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Synthesis and Structure of "Hexametaxylylenetetramine"[1,2)]
A Urotropin-like Cage Compound

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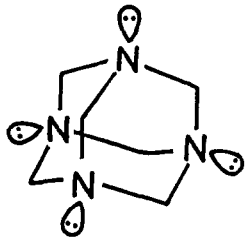
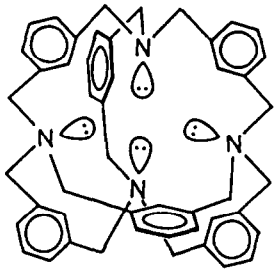
Summary: The title compound was synthesized by the reaction of 1,3-bis-(aminomethyl)benzene with 1,3-bis(bromomethyl)benzene. The urotropin-like cage structure of this compound was established by X-ray crystallographic structure determination.

Urotropin[3)] (or hexamethylenetetramine, $(CH_2)_6N_4$, employed in medicine as a urinary antiseptic), which is the first organic molecule whose structure was determined by X-ray diffraction[4)], has a adamantane-like structure.
In urotropin, four lone pairs on nitrogen atoms at bridgehead are oriented outward with respect to the center of the molecule.



urotropin
(hexamethylenetetramine)
(1,3,5,7-tetraazaadamantane)



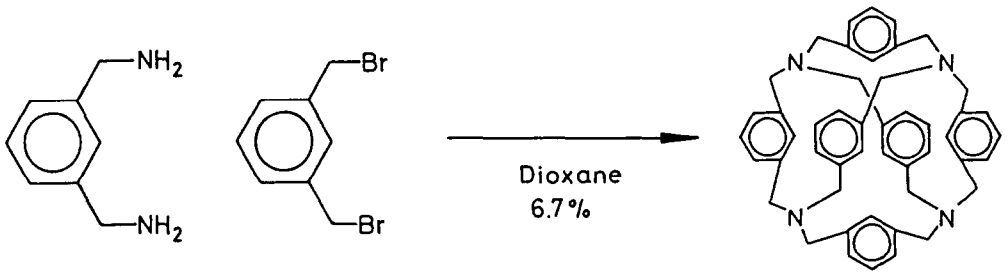
1
"hexametaxylylenetetramine"

Fig. 1.

In this communication we report a synthesis and a structural elucidation of a cage compound 1 which has an urotropin-like structure. This compound also resembles somewhat structurally Lehn's sophisticated tricyclic cryptand known as "soccer ball molecule"[5)] on account of its spherical three-dimensional skeleton. In this compound, contrary to urotropin, four lone pairs of electrons on the bridgehead nitrogen atoms are oriented toward the center of the molecule.

Six aromatic hydrogen atoms placed between two methylene groups are also oriented toward the central intramolecular cavity.

From the molecular model consideration, any cation but proton is too large to fit into the intramolecular cavity. Thus, this compound may serve as a proton cryptand[6].



Scheme 1.

Cage compound 1 was prepared by the reaction of 1,3-bis(aminomethyl)benzene with 1,3-bis(bromomethyl)benzene in one step as shown in Scheme 1.

To a refluxed solution of 1,3-bis(aminomethyl)benzene (16.0 g, 117 mmol) in dioxane (400 ml) was added a solution of 1,3-bis(bromomethyl)benzene (23.8 g, 90.2 mmol) in dioxane (300 ml) over a period of 4 h. After the solution was refluxed for additional 4.5h, the reaction mixture was filtered and the organic layer was concentrated in vacuo. The residue thus obtained was digested with benzene and purified by passing the benzene solution through an alumina short column (WAKO 300, benzene) to furnish white crystalline powder. Recrystallization from n-hexane-$CHCl_3$ mixture gave colorless prisms (1.03 g, 6.7% based on the dibromide), mp 389°C dec(corr). Found: C, 84.42; H, 7.17; N, 8.33%. Calcd for $C_{48}H_{48}N_4$: C, 84.67; H, 7.10; N, 8.23%. PMR[7](CDCl$_3$, δ) 8.36 bs(arom, 6H), 7.08s (arom, 18H), 3.53bs(-$\underline{CH}_2$-N, 24H); CMR[7](CDCl$_3$, δ) 140.83s, 127.91, 127.65, 127.58, 127.52, 127.43, 126.89, 126.59, 59.96t(-$\underline{CH}_2$N-); IR(KBr disk, cm^{-1}) 3020(ν_{C-H} arom), 1600, 1585, 1480($\nu_{C=C}$ arom), 1435(δ_{sC-H}), 1365, 895, 860, 800, 780, 765, 750, 695(δ_{opC-H} arom). MS(m/e) M^+, 680.

Recrystallization from benzene gave the benzene adduct (1:benzene=1:1) as colorless prisms. Found: C, 85.24; H, 7.26; N, 7.42%. Calcd for $C_{48}H_{48}N_4 \cdot C_6H_6$: C, 85.45; H, 7.17; N, 7.38%.

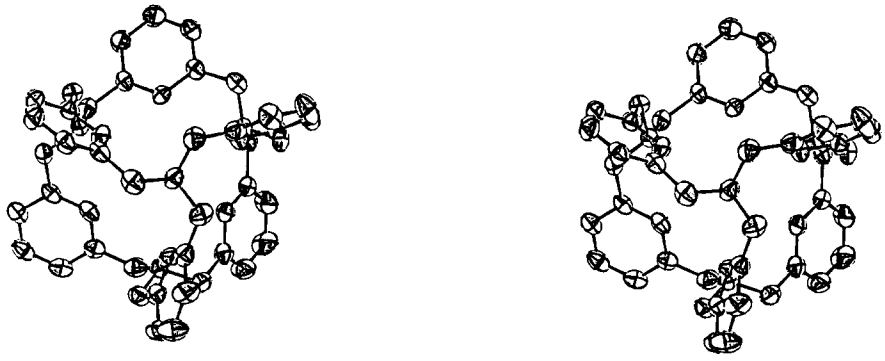


Fig. 2. A computer generated stereoscopic drawing of the molecule 1.

On the basis of usual physical data alone such as PMR, CMR, IR, MS and elemental analysis, it was very difficult to distinguish between this cage structure (1) and another possible cage structure (2)[8,9]. In addition to the unambiguous synthesis of compound 2, the X-ray analysis was used to provide an unequivocal proof for the urotropin-like structure of 1. The crystal data[10] of the benzene adduct ($C_{48}H_{48}N_4 \cdot C_6H_6$) are as follows; monoclinic, space group $P2_1/a$, a=27.871(4), b=15.928(2), C=9.831(1)Å, β=92.25(1)°, V=4360.8(9)Å^3, Z=4, Dc=1.156 (Dm=1.153)g cm^{-3}.
A colorless crystal (0.28×0.44×0.42 mm^3) coated with a thin layer of epoxy cement was used for intensity measurement up to 2θ=55.0° on Rigaku AFC-5 diffractometer with Mo-Kα radiation. A total of 4516 independent reflection with Fo≥3δ(Fo) was considered to be observed. The structure was solved by direct methods using Multan 78[11] and refined[12] with anisotropic non-hydrogen atom and isotropic hydrogen atoms to R=0.082, Rw=0.079 (w=1.0).

Although a structure, in which all four lone pairs on bridgehead nitrogen atoms are oriented outward with respect to the center of molecule as in urotropin, is possible from the CPK model, but at least in crystalline state all lone pairs on nitrogen atoms point toward the center of the tetrahedron constructed of four nitrogens as shown in Fig. 1 and in the ORTEP drawing[13] in Fig. 2.

Further studies on the protonation and quarternization of compound 1 and synthesis of pyridine analogue are in progress.

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References and Notes

1) The trivial name "hexametaxylylenetetramine" is used because of prolixity for nomenclature.

2) 1,9,17,25-tetraazanonacyclo[15.15.7.7^{9,25}1^{3,7}1^{11,15}1^{19,23}1^{27,31}-1^{34,38}1^{41,45}]dopentacont-3,5,7(47),11,13,15(48),19,21,23(49),27,29,31(50),-34,36,38(51),41,43,45(52)-octadecaene.

3) Urotropin can be prepared merely by allowing a mixture of formalin and concentrated ammonia solution to evaporate.

4) R. G. Dickinson and A. L. Raymond, J. Am. Chem. Soc., 45, 22 (1923).

5) E. Graf and J. M. Lehn, J. Am. Chem. Soc., 97, 5022 (1975).

6) J. Cheney and J. M. Lehn, J. Chem. Soc., Chem. Commun., 1972, 487.

7) The problem of the conformational mobility of 1 in solution will be discussed elsewhere.

8) Cage compound 2 was prepared by the reaction of 2,11-diaza[3.3]metacyclophane with 1,3-bis(bromomethyl)benzene.

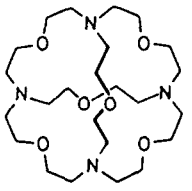
9) To be published elsewhere.

10) Crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre.

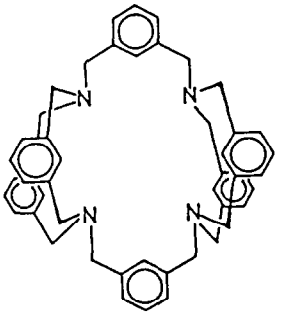
11) R. Main, L. Lessinger, M. M. Woolfson, G. Germain, and J. P. Declercq, 'MULTAN 78, A Program for the Automated Solution of Crystal Structures for X-Ray Diffraction Data', University of York, 1978.

12) T. Sakurai and K. Kobayashi, Rikagaku Kenkyusho Hokoku, 55, 69 (1979).

13) Benzene molecules located between "hexametaxylylenetetramine" molecules are omitted in the stereoscopic drawing in Fig. 2.



"soccer molecule"



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