Cage peroxides having planar bridgehead nitrogen atoms

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Abstract: Three new cage peroxides, 1,6-diaza-3,4,8,9-tetraoxabicyclo[4.4.2]dodecane (**3a**),1,6-diaza-3,4,8,9-tetraoxa-11-methylbicyclo[4.4.2]dodecane (**3b**), and 1,6-diaza-3,4,8,9-tetraoxatricyclo[4.4.2.4^{11,12}]hexadecane (**4**), have been prepared by reaction of 1,2-diaminoethane, 1,2-diaminopropane, and *trans*-1,2-diaminocyclohexane, respectively, with formaldehyde and hydrogen peroxide in aqueous acidic solution. Their structures have been established by X-ray diffraction, and show the bridgehead nitrogen atoms to be predominantly sp^2 hybridized. The structures accord with ^{1}H and ^{13}C NMR spectra. Variable temperature NMR studies show that the diperoxide **3a** begins to undergo rapid inversion (on the NMR time scale) at about 303 K; up to 370 K the diperoxides **3b** and **4** show no conformational change.

Key words: cage compounds, formaldehyde, peroxides, amine nitrogen, hybridization.

Résumé : On a préparé trois nouveaux peroxydes en cage, les 1,6-diaza-3,4,8,9-tétraoxabicyclo[4.4.2]dodécane (**3a**), 1,6-diaza-3,4,8,9-tétraoxa-11-méthylbicyclo[4.4.2]dodécane (**3b**), et 1,6-diaza-3,4,8,9-tétraoxatricyclo[4.4.2.4^{11,12}]hexadé-cane (4) par réaction respectivement des 1,2-diaminoéthane, 1,2-diaminopropane et *trans*-1,2-diaminocyclohexane avec le formaldéhyde et le peroxyde d'hydrogène en solution aqueuse acide. On a identifié les structures par diffraction des rayons X et on a montré que les atomes d'azote en tête de pont sont hybridés principalement sous la forme sp^2. Les structures sont en accord avec les spectres RMN du ^{1}H et du ^{13}C. Des études de RMN à températures variables montrent que le diperoxyde **3a** commence à subir une inversion rapide (à l'échelle de temps de la RMN) à environ 303 K; à des températures allant jusqu'à 370 K, les composés **3b** et **4** ne présentent pas de changements conformationnels.

Mots clés : composés en cage, formaldéhyde, peroxydes, azote d'une amine, hybridation.

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Introduction

Alder and his colleagues (1) prepared the cage compound **1** by a multistep synthesis, and the chemistry of this and other cage compounds having bridgehead nitrogen atoms has been reviewed (2). The formally similar cage triperoxide **2** (hexamethylene triperoxide diamine or HMTD), which also has bridgehead nitrogen atoms joined by three four-atom bridges, was prepared in 1900 by Baeyer and Villiger (3) in a one-pot synthesis (which must involve many steps) in which formaldehyde reacted with ammonium sulfate and hydrogen peroxide in aqueous solution.

At room temperature, Alder's cage diamine **1** exists in several conformations. In the conformation **1** represented

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above, the lone pairs of electrons of both tetrahedral nitrogen atoms point inwards (in–in) into the cage; in other conformations, the lone pairs are in–out and out–out. The tetrahedral nitrogen atoms of **1** are slightly flattened. In a typical tertiary amine, the nitrogen atom is 0.49 Å out of the plane of the three attached carbon atoms; in the diamine **1**, they are 0.31 Å out of this plane (4). This flattening probably takes place because of van der Waals repulsions between the two nitrogen atoms, which have van der Waals radii in the neighbourhood of 1.55 Å (5–8) and are only 2.806 Å apart in **1** (4).

On the other hand, in HMTD (**2**) the nitrogen atoms have been shown in crystallographic studies of Schaefer et al. (9) to be exactly planar with three-fold coordination, and with N—C distances of 1.42 Å, as compared with 1.47 Å for a

typical tertiary amine. The molecule exists as a racemic mixture of two chiral helices having C-O-O-C torsional angles of ±129.3°, and not as the achiral cylinder **2** shown above (for ease of representation) with torsional angles of zero. Schaefer et al. have shown the nonbonded N···N distance in **2** to be 3.193 Å.

The cage compound **1** has two nitrogen atoms joined by three tetramethylene bridges, the cage **2** by three -CH$_2$-O-O-CH$_2$- bridges. Is a "mixed" cage possible, having the nitrogen atoms bridged by one tetramethylene and two -CH$_2$-O-O-CH$_2$- bridges? The attempt to prepare this compound failed, the reaction of 1,4-diaminobutane with formaldehyde and hydrogen peroxide in acidic solution yielding no insoluble product. However, the reactions of some 1,2-diaminoalkanes (1,2-diaminoethane, 1,2-diaminopropane, and *trans*-1,2-diaminocyclohexane) yielded peroxidic products. The structures of these three new peroxides have been established by X-ray crystallography and two-dimensional NMR, and proved to have some of the unusual features noted in the structure of HMTD (**2**).

Experimental

General

Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Combustion analyses for C, H, and N were carried out by Galbraith Laboratories, Knoxville, Tenn. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Unity-500 spectrometer operating at 499.843 MHz for protons and at 125.697 MHz for carbon-13. Chloroform-*d* was used as solvent unless otherwise noted.

Various 2D experiments were carried out to assign the structures: COSY, and the two-phase sensitive experiments: HMQC and NOESY. The phase in these 2D experiments was detected using the hypercomplex mode. For COSY, the acquisition was repeated for four transients, and 256 complex increments were acquired. The data were processed using a pseudo-echo-shaped function. The final data matrix having 1K by 1K points was symmetrized (zero filling was used only in the evolution domain). For NOESY, the data were obtained using a mixing time of 0.3 s and a relaxation delay of 1 s. The acquisition was repeated for 16 transients, and 256 complex increments were acquired. The data were processed using a Gaussian apodization function. The final data matrix had 2K by 1K points (zero filling was used only in the evolution domain).

The HMQC experiment was preceded by a BIRD nulling period. The recycling delay was set to 1 s, while the nulling period (following the BIRD pulse) was set to 0.3 s. The acquisition was repeated eight times and 256 fids were acquired. During acquisition of the proton spectra, ^{13}C broadband WALTZ decoupling was applied. The data were processed with Gaussian function, with zero filling in the evolution domain (^{13}C). The final matrix size was 2K by 1K. The spectral window in the carbon domain was about 100 ppm and in the proton domain about 7 ppm.

1,6-Diaza-3,4,8,9-tetraoxabicyclo[4.4.2]dodecane, **3a**

Aqueous formaldehyde (37%, 22 mL) was added dropwise to a stirred solution of 1,2-diaminoethane (3.0 g)

in acetic acid (12 mL), followed by hydrogen peroxide (30% w/w; 30 mL), the temperature being kept below 20°C by an ice bath. The diperoxide **3a** precipitated immediately and was removed by filtration, washed copiously with water to remove acidity, and dried under reduced pressure in a desiccator: yield 8.0 g (91%), mp 79–80°C, raised to 117°C by recrystallization from ethanol.

1,6-Diaza-3,4,8,9-tetraoxa-11-methylbicyclo[4.4.2]dodecane, **3b**

3a : R$_1$ = R$_2$ = H
3b : R$_1$ = CH$_3$, R$_2$ = H
3c : R$_1$ = R$_2$ = CH$_3$

4

Aqueous formaldehyde (37%, 22 mL) was added dropwise to stirred 1,2-diaminopropane (3.7 g), followed by acetic acid (12 mL), and then hydrogen peroxide (30% w/w; 30 mL), the temperature being kept below 20°C by an ice bath. The diperoxide **3b** precipitated and was removed by filtration and washed with water: yield 6.2 g (72%), mp 80–81°C, decomp with frothing 90°C, unchanged by recrystallization from petroleum ether.

1,6-Diaza-3,4,8,9-tetraoxatricyclo[4.4.2.4^{11,12}]hexadecane, **4**

Aqueous formaldehyde (38%; 11 mL) was added to *trans*-1,2-diaminocyclohexane (2.82 g) in glacial acetic acid (6 mL) – water (10 mL). The solution was cooled below 20°C, and hydrogen peroxide (30%; 30 mL) was added. The peroxide precipitated immediately and was removed by filtration, washed with water, and dried: yield 4.76 g (83%), mp 115–116°C, raised to 123°C by recrystallization from ethanol. Anal. calcd. for C$_{10}$H$_{18}$N$_2$O$_4$: C 52.16, H 7.88, N 12.17; found: C 52.03, H 7.94, N 12.02.

1,3,5,7-Tetraazapentacyclo[3.3.2.4^{9,10}.4^{11,12}]eicosane, **5**

Aqueous formaldehyde (36% w/w; 3.33 g) was added to a solution of 2.28 g of *trans*-1,2-diaminocyclohexane in 10 mL of ethanol. The solution became warm. It was heated to boiling, and 10 mL of water was added. The solution,

5

6

Table 1. Crystallographic data.

Compound	3a	3b	4
Formula	$C_6H_{12}N_2O_4$	$C_7H_{14}N_2O_4$	$C_{10}H_{18}N_2O_4$
Crystal size (mm^3)	$0.3 \times 0.3 \times 0.27$	$0.5 \times 0.45 \times 0.35$	$0.4 \times 0.25 \times 0.15$
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$A2/a$	$P2_1/c$	P-1
Cell params: A (Å)	11.869(4)	11.1141(23)	6.9886(3)
B (Å)	5.8573(22)	6.408(3)	8.1717(17)
C (Å)	11.918(3)	13.1614(24)	11.202(3)
α (°)			73.836(18)
β (°)	109.99(2)	101.404(16)	76.15(3)
γ (°)			68.994(21)
Z	4	4	2
Density (g cm^{-1})	1.50	1.38	1.35
$F(000)$	376.21	408.22	248.12
μ (cm^{-1})	1.2	1.1	1.0
2θ max (°)	50.0	50.0	49.7
No. reflections	721	1275	2150
No. unique	683	1203	1974
No. refs $>2.5\sigma I$	497	911	1235
Decay of standards (%)	0.7	1.0	1.7
Merging R (%)	0.7	0.6	0.7
R_F (%)	3.3	4.0	4.6
R_W (%)	3.3	3.7	4.0
S	1.41	1.97	1.74
Highest peak in difference Fourier (e Å)	0.17	0.40	0.56

when cool, deposited crystals of the product **5** (1.22 g, 44%), mp 238–239°C, raised to 240°C by recrystallization from cyclohexane; ^{1}H NMR (CDCl$_3$): 1.37 (s, 8H, alicyclic CH$_2$), 1.83 (s, 8H, alicyclic CH$_2$), 2.67 (s, 4H, CH-N), 4.23 (m, 8H, N-CH$_2$-N). Anal. calcd. for C$_{16}$H$_{28}$N$_4$: C 69.52, H 10.71; found: C 69.24; H 10.33.

The monopicrate melted at 137–138°C. Anal. calcd. for C$_{22}$H$_{31}$N$_7$O$_7$: C 52.27, H 6.18; found: C 52.18, H 6.27.

Hydrolytic yields of formaldehyde

The di- or triperoxide (about 0.2 g) was hydrolyzed in 45% sulfuric acid (5 mL) for 1 h, and then a saturated solution of dimedone in methanol (30 mL) – water (450 mL) was added. The pH was adjusted to 4.6 by addition of sodium acetate, and the solution was left overnight. The precipitate was removed on a weighed sintered glass filter, washed with water, and dried for more than 24 h in a desiccator. Yields of the formal dimedone derivative were the following: from **2**, 94 and 87%; from **3a**, 93 and 96%; from **3b**, 95% of theoretical.

Analysis for peroxide content

The triperoxide **2** (80–100 mg) and potassium iodide (1 g) were added to 2 N sulfuric acid (5 mL), and after 20 min, the yellow solution was titrated with standard sodium thiosulfate solution using a starch indicator. Active oxygen: calcd. 23.1%; found 23.0, 22.9%.

For diperoxides **3a** and **3b**, the same procedure resulted in a black precipitate and erratic results, and a different titra-

tion procedure was devised. Sulfuric acid (2 N) was added dropwise to a suspension of diperoxide (80–90 mg) in a solution of potassium iodide (1 g) and starch indicator in water (5 mL), and after each drop, standard thiosulfate solution was added to decolourize the solution. After about 1.5 mL of acid had been added, no more colour was produced. For compound **3a**, active oxygen calcd. 18.2%; found 17.7, 17.9%; for **3b**, active oxygen calcd. 16.8%; found 16.6, 16.6%.

X-ray crystallography

Crystals of the cage diperoxides were obtained from solvents noted above, **3a** and **3b** as chunky prisms, **4** as rectangular plates. Details of crystal, data collection, and refinement parameters are given in Table 1. Data were collected on a Rigaku AFC6S diffractometer controlled by TEXRAY software.[4] Molybdenum K$_\alpha$ radiation (λ = 0.7093 Å) was used. The structures were solved using direct methods and refined by full-matrix least squares. Hydrogen atoms were located in a difference Fourier map and refined isotropically. All non-hydrogen atoms were refined anisotropically. Data processing, structure solution, and structure refinement were all carried out using the NRCVAX system of crystallographic software (10). In the structure of **3a**, the molecule lies across a crystallographic two-fold axis that bisects the ethylene carbon–carbon bond. Table 2 contains the atomic coordinates and B_{eq} for compounds **3a** and **3b**, and Table 3 the atomic coordinates and B_{eq} for compound

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[4]Texray diffractometer control software. Molecular Structure Corp., Woodlands, Tex.

Table 2. Final atomic coordinates (fractional) and equivalent isotropic thermal parameters.[a]

Atom	x	y	z	B_{eq}[b]
		Compound **3a**		
O 1	0.878 26 (13)	0.0617 (3)	0.093 09 (13)	2.89 (8)
O 2	0.945 72 (13)	0.2322 (3)	0.051 90 (13)	2.81 (8)
N	0.730 63 (16)	0.3345 (3)	0.113 64 (15)	2.09 (8)
C 1	0.827 35 (22)	0.1855 (4)	0.168 82 (21)	2.73 (11)
C 2	0.888 78 (20)	0.2529 (5)	−0.075 05 (20)	2.55 (10)
C 3	0.753 54 (23)	0.5505 (4)	0.066 31 (20)	2.55 (11)
H 1A	0.8029 (19)	0.059 (4)	0.2100 (19)	2.7 (5)
H 1B	0.8954 (21)	0.275 (4)	0.2286 (21)	3.8 (6)
H 2A	0.8957 (21)	0.100 (5)	−0.1098 (21)	3.7 (6)
H 2B	0.9442 (18)	0.368 (4)	−0.0948 (17)	2.0 (4)
H 3A	0.8354 (22)	0.596 (4)	0.1176 (21)	3.4 (5)
H 3B	0.6967 (20)	0.662 (4)	0.0753 (20).	3.2 (5)
		Compound **3b**		
O 1	0.444 57 (19)	0.8234 (3)	0.091 02 (15)	5.00 (11)
O 2	0.470 61 (17)	0.6330 (4)	0.148 79 (15)	4.96 (11)
O 3	0.185 22 (24)	0.3197 (4)	0.0935 (3)	7.74 (17)
O 4	0.292 43 (23)	0.3059 (3)	0.046 74 (23)	6.81 (15)
N 1	0.271 94 (22)	0.6634 (4)	−0.019 51 (17)	3.86 (12)
N 2	0.270 24 (24)	0.6123 (4)	0.197 70 (18)	4.00 (12)
C 1	0.3836 (3)	0.7704 (6)	−0.011 39 (23)	4.46 (17)
C 2	0.3976 (3)	0.6469 (7)	0.229 14 (25)	5.00 (20)
C 3	0.2261 (5)	0.4078 (7)	0.1951 (4)	6.7 (3)
C 4	0.2666 (4)	0.4482 (6)	−0.0414 (3)	5.77 (22)
C 5	0.1750 (3)	0.7588 (6)	0.0229 (3)	4.65 (17)
C 6	0.1973 (3)	0.7787 (5)	0.1423 (3)	4.36 (17)
C 7	0.0761 (4)	0.8096 (10)	0.1775 (5)	6.7 (3)
H 1A	0.369 (3)	0.917 (5)	−0.0420 (22)	5.9 (8)
H 1B	0.444 (3)	0.692 (4)	−0.0464 (21)	5.4 (8)
H 2A	0.409 (3)	0.795 (6)	0.252 (3)	8.2 (12)
H 2B	0.433 (3)	0.541 (5)	0.2797 (21)	5.3 (8)
H 3A	0.294 (4)	0.321 (7)	0.235 (3)	10.4 (14)
H 3B	0.145 (4)	0.402 (6)	0.215 (3)	10.4 (13)
H 4A	0.328 (3)	0.410 (5)	−0.0794 (23)	6.5 (9)
H 4B	0.191 (3)	0.405 (5)	−0.0741 (24)	6.8 (10)
H 5A	0.104 (3)	0.681 (5)	0.0012 (22)	5.2 (8)
H 5B	0.165 (3)	0.899 (5)	−0.0014 (22)	5.2 (8)
H 6	0.2490 (24)	0.908 (4)	0.1603 (19)	4.4 (7)
H 7A	0.035 (4)	0.693 (6)	0.162 (3)	8.5 (14)
H 7B	0.039 (4)	0.928 (6)	0.144 (3)	8.8 (13)
H 7C	0.087 (3)	0.829 (6)	0.254 (3)	9.0 (12)

[a]esds refer to the last digit printed.

[b]B_{eq} is the mean of the principal axes of the thermal ellipsoid for atoms refined anisotropically (non-hydrogens). For hydrogens, $B_{eq} = B_{iso}$.

4. Anisotropic thermal parameters, torsion angles, and least-squares planes are included as supplementary material.[5]

Results and discussion

Properties of the cage triperoxide 2 and of the cage diperoxides 3a, 3b, and 4

By analogy with the reaction of ammonia with formaldehyde and hydrogen peroxide to give **2**, we assumed that re-action of 1,2-diaminoethane would give the diperoxide **3a**, of 1,2-diaminopropane would give **3b**, and of 1,2-diamino-cyclohexane would give **4**. These assumptions proved to be true.

The triperoxide **2** is a powerful explosive (11) and should be handled with extreme caution. A small amount of it on a steel plate detonates with a loud report when hit with a hammer. The diperoxide **3a** proved to be more difficult to deto-nate, and the diperoxide **3** even more so, as expected from their progressively less favourable oxygen balances (12).

Table 3. Final atom coordinates (fractional) and equivalent isotropic thermal parameters[a] for compound **4**.

Atom	x	y	z	B_{eq}[b]
O 1	0.1566 (4)	0.1551 (3)	0.010 54 (20)	4.41 (13)
O 2	0.2522 (4)	0.2910 (3)	–0.000 24 (21)	4.70 (13)
O 3	0.1744 (4)	0.1115 (3)	–0.313 73 (23)	5.31 (15)
O 4	0.3104 (4)	0.0022 (3)	–0.218 19 (22)	5.14 (14)
N 1	–0.0245 (4)	0.3144 (3)	–0.172 88 (22)	3.06 (12)
N 2	0.4214 (4)	0.2616 (3)	–0.212 87 (23)	3.43 (13)
C 1	–0.0392 (6)	0.2540 (5)	–0.0393 (3)	3.99 (18)
C 2	0.4434 (6)	0.2559 (5)	–0.0919 (3)	4.28 (19)
C 3	–0.0249 (6)	0.2002 (5)	–0.2470 (4)	4.33 (20)
C 4	0.4757 (6)	0.0829 (5)	–0.2457 (4)	4.54 (20)
C 5	0.0578 (4)	0.4648 (4)	–0.2308 (3)	2.75 (15)
C 6	0.2897 (5)	0.4099 (4)	–0.2883 (3)	3.03 (15)
C 7	0.3635 (5)	0.5741 (4)	–0.3203 (3)	3.66 (17)
C 8	0.2382 (6)	0.7245 (4)	–0.4144 (3)	4.14 (19)
C 9	0.0078 (6)	0.7725 (4)	–0.3661 (4)	4.33 (19)
C 10	–0.0683 (6)	0.6087 (4)	–0.3274 (3)	3.72 (18)
H 1A	–0.117 (4)	0.354 (3)	0.0019 (23)	2.8 (6)
H 1B	–0.119 (4)	0.170 (4)	–0.007 (3)	4.1 (7)
H 2A	0.469 (4)	0.360 (4)	–0.081 (3)	4.0 (7)
H 2B	0.548 (5)	0.140 (4)	–0.057 (3)	4.5 (7)
H 3A	–0.077 (4)	0.260 (3)	–0.329 (3)	3.5 (7)
H 3B	–0.091 (5)	0.107 (4)	–0193 (3)	6.4 (9)
H 4A	0.509 (5)	0.093 (4)	–0.338 (3)	4.1 (7)
H 4B	0.574 (5)	–0.001 (4)	–0.194 (3)	3.8 (7)
H 5	0.039 (3)	0.520 (3)	–0.1626 (20)	1.1 (5)
H 6	0.302 (4)	0.378 (3)	–0.3685 (25)	3.1 (6)
H 7A	0.505 (4)	0.547 (3)	–0.3530 (24)	3.0 (6)
H 7B	0.347 (4)	0.616 (4)	–0.240 (3)	4.1 (7)
H 8A	0.273 (5)	0.684 (4)	–0.499 (3)	5.5 (8)
H 8B	0.289 (4)	0.822 (4)	–0.433 (3)	4.2 (8)
H 9A	–0.068 (5)	0.855 (4)	–0.429 (3)	5.9 (9)
H 9B	–0.024 (4)	0.828 (4)	–0.289 (3)	4.1 (7)
H 10A	–0.206 (5)	0.639 (4)	–0.296 (3)	4.1 (8)
H 10B	–0.053 (4)	0.559 (3)	–0.407 (3)	4.0 (7)

[a]esds refer to the last digit printed.

[b]B_{eq} is the mean of the principal axes of the thermal ellipsoids for atoms refined anisotropically. For hydrogens, $B_{eq} = B_{iso}$.

The diperoxide **4** could not be detonated, and was submitted for combustion analysis in the usual way. The peroxides **3a** and **3b** were analyzed (along with **2** as a control) by decomposition of a small amount of the compound in a large excess of aqueous acid to yield formaldehyde (analyzed by formation of the derivative with dimedone (13, 14)) and hydrogen peroxide (titrated by an iodide–thiosulfate method (15)) in amounts close to theoretical. Treatment of the peroxides with aqueous picric acid did not give their picrate salts, but rather monopicrates of the diamines from which they had been made, and treatment of a very small amount of the solid peroxide with a drop of concentrated hydrochloric acid caused instantaneous decomposition to a sticky liquid. The reaction was particularly violent in the case of **2**. The solid compounds left standing on filter paper in the laboratory atmosphere eventually decomposed to a sticky mass. It seems likely that this decomposition was initiated by a trace of acid furnished by a dust or aerosol particle; the formaldehyde and hydrogen peroxide produced at the initial spot of decomposition would react to give formic acid, so that the decomposition would be autocatalytic.

Diffraction studies

The structures **3a**, **3b**, and **4** were established by X-ray diffraction.[5] ORTEP representations (16) are given in Figs. 1– 3, and in Table 4, the bond distances and angles of the three diperoxides are compared with corresponding bond distances and angles of the triperoxide **2**.

The torsional angles of the peroxide groups C-O-O-C in our three diperoxides lie between 113 and 116°, close to the equilibrium torsional angle of about 112° in hydrogen peroxide (17), while the corresponding torsional angle in HMTD is 129.3° (9). Schaefer et al. (9) point out that it takes little energy to open this angle from 112 to 129°, while closing this angle below 129° in HMTD would force nonbonded N···N atoms (3.193 Å apart) and O···O atoms (2.971 Å apart) to move closer together, with steep increases in van der Waals repulsions. Otherwise, most bond distances and an-

Fig. 1. ORTEP plot (16) of compound **3a**, showing numbering scheme. Ellipsoids are shown at 50% probability for non-hydrogen atoms.

Fig. 2. ORTEP plot (16) of compound **3b**, showing numbering scheme. Ellipsoids are shown at 50% probability for non-hydrogen atoms.

Fig. 3. ORTEP plot (16) of compound **4**, showing numbering scheme. Ellipsoids are shown at 50% probability for non-hydrogen atoms.

ergy of the electron pair in the *p* orbital (the anomeric effect (19)). This hybridization explains the shortened N—C distances in **2**. Essentially, the same explanation is offered by Whittleton et al. (19) for N—C distances in the cage diperoxide formed by reaction of formaldehyde with hydrazine and hydrogen peroxide in acidic solution (20, 21). This effect would be expected to be greater in the triperoxide **2** than in the diperoxides **3a**, **3b**, and **4**, which might account for the less complete planarity of the bridgehead nitrogen atoms of the latter. Furthermore, the anomeric effect would explain why the N—C bonds of the peroxide bridges of **3a**, **3b**, and **4** are shortened, while the N—C bonds of the alkane bridges are not. It would also explain the nonbasic character of the tertiary amino groups, so that the compounds separate out of weakly acidic solutions as bases and not salts.

*PMR spectrum of HMTD **2***

The ^{1}H NMR spectrum of the highly symmetrical hexamethylenetetramine $(CH_2)_6N_4$ shows a sharp singlet at δ 4.64 ppm (22), and a similar spectrum would be expected for HMTD $(CH_2)_6N_2O_6$ if it had the symmetrical structure shown in **2** above, with dihedral angles of zero for the peroxide bridges CH_2-O-O-CH_2. However, the dihedral angles of ±129° of these bridges (9) result in HMTD existing as a racemic mixture of chiral helical conformers. The twist of the helix causes one hydrogen of each methylene group to point slightly inward toward the axis of the molecule, and the other slightly outward. The six methylene groups are all identical; each forms an AB system, so that the spectrum of HMTD in DMSO-d_6, shown in Fig. 4, has a pair of doublets (^2J 13.3 Hz) centered at δ 4.65 and 4.78 ppm. At higher temperatures, the helical conformers interconvert, as shown by the broadening of the NMR peaks, which eventually

gles are fairly similar in all four compounds in Table 1. However, the bridgehead nitrogen atoms of the three new diperoxides are not completely planar, lying about 0.12–0.14 Å out of the plane of the three attached carbon atoms, while in **2** the nitrogen atoms lie exactly (within experimental limits) in this plane. Similarly, in the three new diperoxides all except one of the C-N-C angles are slightly less than 120°, whereas in **2** all are exactly 120°.

Schaefer et al. (9) suggested that the bridgehead nitrogen atoms of **2** are sp^2 hybridized because the electronegative peroxide groups withdraw electron density and lower the en-

Table 4. Bond distances (Å) and angles (°) in some cage peroxides.

Atoms	Compound			
	2[a]	3a	3b	4
	Distances			
N—C (peroxide bridge)	1.426 (8)	1.413 (3)	1.403 (4)	1.430 (4)
	1.416 (8)	1.415 (3)	1.412 (5)	1.413 (4)
			1.379 (5)	1.411 (5)
			1.408 (5)	1.421 (4)
N—C (ethylene bridge)	—	1.449 (3)	1.443 (5)	1.465 (3)
			1.447 (4)	1.464 (4)
O—O	1.456 (8)	1.466 (2)	1.437 (3)	1.469 (3)
			1.448 (4)	1.481 (3)
C—O	1.432 (8)	1.442 (3)	1.425 (4)	1.469 (4)
	1.410 (9)	1.436 (3)	1.457 (4)	1.453 (4)
			1.441 (6)	1.450 (5)
			1.459 (6)	1.458 (5)
C—C (ethylene)	—	1.554 (4)	1.547 (5)	1.543 (4)
		Angles		
OOC-N-COO	120.0 (5)	120.5 (2)	119.7 (3)	119.7 (3)
	120.0 (5)		118.8 (3)	119.1 (3)
OOC-N-CC	—	119.3 (2)	118.7 (3)	117.3 (3)
		118.0 (2)	119.3 (3)	119.9 (3)
			117.5 (3)	119.3 (3)
			121.3 (3)	118.5 (3)
N-C-O	116.6 (5)	117.9 (2)	115.9 (2)	116.7 (3)
	115.7 (5)	115.4 (2)	117.1 (3)	116.9 (3)
			116.6 (3)	116.4 (3)
			115.8 (3)	116.3 (3)
N-C-C	—	116.4 (2)	116.5 (3)	114.5 (2)
			114.3 (3)	114.6 (2)
C-O-O	107.3 (5)	105.1 (2)	107.8 (2)	105.4 (2)
	105.2 (5)	107.2 (2)	104.4 (2)	107.7 (2)
			106.5 (3)	107.2 (2)
			104.5 (3)	104 3 (2)
C-O-O-C	129.3 (5)	115.2 (2)	115.4 (3)	113.7 (2)
			115.5 (3)	115.8 (4)
N-C-C-N		25.7 (1)	32.5 (2)	40.7 (2)
		Nonbonded distances		
N···N	3.193 (7)	2.898 (3)	2.878 (4)	3.189 (4)

[a]From ref. 9.

collapse into a broad singlet at about 105°C, illustrated in Fig. 4.

NMR spectrum of compound 3a

This compound, like **2**, is a racemic mixture of chiral conformers. The X-ray crystallographic studies (see Fig. 1) show that the dihedral angles of CH_2-O-O-CH_2 are not zero, as represented in **3a**, but ±115.2° (Table 4). Again, the hydrogen atoms of both N-CH_2-C and N-CH_2-O methylenes form an AB system. However, in $CDCl_3$ at 30°C, the ^{1}H NMR spectrum, shown in Fig. 5, is that of the symmetrical structure **3a**, having a doublet at δ 3.38 (4 H) for the protons of the ethylene bridge and a doublet at δ 4.83 (8 H) for the methylene protons of the peroxide bridges. The four-bond coupling is favoured by the W-configuration of the bonds between the protons of the two different types of methylenes.

Evidently, the interconversion of enantiomeric conformers of **3a**, which requires eclipsing of the bonds of two peroxide

Fig. 4. Effect of temperature on the PMR spectrum of HMTD (**2**).

groups, takes place at a lower temperature than the interconversion of the enantiomeric conformers of **2**, which requires eclipsing of the bonds of three peroxide groups. The

Fig. 5. Effect of temperature on the PMR spectrum of **3a**.

Fig. 6. The PMR spectrum of **3b**.

Table 5. NMR data for compound **3b** in CDCl$_3$.

Position	^{13}C δ (ppm)	^{1}H δ (ppm)	COSY
1	89.4	A 4.689 d of d	1A, 1B, 4B
		B 4.868 d of d	1B, 1A, 5A
2	91.5	A 4.633 d	2A, 2B, 3B, 6
		B 4.818 d	2B, 2A
3	84.3	A 4.720 d	3A, 3B
		B 4.984 d of d	3B, 3A, 2A, 6
4	91.8	A 4.824 d	4A, 4B, 5B
		B 4.616 d of d	4B, 4A, 1A
5	58.4	A 2.955 t	5A, 5B, 6, 1B
		B 3.239 m	5B, 5A, 6, 4A
6	56.3	–3.612 m	6, 5A, 5B, 7, 3A, 2A
7	15.6	–1.160 d	7, 6

by a bond pointing outward; a conformational inversion would end with this bond pointing inward, into a region of steric congestion, and so is not possible. This steric effect also explains why 2-methyl-1,2-diaminopropane does not re-act with formaldehyde and hydrogen peroxide to form the cage diperoxide **3c**.

The ^{1}H NMR spectrum of compound **3b** (Fig. 6; see also Table 5) corroborates the details of structure established by X-ray diffraction and shown in the ORTEP diagram of Fig 2. The signal for the three methyl protons (1.16 ppm) at posi-tion 7 is split by coupling (^3J 6.5 Hz) to the single proton at position 6 (m, 3.61 ppm). This proton in turn is coupled to the A (^3J 14 Hz) and B (^3J 7 Hz) protons at C5. The proxim-ity of the C5 B proton to the C6 proton is shown by the NOESY spectrum.

The signals between δ 4.6 and 5.0 ppm in Fig. 6 are due to the protons at positions 1, 2, 3, and 4. The assignment of signals to positions 1–4 is possible because of their spin-coupling to the protons at positions 5, 6, and 7, as demon-strated by the COSY spectrum. The results are given in Ta-ble 5. The rigid cage structure of the molecule results in many pairs of protons being linked by four bonds in a W-configuration (see Table 5), and hence having measurable coupling constants.

The spectrum of **3b** in DMSO-d_6 has signals shifted very slightly to higher fields, but is essentially identical to the spectrum in CDCl$_3$.

NMR spectrum of compound 4

The *trans* fusion of a cyclohexane ring to the diperoxide ring of **4** results in a rigid compound incapable of any conformational change. Its ^{1}H and ^{13}C NMR (Table 6) and COSY and NOESY spectra are those expected from the structure (Fig. 3) established by X-ray diffraction, and re-quire no comment.

Formaldehyde and cage compounds

The results reported above illustrate the proclivity of formaldehyde to form cage compounds (see also refs. 19, 20, 23–26). A further example is given by the reaction of formaldehyde with *trans*-1,2-diaminocyclohexane to give the compound **5**, analogous to cage compounds given by other 1,2-diamines (23, 24, 27). *cis*-1,2-Diaminocyclohexane does not react in this way, presumably for steric reasons. The reaction of formaldehyde with 1,2-diaminoethane gives

interconversion of **3a** requires also the eclipsing of the at-oms of the ethylene bridge, but this is already more than half complete in the ground state of the molecule: the X-ray data (Table 4) show that the dihedral angle for N-CH$_2$-CH$_2$-N is not about 60°, as required for a staggered conformation, but 25.7° (Table 4).

At lower temperatures, the rate of interconversion drops, as evidenced by the changes in NMR spectra shown in Fig. 5. At –30°C, the ^{1}H peaks of N-CH$_2$-O (carbon atoms C1, C′1, C2, C′2) can be calculated as two AB quartets, one at δ = 4.66 and 4.88 ppm (^2J = 13.5 Hz), the other at δ = 4.70 and 4.77 ppm (^2J = 12.1 Hz). The high field doublet in each quartet shows a long-range splitting (^4J = 2 Hz) due to coupling to one of the ethylene protons. The spectrum for ethylene (C3 and C′3) shows symmetrical multiplets at δ = 3.347 and 3.227 ppm, and additional splitting from long-range coupling.

NMR spectrum of compound 3b

This compound does not show a rapid interconversion of conformers at 30°C, so that its ^{1}H NMR spectrum has a de-tailed structure not found in the spectrum of **3a** until the temperature of the latter has been reduced to about –20°C. The methyl group of **3b** is attached to the two-carbon bridge

Table 6. NMR δ values (ppm) of compound **4**.

Position	^{13}C	^{1}H
1	91.4	4.62[a]
2	84.5	4.68[a]
3	84.5	4.78[a]
4	91.4	4.74[a]
5	65.2	3.08
6	65.2	3.08
7	30.4	1.65
8	25.8	1.29[b]
		1.74[c]
9	25.8	1.29[b]
		1.74[c]
10	30.4	1.65

[a]$^2J = 13.0$ Hz, $^4J = 2.0$ Hz.

[b]Axial hydrogen.

[c]Equatorial hydrogen.

the compound **6**, which may have the two methylenes of the ethylene bridge eclipsed (as represented in **6**) or staggered: the X-ray evidence is equivocal (28). However, the fused cyclohexane ring enforces staggering of the corresponding carbon atoms in **5**. Dreiding-type models show that only two enantiomeric forms of this compound are possible.

General conclusions

Small cycloalkane rings of 5 or 6 carbon atoms are more stable than medium-sized rings of 7–10 carbon atoms, because of steric and torsional effects. This is not true when the rings incorporate a peroxide group: medium-sized rings then become more stable than the five- or six-membered, because of the differing energies attendant on change of torsional angle for C-O-O-C and C-C-C-C chains. This fact has not often been recognized (cf. refs. 19–21, 27, 29). The structures **3a**, **3b**, and **4**, containing fused eight-membered rings, furnish further examples of this rule; alternative structures containing the peroxide groups in five-membered rings can be written for these compounds and for HMTD (20).

Acknowledgment

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