11. Molecular Recognition in Anion Coordination Chemistry

Structure, Binding Constants and Receptor-Substrate Complementarity of a Series of Anion Cryptates of a Macrobicyclic Receptor Molecule

by **Bernard Dietrich**[a]), **Jean Guilhem**[b]), **Jean-Marie Lehn**[a])*, **Claudine Pascard**[b]) and **Etienne Sonveaux**[a])

[a]) Institut Le Bel, Université Louis Pasteur, 4, rue Blaise Pascal, F-67000 Strasbourg[1])

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

Dedicated to Prof. *Jack Dunitz* on the occasion of his 60th birthday

(21.XI.83)

Summary

The crystal structures of four anion cryptates [$X^- \subset$ **BT-6H**$^+$] formed by the protonated macrobicyclic receptor **BT-6H**$^+$ with F^-, Cl^-, Br^- and N_3^- have been determined. They provide a homogeneous series of anion coordination patterns with the same ligand. The small F^--ion is tetra-coordinated, while Cl^- and Br^- are bound in an octahedron of H-bonds. The non-complementarity between these spherical anions and the ellipsoïdal cavity of **BT-6H**$^+$ is reflected in ligand distortions. Structural complementarity is achieved for the linear triatomic substrate N_3^-, which is bound by two pyramidal arrays of three H-bonds, each interacting with a terminal N-atom of N_3^-. The formation constants of the complexes formed by **BT-6H**$^+$ with a variety of anions (halides, N_3^-, NO_3^-, carboxylates, SO_4^{2-}, HPO_4^{2-}, AMP^{2-}, ADP^{3-}, ATP^{4-}, $P_2O_7^{4-}$) have been determined. Very strong complexations are found, as well as marked electrostatic and structural effects on stability and selectivity; in particular the binding of F^-, Cl^-, Br^- and N_3^- may be analyzed in terms of the crystal structure data. The cryptand **BT-6H**$^+$ is a molecular receptor containing an ellipsoïdal recognition site for linear triatomic substrates of size compatible with the size of the molecular cavity. Further developments of various aspects of anion coordination chemistry are considered.

Introduction. – *Anion coordination chemistry,* the complexation of anionic substrates by organic receptor molecules, has been developing in recent years into a new field of generalized coordination chemistry. In view of the role played by anionic species in chemical as well as in biological processes, the discovery of a multitude of new structures, properties and reactions may be expected [1].

---

[1]) E.R.A. N° 265 of the *Centre National de la Recherche Scientifique.*

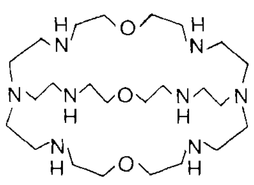
Building up this field requires the design and synthesis of novel receptor molecules, the determination of structures and coordination pattern of their complexes with anions, the measurement of thermodynamics and kinetics of complexation, the elucidation of the structure/stability-selectivity relationships for the complexes, the investigation of molecular catalysis and transport processes on anionic substrates etc.

Several classes of anion ligands and complexes have been reported. Macropolycyclic ammonium salts yield katapinates [2] and anion cryptates [3–5]; acyclic polyguanidinium and polyammonium ions act as anion complexones [6]; polyguanidinium and especially polyammonium macrocycles form strong and selective complexes with a variety of anions [7–12]; ditopic polyammonium macrocycles bind linear dicarboxylates with chain-length selectivity [13].

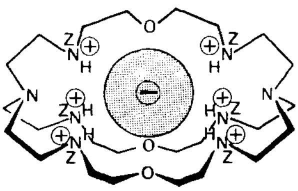
Detailed investigations of the structure of anion complexes and of their coordination patterns are of particular importance for analyzing the intermolecular interactions involved, for understanding the stability and selectivity of anion binding, for designing novel anion receptor molecules. Whereas a wealth of structural data is available on cation complexes, there is little such information on anion binding for the simple reason that only recently strong anion complexes have been discovered, which involve principally macrocyclic and macropolycyclic polycationic ligands [2–13].

Particularly stable and selective are the *anion inclusion complexes,* katapinates [2] and anion cryptates [3–5], in which the anionic substrate is bound inside the intramolecular cavity of a macropolycyclic receptor molecule. Structural data on such species are thus of special interest. Only two crystal structures have been reported until now: a chloride katapinate [2] in which the Cl^--anion is held in a linear arrangement of two $^+N{-}H \cdots Cl^-$ H-bonds inside a macrobicyclic diammonium ion [14]; a chloride cryptate of a spherical macrotricyclic ligand [3] where Cl^- is bound in a tetrahedral set of $^+N{-}H \cdots Cl^-$ H-bonds [15].

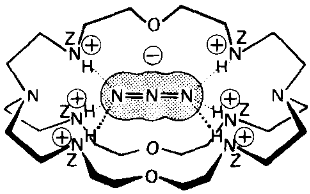
We now report four crystal structures of anion cryptates [$X^- \subset$ **BT**-$6H^+$] formed by the hexaprotonated form of the macrobicyclic ligand 'bis-tren' **BT** [16], with three spherical anions F^-, Cl^- and Br^- and one linear triatomic anion N_3^-. These structures provide a unique homogeneous series allowing to compare related species, to analyze coordination patterns, to assess receptor/substrate structural complementarity. They confirm the structural assignments made earlier on the basis of molecular shapes and complexation data [4]. We also report the stability constants of the complexes formed by protonated **BT** with a number of anions, and discuss their relation with structural features.



BT



[$X^- \subset$ **BT**-$6H^+$]
X = F^-, Cl^-, Br^-



[$N_3^- \subset$ **BT**-$6H^+$]

Structural Results. – In view of the very large number of bond lengths and bond angles present in the structures of the four anion cryptates studied here, only selected values directly relevant to the discussion of these complexes are listed in *Tables 1* and *2* concerning the coordination geometry around the anions and the geometry of the ligand, respectively. The experimental procedures for data collection and refinement and the crystal structure data are given in *Tables 4* and *5*. All the other results are contained in supplementary material available on request (see *Exper. Part*).

Description of the Crystal Assembly. – a) *[$F^- \subset$ **BT-6H$^+$**]*. This complex was obtained in the course of attempts to crystallize the cryptate of the linear FHF$^-$-anion. The product obtained in the conditions employed contained a single F$^-$-anion in the cavity *(Fig. 1)* and corresponds to the formula: $C_{24}H_{60}N_8O_3^{6+}$, F^-, $5ClO_4^-$, ½ H_2O.

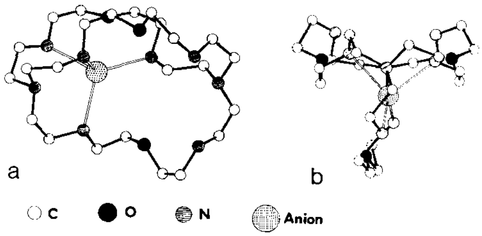


Fig. 1. *ORTEP views of [$F^- \subset$ **BT-6H$^+$**]:* a) into the cavity; b) along the bridgehead NN-axis.

There are two molecules (123 non-H-atoms) in the asymmetric unit. Seven out of ten perchlorate anions are disordered, and the O-atoms have large temperature factors, precluding better refinement. Further attempts to crystallize the cryptate of FHF$^-$ are being made.

b) *[$Cl^- \subset$ **BT-6H$^+$**] and [$Br^- \subset$ **BT-6H$^+$**]*. In the Cl$^-$-cryptate, the ligand uses as symmetry element, a crystallographic diad axis which passes through the included Cl$^-$-anion *(Fig. 2a, b, c)*. Each unit is surrounded by 6 other Cl$^-$-ions (4 of which are crystallographically independent) which lie at binding distances from the protonated nitrogens, completing their tetrahedra. Another Cl$^-$ is located well outside these groups, acting as a sort of counter ion with shortest distance N(11) · · · Cl(2): 4.37 Å.

The molecular arrangement of the bromide complex is identical to the chloride one, the two structures being nearly isomorphous. However, the cryptate unit has lost its binary symmetry (space group $P3_1$) *(Fig. 2d)*.

c) *[$N_3^- \subset$ **BT-6H$^+$**]*. This complex crystallized with 4 PF_6^-, one Cl$^-$ and three H_2O-molecules outside the ligand as well as a linear N_3^--ion occupying the cavity of the ligand *(Fig. 3)*. Each PF_6-octahedron oscillates between two major positions around an F–P–F axis, whose end is bound to HN$^+$ of the ligand or to H_2O-molecules. In the course of the refinement, the F-atoms were split into the differently occupied positions.

Anion Binding Geometry (see distances and angles in *Table 1*). a) *[$F^- \subset$ **BT-6H$^+$**]*. The small F$^-$-ion apparently cannot bind equivalently to the 6 protons and *slides* to-

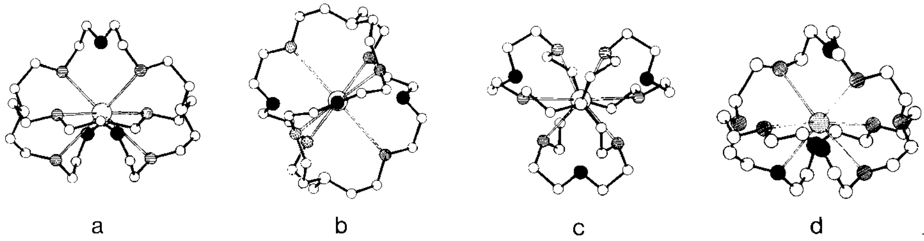


Fig. 2. *ORTEP views of [$Cl^- \subset$ **BT-6H$^+$**]:* a) into the cavity; b) along a Cl,O-direction (binary axis); c) along the bridgehead N Cl N axis; d) *ORTEP view of [$Br^- \subset$ **BT-6H$^+$**].*

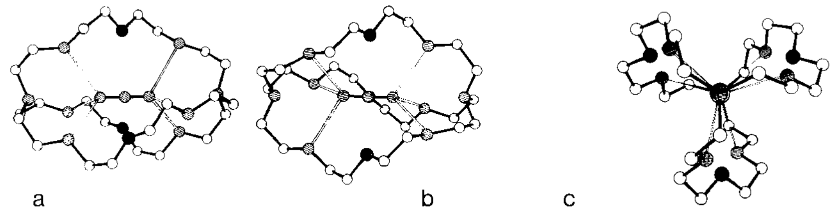
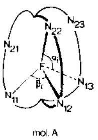
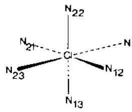
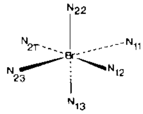
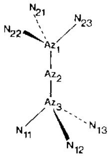


Fig. 3. *ORTEP views of [$N_3^- \subset$ **BT-6H$^+$**]:* a) into the cavity; b) along the direction from an O-atom to the central N-atom of the N_3^--ion; c) along the bridgehead NN_3N-axis.

Table 1. *Anion Coordination Geometry in the Cryptates [$X^- \subset$ **BT-6H$^+$**]* (Distances in Å, Angles in Degrees, with R.m.s. Deviations in Parentheses)[a])

X^-			
F^-	Cl^-	Br^-	N_3^-
			
Mean F···N^+: 2.72 (8) Mean α_i: 118° (5) Mean β_i: 100° (4) (α_i are angles of N_{22} with the other N^+; β_i are the other angles)	Cl···N(11) or N(21): 3.19 (1) Cl···N(12) or N(23): 3.33 (1) Cl···N(22) or N(13): 3.39 (1) Mean $< N^+Cl\ N^+$: 90° (1)	Br···N(11): 3.33 Br···N(21): 3.35 Br···N(12): 3.47 Br···N(23): 3.36 Br···N(22): 3.45 Br···N(13): 3.39 (Mean r.m.s.d: 5) Mean $< N^+Br\ N^+$: 90° (6)	Az_1···N(21): 2.91 Az_1···N(22): 2.92 Az_1···N(23): 2.96 Az_3···N(11): 3.02 Az_3···N(12): 2.98 Az_3···N(13): 2.96 (Mean r.m.s.d: 4) Mean $< Az_2Az_iN^+$:122 (2) $< N^+Az_iN^+$:95 (3) i = 1 or 3

[a]) Numerotation for the ligand heteroatoms in the complexes of:

$$\begin{array}{c} \diagup N(11)-O(1)-N(21) \diagdown \\ N-N(12)-O(2)-N(22)-N' \\ \diagdown N(13)-O(3)-N(23) \diagup \end{array}$$

N^+ stands for the protonated secondary N-sites;
N or N' are the bridgehead N-atoms.

wards one side of the cavity *(Fig. 1a)*, coordinating in a tetrahedral fashion to 4 protonated N-atoms, 2 in one bridge and one in each other. The anion is situated well outside the bridgehead NN axis (1.3 Å). On *Fig. 1*, the non-alignment of the lone pairs of the two bridgehead N-atoms is clearly visible. The average, F,N-distance is 2.72 (0.08) Å. The tetrahedra around the two fluorides in the asymmetric unit are distorted in the same fashion. The two non-F-bonded protonated N-atoms are twice bound to perchlorate O-atoms. All the other N^+-H bonds are oriented towards external binding with ClO_4^--anions.

b) *[$Cl^- \subset$ **BT-6H**$^+$] and [$Br^- \subset$ **BT-6H**$^+$].* The internal Cl^-- and Br^--ions are located almost exactly on the NN-axis joining the two bridgehead N-atoms (Cl^- is off by 0.1 Å) and at equal distances from them: $Cl^- \cdots N = 3.72$ Å; $Br^- \cdots N = 3.76$ Å *(Fig. 2)*. The halide ions are coordinated in an octahedral fashion to the six protonated secondary N-atoms by $^+N-H \cdots X^-$ H-bonds *(Fig. 2a, 2d)*. Each of these N-atoms is in turn tetrahedrally H-bonded to a halide ion located outside the ligand shell *(Fig. 4a)*. The coordination octahedra of Cl^- and Br^- are almost regular, with angles of 90 ± 5°. The N^+, X^- coordination bonds are not equal; they vary in length by about 0.2 Å for Cl^- and 0.15 Å for Br^- *(Table 1)*. These inner $N^+ \cdots X^-$ distances (in Å) are *longer* than the external ones:

	Internal		External	
X	$N^+ \cdots X^-$	$H \cdots X^-$	$N^+ \cdots X^-$	$H \cdots X^-$
Cl	3.19 to 3.39	2.35	3.05 to 3.27	2.16
Br	3.33 to 3.47	2.45	3.16 to 3.37	2.20

c) *[$N_3^- \subset$ **BT-6H**$^+$].* As in the Cl^-- and Br^--cryptates, the N_3^--ion lies on the bridgehead NN-axis. The two terminal N-atoms of N_3^- are at 3.34 and 3.21 Å from the bridgehead N-atoms N and N', respectively; they are H-bonded to the protonated secondary amine functions with nearly equal distances of 2.96 (0.04) Å, the average N^+-Az-N^+ angle being 95(3)° *(Table 1)*. These coordination bonds form two tetrahedra opposed through the common apex (Az_2) and nearly eclipsed (dihedral angle $N_{13}-Az_3-Az_1-N_{23} = 28°$ (see diagram in *Table 1; Fig. 3c)*. Each second H-atom of an N^+-site is directed outwards to H_2O-molecules on the Az_3-side, and bonded to the Cl^- and PF_6^- counter ions on the Az_1-side.

*Geometry of the Hexaprotonated Macrobicyclic Ligand **BT-6H**$^+$ in the Cryptates [$X^- \subset$ **BT-6H**$^+$].* In all four structures the macrobicyclic ligand is in the *endo,endo*-conformation [17, 18] where the bridgehead N-atoms are turned into the cavity *(Fig. 1a, 2a, 2d, 3a)*, with N–N' distances of 7.66, 7.40, 7.50 and 8.84 Å for F^--, Cl^--, Br^-- and N_3^--complexes, respectively *(Table 2)*. All YCH_2CH_2Z (Y, Z = heteroatom) fragments are in the gauche-form and the O-atoms are turned towards the inside of the molecule (mean $X^- \cdots O$ distances, see *Table 2*).

In the *F^--complex* the location of the small anion in one lobe of the bicyclic system distorts completely the ligand to achieve tetrahedral coordination of F^- *(Fig. 1)*.

In the *Cl^-- and Br^--complexes* the ligand adopts the same general shape *(Fig. 2a, 2d)*. The three bridges of the macrobicycle form three rather large lobes not related by

Table 2. *Geometry of the* **BT**-*6H*$^+$ *Ligand in the Anion Cryptates* [$X^- \subset$ **BT**-$6H^+$] (Distances in Å, Angles in degrees)[a])

X$^-$								
	F$^-$		Cl$^-$		Br$^-$		N_3^-	
Cavity dimensions								
	mol. A (mol. B)							
	N–N′	7.66 (8.02)	N–N′	7.40	N–N′	7.50	N–N′	8.84
	O(1)–O(2)	5.15 (4.82)	O(1)–O(2)	5.28	O(1)–O(2)	5.40	O(1)–O(2)	5.60
	O(1)–O(3)	5.98 (5.81)	O(2)–O(3)	6.14	O(1)–O(3)	5.50	O(1)–O(3)	5.40
	O(2)–O(3)	6.20 (6.13)	Cl–O(1)	3.31	O(2)–O(3)	6.20	O(2)–O(3)	5.40
	F–O(1)	4.00 (3.04)	Cl–O(2)	3.22	Br–O(1)	3.71	Az(1)–N′	3.34
	F–O(2)	3.04 (3.82)	Cl–N	3.71	Br–O(2)	3.26	Az(3)–N	3.21
	F–O(3)	3.95 (3.91)			Br–O(3)	3.34	Az(2)–O(1)	3.17
	F–N	3.00 (5.46)			Br–N	3.76	Az(2)–O(2)	3.12
	F–N′	5.40 (3.02)					Az(2)–O(3)	3.18
Interatomic distances and angles. Table of average values								
C–C		1.50 (15)		1.51 (1)		1.59 (5)		1.49 (4)
C–N		1.49 (9)		1.49 (1)		1.47 (4)		1.50 (3)
C–O		1.48 (9)		1.42 (1)		1.46 (4)		1.42 (2)
< CN$^+$C		113.0 (6°)		113.6 (5°)		116.0 (8°)		114.0 (3°)
< CN C		109.5 (4°)		109.1 (5°)		111.0 (5°)		109.9 (3°)
Torsions angles in the ligand								
C–N–C–C		30%: 60°, 70%: 180°		60° or 180°		60° or 180°[b])		–150° to 180°
N–C–C–N		85%: 60°, 15%: 180°		60° to 80°		69° (± 8°)		70° to 80°
N–C–C–O		100%: 60°		50° to 70°		40° to 80°		57° to 70°
C–C–O–C		30%: 90°, 70%: 180°		90° or 180°		90° or 160°		170°

[a]) For numerotation, see footnote in *Table 1*.

[b]) Except angles on each side of N(21).

ternary symmetry. With Cl$^-$ two lobes are identical and related by a binary axis passing through the O-atom of the third bridge *(Fig. 2c)*; this C_{2v}-symmetry is not found in the Br -complex (disorder?).

In the *N_3^--complex*, the ligand is markedly expanded around the enclosed N_3^--ion and the geometrical requirements of the cavity are apparently fulfilled (see torsion angles in *Table 2*). The three lobes of the ligand are much smaller than in the Cl$^-$- and Br$^-$-complexes and they form a perfect trigonal arrangement centered on the NN′-axis *(Fig. 3c)*.

The *packing* in the crystals is shown in *Fig. 4* for the Cl$^-$- and N_3^--complexes.

Stability Constants for Anion Binding by Ligand BT-6H$^+$. – The stability constants of the complexes formed by protonated forms of **BT** with the anions F$^-$, Cl$^-$, Br$^-$, N_3^- as well as with a number of inorganic and organic polyatomic anions, have been determined by computer analysis of the pH-metric titration curves measured in presence of the corresponding anion. The results are listed in *Table 3*. In agreement with earlier results [4] and with the present structural data, 1:1 substrate/ligand stoichiometries were used in all cases. To minimize interference from other anions, TsONa was used as

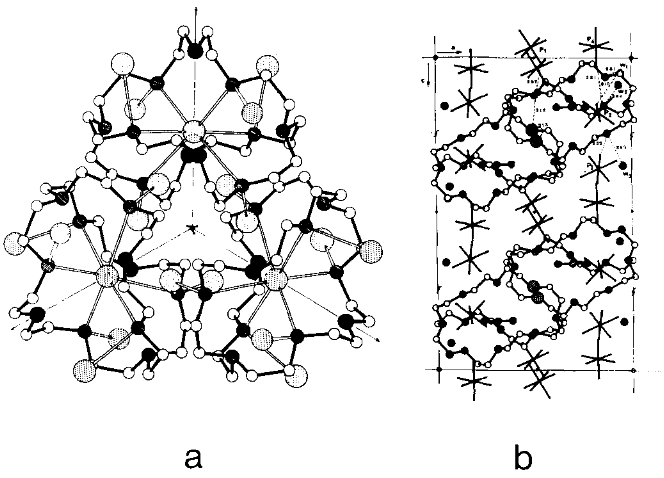


Fig. 4. *Two examples of molecular packing:* a) *for* $[Cl^- \subset$ ***BT*-6H**$^+]$, *5* Cl^-, showing the six external Cl^--ions H-bonded to the protonated N-sites; b) *for* $[N_3^- \subset$ ***BT*-6H**$^+]$ Cl^-, *4* PF_6^-, *3* H_2O, *: PF_6^- anion, ●: H_2O-molecule.

supporting electrolyte (see *Exper. Part*). Earlier anion-binding studies employed spectroscopic (NMR, IR, *Raman* spectra) and potentiometric methods [4]; they gave stability constants in satisfactory agreement with present ones for Br^-, N_3^- and HCO_2^-, taking into account the difference in experimental conditions; the values obtained for Cl^- and I^- using anion selective electrodes were, however, too low, due perhaps to unsufficient electrode response. In the case of F^-, taking into account the equilibrium of F_2H^--formation did not affect the K_s-values.

Discussion. – The present structural data confirm that the anion complexes of the macrobicyclic receptor molecule **BT**-6H$^+$ with F^-, Cl^-, Br^-, N_3^- are indeed *anion cryptates*. $[X^- \subset$ **BT**-6H$^+]$, in which the substrate is contained in the intramolecular cavity and bound by an array of H-bonds; furthermore the structure of the N_3^--complex agrees very well indeed, with that proposed earlier on the basis of geometric considerations and binding studies [4]. Also, the protonation pattern of **BT**-6H$^+$ is found to be that which may be expected on the basis of known pK_a-data [4].

On the basis of size and shape considerations, the smaller polyatomic anions (NO_3^-, HCO_2^-, SO_4^{2-}, HPO_4^{2-}, oxalate, *Table 3*), for which no crystal structure is available, can probably still penetrate more or less completely into the ligand to form cryptate complexes. However, in the case of the larger anions (malonate and especially $P_2O_7^{4-}$, AMP^{2-}, ADP^{3-}, ATP^{4-}, *Table 3*) only the terminal anionic group should be able to enter into the cavity to some extent, resulting in only partial inclusion of the substrate.

Anion Coordination Geometry. A fundamental property of metal cation complexes is their usually well-defined coordination geometry. Clearly, the development of an anion coordination chemistry requires an understanding of the basic geometrical features of anion complexes and of the intermolecular interactions which determine them. In the present series of structures of anion cryptates $[X^- \subset$ **BT**-6H$^+]$, the different anions display indeed characteristic coordination polyhedra: a *tetrahedron* for F^-, an

Table 3. *Stability Constants log* K_s *for Anion Complexation by Two Protonated Forms* ***BT**-nH^+* *(n = 5,6) of the Macrobicyclic Receptor Molecule* ***BT***[a]

Anion[b]	logK_s[c]		Anion[b]	log K_s[c]	
	BT-6H$^+$	**BT**-5H$^+$		**BT**-6H$^+$	**BT**-5H$^+$
F^-	4.10	3.20	$CH_2(CO_2^-)_2$	3.10	2.00
Cl^-[d]	3.00, 2.26 [25]	1.95, 1.7 [25]	SO_4^{2-}	4.90	2.90
Br^-	2.60	1.60	HPO_4^{2-}	5.50	2.75
I^-	2.15	1.55	AMP^{2-}	3.85	2.65
N_3^-	4.30	2.65	ADP^{3-}	5.85	4.15
NO_3^-[d]	2.80, 2.95 [25]	1.65, 2.30 [25]	ATP^{4-}	8.00	5.40
HCO_2^-	2.30	< 1.5	$P_2O_7^{4-}$	10.30	6.45
$(CO_2^-)_2$	4.95	3.35			

[a] Aqueous solution; 25°; see *Exper. Part* for more details; in the present conditions the pK_a-values of the ligand **BT** were: 9.60, 9.35, 8.30, 7.75, 7.00, 5.90, see also [25].

[b] Selected properties of some anions; ionic radius: 1.36 (F^-), 1.81 (Cl^-), 1.95 (Br^-), 2.16 (I^-) Å [19]; average H-bond length N,X in $^+N-H \cdots X^-$: 2.92 (F^-), 3.23 (Cl^-), 3.37 (Br^-), 3.66 (I^-) Å [20, 21], 2.94 (N_3^-) [22, 23]; free energies of hydration: −103.8 (F^-), −75.8 (Cl^-), −72.5 (Br^-), −61.4 (I^-) kcal/mole [24].

[c] K_s in $l\,mol^{-1}$; values below ≈ 2 are not accurate; calculated values of log K_s were < 2.0 for the complexes of **BT**-4H$^+$ with the monovalent and divalent anions.

[d] Binding constants determined previously by pH-metry in somewhat different conditions [25], agree well with the present ones for NO_3^- but less so for Cl^-; ^{35}Cl-NMR studies in again different conditions, agree with the Cl^-- and NO_3^--complexes having similar stabilities (*J. P. Kintzinger & A. Zahidi*, unpublished results).

octahedron for Cl^- and Br^-, two trigonal pyramids forming a somewhat distorted *biprism* for N_3^- *(Fig. 1–3; Table 1)*.

Tetrahedral coordination of F^- is found in the structure of the $(H_4F_5)^-$-anion in $K(H_4F_5)$ [26] and has been proposed for the salt $(Me_3NH^+)(H_3F_4^-)$ [27]. Tetrahedral coordination of Cl^- by $^+N-H \cdots Cl^-$ bonds occurs in spherical macrotricyclic anion cryptates [3] [15]. In $N(CH_2CH_2NH_3^+)_3$, 3 Cl^- [28] and in $NH_3^+CH_2CH_2NH_3^+$, 2 Cl^- [29] each Cl^- has three N-neighbours at about 3.2 Å. Ethylenediammonium dibromide shows $^+N \cdots Br^- \cdots N^+$ angles of 90° [30]. The N_3^--ion of NH_4N_3 is tetra-coordinated forming two H-bonds between each of its terminal N-atoms and NH_4^+-cations [22] [23]. Despite the fragmentary literature data available, it is clear that the large number and the arrangement of the binding sites made available by macropolycyclic anion receptors allows to attain much higher coordination number and much better defined geometries. To what extent these are dependent on the anion on one hand and on the ligand features on the other hand, remains to be established by studying numerous other anion complexes.

Stability and Selectivity of Complexation. As in the case of spherical cation cryptates [1], three-dimensional binding of an anionic substrate with inclusion into a molecular cavity, should yield stable and selective anion cryptates.

Complexation stability in anion binding by **BT**-6H$^+$ should be strongly dependent on *electrostatic interactions*, in view of the fact that it results from formation of zwitterionic H-bonds $^+N-H \cdots X^{n-}$. Thus, the most stable complexes are obtained with substrates of highest charge density, like the small F^- and the multiply charged ions, especially the polyphosphates *(Table 3)*.

The strong binding of F^-, compared to the other halides, may be ascribed to the particularly large electrostatic interactions displayed by this small anion and its propensity to form strong H-bonds. This is reflected for instance in its much larger energy of hydration in the gas phase [31] or in solution *(Table 3)* and in the formation of the very strong H-bond of the $(FHF)^-$-anion, which is about three times stronger than the corresponding H-bond in $(ClHCl)^-$ [31b] [32].

One would expect the polyphosphates to be bound even more strongly by **BT**-$6H^+$ than actually observed, in view of the fact that AMP^{2-}, ADP^{3-} and ATP^{4-} are complexed with log $K_s = 6.95$, 8.30 and 11.00 by the hexa-protonated form of the [24]-N_6O_2 macrocycle, the monocyclic analog of **BT** [33]; very large binding constants are also found with other polyammonium macrocycles [8]. This lower binding of the polyphosphates by **BT**-$6H^+$ may be ascribed to the fact that these large substrates can only be partially included in the ligand cavity (see *above*). The same factor probably plays a role, in addition to charge density, in the weaker complexation of malonate as compared to oxalate *(Table 3)*.

The importance of electrostatic effects is also seen in the large decrease in complex stability which occurs on removal of one or two protons from **BT**-$6H^+$ as shown by the log K_s values found for **BT**-$5H^+$ and **BT**-$4H^+$ *(Table 3)*. Of course, the structure of the complexes formed by these species may also differ from those of **BT**-$6H^+$, in particular with respect to the extent of substrate inclusion. The large decrease in stability of the N_3^-- and SO_4^{2-}-complexes of **BT**-$5H^+$ compared to those of **BT**-$6H^+$ shows that the removal of a single proton has an especially large effect when the substrate is hexa-coordinated and/or highly charged. The appreciably higher stability of [$F^- \subset$ **BT**-$5H^+$] compared to the corresponding Cl^--complex, probably reflects the fact that F^- is only tetra-coordinated.

Among monovalent anions, **BT**-$6H^+$ displays a high *complexation selectivity* for N_3^- (by a factor of about 100), with a sequence $I^- < Br^-$, Cl^-, $NO_3^- \ll N_3^-$ *(Table 3)*. The presence of a Cl^--ion in the lattice of the N_3^--cryptate (see above) is structural indication for the preferential binding of N_3^-. The strong binding of F^- has been discussed above. HCO_2^- is also much less well bound that N_3^- and ClO_4^- even less [4]. Such a pattern (especially ClO_4^-, $I^- < N_3^-$) does not fit the sequence of hydration energies *(Table 3)*, nor the lyotropic series [34] nor the sequence of anion binding to carbonic anhydrase [35], from which one would expect similar (and rather strong) binding of all three weakly hydrated N_3^--, I^--, ClO_4^--ions. It is also rather striking that the doubly charged SO_4^{2-}-anion is not bound much more strongly than N_3^-.

Finally, the presence of a macrobicyclic *cryptate effect* enhancing both the stability and the selectivity of anion binding by **BT**-$6H^+$ is indicated by the absence of any detectable complexation of N_3^- by the tripodal ligand $N(CH_2CH_2NH_3^+)_3$ [4], which constitutes the binding subunits on which **BT**-$6H^+$ is built.

All these binding properties point to the operation of topological discrimination due to the receptor properties of **BT**-$6H^+$, *i.e.* to the shape and size of the intramolecular cavity as well as to the arrangements of the binding sites; they are therefore directly related to the receptor/substrate structural features presented above.

*Receptor/Substrate Structural Complementarity in the Anion Cryptates [$X^- \subset$ **BT**-$6H^+$] ($X^- = F^-$, Cl^-, Br^-, N_3^-).* The three substrate anions F^-, Cl^- and Br^- are *spherical* species of increasing size *(Table 3)*; N_3^- may be considered as grossly *cylindrical* with a length of about 5.5 Å (end-to-end distance: 2.33 Å + 2 × ionic radius of a N-site: 2 × 1.6 Å [23]) and a diameter of 2 × 1.6 = 3.2 Å. The receptor molecule **BT**-$6H^+$ is of *ellipsoïdal* shape, with cavity dimensions of about 4.5 Å and 2.5–3.0 Å for the long and short axes, respectively, in a conformationally relaxed state like that of the N_3^--cryptate *(Table 2)*; this cavity may be approximated by a cylinder of diameter ($\approx$ 5.0 Å) defined by the circles passing through the three protonated N-sites at each pole of the molecule and of length ($\approx$ 5.5 Å) equal to the distance between these circles.

The *structural non-complementarity* between F^-, Cl^- or Br^- and the **BT**-$6H^+$ ligand has direct structural consequences for the complexes and provides an interesting case for analyzing how a receptor molecule responds to a non-ideal substrate. These halide ions differ from the intramolecular cavity both in shape and in size, being spherical and too small along the bridgehead NN-axis.

The F^--ion is so small with respect to the equilibrium cavity, that it does not even occupy its centre but shifts towards one pole *(Fig. 1a)* and 'falls' into one lobe of the macrobicycle, which is completely distorted in order to complete the coordination tetrahedron. This is an indication of the strength of the H-bonds formed and relates to the above discussion of the reasons why the F^--cryptate is nevertheless highly stable.

The Cl^-- and Br^--substrates are larger than F^-, large enough to occupy the cavity center. However, to accommodate these substrates and to form $^+N-H \cdots X^-$ H-bonds with them, the ligand must contract upon itself and render its cavity more or less spherical. This is achieved by a large helical twist around the NN bridgehead axis, which results in the large lobes seen in *Fig. 2c* ('lobe dihedral angles' of about 90°) and makes octahedral coordination possible. However, that despite this pronounced deformation, the resulting ligand conformation is still not ideal and contains appreciable strain, may be adduced from the fact that in the Cl^--complex, the internal $^+N-H \cdots Cl^-$ H-bonds are *longer* than those formed with the Cl^--ions outside the cage (see *above*). As expected, this difference between internal and external H-bonds is less pronounced in the cryptate of the larger Br^--ion.

Receptor-substrate structural complementarity is, in contrast, achieved to a high degree in the N_3^--cryptate [$N_3^- \subset$ **BT**-$6H^+$]. N_3^- bears negative charge and high electron density with cylindrical distribution on both terminal N-atoms [36]; its cylindrical shape and size are such that it may fit tightly into the cavity and form simultaneously two pyramidal arrays of three $^+N-H \cdots N^-$ H-bonds with the three protonated secondary N-sites located at each pole of the macrobicyclic ligand **BT**-$6H^+$. The N_3^--substrate fills out the intramolecular cavity and the ligand adopts an elongated (see the long N–N′ bridgehead distance of 8.84 Å, *Table 2*) and relaxed geometry with only small bridge lobes ('lobe angle' $\approx$ 20°, *Fig. 3c*). The IR and laser-*Raman (Fig. 5)* spectra of the N_3^--cryptate display asymmetric (2085 ± 5 cm^{-1}) and symmetric (1363 ± 1 cm^{-1}) stretching bands shifted towards higher frequencies with respect to free N_3^- (2052 and 1343 cm^{-1}, respectively [37]), indicating that the cryptated N_3^--ion experiences a higher effective force field, as one might expect if tight fit hinders substrate deformation. The cryptand **BT**-$6H^+$ is thus a *molecular receptor containing an ellipsoïdal recognition site for linear triatomic substrates* of size compatible with the size of the molecular cavity.

The [$N_3^- \subset$ **BT**-$6H^+$]-species may also be considered as a cryptate of a *ditopic coreceptor* [38] in which the two tripodal binding subunits of the **BT**-$6H^+$ macrobicycle

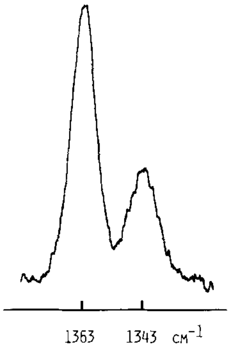


Fig. 5. *Laser*-Raman *spectrum of [$N_3^- \subset$ **BT-6H**$^+$] in presence of excess NaN_3.* Symmetric stretching vibration of free (1343 cm^{-1}) and bound (1363 cm^{-1}) N_3^--anion; aqueous solution at pH = 5.

cooperate in substrate binding, each holding one of the terminal N-atoms of N_3^-. Such ditopic binding is known for complexation of both linear diammonium [38] [39] and dicarboxylate [13] substrates with coreceptor molecules [38].

BT-6H$^+$ also binds the linear anions FHF^- and NCO^- [4]^2) but NCS^- is less well-complexed. NO_2^- ^{2}), NO_3^- and HCO_2^-, which may be considered as substrates with bent triatomic sites, still form stable complexes, probably because they may also bridge the two sets of ammonium sites from pole to pole [25]. Complexation of tetrahedral ClO_4^--ion and especially of the sulfonates RSO_3^- is especially weak, so that the latter is best suited for use in the supporting electrolyte since it interferes least with the binding of other anions. A more detailed description of these cryptates, as well as of those of the other anions listed in *Table 3* must await the determination of the corresponding crystal structures.

Conclusion. – The present results on a series on anion cryptates provide insight into the structural features of anion coordination and allow to analyze the binding properties in terms of receptor-substrate complementarity.

It would be of much interest to take advantage of the available X-ray crystallographic data files for studying the environments and interactions of anions in solids, to recognize regularities in intermolecular binding interactions and to establish anion coordination patterns. The remarkable stability and selectivity of the N_3^--complex with respect to anions of different shape (non-linear, triangular, tetrahedral) are comparable to those of the spherical anion cryptates [3], and may be ascribed again to the cryptate nature of these complexes.

Further developments comprise *inter alia* the design of other selective receptor molecules for anionic substrates of various shapes and sizes; the stabilization of unstable species (F_2H^-, Cl_2F^- *etc.*) or of unusual geometries of a given species (for instance complex anions); the modification of the physical properties of the bound anions like their redox potential [12] or their spectra; the design of molecular catalysts for the activation and transformation of bound anionic substrates (*e.g.* for ATP-hydrolysis

---

^{2}) Because of slow reaction of the corresponding acid with the ligand, accurate values of the stability constants cannot be determined for NCO^- and NO_2^-.

[33]); the development of selective anion transport systems for chemical or biological species (*cf.* [40] and references therein).

In view of the key role played by anions ion chemistry and in biology, the development of the various facets of anion coordination chemistry opens many avenues in pure as well as in applied research.

We thank Dr. *S. J. Abbott* for measuring the *Raman* spectra. *E. Sonveaux* thanks the *Fonds National de la Recherche Scientifique Belge* for financial support.

Experimental Part

Preparation of the Anion Cryptates. The synthesis of the macrobicyclic molecule **BT** has been reported earlier [16].The cryptates of the hexa-protonated ligand, $[X^- \subset$ **BT**$\text{-}6H^+]$ have been crystallized in the following conditions.

*$[F^- \subset$ **BT**$\text{-}6H^+]$, 5 ClO_4^-.* To a solution of **BT**-$6H^+$, 6 ClO_4^- (55 mg, $5 \cdot 10^{-5}$ mol) in 1 ml H_2O F_2HK (3.9 mg, $5 \cdot 10^{-5}$ mol) was added. Vapor diffusion of EtOH into this solutions gave suitable crystals after a few days, m.p. ≈ 200° (dec.). Anal. calc. for $C_{24}H_{60}Cl_5FN_8O_{23}$, ½ H_2O (1034.04): C 27.87, H 5.94, N 10.83; found: C 27.40, H 5.68, N 10.53.

*$[Cl^- \subset$ **BT**$\text{-}6H^+] \cdot 5\ Cl^-$.* The free octamine **BT** was treated by an excess of 1N HCl and the solution was evaporated to dryness. Crystallization was performed in H_2O/EtOH m.p. > 260°. Anal. calc. for $C_{24}H_{60}Cl_6N_8O_3$ (721.49): C 39.95, H 8.38, N 15.53; found: C 39.75, H 8.39, N 15.67.

*$[Br^- \subset$ **BT**$\text{-}6H^+]$, 5 Br^-.* The same procedure as described above for Cl^- was used, m.p. > 260°. Anal. calc. for $C_{24}H_{60}Br_6N_8O_3$ (988.20): C 29.17, H 6.12, N 11.34; found: C 29.18, H 6.24, N 11.29.

*$[N_3^- \subset$ **BT**$\text{-}6H^+]$, Cl^-, 4 PF_6^-.* To a solution of **BT**-$6H^+$, 6 Cl^- (72 mg, 10^-4 mol) in 0.2 ml H_2O a solution of NH_4PF_6 (130 mg, $8 \cdot 10^{-4}$ mole) in 5 ml EtOH was added. Precipitation rapidly occurred. The precipitate was filtered, dried and dissolved in 5 ml of hot H_2O; NaN_3 (6.5 mg, 10^{-4} mol) was added to this hot solution; the crystals which appeared on cooling were filtered off and dried under vacuum at r.t., m.p. ≈ 220° (dec.). Anal. calc. for $C_{24}H_{60}ClF_{24}N_{11}O_3P_4$ (1166.08): C 24.72, H 5.15, N 13.21; found: C 24.50, H 4.92, N 13.32.

The crystals used for the structure determination were obtained by a second crystallization from hot H_2O and were not dried.

pH-metric Measurements. The pH-metric titration and data analysis procedures were similar to those described earlier [6]. The **BT**-ligand [16] was used in its hexa-protonated form, with perchlorate as counterion, **BT**-$6H^+$, $6ClO_4^-$. All measurements were performed at 25° under N_2-atmosphere on aq. solutions containing 10^{-3}M ligand; the concentrations of anions were 1.5×10^{-2}M, 5×10^{-3}M, 2.5×10^{-3}M, 1.5×10^{-3}M for anions of charge 1,2,3,4, respectively. The supporting electrolyte was 0.1M TsONa. Data analysis has been performed assuming 1:1 stoichiometry.

Table 4. *Experimental Parameters for Data Collection for the Cryptates $[X^- \subset$ **BT**$\text{-}6H^+]$*

	X^-			
	F^-	Cl^-	Br^-	N_3^-
Crystal dimensions	2 crystals: 0.6 × 0.4 × 0.05	0.3 × 0.3 × 0.3	0.2 × 0.4 × 0.4	0.4 × 0.4 × 0.1
Wavelength	CuK_a	CuK_a	MoK_a	CuK_α
Registered Domain (ω-2θ) θ max.	68°	68°	31°	68°
Scan speed	0.033° s^{-1}	0.03° s^{-1}	0.035° s^{-1}	0.05° s^{-1}
Scan width	1.3°	1.4° + 0.16 tgθ	1.4°	1.5° + 0.16 tgθ
No. of ind. reflex.	18144	1959	6086	7818
No. of I above backg.	$3535 > 2\sigma$	$1651 > 3\sigma$	$2249 > 2\sigma$	$3240 > 2.5\sigma$
Absorption μ	18 cm^{-1}	69 cm^{-1}	61 cm^{-1}	28 cm^{-1}

Table 5. *Structural Data and Refinement Procedures for Structure Determination of the Cryptates* $[X^- \subset \mathbf{BT\text{-}6H^+}]$

		X^-			
		F^-	Cl^-	Br^-	N_3^-
Crystal system		Monoclinic	Trigonal	Trigonal	Monoclinic
Space group		$P2_1/c$ ($Z = 4$)	$P3_121$ ($Z = 6$)	$P3_1$ ($Z = 3$)	$P2_1/n$ ($Z = 4$)
Formula unit		$C_{24}H_{60}N_8O_3$, F, 5(ClO_4), ½ H_2O	$C_{24}H_{60}Cl_6N_8O_3$	$C_{24}H_{60}Br_6N_8O_3$	$C_{24}H_{60}N_8O_3$, N_3, Cl, 4(PF_6), 3 H_2O
Cell dimensions	a (A)	21.026 (9)	11.186 (7)	11.537 (7)	15.236 (7)
	b (A)	12.611 (6)			14.097 (6)
	c (A)	34.916 (13)	24.801 (7)	25.413 (9)	24.410 (10)
	β (°)	95.67 (9)			90.67 (8)
	V (Å^3)	9239	2690	2929	5242
No. of mol. per asym. unit		n = 2	n = ½	n = 1	n = 1
Structure resolution method		Direct methods	Patterson	Isomorphous replacement	Direct methods
Refinement: programme		SHELX 76	O.R.F.L.S.	SHELX 76	SHELX 76
Thermal parameters		Cl, N, O, F axis, most ClO_4 disordered	Anisotropic	Anisotropic	Anis. but PF_6 iso. in rigid groups with 2 positions for 4F/6
H-atoms		No H	In theoretical position	In theoretical position	No H
R (R_w) %		19.8 (19.8)	5.4 (5.3)	9.2 (11.0)	16.2 (16.2)

Crystal Data and Structure Determination. The cell dimensions and diffraction data were collected on an automatic 4-circle *Philips PW 1100* diffractometer. The experimental procedures and conditions for the determination of the crystal structures of the cryptates $[X^- \subset BT\text{-}6H^+]$ ($X = F, Cl, Br, N_3$) are listed in *Table 4* and *5*. The atomic coordinates, along with the complete lists of bond lengths, bond angles and torsional angles, are available from the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, Lensfield Road, Cambridge CB2, 1EW. Any request should be accompanied by the full literature citation of this publication.

REFERENCES

[1] *J. M. Lehn*, Pure Appl. Chem. *50*, 871 (1978); Acc. Chem. Res. *11*, 49 (1978).
[2] *C. H. Park & H. E. Simmons*, J. Am. Chem. Soc. *90*, 2431 (1968).
[3] *E. Graf & J. M. Lehn*, J. Am. Chem. Soc. *98*, 6403 (1976).
[4] *J. M. Lehn, E. Sonveaux & A. K. Willard*, J. Am. Chem. Soc. *100*, 4914 (1978).
[5] *F. P. Schmidtchen*, Angew. Chem. *89*, 751 (1977).
[6] *B. Dietrich, D. L. Fyles, T. M. Fyles & J. M. Lehn*, Helv. Chim. Acta *62*, 2763 (1979).
[7] *B. Dietrich, T. M. Fyles, J. M. Lehn, L. G. Pease & D. L. Fyles*, J.Chem. Soc., Chem. Commun. *1978*, 934.
[8] *B. Dietrich, M. W. Hosseini, J. M. Lehn & R. B. Sessions*, J. Am. Chem. Soc. *103*, 1282 (1981).
[9] *E. Kimura, A. Sakonaka, T. Yatsunami & M. Kodama*, J. Am. Chem. Soc. *103*, 3041 (1981).
[10] *J. Cullinane, R. I. Gelb, T. N. Margulis & L. J. Zompa*, J.Am. Chem. Soc. *104*, 3048 (1982).
[11] *E. Kimura, M. Kodama & T. Yatsunami*, J. Am.Chem. Soc. *104*, 3182 (1982).
[12] *F. Peter, M. Gross, M. W. Hosseini, J. M. Lehn & R. B. Sessions*, J. Chem. Soc., Chem. Commun. *1981*, 1067; *F. Peter, M. Gross, M. W. Hosseini & J. M. Lehn*, J. Electroanal. Chem. *144*, 279 (1983).
[13] *M. W. Hosseini & J. M. Lehn*, J. Am. Chem. Soc. *104*, 3525 (1982).
[14] *R. A. Bell, G. G. Christoph, F. R. Fronzeck & R. E. Marsh*, Science *190*, 151 (1975).
[15] *B. Metz, J. M. Rosalky & R. Weiss*, J. Chem. Soc., Chem. Commun. *1976*, 533.
[16] *J. M. Lehn, S. H. Pine, E. I. Watanabe & A. K. Willard*, J. Am. Chem. Soc. *99*, 6766 (1977).
[17] *H. E. Simmons & C. H. Park*, J. Am. Chem. Soc. *90*, 2428 (1968).

[18] *B. Dietrich, J.M. Lehn & J.P. Sauvage,* Tetrahedron Lett. *1969,* 2885; ibid. *1969,* 2889.

[19] *L. Pauling,* 'The Nature of the Chemical Bond, 3rd edn., Cornell University Press, Ithaca, N.Y., 1960, p. 514.

[20] *G.C. Pimentel & A.L. McClellan,* Ann. Rev. Phys. Chem. *22,* 347 (1971).

[21] *W.C. Hamilton & J.A. Ibers,* 'Hydrogen Bonding in Solids', Benjamin, New York, 1968.

[22] *L.K. Frevel,* Z. Kristallogr. *94,* 197 (1936).

[23] *U. Müller,* Struct. Bonding *14,* 141 (1973).

[24] *D.R. Rosseinsky,* Chem. Rev. *65,* 467 (1965).

[25] *R.J. Motekaitis, A.E. Martell, J.M. Lehn & E.I. Watanabe,* Inorg. Chem. *21,* 4253 (1982).

[26] *B.A. Coyle, L.W. Schroeder & J.A. Ibers,* J. Solid State Chem. *1,* 386 (1970).

[27] *I. Gennick, K.M. Harmon & M.M. Potvin,* Inorg. Chem. *16,* 2033 (1977).

[28] *S.E. Rasmussen & R. Grønbaek,* Acta Chem. Scand. *17,* 832 (1963); *R. Grønbaek-Hazell & S.E. Rasmussen,* ibid. *22,* 348 (1968).

[29] *T. Ashida & S. Hirokawa,* Bull. Soc. Chim. Jpn. *36,* 704 (1963).

[30] *I. Søtofte,* Acta Chem. Scand. *A30,* 309 (1976).

[31] a) *M. Arshadi, R. Yamdagni & P. Kebarle,* J. Phys. Chem. *74,* 1475 (1970); b) *J.W. Larson & T.B. McMahon,* J. Am. Chem. Soc. *105,* 2944 (1983).

[32] *D.G. Tuck,* in 'Progress in Inorganic Chemistry', Vol. 9, ed. F.A. Cotton, New York, 1968.

[33] *M.W. Hosseini, J.M. Lehn & M.P. Mertes,* Helv. Chim. Acta *66,* 2454 (1983).

[34] *W.P. Jencks,* 'Catalysis in Chemistry and in Enzymology', McGraw Hill, New York, 1969, p. 358.

[35] *Y. Pocker & J.T. Stone,* Biochemistry *7,* 2936 (1968).

[36] *E.D. Stevens, J. Rys & P. Coppens,* J. Am. Chem. Soc. *99,* 265 (1977).

[37] *D.A. Dows, E. Whittle & G.C. Pimentel,* J. Chem. Phys. *23,* 1475 (1955).

[38] *J.M. Lehn,* in 'Biomimetic Chemistry', eds. N. Ise and Z.I. Yoshida, Kodansha, Tokyo; Elsevier, Amsterdam, 1983, p. 163.

[39] *F. Kotzyba-Hibert, J.M. Lehn & P. Vierling,* Tetrahedron Lett. *1980,* 941; *C. Pascard, C. Riche, M. Cesario, F. Kotzyba-Hibert & J.M. Lehn,* J. Chem. Soc., Chem. Commun. *1982,* 557.

[40] *J.M. Lehn,* in 'Physical Chemistry of Transmembrane Ion Motions', ed. G. Spach, Elsevier, Amsterdam, p. 181.