

Molecular Mechanics Calculations and Metal Ion Recognition

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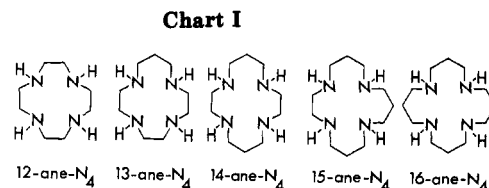
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An important idea in macrocyclic chemistry¹ and also in the chemistry of cryptates² is *size-match selectivity*, the idea that a metal ion will form its most stable complex with the member of a series of macrocycles where match between size of metal ion and macrocyclic cavity is closest. A classic example of size-match selectivity is seen in Figure 1, where formation constants³ of the crown ether 18-crown-6 (see Figure 2 for structures of ligands) are plotted for each metal ion as a function of its ionic radius.⁴ The maximum in complex stability at K⁺ can be interpreted in terms of its ionic radius fitting the cavity in the crown ether most closely. Some criticism of this interpretation⁵ has been offered, since with smaller macrocycles such as 12-crown-4 the maximum in complex stability is still at the K⁺ ion, rather than shifting to smaller ions such as Li⁺. In general, however, size-match selectivity is widely accepted⁶ as the most important factor in controlling metal ion selectivity in macrocyclic ligands.

In expectation of confirming this idea for the tetraaza macrocycles 12-aneN₄ through 15-aneN₄ (Chart I), we determined the missing formation constants with these ligands for the metal ions Ni^{II}, Cu^{II}, Zn^{II}, Cd^{II}, and Pb^{II}, which range in ionic radius⁴ from 0.49 [S = 0 Ni(II)] to 1.18 Å [octahedral Pb(II)]. The best fit hole sizes of the tetraaza macrocycles 12-aneN₄ through 16-aneN₄ had been estimated by De Hayes and Busch⁷ through molecular mechanics (MM) calculations where the M-N force constant *K* had been set to 0 in eq 1 to allow the ligand to dictate M-N bond length, which was then the best fit M-N length for coordinating to that particular macrocycle, as seen in Chart I. (We obtained^{8a} essential agreement with these hole sizes.)

Chart I shows where the metal ions might have been expected to form their most stable complexes on the basis of size-match selectivity. The strain-free M-N lengths are derived from MM calculations⁹ or crystal structures of the simple ammine complexes. The formation constants for each metal ion tended not to peak at the tetraaza macrocycle with a cavity that matched the size of the metal ion. Instead, behavior was as summarized in Figure 3, where the change in stability ($\Delta \log K$) for each metal ion relative to the 12-aneN₄ complex as the size of the macrocyclic ring is increased is plotted against the size of the macrocyclic ring. Figure 3 has a very regular pattern showing that as metal ions became *larger*, so their affinity for the *smallest* macrocycle 12-aneN₄, relative to the others in the series, increased. The ligand that would be expected



ideal bond length (Å) for fitting into ligand:	12-ane-N ₄	13-ane-N ₄	14-ane-N ₄	15-ane-N ₄	16-ane-N ₄
	1.83	1.92	2.07	2.22	2.38
strain-free M-N bond length of metal ion (Å):		Ni(II)(S=O) 1.91	Cu(II) 2.03	Zn(II) 2.15	Cd(II) Pb(II) 2.35 2.6

(metal ions are indicated below ligands into which they should fit best)

from size-match selectivity to form the most stable complex with each metal ion is indicated by an arrow in Figure 3. Only for Cu^{II} does the behavior appear to accord with expectations based on size-match selectivity.

In their estimation of the best fit M-N lengths for the macrocycles seen in Chart I, De Hayes and Busch considered⁷ only the trans-III conformer of the tetraaza macrocycles, seen in Figure 4. While we were obtaining^{8b} our "anomalous" (in terms of size-match selectivity) results for the tetraaza macrocycles, we were carrying out⁹ MM calculations on two other commonly occurring conformers of tetraaza macrocycles, the trans-I and cis-V conformers (Figure 4). These calculations led to a rethinking of what controlled metal ion selectivity in macrocycles and to some ideas that are applicable to metal ion selectivity in all ligands.

Molecular Mechanics Calculations. These have in recent years gained importance in coordination chemistry.^{10,11} For a discussion of the basis of MM, the literature should be consulted.¹²⁻¹⁴ The MM calculation models steric effects in molecules by use of simple equations to represent contributions to steric strain, such as bond-length and bond-angle deformation, tor-

- Pedersen, C. J. *J. Am. Chem. Soc.* 1967, 89, 2459.
- Lehn, J.-M. *Acc. Chem. Res.* 1978, 11, 49.
- Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev.* 1985, 85, 271.
- Shannon, R. D. *Acta Crystallogr., Sect. A* 1976, 32, 751.
- Gokel, G. W.; Goli, D. M.; Minganti, C.; Echevoyen, L. *J. Am. Chem. Soc.* 1983, 105, 6786.
- Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, 1989; pp 4-6, 185-191.
- De Hayes, L. J.; Busch, D. H. *Inorg. Chem.* 1973, 12, 1505.
- (a) Hancock, R. D.; McDougall, G. J. *J. Am. Chem. Soc.* 1980, 102, 6551. (b) Thom, V. J.; Hosken, G. D.; Hancock, R. D. *Inorg. Chem.* 1985, 24, 3378.
- Thom, V. J.; Fox, C. C.; Boeyens, J. C. A.; Hancock, R. D. *J. Am. Chem. Soc.* 1984, 106, 5947.
- Brubaker, G. R.; Johnson, D. W. *Coord. Chem. Rev.* 1984, 53, 1.
- Hancock, R. D. *Prog. Inorg. Chem.* 1989, 37, 187.
- Allinger, N. L.; Yuh, Y. H. *QCPE* 1981, 13, 395. Bulletin of the Quantum Chemistry Program Exchange, c/o Department of Chemistry, Indiana University, Bloomington, IN.
- (a) Burket, U.; Allinger, N. F. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society; Washington DC 1982. (b) Allinger, N. F. *Adv. Phys. Org. Chem.* 1976, 13, 1.
- Boyd, R. H. *J. Chem. Phys.* 1968, 49, 2574.

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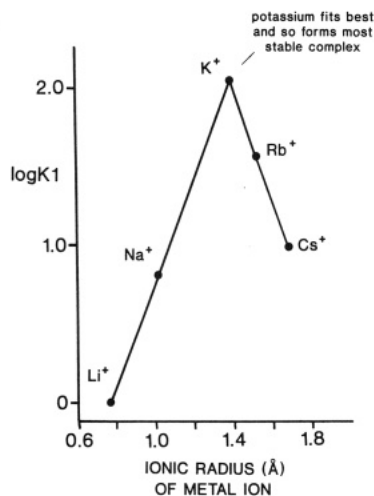


Figure 1. The formation constants³ of the complexes of the alkali-metal ions with 18-crown-6 at 25 °C in water, plotted as a function of their octahedral ionic radii.⁴

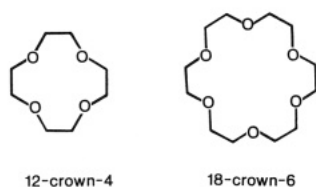


Figure 2. Some ligands discussed in this Account.

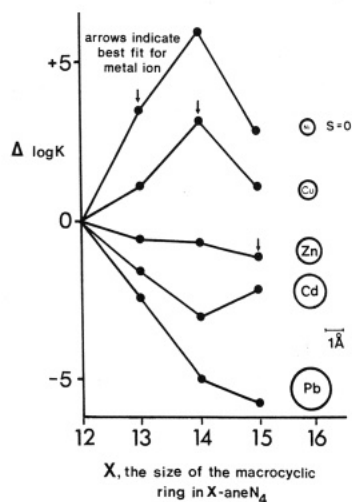


Figure 3. The change in formation constant, $\Delta \log K_1$, of the complexes of the $X\text{-aneN}_4$ macrocycles relative to $\log K_1$ for 12-ane N_4 , plotted as a function of X , the macrocyclic ring size. The metal ions are indicated in circles drawn proportionally to their ionic radii.⁴ Redrawn after ref 9.

sional strain, and van der Waals interactions between nonbonded atoms. Thus, the equation used to calculate strain from bond-length deformation, U_B , is a simple Hooke's law expression,

$$U_B = \frac{1}{2}K(r^\circ - r)^2 \quad (1)$$

where r° is the ideal bond length, r is the observed bond length, and K is the force constant for that particular type of bond.

Molecular Mechanics Calculations on Tetraaza Macrocycles. We have developed^{8,9,11,15} an approach

(15) McDougall, G. J.; Hancock, R. D. *J. Chem. Soc., Dalton Trans.* 1980, 654.

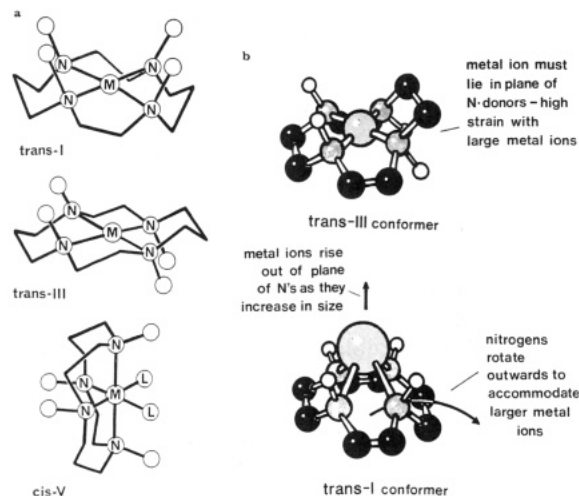


Figure 4. (a) Three conformers of the tetraaza macrocycle type of ligand. The open circles represent the N-H hydrogen atoms. (b) Diagrams illustrating how the trans-I type of conformer is able to adapt to metal ions of different sizes, compared to the more rigid trans-III conformer in tetraaza macrocycles.

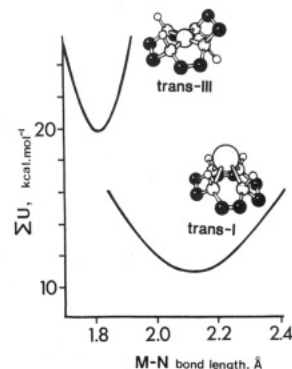


Figure 5. The strain energy, ΔU , of the trans-I and trans-III conformers of $[M(12\text{-aneN}_4)]^{n+}$ as a function of final energy minimized M-N bond length. Redrawn after ref 18.

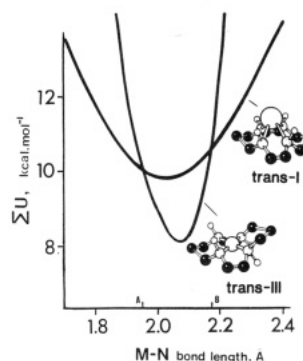


Figure 6. The strain energy, ΔU , of the trans-I and trans-III conformers of $[M(14\text{-aneN}_4)]^{n+}$ as a function of final energy minimized M-N bond length. Redrawn after ref 29.

to finding the best fit metal ions for ligands, in which the strain energy of the complex is calculated as a function of the strain-free M-N length, r° in eq 1, over a suitable range of M-N lengths. All other parameters in the calculation involving the metal ion are kept constant, usually at the values for high-spin Ni(II). The results are not too dependent on choice of metal ion. In Figure 5 and 6 are shown scans of strain energies of the trans-I and trans-III conformers of the 12-ane N_4 and 14-ane N_4 complexes. The minima in the curves in

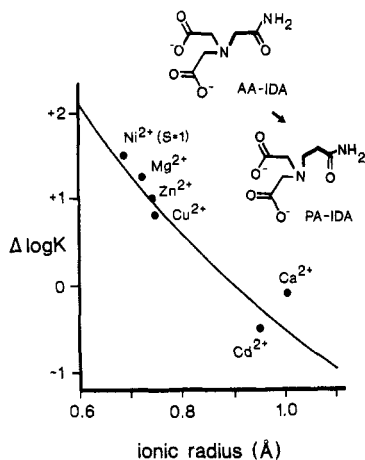


Figure 7. The change in formation constant, $\Delta \log K$, that occurs on increasing the chelate ring size from five membered in the chelate ring containing the amide oxygen in AA-IDA to six membered in PA-IDA, plotted as a function of octahedral ionic radius.⁴

Figures 5 and 6 are the best fit M-N lengths for each conformer. The sharpness of the curves is an indication of the rigidity of the conformer of the complex. Figure 5 shows that for 12-aneN₄ at all M-N bond lengths the trans-I conformer will be of lower energy than the trans-III conformer, so that the trans-III conformer should not occur. All known planar complexes of 12-aneN₄ and its derivatives have¹⁶⁻¹⁹ the trans-I conformation.

Figure 6 shows that, in contrast to 12-aneN₄, for 14-aneN₄ complexes there is a region where the trans-III conformer is of lower energy than the trans-I conformer. This lies between M-N lengths of 1.96 and 2.17 Å (points A and B on the diagram). The Cu(II) complex of 14-aneN₄ with a Cu-N length of 2.04 Å lies in this region and so is observed²⁰ to have the trans-III conformation. In contrast, Hg-N lengths in the Hg^{II} 14-aneN₄ complex lie outside this range at 2.37 Å, and it has²¹ the trans-I conformation.

Calculations have also been carried out⁹ on the cis-V conformer of 14-aneN₄ (Figure 4), which show that this is more stable (relative to the trans-III conformer) at longer M-N lengths. The picture of selectivity in the tetraaza macrocycles that emerges is not one where the ligand has a single preferred conformer with a rigid cavity that leads to size-match selectivity for metal ions. Rather, the ligand has several conformers not greatly different in energy, which have different metal ion size preferences. Metal ions that are too large for the cavity of the macrocycle are simply coordinated out of the plane of the donor atoms in conformers such as the trans-I conformer. In these out-of-plane positions the size of the macrocyclic cavity is unimportant, and stability is controlled by the same geometrical factors that control stability in open-chain ligands, namely, the size of the chelate ring.

(16) Clay, R.; Murray-Rust, P.; Murray-Rust, J. *Acta Crystallogr., Sect. B* **1979**, *B35*, 1894.

(17) Sakurai, T.; Kobayashi, K.; Hasegawa, A.; Tsuboyama, B.; Tsuboyama, K. *Acta Crystallogr., Sect. B* **1982**, *B38*, 107.

(18) Desimone, R. E.; Blinn, E. L.; Mucker, K. F. *Inorg. Nucl. Chem. Lett.* **1980**, *16*, 23.

(19) Coates, J. H.; Hadi, D. M. M. A.; Hambley, T. W.; Lincoln, S. F.; Rodgers, J. R. *Cryst. Struct. Commun.* **1982**, *11*, 815.

(20) Tasker, P. A.; Sklar, L. *Crystallogr. Mol. Struct.* **1975**, *5*, 329.

(21) Alcock, N. W.; Curson, E. H.; Herron, N.; Moore, P. *J. Chem. Soc., Dalton Trans.* **1979**, 1987.

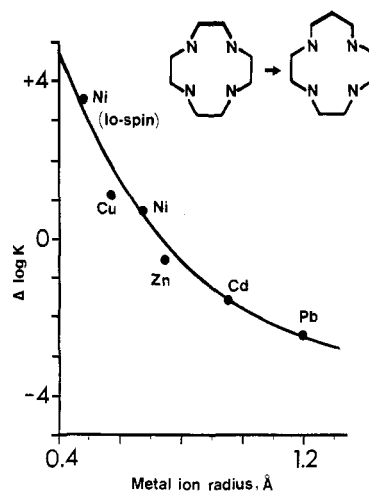
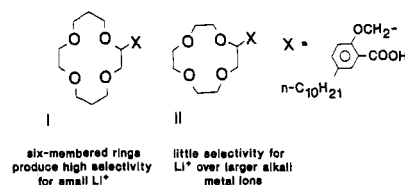


Figure 8. A relationship similar to that depicted in Figure 7, plotted for the pair of ligands 12-aneN₄ and 13-aneN₄.

Chart II



Chelate Ring Size and Metal Ion Selectivity. It was observed²² that in open-chain ligands the familiar destabilization of complexes that occurs when the size of the chelate ring is increased from five membered to six membered was directly related to metal ion size. An example of this dependency is shown in Figure 7, where the change in formation constant, $\Delta \log K$, that occurs on passing from AA-IDA (Figure 7) to PA-IDA is plotted against metal ion octahedral radius.⁴ In AA-IDA all the chelate rings formed are five membered, whereas in PA-IDA the size of the chelate ring involving the amide oxygen is increased to six membered. Many examples of this type of relationship between change of stability on increase of chelate ring size from five to six membered and metal ion radius have been demonstrated.^{22,23} The relationships include also macrocycles where there is an increase of chelate ring size, as seen in Figure 8 for 12-aneN₄ and 13-aneN₄. The widespread occurrence of the type of correlation seen in Figures 7 and 8 leads²² to a rule of ligand design: *Increase of chelate ring size from five membered to six membered in a complex will increase the stability of complexes of smaller relative to larger metal ions.* This rule holds for both macrocyclic and nonmacrocyclic ligands. An example of the rule applied to crown ethers is seen in Chart II. Ligand I shows²⁴ much higher selectivity for the small Li⁺ ion relative to other alkali-metal ions than does ligand II, even though it has a larger macrocyclic cavity. This relates to the presence of six-membered chelate rings in the complexes of crown ether I, so favoring the small Li⁺ ion.

Origin of the Size-Selective Effect of Chelate Ring Size. Metal ion size preferences of five- and

(22) Hancock, R. D. *Pure Appl. Chem.* **1986**, *58*, 1445.

(23) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.

(24) Bartsch, R. A.; Czech, B. P.; Kang, S. I.; Stewart, L. E.; Wolkowiak, W.; Charewicz, W. A.; Heo, G. S.; Son, B. *J. Am. Chem. Soc.* **1985**, *107*, 4997.

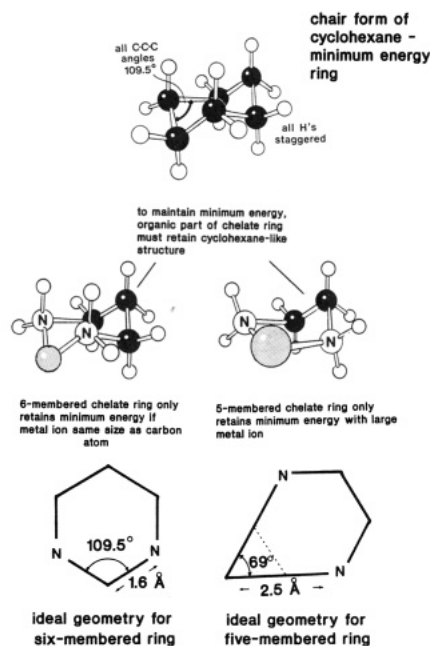
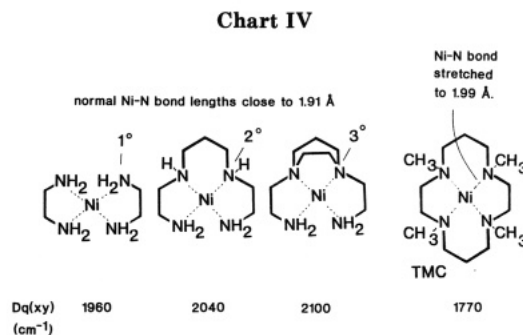
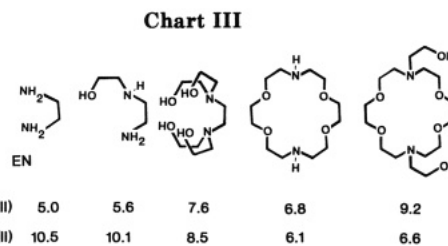


Figure 9. The relationship between minimum strain geometry in cyclohexane and the steric requirements of chelate rings of size five and size six.

six-membered chelate rings relate to the steric requirements of low-strain cycloalkanes. The chair form of the cyclohexane ring has (Figure 9) minimum strain energy because all torsional angles are at the minimum strain value of 60° . A six-membered chelate ring based on TN (1,3-diaminopropane) retains this low-strain geometry as long as the metal ion is about the same size as the tetrahedral carbon atom. MM calculation shows that as the metal ion gets larger, the chelate ring flattens, and the hydrogens rotate into eclipsed positions, with a rise in strain energy. Thus, very small metal ions coordinate best in six-membered chelate rings, while complexes of large metal ions are destabilized by six-membered chelate rings.

MM calculations¹¹ show that the torsion angles in the five-membered chelate ring based on EN (1,2-diaminoethane) approach the minimum strain situation when the metal ion is large (Figure 9) with an M-N length of 2.5 Å and a small N-M-N angle of 69° . Metal ion size based on selectivity is thus controlled by chelate ring size because minimum strain energy is achieved in six-membered chelate rings with the smallest metal ions, with low coordination number and thus large N-M-N angle. Five-membered chelate rings have minimum strain energy with large metal ions of high coordination number and thus small N-M-N angle.

Metal Ion Selectivity of Oxygen-Donor Macrocycles. The oxygen donor found in crown ethers has not been extensively investigated as a donor atom in its own right. We found²⁵⁻²⁷ that in open-chain ligands, addition of neutral oxygen donors as pendent hydroxyethyl groups had effects on complex stability reminiscent of the coordinating properties of crown ethers. Thus, complexes of large metal ions such as Pb^{II} and



Ba^{II} showed strong increases in complex stability when groups containing neutral oxygen donors were added, while small metal ions such as Cu^{II} showed strong decreases in complex stability (Chart III). This behavior relates strongly enough to metal ion radius that plots of $\Delta \log K$ on addition of neutral oxygen donors to a ligand versus ionic radius are of good linearity,²⁵⁻²⁷ resembling Figures 7 and 8, but of opposite slope. An important proviso here is that the added oxygen donors should be part of a five-membered chelate ring, as we have recently demonstrated²⁸ with ligands where 3-hydroxypropyl groups are used to form six-membered chelate rings. With oxygen donors in six-membered chelate rings, the complexes of small metal ions are stabilized relative to those of large metal ions. This is seen also in Chart II and Figure 7. It is suggested that much of the preference displayed by crown ethers and other ligands containing neutral oxygen donors for large metal ions arises because the oxygen donors are usually part of five-membered rather than six-membered chelate rings. An explanation for the fact that peaks in complex stability in correlations such as Figure 1 occur at K^+ regardless of the size of the macrocyclic ring could lie in the idea that potassium is the right size for the five-membered chelate rings of crown ethers.

Ligand Field Strength of Nitrogen Donor Macrocycles. Complexes of nitrogen donor macrocycles usually show higher ligand field (LF) strengths than their open-chain analogues.²⁹ Increased LF strength implies increased overlap in the M-N bond. It is not surprising in terms of the idea of macrocycles as rigid ligands that a widely accepted interpretation³⁰ of this phenomenon is that it is due to compression of the metal ion in the too-small cavity of the ligand. This seems unlikely, however, since crystal structures show²⁹ no shortening of the M-N bond in these situations. A better interpretation is that the increase in LF is due^{23,29} to increasing covalency in the M-N bond accompanying the increase in donor strength, along the series primary

(25) Thom, V. J.; Shaikjee, M. S.; Hancock, R. D. *Inorg. Chem.* **1986**, *25*, 2992.

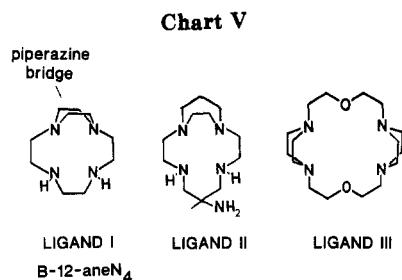
(26) Hancock, R. D.; Bhavan, R.; Wade, P. W.; Boeyens, J. C. A.; Dobson, S. M. *Inorg. Chem.* **1989**, *28*, 187.

(27) Damu, K. V.; Shaikjee, M. S.; Michael, J. P.; Howard, A. S.; Hancock, R. D. *Inorg. Chem.* **1986**, *25*, 3879.

(28) Hancock, R. D.; Maumela, H., to be published.

(29) Thom, V. J.; Fox, C. C.; Boeyens, J. C. A.; Hancock, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 5947.

(30) Busch, D. H.; Farmery, K.; Goedken, V.; Katovic, V.; Melnyk, A. C.; Sperati, C. R.; Tokel, N. *Adv. Chem. Ser.* **1971**, No. 100, 44.



< secondary < tertiary, illustrated in the series in Chart IV. As illustrated in Chart IV, an increase in the basicity of the nitrogens from the addition of methyl groups to give TMC is overcome by the resulting steric strain and a drop in LF strength³¹ corresponding to the lengthening³² of the Ni-N bond is observed. High LF strengths lead to the stabilization of unusual oxidation states,³³ including a report³⁴ of Hg^{III}. To increase complex stability and LF strength, the alkyl groups added should not produce adverse steric effects, which usually means that they should be bridging alkyl groups that are part of a chelate ring.

Structurally Reinforced Macrocycles. The conclusion that macrocycles in general, and the tetraaza macrocycles in particular, were not particularly rigid molecules, and so failed to show size-match selectivity, led us to search for more rigid ligands. The literature yielded brief reports^{35,36} of reinforced macrocycles, such as B-12-aneN₄ shown in Chart V. A crystal structure determination³⁷ for [Ni(B-12-aneN₄)]²⁺ showed that the Ni-N bond lengths had been compressed from the strain-free value¹¹ of 1.91 Å for $S = 0$ Ni^{II} down to a mean length of 1.86 Å, in accord with the suggestion³⁵ that the very high LF strength observed for this complex was due to compression of the metal ion. We have since synthesized^{38,39} a variety of reinforced macrocycles, some of which are shown in Chart V. The complex of ligand II with Ni^{II} shows an even higher LF strength than does B-12-aneN₄, which is attributed³⁸ to the

presence of tertiary nitrogen donors rather than compression. The rigidity of ligand II is such that the Ni^{II} complex is not demetalated even in refluxing cyanide solutions. Ligand III is interesting in that it shows³⁹ total selectivity for the Pb^{II} ion, with no signs of complexing other metal ions tested. Adoption of the low-energy chair form by the piperazine bridges of the free ligand, however, rather than the boat form required for coordination to metal ions, means that overall complex stability is low, even with Pb^{II}.

Concluding Remarks. Space limitations have meant that I have been able to give only a brief look at the application of MM calculations to problems in coordination chemistry, and the interested reader is referred to ref 11. Similarly, the arguments concerning the role in metal ion size-based selectivity of the size of the chelate ring, i.e., whether it is five membered or six membered, have necessarily been brief. The evidence, weighed carefully, seems strong that the size of the chelate ring outweighs the size of the macrocyclic ring in determining thermodynamic complex stability with metal ions of different sizes, at least for saturated unreinforced macrocycles.

One can distinguish the effects of the size of the chelate ring from the effects of the size of the macrocyclic ring because these are often expected to be of opposite effect on complex stability as the size of the metal ion increases. In nonmacrocyclic ligands, an increase in the size of the chelate ring leads to a decrease in complex stability for larger metal ions relative to smaller metal ions. The increase in macrocyclic ring size that accompanies increasing chelate ring size is expected to produce an increase in complex stability for larger metal ions, but invariably it does not. In considering macrocyclic ring size, we are expecting the distance from the metal ion to the donor atoms to control complex stability. MM calculation shows that the macrocyclic ring is generally too flexible for this to be important. In considering chelate ring size, we are actually considering the orientation of the lone pairs on the donor atoms, which for ring size six focus on a point close to the donor atoms, while for ring size five the lone pairs focus on a point a long way from the donor atoms. This fact leads to rules for controlling selectivity of ligands for metal ions on the basis of their size, which, along with other rules developed²³ for ligand design, may lead to an improved ability to design ligands for specific complexation of metal ions.

I thank the University of the Witwatersrand and the Foundation for Research Development for generous support for this work and my colleagues and students for their invaluable contributions to the work reported here.

(31) Herron, N.; Moore, P. *Inorg. Chim. Acta* 1979, 36, 89.

(32) Hambley, T. W. *J. Chem. Soc., Dalton Trans.* 1986, 565.

(33) Fabbrizzi, L. *Comments Inorg. Chem.* 1985, 4, 33.

(34) Deming, R. L.; Allred, A. L.; Dahl, A. E.; Merlinger, A. W.; Kostner, M. O. *J. Am. Chem. Soc.* 1976, 98, 4132.

(35) Wainwright, K. P.; Ramasubbu, A. *J. Chem. Soc., Chem. Commun.* 1982, 277.

(36) Wainwright, K. P. *Inorg. Chem.* 1980, 19, 1396.

(37) Hancock, R. D.; Dobson, S. M.; Evers, A.; Wade, P. W.; Ngwenya, M. P.; Boeyens, J. C. A.; Wainwright, K. P. *J. Am. Chem. Soc.* 1988, 110, 2788.

(38) Hancock, R. D.; Ngwenya, M. P.; Wade, P. W.; Boeyens, J. C. A.; Dobson, S. M. *Inorg. Chim. Acta* 1989, 164, 73.

(39) Wade, P. W.; Hancock, R. D.; Boeyens, J. C. A.; Dobson, S. M. *J. Chem. Soc., Dalton Trans.* 1990, 483.