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Conformational Analysis of (*S,S*)-Dimethyldiketopyridino-18-crown-6†

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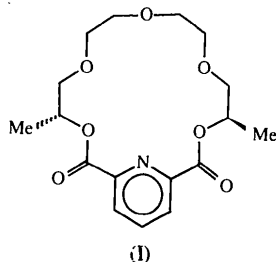
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Abstract

The crystal structure of (*S,S*)-dimethyldiketopyridino-18-crown-6, (I), C₁₇H₂₃NO₇, an effective host for chiral organic ammonium salts is described. A minimum-energy conformation was obtained by a pseudo-Monte-Carlo conformational search in the gas phase and was compared with the crystal structure. Structural changes in chiral recognition processes are also discussed.

Comment

Enantiomeric recognition of chiral organic ammonium salts by chiral macrocyclic compounds is a well known phenomenon. Among many chiral crown ethers (*S,S*)-dimethyldiketopyridino-18-crown-6, (I), displays significant recognition (Davidson *et al.*, 1984). The degree of enantiomeric recognition was studied by NMR spectroscopy, calorimetric titration, solvent extraction, liquid membrane transport and chromatography (Izatt, Zhu, Huszthy & Bradshaw, 1992). The crystal structure analysis of some complexes of (I) was reported recently (Izatt, Zhu, Dalley, Curtis, Kou & Bradshaw, 1992; Zhu, Izatt, Bradshaw & Dalley, 1992) but the structure of the



† Alternative nomenclature: 4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione.

free host molecule has never been determined. We were also interested in studying the conformation of medium size macrocyclic compounds (Böcskei & Keserű, 1994; Keserű, Vásárhelyi & Makara, 1994), which led us to determine the most stable conformation of (I) in the solid state and also in the gas phase.

The preparation of compound (I) is described in the *Experimental* section. The crystallographic asymmetric unit contains two independent molecules which are very similar as far as their overall geometry is concerned. The bond lengths and angles are as expected except for the O_{sp³}–C_{sp³} bond lengths of the macrocycle which are a little shorter than it is usual (average 1.42 Å).

Most of the torsion angles of the macrocycle are in either a *gauche* or *anti* conformation (Fig. 1). It is interesting to note that one of the topologically equivalent carbonyl groups is in the plane of the pyridine ring while the plane of the other forms an angle of 33 or 36° depending on which molecule we consider.

The crystal structure of the isolated host and the solid-state conformations of its complexes with (*R*)- and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate (Davidson, Dalley, Izatt, Christensen & Bradshaw, 1985) [(*R*)- and (*S*)-complex, respectively] are compared (Fig 2). The conformation of the host has changed in both complexation processes as compared to the free form. In addition to the formation of hydrogen bonds, π–π interactions also take place between the pyridine ring of the host and the naphthalene ring of the guest.

There are two major driving forces that could explain the observed behaviour and stability result. For a favourable π–π interaction, the two rings must lie

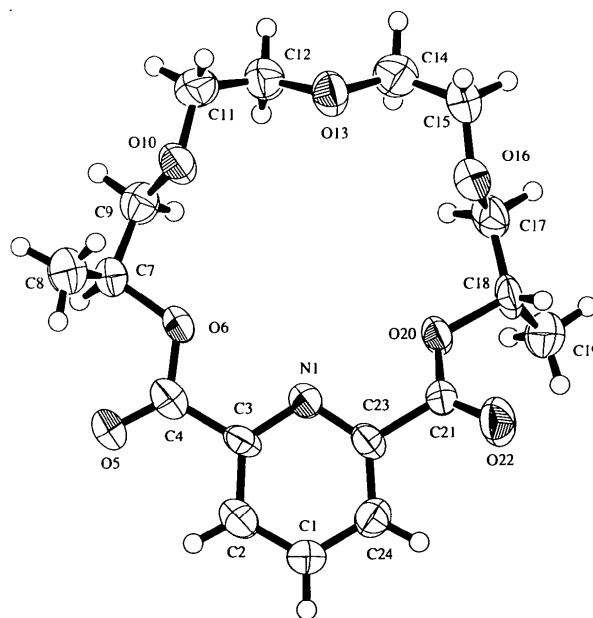


Fig. 1. Molecular structure and atomic numbering for (*S,S*)-dimethyldiketopyridino-18-crown-6, (I). Displacement ellipsoids are plotted at the 50% probability level.

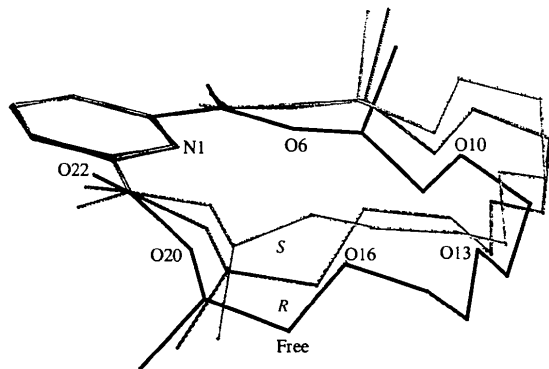


Fig. 2. Superposition of the crystal structure of (I) and the solid-state conformations of the host in (*S*)- and (*R*)-complexes.

stacked and parallel above each other. An upward movement of the ethyleneoxy groups on the opposite sides of the pyridine ring has to take place for the interacting O atoms of the host and the positively charged ammonium group of the guest to come into close proximity.

When complexing with the (*R*)-[α -(1-naphthyl)ethyl]-ammonium ion, little distortion was seen that provided proper distances for the interacting atoms. In the case of the *S* cation, however, the upward movement of the host atoms was so extensive that it resulted in an overall strain of the host. Secondly, it is also worth noting that upon complexation with the *S* cation a conformational change has to take place in the O20—C14 region (our numbering) of the macrocycle so that the guest molecule could be conveniently accommodated. This change results in a relatively unfavourable value (-155.9°) for the torsion angle C18—C17—O16—C15 and adds considerable strain to the ring system. This effect may be partially responsible for the decreased stability of the (*S*) complex.

It is also worth noting that the crystal structure of the free host contains some interesting packing motifs. The crown molecules are ordered into layers along the long *b* axis of the unit cell. Four such layers are formed per unit cell. In all the layers there is an interesting short contact between two of the ether O atoms (O16 and O13) and the C1 atom of the pyridine ring of another neighbouring molecule (Fig. 4.). This may be the result of a weak bifurcated C—H \cdots O-type hydrogen bond.

A conformational analysis of (I) in the gas phase was also carried out *via* an efficient method, the systematic unbounded multiple minimum search technique (SUMM) (Goodman & Still, 1991). This is available in the *MACROMODEL* computational package (Still, 1993). In the SUMM method, the generation of conformers is solved by the pseudo-random (eventually systematic) variation of the torsional angles of the temporarily opened structure followed by reclosure of the ring. The energy of the resulting structures is minimized

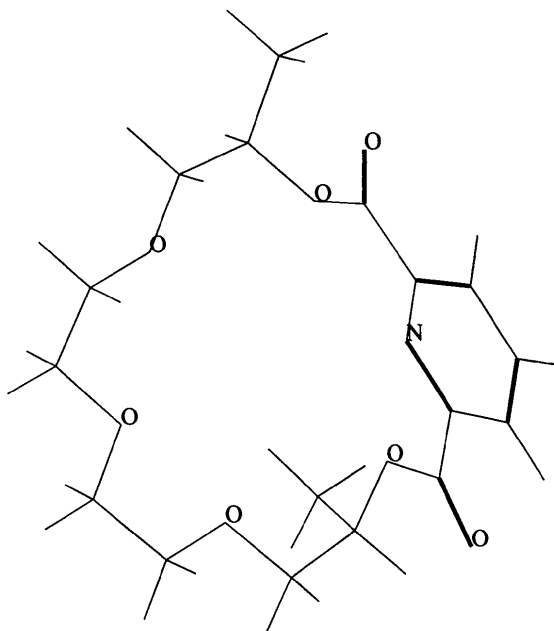


Fig. 3. Minimum-energy conformation of (*S,S*)-dimethyldiketopyridino-18-crown-6, (I), obtained by SUMM conformational search. Dihedral angles in the macrocycle of the minimum-energy conformation starting at N1—C23—C21—O20 and progressing in the direction of C23 (only the first atom is given for each angle): N1 -3.0 , C23 161.4 , C21 -73.5 , O20 -61.1 , C18 175.6 , C17 174.5 , O16 61.8 , C15 -179.2 , C14 179.5 , O13 -61.8 , C12 -174.5 , C11 -175.7 , O10 60.9 , C9 72.5 , C7 -161.6 , O6 4.1 , C4 179.0 , C3 -179° .

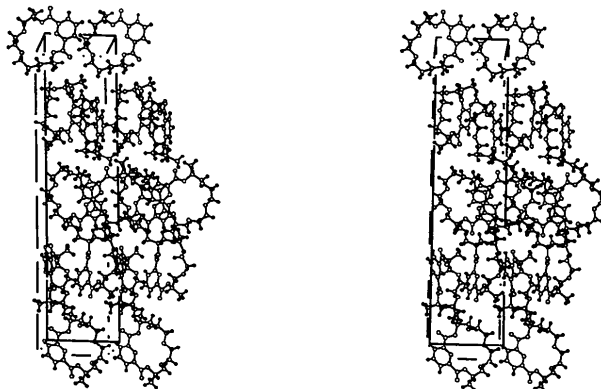


Fig. 4. Intermolecular interactions in the crystal lattice of (I).

to give local minima of the conformational space. The energy hypersurface of (I) was sampled by the SUMM method. The electrostatic treatment of (I) was based on our good experience of reproducing crystal structures of organic molecules by using *in vacuo* calculations with attenuated electrostatics (Keserű, Kolossváry & Nógrádi, 1995). Almost a million conformers were generated and 784 enantiomeric conformations were stored after rejections were made based on the failure of ring closure, unfavourable van der Waals interactions and the energy window (30 kJ mol^{-1} above the global mini-

mum). In addition to the lowest energy conformation ($E = 140.6 \text{ kJ mol}^{-1}$) shown in Fig. 3, the conformation corresponding to the X-ray structure of (I) ($E = 154.1 \text{ kJ mol}^{-1}$) was also found.

The most characteristic difference between the calculated global minimum and the crystal structure is the relative orientation of the carboxylate and the pyridine ring planes. Contrary to the solid-state structure, in the energy minimized conformer both carbonyloxy planes are coplanar with the pyridine ring.

Experimental

Compound (I) was prepared in the same way as described for the preparation of the di-*tert*-butyl analogue (Huszthy, Bradshaw, Zhu, Izatt & Lifson, 1991) and was recrystallized from methanol to give suitable crystals for the X-ray study.

Crystal data

$\text{C}_{17}\text{H}_{23}\text{NO}_7$
 $M_r = 353.36$
 Orthorhombic
 $P2_12_12_1$
 $a = 9.463 (5) \text{ \AA}$
 $b = 42.025 (4) \text{ \AA}$
 $c = 9.089 (4) \text{ \AA}$
 $V = 3614.6 (25) \text{ \AA}^3$
 $Z = 8$
 $D_x = 1.299 \text{ Mg m}^{-3}$

Cu $K\alpha$ radiation
 $\lambda = 1.54180 \text{ \AA}$
 Cell parameters from 23 reflections
 $\theta = 18.84\text{--}25.16^\circ$
 $\mu = 0.851 \text{ mm}^{-1}$
 $T = 293 (2) \text{ K}$
 Plate
 $0.5 \times 0.4 \times 0.1 \text{ mm}$
 Transparent

Data collection

Rigaku AFC-6S four-circle diffractometer
 ω - 2θ scans
 Absorption correction: none
 3970 measured reflections
 3970 independent reflections
 2039 observed reflections
 $[I > 2\sigma(I)]$

$\theta_{\max} = 75.11^\circ$
 $h = -11 \rightarrow 11$
 $k = -34 \rightarrow 52$
 $l = -11 \rightarrow 11$
 3 standard reflections monitored every 150 reflections
 intensity decay: none

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.0574$
 $wR(F^2) = 0.1682$
 $S = 1.282$
 3917 reflections
 451 parameters
 Only H-atom U 's refined
 $w = 1/[\sigma^2(F_o^2) + (0.0420P)^2 + 10.0620P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = -0.001$

$\Delta\rho_{\max} = 0.277 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.311 \text{ e \AA}^{-3}$
 Extinction correction: SHELXL93 (Sheldrick, 1993)
 Extinction coefficient: 0.00086 (14)
 Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)

$$U_{\text{eq}} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*a_i \cdot a_j$$

	x	y	z	U_{eq}
O5	0.6425 (9)	0.66090 (14)	0.1558 (9)	0.077 (3)
O6	0.7421 (7)	0.70250 (13)	0.2698 (7)	0.047 (2)
O10	0.9183 (7)	0.72343 (14)	0.5073 (8)	0.056 (2)

O13	0.9178 (8)	0.79500 (14)	0.5417 (8)	0.059 (2)
O16	0.8298 (7)	0.83963 (15)	0.3080 (8)	0.057 (2)
O20	0.6295 (8)	0.80600 (12)	0.1212 (7)	0.049 (2)
O22	0.6521 (10)	0.8149 (2)	-0.1185 (8)	0.079 (3)
N1	0.6551 (8)	0.7426 (2)	0.0655 (8)	0.045 (2)
C1	0.5068 (11)	0.7213 (2)	-0.1815 (11)	0.057 (3)
C2	0.5509 (11)	0.6999 (2)	-0.0755 (11)	0.060 (3)
C3	0.6256 (10)	0.7119 (2)	0.0439 (10)	0.045 (2)
C4	0.6710 (11)	0.6886 (2)	0.1610 (11)	0.054 (3)
C7	0.7750 (11)	0.6829 (2)	0.3988 (10)	0.052 (3)
C8	0.9022 (12)	0.6630 (2)	0.3704 (13)	0.072 (3)
C9	0.7929 (11)	0.7058 (2)	0.5238 (11)	0.056 (3)
C11	0.9503 (13)	0.7423 (2)	0.6337 (11)	0.067 (3)
C12	0.8715 (13)	0.7727 (2)	0.6472 (11)	0.062 (3)
C14	0.8553 (13)	0.8257 (2)	0.5680 (12)	0.070 (3)
C15	0.8906 (13)	0.8474 (2)	0.4451 (12)	0.069 (3)
C17	0.6812 (11)	0.8450 (2)	0.3036 (11)	0.056 (3)
C18	0.6293 (11)	0.8407 (2)	0.1506 (11)	0.051 (3)
C19	0.4793 (12)	0.8528 (2)	0.1304 (13)	0.074 (4)
C21	0.6353 (11)	0.7973 (2)	-0.0167 (10)	0.046 (2)
C23	0.6091 (10)	0.7622 (2)	-0.0398 (10)	0.043 (2)
C24	0.5363 (11)	0.7533 (2)	-0.1639 (10)	0.055 (3)
O5'	0.9061 (8)	1.08803 (13)	0.0569 (9)	0.072 (2)
O6'	1.0123 (6)	1.04763 (12)	0.1770 (7)	0.047 (2)
O10'	1.2434 (7)	1.02988 (14)	0.3667 (7)	0.052 (2)
O13'	1.2804 (7)	0.95906 (15)	0.3562 (8)	0.055 (2)
O16'	1.0575 (7)	0.91311 (15)	0.2662 (8)	0.055 (2)
O20'	0.8698 (6)	0.94276 (12)	0.0609 (8)	0.049 (2)
O22'	0.6424 (7)	0.93377 (15)	0.1127 (9)	0.066 (2)
N1'	0.8178 (7)	1.00636 (15)	0.0877 (8)	0.042 (2)
C1'	0.5732 (10)	1.0268 (2)	-0.0535 (12)	0.056 (3)
C2'	0.6767 (5)	1.04786 (10)	-0.0146 (6)	0.057 (3)
C3'	0.7955 (5)	1.03680 (10)	0.0563 (6)	0.041 (2)
C4'	0.9091 (5)	1.06023 (10)	0.0967 (6)	0.049 (2)
C7'	1.1297 (5)	1.06886 (10)	0.2155 (6)	0.049 (2)
C8'	1.0896 (11)	1.0886 (2)	0.3489 (11)	0.058 (3)
C9'	1.2554 (10)	1.0486 (2)	0.2384 (11)	0.050 (3)
C11'	1.3663 (10)	1.0118 (2)	0.3996 (12)	0.056 (3)
C12'	1.3820 (9)	0.9821 (2)	0.3114 (12)	0.055 (3)
C14'	1.3056 (10)	0.9291 (2)	0.2893 (13)	0.062 (3)
C15'	1.1902 (10)	0.9061 (2)	0.3283 (14)	0.062 (3)
C17'	1.0512 (10)	0.9052 (2)	0.1144 (11)	0.050 (3)
C18'	0.9007 (10)	0.9087 (2)	0.0639 (11)	0.050 (3)
C19'	0.8779 (13)	0.8957 (2)	-0.0899 (12)	0.066 (3)
C21'	0.7373 (9)	0.9512 (2)	0.0814 (11)	0.044 (2)
C23'	0.7140 (9)	0.9858 (2)	0.0500 (11)	0.041 (2)
C24'	0.5903 (9)	0.9950 (2)	-0.0166 (11)	0.048 (3)

Table 2. Selected geometric parameters (\AA , $^\circ$)

O5—C4	1.198 (9)	O5'—C4'	1.223 (7)
O6—C4	1.330 (10)	O6'—C4'	1.329 (7)
O6—C7	1.466 (10)	O6'—C7'	1.467 (7)
O10—C9	1.407 (11)	O10'—C9'	1.411 (10)
O10—C11	1.429 (11)	O10'—C11'	1.422 (10)
O13—C12	1.409 (11)	O13'—C14'	1.419 (10)
O13—C14	1.439 (11)	O13'—C12'	1.424 (10)
O16—C15	1.410 (11)	O16'—C15'	1.408 (11)
O16—C17	1.425 (11)	O16'—C17'	1.420 (11)
O20—C21	1.307 (10)	O20'—C21'	1.317 (10)
O20—C18	1.482 (8)	O20'—C18'	1.462 (8)
O22—C21	1.194 (10)	O22'—C21'	1.193 (9)
N1—C23	1.336 (10)	N1'—C3'	1.328 (7)
N1—C3	1.332 (9)	N1'—C23'	1.352 (9)
C7—C9	1.498 (12)	C7'—C9'	1.478 (10)
C11—C12	1.486 (13)	C11'—C12'	1.489 (12)
C14—C15	1.480 (13)	C14'—C15'	1.500 (13)
C17—C18	1.486 (13)	C17'—C18'	1.503 (12)
C21—C23	1.514 (10)	C21'—C23'	1.498 (10)
C4—O6—C7	117.2 (6)	C4'—O6'—C7'	116.4 (5)
C9—O10—C11	112.7 (8)	C9'—O10'—C11'	113.9 (7)
C12—O13—C14	110.7 (8)	C14'—O13'—C12'	111.6 (7)
C15—O16—C17	113.0 (8)	C15'—O16'—C17'	112.2 (8)
C21—O20—C18	116.6 (6)	C21'—O20'—C18'	116.9 (7)
C23—N1—C3	115.0 (7)	C3'—N1'—C23'	116.4 (6)
N1—C3—C2	125.0 (8)	N1'—C3'—C4'	117.7 (4)
O6—C4—C3	112.7 (7)	O6'—C4'—C3'	113.5 (3)

O6—C7—C9	105.7 (7)	O6'—C7'—C9'	107.0 (5)
O10—C9—C7	110.6 (8)	O10'—C9'—C7'	111.9 (7)
O10—C11—C12	116.0 (9)	O10'—C11'—C12'	114.6 (8)
O13—C12—C11	111.0 (9)	O13'—C12'—C11'	110.4 (8)
O13—C14—C15	109.5 (9)	O13'—C14'—C15'	110.4 (8)
O16—C15—C14	115.7 (9)	O16'—C15'—C14'	114.8 (8)
O16—C17—C18	109.4 (8)	O16'—C17'—C18'	108.3 (8)
C17—C18—O20	106.8 (7)	O20'—C18'—C17'	106.9 (7)
O20—C21—C23	113.5 (7)	O20'—C21'—C23'	112.0 (7)
N1—C23—C21	116.7 (7)	N1'—C23'—C21'	117.7 (7)
C7—O6—C4—C3	172.1 (8)		
N1—C3—C4—O6	-2.9 (13)		
C4—O6—C7—C9	-155.4 (8)		
C11—O10—C9—C7	-171.7 (8)		
O6—C7—C9—O10	-70.7 (10)		
C9—O10—C11—C12	-79.8 (11)		
C14—O13—C12—C11	-172.1 (9)		
O10—C11—C12—O13	-71.2 (12)		
C12—O13—C14—C15	-172.7 (9)		
C17—O16—C15—C14	70.8 (12)		
O13—C14—C15—O16	67.1 (13)		
C15—O16—C17—C18	172.1 (7)		
O16—C17—C18—O20	74.0 (10)		
C21—O20—C18—C17	-157.2 (9)		
C18—O20—C21—C23	-169.8 (8)		
C3—N1—C23—C21	177.7 (9)		
O20—C21—C23—N1	-33.7 (13)		
C7'—O6'—C4'—C3'	177.7 (4)		
N1'—C3'—C4'—O6'	-8.0 (5)		
C4'—O6'—C7'—C9'	-153.8 (5)		
C11'—O10'—C9'—C7'	-175.4 (7)		
O6'—C7'—C9'—O10'	-69.5 (8)		
C9'—O10'—C11'—C12'	-79.2 (10)		
C14'—O13'—C12'—C11'	-171.5 (8)		
O10'—C11'—C12'—O13'	-71.3 (10)		
C12'—O13'—C14'—C15'	-175.2 (9)		
C17'—O16'—C15'—C14'	75.7 (11)		
O13'—C14'—C15'—O16'	68.7 (12)		
C15'—O16'—C17'—C18'	171.3 (7)		
C21'—O20'—C18'—C17'	-152.1 (9)		
O16'—C17'—C18'—O20'	71.1 (9)		
C18'—O20'—C21'—C23'	-170.0 (8)		
C3'—N1'—C23'—C21'	178.9 (7)		
O20'—C21'—C23'—N1'	-36.7 (13)		

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1992). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KA1127). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1:1 Adduct of Tris(4-hydroxy-3,5-dimethylbenzyl)amine and Hexamethylenetetramine

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Abstract

The title compound {4,4',4''-(nitrotrimethylene)tris(2,6-dimethylphenol)-1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane (1/1), C₂₇H₃₃NO₃.C₆H₁₂N₄} crystallizes in the space group *R*3̄, with hydrogen-bonded layers perpendicular to the symmetry axes. All molecules lie on threefold rotation axes. Each triphenol molecule is hydrogen bonded to three hexamethylenetetramine molecules and each hexamethylenetetramine molecule is hydrogen bonded to three triphenol molecules. The hydrogen bonds are similar to those found in other adducts of hexamethylenetetramine with phenols.