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SYNTHESIS OF DOME-SHAPED CYCLOPHANE TYPE MACROTRICYCLIC ANION RECEPTOR MOLECULES

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Abstract. *Five novel poly-aza macrotricycles 1-5 of cyclophane type, containing amine and amide functional groups have been synthesized; when protonated they may function as anion receptor molecules.*

The design, preparation and study of synthetic organic receptor molecules capable of binding anionic substrates is a relatively new area within the field of supramolecular chemistry[1]. Recently the investigation of anion complexes has received much attention in view of the critical role played by anions in both chemical and biological processes[2].

To date, a number of macrocyclic anion complexing agents containing ammonium[3,4] or guanidinium[5] groups as binding sites, have been described.

Here, we now report the synthesis and some properties of five new triply bridged cyclophane type macrotricycles possessing three amide and three amine groups 1, 2, 3 or six amine sites 4, 5. With the amide functions of the macrocycles 1, 2, 3 fixed in the anti-form, the N-H bonds are expected to be directed towards the interior of the molecules, which should favour inclusion-type binding of anions (see also[6]). We have described earlier the synthesis and anion binding features of macrobicyclic cyclophane anion receptors[7].

Synthesis of the Macrotricycles 1, 2 and 3.

The basic skeleton 2,11,20-triaza[3.3.3]paracyclophane 6[8] was prepared in 50% overall yield in the following manner. p-Toluenesulfonamide was reacted with α-bromo-p-tolunitrile (K_2CO_3, DMF, 60°C, 3h) to give the bis-nitrile 7 (90%). Reduction of 7 with B_2H_6[9] (THF, r.t., 16h), followed by hydrolysis (6N-HCl, r.t., 18h), afforded the amine 8, which on treatment with tosyl chloride (K_2CO_3, THF/H_2O 4/1, 60°C, 14h) was converted to the corresponding tris-tosylate 9 (88% from 7). Cyclization of 8 with α,α'-dibromo-p-xylene (K_2CO_3, DMF, 65°C, 8.5h) produced the N-tosyl-azacyclophane 10 (70%). The removal of the tosyl groups was achieved by treatment with a large excess of $LiAlH_4$ under mild conditions (40-50°C, THF, 18h) to yield the azacyclophane 6 in 90% yield[7,10].

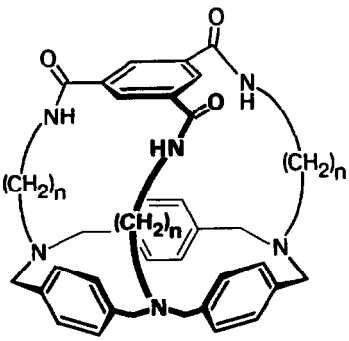
The branched macrocycles 14, 15 and 16 were prepared by the attachment of nitrile bearing side-chains to 6 and subsequent reduction with $LiAlH_4$ 14 or B_2H_6 (15 and 16). The reaction of the sodium salt of 6 (NaH, THF, reflux, 1h) with bromoacetonitrile (DMF, 70°C, 2h) or 4-bromobutyronitrile (DMF, 50°C, 17h) gave the tris-nitriles 11 (90%) and 13 (78%) which were reduced respectively to 14 (70%, $LiAlH_4$, THF, r.t., 24h) and to 16 (82%, a) B_2H_6, THF, r.t., 16h; b) 6N HCl, r.t., 16h). The macrocycle 15 was prepared by addition of

acrylonitrile to 6 in the presence of acetic acid[11] (3.0 eq., reflux, 2h) to give 12 (94%), and subsequent B_2H_6 reduction (THF, r.t., 24h), followed by hydrolysis (90% from 12, 6N HCl, r.t., 16h).

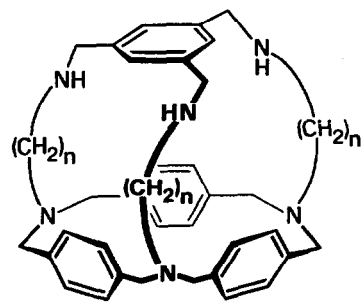
The synthesis of the macrotricycles 1, 2 and 3 was carried out by direct coupling of the above triply branched macrocycles 14, 15 and 16 with 1,3,5-benzenetricarboxylic acid chloride 17 under high dilution conditions. Simultaneous addition of solutions of 14-16 (2.9×10^{-3}M in CH_2Cl_2 plus excess triethylamine as base) and of 17 (2.9×10^{-3}M in CH_2Cl_2) to CH_2Cl_2 at room temperature followed by purification of the crude products by column chromatography (silica gel; eluent: $CHCl_3$/MeOH 98/2) yielded the macrotricycles 1, 2 and 3 in 13%, 33% and 42% yields, respectively[12].

The relative yields of the tripod-tripod direct coupling reactions giving the macrocycles 1, 2 and 3 (1 < 2 < 3) indicate that steric effects hinder the final ring closure step, especially for the formation of 1.

Reduction of the three amide groups of 2 and 3 with B_2H_6 (THF, r.t., 16h) followed by hydrolysis (6N HCl, r.t., 15h) gave the macrotricyclic hexa-amines 4 and 5 in about 90% yield. Similar treatment of 1 gave a mixture of compounds; further work is under way[13].

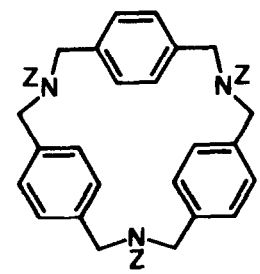


2 n=3
3 n=4



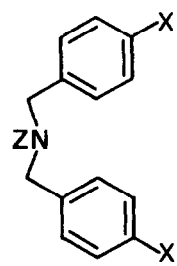
4 n=3
5 n=4

6	Z=H	13	$Z=CH_2CH_2CH_2CN$
10	Z=Tosyl	14	$Z=CH_2CH_2NH_2$
11	$Z=CH_2CN$	15	$Z=CH_2CH_2CH_2NH_2$
12	$Z=CH_2CH_2CN$	16	$Z=CH_2CH_2CH_2CH_2NH_2$

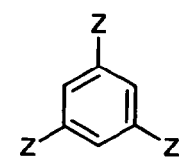


7 X=CN
8 $X=CH_2NH_2$
9 $X=CH_2NHTosyl$

Z = Tosyl



17



Z = COCl

Properties of the Bridged Cyclophane Receptor Molecules 1-5.

Compounds 1-5 possess a dome-shaped structure that delineates an intramolecular cavity whose size increases with the length of the methylene bridges[14]. The proton NMR spectra in $CDCl_3$ show that the three bridges are equivalent in agreement with threefold symmetry. One may expect that all three secondary amide groups of 1-3 are in the anti configuration which is known to be more stable than the syn form. The CH_2-N signals of the azacyclophane 6 contained in 1-5 appear as an AB pattern, indicating that the top 1,3,5-trisubstituted benzene ring does not flip through the basal cyclophane, as may be expected since the size of the cavity of 6 is too small for allowing such a process to occur.

The cavity of the present compounds is lined with three amine and three amide functional groups in the case of 1-3 and with six amines for 4 and 5. When fully protonated, 1-5 could act as receptor molecules for the binding of anionic substrates of suitable type through hydrogen bonding with the amide N-H and/or ammonium $N-H^+$ sites. The three-fold symmetry of these molecules may be well suited for the recognition, i.e. the selective binding, of complementary substrates i.e. trigonal anions of compatible size, such as nitrate.

Anion binding studies were performed by observing the proton NMR spectra of protonated 1-5, in the presence of various anions. The spectrum of (1-$3H^+$) shows that protonation causes a loss of three-fold symmetry and addition of various anions leaves the spectrum unchanged. (2-$3H^+$) has three-fold symmetry but looses it in presence of anions such as chloride, bromide and nitrate. (3-$3H^+$) is symmetric and forms with nitrate a stable and symmetric complex. (4-$6H^+$) and (5-$6H^+$) have three-fold symmetry. Preliminary results indicate that (4-$6H^+$) forms a 1/1 complex of three-fold symmetry in which NO_3^-, in agreement with a cryptate structure in which NO_3^- is included in the ligand cavity. These data indicate that protonation of 1-5 yields polycationic anion receptor molecules that yield different types of protonated species and of anion complexes depending on the ligand and the anion. Further studies are under way in order to characterize the structures of the complexes formed as well as to determine their thermodynamic and kinetic properties.

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8. Recently, the triazaparacyclophane **6** was synthesized using an alternative method: H. Teramura, M. Suenaga, K. Sakai, H. Kawachi, T. Shinmyozu, Y. Miyahara and T. Inazu, J. Incl. Phenom. **2**, 207 (1984).
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12. An alternative synthesis of **4** was achieved by condensation of **6** ($Z=CH_2CH_2CH_2NHTos$) with 1,3,5-trisbromomethylbenzene (Cs_2CO_3, DMF, 60°C, 5h) followed by chromatography (silica gel, chloroform) to give the tris-tosylamide of **4** (20% yield), which was treated with $LiAlH_4$ (THF, 50°C, 18h) to remove the tosyl groups (95% yield).
13. All new compounds had spectral and microanalytical properties in agreement with the assigned structures.
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