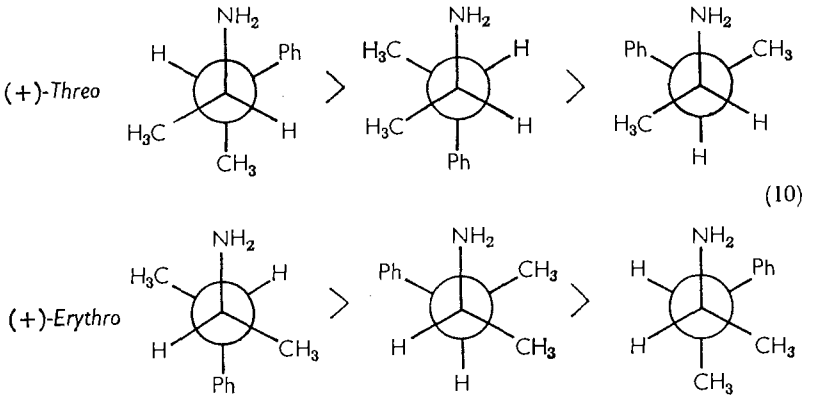
Extension of these conclusions to non-arylated substrates is uncertain as the classical ion may be especially stabilised in these rather unusual structures, and the route utilised may well depend on the reaction conditions. Deamination of 2-amino-3-phenylbutane (**11**), results in stereospecific migration of phenyl with inversion at the origin and terminus (owing to the symmetry of the molecule this rearrangement could only be detected by optical analysis), but the accompanying methyl shift resulted in only about 16% inversion at the migration origin[63]. A bridged ion **12** (reaction 9) was proposed



(9)

here, and also for the phenyl shift, which in the former, but not latter case, either reacted with inversion at the migration origin to give products, or first formed a new classical ion which gave racemic products. It was also recognised that the partial stereospecificity of the methyl shift may result from predominant attack on a classical ion from the less sterically hindered side. At present a decision is not

possible between the two mechanisms, although **12**, in contradistinction to phenonium ions, seems more likely as a transition state than an intermediate. Less ambiguous was the observation that *threo*-**11** gave 32% methyl, 24% phenyl, and 24% hydrogen migration, whereas the *erythro* isomer gave 6, 68, and 20% respectively. These values are in excellent accord with the calculated conformational populations of the substrates, (reaction 10) and with the proposal that an *anti*-



(10)

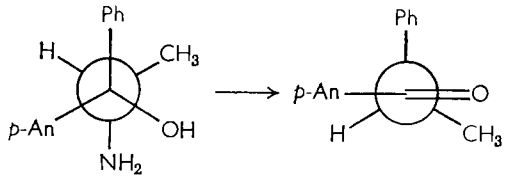
periplanar relationship between migrating and leaving groups is required. Although this is again consistent with a mechanism where migration is synchronous with nitrogen loss from the diazonium ion, the consensus of opinion again is that it refers to a carbonium ion mechanism in which the migration rate is considerably greater than the rate of rotation about the central bond, *i.e.* analogous to reaction (7), with no rotation of the first-formed ion.

E. Migratory Aptitudes

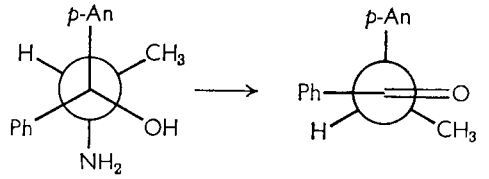
The ease of migration of groups in the pinacol rearrangement varies in a consistent and interpretable manner over a several hundred-fold range, but little selectivity is shown in migration to a hot ionic centre. Accordingly, the relative migratory aptitude (determined by product analyses of substrates carrying groups to be compared in equivalent positions) for *p*-anisyl:phenyl falls from about 500:1 in the former reaction, to 1·6:1 in semipinacolic deamination, and such values are typical for *p*-substituted aryl groups, irrespective of the polarity of the *para* substituent[4,25]. Discrimination between possible migrating groups is also negligible in deamination of 2,2-diarylethylamines[65]. and *N*-nitroso-*N*-acetylamines[7]; for example ratios for *o*-, *m*-, or *p*-tolyl

to phenyl are all 1·2:1. Phenyl has a very much greater migratory tendency in S_N1 than have methyl or hydride ions, in fact the latter have been rarely observed to shift, but in certain deaminations the phenyl:methyl migratory aptitude is only about 6, and phenyl:hydride about 18[25,26]. Alkyl groups also probably have similar aptitudes in deamination; e.g. $PhCH_2{=}CH_3$ = 2:1[66]. $\Delta H^{\ddagger}$ for hydride shift in isobutylamine is 2·5 kcal/mole less than that for methyl shift[19], but the ΔS^* factor favours the latter process by some 5 kcal/mole. The latter factor probably illustrates the small tendency of hydrogen to be situated *anti* periplanar to the leaving group in the ground-state conformations: a much bulkier group usually occupies this position.

In all these compounds, ground-state conformations are equally probable with either of the competing and compared migrating groups in the favourable *anti*-periplanar orientation to the amino group, but in certain diastereoisomers *cis* interactions between bulky non-migrating groups attached to the two asymmetric carbons cause different groups in each isomer to be favourably oriented in the ground state and the closely related (both electronically and structurally) transition state. Thus migration occurs predominantly as shown in **13** and **14** (*p*-An = *p*-Anisyl), (reaction 11), such that any



(13)



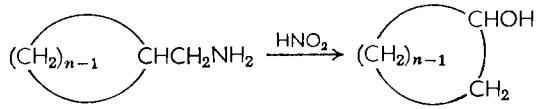
(14)

(11)

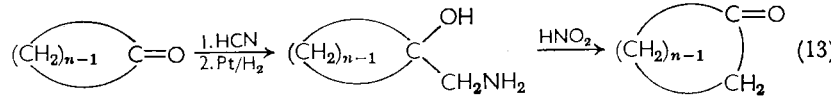
'*cis* effect' of neighbouring aryl and methyl is eliminated[67]. Other unusual relative aptitudes, e.g. Ph > σ-Tolyl[68], Ph > Naphthyl[69], and *t*-Bu ~ Ph[70], also reflect the favoured ground-state conformation rather than inherent migrational ability, and again indicate (on the basis of the carbonium ion model) the preference for migration within, rather than rotation of, the initially formed ion.

F. Cycloalkylamines: Ring Expansion

Alicyclic analogues of the above reactions were discovered in 1901 (Demjanov rearrangement of amines) and 1937 (Tiffeneau rearrangement of aminoalcohols), but although scores of examples have been recorded[71], few mechanistic studies are available. These reactions, shown in (12) and (13), usually give good (30–60%) and sometimes excellent (>80%) yields of rearranged alcohols or ketones and



(12)



(13)

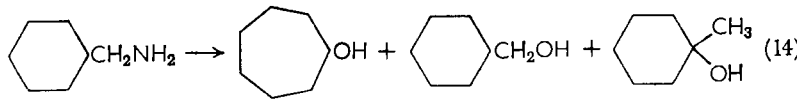
olefins, accompanied by unrearranged products, and three- to twelve-membered carbocyclic rings have been thus expanded: maximum rearrangement occurring with the five to seven membered[71-73]. As a carbon–carbon (ring) bond will predominantly be *anti* periplanar to the leaving group in the substrate, the hindered rearrangement of the larger rings probably reflects an unfavourable entropy factor in the actual migration step, caused by the need to change the conformation of the original ring, when its span is flexed to a new terminus.

The Tiffeneau reaction possesses two properties favouring ring expansion:

(i) No hydrogen is available at $C_{(2)}$ to compete with migration of ring-bond electrons.

(ii) A protonated carbonyl group, $\overset{+}{\text{C}}$—OH, is formed on ring expansion which is a comparatively stable carbonium ion. Consequently expansion is usually more complete, with less olefinic by-products, than in the Demjanov process. In synthesis, the Tiffeneau method is especially valuable for ring enlargement of ketones (see reaction 13).

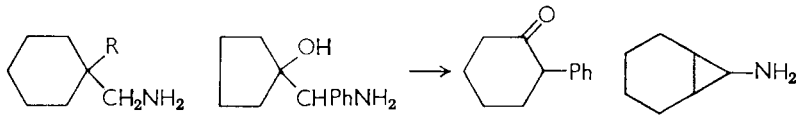
These rearrangements are again manifestations of the tendency to form a more stable carbonium ion. Both ring-bond and hydride shifts (in Demjanov conditions) can occur (reaction 14)[74], but the latter are



(66%) (33%) (1%)

(14)

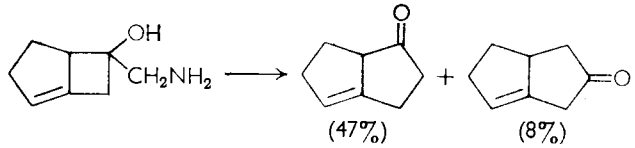
usually unimportant as they require an unfavourable ground-state conformation, even though they lead to a tertiary ion. Nevertheless up to 20% tertiary alcohol results from 1-cyclopentylethylamine[75], and hydride shift can be readily demonstrated in non-rearranged products by tracer studies; for example 1-^{14}C-cyclohexylamine gives a mixture of 1-^{14}C- and 2-^{14}C-cyclohexanol[76]. Methyl and phenyl substituents at $C_{(2)}$ can migrate more efficiently than hydrogen in competition with ring expansion, as their greater size ensures a greater proportion of the ground state having these groups *anti* to the amino group. Thus **15** (R = CH_3) gives 2-methylcycloheptanol (67%) and 1-ethylcyclohexanol (11%); the latter derived from methyl shift[71,77]; whereas **15** (R = Ph) gives only products of phenyl migration[78]. A $C_{(1)}$-attached alkyl or phenyl group stabilises the ion initially formed in



(15) (16) (17)

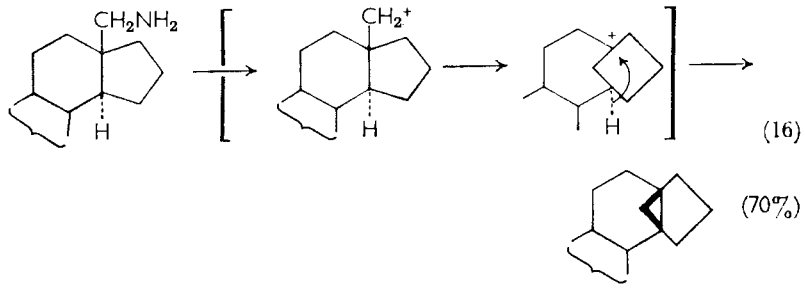
Demjanov deamination and so inhibits ring expansion, even in small rings where strain is released by the latter process[71,75,82]. An intervening methylene group between the ring and the ionic centre (in 3-cycloalkylpropylamines) has the same effect[71]. Tiffeneau reactions are much less affected by such factors, having stronger driving forces, and **16** gives over 50% ring expansion, and the corresponding 1-methylated amine of the cyclohexane series even more[71,83]. Bulky alkyl groups at $C_{(1)}$[84] or the axial/equatorial nature of the aminoethyl group (in conformationally fixed 4-*t*-butyl-1-hydroxy-1-methylaminocyclohexanes) do not prevent up to 80% ring expansion[47].

Asymmetrically substituted rings can expand in two ways to give position isomers, the proportions of which can usually be rationalised by conformational considerations as to which ring bond is suitably placed for migration (however, see reaction 15)[71]. Demjanov–Tiffeneau reactions can be applied to bicyclics (reaction 15)[71].



(47%) (8%) (15)

Reaction (16) is a general route applicable to the C–D rings of steroids[86,87] and to *N*-, *O*-, and *S*-heterocyclics[71,85]. However, certain



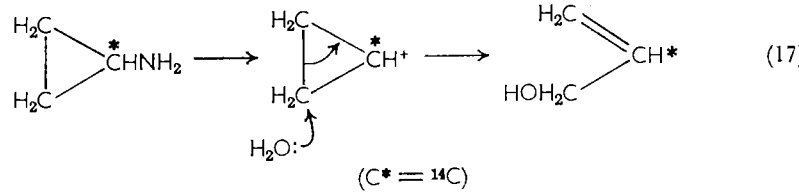
(16)

(70%)

electronegative substituents (2- and 4-Cl, F, and COOEt) inhibit ring expansion in six- and even four-membered rings[71,79-81], perhaps by favouring direct decomposition in the diazonium ion stage.

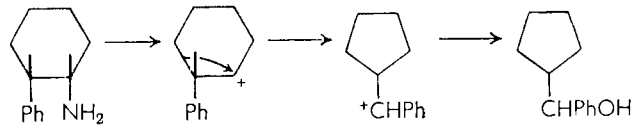
G. Cycloalkylamines: Ring Contraction

In a few structures, the most stable ion results from ring contraction, rather than expansion. Cleavage of the strained ion from cyclopropylamine[88] is a particular case, and ^{14}C labelling has elucidated the mechanism (reaction 17)[89]. The bicyclic (**17**) reacts analogously to



(C* = ^{14}C) (17)

give 2-hydroxycycloheptene[90], but the ion derived from cyclopropylmethylamine is much more stable (see section I), and the strained **18** gives little rearranged product[91].



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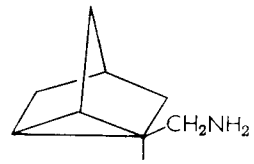
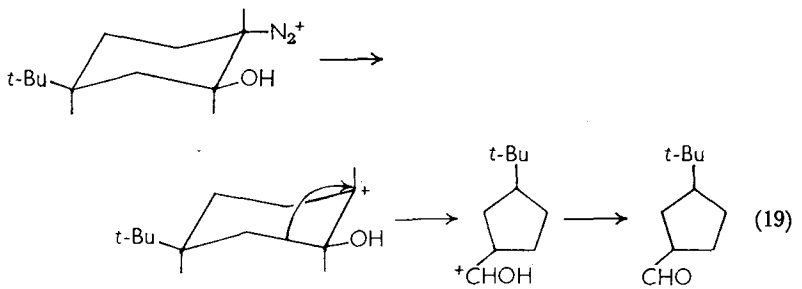


(18)

True contraction is stimulated by a 2-phenyl substituent in cyclohexylamine (reaction 18), which enables a benzyl cation to be formed, but not by 4-phenyl, 4- or 2-alkyl groups[79]. It leads to the major product from 1,2-aminoalcohols in which the amino group is fixed equatorially either by incorporation into a *trans*-decalin skeleton[92] or by the use of a *t*-butyl conformational-holding group in cyclohexanes[10]. The latter reactions are the consequences of the combination of a suitably orientated $C_{(2)}$–$C_{(3)}$ bond, and the possibility of forming a protonated carbonyl group (reaction 19); when the amino group was

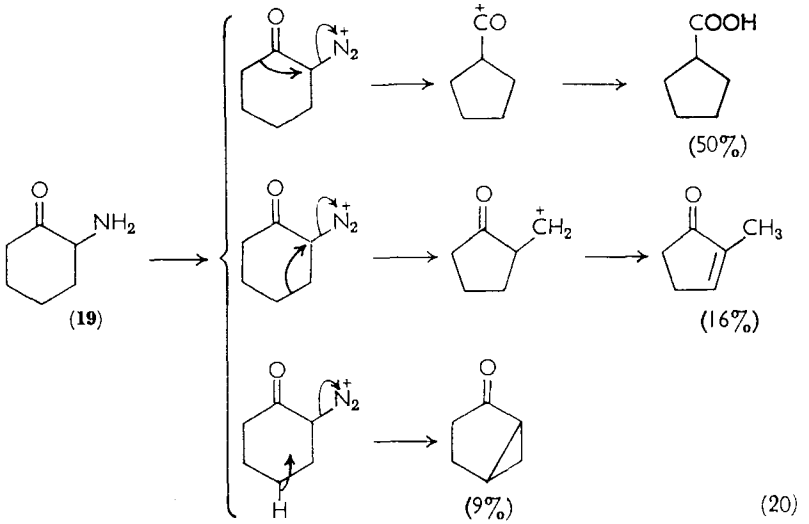


(19)

fixed axially no contraction took place. *trans*-2-Hydroxycyclohexylamine (OH, NH_2 both equatorial in the ground state) gives almost exclusively the ring-contracted aldehyde for the same reasons[93,134], but the *cis* isomer (with a major proportion of NH_2 equatorial) gives 70% contracted and 30% unrearranged products[94-96]. Originally it was believed that these last products corresponded to the conformational populations of the *cis* starting material, but recent work[10] refutes this and interprets products in terms of the equilibrium conformations of diazohydroxides which are supposed to decompose directly to a carbonium ion and to by-pass the diazonium ion. It is not yet clear how general this mechanism is in aliphatic deamination.

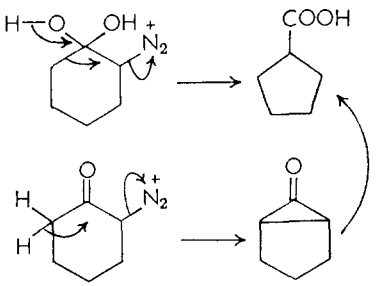
H. α-Aminoketones

The usual deamination mechanism is considered[97] to be energetically unfavourable for these substrates, as it would generate a positive centre adjacent to the positive end of the carbonyl dipole, and rearrangement synchronous with nitrogen loss from the diazonium ion is suggested, to allow incipient charge on $C_{(1)}$ to be delocalised. A detailed product study of **19** delineates three types of bond rearrangement (reaction 20)[97]. The cyclopentane carboxylic acid may also be



(20)

formed by direct rearrangement of the ketone hydrate (reaction 21) but a Favorskii-type mechanism (reaction 22) was excluded by the



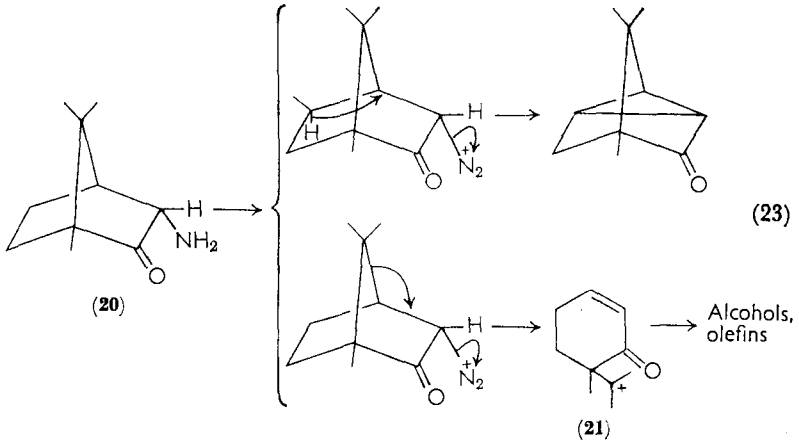
(21)

(22)

observation that 2-amino-6,6-dimethylcyclohexanone and **19** both give similar products. 1,3-Transannular elimination of hydrogen to form the bicyclic ketone as in reaction (20), was also demonstrated in a reinvestigation of products from cyclohexylamine which revealed 2% (3.1.0)-bicyclohexane[97,133]. This may indicate that part, at least, of this substrate decomposes via the diazonium ion with no formation of the hot carbonium ion, as the 2-methyl derivative of **19**, which might be expected to be able to react by the carbonium ion mechanism, gives only unrearranged products[98].

Straight-chain α-aminoketones rearrange analogously to alkylamines by means of methyl shifts[98], but **20** does not undergo 2,6-hydride shift similar to that occurring in the bornylamines (see

section I.J). The ring opens to a classical ion **21** with good charge separation, and some 1,3-hydrogen elimination takes place (reaction 23)[97]. Similar reactions are reported for other bicyclics[99].

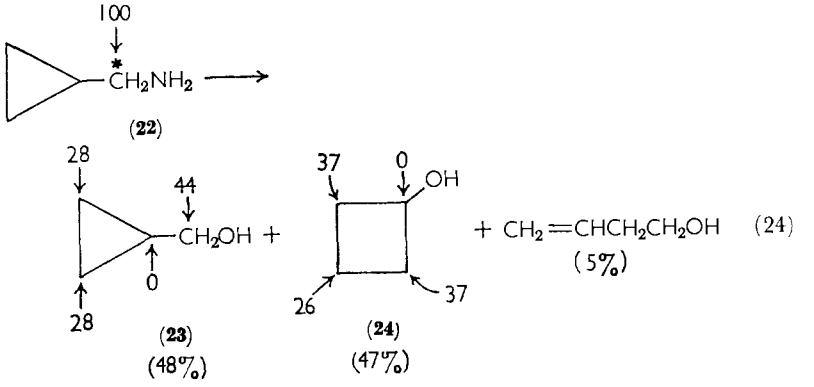


(23)

I. Non-classical Ions from Monocyclic Amines

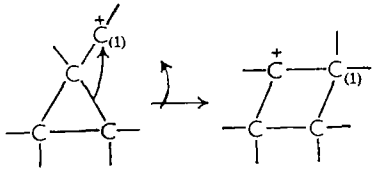
As outlined in section I.D, there is no compelling evidence for non-classical intermediates in the deamination of acyclic amines, but a series of tracer and stereochemical studies have led many workers to postulate their existence in the alicyclic field[100,129]. In forming mesomeric cations monocyclic, and especially bicyclic, ions have important advantages over open-chain compounds as the latter must sustain a large entropy loss in order to achieve the restricted orientation for electron delocalisation.

Cyclopropylmethylamine (**22**) would either be expected to undergo ring expansion to cyclobutyl derivatives or cleavage to allylic products in order to gain advantage from secondary or mesomeric ion formation, but the situation is much more complex. Reaction (24) shows products and tracer distribution from 1-^{14}C-labelled substrate[101]. It is interesting that cyclobutylamine gives the same proportions of products although the equilibrium position of **23** and **24** is nearly 100% in favour of the latter[101], and that 2-phenylated **22** gives 97% ring expansion via a benzylic ion[102]. A simple view of the expansion is that the *p* orbital of $C_{(1)}$ in the carbonium ion overlaps with one of the 'banana' orbitals of the three-membered ring (reaction 25) such that $C_{(1)}$ of **22** becomes $C_{(2)}$ of **24**, but the tracer distribution shows that an intermediate must intervene in which $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ of **24** become



(24)

(figures give % distribution of tracer)



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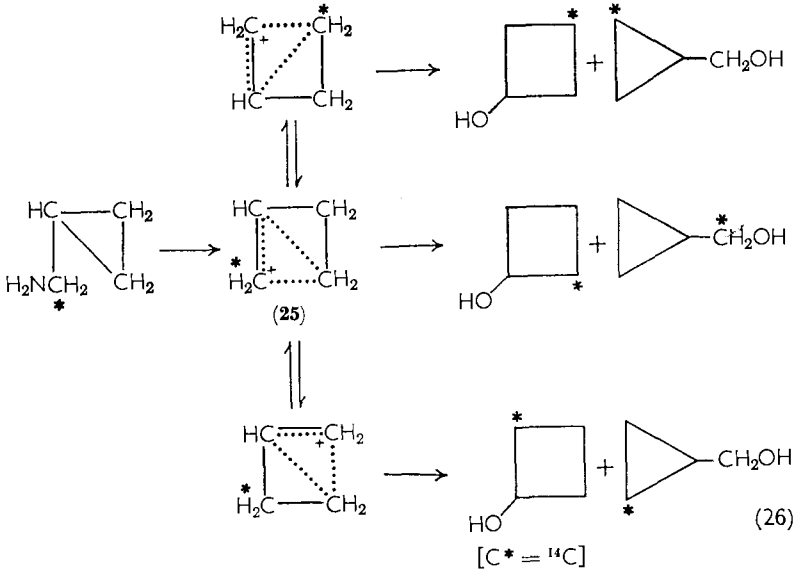
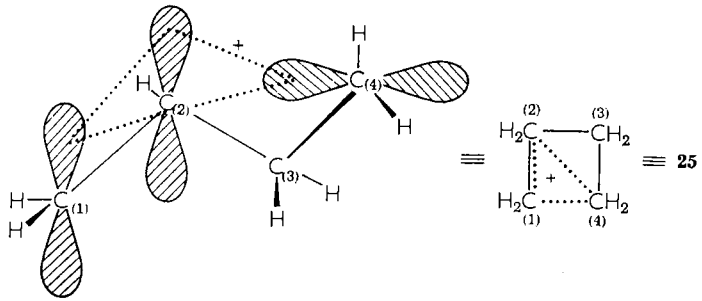
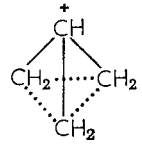


(26)

nearly, but not exactly, geometrically equivalent, as must $C_{(1)}$, $C_{(3)}$, and $C_{(4)}$ of **23**. No classical species fulfills the role, but a scheme of rapidly, but not instantaneously interconverting non-classical ions was proposed (reaction 26). It is important to appreciate that **25**,

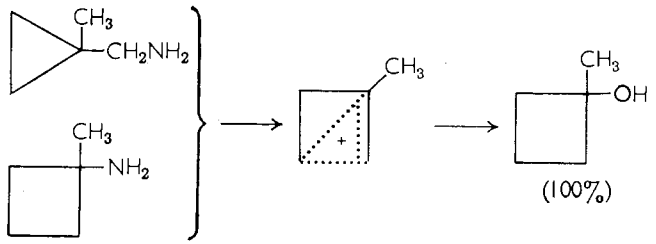


(**26**)



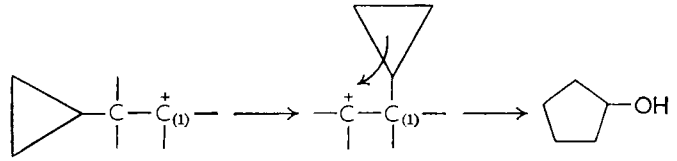
(**27**)

for example, is shorthand notation for a complicated orbital diagram: the geometry of this ion is probably **26**, wherein the $2p$ orbitals of $C_{(1)}$, $C_{(2)}$, and $C_{(4)}$ overlap to form a bonding molecular orbital (containing two electrons) and two vacant antibonding orbitals[101]. Symmetrical ions such as **27** are believed to play a minor role as intermediates, except possibly in the interconversions of **25** and its two isomers. Deamination (and S_N1) of other cyclopropyl derivatives have been similarly interpreted[103], although in some structures tracer work indicates little scrambling from $C_{(1)}$, and an almost classical ion, with a nearly localised charge, is likely (reaction 27)[104].



(27)

An interesting product from 2-cyclopropylethylamine is cyclopentanol, which is believed to result from irreversible migration of the ring to $C_{(1)}$ (reaction 28), although the reactions are complicated by

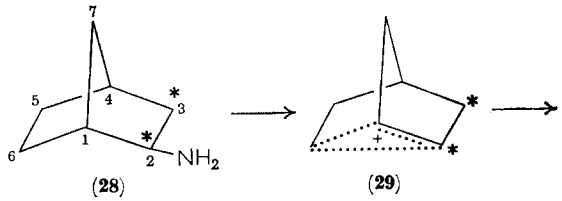


(28)

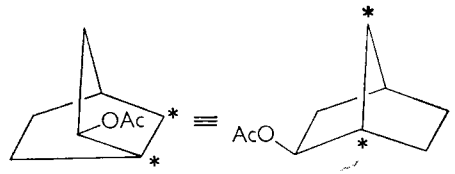
much isotope scrambling from $C_{(1)}$ and probably proceed through non-classical intermediates[105].

J. Non-classical Ions from Bicyclic Amines

Solvolyses and deaminations of *exo*- and *endo*-norbornyl (**28**) and norbornenyl derivatives labelled with ^{14}C at $C_{(2)}$ and $C_{(3)}$ have been held to indicate non-classical intermediates (reaction 29)[106,107]. If **29**

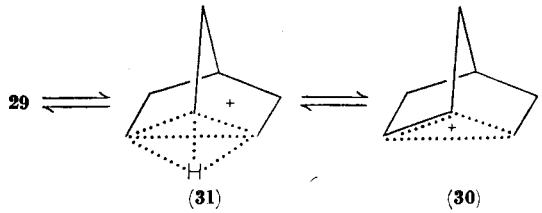


(**28**) (**29**)



(29)

was the sole intermediate, tracer would appear at $C_{(1)}$ and $C_{(7)}$ in the product, but substantial, although not equivalent amounts were found at all positions except $C_{(4)}$. This distribution was accommodated by postulating a 2,6-hydride shift linking non-classical ions **29** and **30**, via the special non-classical symmetrical species **31** (reaction 30), and

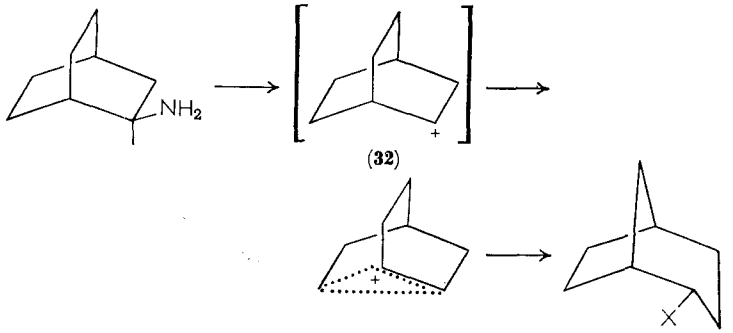


(**31**) (**30**)

(30)

so achieving a system whereby partial or total equilibration of tracer in all positions except $C_{(4)}$ could be realised, before destruction of the intermediates by solvolysis. However, there is no evidence that **31** is anything but a transition state in the equilibration of **29** and **30**, which could both be classical. The above scheme would yield racemic products, and a claim to optically active products led to the proposal of equilibrating classical ions[108], but this work has been validly criticised on both experimental and theoretical grounds[109], and the consensus of opinion favours non-classical intermediates, although not necessarily the existence of **31**[100].

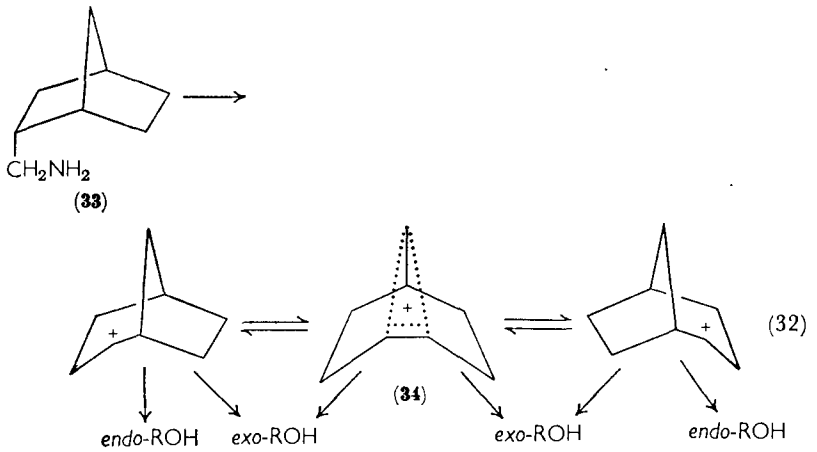
More recently, analyses of tracer distribution or optical activity, and geometric structure (i.e. *endo* or *exo*) of products from various bicyclic amines have presented evidence for non-classical intermediates[100,113]. A typical example is shown in reaction (31)[110]. In both non-solvating (to carbonium ions) acetic acid and solvating aqueous conditions, only *exo* product could be detected and such stereospecificity is difficult to interpret on a classical mechanism[100], wherein **32** is directly destroyed by solvolysis. Optical examination of



(31)

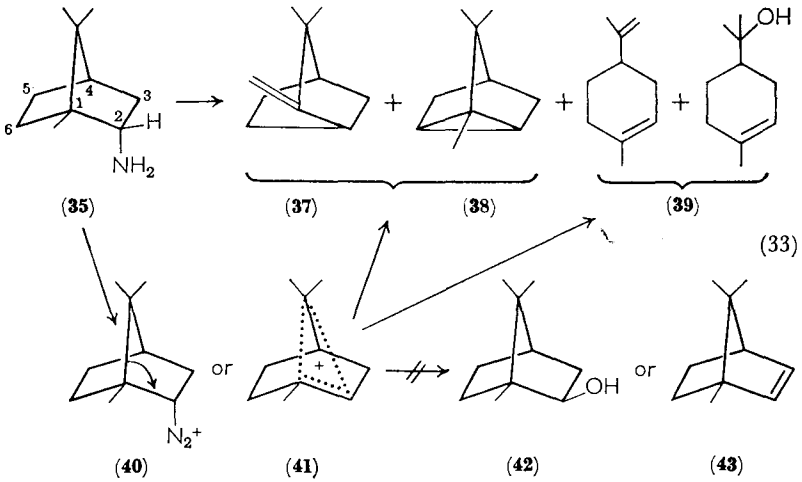
products was not made but a non-classical ion would lead to active *exo* product whereas the *endo–exo* mixture from **32** would be racemic. For other systems it has been adduced that both classical and non-classical ions act as precursors of products: for example **33** gives optically active products and this rules out the symmetrical **34** as sole intermediate. Detailed analysis suggests reaction (32)[111]. The epimeric *exo*-amine, although forming a formally identical carbonium ion, utilises a different sequence of classical and non-classical intermediates which are only converted into those of reaction (32) with difficulty, and which lead to entirely different products[112].

Particularly well studied is the bornylamine system. Both bornylamine (**35**), and its epimer (**36**), give camphene (**37**) and tricyclene



(32)

(**38**) on deamination in aqueous or acetous solvents[114,115], and the former is optically pure, i.e. there is no evidence for Nametkin or 2,6-hydride shifts. However, **35** gives up to 10% of monocyclic products **39**, whereas its epimer gives none (reaction 33). The corresponding



(33)

fencyhlamines behave similarly[116]. It is unlikely that the ring opening occurs by a synchronous elimination-type mechanism in the ion **40**, for as the preferred dihedral angle of either 0° or 180° between the participating bonds cannot be achieved (owing to the rigid geometry) in either the *endo* or *exo* isomer, each isomer should behave similarly. Also, perfect eclipsing (dihedral angle ~0) of the leaving group and a

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Boyd, M. 393 (226), *405*
Boyd, W. F. 123 (456), *156*
Boyer, J. H. 323 (240a), *345*
Boyland, E. 638 (290, 292), *665*
Brabander, H. J. 653 (374), *667*
Brackman, W. 318 (215), *344*
Bradley, W. 255 (265), *273*
Bradshaw, J. S. 366 (113), *401*, 438 (96), 439 (96, 99), *492*
Bradsher, C. K. 59 (111), *74*
Bradstreet, R. B. 82 (43, 44), *146*
Brady, O. L. 294 (99), *341*, 363 (95), *401*
Branch, G. E. K. 229 (105), *268*
Brand, J. C. D. 65 (158), *76*, 95, 131 (168), *149*, 256 (274), *273*
Brandenburg, D. 694 (175), *699*
Brasen, W. R. 708 (28), *746*
Braser, W. R. 621 (183), 662
Bratoz, S. 7 (8), *34*
Braude, E. A. 128 (477–479), 130, 131 (479), *157*, 213 (48), *267*
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Braun, J. von 46 (27), 50 (56), 51 (27), *70, 72*, 106 (304), *152*, 410 (4b), 427 (62), 428 (62, 65, 66), 483 (205, 206), *487, 490, 497*
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Bredeweg, C. J. 335 (292), *347*
Breederveld, H. 431, 432 (81f), *491*
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Bren, V. A. 352 (18), *398*
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Breslow, R. 705 (14–15d), 717, 723 (14), *745, 746*
Bretschneider, H. 689 (139), *698*
Breuer, E. 65 (161a), *76*
Brewster, J. H. 417 (25, 28a), 418 (33b), 432 (28a), *488, 489*, 615 (155), 635 (257), *662, 664*
Brewster, P. 135 (532), *158*
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Brimacombe, D. A. 219 (74), *268*
Brinley, J. E. 102 (256), *151*
Brion, H. 2, 7 (3), *34*
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Britton, H. T. S. 199 (117), *204*
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Broderick, O. J. J. 651 (362), *667*
Brodhag, A. 470 (176), *496*, 590 (38), *659*
Brodie, B. B. 102 (268), *152*
Brönsted, J. N. 167 (7), *201*, 374 (162), *403*
Brooker, L. G. S. 141 (574), *160*
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Brooks, D. W. 367, 386 (134), *402*
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Brower, K. K. 629 (228), *663*
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Brown, E. N. 104 (293), *152*
Brown, E. V. 365 (110), *401*
Brown, F. C. 59 (111), *74*
Brown, G. B. 657 (392), *667*
Brown, H. B. 427 (57c), *490*
Brown, H. C. 39 (8), 46 (33), 47 (34), 65 (161a, 161b), 67 (170b), 68 (175, 178), *70, 71, 76, 77*, 136 137 (552), 141 (577, 580, 581), 142 (580), *159, 160*, 170 (12, 13), 171 (14, 15), 186 (89), 187 (95), 191 (12), 197 (13, 108–111), 198 (111, 112), *201, 203*, 209 (18), 212 (31, 33), 214 (52), 215 (60, 67), 216 (60), 218 (52, 66–69), 219 (71), 222 (18), 223 (79), 224–228 (18), 251, 256 (52), *266–268*, 279 (4), *339*, 416 (21), *488*, 587 (13), *658*
Brown, K. 139 (563), *159*
Brown, L. E. 82 (17), *146*
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Brown, M. E. 512 (7), *580*
Brown, R. 60 (117), *74*
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Brownlee, M. J. 386, 388 (194), *404*
Brownlee, T. H. 416 (24c), *488*
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Bruce, W. F. 598 (78), *660*
Bruckenstein, S. 287 (47), *340*
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Bryner, F. 358 (54), *399*
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Buchler, J. W. 702 (2), 705 (12), 711 (2), 715 (39, 40), 721, 722 (48), 729 (2), 739 (77a, 77b), 740, 741 (77b), 742 (77b, 81), *745, 747, 748*
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Bumgardener, C. L. 417 (29a), 422 (42), 433 (85a), 435, 438 (95a, 95b), *488, 489, 491, 492*, 620 (175), *662*
Bunce, S. C. 605 (105), *660*
Bundel, A. A. 518 (22), *581*
Bunnett, J. F. 55 (93a, 93b), 56 (93a, 93b, 96), 57 (93a, 93b, 103b), 58 (93a, 108b), 60 (114), 63 (103b), *73, 74*, 235 (154–156), 237 (156, 167, 169), 238 (167, 175), 258 (175), *270*, 280 (10), 294 (101, 104), 297 (106, 107), *339, 341*, 381 (176), *403*, 411 (6b), *487*, 650 (353), *666*
Bunton, C. A. 284 (31), 291 (90), 307 (167–169), *339, 341, 343*, 469 (175), *496*, 639, 641 (302), 645 (327), *665, 666*
Burawoy, A. 361 (80), *400*
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Burch, J. E. 307 (168), *343*
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Burr, J. G., Jr. 468, 473, 474 (170a), *495*
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Burton, W. R. 112 (379), *154*
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Calvin, M. 672, 691 (22), *695*
Camerman, N. 142 (582), *160*
Camp, B. J. 102 (257), *152*
Campbell, A. 418 (33a), *489*, 615 (154), 628 (223), *662, 663*
Campbell, D. H. 388 (206), *404*
Campbell, N. 104 (293), *152*
Campbell, R. H. 58 (105b), *74*
Cândea, C. 95 (160), *149*

Cannell, L. G. 440 (103c), 464 (166), *493*, *495*, 587, 588, 596 (19), *658*
Cannon, G. W. 52 (69), *72*
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Capon, B. 56 (97), *73*, 231 (112), *269*, 654 (375), *667*
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Carlton, J. K. 118, 121 (418), *155*
Carmack, M. 132, 133 (503), *158*
Carnahan, J. E. 513 (9), 516 (12, 13), *581*, 704, 711, 712, 715, 728, 729, 733 (9), *745*
Carnahan, R. E. 50 (55a, 55b), *72*
Carothers, W. H. 179 (56), *202*, 675 (49), *695*
Carpenter, F. H. 683 (97, 98), *697*
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Carpenter, W. 736 (73), 741 (79), *748*
Carpino, L. A. 685 (117, 118), 694 (179), *697*, *699*
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Cartier, G. E. 605 (105), *660*
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Cerchez, V. 671 (15), *695*
Černý, V. 473 (184b), *496*, 598 (86), *660*
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Chamberlain, N. F. 113, 125 (393), *155*
Chamberlin, J. W. 683 (103), *697*
Chambers, D. C. 92 (134), *148*
Chambers, R. A. 431, 432, 436 (81d), *491*
Chambers, V. C. 179, 180 (57), *202*
Chambers, W. J. 704, 711 (10), *745*
Chan, J. C. 637 (277), *665*
Chan, T. H. 419 (37), *489*, 616 (159), *662*
Chandra, S. 51 (61a), *72*, 437 (91a) *492*
Chandross, E. A. 733 (69), *748*
Chang, C. H. 62 (134b), *75*
Chang, Ch. F. 82 (29), *146*
Chang, H. W. 394 (246), *405*
Chang, L. H. 104 (282), *152*
Chang, P. K. 368 (144), *402*
Chang, N. Y. C. 122 (438), *156*
Chang, S. H. 104 (283), *152*
Chang, Y. C. 732 (64), *747*
Channing, D. M. 683 (100), *697*
Chao, T. H. 258 (286), *273*
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Chayen, S. 512, (6) *580*
Chen, S. C. 104 (285), *152*
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Clark, R. F. 380 (175), *403*
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Coffin, E. M. 95 (166), *149*
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Cohen, D. 694 (172), *698*
Cohen, J. B. 289 (70), *340*
Cohen, L. A. 679 (79, 83), 680, 681 (84), *696*
Cohen, L. H. 555 (93), *583*
Cohen, M. M. 89 (69), *147*
Cohen, S. G. 484 (215), *497*
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