Tetrahedron Letters,Vol.27,No.35,pp 4099-4102,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

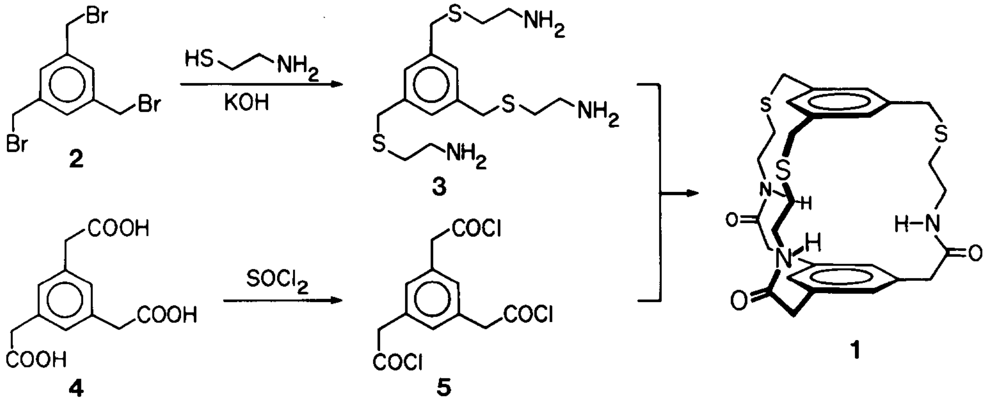
SYNTHESIS AND X-RAY CRYSTALLOGRAPHIC CHARACTERIZATION OF A (1,3,5)CYCLOPHANE WITH THREE AMIDE N-H GROUPS SURROUNDING A CENTRAL CAVITY.

A NEUTRAL HOST FOR ANION COMPLEXATION.

Robert A. Pascal, Jr.,* Jonathan Spergel, and Donna Van Engen
Deparment of Chemistry, Princeton University, Princeton, New Jersey 08544

Summary: *A short synthesis of 2,15,28-trioxo-3,16,29-triaza-6,19,32-trithia-[7.7.7](1,3,5)cyclophane (1) is described. An X-ray crystallographic analysis shows that the cyclophane exists in an extended conformation with three amide N-H groups directed approximately inward toward the central cavity.*

The complexation of anions by organic macrocyclic ligands is by comparison to cation complexation a relatively unexplored area of chemistry. Furthermore, the vast majority of anion-complexing macrocycles are polyammonium compounds[1,2] in which charge-charge interactions presumably provide much of the binding force. In contrast, the X-ray crystal structure of the sulfate-binding protein of *Salmonella typhimurium* shows that the sulfate is bound only by seven hydrogen bonds, five of which are made with amide N-H's of the polypeptide backbone.[3] No cationic groups are present in the binding site, which is 7 Å below the surface of the protein and inaccessible to the solvent. In order to mimic this mode of anion complexation in a simpler system, we wished to synthesize a neutral organic macrocycle containing several inwardly-directed amide N-H groups which might form hydrogen bonds with an encapsulated inorganic anion. We report herein the synthesis and X-ray crystallographic characterization of a macrocycle suitable for such studies: 2,15,28-trioxo-3,16,29-triaza-6,19,32-trithia[7.7.7](1,3,5)cyclophane[4] (1).



Compound **1** may be prepared from the easily accessible precursors 1,3,5-tris-(bromomethyl)benzene[5] (**2**) and 1,3,5-benzenetriacetic acid[6] (**4**) in a short, convergent synthesis, requiring no chromatographic steps, which may be completed in less than 24 hours. Sodium hydroxide (0.30 g, 7.5 mmol) is dissolved in 30 mL of 95% ethanol, and the solution is saturated with argon. Cysteamine (0.58 g, 7.5 mmol) is added, followed by an argon saturated solution of compound **2** (0.89 g, 2.5 mmol) in benzene (20 mL). The solution is stirred for 2 hours, the solvent is evaporated, and the residue is dried under vacuum to give the crude triamine **3**. During this time, compound **4** (0.63 g, 7.5 mmol), thionyl chloride (5 mL), and toluene (20 mL) are refluxed for 1 hour. Another 30 mL of toluene are added, and the thionyl chloride and toluene are distilled away to give the crude triacid chloride **5**. Dry THF (250 mL) is added to the triamine, and the mixture is heated to reflux. Dry THF (50 mL) is added to the triacid chloride, and this solution is added rapidly to the refluxing solution of the triamine. After 10 minutes, triethylamine (2 mL) is added, and the mixture is refluxed for 4 hours. After cooling, the solvent is evaporated to yield a yellow powder. This material is placed in a Soxhlet extraction cup, and it is extracted with carbon tetrachloride for 3 hours followed by chloroform for 4 hours. ^1H NMR analysis has shown that the chloroform fraction contains only the desired cyclophane **1** and triethylammonium chloride. Therefore, the chloroform solution is washed with 1 N HCl, dried, and concentrated to dryness. The remaining white powder is essentially pure cyclophane **1**. Recrystallization from methanol gives 0.150 g (11% yield), mp >350°; ^1H NMR (DMSO-d_6) δ 2.20 (t, J = 7, 6H, $SC\underline{H}_2CH_2NH$), 3.04 (m, 6H, $SCH_2C\underline{H}_2NH$), 3.27 (s, 6H, $Ar(CH_2)_3$), 3.43 (s, 6H, $Ar(CH_2)_3$), 6.93 (s, 3H, $Ar\text{-}H_3$), 7.06 (s, 3H, $Ar\text{-}H_3$), 7.66 (t, J = 6, 3H, NH); MS, m/z 543 (M+, 100), 285 ($M\text{-}C_6H_3(CH_2SCH_2)_3$, 34).

Single crystals of compound **1** were obtained by the slow evaporation of a methanol solution. An X-ray crystallographic analysis[7] yielded the structure illustrated in Figure 1. In the solid state, **1** adopts an extended conformation in which the capping benzene rings are 7.40 Å apart (along an imaginary axis drawn between the centers of the rings) and approximately parallel (the ring planes are inclined by 6° relative to one another). The two aromatic rings and three bridging arms enclose a roughly cylindrical cavity approximately 4 Å in length and 3 Å in diameter. The three N-H groups do not point directly inward, but are inclined by 47, 54, and 68° to radii drawn from the central axis through the nitrogen atoms. The cavity size is such that small anions such as fluoride and hydroxide[1] should be easily accommodated, and the amide N-H groups are well situated to form three strong hydrogen bonds with an encapsulated anion.[8]

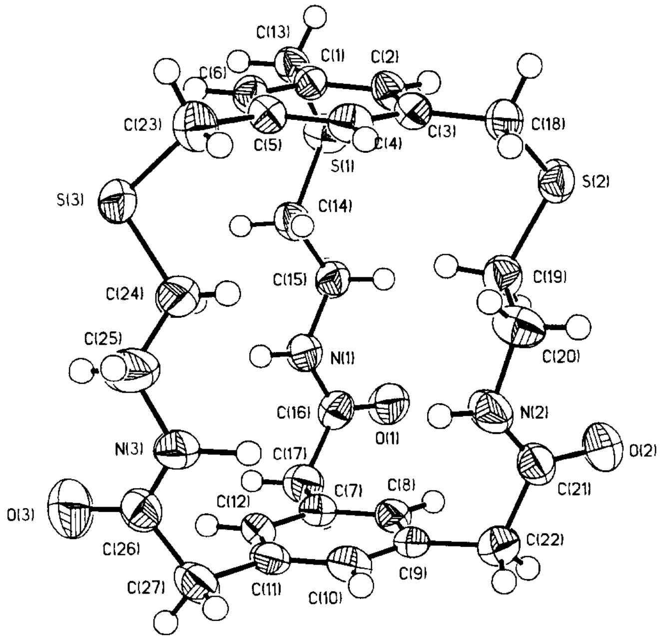


Figure 1. Computer-generated perspective drawing of compound **1**.

Our preliminary ^{1}H and ^{19}F NMR studies of solutions of **1** and tetrabutylammonium fluoride in DMSO-d_6 suggest that there is an association of fluoride ion with the macrocycle **1**, but it is not certain at this time that fluoride is contained within the cavity of the cyclophane.

REFERENCES AND NOTES

1. Recent reviews of anion complexation: (a) Pierre, J.-L., and Baret, P. (1983) Bull. Soc. Chim. Fr., 367; (b) Dietrich, B., "Cryptate Complexes" in Inclusion Compounds, vol. 2, Atwood, J.L., Davies, J.E.D., and MacNicol, D.D., eds.; Academic Press, New York: 1984, p. 337, and references cited therein.
2. X-ray crystal structures of macrocycles containing encapsulated anions: (a) Bell, R.A., Christoph, G.G., Fronczek, F.R., and Marsh, R.E. (1975) Science **190**, 151; (b) Metz, B., Rosalky, J.M., and Weiss, R. (1976) J. Chem. Soc., Chem. Comm., 533; (c) Dietrich, B., Guilhem, J., Lehn, J.-M., Pascard, C., and Sonveaux, E. (1984) Helv. Chim. Acta **67**, 91; (d) Schmidtchen, F.P., and Muller, G. (1984) J. Chem. Soc., Chem. Comm., 1115.
3. Pflugrath, J.W., and Quiocho, F.A. (1985) Nature **314**, 257.
4. The nomenclature of Vogtle is used for the naming of compound 1: Vogtle, F., and Neumann, P. (1969) Tetrahedron Lett., 5329.
5. Vogtle, F., Zuber, M., and Lichtenthaler, R.G. (1973) Chem. Ber. **106**, 717.
6. Newman, M.S., and Lowrie, H.S. (1954) J. Am. Chem. Soc. **76**, 6196.

7. A crystal of compound 1 measuring 0.07 x 0.15 x 0.30 mm^3 was chosen for X-ray measurements. Crystal data: $C_{21}H_{33}N_3O_3S_3$, M_r = 471.8; monoclinic, space group $P2_1/a$ (standard: $P2_1/c$); a = 15.633(4) Å, b = 8.389(3) Å, c = 21.202(5) Å, β = 98.27(2)°, V = 2752(1) Å^3, Z = 4, d_{calcd} = 1.19 g/cm^3. Intensity measurements were made with 3° < 2θ < 114° using graphite monochromated CuKα radiation (λ = 1.54178 Å) at 180 K on a Nicolet R3m diffractometer. A total of 3704 unique reflections were measured, and after applying Lorentz, polarization, and background corrections, 2872 were considered to be observed [$|F_0| > 3\sigma(F_0)$]. The structure was solved by direct methods using the SHELXTL software. In the final cycles of blocked-cascade least-squares refinement, all nonhydrogen atoms were assigned anisotropic temperature factors, the N-H hydrogens were fixed, and a riding model was used for the remaining hydrogens with positions idealized at C-H = 0.960 Å, B(H) = 1.2 x B(C). Final refinement with 325 parameters converged at R = 0.063 and R_w = 0.063 with goodness of fit = 1.44.
8. In the crystal, N(1), N(2), and N(3) (see Figure 1 for numbering) are located 3.2, 2.8, and 3.3 Å, respectively, from the central axis of compound 1. An encapsulated ion should reside on or near this axis. Typical heavy atom to heavy atom distances for N-H···F, N-H···O, and N-H···Cl hydrogen bonds are 2.8, 2.9, and 3.3 Å, respectively,[9] so the dimensions of the central cavity are quite appropriate. The protons attached to N(1), N(2), and N(3) are located approximately 3.0, 2.4, and 2.9 Å, respectively, from the central axis of the molecule. Were the side chains to twist slightly to permit the N-H bonds to point directly inward, these distances could be reduced to as little as 2.0 Å.
9. Huheey, J.E., Inorganic Chemistry, 3rd ed.; Harper & Row: New York, 1983; p. 268.

(Received in USA 16 May 1986)