114. Enthalpy and Entropy of Formation of Alkali and Alkaline-Earth Macrobicyclic Cryptate Complexes [1]

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Summary. The enthalpies and entropies of complexation of alkali and alkaline-earth metal cations by several macrobicyclic ligands have been obtained from calorimetric measurements and from the previously determined stability constants [2]. Both enthalpy and entropy changes play an important role in the stability and selectivity of the complexes. Particularly noteworthy are the *large enthalpies* and the *negative entropies* of complexation obtained for the alkali cation complexes (Na^+, K^+, Rb^+ and Cs^+ cryptates). The Sr^{2+} and Ba^{2+} as well as [$Li^+ \subset$ 2.1.1]¹) and [$Na^+ \subset$ 2.2.1] cryptates are of the enthalpy dominant type with also a favourable entropy change. The Ca^{2+} and [$Li^+ \subset$ 2.2.1] cryptates are entirely entropy stabilized with about zero heat of reaction. The high stability of the macrobicyclic complexes as compared to the macromonocyclic ones, the *cryptate effect*, is of *enthalpic origin*. The enthalpies of complexation display selectivity peaks, as do the stabilities, whereas the entropy changes do not. The high M^{2+}/M^+ selectivities found in terms of free energy, may be reversed when enthalpy is considered in view of the very different role played by the entropy term for M^{2+} and M^+ cations. The enthalpies and entropies of ligation show that whereas the cryptate anions are similar in terms of entropy irrespective of which cation is included, the ligands, despite being more rigid than the hydration shell, are nevertheless able to adjust to some extent to the cation. This conclusion agrees with published X-rays data. The origin of the enthalpies and entropies of complexation is discussed in terms of structural features of the ligands and of solvation effects.

Introduction. – Although alkali and alkaline-earth metal cations play a role of foremost importance both in chemistry and in biology, their coordination chemistry has mainly been developing in recent years with the advent of natural [3] or synthetic [4–6] macrocyclic and synthetic macropolycyclic [5–9] ligands. These ligands form inclusion complexes in which the metal cation is contained in the intramolecular cavity. The stabilities and selectivities [2] of such cryptates [8] complexes have been studied for many ligand/cation pairs and have been related to ligand structural features [1–6].

A deeper understanding of the thermodynamics of cryptate formation may be provided by the analysis of the free energy of complexation, ΔG, into enthalpy, ΔH, and entropy, ΔS, of complexation. Such data have become recently available for a number of natural macrocyclic antibiotic ligands [10–15], for two isomers of the macrocyclic polyether dicyclohexl-18-crown-6 [16–17] as well as for a number of common solvents including the linear polyethers of the 'glyme' type [17].

We present here a calorimetric study [18] of the formation by cryptands **1–4** of the especially stable alkali and alkaline-earth macrobicyclic 1:1 cryptates whose

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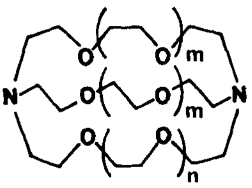
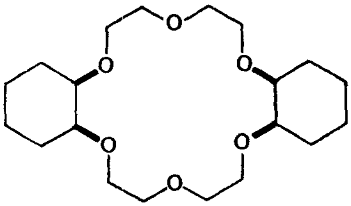
¹) For use of the symbols see [2].

structures [8] and stabilities [2] have been discussed previously. After completion of this work a calorimetric study of cation complexation by ligand **3** has been published. The data reported are in agreement with our results [19][2].



1 $m = 0; n = 1$ [2.1.1]
2 $m = 1; n = 0$ [2.2.1]
3 $m = n = 1$ [2.2.2]
4 $m = 1; n = 2$ (3.2.2]



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1. *Heats of complexation.* The formation of the cryptates in water is represented by equation (1).

$$(L)_{aq} + (M^{n+}, m\,H_2O) \overset{K_s}{\rightleftharpoons} [M^{n+} \subset L]_{aq'} + m\,H_2O \qquad (1)$$

where K_s is the concentration stability constant. In addition to (1), four acid-base equilibria are present. They correspond to the mono- and biprotonation of the free ligand and of the complex (see [2] for more details).

In order to avoid complications which may arise from these protonation equilibria, the measurements have been performed in basic solutions, at a pH higher than the pK_a of the ligands by more than one unit (see exper. part). The determinations have been restricted to those ligand/cation pairs which form stable enough cryptates in water so that complexation of the ligand be almost complete in the present conditions. The necessary corrections have been made when this was not the case.

2. *Enthalpies and entropies of cryptation.* The enthalpies of cryptation ΔH_c have been calculated from the experimental heats of reaction in water solution at fixed ionic strength. The stability constants in similar experimental conditions have been determined previously [2] and lead to the free energies of complexation ΔG_c:

$$\Delta G_c = -4.57\ T \log K_s \qquad (2)$$

The entropies of complexation are:

$$\Delta S_c = (\Delta H_c - \Delta G_c)/T \qquad (3)$$

If one adds the experimental complexation parameters to the corresponding hydration data one obtains the enthalpies and entropies of 'ligation' ΔH_l and ΔS_l, *i.e.*

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[2] A recent study [20] lists thermodynamic parameters for the calcium cryptates of ligands **1–3**, obtained from cation exchange kinetics. The values reported for **1** and **2** do not agree with the present calorimetric data.

of transfer of the cation from the gas phase into the hydrated ligand with formation of the differently hydrated cryptate (equation (4)).

$$(M^{n+})_{gas} + (L)_{aq} \rightarrow [M^{n+} \subset L]_{aq'} \tag{4}$$

$$\Delta H_l = \Delta H_c + \Delta H_h \tag{5}$$

$$\Delta S_l = \Delta S_c + \Delta S_h \tag{6}$$

These parameters provide data for comparing the ligand coordination shell to the hydration shell.

Table 1 lists the thermodynamic parameters ΔG_c, ΔH_c, ΔS_c, ΔH_l, ΔS_l for the alkaline and alkaline-earth cryptates of ligands **1–4**. Data for the crown ether **5** [16] as well as the thermodynamic functions for cation hydration [21] have been added for comparison purposes. Fig. 1 and 2 provide a graphical representation of the variation of the complexation parameters with cation for the ligands [2.2.1] and [2.2.2]. The data listed are valid for the experimental conditions used in this work. Although the values of the parameters will depend on ionic strength, supporting electrolyte *etc.*, the interpretation of the data given below should not be affected since all data have been obtained in similar conditions[3]).

3. *Cryptate stability. Enthalpy and entropy contributions.* It has already been pointed out that the most stable alkali and alkaline-earth cation macrocyclic complexes are found among the macrobicyclic cryptates [2]. The results in Table 1 and in the figures show that these large values of the free energies of complexation may be to various extents of either enthalpic or entropic origin.

Electrostatic complexes between 'hard' (A type) cations and charged ligands are generally entropy stabilized ($T\Delta S$ dominant and positive) [16] [22], whereas the formation of complexes of 'soft' (B type) cations containing bonds with more or less covalent character is generally controlled by the decrease in enthalpy (ΔH dominant and negative) [16] [22].

The cryptates of **1–4** should belong mainly to the enthalpic type since the ligands are uncharged. However, alkali and alkaline-earth cations being of the A-type, entropy dominant behaviour may also be found.

There are altogether four possible combinations of the thermodynamic parameters leading to stable complexes ($\Delta G < 0$): a) $\Delta H < 0$ and dominant, $T\Delta S > 0$; b) $\Delta H < 0$ and dominant, $T\Delta S < 0$; c) $T\Delta S > 0$ and dominant, $\Delta H < 0$; d) $T\Delta S > 0$ and dominant, $\Delta H > 0$.

Cases a) and b) are enthalpy stabilized complexes, c) and d) are entropy stabilized complexes; a) and c) correspond to complex stabilization by both enthalpy and entropy whereas b) and d) correspond to unfavourable changes in entropy and in enthalpy respectively. The complexation features depend on the enthalpies and entropies of cation hydration which are higher for smaller and more highly charged cations (see Table 1). Thus all four types of complexes a)–d) are found among the cryptates studied here depending on ligand and cation.

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[3]) The results reported here may differ from preliminary data previously presented at a meeting [18] and listed in a recent publication [5] (see exper. part).

Table 1. *Free energy ΔG, Enthalpy ΔH, Entropy ΔS of cation hydration and complexation by ligands* **1–5**[a])

Ligand	Thermodynamic Parameter[b])	Cation							
		Li^+	Na^+	K^+	Rb^+	Cs^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
H_2O	$-\Delta G_h$	122.1	98.2	80.6	75.5	67.8	380.8	345.9	315.1
	$-\Delta H_h$	132.1	106.0	85.8	79.8	72.0	398.8	363.5	329.5
	$-\Delta S_h$	33	26	17	14	14	60	59[b])	48
1 [2.1.1]	$-\Delta G_c$	7.5	4.5	–	–	–	3.4	–	–
	$-\Delta H_c$	5.1	5.4	–	–	–	0.1[d])	–	–
	$T\Delta S_c$	2.4	−0.9	–	–	–	3.3	–	–
	$+\Delta S_c$	8	−3	–	–	–	11.1	–	–
	$-\Delta H_l$	137.2	111.4	–	–	–	398.9	–	–
	$-\Delta S_l$	25	29	–	–	–	48.9	–	–
2 [2.2.1]	$-\Delta G_c$	3.4	7.2	5.4	3.45	–	9.5	10.0	8.6
	$-\Delta H_c$	0.0[d])	5.35	6.8	5.4	–	2.9	6.1	6.3
	$T\Delta S_c$	3.4	1.85	−1.4	−1.95	–	6.6	3.9	2.3
	$+\Delta S_c$	11.4	6.2	−4.7	−6.5	–	22	13.1	7.7
	$-\Delta H_l$	132	111.3	92.6	85.2	–	401.7	370	336
	$-\Delta S_l$	21.6	19.8	21.7	20.5	–	38	46	40
3 [2.2.2]	$-\Delta G_c$	–	5.3	7.2	5.9	–	6	10.9	12.9
	$-\Delta H_c$	–	7.4	11.4	11.8	–	0.2	10.3	14.1
		–	7.4[c])	11.0[c])	11.8[c])	–	0.2[c])	10.6[c])	14.3[c])
	$T\Delta S_c$	–	−2.1	−4.2	−5.9	–	5.8	0.6	−1.2
	$+\Delta S_c$	–	−7	−14.1	−19.8	–	19.5	2	−4.0
	$-\Delta H_l$	–	113	97	92	–	399	374	343.6
	$-\Delta S_l$	–	33	31	34	–	40.5	57	52

[a-d]) see next page.

Table 1. (continued)

Ligand	Thermodynamic Parameter[b]	Cation							
		Li^+	Na^+	K^+	Rb^+	Cs^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
3 [2.2.2][e]	$-\Delta G_c$	–	9.82	13.27	11.44	4.82	10.35	15.66	16.3 ± 0.9
	$-\Delta H_c$	–	10.6	19.0	19.6	11.9	6.6	14.1	20.1
	$T\Delta S_c$	–	−0.78	−5.73	−8.16	−7.08	+3.75	+1.56	−3.8
	$+\Delta S_c$	–	−2.6	−19.2	−27.4	−23.7	+12.6	+5.23	−12.75
4 [3.2.2]	$-\Delta G_c$	–	–	3.0	2.8	2.45	2.7	4.6	8.2
	$-\Delta H_c$	–	–	3[d]	4.2[d]	5.4	−0.16[d]	3.3 ± 0.3	6.2 ± 0.3
	$T\Delta S_c$	–	–	0	−1.4	−3	2.86	1.3 ± 0.3	2 ± 0.3
	$+\Delta S_c$	–	–	0	−4.7	−9.9	9.6	4.4 ± 1	6.7 ± 1
	$-\Delta H_1$	–	–	88.8	84	77.4	398.6	367	336
	$-\Delta S_1$	–	–	17	18.7	24	50.4	54.6 ± 1	41 ± 1
5 [16]	$-\Delta G_c$	–	1.65	2.75	2.07	1.31	–	4.41	4.86
	$-\Delta H_c$	–	−0.16	3.88	3.33	2.41	–	3.68	4.92
	$T\Delta S_c$	–	+1.81	−1.13	−1.26	−1.10	–	0.73	−0.006
	$+\Delta S_c$	–	+6.1	−3.8	−4.2	−3.7	–	2.5	−0.2
	$-\Delta H_1$	–	106	89.5	83	74.5	–	367	334.5
	$-\Delta S_1$	–	20	21	18	18	–	56.5	48.2

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[a] ΔG, ΔH in kcal/mol; ΔS in entropy units e.u. Precision $\Delta G_c = \pm 0.3$ kcal/mol; ΔH_c: ±0.2 kcal/mol; ΔS_c: ±2 e.u. All values are for basic aqueous solution at 25.0 ± 0.1° (see experimental part).

[b] ΔH_h and ΔS_h are the enthalpies and entropies of hydration for transfer of 1 mol of cations from the gas at 1 atm. to a 1 M solution in water at 2.5°. The ligation parameters ΔH_1 and ΔS_1 are defined in the text (equations (4)–(6)). The ΔS_h value for Sr^{2+} is probably too large; a value of about −53 e.u. would improve the coherence between the ΔS_1 values.

[c] See [19].

[d] These values include corrections for incomplete complexation and are less accurate (±10%).

[e] Measurements in methanol/water 95:5.

The Sr^{2+} and Ba^{2+} cryptates (except [$Ba^{2+} \subset$ 2.2.2]) as well as [$Na^+ \subset$ 2.2.1] belong to case a). The enthalpic stabilities of the Na^+, K^+, Rb^+ and Cs^+ cryptates are in general several kcal higher than their free energy stabilities because of negative entropy changes (type b)) (see below). The Ca^{2+} complexes are of type c). The stabilities of the [$Li^+ \subset$ 2.2.1], [$Ca^{2+} \subset$ 2.1.1], [$Ca^{2+} \subset$ 2.2.2] and [$Ca^{2+} \subset$ 3.2.2]cryptates are entirely of entropic origin (case c)) but none is appreciably endothermic ($\Delta H > O$) (case d)). Positive entropies of complexation are found for the small Li^+ cation and for the alkaline-earth cations. These cations have large hydration entropies (Table 1), so that release of the hydration shell on complexation gives a positive entropy change and stabilizes the complexes.

The crown ether **5** displays the same general behaviour as the cryptates (Table 1) [16] except that the ΔH and ΔS changes are smaller. The thermodynamic parameters available for the complexes of the macrocyclic antibiotics have been determined in non aqueous solution (in methanol or ethanol) [10–15]. The results are thus not directly comparable to the present ones. However the trends observed are similar; the complexation enthalpies $-\Delta H_c$ are generally much larger than $-\Delta G_c$ and the ΔS_c are less negative for Na^+ than for K^+ complexes.

The *enthalpies of complexation* contain: 1) the variations in nature and energy of the bonds between the cation and either the ligand or the solvent molecules in the first solvation shell; 2) the change in interaction with the solvent molecules outside the complex as compared to those outside the first solvation shell (*Born* term; see also below); 3) the change in inter-binding site repulsions (see also below); 4) the effect of ligand solvation; 5) the steric deformations of the ligand by the cation.

Since dimethyl ether has a smaller dipole moment (1.30 D) than water (1.82 D) and the ligand shell is thicker [6] than the first hydration shell, both terms 1) and 2) should destabilize the complexes with respect to the solvated state. The measured favourable enthalpies of complexation must thus arise in a large part from factors 3) and 4). The latter has been considered to play an important role in the stability of macrocyclic complexes [23]: the macrocyclic structures are less solvated than the non-cyclic ligands and thus complexation requires less solvation bond breaking. This effect certainly contributes also to the cryptate stabilities since macrobicyclic ligands are even less accessible to solvation than macrocyclic ones.

Effect 3) is however also of importance. Repulsions between the solvent molecules forming the solvation shell destabilize the solvated state and this destabilization increases more and more for each new solvent molecule brought into the shell. As we have already pointed out [6], the linkage of all binding sites in a suitable arrangement in a single polydentate ligand first supresses this destabilization effect (since the binding sites are held in place and cannot be pushed out of the shell by the repulsions as is the case for monodentate ligands) and second, allows the introduction of more binding sites than the balance between cation-site attraction and site-site repulsion permits in the solvated state. Thus, the destabilizing effect of inter-binding site (or intrasolvation shell) repulsions has been built into the ligand in the course of the synthesis so that it cannot affect anymore the stability of the complexes.

This repulsion effect, together with progressive bonding saturation, is illustrated by the smaller and smaller gain in binding energy per water molecule for each new molecule introduced in the course of building up the $M^+(H_2O)_n$ species in the gas phase [24]. For $M^+ = K^+$ the gain in stability ($-\Delta H$) is respectively 17.9, 16.1, 13.2, 11.8, 10.7 and 10.0 kcal/mol on the successive introduction of six water molecules [24]. *Ab initio* computations have also shown that the bringing together of four NH_3 molecules from infinitive distance to their arrangement in the $[Li(NH_3)_4]^+$ complex leads to a repulsion of about 20 kcal/mol [25].

Effect 5) will play a role for those cations which are too small or too large for the intramolecular cavity. The zero enthalpies of complexation observed for $[Li^+ \subset 2.2.1]$, $[Ca^{2+} \subset 2.2.2]$ and $[Ca^{2+} \subset 3.2.2]$ may arise from the too small size of the cation. Ca^{2+} is too large for [2.1.1] and gives an appreciably exothermic reaction only with the ligand [2.2.1] into whose cavity it fist best.

The *entropies of complexation* are much less positive than one might expect on complete release of the hydration shell; in fact even marked entropy losses are observed in a number of cases. The entropy changes on complexation incorporate the hydration entropies of the metal cation and of the ligand, the changes in ligand internal entropy (due to orientation, rigidification, conformational changes), the changes in total number of particles and in translational entropy.

In addition, an appreciable negative entropy change on complexation is also expected to arise from a rearrangement of water structure on cryptate formation. Indeed, complexation of a metal cation by a cryptand transforms a small inorganic cation into a large hydrophobic organic cation. This should lead to a marked loss of entropy due to solvation of 'the second kind' [26], *i.e.* the formation of a water structure around the organic cation. Taking NBu_4^+ as a model for a hydrophobic cryptate cation, an estimate of the entropy changes for the process $M^+ \rightarrow NBu_4^+$ may be given by the difference between the respective entropies of transfer of M^+ and NBu_4^+ ions to water [27]. Taking the values listed in Table 5 of ref. [27] one obtains entropy losses of about -10, -17, -24, -27 and -28 e.u. respectively for $M^+ =$ Li^+, Na^+, K^+, Rb^+ and Cs^+. The same effect should also play a role in the alkaline-earth cryptates.

The above factors taken together provide a rationalization for the markedly negative entropy changes displayed by the K^+, Rb^+ and Cs^+ complexes of [2.2.2] and [3.2.2]. Smaller changes in ligand internal entropy may also contribute but are difficult to estimate.

4. *The cryptate effect.* Of much interest is also the question of the thermodynamic origin of the cryptate effect [2], *i.e.* of the very large increase in complex stability of the macrobicyclic complexes compared to the macromonocyclic ones. Comparing the K^+ complexes of [2.2.2] and of the macrocyclic ligand **5**, it is seen that the cryptate effect is entirely of *enthalpic origin*. The entropic term even disfavours the *m*acrobicyclic complex with respect to the monocyclic one. A closer comparison is provided by the thermodynamics of complexation displayed by the monocyclic analog of [2.2.2], $HN(CH_2CH_2OCH_2CH_2OCH_2CH_2)_2NH$ reported by *Anderegg* [19]; the results agree with our present conclusion about the enthalpic nature of the cryptate effect. The cryptate nature of the complexes, *i.e.* the complete tridimensional inclusion of the metal cation into an organic molecule, accounts for both these enthalpic and entropic changes with respect to the macrocyclic effect [23] [28]. Indeed, according to the discussion above the enthalpic terms 3) and 4), as well as the entropy terms considered should lead to more negative ΔH_c and ΔS_c for the macrobicyclic complex than

for the macrocyclic one. The enthalpic stabilization of certain macrocyclic transition metal complexes with respect to complexes with open chain ligands (the macrocyclic effect) has also been found to be of enthalpic nature although other cyclic ligands yield entropy stabilized complexes [29].

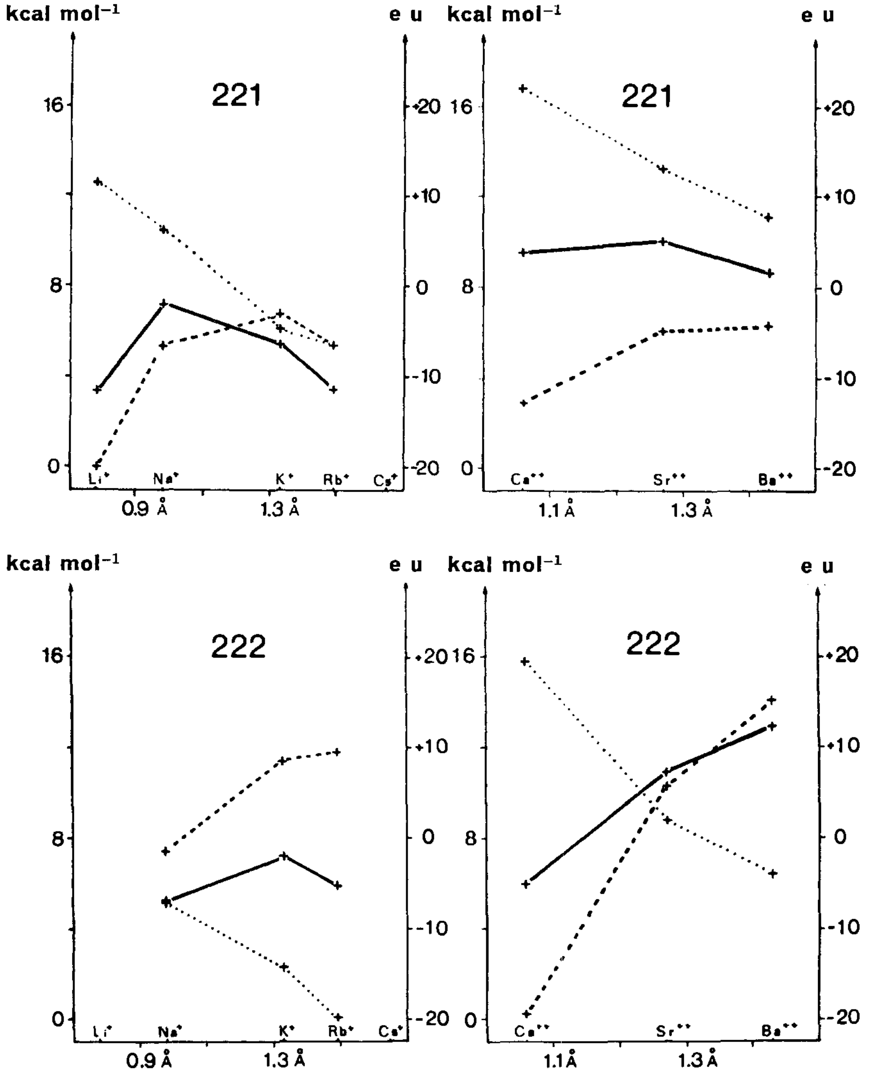

Fig. 1. *Free energies* $-\Delta G^\circ_c$ (solid line), *enthalpies* $-\Delta H^\circ_c$ (dashed line) *and entropies* $+\Delta S^\circ_c$ (dotted line) *of cryptate formation by alkali and alkaline-earth cations with ligands* [*2.2.1*] *and* [*2.2.2*] (in water at 25°; see Table 1 and experimental part).

5. *Cryptate selectivities. Enthalpy and entropy contributions.* The enthalpies of complexation of the cryptates present selectivity peaks and show grossly the same trends as their free energies, although they do not run parallel (Table 1, Fig. 1). By

contrast, the entropies of complexation always present the same sequence, becoming regularly less positive or more negative as the cation becomes larger or has lower charge, in agreement with the larger entropy gain one may expect on complexation of small and highly charged cations which display large entropies of hydration. Thus, the *selectivity peaks* observed in the stability constants of the cryptates are intrinsically of *enthalpic origin*. The entropy term may nevertheless lead to marked differences between enthalpy and free energy selectivities, since it favours the complexes of small and bivalent cations over those of large and monovalent ones.

For cations of the same charge, the selectivity M^+(larger)/M^+(smaller) is higher in terms of enthalpy than in terms of free energy. Whereas [2.1.1] and [2.2.1] have a high free energy selectivity for Li^+ and Na^+ respectively, the [$Na^+ \subset$ 2.1.1] and [$Na^+ \subset$ 2.2.1] cryptates display about the same ΔH_c. The preference of [2.2.1] for Na^+ over K^+ ($\Delta\Delta G_c = 1.8$ kcal/mol) is reversed in terms of enthalpy ($\Delta\Delta H_c = -1.4$ kcal/mol); the preference of [2.2.2] for K^+ over Na^+ ($\Delta\Delta G_c = 1.9$ kcal/mol) is much higher in terms of enthalpy ($\Delta\Delta H_c = 4$ kcal/mol) whereas the reverse holds for K^+ versus Rb^+ ($\Delta\Delta G_c = 1.3$ kcal/mol; $\Delta\Delta H_c \sim -0.5$ kcal/mol). The remarkable $Ca^{2+} \ll Sr^{2+} < Ba^{2+}$ complexation selectivity displayed by ligand [2.2.2] [2] is even much larger in terms of enthalpy alone.

Thus, the cavity-radius/cation-radius effect used as an empirical criterion for discussing the selectivity of complexation [2] incorporates both enthalpic and entropic effects and is not just a measure of steric fit. Of course the cavity radii [2] [6] determined on molecular models may be quite inaccurate and the problem is how they may be used to predict complex stabilities. It seems best to consider that a good fit of cation to cavity is merely an empirical and operational criterion for preferred complexation which contains more than just steric effects.

The M^{2+}/M^+ *selectivity* is completely different in terms of free energy as compared to enthalpy alone. Most striking is the fact that whereas divalent cryptates are much more stable than monovalent ones (with cations of similar radii), their enthalpy of complexation is comparable or smaller, so that the enthalpic M^{2+}/M^+ selectivities may be reversed.

6. *Transfer and entropy of ligation.* The free energies of transfer of a cation from gas phase into the ligand in aqueous solution, $\Delta G_l = \Delta G_c + \Delta G_h$, follow the same sequence as the free energies of hydration and do not yield much information about the difference between hydration and ligation of the cations. Comparing separately the enthalpy and entropy terms is more informative.

If the ligands were perfectly rigid and defining a cavity of constant size, all complexes formed with cations of the same charge and of size smaller or equal to the cavity size should show very similar properties. Indeed once the cations are embedded in the ligand they loose their specific properties and give a very similar cation complex irrespective of which cation is included. Consequently one would expect the ΔH_l and ΔS_l values to be similar for all metal cations, except when the cation is too large and causes severe steric distortions.

The data in the Table 1 indeed show that the entropy change ΔS_l is much more constant for a given ligand than ΔS_c or ΔS_h. The average values are about -27, -20, -32 and -20 e.u. for the [$M^+ \subset$ 2.1.1], [$M^+ \subset$ 2.2.1], [$M^+ \subset$ 2.2.2] and [$M^+ \subset$ 3.2.2] cryptates respectively. A similar situation holds for the Sr^{2+} and Ba^{2+}

cryptates (less so for Ca^{2+}) (Table 1). Thus, in terms of entropy the cryptates of same charge are indeed similar. The strongly negative ΔS_l observed despite the fact that ligation is formally a two particle reaction, may be rationalized by the entropy contributions discussed above, especially by the negative hydration entropy expected for a large hydrophobic cation. The quite different ΔS_l values found for Na^+ and K^+ complexes of the macrotetrolide nonactin [13] might arise from appreciable differences in internal entropy of this larger and more flexible ligand.

The situation is quite different for the ligation enthalpy ΔH_l (Table 1). The enthalpy changes for transfer of a cation from gas phase into the ligand in aqueous solution show the same trends as the hydration enthalpies, *i.e.* the ΔH_l values decrease from small to large cations although not by exactly the same increments from cation to cation, of course. Consequently, despite their limited flexibility with respect to open chain or macrocyclic ligands, or to the hydration shell, the macrobicyclic ligands are not rigid enough to resist deformation and may adjust to some extent to cation size by contraction or expansion of the cavity. Indeed this is not too surprising, if one considers the large interaction energies which come into play (Table 1).

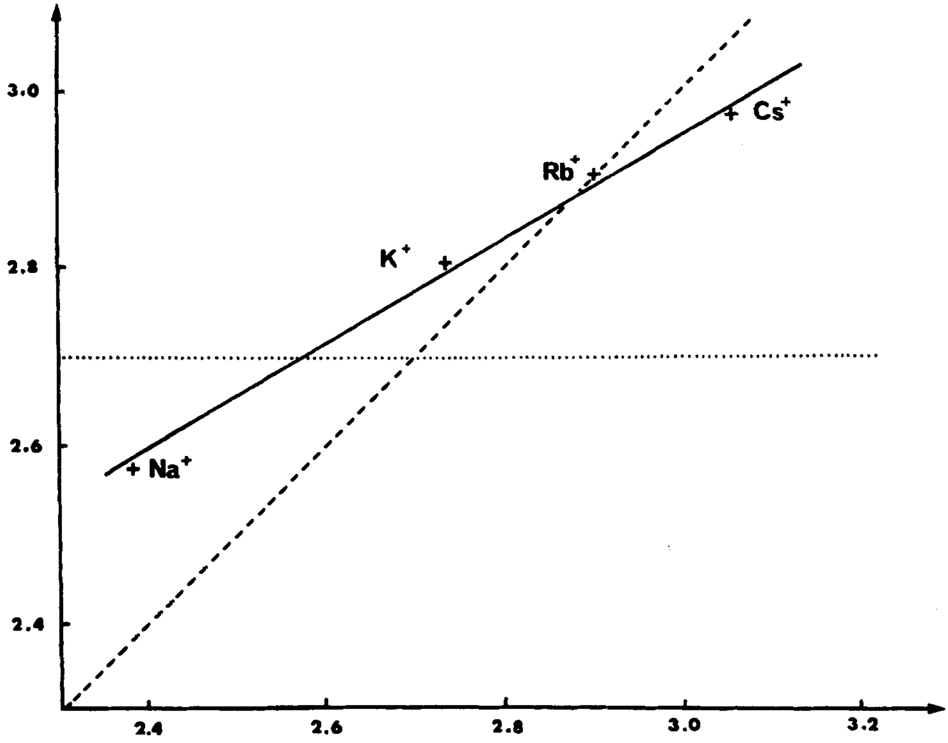

Fig. 2. *Plot of the $M^+ \cdots O$ distances in the alkali cryptates of* [*2.2.2*], *obtained from the crystal structures* [29], *as a function of the $M^+ \cdots O$ distances in the hydrated cations* (cationic radius [2] + 1.4 Å for the oxygen *Van der Waals* radius). The dotted line of slope zero would correspond to a hypothetical infinitely rigid ligand having a cavity of 1.3 Å radius; the dashed line (slope one) corresponds to a ligand as deformable as the hydration shell.

The crystal structure of the Na^+, K^+, Rb^+ and Cs^+ cryptates of ligand [2.2.2] yield the cation-oxygen distances [9]. A plot of these $M^+ \cdots O$ distances *versus* ionic radius of the cation plus oxygen *Van der Waals* radius (1.4 Å) (Fig. 2) should be a straight line of slope 1 for a ligand about as adaptable as the hydration shell and of slope O for an infinitely rigid ligand. The observed slope is about 0.6. The departure of the slope from one gives some measure of the rigidity of the ligand compared to the hydration shell. The ligand does not fit either Na^+ or Cs^+, the cavity being respectively larger and smaller than that required by these cations. Both K^+ and Rb^+ fit approximately the cavity. This is in agreement with the fact that the K^+/Na^+ and K^+/Rb^+ selectivities are respectively larger and smaller in terms of enthalpy than in terms of free energy.

7. *Solvent effects on the thermodynamics of complexation.* It has been shown previously that the transfer from aqueous solution to methanol/water 95:5 or pure methanol solution raises the stabilities of the complexes by factors of the order of 10^3–10^5 [2]. It was of interest to perform some thermodynamic measurements in the same mixed solvent as used previously in order to gain information about the origin of the solvent effect. The results reported in the Table for ligand [2.2.2] clearly show that the very marked stability increase on transfer from water to M/W 95:5 is entirely due to a marked increase in enthalpy of complexation in the mixed solvent, the complexation entropy of K^+, Rb^+, Ca^+, Ba^{2+} becoming even more negative (or less positive) than in water. All complexes studied, including that of Ca^{2+}, are enthalpy stabilized complexes in W/M. Again the enthalpic selectivities are larger than the free energy selectivities and a selectivity peak is only observed for the enthalpies, whereas the entropies become more negative or less positive as the size of the cation increases. Thus the general features of the ΔH and ΔS changes are similar in aqueous and in M/W solutions. The much higher enthalpies of complexation found in M/W may be due in a large part to the increased electrostatic interaction of the cation with the ligand in the medium of lower dielectric constant and its smaller interaction with the solvent.

Conclusion. – The calorimetric data provide a picture of the thermodynamic origin of cryptate stabilities and selectivities. Only the enthalpies of complexation show stability peaks like the stability constants. The entropies of complexation decrease from small to large cations. Entropy changes play a particularly important role for doubly charged and/or small cations. The enthalpy changes indicate that the ligands retain limited adaptability to cation size. The study of even more rigid ligands would shed more light on the effect of this parameter. The results provide a deeper insight into the enthalpic and entropic nature of cation complexation and into the enthalpic origin of the cryptate effect (*i.e.* the generalized, tridimensional, chelate effect).

Experimental part

Materials. The macrobicyclic ligands **1–4** have been obtained from previous work [7]. The salts (chlorides) were commercially available puriss grade reagents.

Method of measurement. The heat of the cryptates formation in water (equation (1)) is:

$$q_c = x \Delta H_c \tag{7}$$

where x is the number of moles of complex formed *i.e.*

$$x = v \cdot |[M^{n+} \subset L]| \tag{8}$$

(v: volume of ligand solution)

$$\Delta H_c = \frac{q_c}{v\,C_L}\left(1 + \frac{1}{K_s\,C_M}\right) \tag{9}$$

(C_L, C_M: total concentrations of ligand and cation respectively; K_s, stability constant of the complex in equation (1) [2]). A large cation to ligand concentration was used (see below) and hence C_M may be considered constant.

For high C_M the term $1/K_s\,C_M$ is small with respect to 1 except for the less stable complexes, for nstance when $\log K_s < 3$ (*e.g.* the K^+, Rb^+, Cs^+ cryptates of [3.2.2]). Corrections taking into account the amount of complex formed have been performed when relevant, using the previously determined stability constants [2].

Experimental procedure. The heats of complexation have been measured at 25.0 ± 0.1° with an LKB 10700 flow microcalorimeter equipped with a recorder and curve integrator and LKB 10200 peristaltic pumps. Since the ligands are bases the measurements have been conducted on basic solutions under argon atmosphere so as to avoid complications from ligand deprotonation on complexation and carbonatation. All solutions were prepared in demineralized distilled water shortly before use, degassed and kept under argon. The ligand solutions are 2.10^{-3}M with regard to the ligand and y M with regard to $N(CH_3)_4OH$. The salt solutions are 2.10^{-2}M (alkali salt) or $0.66\ 10^{-2}$M (alkaline-earth salt) and z M ($N(CH_3)_4Br$, supporting electrolyte); they also are y M with regard to $N(CH_3)_4OH$ in most experiments. The concentrations y and z of base and supporting electrolyte were changed simultaneously depending on the pH desired, so as to keep constant the total ionic strength after mixing. The flow of the salt solutions was 2.5 times faster than the flow of the ligand solutions. After mixing the ionic strength is about 0.057, close to the ionic strength used previously for the determination of the stability constants [2]. The quantity of ligand consumed results from the determination of the exact flow and the injection time of the ligand solution. The base line is given by the mixing of y mol/l $N(CH_3)_4OH$ with the salt solution under argon. The heat of dilution of the ligand solution is found to be negligeable. The measurements were repeated several times and internal consistency was assured by measuring the heat of complexation of K^+ with ligand **3** from time to time. The reproducibility of the ΔH values was ± 0.2 kcal/mol in a given set of conditions. For the least stable complexes, corrections have been performed because of incomplete complexation of the ligand; these values are less accurate and are given in parentheses in Table 1. The lowest and least accurate stability constants are those of the alkali complexes of [3.2.2]; in this case, in order to ensure a high enough degree of complexation (~90%), 0.2M alkali salt solutions were used (no $N(CH_3)_4Br$ present).

Measurements were performed at several pH values. Indeed, the basicities of ligands **1**–**4** are very different, with pK_a's for the first protonation of 10.64, 10.53, 9.60 and 8.50 for **1**, **2**, **3** and **4** respectively [2]. The results reported in Table 1 are for pH 12 (concentrations $y = 10^{-2}$; $z = 4.58\ 10^{-2}$) for the two ligands [2.1.1] and [2.2.1]. For [2.2.2] and [3.2.2] the measurements were performed at pH 10.4 (concentrations $y = 10^{-3}$ in ligand solution; $y = 0$ in salt solution; $z = 6.10^{-2}$). At pH 12, the ΔH_c values for [2.2.2] were 7.1, 11.4, 11.1, 0.4, 9.3, 14.1 for Na^+, K^+, Rb^+, Ca^{2+}, Sr^{2+}, Ba^{2+} respectively; they are close to the pH 10.4 values except for Sr^{2+} (why, is not clear). Hydrolysis of Ca^{2+} at pH 12 does not seem to be a problem, since there is a large excess of salt over ligand.

The measurement with [2.2.2] in the mixed solvent 95% methanol + 5% water (*v/v*) were performed at pH 10.4 using the same concentrations of ligand, salt, base and supporting electrolyte as for the aqueous solutions at the same pH.

It has been checked that mixing of the supporting electrolyte with the ligand does not give any heat of reaction.

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