Tetrahedron Letters,Vol.28,No.30,pp 3489-3492,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

POLYAZA-MACROCYCLES OF CYCLOPHANE TYPE: SYNTHESIS, STRUCTURE OF A CHLOROFORM INCLUSION COMPLEX AND ANION BINDING.

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Abstract. Polyazamacrocycles (1)-(7) have been obtained via efficient (amine + aldehyde) polycondensation processes. The tetraimine (1) forms a chloroform inclusion complex whose crystal structure has been determined; the protonated tetraamine (5) binds dicarboxylate substrates.

Amphiphilic receptor molecules based on the combination of apolar shaping components with polar binding subunits (as in speleands), may be expected to present enhanced substrate complexation abilities due to the synergistic operation of hydrophobic and electrostatic effects[1]. Such is for instance the case for macrocyclic molecules incorporating diphenylmethane groups[2-8] and ammonium[2-6] or carboxylate[7] sites, which possess an internal cavity suitable for inclusion of a variety of substrates.

We report here an efficient, one-step access to related macrocycles (1)-(7) via multiple (amine + aldehyde) condensations and describe some preliminary complexation properties.

Synthesis of Macrocycles (1)-(7).

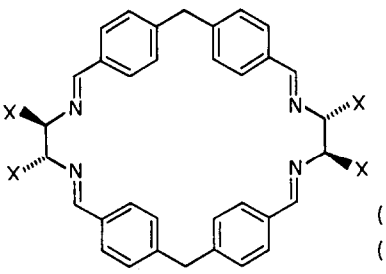
Typically, the dialdehyde (8)[9] derived from diphenylmethane (about 1 mmol) in acetonitrile (20 ml) was added dropwise over 30 min to a stirred solution of a diamine (1 eq.) in acetonitrile (about 40 ml) at room temperature. The mixture was stirred for several hours during which time the corresponding macrocyclic tetraimine precipitated as a white solid. Thus, ethylenediamine and the diamines (9) and (10) gave respectively macrocycles (1) (m.p. ~ 240°dec.), (3) (m.p. 124°) and (4) (m.p. 215°) (about 65-75% yield) which were recrystallized from $CHCl_3/CH_3CN$. Condensation of optically active SS(+)-diamino-succinic acid[10] with (8) in toluene gave the chiral macrocycle (2) (m.p. > 250°) after evaporation of the solvent and crystallization from CH_3CN (about 85% yield)[11].

Reduction of (1) and (4) with $LiAlH_4$ in tetrahydrofurane (reflux; 1h) gave the corresponding macrocyclic polyamines (5) and (7) (60% and 20% yield respectively) which were isolated as their hydrochlorides[12]. Tetraimine (2) was reduced with $NaBH_3CN$[13] in methanol under continuous adjustment of the apparent pH of the reaction mixture to ~ 6 with HCl/MeOH, giving (6) in 60% yield (crystallized from cyclohexane; m.p. > 250°). Hydrolysis of (6) with NaOH in $MeOH/H_2O$ at reflux gave the corresponding tetracarboxylate (6)($X=CO_2^-Na^+$)[14].

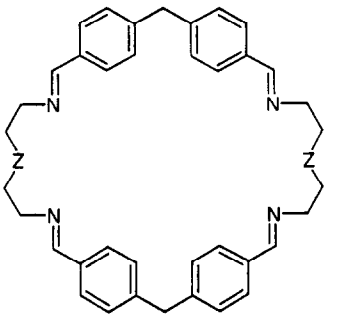
The tetraimino macrocycles (1)-(4) are sensitive to hydrolysis. The highly basic polyamines (5) and (7), are water soluble when protonated in weakly acidic conditions;

(6)(X=COOH) contains four asymmetric centres and four amino-acid groups; the tetraester (6) is water soluble in acidic medium (pH < 3.0), whereas (6)(X=COOH) is soluble either in acidic or basic solution but not around neutral pH where the zwitterionic form is present.

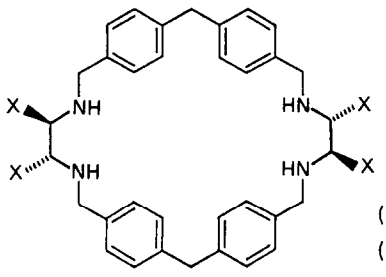
All these new macrocycles are potential receptor molecules of ditopic type[1] since they contain two polyaza binding subunits separated by the diphenylmethane bridges.



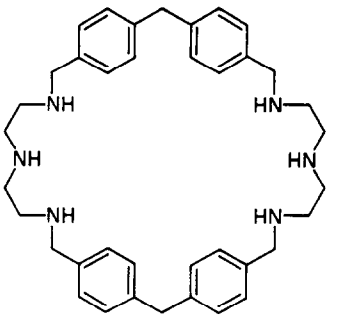
(1) X=H
(2) X=COOMe



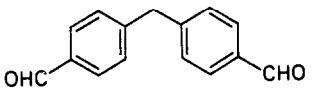
(3) Z=O
(4) Z=N-Tosyl



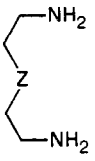
(5) X=H
(6) X=COOMe



(7)



(8)



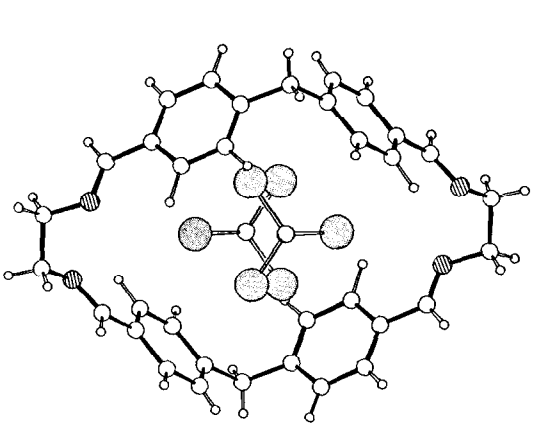
(9) Z=O
(10) Z=N-Tosyl

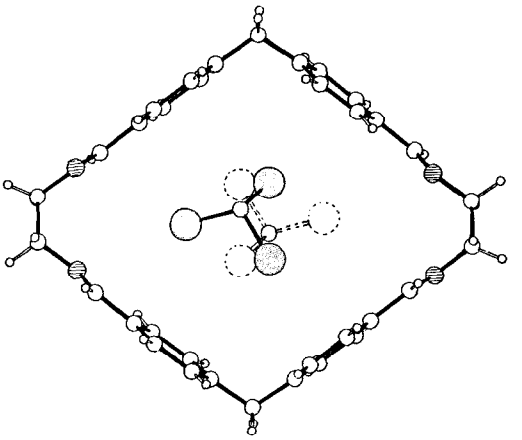
Crystal Structure of the [$CHCl_3 \subset$ (1)] Inclusion Complex.

The structure of macrocycle (1) was confirmed by radiocrystallographic analysis on a crystal grown from a $CHCl_3/CH_3CN$ mixture[15]. This also supports the structural assignment for the other macrocycles. Two views of the structure are shown in Figures 1 and 2.

It is seen that the compound is in fact an inclusion complex containing a neutral substrate, a chloroform molecule in the intramolecular cavity of receptor (1).

The macrocycle exhibits C_{2h} symmetry, with a binary axis passing through the middle of the CH_2-CH_2 bond and a mirror plane perpendicular to it and passing through the two methylene groups. The four nitrogens are located in one plane which is median to the whole structure. The molecule has a diamond shape and the phenyl rings are almost perpendicular (tilt angles of 83° and 87°) to this mean plane, thus delineating a well-defined intramolecular cavity of dimensions 12.8 Å and 10.9 Å from ethylene-to-ethylene and CH_2-to-CH_2 units respectively with a C_6H_4-CH_2-C_6H_4 angle of 107°.





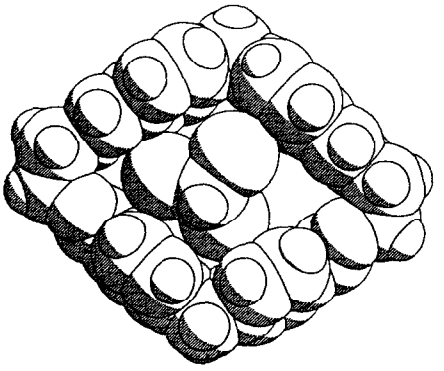


Figure 1 (above). Two perspective views of the chloroform inclusion complex [$CHCl_3 \subset$ (1)] formed by macrocycle (1); the two positions of the chloroform molecule are shown.

Figure 2 (left). Space-filling representation of the complex [$CHCl_3 \subset$ (1)] with the chloroform molecule in one position.

The included chloroform molecule is located in the center of the macrocycle and on the same level, with one chlorine atom tucked in the corner formed by the di-imino chain. The two other chlorines lie in the wider part of the cavity, above and below the ring. The 3-chlorine plane makes a dihedral angle of 39° with the ring mean plane. The shortest distances between the chloroform molecule and the walls of the macrocycle lie in the 3.35-3.61 Å range indicating that the two species are in Van der Waals contact. Chloroform inclusion by cyclophane type polyamine and polyamide macrocycles has been reported[16].

Substrate Binding.

Anion binding may occur with the protonated polyamines (5)-(7) which are ditopic receptor molecules and could form complexes of speleate type with difunctional anionic substrates. Dicarboxylate molecules may interact with each of the binding subunits, as in other ditopic polyammonium macrocycles[17]. Some preliminary binding studies were performed.

Marked upfield shifts of the 200 MHz ^{1}H-NMR signals of succinate (200 Hz), malate (110 Hz) or tartrate (35 Hz) were observed on addition of 1 eq. of (5),4HCl (1.5 mM) at pH=5.8-6.0, indicating that complexation was taking place. Analysis of the shift of the NCH_2CH_2N signal as a function of added succinate gave a stability constant of log K_s = 2.80 ± 0.2 (maximum shift of 126 ± 15 Hz). Thus, (5),4HCl forms a stable complex with this substrate whose length is compatible with the size of the molecular cavity.

Binding of methylviologen by the tetracarboxylate macrocycle (**6**)(X=COO^-) at pH=9 was also detected by ^{1}H-NMR studies, but the shifts were much smaller than found previously with an analogous tetracarboxylate macrocycle containing oxygens in place of the nitrogen atoms[7].

These preliminary results indicate that protonated (**5**) and (**7**) should be able to bind a variety of anionic substrates. Furthermore, variation in both the diphenylmethane and polyamine groups may be expected to affect stability and selectivity of the complexes. Finally, macrocycle (**7**) (and analogues thereof) may also be of interest as catalyst acting on anionic substrates since macrocyclic polyamines have been shown to mediate phosphoryl transfer processes[18,19].

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15. Crystal data: monoclinic, space-group $P2_1/c$; a=8.979(6), b=23.786(10), c=7.469(6) Å; ß=101.94(5) Å; V=1561 Å^3 ; d_c=1.31; Z=2 complexes per unit cell. The structure was solved by direct methods using a local program (C. Riche, 7th European Crystallographic Meeting, Jerusalem, Abstract 25, 1982). All hydrogen atoms were found on difference Fourier syntheses and introduced in the calculations with a constant temperature factor. The final discrepancy factor was 9.1% for 2087 reflections. The highest residue on the final electronic density map was about 0.5e/A^3. Tables of structural data are available from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, Great Britain.
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19. Work supported by the CNRS and the Collège de France (research fellowship to JJ).

(Received in France 24 May 1987)