and finally by nonbonding S 3p levels. The levels introduced by S_2^{2-} diatomics, however, retain their identity, and the interaction of the end S orbitals with the Mo levels is best described in terms of the σ and π MOs of the diatomics. The orbital character of these levels is similar to that studied in ref 9, where X_α calculations are reported for mononuclear Rh and Ir complexes ligated by a S_2^{2-} diatomic and four phosphine ligands. In our calculations, the single Mo-Mo bond lies 1 eV below the π^* levels of the diatomic.

The Mo-S systems differ significantly from nominally similar Fe-S systems,[8] since spin-polarization effects play a very important role in the latter case. For the "thiocubane" clusters[8c] both the HOMO and the LUMO consist mainly of spin-polarized Fe orbitals since both Fe(II) and Fe(III) are present in the ions, while the 1-Fe rubredoxin model[8a] and the Fe_2S_2 ferredoxin model[8b] have a sulfur-derived HOMO and an iron-derived LUMO.

The optical spectrum of $Mo_2O_2(\mu\text{-}S)_2(S_2)_2^{2-}$ [3] shows transitions at 2.7 (21 800) and 3.35 (27 000) eV (cm^{-1}). The corresponding transitions for $Mo_2S_2(\mu\text{-}S)_2(S_2)_2^{2-}$ [5] are at 2.16 (17 400) and 2.65 (21 400) eV (cm^{-1}). We assign the first transition to a charge-transfer excitation from the S_2^{2-} diatomics to the Mo-O and Mo-S_t antibonding orbitals (nominally Mo d orbitals), respectively. The second transition corresponds to a charge-transfer excitation from the bridging sulfur atoms to the same acceptor levels. Note that both the S_2^{2-} to Mo and bridging S to Mo charge-transfer bands are lower in energy than the terminal S→Mo charge-transfer bands. This is due to strong stabilization of S_t bonding levels by strong σ and π bonding with Mo. As mentioned in the previous section, optical transitions have been systematically underestimated by local density theory in solid-state applications. Since the optical transitions described above are between highly delocalized levels, similar effets are expected here. The calculated values are 2.0 and 3.0 eV for $Mo_2O_2(\mu\text{-}S)_2(S_2)_2^{2-}$ and 1.45 and 2.4 for $Mo_2S_2(\mu\text{-}S)_2(S_2)_2^{2-}$.

The reaction of $Mo_2O_2(\mu\text{-}S)_2(S_2)_2^{2-}$ with an activated acetylene,[4] such as dimethylacetylenedicarboxylate, involves insertion of two carbon atoms into one of the Mo-S_2 bonds. This reaction may involve nucleophilic attack of S on C with filled S levels interacting with low-lying empty levels (π^*) on the activated acetylene. It is noteworthy that the site of acetylene reactivity corresponds to the HOMO of **1**. Since the highest lying occupied orbitals in the S analogue, **2**, are very similar, a similar reactivity is expected. Moreover, the reaction may also involve the Mo-S_2 antibonding orbitals, perhaps in a second step. Since the Mo-S_2 antibonding orbital is shifted down in energy in **2** compared to the case of **1**, reactions with $Mo_2S_2(\mu\text{-}S)_2(S_2)_2^{2-}$ that have such a nucleophilic component could have a lower activation energy. Such arguments, however, depend upon detailed mechanisms of the acetylene reactions, which are under experimental study.

Summary

We have carried out a detailed analysis of the differences and similarities between the electronic properties of $Mo_2O_2(\mu\text{-}S)_2(S_2)_2^{2-}$ and $Mo_2S_2(\mu\text{-}S)_2(S_2)_2^{2-}$. We find that the replacement of oxygen atoms by sulfur atoms in the $Mo_2O_2S_2^{2+}$ core does not significantly affect the binding of S_2^{2-} to the core or the binding of the bridging sulfur atoms to the molybdenum atoms within the core. In particular, the S_2^{2-} π^* orbitals in the plane perpendicular to the Mo-S_2 bond remain the HOMOs in $Mo_2S_2(\mu\text{-}S)_2(S_2)_2^{2-}$. Their energies, as well as the energy and the orbital content in the single Mo-Mo bond, 1 eV below the HOMOs, are not significantly affected. For the unoccupied orbitals, the Mo-O π^* orbitals are replaced by Mo-S(terminal) π^* orbitals as the LUMOs. The invariance of the higher lying occupied orbitals and the relatively small changes in the unoccupied orbitals suggest an essentially similar reactivity pattern for $Mo_2S_2(\mu\text{-}S)_2(S_2)_2^{2-}$ toward simple electrophlic reagents. The lowering of the HOMO-LUMO gap, however, suggests a possible lowering of the activation energy for reactions involving the unoccupied orbitals. The results of these calculations together with mechanistic studies currently in progress lead to a better appreciation of reaction pathways available to molybdenum-sulfur systems.

Acknowledgment. It is a pleasure to thank Drs. T. R. Halbert, S. Harris, and W.-H. Pan for useful discussions.

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Contribution from the Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa

Control of Metal Ion Selectivity in Ligands Containing Neutral Oxygen and Pyridyl Groups

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The stabilities of the complexes of the ligand $(py)_2$-18-aneN_2O_4 (*N,N'*-bis(*o*-pyridylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane) at 25 °C in 0.1 M $NaNO_3$ are reported, as well as those of DHEAMP (((bis(2-hydroxyethyl)amino)methyl)-pyridine), with a variety of metal ions. The log K_1 values for the $(py)_2$-18-aneN_2O_4 complexes are as follows: Cu^{2+}, 13.55; Ni^{2+}, 8.80; Zn^{2+}, 6.96; Cd^{2+}, 10.96; Ca^{2+}, 3.63; La^{3+}, 3.53; Sr^{2+}, 4.87; Pb^{2+}, 11.67; Ba^{2+}, 4.99. The constants for the protonation equilibria were, for $H^+ + L = HL^+$, log K = 7.44, for $H^+ + HL^+ = H_2L^{2+}$, log K = 6.26, and for $H^+ + H_2L^{2+} = H_3L^{3+}$, log K = 1.38. For DHEAMP, log K values are as follows: Cu^{2+}, 9.2; Ni^{2+}, 7.34; Zn^{2+}, 5.25; Ca^{2+}, 1.0; La^{3+}, 1.95; Pb^{2+}, 5.43. The protonation equilibria for DHEAMP were, for $H^+ + L = HL^+$, log K = 6.92, and for $H^+ + HL^+ = H_2L^{2+}$, log K = 1.16. The coordinating properties of ligands with neutral oxygen donors are discussed, and the suitability of $(py)_2$-18-aneN_2O_4 as a reagent for the treatment of lead poisoning is considered. The control of metal ion selectivity based on metal ion size is discussed, as well as the coordinating properties of ligands based on the 18-aneN_2O_4 ring, which have pendant donor groups attached to the nitrogens of the macrocyclic ring.

The metals lead, cadmium, and mercury are currently of environmental concern.[1] At present, none of the ligands used for removing these metal ions from the body in cases of metal poisoning can be regarded as very satisfactory.[1] Lead poisoning, which is our interest here, is treated with EDTA (see Figure 1 for structures of ligands), which has the drawback[1] of a lead/zinc selectivity of only 1.6 log units,[2] which means that excessive amounts of zinc are removed from the body during treatment. A further problem with EDTA is its relatively high affinity for

(1) May, P. M.; Bulman, R. A. *Prog. Med. Chem.* **1983**, *20*, 226.

(2) All formation constants referred to in this work, unless otherwise indicated, are from: Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum: New York, 1974-1977, 1979; Vol. 1-5. Where selectivities for one metal ion over another are indicated, the numerical value for the selectivity is simply the logarithm of the formation constant, log K, for the first metal ion minus log K for the second metal ion with the same ligand.

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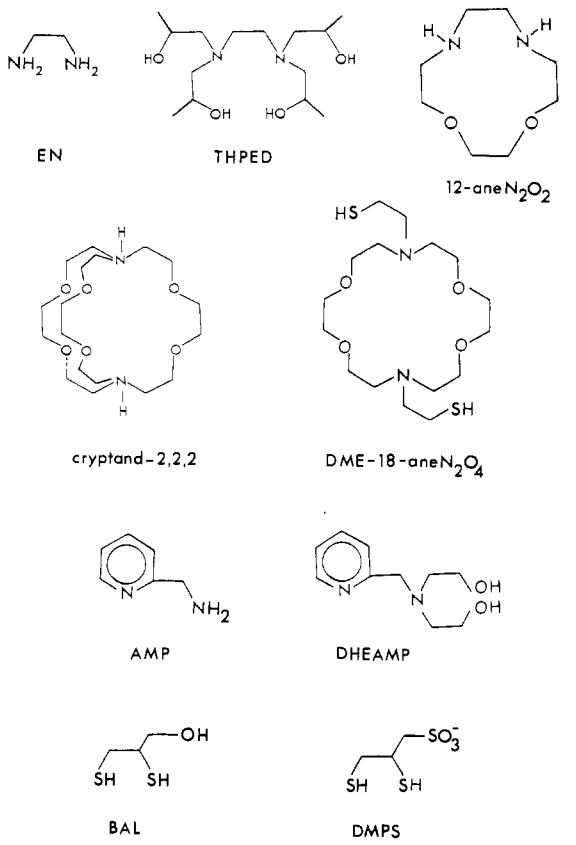

Figure 1. Formulas of the ligands discussed in this work. The optically active carbons on the 2-hydroxypropyl groups are unresolved, so that THPED will be a mixture of enantiomers.

Ca^{2+}, which is, however, overcome by administering EDTA as a calcium complex. An improvement over EDTA would be a ligand with a greatly enhanced Pb^{2+}/Zn^{2+} selectivity, and while not essential, a Pb^{2+}/Ca^{2+} selectivity in excess of the 7.3 log units obtained with EDTA.[2] Lehn[3] has suggested that cryptand-2,2,2 would be a more lead-selective ligand, since its log K_1 value for Pb^{2+} is more than 9 orders of magnitude higher than for Zn^{2+}, which is hardly complexed by the ligand, while its Pb^{2+}/Ca^{2+} selectivity is satisfactory at 7.4 log units. Baudot et al.[4] have tested cryptand-2,2,2 on rats and found its performance to be satisfactory for removing lead. The log K of 12.0 for Pb^{2+} with cryptand-2,2,2 could thus probably be regarded as a strong enough binding constant to aim for. Possible drawbacks to cryptand-2,2,2 are its high cost and its relatively slow rate of complex formation,[5] which could be serious at the low concentrations of metal ions that must be complexed in biological systems. The available data suggest[6,7] that complexation rates of macrocycles with pendent donor groups will be higher than for cryptands, so that these might be more suitable. The ligands THP-12-aneN_3O, DHP-15-aneN_2O_3, and DHP-18-aneN_2O_4 are shown, together with their selectivities for the large Pb^{2+} over the small Zn^{2+} ion, in Figure 2. These results indicate that the large 18-membered ring produces much larger Pb/Zn selectivities than do the smaller 15- and 12-membered rings. However, the actual stabilities of the complexes formed by DHP-18-aneN_2O_4 with Pb^{2+} are probably too low to be effective at complexing lead in biological systems. One should aim to raise the stability to about log K_1 = 12.0 of Pb^{2+} with cryptand-2,2,2, remembering, of course, that the energy required to deprotonate the ligand at biological pH should also be taken into consideration. The stability of the complex formed by Pb^{2+} with the DHP-18-aneN_2O_4 type of ligand could be raised by replacing the 2-hydroxypropyl groups with more strongly coordinating groups, remembering that these should not bind Zn^{2+} significantly more strongly than Pb^{2+} or a loss of Pb/Zn selectivity will occur. The pyridyl group appears suitable, since the affinity of Zn^{2+} for nitrogen donors is[8] only slightly higher than that of Pb^{2+}. At the same time, the low affinity of Ca^{2+} for nitrogen donors should ensure a high Pb/Ca selectivity. Accordingly, in this paper are reported the metal ion complexing properties of $(py)_2$-18-aneN_2O_4. Also reported here are the metal complexing properties of DHEAMP. It has previously been shown[9] that neutral oxygen donors that are not part of a macrocyclic ring can produce size selectivity effects very like those of oxygen-donor-containing macrocyclic rings. The ligand DHEAMP is derived from AMP by addition of *N*-2-hydroxyethyl groups, so that a comparison of the complexing properties of AMP and DHEAMP would allow an evaluation of this effect.

Experimental Section

The ligand $(py)_2$-18-aneN_2O_4 was synthesized according to the method of Kulstad and Malmsten.[10] It was recrystallized from ethanol as the NaI complex. A stock solution of the latter salt was made up and standardized by acid–base titration, which showed the ligand to be approximately 99% pure. The calculated quantity of $AgNO_3$ was added to precipitate out the iodide, and after filtration, the ligand solution was restandardized. This was used to make up the solutions used in the potentiometric studies.

The ligand DHEAMP was synthesized from AMP (Aldrich) by dissolving the latter in isoamyl alcohol and adding a slight excess of ethylene oxide to the cooled solution. After being allowed to stand overnight, the ligand was recovered as a clear oil after removing the solvent and excess ethylene oxide under vacuum. Purification was effected by precipitating DHEAMP as its dihydrochloride from ether, followed by recrystallization from ethanol to give white needles. These needles appeared to lose one HCl molecule at about 126 °C and finally melt at 156.5 °C. Anal. Calcd for $C_{10}H_{18}N_2O_2Cl_2$: C, 44.6; H, 6.74; N, 10.41; Cl, 26.36. Found: C, 44.06; H, 6.72; N, 10.19; Cl, 26.44. NMR spectrum: δ 3.65 (m, 4 H, $-CH_2CH_2OH$); 4.08 (m, 4 H, $-CH_2CH_2OH$); 5.03 (s, 2 H, py-CH_2-N); 8.40 (m, 3 H, py-H); 9.00 (d, 1 H, py-H).

Potentiometry. Glass electrodes were used as described previously[11] in titrations in 0.1 M $NaNO_3$ at 25 °C in the pH range 2–10 with total metal and total ligand concentrations in the range 10^{-2}–10^{-3} M. The second protonation constant for DHEAMP was too low to be determined by glass electrode potentiometry, so that this was determined by following the NMR spectrum of the ligand as a function of pH between pH 1.0 and 2.0, with spectra being recorded in much more concentrated acid solutions to obtain limiting spectra for the diprotonated DHEAMP. The complex of Cu^{2+} with DHEAMP was too stable to break up above a pH of 2.0. The formation constant of Cu^{2+} with DHEAMP was thus determined by following the UV–visible spectrum of solutions of Cu^{2+} and DHEAMP as a function of pH in the pH range 1.0–2.0.

Instrumentation. UV–visible spectra were recorded on a Cary-2300 spectrophotometer, and NMR spectra were recorded on a Varian EM-360 spectrometer.

Results and Discussion

In Table I are seen the protonation constants of the ligands AMP, DHEAMP, and $(py)_2$-18-aneN_2O_4, as well as their formation constants with a variety of metal ions. It is seen that the Pb^{2+}/Zn^{2+} selectivity is 4.7 log units for the ligand $(py)_2$-18-aneN_2O_4, while its Pb^{2+}/Ca^{2+} selectivity is 8.0 log units. The design change, shown in Figure 2, has thus been successful, in that there has been only a small drop in Pb^{2+}/Zn^{2+} selectivity, expected on the basis of the somewhat higher affinity[8] of Zn^{2+} for nitrogen donor ligands than is the case for Pb^{2+}. However, the Pb^{2+}/Ca^{2+} selectivity has been greatly enhanced by the in-

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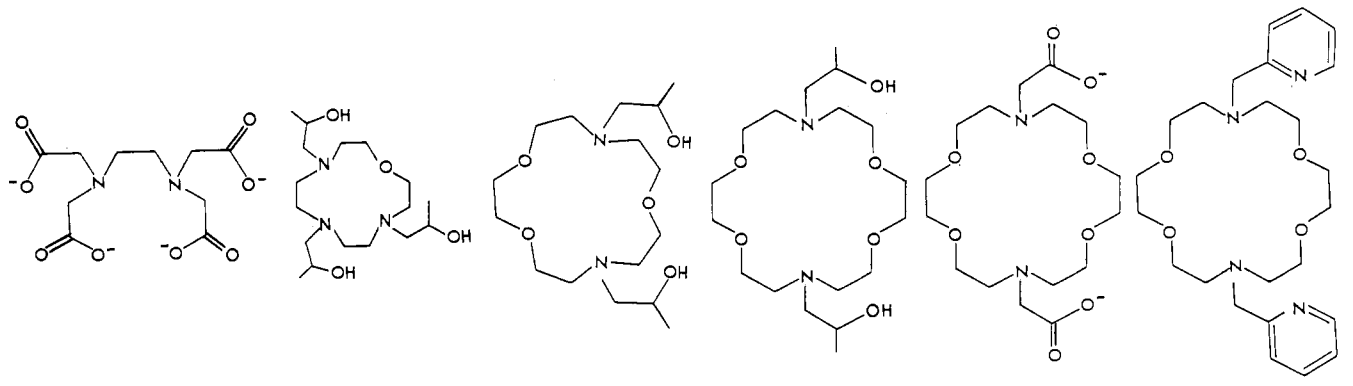

	EDTA	THP-12-aneN$_3$O	DHP-15-aneN$_2$O$_3$	DHP-18-aneN$_2$O$_4$	18-aneN$_2$O$_4$-DA	py$_2$-18-aneN$_2$O$_4$
Pb/Zn	1.6	2.2	1.8	5.6	5.7	4.7
Pb/Ca	7.4	7.5	4.3	5.0	5.1	8.1

Figure 2. Formulas of ligands and their selectivity[2] for Pb^{2+} over Zn^{2+} and Ca^{2+}. The enantiomeric mixtures for ligands such as DHP-15-aneN$_2$O$_3$, THP-12-aneN$_3$O, and DHP-18aneN$_2$O$_4$ are unresolved.[9]

Table I. Logarithms of Protonation and Formation Constants of Ligands Containing the Pyridyl Group

Lewis acid[a]	equilibrium[b]	AMP[c]	DHEAMP[d]	(py)$_2$-18-aneN$_2$O$_4$[e]
H^+	$L + H^+ \rightleftarrows LH^+$	8.61	6.92 ± 0.01	7.44 ± 0.01
	$LH^+ + H^+ \rightleftarrows LH_2^{2+}$	2.00	1.16 ± 0.09[f]	6.26 ± 0.01
	$LH_2^{2+} + H^+ \rightleftarrows LH_3^{3+}$			1.38 ± 0.03
Cu^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	9.5	9.2 ± 0.1[f]	13.55 ± 0.02
	$M^{2+} + 2L \rightleftarrows ML_2^{2+}$	17.2		
Ni^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	7.11	7.34 ± 0.02	8.80 ± 0.02
	$M^{2+} + 2L \rightleftarrows ML_2^{2+}$	13.34		
Zn^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	5.28	5.25 ± 0.02	6.96 ± 0.01
	$M^{2+} + 2L \rightleftarrows ML_2^{2+}$	9.44		
Cd^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	4.4		10.96 ± 0.02
Ca^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	(0.0)[g]	1.0 ± 0.1	3.63 ± 0.02
La^{3+}	$M^{3+} + L \rightleftarrows ML^{3+}$	(1.2)[g]	1.95 ± 0.05	3.53 ± 0.05
Sr^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	(0.0)[g]		4.87 ± 0.01
Pb^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$	3.95 ± 0.05[h]	5.43 ± 0.03	11.67 ± 0.01
	$M^{2+} + 2L \rightleftarrows ML_2^{2+}$	6.0 ± 0.1[h]		
Ba^{2+}	$M^{2+} + L \rightleftarrows ML^{2+}$			4.99 ± 0.01

[a] The Lewis acids are arranged in order of incaresing ionic radius.[15] [b] The ligands are abbreviated as L and each metal ion is indicated as M in the equilibrium indicated. [c] AMP = (aminomethyl)pyridine. Data from ref 2, except where otherwise indicated. [d] DHEAMP = ((bis(2-hydroxyethyl)amino)methyl)pyridine. Constants, this work, at 25 °C, in 0.1 M $NaNO_3$. [e] For structure of ligand, see Figure 1. Constants, this work, at 25 °C, in 0.1 M $NaNO_3$. [f] Determined spectroscopically, as described in the text. [g] Estimated, as discussed in the text. [h] This work, at 25 °C, in 0.1 M $NaNO_3$. Note that the stated uncertainties on the formation constants reported in this work are 3 times the standard deviation indicated by the program MINIQUAD,[17] which was used in calculating the formation constants from the potentiometric data.

troduction of pyridyl groups. The ligand (py)$_2$-18-aneN$_2$O$_4$ may appear to be a little on the low side in complexing strength with Pb^{2+}, since log K_1 is only 11.7 in comparison with the target of 12.0 based on the effectiveness of cryptand-2,2,2 as a lead-detoxifying agent.[4] However, an important point that always has to be borne in mind[1] is that complex formation occurs in aqueous solution in competition with the proton, so that one should really consider the equilibrium

$$M^{2+} + LH_n^{n+} \rightleftharpoons ML^{2+} + nH^+ \quad (1)$$

at a biological pH of 7.3 in order to compare the effectiveness of ligands as complexing agents. Cryptand-2,2,2 has log K values for protonation of 9.71 and 7.31, so that at a pH of 7.3 only the first proton will really offer much resistance to complex formation, and the effective reaction constant for Pb^{2+} at a pH of 7.3 with cryptand-2,2,2 will be 12.0 − (9.71 − 7.3) = 9.6. By comparison, protonation of (py)$_2$-18-aneN$_2$O$_4$ is weak at pH 7.3, and the corresponding effective constant with Pb^{2+} will be 11.5 log units. The same calculation with EDTA yields an effective constant with Pb^{2+} of 15.0 log units. What emerges here is that addition of neutral oxygen donor groups leads to a considerable drop in pK_a values, which leads to a greater effective complexing strength. In this regard it was found[12] that addition of *N*-2-hydroxyethyl groups to 2-(aminomethyl)imidazole functional groups on polystyrene-based ion-exchange resins leads to much greater difficulty in stripping copper(II) off the resin using acid. In fact, whereas the unsubstituted resin loaded copper(II) only at a pH of 2.0, addition of the hydroxyethyl groups lead to a resin that could actually load copper quite efficiently from the 1 M H_2SO_4 used for stripping these resins. It is clear from a comparison of log K_1 values for AMP and DHEAMP that this does not arise from an increase in complexing strength but rather from a considerable drop in the pK_a values of the ligand on adding hydroxyethyl groups. This ability of the hydroxyethyl group to lower the pK_a values of the nitrogen to which it is attached is a useful tool in stabilizing complexes of easily hydrolyzed metal ions. Thus, we were not able to determine the formation constants of AMP or EN with La^{3+} because of hydrolysis problems. However, for DHEAMP and THPED, the lower pK_a values of the ligands coupled with the somewhat higher formation constants of the large La(III) ion in the presence of neutral oxygen donors lead to hydrolysis-resistant complexes in aqueous solution. An important aspect of the only partial protonation of (py)$_2$-18-aneN$_2$O$_4$ at biological pH is that

(12) Green, B. R.; Hancock, R. D., unpublished work.

it might be expected to pass through the cell wall and thus retrieve metal ions from within the cell. By partial protonation here we mean that at pH 7.3 the ligand should exist as an equal mixture of neutral unprotonated and charged monoprotonated species. The importance of neutrality in allowing the molecule to pass into the cell has been postulated[1] to explain the much greater effectiveness of neutral BAL (see Figure 1) than charged DMPS in metal detoxification.

We did not carry out any kinetic studies on $(py)_2$-18-aneN_2O_4 to see how rapidly it formed complexes. However, equilibration in the potentiometric studies was rapid for all the metal ions except Cu^{2+}, Ni^{2+}, and La^{3+}. Slower equilibration with Ni^{2+} and La^{3+} would be expected from their slower rates of water exchange.[13] The slowness of the equilibrium with Cu^{2+} was a little surprising but was probably due to the low free-ligand concentration at which equilibration was occurring. In addition, the ligand might possibly have had to undergo conformational changes of a demanding nature in order to accommodate the very small Cu^{2+} ion. One might guess, however, that the complexation rate of $(py)_2$-18-aneN_2O_4 with metal ions would be superior to that of cryptand-2,2,2, since equilibration in our studies required hours with La^{3+} rather than the month required[14] for attainment of equilibrium with cryptand-2,2,2.

Our qualitative ligand design approach, where we have simply noted the effect of macrocyclic ring size on metal ion selectivity and changed pendent donor groups in accord with noted bonding preferences, has yielded promising results with $(py)_2$-18-aneN_2O_4, which we selected as a potential lead-detoxifying agent. One can, however, analyze the observed selectivities more closely and put the ligand design principles on a more quantitative basis. As noted above, the change in complex stability produced on adding groups containing neutral oxygen donors appears to be governed by metal ion size. The change in complex stability, $\Delta \log K$, is so closely governed by metal ion size that we may in fact obtain a reasonable linear correlation of $\Delta \log K$ vs. the ionic radii of the metal ion. This is seen for DHEAMP, 18-aneN_2O_4, and $(py)_2$-18-aneN_2O_4 in Figure 3. The ionic radii, r^+, are all for six-coordination,[15] except for Cu^{2+}, for which four-coordination has been used as being more appropriate. For DHEAMP, the value of $\Delta \log K$ is calculated as $\log K_1$ for DHEAMP minus $\log K_1$ for AMP. For $(py)_2$-18-aneN_2O_4 the value of $\Delta \log K$ is calculated as $\log K_1$ for $(py)_2$-18-aneN_2O_4 minus $\log \beta_2$ for AMP, since the macrocycle is considered to be formed from two AMP molecules by the addition of bridging diether groups. Similarly, 18-aneN_2O_4 is considered to be formed from two ammonia molecules by the addition of two bridging diether groups, so that $\Delta \log K$ here is calculated as $\log K_1$ for the 18-ane-N_2O_4 complex minus $\log \beta_2$ for the ammonia complex of each metal ion. We will identify each of these relationships as DHEAMP/AMP, $(py)_2$-18-ane-N_2O_4/$(AMP)_2$, and 18-aneN_2O_4/$(NH_3)_2$, respectively. It is seen in Figure III that all three relationships are reasonably linear, differing only in the steepness of the slope. The steeper the slope, the more the structural change has been able to induce metal ion size selectivity. It is seen that size selectivity increases in the order DHEAMP/AMP < 18-aneN_2O_4/$(NH_3)_2$ < $(py)_2$-18-aneN_2O_4/$(AMP)_2$, which is in line with what one would expect on the basis of the increase in steric demand on the metal ion that will be produced by the given structural change. Thus, addition of *N*-hydroxyethyl groups to AMP to give DHEAMP is not very sterically demanding. Thus, even for the smallest metal ion, Cu^{2+}, there is only a slight drop in complex stability, and the slope of DHEAMP/AMP is fairly flat. Formation of a macrocyclic ring in going from two ammonias to 18-aneN_2O_4 is considerably more sterically demanding than adding hydroxyethyl groups, and here we see a much steeper slope of $\Delta \log K$ vs. r^+, plus a considerable drop in stability for the complexes of the smaller metal ions. What is particularly interesting about Figure III is the slope for

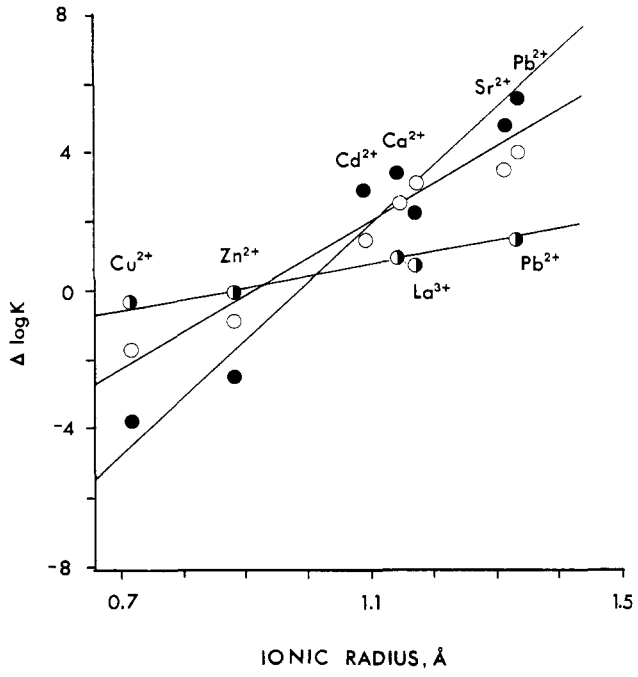

Figure 3. Change in stability, $\Delta \log K$, produced by adding donor groups containing neutral oxygen to amine ligands, as a function of the ionic radius[15] of the metal ions. The relationship of shallowest slope (◑) is that for the change in stability produced by adding two hydroxyethyl groups to AMP to give DHEAMP. The next relationship (○) is the change in stability produced by adding bridging diether groups to two ammonia ligands to give 18-aneN_2O_4, while the steepest slope (●) is for the change in stability produced by adding similar bridging groups to two AMP ligands to give the ligand $(py)_2$-18-aneN_2O_4. For key to abbreviations of ligands, see Figure 1.

$(py)_2$-18-aneN_2O_4/$(AMP)_2$, which is much steeper than that for 18-aneN_2O_4/$(NH_3)_2$. This greater steepness shows that making the same structural change to two AMP molecules to create the macrocyclic ring in $(py)_2$-18-aneN_2O_4 produces a ligand that is much more sterically demanding than if 18-aneN_2O_4 is generated from two ammonia molecules. Thus, metal ion size selectivity is enhanced by the presence of pendent donor groups on macrocycles.

Figure III allows us to quantify the metal ion size selectivity produced by various structural changes in ligands. One finds that the relationship obtained for other analogues of $(py)_2$-18-aneN_2O_4 is roughly superimposable on $(py)_2$-18-aneN_2O_4/$(AMP)_2$. Thus, DA-18-aneN_2O_4/$(glycine)_2$ gives about the same slope and intercept as $(py)_2$-18-aneN_2O_4/$(AMP)_2$, where DA-18-aneN_2O_4 is derived from 18-aneN_2O_4 by addition of two *N*-acetate groups. If it turns out to be generally true that such $\Delta \log K$ vs. r^+ relationships for 18-aneN_2O_4 derivatives are roughly superimposable, then this presents a useful method of predicting stability of complexes of as yet unsynthesized ligands derived from 18-aneN_2O_4 by addition of pendent donor groups to the nitrogens. Thus, for example, we are at present synthesizing the ligand DME-18-aneN_2O_4 (Figure 1), which is derived from 18-aneN_2O_4 by addition of mercaptoethyl groups. The interest here is to try to produce a ligand sufficiently powerful that it might possibly be useful in removing Cd^{2+} from the body, which is extremely difficult to achieve once metallothionein synthesis has begun.[1] Existing ligands such as BAL and EDTA are not able to achieve this.[1] Before going to the trouble of synthesizing DME-18-aneN_2O_4, one would like to have some idea of its complexing properties.

We can use Figure III to gain some idea of what the metal-complexing properties of DME-18-aneN_2O_4 are likely to be. Thus, the $\log \beta_2$ values for (mercaptoethyl)amine are known for many metal ions[2] or can be estimated as approximately $2 \log K_1 - 2.0$ where only $\log K_1$ is known (Pb^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) by comparison with metal ions where both $\log K_1$ and $\log \beta_2$ with (mercaptoethyl)amine are known. Thus, if we assume that the

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Table II. Formation Constants, log K, of Complexes of Ligands Based on the 18-aneN_2O_4 Ring[a]

metal ion	substituent			
	$-H^b$	$-CH_2CH(CH_3)OH^c$	$-CH_2COO^{-d}$	$-CH_2py^e$
Cu^{2+}	6.1	5.97		13.55
Ni^{2+}				8.80
Zn^{2+}	3.1	3.0	8.1	6.96
Cd^{2+}	5.25	7.64	11.9	10.96
Ca^{2+}	1.74[c]	3.59	7.7	3.63
Sr^{2+}	2.6	4.05		4.87
Ba^{2+}	2.97	4.65		4.99
La^{3+}	~3.0[f]	3.24	11.7	3.53
Pb^{2+}	6.8	8.57	13.5	11.67

[a] The donor groups indicated are attached to the two nitrogens of the ring of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane. [b] Taken from ref 2. [c] From ref 9b. [d] From Hancock, R. D.; Shaikjee, M. S., to be submitted for publication. [e] This work. [f] Hancock, R. D.; Hearn, A., unpublished work.

Δ log K vs. r^+ relationship is the same for DME-18-aneN_2O_4/$(HSEtNH_2)_2$ as for $(py)_2$-18-aneN_2O_4/$(AMP)_2$, then we can read off that Δ log K for Pb^{2+} will be 5.9 log units, and adding this to the log β_2 for (mercaptoethyl)amine to predict log K_1 equals 26.1 for DME-18-aneN_2O_4. Similarly, log K_1 for Cd^{2+} and Zn^{2+} can be predicted to be 22.9 and 16.3, respectively, with DME-18-aneN_2O_4, suggesting that this might indeed be a sufficiently powerful ligand for our purposes. In addition, the selectivity for Pb^{2+} and Cd^{2+} over Zn^{2+} should be very high, while log K_1 with the Ca^{2+} ion is predicted to be only about 7.0, so that selectivity over Ca^{2+} will also be very high. We are at present synthesizing DME-18-aneN_2O_4 so that we can study its complexing properties and suitability for treating metal-poisoning problems.

An interesting feature of the complexing properties of $(py)_2$-18-aneN_2O_4 is that (Table II) it binds very hard metal ions like Ca^{2+}, Sr^{2+}, and Ba^{2+}, which are not normally considered to have much affinity for nitrogen donors, more strongly than does DHP-18-aneN_2O_4. The poor affinity of these metal ions for nitrogen donor ligands arises from the fact that in the usual standard state the nitrogen donor ligand is competing with 55.5 M water. By comparison of $(py)_2$-18-aneN_2O_4 with DHP-18-aneN_2O_4, the pyridyl groups of the former ligand are placed on an equal footing with the hydroxypropyl groups of the latter, and it is seen that the pyridyl groups (Table II) are for all metal ions better donors than are the alcoholic groups. This fact suggests that recently reported[16] cryptand ligands that have all pyridyl donor groups will display what may at first sight seem surprisingly high affinity for the alkaline-earth-metal ions. Indeed, the isolation of $(py)_2$-18-aneN_2O_4 as a sodium complex[10] from solution, rather than as the free ligand, suggests that a surprisingly good affinity of pyridyl groups for alkali-metal ions will also be found.

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Registry No. $(py)_2$-18-aneN_2O_4, 103837-13-4; Cu, 7440-50-8; Ni, 7440-02-0; Zn, 7440-66-6; Cd, 7440-43-9; Ca, 7440-70-2; La, 7439-91-0; Sr, 7440-24-6; Pb, 7439-92-1; Ba, 7440-39-3.

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Synthesis and Metal Complexes of Macrocyclic Triamines Bearing a Phenol Pendant

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A novel, one-pot annelation method that "recycles" coumarin with the linear triamine 1,7-diamino-4-azaheptane has been applied to the synthesis of a phenol-pendant 12-membered macrocyclic triamine ([12]ane-N_3, **7**). The simplicity and versatility of this annelation method will be useful in the synthesis of a variety of macrocyclic spermidine alkaloid analogues. With Cu^{II}, Ni^{II}, and Zn^{II} the pendant phenol becomes phenolate at acidic pH to serve as the fourth donor. The resulting 1:1 metal complexes are more stable than the corresponding phenol-less [12]ane-N_3 complexes.

Introduction

Cyclization of saturated triamine ligands has remarkable thermodynamic and kinetic effects on complex formation. Although metal complexes of macrocyclic triamines have been studied extensively,[1-9] they are limited to unsubstituted triamines with various ring sizes. These macrocyclic triamines coordinate with transition-metal ions only facially for three-coordinated 1:1 complexes with the remaining coordination sites unoccupied (or solvated) in solutions or for six-coordinated 2:1 complexes.[6-9] The triamine ligands that posssess a potential fourth donor covalently attached to the macrocyclic rings might greatly affect the structure and properties of the complexes.

Recently,[10] we have discovered a novel annelation method for the synthesis of a new phenol-appended tetraamine macrocycle (**3**) starting from coumarin (**1**) and a linear tetraamine such as **2** and described some of their unique complexes properties. The pendant phenol readily interacts with encapsulated metal ions below in a N_4 macrocycle, which causes dissociation of its proton for an apical coordination (see **4**) to enhance the stability or drastically modify the structure of the complexes. An X-ray crystal structure of Ni^{II} complex **4** has proved the most appro-

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