

## Anion Receptor Molecules : Synthesis of an Octaaza-cryptand and Structure of its Fluoride Cryptate

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The octaaza macrobicyclic polyamine **1** has been synthesized and found to form a fluoride cryptate **9** whose crystal structure shows that the F<sup>-</sup> substrate is hexacoordinated to the 1-6H<sup>+</sup> receptor molecule **8** in a quasi trigonal prismatic array of six F<sup>-</sup>...H-N<sup>+</sup> hydrogen bonds.

The coordination chemistry of anionic species is a rather recent field of research within the general area of supramolecular chemistry<sup>1</sup>. It rests on the design of receptor molecules capable of binding strongly and selectively anionic substrates<sup>1,2</sup>. Protonated polyamines represent the most extensively studied anion ligands. We have investigated earlier the anion complexation features of a number of macrocyclic<sup>3</sup>, macrobicyclic<sup>4-6</sup> and macrotricyclic<sup>7</sup> molecules bearing ammonium groups as binding sites. On the other hand, the corresponding unprotonated species are very effective ligands for metal cations. Thus, polyamines present a double interest for coordination chemistry, being able to bind either cations or anions.

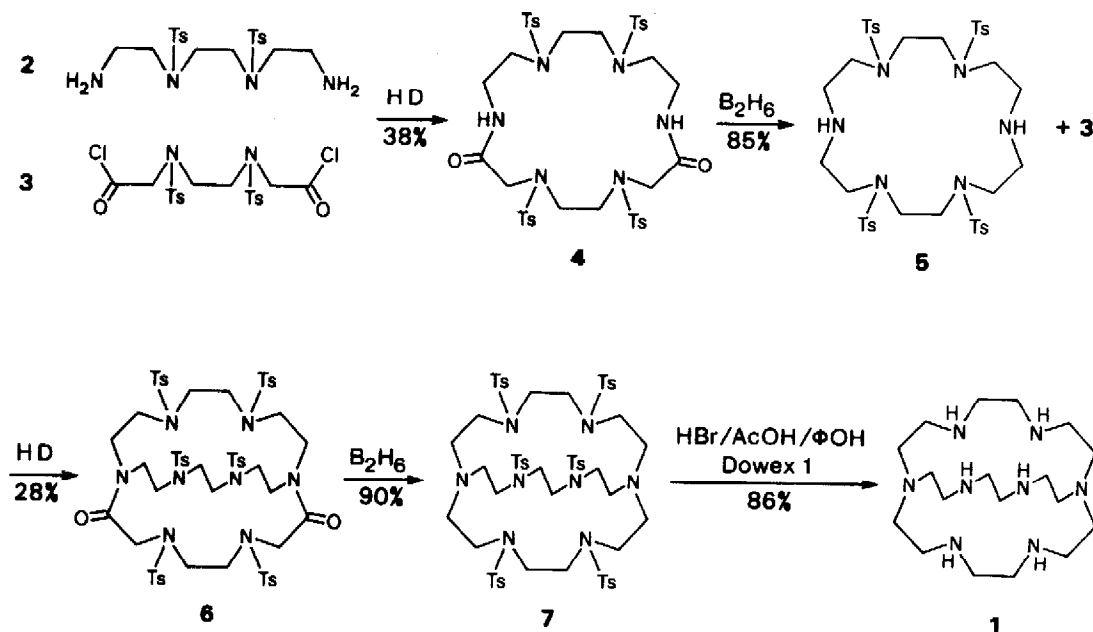
The macrobicyclic Bis-Tren N(CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>N<sup>4,6a</sup> binds a variety of anions in its hexaprotonated state<sup>4,5</sup>, in particular halide ions, forming anion cryptates characterized by a given coordination geometry for the included anion as revealed by the crystal structures<sup>5</sup>. In the case of the small fluoride, the cavity of the ligand is too large, so that the anion is bound on one side of the molecule to only four of the six secondary ammonium sites<sup>5</sup>. A ligand better adapted to the recognition of the fluoride anion, might be the octaaza macrobicyclic **1**, an analogue of the original [2.2.2] cryptand in which all six oxygens are replaced by nitrogens. We report here the synthesis of **1** and the structure of the fluoride complex formed by its hexaprotonated derivative. The synthesis and metal cation binding properties of the tri-, tetra- and hexa-aza analogues of [2.2.2] have been described earlier<sup>8,9</sup>.

### Synthesis of the octaaza macrobicyclic cryptand **1**

The target compound **1** was obtained following the synthetic route represented below<sup>8,12</sup>. The reaction of N,N'-ditosyl-ethylenediamine with monochloroacetonitrile (4 eq. K<sub>2</sub>CO<sub>3</sub>, DMF, r.t.) yielded the dinitrile NC-CH<sub>2</sub>NTosCH<sub>2</sub>CH<sub>2</sub>NTosCH<sub>2</sub>-CN (crystallized from DMF/EtOH ; 78% yield ; m.p. 204°) which was reduced (diborane, THF ; reflux ; 12 h) to the diamine **2** (97% yield ; oil). The condensation of **2** with the diacid dichloride **3**<sup>8a</sup> (1 eq. ; CH<sub>2</sub>Cl<sub>2</sub>/toluene 3/2 ; 2 eq. Et<sub>3</sub>N ; r.t. ; 7 h) in HD<sup>12</sup> conditions gave, after column chromatography (silica ; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99/1), the macrocyclic bis-lactam **4** (38% yield ; m.p. 123-125°) which was reduced (diborane, THF ; reflux ; 20h) to the diamine **5** (85% yield ; m.p. 213°). The reaction of **5** with **3** (1 eq. ; CH<sub>2</sub>Cl<sub>2</sub>/toluene 4/1 ; 2 eq. Et<sub>3</sub>N ; r.t. ; 8h) in HD<sup>12</sup> conditions afforded, after column chromatography (alumina ; CH<sub>2</sub>Cl<sub>2</sub>)

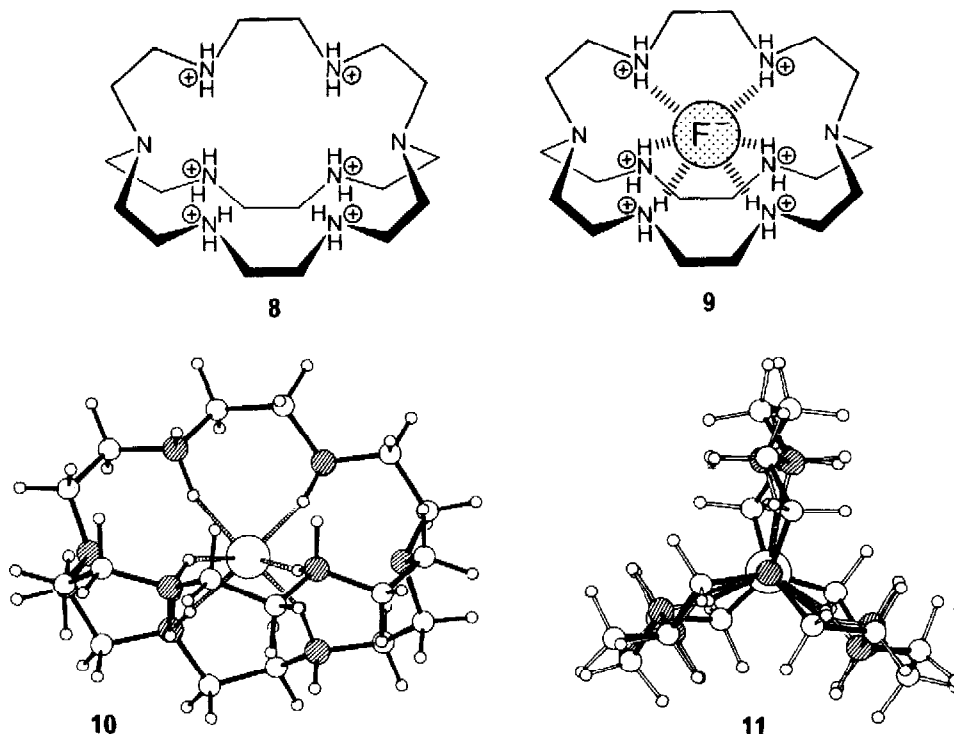
the macrobicyclic bis-lactam **6** (28% yield; m.p. 250°) which was reduced (diborane, THF; reflux; 20h) to the diamine **7** (90% yield; m.p. 178-180°). Detosylation of **7** with 33% HBr in acetic acid in presence of a large excess of phenol (80°; 16 h) gave after passage on a basic ion-exchange column, the macrobicyclic octaamine **1** which was isolated as its hexahydrochloride by treatment of the aqueous solution with excess HCl (86% yield; m.p. > 250°)<sup>13</sup>.

This stepwise synthesis of **1** is more lengthy than direct macrobicyclisation reactions<sup>6a,14</sup> or template condensations<sup>11,15</sup>, but has the advantage to afford intermediates of interest, such as **5** which may be used for the synthesis of polyaza macrotricyclic ligands for instance<sup>16</sup>. The tris-2,2'-bipyridine analogue of **1** in which each nitrogen site is contained in a pyridine ring has been described earlier<sup>15</sup>.



#### Binding of the fluoride anion. Crystal structure of the fluoride cryptate of 1-6H<sup>+</sup>

Fluoride binding has been observed in solution with the protonated derivatives of a spheroidal macrotricyclic<sup>17</sup>, of macrobicyclic<sup>5,9</sup> and of macrocyclic polyamines<sup>18</sup>. In the only crystal structure known, that of the fluoride cryptate of Bis-Tren (see above), the anion is held in a tetrahedral array of hydrogen bonds<sup>5</sup>. Because F<sup>-</sup> forms strong hydrogen bonds and tends to be tetrahedrally coordinated (see ref. in <sup>5</sup>), it was of interest to investigate its binding by protonated **1**. Treatment of the hexahydrochloride of **1** with 1 eq. NMe<sub>4</sub>F and 6 eq. NH<sub>4</sub>PF<sub>6</sub> in H<sub>2</sub>O/EtOH led to the crystallisation of a salt of composition (1-6H<sup>+</sup>, Cl<sup>-</sup>, 3F<sup>-</sup>, 2PF<sub>6</sub><sup>-</sup>), whose crystal structure has been determined<sup>19</sup> and is shown below in two orientations **10** and **11**.



The salt contains a fluoride cryptate  $[F^- \cdot 1-6H^+]$ , **9**, in which a fluoride anion is located inside the molecular cavity of the receptor molecule **8** whose six secondary amine groups, but not the bridgehead nitrogens, are protonated. The anion is hexacoordinated to the six ammonium sites in a *quasi trigonal prismatic geometry*. The lengths of the six  $F^- \cdots H-N^+$  bonds lie between 2.76 Å and 2.86 Å, which is slightly larger than the distance (2.71 Å) observed for instance in  $NH_4F^{22}$ . The distances between  $F^-$  and the unprotonated bridgehead nitrogens are much longer (3.28 and 3.37 Å). Furthermore, as shown by structure **11**, there is little twist of the molecule about the  $N, F^-, N$  axis. These data indicate a good complementarity between the receptor molecule **8** and the substrate, contrary to what is found for the  $F^-$  complex of Bis-Tren<sup>5</sup>. One may also compare the  $F^- \cdots H-N^+$  distances to the  $K^+ \cdots O$  distances ( $\sim 2.79$  Å)<sup>23</sup> in the cryptate formed by  $K^+$  with the macrobicyclic [2.2.2]. Thus the receptor molecule **1-6H+**, **8**, is indeed structurally complementary to the spherical  $F^-$  substrate and effects its molecular recognition. These results represent a further step in the design of anion receptors effecting the *molecular recognition of spherical anionic substrates, the halide ions*.

One may also point out that the polyamine **1** should form cryptates with a variety of metal cations (see ref.<sup>8</sup>). Finally, the hexa-*N*-methyl derivative of **1**<sup>24</sup> should be of interest as cation ligand in the area of alkalides and electrides<sup>25</sup>.

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