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A Novel Macrotricyclic Receptor for the Inclusion of Fluoride Ion

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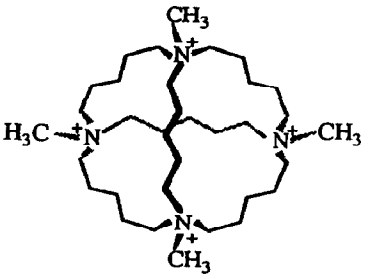
Abstract: A novel macrotricyclic receptor **1** with hydrocarbon chain of $(CH_2)_5$ has been synthesized and the ^{19}F NMR study on the aqueous solution of **1** shows the single coordination geometry of the encapsulated fluoride ion.

The construction of host molecules with predesigned architecture is the vital important for the entry of the supramolecular chemistry in recognition of the substrates. For the selectivity of small ions or neutral molecules by the hosts, the cavity must be well adapted with the corresponding size of the guest species. The macrocyclic polyamines[1] or their protonated forms[2] provide the particular attractive selectivity for the wide range of cationic or anionic guests respectively. The macrotricyclic quaternary ammonium ions with hydrocarbon chain of $(CH_2)_6$, **2** and $(CH_2)_8$ have been demonstrated to bind strongly and selectivity for a variety of anions[3]; in particular, a definite coordination geometry for the encapsulated anion has been characterized by the crystal structures' analyses[4] and ^{35}Cl NMR measurements in liquid phase[5]. The halide ions are encapsulated in the cavity by the strong electrostatic forces exerted by the oppositely charged hetroatomic units arranged tetrahedrally of the rigid blocks. Indeed, these cavities are unfavorable for the selectivity of the small fluoride ion[6]. We, therefore, have tempted to explore in building of a new host containing smaller intramolecular space. In fact, the macrotricyclic ligand bearing the nitrogen atoms represents the multiple interest in the host-guest field. We report here the synthesis of a novel host **1** with hydrocarbon chain of $(CH_2)_5$ as a fluoride receptor.

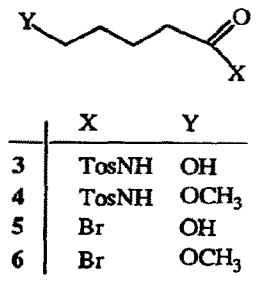


1

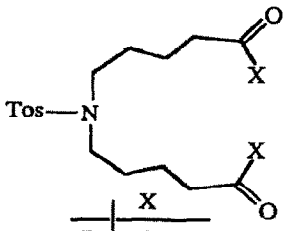
The synthetic plan was based on the progressive cementing of four nitrogen cornerstones with hydrocarbon chain represented as below[7]. The coupling of **4** (obtained by tosylation of 5-aminopentanoic acid followed by the esterification in usual fashion) with **6** was carried out in THF in the presence of butyllithium as

base (reflux for 24 hrs.) to give **7** (70% yield) after purification by column (Al_2O_3, $CHCl_3$). It should be noted that the attempts to obtain the desired diester led to failure employing other reagents used on the synthesis of **2**[6a]. The hydrolysis of the ester groups with sodium hydroxide in ethanol/water (2:1 v/v; reflux for 18 hrs.) and the subsequent addition of barium chloride, followed by extraction with chloroform of acidified filtrate, led to the dicarboxylic acid **8** (crystallized from toluene; 60% yield). The diacid chloride **9** was obtained by the reaction of **8** with oxalyl chloride in benzene (95% yield).

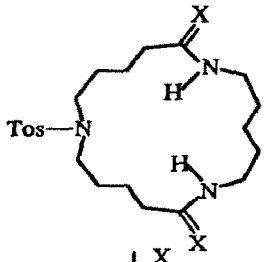
The reaction of **9** (50mM) with 1,5-diaminopentane (51mM) was carried out under the high dilution conditions in toluene (12 hrs. at r.t.) to afford the macrocyclic amide **10** (65% yield), after column chromatography (Al_2O_3, $CHCl_3$) which on reduction with diborane in THF yielded the crystalline amine **11** (95% yield). The condensation of **11** (25mM) with the diacid chloride **9** (26mM) in toluene (12 hrs. at r.t.) using triethylamine (52mM) as base gave, after column chromatography (Al_2O_3, $CHCl_3$), the bicyclic amide **12** (60% yield) which was reduced by diborane in THF (reflux for 7 hrs.) to the bicyclic amine **13** (80% yield).



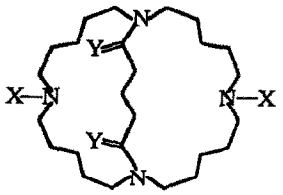
	X	Y
3	TosNH	OH
4	TosNH	OCH_3
5	Br	OH
6	Br	OCH_3



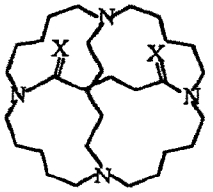
	X
7	OCH_3
8	OH
9	Cl



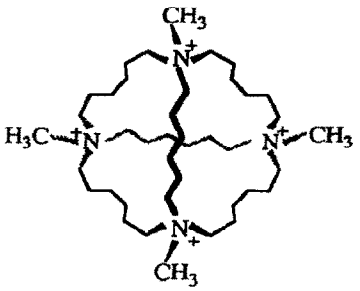
	X
10	O
11	H_2



	X	Y
12	Tos	O
13	Tos	H_2
14	H	H_2



	X
15	O
16	H_2



2

The removal of tosyl group by 48% HBr (reflux for 12 hrs.) converted the bicyclic amine **13** into its tetraprotonated amine which was extracted by 2M HCl from chloroform. The follow-up neutralization by LiOH and the subsequent extraction with hexane gave the macrobicyclic tetramine **14** after passage through the column (Al_2O_3, $CHCl_3$). The final cyclization was achieved by the reaction of **14** (4mM) with glutaryl chloride

(4.1mM) using triethylamine (12 hrs. at r.t.) to give **15** (60% yield) and the subsequent diborane reduction in THF (reflux for 14 hrs.) gave the macrotricyclic tetraamine **16** (80% yield) associated with the intramolecular cavity . The quaternization of the tertiary nitrogen centers with methyl iodide in acetonitrile followed by addition of saturated $NaBF_4$ solution completed the synthesis of crystalline target host **1**[8] (80% yield).

The CPK model inspection of **1** and **16** suggests the maximum possible cavity diameter, ca.3.5 Å which is less than Schmidtchen's quaternary ammonium ion **2** (4.6 Å)[3a]. The neutral amine **16** is itself a very interesting ligand possessing a symmetrical cavity to the alkali or alkaline earth metal ion in size. Compound **1** having the four positive units at its terminal corner is soluble in polar solvents like water, alcohol and acetonitrile. Considering the size factor of the cavity and the fluoride ion with 1.19 Å radius[9], the fluoride inclusion complex is expected.

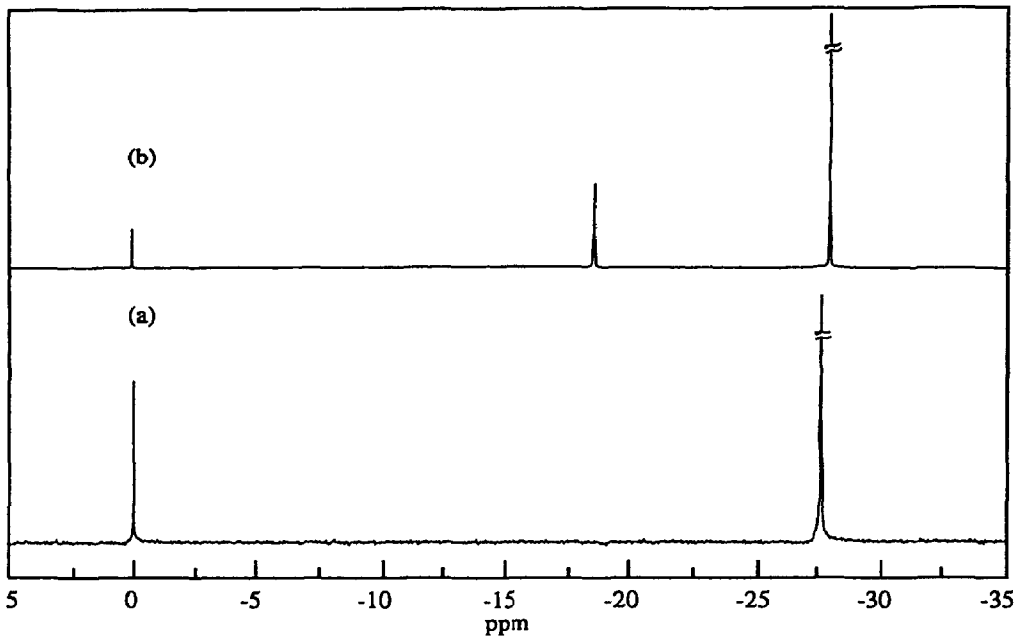


Figure 1. ^{19}F NMR spectra o f **1** (a) and **2** (b) in presence of tetrabutyl ammunium fluoride for R ($=[F^-]_o/[1 \text{ or } 2]_o$) = 1 in aqueous solution at [1 or 2] = $2x10^{-3}$ M and 298 K

The binding ability of **1** towards fluoride ion in the aqueous solution has been conveniently investigated by ^{19}F NMR spectroscopy (Varian XL-400) using tetrabutyl ammonium fluoride (TBAF) as the source of fluoride ions. Upon addition of TBAF to **1** ($2x10^{-3}$ M), two distinct sharps signals were observed at δ=0 and -28 ppm (Fig. 1a) indicating two different environment around the fluoride ions. Since the aqueous TBAF has been used as an external standard sample, the peak at δ=0 is readily assigned to the free fluoride ion solvated by water molecules. The other at upfield suggests that the fluoride ion experiences a strong shielding effect, presumably being bound by the host. The increment addition of the guest to the host solution causes the reduction in the relative ratio of the complexed/uncomplexed fluoride signals without emergence of any new peak and indicates that the fluoride ion near the host is surrounded by only one chemical environment being

centrally encapsulated. The R (=$[F^-]_o/[1]_o$) dependence of ^{19}F NMR spectra allows to give the stability constant of the host-guest complex to be $(1.5\pm0.5)\times10^4$ M^{-1} in water at 298 K.

To contrast this observation we have studied the ^{19}F NMR for the aqueous solution of TBAF and homemade **2**[7a,5]. Upon addition of fluoride salts, the three sharp signals were observed at δ=0, -17 and -28 ppm, as shown in Fig. 1(b). The appearance of a new signal at δ= -17 ppm unlike the host **1** evinces the another different chemical environment around the anion that can be assigned to the fluoride ion, partly solvated by water, in the nearest neighborhood of **2**. The same conclusion was shown in the ^{35}Cl NMR study on the capsulation in the solution of I^-/Cl^- and **2**.[5] Interestingly, the addition of Cl^- to the aqueous solution of **1** in presence of F^- did not lead any change in the ^{19}F NMR spectrum. Specially, the best fitting of a small guest into an intramolecular cavity can lead to the selective complexation with single coordination geometry. The host **1** is thus a selective receptor in binding of fluoride ion.

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