84. Anion-Receptor Molecules: Macrocyclic and Macrobicyclic Effects on Anion Binding by Polyammonium Receptor Molecules

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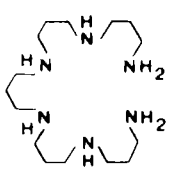
The stability constants for anion binding by the acyclic hexaamine **1**, its macrocyclic analogue **2**, and the bicyclic compound **3** in their protonated forms are reported. Compound **3** forms stable and selective complexes with halide ions, the stability sequence being $I^- > Br^- > Cl^-$. Compound **2** forms more stable complexes with sulfate, oxalate, and malonate dianions than its acyclic analogue **1** and shows a better selectivity pattern. Compound **3** forms stronger complexes with oxalate^{2-} than **2** and shows a remarkably high binding selectivity between oxalate^{2-} and malonate^{2-}. The comparison of the ability of **1–3** to complex anions demonstrates the macrocyclic and macrobicyclic effects on anion binding stability and selectivity.

Introduction. – In view of the role played by anionic species in chemical as well as in biological processes, their binding by synthetic receptor molecules is of wide interest. The complexation of anions by organic receptors has been developing in recent years into a new field of coordination chemistry [1–6]. The development of this field requires the design and synthesis of novel receptor molecules [1] capable of forming various types of complexes presenting characteristic structure/stability-selectivity relationships.

Macropolycyclic polyammonium cations bind anions and yield katapinates [7] and cryptates [8–14]. Acyclic polyguanidinium and polyammonium cations from complexes with anionic species [15]; polyguanidinium [16] and especially polyammonium macrocycles [17–20] bind strongly and selectively a variety of inorganic as well as organic anions. Binding of complex anions, such as $M(CN)_6^{n-}$ by macrocyclic polyammonium receptor molecules modifies their electrochemical [21] [22] and photochemical [23] properties. Macrocyclic polyamines, when protonated, bind nucleotides and polyphosphates [17] [18] [24–26]; furthermore, they catalyse their hydrolytic reactions [26–29], as well as phosphoryl transfer processes, from a phosphate donor to phosphate acceptors [30] [31].



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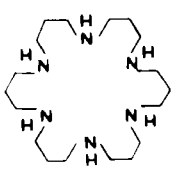

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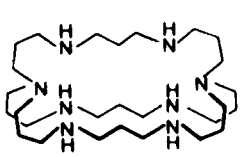

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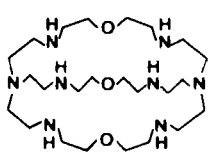

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[1]) U.A. N° 422 of the CNRS.

To better understand the structure/stability-selectivity relationships, *i.e.* the macrocyclic and the macrobicyclic effets in anion binding by polyammonium receptor molecules, the influence of structural variations was investigated. We report here the study of anion binding by the structurally related acyclic **1**, macrocyclic **2**, and macrobicyclic **3** polyamines in their protonated forms.

Design of the Polyaza Receptor Molecules. – The syntheses of **1**, **2** [32], and **3** [33] were reported earlier. The anion binding units of **2** and **3** consist of several positively charged ammonium groups arranged around a cavity defined by their molecular architecture. The choice of the number of CH_2 groups (propylene) separating the binding sites in **1** and **2** has been discussed previously [32]. The compound **3** is based on the tripodal subunits $(CH_2CH_2CH_2NH_2)_3N$ with protonation constants of 5.60, 9.10, 9.95, and 10.50 [15]. It belongs to the same class as the bis-tren cryptand described earlier [12] [13]. Compound **4** contains tren ($(CH_2CH_2NH_2)_3N$) with protonation constants of 2, 8.20, 9.35, and 9.90 [15] as tripodal unit. The incidence of these two subunits on the protonation constants and features of macrobicyclic compounds **3** and **4** will be discussed (see below).

Table 1. *Protonation Equilibrium Constants log* K_n (= pK_a) *of the Macrobicyclic Octaamine* **3**[a])

Supporting electrolyte	*n*							
	1	2	3	4	5	6	7	8
TsONa[b])	10.10	10.45	9.40	8.65	7.00	6.75	4.95	4.15
NMe_4Cl[b])	10.45	10.30	9.55	8.60	7.45	7.30	5.40	4.60

[a]) In H_2O, at 25°, see *Eqns. 1* and *2* for definition of K_n.
[b]) TsONa: sodium *p*-toluene sulfonate; 0.1M.

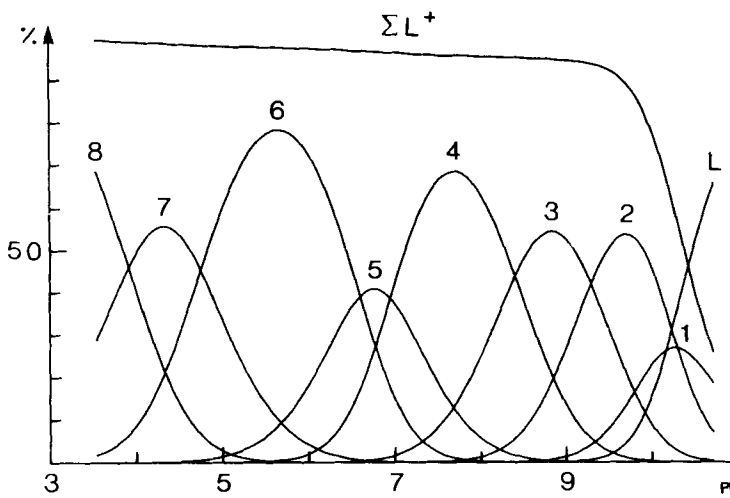

Fig. 1. *Distribution curves of the unprotonated and protonated forms of the macrobicyclic polyamine* **3** *as a function of pH.* L: unprotonated **3**; the numbers 1–8 refer to the successive protonated species bearing 1–8 protons; Σ L^+: summation over all the protonated species.

Results. – *Protonation Features.* The protonation constants log K_n (= pK_a values) corresponding to the equilibria of the polyamine L = **3** (*Eqns. 1* and *2*) are listed in *Table 1*. They lead to the distribution curves of the various species represented in *Fig. 1*.

$$H_{n-1}L^{(n-1)} + H^+ \rightleftharpoons H_nL^{n+} \quad (1)$$

$$K_n = \frac{[H_nL^{n+}]}{[H_{n-1}L^{(n-1)+}][H^+]} \quad (2)$$

The protonation constants for compounds **1** and **2** [32] in 0.1M Me_4NCl or TsONa and **4** in 0.1M TsONa [13] have been reported. Compounds **1–3** in their protonated forms bind anions, thus the pK_a values found depend on the anion present in the supporting electrolyte. The latter was chosen so as to minimize such medium effects. The binding of Cl^- by **1–3** was established by ^{35}Cl-NMR spectroscopy [34]. Compounds **1** and **2** bind Cl^- weakly, whereas **3** binds it strongly. In the case of **3**, complexation of Cl^- was established by pH-metric titration experiments (see *Tables 1* and *2*). Thus, to minimize the interactions between the anion of the supporting electrolyte and the receptor **3**, TsONa was chosen. It is important to note that the pK_a values determined are apparent and hold specifically for the medium used.

Complexation Features of Compounds **1–3**. The stability constants log K_s^n corresponding to the equilibria of the polyammonium ions H_nL^{n+} (L = **1–3**) with various anions A^{m-} (*Eqns. 3* and *4*) were determined by pH-metric titration (see *Experimental*), and are listed in *Tables 2* and *3*.

$$L + nH^+ + A^{m-} \rightleftharpoons (H_nLA)^{(n-m)+} \quad (3)$$

$$K_s^n = \frac{[(H_nLA)^{(n-m)+}]}{[H^+]^n[L]\ [A^{m-}]} \quad (4)$$

To provide a clearer picture of the observed stability and selectivity sequences, graphical representations of the stability constants in comparative series of complexes are shown in *Figs. 2–4*. As mentioned above, weak binding of Cl^- by **1** and **2** and of TsO^- by **3** competes, to some extent, with binding of the anion studied. Consequently, the stability constants determined are apparent constants, the real values for a given anion being even higher than those listed in *Tables 2* and *3*.

Table 2. *Stability Constants log* K_s (± 0.2) *for Halide Binding by the Macrobicyclic Polyammonium Receptor Molecule* **3** *in Aqueous Solution* [a])

Halide	n [b])			
	8	7	6	5
Cl^-	2.40	2.10	1.70	1.50
Br^-	2.95	2.65	2.20	1.70
I^-	3.40	3.00	2.40	1.95

[a]) The log K_s values were determined in the presence of 0.1M TsONa at 25° (*Eqns. 3* and *4*).
[b]) Number of protons involved in the complexes of the type (**3**, nH^+, A^-).

Table 3. *Stability Constants log* K_s (± 0.2) *for Molecular Anions Binding by Polyamines* **1**, **2**, *and* **3** *in Aqueous Solution*[a])

Anion	n[b])	Macro(poly)cyclic and linear polyamines		
		1	**2**	**3**
SO_4^{2-}	8			7.45
	7			5.60
	6	2.50	4.05	4.20
	5	2.00	3.05	3.20
	4	1.15	2.50	2.75
Oxalate^{2-}	8			6.55
	7			5.20
	6	2.40	3.80	4.50
	5	2.05	3.20	3.25
	4	1.40	2.60	
Malonate^{2-}	8			4.00
	7			3.10
	6	–	3.30	2.85
	5	–	2.60	2.20
	4	–	2.45	
Maleate^{2-}	6	2.65	3.70	–
	5	2.30	2.95	–
	4	1.40	2.70	–
Fumarate^{2-}	6	1.95	2.20	–
	5	1.70	1.90	–
	4	1.40	1.75	–

[a]) The log K_s values were determined in the presence of 0.1M Me_4NCl for **1** and **2**, and 0.1M TsONa for **3** at 25° (*Eqns. 3* and *4*).

[b]) Number of protons involved in the complexes of the type (L, nH^+, A^{2-}), L = **1**–**3**.

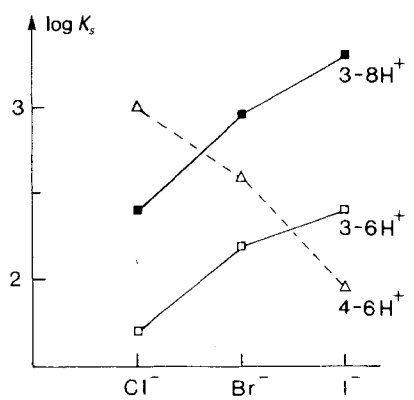

Fig. 2. *Graphical representation of the stability constants log* K_s *of the complexes formed by* **3**-8 H^+ (■), **3**-6 H^+ (□) *and* **4**-6 H^+ (△) [13] *with halide*

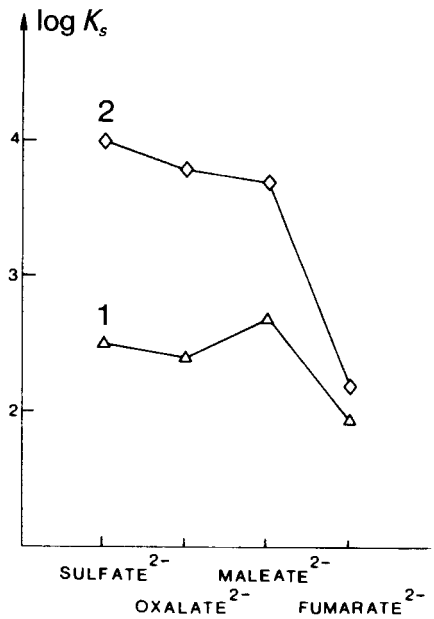

Fig. 3. *Graphical representation of the stability constants log* K_s *of the complexes formed by* **1**-6 H^+ (△) *and* **2**-6 H^+ (◇) [20] *with molecular anions*

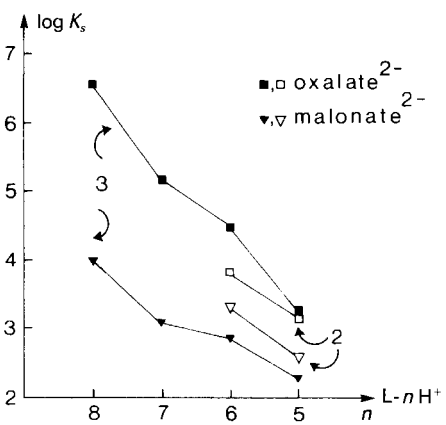

Fig. 4. *Graphical representation of the stability constants log* K_s *of the complexes formed by* **2** (□, ▽) *and* **3** (■, ▼) *with oxalate*$^{2-}$ (■, □) *and malonate* (▼, ▽) *as a function of the number of protons* n *involved in* (L-nH^+, A^{2-}), *with* L = **2**, **3**; n = 5–8 *and* A^{2-} = *oxalate*$^{2-}$, *malonate*$^{2-}$

Discussion. – It may first be noted that the pK_a values for the octa- and hepta-protonated forms of **4** are lower than 2 [13], whereas for compound **3**, they are 4.15 and 4.95, respectively *(Table 1)*. On the other hand, the pK_a values for the hexa-protonated forms of **3** and **4** are 6.05 and 6.75, respectively. Thus, at $3 < pH < 5$, **3**-8 H^+ and **3**-7 H^+ are present for anion complexation and at $5 < pH < 7$, **3**– 6 H^+ is the most abondant species in solution *(Fig. 1)*. This demonstrates clearly the importance of the choice of the tripodal subunits on the number of the ammonium binding sites at a given pH.

Binding of Halides. Binding of halides by polyammonium receptors has been found to occur in katapinates [7], in spherical macrotricyclic cryptates [8–11], in the anion complexes of the bis-tren macrobicyclic compound **4** [12] [13], as well as in those formed by the protonated macrocyclic polyamine hexacyclen ($[18]N_6$) [19].

Whereas complexation of halides by **1** and **2** is rather weak, the protonated macrobicyclic compound **3** forms stable complexes with Cl^-, Br^-, and I^- *(Table 2)*. The comparison of the pK_a values for **3** in the presence of 0.1M Me_4NCl and TsONa *(Table 1)* proves the binding of Cl^- by **3**-$n$$H^+$ for $n = 5$–8. Indeed, the log K_n values for $n = 5$–8 are higher in the presence of Cl^- than in the presence of TsO^-. The fact that log K_1 value is lower in 0.1M TsONa (10.10) than in 0.1M Me_4NCl (10.45) is probably due to the binding of Na^+ by the unprotonated compound **3**. As in the case of protonated macrocyclic polyamines, the most stable complexes are formed by the most highly charged ligands. The stability sequence observed $Cl^- < Br^- < I^-$ demonstrates clearly that halide binding by **3** is not governed simply by electrostatic interactions, but that the size of the substrate plays an important role. The electrostatic interactions alone should lead to stronger complexes with Cl^- than with I^-, since the charge density is higher for Cl^- (ionic radius of 1.81 Å) than for I^- (ionic radius of 2.16 Å).

A comparison of the stability constants for halide binding by **3** and **4** [13] is shown in *Fig. 2*. Whereas for **4** the stability sequence is $I^- < Br^- < Cl^-$, it is opposite for **3**. This may be due to the structural features of **3** and **4**. The structure of **4** is based on two tren subunits linked together by three $CH_2CH_2OCH_2CH_2$ chains. Whereas, the structure of **3** is based on two wider $(CH_2CH_2CH_2NH_2)_3N$ tripods linked together by $CH_2CH_2CH_2$ chains, consequently, compound **3** possesses a larger and more spherical cavity than **4** and forms the most stable complexes with I^-. The same behaviour was observed for macrotricyclic cryptands [11]. Since **4**-8 H^+ and **4**-7 H^+, due to their low pK_a values, are not present, one may compare the complexes (L-6 H^+, A^-) with L = **3** or **4** *(Fig. 3)*. The complex (**4**-6 H^+, Cl^-) (log $K_S^6 = 3.00$ [13]) is more stable than (**3**-6 H^+, I^-) (log $K_S^6 = 2.40$, see *Table 2*). Preference for the larger anion of smaller charge density I^-, may be due to the more symmetrical distribution of charged sites in **3**-6 H^+, whereas charge density is higher in **4**-6 H^+, which contracts in order to fit the included Cl^- [13].

Binding of Molecular Anions. Polyamines **1–3**, when protonated, from stable and selective complexes in aqueous solution with molecular inorganic anions such as sulfate and organic dicarboxylates *(Table 3)*. The acyclic hexaamine **1**, despite the fact that it possesses four secondary and two primary amines, may be considered as a close open-chain analogue of the macrocyclic hexaamine **2** which possesses six secondary amines. A comparison of the stability constants for molecular anion binding by **1** and **2** is shown *Fig. 3*. Complexes of the type (L, $n$$H^+$, A^{2-}) with L = **1** or **2** and $n = 4$–6 may be compared because the pK_a values for $n = 4$–6 are similar for **1** and **2** [32]. When the substrate size is compatible with the cavity defined by the macrocyclic structure, compound **2**, which also

has higher charge density, forms much more stable complexes with the more compact dianions, sulfate, oxalate, malonate, and maleate, than its acyclic analogue **1**, demonstrating a macrocyclic effect. On the other hand, fumarate^{2-} being too long to fit, the macrocycle **2** displays a large drop in stability from maleate to fumarate, whereas the decrease is much smaller for the acyclic compound **1**, which may adapt to the structural change of the substrate. Thus, a marked macrocyclic effect on both stability and selectivity of anion binding is observed, the acyclic ligand **1** displaying both much lower stability and selectivity than the macrocycle **2**. This type of selectivity has been observed previously in the linear recognition of dicarboxylate substrates by ditopic polyammonium receptor molecules [20].

A comparison of the stability constants for oxalate^{2-} and malonate^{2-} binding by **2** and **3** is given in *Fig. 4*. Considering identical protonated states, the hexa-protonated form of **3** binds oxalate^{2-} better than **2**-6 H^+, whereas **2**-6 H^+ forms a stronger complex with malonate^{2-} than with **3**-6 H^+. Higher selectivities between oxalate^{2-} and malonate^{2-} are thus obtained for **3**-6 H^+ and **3**-5 H^+ than for **2**-6 H^+ and **2**-5 H^+. This marked selectivity is due to the fact that oxalate^{2-} fits well into the cavity of **3**, whereas malonate^{2-} cannot be included entirely. Thus, a comparison of the stability constants for molecular anion binding by **2** and **3** demonstrates clearly the macrobicyclic effect on both the stability and the selectivity of complexation.

Conclusion. – The present results on binding of halide anions again demonstrates the importance of the molecular architecture on the complexation features. The results obtained for binding of molecular anions illustrate two major features of supramolecular chemistry, *i.e.* the macrocyclic and macrobicyclic effects on binding stability and selectivity. Indeed, as in the case of cation binding, the greater structural organization of the receptor molecules, *i.e.* macrobicyclic compared to macrocyclic and acyclic structures, provides stronger and more selective complexation of substrate anions. Thus, the present results provide further information on molecular recognition of anionic substrates.

Experimental. – pH-Metric measurements were performed with *Metrohm-637* titrimeter, the cell was thermostated at 25° ± 0.1°, the soln. stirred, and all measurements were performed under N_2. The log K_n values of the compounds were determined by titration with 0.1N NaOH of a soln. containing typically 10^{-3} M of the polyammonium salt in the presence of 0.1M Me_4NCl or TsONa. The log K_s^n values of the complexes were determined by titration with 0.1N NaOH of a soln. containing 10^{-3} M of the HCl salts of **1**, **2**, or TsOH salt of **3**, and 0.015M of the desired Na salt of the halides, or 5×10^{-3}M of the desired dianions in the presence of 0.1M Me_4NCl in the case of **1**, **2**, and 0.1M TsONa in the case of **3**. The data for all titration results was processed by the computer program SCOGS 76 [35].

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