Comments on Inorganic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455155

The Chelate, Cryptate and Macrocyclic Effects

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To cite this Article Hancock, Robert D. and Martell, Arthur E.(1988) 'The Chelate, Cryptate and Macrocyclic Effects', Comments on Inorganic Chemistry, 6: 5, 237 — 284
To link to this Article: DOI: 10.1080/02603598808072293
URL: http://dx.doi.org/10.1080/02603598808072293

The Chelate, Cryptate and Macrocyclic Effects

The chelate, macrocyclic, and cryptate effects are analyzed. It is concluded that for all three effects considerable stabilization is derived from the greater basicity induced in donor atoms as ethylene bridges are added. Further considerations of importance in these effects are (1) desolvation effects, where steric constraints to solvation of the donor atoms in the free ligand lead to increased complex stability, (2) enforced dipole–dipole repulsion in the ligand, which is relieved on complex formation, and (3) structural preorganization of the ligand such that the donor atoms in the free ligand are already correctly oriented for complex formation. Only for the chelate effect is entropy of paramount importance, where it is derived from a cratic effect. It is emphasized that the level of preorganization of macrocycles, and to a lesser extent cryptands, is much lower than commonly realized. Newly emerging types of more highly preorganized ligands are discussed.

INTRODUCTION

The chelate,[1] macrocyclic,[2] and cryptate[3] effects are of major importance in coordination chemistry because they allow for the design of ligands which display greatly enhanced complex stability and metal–ion selectivity. Figure 1 shows the changes in complex stability for the metal ions Cu(II) and Pb(II) as the structure of the simple diammine complexes is elaborated through chelating macrocyclic, and finally cryptand ligands. The selectivity aspect is illustrated by the Cu/Pb selectivity, i.e., log K for the Cu(II) complex minus log K for the Pb(II) complex through this series of complexes. For the simple diammine the Cu/Pb selectivity is five log units in favor of Cu, but by the time the cryptand-2,2,2 is

Comments Inorg. Chem.
1988, Vol. 6, Nos. 5 & 6, pp. 237–284
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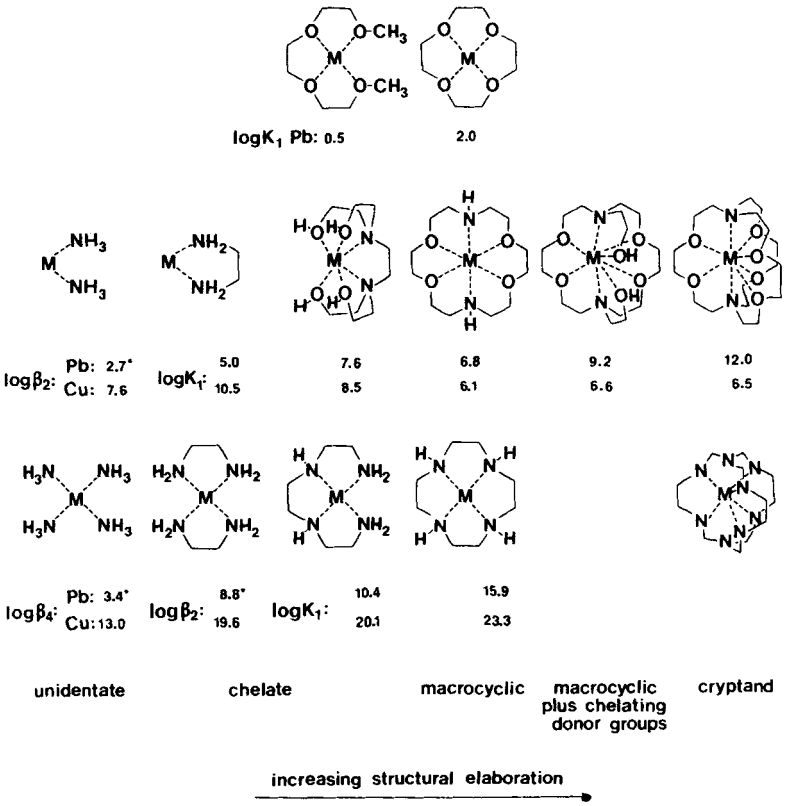


FIGURE 1 A selection of complexes showing the effect on complex stability for Pb(II) and Cu(II) as the complexity of the ligands increases along the series unidentate, chelate, macrocyclic, and cryptate. Formation constants are from Refs. 5, 26, 32, and 71. The log β_n values for Pb(II) marked with an asterisk (*) are estimated from the known (Ref. 26) log K_1 values by comparison with Cd(II).

reached, it has reversed to be some five orders of magnitude in favor of Pb(II).

In this Comment an attempt will be made to synthesize current ideas on the origins of the chelate, macrocyclic, and cryptate effects. In so doing two aspects, not widely considered in analyzing the origins of these effects, will be highlighted. Included in Fig. 1 are ligands which are derived from simpler analogs by the addition of chelating groups where the added donor atom is a neutral oxygen

donor. Thus, from EN is derived THEEN, and from 18-aneN_2O_4 is derived BAE-18-aneN_2O_4. Figure 1 shows that the effects on complex stability of adding neutral oxygen donors in chelating groups are very similar to the effects of adding oxygen donors to form macrocycles or cryptands. Thus, many of the properties of oxygen-donor containing macrocycles are to be understood in terms of the coordinating properties of the neutral oxygen donor atom, and are not solely produced by the presence of a macrocyclic structure. Most important here is the intrinsic basicity along the series H_2O, ROH, R_2O (R = alkyl). Similarly, many of the properties of N-donor macrocycles and chelates are to be understood in terms of the intrinsic basicity along the series NH_3, NH_2R, NHR_2, and R_3N.

The second point considered here is that of steric strain, which so often masks the intrinsic basicities of the O and N donor atoms. The steric strain increase in taking two DPTN ligands (see Fig. 2 for key to ligand abbreviations) from the low-energy conformations for the free ligand and wrapping them around the Ni(II) ion to form the complex $[Ni(DPTN)_2]^{2+}$ is some 15 kcal mol^{-1}.[4] The latter is an unfavorable contribution to complex formation almost as large as the observed[5] free energy of complex formation. One can thus hardly consider profitably the thermodynamics of complex formation for the complexes shown in Fig. 1 without taking steric strain into account. We therefore include some results of molecular mechanics (MM) calculations as an aid to understanding complex stability.

1. THE INTRINSIC BASICITY OF SATURATED NITROGEN AND OXYGEN DONORS

The protonation constants[5] along the series NH_3 through $N(CH_3)_3$ are NH_3, 9.2; NH_2CH_3, 10.6; $NH(CH_3)_2$, 10.8; $N(CH_3)_3$, 9.9. This set of data gives the impression that the intrinsic basicity varies little along this series. How then are the analogous phosphine series: PH_3, −14; $PH_2(CH_3)$, 0.0; $PH(CH_3)_2$, 3.9; $P(CH_3)_3$, 8.7, understood?[6] The measurement of gas-phase basicities of these bases[7–10] using mass and cyclotron resonance spectrometry helps to unravel the origin of these effects. In Fig. 3 is seen the free

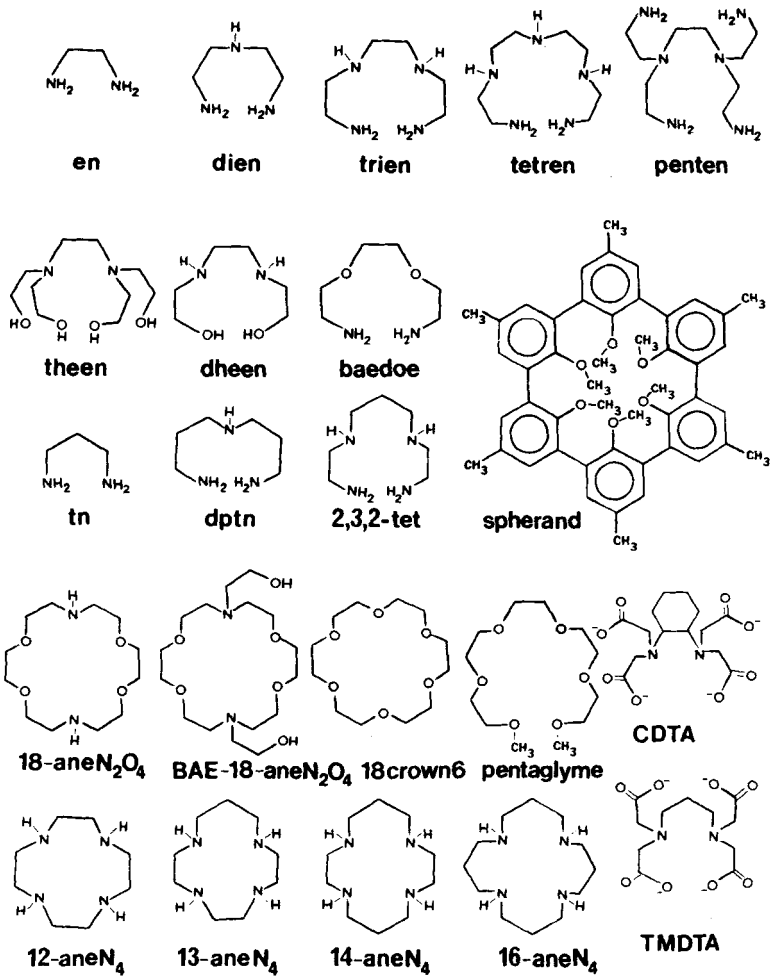


FIGURE 2 Some of the ligands discussed in this paper.

energy of protonation in the gas-phase of the series of bases NH_3 through NR_3, PH_3 through PR_3, OH_2 through OR_2, and SH_2 through SR_2 (R = methyl). It is seen that in all cases there is an increase in intrinsic basicity as hydrogens are replaced by methyl groups. Why then do the protonation constants of the amine series not display this intrinsic basicity order in water, while the phosphine

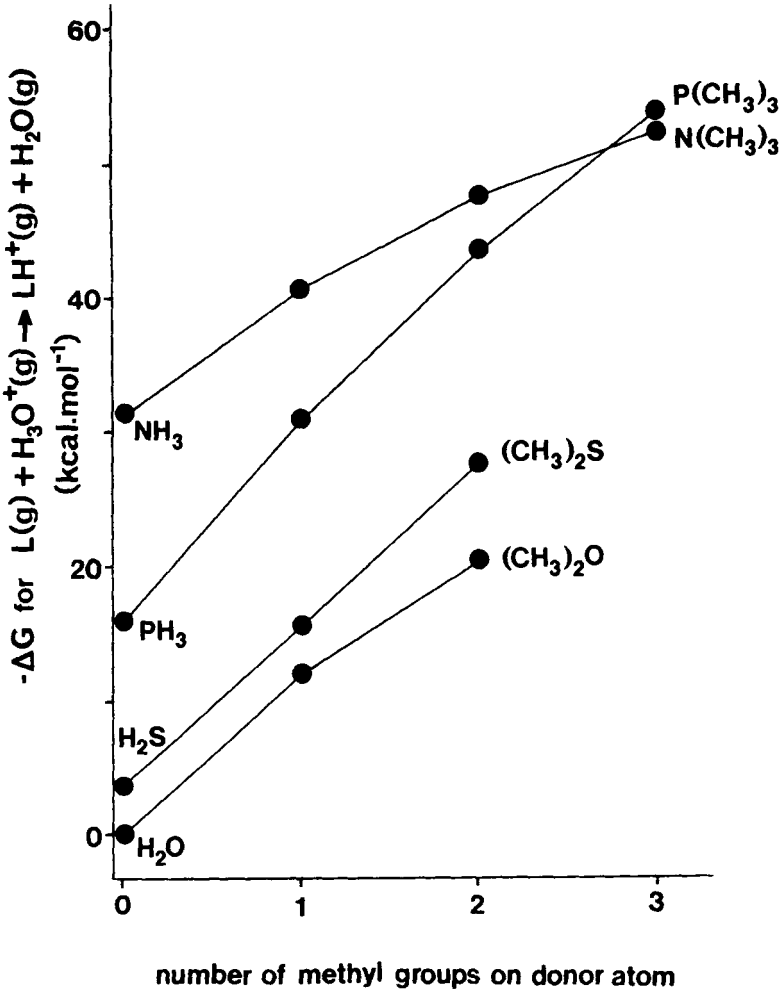
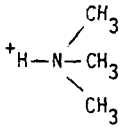


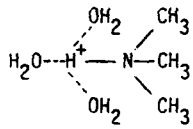
FIGURE 3 Variation of the free energy of protonation in the gas phase for various series of bases as the number of methyl groups attached to the donor atom is varied. All free energies are for the removal by the base in the gas phase of a proton from the H_3O^+ ion as indicated.

series still does? If a Born–Haber cycle is constructed for each of the amines in the above series, it becomes apparent that the poor basicity of $N(CH_3)_3$ (relative to what might be expected from the gas-phase basicities) is due to the lower energy of solvation of the $(CH_3)_3NH^+$ cation. This appears to be caused by two effects.[6] First, the proton in the gas phase is bare, and so experiences much less strain in coordinating to $N(CH_3)_3$. In water, however, the proton has a bulky solvation sheath, which is sterically hindered by the methyl groups.



gas phase

bulky solvation sheath hindered by methyl groups



aqueous solution

The second factor, which is thought[11] to account for the relatively poor basicity of $N(CH_3)_3$, is inability to disperse positive charge to the solvent through hydrogen bonding. Thus, NH_4^+ is stabilized relative to $(CH_3)_3NH^+$ and PH_4^+ by the inability of the CH_3 groups on $(CH_3)_3NH^+$ and the hydrogens on PH_4^+ to hydrogen bond with the solvent. The hydrogens on PH_4^+ through $(CH_3)_3PH^+$ do not hydrogen bond to the solvent at all well. Evidently hydrogen bonding does not, unlike the series NH_4^+ through $(CH_3)_3NH^+$, determine the basicities of PH_4^+ through $(CH_3)_3PH^+$, and the basicity order in water for the phosphines resembles the gas-phase order.

Figure 4 shows the variation in enthalpy of complex formation in the gas-phase of Lewis acids other than the proton, along the series NH_3 through $N(CH_3)_3$, and H_2O through $(CH_3)_2O$. Along these two series all Lewis acids show increasing complex stability in the gas-phase as hydrogens on the donor atoms are replaced by methyl groups. From the above discussion, it might be anticipated that, in the absence of steric effects, Lewis acids in aqueous solution should also show increases in free energies of complex formation along the series $NH_3 < NH_2R < NHR_2 < NR_3$, and $H_2O < ROH < R_2O$. Very germane to this discussion is the E and C analysis of Drago *et al.*,[12] which suggests that there is a strong increase in covalence along these two series. One can find[12] many

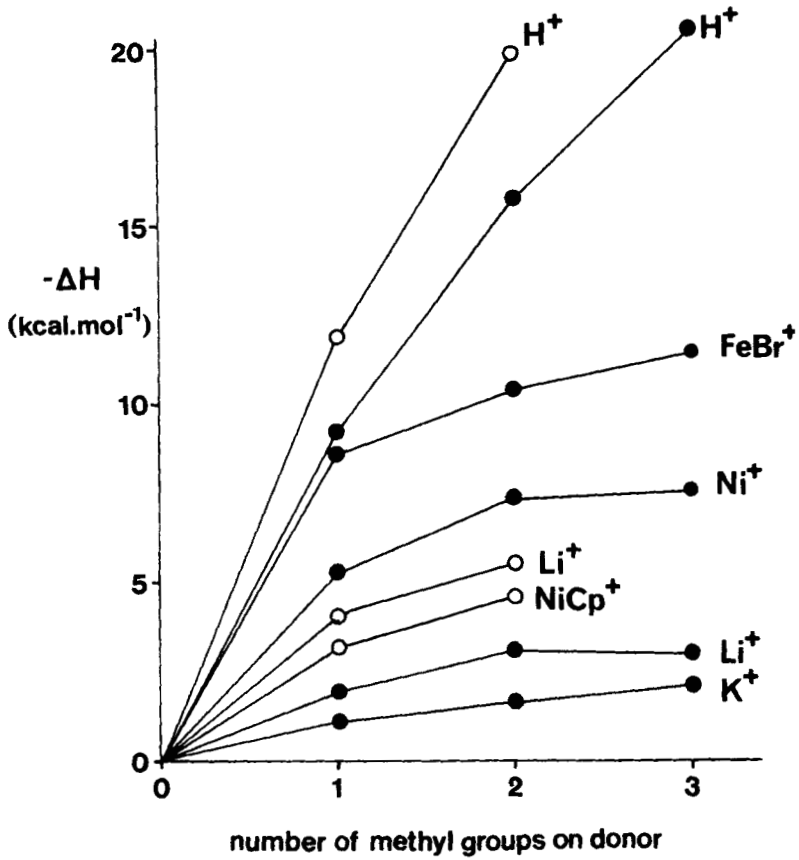


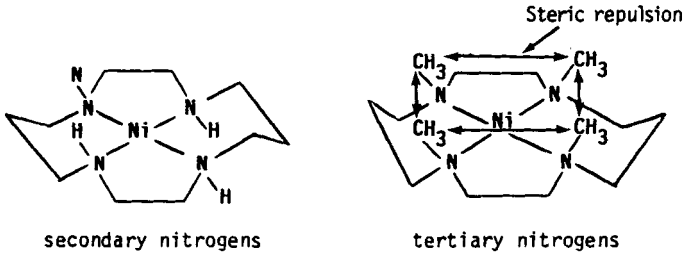
FIGURE 4 Enthalpy of complex formation in the gas phase of a variety of Lewis acids with the series of ligands NH_3, NH_2CH_3, $NH(CH_3)_2$, $N(CH_3)_3$ (●), and H_2O, CH_3OH, $(CH_3)_2O$ (○), as a function of the number of methyl groups attached to the donor atom. All the enthalpies are for the reaction where NH_3 is displaced from the complex by an amine (●), or H_2O is displaced by an alcohol or ether (○). Data from Refs. 7–10. The curvature in each series is a function of steric hindrance. It is noteworthy that the response of most metal ions, as shown by Li^+ here, to the inductive effects of added methyl groups is stronger for the oxygen donor (○) series of ligands than for the nitrogen donors (●).

examples of low steric-strain systems, such as the I_2 complexes, which in solvents of low dielectric constant show stability orders which are very strongly $NH_3 < NH_2CH_3 < NH(CH_3)_2 < N(CH_3)_3$ or $CH_3OH < (CH_3)_2O$.

2. STERIC STRAIN. THE CONSEQUENCE OF REPLACING HYDROGENS ON THE DONOR ATOMS WITH METHYL GROUPS

Molecular mechanics calculations[13] take as their premise the idea that each bond length and angle in a molecule has an ideal strain-free value. The strain-free Ni–N bond length in complexes of polyamines with low-spin Ni(II) is, for example, 1.91 Å, while the strain-free N–Ni–N bond angle is 90°.[14] The tendency of these bonds to retain these lengths and angles is modeled using force constants. Other forces in the molecule, which tend to distort the strain-free lengths and angles, are the van der Waals forces, and torsional forces, which are also simply modeled.[13] The MM calculations are able to predict the gas-phase structures of molecules or ions with a high degree of accuracy by finding the minimum strain energy structure for the complex.[13]

Consider first what happens when secondary nitrogens are turned into tertiary nitrogens by adding methyl groups to them. The MM calculations, using a strain-free Ni–N bond length of 1.91 Å in both cases, predict the Ni–N bond lengths shown.

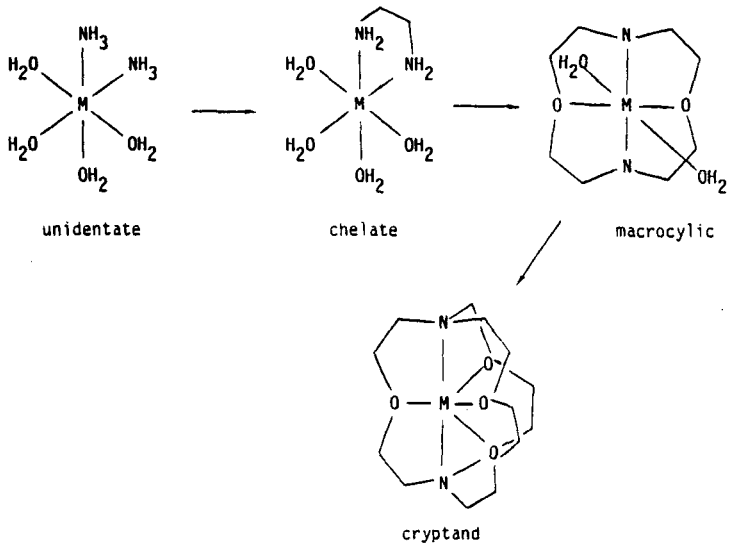


secondary nitrogens tertiary nitrogens

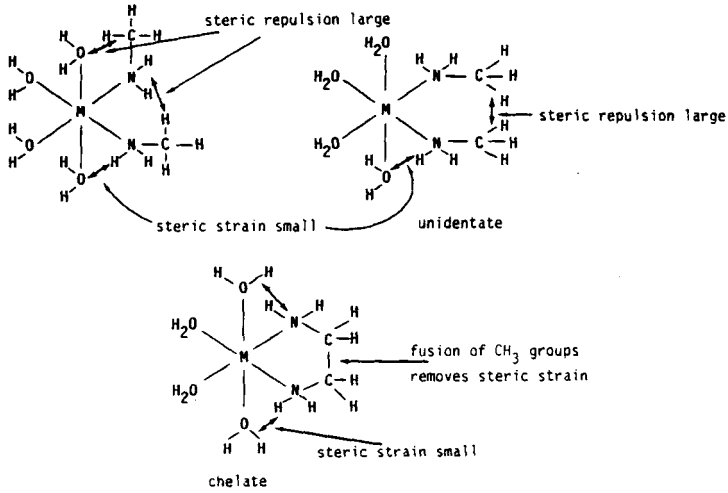
The calculations agree with the results of X-ray crystallography, even down to quite small structural details.[14] The calculations also show that the stretching of the Ni–N bonds in $[Ni(TMC)]^{2+}$ is due to van der Waals repulsions between the N-methyl groups. Accompanying the stretching of the Ni–N bonds is an increase in the total strain energy, ΣU, from 11.3 kcal mol^{-1} in $[Ni(cyclam)]^{2+}$ to 35 kcal mol^{-1} in $[Ni(TMC)]^{2+}$, which seems to be the most probable explanation for the drop in complex stability from log

K_1 = 20 for the cyclam complex[15] to only 8.6 for $[Ni(TMC)]^{2+}$.[16] The drop would be even larger except for the greater basicity of the nitrogens in the TMC complex. One should also note the accompanying drop in the ligand–field splitting parameters[17] from a value of Dq_{xy} = 2043 cm^{-1} in $[Ni(cyclam)]^{2+}$ to 1782 cm^{-1} in $[Ni(TMC)]^{2+}$. This indicates decreasing overlap in the bond as the Ni–N bond is stretched in $[Ni(TMC)]^{2+}$.

If one attaches an extra chelate ring to an existing ligand, the donor atom which acts as the point of attachment moves up one along the series primary, secondary, tertiary. The same is true when an alkyl bridge is added to form a macrocycle or cryptand:



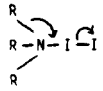
Crystallography shows that in adding a bridging alkyl group there is significantly less steric strain induced than when methyl groups are added. Molecular mechanics calculations yield similar results.[18] One may appreciate the reason for this in a very simple manner. When two methyl groups are fused to give a bridging ethylene group, the main source of van der Waals repulsion, which is between the methyl groups, or the methyl groups and adjacent coordinated groups, is removed:



A contributing factor to the stability of complexes as structural elaboration proceeds along the series unidentate, chelate, macrocyclic, cryptate might thus be expected from the fact that *donor atoms can be made better intrinsic bases by moving along the series zero order, primary, secondary, tertiary, without there being an inordinate increase in steric strain energy.*

3. LIGAND FIELD STRENGTHS OF COMPLEXES WITH UNIDENTATE, CHELATE, AND MACROCYCLIC LIGANDS

It is found[19] that charge-transfer bands in low-strain complexes such as $I_2 \cdot NH_3$ through $I_2 \cdot NR_3$ move in parallel with the heats of complex formation, indicating that increasing complex strength is caused by a process of the type



as NH_3 is changed along the series through to NR_3. This parallels the results found[20] for complexes of Ni(II). It is generally considered[21]

that LF strength in complexes of transition metal ions is a measure of covalence in the M–L bond. Consider the LF splitting parameter, 10 *Dq*, in the following series:

complex:	$[Ni(NH_3)_6]^{2+}$	$[Ni(EN)_3]^{2+}$	$[Ni(9\text{-}aneN_3)_2]^{2+}$
10 *Dq*	10750 cm^{-1}	11500 cm^{-1}	12350 cm^{-1}
	"zeroth" nitrogens	primary nitrogens	secondary nitrogens

complex:	$[Cu(NH_3)_4]^{2+}$	$[Cu(EN)_2]^{2+}$	[Cu(2,3,2-tet)]$^{2+}$	[Cu(cyclam)]$^{2+}$
10 *Dq*	17000	18300	19000	19900
nitrogens:	all "zeroth"	all primary	two primary, two secondary	all secondary

The interpretation placed upon these series is that one is increasing 10 *Dq* because the covalence in the M–N bond is increasing as the nitrogens are changed from "zeroth" to primary and then secondary. The values of 10 *Dq* follow the order of intrinsic basicity of the nitrogens only because here sufficiently low steric strain has been achieved. *A general result in macrocyclic chemistry is that where the macrocycle coordinates to the metal ion with low steric strain, very high LF strengths are observed.*

4. THE CHELATE EFFECT

A problem associated with interpreting enthalpy and entropy changes on complex formation involved in the chelate effect is that there may be differences in the extent of solvation in the two complexation equilibria, i.e., for the unidentate and for the chelate complexes being compared. If, for example, the chelate ligand has one less water of solvation than the two unidentate ligands with which it is being compared, this would lead to an overall more favorable enthalpy of complex formation, because energy would not have to be expended to remove this water molecule before the complex could be formed. However, fewer water molecules would be released on complex formation, resulting in a compensating change in the entropy contribution to the free energy of complex formation. It is thus found that free energy changes[21] are much less affected by solvation effects than are enthalpy or entropy changes. A second point to be borne in mind when analyzing the chelate

effect is the very much greater strain energy likely to be present in the complexes of complex ligands than in those of simple ligands. What is important here, of course, is the increase in strain energy, ΔU, which occurs on complex formation[18]:

$$\mathrm{M} + n\mathrm{L} \xrightarrow{\Delta U} \mathrm{ML}_n$$

$$U_{\mathrm{M}} \quad U_{\mathrm{L}} \qquad U_{\mathrm{ML}}$$

$$\Delta U = U_{\mathrm{ML}} - U_{\mathrm{M}} - nU_{\mathrm{L}}$$

Thus, for example, the value of ΔU has been calculated[18] to be only 0.6 kcal mol^{-1} for $[\mathrm{Ni(EN)_3}]^{2+}$, but some 13 kcal mol^{-1} for $[\mathrm{Ni(PENTEN)}]^{2+}$. Such very large differences in strain energy are not normally considered in simple analyses of the chelate effect. The low values of ΔU for complexes of EN suggest that these are the most appropriate for an analysis of the chelate effect.

In virtually all discussions of the chelate effect, the thermodynamics of complex formation of $[\mathrm{Cd(EN)_2}]^{2+}$ are compared with those of its methylamine or ammonia analogs. The chelate effect in this system is found[22] to be entirely due to entropy. A difficulty with both the Zn(II) and Cd(II) complexes of ammonia and EN is that discontinuities are observed in the thermodynamic parameters as more nitrogens are coordinated,[5] which suggests that the systems being compared are not necessarily similar with respect to the presence of octahedral as against tetrahedral complexes. It is probable then that the Ni(II) and Cu(II) systems with EN and NH_3 represent the best systems in which the chelate effect can be examined. In both these systems, as seen in Table I, the chelate effect is due to both a more favorable enthalpy and more favorable entropy contribution.

The arguments of Schwarzenbach[1] and Adamson[23] on the origins of the entropy contribution to the chelate effect have been covered in detail elsewhere.[24] The model of Schwarzenbach[1] considers the chelate effect to arise because, once one donor atom of a chelating ligand has been attached to a metal ion, the second donor atom is constrained to move in a greatly reduced volume as compared to the situation for the unidentate system. Adamson[23] suggested that the chelate effect arose because of the way in which the stand-

TABLE I

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

Unidentate Complex	ΔG	ΔH	ΔS	Chelate Analog	ΔG	ΔH	ΔS	ΔG^*	ΔH^* (Chelate Effect)[b]	ΔS^*	$7.9n$[c]
$[Ni(NH_3)_2(H_2O)_4]^{2+}$	−6.93	−7.8	−3	$[Ni(EN)(H_2O)_4]^{2+}$	−10.03	−9.0	4	−3.1	−1.2	7	7.9
$[Ni(NH_3)_4(H_2O)_2]^{2+}$	−11.08	−15.6	−15	$[Ni(EN)_2(H_2O)_4]^{2+}$	−18.47	−18.3	3	−7.4	−2.7	18	15.8
$[Ni(NH_3)_6]^{2+}$	−12.39	−24	−39	$[Ni(EN)_3]^{2+}$	−24.16	−28.0	−10	−11.77	−4	29	23.7
$[Cu(NH_3)_2(H_2O)_4]^{2+}$	−10.68	−11.1	−1	$[Cu(EN)(H_2O)_4]^{2+}$	−14.38	−13.1	6	−3.7	−2.0	7	7.9
$[Cu(NH_3)_4(H_2O)_2]^{2+}$	−17.74	−22.0	−14	$[Cu(EN)_2(H_2O)]^{2+}$	−26.74	−25.5	7	−9.0	−3.5	21	15.8

[a]All data from Ref. 5.

[b]The thermodynamic manifestation of the chelate effect, such that $\Delta G^* = \Delta G(\text{EN complex}) - \Delta G(NH_3 \text{ complex})$.

[c]The value of $7.9n$, where n is the number of chelate rings in the complex should be compared with ΔS^*.

ard reference state is defined, and showed that in mole fraction units the chelate effect "disappears." It is not correct to infer from the results of Adamson that the chelate effect does not exist. The chelate effect is largely due to an increase in translational entropy.[24] The translational entropy is a function of the volume of the standard reference state. When the standard reference state is one of unit mole fraction, as employed by Adamson, it refers to a situation where each one of the components of the equilibrium entirely fills the space of the standard reference state, and translational entropy is zero. The ideas of Adamson[23] lead to a very simple approach to the chelate effect, where each extra chelate ring in a complex should give R ln 55.5 (where 55.5 is the molality of pure water) or about 8 entropy units to the entropy of the chelate effect. This may be expressed[25] as Eq. (1) for an n-dentate polydentate ligand:

$$\log K_1(\text{polydentate}) = \log \beta_n(\text{unidentate}) + (n-1)\log 55.5 \quad (1)$$

If log β_n values for ammonia complexes are substituted into Eq. (1), it predicts log K_1 values for the polyamines which are much too low. However, if the greater basicity of the polyamines compared with ammonia is corrected for by inserting an "intrinsic basicity factor" of 1.152 (= $pK(CH_3NH_2)/pK(NH_3)$, i.e., 10.6/9.2), Eq. (2) is obtained which has very good predictive powers:

$$\log K_1(\text{polyamine}) = 1.152 \log \beta_n(NH_3) + (n-1)\log 55.5 \quad (2)$$

Equation (2) is very successful at predicting formation constants for polyamine ligands:

Complex	Ni(EN)	Ni(DIEN)	Ni(TRIEN)	Ni(TETREN)	Ni(PENTEN)
log K_1 (calc)	7.6	11.0	14.1	17.3	19.2
log K_1 (obs)	7.4	11.0	14.0	17.4	19.1

In the case of Pb^{2+} the stability of the ammines were unknown. However, the stability of the known polyamine complexes could be used in Eq. (2) to estimate log $K_1(NH_3)$ = 1.6. Subsequent study of the Pb(II)/NH_3 system yielded[26] log K_1 = 1.55. Equation (2) has been elaborated[25] to include aminocarboxylic acids, and

used to estimate log K_1 for other ammonia complexes, e.g., La^{3+}, 0.2; Sc^{3+}, 0.7; Fe^{3+}, 3.8; and UO_2^{2+}, 2.0.

The entropy contributions to the chelate effect are expected[24] from Adamson's work to be 7.9 cal deg^{-1} mol^{-1} per chelate ring. Table I shows that the entropy contributions to the chelate effect are fairly close to the expected value of $7.9n$. The extra stability due to the electron-releasing properties of the ethylene bridges of the chelate should manifest itself as ligand field stabilization energy (LFSE), if it is assumed that the LFSE is an indication of the extra covalence in the M–L bond.[21,27] In Table II is seen the difference in ΔH between the ethylenediamine complexes and their ammine analogs, for Cu(II) and Ni(II), compared with the differences in LFSE for the same pairs of complexes. It is seen that the differences in LFSE tend to be somewhat too small to account for the whole of the chelate enthalpy. However, excellent correlations between the positions of the electronic band maxima in spectra of amine

TABLE II

A comparison between the differences in enthalpy of complex formation and of ligand field stabilization energy (LFSE) in complexes of Cu(II) and Ni(II) on chelate ring formation[a]

Complex	10 Dq (cm^{-1})	ΔLFSE (kcal mol^{-1})	ΔH (kcal mol^{-1})	$-\Delta(\Delta H)$ (kcal mol^{-1})
$Ni(NH_3)_2$	9250	1.46	−7.8	1.20
Ni(EN)	9800		−9.0	
$Ni(NH_3)_4$	10000	1.33	−15.6	2.7
$Ni(EN)_2$	10500		−18.3	
$Ni(NH_3)_6$	10750	2.26	−24	4.0
$Ni(EN)_3$	11600		−28.0	
$Cu(NH_3)_2$	14800	0.6	−11.1	2.0
Cu(EN)	15200		−13.1	
$Cu(NH_3)_4$	17000	1.7	−22.0	3.5
$Cu(EN)_2$	18300		−25.5	
Cu(2,3,2-tet)	19000	1.7	−27.7	4.7
Cu(cyclam)	19900		−32.4	
Ni(2,3,2-tet)[b]	11200	~1.8	−18.6	5.5
Ni(cyclam)[b]	~11900[c]		−24.1	

[a]10 Dq values from Ref. 28, ΔH from Ref. 5.
[b]High-spin Ni(II).
[c]Estimated from band energies reported in Ref. 17.

complexes of Cu(II) and of Ni(II), and their heats of formation in aqueous solutions, have been reported,[28] which suggest that the increases in ΔH are related to covalence, but that LFSE is not the total indication thereof. This is not surprising, since 10 Dq is but a measure of the energy difference between a probably nonbonding t_{2g} energy level and an antibonding e_g level, and thus all other overlaps in the M–N bonds are ignored.[27] The fact that the LFSE does not account for all of the chelate enthalpy may therefore not signify that any of the chelate enthalpy is derived from some effect other than increased covalency in the M–L bond.

A. The Size of the Chelate Ring

The drop in complex stability which usually accompanies an increase in size of the chelate ring has been modeled by Schwarzenbach[1] and Cotton[29] in terms of models which consider entropy effects. However, the available evidence[5,30] suggests that only for very large rings (above seven-membered) do entropy effects contribute significantly to the drop in stability. The drop in complex stability is, in fact, enthalpy controlled. For six-membered chelate rings, the drop in complex stability relative to the five-membered ring analog is regarded[31] as being due to steric strain. Molecular mechanics calculations on polyamine complexes support this interpretation.[4,18] For high-spin Ni(II), the differences in ΔU, the change in strain energy on complex formation, match very well the differences in ΔH, for pairs of otherwise similar complexes, where one member of the pair has five-membered chelate rings and where the other member of the pair has six-membered chelate rings. This is seen in Table III. Of particular interest in Table III is the value of $-\Delta U$ for the 2,3,2-tet relative to the 2,2,2-tet complex. Here the six-membered ring complex of 2,3,2-tet is more stable with Ni(II) than is that of 2,2,2-tet. In agreement with general opinion, the MM calculations suggest that the greater stability of the complex of 2,3,2-tet is due to release of cumulative ring strain, which in the 2,2,2-tet complex is caused by the bite (N--N distance) of the five-membered chelate ring being too short to bridge the distance between the coordination sites on Ni(II).

TABLE III

The changes in enthalpy of complex formation of polyamine complexes of Ni(II) on increasing the chelate ring size from five- to six-membered, compared[a] with the differences in strain energy calculated by molecular mechanics calculation.[18]

Complex[b]	U^c	$-\Delta U^d$	ΔH^e	$-\Delta(\Delta H)$
Ni(EN)	1.14	1.53	−9.0	1.2
Ni(TN)	3.04		−7.8	
$Ni(EN)_2$	3.35	3.07	−18.3	3.3
$Ni(TN)_2$	7.16		−15.0	
$Ni(EN)_3$	4.57	7.44	−28.0	6.7
$Ni(TN)_3$	13.12		−21.3	
Ni(DIEN)	6.08	1.46	−11.9	1.3
Ni(DPTN)	8.28		−10.6	
$Ni(DIEN)_2$	11.87	7.97	−25.3	7.7
$Ni(DPTN)_2$	21.32		−17.6	
Ni(2,2,2-tet)	9.44	−1.82	−14.0	−3.9
Ni(2,3,2-tet)	7.32		−17.9	

[a]The difference in strain energy, $-\Delta U$, should be compared with the difference in enthalpy of complex formation, $-\Delta(\Delta H)$; units are kcal mol^{-1}.

[b]EN = ethylenediamine, TN = 1,3-diaminopropane, DIEN = 1,4,7-triazaheptane, DPTN = 1,5,9-triazanonane. All high-spin Ni(II), waters and charges neglected for simplicity.

[c]Ref. 18.

[d]Corrected for differences in strain energy of free ligands.[18]

[e]Ref. 5.

B. Metal Ion Size and the Size of the Chelate Ring

The complexes of larger metal ions are destabilized more than those of smaller metal ions by an increase in size of chelate ring.[32] This is found to be true for complexes of EDTA and its analog based on trimethylenediamine, TMDTA.[30] One can obtain a linear relation between the change in complex stability between the TMDTA complex, and the EDTA complex, $\Delta(\log K)$, and the ionic radius of the metal ion.[33] The drop in complex stability is entirely an enthalpy effect, as seen in Table IV. The change in complex stability on increase of chelate ring size is metal-ion related, and is thus not a property of the free ligand, but of the complex. Molecular mechanics calculations show[35] that the ideal size of metal ion for coordination to EN to form a minimum strain

TABLE IV

The effect of increase of chelate ring size on thermodynamics of complex formation in passing from complexes of EDTA to those of TMDTA[a]

		EDTA			TMDTA		
Metal Ion	Ionic Radius[34]	log K	ΔH	ΔS	log K	ΔH	ΔS
Cu^{2+}	0.57	18.70	−8.2	58	18.76	−7.7	60
Cd^{2+}	0.95	16.36	−9.1	44	13.83	−5.4	45
Ca^{2+}	1.00	10.61	−6.6	26	7.26	−1.7	27
La^{3+}	1.03	15.46	−2.9	61	11.28	+3.8	64
Pb^{2+}	1.18	17.88	−13.2	38	13.70	−6.4	41

[a]TMDTA = 1,3,-diaminopropane-N,N,N′, N′-tetraacetate; all data from Ref. 5; units for ΔH, kcal mol^{-1}; ΔS, cal deg^{-1} mol^{-1}.

chelate ring has a M–N bond length of 2.50 Å, and a N–M–N angle of 69°. On the other hand, the minimum strain chelate ring with TN (1,3-diaminopropane) has a M–N bond length of 1.6 Å and an N–M–N angle of 109.5°. This means that the minimum strain-energy stiuation with EN type rings will occur with metal ions such as the large La^{3+} or Pb^{2+}, which have small N–M–N angles because of their high coordination numbers. On the other hand, the lowest strain for TN complexes would occur with, ideally, a small metal ion such as Be^{2+} with its tetrahedral coordination geometry. In between these two extremes a steady progression will be found where, for example, a large metal ion such as Cd^{2+} will show a stronger preference for EN over TN than will a smaller metal ion such as Cu^{2+}.

The metal-ion size-related pattern of the dependence of complex stability on chelate ring size can be observed for many pairs of ligands, such as EDTA and TMDTA, or 2,2,2-tet and 2,3,2-tet. Even more interesting, it is also observed[33] for pairs of macrocyclic ligands, such as 12-aneN_4 and 13-aneN_4, or 13-aneN_4 and 14-aneN_4.

C. The Role of Solvation in Complexes of Charged Ligands

Martell[24] has shown that for aminocarboxylic acids, the entropy change on complex formation is proportional to the charge on the metal ion (Z^+) and on the free ligand (Z^-), and inversely proportional to the crystal radius (r^+) of the metal ion. In Fig. 5 is shown a plot of entropy change on complex formation for a variety of aminocarboxylates, ranging in size from glycine to EDTA, as a function of $-Z^+Z^-/r^+$. It has been pointed out[24] that part of the increase in ΔS with increase in number of negative charges must be due to the favorable entropy of translation effect associated with chelate ring formation. Also plotted in Fig. 5 is the entropy of complex formation for ML_2 complexes of aminocarboxylates as a function of $-Z^+Z^-/r^+$. The value of Z^- is taken as the sum of the charges on 2L. The few data available suggest that a linear relationship between $-Z^+Z^-/r^+$ and ΔS is present for the ML_2 complexes. One would expect the relationship for the ML_2 complexes to run parallel to that for the ML complexes, and be displaced downward by 7.9 cal deg^{-1} mol^{-1}, the entropy of the chelate effect. A broken line has been drawn for the ML_2 relationship to run parallel to that for the ML complexes, although

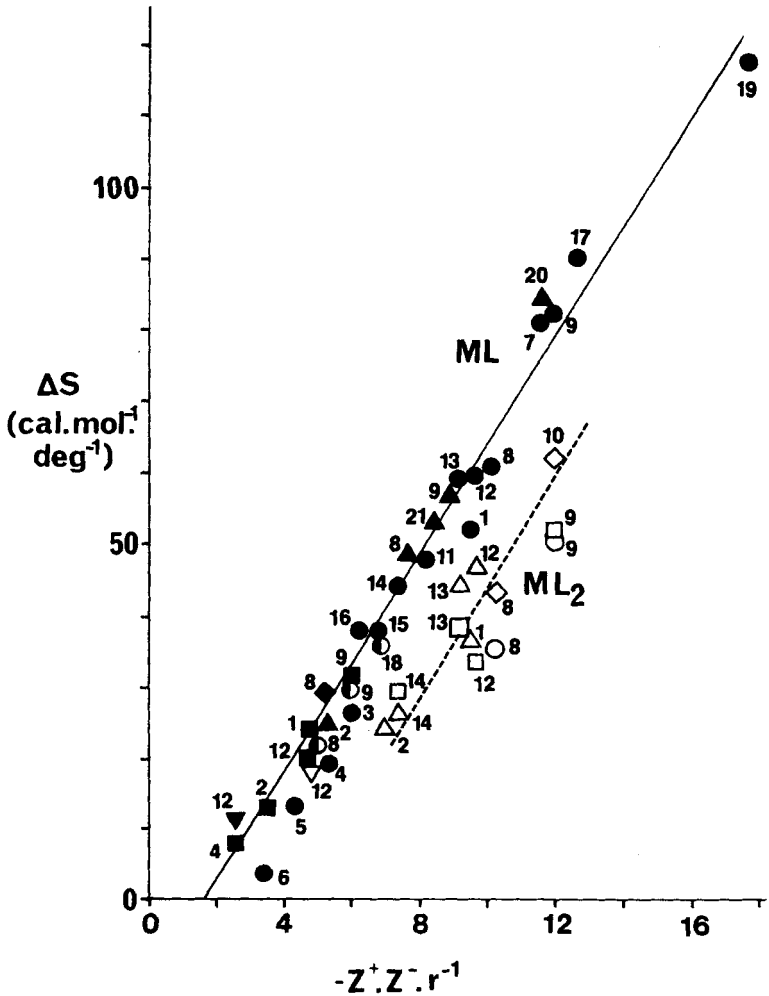


FIGURE 5 Variation of the entropy of complex formation of carboxylate containing ligands as a function of $-Z^+Z^-/r$. Data from Ref. 5. Z^+ is the oxidation state of the uncomplexed metal ion, Z^- is the number of carboxylate groups on the free ligand, and r is the crystal radius (Ref. 34) of the metal ion in Å. The ligands are, for ML complexes: glycine (▼) iminodiacetate (■), nitrilotriacetate (▲), ethylenediamine-N,N′-diacetate (◆), EDTA (●), and oxydiacetate (◐). For the ML_2 complexes, the ligands are: glycine (▽), iminodiacetate (□), ethylenediamine-N,N′-diacetate (◇), N-methyliminodiacetate (△), and oxydiacetate (○). The metal ions are Mg^{2+} (1), Ca^{2+} (2), Sr^{2+} (3), Ba^{2+} (4), Li^+ (5), Na^+ (6), Y^{3+} (7), La^{3+} (8), Lu^{3+} (9), Yb^{3+} (10), Mn^{2+} (11), Ni^{2+} (12), Zn^{2+} (13), Cd^{2+} (14), Hg^{2+} (15), Pb^{2+} (16), In^{3+} (17), Sc^{3+} (18), Al^{3+} (19), Fe^{3+} (20), Cu^{2+} (21).

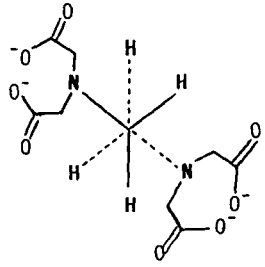
more data may reveal that the best straight line does not run parallel. However, the downward displacement appears to be in the vicinity of 15 cal deg^{-1} mol^{-1}, virtually double the expected displacement. This possibly reflects differences in degree of solvation of the free ligands and of the complexes involved in the two relationships. The actual observation of such good correlations between ΔS and $-Z^+Z^-/r^+$ appears to be derived from the amount of water which is liberated on complex formation, which in turn is a function of the charge on the metal ion, and its size, as well as the charge on the ligand.

D. Effect of Structure of the Chelate Ligand

An important aspect of coordination chemistry is the "architecture" of the ligand, and how this affects coordination to the metal ion. Familiar examples, such as the inability of the tripod ligand TREN to adapt to the planar coordination geometry required by Cu^{2+}, have already been discussed.[24] An important effect to discuss here is that of adding C-alkyl groups to the ethylene bridges of chelating ligands. The C-methylated ethylenediamines show small increases in log K as the degree of C-methylation increases. These increases in log K_1 are accompanied by increases in LF strength,[21] so that it seems reasonable to attribute them to increasing electron-releasing ability as C-methylation increases. However, when the ethylene bridge of EDTA is C-methylated, or alkylated by forming a cyclohexane ring in *trans*-CDTA, there are much larger increases in complex stability which are metal-ion independent, and entropy controlled. The results for Ca^{2+} are typical:

	log K_1	ΔH	ΔS
$[Ca(EDTA)]^{2-}$	10.6	−6.6	26
$[Ca(CDTA)]^{2-}$	13.2	−3.7	48

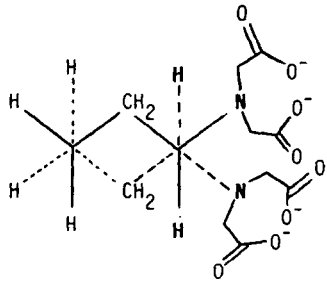
This increase in complex stability has been interpreted[36] in terms of the greater ease of assumption of the skew form of the free ligand, which is required for complex formation, whereas EDTA presumably adopts the lower energy *trans* form as the free ligand.



EDTA

viewed down the C-C axis

trans-arrangement



trans-CDTA

viewed down the C-C axis

skew-arrangement

What is important here in relation to the following discussion on the macrocyclic effect is that these are examples of *preorganization* of the ligand into the correct conformation for complex formation, which leads to higher complex stability. This is possibly an important contribution to the macrocyclic effect, where it is generally regarded that in some way preorganization might be responsible for the greater complex stability observed. It is interesting to note here that high levels of preorganization are not confined to macrocycles or cryptates, and can just as easily occur in chelating ligands.

5. THE MACROCYCLIC EFFECT

It goes without saying that any explanation of the macrocyclic effect has to be consistent with the chemical properties observed for macrocyclic complexes. Properties already mentioned are the greater thermodynamic stability, i.e., the thermodynamic manifestation of the macrocyclic effect, and the greater ligand field strength provided the macrocycle fits the metal ion. Among the more remarkable properties of complexes of macrocycles is the ability to stabilize unusual oxidation states of metal ions, for example Ni(III),[37–40] Ni(I),[41,42] Cu(III),[43,44] Co(I),[37,45,46] Ag(II),[47] Pt(III),[48] and even Hg(III).[49] Another property of interest is the kinetic inertness of

the complexes of macrocycles towards demetallation, the kinetic macrocyclic effect.

In the macrocyclic effect, the stability of the complex of the macrocyclic ligand is compared with that of its open-chain analog. The number of particles in both equilibria is the same so that no translational entropy effects are expected, which is an important difference between the macrocyclic and chelate effects. Contributions which are expected to be important in the macrocyclic effect are:

(1) preorganization of the ligand[2,4,50,51,53]
(2) desolvation of the donor atoms in the confined space of the macrocyclic cavity[2]
(3) intrinsic basicity effects[52]
(4) dipole–dipole repulsion in the cavity of the ligand[52,53,54]

Under effect (1) suggestions such as "prestraining,"[4] "preorienting,"[50] and "multijuxtapositional fixedness" have been grouped.[51] The term "preorganization," suggested by Cram,[53] is used here for all these effects.

A property of macrocycles which is of paramount importance is the cavity in the center of the ligand. An important idea in macrocyclic chemistry is that macrocycles should display selectivity for metal ions on the basis of the match between the size of the metal ion and of the cavity in the ligand, which will be referred to here as size-match selectivity. At the same time, it is of great importance to consider what happens when there is a mismatch between the size of the metal ion and of the cavity, and, in particular, to what extent the macrocycle is able to compress the too-large metal ion.

A. The Thermodynamics of the Macrocyclic Effect

Before proceeding to consider what the relative importance of the contributions to the macrocyclic effect are, it is necessary to establish what are probably the best thermodynamic representations of the effect. In considering the chelate effect, it was possible to select very simple examples such as ethylenediamine versus ammine systems, which minimized the contributions of strain energy and other extraneous effects. Similarly, for the macrocyclic effect,

it is important to minimize differences such as strain energy in making the comparison. Thus, if as an example the Cu(II) complex of 12-aneN$_4$ is selected, the metal ion is too big for the macrocyclic cavity, and strain energy effects will make a large contribution.[50] The choice of cyclam to compare with 2,3,2-tet[2] is probably a good one for Cu(II), high-spin Ni(II), and probably also Zn(II). Molecular mechanics calculations[20] suggest that for these three metal ions, cyclam represents a minimum strain complex out of the set of tetraazamacrocycles from 12-aneN$_2$ through 16-aneN$_4$. In addition, 2,3,2-tet appears to be a best-fit situation for these metal ions, since they all form their most stable complexes with 2,3,2-tet out of the series of ligands 2,2,2-tet through 3,3,3-tet, suggesting that here too there is a minimum strain energy situation.

Table V suggests that the macrocyclic effect is, for all three metal ions, almost entirely due to a more favorable enthalpy contribution for the complex of the macrocycle. In Table VI are seen[55,56] the thermodynamic parameters for the formation of the complexes of 18-crown-6 and its open-chain analog pentaglyme with Na^+, K^+, and Ba^{2+} in 100% methanol. One sees here too that enthalpy makes a major contribution to the macrocyclic effect. For mixed-

TABLE V

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

		Cu(II)	Ni(II)[b]	Zn(II)
log K_1:	cyclam	26.5	~19.4[c]	15.5
	2,3,2-tet	23.2	15.9	12.6
	log K (MAC)	3.3	~3.5	2.9
ΔH:	cyclam	−32.4	−24.1	−14.8
	2,3,2-tet	−27.7	−18.6	−11.9
	ΔH (MAC)	−4.7	−5.5	−2.9
ΔS:	cyclam	13	~8	21
	2,3,2-tet	13	10	18
	ΔS (MAC)	0	~−2	3

[a]For key to ligand abbreviations, see Fig. 2; units ΔH, kcal mol^{-1}, ΔS, cal deg mol^{-1}; the thermodynamic contributions to the macrocyclic effect are log K (MAC), ΔH (MAC), and ΔS (MAC).

[b]All quantities refer to high-spin Ni(II).

[c]This value is somewhat lower than that reported in Ref. 2(b), and is from Ref. 15.

TABLE VI

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

		Na^+	K^+	Ba^{2+}
log K_1	18-crown-6	4.36	6.06	7.04
	pentaglyme[b]	1.44	2.1	2.3
	log K (MAC)	2.92	3.96	4.74
ΔH[c]	18-crown-6	−8.4	−13.4	−10.4
	pentaglyme	−4.0	−8.7	−5.69
	ΔH (MAC)	−4.4	−4.7	−4.8
ΔS[d]	18-crown-6	−8	−17	−3
	pentaglyme	−7	−20	−8
	ΔS (MAC)	−1	3	5

[a]Data from Refs. 55 and 56.
[b]Pentaglyme = $CH_3(OCH_2CH_2)_5OCH_3$.
[c]Units are kcal mol^{-1}.
[d]Units are cal deg^{-1} mol^{-1}.

donor macrocycles containing S, N, and O donors, Arnaud-Neu *et al.*[57] concluded that both enthalpy and entropy contributed to the macrocyclic effect. The evidence appears to suggest, then, that if there is not a serious mismatch between the size of the metal ion and the macrocyclic cavity, there will always be a substantial contribution from enthalpy to the macrocyclic effect, with entropy sometimes contributing, but usually to a lesser extent.

B. The Role of Preorganization, Desolvation, and Dipole–Dipole Repulsion

In the simplest case preorganization of the ligand, as is found for the nonmacrocyclic CDTA ligand,[36] involves the ligand already being in the right conformation for complex formation. In the case of 18-crown-6, and also the cryptand-2,2,2 as seen in Fig. 6, the ligands are not preorgagnized, in the sense that they are not in the same conformation as found in the complex. The conformation for[58] the free 18-crown-6 is the C_i conformation shown in Fig. 6, while that for the K^+ complex is D_{3d}. The conformation of the free ligand[59] cryptand-2,2,2 is similar to that of 18-crown-6, in that in both cases there are methylene groups which are folded into the cavity in the ligand. MM calculations show[60] that these folded

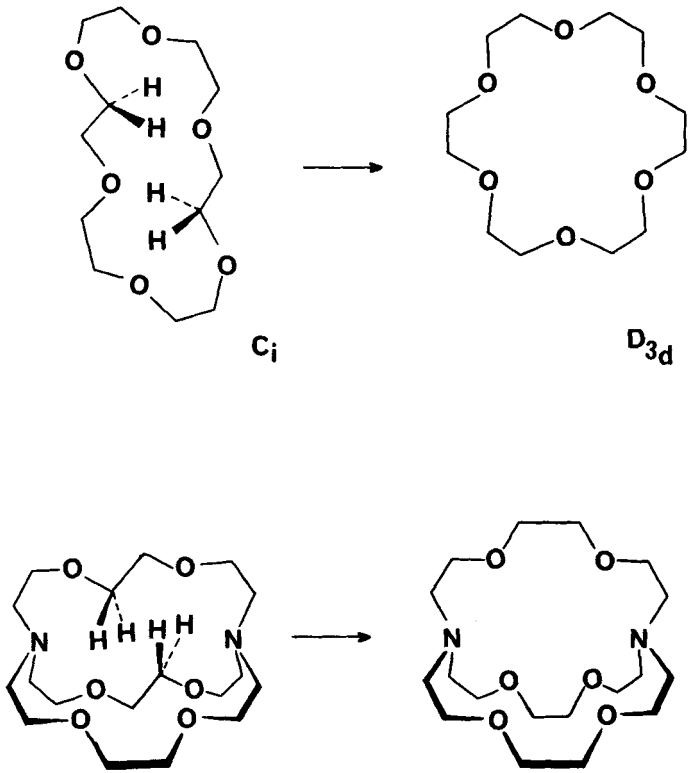


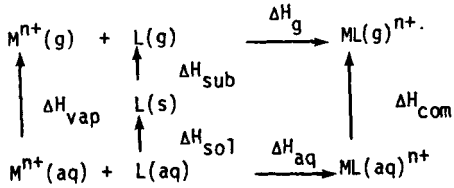
FIGURE 6 Diagrammatic representation of the structures of the free ligands as observed in the crystal structures (Refs. 58, 59) for 18-crown-6 and cryptand-222 (left-hand side), and the conformations required for coordination to metal ions (right-hand side). Modified after Ref. 53.

conformations are adopted in order to lessen dipole–dipole repulsion. Because of dipole–dipole repulsion the energy of the D_{3d} conformation of the free ligand 18-crown-6 is considerably higher than the energy of the C_i. Thus, there will be a considerable increase in strain energy in rearranging the ligand into a conformation suitable for complex formation. However, the MM calculations[60(b)] suggest that this will still be a lesser increase in strain energy than is the case for pentaglyme in forming its complex with K^+. The free ligand 18-crown-6 is thus not preorganized in the sense that it is already in the right conformation for complex

formation. However, it is, even in the C_i conformer, in a high strain energy state. Thus, in the gas phase, the macrocyclic effect here might be derived from the fact that the free ligand is in a higher energy state for the macrocycle than for the open-chain analog. If 18-crown-6 is dissolved in water, it is likely that solvation lessens the dipole–dipole repulsion[60(b)] and a D_{3d}-like conformation is adopted.[60(c)] However, it is here probable that the solvation of 18-crown-6 would be less than that of pentaglyme. Under these differing conditions the macrocyclic effect would be observed in the gas-phase or low dielectric constant solvents because of the higher strain energy in 18-crown-6 than in pentaglyme, but the macrocyclic effect would in water be one due to differential solvation. The structure of 18-crown-6 in the solid state[58] and in solvents of low dielectric constant is C_i, and here dipole–dipole repulsion appears to be minimized by folding of the ligand in on itself. However, if the ligand is sufficiently rigid, as in the spherands, shown in Fig. 2, then it appears that dipole–dipole repulsion cannot be avoided, and in this case the very large affinity which the spherand displays for Li^+ may be traced directly to the relief of dipole–dipole repulsion on complex formation.[53] It thus seems possible that all three of the effects discussed here, namely preorganization, solvation, and dipole–dipole repulsion can contribute to the macrocyclic effect under appropriate conditions. *The important factor here is that all three types of effect lead to a high energy state for the macrocycle, which is relieved on complex formation.*

Molecular mechanics calculations on cyclam and 2,3,2-tet[20,52] show similar results to those on crown ethers. For the free ligands, if the dipole–dipole repulsion in the macrocyclic cavity is ignored, the increase in strain energy on complex formation with Ni(II), ΔU, is about the same for both 2,3,2-tet and cyclam. When dipoles are placed on the nitrogens, the enforced dipole–dipole repulsion in the macrocyclic cavity of cyclam leads to a very much smaller ΔU due to the higher energy state of the free cyclam ligand. It was considered that solvation of these dipoles would simply change the origin of the macrocyclic cavity to an origin in solvation differences.[20] However, these calculations suggested that not all of the macrocyclic enthalpy would be caused by solvation/dipole–dipole repulsion effects.[20,52]

Margerum,[2(b)] in his study of the thermodynamics of complex formation of Ni(II) with cyclam and 2,3,2-tet, found that the macrocyclic effect was caused entirely by a favorable enthalpy effect, with entropy actually making an unfavorable contribution. It was this result which led Margerum to make the insightful proposal regarding the role of ligand solvation, and although the thermodynamics now regarded as being most accurate are somewhat different from those of Margerum,[2(b)] the results in Tables V and VI concur with his in that the enthalpy contribution appears to be the most important. What would be required to better assess the role of ligand solvation, and the other proposals listed above, in producing the macrocyclic effect would be complete Born–Haber cycles of the type shown below for both the formation of the macrocyclic complex and its open-chain analog:



For the ligands cyclam and 2,3,2-tet a recent study[61] has shown that the heat of solution (ΔH_{sol} + ΔH_{sub} in the above cycle) was some 5.2 kcal mol^{-1} smaller for cyclam than for 2,3,2-tet. From this it was tentatively concluded that the entire macrocyclic enthalpy of -4.7 kcal mol^{-1} for the Cu(II) complex of cyclam relative to 2,3,2-tet was due to differential ligand solvation. However, to be more certain of this, it would be necessary to know ΔH_{com} for the Cu^{2+} complexes of both cyclam and 2,3,2-tet, which might also differ by 5 kcal mol^{-1}, thereby canceling out the contribution from differential solvation. Izatt *et al.*[55] measured only the heat of solution of the pure ligands into methanol (ΔH_{sol}), for 18-crown-6 and pentaglyme, and found them to be virtually identical. This tends not to support the idea of a contribution from ligand solvation, although without the heats of vaporization of the free ligands, ΔH_{sub} in the above cycle, one cannot attach too much significance to this result. The same authors also determined the size of the macrocyclic enthalpy for Na^+, K^+, and Ba^{2+} in 90% meth-

anol, and found essentially the same result as in 100% methanol reported in Table VI. This tends to suggest that here solvation effects are not important, since such a change in dielectric constant and solvating power might have been expected to cause a change in the magnitude of the contributions to the macrocyclic effect.[55] However, as discussed above, the origin of the macrocyclic effect may simply change from differential solvation to dipole–dipole repulsion as the dielectric constant is lowered.

No thermodynamics for complex formation of macrocycles and their open-chain analogs are available in the gas phase, and this is a situation which one hopes will be corrected in the not too distant future. However, some theoretical studies are available which give calculated values. Thus, Reibnegger and Rode[62] report LCAO–MO calculations on Li^+ complexes of 12-aneN_4 and its open-chain analog $(CH_3NHCH_2CH_2NHCH_2)_2$. The authors themselves point out the very approximate nature of the calculations, but suggest that a major contribution to the macrocyclic effect arises because of the large energy required to take the open-chain analog from its minimum energy linear conformer to that required for complexation, which is not necessary in the prestrained macrocycle. It is not clear from the paper what the contribution is from dipole–dipole repulsion to the high energy of the open-chain ligand when it is folded so as to coordinate to the metal ion. Of particular interest here are the calculations of Yamabe *et al.*[63] These calculations indicated that there is a considerable contribution from covalence to the stabilization of the M–O bond, suggesting that it is not entirely correct to regard the M–O bond as being purely electrostatic. A recent photoelectron spectroscopic study of crown ethers and N-donor macrocycles and their open-chain analogs[64] has indicated a greater ease of removal of electrons from the dipoles on the donor atoms of the macrocycle than of the open-chain compounds. This might be due to dipole–dipole repulsion within the macrocyclic cavity, although the structures of the macrocyclic ligands (Fig. 6) show that dipole–dipole repulsion is possibly less than might be expected.

C. The Role of Inductive Effects (Intrinsic Basicity)

The relationship betwen enthalpy of complex formation and energies of ligand field bands found[28] for polyamine complexes of Cu(II)

and Ni(II) suggests a relationship between covalence in the M–N bond, produced by inductive effects, and the enthalpy of complex formation. An indication of the importance of this is seen in the enthalpies of complex formation along the following series (compare with LF parameters in Section 3):

Complex:	$[Cu(NH_3)_4]^{2+}$	$[Cu(EN)_2]^{2+}$	$[Cu(2,3,2\text{-tet})]^{2+}$	$[Cu(cyclam)]^{2+}$
ΔH (kcal mol^{-1})	−22.0	−25.5	−27.7	−32.4

If it is assumed that the increase in ΔH along the series from $[Cu(NH_3)_4]^{2+}$ to $[Cu(2,3,2\text{-tet})]^{2+}$ is a function of the number of nitrogens pushed up one place in the series zeroth, primary, secondary, tertiary, by extrapolation a value of ΔH of about −29.9 kcal mol^{-1} for $[Cu(cyclam)]^{2+}$ would be expected. The fact that $-\Delta H$ for $[Cu(cyclam)]^{2+}$ is, at −32.4 kcal mol^{-1} somewhat higher than this suggests that the extra 2.5 kcal mol^{-1} is derived from noninductive-effect-related contributions such as differential solvation, dipole–dipole repulsion, and preorganization. One also obtains a rough estimate that 2.2 kcal mol^{-1} of the macrocyclic effect would be due to inductive effects. Theoretical calculations suggest that this figure is[20] about 3.4 kcal mol^{-1}.

Perhaps the most compelling evidence for the greater covalence of the M–N bonding in the N-donor macrocycles lies, however, in the chemistry of the complexes themselves. Thus, $[Fe(9\text{-ane}N_3)_2]^{2+}$ is low-spin, whereas its open-chain analog $[Fe(DIEN)_2]^{2+}$ is high-spin.[65] The ability of macrocyclic ligands to stabilize Ni(III) and Cu(III) is within the group of macrocycles studied[39] clearly related to ligand-field strength and covalence. If only ligand-related effects (solvation, dipole–dipole, and preorganization) were important in producing the macrocyclic effect, the tetraazamacrocycles would not be expected to be so very much better at stabilizing unusual oxidation states, even where the fit of the metal ions to the macrocycle was poorer than is found for open-chain polyamines.[39]

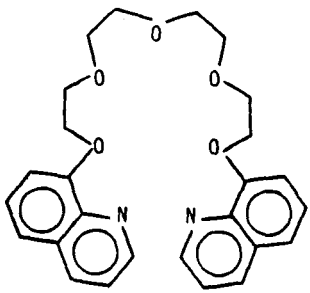
To summarize, then, the macrocyclic effect appears to be predominantly an enthalpy effect. Three ligand-related factors, preorganization, differential solvation, and dipole–dipole repulsion, probably contribute to the macrocyclic enthalpy. The contribution of one type observed under one set of conditions, e.g., low dielectric constant solvent (dipole–dipole repulsion), may change to

another[52,54] in solvents of higher dielectric constant (differential solvation), and the relative importance of each contribution will probably differ from macrocycle to macrocycle, and as a function of solvent.

The fourth contribution, the greater basicity of donor atoms along the series NH_3, NH_2R, NHR_2, NR_3, and H_2O, ROH, R_2O, makes a substantial contribution in the cases of the nitrogen donors, and accounts for many of the properties of the complexes themselves. The important aspect of macrocyclic structure is that the macrocycles are sterically efficient, and allow for the exercising of the greater basicity of the donor atoms of macrocycles without paying the steric penalties that are incurred in open-chain ligands when addition of N-alkyl groups is used to change donor atoms from primary to secondary. One might also tentatively suggest here that the greater basicity of the oxygen donor atom along the series H_2O, ROH, R_2O must contribute something to the macrocyclic effect in crown ethers, and, as discussed below, the cryptands.

D. The Size-Match Selectivity of Macrocycles for Metal Ions

This topic has already been covered in some detail elsewhere,[33] and so it will be covered here only insofar as it casts light on the nature of the macrocyclic effect. For crown ethers, as stated in the Introduction, much of the observed behavior is simply related to the coordinating properties of the neutral oxygen donor, and is not solely the product of the macrocyclic structure. Thus, the open-chain polyethers of the Kryptofix-5 type show complexing properties for the alkali metal ions very similar to those of crown ethers,[66] and even appear to display size-selectivity (Fig. 8).



Kryptofix-5

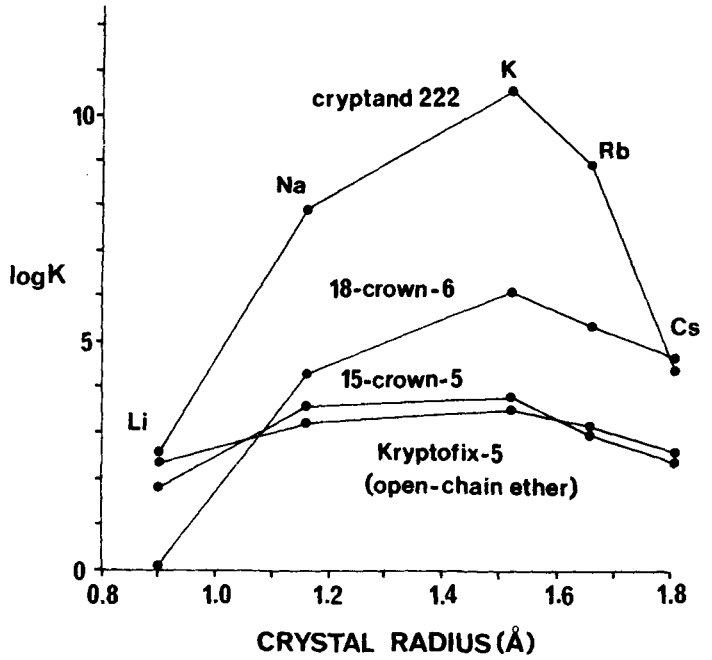
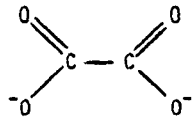
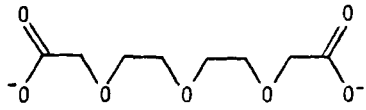


FIGURE 7 Formation constants, log K_1, in methanol of a variety of ligands, complexing with the alkali metal ions, as a function of crystal radius (Ref. 34) of the metal ion. Data from Ref. 78. Kryptofix-5 is an open-chain ether described by Weber and Vogtle (Ref. 66).

Addition of groups containing neutral oxygen donors to existing ligands virtually always has a metal-ion size-related effect on complex stability, shown for the ligands L_1 and L_2 below:



L_1 (oxalate)



L_2

Metal ion:	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
ionic radius[34] (Å):	0.72	1.00	1.18	1.35
log $K_1(L_2)$ − log $K_1(L_1)$:	−1.4	0.0	+0.5	+0.9

This type of effect is independent of the nature of the metal ion, e.g., Cu^{2+}, La^{3+}, Pb^{2+}, and simple metal-ion size appears to be the controlling factor. The interpretation put on this is in accord with ideas on intrinsic M–O bond strengths shown up by theoretical calculations.[60(b),63] Thus, in the gas phase the M–O bond strength order should follow the polarizing power of the metal ion, e.g., $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$ or $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, for both the aquo ions and the macrocycle. However, as the metal ion becomes smaller, so also the steric crowding becomes greater when the ligand is forced to coordinate to it, and it is this which leads to stability orders with macrocycles such as $K^+ > Na^+ > Li^+$. This is illustrated in Fig. 8. There is a subtle difference between selectivity so generated, and genuine size-match selectivity, in that in the former the ligand is quite flexible, and it is only the bulk of the ligand which destabilizes the complexes of smaller metal ions. In classic size-match selectivity, the cavity in the macrocycle is regarded as being rigid, and destabilization of the complexes of small metal ions is produced by their lack of fit to this rigid cavity. The importance of the distinction only becomes clear when one observes that the former type of selectivity should also be observed in the complexes of open-chain ligands, even though their greater flexibility should make it less marked than in crown ethers. This is amply illustrated by the relationship between ionic radius and $\log K_1(L_2) - \log K_1(L_1)$ found for open-chain ligands in the table above.[33] True size-match selectivity would not be observed for open-chain ligands. The drop off in complex stability as size increases for a ligand such as 18-crown-6 is not because Cs^+ or Rb^+ are too big for the macrocyclic cavity. In fact, the MM calculation shows[60(b)] that the Cs^+ ion coordinates to 18-crown-6 with *less* strain than does K^+. The stability order $K^+ > Rb^+ > Cs^+$ reflects the order of M–O bond strength[60,63] $K^+ > Rb^+ > Cs^+$ (Fig. 8), and exactly the same type of "fade" in complex stability can be found[33] with increasing metal-ion size for complexes of open-chain O-donor ligands. The suggestion of Cram[53] that simple crown ethers are too flexible to behave as though rigidly "preorganized" appears to be correct. One should also note that Pedersen[67] in his original paper on crown ethers pointed to the possible importance of differences in M–O bond energy in the aquo ion and in the crown ether complex in apparent size-selectivity.

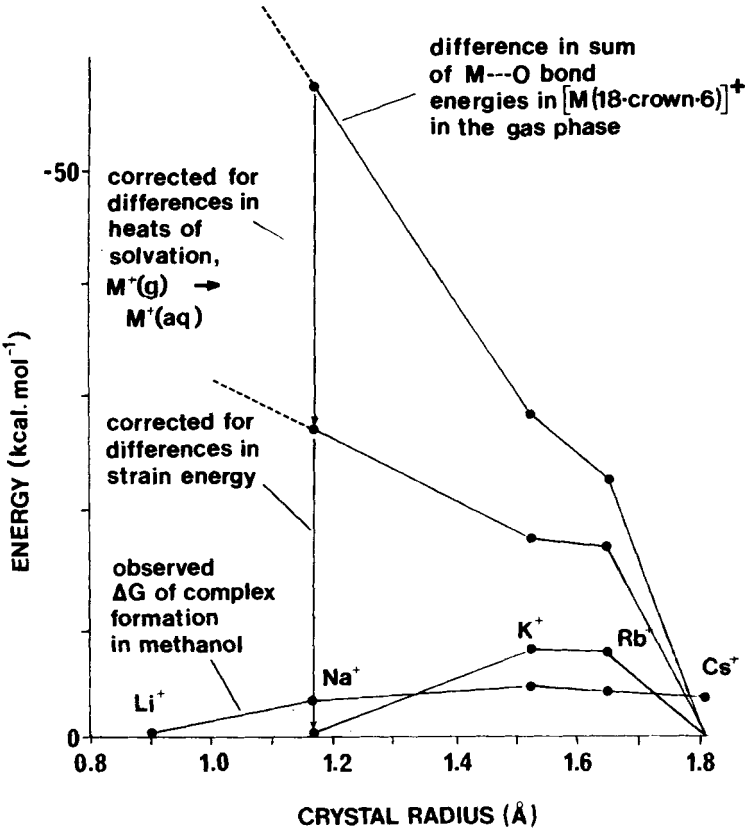


FIGURE 8 The components of the energies contributing to the final stability order observed for 18-crown-6 complexes with the alkali metal ions, as a function of radius. Since some of these individual contributions may exceed 200 kcal mol^{-1}, in order to facilitate comparison, these are plotted relative to the value for Cs^+. The uppermost relation is thus the energy for the process in the gas phase. $M^+(g) + [Cs(18\text{-crown-6})]^+(g) \rightarrow [M(18\text{-crown-6})]^+(g) + Cs^+(g)$. These energies do not contain the strain energies induced in the ligand by the process of complex formation. The next relationship down is corrected for the heats of solvation of the individual ions, and is derived from the upper relation by subtraction of the enthalpies for the process $M^+(g) + Cs^+(aq) \rightarrow M^+(aq) + Cs^+(g)$. Finally, the lowest relationship is derived by subtracting the strain energies induced by the process of complex formation, relative to the strain energy in the Cs^+ complex. This curve now resembles the observed free energies of complex formation in methanol, which are included for comparison, although it is much sharper. All energy values from Ref. 60(b). It is important to note that the strain energy in the Cs^+ complex is less than that in the K^+ complex, i.e., Cs^+ does not fit less well. The lower stability of the Cs^+ complex ultimately is derived from the lower Cs–O as compared to K–O bond strengths.

For the N-donor macrocycles, extensive molecular mechanics calculations have shown the fact that the series 12-aneN_4 through 16-aneN_4 are far more flexible than might have been appreciated.[68] For metal ions small enough to lie in the macrocyclic cavity of the smaller members of the series, something approaching size-match selectivity is observed, e.g., in Cu(II) which complexes most strongly with cyclam, the ligand which MM calculations and models suggest fits Cu(II) with least steric strain. However, for large metal ions such as Cd(II) or Pb(II), the fact that coordination probably occurs lying out of the macrocyclic cavity does not appear to offer any disadvantages, and both of these metal ions form their most stable complexes with 12-aneN_4, the member of the series which has the smallest macrocyclic cavity. The origin of the greater flexibility of the tetraazamacrocycles is to be found in the ability of the complexes to assume a number of different conformers, which differ from each other in the best-fit size of metal ion, whether the metal ion must lie in the cavity or out of it, and in the tolerance of the conformer to change in size of metal ion. The whole effect may be neatly summarized in the *trans*-I and *trans*-III conformers of 12-aneN_4, shown in Fig. 9. The *trans*-I conformer is highly flexible, and coordinates with the metal ion lying out of the plane of the macrocycle,[68] and so is strongly preferred by large metal ions. This is the strongly preferred conformer for 12-aneN_4 complexes, and this factor accounts for the strong preference of large metal ions such as Pb(II) and Cd(II) for 12-aneN_4. On the other hand, the *trans*-III conformer strongly constrains the metal ions to lie in the plane of the four donor atoms, and is therefore disfavored by too large metal ions. This conformer is strongly preferred over the *trans*-I for cyclam, and accounts for the low affinity for larger metal ions such as Pb(II) or Cd(II) for cyclam. Once again, theoretical calculations and experimental results do not support the idea of the rigid cavity in the macrocyclic ligand. Factors other than size-match selectivity are responsible for the selectivity patterns of the tetraazamacrocycles. A closer analysis suggests that the overriding factor here is not macrocyclic ring size, but the size of the chelate rings formed in the complex.[32,33] The behavior of the tetraazamacrocycles in terms of their selectivity patterns thus resembles very strongly that discussed in Section 4.B for chelates where ring size is varied. In order to generate control of ligand selectivity for

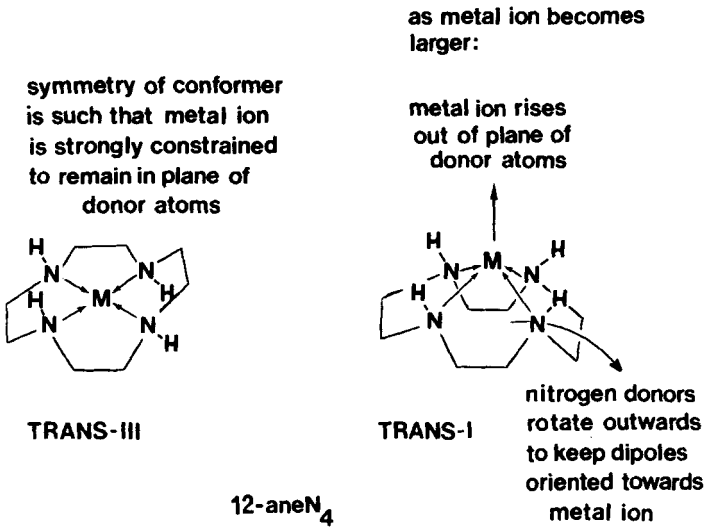


FIGURE 9 The *trans*-I and *trans*-III conformers of 12-aneN$_4$, showing diagrammatically that the *trans*-I conformer is much better able to accommodate large metal ions than is the *trans*-III.

metal ions based on something more nearly approaching size-match selectivity, one must turn to the cryptands.

E. Can Macrocycles Compress Too Large Metal Ions?

Space does not permit a detailed discussion of this question. However, molecular mechanics calculations indicate[20,52] that significant compression of metal ions by saturated macrocycles is rather unlikely. One reason for this relates to the fact that it is easier to distort bond angles and torsion angles than it is to distort bond lengths. Thus, when a metal ion is too big for a macrocyclic cavity, if possible it would prefer to undergo N–M–N bond angle distortion and rise up out of the macrocyclic cavity, than undergo M–N bond length compression.[68] Similarly, the forces in the ligand which tend to make it keep a constant hole size are rather weak, being made up, for example, of C–N–C angle bending, or N–C–C–N torsional effects. Thus, for metal ions which are slightly too big for the cavity (by < 0.05 Å), the steric strain is taken up in many small distortions of the ligand rather than significant M–N bond length compression. Just how difficult it is to compress a

metal ion is seen (Section 7) for a novel rigid macrocyclic ligand[14] where putting low-spin Ni(II) with a strain-free Ni–N length of 1.91 Å into a hole with a best-fit size of 1.73 Å results in a compression of the Ni–N bond of only 0.05 Å. *Far more stretching of the macrocyclic hole than compression of the metal ion occurs.*

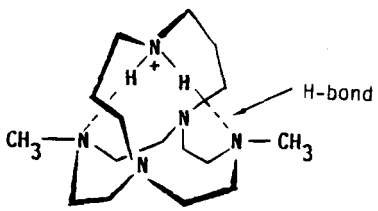
The above ligand is sufficiently rigid that the metal ion cannot escape compression, but for conventional macrocycles, a large mismatch between the size of the metal ion and of the macrocyclic cavity is easily dealt with by change in conformation. Thus, many different conformers of the macrocycle exist, which have different metal-ion size preferences, and the energy differences between these conformers are not large.[68] On the other hand, stretching of metal to ligand bonds is a common occurrence.[4,20] Stretching of the metal to ligand bond is produced by steric crowding. The forces involved in steric crowding are the very strong van der Waals repulsive forces which are easily able to overcome the forces governing M–L bond length deformation.

6. THE CRYPTATE EFFECT

The rigidity of the three-dimensional cryptates appears to be considerably greater than that of the macrocycles, and although the free ligand in cryptates is not totally preorganized, being folded in on itself (Fig. 6), once coordinated to a metal ion it appears to exert far more demanding metal-ion size requirements. This is shown in Fig. 7, where it is seen that the sharpness of the size-selectivity of the cryptand-2,2,2 is much greater than that of macrocycles such as 18-crown-6 or 15-crown-5. Indeed, the size-selectivity of 15-crown-5 is virtually identical to that of the open-chain ether Kryptofix-5 of Weber and Vogtle.[66] The interpretation placed upon the stability order $K^+ > Rb^+ > Cs^+$ for both crown ethers and the open-chain ether is that this reflects the intrinsic M–O bond strength $K^+ > Rb^+ > Cs^+$.[60(b)] However, the very much steeper slope $K^+ >> Rb^+ >> Cs^+$ observed for the cryptand must reflect a genuine steric constraint on fitting the too large Rb^+ and Cs^+ metal ions into the cavity of the cryptand.

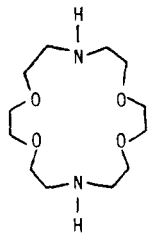
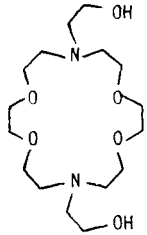
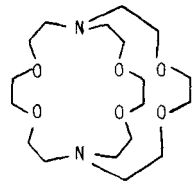
The higher level of preorganization of the cryptands as compared to other ligands leads to remarkable properties,[3] familiar now to most readers. One of the more remarkable results of the high level of preorganization found in cryptands is the first protonation con-

stant of the cryptand shown below, which is in excess of 16![69] Crystallographic analysis[69] of the protonated form of the ligand shows that the proton joins the hydrogen on the secondary nitrogen of the ligand, and that both of these protons are hydrogen bonded to one other nitrogen in the ligand. In addition, the dipoles on the remaining nitrogens are oriented to lie some 0.5 Å beneath these two protons. The H-bonds do not appear to be very unusual, and are even a little long. One might have expected something more dramatic. The structure, however, illustrates the power of preorganization. The two equivalent protons are both held within the cavity—in simple macrocycles such as cyclam one of the two protons on the protonated secondary nitrogen must lie outside the cavity, where it must be solvated by water molecules. Here the cryptand ligand provides all of the solvation for both protons—no solvent molecules have to be organized to provide solvation. As a result the ligand acts as a "proton sponge," and is not deprotonated even in 3M NaOH.[69] [An even higher proton affinity (protonation constant $\sim 10^{18}$] was estimated from rate data for the [1:1:1] macrobicyclic cryptand (P. B. Smith, J. L. Dye, J. Cheney and J. M. Lehn, J. Am. Chem. Soc. **103**, 6044 (1981).]



The first point to be made about the cryptate effect is that even here many of the coordinating properties of the cryptands are those of the neutral oxygen donor atoms. This is seen in the formation constants of the series of ligands below. This set of ligands emphasizes that in deciding on the size of the cryptate effect, one should compare ligands which have the same number of donor atoms, including oxygen donors.[70]

The following table shows that the effect of adding hydroxyethyl arms to 18-aneN_2O_4 to give BHE-18-ane-N_2O_4 can give an increase in complex stability which approaches that produced by cyclizing the two arms of BHE-18-aneN_2O_4 to give cryptand-2,2,2. In cases such as that of Cd^{2+}, where the metal ion appears to be too small

		18-aneN$_2$O$_4$	BHE-18-aneN$_2$O$_4$	cryptand-2,2,2
log K_1[71]	Pb^{2+}	6.8	9.2	12.0
	Ba^{2+}	3.0	(5.3)*	9.5
	Ca^{2+}	1.7	4.1	4.5
	Cd^{2+}	5.3	8.0	6.8
	Cu^{2+}	6.1	6.6	6.5

*The value of Ba^{2+} is estimated from that of the very similar bis(2-hydroxypropyl)analog.[70]

for the cavity of cryptand-2,2,2, the complex with monocyclic BHE-18-aneN$_2$O$_4$ may even be the more stable.

One might ask here why the complexes of BHE-18-aneN$_2$O$_4$ are more stable than those of 18-aneN$_2$O$_4$. Clearly, the presence of the hydroxyethyl arms is providing some sort of chelate effect relative to the complexes of 18-aneN$_2$O$_4$, where instead of the coordinated alcholic oxygens, water molecules might be coordinated to the metal ion. However, it seems unlikely that this chelate effect is due to a cratic term. The reason for saying this is as follows. If one imagines a hypothetical complex with a unidentate ethanol group coordinated to the metal, and supposes that the donor strength of the alcohol to the metal ion is identical to that of water, then a log K_1 for the alcohol of log 1/55.5 or -1.74 is expected, because there are 55.5 times as many water molecules as ethanol molecules in the standard reference state. The cratic contribution to the chelate effect should provide a stabilization of log 55.5, which exactly cancels out the log $K_1 = -1.74$ for ethanol, once the alcohol joins the 18-aneN$_2$O$_4$ to form a chelating group. There should thus be no net complex stabilization due to cratic effects when hydroxyethyl groups are added to existing ligands. It seems more probable that the stabilization of complexes of metal ions with BHE-18aneN$_2$O$_4$ relative to those of 18-aneN$_2$O$_4$ is due to the greater basicity of the alcoholic oxygen than the oxygen of one water

molecule, which is displaced when the alcoholic arm of BHE-18-aneN_2O_4 is coordinated to a metal ion. It is thus predicted that when the thermodynamics of complex formation for BHE-18-aneN_2O_4 become available, the stabilization relative to 18-ane-N_2O_4 will be an enthalpy effect.

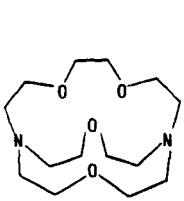
In the absence of enthalpy of complex formation data for BHE-18-aneN_2O_4, the cryptate effect must be evaluated by comparing the enthalpies and free energies of complex formation for 18-aneN_2O_4 relative to cryptand-2,2,2. The available data[5] for 18-aneN_2O_4 and cryptand-2,2,2 show that the cryptate free energy is almost entirely due to enthalpy differences:

Metal ion:	Sr^{2+}	Ba^{2+}	Ag^{+}	Cd^{2+}
ΔH (cryptand-2,2,2)	−10.6	−14.2	−12.8	0.5
ΔH (18-aneN_2O_4)	−2.6	−3.0	−9.2	−0.7
cryptate ΔH	−8.0	−11.2	−3.6	1.2
cryptate ΔG	−7.4	−9.0	−2.5	−2.0

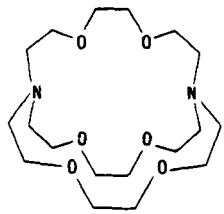
The manifestation of the cryptate ΔG as enthalpy is in accord with interpretation of the cryptate effect in exactly the same terms as the macrocyclic effect, namely differential solvation effects, dipole–dipole repulsion, inductive effects, and also preorganization effects. In the case of preorganization effects one would include prestraining effects (i.e., the cryptand free ligand is in a high state of steric strain before complex formation) as well as favorable entropic effects because of a reduction in the number of conformers possible for the ligand. As with the macrocyclic effect, such favorable entropy contributions appear to be more than cancelled out by unfavorable entropy contributions arising from the weaker solvation of the cryptand. Looking at the stability constants along the series 18-aneN_2O_4, BHE-18-aneN_2O_4, cryptand-2,2,2 it seems likely there is also a considerable contribution from inductive effects. Thus, the complexes of BHE-18-aneN_2O_4 have primary oxygen donors on their alcoholic arms, and these are turned to secondary (ethereal) oxygens on cyclization to turn BHE-18-aneN_2O_4 into cryptand-2,2,2. A considerable portion of the cryptate effect would thus be derived from the greater basicity of the ethereal oxygens of cryptand-2,2,2 as compared with the alcoholic oxygens of BHE-18-aneN_2O_4. However, the importance of this effect should vary with the ionicity of the M–O bond. Thus, with more ionic

bonding, as found for K^+ or Ba^{2+}, the contribution of increased basicity of the donor atoms should be smaller, but for more covalent metal ions such as Pb^{2+}, this contribution is expected to be substantial.

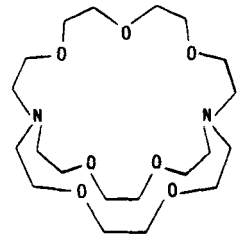
A factor which should be considered here is what effect the oxygen donors should have on the basicity of the bridgehead nitrogen atoms of, for example, cryptand-2,2,2. Most readers will be familiar with the way oxygen atoms two carbons away from a nitrogen donor will tend to decrease proton basicity. This is seen in the series of ligands where protons are progressively replaced by hydroxyethyl groups, where the protonation constants are: NH_3, 9.2; $NH_2CH_2CH_2OH$, 9.5; $NH(CH_2CH_2OH)_2$, 8.9; $N(CH_2CH_2OH)_3$, 7.8. Thus, one might have expected the inductive effects to be unfavorable on the nitrogen bridgehead atoms, and even adjacent oxygen donors, in a ligand such as cryptand 222:



cryptand 211
$pK_1 = 10.7$, $pK_2 = 7.9$



cryptand 222
$pK_1 = 9.6$, $pK_2 = 7.3$



cryptand 322
$pK_1 = 8.2$, $pK_2 = 7.3$

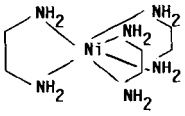
The protonation constants for cryptand-222 and cryptand-211 are much higher than for triethanolamine. Since this is not true for cryptand-322, one must assume that the high pK values for cryptand-222 and cryptand-211 represent a cryptate effect where the cavity in the ligand provides a preorganized structure allowing hydrogen bonding from the proton on the nitrogen to the oxygens, leading to stabilization. The larger cavity in cryptand-322 presumably does not provide correct preorganization for stabilizing the proton bound to the bridgehead nitrogen.

One might thus draw the inference from the low pK value of triethanolamine that oxygens will lead to electron-withdrawing effects, and increased basicity arguments cannot be used to rationalize the cryptate effect. However, if one proposes that ethoxy

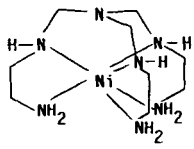
groups are electron withdrawing relative to the proton, how can one then explain the fact that the pK for ethanolamine is higher than that of ammonia? The answer is that the ethoxy group is not electron withdrawing relative to a proton, and the low basicity of triethanolamine is a solvational plus steric problem in exactly the same way as for trimethylamine. The true order of inductive effects for the ethoxy substituent is more closely reflected in the order of protonation constants: NH_3, 9.2; $NH_2CH_2CH_2OH$, 9.5; and $NH_2CH_2CH_3$, 10.8.

7. THE SEPULCHRATES

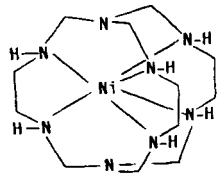
The sepulchrates, first prepared by Sargeson,[72] are formally cryptands. They have shown much interesting chemistry, including the fact that the electron-exchange rate between the Co^{2+} and Co^{3+} complex is many orders of magnitude faster than that for the analogous *tris*-EN system. In other cases where such high rates of electron exchange are found, as in the Co^{2+} and Co^{3+} *tris*-bipyridyl systems, this has been attributed to the high LF strength of the ligand providing easy access to the low-spin state of Co(II).[72] However, the LF strength of the sepulchrates appears to be no different from that of the TRIS-EN analog,[72] since the Co(II) and Co(III) TRIS-EN complexes appear to have LF spectra almost identical to those of the sepulchrate analogs. An important factor to consider here is the postulate (Section 3) that where there are secondary rather than primary nitrogen donor atoms a higher LF is expected if the metal ion is coordinated by the ligand *without excessive strain*. For the Ni(II) complexes, the following LF splitting parameters can be estimated from the reported[73] spectra:



10 Dq = 11500 cm^{-1}



10 Dq = 11990 cm^{-1}
(hemi-sepulchrate)



10 Dq = 12400 cm^{-1}
(sepulchrate)

The Ni(II) complexes follow the expectations from the presence of secondary N-donors that the LF in the sepulchrate will be higher.

High-spin Co(II) (Co–N = 2.16 Å) and Co(III) (Co–N = 1.92 Å) do not show higher LF values because they are, respectively, too big and too small for the cavity in the sepulchrate,[74] causing excessive strain. It appears that low-spin Co(II) (Co–N = 2.07 Å) is about the same size as high-spin Ni(II) (Ni–N = 2.10 Å), and should also fit the cavity in sepulchrates. The low-spin Co(II) in sepulchrate should thus be stabilized by higher LF strength, and could provide a pathway for electron exchange because of a more accessible low-spin Co(II) state in the sepulchrates than in the TRIS-EN complexes.[74]

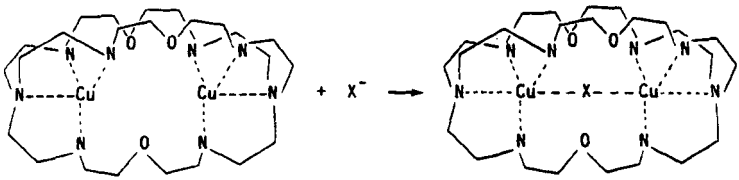
8. CONCLUSIONS AND FUTURE TRENDS

A number of views have been promoted in this review. One is that inductive effects are of importance in generating the macrocyclic and cryptate effects. Another view promoted is that macrocyclic ligands, and to a lesser extent cryptands, are not nearly as rigid or preorganized as generally imagined. The macrocycles, in particular, are relatively flexible molecules. It seems doubtful that conventional macrocycles compress metal ions to any significant extent. Macrocycles are sufficiently flexible that too large metal ions can be easily coordinated lying out of the macrocyclic plane. Size-match selectivity, whereby the most stable complex is formed where there is a closest match between the size of the metal ion and of the cavity in the ligand, appears not to be strong in macrocycles. For example, selectivity patterns with alkali metal ions are very similar in both crown ethers and in open-chain ethers where there is no cavity. The selectivity patterns for tetraaza-macrocycles do not support the idea of size-match selectivity, and the controlling feature here appears to be the size of the chelate rings formed on complex formation.

Cram[53] originally used the term preorganization in a very wide sense to also include desolvation effects and dipole–dipole repulsion effects as contributions to complex stabilization. In this sense, the order of relative preorganization of ligands is: solvents, unidentate ligands < chelates < macrocycles < cryptates. There is considerable flexibility in this order, in that a chelating ligand such as CDTA (see Section 4.D) may be more preorganized than many macrocycles. The few results available on the metal-ion complexing properties of spherands[53] suggest that these ligands, although they

are formally macrocycles, may be more preorganized than cryptands. Unsaturated macrocycles, particularly those of biological origin such as the porphyrins and corrins, also appear to have a high level of preorganization.

In the future, the synthesis of even more highly preorganized ligands than those discussed above should produce even more remarkable coordination chemistry. Pointers to this are seen in the spherands,[53] and in the "proton sponge" type of nitrogen-donor cryptand discussed above.[69] An area of preorganization of particular importance is that of "cascade" complexes, typified by the bis-copper(II) complex of the ligand BISTREN.[75] Whereas the Cu^{2+} ion in solution binds Cl^- only weakly, and there is[5] no evidence for the existence of complexes of the type $[Cu–Cl–Cu]^{3+}$ in aqueous solution, the bis-copper(II) complex of BISTREN binds Cl^- very strongly, and also has a very high affinity for OH^- ion:

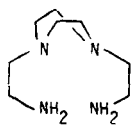


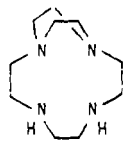
BISTREN

$$Cu^{2+} + X^- \longrightarrow CuX^+$$

X^-	$= OH^-, \log K_1 = 11.6$
X^-	$= Cl^-, \log K_1 = 3.6$
X	$= OH^-, \log K_1 = 6.3$
X	$= Cl^-, \log K_1 = 0.5$

Another interesting ligand, first synthesized by Wainwright,[76] and shown below as II, appears to be very highly preorganized.[77] The ligand shows strong size-selectivity,[77] having stronger preference for metal ions which are small enough to fit into the macrocyclic cavity:





	I	II
$\log K_1$ (Cu^{2+})	11.9	21.5

Ligand II, as seen above, shows the largest macrocyclic effect (or is the ligand a cryptand?) of which the authors are aware, of some 9.6 log units stabilization relative to the complex of I. A space-filling model of II shows hardly any space for a metal ion to fit into the cavity. A contribution to the high stability of the Cu(II) complex of II relative to I is thus probably derived from the small cavity in the free ligand of II, which precludes solvation and enforces dipole–dipole repulsion. Molecular mechanics calculations indicate a very high level of strain in the Ni(II) complex of II, which would ordinarily mean a very weak complex. Crystallographic studies of the Ni(II) complex of II show that the metal ion is actually compressed by some 0.05 Å.[14] However, the high level of strain in the complexes of II with metal ions is apparently more than offset by the high level of strain in the free ligand, so that complexes of high stability are formed.

An important task in coordination chemistry is thus the synthesis of even more highly preorganized ligands. One can only speculate on what remarkable properties might not emerge in terms of such things as size selectivity, complex stability, and the stabilization of unusual oxidation states.

Acknowledgments

The authors thank The Robert A. Welch Foundation, Grant No. A-259 (AEM) and the Foundation for Research Development, the Anderson–Capelli Fund of the University of the Witwatersrand, and the Sir Ernest Oppenheimer Trust (for the award of Travel Fellowship) (RDH) for general financial support of this work.

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References

1. G. Schwarzenbach, Helv. Chim. Acta **35**, 2344 (1952).
2. (a) D. K. Cabbiness and D. W. Margerum, J. Am. Chem. Soc. **91**, 6540 (1969). (b) D. Hinz and D. W. Margerum, Inorg. Chem. **13**, 2941 (1974).

3. J. M. Lehn, Acc. Chem. Res. **11**, 49 (1978).
4. G. J. McDougall, R. D. Hancock and J. C. A. Boeyens, J. Chem. Soc., Dalton Trans., 1438 (1978).
5. A. E. Martell and R. M. Smith, *Critical Stability Constants*, Vols. 1–5 (Plenum, New York, 1974, 1975, 1977, 1976, 1982).
6. (a) W. A. Henderson and C. A. Sperati, J. Am. Chem. Soc. **82**, 5791 (1960). (b) F. M. Jones and E. M. Arnett, Prog. Phys. Org. Chem. **11**, 263 (1974).
7. (a) M. S. B. Munson, J. Am. Chem. Soc. **87**, 2332 (1965). (b) J. I. Braumann, J. M. Riveros and L. K. Blair, *ibid.* **93**, 3914 (1971). (c) M. Taagepera, D. DeFrees, W. J. Hehre and R. W. Taft, *ibid.* **102**, 424 (1980). (d) R. W. Taft, J. F. Wolf, J. L. Beauchamp, G. Scorrano and E. M. Arnett, *ibid.* **100**, 1240 (1978).
8. R. L. Woodin and J. L. Beauchamp, J. Am. Chem. Soc. **100**, 501 (1978); *ibid.* **97**, 5920 (1975).
9. W. R. Davidson and P. Kebarle, J. Am. Chem. Soc. **69**, 6132 (1976).
10. J. S. Uppal and R. H. Staley, J. Am. Chem. Soc. **104**, 1235, 1238 (1982).
11. A. F. Trotman-Dickenson, J. Chem. Soc. 1293 (1949).
12. R. S. Drago, G. C. Vogel and T. E. Needham, J. Am. Chem. Soc. **93**, 6014 (1971).
13. G. Brubaker and D. W. Johnsn, Coord. Chem. Rev. **53**, 1 (1984).
14. R. D. Hancock, S. M. Dobson, A. Evers, M. P. Ngwenya, P. W. Wade, J. C. A. Boeyens and K. P. Wainwright, submitted for publication.
15. R. D. Hancock and A. Evers, to be published. This differs from the value of 22.2 reported by Hinz and Margerum, Ref. 2(b). In the latter study the existence of the complex [Ni(cyclam)(CN_2)] in the solution under study was not taken into account, which makes the calculated value of log K_1 too high.
16. B. S. Nakani and R. D. Hancock, S. Afr. J. Chem. **36**, 117 (1983).
17. N. Herron and P. Moore, Inorg. Chim. Acta **36**, 89 (1979).
18. R. D. Hancock, G. J. McDougall and F. Marsicano, Inorg. Chem. **18**, 2847 (1979).
19. V. Gutmann, Coord. Chem. Rev. **15**, 207 (1975).
20. V. J. Thom. J. C. A. Boeyens, G. J. McDougall and R. D. Hancock, J. Am. Chem. Soc. **106**, 3198 (1984).
21. R. D. Hancock, B. S. Nakani and F. Marsicano, Inorg. Chem. **22**, 2531 (1983).
22. F. A. Cotton and F. E. Harris, J. Phys. Chem. **59**, 1203 (1955).
23. A. W. Adamson, J. Am. Chem. Soc. **76**, 1578 (1954).
24. A. E. Martell, in *Essays in Coordination Chemistry*, eds. W. Schneider, G. Anderegg and R. Gut (Berkhauser Verlag, Basel, 1964), pp. 52–64.
25. R. D. Hancock and F. Marsicano, J. Chem. Soc., Dalton Trans. 1096 (1976).
26. F. Mulla, F. Marsicano, B. S. Nakani and R. D. Hancock, Inorg. Chem. **24**, 3076 (1985).
27. M. Gerloch and R. C. Slade, *Ligand Field Parameters* (Cambridge University Press, Cambridge, 1973).
28. A. B. P. Lever, P. Paoletti and L. Fabbrizzi, Inorg. Chem. **18**, 1324 (1979), and references therein.
29. F. A. Cotton and F. E. Harris, J. Phys. Chem. **60**, 1451 (1956).
30. G. Anderegg, Helv. Chim. Acta **47**, 1801 (1964).
31. P. Paoletti, S. Biagini and M. Cannas, J. Chem. Soc., Chem. Commun. 513 (1969).
32. V. J. Thom, G. D. Hosken and R. D. Hancock, Inorg. Chem. **24**, 3378 (1985).
33. R. D. Hancock, Pure Appl. Chem. **58**, 1445 (1986).
34. R. D. Shannon, Acta Crystallogr. Sect. A. **A32**, 751 (1976).

35. R. D. Hancock, M. P. Ngwenya and P. W. Wade, submitted for publication.
36. N. Okatu, K. Toyoda, Y. Moriguchi and K. Ueno, Bull. Chem. Soc. Jpn. **40**, 2326 (1967).
37. N. F. Curtis and D. F. Cook, J. Chem. Soc., Chem. Commun. 962 (1967).
38. D. C. Olson and J. Vasilevskis, Inorg. Chem. **8**, 1611 (1969).
39. L. Fabbrizzi, Comments Inorg. Chem. **4**, 33 (1985).
40. D. P. Rillema, J. F. Endicott and E. Papacostantinou, Inorg. Chem. **10**, 1973 (1971).
41. (a) E. K. Barefield, F. V. Lovecchio, N. E. Tokel, E. Ochiai and D. H. Busch, Inorg. Chem. **11**, 283 (1972). (b) D. G. Pilsbury and D. H. Busch, J. Am. Chem. Soc. **98**, 7836 (1976).
42. N. Jubran, G. Ginzberg, H. Cohen and D. Meyerstein, J. Chem. Soc., Chem. Commun. 517 (1982); Inorg. Chem. **24**, 251 (1985).
43. D. C. Olson and J. Vasilevskis, Inorg. Chem. **10**, 463 (1973).
44. L. D. Diaddavio, W. R. Robinson and D. W. Margerum, Inorg. Chem. **22**, 1021 (1983).
45. J. Vasilevskis and D. C. Olson, Inorg. Chem. **10**, 1228 (1971).
46. Y. Hung, L. Y. Martin, S. S. Jackels, A. M. Tait and D. H. Busch, J. Am. Chem. Soc. **99**, 4029 (1977).
47. (a) M. O. Kostner and A. L. Allred, J. Am. Chem. Soc. **94**, 7189 (1972). (b) E. K. Barefield and M. T. Mocella, Inorg. Chem. **12**, 2289 (1973).
48. A. J. Blake, R. O. Gould, A. J. Holder, T. I. Hyde, A. J. Lavery, M. O. Odulate and M. Schroder, J. Chem. Soc., Chem. Commun. 119 (1987).
49. R. L. Deming, A. L. Allred, A. E. Dahl, A. W. Merlinger and M. O. Kostner, J. Am. Chem. Soc. **98**, 4132 (1976).
50. A. Anicini, L. Fabbrizzi, P. Paoletti and R. M. Clay, J. Chem. Soc., Dalton 577 (1978).
51. D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperati and N. Tokel, Adv. Chem. Ser. **100**, 52 (1971).
52. R. D. Hancock and G. J. McDougall, J. Am. Chem. Soc. **102**, 6551 (1980).
53. D. J. Cram, T. Kaneda, R. C. Helgeson, S. B. Brown, C. B. Knobler, E. Maverick and K. N. Trueblood, J. Am. Chem. Soc. **107**, 3645 (1985).
54. A. E. Martell, in *Development of Iron Chelators for Clinical Use*, eds. A. E. Martrell, W. F. Anderson and D. G. Badman (Elsevier/North Holland, New York, 1981), pp. 67–79.
55. B. L. Haymore, J. D. Lamb, R. M. Izatt and J. J. Christensen, Inorg. Chem. **21** 1598 (1982).
56. P. U. Fruh and W. Simon, in *Protides of the Biological Fluids—20th Colloquium*, ed. H. Peters (Pergamon, Oxford, 1973), p. 505.
57. F. Arnaud-Neu, M. J. Schwing-Weill, J. Juillard, R. Louis and R. Weiss, Inorg. Nucl. Chem. Lett. **14**, 367 (1978).
58. J. D. Dunitz, M. Dobler, P. Seiler and R. P. Phizackerly, Acta Crystallogr. Sect. B **B30**, 2733 (1974).
59. B. Metz, D. Moran and R. Weiss, *ibid.* **B29**, 1377 (1973).
60. (a) M. J. Bovill, D. J. Chadwick, I. O. Sutherland and D. Watkins, J. Chem. Soc., Perkin II 1529 (1980). (b) G. Wipff, P. Weiner and P. Kollman, J. Am. Chem. Soc. **104**, 3249 (1982). (c) G. Ranghino, S. Romano, J. M. Lehn and G. Wipff, J. Am. Chem. Soc. **107**, 7873 (1985).
61. R. M. Clay, S. Corr, G. Keenan and W. V. Steele, J. Am. Chem. Soc. **105**, 2070 (1983).
62. G. B. Reibnegger and B. M. Rode, Inorg. Chim. Acta **72**, 47 (1983).
63. T. Yamabe, K. Hori, K. Akazi and K. Fukui, Tetrahedron **35**, 1065 (1979).

64. A. D. Baker, G. H. Armen and S. Funaro, J. Chem. Soc., Dalton Trans. 2519 (1983).
65. K. Wieghardt, W. Schmidt, W. Herrmann and H. J. Kuppers, Inorg. Chem. **22**, 2953 (1983).
66. (a) E. Weber and F. Vogtle, Tetrahedron Lett. 2415 (1975). (b) B. Tummler, G. Maass, F. Vogtle, H. Sieger, U. Heimann and E. Weber, J. Am. Chem. Soc. **101**, 2588 (1979).
67. C. J. Pedersen, J. Am. Chem. Soc. **89**, 2459 (1967).
68. V. J. Thom, C. C. Fox, J. C. A. Boeyens and R. D. Hancock, J. Am. Chem. Soc. **106**, 5947 (1984).
69. M. Ciampolini, M. Micheloni, P. Orioli, F. Vizza, S. Mangani and F. Zanobini, Gazz. Chim. Italiana **116**, 189 (1986).
70. R. D. Hancock, R. Bhavan, M. S. Shaikjee, P. W. Wade and A. Hearn, Inorg. Chim. Acta **112**, L23 (1986).
71. (a) S. Kulstad and L. A. Malmsten, J. Inorg. Nucl. Chem. **42**, 573 (1980). (b) See also V. J. Gatto and G. W. Gokel, J. Am. Chem. Soc. **106**, 8240 (1984).
72. A. M. Sargeson, Pure Appl. Chem. **56**, 1603 (1984).
73. M. R. Suh, W. Shin, D. Kim and S. Kim, Inorg. Chem. **23**, 618 (1984).
74. R. D. Hancock, P. W. Wade, A. Evers and V. J. Thom, to be published.
75. R. J. Motekaitis, A. E. Martell, B. Dietrich and J. M. Lehn, Inorg. Chem. **24**, 1588 (1984).
76. K. P. Wainwright and A. Ramasubbu, J. Chem. Soc., Chem. Commun. 277 (1982).
77. R. D. Hancock, A. Evers, M. P. Ngwenya and P. W. Wade, J. Chem. Soc., Chem. Commun., in press.
78. R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. J. Christensen and D. Sen, Chem. Rev. **85**, 271 (1985).