4. Cryptates. XXV[1]). Stability and Selectivity of Cation Inclusion Complexes of Polyaza-macrobicyclic Ligands. Selective Complexation of Toxic Heavy Metal Cations

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Summary

We have measured the stability constants of the cryptate complexes formed by ligands **1-4** with alkali, alkaline-earth, transition metal and toxic heavy metal cations. Stabilities and selectivities of complexation of the alkali and alkaline-earth cations are less pronounced in **1-4** than in the parent compounds **5** and **6** and decrease as the number of nitrogen sites increase. Remarkable complexation properties are found towards transition metal and toxic heavy metal cations. The intramolecular cavity of ligands **1-3** is too large for small cations like Co^{2+}, Ni^{2+}, Zn^{2+} so that the complexes formed are comparatively weak; however these cations are strongly complexed by ligand **4** whose intramolecular cavity has a much smaller size, compatible with their ionic radius. On the other hand, ligands **1-4** all form highly stable cryptates with Cd^{2+}, Hg^{2+}, Pb^{2+}. Thus by the combined operation of the two structural parameters, cavity size and nature of the binding sites, cryptands **2** et **3** present very high selectivities for the complexation of these toxic heavy metal cations with respect to the biologically important ones Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}. The selectivities of ligand **2** for Cd^{2+}, Hg^{2+} and Pb^{2+} with respect to Zn^{2+} are as high as 10^6, 10^{18} and 10^9 respectively. They are much more pronounced than those of previously known complexing agents. Cryptands like **2** and **3** thus present a unique selectivity sequence of special interest in *detoxication* (decorporation, depollution). Further structural elaboration may allow to design ligands which present a given selectivity pattern of potential use in "*cryptatotherapy*" and "*environment pollution control*". The results also provide evidence for the existence, at low pH, of protonated complexes which probably participate in an acid catalysed process for dissociation of the complexes.

Introduction. - Macrobicyclic polyether ligands form very stable and selective cryptate complexes with various metal cations (especially alkali and alkaline-earth cations) in which the cation is contained in the tridimensional intramolecular cavity of the ligand molecule [2-4]. The properties of these complexes may be monitored

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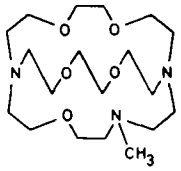
by designing macrobicyclic ligands, cryptands, which incorporate special structural features (topology, nature of the binding sites, *etc.* [2] [5]); stepwise increase in size of the intramolecular cavity is an important factor in the design of the Li^+, Na^+, and K^+ selective cryptands described previously [3] [4] [6]. Unusual sequences of alkaline-earth cation complexation are found as well [2] [3]. Modifying ligand thickness and lipophilicity or changing the number of coordination sites while retaining cavity size, allows monitoring the M^+/M^{2+} complexation selectivities of cryptands for alkali *versus* alkaline-earth cations [2] [7].

Replacing oxygen by sulfur [8] or nitrogen [9] binding sites should also significantly affect complexation selectivities of macrobicyclic ligands. Whereas the highly electrostatic binding of the "hard" alkali and alkaline-earth cations is stronger with "hard", polar and electron rich sites, the binding of group B and transition metal cations is favoured by nitrogen and sulfur sites. Thus, whereas macrocyclic polyethers bind alkali and alkaline-earth cations [10–15], macrocyclic polyamines [11] [16–19] and macrocyclic polysulfides [11] [20] form preferentially complexes with group B and transition metal cations. Similar changes in properties should occur in the macrobicyclic topology. We have described the synthesis of the polyaza-polyoxa-macrobicyclic molecules **1–4** which have been shown to form cryptate-type inclusion complexes with various metal cations [9]. As pointed out [9] these cryptands are of interest from two main points of view: (i) as polyaza derivatives of the initial macrobicyclic ligands [4] [6] on one side and (ii) as polyamines with macrobicyclic topology on the other side. Their complexation properties will allow studying the effect of replacing O by N binding sites in macrobicyclic polyethers as well as the effect of incorporating a polyamine into a macrobicyclic topology.

We report here our results on the determination of the stability constants of the complexes formed by ligands **1–4** with various metal cations. The results should shed light on how the two variables, cavity size (topological information) and nature of the coordination sites (binding information) [2], affect the selectivity sequences.



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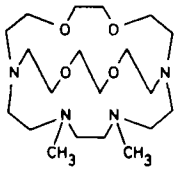

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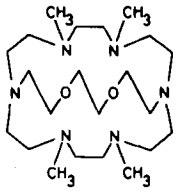

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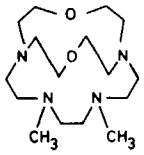

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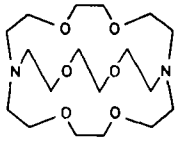

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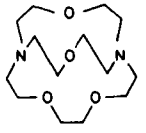

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Especially interesting should be the complexation selectivities for alkali and alkaline-earth cations with respect to transition metal and heavy metal cations.

Heavy metal cations like Tl^+, Cd^{2+}, Hg^{2+}, Pb^{2+} are very toxic [21–23]. The design of highly selective ligands which may remove harmful cations [22] while only minimally affecting the levels of the biologically important ones (Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}) [23] [24] is both of fundamental interest (providing strategies for selectivity control) and of potential practical importance for therapeutical *decorporation* or *administration* (allowing the selective removal of toxic cations from or their transport into organisms) as well as for the control of metal ions in the *environment* [25].

Determination of the stability constants. – *pH-metric titration.* Since cryptands **1–4** are polyamines their aqueous solutions are strongly basic: addition of a complexable cation to such a solution lowers the pH, ΔpH being larger the more stable the complex formed. It is thus possible to determine the stability constants K_s corresponding to the complexation equation (1) *(Fig.1)* by analysis of the pH-metric titratic curves of the ligands L in the presence of the metal cations M^{n+}.

$$(L)_{solv} + (M^{n+}, mS) \overset{K_s}{\rightleftharpoons} (M^{n+} \subset L)_{solv} + mS \tag{1}$$

(*solv:* solvated; S: solvent molecules)

$$K_s = \frac{[(M^{n+} \subset L)]}{[L]\,[M^{n+}]} \tag{2}$$

K_s is the *concentration*-stability constant assuming the activity coefficients of the three species equal to one.

The method [26–28] rests on the fact that the pK of basic or acid functional groups are affected by complex formation; the change being larger the more directly a given group participated in cation binding. The titration curves are thus strongly dependent on cation complexation and their analysis may in principle yield all the equilibrium constants for protonation and complexation of a given system. Very many equilibrium constants have been determined in this way [26–30]. Computer programs have been written for analysing the titration curves of the complicated cases where many protonation and complexation equilibria are present (see for instance [31] [32]). The ligands **1–4** studied here contain N and O binding

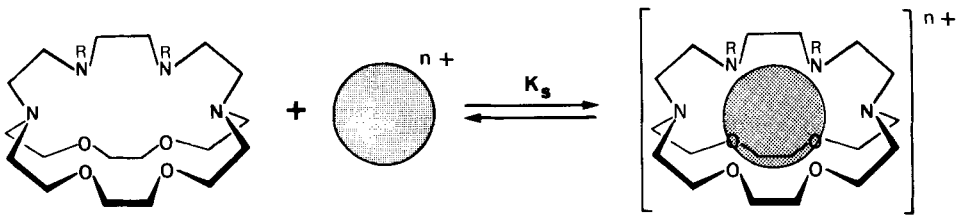


Fig. 1. *Equilibrium equation for the formation of a cryptate inclusion complex between the macrobicyclic ligand* **2** *(represented in the in-in form) and a metal cation*

sites. In the presence of protons and complexable cations several equilibria have to be considered:

a) protonation of the nitrogen sites in the free ligands:

$$(\mathrm{L\,H}_m^{m+}) \rightleftharpoons (\mathrm{L\,H}_{m-1}^{(m-1)+}) + \mathrm{H}^+ \tag{3}$$

defining the parameters $pK_m = -\log K_m$ of the ligands, with

$$K_m = \frac{[(\mathrm{L\,H}_{m-1}^{(m-1)+})]\,[\mathrm{H}^+]}{[(\mathrm{L\,H}_m^{m+})]} \tag{4}$$

b) protonation equilibria of the complexes:

$$(\mathrm{M}^{n+} \subset \mathrm{L\,H}_{m-1}^{(m-1)+}) + \mathrm{H}^+ \rightleftharpoons (\mathrm{M}^{n+} \subset \mathrm{L\,H}_m^{m+}) \tag{5}$$

definig the K_m^{M}-values of the complexes:

$$K_m^{\mathrm{M}} = \frac{[(\mathrm{M}^{n+} \subset \mathrm{L\,H}_m^{m+})]}{[(\mathrm{M}^{n+} \subset \mathrm{L\,H}_{m-1}^{(m-1)+})]\,[\mathrm{H}^+]} \tag{6}$$

c) complexation equilibria:

$$(\mathrm{L\,H}_m^{m+}) + \mathrm{M}^{n+} \rightleftharpoons (\mathrm{M}^{n+} \subset \mathrm{L\,H}_m^{m+}) \tag{7}$$

of which equation (1) is the special case corresponding to $m = 0$. Equations (7) define the concentration stability constants K_s^{m+} for the complexes with unprotonated ($m = 0$, eq. 2) or protonated ligands:

$$K_s^{m+} = \frac{[(\mathrm{M}^{n+} \subset \mathrm{L\,H}_m^{m+})]}{[(\mathrm{L\,H}_m^{m+})]\,[\mathrm{M}^{n+}]} \tag{8}$$

Only complexes of 1:1 ligand/cation stoichiometry are considered since only such complexes are expected to be formed with ligands **1**–**4** [9]. This had been confirmed by analysis of titration curves (see experimental part).

d) conformational equilibria, corresponding to the three possible topologies of the macrobicyclic ligands [2] [6] [9]: *endo-endo, endo-exo* and *exo-exo*. In the cryptates themselves only the *endo-endo* form of the ligand is expected to be present [2] [4] [9], but nothing is known at present about the preferred form of the free ligand.

The equilibria (3) (5) and (7) are not independent; one has $K_s^+ = K_s \cdot K_1^{\mathrm{M}} \cdot K_1$. Furthermore the equilibrium constants which they define correspond to the system at thermodynamic equilibrium with respect to conformational changes d). It is essential that all equilibria (protonation, complexation, conformation) be established in the course of the measurements. While conformational changes should in general be fast, complexation (or dissociation) may be slow in some cases so that it is necessary to wait until the equilibrium state is reached. On the other hand,

time dependent pH changes may be used to measure the kinetics of these slow processes [33].

Titrations. Two types of titrations have been performed: 1) addition of acid to an aqueous solution of the ligand in the presence of excess salt; 2) addition of base to an aqueous solution of the polyprotonated ligand in excess acid in the presence of excess salt.

In the present work we have mainly used the titration with OH^-, which is preferable: a) when the dissociation kinetics of the complex are very slow since method 2) depends on the association rate which is much faster; b) when the salt is subject to hydrolysis, since one may obtain at least part of the titration curve from acid pH up to the pH where hydrolysis occurs, *i.e.* in general up to pH = pK (Hydrolysis)-2[4]). This method also avoids risks of carbonatation of the ligand. The titration base chosen is NMe_4OH whose cation is not complexed by the ligands. The conditions and procedures are described in more detail in the experimental part.

Computations. The pK's of the free ligands have been determined by analysis of the titration curve using a computer program [35]. An iterative computer program has been written for calculating the stability constants from the titration curves. The values have been checked by performing titrations at different ligand/cation ratios; the calculations yield results in agreement within experimental error. Adapted versions [36] of programs described in the literature [32], have also been used.

Determination of the stability constants using cation selective electrodes. Cation selective electrodes allow a direct measurement of the concentrations of free cations. This method has been used for the alkali metal cations and for Ag^+ and Tl^+. The results are in satisfactory agreement with those obtained by pH-metric titration in comparable conditions.

Results. – *Table 1* lists the pK's of the ligands **1**–**4** and the stability constants log K_s *(Fig. 1)* of the unprotonated cryptates (eq. 2). Some stability constants of mono-protonated complexes log K_s^+ (eq. 8, $m=1$; see also below) and mono-protonation constants log K_1^M values (eq. 6, $m=1$) have also been obtained. They are listed in *Table 2*. The accuracy of the data is discussed in the experimental part. The stabilities of the cryptates of ligands **5** and **6** [3] are listed for comparison. *Figures 2* and *3* represent graphically the stability sequences of the complexes.

Protonation equilibrium constants. The pK's determined *(Table 1)* apply to the rapidly interconverting equilibrium mixture of the three possible topological isomers of the ligands and of their various protonated forms. Although up to six such conformationally averaged pK's exist in ligand **3**, pK_5 and pK_6 are too low to be determined in our conditions. Not much can be said with respect to structural effects on the pK's. Comparison with the parent compounds **5** and **6** shows that the present polyamines are generally more basic. Since $(CH_3)_2NCH_2CH_2N(CH_3)_2$ (pK_1 = 9.1) is more basic than $N(CH_2CH_2OH)_3$ (pK = 8.0) the first protonation of **1**–**3** should occur at a bridge nitrogen and not at the bridgeheads. This may account for **1** and **2** being more basic than **5**. However the possibility of hydrogen bonding $N^+-H\ldots N$ between the bridgeheads may change this order

[4]) See [30] for the hydrolysis pK's of the metal cations and [34] for studies of complexes with hydrolyzable cations.

Table 1. *Stability constants, log* K_s, *of the cryptate complexes of ligands* **1**–**6**[a])

Cation	Ionic radius Å [60]		log K_s with ligand					
			1	**2**[b])	**3**	**4**[c])	**5** [3]	**6** [3]
H^+		pK_1	10.55	10.01	9.68	11.18	9.60	10.64
		pK_2	8.57	8.92	9.37	9.75	7.28	7.85
		pK_3	2.55	2.75	5.65	2.42	–	–
		pK_4	–	–	2.26	–	–	–
Li^+	0.78		1.5	2.4	–	3.8	< 2.0	5.5
Li^+ (M)	–		–	> 4.0	> 4.0	> 4.0	2.6	> 6.0
Li^+ (M/W)	–		4.0	3.8	3.5	> 3.8	1.8	7.58
Na^+	0.98		3.2	2.5	–	< 1.0	3.9	3.2
Na^+ (M)	–		–	> 5.0	4.2	–	> 8.0	6.1
K^+	1.33		4.2	2.7	1.7	–	5.4	< 2.0
K^+ (M)	–		–	> 5.0	> 5.0	–	> 8.0	2.3
Rb^+	1.49		3.0	2.3	–	–	4.3	< 2.0
Rb^+ (M)	–	–	–	> 4.0	> 4.0	–	> 6.0	1.9
Cs^+	1.65		< 2.0	< 2.0	–	–	< 2.0	< 2.0
Cs^+ (M)	–		–	3.8	3.3	–	4.4	< 2.0
Mg^{2+}	0.78		1.9	2.6	–	2.4	< 2.0	~ 2.5
Ca^{2+}	1.06		4.6	4.3	1.5	2.2	4.4	2.5
Sr^{2+}	1.27		7.4	6.1	1.5	–	8.0	< 2.0
Ba^{2+}	1.43		9.0	6.7	3.7	–	9.5	< 2.0
Ag^+	1.13		10.8	11.5	13.0	12.7	9.6	8.5[d])
Tl^+	1.49		6.3	5.5	4.1	3.9	6.3	–
Co^{2+}	0.82		5.2	4.9	5.2	9.9	≤ 2.5[d])	≤ 4.7[d])
Ni^{2+}	0.78		5.0	5.1	5.7	10.0	≤ 3.5[d])	≤ 4.5[d])
Cu^{2+}	0.92		9.7	12.7	12.5	16.0	6.8[d])	7.8[d])
Zn^{2+}	0.83		6.3	6.0	6.8	11.2	≤ 2.5[d])	≤ 5.3[d])
Cd^{2+}	1.03		9.7	12.0	10.7	12.4	7.1[d])	≤ 5.5[d])
Hg^{2+}[e])	1.12		21.7	24.9	26.1	26.6	18.2[59]	–
Pb^{2+}	1.32		14.1	15.3	15.5	–	12.7[d])	7.9[d])

[a]) Aqueous solution at 25° unless stated otherwise; ionic strength ~ 0.1. M: methanol solutions; M/W: methanol/water 95:5. K_s in M^{-1}. The precision and experimental conditions are described in the experimental part.

[b]) The parent compound of structure **2** but with $N-CH_3$ replaced by N–H, shows the following log K_s values: < 1.0, Li^+; < 1.0, Na^+; 1.5, K^+; < 1.0, Rb^+; 8.7, Ag^+; 4.2; Tl^+; 12.7, Cd^{2+}; pK values: 10.19, 8.08, 3.76 (aqueous solutions).

[c]) The parent compound of structure **4** but with $N-CH_3$ replaced by N–H, shows the following log K_s values: 1.6, Li^+; 11.5, Ag^+; < 1.0, Tl^+; 1.9, Mg^{2+}; 7.8, Ni^{2+}; 17.9, Cu^{2+}; 11.3, Zn^{2+}; 16.3, Cd^{2+}; pK values: 10.25, 9.55 (aqueous solution).

[d]) See [58].

[e]) Values obtained by competition between the present ligands and chloride anion using the equation $K_s = K'_s(1+\beta_1[Cl^-]+\beta_2[Cl^-]^2+\beta_3[Cl^-]^3+\beta_4[Cl^-]^4)$. Neglecting the first two terms which are comparatively small and using log $\beta_2 = 13.22$, log $\beta_3 = 14.07$, log $\beta_4 = 15.07$ (at $\mu = 0.5$M) [30], the sum at $[Cl^-] = 0.1$ amounts to $\log \sum \beta_i [Cl^-]^i = 11.60$.

and in **4** the high pK_1 might correspond to bridgehead protonation as is the case in **6** which has a high pK and very slow proton exchange kinetics [33]. The inclusion of a water molecule inside the cavity may occur, rendering pK comparisons even more difficult. ^{13}C-NMR. studies as a function of pH could shed some light into the nature of the protonation sites.

Stability and selectivity of the alkali and alkaline-earth cryptates. - As discussed previously [9] alkali and alkaline-earth complexes of ligands **1**–**4** are inclusion complexes of the cryptate type *(Fig. 1)*. The results *(Table 1; Fig. 2)* show that their *stability constants are lower* for the present polyaza ligands **1**–**4** than for the corresponding complexes of the parent compounds **5**, **6**; however the Li^+, Mg^{2+} and Ca^{2+} complexes are less affected. The effect is especially marked for the K^+ complexes of **1**–**3**; progressive replacement of O by $N-CH_3$ sites lowers their stabilities by a factor of 10; the stability constant of the $[K^+ \subset \mathbf{3}]$ cryptate becomes barely measurable being four powers of ten smaller than that of $[K^+ \subset \mathbf{5}]$. Similarly $[Li^+ \subset \mathbf{4}]$ is less stable than $[Li^+ \subset \mathbf{6}]$ by a factor of about 50. The effect seems even larger for the alkaline earth complexes except for cryptand **1** which behaves like **5**. $[Ba^{2+} \subset \mathbf{2}]$ and $[Ba^{2+} \subset \mathbf{3}]$ are less stable than $[Ba^{2+} \subset \mathbf{5}]$ by factors of 600 and $5 \cdot 10^{+5}$ respectively. The stabilities should incorporate the macrobicyclic cryptate effect previously described for the parent cryptand **5** [2] [3]; unfortunately no data for direct comparison are available at present.

The replacement of O by NCH_3 leads to a decrease of electrostatic interaction of the cation with the ligand since the dipole moment of the "softer" [28] [37] [38] NCH_3 sites is smaller than that of the O sites [2] [5]. The *van der Waals* radius of N (1.5 Å) being larger than that of O (1.4 Å) the size of the intramolecular cavity should be somewhat smaller in the polyaza cryptands. Molecular models also show that the methyl groups of the $N-CH_3$ sites increase the thickness of the ligand and shield the cavity (and the complexed cation) from the external polar aqueous medium thus decreasing the interaction between the cation and the solvent (*Born* term) [2] [5] and diminishing the stability of the complexes. Finally the different hydration of N and O sites may also play an important role (see also below) and contribute to lowering the stability of the complexes not only for N replacing O but also for NH as compared to NCH_3 sites. The free energies of

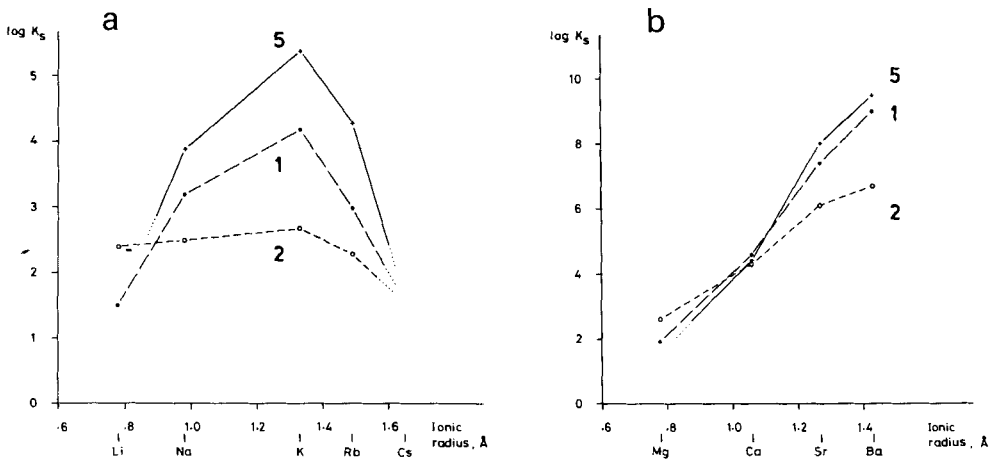


Fig. 2. *Stability constants* (log K_s) *of the cryptates formed by ligands* **1** *and* **2** *with* (a) *alkali and* (b) *alkaline-earth cations as a function of ionic radius* [3]. The results for ligand **5** [3] are added for comparison. (Aqueous solutions at 25°; see also Table 1).

hydration follow the sequence $Et_2O < Et_3N < Et_2NH$ with $\delta\Delta G(Et_3N-Et_2O) = -1.1$ kcal/mol and $\delta\Delta G(Et_2NH-Et_3N) = -1.0$ kcal/mol [39]. The hydration energies of the polyaza-cryptands should thus be larger than those of **5** and **6**. Displacement of these water molecules by the entering cation will disfavour complex formation. The decrease of complex stabilities along the sequence of binding sites O, NCH_3, NH has also been observed in the case of macrocyclic aminoethers [2] [10] [40].

All these effects may contribute to the lowering of cryptate stabilities on going from O to N sites. However, as already noted, the stabilities of the cryptates of the smaller Li^+, Mg^{2+}, Ca^{2+} cations are less affected than those of the larger ones (*e.g.* K^+); this may in part be due to the fact that N sites being more polarizable than O sites, the relative importance of the cation-induced dipole interaction becomes larger the smaller and more highly charged the cation is [2] [5].

The selectivities of complexation decrease as oxygen sites are replaced by nitrogen sites. This is clearly seen from the selectivity curves of **1**, **2** and **5** *(Fig. 2a)*. The peak selectivity of **5** [2] [3] progressively flattens out. Whereas **1** still has appreciable selectivities, **2** is much less selective ($K^+/Na^+ \sim$ 1–2; $K^+/Rb^+ \sim 2$–3) than **5** ($K^+/Na^+ \sim 30$; $K^+/Rb^+ \sim 10$). The same probably holds for **3**. However the Li^+/Na^+ selectivity of **4** seems quite high and comparable to that of **6**. In the case of the alkaline-earth cryptate the selectivities also decrease together with the stabilities. Again the behaviour of **1** is close to that of **5** but **2** and **3** are much less selective (see also *Fig. 2b*). In particular the unique very high selectivity of **5** for Sr^{2+} and Ba^{2+} over Ca^{2+} [3] is reduced by factors of about 100 and 500 in **2**.

The large decrease in *cavity radius* from **5** (1.4 Å) to **6** (0.8 Å) is a major factor in the change from K^+ selectivity to Li^+ selectivity in these two ligands [2] [3]. The same holds for **1**–**3** which, having about the same cavity size as **5**, are K^+ selective; while **4**, whose cavity is comparable to that of **6**, is Li^+ selective.

Finally the *solvent effect* on the stability of the alkali cryptates in methanol as compared to water, provides further insight into the factors responsible for the changes observed on replacing O by N sites.

These changes are smaller in methanol than in water. Indeed, in methanol the stabilities of the alkali cryptates of **2** and **3** are high and closer to the stabilities of the cryptates of **5** than they are in water *(Table 1)*. This may be due to differences in solvation energies, since the solvation of O and N sites by methanol is expected to be less different than their hydration. It is a further indication that desolvation of ligands **1**–**4**, which have larger hydration energies than **5** and **6**, is an important factor in decreasing the stabilities of their cryptates in aqueous solution. The effect of the dielectric constant on the electrostatic interactions of the cation with a nitrogen *versus* an oxygen site, may also contribute.

The high stabilities in methanol of $[Li^+ \subset \mathbf{2}]$ and $[Li^+ \subset \mathbf{3}]$ as compared to $[Li^+ \subset \mathbf{5}]$, may result from the larger contribution of the N site polarisability to the complexation of the small Li^+ cation when solvation of N becomes weaker, *i.e.* in methanol as compared to water.

In the gas phase, Li^+ interacts much more strongly with NH_3 than with H_2O; the interaction of K^+ is slightly larger with NH_3 than with H_2O and slightly smaller

with $N(CH_3)_3$ than with $O(CH_3)_2$ [57]. Thus, one must stress that the effect of nitrogen binding sites on stabilities incorporates an important contribution from the solvent, especially in aqueous solution, on top of the intrinsic properties of the unsolvated species.

Stability and selectivity transition metal and heavy metal complexes. – The stability of the complexes formed by cryptands **1–4** with transition metal and heavy metal cations show characteristic features due to the macrobicyclic topology. That these complexes are of the cryptate type, *i.e.* inclusion complexes, in the case of Ag^+, Tl^+, Pb^{2+} leaves no doubt since such is the case for the cryptates of **5** with Ag^+ [41], Tl^+ and Pb^{2+} [42]. The same should hold for the group IIb cations Zn^{2+} and Cd^{2+}. As previously discussed [9] the cryptate structure of the Ni^{2+} and Cu^{2+} complexes is less sure but still likely. In fact, the lower stability of the Co^{2+}, Ni^{2+} and Cu^{2+} complexes with the ligands **1–3** having a large cavity is indication for the cryptate nature of their more stable complexes with **4**.

In the latter cases only when it is inside the cavity of **4** the transition metal cation can bind to the bridgehead nitrogen atoms as well as to those in the bridge.

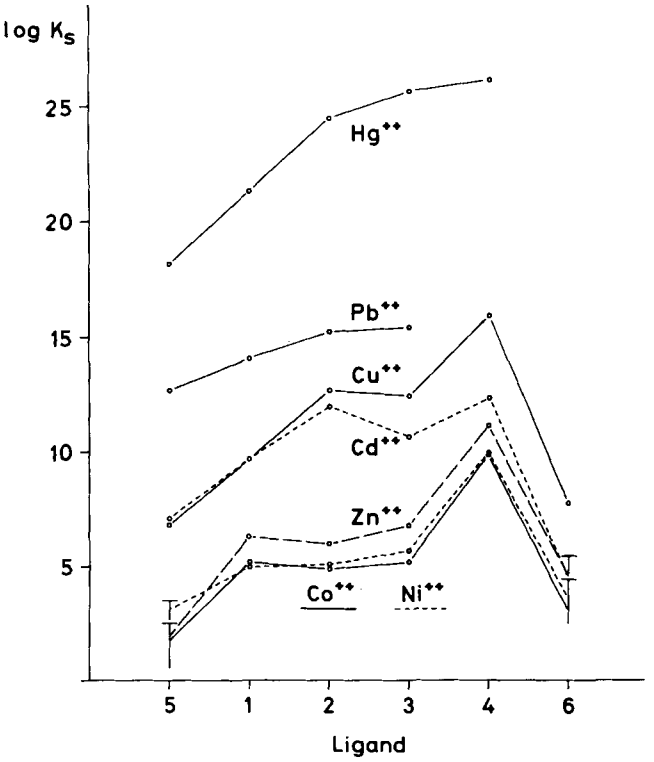


Fig. 3. *Stability constants (log K_s) of the cryptates formed by ligands* **1–6** *(abscissa) with the cations Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Pb^{2+} and Hg^{2+} as a function of ligand structure.* The results for ligands **1–4** are from the present work; the data for ligands **5** and **6** are added for comparison (see *Table 1*) (aqueous solutions at 25°)

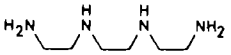
Furthermore, the crystal structure of a Co^{2+} cryptate has been described [43]. In the transition metal complexes of **3** the small cation may be located unsymmetrically more or less on the polyaza face of the macrobicyclic system with perhaps some interaction with suitable anions.

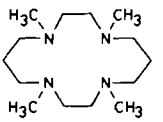
Two main factors are found to influence the stability of the complexes: number of nitrogen sites and cavity size *(Table 1; Fig. 3)*.

a) The stabilities increase with the number of nitrogen sites (except for Tl^+), the effects of the first or the first two sites introduced being the largest (compare the data for ligands **5**, **1**, **2**, **3** and for **4**, **6**; *Fig. 3*). The present cations bind more strongly to N than to O sites. The trend is opposite to that observed for the alkali and alkaline-earth cryptates. The crystal structure of $[Ag^+ \subset \mathbf{5}]$ gives a shortened $N \ldots Ag^+$ distance of 2.48 Å indicating covalent character in the bond [41]. However still shorter distances are observed for $Ag^+ \ldots N$ interactions (about 2.1–2.3 Å) showing that the cavity of **5** and therefore also that of **1**–**3** are too large for Ag^+. This may explain why the complex of Ag^+ with the smaller ligand **4** is so stable.

b) The small cations Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} form appreciably more stable complexes with ligand **4** which has a small cavity (radius of about 0.8 Å [2] [3]) than with ligands **1**–**3** whose cavities are too large (about 1.4 Å [2] [3]). Cavity size effects may explain or at least contribute to the higher stabilities of the Pb^{2+} complexes as compared to the Cd^{2+} complexes of **1**–**3**. A strong cavity size effect is also found for the Cd^{2+}/Zn^{2+} selectivity, which is much larger for ligands **1**–**3** than for **4** (see also below).

Comparing the data for ligands **2** and **5** resp. **4** and **6**, shows that either suitable nitrogen sites or suitable cavity size alone does not lead to high stabilities, but both factors must operate as in **4**.

7 

8 

The Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} complexes of Trien **7** [30] and of 4-Me-Cyclam **8** [44] have stabilities and selectivity patterns similar to those of ligand **4** but are much more stable than the complexes of ligands **1**–**3**. Thus, the macrobicyclic topology does not increase the stability but affects selectivities especially by decreasing the stabilities of the complexes when the cavity size is too large and not flexible enough to adapt to the usual coordination geometry of the cation. A distorted ligand shell is found in a Co^{2+} cryptate [43].

As expected the complexation *selectivity* ("soft" cations)/(alkali and alkaline-earth cations) increases when increasing the number of nitrogen sites in ligands **5**, **1**, **2**, **3** for cations of comparable radius. Two cases deserve special comment since they illustrate well how changing the ligand features allows monitoring their complexation properties.

Complexation selectivity: the thallium/potassium case. Isomorphous replacement is a very useful procedure for the study of biological systems. It consists in replacing a biological cation by another cation of similar size and coordination requirements, which may be used as a physical probe (for instance for NMR. spectros-

copy) while disturbing only negligibly the biological material [24]. K^+ is biologically of prime importance but has unappealing NMR. properties. In a number of K^+ dependent biological systems, K^+ has been replaced by Tl^+ which usually is bound more strongly and provides a very useful UV. and NMR. spectroscopic probe [24] [45]. On the other hand Tl^+ is highly toxic and its specific complexation for decorporation purposes is also of interest.

The results in *Table 1* indicate a way of designing both a stable and selective complex for Tl^+ with respect to the alkali cations of similar size, K^+ and Rb^+. Replacement of oxygen by nitrogen sites should decrease less the stability of the Tl^+ cryptates. Indeed the complexation selectivities are: $Tl^+/K^+ = 130$, 630, 250 and 8 for ligands **1**, **2**, **3** and **5** respectively. One also has $Tl^+/Rb^+ = 1600$, 2000 and 100 for **1**, **2** and **5** respectively. Thus, while retaining stability the introduction of two $N-CH_3$ sites into **5** as in **2** increases the Tl^+/K^+ selectivity of the cryptand by a factor of about 80. However the Tl^+ complex of EDTA although not more stable (log $K_s = 5.8$) than $[Tl^+ \subset \mathbf{2}]$, is about one hundred times more selective. The interaction of Tl^+ with nitrogen sites is reflected in the somewhat shortened $Tl^+ \ldots N$ distances (2.946 Å) found in the crystal structure of $[Tl^+ \subset \mathbf{5}]$ [42] as compared to the sum of the *van der Waals* plus ionic radii: $1.5 + 1.49 = 2.99$ Å.

Complexation selectivity: the cadmium/zinc, and cadmium/calcium cases. These are much more interesting cases than the previous ones. Indeed, Cd^{2+} is an extremely toxic cation and a very important target in *chelatotherapy.* [21–23] [46–49]. In cadmium poisoning Cd^{2+} interfers with zinc, copper, iron and calcium metabolism. For instance Cd^{2+} substitutes for Zn^{2+} in carboxypeptidase (and probably in other zinc metalloenzymes); the modified enzyme still binds the substrate peptide but does not hydrolyse them any more [46]. Among the ligands presently available none seems to be enough cadmium specific for efficient decorporation. The main drawback of the chelating agents (like EDTA, D-penicillamine, $HOCH_2-CH(SH)-CH_2SH$) presently in use against cadmium, lead and mercury contamination is their low selectivity [22] [46–50]. For instance, penicillamine also increases zinc excretion; EDTA does the same and in addition complexes calcium. Leaving aside the question of toxicity of the ligand itself, we may consider the problem of complexing Cd^{2+} selectively with respect to Zn^{2+} and if possible with respect to Ca^{2+}. Among the highest Cd^{2+}/Zn^{2+} selectivities known, is that of $(HOOC-CH_2)_2N-(CH_2-CH_2-O)_2-CH_2-CH_2-N(CH_2-COOH)_2$ (**9**), which displays the following stability constants: log $K_s = 16.73$ (Cd^{2+}); 14.5 (Zn^{2+}); 17.8 (Cu^{2+}); 10.7 (Ca^{2+}) [22] [51] [52].

In the case of the cryptates one may act on two structural parameters: cavity size and binding sites. The Cd^{2+} cation is much larger than Zn^{2+}, but of the same size as Ca^{2+}. On the other hand Cd^{2+} and Zn^{2+}, but not Ca^{2+}, prefer N over O binding sites. Thus, the cryptand desired should contain a cavity too large for efficient Zn^{2+} complexation but containing enough nitrogen sites for strongly favouring Cd^{2+} over Ca^{2+}, since Ca^{2+} is very abundant in biological materials (see also [3] [47]). Starting with **5** which has already a relatively low affinity for Ca^{2+} and a cavity much too large for Li^+, *i.e.* also for Zn^{2+}, introduction of nitrogen sites gives the ligands **1**–**3**. *Indeed, both* **2** resp. **3** *display very high selectivities* $Cd^{2+}/Zn^{2+} = 10^6$ *resp.* 10^4 *and* $Cd^{2+}/Ca^{2+} = 10^8$ *resp.* 10^9.

These Cd^{2+}/Zn^{2+} selectivities are much higher than those of any other known ligand, for instance it is only 170 for the chelating agent **9** [22]. The Cd^{2+}/Co^{2+}, Ni^{2+} and Cu^{2+}/Zn^{2+}, Co^{2+}, Ni^{2+} selectivities of **2** and **3** are also very high $>10^5$, 10^6. The $Cd^{2+}...N$ interaction may be somewhat "covalent", whereas $Ca^{2+}...N$ is not. This may explain the very high Cd^{2+}/Ca^{2+} ratio despite the fact that both cations have similar size.

Further detoxication selectivities: mercury, lead. Hg^{2+} and Pb^{2+} are also highly toxic cations [21] [24] [25] [49] [50]. Cryptands **2** and **3** have very high Pb^{2+}/Ca^{2+} (10^{11} resp. 10^{14}) and Hg^{2+}/Ca^{2+} (10^{20} resp. 10^{24}) selectivities, much higher than those of EDTA (10^7 resp. 10^{11}) or of ligand **9** (10^4 resp. 10^{13}) [22] [51] [52]. Ligand **10**, $HS-CH_2-CH_2-N(CH_2-COOH)_2$, displays log $K_s=4.88$ (Ca^{2+}); 16,72 (Cd^{2+}); 16.16 (Hg^{2+}); 17.03 (Pb^{2+}); 15.92 (Zn^{2+}) [53]; it has very high Pb^{2+}/Ca^{2+} and Hg^{2+}/Ca^{2+} ratios but is unable to distinguish efficiently Cd^{2+} and Zn^{2+}.

One may compare the selectivities found for the complexes of cations of similar size with cryptands **5**, **1**, **2**, **3**: Zn^{2+}/Mg^{2+}, Cd^{2+}/Ca^{2+}, Pb^{2+}/Sr^{2+}; it is seen that they increase with ionic size and with the number of nitrogen sites in the ligand.

Copper is also associated with various diseases and zinc has a protective effect against copper toxicity [21] [23]. Cryptands **2**, **3** and **4** have high Cu^{2+}/Zn^{2+} selectivities, comparable to that of D-penicillamine used for promoting copper removal from patients having *Wilson*'s disease [23].

In conclusion cryptands **2** and **3** present a unique palette of complexation selectivities of special interest in detoxication (decorporation or depollution), since they complex very strongly the toxic heavy metal cations Cd^{2+}, Hg^{2+}, Pb^{2+} and much less the biologically important ones Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}. It would certainly be worth studying further derivatives of this basic system, the [2.2.2] cryptand **5**, into which different binding sites are introduced. Modifications already performed along these lines are the introduction of sulfur sites [8] and the attachment of acetic acid and propionic acid chains [54]. The toxicities of the ligand themselves as well as the stabilities of the complexes in a "plasma" type medium [23] [47] [49] [50] will also have to be investigated in evaluating the potentialities of "*cryptatotherapy*". It is however clear that these cryptates open a new domain of selectivity.

Protonation of the complexes. Stability of protonated complexes. – In the parent cryptands **5**, **6**, where nitrogen sites are only present at the bridgehead, protonation of the complexes is found to be negligible [2]. Since the proton would occupy a position inside the cavity, remove a binding and introduce a positive charge, the resulting protonated complex is unstable for both steric and electrostatic reasons. We may admit that in the present ligands bridgehead protonations of the complexes is also negligible. However, protonation of the nitrogen sites contained in the bridges may be possible similarly to the protonation of complexes with other polyamines. In this case the proton is not penetrating inside the cavity but still removes a binding site and introduces a positive charge. Thus, especially with small cations which may form stable complexes without using up all available

nitrogen sites (like for instance $[Zn^{2+} \subset \mathbf{3}]$[5]), protonated complexes may still have appreciable stability.

Analysis of the titration curves showed that monoprotonation and stable monoprotonated complexes are found for ligands **1**–**4** in conditions where they cannot be observed for the cryptates of **5** and **6**. Higher protonation order could not be detected in the conditions used. Thus only monoprotonation constants of the complexes, log K_1^M, and stability constants of the monoprotonated complexes, log K_s^+, could be determined. They are listed in *Table 2*. There are still a number of complexes (especially the alkali cryptates) for which even the monoprotonated species is present in too small an amount for showing up in the titration curves. In other cases hydrolysis of the free cation hinders the measurement of the titration curve and the determination of K_1^M and of K_s^+ (Ni^{2+}, Zn^{2+}, with **1** and **2**). A further complication is that monoprotonation may occur at different positions in the ligand and in the complex.

K_1^M measures the basicity of the complex and according to their definitions log K_1^M (eq. (6)) and pK_m (eq. (4)) are directly comparable *(Tables 1* and *2)*.

The following observations may be made:

a) The basicity of the complex is lower than that of the free ligand (log $K_1^M < pK_1$), since K_1^M corresponds to protonation of a charged species;

b) The basicity of a complex is generally lower the more stable the cryptate is, *i.e.* when the nitrogen sites are more strongly involved in binding the cation. The same behaviour is found for Trien **7** *(Table 2);*

c) As the oxygen sites of **5** are gradually replaced by nitrogen sites, protonated complexes become more important. Protonated complexes are only detected for complexes having log $K_s > 9$, > 4 and > 3.5 in the case of ligands **1**, **2** and **3** respectively;

Table 2. *Protonation constants log* K_1^M *of the complexes and stability constants log* K_s^+ *of the protonated complexes*[a])

Ligand	log K_1^M (above) and log K_s^+ (below) for the cations									
	Ag^+	Tl^+	Ca^{2+}	Sr^{2+}	Ba^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	Pb^{2+}
1	5.4	–	–	–	4.5	5.4	–	4.7	5.6	2.7
	5.6	–	–	–	2.9	4.5	–	3.8	16.7	6.2
2	5.3	6.4	7.3	6.5	6.0	3.8	–	3.8	3.7	2.7
	6.8	1.9	1.6	2.6	2.7	6.5	–	5.8	18.6	8.0
3	6.4	7.5	–	–	7.2	8.3	6.6	5.0	4.2	3.4
	9.7	1.9	–	–	1.2	11.1	3.7	6.0	20.6	9.2
4	4.8	–	–	–	–	–	–	–	3.9	–
	6.3	–	–	–	–	–	–	–	19.3	–
7[b])	8.0	–	–	–	–	3.5	5.1	6.3	5.6	–
[30]	5.8	–	–	–	–	14.0	7.3	7.1	20.9	–
	(7.7)	–	–	–	–	(20.4)	(12.1)	(10.7)	(25.2)	–

[a]) Aqueous solutions at 25°. See experimental part.

[b]) Values in parentheses are the stability constants log K_s from [30].

[5]) In such cases protonation at the bridgehead may also occur.

d) The stability constants with the protonated ligands are lower than with the unprotonated ones ($\log K_s^+ < \log K_s$). The decrease in stability on protonation tends to be smaller for the same cation when the number of N sites of the ligand increases;

e) With the same ligand, the stability sequences are similar for the protonated and unprotonated complexes.

Decomplexation kinetics. – No detailed kinetic study has been performed for the moment with the present systems but some qualitative observations have been made. The dissociation equilibria are established rapidly when the complexes are not too stable but may become slow for the very stable ones. Thus in titration experiments, time dependent pH changes may occur, which may be used for studying the decomplexation kinetics. Dissociation of the complex can follow two mechanisms: rate determining exit of the cation followed by fast protonation of the ligand [33] [55] or acid catalysed decomposition *via* a protonated complex. The latter is found to be of importance for certain cryptates of **5** and **6** at low pH [56]. Acid catalysed dissociation is more likely to occur for the cryptates of ligands **1**–**3** which contain more nitrogen sites than **5** and may be protonated on a bridge nitrogen more easily than on the less accessible bridgehead. Indeed, in the course of titration experiments the equilibrium pH is established very slowly with [$Ba^{2+} \subset$ **5**] [33], but it is reached immediately with [$Ba^{2+} \subset$ **1**]. Thus, whereas dissociation of the former complex at pH 3 is mainly monomolecular and very slow ($\sim 10^{-5}$ s^{-1}) [33] [55] [56], [$Ba^{2+} \subset$ **1**] must dissociate much faster, probably *via* a (bridge) protonated complex *(Table 2)*.

In back titration experiments with protonated ligand **4** in the presence of metal salts, about one week or more was required for reaching equilibrium with all divalent cations studied except Mg^{2+}. Thus, complex formation in these conditions was very slow. More details about the uncatalysed or acid catalysed cation exchange rates may be obtained using temperature dependent NMR. measurements or other physical methods [55] [56].

Experimental Part

Materials. – The preparation of the ligands has been described previously [9]. The metal salts were the chlorides in all cases except for silver, thallium, cadmium and lead where the nitrates were used. In methanol solution the more soluble iodides were employed. All salts were dried before use.

Apparatus. – The apparatus employed in the present study (pH-meter, electrodes) was the same as previously described [2]. A *Tacussel* TS 60N pH-meter was also used together with a *Tacussel* calomel reference electrode. All measurements were performed in a 10 ml glass cell thermostated at $25 \pm 0.1°$.

pH-Metric Method. – *Procedures.* The measurements were performed by titration with acid (0.1N HCl) or generally back-titration with base (0.1N NMe_4OH, so as to avoid complexation of the cation) of a previously acidified solution. Solutions: 5 ml; 0.005–0.01M ligands; 0.01–0.1M salt; variable concentration of supporting electrolyte (NMe_4Cl or NMe_4NO_3) in order to maintain the ionic strength at 0.1 ± 0.005. In the generally used back-titration procedure the ligand is first dissolved in 0.01N HCl before addition of the salt.

The analysis of the titration curves is performed using the programs mentioned in the results section above. In all cases for which protonated species have been studied (listed in *Table 2*), at least 15% of the complex is protonated in part of the pH domain covered in the titration. When the complexes are not stable enough the required pH may be too low so that they are dissociated and the ligand is protonated. The presence of a protonated complex is detected by comparing the constancy of K_s calculated from different points of the titration curve with and without including a protonated complex.

The absence of significant contribution of complexes of 2:1 stoichiometry was checked by comparing computations with and without inclusion of the corresponding equilibrium equations in the course of the analysis of the titration curves obtained for $[Cu^{2+} \subset \mathbf{3}]$ and $[Ag^{+} \subset \mathbf{3}]$.

In cases of slow kinetics (see above), the measurements were performed on solutions containing different amounts of titrant which were allowed to equilibrate at RT. until the pH remained constant (up to several weeks).

Reproducibility, errors. The precision of the results has been checked: by calculating the mean deviation between K_s values corresponding to different points of a titration curve; by calculating the effects on K_s of various possible experimental errors (concentrations, pK's of the ligands *etc.*); by performing measurements on solutions containing different proportions of ligand and cation. The following limits represent the reproducibility for separate titrations of the same system when log $K_s > 2$:

a) when no protonated complex is present: $\Delta \log K_s = \pm 0.10$;

b) in the presence of protonated complex: $\Delta \log K_s = \pm 0.15$, $\Delta \log K_1^M = \pm 0.20$, $\Delta \log K_s^+ = \pm 0.30$. For stabilities log $K_s < 2$ the error is much larger (± 0.25 or more). The standard deviation for the various log K values calculated at each point along a given titration curve is < 0.05, except for complexes with log $K_s < 2$ and complexes with slow kinetics where it is ~ 0.03.

Method using cation selective electrodes. – *Procedure.* The reference electrode was fitted with a 0.1M NMe_4Br (or NMe_4NO_3 in the presence of Ag^+ or Tl^+) bridge in water or methanol depending on the solution to be measured. The electrodes used were: *Philips* G15 Na (for Na^+ or Ag^+), and *Philips* G15 K (for the other monovalent cations; sensitivity: $K^+ \sim Tl^+ > Rb^+ > Cs^+ \gtrapprox Li^+$). The solutions (5 ml) contained: 0.02M ligand, 0.01M salt, 0.05M supporting electrolyte (NMe_4Br or NMe_4NO_3) in water. No supporting electrolyte is used in methanol. The methanol used contained $< 0.1\%$ water. The electrodes are more stable in methanol than in water.

Reproducibility, errors. The sensitivity limit of the electrodes confine the measurements to the domain $1 < \log K_s < 5$-6 (see also [3]). Δ log $K_s \sim \pm 0.2$ (methanol) and ± 0.3 (water) in the optimal range. Comparison of log K_s values determined by the pH-metric and the cation-electrode methods gives agreement within ± 0.3.

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