Some Multinuclear NMR Studies of the Macrocyclic Effect

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Abstract

Enthalpies and entropies of complexation were determined for thallium(I) and sodium complexes with several linear and cyclic polyethers in *N,N*-dimethylformamide and acetonitrile solutions. As usual, the stabilities of the cyclic complexes were considerably higher than those of their linear analogs. No clear cut conclusions could be reached as to entropic or enthalpic nature of the macrocyclic effect.

Introduction

Some two decades ago, in a series of classical papers, Pedersen described syntheses of some 60 cyclic polyethers (crowns) and their unexpected ability to form stable complexes with the alkali metal ions [1]. Very shortly thereafter, Lehn and co-workers [2] announced the synthesis of several three-dimensional diazapolyoxa ligands (cryptands) with strongly enhanced abilities to complex alkali metal ions. An explosive growth of this field of research in recent years is well recognized and needs no description.

An early study of the stabilities of some polyether complexes by Frensdorff [3] showed that in methanol solutions the stability constants of sodium and potassium ion complexes with a linear polyether, pentaglyme $[CH_3O(CH_2CH_2O)_5CH_3]$, are 3–4 orders of magnitude smaller than those of its cyclic analogue, 18-crown-6. Similar enhancement of stabilities of macrocyclic complexes were observed with transition metal complexes of linear and cyclic polyaza ligands [4]. Some typical results with polyoxa ligands are shown in Table I.

This enhanced stability of cyclic complexes was named 'the macrocyclic effect' by Cabbiness and Margerum [6]. It has been observed by many other investigators particularly in aqueous and methanolic solutions. The nature of the macrocyclic effect, however, still remains controversial.

TABLE I. The Macrocyclic Effect

Ligand	Cation	Solvent	log K_f	Reference
Pentaglyme CH_3O-$(CH_2CH_2O)_5CH_3$	Na^+	methanol	1.5	3
Pentaglyme	K^+	methanol	2.2	3
18-Crown-6	Na^+	methanol	4.32	3
18-Crown-6	K^+	methanol	6.1	3
Cryptand C221	Na^+	95% methanol	8.84	5
Cryptand C222	Na^+	95% methanol	7.21	5
Cryptand C221	K^+	95% methanol	7.45	5
Cryptand C222	K^+	95% methanol	8.40	5

Margerum and co-workers [7] explain the enhanced stability of the cyclic complexes as being due to the difference in the solvation of the cyclic and linear polyaza ligands. In their study of the Ni^{2+} complexes in aqueous solutions the authors found that the cyclic ligands formed complexes with formation constants some six orders of magnitude larger than their linear analogues. This macrocyclic effect results from more favorable enthalpy of complexation for the cyclic ligands. The authors interpreted their results by assuming that the linear ligands are much more solvated than their cyclic analogs. Both types of ligands must be desolvated before a complex is formed; the desolvation of the linear ligands results in a higher enthalpy change and, therefore, the overall enthalpy of complexation favors the cyclic ligands. While the desolvation of the ligand and of the cation increase the translational entropy of the system, there is a negative conformational entropy change upon complexation which must be larger for the flexible linear ligand than for the rigid macrocycle.

On the other hand Paoletti *et al.* [8] neglect the influence of the ligand solvation and ascribe the macrocyclic effect to favorable enthalpic and entropic contributions.

More recently other authors studied the enthalpy and the entropy of complexation [9] of cyclic and linear ligands in aqueous and in methanolic solutions. Some of the typical results are summarized in Table II. It is readily seen that these data do not offer an unambiguous interpretation of the macrocyclic

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TABLE II. Enthalpy and Entropy Contributions to Complexation Reactions in Methanol Solutions

Ligand	Cation	log K_f	H° (kcal mol^{-1})	$T\Delta S^\circ$ (kcal mol^{-1})	Reference
Tetraglyme	Pb^{2+}	2.06	−1.72	−1.08	10a
15-Crown-5	Pb^{2+}	3.92	−5.90	−0.56	10a
Pentaglyme	Ag^+	1.80	−3.78	−1.43	10b
18-Crown-6	Ag^+	4.58	−9.35	−3.10	10b
Hexaglyme	Ba^{2+}	2.65	−6.74	−10.56	10c
21-Crown-7	Ba^{2+}	5.44	−6.81	+0.60	10c

effect. In some cases the effect results from the entropy of complexation, in others the enthalpy is responsible, and yet in others, both entropy and enthalpy contribute to the macrocyclic effect.

Our previous studies have shown that the crown ether 18C6 is strongly solvated in acetonitrile and in nitromethane solutions [11]. The thermodynamics of the complexation reaction, therefore, is related to the solvating ability of the solvent. It was of interest to us to investigate the thermodynamics of complexation reactions of cyclic and linear polyethers in some aprotic solvents, where such comparative studies have not been carried out thus far. Formation constants of several linear and cyclic polyether complexes were determined, as a function of temperature, by the NMR technique described in a previous publication [12]. The enthalpy and entropy of complexation were calculated in the usual way from the temperature dependence of the formation constant.

Experimental

Materials

Sodium tetraphenylborate (Aldrich Chemical Company) was used as received except for drying under vacuum at 45 °C for three days. Sodium perchlorate (Matheson Chemical Company) and sodium chloride (J.T. Baker) were dried at 110 °C for three days. Thallium(I) nitrate (Alfa Chemicals) and thallium(I) perchlorate (K&K Chemical Company) were purified by recrystallization from deionized water and then dried at 120 °C for three days.

Acetonitrile, (AN, Baker) was refluxed over calcium hydride for one week followed by fractional distillation with the middle fraction retained; *N,N*-dimethylformamide (DMF, Fisher), was refluxed over calcium hydride, under reduced pressure, for two days, then fractionally distilled under reduced pressure with the middle 60% fraction retained.

Both solvents were stored over freshly activated Linde 3 Å molecular sieves in brown bottles in a dry box under nitrogen atmosphere. The water content of both solvents was determined by gas chromatography. In all cases it was below 50 ppm.

The macrocyclic ligand 18-crown-6 (18C6, Aldrich), was purified as described previously [13]; the purified ligand was then dried under vacuum for three days at room temperature; 15-crown-5 (15C5) and tetraglyme were obtained from the Aldrich Chemical Company, while 21-crown-7 (21C7) and hexaglyme (HG) were obtained from Parish Chemical Company. These ligands, except hexaglyme, were fractionally distilled under reduced pressure and vacuum dried for three days at room temperature. Hexaglyme was used without further purification except for drying under vacuum for three days at room temperature. Pentaglyme was synthesized by the method described by Haymore and co-workers [14]. It should be noted, however, that the description of the synthesis has a dangerous misprint, namely it calls for dissolution of 46 g of metallic sodium in 70 ml of dry methoxyethanol. The correct volume is 700 ml. Elemental analyses, as well as, ^1H and ^{13}C NMR spectra were used to characterize the final product.

In order to avoid contamination with atmospheric moisture and carbon dioxide all solutions were prepared, and the NMR tubes were filled, in a dry-box under dry nitrogen atmosphere.

NMR Measurements

All nuclear magnetic resonance measurements were made on a Bruker WH-180 superconducting NMR spectrometer with a field strength of 42.3 kG. At this field, sodium-23, and thallium-205, resonate at 47.61 and 103.88 MHz respectively. The spectrometer was interfaced to a Nicolet 1180 computer for time averaging of spectra and for on-line Fourier transformation of data. All solutions were measured in 10 mm o.d. tubes with a 4 mm o.d. insert coaxially placed inside. The insert contained a chemical shift reference and the lock solvent. The references were D_2O solutions 0.1 M in NaCl, and 0.1 M in $TlNO_3$, for sodium-23 and thallium-205, measurements respectively. All measured chemical shifts were corrected for the difference in the bulk diamagnetic susceptibility of the probe solution and the reference.

Data Treatment

Measurement conditions were such that in all cases the cationic exchange between the free and the complexed sites was fast, and only one population

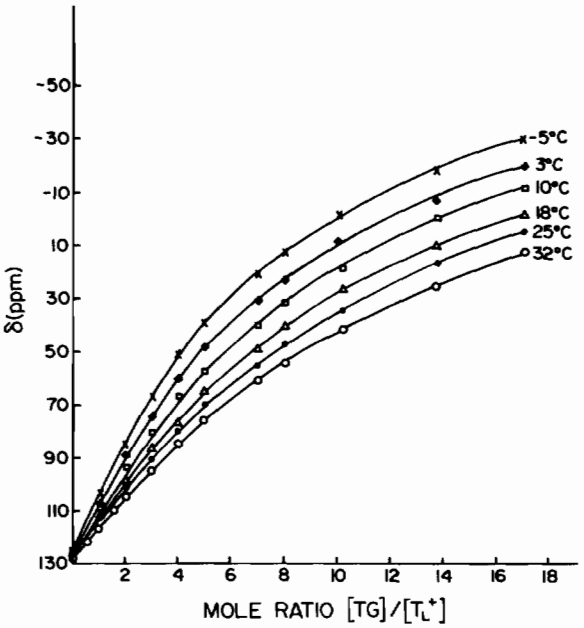

Fig. 1. Chemical shifts *vs.* $[TG]/[Tl^+]$ mole ratio plots at different temperatures for the complexation of the thallium-(I) ion by tetraglyme in *N,N*-dimethylformamide solutions.

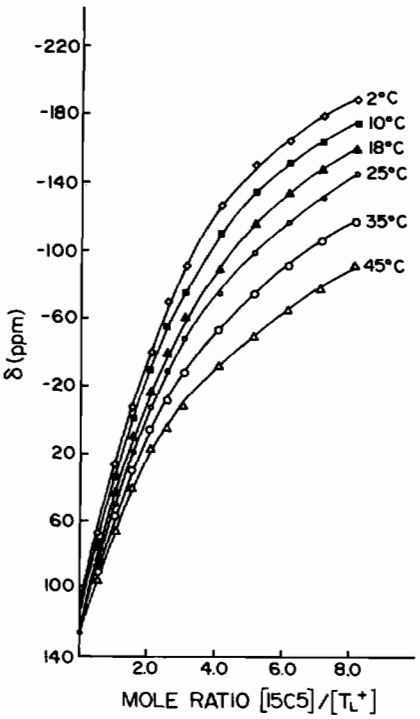

Fig. 2. Chemical shifts *vs.* $[15C5]/[Tl^+]$ mole ratio plots at different temperatures for the complexation of the thallium-(I) ion by 15-crown-5 in *N,N*-dimethylformamide solutions.

averaged signal was observed. An NMR titration was carried out by progressively adding the ligand to a known amount of the metal in an appropriate

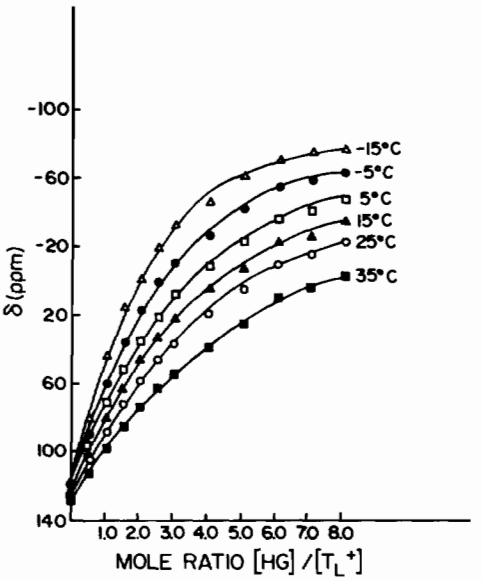

Fig. 3. Plots of chemical shifts as a function of $[Hg]/[Tl^+]$ mole ratio at various temperatures for the complexation of the thallium(I) ion by hexaglyme in *N,N*-dimethylformamide.

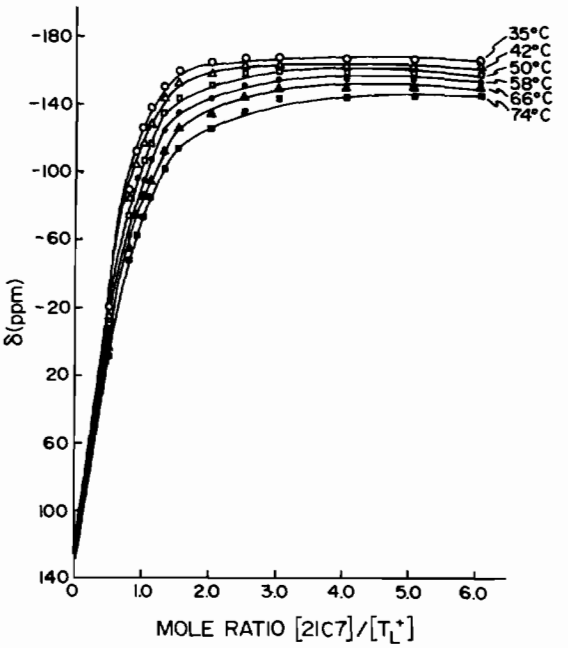

Fig. 4. Plots of chemical shifts as a function of $[21C7]/[Tl^+]$ mole ratio at various temperatures for the complexation of the thallium(I) ion by hexaglyme in *N,N*-dimethylformamide solutions.

solvent. Some typical titration curves are shown in Figs. 1–4. The data were fitted to a previously derived equation which relates the observed chemical shift to the total concentration of the ligand and of the metal ion, to the cationic resonance frequencies at the two sites and to the formation constant [11].

A non-linear least-squares program KINFIT [15] was used to fit the data.

As we have shown previously [16], under the proper set of circumstances, this technique gives adequately accurate results when the $\log K_f$ value varies between ~0.5 and ~4. It becomes quite unreliable with more stable complexes.

It should be noted that in order to compare the stabilities of cyclic and linear complexes, the magnitudes of both formation constants must lie within the above limits. Moreover, metal salts, the ligands and the resulting complexes must be sufficiently soluble in the investigated solvent to give resonance lines with adequate intensities. These restrictions severely limit the number of suitable systems which can be studied in aprotic solvents by the NMR technique.

Another difficulty in such measurements lies in the nearly universally used practice of the neglect of activity corrections. It should be noted that while the formation of a macrocyclic complex is an ion–molecule reaction, neglect of activity corrections is only justifiable within the limits of the Debye–Huckel Limiting Law approximation. In fact, we have shown [17] that at higher ionic strengths ($\sim > 0.05$) the value of the experimental formation constant is influenced by the ionic strength of the solution. Since it is difficult, if not impossible, to calculate activity corrections for neutral species (or even for ions in aprotic solvents), formation constants must be measured in solutions with low ionic strength.

The enthalpy and the entropy of complexation were determined from the temperature dependence of the formation constants. In all cases, measurements were carried out at six different temperatures in a ~50 °C temperature interval. In order to determine the reliability of the calculated ΔH° and ΔS° values each point in the $\ln K_f$ *versus* $1/T$ plots was weighted by the reciprocal of its variance.

Results and Discussion

In order to compare enthalpies and entropies of complexation of cyclic and linear polyethers it was necessary to select solvents with fairly high, but not excessive solvating ability. We have shown previously that a good qualitative guide for the solvation abilities of solvent is given by the Gutmann donicity scale [18]. Strongly solvating solvents, such as dimethylsulfoxide (donor number of 30), depress the stabilities of metal ion complexes. In such cases while it may still be possible to use NMR techniques for the determination of the stability of the macrocyclic complex, the stabilities of the linear polyether become so low that the NMR titration technique can no longer be used for K_f measurements.

The opposite effect is observed in dipolar aprotic non-solvating solvents such as nitromethane (DN = 2.7). In this solvent, titration curves appear as two straight lines intersecting at the 1:1 mole ratio of ligand to the metal ion, and the data can no longer be fitted to our equation.

Of the more common aprotic solvents, *N,N*-dimethylformamide (DN = 26.6) and acetonitrile (DN = 14.1) have intermediate solvating abilities and were used in this investigation. In the first solvent it was possible to study thallium(I) complexes of 15-crown-5, 18-crown-6 and 21-crown-7 as well as of their linear analogues. Typical titration curves are shown in Figs. 1–4 and the van't Hoff's plots are shown in Figs. 5 and 6, while the free energies, enthalpies and entropies of complexation are summarized in Table III and IV. It is seen that, except for tetraglyme and 15C5, the formation constants for the cyclic ligands are ~3 orders of magnitude higher than the ones for the linear polyethers. Relatively small difference in the case of tetraglyme and 15C5 is probably due to the low stability of the 15C5 complex because of the disparity between the cavity size of the macrocycle and the radius of the Tl^+ ion. On the other hand for the flexible linear ligands the stability and the enthalpy of complexation increases with increasing number of ether oxygens, *i.e.* with the number of oxygen–metal ion bonds. It is interesting to note that while the stability of the 15C5 complex clearly results from entropic contribution, the stabilization of the cyclic complexes in the other two cases is due to the much higher enthalpy of complexation.

On the other hand, the macrocyclic effect for sodium ion complexes in acetonitrile solutions is

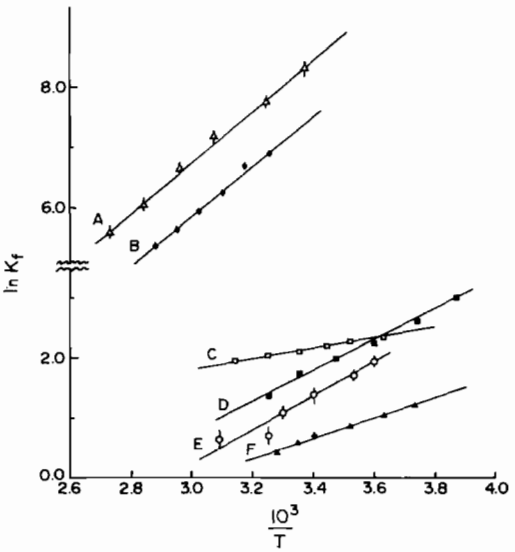

Fig. 5. Van't Hoff plots for the complexation of the Tl^+ ion by various cyclic and analogous linear ligands in *N,N*-dimethylformamide solutions. A: 18C6-Tl^+; B: 21C7-Tl^+; C: 15C5-Tl^+; D: Hg-Tl^+; E: PG-Tl^+; F: TG-Tl^+.

clearly entropic. In fact, in these systems the enthalpies of complexation favor somewhat the linear ligands.

While oure results add new information on the thermodynamics of complexation reactions, they certainly do not resolve the controversy on the nature of the macrocyclic effect. The only conclusion we can draw from our work is that in contrast to the chelation reactions, the macrocyclic effect is neither purely entropic nor is it purely enthalpic. Perhaps it is somewhat naive to expect it to be clearly one or the other. Studies of Petrucci *et al.* on the mechanism of macrocyclic complexation reactions clearly show that they follow the Eigen–Winkler mechanism [19]

$$M^+ + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} M^+\cdots L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ML^+ \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} (ML^+)$$

where M^+ is the free solvated cation, L is the free solvated ligand and $M^+\cdots L$, ML^+ and (ML^+) are three different conformations of the complex. Since the macrocyclic and the linear ligands are solvated to some extent, both the change in ligand conformation and its interaction with the cation must be accompanied by changes in the solution state of the ligand, as well as that of the metal ion. Thus the overall values of the enthalpies and the entropies of complexation are sums of contributions of several processes, and therefore, each step, (and especially the ligand–solvent interaction) must be much better known before the nature of the macrocyclic effect can be elucidated.

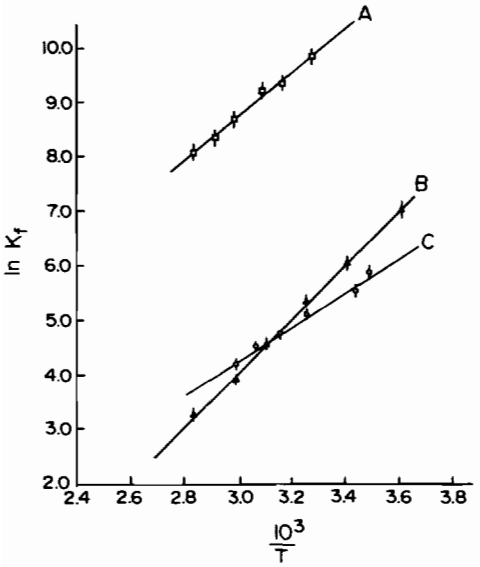

Fig. 6. Van't Hoff plots for the complexation of Na^+ ion by some cyclic and analogous linear ligands in acetonitrile solutions. A: 18C6-Na^+; B: PG.Na^+; C: TG-Na^+.

Acknowledgement

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TABLE III. Thallium Complexes in Dimethylformamide Solutions

Ligand	log K_f [a]	$\Delta G°$ (kcal mol^{-1})	$\Delta H°$ (kcal mol^{-1})	$-T\,\Delta S°$ (kcal mol^{-1})
Tetraglyme	0.27	−0.36 ± 0.04	−3.29 ± 0.13	+2.94 ± 0.13
15-Crown-5	0.91	−1.3 ± 0.18	−1.61 ± 0.01	+0.35 ± 0.06
Pentaglyme	0.50	−0.83 ± 0.05	−4.81 ± 0.50	+4.06 ± 0.11
18-Crown-6	3.73	−4.95 ± 0.30	−8.66 ± 0.22	+3.71 ± 0.20
Hexaglyme	0.76	−1.04 ± 0.06	−5.00 ± 0.15	+3.99 ± 0.10
21-Crown-7	3.01	−4.44 ± 0.24	−8.64 ± 0.20	+4.23 ± 0.13

[a]At 25 °C unless noted otherwise.

TABLE IV. Sodium Complexes in Acetonitrile Solutions

Ligand	log K_f	$\Delta G°$ (kcal mol^{-1})	$\Delta H°$ (kcal mol^{-1})	$-T\,\Delta S°$ (kcal mol^{-1})
Tetraglyme	2.30	−3.13 ± 0.08	−6.33 ± 0.08	+3.09 ± 0.05
15-Crown-5	4.92	−6.79 ± 0.02	−5.76 ± 0.48	−1.17 ± 0.11
Pentaglyme	2.63	−3.59 ± 0.11	−9.47 ± 0.18	+6.05 ± 0.17
18-Crown-6	4.39	−6.02 ± 0.13	−7.86 ± 0.24	+1.79 ± 0.21

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