The development of mixed donor macrocyclic systems for metal-ion discrimination

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Abstract - As part of an overall program concerned with investigating the factors underlying heavy-metal ion recognition, we have developed strategies for observing and maximizing discrimination between transition and other heavy metal ions of interest. One aspect of our research program has been to investigate metal ion complexation across a matrix (or part of a matrix) of related mixed donor macrocycles and to search for stability maxima at different points of the matrix.

The present discussion has been limited to consideration of (pentadentate) ligand systems of types (1)-(16) in which (I) the donor atom pattern, (II) the macrocyclic hole size, and (III) the degree of ring substitution are varied. By reference to specific studies, the influence of each of these parameters in turn on the properties of particular metal ion systems is discussed.

The donor atom pattern present may have a dramatic effect on complex stability. A comparison of the log K values for the 1:1 Cu(II) complexes of nine 17-membered macrocyclic ligands (in which the donor atom set is systematically varied) indicates that the stabilities vary by up to ten orders of magnitude along the series. The use of related donor set variation to achieve high discrimination for Ag(I) over Pb(II) is also described.

Previous studies have shown that macrocyclic ring size variation may induce dislocation behaviour (leading to metal-ion discrimination) for Zn(II) and Cd(II) complexes of the present type. In an extension of these studies, involving a wider range of ligand derivatives, additional examples of such dislocation behaviour have been documented.

In another study, the effect on the metal ion discrimination behaviour of appending N-benzyl substituents to the 17-membered O_2N_3 donor macrocycle (7) has been investigated. Log K data for the 1:1 complexes of this ligand with Co(II), Ni(II), Zn(II), Cd(II), Pb(II), and Ag(I) have been obtained in 95% methanol. As expected, most of the stability constants for this hindered species tend to be much lower than those for the corresponding parent (unsubstituted) macrocycle. Indeed, for the first five metals mentioned above, log K values of 4.3 or less were obtained for the complexes of the benzylated ligand. In contrast, for the Ag(I) complex of this species, the log K value is 9.3. Inspection of a molecular model suggests that this high selectivity for Ag(I) may arise because this ion "triggers" a major ligand conformational change to produce a sterically locked conformation ideally suited for Ag(I).

INTRODUCTION

The coordination chemistry of polydentate organic ligands has now been investigated for about a century. In view of this it is perhaps surprising that it is still often difficult to predict with confidence the relative binding preferences of many such ligands towards particular metal ions. This is especially so when mixed donor atom sets are present. Much of the difficulty arises because of the number of (often interdependent) variables associated with multidonor ligand types. These include the particular donor atom set present, the number and sizes of the chelate rings formed, the flexibility of the system, the relative positions of the donor atoms and the nature of the ligand backbone (including the types of substituents present). For macrocyclic systems, the macrocyclic ring size may be another important parameter. Thus, compared to their open chain analogues, cyclic ligands have additional stereochemical constraints resulting from their cyclic nature which may influence metal-ion binding and hence thermodynamic discrimination.

There are advantages in the use of mixed donor macrocycles for metal-ion recognition
studies. First, the complexes do not show the extreme kinetic and thermodynamic
stability often exhibited by, for example, N_4-donor systems. Secondly, with cyclic
systems solution speciation tends to be simpler than for open chain ligands; in many
instances, 1:1 (metal:ligand) complex formation predominates.

It is noted that a range of "classical" reagents already exist which exhibit specificity
towards particular heavy metals; however, frequently their development has been largely
fortuitous rather than the outcome of a systematic program of research.

Design strategies

Over recent years, we have been concerned with the development of design strategies for
new macrocyclic ligand systems which are able to recognize particular transition and
post-transition metal ions (ref. 1). An important aspect of our approach has been to use
differences in log K values as both a monitor and a control of the organic synthetic
program. That is, starting from a particular macrocyclic ligand chosen on the basis of
its likelihood of giving rise to discrimination, related derivatives are synthesized in a
systematic "tuning up" process of any discrimination observed. A typical three-
dimensional structural matrix might exhibit variation of macrocyclic hole size along one
direction, increasing macrocyclic ring substitution along another and variation of donor
atom type along a third; however other combinations are also possible.

The "matrix" procedure enables the effects of incremental structural variations on log K
differences to be followed; this very often leads to a fuller understanding of the subtle
factors controlling particular observed behaviour. Thus the aim of the studies has not
only been to achieve metal-ion recognition (and/or discrimination) but also to understand
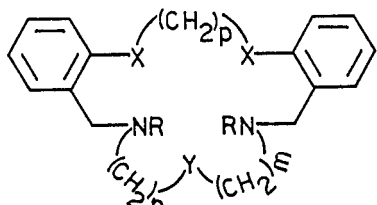the nature of such recognition when it is observed.

Emphasis in our studies has usually been given to full elucidation of the relevant metal-
ion chemistry of the ligand systems. In particular, as well as thermodynamic (mainly log
K) measurements, formation and dissociation kinetics, X-ray and molecular mechanics have
all contributed to the "tuning" process in particular studies.

By reference to individual studies, three features of the use of the above approach to
achieve metal ion recognition are now illustrated. These involve the effect of variation
of (i) the donor atom set present, of (ii) the macrocyclic ring size, and of (iii) the
ligand substitution pattern, on particular metal ion recognition and/or discrimination
behaviour.

DONOR ATOM SET DISCRIMINATION

Cu(II) complexes

The effect of donor atom variation on complex stability is well illustrated by the Cu(II)
complexes of (1)-(9) in which the donor atom sequence is systematically varied (ref. 2).
Stability constants for the 1:1 copper complexes were determined in 95% methanol and a
summary of the respective values is given in Fig. 1. As expected, the stabilities are
quite dependent on the donor atom set present - with the values spanning 10 orders of
magnitude! It is evident from the data that the contribution of the respective donor
atom types to particular copper complex stability falls in the order NH(aliphatic) >
NH(anilino) > S > O.

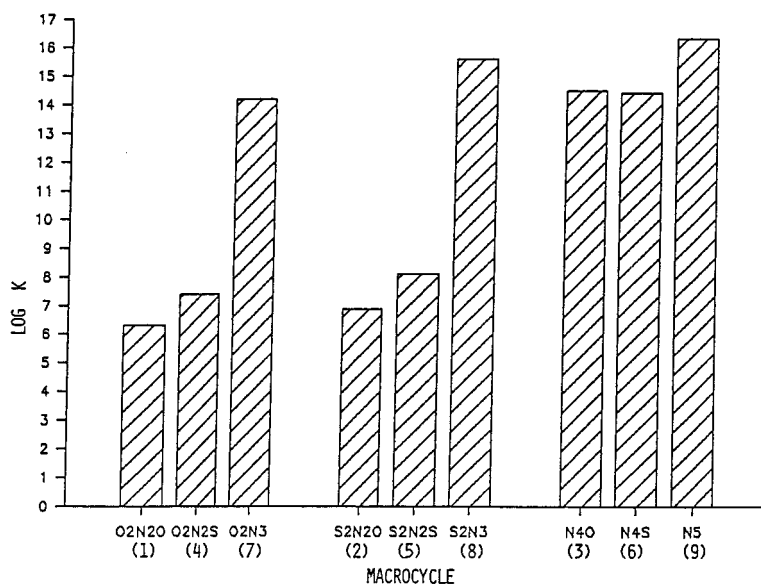|	X	Y	m	n	p	R
(1)	O	O	2	2	2	H
(2)	S	O	2	2	2	H
(3)	NH	O	2	2	2	H
(4)	O	S	2	2	2	H
(5)	S	S	2	2	2	H
(6)	NH	S	2	2	2	H
(7)	O	NH	2	2	2	H
(8)	S	NH	2	2	2	H
(9)	NH	NH	2	2	2	H
(10)	O	NH	2	4	2	H
(11)	O	NH	3	3	2	H
(12)	O	NH	2	2	4	H
(13)	O	NCH3	2	2	2	CH3
(14)	O	NCH3	3	3	2	H
(15)	O	NH	2	4	2	H

Fig. 1. The relative stabilities of the 1:1 Cu(II) complexes of (1)-(9) in
95% methanol [L = 0.1; (C2H5)4ClO4] at 25 °C.

Ag(I) and Pb(II) complexes

Studies of the interaction of Ag(I) and Pb(II) with ligands of the type just discussed
have also been performed. Calorimetric investigations of the interaction of silver
nitrate with a number of these macrocycles in acetonitrile clearly demonstrated the
marked preference of a thioether over an ether donor for this soft metal ion (ref. 2).
From the enthalpic data, it was deduced that the silver-thioether affinity is comparable
to that of a secondary amine group for this ion.

In agreement with the above, it is apparent from the log K data given in Fig. 2 that
substitution of a sulfur for an oxygen donor in the 17-membered ring framework does
result in the expected increase in stability for the silver complexes; moreover, a
similar enhancement does not occur for the complexes of Pb(II) (ref. 4). Thus such a
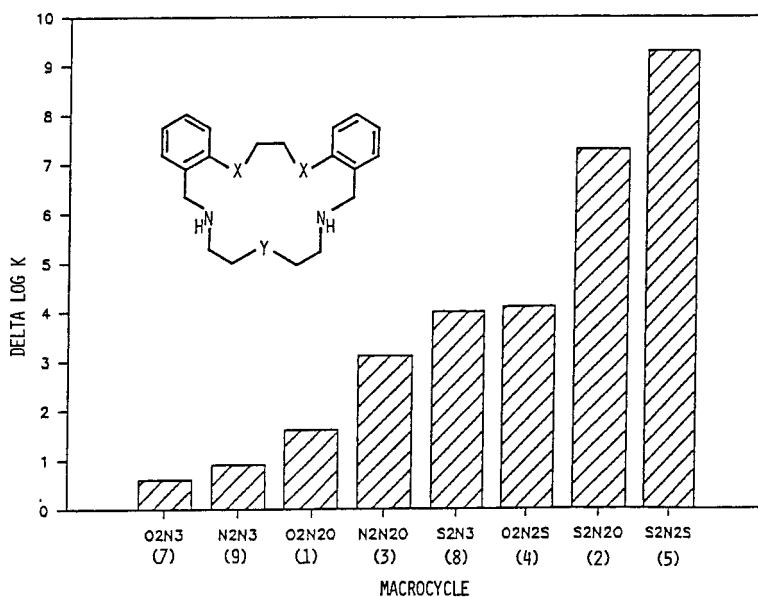situation is ideal for maximizing discrimination between these ions by donor set

Fig. 2. Stability differences (Δlog K) between corresponding Ag(I) and
Pb(II) complexes - in each case the Ag(I) complex is more stable. Log K
values determined in 95% methanol [L = 0.1; (C2H5)4ClO4].

"tuning". Hence the stability difference between the complexes of these metals with the O_2N_3-donor ring (7) is of the order of 10 in favour of Ag(I). However, stepwise incorporation of thioether sulfur donors in the ligand framework results in increasing discrimination for this ion. In the case of the (terminal) S_3N_2-ligand system (5), a discrimination of about 10^9 is achieved. Another aspect of the data presented in Fig. 2 needs to be noted. Inspection of the respective log K values indicates that replacement of a N_3-fragment by an N_2Y-one (Y=O or S) results in a consistent lowering of the stabilities of the various Pb(II) species but has much less effect on the corresponding Ag(I) complexes. The latter effect, which aids the discrimination process, may be a reflection of the well known affinity of Ag(I) for a "linear diammine" coordination geometry.

In summary, both the above studies demonstrate the extremely large stability differentials that may be achieved solely through donor atom variation within a given ligand framework. When used in conjunction with ring-size variation (see below), the combined procedures provide a potentially very powerful means for achieving metal-ion discrimination.

RING SIZE VARIATION AND DISLOCATION DISCRIMINATION

A mechanism for discrimination studied in some depth by the author's group involves the occurrence of "dislocations" along a series of closely related ligands (refs. 5-7). Such "dislocations" occur when the gradual change of properties along the ligand series induces a sudden change in coordination geometry for the complexes of adjacent ligands.

The occurrence of dislocation behaviour at different points along a ligand series for different metal ions may form a basis for discriminating between these ions. Recently, we have expanded our initial investigations (refs. 4 and 8) of this mechanism by extending the range of mixed-donor ligand systems used in the study. The subtle factors underlying such discrimination have been elucidated using a combination of solution equilibrium, kinetic, nmr, molecular mechanics, and X-ray diffraction techniques. The results have allowed a more complete evaluation of structural influences on the inducement of dislocation behaviour within this general category of ligand.

Ni(II) complexes

In the previous study, the thermodynamic stabilities of the Ni(II) complexes of the 17- to 19-membered rings (7), (10) and (11) were determined in 95% methanol: the respective log K values along this series are 10.0, 9.8 and 6.4 (ref. 5). The drop in stability between the complex of the 18- and that of the 19-membered ring appears greater than expected solely for the substitution of a six-membered chelate ring for a five-membered ring. Hence, the behaviour is in accordance with a structural dislocation having occurred between these complexes.

Molecular mechanics and other evidence suggests that the 17- and 18-membered ring complexes have similar octahedral geometries in which all donor groups of the respective macrocycles coordinate and in which the three nitrogen donors are arranged facially. In each case one coordination site appears to be filled by a solvent molecule. Indeed, an X-ray study shows that this occurs in the complex of (7) and also confirms that the three amine donors in this species are facial. In contrast, for the complex of (11), the evidence suggests that the amine donors are arranged meridionally.

From the molecular mechanics investigations it is evident that the above dislocation behaviour is largely associated with steric crowding involving the two 6-membered chelate rings formed by the three amine donors of (11). With respect to this, it is significant that a similar dislocation was not observed between the complexes of the 17- and 19-membered ring structures (7) and (12); however, two 5-membered chelate rings (involving the N_3-chain) are retained in the latter complex. That is, in this species the 19-membered ring is achieved by increasing the number of methylene carbons between the oxygen rather than between the amine donors; in this case, the log K difference between the nickel complexes of (7) and (12) is only about 0.3. This result thus supports the conclusion that the coordination geometries adopted by the O_2N_3-donor ligand series are largely dictated by steric factors involving the chelate rings formed by the respective N_3-backbones.

Zn(II) and Cd(II) complexes

Based on the results of a preliminary investigation (ref. 6), an extensive series of studies involving the Zn(II) and Cd(II) complexes of the 17- to 19-membered macrocycles (7), (10), (11), (13)-(15) are now complete (ref. 8). Fig. 3 summarizes the stabilities of all the 1:1 species studied.
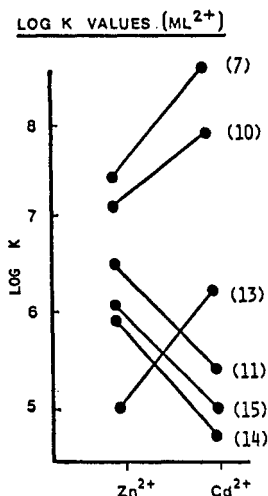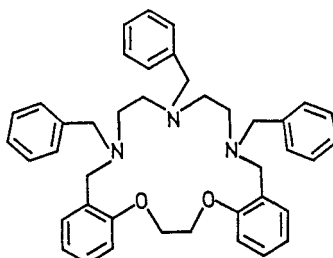
LOG K VALUES (ML^{2+})

Fig. 3. Comparison of the log K values for corresponding Zn(II) and Cd(II) complexes of a range of the present ligands showing the dislocation which occurs along the Cd(II) series. Log K values were obtained in 95% methanol [L = 0.1; (C$_2$H$_5$)$_4$NClO$_4$].

Each 17- and 18-membered ring yields a Cd(II) complex which is more stable than its Zn(II) analogue whereas this order is reversed for the respective complexes of the (three) 19-membered rings. Indeed, this latter order is that expected for simple polyamine species. X-ray diffraction structures of [Zn(NO$_3$)$_2$L] and [Cd(NO$_3$)$_2$L], [where L = (7)], have been obtained. In the Cd(II) complex the five donors of the macrocycle are bound to the metal while, for the Zn(II) species, the ether oxygens do not coordinate. Nmr and molecular mechanics evidence suggest that a similar situation persists in solution. Indeed, it seems likely that the ether oxygens make little contribution to the stability of any of the Zn(II) species shown in Fig. 3. In contrast, coordination of the ether donors does appear to occur in the Cd(II) complexes of the 17- and 18-membered rings. Namely, inspection of the log K values for the respective Cd(II) complexes (Fig.3) strongly suggests that a dislocation occurs between the complexes of the 18- and 19-membered rings. The molecular mechanics calculations are in accord with the observed dislocation being due to a change from coordination to non coordination of the ether oxygens (refs. 6 and 8). This behaviour may reflect the larger macrocyclic cavity associated with the 19-membered rings. Indeed, an X-ray structure determination of the Cd(II) nitrate complex of (11) shows that the ether functions do not coordinate in the solid state (ref. 8).

MACROCYCLE SUBSTITUTION AND DISCRIMINATION

In another investigation, oxygen-nitrogen donor macrocycles containing N-benzyl substitutents have been synthesized from the corresponding unsubstituted cyclic species (ref. 9). Macrocycle (16) is one such derivative. From X-ray data (ref. 10) and from inspection of a molecular model, it is clear that the tribenzyl substituents will greatly restrict the possible conformations able to be adopted by (16) on coordination to a metal ion.

(16)

Table 1. A comparison of log K values for the complexes of (7) and its
tribenzylated derivative (16).[a]

| | Macrocycle | |
	(7)	(16)
Co(II)	7.6[b]	<3.5
Ni(II)	10.0[b]	<3.5
Cu(II)	14.4[b]	_[c]
Zn(II)	7.5	∿3.5
Cd(II)	8.7	∿3.5
Ag(I)	8.7	9.3
Pb(II)	8.1	∿4.3

[a]Log K values determined in 95% methanol at 25 °C with I = 0.1;
$(C_2H_5)_4NClO_4$. [b]I = 0.1, $(CH_3)_4NCl$. [c]Precipitation.

Stability data for the complexes of (16) with Co(II), Ni(II), Zn(II), Cd(II), Pb(II) and
Ag(I) have been obtained. Table 1 gives a comparison of the respective values with those
for the parent (unsubstituted) ring (7). As expected, the stabilities of the complexes
of the sterically hindered ligand are generally much lower than those for the
unsubstituted parent ring; further, in general, little discrimination between individual
metal ions is evident. However, an exception is the observed considerable discrimination
for Ag(I) relative to the other metal ions investigated.

From a study of a space-filling molecular model, it appears that Ag(I) may induce a
major conformational change in the ring system to yield a rigid macrocyclic cavity [which
is apparently ideal for the binding of Ag(I)]. That is, the model can be adjusted into a
form which locks the five donors into an approximately pentagonal arrangement with all
the donor atoms suitably orientated for coordination to a central ion. Clearly, an
interconversion of this type will tend to be a high energy process and, once the latter
conformation is attained, there is little opportunity for the donor atoms to vary their
positions further.

A process of the type just described approximates to metal ion induced "conformational
switching". In the present case, this may be influenced by both the known moderate
stability of Ag(I) to ether bonds and possibly also by the induced cavity size being
close to the radius of Ag(I). However, it is stressed that in the absence of structural
data for the Ag(I) complex, the proposed mechanism must remain tentative.

Acknowledgement

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