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Factors affecting stabilities of chelate, macrocyclic and macrobicyclic complexes in solution

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CONTENTS

ABSTRACT

The factors which contribute to the chelate, macrocyclic and cryptate effects are described. These include the dilution effect, translational entropy, intrinsic basicities of donor atoms, coulombic attractions and repulsions of charged ions and groups, and covalent character of the coordinate bonds. The reduction in hydration/solvation energies and the related coulombic repulsions of the donor atoms of multidentate ligands are related to preorganization of the ligands for complexation of metal ions. A not insignificant part of the chelate and macrocyclic effects is due to increase in the basicities of the donor atoms that occurs on ring formation, as well as to reduction of the steric repulsions of alkyl groups. The effects of ring size on stabilities are described. These factors are illustrated with stabilities of chelates, macrocyclic complexes and cryptates taken from the literature.

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1. INTRODUCTION

The factors which influence complex formation in solution are summarized in Table 1. The stability constant is taken as a measure of the stability of the complex in solution and can be considered as involving both enthalpy and the entropy of complex formation. Enthalpy factors have to do with the energy of formation of the coordinate bond, which includes both the covalent tendency of the metal ion and of the ligand, as well as the charge neutralization that occurs when they combine. In addition, one must consider the effects of desolvation of both the metal ion and ligand that occurs on complex formation. Entropy effects are associated with freedom of motion in both the metal ion and the ligand, and consist of translational entropy of the solutes involved as well as the internal forms of entropy such as freedom of vibration and rotation. Preorganization of the ligand involves the freedom of motion of the ligand which increases with entropy. A highly preorganized ligand, therefore, has low entropy because it is frozen approximately in the conformation that exists in the metal complex that is to be formed. All of these factors must be taken into consideration in the formation of metal complexes in solution.

TABLE 1

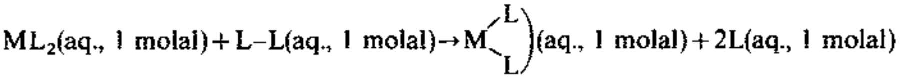
Summary of factors influencing stabilities of metal complexes

1. Intrinsic basicity of donor atom.
2. Covalent tendency of metal ion.
3. Charge neutralization on complex formation.
4. Increase in translational entropy (the classical chelate effect).
5. Steric effects.
6. Preorganization of the ligand.
   (a) Decreases solvation energies.
   (b) Decreases dipole–dipole repulsions.
   (c) Decreases steric strain.
   (d) Lower entropy of ligand favors complex formation.

2. METAL CHELATE COMPLEXES

2.1. The classical chelate effect

In 1952, Schwarzenbach [1] used a model system to explain the higher stability of metal chelate compounds over compounds containing fewer chelate rings. The model assumes that ΔH° is zero for the following reaction involving the formation of one chelate ring:



$$\mathrm{ML_2(aq.,\ 1\ molal) + L{-}L(aq.,\ 1\ molal) \rightarrow M}\left\langle\begin{matrix}\mathrm{L}\\ \mathrm{L}\end{matrix}\right)\mathrm{(aq.,\ 1\ molal) + 2L(aq.,\ 1\ molal)}$$

Assuming solvation energies of complexes, ligand groups L, and energies of all coordinate bonds to be equivalent

$$\Delta H^\circ = H^\circ\text{M}\left(\begin{array}{c}\diagup\text{L}\\ \diagdown\text{L}\end{array}\right) - H^\circ_{\text{ML}_2} - H^\circ_{\text{L-L}} + 2H^\circ_{\text{L}} = 0$$

The entropy change of the reaction is:

$$\Delta S^\circ = S^\circ\text{M}\left(\begin{array}{c}\diagup\text{L}\\ \diagdown\text{L}\end{array}\right) - S^\circ_{\text{ML}_2} - S^\circ_{\text{L-L}} + 2S^\circ_{\text{L}}$$

Assuming internal and solvation entropies to be equivalent, ΔS° becomes equal to the translational entropy of the solute generated in the reaction. Adamson [2] pointed out that this increase in entropy of translation for the generation of one mole of solute at the standard state of 1.00 molal is expressed by

$$\Delta S^\circ = R \ln 55.5 = 7.9 \text{ e.u.} \tag{1}$$

For n chelate rings

$$\Delta S^\circ = 7.9n \text{ e.u.} \tag{2}$$

at 25°C, ΔS° contributes $\sim 2 \log K$ units per chelate ring formed.

Schwarzenbach [1] also used this model to explain the lower stability of chelate compounds with larger rings. Thus the free donor group of the bidentate ligand for the intermediate in which only one of the two donor groups is coordinated to the metal ion is restricted in its freedom of motion to a greater extent when the ring to be formed is smaller. Thus with a potential six-membered chelate ring, the free donor group of the intermediate has greater entropy in that form, which is only partly lost on completion of the chelate ring. Therefore, according to the Schwarzenbach [1] model the smallest chelate ring will show the greatest entropy increase and the formation of larger rings will decrease the entropy of reaction to an increasing amount as the ring becomes larger.

Closely related to Schwarzenbach's [1] chelate effect is the strong dilution effect of metal complexes in solution. Adamson [2] pointed out that the use of unit mole fraction as the standard state of the metal ion, ligand and complex formed would eliminate the entropy factor calculated by Schwarzenbach as the chelate effect. In other words, there is no chelate effect if mole fraction is used as the unit of concentration. Thus the so-called chelate effect is actually the entropy of dilution resulting from the use of one molal as the standard state for the solute.

There have been many articles concerned with the nature of the chelate effect, three of which are referenced here [3–5]. In essence, the articles point out that one can compare $\log K_1$ (polydentate) with $\log \beta_n$ (monodentate) even though the units are different, because the difference itself has units which are some power of the units used for the formation constants. Munro [3] has pointed out that a state of unit mole fraction for all the constituents of an equilibrium is unattainable. Also, the more dilute the standard reference state, the larger is the numerical value of the chelate effect [6]. This corresponds to the fact that the more dilute the solution, the greater the relative advantage (the less the dissociation) that the chelate has over its unidentate analogs. This discussion (and eqns. (1) and (2)) applies only to the change of entropy of translation of the solute that occurs in going from unit mole fraction (at which the entropy of translation is zero) to that of the one molal standard state. There are many other entropy contributions to the chelate effect [3–5], having to do with changes of internal entropy of complex and chelate, which have been extensively discussed in the literature. In order to clarify the distinction between these different types of entropy, this paper will refer to the entropy expressed by eqns. (1) and (2), as the "translational entropy contribution to the chelate effect".

Table 2 illustrates a model calculation of three representative complexes. With a metal ion of coordination number six, a unidentate ligand will form the complex MA_6, a bidentate ligand will form MB_3, and a hexadentate ligand will form the complex indicated as ML with 0, 3 and 5 metal chelate rings, respectively. An initial chelate effect of ~ 2 log units per chelate ring, assuming a value of 10^{12} as the stability constant of the non-chelated complex, gives stability constants of 10^{12}, 10^{18}, and 10^{22} for MA_6, MB_3 and ML, respectively. It is seen that the dilution effect is very strong for the metal complex, with complete dissociation of the complex at 10^{-6} molar, while the metal chelate with five chelate rings undergoes only slight, in fact practically no dissociation under the same conditions. Therefore, in order to form a complex that retains its integrity in very dilute solution, it is important to have as many chelate rings as possible. This dilution effect was pointed out previously by Martell [6].

3. THERMODYNAMICS OF METAL CHELATE FORMATION

The thermodynamics of formation of the ammonia and ethylenediamine complexes of Cu(II) and Ni(II) illustrated in Table 3 show both enthalpic and entropic contributions to the chelate effect [7]. The replacement of two ammonias by one ethylenediamine shows about the expected increase in entropy predicted by Adamson [2] (the experimental values do not differ very greatly from the values obtained by multiplying 7.9 by the number of chelate rings formed). It should be pointed out that simply multiplying the number of rings formed by 7.9 e.u. is an oversimplification since the entropy change on chelate ring formation also results from additional factors, as mentioned above, involving changes in entropy accompanying changes in entropies of vibration and rotation. However, in practical terms one can account very successfully for the entropy part of the chelate effect with multiples of 7.9 e.u.

The data in Table 3 also indicate a considerable contribution from the enthalpy change on chelate formation. Part of this is due to the fact that the polar groups

TABLE 2

Comparison of dissociation of metal complexes and metal chelates in dilute solution

Donor groups per ligand	Number of chelate rings	Equilibrium quotient	*B*	Total concentration of complex and metal ion					
				1.0 M		1.0×10^{-3} M		1.0×10^{-6} M	
				pM[a]	%Diss.	pM[a]	%Diss.	pM[a]	%Diss.
1	0	$\frac{[MA_6]}{[M][A]^6}$	10^{12} M^{-6}	16.67	2.1×10^{-15}	3.75	18	6.00	100
2	3	$\frac{[MB_3]}{[M][B]^3}$	10^{18} M^{-3}	19.43	3.7×10^{-18}	13.43	3.7×10^{-9}	7.74	1.8
6	5	$\frac{[ML]}{[M][L]}$	10^{22} M^{-1}	22.00	1×10^{-20}	22.00	1×10^{-17}	22.00	1×10^{-14}

[a] For 100% excess ligand.

TABLE 3

Thermodynamic contributions to the chelate effect in complexes of ethylenediamine with Cu(II) and Ni(II) [7]

	ΔG^0	ΔH^0	ΔS^0
Unidentate complex			
$[Ni(NH_3)_2(H_2O)_4]^{2+}$	−6.93	−7.8	−3
$[Ni(NH_3)_4(H_2O)_2]^{2+}$	−11.07	−15.6	−15
$[Ni(NH_3)_6]^{2+}$	−12.39	−24	−39
$[Cu(NH_3)_2(H_2O)_4]^{2+}$	−10.68	−11.1	−1
$[Cu(NH_3)_4(H_2O)_2]^{2+}$	−17.74	−22.0	−14
Chelate analog			
$[Ni(En)(H_2O)_4]^{2+}$	−10.31	−9.0	4
$[Ni(En)_2(H_2O)_2]^{2+}$	−19.09	−18.3	3
$[Ni(En)_3]^{2+}$	−25.09	−28.0	−10
$[Cu(En)(H_2O)_4]^{2+}$	−14.64	−13.1	5
$[Cu(En)_2(H_2O)_2]^{2+}$	−27.54	−25.5	7

	ΔG^*	ΔH^*	ΔS^*	$7.9n$
Chelate effect				
Ni(En)	−3.4	−1.2	7	7.9
$Ni(En)_2$	−8.0	−2.7	18	15.8
$Ni(En)_3$	−12.70	−4	29	23.7
Cu(En)	−4.0	−2.0	6	7.9
$Cu(En)_2$	−9.8	−3.5	21	15.8

which are widely separated in ammonia are brought together in the bidentate ligand ethylenediamine so that part of their mutual repulsions are overcome in formation of the ligand. Another factor which is not obvious at first but which is discussed in detail later on in this paper is the increase in the intrinsic basicity of the amino groups resulting from the negative charge donation effect of the alkalene bridge. Thus it is seen that, for metal ions which have considerable tendency for covalent coordinate bond formation (if their electronegativities are appreciable), the enthalpic contribution to chelate formation can be important.

Comparison of the thermodynamics of metal complexation of unidentate amines and bidentate amines has been used by others [5,8–10], and in one case a detailed analysis of the chelate effect on replacing methylamine by ethylenediamine [10] has been given. For the comparison of methylamine with ethylenediamine, it has been pointed out by Hancock [11] that there are difficulties arising from the fact that methylamine produces such serious steric problems.

The enthalpy contribution to the chelate effect may be seen in the variation of chelate ring size with stability indicated in Table 4 [6]. In the examples given, the decrease in stability as the length of the chain between the iminodiacetate groups is increased from 2 to 5 is due mainly to changes in the enthalpy of the reaction rather than changes in the entropy. Assuming that all the donor groups become coordinated to the metal ion, the main feature operating in the complexes formed involving different values of *n* is the variation in the distances between the charged donor groups of the free ligand in solution and the difference in distance between coordinating tertiary nitrogen atoms. As *n* increases, it is necessary to bring these groups together from greater distances to form the complex, so that the coulombic repulsive forces that must be overcome become greater and the formation of these complexes becomes less exothermic as the chain length increases. Therefore, it is seen that, in a more compact ligand such as ethylenediaminetetraacetic acid (EDTA), the internal mutual repulsive forces are already partially overcome in the synthesis of the ligand itself.

The entropies of formation of positively charged metal ions with negatively charged ligands is illustrated in Table 5 and plotted in Fig. 1 [6]. The correlation involving the increase in the value of $\Delta S°$ with the charge of the metal ion and the square of the reciprocal of the ionic radius is truly remarkable and indicates that the entropy increase associated with the combination of positive and negative ions is a major factor in determining the stabilities of these complexes. The radius of the ligand donor group does not enter into this correlation since only one type of donor, the carboxylate group, is involved in charge neutralization with the metal ion. It is

TABLE 4

Thermodynamics of formation of metal chelates of EDTA homologs. Data from ref. 7 at $\mu = 0.10$ M and $T = 25.0°$C.

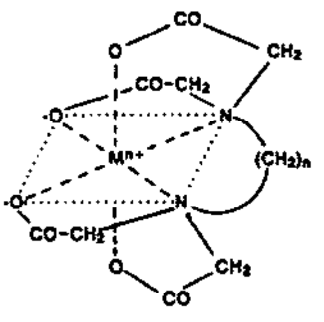
	n	Quantity	Metal ion					
			Mg^{2+}	Ca^{2+}	La^{3+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
	2	log *K*	8.8	10.6	15.5	18.4	18.8	16.5
		ΔH^0	3.3	−6.1	−2.9	−7.4	−8.3	−4.6
		ΔS^0	52	28	61	59	58	60
	3	log *K*	6.3	7.3	11.3	18.1	18.8	15.2
		ΔH^0	9.1	−1.7	3.8	−6.7	−7.7	−2.3
		ΔS^0	59	27	64	60	60	62
	4	log *K*	6.3	5.6	9.2	17.3	17.2	15.0
		ΔH^0	8.5	−0.9	1.9	−7.0	−6.5	−3.5
		ΔS^0	57	23	48	56	57	57
	5	log *K*	5.2	4.6	9.0	13.8	16.1	12.6
		ΔH^0	–	–	–	−6.7	−10.9	−2.7
		ΔS^0	–	–	–	41	37	49

TABLE 5

Correlation of entropy of chelate formation with radius of metal ion and effective charge of ligand[a]

Ligand anion	Metal ion	ΔS^0 (e.u.)	r (Å)	Ligand coordination no.	Z_e^{b}	Z_e/r_e^2
EDTA	Mg^{2+}	52	0.65	6	4	1.47
	Ca^{2+}	28	0.99	5	3	0.76
	Sr^{2-}	26	1.13	5	3	0.66
	Ba^{2+}	20	1.35	5	3	0.54
	Mn^{2+}	48	0.80	6	4	1.23
	Fe^{2+}	52	0.75	6	4	1.31
	Co^{2+}	62	0.72	6	4	1.35
	Ni^{2+}	59	0.69	6	4	1.40
	Cu^{2+}	58	0.65	6	4	1.47
	Zn^{2+}	60	0.74	6	4	1.32
	Cd^{2+}	45	0.97	6	4	1.03
	Hg^{2+}	35	1.10	6	4	0.91
	Pb^{2+}	39	1.21	6	4	0.82
NTA	Mg^{2+}	40	0.65	4	3	1.10
	Ca^{2+}	25	0.99	4	3	0.76
	Ba^{2+}	17	1.35	4	3	0.54
MIMDA	Mg^{2+}	26	0.65	3	2	0.73
	Sr^{2+}	10	1.13	3	2	0.44
	Mn^{2+}	27	0.80	3	2	0.62
DMEDDA	Mg^{2+}	27	0.65	4	2	0.73
DMG	Mg^{2+}	16	0.65	2	1	0.37

[a] r = Pauling ionic radii, Å; r_e = ionic radius + 1.0 Å; Z_e = number of coordinated negative carboxylate groups of ligand.

[b] Data from ref. 6. EDTA = ethylenediaminetetraacetic acid; NTA = nitrilotriacetic acid; MIMDA = *N*-methyliminodiacetic acid; DMEDDA = *N*,*N*′-dimethylethylenediaminediacetic acid; DMG = *N*,*N*-dimethylglycine.

important to note that the entropy may be greater, especially for highly charged metal ions, than that associated with the number of chelate rings formed (the classical chelate effect) which could be visualized by the negative entropy of solvated water molecules held around the metal ion but released to the solvent on complex formation. This effect is due to the fact that more than one molecule of solvated water per chelate ring formed is released from the solvation sheath of the metal ion on complex formation. This factor results from rapidly increasing solvation of the metal ion with ionic charge and is taken into account in the following empirical entropy relationship developed by Powell and Latimer [12].

$$\bar{S}^{\circ}=\frac{3}{2}R\ln M+37-270\frac{z}{r_e^2} \qquad (3)$$

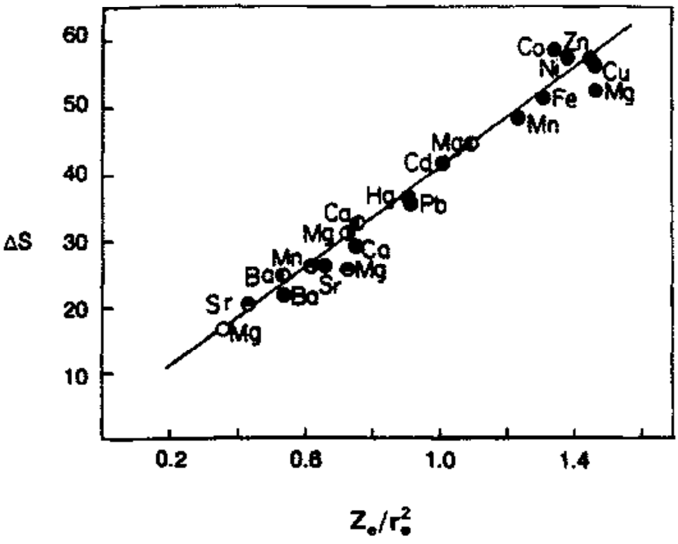


Fig. 1. Correlation of entropies of formation of aminopolycarboxylic acid chelates in aqueous solution with effective radius of the metal ion, r_e, and number of negative carboxylate groups of the ligand, Z_e, that become coordinated with the metal ion; r_e = crystal (Pauling) radius + 1.0 A; ●, EDTA = ethylenediaminetetraacetic acid; ◐, NTA = nitrilotriacetic acid; ⊖, MIMDA = *N*-methyliminodiacetic acid; ◑, DMEDDA = *N,N′*-di-methylethylenediaminediacetic acid; ○, DMG = *N,N*-dimethylglycine.

where M is the molecular weight, z the ionic charge, and r_e the effective ionic radius. In this equation, the entropy of the metal ion is made very negative by the term containing the reciprocal of the effective ionic radius of the metal ion, which decreases rapidly with ionic charge. This term indicates the increase in entropy that occurs when charge neutralization takes place.

3.1 *The size of the chelate ring*

The effect on chelate stability of the size of the chelate ring formed was considered qualitatively by Schwarzenbach [1] and is reflected in the data of Table 4 describing the enthalpy increases in the complexes formed by EDTA homologs [7,13]. Various factors lead to the decrease in stability that is observed in almost all cases as the size of the chelate ring increases. However, there are notable exceptions and they can be understood most readily by looking at the conformations of 5- and 6-membered chelate rings illustrated in Fig. 2 [14]. Through the use of molecular mechanics and the models shown in Fig. 2 involving the most stable conformations of the 5- and 6-membered rings, it is obvious that the "bite-size" of the 5-membered ring is greater than that of the 6-membered ring and the angle of the metal ion which is subtended in the 5-membered ring is smaller with a greater metal donor distance. The cyclohexane model for the 6-membered ring shows a larger angle but a smaller distance between the donor groups and between the metal ion and the donor groups.

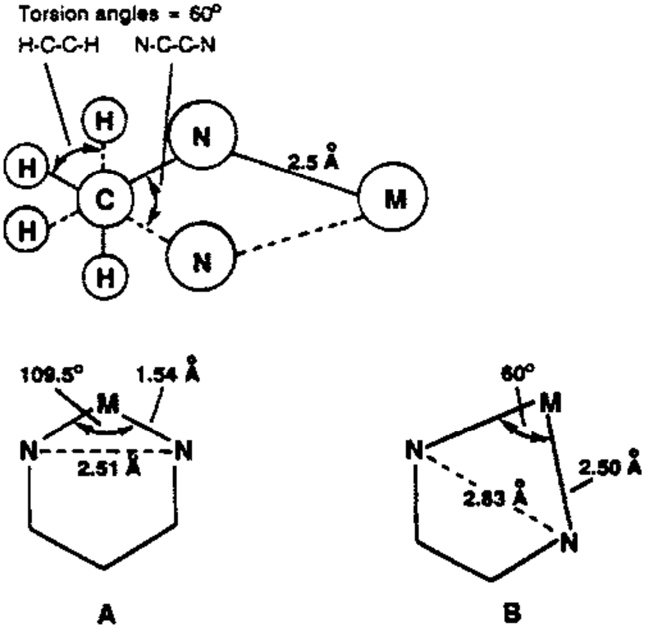


Fig. 2. The lowest strain energy geometry calculated using molecular mechanics for (A) the six-membered chelate ring, and (B) the five-membered chelate ring.

Therefore it would seem that, for smaller metal ions, the 6-membered ring would form the most stable complexes while for large metal ions, the 5-membered ring would form more stable complexes. An illustration of this effect for metal chelate compounds is seen in Fig. 3, which shows the increase in stabilities in going from 2,2,2-tet (triethylene-tetramine) to 2,3,2-tet, and the comparison of the stability of EDTA with the homolog in which there are three carbons between the nitrogens. In most cases, an increase in ring size causes a decrease in stability as the size of the metal ion increases. However, for small metal ions such as Cu(II), Ni(II) and even Zn(II) the tetramine with the 6-membered ring forms a complex which is more stable than the complex in which all the rings are 5-membered. Also, for the EDTA conversion to the homolog containing three carbon atoms between the nitrogens, the chelate containing a six-membered ring is more stable than that of EDTA for the Cu(II) complex.

3.2 Preorganization

Although preorganization is a concept usually applied to macrocyclic and cryptate complexes, it is also of some importance for open-chain ligands that form chelate rings. To illustrate this effect, the stability of the EDTA, **1**, complex is compared with that of *trans*-cyclohexanediaminetetraacetic acid (CDTA, sometimes

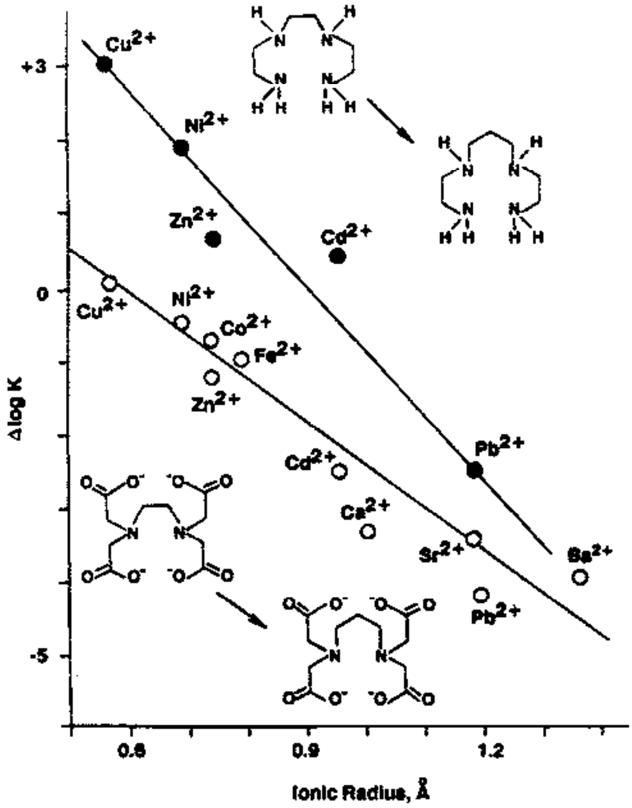
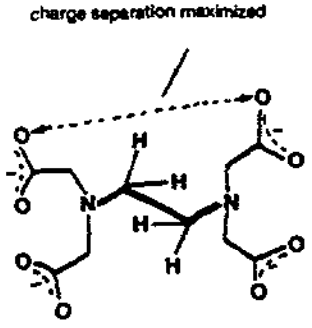


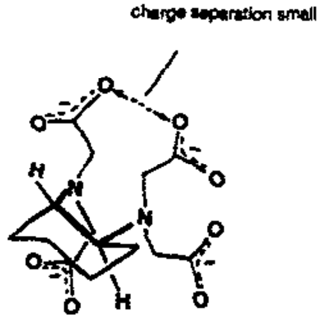
Fig. 3. The effect on complex stability of increase in chelate ring size from 5-membered to 6-membered in open-chain ligands, as a function of metal ion size. Δ log $K = \log K_{ML}$ (6-membered); $-\log K_{ML}$ (5-membered).

labeled CYDTA), **2** [14]. In solution, the EDTA anion is in the extended form with the donor groups as far apart as possible to minimize the repulsions between these groups. These have to be drawn together around the metal ion to form the complex. In *trans*-CDTA the donor groups shown are much closer together so that the mutual repulsions to be overcome are much less since they have already been partially overcome in the synthesis of the ligand. The freedom of motion of the iminodiacetate groups is also greatly restricted so that the entropy of CDTA is much lower than it would otherwise be, and the loss of entropy in forming the complex is much less. The CDTA complexes are therefore more stable than those of EDTA and, in fact, the increase of stability observed is usually from two to three log units. This shows that the concept of preorganization, in which the ligand has a conformation more nearly like the conformation of the metal complex, can be an important factor governing the stabilities of open-chain chelating ligands.

Another ligand which owes part of its affinity for the ferric ion to preorganization is the siderophore enterobactin, **3**. Shanzer et al. [15] performed force field

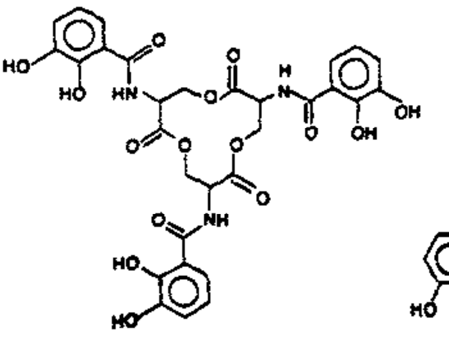


1 EDTA trans form

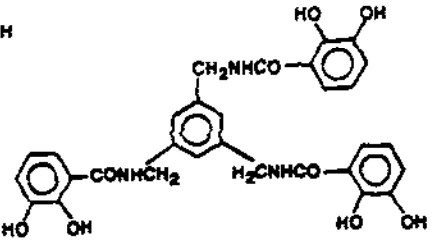


2 CDTA skew form

calculations to compare the complexation of Fe(III) by fully deprotonated enterobactin and complexation by a fully deprotonated MECAM, 4 [16]. Shanzer et al. suggested that the hydrogen bonding network of the cyclic triester ring and the attached amide groups of enterobactin influence the conformation of the free ligand so that it is sterically similar to its conformation in the iron complex. The result of this preorganization is that the constant for enterobactin complexation is about 2 kcal mol^{-1} greater than for the synthetic analog MECAM. The calculations of Shanzer et al. [15] suggested that the observed enthalpic differences can probably be attributed to differences in ring strain of Fe(III) coordination, and that the siderophore enterobactin is more highly preorganized than is the synthetic analog MECAM.



3 Enterobactin



4 MECAM

4. THE MACROCYCLIC EFFECT

4.1 Thermodynamics of macrocyclic complexes

The enthalpy and entropy contributions to the macrocyclic effect in going from the complex formed from the open-chain pentaglyme to the analogous macrocyclic complex containing the same number of oxygen donors, 18-crown-6, is shown in Table 6 [7,13]. In all cases, the macrocyclic complexes of Na^+, K^+, and Ba^{2+} are much more stable than the analogous complexes formed from the open-chain ligand. The entropy contribution to this increase in stability is rather small, increasing considerably with Ba^{2+}, as one might expect from the combination of positive ions with a neutral oxygen donor from the data in Table 6 and eqn. (1). Apparently, the release of water molecules to the solvent on the formation of the macrocyclic complex is slightly more than the negative entropy that would be expected from the greater rigidity of the complex. The major factor in the increased stability of the complex formed by the macrocyclic ligand over that of the open-chain compound, however, can be found in the enthalpy of complex formation. For many other carefully chosen examples [11], the effect of macrocyclic ring formation is mainly to increase the enthalpy of the reaction. Major contributions to the favorable $\Delta H°$ of macrocyclic complex formation are the preorganization of the ligand and the greater basicity of the oxygen donors due to increased alkylation. The preorganization, which is achieved in the synthesis of the macrocyclic donor, involves overcoming the repulsive forces between the polar donor groups. In the open-chain analog, the repulsive forces have to be overcome because the oxygen donor groups are far apart in the free ligand and must be forced closer together to form the complex. A similar macrocyclic effect is shown in Table 7, for the comparison of cyclam and the analogous open-chain ligand with the same number of coordinating nitrogens 2,3,2-tet [7,13]. The main contributions to the favorable $\Delta H°$ of macrocyclic complex formation is again due to preorganization of the ligand and the increased basicity of the donor nitrogens due to increased alkylation. The effect of increased alkylation on the stability is discussed in more detail below.

It is noteworthy that the ligands compared in Tables 6 and 7 contain the same number of donor atoms and form the same number of coordinate bonds, for the

TABLE 6

Thermodynamics of complex formation of Na^+, K^+, and Ba^{2+} with 18-crown-6 and its open-chain analog (pentaglyme) in 100% methanol

		Na^+	K^+	Ba^{2+}
log K_1	18-crown-6	4.36	6.06	7.04
	pentaglyme	1.44	2.1	2.3
	log K (MAC)	2.92	3.96	4.74
ΔH	18-crown-6	−8.4	−13.4	−10.4
	pentaglyme	−4.0	−8.7	−5.6
	ΔH (MAC)	−4.4	−4.7	−4.8
ΔS	18-crown-6	−8	−17	−3
	pentaglyme	−7	−20	−8
	ΔS (MAC)	−1	3	5

TABLE 7

Thermodynamics contributions to the macrocyclic effect in complexes of tetraazamacrocycles[a]

		Cu(II)	Ni(II)	Zn(II)
log K_1	cyclam	27.2	22.2	15.5
	2,3,2-tet	23.2	16.1	12.7
	log K (MAC)	4.0	6.1	2.8
ΔH	cyclam	−32.4	−24.1	−14.8
	2,3,2-tet	−26.5	−17.9	−11.6
	ΔH (MAC)	−5.9	−6.2	−3.2
ΔS	cyclam	12	21	21
	2,3,2-tet	16	15	19
	ΔS (MAC)	−4	6	2

[a] Since stability constants and heats were variously reported at $\mu = 0.1$, 0.5, and 1.0, all differences were matched to similar conditions.

macrocyclic ligands and the corresponding open-chain ligand. In both cases, the complexes formed by the macrocyclic ligand contains one more chelate ring than the complexes formed from the open-chain ligands. Yet the entropy increase in forming the macrocyclic complex from the complex formed by the non-cyclic ligand is close to zero and not the increase in entropy due to the increase of translational entropy associated with the classical chelate effect. It should be noted that there is no change in the number of solute molecules when the chelate containing the open-chain ligand is converted to the macrocyclic complex. It is apparent, therefore, that the entropy increase associated with the classical chelate effect is a valid concept only if formation of a chelate ring also releases a mole of solute. Therefore the increase in entropy that has been used as a measure of the number of chelate rings formed is not that at all, and should be applied with caution, since it is really the consequence of the number of moles of solute released to the solvent.

4.2 Increase in intrinsic basicity of donor atom due to increased alkylation

Although the basicities of trimethylamine and ammonia in water do not seem to be very different as measured by the corresponding pK values, the intrinsic basicities that are important in metal complex formation are masked in aqueous solution by solvation effects. The ammonium ion is stabilized in water by hydrogen bonding with the solvent while in trimethylamine the metal groups cannot hydrogen bond to the solvent and also exert steric effects on the $(CH_3)_3N^+H$ group that is formed on protonation and destabilizes its hydrogen bonding to the solvent. In the gas phase, however, one need not worry about solvation effects and therefore the intrinsic basicities can be observed by mass spectrometry.

In Fig. 4 are plotted the free energies of protonation by H_3O^+ of H_2O, H_2S,

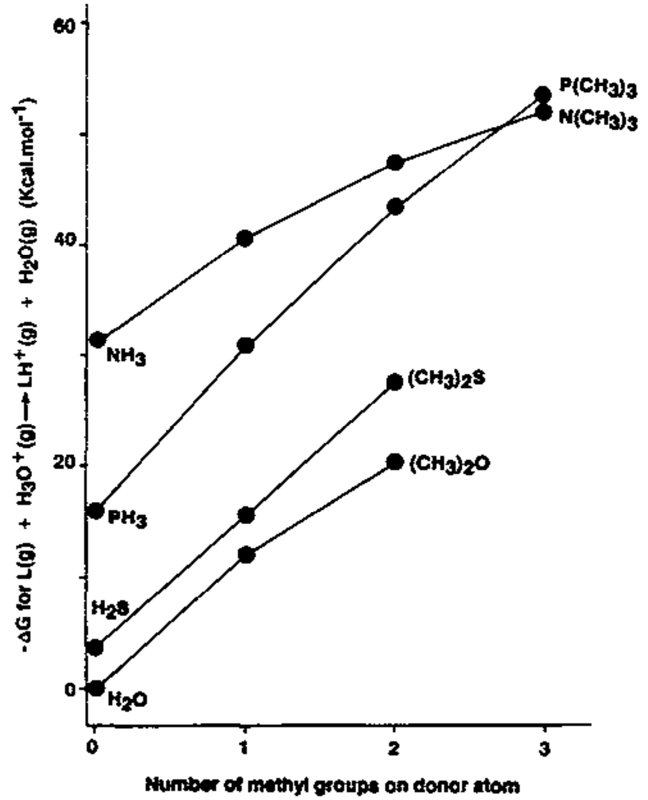
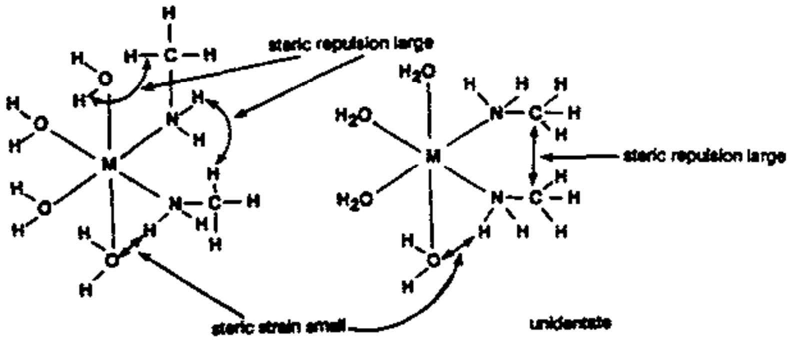
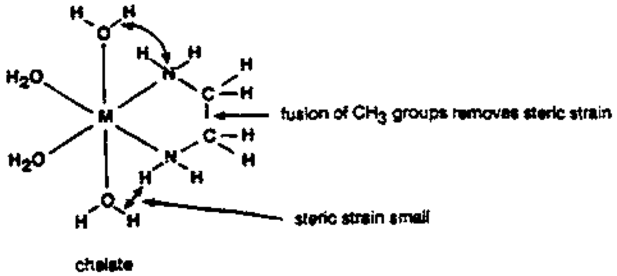


Fig. 4. The effect of methylation of donor atom on basicity in the gas phase.

NH_3 and PH_3 and their methyl derivatives [13]. In all cases, the addition of a methyl group to give an alcohol or ether or a methylated phosphine or amine increases the basicity of the donor atom by a considerable amount. This is due to the increase in the inductive electron release by the methyl group. Combination of these donors with a metal ion would be expected to increase in binding strength in accordance with the data on protonation shown in this graph.

While it is agreed that trimethylamine would be a better donor for metal complex formation than ammonia, this effect is not observed in aqueous solution because of the steric repulsion of methyl groups for each other and the fact that they break up the hydrogen bonding pattern which stabilizes the ammonia complex because the methyl groups do not hydrogen bond with the solvent. On the other hand, the steric repulsions are minimized in the formation of the ligand ethylenediamine in which the alkyl groups are bridging groups and their interference with solvation of the metal complex is minimized. The steric repulsions between the methyl groups in methylamine complexes and the reduction of these steric repulsions by their fusion into an ethylenediamine donor may be visualized by the following [13]:

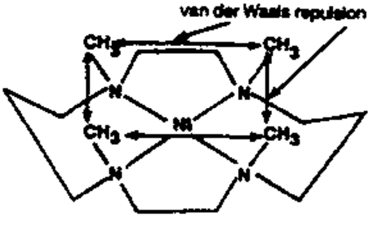




Therefore the increase in stability of an ethylenediamine complex is due in part to the increased affinity for the metal ion of the donor nitrogen atoms of the ligand. Thus the increased affinity of macrocyclic donors such as 18-crown-6 and cyclam is due in part to the greater basicity of the donor oxygen or nitrogen atoms and the consequent greater strength of the coordinate bonds formed with the metal ion.

From the above considerations, one would expect to increase the basicity of macrocyclic ligands such as cyclam by methylation of the nitrogen atoms. However, in tetramethyl cyclam, the stability constants are seen to decrease considerably on methylation, as is indicated in Table 8. This effect is due to the steric repulsions between the methyl groups and also between the methyl groups and the carbon atoms of the macrocycle. This effect is also seen in the following comparison of the low-spin Ni(II) complexes of cyclam and tetramethyl cyclam [13]. The relative strain energies, in other words the repulsive forces in the nickel(II) complexes, reported by Hancock et al. [17] were estimated by the use of molecular mechanics. ΔU, strain energies, for cyclam, **5**, and tetramethylcyclam, **6**, are:

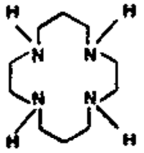
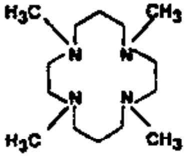
5 $\Delta U = 11.3$ kcal.mol^{-1}



6 $\Delta U = 35$ kcal.mol^{-1}

TABLE 8

N-Alkylation leads to a dramatic drop in log K_1 when cyclam is *N*-methylated to give TMC[a]

	 Cyclam	 TMC	Δ log *K*	Ionic radius (Å)
log K_1 [Cu(II)]	27.2	18.3	8.9	0.65
log K_1 [Ni(II)]	22.2	8.6	13.6	0.69
log K_1 [Co(II)]	12.7	7.6	5.1	0.72
log K_1 [Zn(II)]	15.5	10.4	5.1	0.74
log K_1 [Cd(II)]	11.7	9.0	2.7	0.97
log K_1 [Pb(II)]	11.3	(~7.5)	(~3.8)	1.21

[a] $\mu = 0.10$ M, $T = 25.0$°C.

It is seen that the strain energies of the tetramethyl cyclam are very much higher than those of cyclam itself. This energy must be overcome in complex formation and is due mainly to the steric repulsions of the methyl groups.

4.3 Preorganization

Macrocyclic complexes are not as fully preorganized as the literature sometimes indicates. A typical macrocycle such as 18-crown-6, in the solid state [18] and in solvents of low dielectric constant, is folded in on itself to minimize dipole–dipole repulsions. Thus the folded ligand would have to open up considerably to form the configuration which is necessary to complex metal ions as indicated in Fig. 5 [13]. If 18-crown-6 is dissolved in water, it is likely that solvation lessens the dipole–dipole repulsions [19] and a D_{3d}-like conformation is adopted [20,21]. In this case, the water of solvation would have to be displaced before complex formation could occur.

A good example of a highly preorganized macrocyclic ligand has been reported recently by Hancock et al. [17,22] and is indicated in Fig. 6. The open-chain compound is less stable than the macrocyclic complex shown in Fig. 6 by almost ten orders of magnitude. The increase is due only in part to the increased alkylation of the nitrogen donor atoms in the macrocyclic ring. The effect shown is due mostly to the lack of preorganization of the open-chain compound relative to the macrocyclic ligand. The additional ethylene bridge between two of the nitrogens as shown has the effect of stiffening the macrocyclic ring and decreasing its entropy by not allowing the donor nitrogens as much freedom of motion as they would otherwise have.

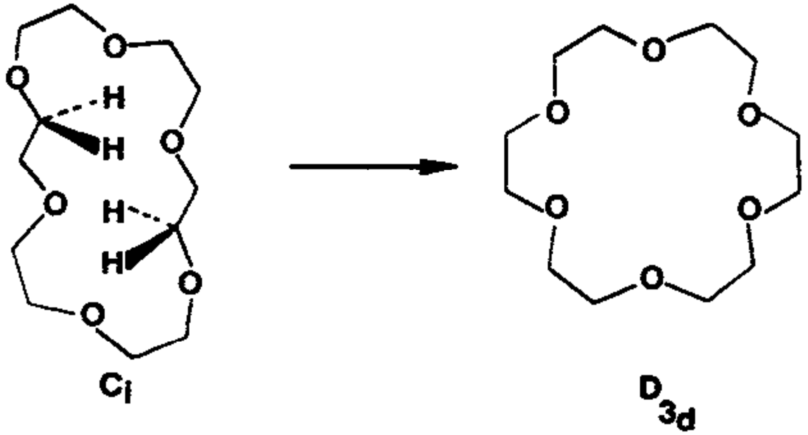


Fig. 5. Representation of the relative structures of the free ligand 18-crown-6 (left) and the conformation required for its coordination to metal ions (right).

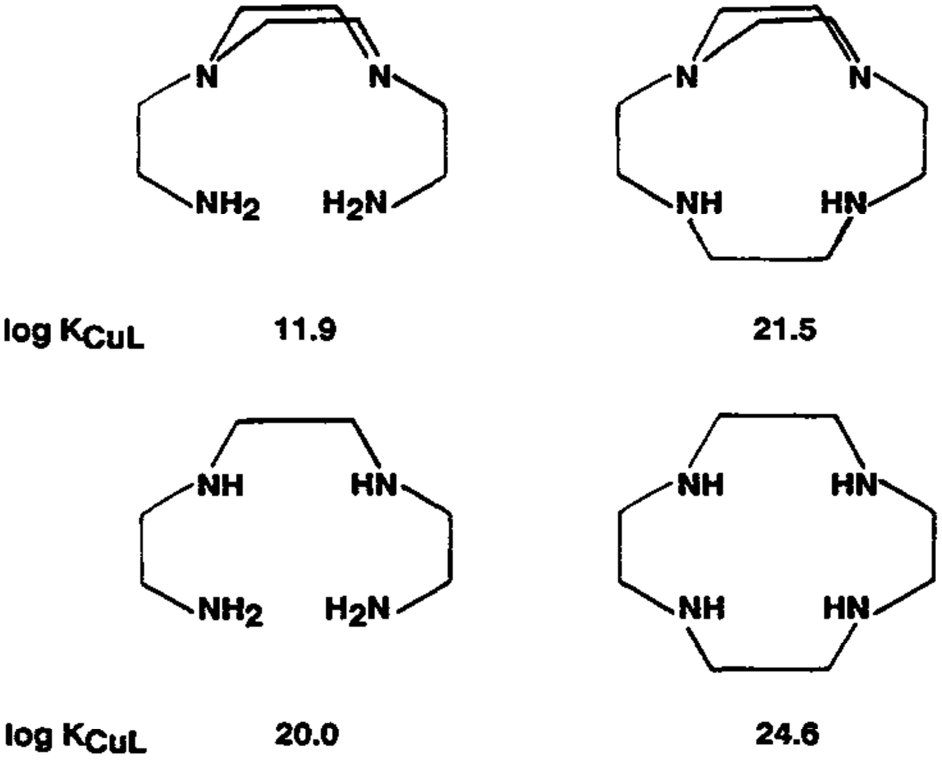


Fig. 6. A large macrocyclic effect.

However, the greatest effect is due to the fact that the piperidine side ring is no doubt in the chair form in the free ligand while it is necessarily in the boat form in the macrocyclic ligand. Conversion of the chair form to the boat form would require considerable energy, which must be overcome in metal complex formation. Therefore, the free open-chain ligand containing the piperidine ring is a good indication of lack of preorganization while the macrocyclic ligand is highly preorganized for complex formation. The open-chain ligand containing the piperidine ring may be described as preorganized in an unfavorable manner relative to the unconstrained triethylenetetraamine molecule. The stability constant of the rigid open-chain polyamine with Cu^{2+} is 8.1 log units lower than its flexible open-chain analog. That there is a very large effect in going from triethylenetetramine to cyclen is obvious.

To summarize, the effects of increased basicity due to alkylation and of preorganization may be seen in Fig. 7 [14]. The increased basicity of the donor atoms in the series of compounds shown is due to increased alkylation for the open-chain ligands. The final step in closing the macrocyclic ring, which involves the conversion of formula III to IV, is in part due to increased basicity of the donor nitrogens tied together by the additional alkylene group. The remainder of the large increase in stability is due to preorganization of the macrocycle compared to the open-chain ligands.

4.4 Metal chelate ring size

It has been shown above that, because of the "bite-size" and angles of 5- and 6-membered rings, metal complexes that form six-membered chelate rings are more stable for small metal ions than for large metal ions, and that larger metal ions prefer to form five-membered chelate rings. These effects are clearly seen in the stabilities of the tetraaza macrocycles in Fig. 8 in which one of the chelate rings is steadily increased from five to six, seven and eight atoms [7,23]. It is seen that the stabilities

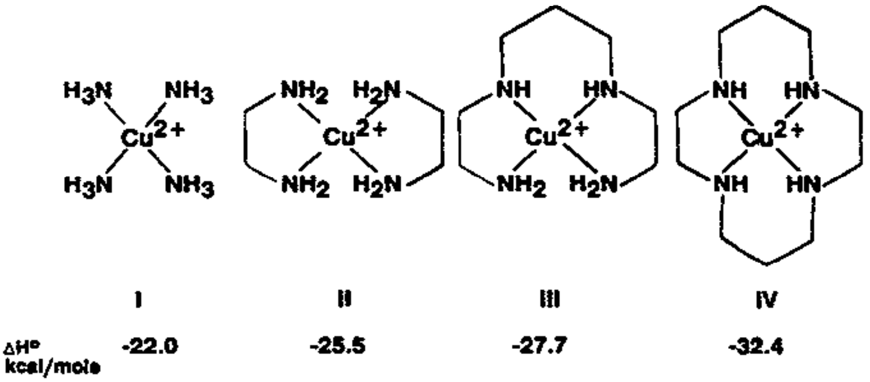


Fig. 7. Increase in covalence of M–N bond resulting from increased alkylation.

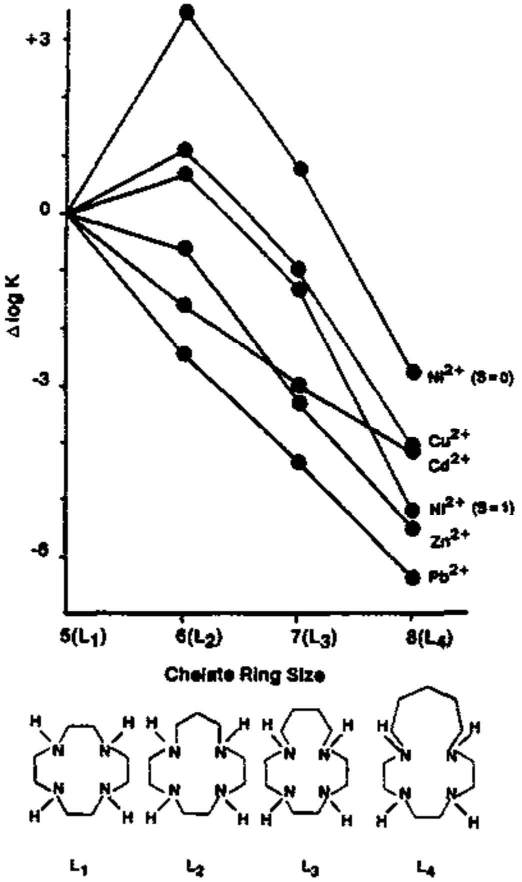


Fig. 8. The effect of increasing chelate ring size on the stability constants of metal complexes of tetraaza macrocyclic ligands.

of the complexes of low-spin nickel(II), copper(II), and high-spin nickel(II) are more stable when the size of one of the chelate rings is expanded from five to six. Beyond that point, all the stabilities decrease with the increase of the metal chelate ring size, as would be expected. An important point is that this decrease also occurs in the first step in which the chelate ring is increased from five- to six-membered for the larger metal ions. A similar effect is seen in Fig. 9 in which the stability constants of the metal complexes of the twelve-membered tetraaza macrocycle ([12]aneN_4) are compared with the stability constants of cyclam complexes which have two six-membered chelate rings [7,14]. In this case also, going from a 5- to a 6-membered chelate ring increases the stability of the low-spin nickel(II), high-spin nickel(II) and Cu(II) complexes, while larger metal ions generally show a decrease in stability. Figures 8 and 9, therefore, show that large metal ions prefer 5-membered chelate rings over 6-membered chelate rings while the reverse is true of small metal ions.

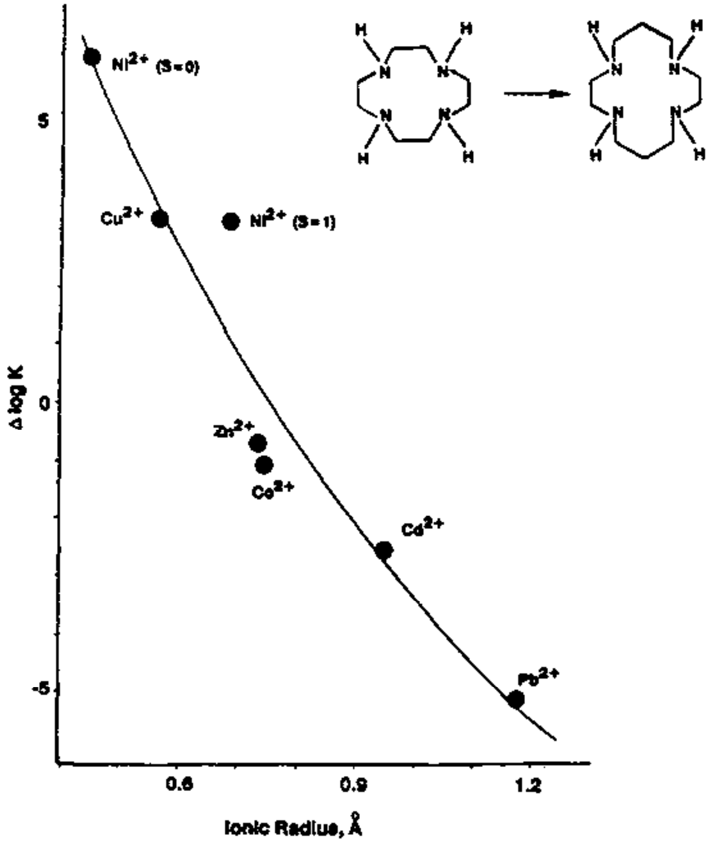
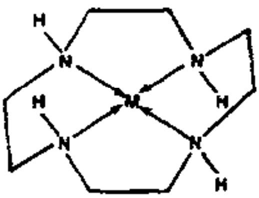


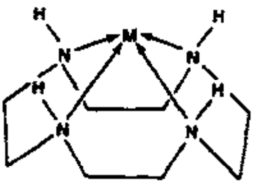
Fig. 9. The effect of increase in chelate ring size on the stability of complexes of tetraaza macrocycles as a function of metal ion size.

4.5 Size-fit relationships

The size-fit concept has been very popular for explaining why macrocyclic complexes of a given size show a maximum affinity for metal ions that fit into the macrocyclic ring most closely. It should be pointed out, however, that what appears to be the size-fit relationship in stability constants has alternative explanations. For example, a 12-membered macrocyclic ring indicated below can accommodate a small metal ion in the plane of the macrocyclic donor atoms (as illustrated by the *trans*-III structure) but the same macrocycle ([12]aneN_4) can assume a different conformation which will allow it to complex larger metal ions quite strongly [13]. This can happen in the conformer shown on the right (*trans*-I) in which the coordination tendencies of the macrocyclic ring are directed above the plane of the ring so the larger metal ion can rise above the nitrogen plane and still be coordinated by the macrocyclic ring donor atoms.



7 *Trans*-III



8 *Trans*-I

Thus it is seen that a metal ion that is too large to fit into the macrocyclic ring can also be coordinated very strongly by the macrocycle. In Fig. 10 are plotted the stabilities of the complexes formed between alkali metal ions and various oxygen macrocycles as well as an open-chain analog and a cryptand structure [13]. It is seen that, in all cases, the stability constant increases with ion size to a maximum at potassium ion and then decreases, the sharpness of the decrease varying considerably with the type of macrocycle involved. The same kind of behavior is seen with the open-chain analog, Kryptofix, which has five oxygen donors and is thus analogous to the macrocyclic ligand 15-crown-5. While it is tempting to assume that the size of the potassium ion best fits into the macrocyclic rings, the effect of the open-chain

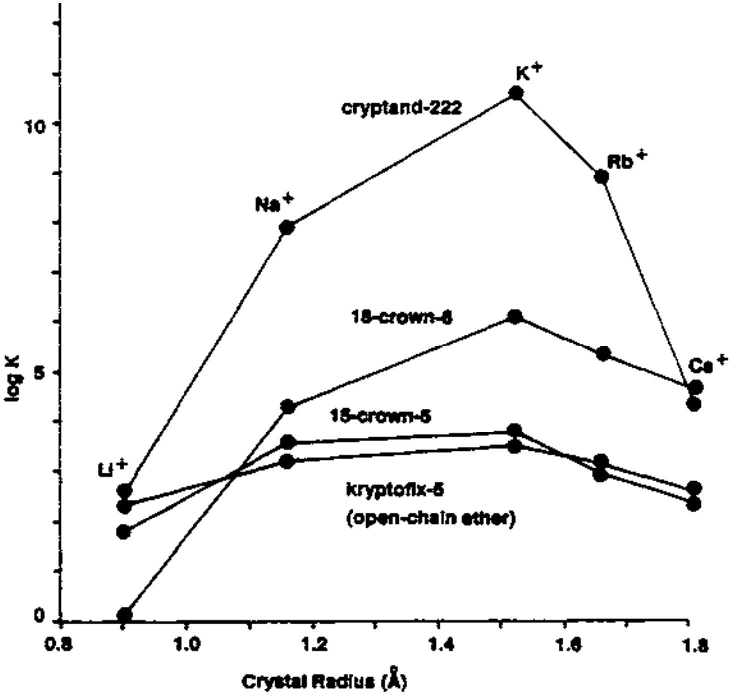


Fig. 10. Formation constants, log K_1, in methanol of a variety of ligands, complexing with the alkali metal ions, as a function of crystal radius of the metal ion.

ligand cannot be explained in a similar fashion. There is an alternative explanation for the behavior illustrated in Fig. 10 in that the small metal ions can not take advantage of all of the donor atoms of the ligand because their coordination numbers are smaller. Thus the stability would increase with coordination number and ion size. Beyond potassium ion, however, the effect of weaker coordinate bonding of the larger metal ions is seen in the decrease of the stability of the complexes formed. Thus the stabilities of the rubidium and cesium complexes would be lower than that produced by the potassium ion, as expected. Therefore the effects seen in Fig. 10 are explained easily on the basis of the coordination reactions between the metal ion and the ligand and a size-fit concept is not necessary to explain the relative stabilities of these complexes. It should also be noted that all of the crown ethers, as well as the open-chain analog, Kryptofix, form five-membered chelate rings with metal ions, which correlates with the data plotted in Fig. 10, which shows maxima at K^+ rather than the somewhat smaller Na^+ ion, as Hancock [24] has pointed out.

5. THE CRYPTATE EFFECT

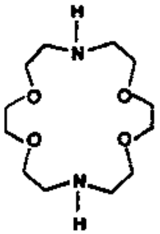
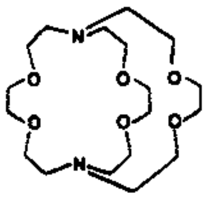
The factors which contribute to the higher stability of macrocyclic complexes over the complexes of open-chain donors are also responsible for the still higher stability of the cryptate complexes over the corresponding macrocyclic compounds. These involve greater intrinsic basicity of the donor atoms of the cryptand due to the alkyl groups which form the additional bridging linkage connecting the donor atoms. In addition to this, of course, there is additional preorganization of the ligand since the three-dimensional structure greatly reduces the freedom of motion of the ligand and donor atoms of the cryptand over that of the macrocyclic ligand. Cryptands are also characterized by a low entropy of formation due to the restriction of vibrational motion and a low degree of solvation (per donor group) due to the proximity of the polar cryptand donor groups to each other. These factors all work towards increased stability of the metal complex that is formed from the cryptand over that of the analogous macrocyclic ligand. The increase in stability of complexes of cryptand-222 over the analogous macrocyclic ligand [18]aneN_2O_4 can be seen in Table 9 [7,25], which shows that the free energy of formation of the cryptate from the cryptand and various metal ions is almost entirely due to changes in ΔH and entropy plays only a minor role in the differences in stabilities that have been measured. These effects are most clearly seen in stabilities and enthalpies of formation of the Sr^{2+}, Ba^{2+} and Ag^+ cryptates. In the case of Cd(II) the metal ion seems to be a bit too small for the cavity in cryptand-222.

5.1 *Size-fit concept*

The size-fit idea, which seems to be unnecessary in many cases for explaining the stabilities of macrocyclic complexes, appears to be very important in explaining

TABLE 9

Thermodynamics of the cryptate effect

Metal ion					
	Sr^{2+}	Ba^{2+}	Ag^{+}	Cd^{2+}	Hg^{2+}
ΔH^0 (cryptand-222)	−10.6	−14.2	−12.8	0.5	−16.0
ΔH^0 ([18]aneN_2O_4)	−2.6	−3.0	−9.2	−0.7	−17.2
Cryptate effect ΔH^0	−8.0	−11.2	−3.6	1.2	1.2
Cryptate effect ΔG^0	−7.4	−9.0	−2.5	−2.0	−0.5

the stabilities of cryptate complexes. The three-dimensional structure of the cryptate molecule and the arrangement of donor atoms in three-dimensional positions around a central metal ion is achieved by the macrobicyclic structure. The complex thus formed achieves maximum stability when the donor atoms provided by the cryptand ligand match the coordination requirements of the metal ion with respect to coordination number and to the lengths and angles of the coordinate bonds formed. For a symmetrical structure, movement of the metal ion from the central position would lengthen the coordinate bonds to some of the donor groups and thus weaken the complex. In other words, the most favorable position for the metal ion is at the very center of the macrobicyclic array of donor groups. Thus a metal ion that is large enough to fit within the macrobicyclic structure and to take advantage of all the coordinate bonds formed by the donor groups of the cryptand provides the complex of maximum stability. Any metal ion that is too large to fit into the macrobicyclic structure will, of course, not be effectively complexed by the ligand. Any metal ion that is too small to take advantage of all the donor groups of the cryptand (has a coordinate number smaller than the number of donor groups of the cryptand ligand) will, of course, form weaker complexes than metal ions which take full advantage of the ligand, other factors being equal.

5.2 Incomplete preorganization

Although the degree of preorganization in the macrobicyclic (cryptand) ligand is greater than that of a macrocyclic ligand, and much greater than that of an open-chain chelating ligand, preorganization in macrobicyclic complexes is, in many cases, far from complete. An example is shown in the conversion of the natural form of the

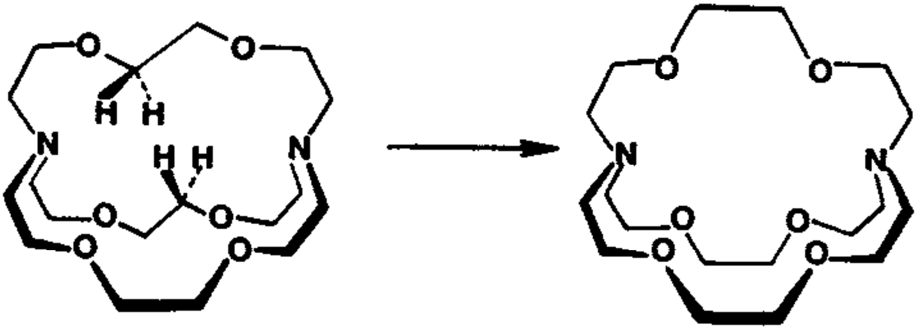


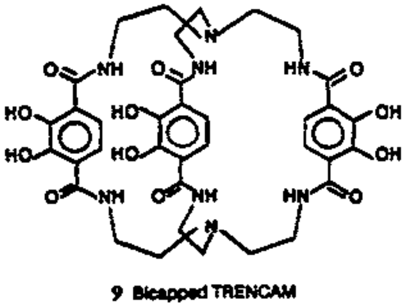
Fig. 11. Representation of the structures of the free ligands as for cryptand-222 (left) and the conformations required for coordination to the metal ions (right).

cryptand-222 ligand, which contains six coordinating ether oxygen atoms from the natural structure to the structure that will allow it effectively to coordinate the central metal ion, as is indicated in Fig. 11 [13,26].

The macrobicyclic ligand exists in a collapsed form in polar solvents in order to maximize the hydrophobic interactions of the hydrocarbon groups, and with the ether oxygens extending as much as possible into the solvent to maximize the solvation of the polar groups with solvent molecules. Thus the ligand is not preorganized for metal complex formation and must be converted to the formula on the right at the expense of a considerable amount of energy, resulting from the greater separation of dipoles and the release of solvated solvent molecules.

Raymond and co-workers [27,28] recently prepared a macrobicyclic (cryptand) triscatechol which they called bicapped TRENCAM, 9, in the hope that it would produce an iron chelate of exceptionally high stability. No appreciable cryptate effect was found (stability constant $10^{43.1}$ compared with a stability constant of the open-chain analog, TRENCAM, of $10^{43.6}$), although its binding of iron(III) at physiological pH is considerably higher than that of the open-chain analog because of the fact that it has considerably lower pK values.

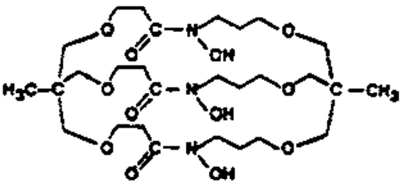
The lack of a cryptate effect in this case is due mainly to the fact that the ligand is not completely preorganized in that the uncomplexed catecholate groups



9 Bicapped TRENCAM

face into the solution to maximize their interactions with the polar solvent molecules instead of taking up the position they would have for complexing the ferric ion. Also, the lengths of the covalent linkages holding the donor groups together are not ideal for the formation of a complex of maximum stability, as indicated by the fact that the crystal structure of ferric chelate of bicapped TRENCAM has a trigonal prismatic arrangement of the donor groups [17] rather than the preferred lower-energy octahedral arrangement.

A similar effect has been observed by Sun and Martell [29] and by Motekaitis et al. [30] for a cryptate, **10**, containing 3-bidentate hydroxamate donor groups. Here, the measured stability constant is only $10^{29.1}$ as compared with $10^{28.1}$ and $10^{31.0}$ for the open-chain analogs.



10 Trishydroxamate cryptand

The lack of a cryptate effect here is probably due to the same reasons as those noted above for bicapped TRENCAM: the donor groups are not preorganized by facing into the crypt in the positions that would be used for coordinating a central metal ion (such as Fe(III)) but rather face out into the solution to maximize the polar interactions with solvent molecules. Also, the use of molecular models indicates that the arms connecting the hydroxamate moieties in the cryptand ligand are not of the ideal size for placing the hydroxamate donor groups around the metal ion in the most favorable position. The use of molecular models indicates that bridging groups containing two carbon atoms would produce a closer fit. The obtaining of a very close fit, resulting in a higher degree of preorganization, is probably not possible due to limitations in the synthetic methods available and the fact that, even with the changes suggested, the fit is not a perfect one.

Thus it is seen that, in macrobicyclic ligands (cryptands) which have the highest degree of preorganization of all the ligand types described above, the degree of preorganization of macrobicyclic complexes is far from perfect. Ideally, the ligand should fit around the metal ion so as to provide donor groups at the right distance and geometrical arrangement for the maximum stability of a metal complex formed. Here the size-fit concept is valid and applies directly to explaining maximization of complex formation of stability constants. However, the donor groups of the free cryptand ligand are solvated to a considerable extent by rotation away from their most favored positions for complex formation, and the synthetic limitations for building the connecting arms of the cryptand severely limit the number of choices that are possible and the closeness of fit of the ligand donor groups around the metal ion.

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