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MULTISITE MOLECULAR RECEPTORS AND CO-SYSTEMS AMMONIUM CRYPTATES OF MACROTRICYCLIC STRUCTURES

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ABSTRACT. Macrotricyclic receptor molecules incorporating [18]-N_2O_4 units have been synthesized. They form mono- and dinuclear ammonium cryptates. Such structures are prototypes of CO-SYSTEMS, whose wide scope as co-receptors, co-catalysts and co-carriers is briefly outlined.

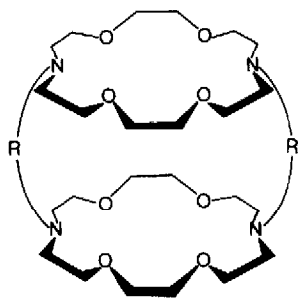
CO-SYSTEMS are supramolecular entities possessing several discrete receptor sites to which several substrates bind simultaneously, thus enabling mutual interaction within a single superstructure. In terms of the general functions of *supramolecular systems*, recognition, catalysis and transport[1] they may act as *co-receptors*, *co-catalysts* or *co-carriers*, and display higher levels of molecular organization and function, *cooperativity*, *allostery*, *regulation*. Such systems add new dimensions to the chemistry of synthetic molecular receptors, catalysts and carriers[1].

Cylindrical macrotricyclic molecules[1-6] contain *two* receptor sites, two macrocycles, linked by bridges which maintain the structure. They define *three cavities:* two lateral circular cavities inside the macrocycles and a central cavity limited by the rings and the bridges. Their properties may be controlled by modifying the size and/or the heteroatoms of the macrocycles and of the bridges. It has been shown earlier that such macrotricycles are able to complex two metal cations, which are bound to the lateral macrocycles and *held inside the central cavity*, thus forming *dinuclear cryptates*[4-9].

Since aza-oxamacrocycles[10-12], like polyether macrocycles[13], complex ammonium ions, it appeared that macrotricycles containing suitable aza-oxa-macrocyclic subunits might form cryptates of organic ammonium cations. The complexation of ammonium salts by a chiral macrotricycle has indeed been demonstrated in earlier work[5-10] and recent NMR studies led to the characterization of several macrotricyclic ammonium cryptates[14,15].

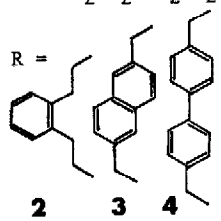
We report here some of our results on the synthesis and properties of the macrotricyclic receptors **1-5** containing the diaza-tetraoxa-macrocycle [18]-N_2O_4 **6** as subunit. Its derivative **7** complexes $R\text{-}NH_3^+$ species as strongly as its polyether analog [18]-crown-6[11]; its nitrogen sites serve for connection in constructing the tricyclic structure and for orientation of the bound substrate(s) inside the central molecular cavity, as in the macrotricyclic metal cation cryptates[4-9].

SYNTHESIS OF CYLINDRICAL MACROTRICYCLES **1-5**. The synthesis and metal cation complexation properties of the macrotricycles **1** and **2** have been reported previously[3,4]. Cryptands **3** and **4** have been obtained as follows.



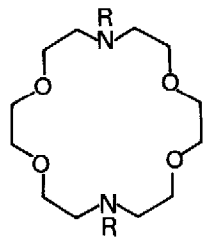
1 R = $CH_2CH_2OCH_2CH_2$

R =



2 **3** **4**

5 R = $(CH_2)_8$



6 R = H

7 R = CH_3

8 R = $CO(CH_2)_6CO_2CH_3$

9 R = $CO(CH_2)_6CO_2H$

10 R = $CO(CH_2)_6COCl$

High dilution condensation[16] of **6** with the chloride of naphthalene-2,6-dicarboxylic acid affords a macrotricyclic tetramide (mp 254°; 70% yield) which, by reduction with diborane gives the macrotricycle **3** (mp 210°; 93% yield). In a similar way, reaction of **6** with biphenyl-4,4'-dicarboxylic acid dichloride yields a tetramide (mp 192°; 85% yield) (see also ref. 17) which on reduction affords the macrotricyclic cryptand **4** (mp 174°; 92% yield).

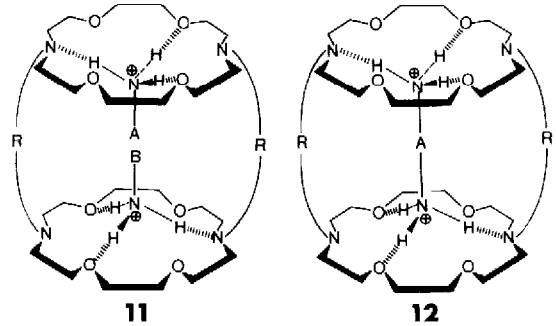
Another scheme was required for synthesizing the macrotricycle **5**, since condensation of **6** with suberic acid dichloride leads to closure to a macrobicyclic structure[16]. Reaction of $ClCO-(CH_2)_6-CO_2CH_3$[18] with **6** gives the diamide diester **8** (mp=42°C; 97% yield) which is quantitatively hydrolysed with 2N KOH to the diacid **9** (mp 106°) and converted to the dichloride **10** with $SOCl_2$ at room temperature. High dilution condensation of **10** with **6** affords the desired macrotricyclic tetramide (colourless glass; 65% yield) which is converted to the macrotricycle **5** (oil; 92% yield) by diborane reduction. This procedure allows the introduction of two different macrocycles and thus represents a route to *dissymetric macrotricycles* as already described earlier[6]. The length of the bridges R in macrotricycles **1-5** determines the size of the central molecular cavity.

MACROTRICYCLIC AMMONIUM CRYPTATES. The formation of ammonium complexes with macrotricycles **1-5** have been studied by proton NMR spectroscopy at 250 MHz in $CDCl_3/CD_3OD$ 9/1 using the ammonium salts as picrates. Marked shifts of the proton signals of both receptor and substrates are observed with respect to the free receptor and to the corresponding complexes of the macrocycle **7** taken as reference. It has been checked that these shifts do not correspond to simple protonation of an amino group of the receptor by proton transfer from the ammonium substrates.

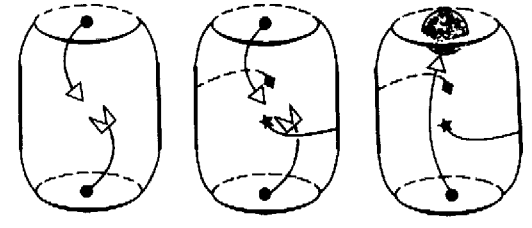
1) Addition of 2 equivalents of $CH_3NH_3^+$ picrate leads to the formation of complexes of 2/1 stoichiometry with all receptors **1-5**. The large cavities of **3** and **4** also accomodate two $EtNH_3^+$ cations. The CH_3 signal in the $EtNH_3^+$/**3** 2/1 complex is shifted upfield by 0.18 ppm with respect to the $EtNH_3^+$/**7** 1/1 complex taken as reference. This may be ascribed to a shielding effect due to the aromatic groups, and taken as indication for the inclusion of both substrate molecules in the central cavity of the macrotricycle, thus forming a *dinuclear monohapto cryptate* [2 $EtNH_3^+ \subset$**3**], structure **11**. Furthermore, only a single cation is complexed when it becomes too large for inclusion of two species. This occurs for

$HOCH_2CH_2CH_2NH_3^+$/**3**, *dopamine-H*$^+$/**4** and $PhCH_2CH_2NH_3^+$/**5**. In the former two cases hydrogen bonding by the -OH groups may also help holding the substrate in the cavity; thus, with dopamine-H^+ the $-NH_3^+$ binds to one macrocycle and the catechol hydroxyl groups may interact with the other one. For $HOCH_2CH_2CH_2NH_3^+$/**3** the PMR signals of the CH_2 groups show downfield (αCH_2, 0.1ppm) and upfield (βCH_2, -0.08 ppm); γCH_2, -0.16 ppm) shifts. This pattern appears general: the αCH protons of the substrate shift slightly downfield while those further removed from the $-NH_3^+$ site shift upfield, and more so as they extend inside the cavity between the aromatic groups forming the walls. The occurence of some external complexation cannot be excluded at present.

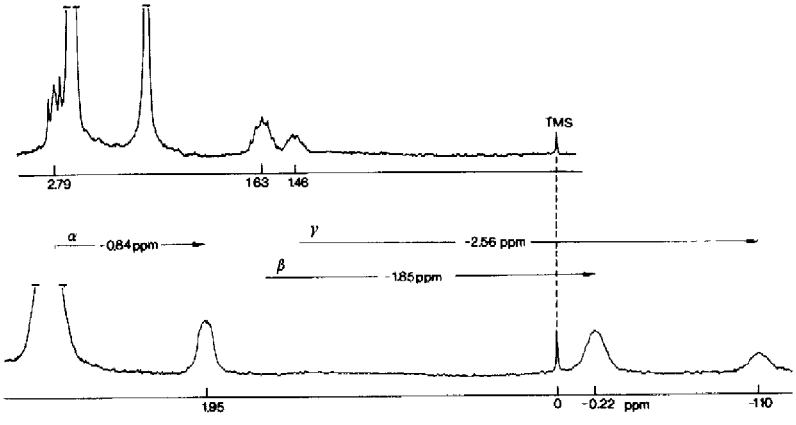
2) With diammonium cations $^+H_3N-(CH_2)_n-NH_3^+$, complexes of 1/1 stoichiometry are formed, for instance (n=4)/**1**, (n=5)/**3**, (n=6)/**4**. In the latter two cases, remarkable upfield shifts of the $-CH_2-$ PMR resonances, increasing in the sequence $\alpha<\beta<\gamma$, are observed with respect to the corresponding 1/2 $^+H_3N-(CH_2)_n-NH_3^+$/**7** complex. They are particularly striking for the (n=5)/**3** complex where the $\gamma-CH_2$ signal is found 1.10 ppm *upfield* from TMS, an upfield shift of 2.56 ppm with respect to the reference! (see Figure). They indicate that the dication must be contained inside the central cavity of the macrotricycle, with each $-NH_3^+$ group bound to one of the macrocycles, thus forming a *mononuclear dihapto cryptate* [$^+H_3N-(CH_2)_n-NH_3^+ \subset$Receptor], structure **12**. For a (n=5)/**3** ratio of 1/2 separate NMR signals are observed for free and complexed receptor, indicating slow substrate exchange at 25°. Diammonium salts have also been found to bind to other macrotricycles[14,15] as well as to the rings of a binaphthyl-bis-crown-ether[19,20].



11 **12**



13 **14** **15**



FIGURE

250 MHz PMR spectra of the complexes of $H_3N^+-(CH_2)_5-NH_3^+$ picrate with: (top) two equivalents of **7**; (bottom) one equivalent of **3** (in $CDCl_3/CD_3OD$ 9/1). Upfield shifts of the substrate α, β and γ CH_2 signals in the latter complex are given with respect to the former taken as reference.

3) Potentiometric determination of displaced Na^+ with an Na^+-selective electrode in $R\text{-}NH_3^+/Na^+$ competition experiments indicates that the approximate contribution per $-NH_3^+$ site to the stability constants of the ammonium complexes of receptor **1** is comparable to the Na^+ binding (see also ref. 4) and may be estimated to ∿500 (in methanol/water 9/1); furthermore comparative studies indicate a stability sequence n=8<6<5<4 for the binding of $^+H_3N\text{-}(CH_2)_n\text{-}NH_3^+$ to **1**.

CONCLUSION AND PROSPECTS. It is clear that macrotricyclic molecules are highly versatile ligands capable of binding a variety of organic (as well as inorganic[4-9]) cations in a *toposelective* manner, orienting the substrate into the cavity and thus forming *cryptate* complexes. Substrate selection may be controlled via the structure of the macrocyclic and of the bridging subunits. As members of the general class of co-systems they may function as:

- *co-receptors*, by their ability to bring together two substrates (structure **13**);
- *co-catalysts*, by promoting reactions between the bound substrates with or without participation of catalytic groups borne by side-chains (e.g. ligase models; structure **14**);
- *metallo-receptors* and *metallo-catalysts*[5], by binding both an organic substrate and a metal cation which interacts with it (structure **15**);
- *co-carriers*, by simultaneously transporting two substrates through membrane barriers.

The design of such systems is being actively pursued.

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