# Molecular Recognition of Anionic Substrates. Binding of Carboxylates by a Macrobicyclic Coreceptor and Crystal Structure of its Supramolecular Cryptate with the Terephthalate Dianion

**Jean-Marie Lehn,*[a] Robert Méric,[a] Jean-Pierre Vigneron,[a] I. Bkouche-Waksman[b] and Claudine Pascard*[b]**

[a] *Laboratoire de Chimie des Interactions Moléculaires, Collège de France, 11, Place Marcelin Berthelot, 75005 Paris, France*†

[b] *Laboratoire de Cristallochimie, Institut de Chimie des Substances Naturelles du CNRS, 91190 Gif-sur-Yvette, France*

The macrobicyclic polyammonium receptor molecule **1**–6H$^+$ binds dicarboxylate substrates with linear recognition and forms with terephthalate a very stable dianion cryptate the crystal structure of which has been determined.

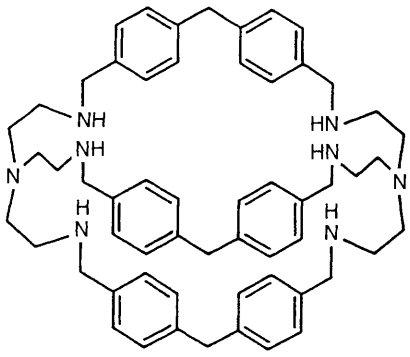
Anion coordination and molecular recognition of anionic substrates have been much less studied than cation complexation despite the very important role played by negatively charged species in chemistry and biology.

In recent years, several classes of anion receptor molecules have been designed, that form strong and selective complexes.[1,2] In particular, anion cryptates have been obtained in which the substrate is bound by multiple hydrogen bonds inside the cavity of a macropolycyclic polyammonium ligand. Their structure has however been determined by X-ray crystallography in only a few cases, of which just a single one concerns a substrate other than a spherical halide ion, the linear triatomic species $N_3^{-3}$.

There is thus a great need for designing novel anion receptors in order better to characterize anion coordination patterns and to obtain novel binding features.

We now report the complexation of dicarboxylate ions by the macrobicyclic polyammonium receptor molecule **1**–6H$^+$ as well as the crystal structure of the cryptate supermolecule that it forms with a polyatomic substrate, the terephthalate dianion.

† ER 285 du CNRS.



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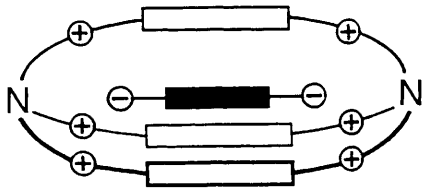

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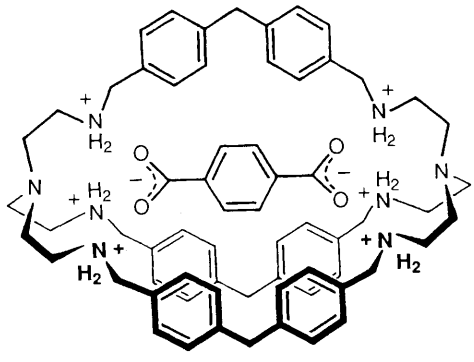

3 $[T^{2-} \subset 1\text{-}6H^{+}]^{4+}$

Ligand **1** has been obtained previously and its ability to bind anions has been mentioned briefly.[4] It possesses two subunits of the tren (tris-2-aminoethylamine) type and thus represents an elongated, cyclophane analogue of the bis-tren macrobicycle studied earlier.[3,5] By analogy, it may be expected to give a hexaprotonated form containing two triprotonated tripodal subunits (as shown in **3**) which should be able to bind dianionic substrates in a coreceptor manner schematically represented by structure **2**. Ditopic macrocyclic polyamines have been shown selectively to bind α,ω-dicarboxylates $^{-}O_2C\text{-}A\text{-}CO_2^{-}$ with length-dependent stability, thus performing chain-length recognition.[6,7]

In the presence of increasing amounts of protonated **1**, the $^1H$ NMR signals of various dianionic substrates were found to undergo marked upfield shifts, indicating that complexation occurred. Analysis of the data showed that the complexes formed had 1:1 stoichiometry and allowed their stability constants to be calculated (Table 1).

Receptor **1** forms *stable complexes* with dicarboxylates in aqueous solution at weakly acidic pH; the higher stabilities at pH 5.5 as compared to pH 6.0 may be attributed to more complete protonation.‡ The shielding effects observed indicate that inclusion of the substrate into the cavity of the receptor molecule probably takes place, yielding a supramolecular species of cryptate type **2**.

The complexes present *structural selectivity*. In the α,ω-dicarboxylate series $^{-}O_2C\text{-}(CH_2)_n\text{-}CO_2^{-}$, adipate ($n = 4$) is bound more strongly than either the shorter or the longer species. Thus, receptor **1** performs *linear recognition* of the substrate whose length probably corresponds best to the size of the intramolecular cavity. The stronger binding of fumarate as compared to maleate shows that structural effects dominate purely electrostatic interactions which should favour maleate, the substrate of higher charge density.

The very strong binding of the terephthalate anion $T^{2-}$ is remarkable. It indicates significant structural complementarity between the receptor and the substrate and results from both electrostatic and hydrophobic effects. The complex formed may be schematically represented by the cryptate structure **3**. The exact nature of this species was ascertained by determination of the crystal structure of a compound containing **1**–$6H^+$ and three terephthalate dianions.§

The structure shows that one $T^{2-}$ anion is located inside the molecular cavity while the other two are outside. Fig. 1 presents three views of the complex species. It is indeed a supramolecular species of cryptate nature $[T^{2-} \subset \mathbf{1}\text{–}6H^+]^{4+}$, **3**, in which the two binding subunits of the ditopic coreceptor molecule cooperate in substrate binding. It represents the dianionic substrate counterpart of the binding of a diammonium cation inside a cylindrical macrotricyclic coreceptor molecule.[8]

‡ Because of the low solubility of the unprotonated ligand **1** in water, its $pK_a$ values were not determined; on the basis of the acidity constants of tren and bis-tren one may expect that species **1**–$6H^+$ and **1**–$5H^+$ predominate at pH 5.5–6.0.

§ $C_{81}H_{118}N_8O_{26}$, $M_r = 1619.9$, orthorhombic, space group *Pnna*; $a = 20.01(1)$, $b = 34.80(1)$, $c = 13.08(1)$ Å, $V = 9108$ Å$^3$, $Z = 4$, $D_c = 1.18$ g cm$^{-3}$, $F(000) = 3472$, λ(Cu-Kα) = 1.5418 Å, μ = 6.50 cm$^{-1}$. A crystal (*ca.* 0.25 × 0.4 × 0.5 mm) was mounted on a four-circle Philips PW1100 diffractometer. Data collection conditions were: scan speed: 0.05° s$^{-1}$, scan width: 1.30°, $2°<\theta<68°$; the intensities of three standard reflexions were monitored every three hours and showed no decay in intensity. Lorentz and polarization corrections were applied, but none for absorption. From 8416 measured reflexions, 4353 with $I>3\sigma(I)$ were used in refinement. The structure was solved by direct methods (SHELX86[9]) and refined using large blocks (SHELX76[10]) programs. The weights were in the form: $w = 1/[\sigma^2(F) + 0.002\,F^2]$ where $\sigma(F)$ is taken from diffractometer counting statistics. The refinement of the disordered terephthalate anion (**T**3) (occupation factor = 0.5) required constraints on its angles and distances. The successive difference-Fourier syntheses showed first five water molecules in the asymmetric unit. At this stage of the isotropic refinement the *R* factor was 21.8%. The anistropic refinement was introduced for all the atoms except those of the **T**3 anion and four additional disordered water molecules (OW6, OW7, OW8, OW9, occupation factor of 0.5). The hydrogens of the macrobicycle and of the three terephthalates were introduced in calculated positions with a conventional distance of 1 Å from the bound atom and an isotropic thermal parameter set equal to that of the latter. The refinement led to $R = 11.5\%$, goodness of fit = 1.06. The last Fourier-synthesis showed a maximum electron density of 0.69 e Å$^{-3}$. The high final *R* factor can be explained by the numerous disordered atoms and the poor data set due to the low crystal quality. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

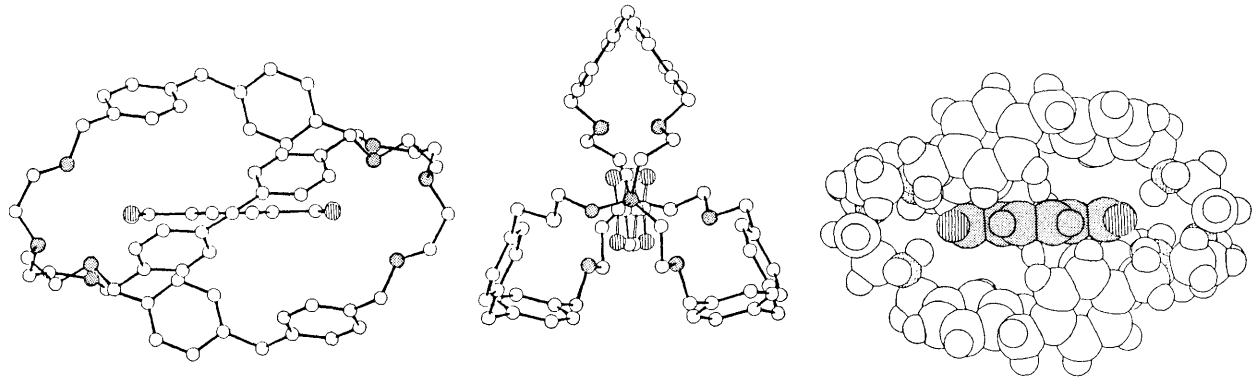

**Fig. 1** Crystal structure of the macrobicyclic cryptate $[T^{2-} \subset 1\text{-}6H^{+}]^{4+}$ formed by the protonated ligand **1**–$6H^{+}$ with the terephthalate dianion $T^{2-}$, viewed from the side (left) and along the bridgehead N,N axis (centre); space filling model representation of side-view (right); N: dotted, O: hatched.

**Table 1** Chemical shifts $\Delta\delta_{max}$ and stability constants $K_s$ for the binding of dicarboxylate substrates by the receptor molecule **1**[a]

| Substrate $^{-}O_2C\text{-}(CH_2)_n\text{-}CO_2^{-}$ | $\Delta\delta_{max}$/Hz[b] | $K_s$/ $dm^3\ mol^{-1}$ [c] |
|---|---|---|
| $n = 2$ | 125[d] | 1400[d] |
| $n = 3$ | 188 | 2300 (5300) |
| $n = 4$ | 195 | 2600 (5900) |
| $n = 5$ | 120 | 2100 (3200) |
| $n = 6$ | 78 | 1900 |
| $n = 7$ | 66 | 1400 |
| $n = 8$ | 57 | 1500 |
| Fumarate | 100 | 4100 |
| Maleate | 200 | 2400 |
| Terephthalate | 188 | 25 000 (60 000)[e] |

[a] In aqueous solution at 20 °C; buffer: pyridine + $CF_3CO_2D$, $10^{-2}$ mol $dm^{-3}$; concentration of **1**–6HCl: $2.6 \times 10^{4}$ mol $dm^{-3}$. [b] Calculated maximum upfield chemical shifts induced by binding on the α-$CH_2$ or vinylic or aromatic protons of the substrate. [c] Stability constant at pH 6.0 or (in parentheses 5.5) adjusted with $CF_3CO_2D$; estimated accuracy ± 10%. [d] The discrepancy with the preliminary value reported for succinate ($n = 2$)[4] may be due to a change in medium composition with respect to the earlier experiments, which did not use a buffer. [e] At pH 6.0 in more dilute solution: $1.0 \times 10^{-4}$ mol $dm^{-3}$ **1**–6HCl; same buffer.

The included substrate $T^{2-}$ extends along the N,N bridgehead axis (angle of ≈ 8° between the N,N axis and the plane of the anion) forming a complex that possesses a single twofold axis in the $T^{2-}$ plane, perpendicular to the N,N axis and passing through the central methylene group of one of the bridges. The anion is bound by N–$H^{+}$ · · · $O^{-}$ hydrogen bonds between each carboxylate group and the three ammonium sites of the corresponding tripodal binding subunit. For a given $-CO_2^{-}$ group, one oxygen is bound to two ammonium sites (N–O 2.96 and 2.77 Å) and the other oxygen to the third one (N–O 2.87 Å); in addition each oxygen accepts a hydrogen bond from one of the four water molecules that closely surround the cryptate resulting in two different irregular coordinations. The N–$H^{+}$ · · · $O^{-}$ distances correspond to strong hydrogen bonds, implying a satisfactory accommodation of the bound species inside the ligand cavity and receptor–substrate length complementarity.

The geometric features of the protonated ligand in the complex are modified with respect to those of the hexaimine compound from which it is derived.[4] The N,N bridgehead distance is shortened (13.77 Å compared to 15.5 Å[4]) and the three 'faces' of the bicyclic structure are enlarged (distances of 11.40, 11.40 and 9.77 Å between the central methylene groups in the three bridges compared to three identical distances of 7.5 Å[4]).¶

Since the receptor **1**–$6H^{+}$ is of ellipsoidal shape and the dianionic substrate is linear or planar, the structural recognition between the two species is mainly of mono-dimensional type, *i.e.* it is determined by the distances between the respective binding sites in the receptor and the substrate. Nevertheless, strong complexation and a well defined supramolecular species are obtained. Such multifunctional binding together with higher order structural complementarity should lead to even more stable and more selective complexes and provide further insight into the factors defining anion coordination and recognition.

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¶ *Environment of the cryptate.* The second terephthalate (**T2**) located on a symmetry centre forms a bridge between two centrosymmetrically related cages *via* two of its oxygens involved in H-bonds. This results in the stacking of the planar anion and the other two oxygens participate in bridging with the cages through chains with water molecules. The third terephthalate (**T3**) extends approximately perpendicularly to the bridgehead N–N axis, with its plane perpendicular to that of $T^{2-}$, with a dihedral angle of 35° with respect to (**T2**); its peculiar position on the bridgehead side makes any direct bonding with the ligand impossible; this is achieved only through water molecules. In addition to the ionic interactions between the macrobicyclic ligand and the terephthalate anions, the structure is built on a very complex hydrogen bonding network where the nine crystallographically different water molecules play an important part to ensure the packing in the cell.