

nm, (+) CE near 385 nm; UV  $\lambda_{\max} \sim 415$  nm] of Figure 4 and Table IV are in accord with selective complexation of cyclodextrin with the left-handed chiral conformation, viz., 1A/C (Figure 1).

Similar conclusions favoring predominance of the left-handed chiral conformation (Figure 1) are in accord with the following: (1) the previously reported ICD bisignate CE [ $\Delta\epsilon_{466} \sim -4.7$ ,  $\Delta\epsilon_{416} \sim +3.0$ ] of  $3.4 \times 10^{-5}$  M bilirubin IX $\alpha$  in  $7.24 \times 10^{-2}$  M sodium deoxycholate at pH 8.0,<sup>14</sup> and (2) the CD data of Harmatz and Blauer<sup>35</sup> for selected albumin-bilirubin complexes, e.g., the powerful bisignate CE [ $\Delta\epsilon_{467} \sim -80$ ,  $\Delta\epsilon_{415} \sim +21$ ] for  $2.5 \times 10^{-5}$  M bilirubin IX $\alpha$  in  $5.0 \times 10^{-5}$  M goat albumin at pH 9.8. However, a predominance of a right-handed chiral conformation appears to be indicated [bisignate ICD CE:  $\Delta\epsilon_{460} \sim +53$ ,  $\Delta\epsilon_{410} \sim -33$ ] for bilirubin IX $\alpha$  ( $2.5 \times 10^{-5}$  M) bound to human serum albumin ( $5.0 \times 10^{-5}$  M) at pH 9.8. The order of magnitude larger ICDs associated with the protein-bound bilirubin suggest a relatively larger enantiomeric excess of pigment in the aqueous albumin solutions than in the cyclodextrin or sodium deoxycholate solutions. The stereochemical facets of the interaction of bilirubins and pyromethenones with protein (chiral solute), sodium deoxycholate (chiral micelle), and similar systems are currently under further investigation in our laboratory.

The major, bisignate CEs observed for chiral conformations of bilirubin and discussed above are not the only CEs observed in bilirubin-cyclodextrin solutions. Other weak CEs can be seen near 520 nm for solutions of 1 with C7A and C8A, but not C6A (Tables I-III). These data suggest weak intermolecular electric dipole coupling with other bilirubin pyromethenone chromophores—possibly the presence of dimers or higher aggregates<sup>3,26</sup> complexed with the larger cyclodextrins. Compared with the aqueous solution data, however, complexation of bilirubin to cyclodextrins in Me<sub>2</sub>SO solvent gives relatively weak mono-

signate ICDs with CE  $\lambda_{\max}$  nearly coincident with the UV-vis  $\lambda_{\max}$ . It thus appears that in Me<sub>2</sub>SO well-defined minimum-energy conformers of 1 are not available for complexation with cyclodextrin or complexation is more limited or less discerning than in aqueous buffers.<sup>36</sup> Curiously, when the Me<sub>2</sub>SO solutions are slightly basified, weak ICDs that have signs opposite to those in aqueous buffers can be detected.

### Conclusion

Our CD studies show that enantiomeric intramolecularly hydrogen-bonded conformations of bilirubin can be complexed selectively with cyclodextrins, with the left-handed chirality enantiomer (1A/C) complexed preferentially. These results find close parallels with and can explain the previously observed ICD of bilirubin in sodium deoxycholate solution.<sup>14</sup> Similar parallels may be drawn to the complexation of bilirubin to albumin,<sup>13</sup> where bisignate ICDs are also found, and where selective association of the protein with enantiomeric conformations of bilirubin is probably also important.

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**Registry No.** 1, 635-65-4; mesobilirubin IV $\alpha$ , 94732-74-8; xanthobilirubin acid, 15770-19-1; mesobilirubin XIII $\alpha$ , 79719-28-1;  $\alpha$ -cyclodextrin, 10016-20-3;  $\beta$ -cyclodextrin, 7585-39-9;  $\gamma$ -cyclodextrin, 17465-86-0.

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(36) Me<sub>2</sub>SO is expected to interfere with intramolecular H bonding and probably destabilizes conformations like 1A and 1B, see ref 5 and 6. Bilirubin is much more soluble in Me<sub>2</sub>SO than in water.

## Structure of Hexamethylene Triperoxide Diamine

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**Abstract:** The structure of 1,6-diaza-3,4,8,9,12,13-hexaoxabicyclo[4.4.4]tetradecane (hexamethylene triperoxide diamine or HMTD) has been determined. The compound has a most unusual, exactly planar 3-fold coordination about the two bridgehead nitrogen atoms, with N-C distances of 1.421 (8) Å. It crystallizes in the trigonal space group  $R\bar{3}m$ :  $a = 10.417$  (5) Å,  $c = 6.975$  (3) Å,  $z = 3$ . The structure was refined by least squares to an  $R$  index of 0.034.

1,6-Diaza-3,4,8,9,12,13-hexaoxabicyclo[4.4.4]tetradecane (hexamethylene triperoxide diamine or HMTD) was first synthesized in 1885 by Legler.<sup>1</sup> It was soon found to be a powerful initiating explosive and as such was studied by Taylor and Rinkenbach of the Bureau of Mines.<sup>2</sup> Although it is inexpensive, easy to synthesize, relatively insensitive to shock (it requires a 3-cm drop of a 2-kg weight to detonate, as compared to 0.25 cm for mercury fulminate), and more powerful than most initiating explosives, HMTD slowly decomposes when stored and so is not now of commercial or military importance.

We were first attracted to HMTD by a stick model of the molecule that suggested there might be a central cavity toward which some lone pair electrons from the oxygen atoms were pointing (Figure 1). The possibility of capturing protons in the cavity, as is known for 1,6-diazabicyclo[4.4.4]tetradecane,<sup>3</sup> immediately came to mind. We began a crystallographic study to

Table I. Crystal Data for Hexamethylene Triperoxide Diamine

N(CH <sub>2</sub> O <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> N (C <sub>6</sub> H <sub>12</sub> N <sub>2</sub> O <sub>6</sub> )	
$M_r$ 208.17	
space group $R\bar{3}m$ No. 160	
$a = 10.417$ (5) Å	rhombohedral axes
$c = 6.975$ (3) Å	$a = 6.448$ (3) Å
$V = 655.5$ (12) Å <sup>3</sup>	$\alpha = 107.76$ (3)°
$F(000) = 330e$	$V = 218.5$ (4) Å <sup>3</sup>
$Z = 3$	$Z = 1$
$\rho(\text{calcd}) = 1.58$ g cm <sup>-3</sup>	$\rho(\text{obsd}) = 1.57$ g cm <sup>-3</sup> (ref 2)
Mo K $\alpha$ , 0.710 73 Å	$\mu(\text{Mo K}\alpha), 1.53$ cm <sup>-1</sup>
$T = 21$ °C	( $\mu r_{\max} = 0.03$ )

determine the size and configuration of the cavity; our results are reported in this paper.

### Experimental Section

**Caution:** HMTD is a powerful explosive. The synthesis of HMTD itself is quite facile.<sup>4</sup> Fourteen grams of hexamethylenetetramine is

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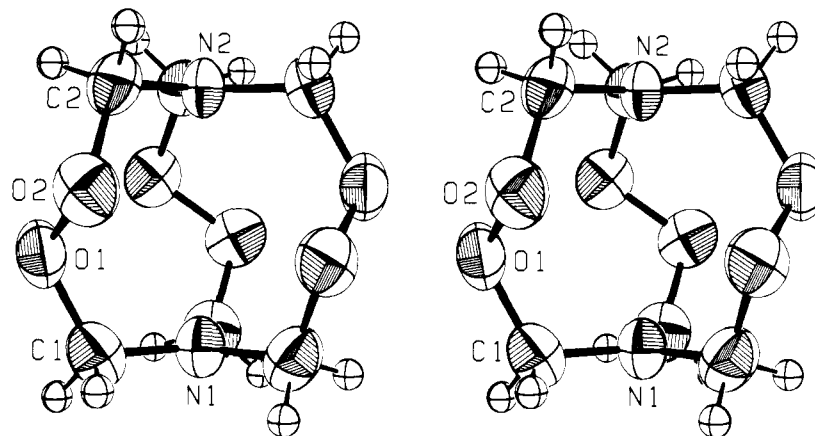


Figure 1. Stereoview of HMTD prepared by ORTEP.<sup>8</sup> Thermal ellipsoids enclose 60% of the electron probability; hydrogen atoms were assigned an arbitrary, small thermal parameter.

Table II. Final Heavy-Atom Parameters for HMTD

atom	x	y	z	$U_{eq}^a$	POP <sup>b</sup>
N(1)	0	0	-0.2309	0.0410 (10)	3.0
C(1)	0.1156 (6)	0.1512 (7)	-0.2301 (11)	0.0518 (16)	9.0
O(1)	0.1864 (4)	0.2090 (4)	-0.0531 (10)	0.0525 (11)	9.0
O(2)	0.0829 (5)	0.2281 (4)	0.0673 (11)	0.0511 (12)	9.0
C(2)	0.0785 (2)	-x	0.2448 (8)	0.0420 (8)	9.0
N(2)	0	0	0.2413 (10)	0.0337 (9)	3.0

<sup>a</sup>  $U_{eq} = 1/3 \sum_i \sum_j [U_{ij}(a_i^* a_j^*) \bar{a}_i \bar{a}_j]$ .  $\sigma U_{eq} = (1/6^{1/2}) (\sigma U_{ii}/U_{ii}) U_{eq}$ .  
<sup>b</sup> The number of atoms in the unit cell.

dissolved in 45 g of 30% hydrogen peroxide and stirred mechanically at 0 °C. Twenty one grams of powdered citric acid is slowly added while the stirring continues. The mixture is stirred for 3 h at 0 °C and then is allowed to warm to room temperature and stand for 2 h. The white crystalline product is filtered off, washed thoroughly with water, rinsed with methanol, and air dried. Yield is 50–70%. If larger portions are made (greater than double the recommended amount), the product will decompose exothermally while the solution warms. HMTD may be stored under water with no risk of explosion and no increase in the rate of decomposition. The rate of decomposition may be lowered by refrigeration. Anal. (C<sub>6</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

A crystal (0.16 × 0.19 × 0.21 mm) that appeared satisfactory from oscillation photographs was centered on a CAD-4 diffractometer and a rhombohedral cell was found (Table I). Unit cell dimensions were calculated from the setting angles of 25 strong reflections with 22° < 2θ (Mo Kα) < 36°; data were collected with graphite-monochromatized Mo Kα radiation for all ±h, ±k, ±l with 2θ < 50°, giving 1620 reflections. The possible space groups (no systematic absences) were R32, R3m, and R3m. The structure was solved by Patterson and structure factor-Fourier techniques. The nitrogen atoms were located from a Patterson map; attempts to find an ordered solution in space group R32 failed, but a model in R3m refined to a final R index of 0.034 ( $R = \sum |F_o - |F_d|| / \sum F_o$ ) and a goodness of fit of 2.84 ( $GOF = [\sum w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}$ , where n = number of independent reflections = 155 and p = number of parameters = 39). The molecule was positioned with the two

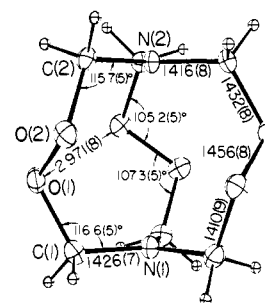


Figure 2. View of the HMTD molecule showing some important distances and angles.

nitrogen atoms on a 3-fold axis and one carbon atom on a mirror plane. The other carbon atom and the two oxygen atoms are disordered across this mirror plane. All six atoms were refined with anisotropic thermal parameters. The four hydrogen atoms were introduced at calculated positions 0.95 Å from the carbon atoms; they were repositioned twice but their positions and assigned isotropic thermal parameters were never refined. Final parameters are given in Table II, bond lengths and angles are in Table III or are shown in Figure 2, and the structure factors, hydrogen parameters, and anisotropic thermal parameters are in the supplementary material.

Bicyclic diaza compounds are conventionally described as having the nitrogen atoms out or in, depending on whether the nitrogen lone pair points away from or toward the "cavity" of the compound. HMTD, with planar nitrogen atoms, cannot be described as out or in. We considered the possibility that the planar geometry observed was the result of the nitrogen atom being disordered between the in and out conformations. Even though the anisotropic thermal parameters did not support such a model, we positioned isotropic half-nitrogen atoms on either side of the carbon atom planes and refined the entire structure; at convergence the half-nitrogen atoms were only 0.26 (3) [N(1)] and 0.30 (3) Å [N(2)] apart or about 0.15 Å from the carbon atom plane. This is the maximum

Table III. Bond distances (Å) and Angles (deg) in HMTD and Some Related Compounds

bond or angle	compound			
	HMTD	carbon analogue <sup>a</sup>	tricyclo-tetradecane <sup>b</sup>	macrobicyclic cryptand <sup>c</sup>
N(1)-C(1)	1.426 (8)	1.443 (3)	1.434 (1)	1.442 (2)
N(2)-C(2)	1.416 (8)	1.443 (3)	1.459 (1)	
O(1)-O(2)	1.456 (8)		1.472 (1)	
C(1)-O(1)	1.432 (8)	1.520 (4) (C-C)	1.445 (1)	
C(2)-O(2)	1.410 (9)		1.428 (1)	
C(1)-N(1)-C(1)	120.0 (5)	115.5 (2)		120.0 (1)
C(2)-N(2)-C(2)	120.0 (5)			
N(1)-C(1)-O(1)	116.6 (5)	114.1 (2) (N-C-C)	115.5 (1)	112.8 (1) (N-C-C)
C(1)-O(1)-O(2)	107.3 (5)	116.4 (2) (C-C-C)	106.0 (1)	
O(1)-O(2)-C(2)	105.2 (5)		109.2 (1)	
O(2)-C(2)-N(2)	115.7 (5)		111.5 (1)	
N(1)-N(2)	3.193 (7)	2.806 (3)		
C(1)-O(1)-O(2)-C(2)	129.3 (5)	90.1 (2) (C-C-C-C)	100	

<sup>a</sup> Reference 3. <sup>b</sup> 1,2,7,8-Tetraaza-4,5,10,11-tetraoxatricyclo[6.4.1.1.2<sup>7</sup>]tetradecane. <sup>c</sup> N[(CH<sub>2</sub>)<sub>2</sub>O(2,6-C<sub>5</sub>H<sub>3</sub>N)O(CH<sub>2</sub>)<sub>2</sub>]<sub>3</sub>N.<sup>5</sup>

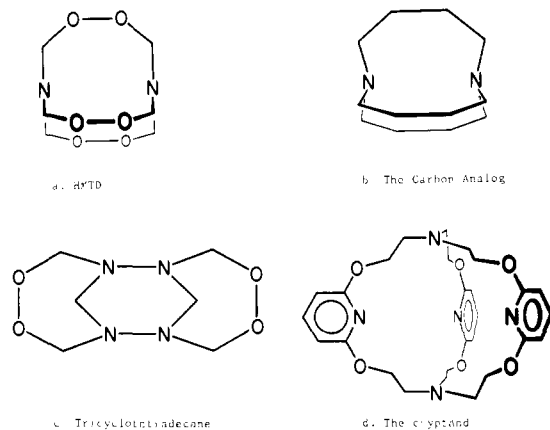


Figure 3. Drawings of the compounds mentioned in Table III.

separation we would expect based on the refinement with anisotropic thermal parameters; we conclude that the appropriate model is the one with single nitrogen atoms and a planar arrangement of carbon atoms about each of them.

### Results and Discussion

The unexpected finding of this structural analysis is the unusual geometry about the two nitrogen atoms: each is planar within experimental error. N(1) is only 0.006 (7) Å out of the plane of the C(1) atoms, while N(2) is 0.025 (8) Å from the C(2) plane; the angles C–N–C are all 120.0 (5)°. A normal tetrahedral nitrogen atom with N–C bonds of 1.47 Å would be 0.49 Å out of the carbon atom plane. The best examples we have found of similar geometries are in the closely related carbon analogues of HMTD that have an in,in configuration<sup>3</sup> and the planar macrobicyclic cryptand prepared by Newkome<sup>5</sup> (see Figure 3). Other compounds with out,in or out,out configurations or with the coordination about nitrogen approaching planarity are known.<sup>6</sup> In 1,6-diazabicyclo[4.4.4]tetradecane (the "carbon analogue") the nitrogen atom is 0.311 (3) Å from the carbon atom plane and the C–N–C angles average 115.5 (2)°. While these values are far from normal, the 120.0° angles found for the cryptand and HMTD are even more unusual.

We can seek an explanation for this geometry in either steric or electronic factors. Table III offers some insight into possible steric differences among HMTD, the carbon analogue, and other compounds with comparable structural features. If the explanation is steric, one might expect that the strain that forces the nitrogen atoms to be planar would evidence itself in other bond length or angle distortions. But bond lengths, where directly comparable, are shorter in HMTD than in the carbon analogue,<sup>3</sup> and they are everywhere shorter than in the relatively unconstrained tricyclotetradecane.<sup>7</sup> Moreover, the bond lengths in the cryptand are all close to normal values. The C–O–O angles in HMTD are normal, whereas the C–C–C angles in the carbon analogue are 7° larger than expected (and 10° larger than the HMTD angles). We may partially rationalize this in terms of qualitative molecular orbital models,<sup>9,10</sup> which suggest that the lone pair–lone pair interactions between oxygen atoms in HMTD make enlarging the bond angle more difficult than do the methylene bond pair–bond pair interactions in the carbon analogue. Models show that de-

creasing this angle moves the nitrogen atoms closer together, which should be energetically unfavorable. The nitrogen atoms of the carbon analogue are much closer together than those of HMTD, however, an indication that it is not simply a nitrogen–nitrogen repulsion that determines the geometry about the nitrogen atom.

The largest difference between HMTD and the comparable compounds is found in the torsion angle C–O–O–C (or C–C–C–C in the carbon analogue). In HMTD this angle is 130°, 30° larger than expected in the absence of other effects. Closing this angle down forces the two nitrogen atoms closer together and also decreases the nonbonded O(1)···O(2) distance; both of these interactions are unfavorable. In HMTD there is an additional electrostatic repulsion between nitrogen atoms and oxygen atoms that is not present in the carbon analogue, tending to keep the torsion angle large. It takes little energy to open this angle<sup>11,12</sup> so this cannot be a major steric factor.

Electronic effects must represent some balance between the loss in energy caused by the sp<sup>2</sup> hybridization of the nitrogen atoms (rather than sp<sup>3</sup>) and the gain obtained by shorter C–N bonds. Since isolated C<sub>3</sub>N systems are not planar, this balance must be net negative, but it is more than compensated for by the other factors. Considering only the differences between the carbon analogue and HMTD, any electronic effects are limited to those caused by a substitution of electronegative oxygen atoms for carbon atoms in the bridges. The oxygen atoms would tend to withdraw electron density from the region of the nitrogen atoms; if these are sp<sup>2</sup> hybridized, the effect of the oxygen atoms is to lower the energy of the electron pair in the p orbital. The N–C distances are what one would expect for this situation; they are so short that any pure sp<sup>3</sup> hybridization is ruled out. Evidently the loss of stabilization in changing from sp<sup>3</sup> to sp<sup>2</sup> hybridization at the nitrogen atoms is more than made up for by this effect and by a decrease in unfavorable steric effects, primarily lone pair–lone pair interactions. The fact that this planar arrangement has been observed once before, in the macrobicyclic cryptand,<sup>5</sup> leads us to believe that it is a stable electronic arrangement for an attached C<sub>3</sub>N fragment.

There is still the question of inserting a proton in the central cavity of HMTD. The carbon analogue is protonated not by a simple proton insertion but by a complicated transfer of a proton from an α-carbon atom to the cavity, followed by protonation of the carbon atom.<sup>13</sup> Such a mechanism may not work for HMTD because the lone pairs on the oxygen atoms will behave differently than will the protons on carbon atoms, making the deprotonation of the α-carbon atom more difficult. Evidently direct protonation is not effective either; the material was synthesized in acidic solution, but no evidence for a proton between the nitrogen atoms can be found in the electron density maps. Thus, although the cavity appears to be large enough to contain a proton, because we have not been able to protonate it we infer that the oxygen atoms protect the cavity well.

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**Registry No.** HMTD, 283-66-9.

**Supplementary Material Available:** Further experimental data and tables of anisotropic thermal parameters, hydrogen parameters, and structure factors (6 pages). Ordering information is given on any current masthead page.

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