

## Macrocycles and their selectivity for metal ions on the basis of size

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**Abstract** - The metal ion size selectivity of the oxygen- and nitrogen-donor macrocycles is examined. It is shown that the presence of the neutral oxygen donor in ligands leads to stronger complexation of large metal ions, with less favourable complexation of small, irrespective of whether the oxygen donor is part of a macrocyclic ring or not. Molecular Mechanics calculations indicate that the size-dependence of the complexing of metal ions by the neutral oxygen donors is controlled by a balance between the steric strain produced by the group bearing the oxygen donor, and its inductive effects. For tetraazamacrocycles the stability is controlled by the size of the chelate ring formed on complex-formation. Larger chelate rings lead to greater complex stabilisation for small metal ions, while larger metal ions show progressively greater complex destabilisation with larger chelate rings. This apparent paradox is also examined using molecular mechanics calculations. The use of neutral oxygen donors and chelate ring size to control metal ion size selectivity in ligand design is discussed.

### INTRODUCTION

Macrocyclic Chemistry has aroused great interest for several reasons. One reason is the unprecedented coordinating ability of the oxygen-donor macrocycles to complex strongly with the alkali and alkaline-earth metal ions. Coupled with this is the unusual property that only very weak coordinating properties are observed with the transition metal ions. The nitrogen-donor macrocycles display more usual properties in that they complex most strongly with the transition and post-transition metal ions. A second interesting property of the macrocycles is the cavity, which might enable the ligand to display selectivity towards metal ions which fit best into it. Much work (ref. 1,2) supports this idea, although results with very large crown ethers (ref. 3,4) suggest that a "plateau" of stability is reached with very large rings, which does not correspond to strongest complexation of the largest metal ions by the largest rings. For the oxygen-donor macrocycles, variation in "cavity size" is accompanied by a variation in the number of oxygen donors, plus their connecting ethylene groups. Variation in cavity size for the tetraaza-macrocycles is achieved, however, by varying the size of the bridging group from ethylene to trimethylene. Hole sizes have been calculated in various ways, such as the Molecular Mechanics calculations, which have yielded (ref. 5,6) the hole sizes for the tetraaza-macrocycles shown in Fig. 1.

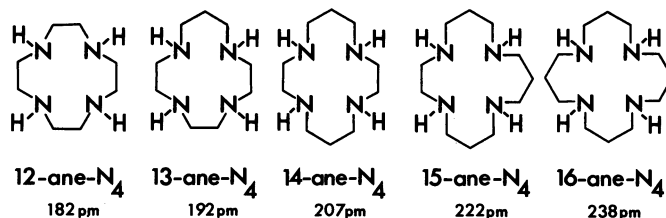


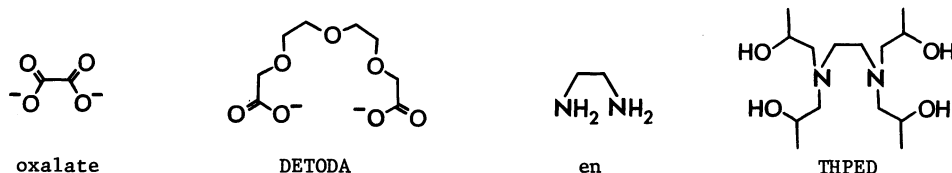
Fig. 1. The tetraaza-macrocycles and their hole-sizes as calculated by Molecular Mechanics for the metal ion lying in the plane of the nitrogen donors. Hole size is the best-fit M-N bond length for fitting into the macrocyclic cavity.

Because of the interest in the properties of the oxygen-donor macrocycles, we have taken a special interest in oxygen as a donor atom. This has involved open-chain ligands containing oxygen-donors (ref. 7,8), macrocycles containing pendent oxygen-donor groups (ref. 8,9), and macrocycles with both oxygen and nitrogen donor atoms in the ring (ref. 10-12). At the same

time, we have investigated the question of hole-sizes in tetraaza-macrocycles, both from the point of view of formation constant studies (ref. 13-14), and of Molecular Mechanics calculations aimed at elucidating the factors involved in metal ion size-selectivity displayed by these ligands (ref. 15-16). From these studies have emerged some patterns with regard to controlling selectivity for metal ions which we believe may be useful. Our own immediate interest here lies in the development of ligands as therapeutic agents for the treatment of metal intoxication. Existing reagents for most applications have severe limitations (ref. 17), and it is clear that improved selectivity for toxic metal ions would be an advantage.

### THE NEUTRAL OXYGEN DONOR

Open-chain ligands containing neutral oxygen donor atoms only are generally poor ligands, and their complexing properties are therefore difficult to study. However, where the neutral oxygens are part of a ligand which contains other, more strongly coordinating groups, overall strength of complexation may be enhanced, and we may complex a wide variety of metal ions. Further, the effects of the oxygen-donor groups alone on complex-stability may be discerned by comparison with ligands which do not contain the neutral oxygen donors, but are otherwise similar. Such a pair of ligands is oxalate and DETODA below, where DETODA is a dicarboxylic acid like oxalate, but contains in addition three ethereal oxygen donors. Another such pair is en and THPED, shown below. The ligand THPED is, like en, a diamine, but contains in addition four pendent "arms" bearing oxygen-donors.



We may calculate the change in complex stability,  $\Delta \log K$ , produced by a particular change in ligand structure. Thus,  $\Delta \log K$  for the pair of ligands oxalate and DETODA is  $\log K_1$  for the DETODA complex minus  $\log K_1$  for the oxalate complex for any given metal ion. In Fig. 2 is shown  $\Delta \log K$  for the pairs of ligands oxalate and DETODA, and en and THPED, as a function of metal ion radius (ref. 18). It is seen that the addition of the neutral oxygen donors produces a size-related change in complex-stability such that large metal ions show more favourable changes than do small. This pattern of stabilisation of complexes resembles very closely that found for crown ethers. Thus, large metal ions such as Pb(II) or Sr(II) show enhanced complex stability on addition of neutral oxygen donors, and also complex well with crown ethers. On the other hand, small metal ions such as Cu(II) or Mg(II) show much less favourable changes in complex stability on addition of neutral oxygen donors, and are also not complexed well by crown ethers.

In Fig. 3 is shown a plot of  $\Delta \log K$  versus  $r^+$  for the pairs of ligands BAEDOE and 18-aneN<sub>2</sub>O<sub>4</sub>, and 18-aneN<sub>2</sub>O<sub>4</sub> and cryptand-2,2,2. What we are in effect doing in Fig. 3 is to take an open chain ligand (BAEDOE) and add a bridge containing two ether groups to give the macrocycle

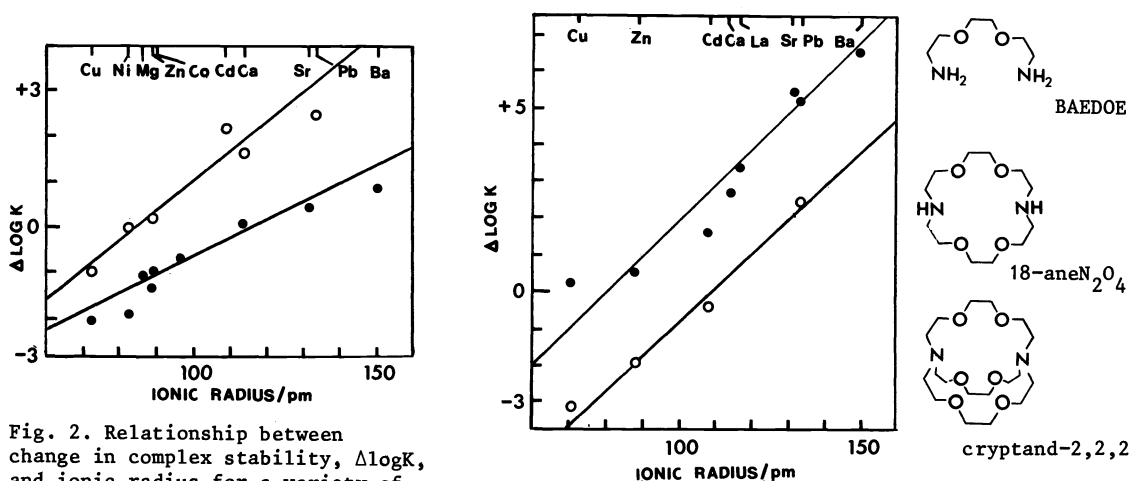


Fig. 2. Relationship between change in complex stability,  $\Delta \log K$ , and ionic radius for a variety of divalent metal ions. The  $\Delta \log K$  values are for passing from the oxalate to the DETODA complexes (●), and from the en to the THPED complexes (○). Formation constant data from ref. 19.

Fig. 3. Relationship between change in complex stability,  $\Delta \log K$ , and ionic radius, for a variety of metal ions. The  $\Delta \log K$  values are for passing from the BAEDOE complex to that of 18-aneN<sub>2</sub>O<sub>4</sub> (○), and from 18-aneN<sub>2</sub>O<sub>4</sub> to cryptand-2,2,2 (●). Data from ref. 19.

18-aneN<sub>2</sub>O<sub>4</sub>, and then repeat the operation with 18-aneN<sub>2</sub>O<sub>4</sub> to give the cryptand-2,2,2. The change in complex stability,  $\Delta\log K$  accompanying the changes in structure is seen to be a function of the size of the metal ion. As with the simpler ligand changes shown in Fig. 2, smaller metal ions show less favourable changes in complex stability than do larger metal ions when groups containing neutral oxygen donors are added to an existing ligand.

The relationships shown in Figs. 2 and 3 appear to be general as far as adding groups containing neutral oxygen donors to existing ligands is concerned. An alternate type of behaviour is seen in Fig. 4, where linearity has been lost. In the upper relationship,  $\Delta\log K$  has been calculated for cryptand-2,2,1 relative to 18-aneN<sub>2</sub>O<sub>4</sub>. Unlike the analogous relationship for cryptand-2,2,2, there appears to be a peak in  $\Delta\log K$  at about 120 pm. This peak must represent the best-fit size for metal ions for fitting into the cavity of cryptand-2,2,1, which accords with estimates made from models. At metal ion sizes above 120 pm, therefore, the metal is too large to fit into the cavity of the macrocycle without causing constriction. The lower relationship shows  $\Delta\log K$  as a function of  $r^+$  for the pair of ligands oxalate and oxydiacetate. Unlike that shown for DETODA relative to oxalate in Fig. 2, there is here a peak in  $\Delta\log K$  at about 115 pm. This is hard to explain in terms of constriction, since ODA should be sterically much less demanding than DETODA, which does not show such a peak. The same levelling off in selectivity with increasing ring size has been noted in crown ethers (ref. 3-4) and referred to as a "plateau" in stability.

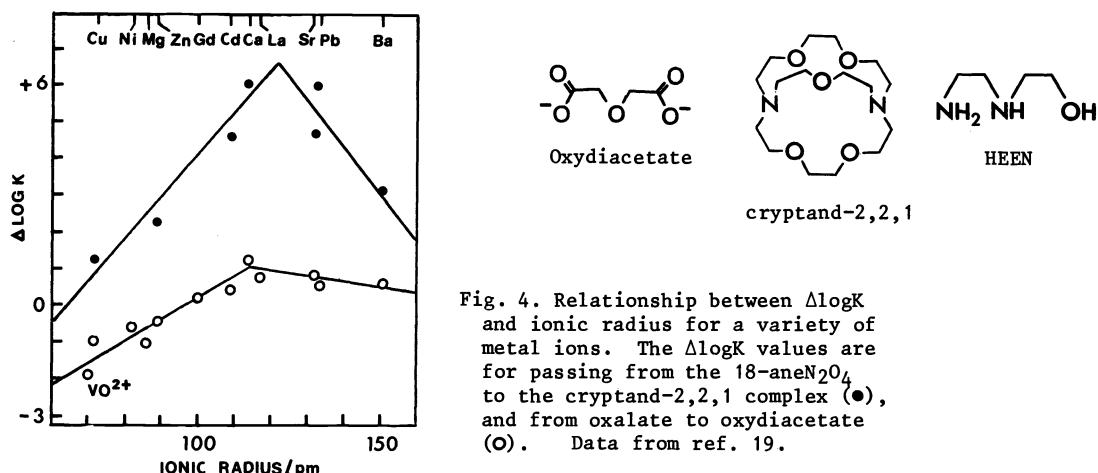


Fig. 4. Relationship between  $\Delta\log K$  and ionic radius for a variety of metal ions. The  $\Delta\log K$  values are for passing from the 18-aneN<sub>2</sub>O<sub>4</sub> to the cryptand-2,2,1 complex (●), and from oxalate to oxydiacetate (○). Data from ref. 19.

### THE ROLE OF STERIC STRAIN

One can readily understand the above behaviour in terms of the balance which exists between steric and inductive effects on complex formation. In particular, Molecular Mechanics (MM) calculations (ref. 16, 20) show that the coordination sphere around a small metal ion is extremely crowded. In the extreme case, such as in octahedral Co(III), v.d. Waals repulsion between the ligands prevents the donor atoms of the ligand from approaching the metal ion to the strain-free Co-N bond length of 193 pm (ref. 20). In actual complexes of Co(III) with amines, the observed Co-N bond lengths fall in the range 194 - 204 pm. The fact that the Co-N bond lengths are longer than that which would be observed in a strain-free situation, i.e. 193 pm, is caused by the Co-N bond stretching associated with steric crowding around the metal ion. *Addition of any organic substituents leads to a dramatic increase in steric crowding.* This is true even if we simply add in an ethylene bridge to create a chelate. This is shown in Fig. 5 for the progressive addition of more and more ethylene groups to

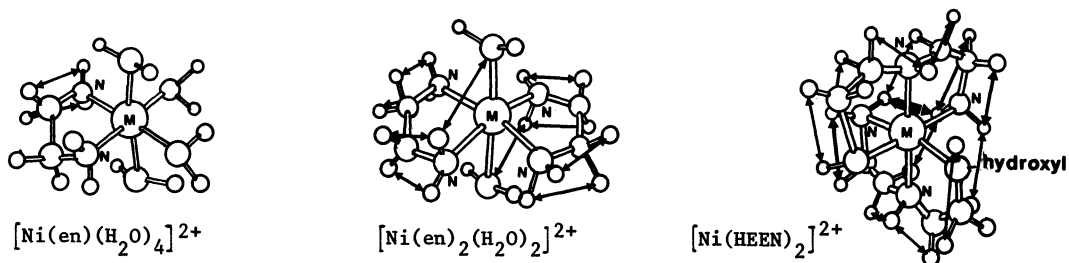


Fig. 5. Drawings of three complexes of Ni(II) showing the build-up of steric strain as the number of bridging ethylene groups is increased. The double-ended arrows indicate v.d. Waals repulsions of more than 0.5 kJ/mol as calculated by Molecular Mechanics. The very thick arrow indicates a repulsion in excess of 2.0 kJ/mol. The small circles are H atoms, the larger are C, unless attached to the metal atom (M), when they are oxygen, except when indicated as N (nitrogen).

Ni(II) complexes. The light double-headed arrow in Fig. 5 indicate v.d. Waals repulsions of over 0.5 kJ/mol. It is seen that in the mono-en complex, there are only two repulsions of this magnitude, when we put in a second ethylenediamine the number increases to ten, and in the bis-HEEN complex, where we now have four bridging ethylene groups, the number has increased to fourteen. In addition, there is in the latter complex a v.d. Waals repulsion of over 2 kJ/mol. The increasing steric repulsion in the complex is caused by steric crowding as the number of ethylene groups increases. The response of the complex to this steric crowding (ref. 16) is principally one of metal to ligand bond stretching, which allows for a decrease in the number of ligand atoms in the immediate vicinity of the metal ion. Thus, the Ni-O bond lengths in Fig. 5 increase from 208 to 215 pm as the number of bridging ethylene groups increases from one to four.

The effect on complex stability of adding a bridging ethylene group will thus be controlled by the balance between the steric effects described above, and the inductive effects produced. Studies of gas-phase basicities (ref. 21-24) show that for neutral oxygen donors the donor strength increases  $H_2O < ROH < R_2O$ , and for amines  $NH_3 < RNH_2 < R_2NH < R_3N$ , where R is an alkyl group. Insertion of a bridging ethylene group between, say, an oxygen and a saturated nitrogen donor will thus produce favourable inductive effects. *The effect on complex stability will thus be the nett balance of the steric and inductive effects produced as we modify a complex by adding organic structural elements such as bridging ethylene groups.* Figures 2 and 3 suggest, as is supported by MM calculations, that steric crowding increases with decreasing metal ion size to the extent that it outweighs the inductive effects, as we add groups containing neutral oxygen donors to existing ligands. For large metal ions, even though coordination number tends to increase, steric effects appear to be outweighed by inductive effects, and increases in complex stability occur. Of course, where the addition of the group bearing neutral oxygen donors results in the formation of a new macrocyclic ring, there will be an additional contribution from the reduced configurational entropy of the free ligand to the resulting complex stability. What is remarkable, as seen in Figs. 2 and 3, is that the change in complex stability should be a linear function of metal ion size. The linearity of the type of relationship seen in Figs. 2 and 3 appears to be a general phenomenon when groups containing neutral oxygen donors are added. This is found even though the changes in complex structure are undoubtedly very complex. Thus, for example, the structure (ref. 25) of the complex of Cu(II) with the ligand DAK-22 shown in Fig. 6 reveals that not all of the donor atoms of the potentially octadentate ligand are coordinated to the small metal ion, which is undoubtedly true for most of the complexes of the smaller metal ions where the number of donor atoms exceeds the commonly found coordination numbers of the small metal ion.

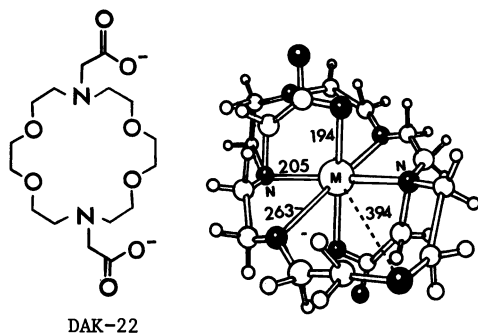


Fig. 6. Drawing of the DAK-22 complex of Cu(II), showing the non-bonded etheral oxygens of the macrocyclic ring. The small circles are hydrogen atoms, the large open circles are carbon, and the coloured are oxygen, or where indicated nitrogen. The numbers indicate bond lengths in pm, or for the dotted line a non-bonded distance.

The peak for the relationship between  $\Delta \log K$  for ODA and oxalate, and  $r^+$ , at an  $r^+$  value of about 115 pm, seen in Figure 4 is thus not interpreted as a best-fit size of metal ion as for the relationship involving cryptand-2,2,1 and 18-ane $N_2O_4$ , but rather as a shift in the balance between steric and inductive effects. Thus, the rate of fall-off in steric effects beyond an  $r^+$  value of 115 pm for the ODA/oxalate relationship drops off, and for larger metal ions electronic effects dominate. With further increases in size there is thus a levelling out or even fall-off in complex stability as the stability is now controlled by electronic effects.

### SIZE-SELECTIVITY IN THE TETRAAZAMACROCYCLES

Molecular mechanics (MM) has indicated that the hole-sizes of the tetraazamacrocycles increases monotonically with increasing size of the macrocyclic ring as shown in Fig. 1. If the metal ions are constrained to lie in the plane of the macrocycle, we would expect that large metal ions would be complexed most strongly by the larger tetraazamacrocycles, while smaller metal ions would be most strongly complexed by the smaller tetraazamacrocycles. Figure 7 shows that this is not so. The change in complex stability,  $\Delta \log K$ , for passing from the macrocycle 12-ane $N_4$  to 13-ane $N_4$  is plotted as a function of  $r^+$  in Fig. 7, and it is seen that as macrocyclic ring size is increased, so the complexes of the metal ions decrease in stability with increasing size. This result appears to be generally true for increasing macrocyclic ring size, as is also seen in Fig. 7 for the pair of ligands DOTA and CYTA, which are

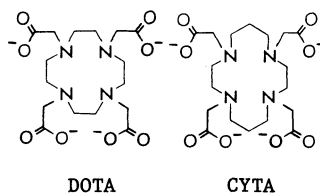
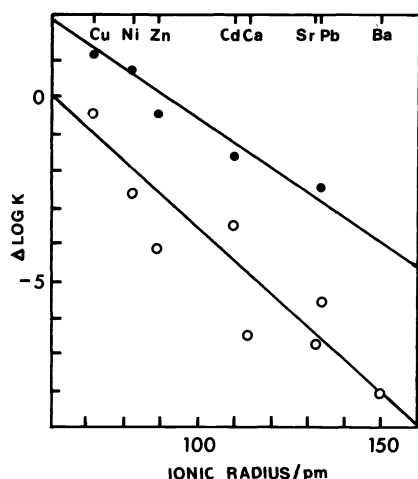


Fig. 7. Change in complex stability,  $\Delta\log K$ , as a function of metal ionic radius, as the size of the chelate ring is increased from five- to six-membered in macrocyclic complexes. The pairs of ligands where the increases are occurring are 12-aneN<sub>4</sub> and 13-aneN<sub>4</sub> (●) (see Fig. 1) and DOTA and CYTA (shown at right) (○).

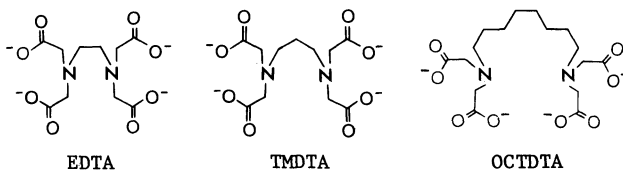
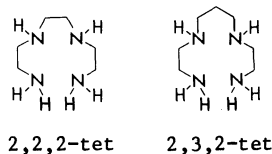
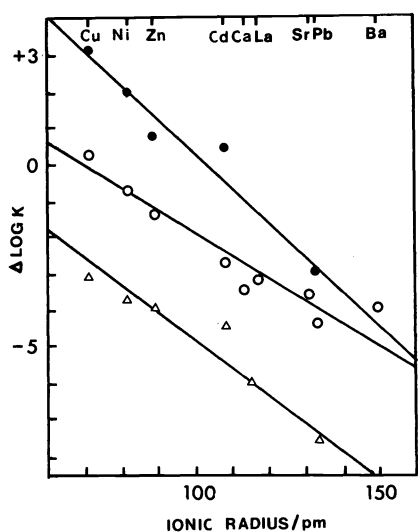


Fig. 8. Similar relationships to Fig. 7, for open-chain ligands. Ligand pairs are 2,2,2-tet and 2,3,2-tet (●), EDTA and TMDTA (○), and EDTA and OCTDTA (Δ).

tetraazamacrocycles with N-acetate groups. However, as seen in Figure 8, exactly the same type of result is found for open-chain ligands. In Fig. 8 is plotted  $\Delta\log K$  for the pairs of ligands 2,2,2-tet and 2,3,2-tet, and EDTA and TMDTA, as a function of  $r^+$ . Figure 8 suggests that the important factor in controlling complex stability in the tetraazamacrocycles is not the size of the macrocyclic ring *per se*, but rather the size of the chelate rings formed on complex-formation. Increase of chelate ring size leads to a greater degree of complex destabilisation for larger than for smaller metal ions, and is independent of whether the chelate ring is part of a macrocyclic ring or not. Examination of a large amount of literature data on formation constants suggests that this statement is generally true, at least where the donor atoms in the chelate ring whose size is being varied are nitrogen and/or oxygen.

The effect on complex stability of increasing chelate ring size appears to carry over to ring sizes larger than six. In Fig. 8 is shown the relationship of  $\Delta\log K$  versus metal ionic radius for the pair of ligands EDTA and OCTDTA. The relationship between  $\Delta\log K$  and  $r^+$  for EDTA and OCTDTA is very similar to that for EDTA and TMDTA, except that it is displaced downwards from the latter relationship, running almost parallel to it. Examination of the literature (ref. 19) shows that the drop in complex stability with increasing metal ion size in passing from EDTA to TMDTA is due entirely to a drop in the enthalpy contribution to the free energy of complex-formation. It is thus reasonable to interpret (ref. 13) such a drop in terms of steric strain. Further increases in chelate ring size produce drops in complex stability which are entirely due to entropy changes. It thus seems that the latter effects are caused by the increase in configurational entropy of the ligand as the chain length of the bridging polymethylene group increases. We have used Molecular Mechanics (ref. 13) to rationalize the metal ion size-selectivity of 14-aneN<sub>4</sub> relative to 12-aneN<sub>4</sub> complexes. These calculations suggest that the six-membered chelate ring is able with very small metal ions to have all its hydrogen atoms in the energetically more favoured staggered position. However, as the size of the metal ion increases, the hydrogens are increasingly forced into the less favourable eclipsed position. There is thus an increase in strain energy, and a decrease in complex stability. For five-membered chelate rings, no such favourable arrangement with all

the hydrogens staggered is possible, and the effect of increase of metal ion size is much less marked. A particularly satisfying aspect of the MM calculations was that the preference for larger metal ions to coordinate to 12-aneN<sub>4</sub>, rather than 14-aneN<sub>4</sub>, was indicated by these calculations *before* the formation constant data became available (ref. 13,15) to substantiate this. The MM approach can be used to calculate total strain energy,  $\Sigma U$ , of the complex as a function of metal ion size, as seen in Fig. 9 (ref. 6, 13, 15). The sharper the curve of  $\Sigma U$  versus M-N bond length, the sharper the metal ion size-selectivity. Figure 9 shows that the best-fit size of metal ion for fitting into the small 12-aneN<sub>4</sub> is actually larger than for 14-aneN<sub>4</sub>, as indicated by the minima in the respective  $\Sigma U$  versus M-N length curves. At the same time, the  $\Sigma U$  versus M-N length curve for 12-aneN<sub>4</sub> is flatter than that for 14-aneN<sub>4</sub>, so that 12-aneN<sub>4</sub> should display a greater tolerance to variation in metal ion size, in accord with experience. The smaller macrocycle achieves this by adopting the +++ conformation, shown in Fig. 9. The metal ion wears the +++ conformer of 12-aneN<sub>4</sub>, like a hat, and lies some 50 pm above the plane of the four nitrogen donors. Models show that the +++ conformer of 12-aneN<sub>4</sub> is very flexible, unlike any of the conformers of 14-aneN<sub>4</sub>, so that 12-aneN<sub>4</sub> is much more able to adapt to a wide range of metal ion sizes. The most stable conformer for 14-aneN<sub>4</sub> complexes is, except for very large metal ions, the +--+ conformer, shown in Fig. 9, which is rather rigid.

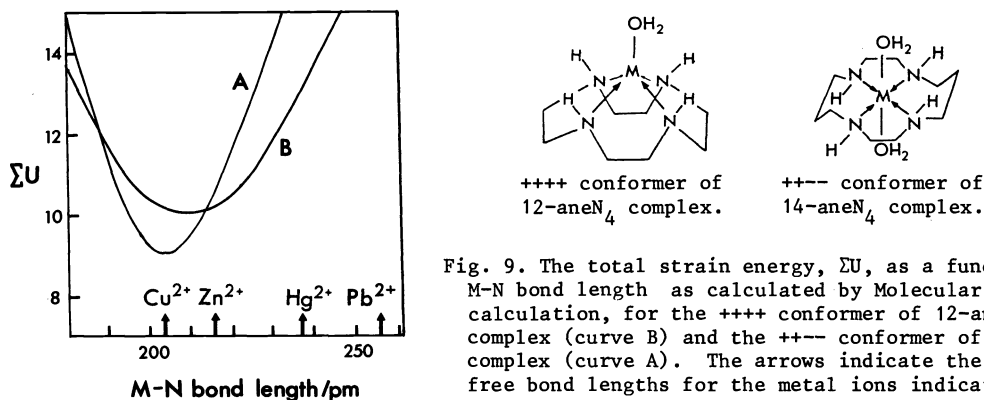
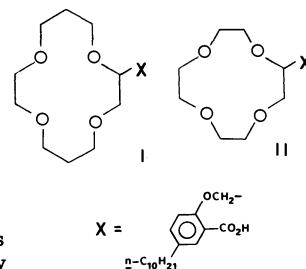


Fig. 9. The total strain energy,  $\Sigma U$ , as a function of M-N bond length as calculated by Molecular Mechanics calculation, for the +++ conformer of 12-aneN<sub>4</sub> complex (curve B) and the +--+ conformer of 14-aneN<sub>4</sub> complex (curve A). The arrows indicate the strain-free bond lengths for the metal ions indicated.

The effect of increasing chelate ring size on metal ion size selectivity of the ligand appears to be present for all ligands so far examined which have nitrogen and/or oxygen donors. Thus, we can now expect to find, which was previously rather puzzling, that a small metal ion such as beryllium(II) complexes more strongly with the malonate ion, which forms a six-membered chelate ring, than the analogous oxalate, which forms a five-membered ring (ref. 19). Similarly, the fact that the crown ether I extracts the small lithium ion from the aqueous to the organic phase with an unprecedentedly high selectivity over the other alkali metal ions is to be expected, whereas crown ether II shows only a small selectivity for lithium (ref. 26).



The increasing selectivity for small metal ions as chelate ring size increases appears to level off or even reverse after a number of five-membered chelate rings have been converted into six-membered. For the tetraazamacrocycles this occurs after two such increases in ring size have been made, as seen in Fig. 10 below. For the open-chain tetraamines the reversal occurs after one such ring-size change (ref. 14), whereas for increasing chelate ring size in EDTA complexes by exchanging the acetate groups for propionate, the progressive favouring of small metal ions persists all the way up to the maximum number of four such changes. It seems likely that the reversals are due to steric crowding caused by the extra methylene

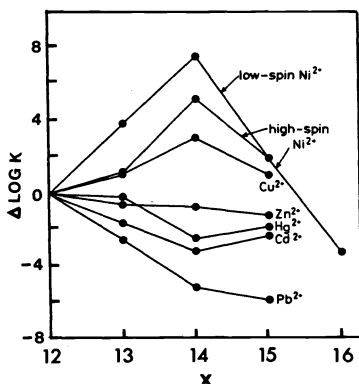


Fig. 10. The change in complex stability,  $\Delta \log K$ , for the X-aneN<sub>4</sub> tetraazamacrocycles, relative to  $\log K_1$  for the 12-aneN<sub>4</sub> complex, as X increases from 12 through 15, plotted as a function of X. Reproduced with permission from reference 14.

groups, which for small metal ions overwhelms the effects caused by whether the hydrogens are able to adopt staggered, or are forced into eclipsed, orientations. The steric crowding effects where a large number of six-membered chelate rings are present has been demonstrated by MM calculations on polyamine complexes of Ni(II) (ref. 20).

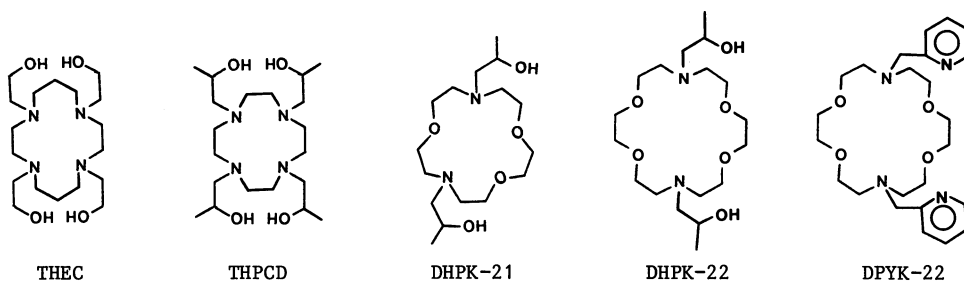
### APPLICATIONS IN LIGAND DESIGN

From the foregoing discussion one can conclude that the following two general rules hold in relation to control of selectivity on the basis of metal ion size:

- 1) The addition of neutral oxygen donor containing groups to ligands will increase the selectivity of the ligand for large metal ions relative to small. This change will occur irrespective of whether the neutral oxygen donor forms part of a macrocyclic ring or not in the newly formed ligand. However, in general the size-selectivity produced will be sharper for macrocyclic structures than for open-chain ligands.
- 2) Increase of chelate ring size from five- to six-membered will favour ligand selectivity for small metal ions over large. This effect is also independent of whether the ligand is a macrocycle or not. The increase in selectivity for small metal ions with increasing chelate ring size may slow or even reverse after a number of such increases in chelate ring size have been made. So far the effect has not been established for chelate rings containing donor atoms other than nitrogen and/or oxygen.

#### Ligands with pendent donor groups

In terms of the above two ligand design rules, the ligand THEC, synthesized by us (ref. 9), is something of a contradiction. It has pendent donor groups bearing neutral oxygen donors, which should favour large metal ions but disfavour small, while the formation of six-membered chelate rings should have the opposite effect on complex stability with respect to metal ion size. The outcome of these features is that THEC does not complex particularly well with anything, although it does have the merit of complexing metal ions very rapidly. In terms of the above two rules, an obvious design change to THEC is to bring down all the chelate rings to five-membered, which should shift the selectivity in favour of large metal ions. This is a worthwhile change in terms of our current interest in developing reagents for the treatment of lead poisoning. A current drawback with the presently used reagent, EDTA, is its low Pb(II)/Zn(II) selectivity (ref. 17) (i.e.  $\log K_1$  for EDTA with Pb(II) minus  $\log K_1$  for Zn(II)) of only 1.6 log units. Thus, the selectivity for the large Pb(II) ion over the small Zn(II) ion changes from -0.2 in THEC to +2.2 log units in THPCD. What is even more remarkable is that this apparently small structural change takes  $\log K_1$  for Pb(II) from 6.3 in the THEC complex (ref. 9) to 15.7 in the THPCD complex (ref. 25), an increase in stability of 9.6 log units. However, the Pb(II)/Zn(II) selectivity of THPCD at 2.2 log units is still too low. We suspected that what was needed here was an increase in macrocyclic ring size, and so turned to macrocycles with pendent donor groups based on fifteen- and eighteen-membered rings.



One finds (ref. 27) that Pb(II)/Zn(II) selectivity in macrocycles with fifteen-membered rings such as DHPK-21 is still too low, being 1.8 log units in DHPK-21 itself. A switch to eighteen membered rings such as those in DHPK-22, DAK-22, and DPYK-22 brings much better Pb(II)/Zn(II) selectivities in the vicinity of 5 log units (ref. 8, 25, 28), and in the case of DPYK-22 and DAK-22 sufficiently strong complexing of Pb(II), so that these two ligands are currently being tested for use in the treatment of lead poisoning.

#### The nine-membered macrocyclic ring

Molecular mechanics calculations show (ref. 16) that the nine-membered macrocyclic ring of the 9-aneN<sub>3</sub> type fits best onto small metal ions. The small ring is more rigid than larger macrocyclic rings, and steric strain increases rapidly with increasing metal ion size. The presence of these very small macrocyclic rings may thus outweigh other considerations which might have favoured large metal ions. Thus, if we add a bridging ethereal oxygen to en to give 9-aneN<sub>2</sub>O (ref. 11), the tendency is towards greater increases in complex stability for smaller metal ions, rather than for larger metal ions as might have been expected.

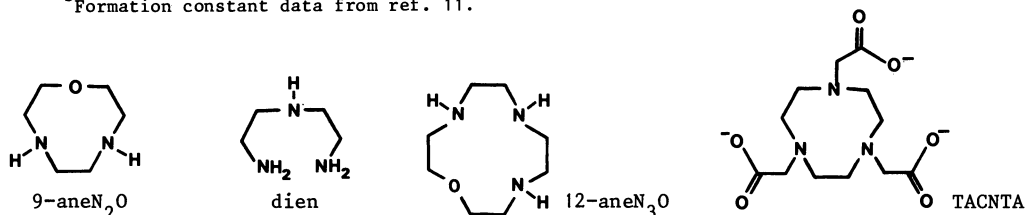
The value of  $\Delta \log K$  for going from en to 9-aneN<sub>2</sub>O varies a little erratically with  $r^+$ . Just how much the nine-membered ring perturbs the normal variation of  $\Delta \log K$  with  $r^+$  is seen for adding a neutral oxygen to dien to give 12-aneN<sub>3</sub>O in Table 1, where a strong increase in  $\Delta \log K$  with  $r^+$  is observed.

TABLE 1. Change in complex stability on addition of a bridging ether group to polyamines to give the corresponding mixed-donor macrocycles

metal ion	$r^+$ (pm)	$\log K_1$		$\Delta \log K$	$\log K_1$		$\Delta \log K$
		en	9-aneN <sub>2</sub> O		dien	12-aneN <sub>3</sub> O	
Cu(II)	71	10.50	10.86	+0.36	15.90	15.85	-0.05
Ni(II)	82	7.31	8.49	+1.18	10.50	12.15	+1.65
Zn(II)	88	5.87	6.36	+0.49	8.80	10.53	+1.73
Cd(II)	109	5.62	4.48	-1.14	8.30	10.78	+2.48
Pb(II)	133	5.04	5.17	+0.13	7.56	11.54	+3.98

<sup>a</sup>Formation constant data from ref. 19, except for Pb(II), ref. 29.

<sup>b</sup>Formation constant data from ref. 11.



The Ni(III) ion is very small, and appears to experience difficulty, like the Co(III) ion, in packing ligands around itself. An important factor in stabilising Ni(III) and Co(III) against reduction to the larger and less sterically troubled Ni(II) and Co(II) ions is thus going to be how well the ligand can pack around the small metal ion. The ligand TACNTA above packs very efficiently (ref. 30), both because of the 9-aneN<sub>3</sub> ring, and also because the acetate group packs very efficiently. We were thus able (ref. 30) to determine the crystal structure of the stable Ni(III) complex of TACNTA, which has extremely short Ni-N bonds of 193 pm, which MM calculations show is permitted only by the packing efficiency of the ligand.

We are at present continuing with our program of MM calculations aimed at understanding the role of steric crowding of ligands around metal ions in complex stability. At the same time, we are attempting to synthesize novel ligands to test out ideas on metal ion size-selectivity and improve our understanding of ligand design.

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