Ligand Design for Selective Complexation of Metal Ions in Aqueous Solution

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Introduction

There is at present a need in several areas for a rational approach toward ligand design for selective complexation of metal ions in solution. Such areas would be, for example, design of ligands as therapeutic reagents for the treatment of metal intoxication,[1,2] design of antibiotics that owe their antibiotic action to specific metal complexation,[3] design of complexes to act as imaging agents[4,5] in the body, design of functional groups for chelating ion-exchange materials,[6] selective metal extractants in hydrometallurgy,[7] and metal ion sequestering agents in detergents.[8] At the same time, an understanding of the principles of selectivity would be invaluable in understanding the metal ion selectivity displayed by biological cation transport systems such as in the cell wall,[9] metal ion binding proteins such as metallothionein, or siderophores such as enterobactin and how metal ions are distributed in the environment.[10]

At present, selection of donor atoms is considered to be fairly well understood,[1] and selection is based on ideas such as the hard and soft acid and base principle of Pearson[11] or the A and B type acids of Schwarzenbach[12] or Ahrland et al.[13] However, the role of ligand architecture is much less well understood[1] and is limited to such ideas as size-match selectivity in macrocycles (by size-match selectivity is meant the idea that a metal ion will form its most stable complex with the member of a series of macrocycles where the match in size between the metal ion and the cavity in the ligand is closest).

In this review an important theme is the role of steric strain in complex formation. The tool used for examining steric strain has been molecular mechanics (MM),[14] which treats a molecule or complex as an assembly of atoms held together by classical forces. Thus, bonds are regarded as having ideal lengths, and deformation of these bond lengths away from the ideal value is modeled by using a Hooke's law expression involving force constants similar to those used in infrared spectroscopy. Bond angles are treated similarly and simple expressions are used to model other forces involved in determining the structure of the molecule or complex, such as torsional forces, van der Waals forces, and in some situations, dipole–dipole repulsion or hydrogen bonding. What is important from the view of ligand design is that a strain energy may be calculated as the sum of all the bond length, bond angle, and torsional distortions in the molecule, plus all the nonbonded (van der Waals) interactions. The strain energy in the complex is an unfavorable contribution to complex formation. Thus, MM calculations can be used to give an idea of how well a particular ligand coordinates to a metal ion from the steric strain point of view. The lower the steric strain in the complex, the more favorable will be the complex formation reaction. This gives rise to the concept of steric efficiency. The lower the steric strain generated in the complex on coordination of the ligand to the metal ion, the more sterically efficient is the ligand. Thus, part of the effort to design ligands that will complex metal ions more strongly is the design of more sterically efficient ligands, and the effort to increase selectivity of the ligand for one metal ion over others is the aim of making the ligand sterically efficient with that metal ion only. The MM calculation is a modern tool that should not be neglected in the effort

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Robert D. Hancock was born in 1944 at Fort Beaufort, Cape Province, South Africa. He attended Rhodes University in Grahamstown, receiving the B.Sc. (Honours) degree in chemistry in 1965, and the University of Cape Town, obtaining a Ph.D. in inorganic chemistry in 1969. In 1970 he joined the National Institute of Metallurgy, Johannesburg, leaving in 1980 with the rank of Assistant Director. Research there involved coordination chemistry of noble metals; awards were (1976) the Raikes Medal of the South African Chemical Institute, awarded annually to the most promising chemist under age 35, and (1980) the Gold Medal of the National Institute of Metallurgy. In 1980 he moved to the University of the Witwatersrand, in 1984 was awarded a Personal Chair in Coordination Chemistry, and in 1988 became Professor of Inorganic Chemistry. In 1987/1988 he was awarded the Sir Earnest Oppenheimer Travel Fellowship, and spent a year as Visiting Professor at Texas A&M University, hosted by Professor A. E. Martell. His research interests center on ligand design and synthesis, molecular mechanics calculations, the structure of complexes of metal ions, and their coordinating properties in aqueous solution. He is married and has two sons.

Arthur E. Martell, Distinguished Professor of Chemistry at Texas A&M since 1973, was also Head of the Chemistry Department there from 1966 to 1980. Formerly he was Professor of Chemistry and Chemistry Department Head or Chairman at the Illinois Institute of Technology (1961–1966) and Clark University (1942–1961). Born in Natick, MA, October 18, 1916, he attended Worcester Polytechnic Institute, receiving the B.S. degree with high honors in 1938. After receiving the Ph.D. degree from New York University (University Heights) in 1941, he entered academic work as Instructor in Chemistry at WPI. He moved to Clark in 1942, where he undertook research on metal chelate compounds and has remained active in that and related fields of biocoordination chemistry. He has held Guggenheim, NIH, and NSF fellowships for postdoctoral work at Zurich, Switzerland, Berkeley, and MIT. He has authored, coauthored, and edited 15 books and 435 research papers on the stabilities, kinetics, and catalytic effects of metal chelate, macrocyclic, and cryptate complexes.

to achieve high complex stability and metal ion selectivity.

Although selection of donor atoms may seem quite well understood, it will be reviewed here, with some more recent observations that might aid in making choices of donor atoms.

TABLE 1. A Classification of Acids and Bases According to the HSAB Principle of Pearson[11] [a]

Acids

Hard	Soft
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}	$CH_3{}^+Hg$, $Co(CN)_5{}^{2-}$, Pt^{4+}
Gd^{3+}, Lu^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}	Te^{4+}, Br^+, I^+
Si^{4+}, Ti^{4+}, Zr^{4+}, Hf^{4+}, Th^{4+}, U^{4+}	
Pu^{4+}, Ce^{4+}, WO^{4+}, Sn^{4+}	
UO^{2+}, VO^{2+}, MoO^{3+}	

Borderline

Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, Sb^{3+}, Bi^{3+}, Rh^{3+},[b] Ir^{3+},[b] $B(CH_3)_3$

Bases

Hard	Soft
H_2O, OH^-, F^-, $CH_3CO_2^-$, PO_4^{3-}	R_2S, RSH, RS^-, I^-, SCN
SO_4^{2-}, Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-	$S_2O_3^{2-}$, R_3P, R_3As, $(RO)_3P$
ROH, RO^-, R_2O, NH_3, RNH_2, NH_2NH_2	CN^-, RNC, CO, C_2H_4, H^-, R^-

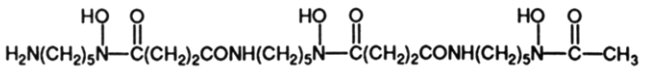
Borderline

$C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_2^-, N_2, SO_3^{2-}

[a] The metal ions refer generally to the aquo ions or complexes in which no very soft donor atoms are already present. [b] A good argument could be made that these are soft.

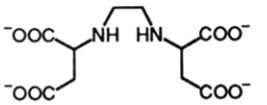
A. The Selection of Donor Atoms

In Table 1 is reproduced a classification of acids and bases into hard, soft, and intermediate (HSAB), according to Pearson.[11] The table is a useful starting point for donor atom selection. Thus if it were decided to design a ligand specific for Fe^{3+}, the table indicates that Fe^{3+} is hard, and thus a hard donor atom such as the negative oxygen donor would be chosen, in accord with experience that ligands such as DFB (desferriferrioxamine-B) are good at complexing iron, having

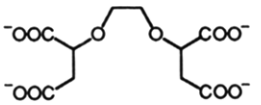


desferriferrioxamine-B (DFB)

negatively charged oxygen donor atoms. However, the HSAB classification as a basis for selecting donor atoms is rather incomplete. For example, neutral oxygen donors (ROH and R_2O) are listed as hard, but experience shows that Fe^{3+} has little affinity for crown ethers with their hard oxygen donors. One cannot be sure whether Fe^{3+} complexing will be strengthened by the presence of neutral oxygens even in a ligand such as EDODS. Further, which would the Fe^{3+} ion prefer, the hard oxygen donors in EDODS or the hard nitrogen donors in EDDS?



EDDS



EDODS

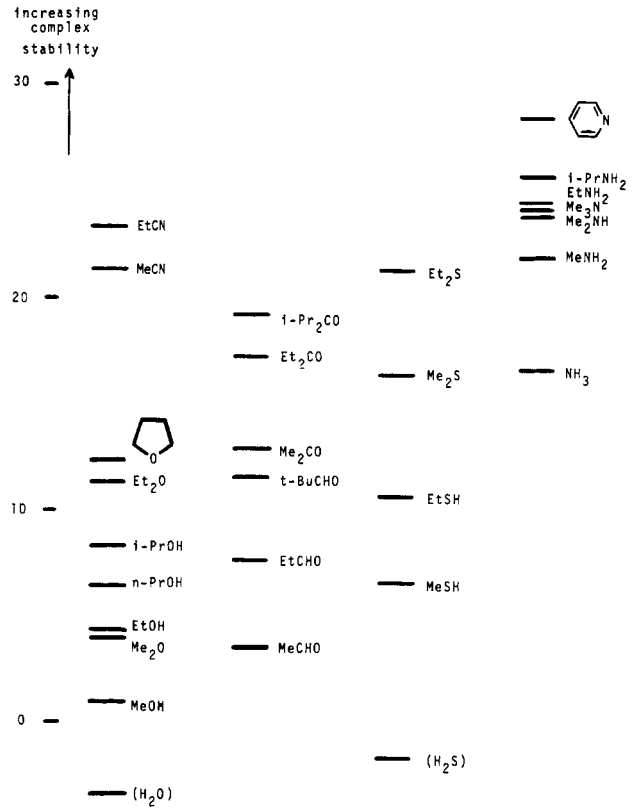
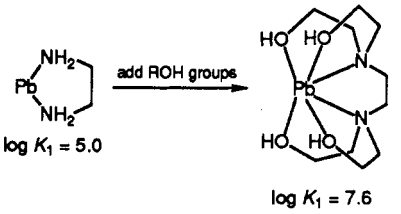


Figure 1. Free energies of formation of Ni(I) bis-ligand complexes with a variety of ligands in the gas phase. Data are in kcal mol^{-1} and are from ref 15. The values of H_2O and H_2S have been estimated by comparison with other Lewis acids in the gas phase.

The HSAB classification may provide a preliminary guide for donor atom selection, but in fact, for effective ligand design, a much more detailed consideration of each type of donor atom is needed.

B. The Neutral Oxygen Donor Atom

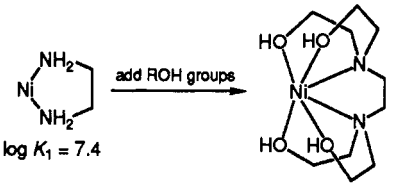
The neutral oxygen donor atom is of especial interest for coordination chemistry in aqueous solution, since it is the donor atom of the solvent, water. It must be stated at once, however, that the coordinating properties of the oxygen donor atom in water and in the other ligands such as alcohols, ethers, ketones, or amides are not identical. This is demonstrated by studies in the gas phase which show that,[15] in general, the donor strength for sp^3-hybridized oxygens increases in the order $H_2O < ROH < R_2O$. Typical examples of gas-phase bond dissociation energies for bis-ligand complexes of Ni(I)[15] are seen in Figure 1. One might expect from the increased donor strength for ROH or R_2O relative to H_2O indicated by gas-phase studies, such as shown in Figure 1, that addition of groups containing ROH or R_2O to existing ligands might increase the stability of the complexes they form. For many metal ions this is true, as seen for the following complexes of Pb^{2+}:[16,17]



log K_1 = 5.0

log K_1 = 7.6

On the other hand, many metal ions show a drop in complex stability when groups containing neutral oxygen donors are added:



log K_1 = 7.4

log K_1 = 6.5

Examination of a large amount of data pertaining to what happens to complex stability when groups bearing neutral oxygen donors are added to existing ligands reveals a very simple pattern of behavior.[16] The response of complex stability to the neutral oxygen donor is a function of metal ion size.[16] This gives rise to a rule of ligand design: *Addition of groups containing neutral oxygen donor atoms to an existing ligand leads to an increase in selectivity of the ligand for large metal ions over small metal ions.*

The rule may be expressed graphically, as seen in Figure 2. In Figure 2A the change in complex stability, $\Delta \log K$, produced by adding ethereal oxygens to oxalate to give diethylenetrioxydiacetate (DETODA) is plotted against r^{n+}, the ionic radius of the metal ions. Also plotted in Figure 2A is $\Delta \log K$ for addition of hydroxyethyl groups to alanine to give *N,N*-bis(2-hydroxyethyl)alanine. In both cases the linear relationship indicates that $\Delta \log K$ is more positive for larger metal ions. Many relationships of this kind can be drawn up and are found to hold in the same way as seen in Figure 2A. In line with this it is found that addition of oxygen donors in such a way as to create a macrocyclic ring also leads to size-dependent increases in complex stability, as seen in Figure 2B. In Figure 2B is plotted $\Delta \log K$ for going from the complex of 18-aneN_2O_4 to cryptand-2,2,2 as a function of ionic radius. It is seen that a linear relationship is observed. It thus appears that part of the selectivity displayed by macrocyclic or cryptand ligands for metal ions of different sizes, namely their selectivity against metal ions that are "too small for the cavity in the ligands", is a property shared with open-chain ligands. As discussed in section M, the metal ion size-related response of complex stability to the presence of neutral oxygen donors relates to steric crowding. Thus in Figure 2A the M–O bond strength for the alkaline earth metal ions with neutral oxygen donors is almost certain to be $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$ in the gas phase. However, the level of steric crowding must become larger as the metal ions become smaller, and the ease of accommodating the extra bulk of DETODA as compared with oxalate must vary as $Mg^{2+} \ll Ca^{2+} < Sr^{2+} < Ba^{2+}$. The net result is that the greater steric difficulties of the smaller metal ions outweigh the stronger M–O bond strengths, and the order of stabilization due to the presence of added neutral oxygen donor groups is $Mg^{2+} \ll Ca^{2+} < Sr^{2+} < Ba^{2+}$. What is remarkable about the empirical correlations observed in Figure 2 is that they do not appear to be sensitive to the nature of the metal ion; i.e., the correlation contains metal ions with very different complexing properties such as Cu^{2+}, Mg^{2+}, La^{3+}, and Pb^{2+}. However, the existence of a large number of empirical correlations such as those in Figure 2 dem-

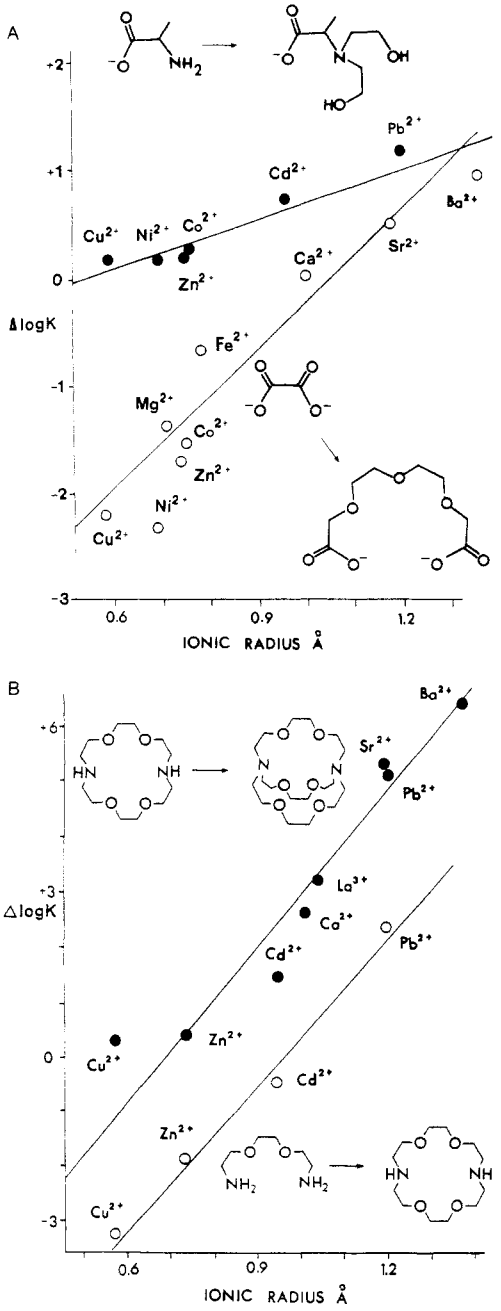


Figure 2. Effect on complex stability of the neutral oxygen donor group. The change in complex stability, Δ log K, produced by adding neutral oxygen donors to existing ligands is plotted as a function of ionic radius[54] of the metal ion. In A the change in complex stability is plotted for *N,N*-bis(2-hydroxyethyl)alanine relative to alanine and for diethylenetrioxydiacetic acid relative to oxalate. In B the change in complex stability has been plotted for cryptand-2,2,2 relative to 18-aneN_2O_4 and for 18-aneN_2O_4 relative to ethylenebis(oxy-2-ethylamine). Formation constant data are from ref 21.

onstrates that the dominant factor in determining how a metal ion will respond in terms of complex stability to the presence of neutral oxygen donors is largely the metal ion radius. This observation extends also to the simple crown ethers, where it is observed that large metal ions such as Sr^{2+}, Ba^{2+}, and Pb^{2+} are well complexed by crown ethers, while smaller metal ions are not, even when the cavity in the ligand appears to be small, as in 12-crown-4.

Deviations from the simple linear relationships seen in Figure 2 are observed in some cases when O-donor groups are added. An example of this is seen in Figure

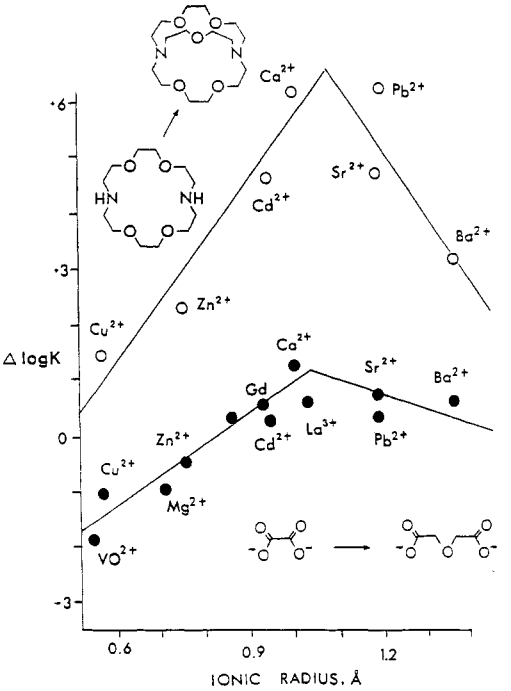
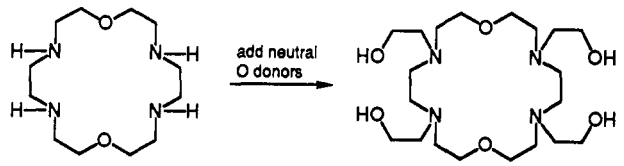


Figure 3. Ligands where addition of neutral oxygen donors produces a peak in change in complex stability. The change in formation constants, Δ log K, produced by adding neutral oxygen donors to existing ligands is plotted as a function of ionic radius[54] of the metal ion. The top relationship (○) is for cryptand-2,2,1 relative to 18-aneN_2O_4, while the relationship at the bottom (●) is for oxydiacetate relative to oxalate. Formation constant data are from ref 21.

3, where addition of a single bridging O atom to 18-aneN_2O_4 to give cryptand-2,2,1 gives a Δ log K vs r^{n+} plot that displays a clear maximum in Δ log K at an r^{n+} value of about 1.1 Å. In this case the peak in Δ log K at this specific value of r^{n+} can be explained in terms of the idea that the size of the cavity in cryptand-2,2,1 is such that metal ions of an ionic radius of ~1.1 Å fit best. Metal ions with an ionic radius >1.1 Å thus are too large, and their complexes are destabilized by steric strain. However, peaks in plots of Δ log K vs r^{n+} are observed for many ligand systems where no such steric constraints appear to be present. Thus, as seen in Figure 3, the plot of Δ log K for oxydiacetate (ODA) relative to oxalate shows a distinct peak, also, coincidentally, at a value of r^{n+} of 1.1 Å. In this case, the interpretation is that at r^{n+} values above 1.1 Å, steric strain in the ODA complexes is so low that it is not significantly decreased by further increases in metal ion radius, and the stability order now reflects the intrinsic M–O bond strength to the ethereal oxygen donor in ODA. Much of the apparent size selectivity of O-donor macrocycles is due to this type of behavior, rather than the exercising of any real "size-match selectivity" by the ligands.[17,18]

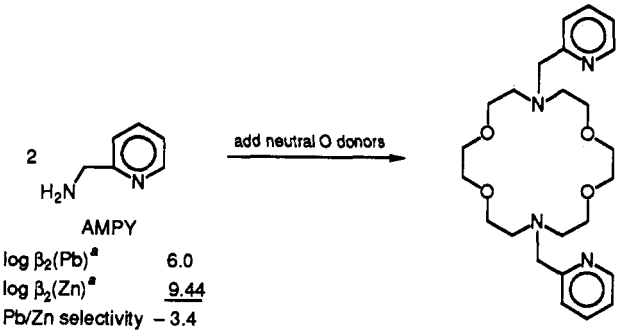
What is of importance here is the existence of a rule of ligand design that allows for fairly predictable control of selectivity on the basis of metal ion size. One may use as examples of the application of this rule ligands recently designed for the selective complexation of lead.[19] The important selectivity to achieve here is for the large Pb^{2+} ion over the small Zn^{2+} ion[1] for use in cases of lead intoxication. The obvious strategy to use in the light of the rule regarding neutral oxygen donors is to attach the latter groups to any ligands that appear to present a useful starting point. Thus, one approach[20]

is to add 2-hydroxyethyl groups to ligands such as 18-aneN$_4$O$_2$ to give THE-18-aneN$_4$O$_2$. It is found[20] that this increases the Pb^{2+}/Zn^{2+} selectivity by some 5.7 log units. A similar result is obtained by taking two (aminomethyl)pyridine (AMPY) groups and bridging them with neutral oxygen donor containing groups to give the ligand (PY)$_2$-18-aneN$_2$O$_4$:



18-aneN$_4$O$_2$		THE-18-aneN$_4$O$_2$	
log K_1(Pb)[a]	9.0	log K_1(Pb)[a]	10.6
log K_1(Zn)[a]	10.5	log K_1(Zn)[a]	6.4
Pb/Zn selectivity	−1.5	Pb/Zn selectivity	+4.2

[a] 0.1 M $NaNO_3$, 25 °C.[20]



AMPY

		(PY)$_2$-18-aneN$_2$O$_4$	
log β_2(Pb)[a]	6.0	log K_1(Pb)[a]	11.7
log β_2(Zn)[a]	9.44	log K_1(Zn)[a]	7.0
Pb/Zn selectivity	−3.4	Pb/Zn selectivity	+4.7

[a] 0.1 M $NaNO_3$, 25 °C.[19]

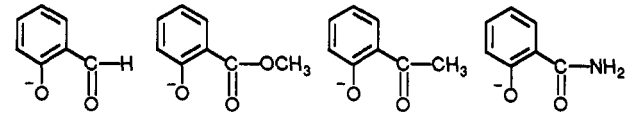
The rule regarding the size-selective effects of neutral oxygen donors appears to hold in a wide variety of cases. As discussed later, there are some situations where it is overruled by other effects, particularly where rigid macrocycles with small cavities are able to produce selectivity for small metal ions when oxygen donors are added.

For neutral oxygen donors other than the alcoholic and ethereal groups, there is much less in the way of formation constant data that would allow an evaluation in relation to metal ion size selectivity and basicity. Figure 1 indicates that carbonyl compounds are stronger bases in the gas phase than alcohols, and accordingly they usually produce larger increases in complex stability than does an alcoholic oxygen. Part of this may be due to the steric efficiency of the carbonyl group, where the oxygen donor bears no sterically crowding hydrogen atom, as does the alcoholic group. The relatively larger increase in log K_1 for the large Cd(II) ion with glycinamide may indicate that the response of log K_1 to the addition of the amide carbonyl oxygen donor may be size related:

metal ion	Cu(II)	Ni(II)	Zn(II)	Cd(II)
metal ion radius (Å)	0.57	0.69	0.74	0.95
log K_1(ethanolamine)[a]	4.5	3.1	2.4	2.8
log K_1(glycinamide)[a]	5.4	4.2	3.3	5.2
Δ log K	0.9	1.1	0.9	2.4

[a] 0.1 M, 25 °C.[21]

The acetyl group appears to be of about the same donor strength as the amide group. One important consequence of the apparently greater steric efficiency of the carbonyl type of oxygen donor is that the inductive effects apparent in Figure 1 may still be observed in aqueous solution; i.e., the increased basicity produced by adding larger donor groups is not canceled by the accompanying adverse steric effects. Thus, for example, *N,N*-diethylglycinamide appears to be a better ligand than glycinamide itself, since log K_1 for the Cu(II) complex of *N,N*-diethylglycinamide is 6.18 as compared with log K_1 = 5.2 for the complex of glycinamide.[21] The relative complexing strength of different carbonyl donors is illustrated by the formation constants of the Fe(III) chelates of substituted phenols:



log K_1	8.75	9.73	10.52	10.02

Taking into account such things as the effect of the carbonyl substituent on the pK_a of the ligand as an indication of effects on complex stability which derive from inductive effects on the phenolic rather than the carbonyl oxygen, one may conclude that the donor strength of the carbonyl groups is probably amide > ketone > aldehydic > ester. However, it is clear that more work needs to be done in this area so as to establish the relative coordinating abilities of carbonyl type oxygens in a variety of situations and with metal ions of different types and sizes. This is particularly important in view of the occurrence of a variety of neutral oxygen donor types in naturally occurring antibiotics,[3] including ethereal, alcoholic, amidic, ester, and ketonic oxygens.

C. The Negatively Charged Oxygen Donor

The negatively charged oxygen donor occurs commonly in the form of the carboxylate group, the phenolate group, the hydroxamic acid group, and the phosphonic acid group as well as in ligands such as acetylacetonate and tropolonate. Also considered here is the effect of very weakly basic negatively charged oxygen-donor groups such as the sulfonic acid group. The effect of the negatively charged oxygen-donor group on complex stability appears[22,23] to depend on the acidity of the metal ion concerned, i.e., the affinity of the metal ion for the archetypal negative O-donor ligand, the OH^- ion. This is shown in Figures 4 and 5, where the log K_1 for a variety of ligands containing negatively charged RO^- donors is plotted against log $K_1(OH^-)$ for each metal ion. In Figure 4 log K_1 for selected ligands is plotted against log $K_1(OH^-)$ for the metal ions concerned. Thus, included in Figure 4 is catecholate with its two phenolate oxygens, malonate with its two much lower basicity carboxylate oxygens, 5-nitrosalicylate with one phenolate and one carboxylate oxygen, and kojate, which has one quasiphenolate oxygen, and ketonic oxygen (see Figure 7 for structures of ligands). It is seen in Figure 4 that a good linear relationship results, with the slopes of the relationships relating to the basicities of the oxygens on the ligands. In Figure 5 is shown a similar relationship of log K_1 for the bidentate acetohydroxamic acid, log K_1 for the

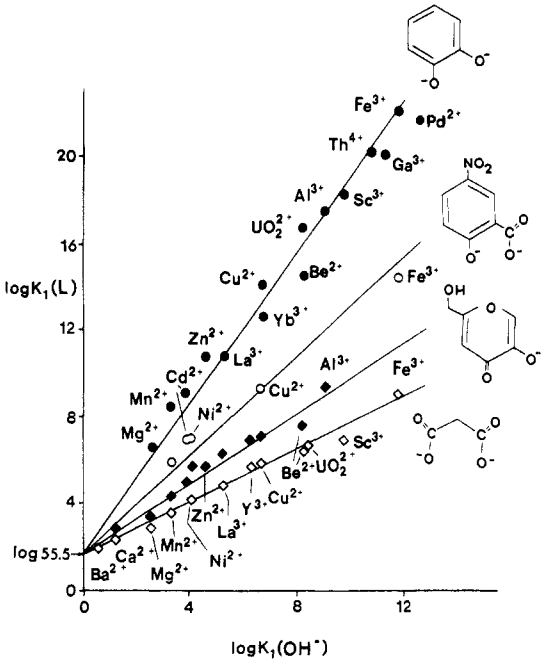


Figure 4. Relationship between stability of complexes of metal ions with ligands with negatively charged oxygen donor groups and the affinity of the metal ion for the hydroxide ion. The intercept of log 55.5 is that required from theories on the origin of the chelate effect[30,31] for a bidentate chelating ligand. The ligands from top to bottom are catecholate, 5-nitrosalicylate, kojate, and malonate. Data from ref 21, ionic strength 0, 25 °C.

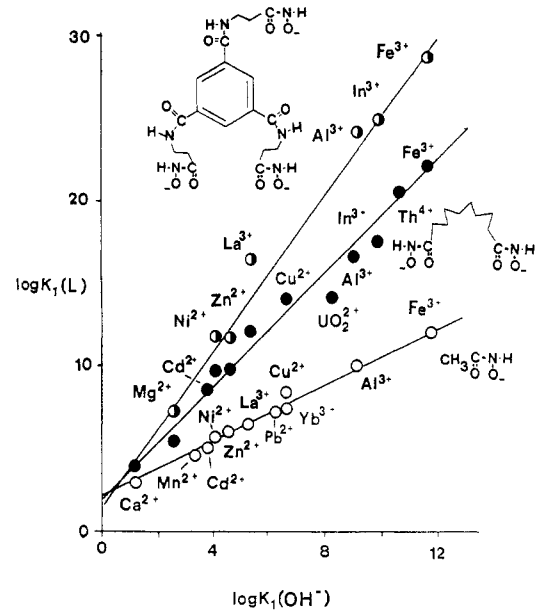


Figure 5. Relationship between the formation constants of ligands containing negatively charged oxygen donor hydroxamate groups and log $K_1(OH^-)$ for the metal ions. The ligands are (top) BAMTPH, ODHA, and (bottom) acetohydroxamic acid. Formation constant data from ref 21, ionic strength 0, 25 °C.

tetradentate ODHA, and log K_1 for the hexadentate BAMTPH against log $K_1(OH^-)$.

The behavior seen in Figure 4 is the simplest type of behavior found for negatively charged O-donor ligands. Numerous examples can be drawn up displaying simple relationships[22,23] with excellent linearity. Design of ligands containing negatively charged groups is thus largely based on metal ion acidity.

To decide whether oxygen-donor groups will enhance the complexing ability of a ligand for one metal ion over another, it is necessary to examine the relative affinity of the two metal ions for the OH^- ion. Thus (Figure 5) the poly(hydroxamic acid) BAMTPH has excellent selectivity for the highly acidic Fe^{3+} ion over other metal ions commonly found in biological systems such as Zn^{2+} or Cu^{2+}, which is also found[24] to be true for the naturally occurring polyhydroxamate DFB. Ligands designed for selective complexation for Fe^{3+} in biological systems have thus involved ligands with several negatively charged oxygen-donor groups, such as catecholates,[25] phenolate,[26] pyridoxyl groups,[27] phosphonic acid groups,[28] and hydroxamic acid groups.[29] Figure 5 also shows how selectivity is increased by increasing the total number of oxygen donors and suggests that ligands containing negatively charged oxygen donors only will always complex Fe(III) more strongly than other metal ions such as Al(III). However, the final ability to remove other metal ions without removing Fe(III) might also depend on relative affinities for iron transport proteins present in the body such as transferrin, so that ligands containing RO^- type donors might still be useful for complexing other acidic metal ions, such as Al(III) (log $K_1(OH^-) = 9.0$[21]) in cases of Al(III) poisoning, and also complex Ga^{3+} (log $K_1(OH^-) = 11.3$) and In^{3+} (log $K_1(OH^-) = 10.0$) successfully for use as imaging agents.

The common intercept of the relationships in Figure 4 is of interest. As discussed in section G on the chelate effect, the intercept is close to log 55.5, the theoretical value[30,31] in terms of the role of the standard reference state in producing the chelate effect.[31] For virtually all bidentate ligands containing two negative oxygen donors, or one negative oxygen donor plus a second that shares in the negative charge by resonance (e.g., acetylacetonate and tropolonate), intercepts close to log 55.5 on plots such as those in Figure 4 are found. Ligands such as kojic acid and acetohydroxamic acid also show intercepts close to log 55.5 (Figure 5), even though they are not formally able to localize charge onto their carbonyl oxygens by resonance. This does not always hold true, however, in that near-zero intercepts may be obtained with ligands such as salicylaldehyde. This point clearly needs further investigation. However, when the size of the chelate ring in the ligand increases beyond six membered, this simple pattern may be lost.

The relationship between log K_1 for succinate, which should form seven-membered chelate rings on complex formation, and log $K_1(OH^-)$ for a variety of metal ions is seen in Figure 6. Instead of the usual linear relationship, a broken relationship is found. The leveled-off part of the relationship at low log $K_1(OH^-)$ values has been interpreted in terms of outer-sphere complex formation. The dotted horizontal line shows the expected value of log K_1 for an outer-sphere complex[32] formed between a dipositive cation and a dinegative anion, and it is seen that the log K_1 values at low complex stability follow this line very well.[22] When the log K_1 for inner-sphere complexes rises above that for outer sphere, then the relationship turns upward, and log K_1 for succinate increases with increasing log $K_1(OH^-)$. Extrapolation of this line indicates that an intercept much lower than the expected log 55.5 would be obtained. This behavior is typical for ligands with large

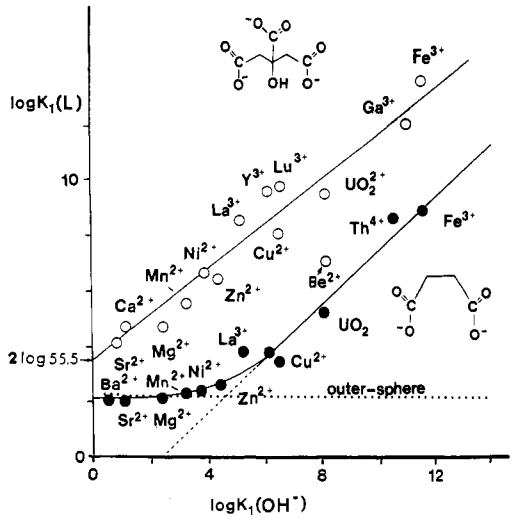
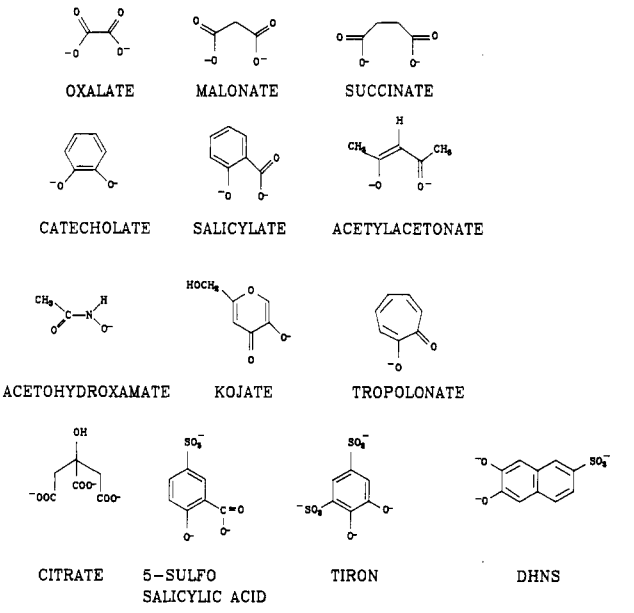


Figure 6. Relationship between the formation constants for citrate (O) and for succinate (●) and log $K_1(OH^-)$ for a variety of metal ions. The relationship for citrate shows the intercept of 2 log 55.5 as expected[30,31] for tridentate ligands, but the Be^{2+} ion shows a drop in complex stability because of steric difficulties in coordinating all three donor atoms. The relationship for succinate shows a negative intercept because of the entropy associated with immobilizing the long bridge between the donor groups. The dotted line is the calculated[32] stability for the outer-sphere complexes between dipositive cations and dinegative anions. Data from ref 21, ionic strength, 0, 25 °C.

chelate rings. The interpretation here is that the unfavorable entropy contributions associated with immobilizing the longer chelating groups diminish the intercept down below the value expected from the chelate effect of log 55.5 in relationships such as those seen in Figure 6.

As seen in Figure 6 the tridentate ligand citrate gives the expected intercept of 2 log 55.5. However, ligands such as BAMTPH or octane-1,8-dihydroxamic acid (ODHA) give intercepts much lower than expected. Thus, for tetradentate ODHA an intercept of 3 log 55.5 would be expected,[30] whereas those observed (Figure 5) are much smaller. This seems to be related to the very long connecting groups necessary for the hydroxamic acid group to coordinate to the metal ion in a bidentate fashion and encompass the metal ion in a relatively strain-free fashion. The unfavorable entropy effects of these very long connecting groups are thus likely to be responsible for the smaller than expected intercepts. The same considerations must apply to the polycatecholate ligands developed by Raymond et al.,[25] where long connecting groups are necessary to allow coordination to the metal ion (see section P). This leads to the speculation that these ligands would be improved by making them more rigid, with the coordinating groups correctly preoriented for coordination to the metal ion so as to decrease the unfavorable entropy contributions expected from the flexible long connecting groups. A possible answer might be cryptand ligands such as those described recently by Vogtle et al.[33] or Raymond et al.[34] (see section P). An important point is the orientation of the donor atoms. In the structure of the hexadentate cryptand with three catecholate groups reported by Raymond et al.,[34] the Fe^{3+} is forced to adopt a trigonal-prismatic mode of coordination, which may be energetically highly unfavorable. This leads to the second point about relationships such as those in Figures 4–6. If the ligand produces a situation

A. Ligands with Negative O-Donor Groups



B. Ligands with Pyridyl Donor Groups

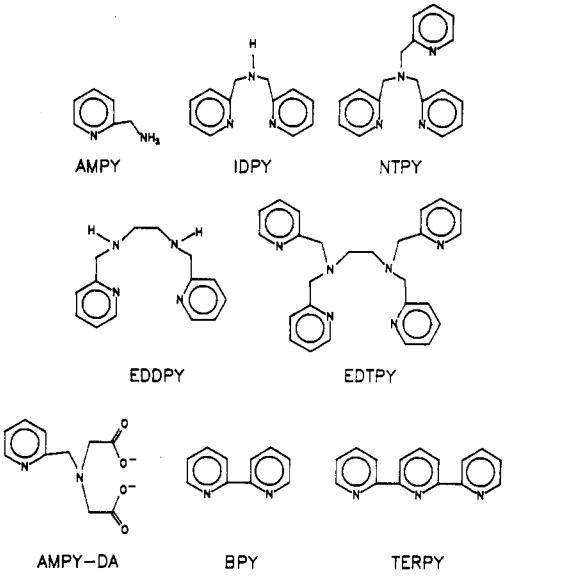


Figure 7. (A) Some ligands with negative O-donor groups discussed in this review. (B) Ligands with pyridyl donor groups.

of high steric strain, then the linearity of the relationship may be disrupted. This is seen for citrate in Figure 6. The intercept has close to the correct value of 2 log 55.5 for a tridentate ligand, but the points for very small metal ions (e.g., Be^{2+}) are displaced downward considerably from their expected values. Examination of a large number of relationships like those seen in Figures 4–6 indicates that a more sterically demanding situation usually affects small metal ions more seriously than it does large ones. If there is any steric difficulty in coordinating to the ligand, this shows up first in the Be^{2+} complex (Figure 6), and if it becomes serious enough, other small metal ions such as Cu^{2+} or Mg^{2+} will be affected. This reflects the situation with neutral oxygen donors, where large metal ions are usually less seriously affected by steric factors than small metal ions. A further point to be considered is the effect of very weakly basic donor groups such as the sulfonate group. It is found that for ligands such as 5-sulfosalicylic acid

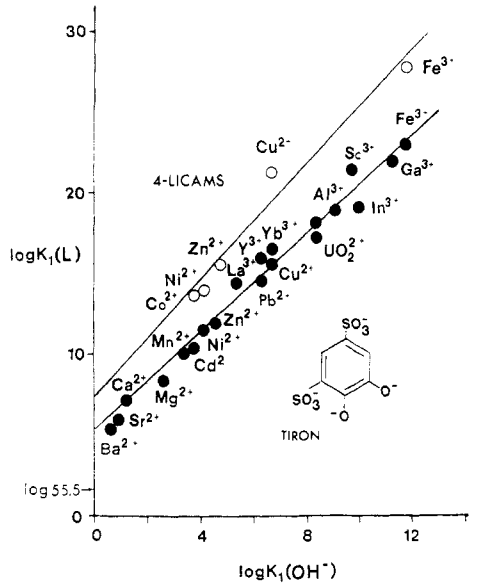


Figure 8. Effect of sulfonic acid groups on complex stability of ligands with negatively charged O donors. A plot of the formation constants of TIRON (●) and of 4-LICAMS (○) vs the log $K_1(OH^-)$ values for the metal ions is shown. The effect of the sulfonic acid groups is that the intercept is much higher than the log 55.5 expected for TIRON, as discussed in the text. Data from ref 21, ionic strength 0, 25 °C.

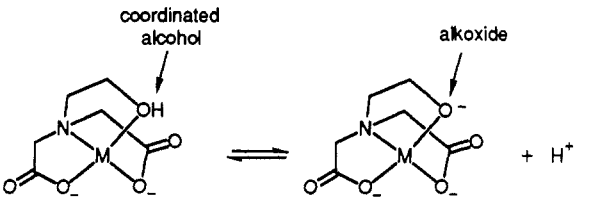
or Tiron (see Figure 8), linear relationships for log K_1 vs log $K_1(OH^-)$ are found, but that the intercepts are much larger[23b] than expected for bidentate ligands. Thus, for Tiron, an intercept of about 3 log 55.5 is found, as though the ligand were tetradentate with both the sulfonic acid and the phenolate groups coordinated to the metal ion. This seems sterically impossible, and it has been found[23b] that siting the sulfonic acid group further away, as in DHNS (Figure 7), does not lower the value of the intercept. In view of this it seems possible that the effect of the sulfonic acid groups on complex stability is an electronic one rather than a through-space type of outer-sphere electrostatic attraction as was suggested previously.[23b] A final and fairly obvious point to be made about relationships such as those seen in Figure 4 is that the slope of the relationship will be dependent on the basicity of the donor groups. Thus, the slopes for the ligands in Figure 4 are compared with the protonation constants as follows:

ligand	catecholate	5-nitrosalicylate	kojate	malonate
slope	1.72	1.14	0.81	0.62
pK_1[a]	12.8	10.33	7.67	4.27
pK_2[a]	9.40	2.12		1.25

[a] Ionic strength 0.1 M, 25 °C.[21]

This behavior follows the expected effect, on the basis of Hammett σ functions,[35] of substituents on the ligands, with electron-withdrawing groups lowering the basicity of the oxygen donors and leading to lower slopes and electron-releasing groups leading to higher slopes. Thus, electron-releasing groups such as methyl groups will lead to greater selectivity for highly acidic metal ions such as Fe^{3+} over less acidic metal ions such as Zn^{2+}, while electron-withdrawing groups will lead to lower selectivity for more acidic metal ions.

The alkoxy group bears a negatively charged oxygen donor and so should also be considered here. The very high protonation constants of alkoxides mean that one can really only examine generally the deprotonation constant of the coordinated ethanolic group, as for example for HIDA complexes:



It is difficult to be sure that the proton is actually coming from the alcoholic group rather than a coordinated water molecule. However, points to the proton originating from the alcohol are the fact that the deprotonation constants for the HIDA complexes are[21] larger than for the IDA complexes, where no alcoholic group is present. As expected, the pK_a for HIDA complexes giving a good linear relationship with log $K_1(OH^-)$ for the metal ions concerned, paralleling the correlations in Figures 4 and 5. One may suppose, therefore, that the affinities of metal ions for alkoxide groups parallel their affinities for hydroxide ion, as is found for other ligands with RO^- groups. Thus in citrate, it appears that coordination occurs through the deprotonated hydroxy group and two carboxylate groups, rather than through three carboxylate groups. In a ligand such as triethanolamine, deprotonation of the alcoholic groups occurs for many of its complexes,[21] and this may stabilize complexes to the extent that the complex formed between Fe(III) and $N(CH_2CH_2O^-)_3$ is able to prevent[36] precipitation of ferric hydroxide at pH 14!

The following is a summary of coordinating properties of oxygen donors:

1. Adding neutral oxygen donors to ligands leads to an increase in selectivity for large metal ions over small metal ions.

2. The strength of coordination of negatively charged groups is related to the acidity (affinity for the OH^- ion) of the metal ion and the proton basicity of the oxygen donor. The selectivity of the ligand for a more acidic metal ion (e.g., Fe^{3+}, Al^{3+}) over a less acidic metal ion (e.g., Zn^{2+}, Cu^{2+}) will be increased by an increase in the number and basicity of the charged oxygen groups. Steric effects usually lead to a drop in complex stability of smaller metal ions such as Be^{2+}.

D. The Neutral Saturated Nitrogen Donor

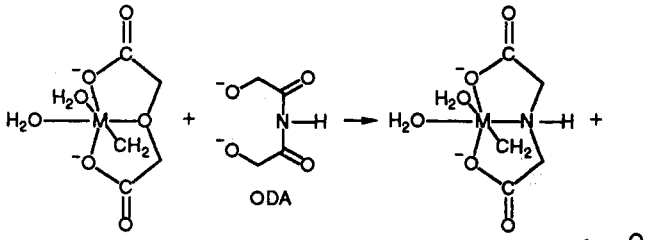
The neutral saturated nitrogen donor is widespread in ligands used in coordination chemistry. This is partly because it provides a synthetically convenient point of attachment for three other chelating groups, as in NTA or EDTA. However, the neutral nitrogen donor displays stronger coordinating properties with many metal ions than does the neutral oxygen donor, and it is of interest here to examine the coordinating properties of the neutral nitrogen donor. First, as seen in Figure 1, in the gas phase[15] the order of basicity toward metal ions is $NH_3 < RNH_2 < R_2NH < R_3N$. This has important implications for the coordinating properties of ligands containing the nitrogen donor atom, which will become apparent as the discussion proceeds. The first point of interest is to characterize the affinity of each individual metal ion for the N-donor group. By analogy

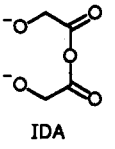
TABLE 2. Formation Constants for Ammine Complexes of Metal Ions

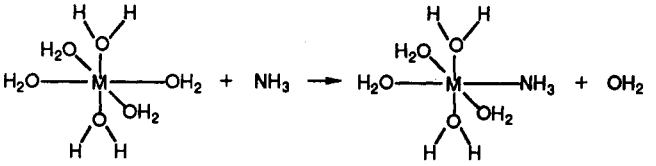
metal ion	Li^+	Na^+	K^+	Cu^+	Ag^+	Au^+			
log $K_1(NH_3)$	−0.3	−1.1	−2.8	5.9	3.3	5.6			
metal ion	Be^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	
log $K_1(NH_3)$	2.6[a]	0.26	−0.2	−0.2[a]	−0.2[a]	2.18	2.65 (1.9[a])[b]	8.8 (4.1[a])[b]	
metal ion	Al^{3+}	Ga^{3+}	In^{3+}	Tl^{3+}	Sc^{3+}	Y^{3+}	La^{3+}	Gd^{3+}	Lu^{3+}
log $K_1(NH_3)$	0.8[a]	4.1[a]	4.0[a]	9.1[a]	0.7[a]	0.4[a]	0.2[a]	0.45[a]	0.7[a]
metal ion	Cr^{2+}	Mn^{2+}	Fe^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Pd^{2+}		
log $K_1(NH_3)$	1.7[a]	1.0	1.4[a]	2.1	2.7	4.1	9.6		
metal ion	V^{3+}	Cr^{3+}	Mn^{3+}	Fe^{3+}	Co^{3+}	VO^{2+}			
log $K_1(NH_3)$	3.8[a]	3.4[a]	6.6[a](?)	3.8[a]	7.3[a]	3.2[a]			
metal ion	Th^{4+}	U^{4+}	Zr^{4+}	Hf^{4+}	UO_2^{2+}				
log $K_1(NH_3)$	0.4[a]	4.2[a]	2.0[a]	2.4[a]	2.0[a]				
metal ion	Tl^+	Sn^{2+}	Pb^{2+}	Bi^{3+}					
log $K_1(NH_3)$	−0.98	2.58[a]	1.6	5.08[a]					

[a] Estimated as described in the text and ref 37. [b] The experimental log K_1 values appear to apply for Hg^{2+} to linear coordination and for Cd^{2+} to tetrahedral coordination. For multidentate ligands these geometries appear not to be maintained and the values in parentheses appear to be more appropriate for use in eq 6 and 7.

with the use of the OH^- ligand to characterize the affinity of all RO^- donors for metal ions, one might start by using log $K_1(NH_3)$ values as indicators of the affinity for N donors. A serious problem arises in that most metal ions do not form complexes with NH_3 in aqueous solution. An approach has been developed[37] for estimating log $K_1(NH_3)$ values that are not known. In this approach it is assumed that a complex formation reaction such as that where an IDA ligand displaces an ODA ligand is rather like the complex formation process where a water molecule is displaced by an ammonia:







In both cases an oxygen donor is effectively replaced by a saturated N donor. In Figure 9 is seen a plot of log K_1(IDA) − log K_1(ODA) vs log $K_1(NH_3)$ for a selection of metal ions. Those points represented by filled circles are for metal ions with experimentally known log $K_1(NH_3)$ values, while those represented by open circles are for estimated log $K_1(NH_3)$ values, which have been estimated from several diagrams such as that in Figure 9, where the log K_1(IDA) and log K_1(ODA) values are known but not the log $K_1(NH_3)$ value. The values for log $K_1(NH_3)$ that have been estimated by this method are listed in Table 2. They are of interest in that they are consistent with the nonexistence of the ammonia complexes with the particular metal ions concerned. For example, addition of ammonia to a solution of Fe^{3+} in water gives only the hydroxide. If one takes the estimated log $K_1(NH_3)$ value of 3.8 for Fe^{3+}, it is seen

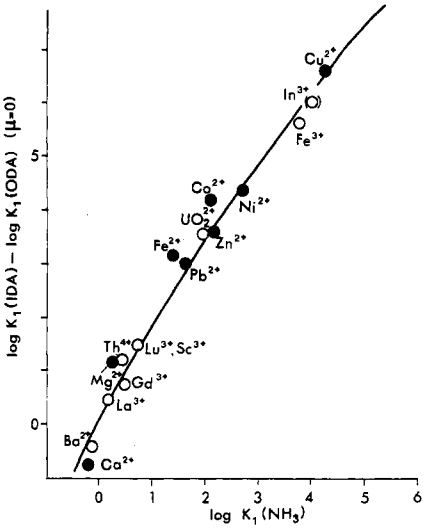


Figure 9. Relationship between the effects on complex stability of substitution of nitrogen donors for oxygen donors in chelating ligands and the stabilities of the simple ammine complexes. Here log K_1 for the iminodiacetate complexes minus log K_1 for the oxydiacetate complexes has been plotted against log $K_1(NH_3)$; experimental values are from ref 21 (ionic strength 0.1 M, 25 °C (●)) or estimated as discussed in the text (○).

that the ammonia complex is highly unstable with respect to decomposition to monohydroxo ferric complex species plus ammonium ion in water:

$$Fe(NH_3)^{3+} + H_2O \rightleftharpoons Fe(OH)^{2+} + NH_4^+ \quad (1)$$

Taking pK_w as −14, log $K_1(OH^-)$ as 11.8 for Fe^{3+}, and the pK_a of ammonia as 9.2 gives an equilibrium quotient for eq 1 of 3.2 log units. One can in fact deduce that for any metal ion where log $K_1(NH_3)$ is less than log $K_1(OH^-)$ by more than 4.8 log units (the difference in pK_w and pK_a for NH_3), the ammonia complex will not exist in water to any appreciable level. A point of interest is that log K_1 for Pb^{2+} was predicted to be 1.68, which means that with log $K_1(OH^-)$ = 6.3, Pb(II) is just on the borderline of being able to produce reasonable concentrations of the $Pb(NH_3)^{2+}$ complex in aqueous solution. In the presence of 5 M NH_4^+ to drive back the equivalent reaction for Pb(II) as shown for Fe(III) in eq 1, it was found[37] that log $K_1(NH_3)$ for Pb(II) is 1.55.

Figure 9 illustrates several important points. The first, which will be elaborated later, is that in many ways

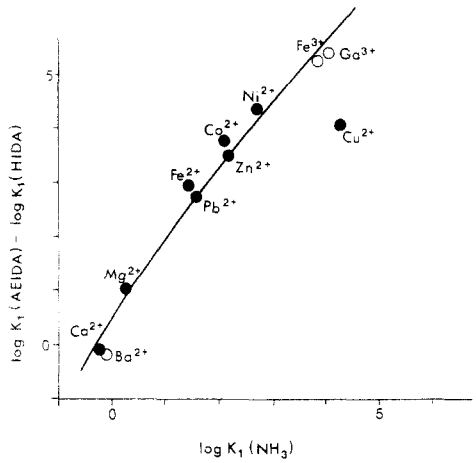


Figure 10. Effect of differing coordination geometries in the Cu(II) complexes on correlations such as that in Figure 9. The correlation here is for log K_1 for (*N*-(2-aminoethyl)imino)diacetate minus (*N*-(2-hydroxyethyl)imino)diacetate vs log $K_1(NH_3)$. Data from ref 21, ionic strength 0.1 M, 25 °C ((●) measured values; (○) estimated).

chelating ligands behave in a fairly additive way as far as their complex stability goes, in comparison with unidentate ligands. Thus, the effect on complex stability that is produced by replacing an O donor with an N donor is directly and simply related to the affinity the metal ion has for the archetypcal saturated N donor, the ammonia ligand. The second point of importance is that the slope in Figure 9 is well above unity. The best explanation in terms of the ideas developed in this review is that this reflects the greater basicity of the secondary nitrogens in IDA compared with the zeroth-order nitrogen of ammonia.[37] Ordinarily, steric strain effects mask the fact that secondary nitrogens are much stronger bases than ammonia. However, by looking at log K_1 for IDA minus log K_1 for ODA, the contributions of steric strain (which must be similar in the IDA and ODA complexes) are effectively canceled out, and the pure inductive effects become apparent in Figure 9. The third point is that there is a crossover as log K_1-(NH_3) equals zero. Above this point metal ions prefer ammonia to water and also prefer N donors to O donors. Metal ions below this point, Ca^{2+}, Sr^{2+}, Ba^{2+}, and the alkali metal ions, prefer oxygen donors to nitrogen donors. The latter metal ions would thus prefer EDODS to EDDS (see section A), but all other metal ions would prefer EDDS to EDODS. Only in special cases, such as macrocyclic complexes, is this preference of each type of metal ion altered, in that even very hard metal ions such as Ca^{2+} may come to complex more strongly with N donors than O donors (see section K).

Figure 10 shows a plot of log K_1 for (*N*-(2-aminoethyl)imino)diacetate (AE-IDA) minus log K_1 for (*N*-(2-hydroxyethyl)imino)diacetate (HIDA) vs log K_1(N-H_3). A linear relationship is found, except that the point for the Cu^{2+} complex is displaced downward. This can be understood in terms of the Jahn–Teller distortion present in Cu(II) complexes. In the HIDA complex, the one nitrogen and two acetate oxygen donors should occupy the more favored in-plane coordination sites, with the weak neutral O donor occupying the axial site with its long M–L bond. However, for the AE-IDA complex, the strongest N donors and one acetate would occupy the in-plane sites, while an acetate would be forced into the less favored axial site:

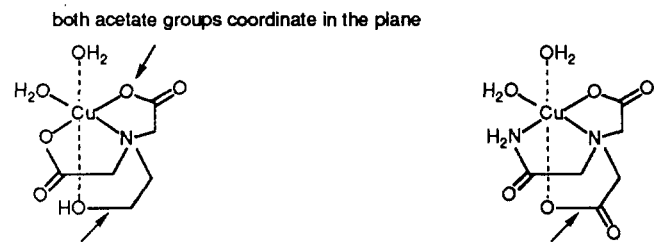
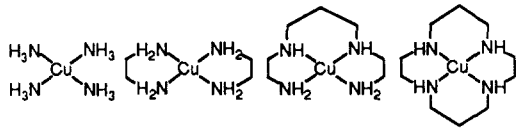


Figure 10 thus demonstrates how sensitive the type of plot seen in Figure 9 is to changes in structure of the complex. An important aspect of Figures 9 and 10 is the idea that the structure in the pair of complexes, e.g., IDA and ODA, or AE-IDA and HIDA, should be closely similar with the same metal ion. This is important in that it keeps the steric strain similar in the two complexes, which is an important contribution to the thermodynamics of complex formation. As will become apparent, steric strain is of paramount importance in complex formation, and an understanding of it is vital for effective ligand design.

The effects of donor atom basicity on the complexes of ligands with saturated N donors are readily apparent. Consider the enthalpies of complex formation plus the energies of the d–d band along the following series of Cu(II) complexes of polyamines:



nitrogens:	all zeroth	all primary	2 primary 2 secondary	all secondary
ΔH,[a] kcal mol^{-1}	−22.0	−25.5	−27.7	−32.4
ν(d–d), cm^{-1}	17000	18300	19000	19900

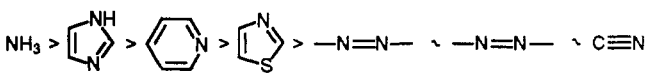
[a] Ionic strength 0.5 M, 25 °C.[21]

The most reasonable explanation[38] for the variation in ΔH and in ligand field strength (ν(d–d)) along the above series is that the increase is caused by the greater donor strength as zeroth nitrogens are first replaced by primary and then by secondary nitrogens. The implications for ligand design would seem to be clear. In order to increase the strength of complex formation, the basicity of the donor atoms must be increased. However, this cannot be done in just any fashion with some chance of success. For example, one might believe that turning the nitrogens on cyclams from secondary into tertiary by adding *N*-methyl groups might increase the complexing ability. However, exactly the opposite happens, in that log K_1 drops from a value of 26.5 for Cu(II) with cyclam to a value of 18.3 with TMC (tetra-*N*-methylcyclam).[39] The reason for this is almost certain to be the large increase in steric strain found when complexes have *N*-alkyl groups added. This is accompanied by large drops in both complex stability and ligand field (LF) strength. The LF strength is a measure of the overlap in the M–L bond,[40] which is decreased when the M–L bonds are stretched in response to the steric crowding produced by *N*-alkyl groups. Figure 1 shows the Ni–N bonding in the gas phase becomes stronger along the series of ligands $MeNH_2 < EtNH_2 < i\text{-}PrNH_2$. In water, the solvation of the metal ion, or the proton, means that the steric

hindrance between the added alkyl groups and the waters of solvation leads[39a] to a decrease in complex stability along this series. Only for the Ag(I) ion[39b] with its long Ag–N bonds and linear coordination geometry does the intrinsic gas-phase order of basicity persist in aqueous solution, with log K_1 values as follows: $MeNH_2$, 3.06; $EtNH_2$, 3.44; *i*-$PrNH_2$, 3.64; *t*-$BuNH_2$, 3.69. The C-alkylation of chelating amines such as EN to give ligands such as TMEEN can also lead[39c,41] to an increase in complex stability[21] and LF strength for the complexes of square-planar low-spin Ni(II) and for Cu(II), where steric hindrance will be less, but for octahedral metal ions such as Zn(II)or Mn(II) the steric hindrance still overwhelms the gains in inductive effect.[39c]

E. Unsaturated Nitrogen Donors

Figure 1 shows that in the gas phase, the unsaturated nitrogen donor pyridine is a stronger base than any of the saturated N donors. However, in aqueous solution, pyridine is a weaker base than the saturated nitrogen donors. This must arise partly because pyridine is a tertiary amine, unable to disperse the charge from Lewis acids to the solvent by hydrogen bonding. Other unsaturated bases such as the nitriles (Figure 1) also show surprisingly strong coordinating properties in the gas phase but are relatively poor ligands in water. Here again, there is inability to disperse charge to the solvent. The order of basicity of N donors in water appears to be



The nitrogen is sp^2 (or sp) hybridized in these ligands, which leads to greater character in the orbitals used for bonding to the metal ion and hence more covalent bonding. These ligands can thus exert very high ligand field strengths, even though their proton basicity may be significantly less than that of the sp^3-hybridized saturated nitrogens. The low proton basicity of the unsaturated nitrogen donor can be of considerable help in designing ligands, since what ultimately counts in many situations is not the formation constant of the metal ion with the ligand alone but also the relative difficulty of removing protons from the donor groups of the ligand so as to permit complex formation. Another important aspect of the unsaturated nitrogen donors is the possibility of π bonding between the ligand and the metal ion. Thus, with the pyrazine ligand, it has been found[42] that the Ru(II) and Os(III) complexes are greatly stabilized relative to the complexes of other nitrogen donors by what can best be rationalized as a π-bonding component:

The evidence for this is the fact that the protonation constant of the pyrazine bound to the Ru(II) is *higher* than for the free ligand and the fact that the formation constant for Ru(II) with pyrazine is much higher than that with ammonia, even though the proton basicity of ammonia (pK_a = 9.2) is very much higher than that of pyrazine (pK_a = 0.6). This ability may be important in the coordinating properties of other systems containing unsaturated nitrogens, although, apart from the case of this unsaturated ligand with Ru(II) and Os(II), there is as yet no irrefutable evidence for this important effect.

Unsaturated donors such as the pyridyl or imidazole group have the ability to impart rigidity to the ligand system, due to the rigidity of aromatic ring systems. The ligand 1,10-phenanthroline (PHEN) forms complexes that are a fairly constant 1.4 log units more stable than those formed by BPY (2,2′-bipyridyl) with the same metal ion:

metal ion	log K_1(BPY)[a]	log K_1(PHEN)
Pb^{2+}	2.9	4.7
Mn^{2+}	2.6	4.0
Ni^{2+}	7.0	8.6
Cu^{2+}	8.0	9.1
Zn^{2+}	5.1	6.4
Ga^{2+}	4.5	5.6
Mg^{2+}		1.5
Ca^{2+}		0.7
La^{3+}	1.0	

[a] Ionic strength 0.1 M, 25 °C.[21]

It seems reasonable to suggest that this effect is due to the fact that the PHEN is more effectively *preorganized* for coordination relative to the BPY. The BPY is highly strained in the conformer with the nitrogens cis to each other, as required for coordination to metal ions,[43] because of the steric hindrance between the hydrogens in the 3- and 3′- positions, as seen in Figure 11A. However, in PHEN this problem is overcome by fusing the two rings and forcing the ligand to remain in the correct conformation for coordination to a metal ion. This idea of *preorganization*[44] is of considerable importance in ligand design and will be more fully discussed in section L.

F. The Heavier Donor Atoms P, As, S, and Se

Figure 1 shows once again that the neutral sulfur donor in the gas phase is a stronger base than are the analogous oxygen-donor ligands; this is true even for the proton.[15] In water, however, this is not the case. This difference is due to the inability of the sulfur to hydrogen bond to the solvent and so disperse the charge on the metal ion.[39b] A further factor may be[45,46] the large size of the S (and also Se, P, and As) donor atoms, which hampers coordination to small metal ions with tightly packed solvation spheres. The heavier donor atoms S, Se, P, and As when neutral coordinate well only to the soft metal ions, which tend to be large and often poorly solvated, such as Ag(I), Au(I), Hg(II), or Pd(II). Addition of S and Se groups to ligands leads to a modest increase in log K_1 for many metal ions (Cu^{2+}, Ni^{2+}) or a large (Ca^{2+}, La^{3+}) to small (Cd^{2+}, Pb^{2+}) decrease in log K_1. Only for really soft metal ions such as Ag(I) and Hg(II) are log K_1 values increased substantially by added thioether groups. The pattern, as far as can be judged from the limited amount of data available, is similar for arsine and phosphine groups, except that much larger stabilizations are produced by phosphine groups with soft metal ions.

A group of considerable importance is the mercapto or thiol group. The thiol group is weakly acidic (pK usually about 9 or 10) but binds to many metal ions with enormous complexing strength. It is, like the neutral soft donors, particularly strongly bound by soft metal ions such as Ag(I) and Hg(II), and ligands such

TABLE 3. Values of H_A, E_A^{aq}, C_A^{aq}, and D_A for Lewis Acids[a]

Lewis acids[b]	H_A	E_A^{aq}	C_A^{aq}	D_A	Lewis acid[b]	H_A	E_A^{aq}	C_A^{aq}	D_A
Au^+	−16	−3.0	0.190	0.0	Bi^{3+}	6.39	5.92	0.926	0.0
Ag^+	−10.6	−1.52	0.143	0.0	Pb^{2+}	6.69	2.76	0.413	0.0
Cu^+	−1.30	−0.56	0.430	2.5	Mn^{2+}	7.09	1.58	0.223	1.0
Hg^{2+}	1.63	1.35	0.826	0.0	Cr^{3+}	7.14	5.15	0.721	1.5
CH_3Hg^+	2.50	1.60	0.640	0.0	Fe^{3+}	7.22	6.07	0.841	1.5
Tl^{3+}	2.66	2.55	0.960	0.0	Ga^{3+}	7.69	6.06	0.788	1.5
Cu^{2+}	2.68	1.25	0.466	6.0	U^{4+}	7.80	7.55	0.968	3.0
H^+	3.04	3.07	1.009	20.0	Sn^{2+}	8.07	5.65	0.700	0.0
Cd^{2+}	3.31	0.99	0.300	0.6	UO_2^{2+}	8.40	4.95	0.589	1.0
Ni^{2+}	3.37	1.01	0.300	4.5	Lu^{3+}	10.07	4.57	0.454	0.0
Co^{3+}	3.77	3.30	0.875	7.0	La^{3+}	10.30	3.90	0.379	0.0
Zn^{2+}	4.26	1.33	0.312	4.0	Mg^{2+}	10.46	1.86	0.178	1.5
Co^{2+}	4.34	1.20	0.276	3.0	Sc^{3+}	10.49	7.03	0.671	0.0
Fe^{2+}	5.94	1.52	0.256	2.0	Al^{3+}	10.50	6.90	0.657	2.0
VO^{2+}	5.97	3.96	0.664	3.5	Y^{3+}	10.64	4.76	0.477	0.0
In^{3+}	6.30	4.49	0.714	0.5	Ca^{2+}	12.16	0.98	0.081	0.0

[a] Data from ref 45 and 46. E_A^{aq} and C_A^{eq} are for use in eq 3 and are the tendency of the Lewis acid to undergo ionic and covalent bonding. The D_A parameter is thought to represent steric and solvation effects on complex formation. [b] H_A is the hardness parameter, and the metal ions are placed in order of increasing hardness so that Au^+ is the softest and Ca^{2+} the hardest metal ion. Note that increased hardness implies decreased softness.

as dimercaptosuccinic acid, which has two thiol groups, are used in the treatment of mercury poisoning.[1]

G. Dual Basicity Scale Equations as an Aid in Selecting Donor Atoms

As pointed out in the Introduction, the HSAB idea of Pearson forms the basis of choice of donor atom for ligands but is limited in that the direction which it gives may be incomplete. There have been several attempts to quantify the ideas of HSAB, starting with the pioneering work of Edwards[47] and including other similar attempts by Yingst and McDaniel[48] and Yamada and Tanaka.[50] As has been discussed,[45,46] these empirical equations fail to predict data outside of the data set used for fitting the empirical constants in the equations, particularly some of the constants in Table 2. A more recent fitting of a dual-basicity scale[45,46] has incorporated the data in Table 2, and it was found that a two-parameter scale of the type used by Edwards[47] (eq 2) was incapable of correlating the large data set used.

$$\log (K/K_0) = \alpha E_n + \beta H \qquad (2)$$

In eq 2 log K is the formation constant of the complex between the metal ion and a unidentate ligand, whereas log K_0 is the constant with the water molecule and is taken to be −1.74. E_n is the nucleophilicity constant and is derived from the oxidation potential of the base. H is the protonation constant of the base relative to that of water, and α and β are empirical constants characteristic of the base. It was found[45,46] that in order to fit the set of formation constants for unidentate ligands with metal ions in aqueous solution an equation with three pairs of parameters was necessary (eq 3). E_A^{aq}

$$\log K_1 = E_A^{aq}E_B^{aq} + C_A^{aq}C_B^{aq} - D_AD_B \qquad (3)$$

and E_B^{aq} are a measure of the strength of the ionic contribution to M–L bond formation for acid A and base B, C_A^{aq} and C_B^{aq} are a measure of the strength of covalence in the M–L bond, and D_A and D_B are a measure of the steric hindrance on formation of the M–L bond.[45,46] Fitting of eq 3 for a large number of Lewis acids and bases gave the set of parameters in Tables 3 and 4. In order to predict the log K_1 values for any acid–base pair, all that is necessary is to sub-

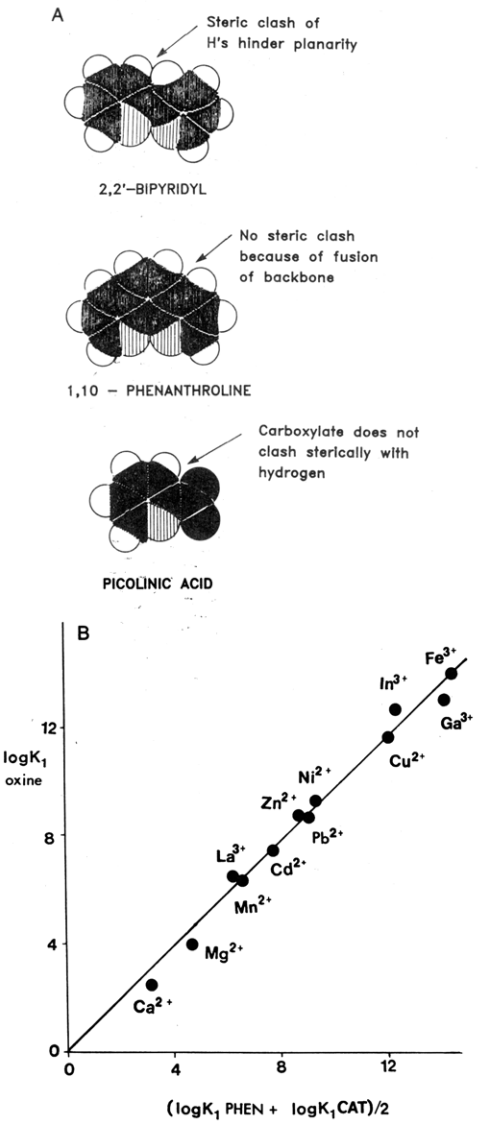


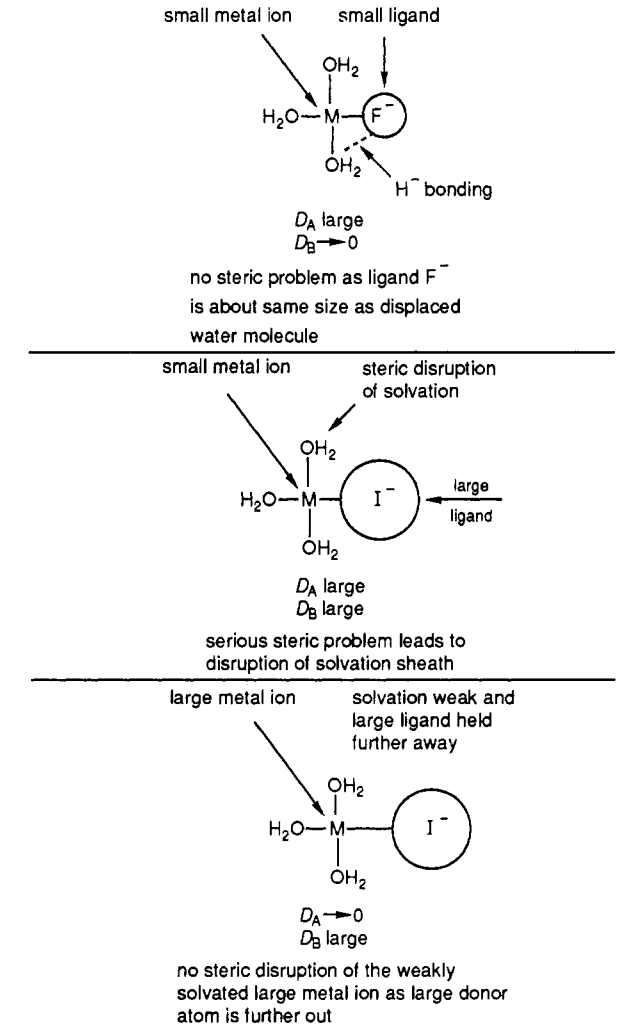
Figure 11. (A) Steric clash in 2,2-bipyridyl which hinders planarity and lowers complex stability relative to 1,10-phenanthroline and picolinic acid, where the clash is not present. (B) The rule of average environment in complex stability, as exemplified by the relationship between log K_1 for the 8-hydroxyquinoline (oxine) complex and the average of log K_1 for the 1,10-phenanthroline (PHEN) complex + log K_1 for the catecholate (CAT) complex. Data from ref 21, ionic strength 0.1 M, 25 °C.

stitute the parameters from Tables 3 and 4 into eq 3. For example, there are currently no formation constant data that would allow a decision on whether a tertiary phosphine donor atom would be effective in a proposed ligand for enhancing selectivity for In(III) relative to Fe(III). Both metal ions are listed in Table 1 as hard, while the phosphine is listed as soft, which does not allow for a decision. However, substitution of the relevant values from Tables 3 and 4 into eq 3 predicts log K_1 with a triphenylphosphine type of ligand as 2.5 for In(III) and −0.1 for Fe(III), which would indeed lead to greater selectivity for In(III). On the same basis one would also expect use of SR_2 or RS^- groups to lead to improved selectivity for In(III) relative to Fe(III).

Equation 3 has considerable power of prediction and generally predicts formation constants to within 0.2 log unit where known, and where there are no known values against which to check, the predictions are at least in accord with chemical experience. However, the reader might wonder what physical meaning can be attached to the parameters in eq 3. Is eq 3, in fact, simply an exercise in numerology without any real chemical significance? First, it should be pointed out that use of a pattern-recognition computer program[50] confirms that a dual-basicity equation is insufficient to correlate formation constant data for complexes of unidentate ligands in aqueous solution and further that a four-pair parameter equation produces only a very small statistically insignificant improvement (within the estimated reliability of the log K_1 values) in predictive ability. Even so, do the parameters mean anything? They are certainly cross-correlated, in that for such types of equations matrix algebra can be used[45,51] to express new sets of C_A, E_A, C_B, and E_B constants in terms of the existing C_A, E_A, C_B, and E_B constants, for example. However, it can be shown from the same matrices that if certain conditions are met in the data set, the order of the *ratios* of the constants, particularly the ratios E_A/C_A and E_B/C_B is unique. These ratios are measures of the relative ionicity versus covalence in the M–L bond and are listed in Table 3 as H_A, the hardness of the Lewis acids, and in Table 4 as H_B, the hardness of the Lewis bases. It should be noted that increasing hardness implies decreasing softness. These hardness parameters correlate well[52,53] with a large variety of physical properties of the acids and bases (e.g., gas-phase affinities, NMR coupling constants, and standard reduction potentials) which might reasonably be expected to correlate with tendencies toward ionicity/covalence in the M–L bond.

Of particular interest are the D_A and D_B parameters, whose equivalent does not appear in other attempts at correlating formation constants.[47-49] In many cases, particularly in the case of the proton, these D_A and D_B constants dominate the chemistry. Thus, without the very large D_A parameter for the proton, HCl would be a weak acid (pK = 7.3). In fact, it has been shown above that gas-phase chemistry[15] does not resemble aqueous-phase chemistry very strongly for most metal ions except very soft metal ions. Soft metal ions have an aqueous-phase chemistry that comes closer to resembling the gas-phase chemistry shown in Figure 1. Thus, Ag(I) has a higher affinity for neutral S than O donor ligands and also shows[39b] affinities in aqueous solution for primary amines which are $MeNH_2 < EtNH_2 < i\text{-}PrNH_2$, as seen for Ni(I) in the gas phase.[15] One notices that for very large Lewis acids, with cation radii[156] above 1.0 Å[54] (e.g., Ag^+, La^{3+}, and Ca^{2+}), D_A is zero, and for small metal ions D_A becomes progressively larger and is uniquely large for the very small proton. Similarly, for bases with small donor atoms, NH_3, OH_2, and F^-, D_B is zero, but becomes larger for larger donor atoms such as S, Se, P, As, Cl, Br, and I. The D_B parameter correlates closely with the covalent radius of the donor atom and is largest for the very large iodide ion. The D_A parameter thus increases with decreasing metal ion radius, while the D_B parameter increases with increasing donor atom radius.

The role of size in the D_A and D_B parameters suggests[46] the following interpretation:



The D_A and D_B parameters are thus essentially concerned with disruption of the solvation sheath on the cation by large donor atoms. This may also involve inability of the large donor atom to H-bond with the solvation sheath, as seen above. Thus, as has already been noted (section D), the Ag(I) ion behaves, because of its large size and weak solvation, like an ion in the gas phase. Other metal ions such as La^{3+} and Ca^{2+} have little affinity for soft donor atoms, even though they have $D_A = 0$. Such metal ions are intrinsically hard with little ability to form covalent bonds. On the other hand, the low affinity that a metal ion such as Cu(II) has for soft donor atoms derives entirely from its small size, with resulting disruption of its solvation sphere by large donor atoms. It has been found[55] that Cu(II) in its TETB complex has a quite different HSAB behavior

TABLE 4. Values of H_A, E_A^{aq}, C_A^{aq}, and D_A for Lewis Bases[a]

Lewis base[b]	H_A	E_A^{aq}	C_A^{aq}	D_A
F^-	0.0	1.00	0	0.0
CH_3COO^-	0.0	0.0	4.76	0.0
OH^-	0.0	0.0	14.00	0.0
N_3^-	−0.064	−0.067	10.4	0.2
$S{=}C{=}N^-$	−0.082	−0.76	9.3	0.2
NH_3	−0.088	−1.08	12.34	0.0
C_5H_5N	−0.102	−0.74	7.0	0.0
Cl^-	−0.100	−1.04	10.4	0.6
SO_3^{2-}	−0.107	−1.94	18.2	0.4
Br^-	−0.108	−1.54	14.2	1.0
$S_2O_3^{2-}$	−0.119	−3.15	26.5	1.1
I^-	−0.122	−2.43	20.0	1.7
NCS^-	−0.128	−1.83	14.3	1.0
$(HOCH_2CH_2)_2S$	−0.135	−1.36	10.1	0.6
$PPh_2(4\text{-}C_6H_4SO_3^-)$	−0.132	−3.03	23.0	0.7
$As(3\text{-}C_6H_4SO_3^-)_3$	−0.135	−1.93	14.3	
$(NH_2)_2C{=}S$	−0.135	−2.46	18.2	0.6
$HOCH_2CH_2P(C_2H_5)_2$	−0.141	−4.89	34.7	0.6
CN^-	−0.148	−4.43	30.0	0.38

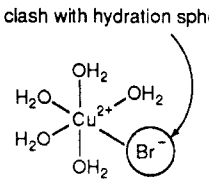
[a] Data from ref 46. [b] The Lewis bases are arranged in order of decreasing hardness, with fluoride the hardest and cyanide the softest ion.

in relation to the formation constants of its complexes with unidentate ligands than is found for the Cu(II) aquo ion:

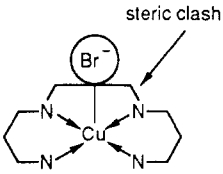
ligand	log $K_1(Cu^{2+})$	log $K_1(CuTETB^{2+})$[55]
Cl^-	0.4	0.04
Br^-	0.03	0.30
I^-	(−3.0)[a]	0.81
N_3^-	2.86	0.89
SCN^-	2.33	1.13
AcO^-	2.22	0.40

[a] Calculated from eq 3, since I^- reduces Cu(II) aquo ion to Cu(I), making measurement of log K_1 impossible.

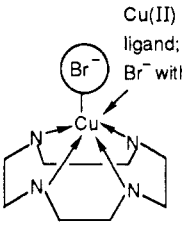
One sees that the Cu^{2+} aquo ion should be hard according to Pearson's criteria,[11] since the order of complex stability with halide ions is $Cl^- > Br^- > I^-$. It is actually classified as intermediate in Table 1 on the basis of other criteria. On the other hand, for the Cu(II) in the complex $[Cu(TETB)]^{2+}$, where the extra ligands bind to the axial site as shown below, the order of complex stability with halide ions of $Cl^- < Br^- < I^-$ means that the Cu(II) should now be classified as soft. Fitting the set of formation constants for $[Cu(TETB)]^{2+}$ binding to unidentate ligands above shows that the change in HSAB behavior from hard to soft is caused by a dramatic drop in the D_A parameter from 6.5 for the Cu^{2+} aquo ion to 0.3 for $[Cu(TETB)]^{2+}$. The interpretation put on this is that the extent of solvation at the axial site of $[Cu(TETB)]^{2+}$ is much less than on the coordination site of the Cu^{2+} aquo ion and that this contributes to the greater affinity that the $[Cu(TETB)]^{2+}$ has for the large donor ligand I^-. If this interpretation is correct, then further removal of steric impediments to coordination of large donor atoms should produce quite dramatic effects on the coordination properties of the Cu(II) ion. Accordingly, it is found for the complex $[Cu(12\text{-}aneN_4)]^{2+}$,[56] where the Cu(II) should be extruded much further out of the plane of the ligand than is true of $[Cu(TETB)]^{2+}$, that even softer behavior should be found. Thus, $[Cu(12\text{-}aneN_4)]^{2+}$ shows[56] an even more marked preference for I^- over Cl^- and binds strongly to such traditionally soft ligands as isonitriles.



Cu(II) aquo ion. Complexes of large donor atom ligands are destabilized sterically, resulting in "hard" behavior.



Cu(II) TETB complex. Steric effects are diminished because of weaker solvation of complex; behavior is weakly "soft".



Cu(II) complex with 12-aneN$_4$. Metal ion is held well out of plane of macrocycle, steric effects are further diminished, and Cu(II) is still softer.

The change of Cu(II) from hard to soft in the above series of complexes is, of course, open to other interpretations. One immediately thinks of the effect of being coordinated to the softer nitrogen donors of the macrocycles on the bonding properties of Cu(II) or the fact that the coordination unidentate ligand must on the macrocyclic complex occupy the axial coordination site, whereas on the Cu(II) aquo ion it presumably coordinates lying in the plane of the tetragonally distorted Cu(II) ion. However, what is clear is that the change in hard–soft behavior of the Cu(II) in passing from the aquo ion through the macrocyclic complexes relates to a change in the D_A parameter, and in order to understand eq 3 more fully, it is necessary to study the binding of unidentate ligands to a wider selection of metal ion complexes such as those[55,56] discussed above.

H. Chelating Ligands

The chelate effect has caused considerable controversy in the past.[57] On the one hand, the model proposed by Schwarzenbach[58] suggested that it could be understood in terms of the restricted volume in which the second donor atom of the chelating ligand could move once the first donor atom had been coordinated. On the other hand, Adamson[31] suggested that the chelate effect arises because of the way the standard reference state is defined and that it disappears once the formation constant is expressed in terms of mole fractions, a more appropriate way of making the comparison. In fact, both approaches are essentially the same, since in the Schwarzenbach approach the translational entropy of the second unidentate ligand is set close to zero by making it move in a restricted volume, while in the Adamson approach the translational entropy is set at zero by making the reactants fill completely the space of the standard reference state once the constants are expressed as mole fractions. However, in practical terms the Adamson approach seems to be simpler, in that it requires no assumptions about ligand

TABLE 5. Values for log K_1 for Polyamine Ligands Observed and Calculated with Eq 5

metal ion		log K_1				
		EN	DIEN	TRIEN	TETREN	PENTEN
Cu(II)	calcd	10.76	15.92	20.20	21.28	
	obsd[21]	10.54	15.9	20.1	22.8	
Ni(II)	calcd	7.59	11.33	14.57	17.24	19.16
	obsd[21]	7.35	10.7	14.4	17.4	19.1
Fe(II)	calcd	4.38	6.82	8.67	10.02	10.87
	obsd[21]	4.34	6.23	7.76	9.85	11.1
Pb(II)	calcd	4.92	7.51	9.59	11.18	12.26
	obsd[21]	5.04	7.56	10.35	10.5	

geometry or the length of the bridge connecting the two or more donor atoms. This approach leads to the following equation for the chelate effect[30]

$$\log K_1(\text{polydentate}) = \log \beta_n(\text{unidentate}) + (n-1)\log 55.5 \quad (4)$$

where log K_1(polydentate) refers to the stability of the complex of an n-dentate polydentate ligand, log β_n(unidentate) refers to the stability of the complex containing n unidentate analogues of the polydentate ligand, and 55.5 is the molarity of water. The log 55.5 represents, in fact, the entropy of translation of 1 mol of solute generated at 1 m concentration.[57]

The first consequence of eq 4 has already been demonstrated in Figures 4–6. When log β_n is zero in eq 4, then the chelate effect should have the value $(n-1)$ log 55.5. In other words, when the donor strength of the two unidentate ligands is weakened to the point that they enjoy no extra stability relative to the water molecules with which they are competing for binding sites on the metal ion, all that should be left as an advantage when they are joined together to give a single chelating ligand is the log 55.5 entropy contribution to the chelate effect. Thus, in Figures 4–6, the intercepts have the value $(n-1)$ log 55.5, or values very close to this, except when other unfavorable entropy effects make themselves felt. Thus, the failure of the correlation for BAMTPH in Figure 5 to produce an intercept of log 55.5 may be accounted for by the unfavorable loss of entropy produced on coordinating the long connecting arms of the ligand. Clearly, to resolve this question ligands with more rigid structures need to be investigated to see whether higher intercepts are obtained in correlations such as that in Figure 5.

For polyamine ligands, eq 1 as it stands predicts formation constants that are much too low, if the ammonia complexes are used as unidentate analogues for the polyamines. However, if the greater basicity of aliphatic amines is taken into account, as evidenced by the pK_a for NH_3 of 9.22 as compared with 10.6 for methylamine, the greater basicity of the nitrogens on polyamines can be corrected for by the inductive effect factor[30] of 1.152 (=10.6/9.22):

$$\log K_1(\text{polyamine}) - 1.152 \log \beta_n(NH_3) + (n-1)\log 55.5 \quad (5)$$

This equation, as seen below, works very well at predicting log K_1 for the polyamine complexes for a variety of metal ions (Table 5). Equation 5 is remarkably successful at predicting log K_1 values for polyamine complexes, considering its simplicity. It should be noted that only log $K_1(NH_3)$ values are known for Fe(II) and Pb(II). In this instance it is necessary to include a term λ_N, which is the stepwise decrease between log K_n and log K_{n+1} values for ammonia complexes and has[30] a value of 0.5. Thus, eq 3 becomes

$$\log K_1(\text{polyamine}) = 1.152n \log K_1(NH_3) - \sum_{i=1}^{n-1} i\lambda_N + (n-1)\log 55.5 \quad (6)$$

Equation 6 is thus equivalent to eq 5, except that λ_N is no longer experimental but is given a fixed value of 0.5.

Equation 6 has been extended[30] to include acetate groups. This has been done by adding a second set of terms analogous to those for the nitrogen donors, with a separate λ_0 term that handles the stepwise decrease of log K_n as more acetate groups are added. Initially, λ_0 was set equal to 0.19 log K_1(acetate) but was later found to be better obtained by empirically adjusting it to a best fit for each metal ion. Some values of λ_0 and log K_1 for amino acids calculated from eq 7 are seen in

$$\log K_1(\text{amino acid}) = 1.152n \log K_1(NH_3) - \sum_{i=1}^{n-1} i\lambda_N + m \log K_1(CH_3COO^-) - \sum_{i=1}^{m} i\lambda_0 + (m+n-1)\log 55.5 \quad (7)$$

Table 6. In eq 7 m is the number of acetate groups on the ligand (e.g., m is 4 for EDTA). The empirically adjusted values of λ_0 are much smaller than those found as log $K_1(CH_3COO^-)$ – log $K_2(CH_3COO^-)$ for metal ions. This was initially rationalized in terms of the large experimental values of λ_0 reflecting the effect on log K_n of electrostatic repulsion between the negatively charged acetate groups, which is removed once the groups are joined together into a single ligand. Table 6 shows the usefulness of eq 7 in predicting log K_1 values for amino acid type ligands. Attempts have been made to extend eq 7 to other types of donor groups, and some success has been found[59] for groups such as pyridyl, imidazolate, and phenolate.

If log β_2 for pyridine is used to calculate log K_1 for BPY with eq 5, it is once again found that the predicted log K_1 values are too low. Similarly, the predicted log

TABLE 6. Values for log K_1 for Various Polyaminocarboxylate Ligands Observed and Calculated with Eq 7[a]

metal ion		Ca(II)	La(III)	Ni(II)	Pb(II)	Al(III)	Fe(III)
GLY[b]	calcd	2.19	4.06	6.26	5.65	5.43	9.57
	obsd	1.39	4.00	5.23	6.18	5.47	10.66
IDA	calcd	4.85	8.04	9.37	9.39	9.61	13.99
	obsd	3.47	7.20	9.14	8.29	9.42	14.08
NTA	calcd	7.75	12.17	12.45	13.06	13.46	18.14
	obsd	7.71	12.45	12.83	12.66	13.38	17.88
EDMA	calcd	3.70	6.03	10.62	8.74	7.59	15.18
	obsd			10.88	8.67		
EDDA	calcd	5.86	9.51	13.73	12.48	11.77	19.78
	obsd	(5.51)[c]	(8.36)[c]	14.53	11.58		(18.24)[c]
EDTA	calcd	11.90	17.92	19.86	19.75	19.14	27.65
	obsd	12.37	18.14	20.36	19.80	19.20	27.64
DTMA	calcd	3.71	6.50	14.49	11.32	9.25	20.30
	obsd			14.81			

[a] At ionic strength of zero. Where values are reported at other ionic strengths, they have been corrected to zero by comparison with metal ions and ligands of the same charge reported at both ionic strengths. Observed values are from ref 21. The log $K_1(NH_3)$ values used in eq 7 are from Table 2. The log $K_1(CH_3COO^-)$ values used are calculated as 0.34 × log $K_1(OH^-)$, which overcomes problems[63] associated with the possibility of acetate itself coordinating as a chelating ligand with larger metal ions. The values of λ_0 used are as follows: Ca(II), –0.24; La(III), –0.15; Ni(II), 0.03; Pb(II), 0.07; Al(III), 0.33; Fe(III), 0.60. [b] Ligand abbreviations: see Glossary. [c] Actually for ethylenediamine-*N*,*N*-diacetate.

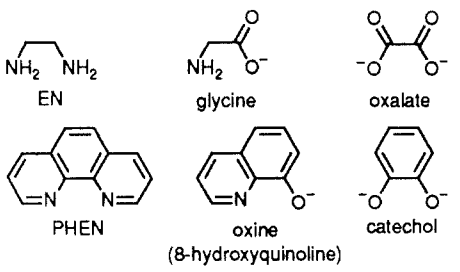
TABLE 7

metal ion		log K,[d] AMPY[a]	IDPY	NTPY	EDDPY	EDTPY	AMPY-DA	BPY	TERPY
Ni(II)[b]	calcd	7.26	10.84	14.04	14.26	19.04	12.77	(7.04)	10.64
	obsd	7.11	8.70	14.45	14.40	18.0	12.1	7.04	10.7
Mn(II)[b]	calcd	2.85	4.24	5.21	5.44	5.8		(2.62)	4.01
	obsd	2.66	4.16	5.6	5.90	10.3[c]		2.62	4.4

[a] For ligand abbreviations, see Figure 7B. [b] "log K_1(py)" = 2.9 for Ni(II), 0.69 for Mn(II). These are empirically derived values, higher than observed, as discussed in text. [c] The value of EDTPY with Mn(II) is also anomalously high, which may reflect something such as a change in coordination number once six nitrogen donor atoms are present. [d] Ionic strength 0.1 M, 25 °C.[21]

K_1 values for ligands containing mixed saturated amine and pyridine groups are predicted to be much too low. This can be remedied by calculating log K_1(py) from eq 4 using log K_1 for BPY, which gives "log K_1(py)" values higher than those observed in practice. This parallels the use of a factor of 1.152 in eq 5 to take into account the higher basicity of nitrogens in polyamines than in ammonia. However, the higher apparent "log K_1(py)" values probably do not reflect greater basicity but rather a diminution of the steric interference produced by the ortho hydrogens on pyridine rings. Thus, the ortho hydrogens on pyridine rings must produce considerable steric hindrance once coordinated to a metal ion, and this will be greatly reduced when the pyridines are bonded to other coordinating groups at the ortho position. Some calculated and observed values for ligands containing pyridyl groups coordinate to Ni(II) and Mn(II) are listed in Table 7.

The type of approach used to estimate log K_1 values based on donor group additivity can be very successful.[30,59] The observation of donor group additivity leads in a logical way to what might be called a "rule of average environment".[60] This states that the formation constant of a ligand containing two different types of donor groups will be the average of the formation constants of a pair of similar ligands each containing only one of the two donor types; e.g., glycine is the average of EN and oxalate, or 8-hydroxyquinoline is the average of catechol and 1,10-phenanthroline (PHEN):



This rule leads to usefully accurate predictions of formation constants. In Figure 11B is seen a plot of [log K_1(catechol) + log K_1(PHEN)]/2 against log K_1(oxine) for all the metal ions for which data are available.[21] No values of log K_1(catechol) for Ca^{2+}, In^{3+}, and Pb^{2+} are currently available, so that these were estimated with the help of Figure 4 as 3.5, 19.5, and 12.5, respectively. Figure 11B can now be used to make predictions that would be very hard to arrive at by any other means. For example, no data are available that would even allow a guess at what log K_1(PHEN) might be for Th(IV). However, log K_1(oxine) is 10.5 for Th(IV), and one can estimate log K_1(catecholate) from Figure 4 as 20.6 from the known value of log $K_1(OH^-)$ = 10.8.[21] This leads to a prediction of log K_1(PHEN) for Th(IV) as 10.5 × 2 − 20.6, or 0.4. As would be expected, Th(IV) has only a very small affinity for PHEN.

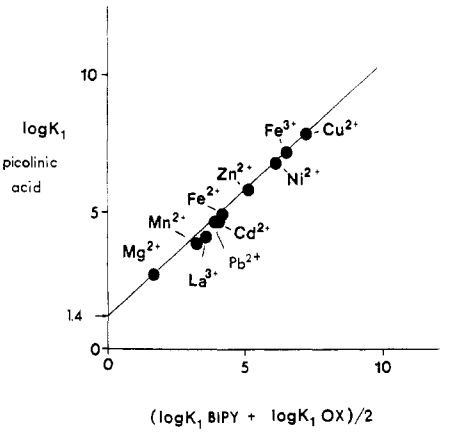


Figure 12. Modification to the rule of average environment brought about by the steric clashes in 2,2′-bipyridyl (BPY) on becoming planar. The intercept on the vertical axis for log K_1 for picolinic acid is produced by the fact that, unlike BPY, there are no steric problems associated with assuming planarity in picolinate so as to coordinate to metal ions, as seen in Figure 11A.

For some systems, such as bipyridyl, picolinic acid (PIC), and oxalate, the rule does not hold without some modification. As seen in Figure 12, there is a good linear relationship between log K_1(PIC) and [log K_1(BPY) + log K_1(oxalate)]/2, and it even has a slope very close to unity, but it has an intercept of about 1.4 log units. This can be understood in terms of the arguments (section E) on the role of steric hindrance between the ortho hydrogens of the BPY ligand, which destabilizes it by a constant 1.4 log units relative to PHEN, as seen in Figure 11A. The intercept in Figure 12 thus corresponds[60] to a reduction in steric strain in PIC relative to BPY because the adjacent hydrogen on PIC is not interfered with sterically by the carboxylate group. Once again, Figure 12 can be used to make a variety of predictions, such as log K_1(BPY) for UO_2^{2+}, PuO_2^{2+}, and Ba^{2+} which are 2.2, 2.9, and −0.7, respectively. Interestingly, it was the correlation in Figure 12 that suggested that log K_1(BPY) for La^{3+} should be 1.2. Experimentally, a value of 1.1 was obtained.[61]

Other approaches to estimating formation constants of chelating ligands have been detailed elsewhere.[62] It is seen that in the approaches described in this section, all the chelates have involved five-membered chelate rings only. None of the models employed take into consideration large chelate rings, and as is evident from the literature,[21] the complexes of chelating ligands that form six-membered chelate rings tend to be of lower stability than those that form five-membered chelate rings. One can take this into account empirically by, for example, altering the values of λ_N and λ_0 in eq 6 and 7. However, such an approach offers no real insights and does not correctly predict the few examples where

TABLE 8[a]

metal ion	complex	L = EN ΔG	ΔH	ΔS	L = TN ΔG	ΔH	ΔS
Cu(II)	ML	-14.3	-12.6	6	-13.2	-11.4	6
	ML_2	-26.7	-25.2	5	-22.9	-22.4	2
Ni(II)	ML	-10.0	-9.0	3	-8.6	-7.8	3
	ML_2	-18.3	-18.3	0	-14.3	-15.0	-2
Cd(II)	ML	-7.4	-6	5	-6.1	-5	4
	ML_2	-13.1	-13.3	-1	-9.8	-10	-1
metal ion	complex	L = EDTA ΔG	ΔH	ΔS	L = TMDTA ΔG	ΔH	ΔS
Cu(II)	ML	-25.5	-8.2	58	-25.6	-7.7	60
Cd(II)	ML	-22.3	-9.1	44	-18.9	-5.4	45
Ca(II)	ML	-14.5	-6.6	26	-9.9	-1.7	27
La(III)	ML	-21.1	-2.9	61	-15.4	+3.8	64
Pb(III)	ML	-24.4	-13.2	38	-18.6	-6.4	41

[a] All data are at 25 °C and ionic strength 0.1 M. Units for ΔG and ΔH are kcal mol^{-1}, and for ΔS are cal deg^{-1} mol^{-1}. Data are from ref 21.

increase of chelate ring size leads to an increase in complex stability. The effect of chelate ring size is of paramount importance in controlling complex stability and selectivity. The changes that occur in formation constant on change of chelate ring size appear to be[63] largely steric in origin, and so to understand them more fully, the steric aspects of complex formation must be considered.

I. The Size of the Chelate Ring and the Size of the Metal Ion

It is a well-known fact of coordination chemistry that an increase in the size of the chelate ring usually leads to a drop in complex stability. This observation was originally modeled[58] in terms of entropy effects associated with the longer connecting link between the donor atoms of ligands that form six-membered as opposed to five-membered chelate rings. However, the available[21] evidence shows that such drops in complex stability, associated with increases in the size of the chelate ring, are almost entirely due to less favorable enthalpy contributions as seen in the thermodynamics of complex formation of EN and PN complexes or of EDTA and TMDTA complexes (see Table 8). There is thus a general opinion that decreases in complex stability associated with increases in the size of the chelate ring are due to the greater difficulty of bringing together dipoles and charges on donor atoms as chelate ring size increases and to steric strain. The role of steric strain has been demonstrated[63] by means of MM calculations for pairs of polyamine ligands where one ligand has a five-membered chelated ring in its complex with metal ions.

The importance of strain energy to the thermodynamics of complex formation lies in the *increase* (ΔU) in strain energy that occurs on complex formation, as in eq 8.

$$\underset{U_M}{M} + n\underset{U_L}{L} \xrightarrow{\Delta U} \underset{U_{ML_n}}{ML_n}$$

$$\Delta U = U_{ML_n} - U_M - nU_L \qquad (8)$$

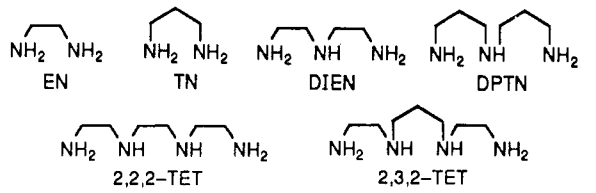
In eq 8, ΔU is the change in strain energy of the ligand plus metal ion on complex formation, U_M, U_L, and U_{ML_n} are the strain energies of the free metal ion, the ligand L, and the complex formed between the metal ions and n ligands, respectively. The complexes involving Ni(II) with polyamines with different sizes of chelate rings are ideal to test the hypothesis that decrease of complex stability, which is almost entirely an enthalpy effect, is largely due to steric strain. There is available[21] a large quantity of data on the formation constants and enthalpies of complex formation of these complexes, as well[64] as crystallographic studies, which allow for the development of appropriate force field parameters for the bonds involving the high-spin Ni(II) ion. Of particular interest here is the pair of complexes $[Ni(2,2,2\text{-TET})(H_2O)_2]^{2+}$ and $[Ni(2,3,2\text{-TET})(H_2O)_2]^{2+}$, because, unlike the usual situation, the complex with 2,3,2-TET, which has a six-membered chelate ring, is more stable than that with 2,2,2-TET, which has only five-membered rings.

TABLE 9. 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 Calculations[63-65]

complex[b]	U[c]	$-\Delta U$[d]	ΔH[e]	$-\Delta(\Delta H)$
Ni(EN)	1.14		-9.0	
		1.53		1.2
Ni(TN)	3.04		-7.8	
$Ni(EN)_2$	3.35		-18.3	
		3.07		3.3
$Ni(TN)_2$	7.16		-15.0	
$Ni(EN)_3$	4.57		-28.0	
		7.44		6.7
$Ni(TN)_3$	13.12		-21.3	
Ni(DIEN)	6.08		-11.9	
		1.46		1.3
Ni(DPTN)	8.28		-10.6	
Ni(DIEN)	11.87		-25.3	
		7.97		7.7
$Ni(DPTN)_2$	21.32		-17.6	
Ni(2,2,2-TET)	9.44		-14.0	
		-2.49		-3.9
Ni(2,3,2-TET)	7.32		-17.9	

[a] The difference in strain energy, $-\Delta H$, 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, and DPTN = 1,5,9-triazanonane. All high-spin Ni(II) waters and charges are neglected for simplicity. [c] Reference 63. [d] Corrected for differences in strain energy of free ligands of 0.37 kcal mol^{-1} per extra methylene group.[63] [e] Reference 21, ionic strength 0.1 , 25 °C.

Accordingly, values of U_L were calculated for the free ligands EN and TN, and U_L was estimated to differ for DIEN and DPTN by 0.37 kcal mol^{-1} per extra methylene group,[63] which was the calculated difference in U_L for EN and TN. Values of U_{ML} were calculated for the



pairs of complexes illustrated in Table 9. It is seen that the differences in ΔU in Table 9 correspond very closely to the differences in ΔH. Of particular interest is the fact that the calculations[65] reproduce the observation that the complex of the ligand 2,3,2-TET, which forms a six-membered chelate ring, is more stable than that

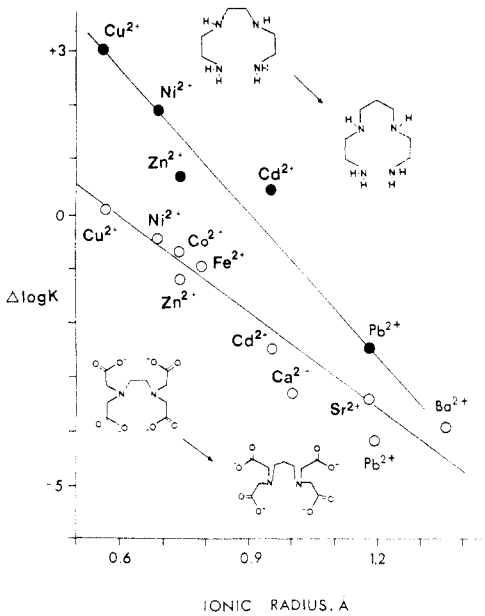


Figure 13. Effect on complex stability of increase in chelate ring size from five-membered and six-membered in open-chain ligands as a function of metal ion size. The change in formation constant, $\Delta \log K_1$, in passing from 2,2,2-TET to 2,3,2-TET (●) and in passing from EDTA to TMDTA (○) is plotted against the ionic radii[54] of the metal ions. It should be noted that increase in chelate ring size leads to greater decreases in complex stability with larger metal ions. Data from ref 21, ionic strength 0.1 M, 25 °C.

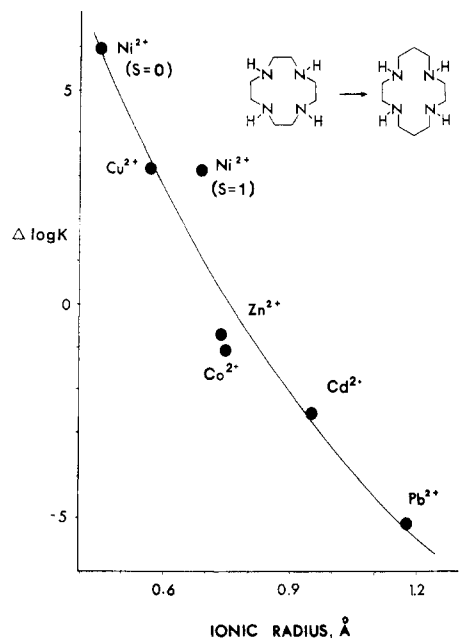
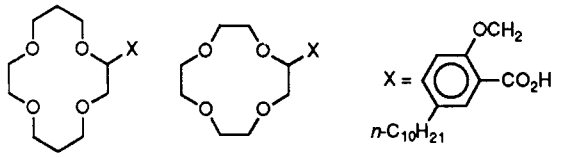


Figure 14. Effect of increase in chelate ring size on the stability of complexes of macrocycles as a function of metal ion size. The change in formation constant, $\Delta \log K_1$, in passing from 12-aneN$_4$ to 14-aneN$_4$ has been plotted as a function of metal ionic radius.[54] This correlation should be compared with those in Figure 13. It should be noted that $\Delta \log K_1$ for these macrocycles decreases with increasing metal ion size, as found for open-chain ligands, but opposite to what would be expected on the basis of macrocyclic hole size. Data from ref 21, ionic strength 0.1 M, 25 °C.

of 2,2,2-TET, which forms only five-membered chelate rings. In accordance with general opinion, the greater complex stability of the 2,3,2-TET complex than of the 2,2,2-TET complex is a steric effect and is associated with the release of steric strain in the 2,2,2-TET complex, which is too short to span the Ni(II) ion effectively, on adding another methylene group to give 2,3,2-TET. Table 9 demonstrates the potential of MM calculations for predicting and rationalizing the thermodynamics of complex formation.

Crystal structures of Ni(II) complexes with polyamines with five-membered or six-membered chelate rings suggest that the bite size (N···N distance across the chelate ring) of TN is greater than that of EN.[64] One might logically expect, therefore, that one way in which to increase selectivity for large metal ions over small metal ions would be increase the size of the chelate ring. However, a large amount of formation constant data reveals that precisely the opposite is true; i.e., an increase of chelate ring size leads to large drops in complex stability for the complexes of large metal ions and may even lead to increases in complex stability for small metal ions. So closely related to metal ion size is this effect that it can be quantified as seen in Figure 13. In Figure 13 has been plotted against metal ion radius[54] the change in complex stability $\Delta \log K$, on going from the EDTA to the TMDTA complex or from the 2,2,2-TET complex to the 2,3,2-TET complex, for a wide variety of metal ions. It is seen that as metal ion radius increases, so the drop in complex stability on passing from the five-membered chelate ring to the six-membered chelate ring becomes more marked. This observation leads to a second rule of ligand design,[16] which relates complex stability to metal ion size and states that "increase of chelate ring size leads to a greater degree of complex destabilization for larger metal ions than for smaller metal ions".

This rule even holds to a considerable degree in the complexes of macrocyclic ligands and usually takes precedence over expectations based on macrocyclic ring size. Thus,[16] crown ether I has a larger macrocyclic ring



I II

than crown ether II but shows[66] greater selectivity for the small Li^+ ion over the large Na^+ ion. This suggests that the greater selectivity of I for the small Li^+ ion arises because I forms six-membered chelate rings on complex formation, whereas II forms only five-membered chelate rings. The same type of effect is observed[16] for the tetraazamacrocycles. In Figure 14 is seen a plot against metal ionic radius of the change in complex stability, $\Delta \log K$, which occurs in going from the complexes of the tetraazamacrocycle 12-aneN$_4$ to 14-aneN$_4$. It is seen that the behavior is not very different from that observed for nonmacrocyclic ligands in Figure 13. The essence of the behavior seen in Figure 14 is that as the macrocyclic cavity gets larger, so the affinity for large metal ions decreases and that for small metal ions increases. This is quite contrary[67,68] to expectations based on the current idea of size-match selectivity in macrocyclic ligands. It is, however, entirely in keeping with expectations based[16] on the rule regarding the response in terms of complex stability of metal ions to changes in chelate ring size as the size of the metal ion is varied.

In order to understand this effect, one needs to examine MM calculations on chelate rings of different

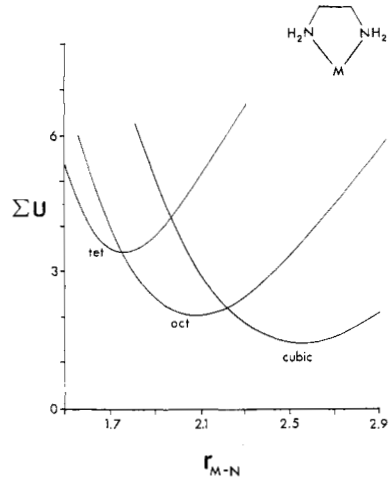


Figure 15. Strain energy, $\sum U$, of an isolated five-membered chelate ring involving ethylenediamine, calculated using molecular mechanics, as a function of metal–nitrogen bond length and N–M–N bond angles appropriate to different coordination geometries.[69] The N–M–N angles used were 109.5° for tetrahedral, 90° for octahedral (or square planar), and 70° for cubic. As metal ions become larger, coordination numbers increase, and so preferred N–M–N angle decreases. The diagram shows that the lowest strain energy for the ethylenediamine type of chelate ring is achieved with metal ions with longer M–N bond lengths (and smaller N–M–N angles), i.e., large metal ions.

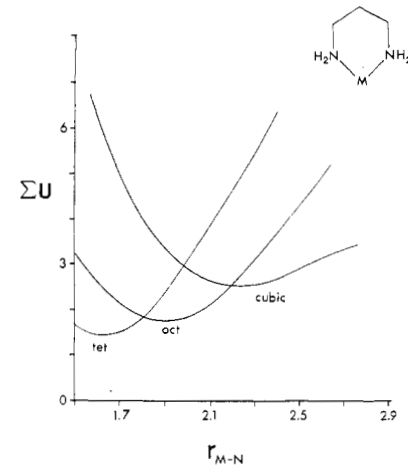


Figure 16. Strain energy of an isolated six-membered chelate ring involving 1,3-diaminopropane calculated as a function of metal–nitrogen bond length for N–M–N angles appropriate to different coordination geometries.[69] The diagram should be compared with Figure 15, when it becomes apparent that, in contrast to the five-membered chelate ring, lower strain energy is achieved for the six-membered chelate ring with metal ions with shorter M–N bond lengths (and larger N–M–N bond angles), i.e., small metal ions.

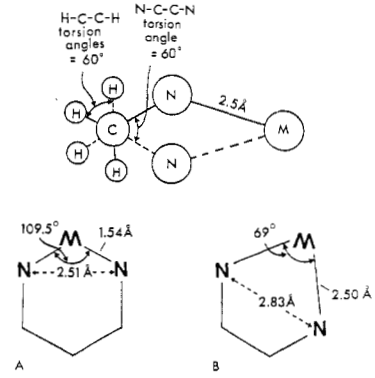


Figure 17. Lowest strain energy geometry calculated by using molecular mechanics[68] for (A) the six-membered chelate ring and (B) the five-membered chelate ring. The result in A can be easily understood from the fact that cyclohexane represents a minimum-strain situation for cycloalkanes, and in order to preserve this, the chelate rings should be close to the same dimensions as a cyclohexane ring. The result in B can be best understood in terms of the organic part of the chelate ring requiring the same geometry as the cyclohexane ring, with the metal ion placed at the focus of the lone pairs on the nitrogen donor atoms. The upper drawing shows in side view ideal geometry for a five-membered ethylenediamine type chelate ring.

size. In general, as metal ions increase in size, so their coordination number increases. As coordination number increases, so the L–M–L bond angles within the chelate ring become smaller (L–M–L = 109.5° for tetrahedral, 90° for octahedral, ~70° for eight-coordinate, and so on). The pattern will thus be that as M–L bond length increases, so the L–M–L angle will tend to decrease. In Figure 15 is seen[69] the strain energy, $\sum U$, calculated for a single EN chelate ring with a generalized metal ion as the M–L bond length is varied, with the strain-free M–L length set to 109.5° to present tetrahedral coordination geometry, 90° for octahedral, and 70° for square-prismatic eight-coordination. It is seen that the trend is for the strain energy to decrease as the M–L bond length increases and the L–M–L bond angle decreases. Use of MM to explore the potential energy surface for the EN chelate ring shows that the lowest strain energy will occur for a metal ion with a M–N bond length of 2.50 Å, and a N–M–N bond angle of 60°. On the other hand, as seen in Figure 16, the same calculations for the isolated TN ring indicate exactly the opposite, that minimum strain energy will occur for a metal ion with a M–N bond length of 1.6 Å and a N–M–N bond angle of 109.5°. The MM calculations thus account very satisfactorily for the empirical observation that large metal ions prefer five-membered chelate rings, while small metal ions show a smaller aversion toward six-membered chelate rings than do large metal ions.

The whole effect of chelate ring size can be easily understood by reference to the cyclohexane ring. The cyclohexane ring represents a minimum strain energy situation in that all the torsion angles are the ideal 60° and all the bond angles are 109.5°. Any ring that can come close to this arrangement will thus be of very low strain energy. As seen in Figure 17, the six-membered chelate ring comes closest to being like the cyclohexane ring when the metal atom of the chelate ring is the same as a carbon atom and has N–M–N angles of 109.5° as does a carbon atom. On the other hand, for five-membered chelate rings, the ring can come closest to achieving strain-free geometry when the metal atom lies out on the projection of the two C–C bonds of the cyclohexane ring as shown, and this requires long M–N bonds and a small N–M–N angle. It should also be noted that the "bite" (N···N distance across the chelate ring) of the strain-free EN ring should be 2.83 Å, *larger* than for the six-membered chelate ring, where it should be 2.51 Å. However, when both chelate rings involve a metal ion of the size of Ni(II), the distortions involved increase the bite size of the TN complex so as to be larger than that of the EN complex, which is decreased. The changes in bite size in the EN and TN complexes arise mainly as a result of the need to maximize overlap in the Ni–N bond, which involves opening up the TN bite and compressing down the EN bite.

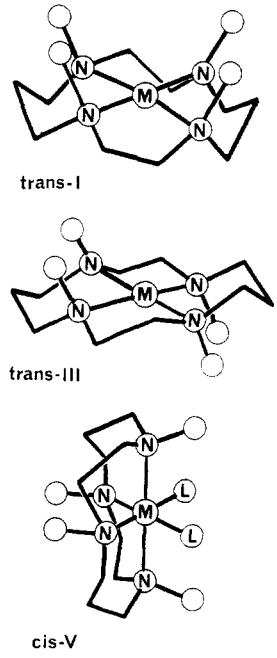


Figure 18. Conformers of cyclam complexes. The open circles represent the hydrogen atoms on the nitrogens or other N substituents present.

The empirical observation that the stabilities of complexes formed by tetraazamacrocycles do not show much evidence in their selectivity patterns suggestive of size-match selectivity is important as a factor in ligand design and is examined in the next section.

J. The Metal Ion Selectivity of Macrocyclic Ligands

In the previous section it was shown that the stability constant patterns of tetraazamacrocylic complexes are not interpretable in terms of size-match selectivity. In addition, in section B it was shown that much of the apparent size-match selectivity of crown ethers is a property of the neutral oxygen donor and is not dependent on the presence of a macrocyclic ring. Open-chain ligands with neutral oxygen donor groups show size selectivity patterns similar to those of crown ethers. In this section an inquiry is made into the origin of this lack of size-match selectivity.

For the tetraazamacrocycles, hole sizes have been calculated by using molecular mechanics[38,70] on the basis that hole size is the M–N bond length that produces minimum strain in the complex. These two studies give best-fit M–N lengths in good agreement with each other:

	best-fit M–N length, Å	
macrocycle	Busch et al.[70]	Hancock et al.[38]
12-aneN$_4$	1.83	1.81
13-aneN$_4$	1.92	1.92
14-aneN$_4$	2.07	2.05
15-aneN$_4$	2.22	
16-aneN$_4$	2.38	

These calculations were carried out for the planar trans-III conformer of all the complexes (see Figure 18) and have been widely used in rationalizing much of the chemistry of the tetraazamacrocycles. However, these hole sizes make no sense at all for the selectivity patterns for tetraazamacrocyclic complexes seen in Figure 14. In order to understand the behavior illustrated in Figure 14, it is necessary to consider other possible conformers of the complexes of these ligands. Particularly important are the planar trans-I and folded cis-V conformers seen in Figure 18. Calculations on these additional conformers reveal[71] a completely different selectivity pattern. In Table 10 are seen the best-fit M–N lengths in complexes of the macrocycles 12-aneN$_4$, 13-ane N$_4$, and 14-aneN$_4$, together with the strain energies of the complexes at the best-fit M–N length for both the trans-I and trans-III conformers (Figure 18) of each complex. It is seen that for 12-aneN$_4$ the trans-III conformer is much higher in strain energy than the trans-I conformer, and it has been predicted[71] that no complex of 12-aneN$_4$ with the trans-III conformer will ever be found. The trans-I conformer of 12-aneN$_4$ has, in fact, a preference (Table 10) for large metal ions, which accounts for the preference of large metal ions for this ligand. As one passes from 12-aneN$_4$ through 13-aneN$_4$ to 14-ane$_4$, the trans-III conformer increases in stability relative to the trans-I conformer. The trans-III conformer is much more rigid than the trans-I conformer[71] and does not coordinate very well to large metal ions such as Pb(II) or Cd(II). *The selectivity patterns of the complexes of the tetraazamacrocycles are thus governed by the relative stability of two or more conformers that have different metal ion size preferences.* This is rather different from the idea of a ligand having a fixed cavity size, and metal ions coordinate well or badly depending on how well they fit into the cavity. Moreover, when metal ions are too large for the cavities of the tetraazamacrocycles, MM calculations show that,[71] particularly in the trans-I conformer, they are simply coordinated lying out of the plane of the donor atoms, which does not necessarily have any adverse strain effects. This is seen in Figure 19 for the complex of Cu(II) with 13-aneN$_3$O. The Cu(II) ion is, with Cu–N bond lengths of 2.03 Å, too big for the cavity of the ligand (ideal M–N length = 1.92 Å) and so is coordinated lying out of the cavity of the ligand, which has the trans-I conformation. Another way in which too-large metal ions relieve steric strain is in the folding of the macrocycle[71] to give cis-V folded conformers (Figure 18).

TABLE 10. Best-Fit M–N Bond Lengths (Å) for Tetraazamacrocycles and the Strain Energies (kcal mol^{-1}) of the Complexes at the Best-Fit Size

	conformer[a]	
	trans-I	trans-III
	12-aneN$_4$	
best-fit M–N[b]	2.11	1.81
strain energy	10.8	19.7
	13-aneN$_4$	
best-fit M–N	2.03	1.92
strain energy	11.5	13.5
	14-aneN$_4$	
best-fit M–N	2.00	2.05
strain energy	9.4	8.1

[a] For explanation of structure of conformers, see Figure 18. [b] Best-fit M–N length is M–N length that in molecular mechanics calculation of strain energy of complex gives minimum energy.

The picture that emerges from MM calculations on the tetraazamacrocycles is that these macrocycles are easily able to change conformation to accommodate too-large metal ions, which are coordinated lying out

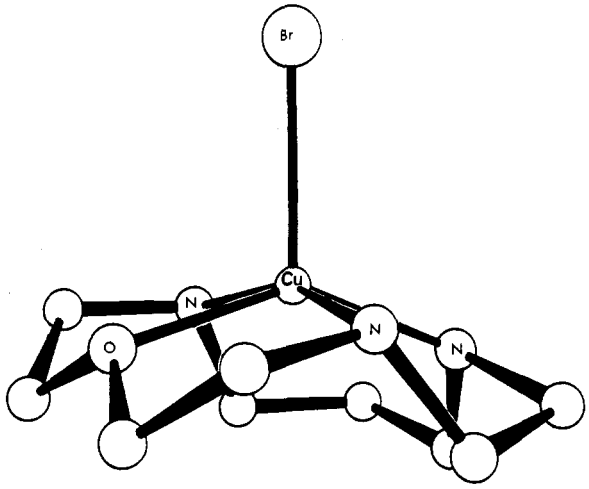


Figure 19. Structure[71] of the Cu(II) complex of 13-aneN_3O, showing how the too-small cavity of the ligand results in the Cu(II) ion being coordinated lying out of the plane of the donor atoms. To accommodate the too-large metal ion, the ligand is in the trans-I conformation. Redrawn after ref 71.

of the plane of the donor atoms of the ligand. In this situation, the factors that control metal ion size selectivity are the same as those that control selectivity in open-chain polyamine ligands, namely, the size of the chelate rings formed on complex formation.

Molecular mechanics calculations on crown ethers highlight several important points. As seen in Figure 20, a free ligand such as 18-crown-6 has as its lowest energy conformer the C_i conformer (Figure 20B), which is not that required for complex formation.[72,73] The D_{3d} conformer (Figure 20A) required for complex formation is, in solvents of low dielectric constant and in the solid state, of much higher energy than the C_i conformer and only becomes of lower energy in solvents of high dielectric constant, where the dipole–dipole repulsion between the dipoles on the donor atoms of 18-crown-6 is lowered.

A further important point shown by the MM calculations is the importance of solvation energy in producing the observed order of selectivity for the alkali metal ions of a ligand such as 18-crown-6. Thus, in the gas phase, the order of binding strength for the alkali metal ions with 18-crown-6 would be $Li^+ \gg Na^+ \gg K^+ \gg Rb^+ \gg Cs^+$, which is largely reversed[72] by the order of heats of solvation, which decrease in the same order. The order of log K_1 of the 18-crown-6, $K^+ > Rb^+ > Cs^+$, probably contains a large contribution from the fact that the affinity for the ethereal oxygen donor would also decrease from Li^+ to Cs^+. The reversal in complex stability away from the intrinsic gas-phase order of M–O bond strength such that complex stability varies $Li^+ < Na^+ < K^+$ for the lighter alkali metals is due to an increase in steric strain in the complexes of these metal ions as the size of the metal ion decreases. However, this increase in steric strain is not simply a case of the hole in the cavity of the macrocycle becoming too large for the metal ion, with an accompanying increase in steric strain. The molecular mechanics calculations show that,[72] as with the tetraazamacrocycles, there is a change in conformation of the ligand in its complexes with the metal ions in response to a change in size. Thus, 18-crown-6 forms complexes of D_{3d} symmetry (Figure 20A) with K^+ and the larger alkali metal ions, but with the smaller Na^+ ion a conformer of lower symmetry becomes more stable. Calculations of one of the authors (R.D.H.) show that the Li^+ ion coordinates to this same conformer with lower strain energy than does the Na^+ ion and that it is only the higher heat of solvation of Li^+ than that of Na^+ which leads to lower complex stability with 18-crown-6.

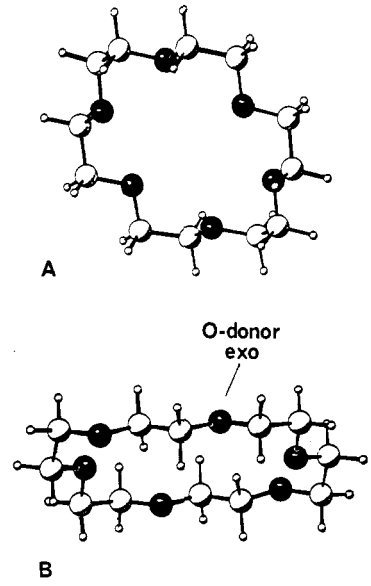


Figure 20. Conformers of the 18-crown-6 ligand. At A is the D_{3d} conformer required for complex formation. At B is the lower strain energy[72,73] C_i conformer observed in crystal structures, which is unsuitable for complexing metal ions since some of the oxygen donors are exo, i.e., directed out of the macrocyclic cavity. Redrawn after ref 73.

The evidence suggests then that the macrocycles are too flexible to be regarded as being highly preorganized. However, as a rule, and in line with what one might expect intuitively, smaller ligands tend to be more rigid than larger ligands. It is thus found that 9-aneS_3,[74,75] 9-aneN_2O,[76] and 9-aneN_2S[77,78] tend to show size selectivity. This is not classic size-match selectivity of metal ions of the right size fitting into holes. Rather, the rigidity of the 9-aneN_3 type of ring sets[78–80] fairly stringent requirements as to the preferred size of metal ion for coordination to the three donor atoms. MM calculations show that metal ions with a M–N bond length of 2.08 Å will fit best in the bis-9-aneN_3 type of complex seen in Figure 21A. In contrast to the tetraazamacrocycles, macrocycles of the 9-aneX_3 type almost invariably have only one conformer,[77] the [333] conformer (see Figure 21). The only other conformer that has been observed[77] is the [234] conformer, found in a Cu(II) complex of 9-aneN_2S. It appears that this unusual conformer may be due to such factors as the mismatch in bond length between the Cu–N and Cu–S bonds, which is unusually large because the S donor occupies the axial site on the tetragonally distorted Cu(II).[77] The MM calculations show, however, that ordinarily the [333] conformer will be of much lower energy than any other conformer when coordinated to the metal ion. This means that the 9-aneX_3 macrocycles do not have the possibility, found in the tetraazamacrocycles, of changing conformation to accommodate too-large metal ions. As seen in Figure 22, a plot of Δ log K versus ionic radius for the change in complex stability that occurs in passing from the open-chain analogue (DIEN, DAES, ODEN) to the macrocycle (9-aneN_3, 9-aneN_2S, 9-aneN_2O) behaves as would be

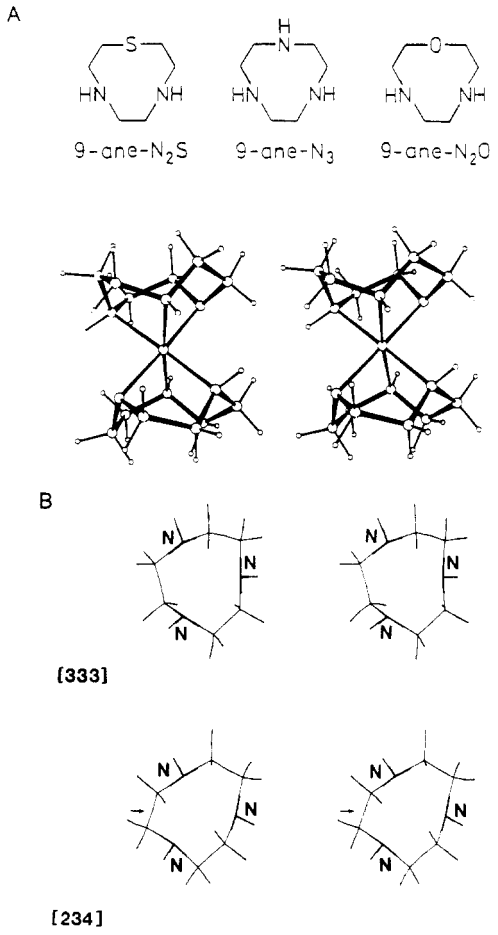


Figure 21. (A) Some 9-aneX_3 macrocycles (above) and (below) a stereoview of a bis-9-aneN_2O complex of Ni(II) showing the typical puckered nine-membered ring of coordinated 9-aneX_3 type ligands. (B) Stereoviews of (above) the usual [333] conformation of the 9-aneX_3 type of ligand when coordinated to a metal ion and (below) the only other conformation observed for coordinated 9-aneX_3 type ligands, the [234] conformer found[78] so far only with Cu(II) complexes of 9-aneN_2S. The arrow indicates the ethylene bridge which is oriented in an opposite fashion to that in the more symmetrical [333] conformer.

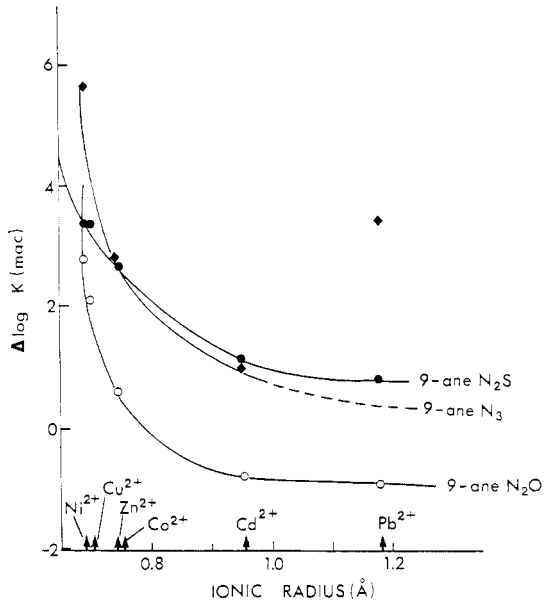


Figure 22. Size-match selectivity of 9-aneX_3 type macrocycles. The change in formation constant, $\Delta \log K_1$, produced by adding an ethylene bridge to an open-chain $NH_2CH_2CH_2XCH_2CH_2NH_2$ ligand to produce a 9-aneN_2X macrocycle, where X = S (●), O (○), or NH (◆), is plotted against metal ionic radius. After ref 78. The values of $\Delta \log K_1$ are a maximum for metal ions of the size of high-spin Ni(II), which molecular mechanics calculations[78] show to be the optimum size for coordinating to 9-aneN_2X type macrocycles. Data from ref 21 and 78, ionic strength 0.1 M, 25 °C.

expected if the preference for 9-aneX_3 types of macrocycles is for small metal ions. Thus, $\Delta \log K$ is positive for small metal ions and becomes negative for large metal ions. The only exception to this behavior is for the Pb(II) complex of 9-aneN_3, which is too stable in terms of the size-selectivity idea. As will be discussed in section P, this appears to relate to the change in the unshared pair of electrons on Pb(II) from stereochemically inactive to active.[20,81]

Taking the idea of small macrocycles being more rigid one step further, then "macrocycles" such as the bidentate DACO (1,5-diazacyclooctane) should be even more selective. The ligand DACO is not really a macrocycle, but it displays in its complexes and complexing properties the behavior associated with tetraazamacrocycles. Thus, the log β_2 values for DACO with Cu(II) and Ni(II) are higher than for TN (1,3-propanediamine), which must be regarded as the open-chain analogue, and the LF strengths are higher than for the open-chain bis-EN complexes. Indeed, the LF strengths of the bis-DACO complexes are actually higher than those of the macrocycle cyclam. This would be interpreted[82,83] in terms of the presence of secondary nitrogen donors on DACO in a reasonably low strain energy situation:

	Ni(II)	Cu(II)
log β_2(DACO)[a]	13.1[b]	17.8[c]
log β_2(TN)[a]	10.5[d]	16.8[d]
ν(d–d), cm^{-1}		
bis-DACO[e]	22500	19950
cyclam	22470	19900
bis-EN[e]	21600	18200

[a] Ionic strength 0.1 M, 25 °C. [b] Reference 83. [c] Reference 82. [d] Reference 21. [e] Reference 79.

The rates of equilibration of Ni(II) with DACO in water are very slow,[82,83] as is found with tetraazamacrocycles. What is particularly remarkable about DACO is the fact that it forms stable complexes with the small metal ions Cu(II) and low-spin Ni(II) but not with the larger metal ions Zn(II), Cd(II), and Pb(II).[83] This must come about because the coordinated DACO ligand effectively forms a double six-membered ring and so should show markedly stronger preference for small metal ions than do open-chain ligands such as EN or TN, since (section I) small metal ions are preferred for coordination relative to large metal ions by six-membered chelate rings. The fused nature of the double chelate ring of DACO should give it much greater rigidity and hence account for its more marked size-based selectivity for small metal ions. It is predicted that very small metal ions such as Be(II) would form complexes of high stability with DACO, which, unlike $[Be(NH_3)]^{2+}$, probably would not be hydrolyzed in water.

Lindoy and co-workers[84-91] have reported an extensive investigation of the role of hole size in controlling the complex stability and rates of complexation[92,93] of the 14- to 17-membered macrocycles seen in Figure 23. A basic presumption in this work is that size-match selectivity is operative in controlling the stability of

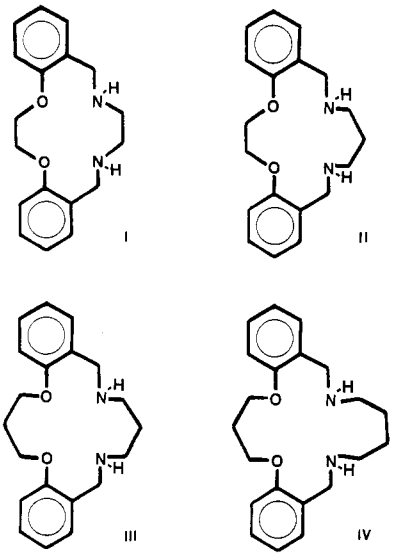


Figure 23. Some ligands studied by Lindoy et al.[84-93]

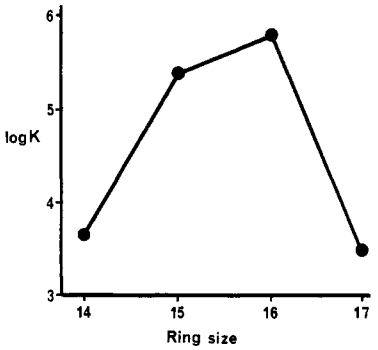


Figure 24. Stabilities of the Ni(II) complexes of ligands of the type shown in Figure 23 as a function of macrocyclic ring size. Redrawn after ref 84 and 91.

complexes formed with these macrocycles. In support of this, the plot of log K_1 for the series of macrocycles shows a peak in complex stability (Figure 24) at the ligand (the 16-membered-ring macrocycle III, Figure 23) that forms the most stable complex with high-spin Ni(II).[84-91] That this represents a best-fit size for Ni(II) is supported[84-91] by crystallographic studies of both the free ligand and the complex. It seems probable for Ni(II) that the interpretation presented by Lindoy et al. is correct. However, an apparently similar result is found for the tetraazamacrocycles 12-aneN_4 through 16-aneN_4 with Cu(II).[94] The observation[94] of behavior apparently consistent with size-match selectivity for Cu(II) with the macrocycles 12-aneN_4 through 16-aneN_4 is, however, no guarantee that behavior resembling size-match selectivity will be observed with metal ions of other sizes, as indeed it is not.[67,68,71] In the same way it seems far from clear that the ligands in Figure 23 will display behavior consistent with size-match selectivity with other metal ions, such as Pb(II). One would expect that with Pb(II) the most stable complex would be formed with the smallest member of the series in Figure 23, since this forms fewer six-membered chelate rings. The role played by macrocyclic ring size in the ligands seen in Figure 23 is further cast into doubt by the behavior of the complexes with Zn(II) and Cu(II). NMR shift studies have shown[84-91] that the O donors of the ligands seen in Figure 23 probably do not coordinate to Zn(II) and Cu(II). The structure of one such Zn(II)

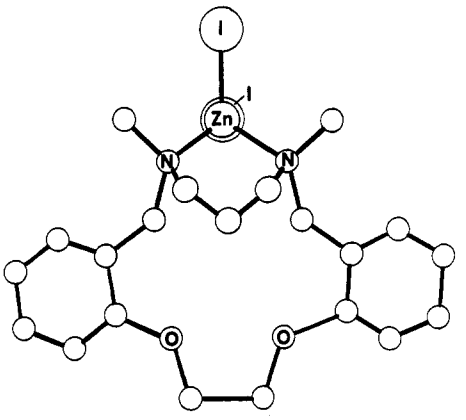


Figure 25. Structure of the complex of Zn(II) with an N-methylated version of ligand II in Figure 23, showing how the oxygen donors of the macrocycle are not coordinated. Redrawn after ref 86.

complex, of the N-methylated version of II in Figure 23, is seen in Figure 25,[88] showing how bidentate coordination is achieved. From the formation constants for the Cu(II), Ni(II), and Zn(II) complexes of the ligands[84-91] seen in Figure 23, the probability of only partial coordination of at least some of the complexes appears to have no detrimental effects on complex stability, as seen in the following table.

macrocyclic ring size[b]	log K_1[a]		
	Ni(II)	Cu(II)[c]	Zn(II)[c]
14 (ligand I)	3.7	8.2	3.0
15 (ligand II)	5.4	7.2	4.1
16 (ligand III)	5.8	7.7	4.3
17 (ligand IV)	3.5	7.2	4.2

[a] References 85–92, 95% methanol. [b] Ligands I–IV in Figure 23. [c] O donors probably not coordinated, as in Figure 25.

Thus, the formation constants for Ni(II) appear normal in relation to the Zn(II) and Cu(II) constants; i.e., there does not appear to be any destabilization of the complexes of Cu(II) and Zn(II) by the fact of only partial coordination of the macrocycle. One may point out that[84-91] Ni(II) shows some trend in its formation constants with the set of ligands seen in Figure 23, while Cu(II) and Zn(II) show no real trend, consistent with the absence of coordination in the macrocyclic ring. However, apparent size-match selectivity in the complexes of one metal ion with a series of ligands because that metal ion coordinates in the macrocyclic cavity of the ligands is of little practical value if other metal ions suffer no penalties as far as complex stability is concerned for not coordinating in the macrocyclic cavity. Thus one could not use the noncoordination of Cu(II) in the macrocyclic cavity as a device for producing selectivity for the Ni(II) ion which does coordinate lying in the macrocyclic cavity.

An interesting aspect of Figure 24 is that the peak in complex stability occurs at the 16-membered-ring macrocycle for Ni(II), in contrast to the tetraazamacrocycles where it occurs[68,95,96] with the 14-membered-ring macrocycle. Although there is not yet complete information on the formation constants across the series of macrocycles 12-aneN_2O_2 to 16-aneN_2O_2, the behavior of the pair of ligands 12-aneN_2O_2 and 13-aneN_2O_2[97] with respect to complex stability and metal ion size is almost identical with that of the pair 12-aneN_4 and 13-aneN_4. It therefore seems unlikely that the difference in donor

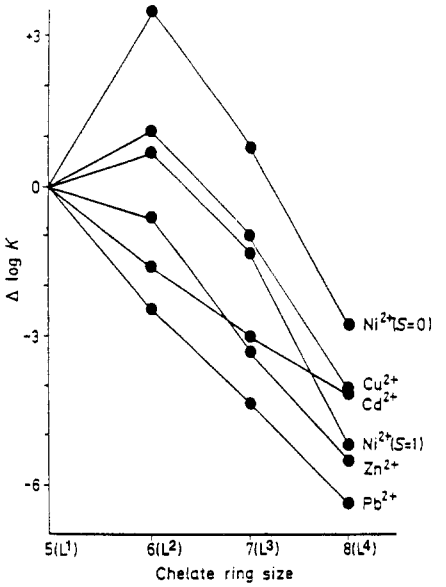
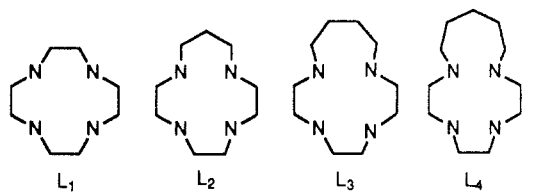


Figure 26. Effect on complex stability of increasing chelate ring size in tetraazamacrocycles. For each metal ion the change in complex stability, Δ log K_1, is plotted relative to log K_1 with 12-aneN$_4$ (chelate ring size 5) as one chelate ring is increased in size to 6 (13-aneN$_4$), then 7 (C(7)-14-aneN$_4$)), and finally 8 (C-(8)-15-aneN$_4$)). For structures of ligand, see Figure 7. Redrawn after ref 98.

atoms between the ligands seen in Figure 23 and the tetraazamacrocycles is the cause. One possibility is that even for Ni(II), the O donors are not coordinated in solution in the series in Figure 23. If it turns out that they are coordinated, however, this would then point to interesting differences produced by the presence of benzo groups fused into the macrocyclic ring and suggests that MM calculations might be of interest in unraveling this behavior.

One chelate ring formed by the ligand IV in Figure 23 in its complexes must be seven-membered, and this raises the point of what happens to metal ion selectivity as chelate rings are increased in size beyond six-membered. The available evidence[16] suggests that for larger chelate rings, there is a uniform decrease in complex stability as compared to analogous ligands with six-membered chelate rings. Thus, little further discrimination between metal ions on the basis of size occurs as chelate ring size is increased beyond six-membered, and there is a perhaps unuseful drop in complex stability with all metal ions. This is seen for the series of ligands below, in Figure 26, where the size of one chelate ring is steadily increased[98] from five-membered to eight-membered.



Thus, in Figure 26, the change in complex stability in passing from L_1 to L_2 produces the expected spread of metal ion complex stability with the smallest metal ions (Cu(II), $S = 0$ Ni(II)) showing an increase in log K_1 and large metal ions such as Pb(II) showing a decrease. As the chelate ring size increases from six-membered to seven-membered and beyond, there is a fairly constant decrease in complex stability which results in little further discrimination in complex stability according to metal ion size. The same result is observed[98] for other sets of ligands such as the 2,2,2-TET or EDTA series, where the central chelate ring is progressively increased in size. The response of Cd(II) is unusual, however, in that in all these series of ligands it shows decreases in complex stability that are smaller than those of other metal ions. The behavior of Cd(II) may reflect its ability to adopt tetrahedral coordination geometry where its ionic radius is smaller,[54] and it may increasingly be able to adapt to the larger chelate rings by switching from octahedral to tetrahedral coordination geometry. It is not clear at this stage whether any other metal ion might show behavior like Cd(II). This would be of importance in the design of siderophores, as discussed in section P.

In this section the point has been made[16,67,98] that the selectivity patterns of N-donor and O-donor macrocycles as far as size selectivity is concerned are not very different from those of their open-chain analogues. This arises chiefly because of the ability of the macrocycles to adopt a wide range of conformers of fairly similar energy which present the metal ions with a range of best-fit M–L lengths, allowing strong complexation by metal ions while lying coordinated out of the macrocyclic cavity. The macrocycles are thus rather too flexible to show genuine size-match selectivity, and their selectivity patterns are controlled by the same factors that control the selectivity patterns of open-chain ligands, such as chelate ring size and the size selectivity inherent in the coordinating properties of the neutral oxygen donor atom. In the next section consideration is given to ways in which the metal ion selectivity of macrocyclic ligands might be enhanced.

K. Macrocyclic Ligands with Pendent Donor Groups

The field of macrocycles with pendent donor groups has grown rapidly, even since the appearance of a recent review[99] on these ligands. It is not our intention to review all these ligands here but rather to consider how the presence of the pendent donor groups affects metal ion selectivity. Ligands with pendent donor groups discussed here are seen in Figure 27.

Ligands that have neutral oxygen donors (alcohols and ethers) on pendent groups[80,100–106] on macrocycles have been synthesized in abundance. A chief attraction here is the synthetic simplicity, particularly for adding hydroxyethyl groups. For THEC (Figure 27)[102] the synthesis consists simply of adding a slight excess of ethylene oxide to cyclam in chilled 2-propanol and allowing it to stand in the refrigerator overnight. The procedure gives close to a 100% yield of crystalline material. The effect of these hydroxyethyl groups on metal ion size selectivity patterns appears to be identical with the effect in other situations where groups bearing neutral oxygen donors are added to existing ligands. Thus, in Figure 28 is seen the change in complex stability, Δ log K, produced by adding hydroxyethyl groups to 18-aneN$_4$O$_2$ to give THF-18-aneN$_4$O$_2$ (Figure 27) as a function of metal ionic radius.[105] It is seen that the added hydroxyethyl groups produce a marked decrease in complex stability for small metal ions and a moderate increase in complex stability for

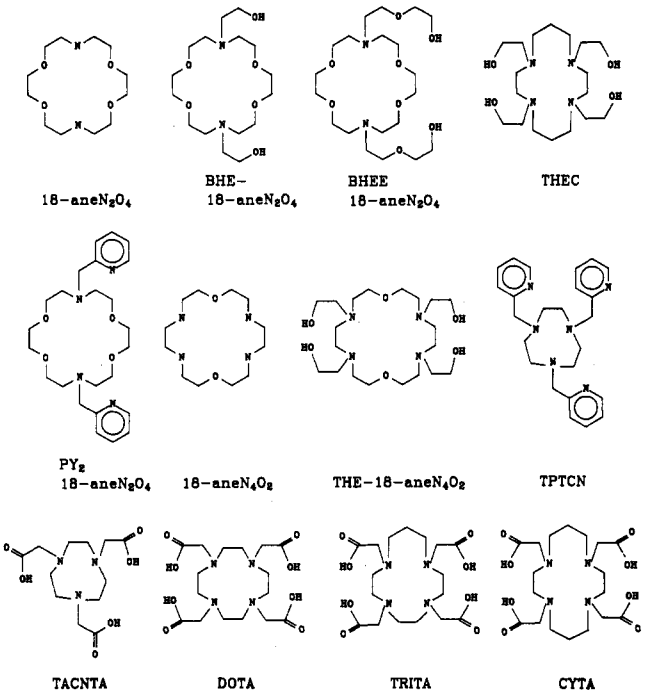


Figure 27. Structures of some ligands discussed in this review.

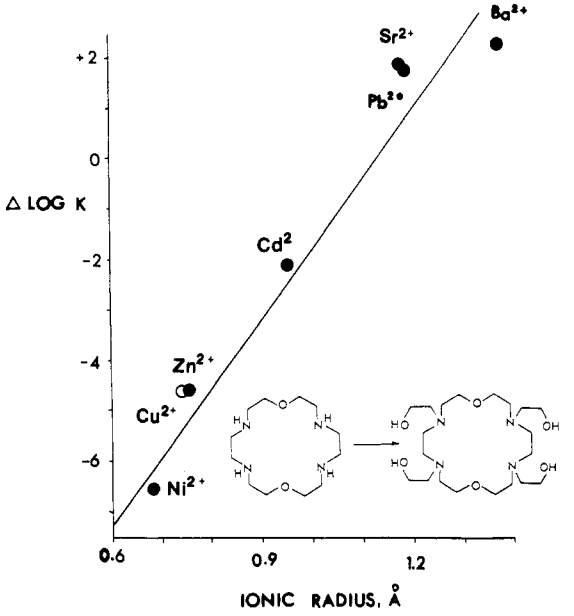


Figure 28. Effect on the stability of the complexes of 18-aneN$_2$O$_4$ of adding neutral oxygen donors (*N*-hydroxyethyl groups) to give THE-18-aneN$_2$O$_4$. (For key to ligand abbreviations, see Figure 27). The change in complex stability, $\Delta \log K_1$, on passing from 18-aneN$_2$O$_4$ to THE-18-aneN$_2$O$_4$ is plotted against the ionic radii[54] of the metal ions. Data from ref 105, 0.1 M $NaNO_3$, 25 °C. The octahedral radius of the Cu^{2+} ion has been used here as more appropriate than that for the square-planar coordination.

the very large Pb(II) ion, in accordance with the rule (section B) regarding the effect of neutral oxygen donors on complex stability in relation to metal ion size. The behavior is very similar to the situation where neutral oxygen donor bearing groups are added to open-chain ligands (Figure 2A) or bridging ethereal oxygen donor bearing groups are added to open-chain ligands to produce a macrocycle or cryptand (Figure 2B). One can thus say that in order to increase the selectivity of macrocycles for large metal ions, all that is necessary is to add groups bearing neutral oxygen donors. This is attractive in that it is synthetically much simpler than creating a cryptand type of structure. The slopes of relationships such as those seen in Figures 2 and 28 become steeper as a general rule as more oxygen donors are added, so that higher selectivity can usually be achieved by adding more O donors. This is illustrated for the ligand BHE-18-aneN$_2$O$_4$, which has a modest selectivity for the large Pb(II) ion over other, smaller, metal ions. Greater selectivity is simply produced by adding more oxygen donors to BHE-18-aneN$_2$O$_4$ to give BHEE-18-aneN$_2$O$_4$,[105] which leads to the following metal ion size related changes in complex stability:

metal ion	Cu^{2+}	Cd^{2+}	Ca^{2+}	Sr^{2+}	Pb^{2+}	Ba^{2+}
ionic radius, Å	0.57	0.95	1.00	1.17	1.18	1.36
log K_1(BHE-18-aneN$_2$O$_4$)[a]	6.6	8.0	4.1	5.0	9.2	5.4
log K_1(BHEE-18-aneN$_2$O$_4$)	*b*	3.3	*b*	3.3	7.2	4.9
$\Delta \log K$	large	−4.7		−1.7	−2.0	−0.5

[a] Ionic strength 0.1 M, 25 °C. [b] No evidence for complex formation.

Thus, it is not always clear just how much change in selectivity in favor of large metal ions will occur when O-donor groups are added to a ligand, but if this is not sufficient, one should try adding more neutral oxygen donors.

A large amount of work has also been reported[107-117] on the complexing properties of *N*-acetate-substituted macrocycles. An area of considerable interest has been tetraazamacrocycles with four added *N*-acetates.[107-110] These ligands present a problem for metal ions that cannot expand their coordination numbers to meet the potential octadentate coordination provided by these ligands but allow for very strong complexation of large metal ions that can achieve the coordination number of 8 required for full coordination of the donor atoms of the ligand. Thus, the Ca(II) complex of DOTA is[107,108] the most stable known complex of Ca(II), with a log K_1 of approximately 16.5[107,108] as compared to log K_1 of only 10.6 of EDTA.[21] The Ca(II) ion normally has little affinity for N donors, so that it would seem that it is the macrocyclic structure of the amine part of the ligand that is responsible for the large increase in complex stability. This is confirmed in that[97] Ca(II) actually has log K_1 = 3.1 with 12-aneN$_4$, the parent macrocycle of DOTA, but does not appear to form complexes with noncyclic polyamines in aqueous solution. If one examines the changes in complex stability that occur when four acetate groups are added to 12-aneN$_4$, the following picture emerges:

metal ion	Cu^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Ca^{2+}	Pb^{2+}
ionic radius	0.57	0.69	0.74	0.95	1.00	1.18
log K_1(12-aneN$_4$)[b]	23.3	16.4	16.2	14.3	3.1	15.9
log K_1(DOTA)[a,b]	20.3	18.7	20.0	19.0	16.5	19.0
$\Delta \log K$	−3.0	+1.7	+3.8	+4.7	+13.4	+3.1

[a] Mean of values reported in ref 107 and 108. [b] Ionic strength 0.1 M, 25 °C. By comparison log K is fairly constant for EN → EDTA for all these metal ions at 9–12 log units.

There is no relationship between the values of $\Delta \log K$, the changes in complex stability between 12-aneN$_4$ and DOTA, and the affinity of each of the metal ions for acetate groups. The Ca(II) ion in fact shows the least affinity for acetate itself[21] of the metal ions shown but shows a massive increase in log K_1 when the four acetate groups are added to 12-aneN$_4$ to give DOTA. This presumably reflects the ability of the very ionically bound Ca(II) ion to adapt to the required coordination geometry for complexing with DOTA, which is most

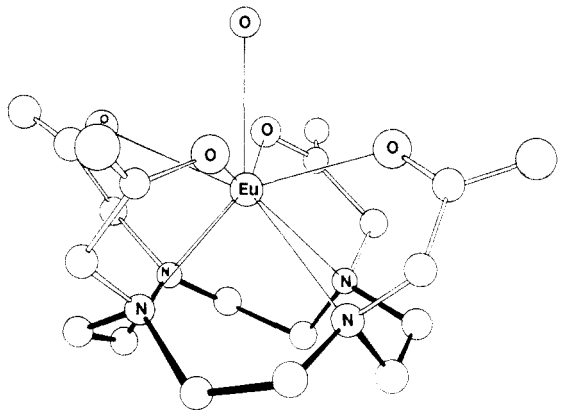


Figure 29. Structure of the Eu(III) complex of DOTA (see Figure 27 for ligand abbreviations); redrawn after ref 111. The bonds in the 12-aneN$_4$ ring are drawn as solid, while those of the acetate arms are drawn as open. Only the donor atoms are labeled. The axial oxygen is a coordinated water molecule.

difficult for metal ions such as Cu(II), Ni(II), or Zn(II) with their lower coordination numbers. Possibly the bonding in the Pb(II)/DOTA complex is too covalent to allow for good adaptation to the needs of the DOTA ligand. Other metal ions that have ionic M–L bonding and appear to coordinate well to DOTA are the lanthanides,[111] which appear[110,111] to have log K_1 values in the vicinity of 20 and above with DOTA. The structure of the Eu(III) complex of DOTA is seen in Figure 29.[111]

The tetraazamacrocycle tetraacetates studied so far are DOTA, TRITA (the 13-aneN$_4$ derivative), and TETA. It should be pointed out here that the lack of agreement[107,108] in the formation constants of the complexes of these ligands appears to be due to the slow rates of equilibration of these ligands with metal ions. At present, a study of the formation constants of these complexes with allowance for long equilibration times is being carried out in the hope of obtaining more reliable log K values.[112] What can be discerned in the currently available formation constants is that these appear roughly to obey the rule regarding the effect of chelate ring size on complex stability as related to metal ion size (section I). Thus, as one passes from DOTA, forming only five-membered chelate rings, to TETA, which forms two six-membered chelate rings, there is a metal ion size related drop in log K_1:

metal ion	Be^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Ca^{2+}	Pb^{2+}	Ba^{2+}
radius of M^{n+}, Å	0.31	0.69	0.74	0.95	1.00	1.18	1.36
log K_1(DOTA)[a,b]	13.6	18.7	20.0	19.0	16.5	19.0	12.1
log K_1(TETA)[a,b]	13.4	17.6	16.0	15.5	8.9	14.7	4.1
Δ log K	−0.2	−0.9	−4.0	−3.5	−7.6	−4.3	−8.0

[a] Ionic strength 0.1 M, 25 °C. [b] Average of those reported in ref 107 and 108.

In general, therefore, the rule regarding the relationship between chelate ring size, metal ion size, and stability constant holds even in these relatively more complicated ligands. An exception would appear to be the Mg(II) ion, which is small but shows a massive difference in log K_1 between DOTA and TETA of about 8 log units. This may reflect modes of coordination that are completely different in the two complexes, although the difference does seem very large even if this were the case. Perhaps a crystallographic study would reveal the cause of this very large difference in complex stability, or possibly the TETA system, in particular, had not equilibrated with the small Mg(II) ion.

The tetraazamacrocyclic tetraacetates have shown how selectivity patterns can break away from those found in nonmacrocyclic and simple macrocyclic ligands with the addition of pendent donor groups. Now a massive shift in the direction of selectivity for the large Ca(II) ion can be engineered because it appears to fit the required coordination geometry of the DOTA ligand. However, by and large, some selectivity patterns of open-chain ligands still persist, as seen in the effect of size of chelate ring on selectivity in DOTA and TETA complexes. It has been seen, however, that the 9-aneN$_3$ type of ligand (section J) is more rigid than the 12-aneN$_4$ type of ligand. It might therefore be expected from this greater rigidity that ligands based on the 9-aneN$_3$ unit, with attached *N*-acetates, such as TACNTA in Figure 27 would show even more remarkable metal ion selectivity effects.

The ligand TACNTA[113–116] is hexadentate and has[80] a preference for small metal ions with M–L bond lengths in the vicinity of 2.00 Å. This means that, whereas DOTA shows a strong preference for larger eight-coordinate metal ions such as Ca^{2+} or lanthanide(III) ions, so TACNTA should prefer small hexacoordinate metal ions. This expectation is fulfilled, with truly remarkable selectivities:

metal ion	Cu^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Ca^{2+}	Pb^{2+}
log K_1(9-aneN$_3$)[a,d]	15.5	16.2	11.6	9.5		11.0
log K_1(TACNTA)[b,d]	19.5	28.3	(22.5)[c]	16.8	8.8	16.6
Δ log K	+4.0	+12.1	(+10.9)	+7.3		+5.6

[a] Reference 21. [b] Mostly from the thesis of R. Weber, quoted in ref 117. [c] Mean of two rather disparate values of 18.3 and 26.6.[117] [d] Ionic strength 0.1 M, 25 °C.

The chemistry of TACNTA has recently been described by Chaudhuri and Wieghardt[117] in a general review on the 9-aneN$_3$ type and related ligands. The selectivity of TACNTA for the six-coordinate Ni(II) over Cu(II) is quite remarkable. The log K values for Zn(II) with TACNTA present a problem in that two very disparate log K_1 values have been reported,[113,117] so that the correct log K_1 value must be regarded as being still uncertain. However, the present authors have some evidence that the very high log K_1 for the Ni(II) complex of TACNTA is correct.

The origin of the remarkable stability of the TACNTA complex of Ni(II) and the selectivity against other metal ions studied lie in the preference of the ligand for small metal ions. But there is more to this than just simple size-match selectivity. If one lowers the pH in solutions of EDTA complexes, at about pH 4 one of the carboxylate groups becomes protonated to give complexes of the MLH type.[21] By contrast, [Ni(TACNTA)]$^-$ is not protonated even in 0.100 M HNO_3 and can be crystallized out as the strong acid[80] H_3O[Ni(TACNTA)], which contains a hydronium ion, as seen in Figure 30. This unusual behavior reflects a fact about coordination of carboxylate groups that is very important. *The carboxylate group is sterically very efficient*, which is to say that it coordinates to metal ions without bringing a large number of atoms to lie close in to the metal ion. Thus, amine groups have hydrogens attached to the nitrogen donors, and the carbon atoms attached to the nitrogen also have hydrogen atoms attached to them. In contrast, the oxygen of the carboxylate group has no hydrogens attached to it, and the carbon atom to which it is attached also has no hydrogens, but only an oxygen directed away from

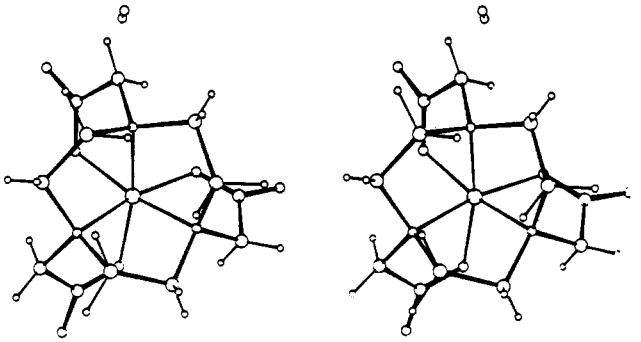
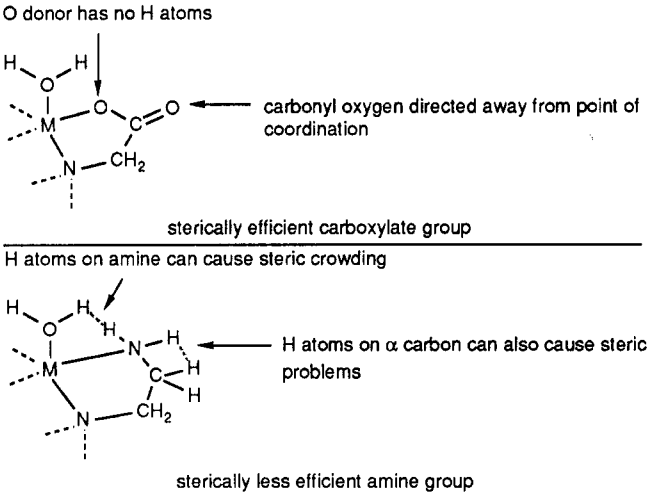


Figure 30. Stereoview of the complex H_3O[Ni(TACNTA)] from ref 115, viewed down the threefold axis. The disordered hydronium ion is the dumbbell-like object at the top of the diagram. Two half-oxygens are present since the hydronium ion has 50% occupation of each of the two sites. The hydrogens on the hydronium ions were not found.

the point of coordination at much longer distances than the hydrogens on a group such as an amine. Thus, carboxylates allow for the design of sterically efficient ligands such as TACNTA or DOTA, where unusual stabilities can be achieved because of the ability of the carboxylate to occupy little space close in to the metal ion, allowing for the more efficient coordination of other donor groups present. The origin of the greater steric efficiency of the carboxylate donor than the amine donors (or alcohols) is shown diagramatically below.

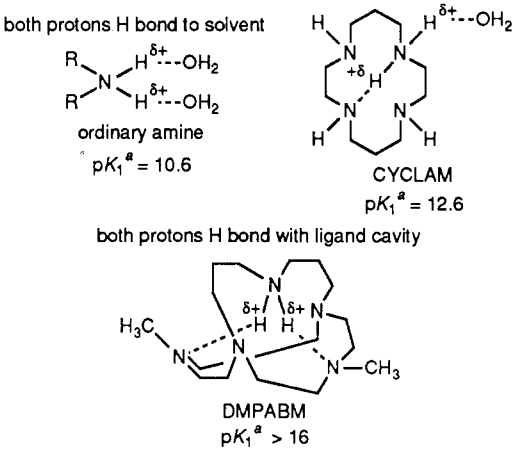


Many other types of donor groups have been attached to macrocycles as pendent groups, among which are pyridyl groups,[19,118] phenolate groups,[119] and 2-aminoethyl groups.[120,121] There is insufficient evidence at this stage to say definitely that these groups do or do not produce remarkable selectivities or complex stabilities. However, it would appear that the pyridyl and aminoethyl groups are not sterically efficient to any degree approaching the carboxylate group. Thus, in the crystal structure of $[Fe(TPTCN)]^{2+}$ (TPTCN is shown in Figure 27), the Fe(II)–N bonds of the macrocyclic ring are not particularly short,[118] which would be expected if the pyridyl groups were sterically efficient. The phenolate group as a pendent group may very well be sterically efficient in the same way as a carboxylate group, since its donor atom is an oxygen without any attached hydrogens or other atoms.

In the next section the stabilities and selectivity of ligands of the highest level of preorganization are discussed.

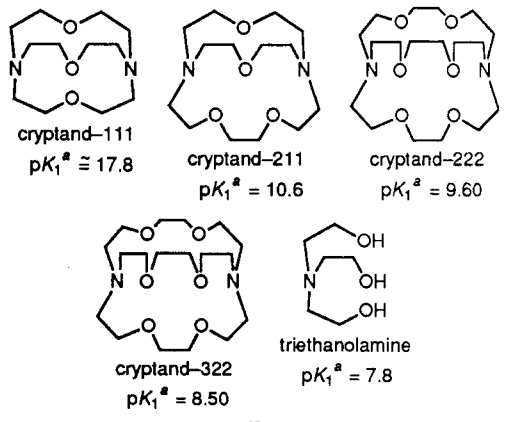
L. More Highly Preorganized Ligands: Cryptands, Spherands, and Other More Rigid Ligands

It is not the intention to attempt to review here the chemistry of bicyclic and other more preorganized ligands. There is currently an extensive literature on the subject, covered in several recent reviews.[122] What is of importance here is to consider the effect of higher levels of preorganization on complex stability and selectivity for different metal ions, so as to draw forth the ligand design principles involved. As has been stated earlier, macrocyclic ligands show modest levels of preorganization, which lead to significant but not remarkable effects. Thus, as an example, the ligand cyclam shows higher protonation constants[123] than do normal secondary amines, and this has been attributed[123] to hydrogen bonding within the cavity of the ligand, which does away with the need for one of the protons on the protonated secondary nitrogen donor to immobilize a solvent molecule required for its solvation. However, the other proton must still be solvated by a solvent molecule, as shown below. In contrast, when the ligand can provide both solvating Lewis bases for the two protons, as in DMPABM, one sees a remarkably high protonation constant:



[a] Ionic strength 0.5 M, 25 °C.[123,124]

The ligand DMPABM is also well preorganized for complex metal ions of the size of Cu(II)[124] and appears to form complexes of extraordinarily high stability. This type of effect was first noted, of course, by Smith et al.[125] in the small cryptand-111, as seen in the following series:



[a] Ionic strength 0.1 M, 25 °C.[125]

TABLE 11

properties of ligands	classes of ligands	some examples
solvent excluded from ligand cavity	spherands, small cryptands, porphyrins, corrins	$[Ni(DMPABN)]^{2+}$, $\log K_1$ = ?
structurally rigid with donor atoms correctly placed for coordination to sites on metal ion	sepulchrates small macrocycles rigid chelates	$[Ni(9\text{-}aneN_3)_2]^{2+}$, $\log \beta_2 = 30$; $[Ca(DOTA)]^{2-}$, $\log K_1 = 16.5$ $[Ni(CYCLAM)]^{2+}$, $\log K_1 = 20.1$; $[Ca(TETA)]^{2-}$, $\log K_1 = 13.2$
lower rigidity	large cryptands, large macrocycles	
donor atoms joined together to decrease translation entropy	chelating ligands	$[Ni(2,3,2\text{-}TET)]^{2+}$, $\log K_1 = 16.4$; $[Ni(EN)_2]^{2+}$, $\log \beta_2 = 13.4$; $[Ca(EDTA)]^{2-}$, $\log K_1 = 10.6$; $[Ca(OMDTA)]^{2-}$, $\log K_1 = 4.6$; $[Ca(IDA)_2]^{2-}$, $\log \beta_2 = 3.9$
low preorganization	chelating ligands with very long bridges	
donor groups move randomly and have no preorganization	solvents unidentate ligands	$[Ni(NH_3)_4]^{2+}$, $\log \beta_4 = 8.1$

level of preorganization ↑ ; approximate increasing complex lability ↓

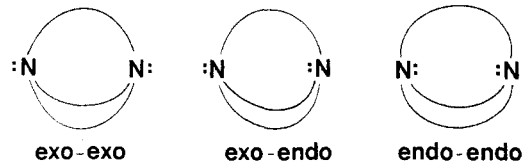
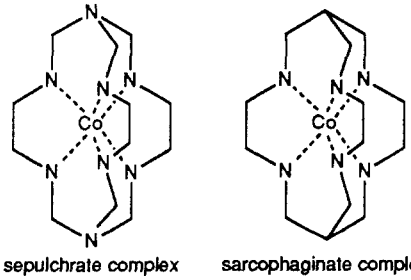


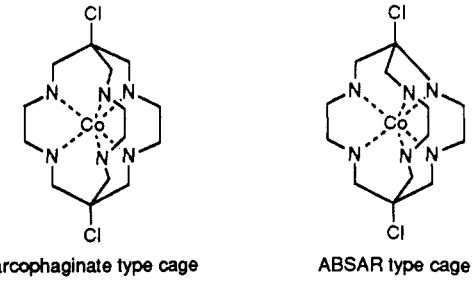
Figure 31. Diagrammatic representation of the three orientations of the nitrogen donors in conformations of cryptand-like ligands.

one sees how dramatic is the effect of preorganization on the protonation constant of the cryptand-111 and how critical the dimensions of the cryptand cavity are, since the effect on the pK_1 value of cryptand-211 relative to the open-chain ligand triethanolamine is quite modest when compared to the effect on the pK_1 of cryptand-111. In a large cryptand such as cryptand-322 there appears to be little or no preorganization for complexing the proton. Molecular mechanics calculations[126] show that cryptand-111 has only one low strain energy conformer, with both nitrogens in the endo position, whereas cryptand-222 is a much less rigid molecule with endo–endo, endo–exo, and exo–exo conformers (Figure 31), all of fairly low energy.

Other ligands that are highly preorganized are clearly the sepulchrates and sarcophaginates, which are structurally similar to cryptands.[127] Molecular me-



chanics calculations[128] have shown the sepulchrate type of ligand to be sterically quite rigid and capable of significant compression of too-large metal ions. Thus, the cavity in sepulchrates (or sarcophaginates) is of such a size that metal ions with a M–N bond length of 2.10 Å (or ionic radius of 0.7 Å) should fit best. The MM calculations show that the sepulchrate is unable to assume conformations that allow for low-strain complexation of metal ions of significantly different size from the best-fit size. Therefore, a too-large metal ion such as Hg(II) is compressed in its sarcophaginate complex by[127] some 0.1 Å, which is a very large amount of compression indeed. There are no published formation constant data on sarcophaginates (the free ligand sepulchrate is stable only when coordinated to a metal ion) and this relates to the kinetic inertness of these complexes with respect to metalation and demetalation.[127] However, a value for $\log K_1 \sim 18$ has been mentioned[127] for the Hg(II) complex of sarcophagine, which is very much lower than the $\log K_1 = 29.6$ for the Hg(II) complex of PENTEN,[21] which has a similar donor set of six nitrogens. This low complex stability for the Hg(II) sarcophagine complex is only to be expected in view of the fact that the metal ion is far too large for the cavity and appears to be severely compressed by the ligand. The metal ion that would fit perfectly into the sarcophagine cavity is high-spin Ni(II),[128] and it would be of considerable interest to know the complex stability constant for metal ions in this size range, which one would anticipate to be very high. It should be pointed out here that, although the sepulchrate complexes are formed by template reaction on Co^{III} (EN) complexes, the Co(III) ion is, with a strain-free Co–N length of 1.925 Å,[79] much too small for the sepulchrate cavity and the Co–N bond lengths are stretched[128] out to a length of 1.99 Å.[127] In line with this, it is found that the chlorinated sarcophaginate type of complex[127] undergoes an unusual cage contraction reaction, which one would surmise is driven by the need for the Co(III) to achieve shorter Co–N bond lengths:



It would be of considerable interest to see what the metal ion selectivity for the ABSAR type of cage relative to the sepulchrate type of cage would be.

The most highly preorganized ligands to date are probably the spherands (Figure 32) of Cram et al.,[44] in that they offer six donor atoms arranged in a nearly perfect octahedral array, and water molecules are ex-

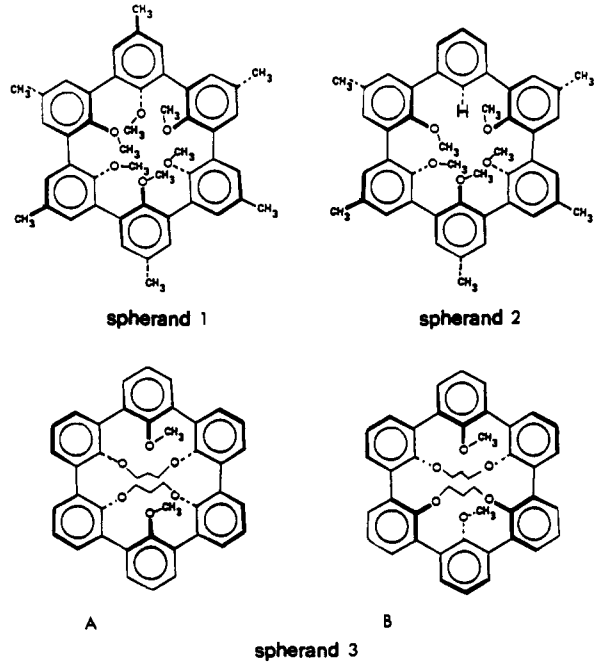
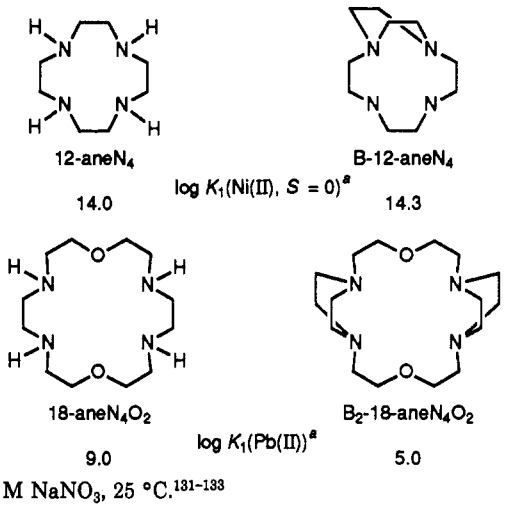


Figure 32. The spherands[44] discussed in this article.

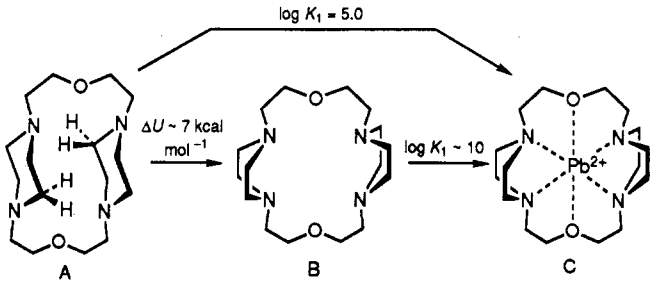
cluded from the cavity of the ligand. As summarized in Table 11, this is probably the highest attainable level of preorganization for ligands. The effects on complex stability and selectivity for Na(I) and Li(I), the two metal ions that MM calculations indicate fit the cavity best,[129] are quite dramatic. Thus, spherand I is able to extract the traces of Li^+ and Na^+ present from reagent grade KOH. Crystallography shows that the cavity of the spherand is void;[44] i.e., there are no water molecules solvating the donor atoms. This means that the water molecules which have to be removed from the donor atoms of ligands of low levels of preorganization do not have to be removed here. When one considers that hydrogen bonds normally have energies of bond formation of about 7 kcal mol^{-1}, one can see how substantial a contribution this can be, which does not have to be overcome for the spherands. The desolvation of the donor atoms within the ligand cavity is obviously not an all-or-nothing factor in complex stability. The idea was originally proposed by Cabbiness and Margerum[130] to account for the macrocyclic effect in complexes of tetraazamacrocycles, where these authors first identified the macrocyclic effect. Tetraazamacrocycles are only partially desolvated,[130] which contributes to the macrocyclic effect, but not to the extent that it appears to do for spherands. It is even possible that desolvation effects may contribute[130] to the higher complex stability where the donor atoms on a chelating ligand such as PHEN are pressed close together.

Ligands of the highest level of preorganization thus hold forth the promise of forming complexes with unprecedented complex stabilities and selectivities. However, some of the problems associated with high levels of preorganization should be pointed out. The first is the difficulty of creating ligands with larger cavities that are highly preorganized. As has been seen repeatedly in this review, small ligands tend to show higher levels of preorganization (see Table 11), but ligands with larger cavities tend to collapse in on themselves, and the cavity is lost, or else the cavity is filled with solvent. This type of effect is illustrated for the pair of ligands B-12-aneN$_4$ and B$_2$-18-aneN$_4$O$_2$ and their nonbridged analogues:[131-133]



[a] 0.1 M $NaNO_3$, 25 °C.[131-133]

It is seen that bridging 12-aneN$_4$ to give B-12-aneN$_4$ leads to a modest increase in complex stability for low-spin Ni(II), even though MM calculations show the complex [Ni(B-12-aneN$_4$)]$^{2+}$ to be highly strained, with the too-large Ni(II) ion being compressed by some 0.05 Å.[129] The fact that the high strain in the complex of low-spin Ni(II) with B-12-aneN$_4$ does not lead to a drop in complex stability is because the free ligand itself is[133] so highly strained. In other words, ΔU in eq 8 is small for the formation of the complex with B-12-aneN$_4$, although other evidence[133] suggests that the ligand may be in a highly strained exo conformation, with the dipoles on the outside of the ligand. By contrast, the ligand B$_2$-18-aneN$_4$O$_2$ with its much larger cavity shows a drop in complex stability for the Pb(II) complex[133] relative to the complex with 18-aneN$_4$O$_2$. This would appear to correspond to the energy required to "uncollapse" the free B$_2$-18-aneN$_4$O$_2$ ligand, so as to create a cavity suitable for coordinating the Pb(II) ion, as indicated below:



"collapsed" form of B$_2$-18-aneN$_4$O$_2$, cavity filled with methylene H's, and piperazine type rings in low-energy chair form (crystal structure)[134]

"uncollapsed" form of B$_2$-18-aneN$_4$O$_2$ with piperazine type rings in boat form, generated by MM calculation,[134] with large metal ion, e.g., Pb(II)

complex of Pb(II) in B$_2$-18-aneN$_4$O$_2$; stability lower than that of 18-aneN$_4$O$_2$ by approximate ΔU

Thus the inability of the large-cavity B$_2$-18-aneN$_4$O$_2$ ligand to maintain as the free ligand the conformation required for complex formation costs the formation constant with Pb(II) the 7 kcal mol^{-1} in strain energy required[134] to produce the higher energy conformer required for complex formation. The small-cavity β-12-aneN$_4$ appears unable to collapse back into a low-

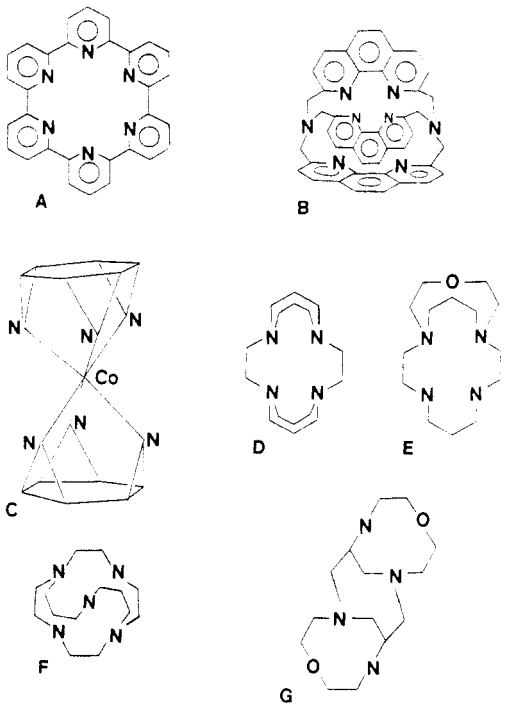


Figure 33. Some highly preorganized nitrogen donor ligands. Ligand A is sexipyridine[135] which should be selective for large metal ions. Ligand B has been reported by Lehn et al.[136] Ligand C[137] is remarkably sterically efficient with Co(III). Ligands D, E, and G are proposed highly structurally reinforced ligands, and the very rigid ligand F has been reported.[138]

energy conformer and so forms complexes of high stability. The potential value of ligands with large cavities is seen, however, in that B_2-18-aneN_4O_2 shows total selectivity for Pb(II)—it shows no sign of complexation with any other metal ion. The above scheme suggests that if the ligand could be stabilized in the "uncollapsed" form, complexes with log K_1 for Pb(II) of approximately 10 and very high selectivity against other metal ions such as Cu(II) and Ni(II) would be produced that bind nonbridged ligands such as 18-aneN_4O_2 very strongly.

In order to synthesize highly preorganized ligands with larger cavities, more rigid groups connecting the donor atoms together will have to be used. This suggests extensive use of aromatic rings fused into the ligand skeleton, particularly of the pyridyl group, as seen for "sexipyridine"[135], A, and the cryptand, B, having 1,10-phenanthroline bridges[136] in Figure 33. A particularly interesting ligand[137] is the cyclic "triaziridine" shown in Figure 33, which is so sterically efficient that, as confirmed by MM calculations (see section M), the Co(III) has very short Co–N bond lengths. A further approach to greater ligand rigidity is reinforcement, with bridges between adjacent donor atoms[133] (D in Figure 33) or with additional donor atoms in bridges between adjacent donor atoms (E in Figure 33) or bridging diagonally across the macrocycle (F in Figure 33).[124] Ligand F forms complexes with Cu(II) that appear[124] to be totally resistant to removal even by concentrated acid. Ligand G contains two rigid nine-membered macrocyclic rings joined (section M) in a highly sterically efficient manner and would be highly preorganized for complexing metal ions the size of Co(III). A third bridge of the type shown in G would lead to a highly rigid sepulchrate type of ligand, totally resistant to demetalation, since models suggest that there would be insufficient room for a metal ion to escape between the connecting strands.

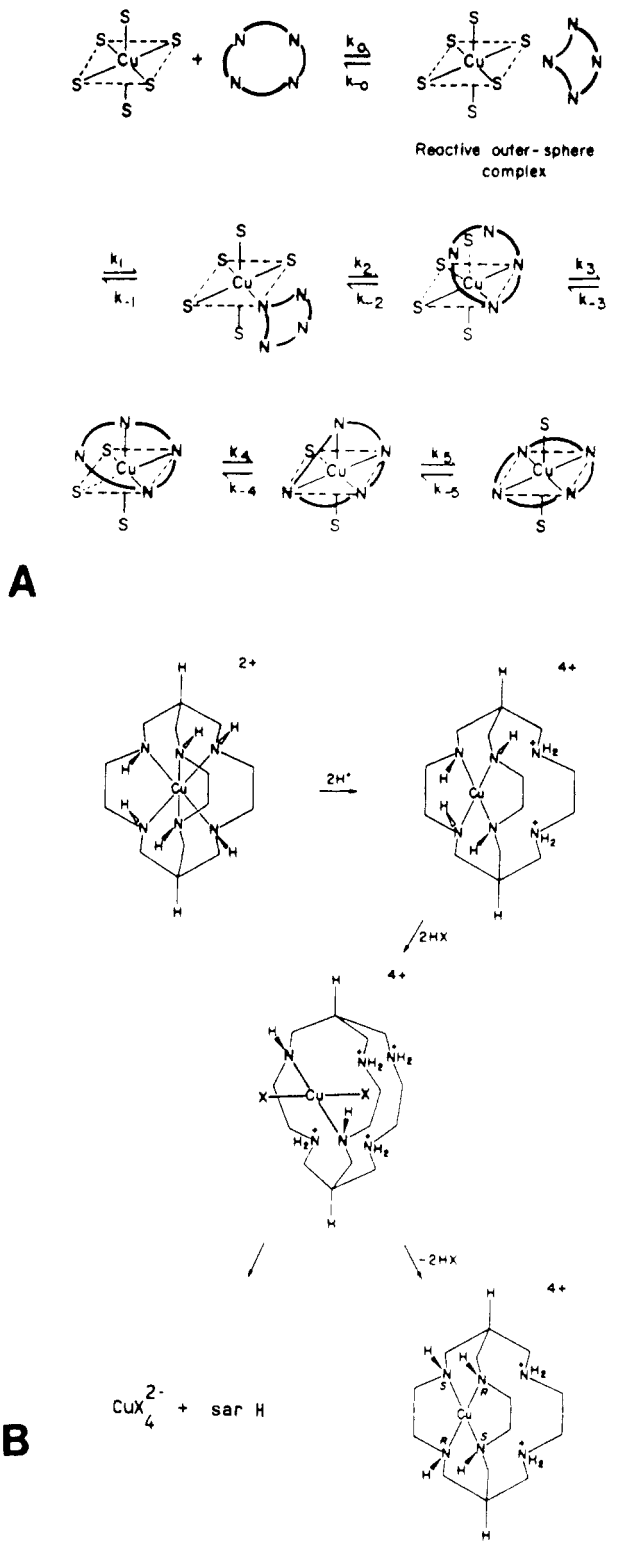
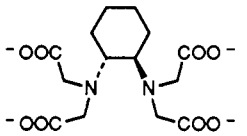


Figure 34. The flexibility required for more preorganized ligands in their interactions with metal ions, illustrated by the proposed mechanisms for (A) the complex formation reaction of Cu(II) with a tetraazamacrocycle[138] (S = solvent molecule) and (B) the removal of Cu(II) from its sarcophaginate complex in HCl.[127]

A second problem with highly preorganized ligands, if they are to be used for complexation rather than encapsulation, is that, as a rule, the level of complex lability (Table 11) drops off roughly as the level of

preorganization of the ligand increases. This can be readily appreciated from kinetic studies which show that ligand flexibility is necessary[44,127,138] to allow the metal ion to enter or leave the cavity of more preorganized ligands, as seen in Figure 34. The entry of the Cu(II) into a tetraazamacrocycle in Figure 34A involves a series of conformational changes that require considerable ligand flexibility, particularly for the later steps where coordinated nitrogens have to move from axial to equatorial coordination sites in Figure 34B. The Cu(II) emerges from the sarcophaginate by initially forming a square-planar complex. Protonation of further nitrogens leads to a complex in which the copper sits between two bridges of the ligand coordinated to only two nitrogens. The copper may then be completely displaced or undergo a competing reaction in which it is held by four nitrogens in a thermodynamically more stable conformation than is true for the initial square-planar complex. Even the relatively low levels of preorganization found in nonmacrocyclic ligands such as CDTA can lead[139] to drops in rates of metalation and



CDTA

ligand exchange reactions of several orders of magnitude compared to the less preorganized EDTA. As seen in Table 11, the increase in level of preorganization in the Ca(II) complex of CDTA leads to an increase in complex stability relative to the EDTA complex of 2.6 log units,[21] which is not a great deal less than is produced by the macrocyclic effect for many ligands. (See section O for further discussion of CDTA.) At the other end of the scale of level of preorganization, ligands undergo metalation and demetalation reactions very slowly. Thus, the cobalt can only be removed from sarcophaginate once reduced to the more labile Co(II), and then only[127] after refluxing in concentrated HCl for several days. The spherand complexes appear to be even more kinetically inert than the cryptands, reacting very slowly[44] even with the normally very labile Li^+ and Ni^+ ions.

The level of preorganization that is useful thus depends on the use to which the ligand or complex will be put. If the ligand is to be used to sequester metal ions, e.g., to remove them from the body or the environment, then slow rates of metalation are not acceptable. On the other hand, if it is required that the complex simply act to hold the metal ion, for example, in use as an NMR imaging agent, where the complex can be prepared well before use, then inertness may be a positive advantage in that such inert complexes could be used even in the presence of other metal ions that could thermodynamically displace the initial metal ion from its complex. It would appear that for active complexation of metal ions, where a high rate of complex formation is important, macrocyclic ligands with pendent donor groups offer the best combination of high levels of preorganization so as to produce high complex stability and adequate rates of complex formation. Thus, even porphyrin type molecules with suitably positioned pendent acetate groups show[140] reasonably high rates of metalation.

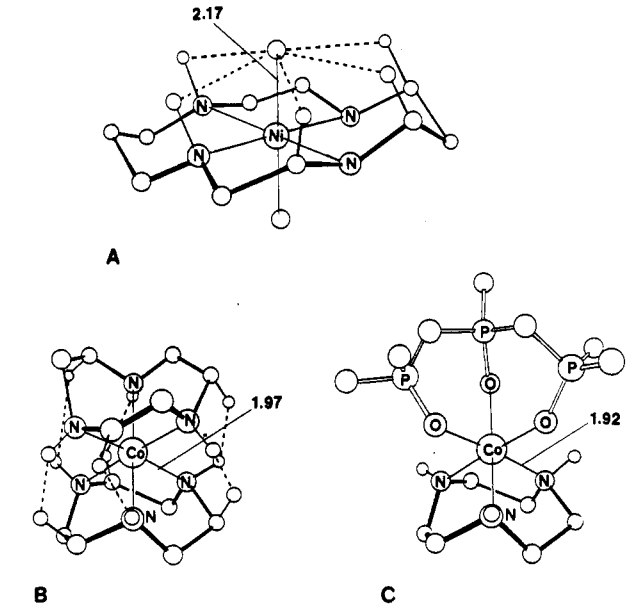


Figure 35. The stretching of M–L bonds by van der Waals repulsions (- - -) between ligands. For simplicity only those hydrogens involved in steric interactions are shown. In A (redrawn after ref 71) the Ni–O bond to the axial ligand (a nitrate) is stretched from the normal 2.10 Å out to a value of 2.17 Å. Only the oxygen donor atoms of the nitrates are shown, and the steric interactions of only one nitrate are shown. In B (redrawn after ref 79) the Co–N bonds of $[Co\text{-}9\text{-}aneN_3)_2]^{3+}$ are stretched from the ideal value of 1.92 Å out to 1.97 Å by the van der Waals repulsions between the two ligands. In C (redrawn after ref 139) the meshing between the tripolyphosphate and the 9-aneN$_3$ is greatly improved, and the structure[139] shows the unusually short Co–N bond length of 1.92 Å.

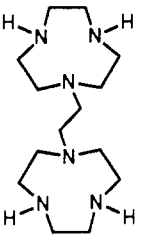
M. The Analysis of Steric Effects and Steric Efficiency

Molecular mechanics calculations are now beginning to be a useful tool in coordination chemistry.[14] In section I it was shown how MM calculations could be used to understand the size selectivity effects of chelate ring size, and in section J it was shown how MM could be used to understand the role of the relative stabilities of different conformers of macrocycles in producing metal ion selectivity. In this section a further point is examined, namely, the analysis of steric efficiency. By steric efficiency is meant the meshing together of different donor groups or different ligands around a metal ion so as to form a complex with the minimum of steric strain. The TACNTA ligand discussed in section K is an example of a ligand of extremely high steric efficiency.

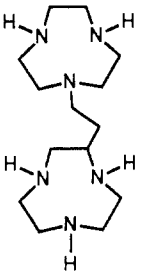
As a concrete example, the ligand cyclam generally forms[67,68] complexes that are more stable than the 2,3,2-TET analogue by some 3 log units, which is the manifestation of its macrocyclic effect. On the other hand, 9-aneN$_3$ forms complexes that are some 6 log units more stable than its open-chain analogue DIEN. The origin of this difference seems to lie, at least in part, in differences in steric efficiency, as suggested by MM calculations. As seen in Figure 35, the cyclam complex of Ni(II) has two serious steric problems. One is the fact that high-spin Ni(II) is too large for the cavity in the ligand, and the other is the steric repulsion from hydrogens on the macrocyclic ring against the ligands, such as solvent molecules, which must occupy the axial

coordination sites. The steric hindrance to axial ligands on the cyclam complex of Ni(II) results[71] in long Ni–O bonds which are 2.17 Å in $[Ni(cyclam)(NO_3)_2]$, as compared with more usual Ni–O bond lengths of ~2.10 Å. On the other hand, Ni(II) fits the bis-9-aneN_3 complex almost perfectly,[79] and all of the Ni–N bond lengths[141] are close to the ideal length of 2.10 Å. The MM calculation can be used to identify steric problems in a complex more accurately than can be achieved by inspection of space-filling models, and will pinpoint all of the large van der Waals repulsive contributions. Thus, as seen in Figure 35B,C, when a bis-9-aneN_3 complex of a smaller metal ion such as Co(III) is formed, steric repulsions between the hydrogens on the two 9-aneN_3 rings result in stretching of the Co–N bond out to 1.97 Å as compared with the strain-free Co–N length[142] of 1.92 Å. It can be seen from the illustration of the $[Co(9\text{-ane}N_3)_2]^{3+}$ complex (generated by MM calculation) that the way to remove the steric clash between the two 9-aneN_3 ligands is to replace one of them with a ligand that meshes better with 9-aneN_3. As has been mentioned already, donor groups with negatively charged oxygen donors are sterically efficient because the oxygens carry no hydrogen atoms. A ligand such as tripolyphosphate is therefore likely to be sterically efficient, particularly in view of the long P–O bonds which keep most of the ligand far from the donor oxygen atoms. In line with this, it is found that the Co–N bonds in the complex with one 9-aneN_3 and tripolyphosphate coordinated to Co(III) has the unusually short Co–N bond length, where N is a saturated nitrogen, of 1.922 Å,[143] which is thus an example of a Co(III) complex where the packing of the ligands around the Co(III) is efficient enough to allow observation of a strain-free Co–N length. Even in a complex such as $[Co(NH_3)_6]^{3+}$ the Co–N bonds are stretched by van der Waals repulsions out to a length of 1.96 Å.

An important way of overcoming steric clashes[38] is either to look for different groups that mesh well or, perhaps more simply, wherever there is a steric clash, to overcome it by joining the point of clash together. This is already done in a sense in creating more stable complexes along a series where steric crowding in a complex such as $[Ni(DIEN)_2]^{2+}$ is reduced by joining the terminal NH_2 groups together with an ethylene bridge to form a macrocyclic complex such as $[Ni(9\text{-ane}N_3)_2]^{2+}$. Thus, the steric clashes between the N–H hydrogens and the C–H hydrogens on the two 9-aneN_3 rings of $[Co(9\text{-ane}N_3)_2]^{3+}$ shown in Figure 35 could be removed in a sterically very efficient way by replacing each pair of sterically clashing hydrogens with an ethylene bridge, as shown below. It should be noted, which can also be readily discerned from models, that connecting two 9-aneN_3 groups together via the N donors to give the ligand DTNE actually lowers complex stability very considerably compared to the unbridged bis-9-aneN_3 complex, because this leads to a considerable trigonal twist distortion of the metal ion.[144,145] The ethylene bridge between two nitrogens is too short and so pulls the two 9-aneN_3 rings in DTNE around so as to give more nearly trigonal-prismatic coordination. However, replacement of the ethylene bridge with a possible longer trimethylene bridge will lead to no improvement, since an alternate problem of steric crowding will result.



DTNE
sterically inefficient



ligand "B"
sterically efficient

The stability constants and LF parameters for the complexes $[Ni(DTNE)]^{2+}$ and $[Ni(9\text{-ane}N_3)_2]^{2+}$ illustrate very well the effects of the steric strain induced by trigonal twist of the DTNE complex:

	$[Ni(9\text{-ane}N_3)_2]^{2+}$	$[Ni(DTNE)]^{2+}$
$\log \beta_n$[Ni(II)]	30[a] (n = 2)	21.5[b] (n = 1)
$10Dq$, cm^{-1}	12350[c]	12000[b]

[a] Marsicano and Hancock, to be published. [b] Reference 144. [c] Reference 79.

A very important ligand design tool is apparent in the lower LF of the Ni(II) complex of DTNE. The LF strength for similar donor sets is an indicator of the relative amount of overlap in the M–L bond.[40] The donor set in DTNE consists of two tertiary and four secondary nitrogens, so that, all else being equal, one would have expected DTNE to produce a stronger LF than would two 9-aneN_3 ligands, which have six less strongly basic secondary nitrogens (see section D). The fact that the LF strength of the DTNE complex is so low is a strong indicator that the steric strain situation is very much worse than is the case for the bis-9-aneN_3 complex. Thus, LF strength is an important pointer to steric efficiency.

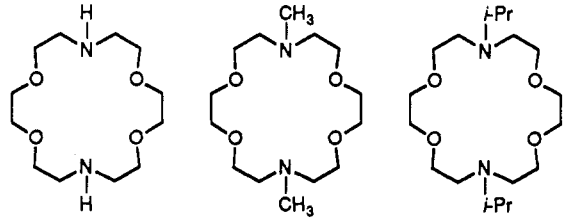
A dramatic example of the use of MM calculations as a ligand design tool is found in the work of Kollman et al.[129] on the spherands. MM analysis of the conformation of spherand complexes of Li^+ with spherand 2 in Figure 32 showed that complexes of much lower strain energy would be obtained for the Li^+ spherand 3, which has a different conformation to spherand 2. Study of this ligand[129] has shown that spherand 3 does indeed complex Li^+ much more strongly than is found to be the case for spherand 2.

As will be discussed in the next section, MM calculations have been used as a tool to examine the effect of sterically crowding alkyl groups on selectivity for Cu(II) relative to Ni(II).

N. The Use of Sterically Crowding Groups To Improve Selectivity

As already mentioned, addition of *N*-alkyl or *C*-alkyl groups (section D) to a ligand has two opposing effects. In the first instance, both types of alkyl addition lead to an increase in the donor strength of the nitrogen (or other type of) donor atom. The second effect is that there is also an increase in steric crowding, with resulting unusually high steric strain. The resulting complex stability is a delicate balance between these two effects. Strangely, these seemingly simple alterations in ligand structure provide the most difficult examples in which to predict with any degree of reliability which way the effect will go. Thus, for the sterically

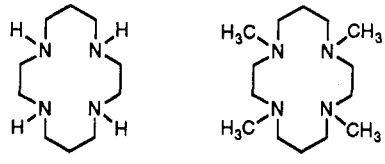
efficient arrangement of coordinating primary amines RHN_2 to the large Ag(I) ion,[39b] the inductive effects along the series $MeNH_2 < EtNH_2 < i\text{-}PrNH_2 < t\text{-}BuNH_2$ prevail. Similarly, C-methylation of EN to give TMEEN (section D) leads to an increase in complex stability for square-planar metal ions such as low-spin Ni(II) and Cu(II), but not so for presumably octahedral Zn(II) and Mn(II).[39c] The subtlety of the effects of sterically hindering alkyl groups is illustrated[146] by the effects of alkyl groups of differing sizes on the complexes of 18-aneN_2O_4 ligands:



log K_1[Cu(II)][a]	6.1	6.8	no evidence of complex formation
log K_1[Pb(II)][a]	6.8	7.2	6.2
log K_1[Ba(II)][a]	3.0	3.8	no evidence of complex formation

[a] 0.1 M $NaNO_3$, 25 °C.[146]

One sees that for all the metal ions, replacement of the hydrogens of 18-aneN_2O_4 by methyl groups leads to a modest increase in complex stability, so that for the methyl substituent, inductive effects appear to prevail. However, when the methyl group is replaced[146] by an isopropyl group, only for the Pb(II) complex is the balance still reasonable, although alkylation produces a moderate decrease in stability. For both the small Cu(II) ion and the very large Ba(II) ion the balance tips the other way, and no complex formation can be detected at all.[146] In other situations, however, N-alkylation may lead to a dramatic drop in log K_1 for complexes of all metal ions, as when cyclam is methylated so as to give TMC:



cyclam TMC

	cyclam	TMC[a]	Δ log K	ionic radius, Å
log K_1[Cu(II)]	26.5	18.3	8.2	0.57
log K_1[Ni(II)]	20.1[b]	8.6	11.5	0.69
log K_1[Zn(II)]	15.5	10.4	5.1	0.74
log K_1[Cd(II)]	11.3	9.0	2.3	0.95
log K_1[Pb(II)]	10.8	(~7.5)[c]	(~3.3)[c]	1.18

[a] Reference 39a, ionic strength 0.1 M, 25 °C. [b] Work involving competition between the proton and Ni(II) for cyclam suggests (Hancock and Evers, unpublished work) that log K_1 is slightly lower than the published value of 22.2. [c] Estimated by comparison with the tetra-*N*-methylcyclen complex.

One sees that there is a rough trend in the drop in complex stability, Δ log K, on adding the four *N*-methyl groups to cyclam to give TMC such that small metal ions appear to be more adversely affected by the change. The formation constant of the Pb(II) complex of TMC is estimated by comparison with the tetra-*N*-methylcyclen complex, which, because it forms five-membered chelate rings, complexes much more strongly

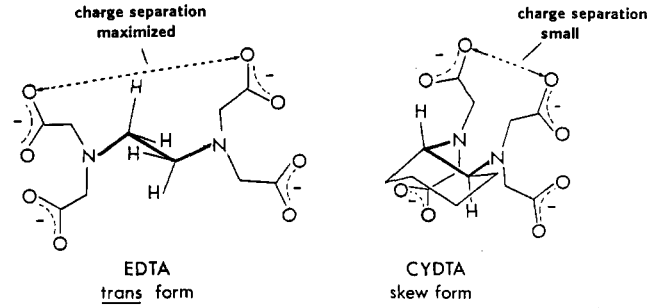
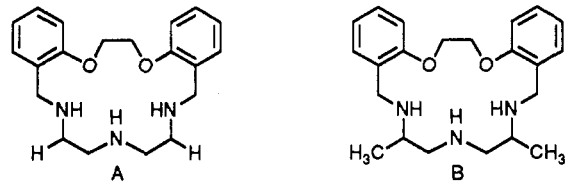


Figure 36. Role of preorganization in the complex stability of EDTA type ligands. In EDTA it appears[143] that the free ligand in solution adopts the trans form so as to maximize charge separation, whereas CYDTA is preorganized into the skew form required for complex formation, which leads to increases in complex stability.[21]

with the large Pb(II) ion. What is particularly noteworthy[39a] is the very large selectivity for Cu(II) displayed by TMC, which appears to be the largest reported to date. Use of alkyl substitution appears able to produce interesting selectivity effects, even if these are hard to predict.

Adam et al. have made a start on analyzing selectivity effects produced by methyl substitution, using MM calculations on the complexes of Cu(II) and Ni(II) with the following pair of ligands:[147,148]

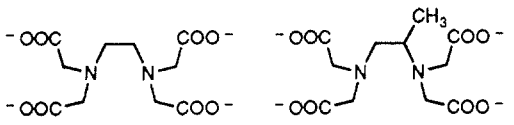


A B

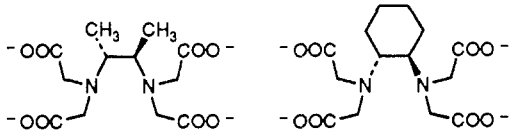
Ligands A and B form complexes of equal stability with Cu(II), while the Ni(II) complexes are considerably destabilized by the presence of the methyl groups on B. MM calculations show[148] that the destabilization of the Ni(II) complexes is brought about by the fact that the methyl groups destabilize the preferred *fac* isomer of the complex with ligand A, and with ligand B the Ni(II) is forced to adopt the less favored *mer* conformer. No MM analysis was reported that explains the lack of response of the stability of the Cu(II) complexes to the presence of methyl groups, which one assumes will be reported in a future more complete paper.

O. The Effect of Restricted Rotation of the Ligand on Complex Stability

It is found that addition[149] of *C*-methyl or other alkyl groups to the ethylene bridge of EDTA gives complexes of uniformly higher complex stability.[21] Such increases in complex stability must have a contribution from the inductive effects of the added methyl groups (see section D), but the major contribution appears[149] to be a decrease in the barrier to rotation from the trans form of EDTA, which minimizes the steric and electrostatic repulsion between the acetate groups, to the skew form, which is required for complexing the metal ion. With methyl substitution, the van der Waals repulsion between the methyl groups when the N donors are in the trans form means that the increase in energy that occurs when the ligand changes to the skew form is much less. This is seen in Figure 36. The highest level of stabilization is produced by the ligand CDTA, where the



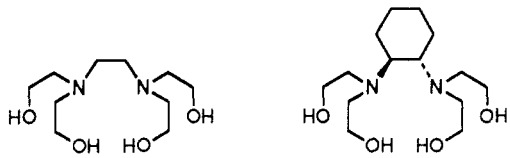
log K_1	EDTA	PMDTA
Ca(II)[a]	10.6	11.6
Cu(II)	18.7	19.8
Fe(III)	25.0	26.0



log K_1	DMEDTA	CDTA
Ca(II)[a]	12.3	13.2
Cu(II)	21.6	21.9
Fe(III)	28.2	30.0

[a] Reference 21, ionic strength 0.1 M, 25 °C.

cyclohexane ring preorganizes the two iminodiacetate type groups so that they must be in the skew position. In contrast, the ligand THECHDA shows very little



THEEN THECHDA

stabilization of its complexes relative to those of THEEN.[150] It thus seems that the effect of restricted rotation probably derives from the importance of the electrostatic repulsion that must be overcome in EDTA type ligands in rotating them around from the trans conformation to the skew conformation so as to form a complex. Rotation of the neutral groups in THEEN from trans to a skew conformation appears to present much less of an energy barrier. This consideration would seem to be particularly important in the design of siderophores, where large numbers of presumably mutually repelling charged oxygen donors are present, and energies required to assume the correct conformation for complex formation could also be large.

P. Some Specific Examples

In this section no attempt will be made to provide a complete picture of the current state of ligand design in the many fields where it is important, and the reader is referred to current reviews of these fields.[1-9] Rather, a few examples will be discussed to show how the ligand design principles outlined in this review can be used to understand the problems and potential solutions in the examples discussed. Other considerations such as toxicity, biodegradability, lipophilicity, etc., which may be needed in the ligand, are not dealt with here.

1. Specific Complexation of Larger Metal Ions Such As Ca(II) and Pb(II)

Considerable effort has been devoted to the development[8] of "detergent builders", i.e., ligands that can complex Ca^{2+} and Mg^{2+} ions and disperse precipitates and so reinforce detergent action. The eutrophication of natural waters by the sodium tripolyphosphate builders used in the past led to the use of nitrilotriacetate, which was in turn temporarily rejected (in the U.S.A. only) because of claims of weak carcinogenicity. Subsequent research was focused on ligands with combinations of carboxylate groups and neutral oxygen donors and which contain no nitrogen and phosphorus, which stimulate plant and algae growth. A correlation between the stability of the calcium complex and builder action has been found,[8] and it appears that a log K_1 of at least 5, but probably closer to 6 as is found for log K_1 for the Ca^{2+} tripolyphosphate complex, is required. (These constants refer to an ionic strength of ~0.05 M.)

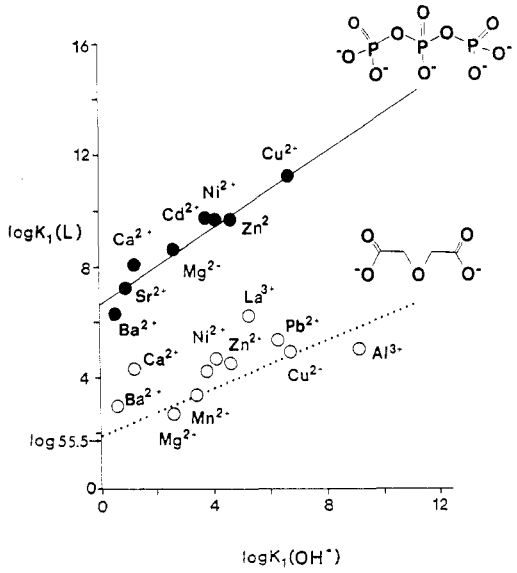
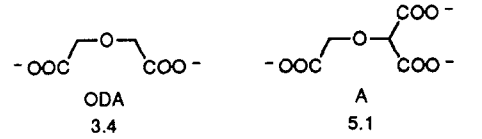
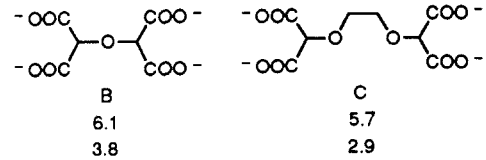


Figure 37. Relationship between log K_1 for the tripolyphosphate anion (●) and log $K_1(OH^-)$ and between log K_1 for oxydiacetate (○) and log $K_1(OH^-)$ for a variety of metal ions. Data from ref 21, ionic strength 0, 25 °C. The upward deviation for metal ions with ionic radii close to 1.00 Å (Ca^{2+}, La^{3+}) for the correlation involving oxydiacetate are useful in generating selectivity for metal ions of about this size.

The tripolyphosphate anion behaves very well as a typical negatively charged O-donor ligand, as seen in Figure 37, where log K_1 for complexes of tripolyphosphate with a variety of metal ions has been plotted against log $K_1(OH^-)$ for those metal ions (compare with Figures 4–6). The intercept in Figure 37 is close to the theoretical value of a pentacoordinate ligand of 4 log 55.5. One sees that the Mg^{2+} ion forms a more stable complex than is true for Ca^{2+}, which is to be expected from the higher log $K_1(OH^-)$ of Mg^{2+}. In contrast, for the types of ligands investigated as potential builders,[8] the stability of the Mg^{2+} complexes has been very much lower than the Ca^{2+}, as seen in the following examples:



	ODA	A
log $K_1(Ca^{2+})$[a]	3.4	5.1
log $K_1(Mg^{2+})$[a]	1.8	–



	B	C
log $K_1(Ca^{2+})$[a]	6.1	5.7
log $K_1(Mg^{2+})$[a]	3.8	2.9

[a] Ionic strength 0.05 M, 25 °C.[8]

This low stability of the Mg^{2+} complexes can be un-

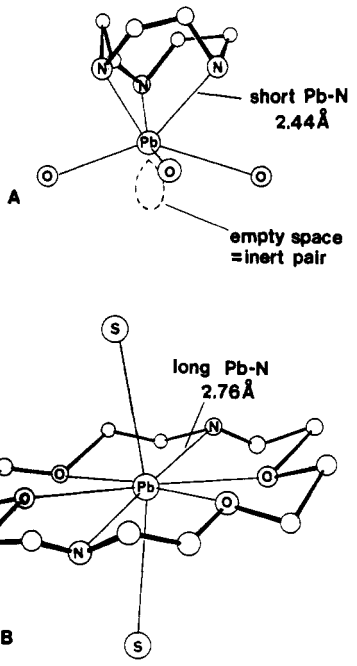
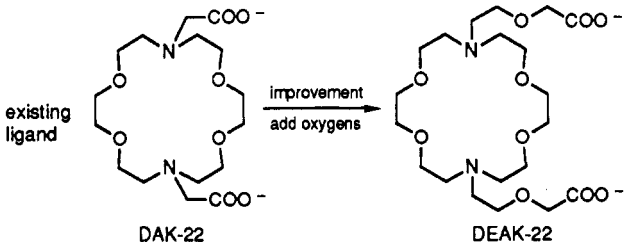


Figure 38. Effect of the inert pair of electrons of lead(II) on bond length and coordination geometry. In A the inert pair is stereochemically active, and it is inferred[81] that the inert pair is localized in the apparent gap in the coordination sphere. The bonds opposite the localized inert pair, in this case the Pb–N bonds, are shortened. After ref 81. In B it is inferred[20] that the inert pair is inactive. There is no gap in the coordination sphere, and the Pb–N bonds are long. As discussed in the text, the extent of localization of the inert pair has a marked effect on complex stability and the selectivity behavior of the Pb(II) ion.[20] After ref 152.

derstood directly from the presence of neutral oxygen donors. The Mg^{2+} ion is small, and therefore its complexes are destabilized by the presence of neutral oxygen donors (section B). It is noted that the stabilities of the complexes of the Ca^{2+} ion increase strongly with increasing numbers of carboxylate groups. This is the correct design approach in terms of correlations such as Figures 4–6. Since the Ca^{2+} ion has a low affinity for the RO^- type of donor, the stability of its complexes does not increase markedly with increasing basicity of the RO^- groups. Complex stability relates rather to the $(n-1)$ log 55.5 intercept expected from theories of the chelate effect (section H), where n is the number of donor atoms. The Ca^{2+} benefits greatly from the introduction of a single neutral oxygen donor. The Ca^{2+} ion is medium-sized, and ligands such as B appear to present it with a reasonably low strain situation. Thus, as seen in Figure 37, medium-large metal ions with ionic radii of about 1.0 Å such as Ca^{2+} and La^{3+} show the greatest stabilization upon introduction of a single oxygen donor group, as seen from the complexes with ODA. However, for these medium-large metal ions (see section B) the introduction of more than one oxygen donor leads to a situation where the added steric crowding cancels out any expected increase in complex stability from the extra donor atom, and accordingly ligand C with its two donor atoms complexes Ca^{2+} more weakly than does ligand B with its single oxygen donor. The considerations that should be addressed in designing ligands as complexing agents for Ca^{2+} are thus that the ligand should have (a) only one neutral oxygen donor and (b) as many carboxylate groups as can be placed so as to be able to coordinate with a minimum of steric strain to the Ca^{2+} ion. NTA meets the requirements of a large number of carboxylate groups in a sterically efficient arrangement and so complexes Ca^{2+} well. It seems clear that MM calculations would be invaluable in maximizing the steric efficiency with which the ligand complexes the metal ion and possibly in designing more highly preorganized ligands.

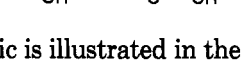
As already mentioned in section B, the design of ligands selective for Pb(II) for the treatment of lead intoxication involves ligands selective for the large Pb(II) ion over the small Zn(II) ion, an essential ion that should not be removed from the body. Design of ligands selective for the large Pb(II) ion means avoidance of six-membered chelate rings, and addition of as many neutral oxygen donor groups as necessary to depress Zn(II) binding to the desired level. It would appear[19] that a log K_1 with Pb(II) of about 12 is necessary, with a selectivity against Zn(II) of at least 5 log units. Affinity for Ca(II) should also be low. Such requirements appear to be satisfied (section B) by ligands such as $(PY)_2$-18-aneN_2O_4, which has log K_1 with the metal ions indicated as follows:[19] Pb(II), 11.7; Zn(II), 7.0; Ca(II), 3.6.

The design principles outlined in sections B (neutral donors) and I (avoid large chelate rings) may be used to suggest many ligands that should have even better selectivity than $(PY)_2$-18-aneN_2O_4, as in, e.g.



	DAK-22	DEAK-22
log K_1[Pb(II)][a]	14.5	(12)[b]
log K_1[Zn(II)][a]	8.9	(2)[b]
log K_1[Ca(II)][a]	8.6	(4)[b]

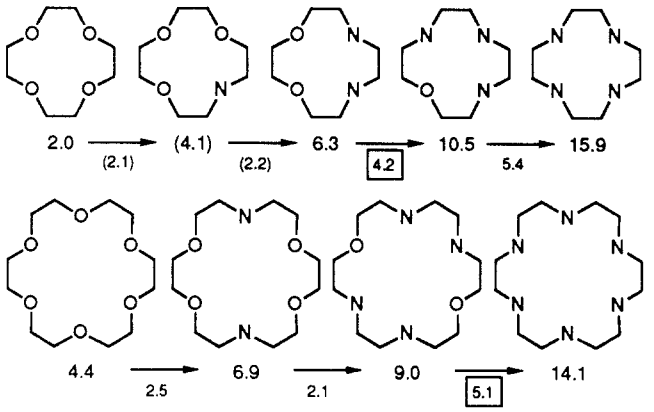
[a] Ionic strength 0.1 M, 25 °C.[20] [b] Estimated by comparison with 18-aneN_2O_4 derivatives where N substituents changed from



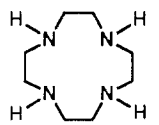
An important tactic is illustrated in the above example. When adding the neutral oxygens, one should do so in such a way as to break up adjacent groups which might coordinate well to a small metal ion. Thus, the two oxygens added to DAK-22 above are not added into the macrocyclic ring, as this would leave the Zn(II) ion the option of binding to a glycine-like arm of the ligand. Placement of the oxygen between the main ring and the carboxylate breaks up this option, as in coordinating to one carboxylate and one nitrogen donor on one arm of the ligand the Zn(II) cannot avoid also binding to a neutral oxygen.

However, all is not always so simple in controlling selectivity for the Pb(II) ion. When there are three or more nitrogen donors present in the ligand, a change appears to be possible such that the stereochemically inactive inert pair of electrons on the Pb(II) ion becomes stereochemically active.[20] This change from an inactive to an active (i.e., from the point of view of the inert pair of electrons) form is accompanied by shortening of the Pb–N bond lengths by approximately 0.3 Å, with much more covalent M–L bonding.[20] The

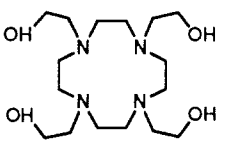
phenomenon is similar in some ways to the changes in coordinating properties that occur on spin-pairing of the d electrons in metal ions such as Fe(II) or Ni(II). The effect appears[20] to account for discontinuities in stability sequences such as the one below, where the incremental change in log K_1 for the Pb(II) complex along the series of ligands suddenly becomes much larger as oxygens are replaced by nitrogens (ref 20, 21, and 105, the ionic strength 0.1 M, 25 °C):



The number enclosed in a box in each sequence indicates the point at which it is thought that the change from an inactive to an active inert pair of electrons occurs on Pb(II).[20] This idea could be ascertained crystallographically and has already been demonstrated[81] to be the case for Pb(II) complexes of 9-aneN$_3$. As seen in Figure 38, the structure of the complex of Pb(II) with the ligand 9-aneN$_3$ has very much shorter Pb–N bond lengths than does that with 18-aneN$_2$O$_4$, a lower coordination number, and a distinct "gap" that is occupied by the unshared pair of electrons. The important point about this change in size is that it changes the responses of the Pb(II) in terms of rules for selectivity of ligands for metal ions based on metal ion size. If the Pb(II) has not changed from having an inactive to an active inert pair of electrons, then it behaves as a large metal ion with ionic radius about 1.18 Å. However, once it has undergone the change to an active inert pair, it responds more like a metal ion of ionic radius about 0.75 Å. Thus, the increase in complex stability for [Pb(12-aneN$_4$)]$^{2+}$ is due to a stereochemically active lone pair and short Pb–N bonds, because of the large number of nitrogen donor atoms. Addition of hydroxyethyl groups to 12-aneN$_4$ to give THE-12-aneN$_4$ thus gives a response like that of a smaller metal



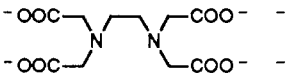
12-aneN$_4$
log K_1[Pb(II)]^a = 15.9



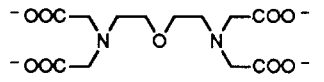
THE-12-aneN$_4$
log K_1[Pb(II)]^a = 15.1

^{a} Ionic strength 0.1 M, 25 °C.[20,21]

ion with ionic radius of about 0.75 Å, and log K_1 drops instead of rising. This type of effect also seems to be induced when a large number of acetate groups are present, as can be seen in comparing the effect of inserting an oxygen donor into EDTA to give EEDTA on the log K_1 values of Pb(II), and the similarity sized Sr(II) (which behaves like Pb(II) without a stereochemically active inert pair).



EDTA



EEDTA

	EDTA	EEDTA
log K_1[Sr(II)]^a	8.68	9.24
log K_1[Pb(II)]^a	17.88	14.8

^{a} Ionic strength 0.1 M, 25 °C.[21]

Crystallographic studies[151] support the idea that the inert pair on [Pb(EDTA)]$^{2-}$ is stereochemically active. Thus, an important factor in designing ligands for selective complexation of Pb(II) is the activity or inactivity of the inert pair of electrons, and the presence of an active inert pair must be considered as a possibility when there are several donor groups that are not neutral oxygen donors.

2. Ligands for Complexing More Highly Charged Metal Ions Such As Al(III), In(III), Ga(III), or Fe(III)

The discussion in section C indicates that ligands for complexing more highly charged metal ions should contain negatively charged oxygen donors. The problems that became apparent in section C were the following: (a) the correlation of log K_1 for such ligands with log K_1(OH$^-$) for the metal ions involved means that the selectivity orders of these ligands are more or less fixed; (b) the fact that the negatively charged oxygen donor cannot act as a point for connecting two chelate rings means that unfavorable entropy effects are produced by the very long connecting bridges, which leads to lowered complex stability.

The first problem, the ligand selectivity order, can be attacked by including other types of donor atoms (e.g., N, S, or neutral O) or by arranging the geometry of the negative O donors so that one metal ion is favored. The latter approach has been most elegantly used by Shinkai et al.[152] in the substituted calixarene seen in Figure 39. The six acetate donors of the ligand require that the metal ion be able to accept planar six-coordination. It is thus found that the UO_2^{2+} ion is very strongly complexed by this ligand but that other metal ions such as Cu^{2+}, which cannot adapt to the steric requirements of the ligand, are only weakly coordinated. The ligand shows a selectivity for UO_2^{2+} over Cu^{2+} of some 14 log units, which is much larger than would be expected from correlations such as those in Figures 3–6, and the relatively small difference in log K_1(OH$^-$), which is[21] 8.4 for UO_2^{2+} and 6.7 for Cu^{2+}. The ligand of Shinkai et al.[152] is thus preorganized for coordinating to UO_2^{2+}.

The use of other donor atoms to alter selectivities may in some cases turn out to be quite straightforward. Larger metal ions of reasonable affinity for negatively charged O donors such as La^{3+}, In^{3+}, or Th^{4+} might have ligand selectivity altered in their favor by the addition of neutral O donors, as discussed in section B. An example of such an alteration is seen in ligands A and B in Figure 39. Alternatively, addition of nitrogen donors (Table 2) might lead to greater selectivity for metal ions that have a high affinity for nitrogen such as In(III), Ga(III), or Fe(III), as discussed in section D. Unfortunately, Al(III) presents a considerable challenge in designing ligands selective against Fe(III), for exam-

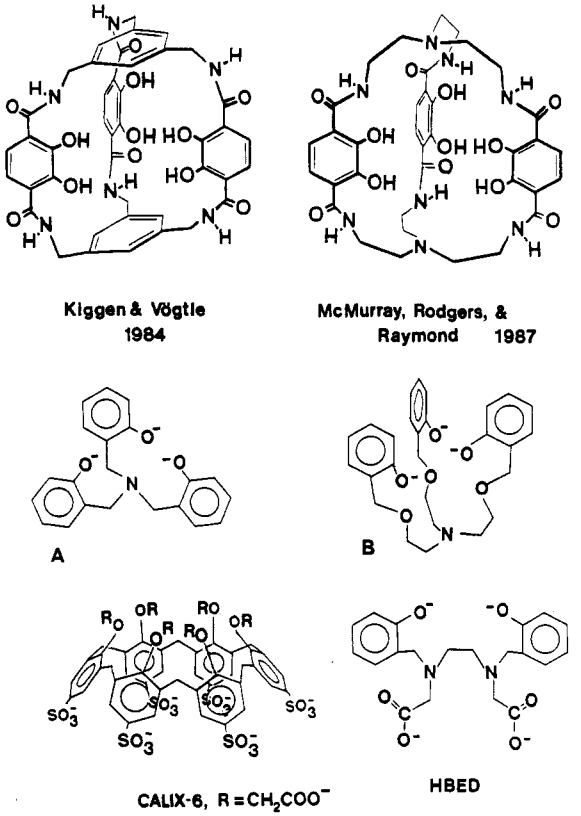


Figure 39. Ligands containing negative oxygen donors discussed in the text. At top are cryptand-like triscatecholates. At center is shown how addition of neutral O donors to A to yield B might give a ligand more selective for larger metal ions such as In(III) or Gd(III). At bottom is the CALIX-6 of Shinkai et al.,[148] which is selective for the uranyl ion, and HBED, which may turn out to be the best for Fe(III).[155]

ple. The Al(III) ion is small, so neutral O donors will not improve selectivity for it. Table 2 shows that it has much lower affinity for nitrogen than does Fe(III), and Table 3 shows Al(III) to be extremely hard, so that soft donors will not improve ligand selectivity for aluminum. Possibly preorganization of the ligand to favor very small metal ions will enhance selectivity for Al(III), and use of six-membered chelate rings (section I) is indicated.

Problems of low levels of preorganization in negatively charged oxygen donor ligands brought about by the long connecting bridges are addressed in the naturally occurring ligand rhodotorulic acid. It is found that log K_1 for Fe(III) with rhodotorulic acid is 21.9,[153] higher than other dihydroxamates such as octane-1,8-dihydroxamic acid, where it is only 20.3.[154] The greater stability of the rhodotorulic acid complex is attributed to the partial immobilization of the bridge between the hydroxamate groups by the diketopiperazine portion of the bridge and the fact that the two hydroxamate groups are preorganized on the same side of the diketopiperazine group, as seen in Figure 40.

Vogtle et al.[33] and Raymond et al.[34] have synthesized cryptand-like triscatecholates, as seen in Figure 39, which represent attempts to improve the level of preorganization in triscatecholate ligands. Martell et al.[155] have reported cyclic dihydroxamic acids. It may turn out, however, that the easiest way to overcome the need for long connecting bridges in negative O-donor ligands is to include N donors, which can connect adjacent chelate rings together, and ligands such as HBED

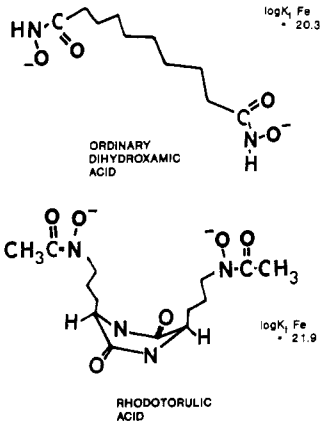


Figure 40. Comparison of a synthetic aliphatic bis(hydroxamic acid) with the naturally occurring partially preorganized bis(hydroxamic acid) rhodotorulic acid. Data from ref 153 and 154, ionic strength 0.1 M, 25 °C.

(Figure 39) will turn out to be the simplest to make and be highly effective complexing agents for metal ions such as Fe(III).

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Glossary

9-aneN_2O	1-oxa-4,7-diazacyclononane
9-aneN_2S	1-thia-4,7-diazacyclononane
9-aneN_3	1,4,7-triazacyclononane
12-aneN_4	1,4,7,10-tetraazacyclododecane
13-aneN_3O	4-oxa-1,7,10-triazacyclotridecane
14-aneN_4	1,4,8,11-tetraazacyclotetradecane
18-aneN_2O_4	1,1,10,13-tetraoxa-7,16-diazacyclooctadecane
18-aneN_4O_2	1,10-dioxa-4,7,13,16-tetraazacyclooctadecane
ABSAR	1-(chloromethyl)-8-chloro-3,6,9,13,15,18-hexaazabicyclo[6.6.5]nonadecane
AE-IDA	1,2-diaminoethane-*N*,*N*-diacetic acid
AMPY	(aminomethyl)pyridine
AMPY-DA	(aminomethyl)pyridine-*N*,*N*-diacetic acid
B-12-aneN_4	1,4,7,10-tetraazabicyclo[8.2.2]tetradecane
BAMTPH	*N*,*N*′,*N*″-tris(3-*N*-hydroxypropanamido)-1,3,5-benzenetricarboxamide
BHE-18-aneN_2O_4	*N*,*N*′-bis(2-hydroxyethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane
BHEE-18-aneN_2O_4	1,10-bis(2-(2-hydroxyethoxy)ethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane
BPY	2,2′-bipyridyl
CAT	catechol
CDTA, CYDTA	*trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid
18-crown-6	1,4,7,10,13,16-hexaazacyclooctadecane

cyclam	1,4,8,11-tetraazacyclotetradecane
cyclen	1,4,7,10-tetraazacyclododecane
DACO	1,5-diazacyclooctane
DAES	4-thia-1,7-diazaheptane
DAK-22	4,7,13,16-tetraoxa-1,10-diazacyclooctadecane-1,10-diacetate
DEAK-22	4,7,13,16-tetraoxa-1,10-diazacyclooctadecane-1,10-diylbis((ethyleneoxy)acetate)
DETODA	3,6,9-trioxaundecanedioic acid
DFB	desferriferrioxamine-B
DHNS	2,3-dihydroxynaphthalene-6-sulfonic acid
DIEN	1,4,7-triazaheptane (diethylenetriamine)
DMEDTA	DL-(2,3-butylenedinitrilo)tetraacetic acid
DMPABM	12,17-dimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane
DOTA	1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid
DPTN	1,5,9-triazanonane
DTMA	diethylenetriaminemonoacetic acid
DTNE	1,1′-ethylenebis(1,4,7-triazacyclononane)
DTPA	diethylenetriaminepentaacetic acid
EDDA	ethylenediamine-*N*,*N*′-diacetic acid
EDDPY	2,2′-ethylenebis(iminomethylene)dipyridine)
EDDS	ethylenediamine-*N*,*N*′-disuccinic acid
EDMA	ethylenediaminemonoacetic acid
EDODS	(ethylenedioxy)disuccinic acid
EDTA	ethylenediaminetetraacetic acid
EDTPY	2,2′,2″,2‴-(ethylenedinitrilo)tetramethylenetetrapyridine
EEDTA	1,7-diaza-4-oxaheptane-1,1,7,7-tetraacetic acid
EN	ethylenediamine
GLY	glycine
HBED	*N*,*N*′-bis(2-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic acid
HIDA	(*N*-(2-hydroxyethyl)imino)diacetic acid
HSAB	hard and soft acid and base principle
IDA	iminodiacetic acid
IDPY	2,2′-iminodimethylenedipyridine
MM	molecular mechanics
NTA	nitrilotriacetic acid
NTPY	2,2′,2″-nitrilotrimethylenetripyridine
ODA	oxydiacetic acid
ODEN	4-oxa-1,7-diazaheptane
ODHA	octane-1,8-dihydroxamic acid
OMDTA	octamethylenediaminetetraacetic acid
PENTEN	pentaethylenehexamine
PHEN	1,10-phenanthroline
PIC	picolinic acid
PMDTA	DL-(propylenedinitrilo)tetraacetic acid
$(PY)_2$-18-aneN$_2$O$_4$	*N*,*N*′-bis(2-pyridylmethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane
TACNTA	1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid
TERPY	2,2′,2″-terpyridyl
2,2,2-TET	triethylenetetramine (TRIEN)
2,3,2-TET	1,4,8,11-tetraazaundecane
TETB	*rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane
TETA	1,4,8,11-tetraazacyclotetradecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid
TETREN	1,4,7,10,13-pentaazatridecane (tetraethylenepentamine)
THE-12-aneN$_4$	1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane
THE-18-aneN$_4$O$_2$	1,4,10,13-tetrakis(2-hydroxyethyl)-7,16-dioxa-1,4,10,13-tetraazacyclooctadecane
THEC	1,4,8,11-tetrakis(2-hydroxyethyl)-1,4,8,11-tetraazacyclotetradecane
THECHDA	*N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)-*trans*-1,2-diaminocyclohexane
THEEN	*N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)-1,2-diaminoethane
Tiron	3,5-disulfocatechol
TMC	*N*,*N*′,*N*″,*N*‴-tetramethylcyclam
TMDTA	trimethylenediaminetetraacetic acid
TMEEN	tetramethylethylenediamine
TN	1,3-diaminopropane (trimethylenediamine)
TPTCN	1,4,7-tris(2-pyridylmethyl)-1,4,7-triazacyclononane
TRIEN	triethylenetetramine
TRITA	1,4,7,10-tetraazacyclotridecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid

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