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NEW MOLECULAR RECEPTORS FOR SMALL MOLECULES AND IONS

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The Royal Society of New South Wales

Leonard Francis Lindoy

LEONARD FRANCIS LINDOY 1937 -

Leonard Francis Lindoy was born on 20 April, 1937 in Wollongong, NSW. After secondary education at Marist Brothers High School, Kogarah, N.S.W., he studied at the University of New South Wales, graduating B.Sc. in 1963, and M.Sc. in 1966, working under the supervision of Professor S.E. Livingstone. With an American Army Scholarship he carried out research on metal complexes of sulfur-containing ligands with Stanley Livingstone as supervisor and graduated Ph.D. in 1968. He then proceeded to Ohio State University, Columbus, Ohio, where he worked on macrocyclic ligand complexes with Professor Daryle Busch. His first academic appointment was as Lecturer in Inorganic Chemistry at James Cook University in 1970, being promoted to Senior Lecturer (1974), Reader (1977), and then to a Personal Chair in 1987. In 1985 he was awarded the degree of D.Sc. by the University of New South Wales. In 1996 he was appointed as Professor and Head of Inorganic Chemistry at the University of Sydney, and since 1997 he has been Deputy Head of the School of Chemistry there. During periods of study leave he has been Visiting Professor at ETH, Zurich, and the University of Cincinnati, Cincinnati, Ohio, and he has spent many periods at Cambridge University, where he is currently a Senior Member of Robinson College. His main research interests have been in coordination chemistry, particularly in the design and synthesis of novel macrocyclic ligands and the chemistry of their metal coordination complexes, host-guest chemistry, metal ion and small molecule recognition and supramolecular chemistry, and he and his colleagues hold several chemical patents. He has been a Plenary Lecturer at numerous international conferences on macrocyclic and coordination chemistry. In 1993 he was President of the Australian Institute of Nuclear Science and Engineering.

Len Lindoy has been involved in numerous extramural activities concerned with various aspects of research management and funding, both nationally and internationally. He is a member of several national and international journal editorial boards, and is currently Chair of the Editorial Advisory Board of the *Australian Journal of Chemistry*, and Associate Editor of Molecular Engineering - *Supramolecular Science and Technology Reviews*. He has been involved in the organisation of several international conferences and seminars, and in 1994 was appointed as the Australian representative on the International Organizing Committee of the International Coordination Chemistry Conference (ICCC). He has acted as a Member or Chair of several institutional review panels, and in 1994 he was appointed Chair of the Physical Sciences Panel of the Australian Research Council (ARC), Large Grants.

Honours and Awards (Pre-2014)

1980	FRACI (Fellow of the Royal Australian Chemical Institute)
1988	Archibald Ollé Prize, RACI
1991	Burrows Award for Inorganic Chemistry, RACI
1991	Fellow of the Royal Society of Chemistry (UK)
1993	FAA (Fellow of the Australian Academy of Science)

1995	Gold Medal for Excellence in Research, Australian Institute of Nuclear Science & Engineering (AINSE)
1995	H.G. Smith Medal, RACI
1998	Visiting/Senior Member, with life tenure, Robinson College, Cambridge
1998	Liversidge Research Lecture, Royal Society of New South Wales
2000	Royal Society of Chemistry (UK) Lecturer for Australia and New Zealand.
2001	Archibald D. Ollé Prize (RACI), jointly with Dr. I.M. Atkinson
2003	Centenary Medal (Australian Government)
2004	Appointed Australian Representative, IUPAC Committee Division (VIII) of Nomenclature and Structure
2005	Honorary D.Sc., University of Woollongong
2005	Inaugural EastChem (Scotland) International Visiting Fellowship, Universities of Edinburgh and St. Andrews
2005	RACI Distinguished Fellowship Award
2006	Guest Professor, East China University of Science and Technology
2006	Honorary Professorships at Guizhou Normal University and Guizhou University, China
2006	Mercator Guest Professor at the Technical University, Dresden
2006	Lecture tour of five Universities in New Zealand (New Zealand Institute of Chemistry)
2008	Leighton Medal (RACI)
2008/2009	Royal Society of Chemistry Journal Grant, Foreign Chemistry, one month visits to University of Edinburgh
2008/2009	KOSEF Brain Pool Research Fellowship (Korea Science and Engineering Foundation, South Korea)
2008	Visiting Professor in Chemistry, University of Singapore
2009/2010	Centenary Lectureship and Silver Medal, Royal Society of Chemistry
2009	David Craig Medal, Australian Academy of Science
2010	Honorary D.Sc., Senatus Academicus, University of Edinburgh
2011	AINSE Honorary Fellow, Council of the Australian Institute of Nuclear Science and Engineering
2012	Appointed to the first Endowed Chair Professor of Gyeongsang National University, Jinju, South Korea
2012	'Leonard Lindoy 75th birthday' issue of Journal of Inclusion Phenomena and Macrocyclic Chemistry
2012	Guest of Honour, Fourth International Symposium on Coordination and

Supramolecular Chemistry, Chulalongkorn University, Bankok, Thailand

2012/2013 Erskine Fellow, University of Canterbury (NZ), for 3 months

2013 L.F. Power Lecture, James Cook University

2013 Honoured as an "Asian Pioneer" at the 15th Asian Chemical Society Congress

2013 Delivered an "Open Lecture" – On Knowledge Partnership" on nanotechnology at the Universitas Gadjah Mada, Yogyakarta, Indonesia

Biographical Source

Personal communication

Scientific Publications by L.F. Lindoy

Between 1964 and 2014 L.F. Lindoy had some 360 publications, including 2 books; he also had several patents.

NEW MOLECULAR RECEPTORS FOR SMALL MOLECULES AND IONS*

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ABSTRACT. New macrocyclic and cage-like receptors have been synthesised. The host-guest complexation behaviour of these species with metal cations and, in one instance, organic guests has been investigated using a range of physical and computational techniques. Emphasis in these studies has been given to the development of systems showing selective host-guest complexation behaviour.

KEYWORDS: heavy metal, selectivity, host-guest, macrocycle, cage.

Introduction

Although the recognition of ionic and molecular species is a unifying theme throughout nature's chemistry, it is only in comparatively recent times that a substantial effort has been expended on the design and synthesis of synthetic systems that might exhibit comparable recognition behaviour (Izatt *et al.*, 1991) (Martell *et al.*, 1994). In this paper, selected results from our ongoing studies are presented illustrating how organic systems have been designed to recognise, and in some cases discriminate for (or against), both individual transition metal ions as well as small neutral molecules.

Metal-Ion Recognition

It is now around one hundred years since Alfred Werner first elucidated the nature of metal-ion complexes. Despite this, and the innumerable studies that have taken place in the area since Werner's time, it still often remains rather difficult to predict the metal binding preferences of individual binding sites, especially when mixed donor atom patterns and/or irregular coordination site geometries are involved. It is worthy of note that sites of these latter types tend to be the rule rather than the exception in biochemical systems. Apart from gaining a fuller understanding of the role of metals in biology, there is a host of more practical reasons for undertaking studies of metal-ion recognition. An understanding of the area has implications for each of the following: the design and construction of sensing elements for metal-ion detection and measurement, the design of metal-ion separation processes in a range of industrial (including mining) applications, the control and clean-up of heavy metal pollution as well as for medical use in the treatment of heavy metal poisoning in humans. Laboratory applications include chromatographic separations and a range of classical metal analysis procedures.

How does one tackle the problem of designing new reagents for metal ions of interest? First there are some long established guidelines that one can heed. The HASB (hard acid/soft base) proposal of Pearson (Pearson, 1990) along with the older 'a' and 'b'

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classifications (Ahrland *et al.*, 1958; Ahrland, 1996) provide a general guide as to what donor types will show especial affinities for what metal ions. This is a useful guide, particularly when single donor atom types are present; however, in the author's experience these classifications are not without problems (the unexpected low affinity of thioether groups for some soft metals but not others provides an example). The Irving-Williams stability order (Irving and Williams, 1953), also proposed by the Australians D. P. Mellor and L. Maley from work performed at Sydney (Mellor and Maley, 1947), in many instances also aids the prediction of the relative stabilities of the divalent metal complexes of metals from the latter half of the first-row transition series (namely, from manganese to zinc).

For some time our research has involved an investigation of the recognition behaviour of mixed donor macrocyclic ligands towards a range of industrially important metal ions such as cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), silver(I) and lead(II) (Ahearn *et al.*, 1996). A focus of our investigations has been the development of strategies for achieving discrimination between these ions but, more importantly, for understanding the nature of such discrimination when it is achieved. The use of macrocyclic ligands in such studies has two major advantages. First, it provides another parameter - the macrocyclic ring size - that can be employed in the tuning of a given ring for a metal ion of interest. Secondly, because of the inherent configurational restrictions associated with their cyclic nature, macrocyclic ligands tend to give rise to simpler solution speciation patterns for metal complexation than do their open chain analogues (Lindoy, 1989). Indeed, the former frequently yield simple 1:1 (metal:ligand) complexes as the only complex species present in solution. Such absence of complicated speciation considerably aids the investigation of stability patterns.

A very wide range of mixed-donor cyclic systems has now been investigated, with typical examples being illustrated by the four- and five-donor structures (**1**) and (**2**)*, where X and Y are nitrogen, oxygen and/or sulfur donors. It has proved advantageous in our studies to employ cyclic systems such as these that are of intermediate flexibility. This tends to limit the number of ligand conformations/configurations possible on binding to a metal, while still permitting ready uptake (and/or loss) of the metal with respect to the macrocyclic ring. Mixed donor sets are also often an advantage in this regard since they tend to reduce the very high kinetic and thermodynamic stabilities that are characteristic of, for example, many all nitrogen donor macrocyclic systems. Such high stabilities generally cause difficulties when undertaking solution equilibrium studies using conventional techniques.

Small Molecule Recognition

The strategies for designing synthetic receptors ('hosts') for binding small molecules ('guests') to a large degree parallel those discussed so far for obtaining new metal-ion receptors. However, in the former case, more complex-shape recognition may need to take place and covalent host-guest linkages are no longer appropriate if reversible binding is to be achieved. Weaker intermolecular forces (including hydrogen bonds, □-interactions and van der Waals interactions) between host and guest now become the order of the day (Whitesides *et al.*,1995).

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*Numbers in parentheses and in bold type here and in the rest of the text refer to the molecular structures illustrated in Fig. 1.

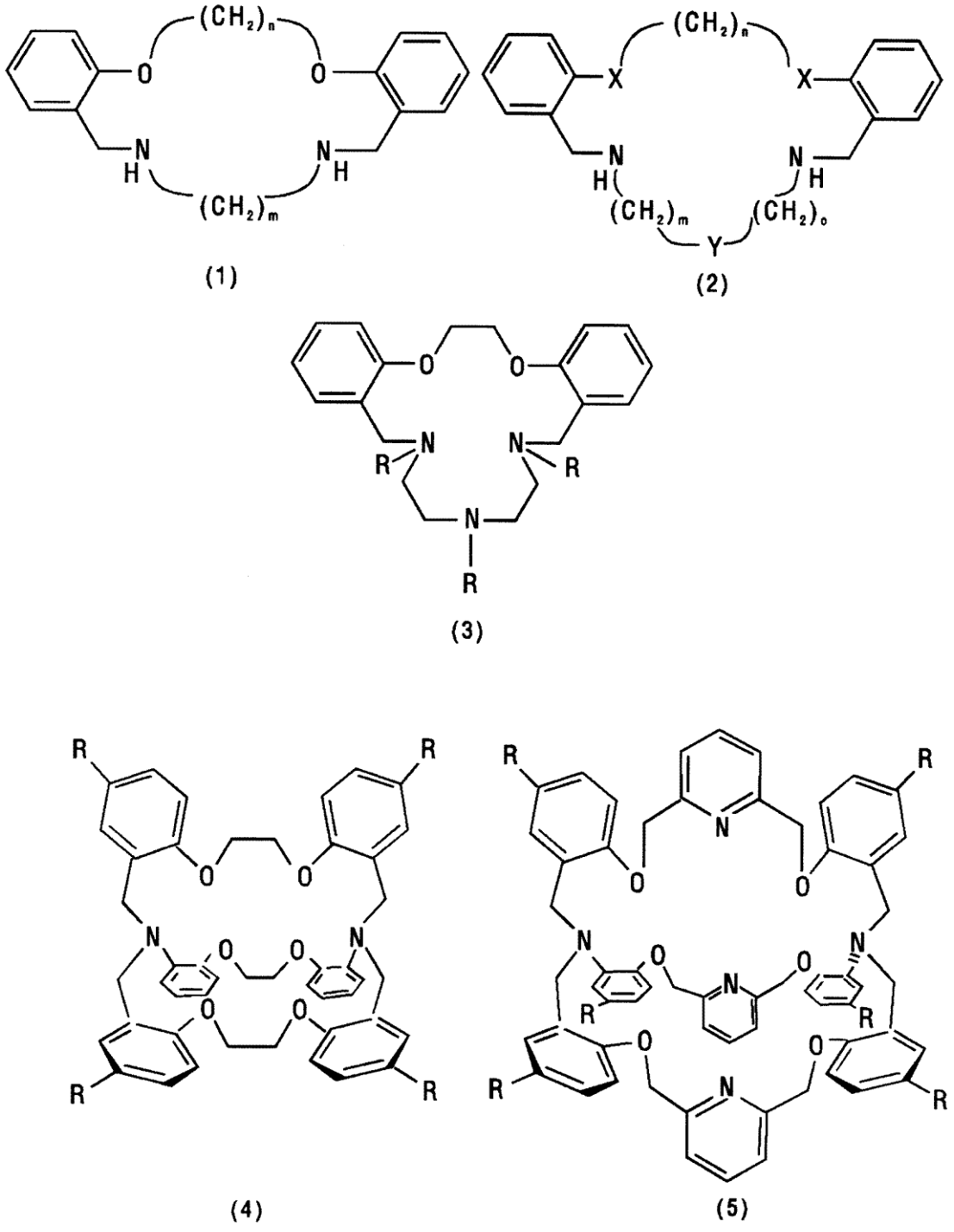

FIGURE 1. Structures of Molecular Receptors.

Variation of Structural Parameters to Achieve Metal-Ion Recognition

In our studies we have employed a general strategy for achieving metal-ion recognition that has involved the regular variation of structural parameters within a series of macrocyclic ligands of related type (Adam and Lindoy, 1992). More specifically, we have employed systematic variation of the macrocyclic ring size, the donor set present and/or the degree of substitution of the parent ring structure to 'tune' the affinity of a given ring type for a chosen metal ion. It is convenient here to exemplify each of these approaches separately; however, in many instances it is clearly advantageous to use variations of all three parameters simultaneously in order to maximise metal ion recognition. This is perhaps best illustrated by considering the process as one in which one moves stepwise within a ligand 3D structural matrix for which the axes are: macrocycle ring size, donor set type and degree of ring substitution. That is, stepwise movement within the matrix is used to maximise recognition behaviour.

Variation of Macrocyclic Ring Size

The variation of macrocyclic ring size in order to provide a macrocyclic cavity that matches the radius of a particular metal ion has long been employed (Lindoy, 1989) as a strategy for obtaining selectivity for individual metals based on their respective ionic or covalent radii. In general, strongest metal-ion binding occurs when the ligand's cavity best matches the radius of the bound metal ion. Despite this, it needs to be noted that such an approach is often far from straightforward. For systems that are not completely rigid, some contraction or expansion of the macrocyclic cavity may occur to meet the dictates of the bound metal which, in any case, may choose not to fully occupy the macrocyclic cavity.

In an earlier study, we employed the above 'hole-size match' strategy to obtain metal-ion recognition. Thus, X-ray structural analyses (and associated molecular mechanics modelling) indicated that the 14 - to 17-membered rings (**1**; n = m = 2), (**1**; n = 2, m = 3), (**1**; n = 3, m = 3) and (**1**; n = 2, m = 4) yield nickel(II) complexes of type $[NiLX_2]$ (X = Cl or Br) in which the metal ion occupies the respective macrocyclic cavities, with the X groups occupying *trans* (axial) positions such that each complex has a similar pseudo octahedral coordination geometry (Adam *et al.*, 1988).

The structural studies coupled with hole size calculations indicate that the 16-membered ring makes available a near ideal coordination cavity for this ion in its high-spin state. Accordingly, the respective stability constants (log *K* values corresponding to the formation of 1:1 complexes) for the interaction of this ligand series with nickel(II) in 95% methanol are 3.7 (14-membered ring), 5.4 (15-membered ring), 5.8 (16-membered ring) and ~3.5 (17-membered ring). Not unexpectedly, the rate constants for the dissociation of these complexes in acid follow the reverse order to these log *K* values.

A second strategy introduced by us uses variation of macrocyclic ring size to induce what we term 'dislocation discrimination'. This depends on an abrupt structural change in coordination behaviour being induced for one metal ion relative to another as the macrocyclic ring size is progressively altered. At the point of dislocation, the coordination geometry change may lead to an enhanced stability differential (or unusual stability order) between the complexes of the respective metals. This is best illustrated by means of an example.

An investigation of the formation of the zinc(II) and cadmium(II) complexes of the 16- to 19-membered macrocycles of type (**2**; X = O, Y = NH) (Adam, Dancey*et al.*, 1988)

TABLE 1

Log K *values (ML^{2+}) for the zinc II) and cadmium(II) complexes of the N_3O_2- donor (X = O, Y = NH) macrocycles of type (2) in 95% methanol,* I = *0.1 (Et_4NClO_4). at 25˚C*

Macrocycle	Ring Size	log*K* values Zinc(II)	Cadmium(II)
2; n = m = n = 2	17	7.5	8.5
2; n = 2, m = 2, o = 3	18	7.1	7.9
2; n = 2, m = 3, o = 3	19	6.6	5.3
2; n = 2, m = 2, o = 4	19	6.0	5.0

(Adam *et al.*, 1994) revealed that the relative stabilities of the 1:1 zinc(II) and cadmium(II) complexes in 95 percent methanol followed the overall pattern shown in Table 1. Thus, the 17- and 18-membered ring species yield cadmium(II) complexes which are in each case more stable than the corresponding zinc(II) complexes. However, for both 19-membered ring species this order is reversed. The crystal structures of $[Zn(NO_3)_2L]NO_3$ and $[Cd(NO_3)_2L]$, where L = (**2**; X = O, Y = NH, n = m = o = 2), show that all five donors of the macrocyclic ligand are bound to the metal in the case of the cadmium(II) complex while, for the zinc(II) species, the ether oxygens do not coordinate. The relative thermodynamic stabilities of these complexes [the cadmium(II) species is more stable than the zinc(II) species] is in accordance with similar structures to those found in the solid state persisting in solution - with donation from the ether oxygens appearing to make little (if any) contribution to the stability of the zinc(II) species. In contrast, a contribution does appear to be made in the case of the cadmium(II) complex. The overall stability pattern also suggests that the above situation (non-coordination of the ether donors in the case of the 17-membered zinc complex) also occurs for the corresponding 18- and 19-membered zinc(II) complexes.

Inspection of the log *K* values for the respective cadmium(II) complexes (Table 1) accords with the presence of a structural 'dislocation' occurring between the complexes of the 18- and 19-membered rings. Inspection of molecular models suggested that the observed dislocation may reflect a change from coordination to non-coordination of the ether oxygens on passing from the complex of the 18- to that of the larger 19-membered ring. In accordance with this, an X-ray structure determination of the cadmium(II) nitrate complex of this latter ring shows that non-coordination of the ether functions does occur in the solid state.

It should be noted that a similar stability pattern is observed for the related zinc(II) and cadmium(II) complexes of the analogous 17- to 19-membered, N_3S_2- donor macrocycles of type (**2**; with X = S, Y = NH) (Adam, Arshad *et al.*, 1994). That is, the 17- and 18-members of this series yield cadmium(II) complexes which are once again more stable than their zinc(II) analogues. While, as before, for the complexes of the 19-membered ring (**2**; X = S, Y = NH, n = 2; m = o =3), this order is reversed.

In summary, for both the N_3O_2- and N_3S_2-donor ring systems discussed above, it can be seen that the occurrence of a structural dislocation in the formation of the cadmium(II) complexes of the respective 19-membered rings, is reflected by a change in the metal recognition properties of these ligands (19-membered: cadmium < zinc) relative to their smaller ring analogues (17- and 18-membered: zinc < cadmium).

Variation of Donor Atom Set

As mentioned earlier, donor set variation has traditionally been employed in the design of ligands for the selective binding of metal ions of interest. In our metal discrimination studies we have also employed such a procedure; for example, we have employed donor atom variation within the 17-membered rings of type (**2**) in which X and Y were varied in a regular manner from NH to O to S. In one study of this type, it was our aim to maximise discrimination for silver(I) over lead(II) - two metals that are found together in nature.

The thermodynamic stabilities of the complexes of these metals were again measured potentiometrically in 95 percent methanol (I = 0.1, Et_4NClO_4) as the nature of X and Y in (**2**) was varied in a stepwise manner. The results are summarised in Table 2.

TABLE 2

Effect of donor set on log K *values on silver(I)/lead(II) discrimination for the complexes (ML^{n+}) of the 17-membered ring (**2**, n-m-o = 2) in 95% methanol,* I *= 0.1 (Et_4NClO_4), 25˚C.*

Ligand	Silver(I)	Lead(II)	Δlog*K*
2; X=S, Y=S (S_2N_3)	12.4	~3.1	~9.4
2; X=S, Y=O (S_2N_2O)	10.3	----	~7.3
2; X=S, Y=NH (S_2N_3)	~11.7	8.0	~3.7
2; X=S, Y=NH (O_2N_2S)	8.6	4.5	4.1
2; X=O, Y=O (O_3N_2)	7.1	5.5	1.6
2; X=O, Y=NH (O_2N_3)	8.7	8.1	0.6
2; X=Y=NH (N_5)	10.3	9.4	0.9

In the initial log *K* determinations, the values for the complexes of the 'parent' (17-membered) N_3O_2-donor ligand (**2**; X = O, Y = NH) indicated that little discrimination was evident between the complexes of the above metal ions (the Δlog *K* for the silver complex over the lead complex is less than an order of magnitude). On moving to the related 17-membered N_5-donor system (**2**; X = Y = NH), little improvement was observed even though the absolute log *K* values are higher in both cases. However, on moving to the system with X = O, Y = O, then discrimination for silver(I) increases (even though the overall values are lower). It is clear from this that the silver(I) ion is more tolerant towards a $NHCH_2CH_2XCH_2CH_2NH$ bridge (where X = O, in this case) than is lead(II); perhaps paralleling the well known tendency for silver(I) to form a simple diammine species.

Silver(I) is a soft metal ion while lead(II) is borderline (Ahrland, Chat and Davies, 1958) and hence it was reasoned that substitution of a thioether group for an ether group might further enhance the stability differential between the complexes of these ions. This was clearly found to be the case (Table 2). The stepwise replacement of sulfur for oxygen or nitrogen in positions X and Y of (**2**) results in a steady increase in the $\Delta\log K$ value in favour of silver. For the final compound in the series, namely the N_2S_3-donor ligand (which it is noted also contains a heteroatom other than NH in the X-position), the stability difference is now ~10^9!

The above result provides a powerful illustration of the effect that a 'tuning' strategy, involving the systematic variation of just one structural parameter (in this case the donor atom set), may have on achieving metal-ion discrimination of a high order.

X-ray diffraction structure determinations on the solid silver complexes of type $[AgL]NO_3$ [where L is a 17-membered ring of type (**2**) with X = S, Y = O] (Adam, Baldwin *et al.*, 1994; X = S; Y = NH (Kallert and Mattes, 1991); and X = S, Y = S (Kallert and Mattes, 1992) and the lead complex $[PbL(ClO_4)_2]$ [where L = (2), X = S, Y = NH] (Adam *et al.*, 1994) clearly reflect the results obtained from the solution stability studies. Namely, while all three silver complexes have similar structures in which the ligand 'wraps' tightly around the central metal ion such that all donor atoms of the respective ligands bind to silver to yield five-coordinate geometries, in the case of the lead complex the structure shows that macrocycle binding is much weaker. The cyclic ligand does not 'wrap' around the lead(II) ion but rather coordinates in an approximately planar fashion in which particular metal-donor atom contacts are somewhat elongated. Further, the coordination number in this complex is expanded to seven by the coordination of two perchlorate anions in 'axial' positions.

The difference between the X-ray structures of the lead complex and the silver complexes, thus accords with a weaker binding of (**2**; X = S, Y = S) in the case of the lead complex - a situation that fits well with the stability trends summarised in Table 1.

Ring Substitution

Effect of Ring Substituents

In an ongoing study, the effects of *N*-methylation and *N*-benzylation of the nitrogen sites of the parent 17-membered, N_3O_2-donor macrocycle (**2**; X = O, Y = NH) on the thermodynamic stabilities of the corresponding complexes of nickel(II), copper(II), zinc(II), cadmium(II), lead(II) and silver(I) have been determined under the conditions mentioned previously. The results are illustrated in Table 3. For the first five metal ions,

TABLE 3

Effect of N-substitution on log K *values* (ML^{2+}) *for the complexes of (**3**) with the metal ions shown in 95% methanol,* I = *0.1* (Et_4NClO_4), *25°C.*

Ligand	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Ag(I)	Pb(II)
3; R = H	7.6	10.0	14.4	7.5	8.7	8.7	8.1
3; R = CH3	<3.5	<3.5	----	5.1	6.1	10.3	6.6
3; R = Benzyl	<3.5	<3.5	----	~3.5	~3.5	9.3	4.3

the presence of the substituents [see (**3**)] leads to metal complexes of lower stability, with, in general, the presence of the bulky benzyl groups causing a larger reduction than the corresponding *N*-methyl substituents. This is the expected situation, reflecting the presence of steric hindrance to metal coordination. However, somewhat surprisingly, in the case of silver(I) a similar effect is not observed - there is even a small increase in stability for the complex of the benzylated ligand derivative with this ion.

In effect, the above behaviour amounts to the selective 'detuning' of the parent ring by *N*-alkylation for all the divalent metals, but not for monovalent silver(I). While the origins of this behaviour remain uncertain, they may parallel a previously documented observation that tetra-*N*-methylation of the N_4-macrocycle, cyclam, results in a product that stabilises the monovalent oxidation state of copper relative to its divalent state (Golub *et al*., 1995). Further work is in progress in our laboratory to confirm or otherwise whether this suggested parallel is in fact the case.

Overall, the discussion so far illustrates how macrocycle hole size, donor set type and degree of substitution can all be employed to influence markedly the discrimination behaviour of a macrocyclic ligand. Once again, it is stressed that the opportunity exists to vary more than one of these parameters during the tuning process, leading to 'synergisticly' enhanced discrimination in suitable cases.

Molecular Cages

We have also been involved in the design and synthesis of new 'cage' structures that contain three dimensional cavities for selectively binding 'guest' metal ions or small molecules. Relative to simple ligands, cages such as (**4**) are potentially able to present a more 'defined' cavity to an incoming guest of the above type. Namely, complementarity (both steric and electronic) with the guest ion or molecule is in principle able to be obtained more readily due to the three dimensional nature of the cage structure. This is an important advantage in terms of designing such systems for selectively binding a guest of interest.

In our initial studies, we observed that cages of type (**4**) are generally poor coordinating agents for metals such as the alkali metals (Atkinson *et al.,* 1996). From structural studies (Atkinson *et al.,* 1994) coupled with a molecular modelling investigation (that included DFT calculations) (Atkinson and Lindoy, 1998), the reason for the poor affinity of such cages for alkali metals has been elucidated. It is clear that these systems do not have an *endo* arrangement of the lone pairs on the nitrogen caps [as is illustrated by (**3**)] but rather an *exo-exo* arrangement is dictated by steric factors and this results in the lone pairs being orientated away from the central cavity. In turn, this has the consequence of forcing the benzyl $-CH_2-$ groups into the central cavity such that its volume is much reduced; the cavity is no longer large enough to accommodate an alkali metal ion.

As an aside, when one or two of the aromatic ring-containing 'straps' linking the terminal nitrogen atoms of the N_2O_6-cage (**4**; R = *t*-Bu) was replaced by an aliphatic strap of type $-CH_2CH_2OCH_2CH_2OCH_2CH_2-$, then uptake of individual alkali metals was observed to occur (Adam *et al.*, 1998). This behaviour is a direct consequence of the additional flexibility present in the new derivatives. This enables them to achieve *endo-endo* arrangements of the nitrogen bridgeheads (White and Skelton, 1998), with a concomitant increase in the cavity size available for binding an alkali metal ion. A series of solvent extraction experiments ($H_2O/CHCl_3$) involving the differential extraction of alkali picrate salts is now complete. These indicated that, under the conditions employed,

only the cages incorporating the aliphatic 'straps' were effective extractants of alkali metal picrates into the chloroform phase.

Small Molecule Recognition

As a direct extension of the above studies it was decided to expand the available cavity in the N_3O_2-cage in another way; namely, by insertion of a pyridyl moiety in the centre of each 'strap' [between the ether heteroatoms of (**4**)] to yield an extended cage of type (**5**) (Atkinson *et al*., 1997). For this product, molecular modelling indicated that the central cavity now approximated that of a 'slot', centred on the plane passing through the three pyridyl nitrogens (the calculations also confirmed that the *exo-exo* arrangement of the nitrogen caps remains strongly favoured).

The new cavity appeared ideal for insertion of flat aromatic-like rings. Indeed, consideration of its diameter as defined by the positions of the heterocyclic nitrogen atoms suggested that its dimensions were ideal for accepting a phloroglucinol guest which should be able to be suitably positioned to undergo hydrogen bonding, via its phenol hydrogens, to the trigonally orientated nitrogens. Accordingly, (**5**; R = *t*-Bu) was found to solubilise phloroglucinol in dichloromethane and chloroform. NMR evidence showed that it interacts in a 1:1 ratio with phloroglucinol, with the data in accord with this guest occupying the central cavity as postulated above. Molecular mechanics and semi-empirical molecular orbital (AM1) calculations also supported the reasonableness of such a host-guest structure. Further evidence for the role of hydrogen bonding in stabilising the above host-guest complex was obtained by repeating the experiment using the corresponding cage in which the pyridyl groups of (**5**) were replaced by three *m*-xylyl groups. In contrast to the previous case, there was no evidence for host-guest formation when this new cage was mixed with phloroglucinol.

Finally, NMR induced chemical shift data confirms that (**5**; R = *t*-Bu) interacts more strongly with phloroglucinol relative to a wide range of other mono-, bi- and tri-phenolic derivatives whose steric properties make them less than ideal for simultaneous binding to the trigonally disposed pyridyl nitrogens of (**5**). Clearly, both the steric and electronic properties of (**5**) result in it being an ideal synthetic receptor for phloroglucinol.

Acknowledgments

The author sincerely thanks his many students and collaborators, both past and present, for their contributions to the work outlined in this paper. Their names are given in the references cited in the text. In particular, he also acknowledges a major contribution from Assoc. Professor G.V. Meehan of James Cook University to the development of the 'cage' chemistry discussed in the latter section of this paper. The author also thanks the Australian Research Council for financial support.

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