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THE SELECTIVE COMPLEXATION OF METAL IONS BY LIGANDS BEARING CYCLOHEXYL SUBSTITUENTS

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A Dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Science.

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ABSTRACT

The addition of cyclohexyl substituents to existing ligands was investigated for its potential use as a factor in ligand design for achieving high specificity for particular metal ions. This work therefore gives the synthesis and stability constants of 7,16-bis(trans-2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (CY_2-K22) and 2-[bis(2-hydroxyethyl)amino]cyclohexanol (BHEAC). An attempt was also made at synthesizing the ligand 2,5,8-triazabicyclo [7,4,0] tridecane. However attempts to prepare this material from its tosylate precursor using standard methods of detosylation proved unsuccessful. An inverse relationship between the effect on complex stability of introducing a cyclohexyl bridge to a chelate ring, and metal ion radius was discovered. Small metal ions (Cu^{2+}, Ni^{2+}) showed larger stabilization in complex stability on the introduction of a trans-cyclohexyl bridge than large metal ions (Pb^{2+}, Ba^{2+}).

A potentiometric study was also undertaken into the complexes of open chain hydroxyethyl substituted amines which differed only in the degree and type of substitution on the hydroxyethyl substituent. The aim was to obtain a better analysis of the relative importance of inductive and

strain effects in the ethanolamine-type chelate ring - which is also present in CY_2-K22 and BHEAC. The stability constants of the ligands, namely: (1) 2-amino-1-propanol, (2) 1-amino-2-propanol, (3) tris(hydroxymethyl)aminomethane, (4) 2-amino-2-methyl-1,3-propanediol, (5) 2-amino-2-methyl-1-propanol and (6) tertiary-butylamine, were determined at 25°C and 0.1M ionic strength for comparative purposes. The results obtained emphasized the fine balance that exists between inductive and strain effects in the binding of Lewis acids in aqueous solution. It is therefore expected that molecular mechanics calculations will be utilized extensively as a predictive tool in ligand design. This will enable the co-ordination chemist to predict the steric strain involved in his/her research.

DECLARATION

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg, and has not been submitted before for any degree or examination at any other University.

G.J.B. Croft

March 1991

To my family

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LIST OF ABBREVIATIONS

AMP	2-(aminomethyl)pyridine
AMPDOL	2-amino-2-methyl-1,3-propanediol
AMPOL	2-amino-2-methyl-1-propanol
AP_2OL	1-amino-2-propanol
A_2POL	2-amino-1-propanol
BHEAC	2-[bis(2-hydroxyethyl)amino]cyclohexanol
BHE-K22	7,16-bis(hydroxyethyl)-1,4,10,13-tetra=oxa-7,16-diazacyclooctadecane
BHP-K22	7,16-bis(2-hydroxypropyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane
CDTA	1,2-diaminocyclohexanetetraacetic acid
CY_2-K22	7,16-bis(trans-2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane
DHEAMP	2-[di(2-hydroxyethyl)aminomethyl]pyridine
EA	ethanolamine
EDTA	ethylenediaminetetraacetic acid
EN	ethylenediamine
K_1	first equilibrium constant
K22	1,4,10,13-tetraoxa-7,16-diazacyclooctadecane
L	ligand molecule
M	metal atom
OH	hydroxide ion
pK_a	protonation constant
r^+	ionic radius

TEA	triethanolamine
THAM	tris(hydroxymethyl)aminomethane
THPED	tetra(2-hydroxypropyl)ethylenediamine
$\bar{n}$	average number of ligands per metal

INTRODUCTION

A.1 AN OVERVIEW OF MACROCYCLIC CHEMISTRY

Although metal complexes of naturally occurring macrocyclic ligands have been known for over seventy years, e.g., the unsaturated porphyrin and corrin ring derivatives, it has been only during the last thirty years that a large number of synthetic macrocyclic compounds capable of binding cations or anions have been prepared and investigated[1,2]. Many of these synthetic macrocyclic polyethers, polyamines, polythioethers, and other related molecules have been shown to possess very interesting and unusual ion binding properties. The novel macrocycles typically contain central hydrophilic cavities ringed with either electronegative or electropositive binding atoms and exterior flexible frameworks exhibiting hydrophobic behaviour. They show a pronounced ability to bind a wide variety of cations or anions and in many cases to undergo marked conformational changes during binding. Their hydrophobic exteriors allow them to solubilize ionic substances in nonaqueous solvents and in membrane media[1].

Macrocyclic chemistry has aroused great interest for several reasons[3]. One reason is the unprecedented co-ordinating ability of the oxygen-donor macrocycles to complex strongly with the alkali and alkaline-earth metal ions. Coupled with this is the unusual property that only very weak co-ordinating properties of oxygen-donor macrocycles are observed with the transition metal ions. The nitrogen-donor

macrocycles display more usual properties in that they complex most strongly with the transition and post-transition metal ions[3]. As a result of this behaviour Lindoy[4] suggests that the chemistry of synthetic macrocyclic ligands can be divided into two broad divisions. Firstly, there are the cyclic polyethers which complex strongly with the alkali and alkaline-earth metal ions, but preclude strong complexation with transition metal ions. Lindoy's[4] second category of synthetic macrocyclic ligands incorporates the ring systems containing donor atoms other than oxygen. The majority of such ligands contain nitrogen donor atoms, although ligands incorporating sulphur donors as well as phosphorous donors are also known. As mentioned above, these ligands typically form strong complexes with transition metal ions.

A second interesting property of the macrocycles is the cavity, which might enable the ligand to display selectivity towards metal ions which fit best into it[3]. Much work[5,6] supports this idea, although results with very large crown ethers[1,7] suggest that a "plateau" of stability is reached with very large rings, which does not correspond to strongest complexation of the largest metal ions by the largest rings.

Because of the interest in the properties of the oxygen-donor macrocycles, a special interest in oxygen as a donor atom has evolved. This involves open-chain

ligands containing oxygen-donors[8,9], macrocycles containing pendent oxygen-donor groups[9,10], and macrocycles with both oxygen and nitrogen donor atoms in the ring[11,13]. As a continuation of this investigation, the present work involves the examination of the cyclohexanol substituent. Hence in order to elucidate the role of the oxygen donor of cyclohexanol, an investigation into open-chain ligands bearing similar structural groups will give a greater understanding of the properties of cyclohexyl substituents and, in particular, cyclohexanol substituents.

It is pertinent, at this point, to consider why macrocyclic ligands often yield complexes which show unusual properties (compared with similar complexes of related open-chain ligands). Studies are still underway concerning these unusual properties[2,14]. However Lindoy[4], as early as the mid-seventies, considered there to be three main considerations. Firstly, on complex formation, geometrical factors arising from the cyclic nature of the ligands often impose additional constraints on the positions of the donor atoms. As a reflection of these constraints, macrocyclic ligand complexes containing unusual metal-donor atom bond distances, unusual bond angles, or grossly strained chelate-ring conformations are all known. Secondly, if the cyclic ligand is fully conjugated and incorporates $(4n + 2)\pi$ electrons, then enhanced electron delocalization and ligand stability are characteristic of the resulting Hückel aromatic system. Thirdly, and perhaps most importantly,

cyclic-ligand complexes are almost always found to be considerably more stable thermodynamically and kinetically (with respect to disassociation of the ligand from the metal ion) than their corresponding open-chain analogues. Such properties seem to be an intrinsic feature related to the cyclic nature of the ligands and have been collectively referred to as the macrocyclic effect. According to Hancock & Martell[2] the contributions which are expected to be important in the macrocyclic effect are:

1) Pre-organization of the ligand
2) Desolvation of the donor atoms in the confined space of the macrocyclic cavity
3) Intrinsic basicity effects
4) Dipole-dipole repulsion in the cavity of the ligand.

Macrocycles have been utilized in several practical fields. These include the fields of therapeutics[3,15], solubilization[16], catalysis[17] and those involving the biological processes of active ion transport across membranes (biomimetic membrane chemistry)[18,19].

Cyclic polyethers and the structurally related antibiotics such as valinomycin, nonactin, monactin, and other macrocyclic molecules, both biological and synthetic in origin, exhibit varying degrees of biological activity as related to the processes of active ion transport,

photosynthesis, and oxidative phosphorylation[18]. Recognition and transportation of ionic substrates by membrane carriers are of great importance in chemistry, biology and separation science[19]. The biological activity of these compounds appears to be related to their macrocyclic structure, which consists of a lipophilic exterior and a hydrophilic central cavity ringed with electronegative donor atoms, and their ability to assume highly specific conformations in the presence of metal ions. The macrocyclic nature of these compounds allows charged cations to be held in the central cavity, thus rendering the cations soluble in the lipid region of the membrane[18]. Recently anion transport has received much attention[19]. The anion carriers, which possess appropriate anion binding sites, such as quartemary ammonium cations and metal ions, interact with anionic substrates by inclusion, electro-static forces, co-ordination interactions, and/or hydrogen bonding. Proton-assisted transport of amino acid and related polycarboxylate anions via polyammonium macrocycles has been investigated by Tsukube[19]. The extent to which macrocyclic molecules influence alkali metal ion transport across intact mitochondrial and chromatophore membranes has been studied[19]. Research suggests that cyclic polyethers promote selective transport of alkali metal cations across membranes[19].

It has been reported[20] that simple lipophilic diaza-crown ethers show unique transport properties for primary and

secondary ammonium salts, which are markedly different from those observed with common crown ether systems. Certain diaza-crown ethers show high transport abilities for various ammonium cations of amino acid esters, while they offer low transport rates for potassium(I) and other metal ions. Because diaza-crown ethers having 15 to 21-membered ring sizes show potential transport properties for ammonium salts, it has been postulated that they may provide wide applications in the cation transport and in the related biomimetic systems[20].

Another important usage of macrocycles is their importance to bioinorganic modelling and catalysis. Cascade complexes formed by substrate inclusion between metal cations of bi- or polynuclear macropolycyclic complexes, subsequent to the inclusion of these cations themselves into the ligand, allows for the development of receptors with recognition sites. These complexes allow the study of cascade recognition[19]. It does not seem too daring a prediction, that the symbiosis of the architectural power of organic synthesis with the multiform properties of inorganic ions and molecules, provided by macropolycyclic ligands, should assure a bright future for this field of chemistry.

Lead, cadmium and mercury are metals which are currently of environmental concern[21]. 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[21].

Hancock[3,15] is currently involved in the development of ligands as therapeutic agents for the treatment of metal intoxication. Existing reagents for most applications have severe limitations[21], and it is clear that improved selectivity for toxic metal ions would be an advantage. The use of macrocyclic ligands in order to achieve this goal has been investigated[3,15] and this forms the basis of the current investigation.

The capacity of crown ethers to form complexes with alkali metal and alkaline earth metal cations has been investigated extensively[22,23] and utilized - often successfully - to solubilize sparingly soluble salts into apolar solvents, and for the solubilization of water-insoluble salts into water. As an example of the latter case it was found that bis(carboxymethyl)diaza-18-crown-6 and bis(phosphonomethyl)-diaza-18-crown-6 are efficient solubilizers of $BaSO_4$ in water[16]. Problems caused by precipitation of salts from aqueous phases are frequently encountered in those industrial operations in which local non-purified water has to be used. For example, the use of seawater as injection fluid in oil-producing locations often leads to clogging of wells as a result of $BaSO_4$-scale formation[16]. Consequently the synthesis of macrocyclic complexants specifically designed to solubilize $BaSO_4$ efficiently into water went a long way towards solving the problem of $BaSO_4$-scale formation. Of particular interest was the approach of the authors in solving this problem. In designing crown ethers for the complexation of barium cations, numerous parameters

of importance were first identified. From this sound basis the authors[16] were able to successfully design ligands capable of efficiently solubilizing $BaSO_4$ into water.

This overview provides the reader with an understanding of some of the history, properties and potential uses of macrocycles. Although it only covers a small section of the huge literature on macrocycles, the reader should appreciate the reasons behind the continuation of research into macrocyclic chemistry. One objective of this study was to synthesize ligands for specific complexation of metal ions of interest in biological systems.

(A.2) THE BINDING OF LEWIS ACIDS IN AQUEOUS SOLUTION

Aqueous pK_a values of amines (given in parentheses below) show little response to the increasing inductive effect of substituents, whether substitution is directly on the nitrogen[24] in the series ammonia (9.2), methylamine (10.6), dimethylamine (10.8), and trimethylamine (9.8), or on the α-carbon atom in the series methylamine, ethylamine (10.7), isopropylamine (10.6) and tert-butylamine (10.7)[25]. A similar effect has been found in carbon-methylated ethylenediamines[26] in that the pK_a values are insensitive to increasing inductive effects of methyl groups in passing from ethylenediamine through DL-2,3-butylenediamine to 1,1,2,2-tetramethylethylenediamine. This gives the impression that alkyl substitution has little effect on nitrogen donor basicity. It is thus with surprise that increasing stability is found for aqueous formation constants (logK) of Ag(I) with the above set of α-C-methylated primary amines[25] and metal ions such as Cu(II) and Ni(II) with C-methylated ethylenediamines[27].

It was only with advances in gas-phase chemistry[28-34] that a fairly detailed understanding of such phenomena as reversal of relative basicity orders with successive methyl substitution in transferring from gas-phase to water could be explained. An examination of the free energy of protonation in the gas phase of the series of bases NH_3 through to $N(CH_3)_3$ will reveal that there is an increase in intrinsic basicity as hydrogens are replaced by methyl groups. Why then do the protonation constants of the amine

series not display this intrinsic basicity order in water? The pKa values of the amine series NH_3 through to $N(CH_3)_3$ in water give the impression that the intrinsic basicity varies little along this series. If a Born-Haber cycle is constructed for each of the amines in this series, it becomes apparent that the poor basicity of $N(CH_3)_3$ (relative to what might be expected from the gas-phase basicities) is due to the lower energy of solvation of the $(CH_3)_3NH^+$ cation. This appears to be caused by two affects[35,36]. Firstly, the proton in the gas phase is bare, so it experiences much less strain in co-ordinating to $N(CH_3)_3$. In water, however, the proton has a bulky solvation sheath, which is sterically hindered by the methyl groups of trimethylamine. The second factor which is thought[37] to account for the relatively poor basicity of $N(CH_3)_3$ is its inability to disperse positive charge to the solvent through hydrogen bonding. Thus, N_4^+ is stabilized relative to $(CH_3)_3NH^+$ by the inability of the CH_3 groups on $(CH_3)_3NH^+$ to hydrogen bond to the solvent.

Taft <u>et al</u>[38] have shown that inductive effects of methyl substituents are quenched to about 50% in aqueous solution, while polarizability effects are neutralized as the highly polar co-ordinated water molecules take over charge dispersion in protonated amines. The extra stabilization of the more solvated protonated amines must, therefore, be attributed to specific solvation, which arises because of the solvent having specific sites of attachment on the

solute. The polarizability effects that account for stability of ions in the gas-phase are removed by hydrogen bonding as protonated nitrogen donor bases are stabilized by co-ordinated water molecules which take over charge delocalization.

Because the pK_a values of primary and secondary amines in water are very similar it has led to a strong intuitive feeling among many chemists that the basicities of primary and secondary nitrogens are not intrinsically very different[39]. This is evidenced, for example, in the rejection[40] of the idea that greater basicity of the secondary nitrogens contributes to the macrocyclic effect. The data on the binding of amines to metal ions in the gas-phase[28-34], mentioned earlier, clarifies this situation. There is evidence that in the gas-phase all metal ions respond favourably to a change from primary to secondary amines. This supports the contention by Hancock et al[41] that metal-nitrogen bonds to secondary nitrogens are intrinsically stronger than those to primary nitrogens. Currently it appears that the complexing tendencies of Lewis acids in aqueous solution[42-44] suggest that, for most metal ions, steric effects are of paramount importance in their complex formation reactions. The inability of some Lewis acids, such as the small and highly solvated ions H^+, Cu(II) and Ni(II), to form strong complexes with soft[45] ligands such as I^-, seems not to derive from an inherent weakness of the M-L bond (i.e. the hardness[45] of the Lewis acid), but from steric interactions between the ligand and the water

molecules co-ordinated to the metal ion. This is illustrated by the large Ag(I) ion, which, because of its linear co-ordination geometry, is only slightly affected by steric effects. Hence it has been suggested[42] that the Ag(I) ion is less susceptible than the proton to steric hindrance to co-ordination, caused by the large hydration sphere and small size of the latter. This allows Ag(I) to form strong complexes with Cl^- compared with Cu(II)[48]. The implication is that a system may be developed which allows the steric environment around a metal ion to be controlled in such a manner that the chemistry (complex formation reactions) of Lewis acids can be altered or even reversed.

Steric hindrance and specific solvation effects are therefore of importance in determining aqueous Lewis acid-base behaviour. The binding of the proton to ligands in water is not always a good indicator of inductive effects, which may be "hidden". Gas-phase results show up these hidden inductive effects very strongly, for both the proton and other Lewis acids. For both the proton and other Lewis acids, these inductive effects may be masked in aqueous solution by steric hindrance. For metal ions with low susceptibility to steric hindrance such as Ag(I) with primary amines or square-planar Cu(II) and Ni(II) with symmetrically C-methylated ethylenediamine ligands, the inductive effects may be able to overcome steric effects and manifest themselves as increasing complex stability and

stronger ligand fields[46]. It was therefore proposed that the proton may no longer be used, as has so often been the case, as an indication of inductive effects in aqueous complex formation reactions, because these effects are often masked by steric hindrance and are therefore called "hidden" inductive effects[47].

The fine balance that exists between the contributions of inductive and steric effects, is emphasised by the work done on adding C-methyl groups to ethylenediamines[46]. Such a seemingly small change as placing both methyl groups on the same C atom of the bridge in 1,1-dimethylethylenediamine can destabilize the Ni(II) and Cu(II) complexes relative to that of ethylenediamine, whereas placing them on separate carbon atoms, as in L-2,3-butylenediamine can stabilize the Cu(II) and Ni(II) complexes.

Crystallographic studies and molecular mechanics calculations[49] have shown that the planar ring of cyclam has a considerable thickness and that there is significant steric hindrance to co-ordination at the axial sites of the planar complexes of cyclam. The inability of ligands with large donor atoms (Cl^-, thiourea) to co-ordinate to the Cu(II) complex of cyclam[50] is, therefore, in agreement with sterically hindered axial co-ordination sites in this complex. This emphasizes the role of steric effects in aqueous Lewis acid-base complex formation reactions. It is, however, with surprise that some of the ligands which are

expected to form quite strong complexes with the Cu(II) complex of cyclam, since these have small donor atoms (F^-, OH^- or NH_3), also do not co-ordinate, whereas ligands such as N_3^-, SCN^- and CN^- which have small donor atoms, do bind[47]. It appears that the former ligands are those which are expected to form strong hydrogen bonds to the solvent, while the latter are ligands which are not expected to bind the solvent very strongly, suggesting that the co-ordinated water molecules must, in aqueous solution, be able to enter into structuring the hydrogen-bonded water around ligands such as F^-, OH^- or NH_3, which is not possible with the hydrophobic alkyl bridges of the cyclam ring[47]. The apparent role of hydrophobicity in weakening the binding of hydrophilic ligands emphasizes the role that specific solvation effects play in aqueous Lewis acid-base complex formation reactions. As discussed earlier, increasing stability with increasing C-methylation in symmetrically substituted diamine square-planar complexes of Cu(II) and Ni(II) has been found[27]. One of the reasons for this has been attributed to low steric interactions between groups in the co-ordination sphere of the metal ions. The hydrophobic nature of the C-methylated ethylenediamine skeleton leads to a loss of water molecules from the co-ordination sphere of the metal ion, resulting in rearrangement of the co-ordinated groups to form the less sterically strained planar configuration, where substituents are on either side of the ring. Consequently, there is a greater overlap between the orbitals and therefore stronger M-N bond strengths which manifest themselves in the increased

stabilities of these complexes. This is another example of hydrophobicity playing a part in aqueous Lewis acid-base complex formation reactions.

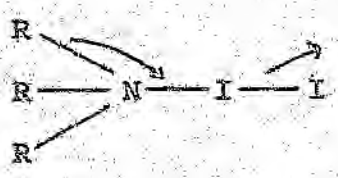
It has been found[47] that for Co(II), Zn(II) and Cd(II) metal ions $\log K_1(OH^-)$ for the tetramethylcyclam (TMC) and tetraethylcyclam (TEC) complexes is larger than the corresponding $\log K_1(OH^-)$ for the formation of the monohydroxo complexes of the aqua ions. This has been attributed to the unusual five co-ordinate geometry imposed on metal ions in the TMC and TEC complexes. The metals cannot adapt to this strained arrangement, thus leading to a stronger bond between the metal ion and the axially co-ordinated water molecule, presumably because of poor overlap of the orbitals of the metal ion and those of the in-plane nitrogens. It is clear that, by only altering the co-ordination sphere around these Lewis acids, a change in their aqueous complex formation properties has been effected.

Molecular mechanics calculations[3] show that the co-ordination sphere around a small metal ion is extremely crowded. In the extreme case, such as in octahedral Co(III), van der Waal's repulsion between the ligands prevents the donor atoms of the ligand from approaching the metal ion to the strain-free Co-N bond length of 193pm [3].

In actual complexes of Co(III) with amines, the observed Co-N bond lengths fall in the range 194-204 pm. The fact that the Co-N bond lengths are longer than those which would be observed in a strain-free situation, i.e. 193 pm, is caused by the Co-N bond stretching associated with steric crowding around the metal ion. Addition of any organic substituents leads to a dramatic increase in steric crowding[3]. The response of the complex to this steric crowding is principally one of metal to ligand bond stretching, which allows for a decrease in the number of ligand atoms in the immediate vicinity of the metal ion. Steric crowding and the resulting steric strain produce an unfavourable contribution to complex stability. Leussing[51] suggested that the enhanced stability observed in symmetrically c-methylated complexes of Cu(II and Ni(II) was due to the inductive effects of the methyl groups overcoming steric hindrance. The destabilizing effect of N-methylation on ethylenediamine compared with c-methylation[51] supports this suggestion by Leussing, because with substitution on the nitrogen the substituents become very much closer to the co-ordination site than in the latter case. This close proximity of co-ordinated groups in the complex leads to crowding, hence the adverse steric effects.

It is found[52] that charge transfer bands in low strain complexes such as $I_2.NH_3$ through $I_2.NR_3$ move in parallel with the heats of complex-formation, indicating that

increasing complex strength is caused by a process of the type



as NH_3 is changed along the series through to NR_3. It is generally considered[46] that LF strength in complexes of transition metal ions is a measure of covalence in the M-L bond. Consider the LF splitting parameter, 10 Dq, in the following series[2]:

complex:	$[Ni(NH_3)_6]^{2+}$	$[Ni(EN)_3]^{2+}$	$[Ni(9\text{-}aneN_3)_2]^{2+}$
10 Dq	10750 cm^{-1}	11500 cm^{-1}	12350 cm^{-1}
	"zeroth" nitrogens	primary nitrogens	secondary nitrogens

complex:	$[Cu(NH_3)_4]^{2+}$	$[Cu(EN)_2]^{2+}$	[Cu(2,3,2-tet)]$^{2+}$	[Cu(cyclam)]$^{2+}$
10 Dq	17000	18300	19000	19900
nitrogens:	"zeroth"	all primary	two primary two secondary	all secondary

The interpretation placed upon these series is that one is increasing 10 Dq because the covalence in the M-N bond is increasing as the nitrogens are changed from "zeroth" to primary and then secondary. The important aspect here is that the values of 10 Dq follow the order of intrinsic basicity of the nitrogens, only because here sufficiently low steric strain has been achieved. A general result in

macrocyclic chemistry is that where the macrocycle co-ordinates to the metal ion with low steric strain, very high LF strengths are observed[2]. The increased ligand field strength found in complexes of macrocyclic ligands is at a maximum in the macrocycles which fit with the least steric strain around the metal ions[39]. If the metal-donor atom bond is strained, this leads to a diminishing of the overlap between the donor atom and metal orbitals forming the bond, and hence a decrease in 10 Dq, if we consider the molecular orbital interpretation[53] of ligand field (LF) theory. The effect of steric strain on LF strength was investigated[39], and a simple model was developed which relates strain in the metal-nitrogen bond to the LF strength. This model supports the idea that the high LF strength in complexes of macrocyclic ligands is due to a large number of secondary nitrogen donors in a situation of comparatively low strain in the metal-nitrogen bond. The increased LF strength is caused by the inductive effect of the increased number of secondary nitrogen donors present in a low-strain situation, which also contributes to the macrocyclic enthalpy[39]. An example where LF does not increase with increasing basicity of the ligand, as a result of steric strain, can be found in the complexation of high spin Co(II) and Co(III) by sepulchrates[54], formally cryptands. The LF strength of the sepulchrates appears to be no different from that of the TRIS-EN analogue[54], since Co(II) and Co(III) TRIS-EN complexes appear to have LF spectra almost identical to those of the sepulchrate analogues[2]. An important factor to

consider here is the postulate that where there are secondary rather than primary nitrogen donor atoms, a higher LF is expected if the metal ion is co-ordinated by the ligand without excessive strain. High-spin Co(II) and Co(III) do not show higher LF values because they are respectively too big and too small for the cavity in the sepulcrate[55], causing excessive strain. It is clear from the above discussion that the effect on ligand field strength, and in particular complex stability, will thus be the nett balance of the steric and inductive effects produced by the ligand on complex formation.

The equation of Pavelich and Taft[56] below, which takes polar (inductive) and steric effects into account, has been used highly successfully to separate and correlate these effects.

$$\log K = \log K^{o} + p^{*}\sigma^{*} + \delta E_{s} \qquad (1)$$

logK is the formation constant for the base with any given substituent and $\log K^{o}$ for that with the methyl group as substituent. The Taft inductive effect parameter, σ^{*}, becomes more negative as the substituent becomes more electron releasing, while p^{*} is analogous to the Hammett p constant. A more negative p^{*} indicates increasing ability on the part of the Lewis acid to respond to the inductive effect of a substituent. E_s is a measure of the ability of the substituent to cause steric hindrance, taken as zero for the methyl substituent, while δ measures the susceptibility

of the Lewis acid to steric hindrance[25,46]. Hancock, et al[46] found by fitting equation 1 to the data for Ag(I), Hg(II), and the proton with a selection of primary amines, designed to give as wide a range of σ^* and E_s values as possible, values of p^* of -1.1,-2.83 and -3.95 and of δ of -0.09, 0.37 and 0.68, respectively. The values indicate a very low susceptibility to steric effects on the part of Ag(I) whereas the p^* values show that the proton responds best to an increased inductive effect of the substituent. This supports the proposal[42] that susceptibility to steric hindrance is an important factor in accounting for the low affinity of the proton or Ni(II) for ligands such as chloride ion in water, as compared with that displayed by large ions such as Ag(I).

Another interesting phenomenon in aqueous Lewis acid-base complex formation reactions can be found by examining the values of $\log K_1(NH_3)$ and the corresponding ionic radii for the metals Cu(II), Ni(II), Zn(II), Cd(II), and Pb(II). These can be found in Table A.1.

Table A.1 : $\log K_1$ values, at 25°C and ionic strength 0.1M, for ammonia and ionic radii for a selection of metal ions

Metal ion	Ionic radii[a] (pm)	$\log K_1(NH_3)$[b]
Mn^{2+}	71	4.10
Ni^{2+}	83	2.70
Zn^{2+}	88	2.18
Cd^{2+}	109	1.9
Pb^{2+}	133	1.6

[a]Data from reference 59. All six co-ordination except for Cu^{2+} which is four co-ordination. [b]Reference 26 except for Pb^{2+} reference 57 and Cd^{2+} reference 58.

It is clear that as the ionic radius increases so $\log K_1(NH_3)$ decreases. Since this is the case, it is possible that small metal ions react more favourably than large metal ions to inductive effects on amine ligands. Hence increasing the electron donating ability of the amine substituent is expected to produce a more favourable change in the stability constants of small metal ions than that for large metal ions.

(A.3) THE IMPORTANCE OF MOLECULAR MECHANICS (MM)

An important consideration in analyzing effects such as the chelate effect, is the increase in strain energy, ΔU, which occurs on complex formation[41]. Molecular mechanics calculations serve as a tool for the determination of the change in strain energy on complex formation. For example, work done by Hancock et al[60,62] on the Ni(II) complex of cyclam and tetramethylcyclam (TMC) showed that by replacing hydrogens on the donor atoms of cyclam with methyl groups to produce TMC produces a concomitant decrease in complex stability from $\log K_1 = 20$ for the cyclam complex[61] to only 8.6 for $[Ni(TMC)]^{2+}$. The MM calculations using a strain-free Ni-N bond length of 1.91 Å, in both cases, predicted a Ni-N bond length of 1.93 Å for the $[Ni(cyclam)]^{2+}$ complex and a Ni-N bond length of 1.99 Å for the $[Ni(TMC)]^{2+}$ complex. The calculations agreed with the results of X-ray crystallography, even down to quite small structural details[60]. The calculations also showed that the stretching of the Ni-N bonds in $[Ni(TMC)]^{2+}$ is due to v.d. Waal's repulsions between the N-methyl groups. Accompanying the stretching of the Ni-N bonds is an increase in the total strain energy, ΣU, from 11.3 kcal mol^{-1} in $[Ni(cyclam)]^{2+}$ to 35 kcal mol^{-1} in $[Ni(TMC)]^{2+}$, which seems to be the most probable explanation for the drop in complex stability for Ni(II) in going from the cyclam complex to the tetramethylcyclam complex. It has also been found[63] that there is an accompanying drop in the ligand-field splitting parameters in going from $[Ni(cyclam)]^{2+}$ to $[Ni(TMC)]^{2+}$.

This indicates decreasing overlap in the bond as the Ni-N bond is stretched in $[Ni(TMC)]^{2+}$. Hence molecular mechanics calculations of this nature can help to explain such phenomena as decreasing complex stability and a drop in ligand-field splitting parameters, since they can be used to calculate strain energies of complexes. One can thus hardly profitably consider the thermodynamics of complex formation without taking steric strain into account. Consequently molecular mechanics (MM) calculations are used as an aid to understanding complex stability.

The apparent paradox that larger metal ions co-ordinate more strongly to the small macrocycle 12-aneN_4 than to the large 14-aneN_4 was examined by performing molecular mechanics calculations[64]. These calculations showed that, in its trans-I conformer, 12-aneN_4 has a larger cavity, with best-fit M-N lengths of 2.11 Å, compared with 2.05 Å for the trans-III conformer of 14-aneN_4. In addition, it was found that the macrocyclic ring of 12-aneN_4 is more flexible than that of 14-aneN_4, thus allowing better response to a change of metal ion size. Thus MM calculations were able to help explain the paradox that most metal ions complex most strongly to 12-aneN_4, with only small metal ions, such as Cu(II), prefering the large 14-aneN_4. Molecular mechanics calculations[41,65] have also been used to support the idea[66] that the drop in complex stability in going from five to six-membered chelate rings is due to steric strain. In

addition plots of the strain energy of a complex, U, as a function of the metal-donor atom bond length, r, obtained through MM calculations, have been found[49] to be able to predict with success the configuration of co-ordinated tetraaza macrocycles. It is therefore apparent that the use of MM calculations has aided the co-ordination chemist in understanding various complex formation phenomena.

In the future an important task in co-ordination chemistry will be the synthesis of highly pre-organized ligands[2]. Molecular mechanics will be used as a tool in ligand design, in order to predict the properties of a ligand before one gets involved in the more difficult task of synthesizing the ligand. In this way MM calculations could save the co-ordination chemist from synthesizing many ligands. In the endeavour to produce ligands with remarkable properties, such as size selectivity, and the stabilization of unusual oxidation states, this will mean that much time would be saved.

(A.4) EFFECT OF ADDING NEUTRAL OXYGEN DONORS TO EXISTING LIGANDS

Neutral oxygen as a donor atom, in the form of alcoholic and ethereal oxygens, is of considerable interest because of the macrocyclic effect found in complexes of crown ethers with metal ions such as the alkali and alkaline-earths[5]. The relatively high stability[67] of these complexes is of particular interest, as it appears to have no precedent in open-chain ligands. As a first step to an understanding of the complexing properties of crown ethers, the stability of complexes with neutral oxygen-donors in open-chain ligands has been examined[8]. It has been found[8] that investigations of ligands with neutral oxygen-donors can lead to a greater understanding of the macrocyclic effect in oxygen-donor macrocycles. Because of the interest in the properties of the oxygen-donor macrocycles, Hancock[3] has taken a special interest in oxygen as a donor atom. As mentioned previously (Section A.1), this has involved open-chain ligands containing oxygen-donors, macrocycles containing pendant oxygen-donor groups, and macrocycles with both oxygen and nitrogen donor atoms in the ring. It has been found[2] that the effects on complex stability of adding neutral oxygen donors in chelating groups to produce open-chain ligands containing oxygen-donors, are very similar to the effects of adding oxygen-donors to form macrocycles or cryptands. Thus, many of the properties of oxygen-donor containing macrocycles are to be understood in terms of the

co-ordinating properties of the neutral oxygen donor atom, and are not solely produced by the presence of a macrocyclic structure. Most important here is the intrinsic basicity along the series H_2O, ROH, R_2O (R = alkyl).

An interesting effect which emerges is found[8] on passing from oxalate to oxydiacetate (ODA). In passing from oxalate to ODA an ethereal oxygen-donor held in position by two methylene groups is inserted. Those metal ions, whose complexes increase in stability on inserting the ethereal oxygen donor atom into oxalate to give ODA, are precisely those metal ions which form stable complexes with crown ethers. On the other hand, those metal ions whose complexes decrease in stability are those which do not. The interpretation here[8] is that for all the metal ions studied, the inductive effect of the ethereal oxygen-donor atom should lead to an increase in complex stability, in the absence of steric effects. For metal ions such as Pb(II), La(III) or Ca(II), the increase in steric strain is not sufficient to counter the inductive effect, and increases in complex stability occur, while for Cu(II) and Fe(III) it is, and decreases in complex stability result. The behaviour of Pb(II) and La(III) on adding a neutral oxygen-donor in going from oxalate to ODA is thus of importance in understanding the high stability of their complexes with the ligand tetrahydroxyethylcyclam[68], where the hydroxyethyl "arms" of the macrocycle lead to considerable stabilization. It also accounts for the high stability of ethanolamine and

triethanolamine complexes of Pb(II)[8]. For ethanolamine and triethanolamine, $\log K_1$, for all the metal ions in Table A.2, is approximately the same as $\log K_1(NH_3)$, except for Pb(II) where it is much higher. This suggests[8] that the hydroxyethyl groups of triethanolamine, and the single hydroxyethyl group of ethanolamine, lead to a stabilization of the Pb(II) complex, whereas in the complexes of the other metal ions no such stabilization is present.

It has been found[3] that the addition of neutral oxygen donors to existing ligands produces a size-related change in complex stability such that large metal ions show more favourable changes than do small. In general, two types of relationships have been found between $\Delta\log K$, the change in complex stability, and r^+, the ionic radius of the metal ion. Either linear or peak relationships have been found[3],

Table A.2 : Comparison of $\log K_1$ values for ammonia, ethanolamine and triethanolamine at 25°C and ionic strength 0.1 M.[a]

Metal ion	$\log K_1(NH_3)$	$\log K_1$(ethanolamine)	$\log K_1$(triethanolamine)
Cu^{2+}	4.10	4.50	4.07
Ni^{2+}	2.70	3.05	2.76
Co^{2+}	2.10	2.20	2.25
Zn^{2+}	2.18	2.41	2.05
Pb^{2+}	1.6	4.10	3.39

[a]Data from reference 8.

with smaller metal ions showing less favourable changes in complex stability than larger metal ions, when groups containing neutral oxygen donors are added to an existing ligand.

Studies of gas-phase basicities[28-34] show that for neutral oxygen donors the donor strength increases $H_2O < ROH < R_2O$, and for amines $NH_3 < RNH_2 < R_2NH < R_3N$, where R is an alkyl group. Insertion of a bridging ethylene group between, say, an oxygen and a saturated nitrogen donor will thus produce favourable inductive effects. The effect on complex stability will be the nett balance of the steric and inductive effects produced as we modify a complex by adding organic structural elements such as bridging ethylene groups[3]. Linear $\Delta\log K$ versus r^+ relationships on adding neutral oxygen donors to existing ligands suggest, as is supported by MM calculations[39,69], that steric crowding increases with decreasing metal ion size to the extent that it outweighs the inductive effects (negative values of $\Delta\log K$), as we add groups containing neutral oxygen donors to existing ligands. For large metal ions, even though the co-ordination number tends to increase, steric effects appear to be outweighed by inductive effects, and increases in complex stability occur. What is remarkable is that the change in complex stability, in some cases, is a linear function of metal ion size[3]. The linearity appears to be a general phenomenon when groups containing neutral oxygen donors are added. This behaviour has often been referred to as the "steric bulk" theory of complex stability.

In explaining the peak in the relationship of ΔlogK versus r^+ on adding neutral oxygen donors to existing ligands, which is found in cases where linearity has been lost, two explanations are possible. In the case where a macrocyclic ring is formed on addition, as is found in passing from 18-ane-N_2O_4 to cryptand-2,2,1, the peak at 120 pm must represent the size of metal ions for fitting into the cavity of cryptand-2,2,1 which accords with estimates made from models. At metal ion sizes above 120 pm, therefore, the metal is too large to fit into the cavity of the macrocycle without causing constriction[3]. It is worth mentioning here, however, that size match selectivity, whereby the most stable complex is formed where there is a closest match between the size of the metal ion and the size of the cavity in the ligand, appears not to be strong in macrocycles[2]. For example, selectivity patterns with alkali metal ions are very similar in both crown ethers and in open chain ethers where there is no cavity.

The second explanation for a peak in the relationship between ΔlogK and r^+, on adding neutral oxygen donors to existing ligands, can be found when explaining the peak for the relationship between ΔlogK for ODA and oxalate and r^+, at an r^+ value of about 115 pm. Since there is no cavity, this is thus not interpreted as a best fit size of metal ion, as for the relationship involving cryptand-2,2,1 and 18-ane-N_2O_4, but rather as a shift in the balance between steric and inductive effects. Thus, the rate of fall-off of steric effects beyond an r^+ value of 115 pm for the

ODA/oxalate relationship decreases, and for large metal ions electronic effects dominate. With further increases in size there is thus a levelling out or even fall-off in complex stability, as the stability is now controlled by electronic effects.

Interestingly, the complexes of larger metal ions are destabilized more than those of smaller metal ions by an increase in the size of the chelate ring[2]. This is found to be true for complexes of EDTA (ethylenediaminetetraacetic acid) and its analogue based on trimethylenediamine, TMDTA. One can obtain a linear relationship between the change in complex stability between the TMDTA complex, and the EDTA complex, $\Delta \log K$, and the ionic radius of the metal ion. The change in complex stability on increase of chelate ring size is metal ion related, and is thus not a property of the free ligand, but of the complex. The metal ion size related pattern of the dependance of complex stability on chelate ring size can be observed for many pairs of ligands, such as EDTA and TMDTA, or 13-aneN_4 and 14-aneN_4. Hence it is also observed for pairs of macrocyclic ligands[2]. From the foregoing discussion one can conclude[3] that the following two general rules hold in relation to control of selectivity on the basis of metal ion size.

1. The addition of neutral oxygen-donor groups to ligands will increase the selectivity of the ligand for large metal ions relative to small. In general, the

size-selectivity produced will be sharper for macrocyclic structures than for open chain ligands.

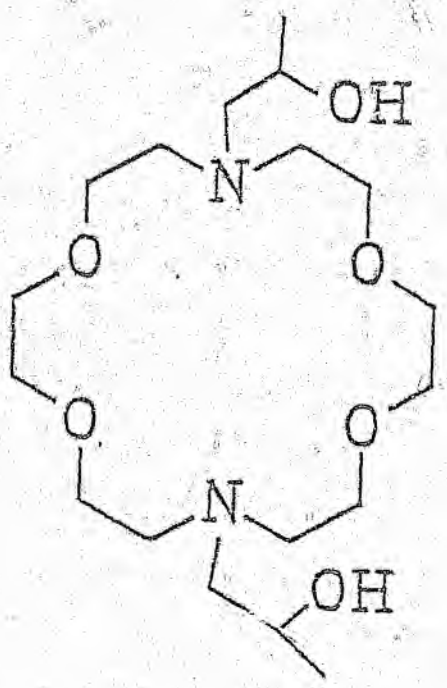
2. Increase of chelate ring size from five to six-membered will favour ligand selectivity for small metal ions over large.

These two general rules are borne in mind during ligand design. Consequently they are often referred to as ligand design rules. Recently[70] the view has been taken that for oxygen donors there exists only one rule and not two as described above. The belief is that the dominant effect is controlled by a change in chelate ring size only.

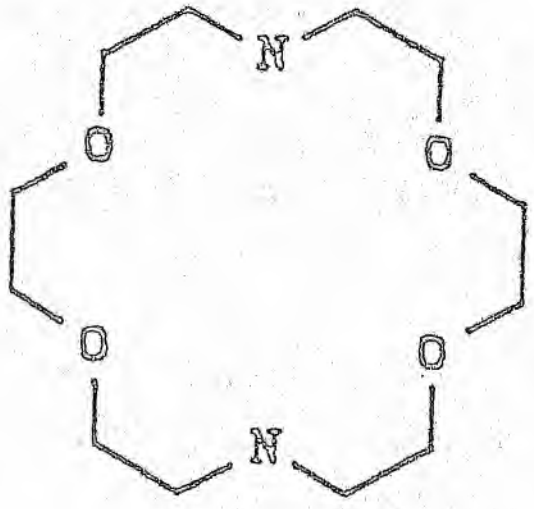
It is generally accepted[3] that the addition of pendent donor groups bearing neutral oxygen donors to macrocycles should favour large metal ions but disfavour small. Interestingly, the addition of neutral oxygen donors via pendents attached to secondary nitrogen donors of macrocycles is expected to increase the basicity of the nitrogen donor and not decrease it as commonly thought[2]. This is seen in the series of ligands where protons are progressively replaced by hydroxyethyl groups, where the protonation constants are: NH_3, 9.2; $NH_2CH_2CH_2OH$, 9.5; $NH(CH_2CH_2OH)_2$, 8.9; $N(CH_2CH_2OH)_3$, 7.8. Thus, one might have expected the inductive effects to be unfavourable on the tertiary nitrogen atoms produced by addition of pendents bearing neutral oxygen donors. One might thus draw the inference from the low pK_a value of

triethanolamine, that oxygens will lead to electron-withdrawing effects, and increased basicity arguments are not correct. However, if one proposes that ethoxy groups are electron withdrawing relative to the proton, how can one then explain the fact that the pK_a for ethanolamine is higher than that of ammonia? The answer is that the ethoxy group is not electron-withdrawing relative to a proton, and the low basicity of triethanolamine is a solvational and a steric problem in exactly the same way as for trimethylamine (section A.2). The true order of inductive effects for the ethoxy substituent is more closely reflected in the order of protonation constants: NH_3, 9.2; $NH_2CH_2CH_2OH$, 9.5; and $NH_2CH_3CH_3$, 10.8.

It has been found[15] that metal ion size selectivity is enhanced by the presence of pendent donor groups on macrocycles. As a consequence of this, numerous macrocycles with pendent donor groups have been synthesized[15] in order to obtain the high selectivity required by therapeutic agents for removing specific metal ions from the body in cases of metal poisoning. Many of these macrocycles have been derived from the macrocycle 18-aneN_2O_4 by addition of pendent donor groups to the nitrogens[15]. One of these is the macrocyclic ligand[9] 7,16-bis(2-hydroxypropyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, more commonly referred to as BHP-K22. Figure A.1 gives a pictorial representation of BHP-K22 together with its unsubstituted analogue 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, commonly called 18-ane-N_2O_4 or just kryptofix 22 (K22).



A



B

Figure A.1 : Macrocylic structures of BHP-K22 (A) and K22 (B)

It is apparent from Figure A.1 that in effect BHP-K22 is derived from K22 by addition of neutral oxygen donors in the form of 2-hydroxy propyl pendents. Figure A.2 shows the change in complex stability, $\Delta \log K$, produced by this addition as a function of the ionic radius of the metal ions investigated[9]. It is clear that the hydroxy propyl pendents on the BHP-K22 macrocycle offer increased steric bulk and hence steric crowding with small metal ions. Thus the ligand favours complexation with larger ions (inductive effects dominating), as is seen by the relative increase in stability for its complexes with Pb^{2+}, Ba^{2+} and Sr^{2+} over those for 2. For large metal ions steric effects appear to be outweighed by inductive effects and increases in complex stability occur for BHP-K22.

It is clear from Figure A.2 that the addition of neutral oxygen-donors to K22 to produce BHP-K22 produced a size-related change in complex stability which supports the general behaviour, as discussed earlier in this section, found[3] when neutral oxygen-donors are added to existing ligands. The peak for Cd^{2+} seen in figure A.2 is interpreted in the same way as the peak found for the ODA/oxalate relationship[3], discussed earlier. The peak is due to a shift in the balance between steric and inductive effects. Thus the rate of fall-off in steric effects beyond an r^+ value of 110 pm for the BHP-K22/K22 relationship drops off, and for larger metal ions electronic effects dominate. With further increasses in size there is thus a levelling out or even fall-off in complex stability as the stability is now controlled by electronic effects.

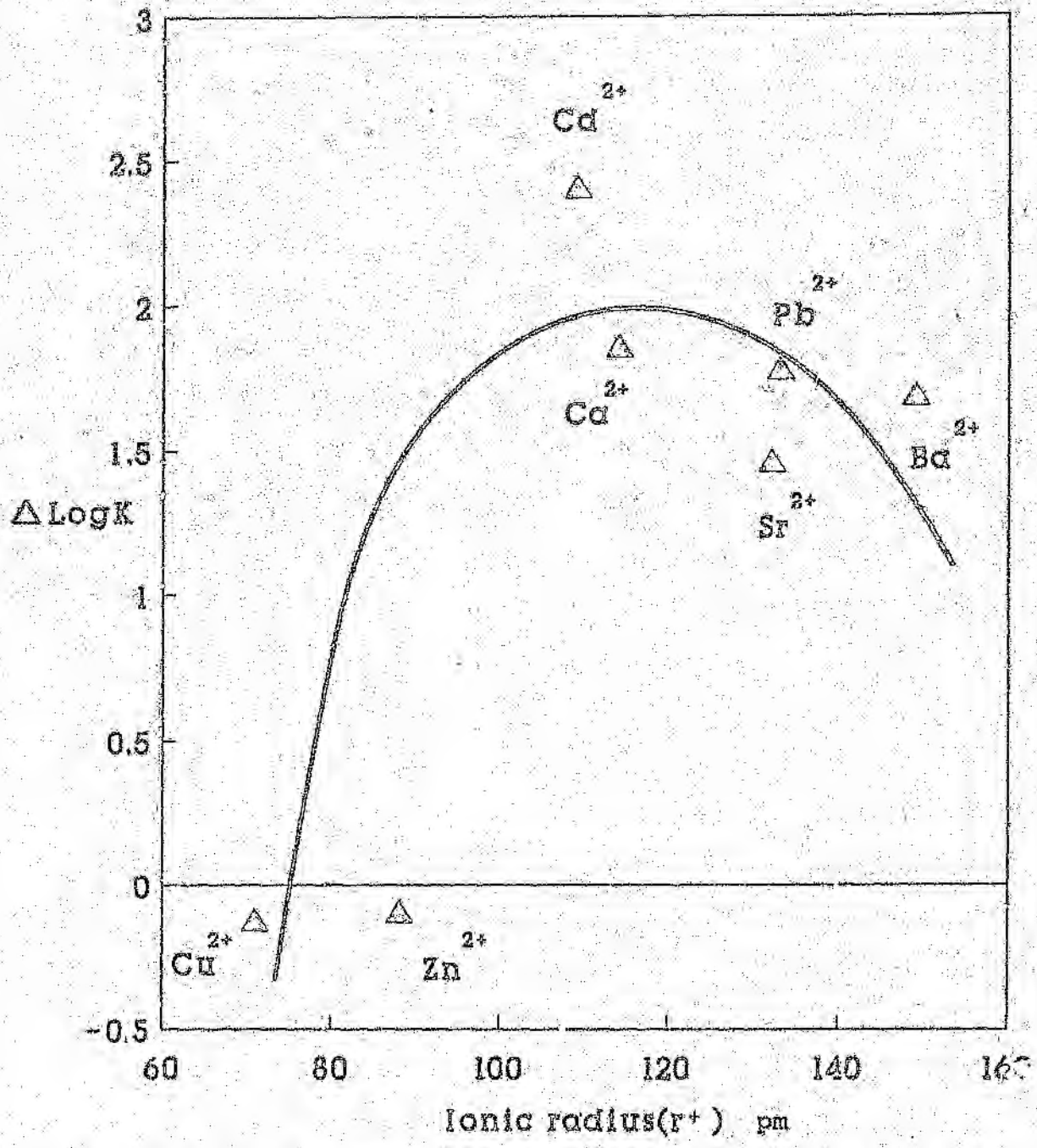


Figure A.2: ΔLogK(BHP-K22/K22) vs metal ionic radius (r^+)

(A.5) THE SIMPLE ANALYSIS OF THE CHELATE EFFECT

The alcoholic hydroxyl group is a particularly interesting donor group in co-ordination chemistry, because it is related to water in the same way as the alkylamine group in ethylenediamine is related to ammonia[71]. For reactions studied in aqueous solution, co-ordination of a hydroxyl group produced a chelate effect with unusual properties. If the donor abilities of the oxygen in water and the chelated hydroxyl group were identical and steric effects are neglected, two important considerations would remain.

Firstly, in the usual standard state, i.e. the one molar standard state, there are 55.5 times as many water molecules as ligand molecules, which, without the chelate effect, would mean that a water molecule would be attached with a probability 55.5 times greater than that of the alcoholic group. Thus, one finds that for the co-ordination of methanol to Cu(II), $\log K_1$ in molarity units is -1.48, not much larger than the -1.74, i.e. -log 55.5, expected from this consideration alone[71]. For chelated hydroxyl groups, the chelate effect counters this unfavourable contribution, leading to weak, but important, stabilization.

The second consideration, the chelate effect, is largely due to an increase in translational entropy[2]. The ideas of Adamson[72] lead to a very simple approach to the chelate effect, where each extra chelate ring in a complex should

inserting an "intrinsic basicity factor" of 1.152 (= $pK_a(CH_3NH_2)/pK_a(NH_3)$, i.e. 10.6/9.2) equation (2) is obtained, which has very good predictive powers[2]:

$$\log K_1 \text{ (polyamine)} = 1.152.\log\beta_n(NH_3) + (n-1)\log 55.5 \quad (2)$$

In Figure A.3 a plot of $\log K_1$(ethanolamine) versus $\log K_1(NH_3)$ is shown. The line drawn in has a slope of 1.152, which is that expected on the basis of the simple model[73] of the chelate effect discussed above. The slightly lower slope which would be obtained from a best-fit line drawn through the experimental points possibly relates to the lower basicity of the nitrogen in ethanolamine (pK_a = 9.45), as compared with a polyamine such as ethylenediamine (pK_a = 9.9)[71]. Figure A.3 suggested[71] that the chelate effect in complexes of ethanolamine can be analysed very simply.

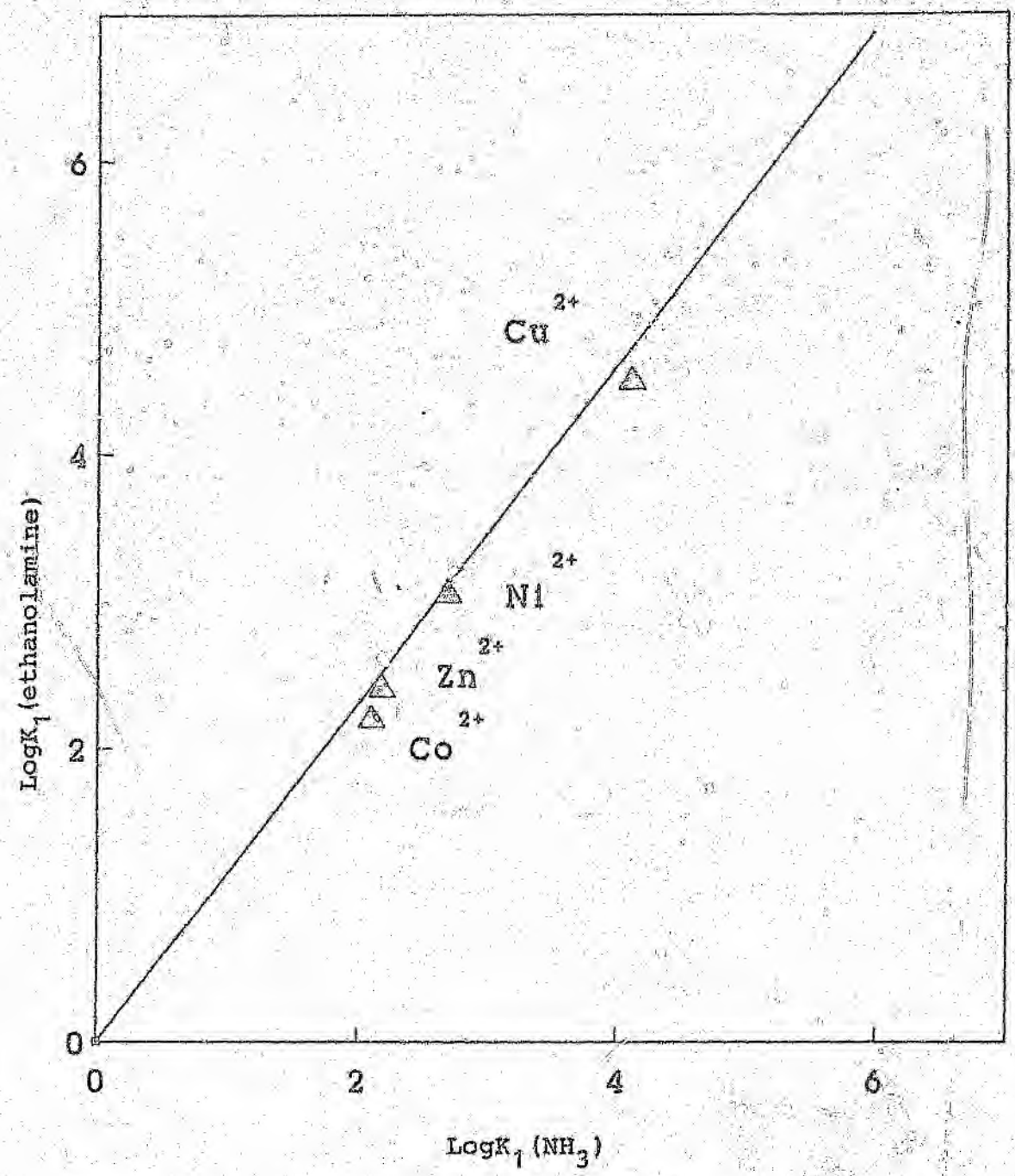


Figure A.3: $LogK_1$ (ethanolamine) vs $LogK_1$ (NH_3). The solid line drawn in has a slope of 1.152, which is the inductive effect factor discussed in the text

The increase in ΣU (steric strain) was not included in the simple analysis of the chelate effect in complexes of ethanolamine, discussed above. The fact that Figure A.3 shows that it has not made itself apparent suggests[71] that this unfavourable contribution is probably counterbalanced by the increased basicity of the alcoholic oxygen as compared with that in the water molecule displaced on co-ordination[71]. As discussed earlier (Section A.4) this is a plausible explanation[47] of the effects observed on adding a neutral oxygen donor in going from oxalate to oxydiacetate (ODA), since the complexes of large metal ions such as Pb^{2+} are stabilized, whereas those of small metal ions such as Cu^{2+} are destabilized by the co-ordinated ethereal oxygen donor atom of ODA.

The important factor[12] is that water and alcohols are not inherently equally strong bases. Results in the gas-phase[28-34] indicate a strongly increasing order of basicity $H_2O < ROH < R_2O$ (R = alkyl), both towards the proton and towards metal ions. From this it is expected[12] that all metal ions will show an increase in complex stability when hydroxyalkyl groups, or groups bearing ethereal oxygens, are added to an existing ligand. However, in general[12] only large metal ions show such an increase in complex stability. The most reasonable explanation for this is that for small metal ions, the increase in steric strain which normally accompanies complex formation[12], outweighs any benefits from greater donor strength in passing from water to a

hydroxyalkyl chelating group. This would relate to greater steric crowding around a small metal ion, as well as the higher strain resulting from distorting the co-ordination polyhedron of small metal ions, which generally have more covalent, and hence more directional bonding than is the case for the larger, more ionically bound metal ions[12].

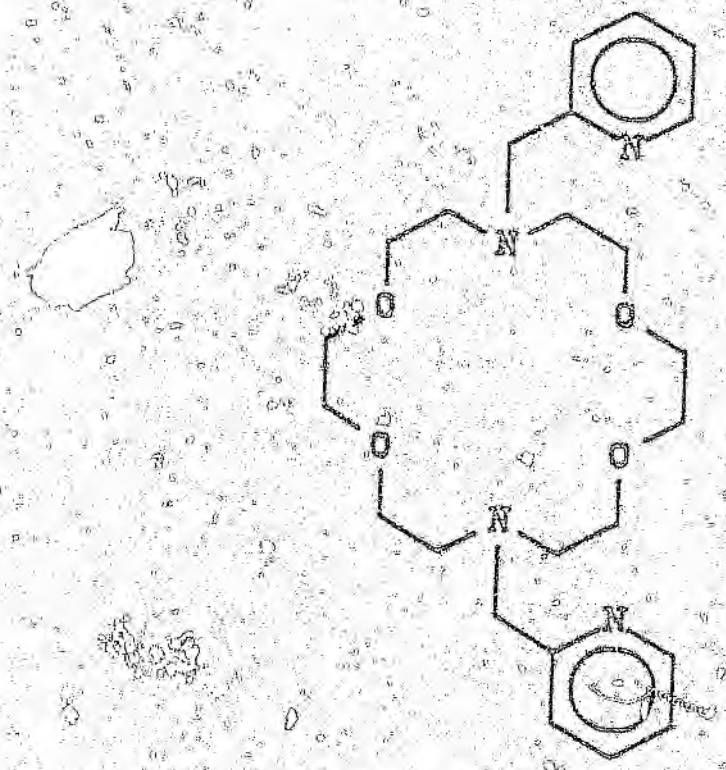
A similar explanation[2] has been given for the greater stability of BHE-K22 complexes than those of K22, where BHE-K22 is derived from K22 by the addition of hydroxyethyl groups to the nitrogen donor atoms. According to the simple analysis of the chelate effect discussed above, there should be no nett complex stabilization due to cratic effects when hydroxyethyl groups are added to existing ligands. It is probable[2] that the stabilization of complexes of metal ions with BHE-K22 relative to those of K22 is due to the greater basicity of the alcoholic oxygen than the oxygen of the water molecule, which is displaced when the alcoholic arm of BHE-K22 is co-ordinated to a metal ion. In order to obtain a better analysis of the relative importance of inductive and strain effects in the ethanolamine-type chelate ring, it will be necessary to extend the study to complexes of other hydroxyethyl substituted amines[71].

(A.6) EFFECTIVE COMPLEXING STRENGTHS

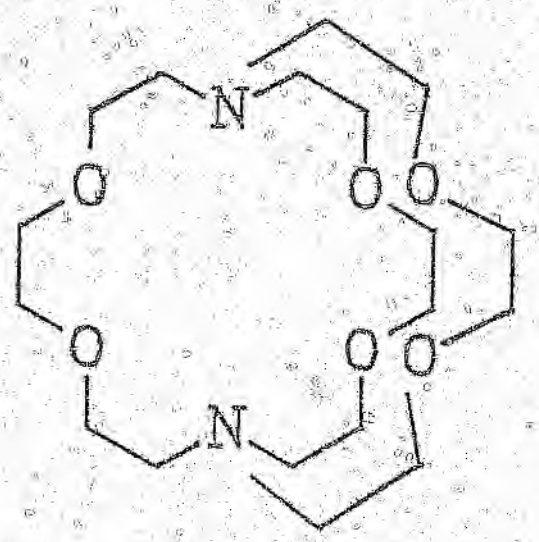
An important point that always has to be borne in mind[15] is that complex formation occurs in aqueous solution in competition with the proton, so that one should really consider the equilibrium

$$M^{x+} + LH_n^{n+} \rightleftharpoons ML^{x+} + nH^{+} \qquad (1)$$

at a biological pH of 7.3 in order to compare the effectiveness of ligands as complexing agents. For example, the ligands $(py)_2$-18-ane-N_2O_4 and cryptand-2,2,2 (Figure A.4) have $\log K_1$ values for Pb^{2+} of 11.7 and 12.0 respectively[15]. Cryptand-2,2,2 has logK 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, whereas for $(py)_2$-18-ane-N_2O_4 the logK values for protonation are 7.44, 6.26 and 1.38, so that protonation of $(py)_2$-18-ane-N_2O_4 is weak at pH 7.3. This greater affinity of cryptand-2,2,2 for the proton, at a biological pH of 7.3, relative to that found for $(py)_2$-18-ane-N_2O_4, leads to an effective reaction constant for Pb^{2+} with cryptand-2,2,2 (9.6 log units) which is less than the corresponding effective constant for Pb^{2+} with $(py)_2$-18-ane-N_2O_4 (11.5 log units)[15].



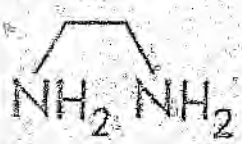
A



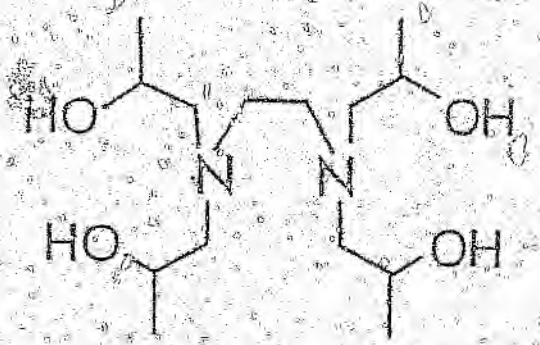
B

Figure A.4 : Structures of $(py)_2$-18-ane-N_2O_4 (A) and cryptand-2,2,2 (B)

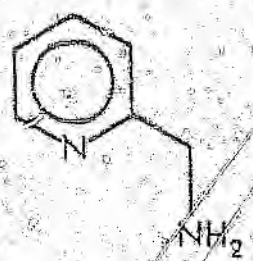
This leads to two important considerations. Firstly it is clear that where the addition of neutral oxygen donor groups, to existing ligands, leads to a considerable drop in pK_a values, greater effective complexing strengths are also obtained. Secondly the ability, in most cases, of the hydroxyethyl 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, it was not possible[15] to determine the formation constants of AMP or EN (Figure A.5) with La^{3+} because of hydrolysis problems. However, for DHEAMP and THPED (Figure A.5), the lower pK_a values of the ligands coupled with the somewhat higher formation constants of the large La^{3+} ion in the presence of neutral oxygen donors lead to hydrolysis-resistant complexes in aqueous solution.



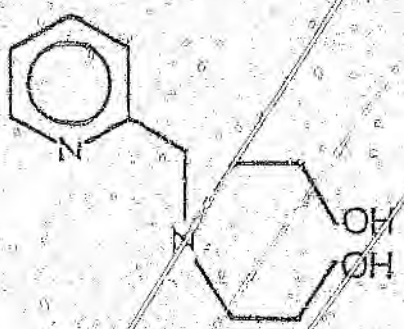
A



B



C



D

Figure A.5 : Structures of EN (A), THPED (B), AMP (C) and DHEAMP (D)

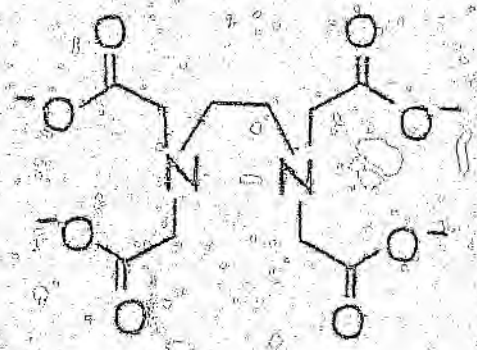
(A.7) LIGAND PRE-ORGANIZATION, FLEXIBILITY AND RIGIDITY

The term pre-organization suggested by Cram[74] is used here to represent effects such as pre-straining and pre-orientating. Cram[74] originally used the term pre-organization in a very wide sense to include also desolvation effects and dipole-dipole repulsion effects as contributions to complex stabilization. In this sense, the order of relative pre- organization of ligands is: solvents, unidentate ligands <chelates <macrocycles <cryptates. There is considerable flexibility in this order, in that a chelating ligand such as CDTA (Figure A.6) may be more pre-organized than many macrocycles. Unsaturated macrocycles, particularly those of biological origin such as the porphyrins and corrins, appear also to have a high level of pre-organization[2].

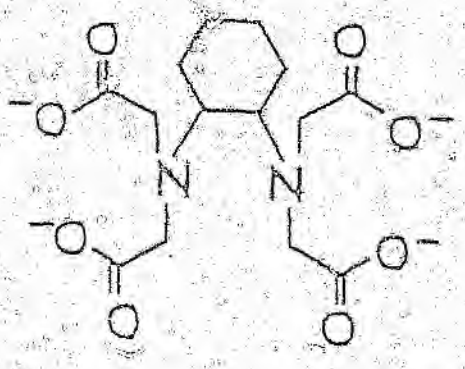
An important aspect of co-ordination chemistry is the "architecture" of the ligand, and how this affects co-ordination to the metal ion[2]. When the ethylene bridge of EDTA (Figure A.6) is alkylated by forming a cyclohexane ring in trans-CDTA, there are large increases in complex stability, which are metal ion independent and entropy controlled. The increase in complex stability has been interpreted in terms of the greater ease of assumption for the skew form of the free ligand, which is required for complex formation, whereas EDTA presumably adopts the lower energy <u>trans</u> form as the free ligand. This is an example of pre-organization of the ligand into the correct conformation

for complex-formation, which leads to higher complex stability. This is possibly[2] an important contribution to the macrocyclic effect, where it is generally regarded that, in some way, pre-organization might be responsible for the greater complex stability observed. It is interesting to note that high levels of pre-organization are not confined to macrocycles or cryptates, and can just as easily occur in chelating ligands. Pre-organization of the ligand, as is found in the non-macrocyclic CDTA ligand, involves the ligand already being in the right conformation for complex formation, in the simplest case. The important factor is that pre-organization leads to a high energy state for the ligand, which is relieved on complex-formation[2].

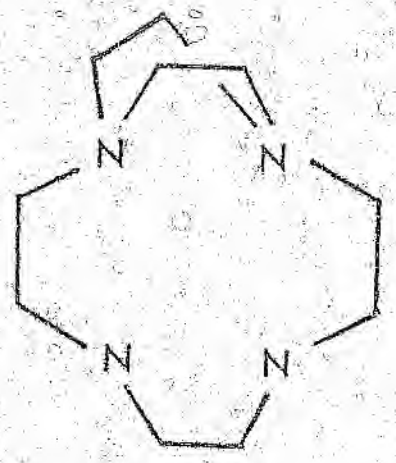
In general, the rigidity of the three dimensional cryptates (Figure A.4) appears to be considerably greater than that of the macrocycles[2]. This is evidenced in their demanding metal ion size requirements. Wainwright[75], in his work on the bridging alkylation of saturated polyazamacrocycles, found that introducing alkyl bridges was a means for imparting structural rigidity. The introduction of a bridge, or bridges, effectively creates a steric barrier, which may be sufficient to limit the co-ordination geometry to only one configuration. Also, the effect of the bridge may be to reduce ligand flexibility to the point where the macrocyclic hole is incapable of expanding[75] to accept larger metal ions. Consequently metal ion size selectivity will be enhanced under such circumstances.



A



B



C

Figure A.6 : Structures of EDTA (A), CDTA (B) and 12-aneN_4 with a bridge (C)

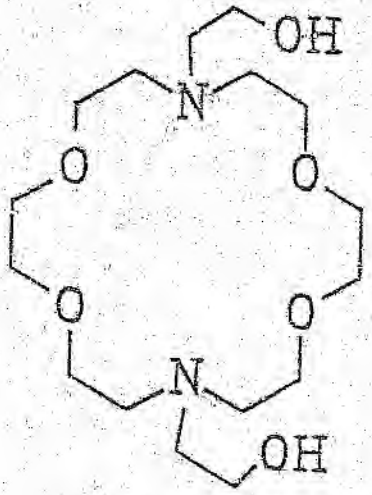
The ligand shown in Figure A.6 as C, appears to be very highly pre-organized[2]. The ligand shows strong size selectivity[2], having stronger preference for metal ions which are small enough to fit into the macrocyclic cavity. A space-filling model of C shows hardly any space for a metal ion to fit into the cavity[2]. Molecular mechanics calculations indicate a very high level of strain in the Ni(II) complex of C, which would ordinarily mean a very weak complex. However, the high level of strain in the complexes of C with metal ions is apparently more than offset by the high level of strain in the free ligand, so that complexes of high stability are formed[2].

An important task in co-ordination chemistry is thus the synthesis of even more highly pre-organized ligands[2]. One can only speculate on what remarkable properties might not emerge in terms of such things as size selectivity, complex stability, and the stabilization of unusual oxidation states.

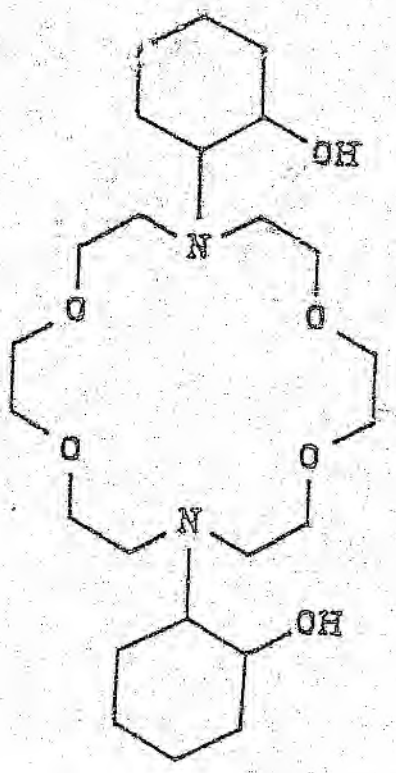
A.8 THE AIMS OF THIS STUDY

When the cyclohexyl group is used as the bridge connecting the two nitrogen donors in place of the ethylene bridge of EDTA (Figure A.6), there are substantial increases in complex stability[77] as measured by the formation constants, $\log K_1$ of the complexes formed for trans-CDTA (Figure A.6).

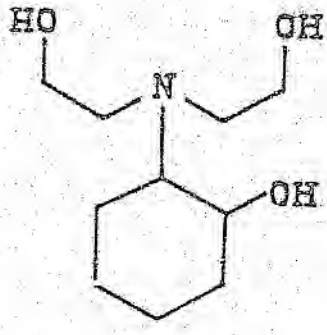
This is an example[78] of pre-organisation[74], in which it is thought[78] that the rigid cyclohexyl ring of CDTA holds the two trans nitrogens in the skew arrangement required for co-ordination to metal ions. In EDTA, by contrast, the low energy form of the free ligand is thought to be the trans, and considerable energy must be expended in transforming it to the skew form required for complex-formation. It therefore seemed that introduction of cyclohexyl groups as bridging groups in other chelating ligands would produce ligands of greatly increased complexing ability. As a start in this direction, the ligand CY_2-K22 was studied (Figure A.7). This ligand has cyclohexyl groups bridging the nitrogen donors of the macrocyclic ring and the pendent alcoholic oxygen donors. This might give interesting effects on complex stability compared with BHE-K22 (Figure A.7) which has simple ethylene bridges linking the donor atoms of the pendent "arms" to the nitrogens of the macrocyclic ring. The same may also be true if compared with the very similar BHP-K22 macrocycle (Figure A.1) which has 2-hydroxypropyl pendents.



A



B



C

Figure A.7 : Structures of BHE-K22 (A), CY_2-K22 (B) and BFEAC (C)

It is found[77] that a cis conformation of the amines on the cyclohexyl group, as in cis-CDTA, leads to incorrect orientation of the nitrogen donor atoms for co-ordination to metal ions, and cis-CDTA shows little increase in complex stability as compared with EDTA. It is thus important that the hydroxyl group be trans to the nitrogen donors of CY_2-K22. The method of synthesis employed here was the same as for many other nitrogen donor macrocycles with hydroxyalkyl pendent donor groups, namely reaction of the parent macrocycle with the epoxide[10]. In this case, the epoxide is cyclohexene oxide, and the mechanism of opening[79-84] of the epoxide ring on this molecule should certainly lead to a trans arrangement of the two substituents on the cyclohexyl group. This work therefore describes the synthesis of the ligand CY_2-K22, and a potentiometric study of its formation constants with Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Ni^{2+}, Cd^{2+}, Cu^{2+}, Pb^{2+}, La^{3+} and Ag^{+}. The results obtained were somewhat surprising in terms of the idea[85] that selectivity for large metal ions relative to small metal ions was increased when pendent groups containing neutral oxygen donor ligands were added to a ligand. In order to see whether the unusual pattern of selectivity for metal ions in relation to their size was dependent on the presence of the macrocyclic ring, the simple ligand BHRAC (Figure A.7), which contains only a single 2-hydroxycyclohexyl group, a single nitrogen donor, and two pendent 2-hydroxyethyl groups was synthesized and the formation constants of this ligand with Ni^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+}, and Ag^{+} were determined.

An attempt was also made at introducing a cyclohexyl group as a bridging group in 1,4,7-triazacyclononane (9-aneN$_3$)[26] to produce the macrocycle 2,5,8-triazabicyclo[7,4,0]tridec=ane. Once again the idea was to observe whether the introduction of cyclohexyl groups as bridging groups in chelating ligands produced ligands of greatly increased complexing ability. However, attempts to prepare this material from its tosylate precursor using standard methods of detosylation proved unsuccessful (see Experimental Section).

In order to obtain a better analysis of the relative importance of inductive and strain effects in the ethanolamine-type chelate ring - which is also present in CY$_2$-K22 and BHEAC - a potentiometric study was undertaken into the complexes of open chain hydroxyethyl substituted amines which differed only in the degree and type of substitution on the hydroxyethyl substituent. The simple ligand tertiary-butylamine was investigated for comparative reasons. This investigation supplemented work already done[71] on the chelate effect in complexes of ethanolamine, where it was found that it could be simply analysed (Section A.5).

B EXPERIMENTAL

B.1 MATERIALS LIST

B.1.1 APPARATUS

B.1.1.1 Apparatus for Synthesis

Varian EM360A NMR spectrophotometer
Edwards Spe divac vacuum pump
Buchi fontavapor 285 distillation unit
Millipore Milli-Q water purification system
Buchi Rotavapor RE120

B.1.1.2 Titrimetric apparatus

HAAK G constant temperature bath
EYELA stirrer
RADIOMETER PHM 84 Research pH meter
CRISON DIGILAB 517 pH meter
CRISON DIGIT 501 pH meter
Calomel reference electrode
Silver-Silver chloride reference electrode
RADIOMETER GK2401B combination pH electrode
RADIOMETER G202B glass electrode
Microburette grade A
Nitrogen bubbler apparatus.

B.1.1.3 Calculation and word processing

Apple IIe microprocessor

Elf ICL computer

CDC CY750 mainframe computer

COPAM AT Personal computer

DEFINICON maths coprocessor card.

B.1.2 CHEMICALS

B.1.2.1 Amines used in Potentiometric study

Amine	Manufacturer
(I)-2-amino-1-propanol (98%)	Aldrich
(±)-1-amino-2-propanol (95%)	Aldrich
tert-butylamine (98%)	Aldrich
2-amino-2-(hydroxymethyl)-1,3-propanediol (99%)	BDH
2-amino-2-methyl-1,3-propanediol (99%)	Eastman
2-amino-2-methyl-1-propanol (99%)	Merck

B.1.2.2 Organic chemicals used in synthesis

Chemical name	Trivial name	Manufacturer
1) 1,2-epoxy-cyclohexane; 7-oxabicyclo [4.1.0] heptane	Cyclohexene oxid	Fluka
2) Diethanolamine		Saarchem
3) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane	Kryptofix 22	Merck
4) 1,4,10-trioxa-7,13-diazacyclopentadecane	Kryptofix 21	Merck

B.1.2.3 Inorganic Chemicals

AR grade MERCK salts of nitrates of copper, nickel, cadmium, zinc, lead, lanthanum, strontium, barium and silver.

B.1.2.4 Abbreviations of Chemical names

Table B.1 gives a list of the abbreviations used in this work for the open chain ligands studied.

Table B.1: Abbreviations of the open chain ligands

Amine	Abbreviation
(I)-2-amino-1-propanol	A_2POL
(±)-1-amino-2-propanol	AP_2OL
tert-butylamine	t-BUTYLAMINE
tris(hydroxymethyl)aminomethane[a]	THAM
2-amino-2-methyl-1,3-propanediol	AMPDOL
2-amino-2-methyl-1-propanol	AMPOL
2-[bis(2-hydroxyethyl)amino]cyclohexanol	BHEAC

[a] 2-amino-2-(hydroxymethyl)-1,3-propanediol

B.2 PROCEDURES

B.2.1 LIGAND SYNTHESIS

B.2.1.1 Synthesis and characterisation of 2,5,8-tritosyl-2,5,8-triazabicyclo[7,4,0]tridecan.

Use was made of the Richman and Atkins method [86,87] for the preparation of the macrocyclic amine. Graham and Weatherburn [88] have shown that the Richman and Atkins method can be used for the preparation of c-methyl-substituted triazamacrocycles, provided that cyclization is accomplished by cyclizing the sodium salt of the methyl- substituted bissulfonamide and the tosyl derivative of the amine-diol. The yields are much smaller than those obtained with the unsubstituted macrocycles and the quantity and variety of co-products are greater.

Consequently it was decided to react the sodium salt of trans-1,2-ditosyl-1,2-diaminecyclohexane with the tosylated derivative of diethanolamine. The tosylated precursors for the cyclization reaction were prepared by reacting p-toluenesulfonylchloride with trans-1,2-diaminecyclo=hexane and diethanolamine in the usual manner[86,89].

(a) Disodium salt of trans-1,2-ditosyl-1,2-diamine-cyclohexane.

To trans-1,2-ditosyl-1,2-diaminecyclohexane (20.60g, 0.05 mol) in a round-bottomed flask was added a solution of sodium (3.90g, 0.17 mol) in 390 cm^3 of absolute alcohol. The solution was kept dry by using a drying tube and left overnight with stirring. The disodium salt crystallized overnight. The salt was filtered, washed with ethanol and placed in a round-bottomed flask. The excess ethanol was evaporated under vacuum. Yield: 20g (88%).

(b) 2,5,8-Tritosyl-2,5,8-triazabicyclo [7,4,0] tridecane

To 430 ml of a 0.1 M solution of the disodium salt (20g, 0,04 mol) dissolved in DMF in a one litre round-bottomed flask was added one equivalent of a 0.2 M diethanolaminetritosylate solution (24g, 0.04 mole) in DMF solvent. A separating funnel was used for the addition of 215 ml of the diethanolaminetritosylate solution over a period of 2 hours. Reaction occured at 110°C for a total of 3 hours. Deionized water (1500 ml) was then slowly added to the hot solution (70-80°C) in a five litre beaker. The solution was then left overnight, giving a white solid on cooling. The white solid was filtered and then washed in warm methanol. Finally it was dried under vacuum

overnight. Yield: 13.41g (48.28%), m.pt. 213-216°C (Found: C, 57.38; H, 6.43, N, 6.45%. Calc. for $C_{31}H_{39}N_3O_6S_3$: C, 57.64; H, 6.10; N, 6.51%). The nmr spectrum of this material in $C_2F_3O_2H$ without the use of an internal reference, at 60 m|z using a Varian Em 360A spectrophotometer consists of the following peaks (given in increasingly upfield order); multiplet (12H); broad singlet (10H); singlet (9H); multiplet (8H).

The relatively low yield obtained can be explained in terms of a decrease of the template effect, since a softer N-donor than O-donor is not apt to complex with a hard alkali metal cation[90].

Also attempted was the cyclization method of Gatto and Gokel[91] which involves a one step cyclization process in acetonitrile solvent in the presence of a base. Diethanolaminetritosylate was refluxed with trans-1,2-diaminecyclohexane. This cyclization process proved unsuccessful. It was hoped that the product, which would have contained only one tosylate group, would have been detosylated under mild conditions.

(c) 2,5,8-Triazabicyclo[7,4,0]tridecane

Attempts to prepare this material from its tosylate precursor using standard methods of detosylation[14,86-88,92-97] proved unsuccessful.

B.2.1.2 Synthesis and characterisation of 7,16-bis(trans-2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (CY_2-K22).

Kryptofix 22 (1.51g; 5.76 mmol) was dissolved in ethanol (26 ml) in a 50 ml round bottomed flask. Cyclohexane oxide (3.5 ml; 34.59 mmol) was pipetted in excess (3 equivalents) into the solution. The mixture was refluxed at 110°C for two weeks.

The solvent (ethanol) was then stripped on a rotary evaporator and the resulting oil put on a vacuum pump (2 hours) to remove any remaining solvent.

Purification was by a standard method of recrystallization[98] whereby the resultant yellow solid was dissolved in a minimum quantity of hot dry n-hexane and filtered through fluted filter paper. Recrystallization occured overnight to give colourless crystals (1.95g); Yield: 73.96%, m.pt. 82-84°C. Purity from potentiometric standardization 99.5%. The nmr spectrum of this

material in $CDCl_3$ and TMS, as an internal reference, at 60 MHz using a Varian EM 360A spectrophotometer consists of the following peaks (ppm from TMS), 1.10-1.28 (m,8H); 1.38-1.86 (m,6H); 2.07-2.30 (m,4H); 2.61-2.90 (m,8H); 3.48-3.61 (m,10H); 4.21(s,2H). The microanalysis was done by the Analytical Division of the National Chemical Research Laboratory, CSIR, Pretoria, (Found: C,62.86; H, 10.51; N, 6.23%; Calc. for $C_{24}H_{46}N_2O_6$: C, 62.84; H, 10.13; N, 6.11%).

B.2.1.3 Synthesis of 2-[bis(2-hydroxyethyl)amino] cyclohexanol : (BHEAC)

The ligand 2-[bis(2-hydroxyethyl)amino]cyclo-hexanol was synthesized according to the method of Ponomarev and Sablina[99]. In a round-bottomed flask fitted with a reflux condenser, a mixture of 98g (100 mmols) of cyclohexene oxid and 10.5g (100 mmols) of diethanolamine was heated on an oil bath at 125°C for 2½ hours, and afterwards for a short time at 150°C. In this way a homogeneous liquid was obtained - the initial components did not mix before heating together. The reaction mixture was cooled and subsequently crystallization of the mass commenced.

To purify the substance it was distilled in a vacuum[99]. A fraction weighing 12.58g and boiling at 206-208°C at 3 mm Hg, was obtained. The product distilled was a colourless oil, which, on standing, crystallized once again; Yield: 61.9%; m.pt. 46-47°C. A stock solution of the ligand was made up and standardized by acid - base titration, which showed the ligand to be 97.85% pure. The nmr spectrum of this material in $CDCl_3$ and TMS, as an internal reference, at 60 MHz using a Varian EM 360A spectrophotometer consists of the following peaks (ppm from TMS), 0.82-2.30 (m, 8H); 2.30-3.14 (m, 5H); 3.3-4.0 (m, 5H); 4.10-4.68 (broad s, 3H). On addition of D_2O the broad singlet disappears completely indicating that the peak (4.10-4.68) represents the three hydroxy groups.

B.2.2 EQUILIBRIUM CONSTANTS

In order to facilitate comparison with stability constants already published by Martell[26] all constants were determined at an ionic strength of 0.1M and at a temperature of 25°C.

B.2.2.1 Solution Standardizations

Analytical reagent grade $AgNO_3$ (Saarchem) and Merck nitrate salts of the metal ions Cu^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, Ba^{2+}, Sr^{2+} and La^{3+} were used to prepare standard solutions of the metal ions. All metal solutions except for silver - which was standardized by titration against dried AR grade NaCl - were standardized by titration with EDTA, using appropriate indicators[100].

Nitric acid used in the potentiometric titrations was prepared from a 1M BDH c.v.s. solution and standardized against recrystallized borax[100]. Standard solutions of the base sodium hydroxide were prepared from BDH c.v.s. ampoules and standardized against standard HNO_3.

The hydroxyamine ligands studied, as well as tertiary butylamine and the macrocycle CY_2-K22, were all standardized potentiometrically[100] with either standard acid or base, depending on the nature of the stock solutions of the ligands prepared.

B.2.2.2 Titration Procedures

B.2.2.2.1 Hydroxyamines and tert-Butylamine

For the hydroxyamines studied, which include A_2FOL, AP_2OL, THAM, AMPDOL, AMPOL and BHEAC and for tert-butylamine, metal stability constants were determined for the metals Zn(II), Ni(II), Cu(II), Ag(I), Cd(II) and Pb(II).

Initially the method employed was the titration of a solution of acid, metal and ligand with standard sodium hydroxide. For all ligands, three different metal-ligand ratios were used to check for polymeric and hydrolysed species. Stock solutions of the ligand (0.01 M) in 0.1 M $NaNO_3$ were prepared and standardized. Stock solutions of the acid and base used were 0.05 M in HNO_3 or NaOH respectively. $NaNO_3$ (0.05 M) was added to the acid and base solutions to adjust the ionic strength to 0.1M.

The apparatus consisted of a titration cell that was thermostated at 25 ± 0.1°C using a Haake thermostat bath. Nitrogen was bubbled through the cell to remove CO_2. Ionic strengths (μ) were kept at 0.1M by the preparation of stock solutions with μ = 0.1 and, where necessary, the initial volume in the titration cell was increased with the use of 0.1 M $NaNO_3$. A Radiometer PHM 84 research pH meter in conjunction with a Radiometer GK2401B combination pH electrode was used to monitor pH changes during the course of the titration. Grade A microburettes were used and the solution was continuously stirred with the use of an EYELA stirrer and a magnetic stirrer.

Although this technique was used for three ligand-metal ratios, very little success was obtained with it. From the outset it was clear that the stability constants that were being measured were relatively low (logK<6). Consequently, complex formation was in competition with the hydrolysis of the metal ion. Another likelihood was the hydrolysis of the metal-ligand complex. With a few exceptions, the end result was that the titrations had to be abandoned due to the formation of metal hydroxide precipitation. In many instances precipitation occured at low n-bar values ($\bar{n}$ <0.5). The refined stability constant

values obtained could therefore not be regarded with much confidence and in most cases the standard deviations were high. An exception to this was the titration of BHEAC with the metal ions Cu(II), Ni(II) and Zn(II). In these cases constants could be determined - using the method described above - with a greater degree of accuracy. As a result of the problems associated with the titration method mentioned above, it was decided to attempt other methods of titration in order to determine the stability constants.

A method whereby a solution of acid and metal was titrated with 0.01 M ligand solution in order to suppress hydrolysis of the metal ions was attempted. This however also proved unsuccessful.

Finally, in general, the approach employed was to titrate 10 ml of 0.1 N HNO_3 plus x ml metal solution (x ranges from 2 to 12) with 0.2 M ligand in 0.1 M HNO_3. For titrations involving Ag(I) the concentration of $AgNO_3$ employed was 0.1 M. The remaining metal solutions were prepared from their corresponding nitrate salts and all had the general formula $M(NO_3)_2$. Consequently, in order to keep the ionic strength constant at μ = 0.1 M the concentrations of these metal solutions were 0.033 M. The initial volume in the titration cell was increased by using 0.1 M $NaNO_3$.

Under these conditions, the background electrolyte to keep the ionic strength constant, consisted mainly of the protonated ligand being studied, so as to suppress hydrolysis of the metal ion. A high acid content in the system was required to suppress hydrolysis of the metal or of the metal-ligand complex, i.e.

$$M + H_2O \rightleftharpoons MOH + H^+$$
$$ML + H_2O \rightleftharpoons MLOH + H^+$$

In most cases the hydrolysis reactions were unavoidable, and the titration data had to be refined by MINIQUAD[101] (Section B.3).

In the determination of the stability constants of BHEAC and A_2POL the method was slightly modified as a result of a shortage of the pure ligands. In the case of the ligand BHEAC the amount of acid added initially to the cell was 3 ml 0.1 M HNO_3 and the titration was performed with 0.16 M BHEAC in 0.1 M HNO_3. For A_2POL 5 ml 0.1 M HNO_3 was added to the cell plus x ml metal solution (x = 10, 7, 5) and the titrand was 0.1 M A_2POL in 0.05 M HNO_3 and 0.05 M $NaNO_3$ to adjust the ionic strength to 0.1.

The apparatus utilized in this method was exactly the same as that used for the previous methods attempted. However, in the case of the Ag(I) titrations, use was made of externally referenced electrode systems. Either a Calomel reference electrode or a Ag/AgCl reference electrode was employed in combination with a Radiometer G202B glass indicator electrode to monitor pH changes during the course of the titration. The reference electrodes were connected to the titration cell via a salt bridge. Junction potentials were minimized by using 0.1M $NaNO_3$ in the salt bridge. Either a Crison Digilab 517 or a Crison Digit 501 pH meter was used.

The results obtained were superior to those obtained in the previous methods. In the titrations where precipitation occured, this only commenced at n-bar values which were far higher than the corresponding values for the other titrations. Consequently a greater degree of confidence could be associated with the refined stability constants. This could be seen with the good agreement obtained with already published literature values - in those cases where such data were available.

For pK_a determinations the ligand solution was titrated with standard 0.05 M HNO_3. The cell volume was adjusted with 0.1 M $NaNO_3$. For each pK_a determination three titrations were performed. In many instances more than one pK_a determination was attempted for a ligand. In the course of finding a useful method to determine the stability constants, as discussed earlier, pK_a determinations proceeded without any problems. Hence, for each different ligand stock solution prepared - as a result of the different titration techniques - a pK_a titration was performed. Also after the preparation of additional ligand stock solution, of a particular type, another pKa determination was performed. Consequently two and sometimes three pK_a values were determined for each ligand. Averages only are reported in the results. An exception to the technique described above for the determination of pK_a values was employed for the pK_a of tert-butylamine. Problems due to the volatility of tert-butylamine were experienced. In order to suppress this, it was decided to titrate a solution of acid with 0.2M tert-butylamine in 0.1 M HNO_3. The volume of the cell was adjusted with 0.1 M $NaNO_3$. The result obtained with this technique was in agreement with that already published[26].

B.2.2.2 CY_2-K22

A 0.005 M solution of the macrocycle in 0.01 M HNO_3 and 0.09 M $NaNO_3$ was prepared and standardized. This solution was used as the stock solution for the determination of the pK_a values and the stability constants of the macrocycle. The apparatus used was the same as that used in the titration methods involving the hydroxyamines and tert-butylamine. A Radiometer GK 2401B combination pH electrode was used in conjunction with a Radiometer PHM 84 research pH meter. In order to keep the ionic strength constant, metal stock solutions were prepared with μ = 0.1 M. Metal stock solutions containing Cu(II), La(III), Ba(II), Pb(II), Cd(II), Ca(II), Sr(II), Ni(II), Zn(II) and Ag(I) were used during the course of the titrations.

In all the titrations a solution of ligand and metal - in excess acid - was titrated with standard 0.05 M NaOH. The ionic strength was maintained at 0.1 M by adjusting the cell volume with 0.1 M $NaNO_3$. As for the titration of the previous ligands discussed, three different ratios of metal and ligand were used to check for polymeric and hydrolysed species. In the determination of the pK_a values of the macrocycle

no metal was added initially to the titration cell. However, in the determination of the stability constants of the metal ions with the macrocycle, metal was added initially to the cell. Except for the titration of Ag(I) with the macrocycle, where only one titration was performed, three titrations were performed for the determination of each constant. Unfortunately there was not enough stock sclution to complete the Ag(I) titrations with the macrocycle. At all times, presaturated nitrogen was bubbled through the cell to exclude oxygen and carbon dioxide.

B.3 CALCULATIONS

Where hydrolysis of the metal ion or of the metal-ligand complex did not occur, use was made of a BASIC program called EQUILIBRIA[102]. This program automatically refined the stability constants. EQUILIBRIA was also used to determine the pK_a's of all the ligands studied.

A shortfall of EQUILIBRIA is its inability to cope with more complex systems. These more complex systems include situations where hydrolysis of the metal ion or of the metal-ligand complex occur. Examples of representative $\bar{n}$ curves are given in appendix A. Computer programs such as MINIQUAD[101] makes investigation of these complex equilibria a much less daunting task. In addition, inclusion of all the constants for the hydrolysis of the metal ions themselves in the refinement removed the problem that take-up of base was due to metal ion hydrolysis rather than complex formation, which is a real possibility with the systems studied in this work. In instances where metal hydroxide constants at an ionic strength of $\mu = 0.1$ were not available, but constants were available at other ionic strengths, corrections were made. Use was made of the Davies equation, which is an extended form of the Debye-Hückel equation, to correct such constants. The objective was to obtain an approximation for their values at $\mu = 0.1$ M which is the ionic strength at which the experimentation

occurred. These adjusted metal hydroxide constants were then included in the refinement of the stability constants, using the program MINIQUAD. MINIQUAD is a non-linear least-squares program which utilizes potentiometric data. It minimises the sum of the squared analytical concentrations, using the Gauss-Newton iterative method[103].

Data reduction consisted of a "pqr" analysis, whereby a large number of complexes were proposed for the initial guesses of logK values. These logK values were then reduced by the program, in successive cycles of refinement, to those reported in the results. Complexes which were included in the analysis were the ML and ML_x complexes, as well as all possible deprotonated forms of these species.

Strain energy values, U, were calculated using a commercially available molecular mechanics program called Alchemy[104].

C. RESULTS AND DISCUSSION

C.1 SYNTHESIS AND CHARACTERISATION OF BHEAC AND CY_2-K22

The yield and the ease with which BHEAC and CY_2-K22 were obtained proved the success of the two syntheses. The reactions proceed by the opening up of cyclohexene oxide by the lone pair of electrons on the nitrogen atoms of diethanolamine and K22. Like ethers, epoxides undergo c-o bond cleavage. However, because of the large ring strain associated with the three-membered ring (about 25 kcal/mole) they are much more reactive than normal ethers. Most evidence[106] indicates that epoxide reactions take place by a bimolecular mechanism (S_N2), although there may be a few extreme cases which take place by S_N1 mechanisms. Hence the most likely mechanism for ring opening of an epoxide in the formation of BHEAC and CY_2-K22 is the S_N2 mechanism. The stereochemical outcome of the reaction is inversion at the reaction centre. Thus cyclohexene oxide reacts to give exclusively trans-cyclohexane 1-2 substituted products.

If one examines the conformations of cyclohexane, one finds that there are three which are free of angle strain. Of these the chair form is the most stable conformation of cyclohexane, and indeed of nearly every derivative of cyclohexane[105]. If a hydrogen on cyclohexane is replaced by a larger atom or group, crowding will occur. The most

severe crowding is among atoms held by the three axial bonds on the same side of the molecule. This resulting interaction is called 1.3 diaxial interaction. Also, as a consequence of this crowding the energy of the diaxial transition state will often be greater than the energy of the diequatorial transition state[106]. It is therefore expected that the S_N2 mechanism will favour the formation of a trans-diequatorial product. Except for hydrogen, a given atom or group has more room in an equatorial position than in an axial position.

Consequently it is certain that, in the formation of CY_2-K22, the cyclohexene oxide, after reaction, adopts a rigid chair conformation with the macrocycle and hydroxyl groups equatorial and trans to one another. Similarly, in the case of BHEAC, the diethanolamine and hydroxyl groups are also expected to be equitorial and trans to one another.

C.2 EQUILIBRIUM CONSTANTS OF CY_2-K22

The macrocycles referred to in this section are graphically represented in Figures A.1 and A.7 in the Introduction. Statistics from the computer analysis of the results are given in Appendix B.

C.2.1 RESULTS

C.2.1.1 Protonation constants

The protonation constants of 7,16-bis(trans-2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane or simply CY_2-K22 are given in Table C.1, as well as those for 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane or simply kryptofix 22 (K22)[107] and 7,16-bis(2-hydroxypropyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane or simply BHP-K22, for comparative purposes[9].

Table C.1: Protonation constants of CY_2-K22, BHP-K22 and K22

Ligand	pKa_1	pKa_2
CY_2-K22[a]	8.38 ± 0.01	8.04 ± 0.01
BHP-K22[b]	8.46 ± 0.02	6.98 ± 0.02
K22[c]	9.08 ± 0.01	7.94 ± 0.03

[a]This work at = 0.1M and 25°C. [b]Data from reference 9. [c]Data from reference 107.

C.2.1.2 ML Constants

The stability constants of K22 and BHP-K22, as well as those for 7,16-bis(hydroxyethyl)-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane or simply BHE-K22, are given in Table C.2 with those for CY_2-K22 for comparative purposes.

TABLE C.2: $LogK_1$ ($M + L \rightleftharpoons ML$) for K22, BHP-K22, BHE-K22 and CY_2-K22.

Metal ion	$LogK_1$ K22[a]	BHP-K22[b]	BHE-K22[c]	CY_2-K22[d]
Cu^{2+}	6.1	5.97	6.60	7.63(3)
Ag^{+}				5.20(1)
Ba^{2+}	2.97	4.65	5.3	4.59(1)
Zn^{2+}	3.1	3.0		e
Cd^{2+}	5.25	7.65	7.96	8.64(2)
Ca^{2+}	1.74	3.59	4.08	4.72(1)
La^{3+}		3.24		4.08(3)
Sr^{2+}	2.6	4.05		4.13(2)
Pb^{2+}	6.8	8.57	9.20	8.59(1)
Ni^{2+}				e

[a]Data from reference 107. [b]Data from reference 9. [c]Data from references 108 and 26. [d]This work at μ = 0.1 M and 25°C. Standard deviations are given in parentheses. [e]Metal hydrolysis problems during the titrations prevented the determination of reliable constants.

C.2.1.3 MLOH Constants

Deprotonation of the metal CY_2-K22 complexes occurred. The refined constants representing the deprotonation reaction for the CY_2-K22 complexes, as well as the available[26] constants for the formation of the monohydroxo complexes of aqua ions, are given in Table C.3.

Table C.3: $LogK(ML+OH^- \rightleftharpoons MLOH)$ for CY_2-K22

Metal ion	$LogK_1(OH^-)^a$ $M + OH^- \rightleftharpoons MOH$[c]	$LogK_1(OH^-)^b$ $ML + OH^- \rightleftharpoons MLOH$[c]
Cu^{2+}	6.65	7.24(2)
Pb^{2+}	5.86	5.20(3)
La^{3+}	4.84	5.97(2)
Cd^{2+}	3.46	5.29(7)
Ca^{2+}	0.86	5.05(1)
Ba^{2+}	0.4	4.74(2)
Sr^{2+}	0.36	5.11(2)

[a]Data from reference 26 and where necessary corrected for ionic strength to μ = 0.1 M using the Davies form of the Debye-Huckel equation[109]. [b]Refined by MINIQUAD[101]. Numbers in parentheses are standard deviations. [c]M = metal ion; L = Ligand; OH = hydroxide ion. Charges on species omitted for simplicity.

C.2.2 DISCUSSION

It can be seen in Table C.1 that the addition of neutral oxygen pendents to K22 has, in the case of BHP-K22, lowered the pK_a values. This is in keeping with the idea that the addition of neutral oxygen donor groups leads to a considerable drop in pKa values[15]. However, in the case of CY_2-K22 the pK_a values have not dropped as expected. This is possibly due to the greater inductive effect of the cyclohexyl arms countering the electron-withdrawing properties of the neutral oxygen donors. The importance of such behaviour at a biological pH of 7.3 is the effect on the effective complexing strengths of these macrocyclic ligands. Although both BHP-K22 and CY_2-K22 have the same $logK_1$ value for Pb^{2+} (Table C.2), their effective complexing strengths will differ because the pK_a values of the former ligand are lower than those of the latter ligand. Consequently BHP-K22 will complex significantly more Pb^{2+} than CY_2-K22 at a biological pH of 7.3.

Looking at the logK values for CY_2-K22 relative to K22 (Table C.2), one notices the increase in stability for all metal ions for the ligand CY_2-K22 relative to K22. The behaviour of N-substituted macrocycle complexes has not always reached the stability expected[110]. It was originally thought that monocyclic ligands with co-ordinating side

chains on the nitrogens ought to approach the high selectivity and stability of bicyclic ligands.

Table C.24 $\Delta LogK$ versus metal ionic radius (r^+) relationships for CY_2-K22

Metal ion	r^+ (pm)[a]	$\Delta LogK$[b]	$\Delta LogK$[c]	$\Delta LogK$[d]
Cu^{2+}	71	1.53	1.66	1.03
Cd^{2+}	109	3.38	0.99	0.68
Ca^{2+}	114	2.98	1.13	0.64
La^{3+}	117.2		0.84	
Sr^{2+}	132	1.53	0.08	
Pb^{2+}	133	1.79	0.02	-0.61
Ba^{2+}	149	1.62	-0.06	-0.71

[a] Data from reference 59. All six co-ordination except for Cu^{2+} which is four co-ordination.

[b] $\Delta LogK = LogK_1(CY_2\text{-K22}) - LogK_1(\text{K22})$.

[c] $\Delta LogK = LogK_1(CY_2\text{-K22}) - LogK_1(\text{BHP-K22})$.

[d] $\Delta LogK = LogK_1(CY_2\text{-K22}) - LogK_1(\text{BHE-K22})$.

Results, however, have generally been disappointing, with N substituted macrocycles not having the desired complexing properties of bicyclic macrocycles. The ligand CY_2-K22 however, does show increased stability for all its complexes studied relative to that for its unsubstituted analogue K22.

Table C.4 gives the $\Delta LogK$ values for CY_2-K22 relative to K22 and BHP-K22 for a variety of metal ions. Also given in Table C.4 are the ionic radius values, in picometres, of the metal ions studied, in order to examine the relationships that exist between $\Delta LogK$ and ionic radius for these macrocyclic ligands. As mentioned in the introduction the addition of neutral oxygen donors to existing ligands has been extensively studied[3,12,15]. Previous work showed that such structural changes to ligands invariably cause a change in the stability constants of the substituted ligands relative to the unsubstituted ligands, which were metal ion size dependent. In general the size selective behaviour produced on adding neutral oxygen donors to existing ligands was found to be as a result of steric effects. The increased steric strain produced by the sterically bulky substituted ligand was at a maximum in complexes with small metal ions, and with large metal ions this steric strain was relieved. Hence, the addition of neutral oxygen donors favoured the complexation of large metal ions over small metal ions. Two types of behaviour are observed. The relationship between $\Delta LogK$ and ionic radius may be linear or a peak may exist at higher values of the ionic radius.

The results of Table C.4 are shown graphically in Figure C.1. It is immediately evident that the addition of two

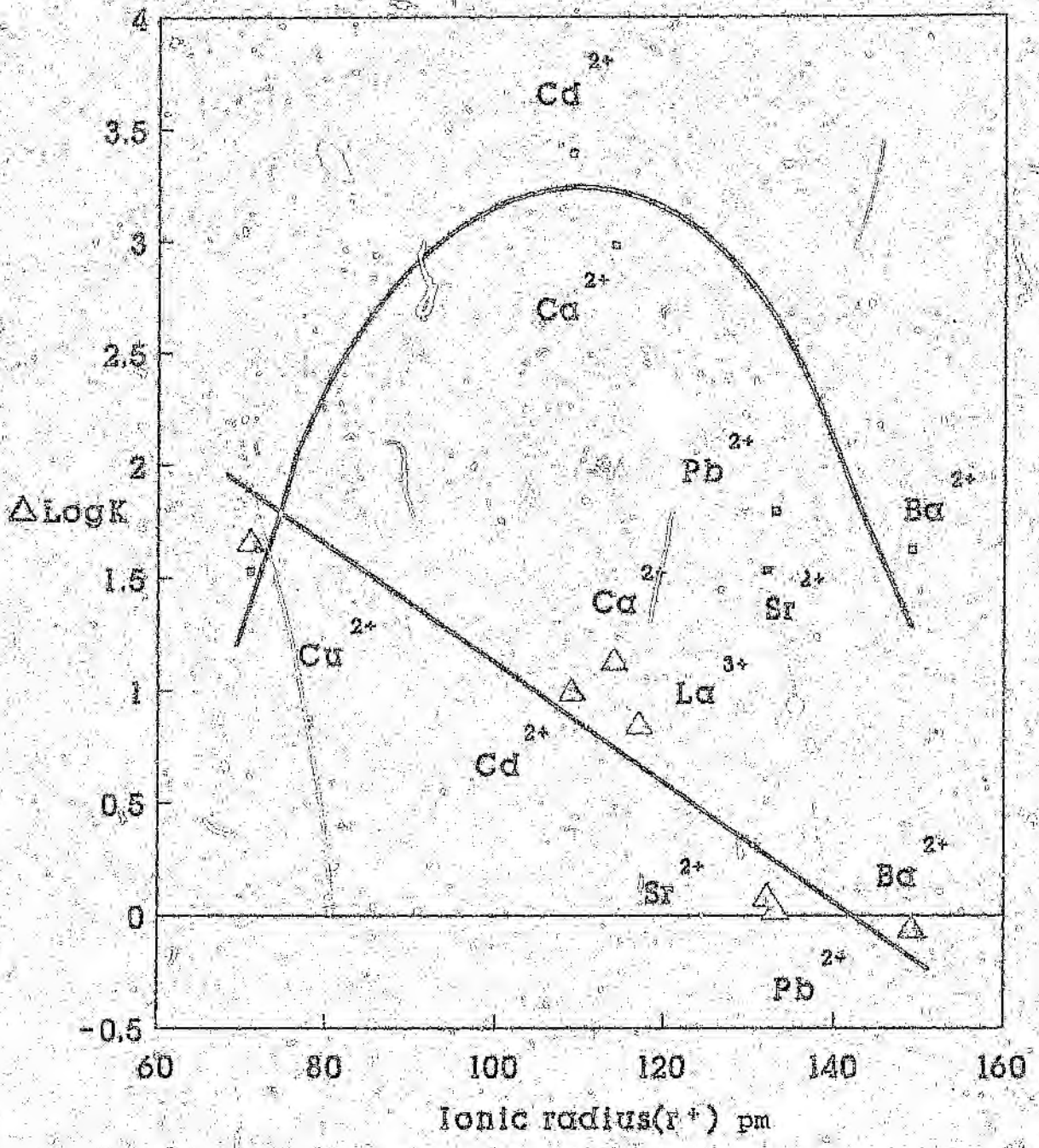


Figure C.1: ΔLogK $(CY_2\text{-K22/K22})$ □ and $(CY_2\text{-K22/BHP-K22})$ △ vs metal ionic radius (r^+)

cyclohexanol groups to K22 has produced extra complex stability over the wide range of metal ion sizes studied in this work. Unlike in previous work[3,12,15] there is also significant stabilization on adding neutral oxygen donors for small metal ions such as Cu^{2+}. As previously mentioned it is expected that small metal ions will react more favourably than large metal ions to inductive effects on amine ligands. Hence, the cyclohexanol substituents on the nitrogens of K22 may produce a favourable inductive effect which counteracts the unfavourable steric strain produced on co-ordination to small metal ions. Addition of any organic substituents leads to a dramatic increase in steric crowding[3] and in particular, molecular mechanics (MM) calculations[39,69] show that the co-ordination sphere around a small metal ion is extremely crowded. The fact that there is an increase in complex stability even for small metal ions emphasises the degree to which the proposed inductive effects are able to overcome these adverse steric effects.

The peak for the relationship between $\Delta \log K$ for the CY_2-K22/K22 comparison, and r^+, at an r^+ value of about 110 pm, seen in Figure C.1 is not interpreted as a best-fit size of metal ion as for the relationship[3] involving cryptand-2,2,1 and K22, but rather as a shift in the balance between steric and inductive effects. Thus, the rate of fall-off in steric effects beyond an r^+ value of 110 pm for the CY_2-K22/K22 relationship drops off, and for larger metal ions electronic effects dominate. With further increases in size there is thus a fall-off in complex stability as the

stability is now controlled by electronic effects. If larger metal ions react less favourably than small metal ions to inductive effects on amine ligands, as expected, the extra stability produced by the cyclohexanol substituents for larger metal ions may be less than or equal to that for small metal ions, even though steric effects are far less pronounced[3] for larger metal ions.

The macrocycle[9] BHP-K22, which has 2-hydroxy propyl substituents attached to both the nitrogens of K22, is structurally very similar to the macrocycle CY_2-K22 (Figures A.1 and A.7). CY_2-K22 has cyclohexyl groups bridging the nitrogen donors of the macrocyclic ring and the pendent alcoholic oxygen donors. Figure C.1 also shows a plot of ΔlogK versus r^+ where ΔlogK represents the relationship $logK_1(CY_2\text{-}K22)-logK_1(BHP\text{-}K22)$. The correlation coefficient is 0.94, showing a fairly strong inverse relationship between the effect on $logK_1$ of introducing a cyclohexyl bridge to the chelate ring, and metal ion size. Thus ΔLogK for small metal ions is larger than ΔLogK for large metal ions and, in the case of the largest ion studied, Ba^{2+}, it is negative. Hence, selectivity has been introduced on the basis of metal ion size, not through steric bulk of cyclohexanol "side arms" as originally it was thought would occur, but partly through the proposed inductive effect of the cyclohexanol arms on the nitrogens. Since small metal ions react more favourably than large metal ions to inductive effects on amine ligands, as discussed previously,

this has had the result that ΔLogK is largest for small metal ions since cyclohexanol pendent arms are expected to be more electron donating than the 2-hydroxy propyl pendent arms. Hence, the assumption that the inductive effect on the nitrogens in CY_2-K22 is greater than that found in BHP-K22, has been given as an explanation for the behaviour of ΔLogK, on changing the ionic radius of the metal ion for the CY_2-K22/BHP-K22 relationship shown in Figure C.1.

Table C.2 shows a selection of formation constants for CY_2-K22, as well as literature values[26,107,108] for BHE-K22 and K22, for purposes of comparison. Table C.4 gives the results of ΔlogK for CY_2-K22 relative to BHE-K22. The ΔlogK value is simply $logK_1$ for the CY_2-K22 complex of each metal ion minus $logK_1$ for the corresponding BHE-K22 complex. These results have been plotted as a function of the ionic radius[59] of the metal ions (Figure C.2). The ionic radii are all for six co-ordination except for Cu^{2+}, which is four co-ordination. The correlation coefficient in Figure C.2 is 0.90, showing a fairly strong relationship once again, between the effect on $logK_1$, of introducing a cyclohexyl bridge to the chelate ring, and metal ion size. It appears that the increase in formation constant in passing from BHE-K22 to CY_2K22 is related to size, but in such a way that the smallest metal ions show the strongest increase in $logK_1$ in changing the 2-hydroxyethyl groups to 2-hydroxycyclohexyl groups. This is an unexpected result since previous work[2,111,112] has shown that a five-membered

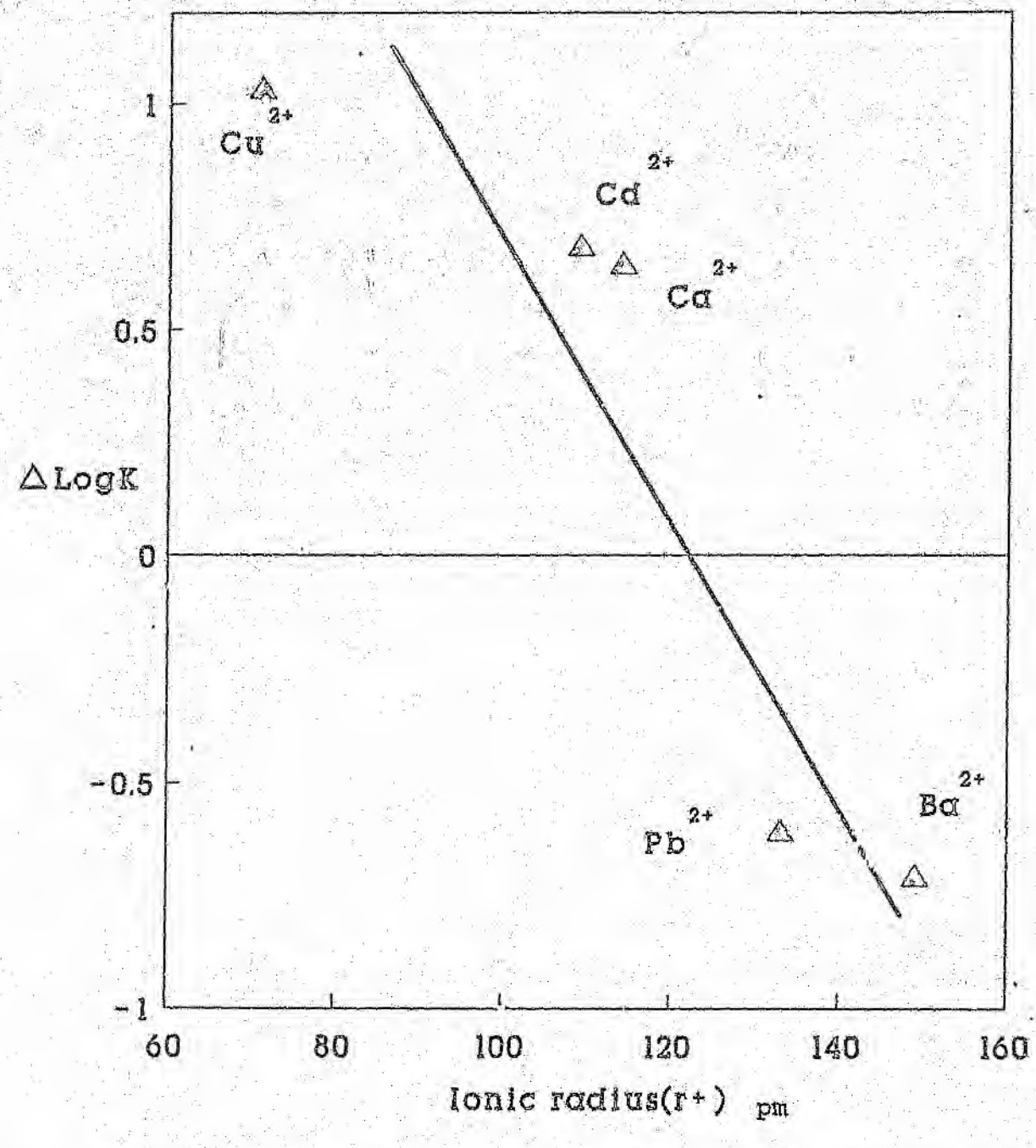


Figure C.2: $\Delta LogK(CY_2\text{-}K22/BHE\text{-}K22)$ vs metal ionic radius (r^+)

chelate ring promotes complex stability for large metal ions relative to small metal ions. In this view, the geometry of the five-membered ring is such that in the minimum strain arrangement the lone pairs on the donor atoms focus on a point some distance away, so that only large metal ions can co-ordinate with a minimum of steric strain. Increasing the rigidity of the five-membered chelate ring by fusing a cyclohexyl group to the bridge of the chelate ring should thus serve only to sharpen this effect. In ethylenediamine complexes small metal ions are accommodated[69] by decrease of the N-C-C-N torsion angle from the minimum strain value of 60, which now becomes impossible with fusion to the rigid cyclohexyl group in ligands such as trans-CDTA or CY_2-K22.

Another reason has been postulated for the behaviour of CY_2-K22. The presence of the bulky cyclohexanol "side arms" on the macrocycle should remarkably increase steric crowding with small ions thereby decreasing complex stability and thus favouring complex stability with the large metal ions. As seen in Figures C.1 and C.2 exactly the opposite happens. It has therefore been postulated that the rigid conformation of the "side arms" on CY_2-K22 over-rides steric effects by limiting steric crowding and thus favouring complex formation with small metal ions, disfavouring large. This aspect was supported by a molecular model of the Cu^{2+}/CY_2-K22 complex which showed that the sterically bulky "side arms" could co-ordinate perfectly well through the oxygen atom to the small Cu^{2+} ion without steric crowding

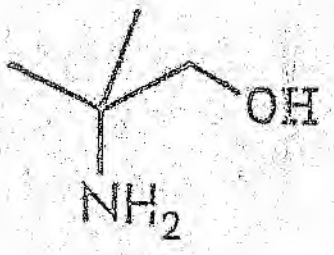
becoming significant. However, a more intensive investigation of the rigid nature adopted by the cyclohexanol pendent arms is necessary in order to verify this hypothesis. A crystallographic study as well as a study into the ligand field strengths of the complexes will serve as a tool in elucidating the role of rigidity in the complexes of CY

Treating the CY_2-K22 data as simple equilibria involving the neutral ligand reacting with the metal ion produced n-bar, the average number of ligands which are bound to the metal ion, plots as a function of the log of the free ligand concentration, which were non-superimposable as the ratio of ligand to metal was varied. The values of n-bar were calculated assuming no deprotonation of the complex, and their almost total non-superimposability, as the ratio of ligand to metal is varied, shows that this is not a tenable hypothesis for CY_2-K22. In order to investigate these more complex equilibria, the computer program MINIQUAD[101] was used. Table C.3 lists the refined deprotonation constants for the CY_2-K22 complexes studied. Figure C.3 shows a species distribution diagram for CY_2-K22 with copper(II) as a function of pH. It can be seen that, in the case of Cu(II), the complex begins to deprotonate at a pH of approximately 5.6. Consequently, it was important to include such species in the refinement of the equilibrium constants for CY_2-K22. The deprotonation reaction, in all cases, most probably represents deprotonation of the

A



B



C

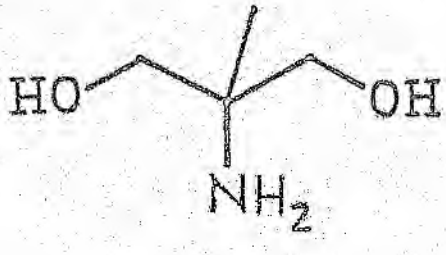


Figure C.4: Representation of the t-BUTYLAMINE (A), AMPOL (B) and AMPDOL (C) compounds

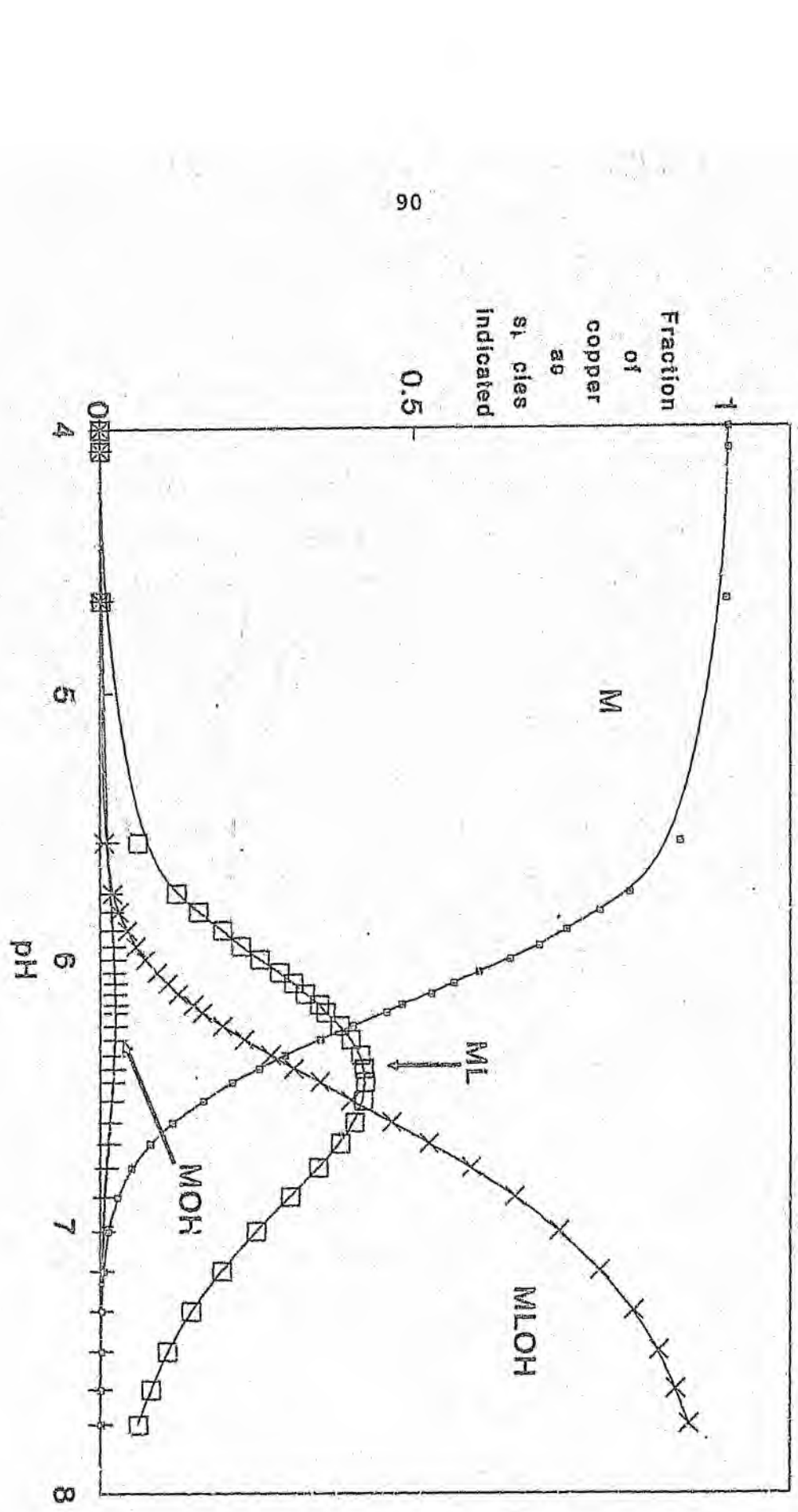


Figure C.3 : Species distribution diagram for the CY_2-K22/Cu(II) system as a function of pH. M = metal ion; L = ligand; OH = hydroxide ion. Charges on species omitted for simplicity.

cyclohexanol pendents to give alkoxide groups. Examination of Table C.3 shows that for all the metal ions studied, except Pb(II), $LogK_1(OH^-)$ for the CY_2-K22 complexes is significantly larger than the corresponding $LogK_1(OH^-)$ for the formation of the monohydroxo complexes of aqua ions. This has been interpreted as a specific solvation effect. The hydrophobic environment created by the alkyl groups of the CY_2-K22 macrocycle effectively reduces the solvation of the alcoholic hydrogen on the cyclohexanol pendents. Since the proton must be solvated in order to remain bonded to the alcoholic oxygen of cyclohexanol, this causes the proton to be more prone to being expelled from the cyclohexanol pendent. Hence, the concomitant increase for all metal ions except Pb(II), in $LogK_1(OH^-)$ for CY_2-K22 complexes relative to that found for the formation of the monohydroxo complexes of the aqua ions. Previous work[47] clearly demonstrates that hydrophobicity plays an important role in aqueous Lewis acid-base complex formation reactions. This work has therefore emphasised the importance of specific solvation effects in such reactions.

C.3 EQUILIBRIUM CONSTANTS OF THE OPEN CHAIN LIGANDS

The compounds referred to below are pictorialy represented in Figures C.4 and C.5. Statistics from the computer analysis of the results are given in appendix B.

C.3.1 RESULTS

Table C.5 through to Table C.11 give lists of equilibrium constants determined for the open chain ligands studied. Standard deviations are given in parentheses and literature values, where available, are given for comparative purposes.

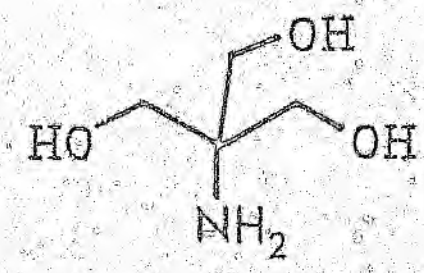
C.3.1.1 t-BUTYLAMINE

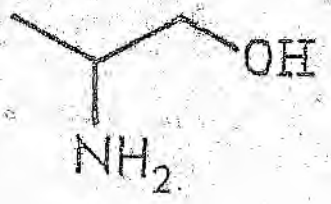
Table C.5: Equilibrium constants determined for t-BUTYLAMINE at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[c]	Log K	Literature values	References
H^+	L + H ---> LH	10.613(1)	10.685[a]	26
			10.66[b]	25
Ni^{2+}	M + L ---> ML	3.05(6)		
Cd^{2+}	M + L ---> ML	2.78(4)		
Pb^{2+}	M + L ---> ML	4.80(4)		
	ML+OH ---> MLOH	6.75(4)		
Ag^+	M + L ---> ML	3.65(2)	3.69[b]	25
	M + 2L --> ML_2	7.80(2)	7.87[b]	25

[a] μ = 0M, 25°C. [b] μ = 0.1M, 25°C. [c] M = metal ion; L = ligand; H = Proton; OH = hydroxide ion. Charges on species omitted for simplicity.

A





C

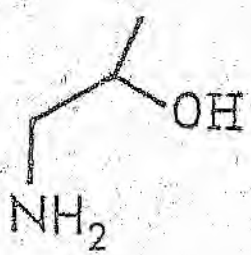


Figure C.5: Representation of the THAM (A), A_2POL (B) and AP OL (C) compounds

C.3.1.2 AMPOL

Table C.6: Equilibrium constants determined for AMPOL at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[b]	Log K	Literature values	References
H^+	L + H ---> LH	9.525(6)	9.7[a]	26
Cu^{2+}	M + L ---> ML	4.30(5)		
Ni^{2+}	M + L ---> ML	2.03(2)		
Zn^{2+}	M + L ---> ML	2.56(3)		
Cd^{2+}	M + L ---> ML	1.65(3)		
Pb^{2+}	M + L ---> ML	3.63(4)		
Ag^+	M + L ---> ML	3.40(3)		
	M + 2L ---> ML_2	7.[illegible](4)		25

[a] μ = 0M, 25°C. [b] M = metal ion; L = ligand; H = proton. Charges on species omitted for simplicity.

C.3.1.3 AMPDOL

Table C.7: Equilibrium constants determined for AMPDOL at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[c]	Log K	Literature values	References
H^+	L + H ---> LH	8.678(5)	8.82[b]	26
Cu^{2+}	M + L ---> ML	3.76(1)		
	ML+OH ---->MLOH	8.017(4)		
Ni^{2+}	M + L ---> ML	2.38(1)		
	ML+OH ---> MLOH	5.51(1)		
Zn^{2+}	M + L ---> ML	1.87(2)		
Cd^{2+}	M + L ---> ML	1.90(1)		
Pb^{2+}	M + L ---> ML	3.15(2)		
Ag^+	M + L ---> ML	3.03(2)		
	M + 2L ---> ML_2	6.81(2)	6.90[a]	26

[a] μ = OM, 25°C. [b] μ = 0.1M, 25°C. [c] M = metal ion; H = proton; L = ligand; OH = hydroxide ion. Charges on species omitted for simplicity.

C.3.1.4 THAM

Table C.8: Equilibrium constants determined for THAM at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[c]	Log K	Literature values	References
H^+	L + H ---> LH	8.023(4)	8.09[b]	26
Cu^{2+}	M + L ---> ML	3.90(1)	3.95[b]	26
	M + 2L --> ML_2	7.31(1)	7.63[b]	26
	M + 3L --> ML_3	10.57(1)	11.10[b]	26
Ni^{2+}	M + L ---> ML	2.53(1)	2.63[b]	26
	M + 2L --> ML_2	4.32(1)	4.5[b]	26
Zn^{2+}	M + L ---> ML	2.032(4)		
Cd^{2+}	M + L ---> ML	1.98(1)		
Pb^{2+}	M + L ---> ML	2.21(2)		
Ag^+	M + L ---> ML	3.05(1)	3.14[a]	25
	M + 2L --> ML_2	6.44(1)	6.57[a]	26

[a] μ = 0.05M, 25°C. [b] μ = 0.1M, 25°C. [c] M = metal ion; L = ligand; H = proton. Charges on species omitted for simplicity.

C.3.1.5 A_2POL

Table C.9: Equilibrium constants determined for A_2POL at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[a]	Log K
H^+	L + H ---> LH	9.42(1)
Cu^{2+}	M + L ---> ML	4.61(1)
Ni^{2+}	M + L ---> ML	2.91(1)
Zn^{2+}	M + L ---> ML	2.48(2)[b]
Cd^{2+}	M + L ---> ML	2.12(1)
Pb^{2+}	M + L ---> ML	3.59(2)
Ag^+	M + L ---> ML	3.24(3)
	M + 2L --> ML_2	6.90(3)

[a] M = metal ion; L = ligand; H = proton. Charges on species omitted for simplicity. [b] Hydroxide precipitation prevented the n-bar value rising above 0.1.

C.3.1.6 AP_2OL

Table C.10: Equilibrium constants determined for AP_2OL at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[a]	Log K	Literature values	References
H^+	L + H ---> LH^b	9.34(1)	9.49(0)[b]	26
Cu^{2+}	M + L ---> ML	4.57(2)		
Ni^{2+}	M + L ---> ML	2.88(2)		
	M + 2L ---> ML_2	5.25(2)		
Zn^{2+}	M + L ---> ML	2.30(4)[d]		
Cd^{2+}	M + L ---> ML	2.10(1)		
Pb^{2+}	M + L ---> ML	2.98(9)		
Ag^+	M + L ---> ML	3.00(2)	3.23[c]	26
	M + 2L ---> ML_2	6.53(2)	6.78[c]	26

[a] M = metal ion; L = ligand; H = proton. Charges on species omitted for simplicity. [b] μ = 0.1M, 25°C. [c] μ = 0 M, 20°C. [d] Hydroxide precipitation prevented a n-bar value greater than 0.86.

C.3 4.7 BHEAC

Table C.11: Equilibrium constants determined for BHEAC at μ = 0.1M and 25°C

Lewis Acid	Equilibrium[a]	Log K
H^+	L + H ---> LH	8.48(1)
Cu^{2+}	M + L ---> ML	4.99(3)
	ML+OH ---> MLOH	8.23(1)
Ni^{2+}	M + L ---> ML	3.60(1)
	ML+OH ---> MLOH	5.06(2)
Zn^{2+}	M + L ---> ML	2.70(5)
Cd^{2+}	M + L ---> ML	3.230(3)
Pb^{2+}	M + L ---> ML	3.72(1)
	M +2L ---> ML_2	6.87(1)
Ag^+	M + L ---> ML	2.09(1)

[a] M = metal ion; L = ligand; H = proton; OH = hydroxide ion. Charges on species omitted for simplicity.

C.4 ANALYSIS OF THE RESULTS OBTAINED FOR BHEAC

C.4.1 The size selective behaviour of BHEAC

Table C.12: Stability constants of BHEAC and triethanolamine (TEA), ionic radii and $\Delta Log\ K^a$

Metal ion	Ionic radii[b] (pm)	Log K[c] BHEAC	Log K[d] TEA	$\Delta Log\ K^a$
Cu^{2+}	71	4.99	4.07	0.92
Ni^{2+}	83	3.60	2.76	0.84
Zn^{2+}	88	2.78	2.05	0.73
Cd^{2+}	109	3.23	2.70	0.53
Pb^{2+}	133	3.72	3.39	0.33

[a] $\Delta LogK = [LogK_1\ (BHEAC) - LogK_1\ (TEA)]$. [b]Data from reference 59. All six co-ordination except for Cu^{2+} which is four co-ordination. [c]This work. μ = 0.1M and 25°C. [d]Reference 8 except for Cd^{2+} reference 26.

A comparison of the two ligands BHEAC and triethanolamine will reveal that the only structural difference is the added cyclohexyl bridge to a chelate ring on one of the hydroxyethyl arms of BHEAC. This extra structural group on

BHEAC possibly makes it more rigid and hence more "pre-organized" than the ligand triethanolamine.

Table C.11 lists all the equilibrium constants obtained in this work for BHEAC. A comparison of the stability constants of BHEAC and triethanolamine (Table C.12) reveals that introducing a cyclohexyl bridge to a chelate ring in triethanolamine to produce BHEAC favours the complexation of small metal ions over large metal ions. This size selective behaviour of BHEAC is diagramatically represented in Figure C.6. The correlation coefficient in Figure C.6 is 0.99, showing a strong inverse relationship between the effect on $\log K_1$ of introducing a cyclohexyl bridge to the chelate ring, and metal ion size. This is a surprising result in terms of the view[1,111,112] that a five-membered chelate ring should promote complex stability for large metal ions relative to small metal ions. The unusual pattern of selectivity for metal ions in relation to their size, found for CY_2-K22 relative to BHE-K22 and BHP-K22, is therefore not dependent on the presence of a macrocyclic ring (Section C.2).

As mentioned in the Introduction, it is expected that small metal ions will react more favourably than large metal ions to inductive effects on amine ligands. Extra electron donating ability of the cyclohexanol group in BHEAC compared to that found for a hydroxyethyl group of triethanolamine is also expected. According to the Taft and Pavelich[56]

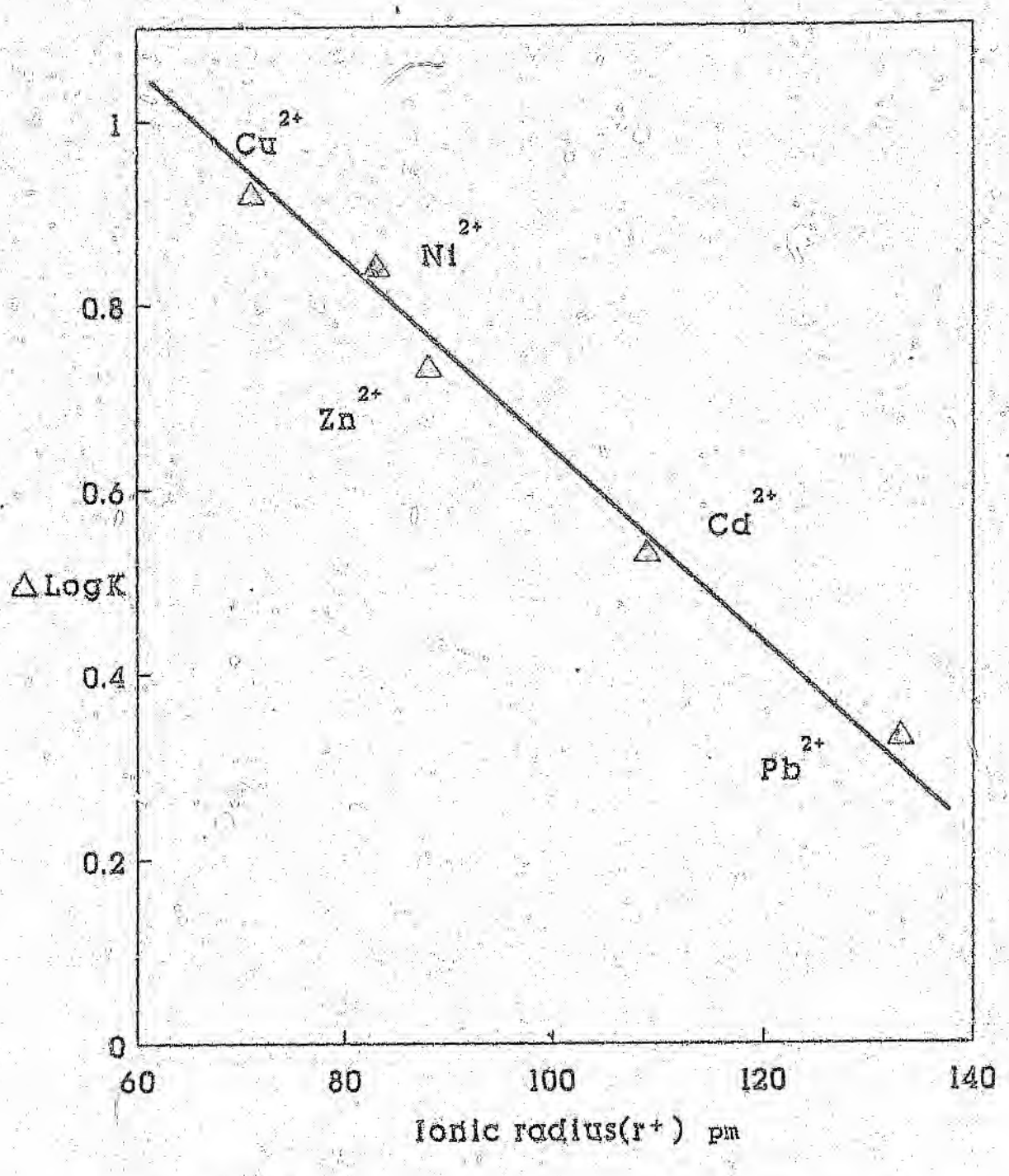


Figure C.6: ΔLogK(BHEAC/TEA) vs metal ionic radius (r^+)

equation for the separation of polar (inductive) and steric effects, this means that the cyclohexanol substituent will have a more negative σ^* (Taft inductive effect parameter) value than that for hydroxyethyl as substituent. The implication is that the inductive effect due to cyclohexanol as substituent is expected to be greater than that with a hydroxyethyl group as substituent. Hence the size selective behaviour of BHEAC in relation to triethanolamine (TEA) can be partly explained in terms of the different inductive effects expected from these two ligands.

The greater inductive effect from the cyclohexanol substituent of the amine BHEAC relative to that found for the hydroxyethyl substituent of triethanolamine results in small metal ions being complexed more favourably than large metal ions. This result is in keeping with the behaviour of ammonia on increasing the size of the metal ion. As mentioned in the Introduction, $\log K_1(NH_3)$ decreases as the ionic radius increases. This behaviour indicates that small metal ions may react more favourably than large metal ions to inductive effects on amine ligands.

Interestingly, in the extreme case of the large silver (I) ion, which has linear co-ordination and therefore minimum steric effects[25], a decrease in complex stability on going from triethanolamine to BHEAC is observed. A value of $\log K_1 = 2.30$ for silver (I) with triethanolamine is given in the literature[26] and in this work a value of $\log K_1 = 2.09$ was obtained for silver (I) with BHEAC.

An important point to be borne in mind when analysing the effect of changes in ligand structure on complex stability, is the very much greater strain energy likely to be present in the complexes of complex than of simple ligands. What is important here is the increase in strain energy, ΔU, which occurs on complex formation[41]. For this reason molecular mechanics calculations were performed on metal complexes of BHEAC and triethanolamine (TEA). For this purpose use was made of the program ALCHEMY[104]. It was assumed that both BHEAC and triethanolamine bound as tetradentate ligands through their nitrogen and oxygen donor atoms. To model the effect of increasing metal ion size on the minimum total strain energy of the complex, ΣU, five different metal to nitrogen and metal to oxygen bond lengths were chosen. The metal to nitrogen bond lengths were made 0.04Å larger than the metal to oxygen bond lengths and octahedral co-ordination geometry around the metal ion was assumed in all cases. The remaining co-ordination sites around the metal ion were filled by co-ordinated water molecules. In order to calculate U one must also calculate U_L for the free ligands. U_M is the same for both ligands and since a comparative study was undertaken its value was assumed to be zero.

The molecular mechanics results obtained from the program ALCHEMY[104] are given in Table C.13. It is evident that the increase in strain energy, ΔU, for the BHEAC complex is in all cases greater than that for the corresponding triethanolamine complex. It must be remembered that molecular mechanics calculations of this nature consider just structural factors. No other effects such as inductive

Table C.13: Strain energy (U) for BHEAC and TEA and the increases in strain energy (ΔU) on complex formation with increasing size of the metal ion[a]

	BHEAC		TEA	
	U	ΔU^e	U	ΔU^e
	(K.cal.mol^{-1})			
U_L[b]	-16.004		-4.469	
MN MO[d]				
1.96 1.92				
U_{ML}[c]	- 8.243	7.761	-6.221	-1.752
MN MO				
2.16 2.12				
U_{ML}	- 4.008	11.996	-1.255	3.214
MN MO				
2.36 2.32				
U_{ML}	2.947	18.951	6.314	10.783
MN MO				
2.56 2.52				
U_{ML}	11.637	27.641	15.306	19.775
MN MO				
2.76 2.72				
U_{ML}	20.753	36.757	25.149	29.618

[a]Data from the molecular mechanics program ALCHEMY[104]. Increases in metal ion size were modelled by increasing the size of the metal to nitrogen and metal to oxygen bond lengths in the program. [b]Strain energy of the free ligand. [c]M = metal; L = ligand. Strain energy of the complex. [d]Bond lengths in Angströms. MN = metal-nitrogen bond length. MO = metal-oxygen bond length. [e]$\Delta U = U_{ML} - U_L$.

effects are taken into account. The molecular mechanics results indicate that, considering structural effects alone, the complexes of triethanolamine should be thermodynamically more stable than those of BHEAC. However from the stability constant data obtained, it is clear that, from a free energy point of view, the more thermodynamically stable complexes are those with BHEAC, with the exception of silver (I). From the molecular mechanics results obtained (Table C.13) one would expect that inductive and not structural effects give it this advantage over triethanolamine.

Molecular mechanics calculations[39,69] show that the co-ordination sphere around a small metal ion is extremely crowded and leads to metal-to-ligand bond stretching, which allows a decrease in the number of ligand atoms in the immediate vicinity of the metal ion and, therefore, a lowering of stability of the complex. Initially it was thought[113] that a cyclohexanol group would add a certain degree of rigidity and pre-organization to ligands. This rigidity would then reduce steric crowding in the co-ordination sphere of small metals with a concomitant increase in complex stability. This work, however, has shown that in passing from triethanolamine to BHEAC there is an increase in ΔU on complex formation. This is presumably due to the cyclohexanol arm of BHEAC. Consequently the theory of rigidity has been discounted as a reason for the selectivity of BHEAC for small metal ions in relation to that found for triethanolamine.

C.4.2 OTHER RESULTS OF INTEREST

Interestingly, like the triethanolamine complex with Cu(II), the BHEAC Cu(II) complex also becomes deprotonated[8]. The similarity of the constants, 8.37 and 8.23 for triethanolamine and BHEAC respectively, representing the equilibrium $ML + OH^- \longrightarrow MLOH$, is probably due to the fact that the same deprotonation reaction is occuring in both cases. This could either be a loss of a proton from a co-ordinated water molecule or, most likely, the loss of a proton from a hydroxyethyl arm of the ligands.

It is also worth mentioning the apparent non-agreement of the results obtained for Ni(II) with BHEAC and triethanolamine. Previous work[8] on triethanolamine (TEA) showed the presence of a $[Ni(TEA)_2]^{2+}$ complex in solution, whereas no equivalent complex formed with BHEAC in solution. Rather, deprotonation of the BHEAC complex occurs with Ni(II). However, the high standard deviation of ± 0.1 reported[8] for the $[Ni(TEA)_2]^{2+}$ complex suggests that at higher pH values the actual equilibrium occurring is not the addition of two triethanolamine ligands to Ni(II), but rather the deprotonation of the triethanolamine complex with Ni(II), as in the case of BHEAC with Ni(II).

The behaviour of Pb(II) and Zn(II) with BHEAC in solution closely matches that found with triethanolamine in solution.

However, precipitation of metal hydroxides during the BHEAC titrations prevented the determination of higher order complexes in solution. Previous work[8] on triethanolamine reported a third order complex in the case of Pb(II) and a second order complex in the case of Zn(II).

C.5 THE SIMPLE ANALYSIS OF THE CHELATE EFFECT IN COMPLEXES OF ETHANOLAMINE-TYPE LIGANDS

In the introduction it was mentioned that previous work on ethanolamine[71] found that the chelate effect in its complexes was very simply analysed. For reasons given in the introduction, it is expected that the chelated alcoholic hydroxyl group will cause no extra stabilization for the amine group in ethanolamine. Any alteration in stability as compared with ammonia can thus be discussed in terms of the inductive effect of the bridging ethylene group[73], somewhat modified by steric effects[72]. Table C.14 lists the stability constants ($\log K_1$) of ammonia and the ethanolamine-type hydroxyethyl substituted amines studied in this work with Cd(II), Zn(II), Ni(II), Cu(II) and Pb(II).

It is clear from an examination of Table C.14 that $\log K_1$ (ammonia) for all metal ions except Pb(II) closely matches $\log K_1$ for the ethanolamine-type ligands studied.

Table C.14: Comparison of $\log K_1$ values for ammonia, A_2POL, AP_2OL and AMPOL at 25°C and ionic strength 0.1 M

Metal ion	$\log K_1$[a] NH_3	$\log K_1$[b] A_2POL	$\log K_1$[b] AP_2OL	$\log K_1$[b] AMPOL
Cd^{2+}	1.9	2.12	2.10	1.64
Zn^{2+}	2.18	2.48[c]	2.30[c]	2.56
Ni^{2+}	2.7	2.91	2.88	2.03
Cu^{2+}	4.1	4.61	4.57	4.30
Pb^{2+}	3.6	3.59	2.98	3.63

[a]Reference 26 except for Pb^{2+} reference 57 and Cd^{2+} reference 58. [b]This work at 25°C and ionic strength 0.1M. [c]The titrations of Zn^{2+} with A_2POL and AP_2OL were plagued by precipitation of hydroxide. The highest $\bar{n}$ values obtained before precipitation set in were not in excess of 0.1 for A_2POL and for AP_2OL precipitation commenced at about $\bar{n}$ equals 0.15.

C.5.1 ANALYSIS OF A_2POL AND AP_2OL COMPLEXES

A plot of $\log K_1$ (ammonia) versus $\log K_1$ (A_2POL) for Cd(II), Zn(II), Ni(II) and Cu(II) is shown in Figure C.7. A similar plot using the stability constants of the same metal ions for the ligand AP_2OL is shown in Figure C.8. In each plot a line of slope 1.152 (inductive effect factor) is shown, which is that expected on the basis of the simple model of the chelate effect[73] discussed in the Introduction.

It can be seen that most points lie on or just below this line. Figure C.7 and Figure C.8 suggest that the chelate effect in complexes of A_2POL and AP_2OL is very simply analysed, as found for ethanolamine in previous work[71]. There are, however, deviations from the model proposed. The fact that most points lie below the line possibly relates to the lower basicity of the nitrogens in the ligands studied as compared with a polyamine such as ethylenediamine (pK_a = 9.9). An inductive term has already been placed into the analyses of the chelate effect in the sense that an inductive effect factor has been used. This inductive effect factor has been assumed to be well represented by the ratio of the protonation constants of methylamine and ammonia[73].

A drawback of the simple approach to the analysis of the chelate effect is that it does not take into account steric effects. The importance of steric effects in controlling complex stability has been emphasised in previous work[2,60,74,76,114].

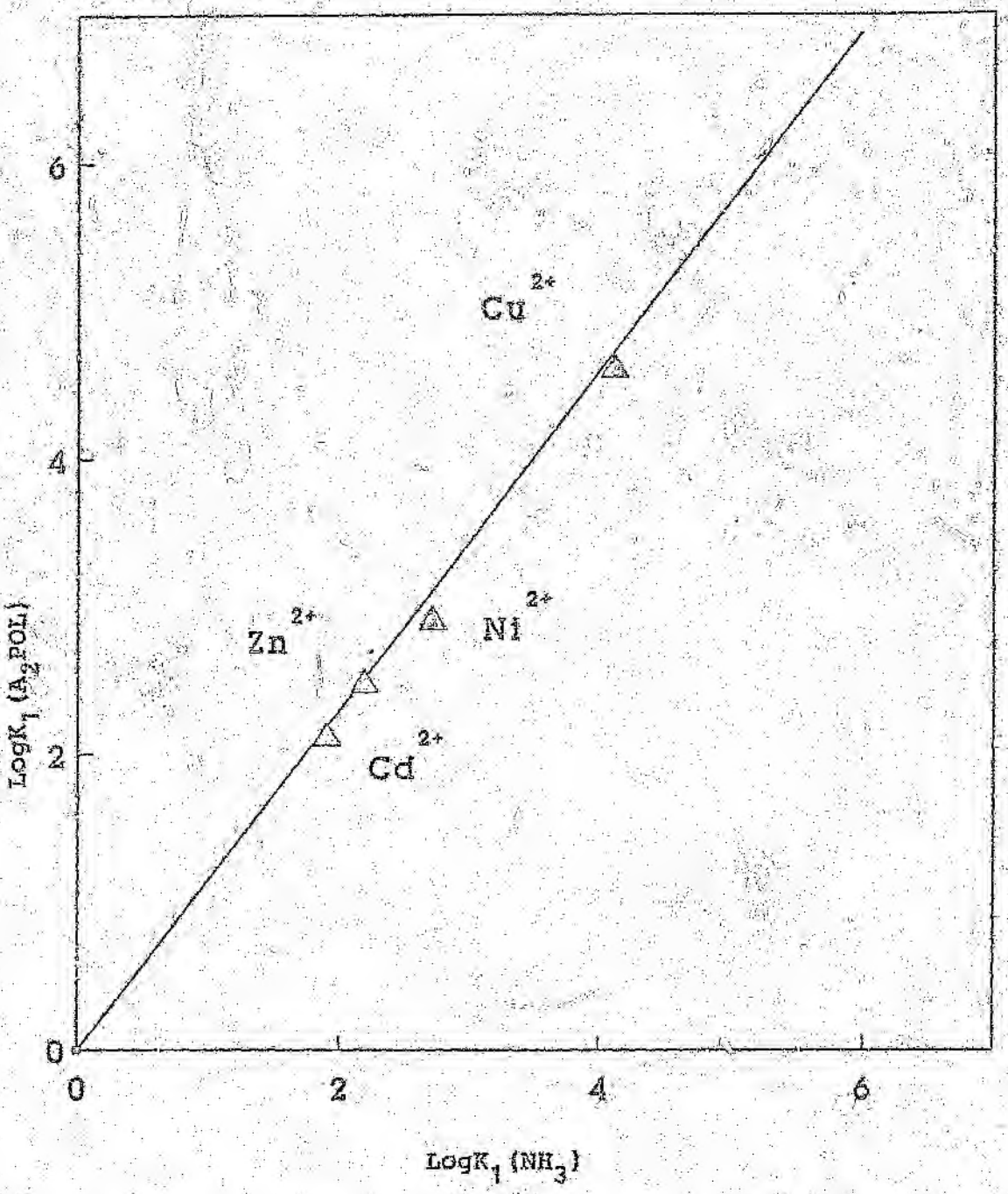


Figure C.7: $LogK_1(A_2POL)$ vs $LogK_1(NH_3)$. The solid line drawn in has a slope of 1.152, which is the inductive effect factor

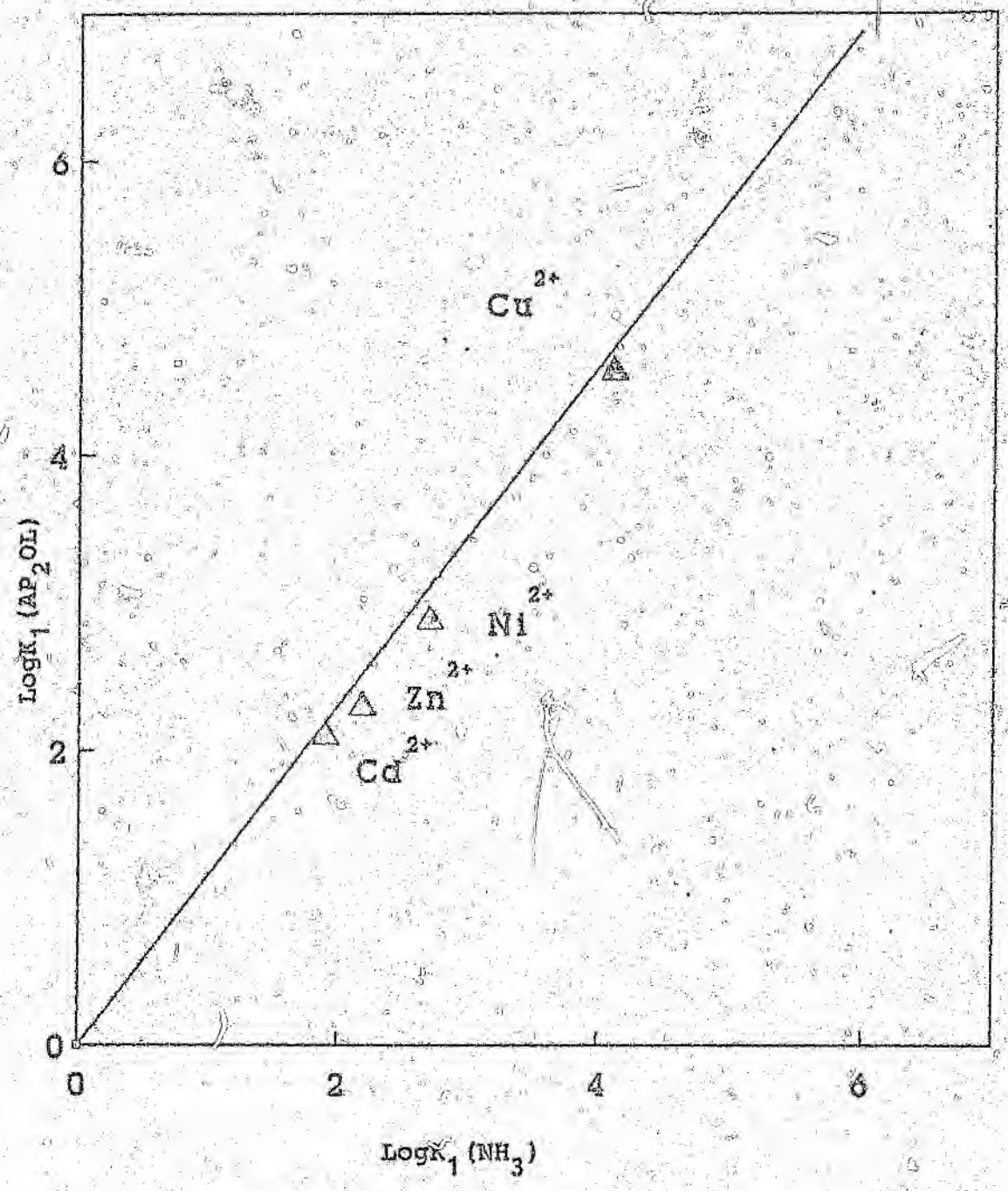


Figure C.8: $LogK_1(AP_2CL)$ vs $LogK_1(NH_3)$. The solid line drawn in has a slope of 1.152, which is the inductive effect factor

Important to the discussion on steric effects is the strain energy U and in particular the increase in strain energy, ΔU, which occurs on complex formation[41]. Empirical force field calculations[41] on the very similar ethylenediamine complexes have shown that for Ni(II) there is an increase of 0.61 Kcal mol^{-1} in the strain energy, U, of the ligand on forming the $[Ni(en)(H_2O)_4]^{2+}$ complex. One would expect that there would also be an increase in U for the formation of the complexes formed by the ethanolamine-type ligands studied in this work. The increase in U was not included in the simple analysis of the chelate effect[73] discussed in the introduction. However, the fact that Figure C.7 and Figure C.8 show that for Cd(II), Zn(II), Ni(II) and Cu(II) complexes of A_2POL and AP_2OL it has not made itself apparent - as found for ethanolamine[71] - suggests that this unfavourable contribution is probably counterbalanced by the increased basicity of the alcoholic oxygen of these two ligands as compared with that in the water molecule displaced on co-ordination. In other words[26] the favourable contribution from the inductive effect of the ethylene bridge is being cancelled out by the steric strain produced by co-ordination of the alcoholic oxygen atom.

C.5.2 ANALYSIS OF AMPOL COMPLEXES

The relationship between $\log K_1$ (AMPOL) and $\log K_1$ (ammonia) for Cd(II), Ni(II), Zn(II) and Cu(II) is shown in Figure C.9. It is evident that for AMPOL there is significant deviation of the points from the theoretical line expected from the simple analysis of the chelate effect. The behaviour of AMPOL is therefore unlike that found for A_2POL and AP_2OL.

It is possible that in the formation of the metal complexes of AMPOL the increase in strain energy, ΔU, may not be counterbalanced by the increased basicity of the alcoholic oxygen as suggested for A_2POL and AP_2OL. This would then explain the deviation to lower values of stability for AMPOL. Remarkably, the ligand AMPOL, which shows the most deviation of all the ligands analysed, is expected to display the largest increase in strain energy on co-ordination. This is due to the extent of α-carbon methylation in AMPOL. Tetrahedrally co-ordinated Cu(II), which shows remarkable agreement with the simple analysis of the chelate effect for all the ligands analysed in this work, should display less steric hindrance than that found in octahedral co-ordination. It is however seen in Figures C.7 to C.9 that the most deviation from the line of gradient equal to 1.152, for Cu(II), is found in its complex with AMPOL, supporting the idea that ΔU, for this ligand, is relatively higher than that expected for A_2POL and AP_2OL.

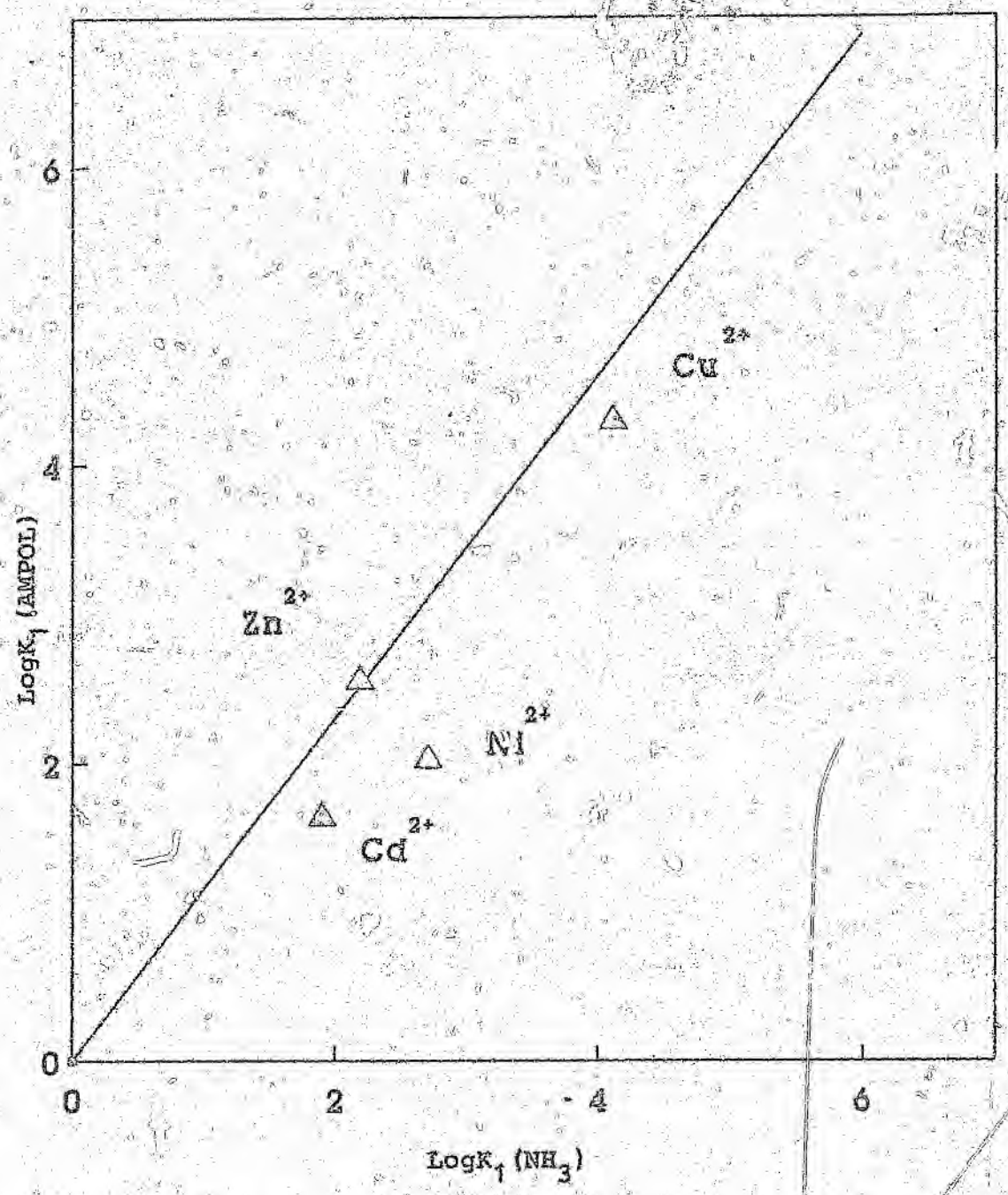


Figure C.9: $LogK_1$ (AMPOL) vs $LogK_1$ (NH_3). The solid line drawn in ha[illegible] a slope of 1.152, which is the inductive effect factor

C.6 FACTORS INFLUENCING THE STABILITY OF COMPLEXES WITH LIGANDS CONTAINING NEUTRAL OXYGEN DONORS

A comparison of the $\log K_1$ values for ammonia, A_2POL, AP_2OL and AMPOL can be made by analysis of Table C.14. Likewise a comparison of $\log K_1$ values for THAM, AMPDOL, ethanolamine, triethanolamine and ammonia can be made using Table C.15. Of particular interest is that $\log K_1$ for all the metal ions in Table C.14 and C.15 except Pb(II) is about the same as for $\log K_1(NH_3)$, with some exceptions, notably the Cd(II) and Ni(II) stability constants of AMPOL, which are significantly lower. This behaviour closely matches that found for ethanolamine and triethanolamine. Previous work[8] found that for Cu(II), Ni(II), Co(II) and Zn(II) $\log K_1$ for ethanolamine and triethanolamine is about the same as $\log K_1(NH_3)$. In these cases the increased basicity of the alcoholic oxygen(s) and amine group is either counterbalanced by the unfavourable increase in strain energy, ΔU, produced on co-ordination to the metal ion, or countered to such an extent that the steric strain produced on formation of the complex outweighs the inductive effects, thereby decreasing complex stability relative to that for ammonia.

Table C.15: Comparison of $\log K_1$ values for ammonia, THAM, AMPDOL, ethanolamine (EA) and triethanolamine (TEA)

Metal ion	$\log K_1$ [a] NH_3	$\log K_1$ [b] THAM	$\log K_1$ [b] AMPDOL	$\log K_1$ [c] EA	$\log K_1$ [d] TEA
Cu^{2+}	4.10	3.90	3.76	4.50	4.07
Ni^{2+}	2.70	2.53	2.38	3.05	2.76
Zn^{2+}	2.18	2.03	1.87	2.41	2.05
Cd^{2+}	1.9	1.98	1.90	2.77	2.70
Pb^{2+}	1.55	2.21	3.14	4.10	3.39

[a]Data from reference 26 except for Cd^{2+} reference 58 and Pb^{2+} reference 57. [b]This work at 25°C and ionic strength 0.1 M. [c]Reference 71 except for Pb^{2+} reference 8 and Cd^{2+} reference 26. [d]Reference 8 except for Cd^{2+} reference 26.

For the ethanolamine-type ligands studied in this work (Table C.14 and Table C.15) $\log K_1$ for Pb(II) is much higher than $\log K_1$ for Pb(II) with ammonia. This suggests that the hydroxyethyl groups of the ethanolamine-type ligands studied lead to stabilization of the Pb(II) complex on forming a chelate, in exactly the same way as was found for ethanolamine and triethanolamine, as discussed in the introduction. Once again[8], in the case of Pb(II), the inductive effect of the alcohols outweighs the unfavourable increase in strain energy, ΔU, produced on formation of the chelate ring, with a resulting increase in the stability of the complex.

A possible explanation for the higher values of $\log K_1$ for Cd(II) with triethanolamine (2.70) and ethanolamine (2.77)[26], as compared to the stability constants found for Cd(II) with the ethanolamine-type ligands studied in this work, may be the lack of considering hydrolysis of the metal ion itself in the former cases. This is a problem, as take-up of base during the titrations could be due, in this case, to metal ion hydrolysis rather than complex formation, which is a possibility with the Cd(II) ion. This would increase the value of the stability constant for Cd(II) in exactly the same way as was found for ethanolamine with Zn(II). Hancock[71] found a value of $\log K_1$ equals 2.41 for the complex of ethanolamine with Zn(II). The surprisingly high value of 3.7 for $\log K_1$ reported[115] for Zn(II) was attributed to hydroxide formation or else deprotonation of the co-ordinated ligand. The titrations of ethanolamine with Zn(II) were plagued by precipitation of hydroxide, which relates to the high acidity of the Zn(II) ion, coupled with its small affinity for ethanolamine. Interestingly, similar precipitation problems were encountered in the titrations of Zn(II) with A_2POL and AP_2OL in this work. Even the use in the titrations of a background salt, being mainly ligand ammonium nitrate, which suppresses both deprotonation of the alcoholic hydroxyl group of the co-ordinated ligand and hydrolysis of the metal ion, did not prevent precipitation problems with Zn(II) in this work and the work done by Hancock[71] on ethanolamine. The highest n-bar values obtained before precipitation set in were not

in excess of 0.1 for A_2POL, and for AP_2OL precipitation commenced at about 0.15 n-bar. Stability constants for these ligands with Zn(II) were calculated using the n-bar values obtained experimentally, and are given in Table C.14.

The constants reported in this work were refined using the computer programme Miniquad[111], which makes investigation of more complex equilibria a much less daunting task. In addition, constants for the hydrolysis of the metal ions themselves may be included in the refinement, which prevents the problem of obtaining misleading stability constant values when working with ligands which do not have high affinities for metal ions.

C.7 THE INFLUENCE OF POLAR AND STERIC EFFECTS ON THE PROTONATION CONSTANTS AND SILVER STABILITY CONSTANTS OF AMINOALCOHOLS

As mentioned in the introduction, previous work[25,46] on primary amines with the proton and silver (I) ion in aqueous solution found a very fine balance between the contributions of inductive and steric effects, in controlling the stability of these complexes.

C.7.1 Effect of the addition of hydroxy groups to tertiary butylamine

Considering the series of primary amine ligands, namely THAM, AMPDOL, AMPOL and tertiary butylamine, one would expect an increase in the electron donating ability of the amine substituent as one successively removes hydroxy groups. This would result in a greater inductive effect of the substituent, which, quantified using Taft and Pavelich's equation[56] for the separation of polar and steric effects, would mean more negative σ^* values. Hence, it might be anticipated that, in the absence of steric effects, Lewis acids in aqueous solution should show increases in their free energies of complex formation with increases in the inductive effect of the substituent[2].

Table C.16 gives the pK_a and complex-formation constants with Ag(I) for the series of primary amines discussed above.

When available, literature values have been included for comparative purposes. It is evident that for this series of ligands both the proton and Ag(I) ion show increasing complex stability as the inductive effect of the substituent increases. The fact that Ag(I) is less susceptible than the proton to steric hindrance to co-ordination[42], for reasons given in the introduction, emphasises the degree to which the steric effects are overcome by the inductive effects in the above series of ligands with the proton. This is possibly due to the fact that the steric environment around the amine co-ordination site for this series of ligands remains constant, since the α-carbon in all cases remains attached to three ß-carbon groups, regardless of the extent of substitution of hydroxy groups onto the ß-carbons.

Table C.16: Values of pK_a and complex-formation constants with Ag(I) for THAM, AMPDOL, AMPOL and t-Butylamine

Stability constants	THAM	AMPDOL	AMPOL	t-BUTYLAMINE
pKa[a]	8.02	8.68	9.53	10.61
pKa(lit)	8.09[b]	8.82[b]	9.72[b]	10.66[c]
$\log K_1$ [a]	3.05	3.03	3.40	3.65
$\log K_1$(lit)	3.14[b]			3.69[c]
$\log ß_2$ [a]	6.44	6.81	7.09	7.80
$\log ß_2$(lit)	6.57[b]	6.90[b]		7.87[c]

[a]This work at 25°C and I = 0.1M. [b] Lit = literature. Data from reference 26. [c]Data from reference 25.

C.7.2 Effect of methylating the α-carbon of ethanolamine

Another series of primary amine ligands investigated displays quite different behaviour from that found in Section C.7.1, on increasing the electron donating ability of the substituent. This series includes the ligands ethanolamine, A_2POL and AMPOL. Table C.1[illegible] the values of pKa and complex-formation constants with Ag(I) for this series of primary amines. Literature values, where available, are also given. All three of these ligands contain an ethanolamine backbone and differ only in the degree of substitution of methyl groups onto the α-carbon atom of ethanolamine. It would therefore be expected that the added methyl groups would increase the inductive effect of the amine substituents. The order of increasing inductive effect, displayed by this series of ligands, would then be expected to be as follows: ethanolamine < A_2POL < AMPOL. Obviously an investigation into the gas phase basicities of these primary amines would serve to give more information on the intrinsic basicity order.

Table C.17 : Values of pK_a and complex-formation constants with Ag(I) for ethanolamine (EA), A_2POL and AMPOL

Stability constants	EA	A_2POL	AMPOL
pKa[a]		9.42	9.53
pKa(lit)	9.45[c]		9.72[b]
$logK_1$ [a]		3.24	3.40
$logK_1$(lit)	3.2[b]		
$log\beta_2$ [a]		6.90	7.09
$log\beta_2$(lit)	6.76[b]		

[a]This work at 25°C and I = 0.1M. [b]Lit = literature. Data from reference 26. [c]Data from reference 71.

It should be noted that the pK_a values of this series of ligands (Table. C.17) show no response to the changes in inductive effect. On the other hand the $logK_1$ and $log\beta_2$ values with Ag(I) increase, very slightly, with increasing inductive effect of the substituent. The behaviour of the pK_a values matches that found for the series of primary amines, as we change the alkyl substituent from methyl to ethyl, isopropyl and finally tert-butylamine[25]. It can be explained in terms of a balance between polar (inductive) and steric effects. Adding a methyl group has a favourable polar contribution, but, because of its bulkiness, has an unfavourable steric contribution. Hence the increased

inductive effects are cancelled out by the increased steric effects, so that there is little difference in pK_a between the amines in this series (Table C.17). Unlike the previous series investigated (THAM to t-BUTYLAMINE), the steric environment around the amine co-ordination site, in this series, changes as methyl groups are substituted onto the α-carbon atom of ethanolamine. Consequently the unfavourable steric interactions produced around the amine co-ordination site by the added methyl group(s) prevent increases in the protonation constants, as methyl groups are successively substituted onto the α-carbon atom of ethanolamine. The behaviour of Ag(I) and the proton with this series of ligands is in keeping with the suggestion[42] that the Ag(I) ion is less susceptible than the proton to steric hindrance to co-ordination caused by the large hydration sphere and small size of the latter. Since the proton is often used as an indication of inductive effects in aqueous solution and steric effects tended to mask these inductive effects, it was proposed[46] that these should be called "hidden" inductive effects. The series of ligands ethanolamine, A_2POL and AMPOL gives yet another example of these hidden inductive effects.

C.8 RELATIONSHIP BETWEEN METAL HYDROLYSIS AND pK_a IN AQUEOUS SOLUTION

In this work an investigation was carried out into the complexing strengths of the series of ligands t-butylamine, AMPOL, AMPDOL and THAM. The series of ligands is generated by successive additions of hydroxy groups onto the methyl groups of tertiary-butylamine. Previous[26] work on these ligands involved, in most cases, a simple analysis of the equilibrium constants, where hydrolysis of the metal ion or metal ligand complexes - which is a very real possibility in these cases - was not considered. In this work the programme Miniquad[101] was used to identify the species distribution in solution. It allows one to take into consideration metal ion hydrolysis and the hydrolysis of metal ligand complexes.

For the series of ligands mentioned above, Table C.16 gives the pK_a values that were determined in this work, as well as those reported in the literature. Good agreement exists between the two sets of values. It is clear that addition of hydroxy groups to the methyl groups of tertiary-butylamine leads to a considerable drop in pK_a values, which will lead to greater effective complexing strengths[15], as discussed in the Introduction. Thus it was not possible to determine the formation constants of tertiary-butylamine with Cu(II) and Zn(II), because of metal hydrolysis problems.

Metal hydrolysis prevented the determination of these constants, even when a high background concentration of tertiary butylammonium nitrate was used in the titrations. However, as hydroxy groups are added to the methyl groups of tertiary-butylamine, so more hydrolysis-resistant complexes in aqueous solution are formed. In the extreme case, where three hydroxy groups have been added to produce the ligand THAM, a high degree of hydrolysis resistance is found. Evidence for this is shown by the relatively higher n-bar values formed during formation of its complexes and, in the case of Cu(II), the presence of a third order complex.

It is clear from a comparison of $\log K_1$ values for this series of ligands (Tables C.5 to C.8) that this does not arise from an increase in complexing strength, but rather from a considerable drop in the pK_a values of the ligands on adding hydroxy groups. This drop in pK_a values produces greater effective complexing strengths, which lead to hydrolysis-resistant complexes in aqueous solution. A similar explanation is given in the literature[15] for the high affinity of Cu(II) for N-2-hydroxyethyl substituted 2-(amino-methyl) imidazole functional groups on polystyrene-based ion-exchange resins[116].

C.9 THE INFLUENCE OF STERIC STRAIN ON THE FORMATION OF TRIETHANOLAMINE AND THAM Cu(II) COMPLEXES

In a study into the complexing properties of triethanolamine (TEA) with Cu(II), it was found that deprotonation of the complex occurred[8]. Interestingly, as in the case of triethanolamine, deprotonation of the Cu(II) complex of BHEAC was found to occur in this work. BHEAC, in a sense, is a more rigid version of TEA. A study was also undertaken, in this work, into the complexing properties of THAM with Cu(II). It was found, in agreement with previous work[26], that no deprotonation of the Cu(II) complex of THAM occurred. The literature[26] refers to the formation of a $[Cu(THAM)_4]^{2+}$ complex and in this work a $[Cu(THAM)_3]^{2+}$ complex was detected. For comparative purposes the formation constants of Cu(II) with triethanolamine, BHEAC and THAM are given in Table C.18.

Table C.18: Equilibrium constants of Cu(II) with triethanolamine (TEA), BHEAC and THAM

Ligand	Equilibrium[a]	logK[b]	References
TEA	M + L ---> ML	4.1, 3.9	8,115
	ML+OH --->MLOH	8.4, 7.6, 7.6	8,117,118
	MLOH+L --->ML_2OH	2.0	8
BHEAC	M + L ---> ML	4.99	c
	ML+OH --->MLOH	7.23	c
THAM	M + L ---> ML	3.90, 3.95	c, 26
	ML+ L ---> ML_2	3.41, 3.68	c, 26
	ML_2+L ---> ML_3	3.26, 3.47	c, 26
	ML_3+L --->ML_4	3.00	26

[a] M = metal ion; L= ligand; OH = hydroxide ion. Charges on species omitted for simplicity. [b] All at ionic strength = 0.1M except for ref.117 and ref.118 which are at 0.5M. [c] This work at 25°C and ionic strength 0.1M.

Molecular mechanics calculations were performed on the ligands THAM and triethanolamine. It was hoped that such a study might provide an insight into the steric constraints involved in placing four ligands around a single metal ion. Use was made of the program Alchemy[104]. Square planar co-ordination was assumed, which is appropriate in the case of Cu(II), for an investigation into the complexes of these

ligands. A strain free metal-nitrogen bond length of 1.96Å was used, as well as a strain free nitrogen-metal-nitrogen bond angle, between adjacent nitrogens, of 90°. Since the increase in strain energy, ΔU, which occurs on complex formation is important[41], the strain energy present in the free ligands was also calculated. Finally it was assumed that no chelation occurred. Hence only monodentate co-ordination occurred through the nitrogen donors on the ligands. The total strain energy, ΣU, in complexes of these ligands, formed by placing four ligands around a single metal ion and where co-ordination took place only through the nitrogen donors, was calculated. Table C.19 gives the refined strain energy values, U, for the above complexes, as well as for the free ligands. In addition the table includes final metal-to-nitrogen bond lengths and nitrogen-metal-nitrogen bond angles, as predicted by the program Alchemy.

Table C.19 Strain energy, increase in strain energy, ΔU, bond lengths and bond angles predicted for two hypothetical complexes with Cu(II)[a].

Complex	U_{ML_4} K.cal.mol^{-1}	ΔU[b] K.cal.mol^{-1}	Bond lengths[c] Å	Bond angles[d] Degrees
$[Cu(TEA)_4]^{2+}$	61.69	79.57	2.075	101.18
			2.115	98.46
			2.093	96.59
			2.130	95.22
$[Cu(THAM)_4]^{2+}$	8.86	31.58	1.991	92.34
			1.979	89.98
			1.984	88.83
			1.986	89.58

[a]Predicted by the molecular mechanics program Alchemy[104].
[b] $\Delta U = U_{ML_4} - 4.U_L$. U_{ML_4} = strain energy for complex. U_L = strain energy for free ligand. U_L (TEA) = -4.47 K.cal.mol^{-1}. U_L(THAM) = -5.68 K.cal.mol^{-1}. U_M is considered to be zero for comparative purposes. [c]The strain free metal to nitrogen bond length is 1.96 Å. [d]The strain free nitrogen-metal-nitrogen bond angle between adjacent nitrogens is 90 degrees.

The results from this simple analysis make it clear that the increase in strain energy, ΔU, which occurs for the formation of the $[Cu(TEA)_4]^{2+}$ complex, is greater than that found for the $[Cu(THAM)_4]^{2+}$ complex. The accompanying stretching of the metal-to-nitrogen bonds and nitrogen-metal-nitrogen angles emphasizes the degree of steric strain in the $[Cu(TEA)_4]^{2+}$ complex. These results offer an explanation for the tendency of triethanolamine not to form the above complex, but rather to favour deprotonation[8]. On the other hand, the accompanying stretching of the metal to nitrogen bonds and nitrogen-metal-nitrogen angles in $[Cu(THAM)_4]^{2+}$ is significantly less than that found in the hypothetical $[Cu(TEA)_4]^{2+}$ complex. The reported[26] formation of a $[Cu(THAM)_4]^{2+}$ complex, as well as the formation of a $[Cu(THAM)_3]^{2+}$ complex, found in this work, is, from a steric point of view, far more acceptable than the previous example of the hypothetical formation of $[Cu(TEA)_4]^{2+}$. The ability of molecular mechanics calculations of this nature, to offer explanations for the behaviour of ligands towards metal ions in solution, is useful to the co-ordination chemist. Such calculations allow the prediction of solution equilibria and serve as a tool in ligand design.

D. CONCLUSIONS AND FUTURE RESEARCH

The relationship between $\Delta\log K$ and the ionic radius of the metal ions for CY_2-K22 relative to BHE-K22, and BHEAC relative to triethanolamine both show an inverse relationship between the effect on complex stability of introducing a cyclohexyl bridge to a chelate ring, and metal ion radius. Figure C.10 shows a similar relationship of $\Delta\log K$ for trans-CDTA and EDTA, with a correlation coefficient of 0.83. The metal ion size-related effect on complex stability, of the introduction of a trans-cyclohexyl bridge thus appears to be fairly general. Why this should be so is not apparent at this stage. One possibility is that the effect is inductive in origin, as N-cyclohexyl groups do produce increases in $\log K_1$ for simple unidentate ligands such as cyclohexylamine relative to methylamine for metal ions such as Ag(I)[25]. This does not seem likely to be the major contribution, however, and future work will involve molecular mechanics calculations aimed at understanding the origin of the effect of the cyclohexane bridge on metal ion size-based selectivity.

The research work done on open chain hydroxyethyl substituted amines, which differed only in the degree and type of substitution on the hydroxyethyl substituent, emphasised, once again[46,47], the fine balance that exists between inductive and strain effects in the binding of Lewis acids in aqueous solution. As a consequence of this fine

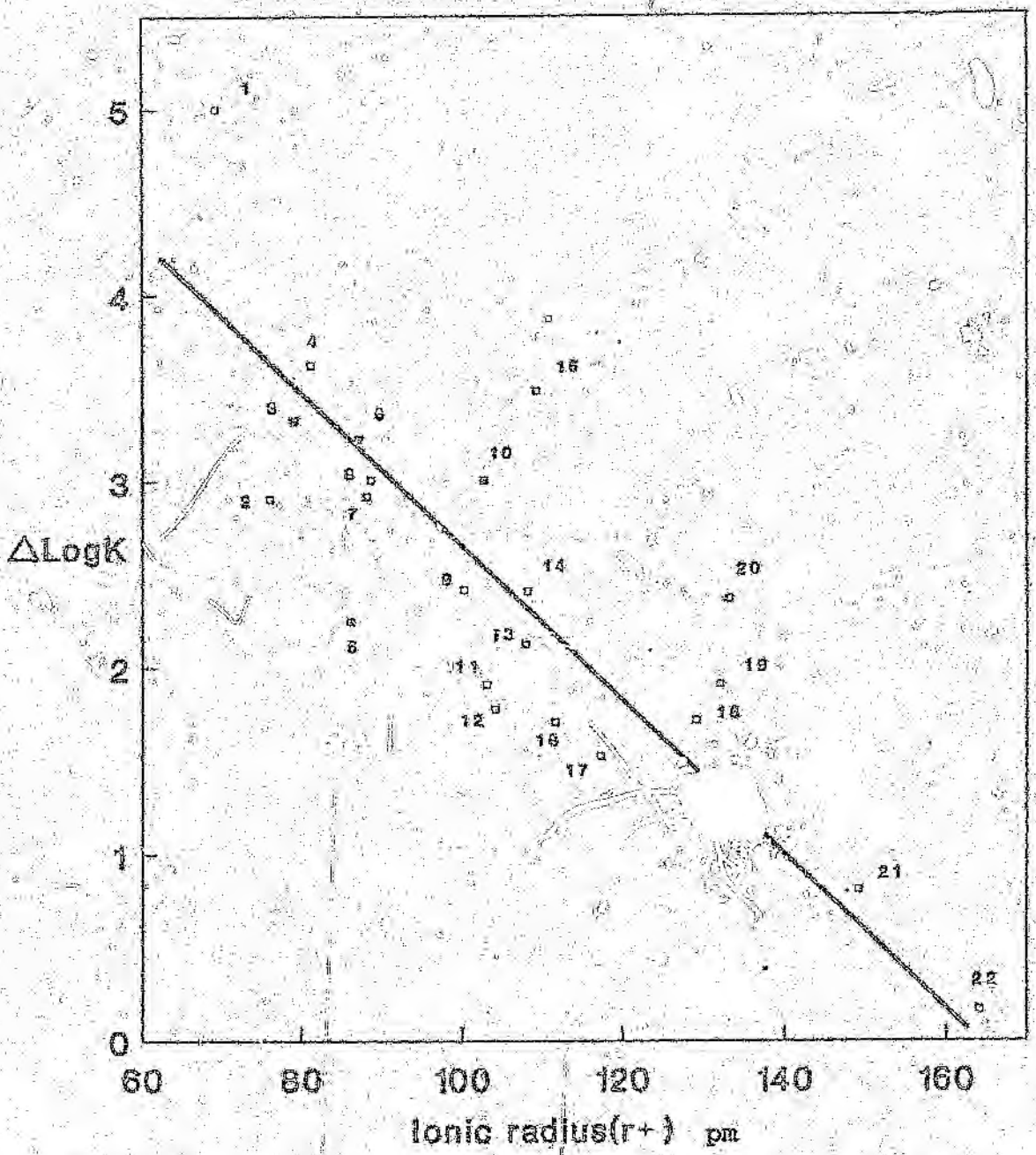


Figure C.10: ΔLogK(CDTA/EDTA) vs metal ionic radius (r^+). Key to metal ions is: 1, Fe^{3+}; 2, Ga^{3+}; 3, Co^{2+}; 4, Mn^{2+}; 5, Mg^{2+}; 6, Cu^{2+}; 7, Zn^{2+}; 8, Sc^{3+}; 9, Lu^{3+}; 10, Tl^{3+}; 11, U^{4+}; 12, Y^{3+}; 13, Gd^{3+}; 14, Th^{4+}; 15, Ca^{2+}; 16, Am^{3+}; 17, La^{3+}; 18, Ag^{+}; 19, Sr^{2+}; 20, Pb^{2+}, 21, Ba^{2+}; 22, Tl^{+}. Data from references 26 and 59. All ionic radii are for octahedral coordination.

balance, it is expected that molecular mechanics calculations will be utilized extensively as a predictive tool in ligand design. The co-ordination chemist can, with the aid of molecular mechanics calculations, estimate the steric constraints involved in adding structural groups to existing ligands and also estimate the effect of such structural changes on the strain energy of its complexes. As shown by this work (Section C.9) such calculations could even offer insight into the type of complexes which could form with as yet unsynthesized ligands. This would save the co-ordination chemist valuable time, since much of his/her effort is spent on synthesizing ligands.

A large proportion of time was spent, during this project, on trying to synthesize saturated nitrogen-donor ligands bearing cyclohexyl substituents. Replacing ethylene bridges in saturated nitrogen-donor macrocycles with cyclohexyl bridges is by no means a simple task. As far as the author is aware, very little success has been achieved in synthesizing such ligands. Surprisingly, Pedersen[5] was able to synthesize, without much difficulty, oxygen-donor macrocycles with cyclohexyl bridges. The reasons for the failure in synthesizing similar nitrogen-donor ligands, are not clear. Future work must, therefore, take this into consideration.

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F. APPENDIXES

APPENDIX A : Representative ñ curves

Figures A1 to A6 show plots of ñ, the average number of ligand molecules that are bound to the metal ion, as a function of the concentration of free ligand in solution. The values of ñ have been calculated assuming no deprotonation of the complex. Three different ratios of ligand to metal ion have been used, for each system, to check for deprotonation of the complex. Where non-superimposability of the plots occurs deprotonation is likely. The figures were obtained from the use of the computer program Equilibria[102].

The advent of computer programs such as Miniquad[101] makes investigation of these complex equilibria a much less daunting task. In addition, inclusion of all the constants for the hydrolysis of the metal ions themselves in the refinement, obviated the problem that take-up of base was due to metal ion hydrolysis rather than complex formation, which is a real possibility with the Pb^{2+} ion.

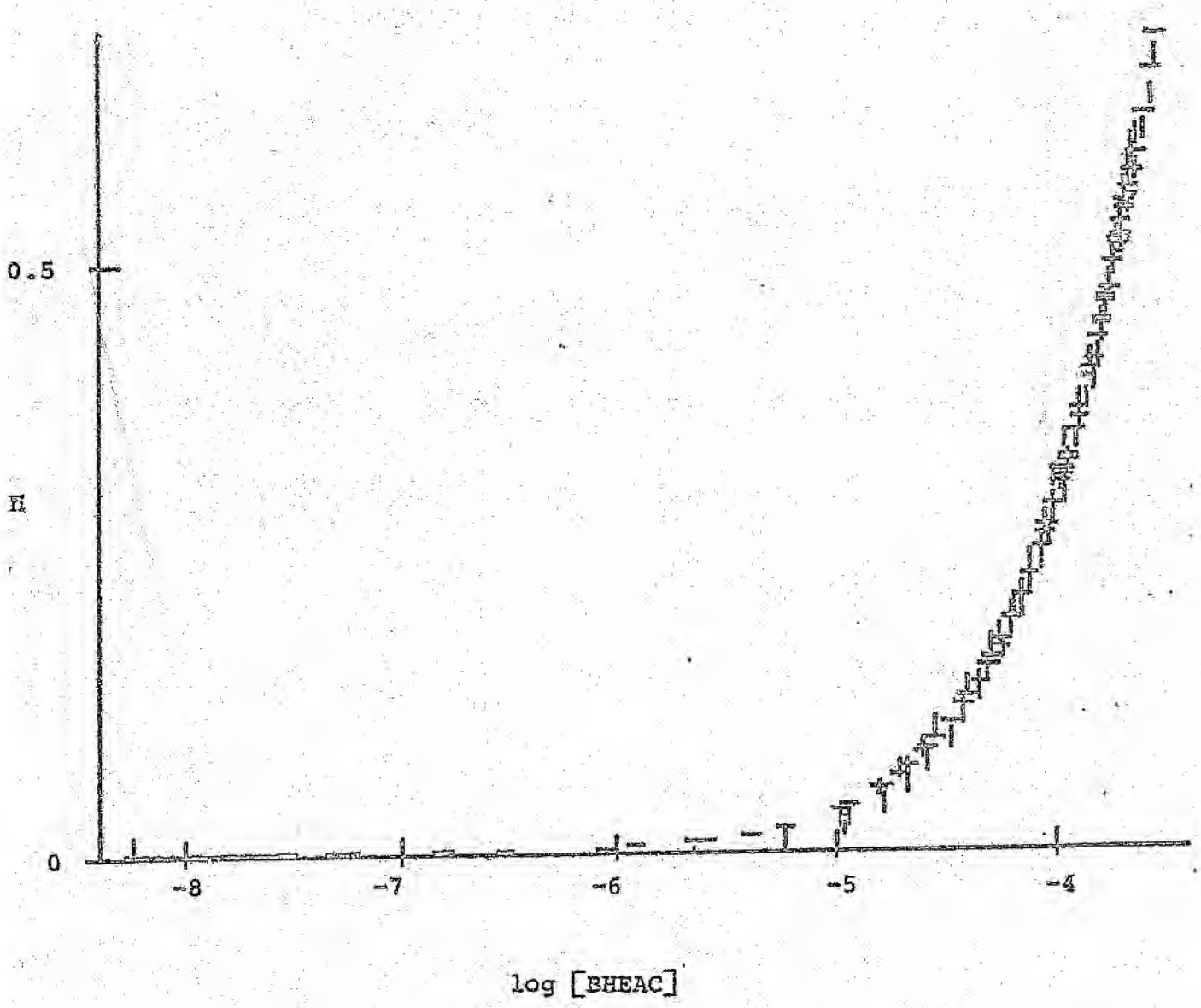


Figure A1: A plot of n̄ versus log [free BHEAC] for Ni(II). | = Experimental n̄ calculated from potentiometric results. — = theoretical n̄ calculated on refinement of stability constants. Both calculations assumed that no deprotonation occurred.

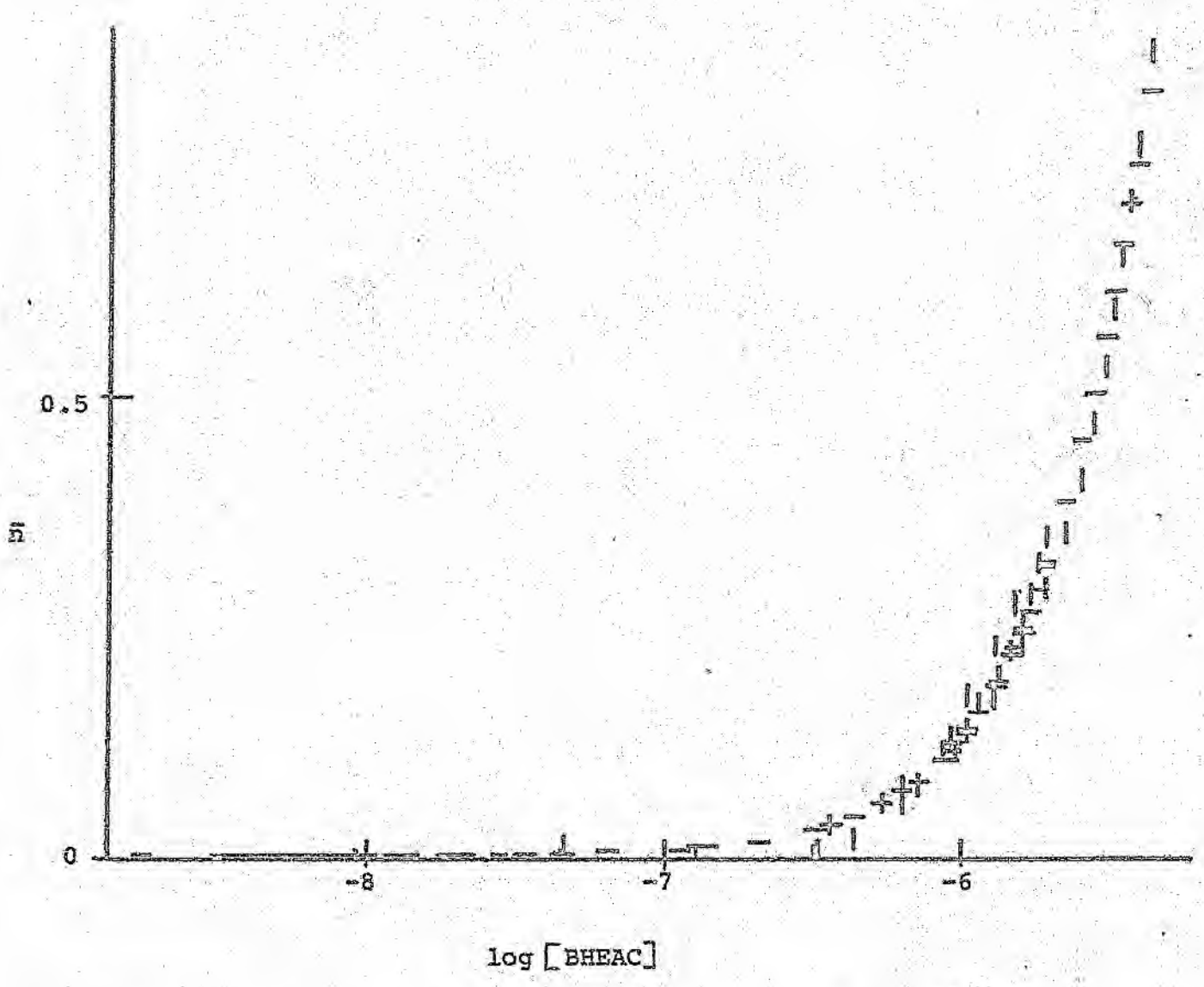


Figure A2 : A plot of n̄ versus log [free BHEAC] for Cu (II). | = Experimental n̄ calculated from potentiometric results. — = theoretical n̄ calculated on refinement of stability constants. Both calculations assumed that no deprotonation occurred.

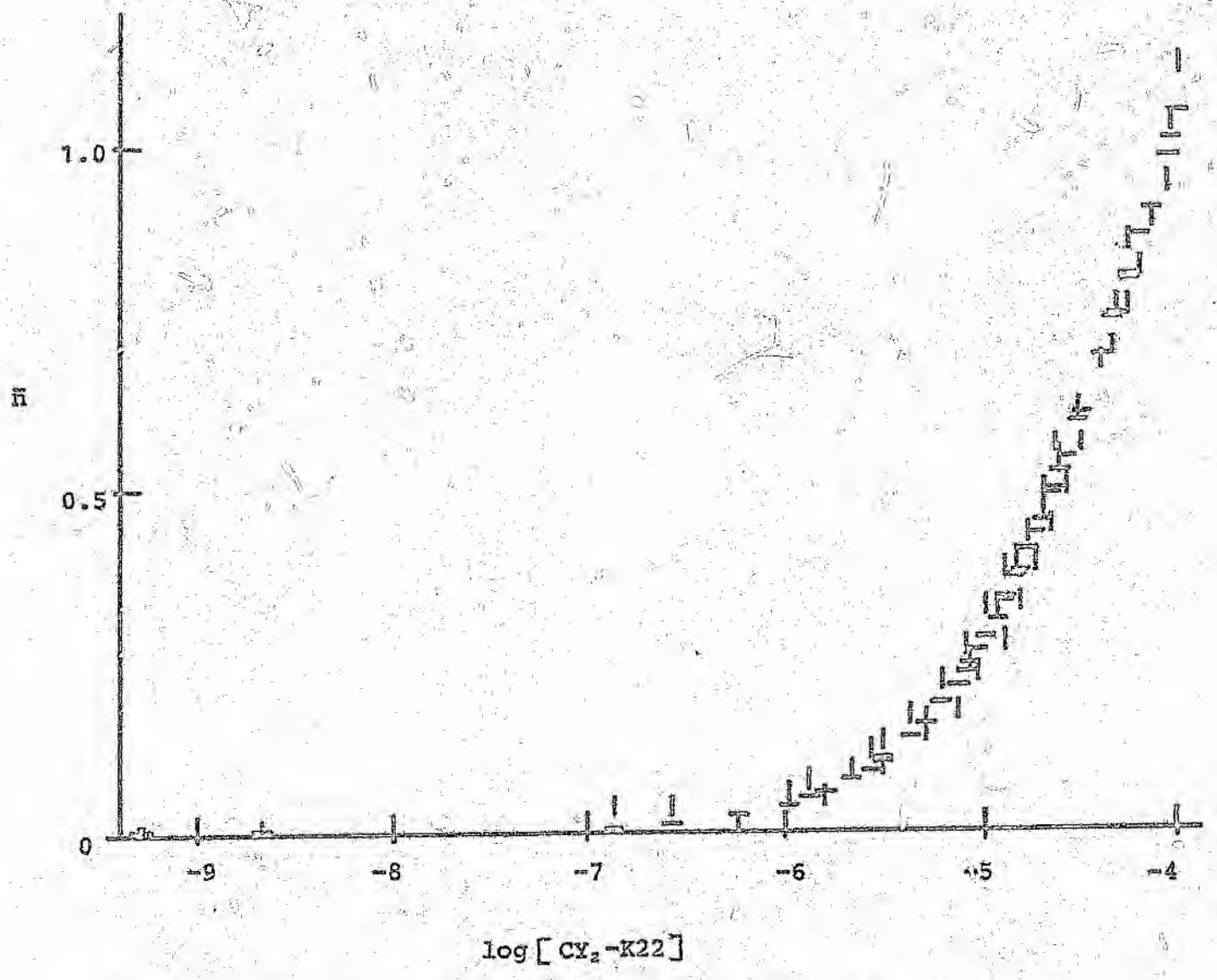


Figure A3 : A plot of n̄ versus log [free CY_2-K22] for Ba(II). | = Experimental n̄ calculated from potentiometric results. — = theoretical n̄ calculated on refinement of stability constants. Both calculations assumed that no deprotonation occurred.

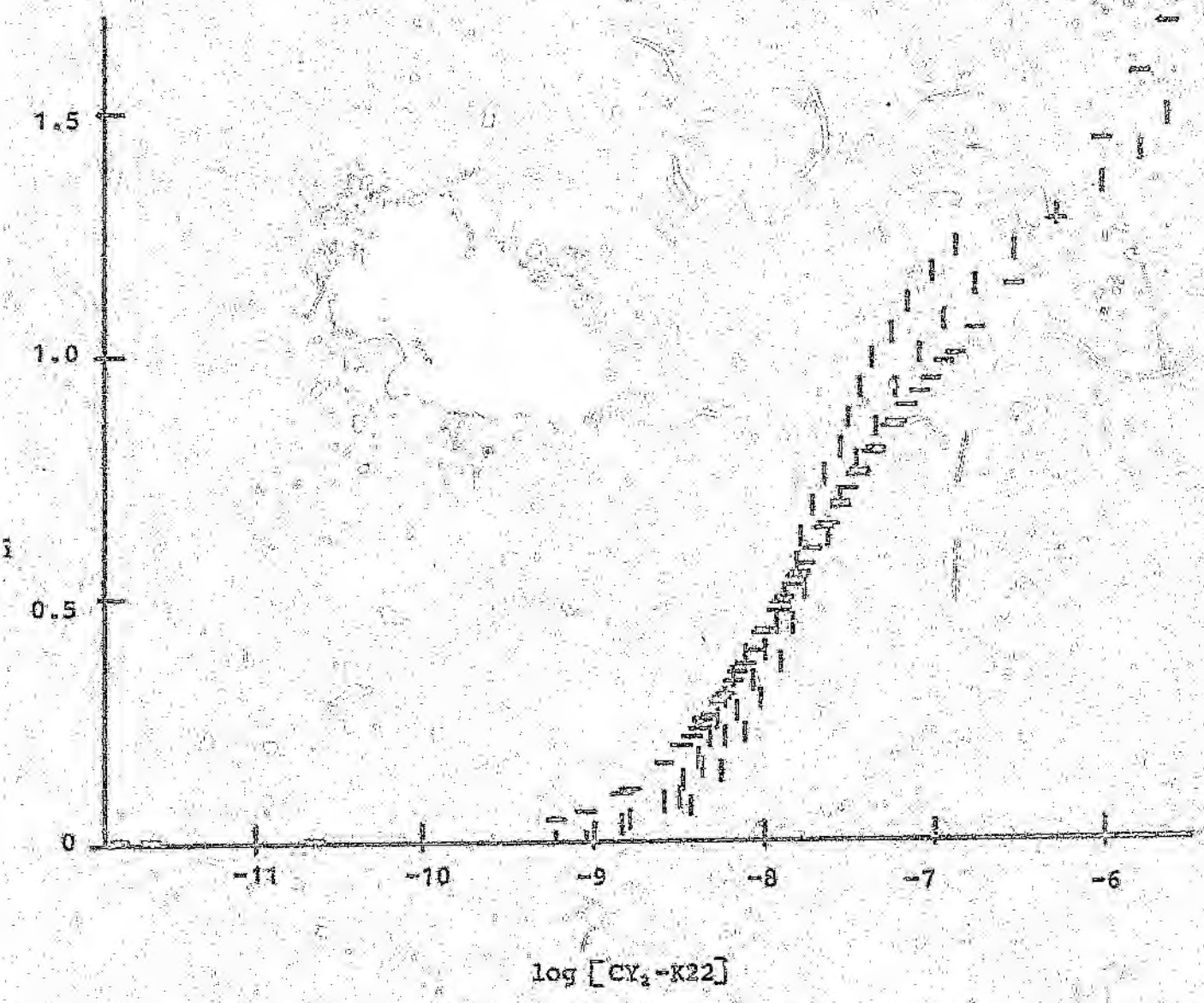


Figure A1 : A plot of $\bar{n}$ versus log [free CY_2-K22] for Cu(II). | = Experimental $\bar{n}$ calculated from potentiometric results. — = theoretical $\bar{n}$ calculated on refinement of stability constants. Both calculations assumed that no deprotonation occurred.

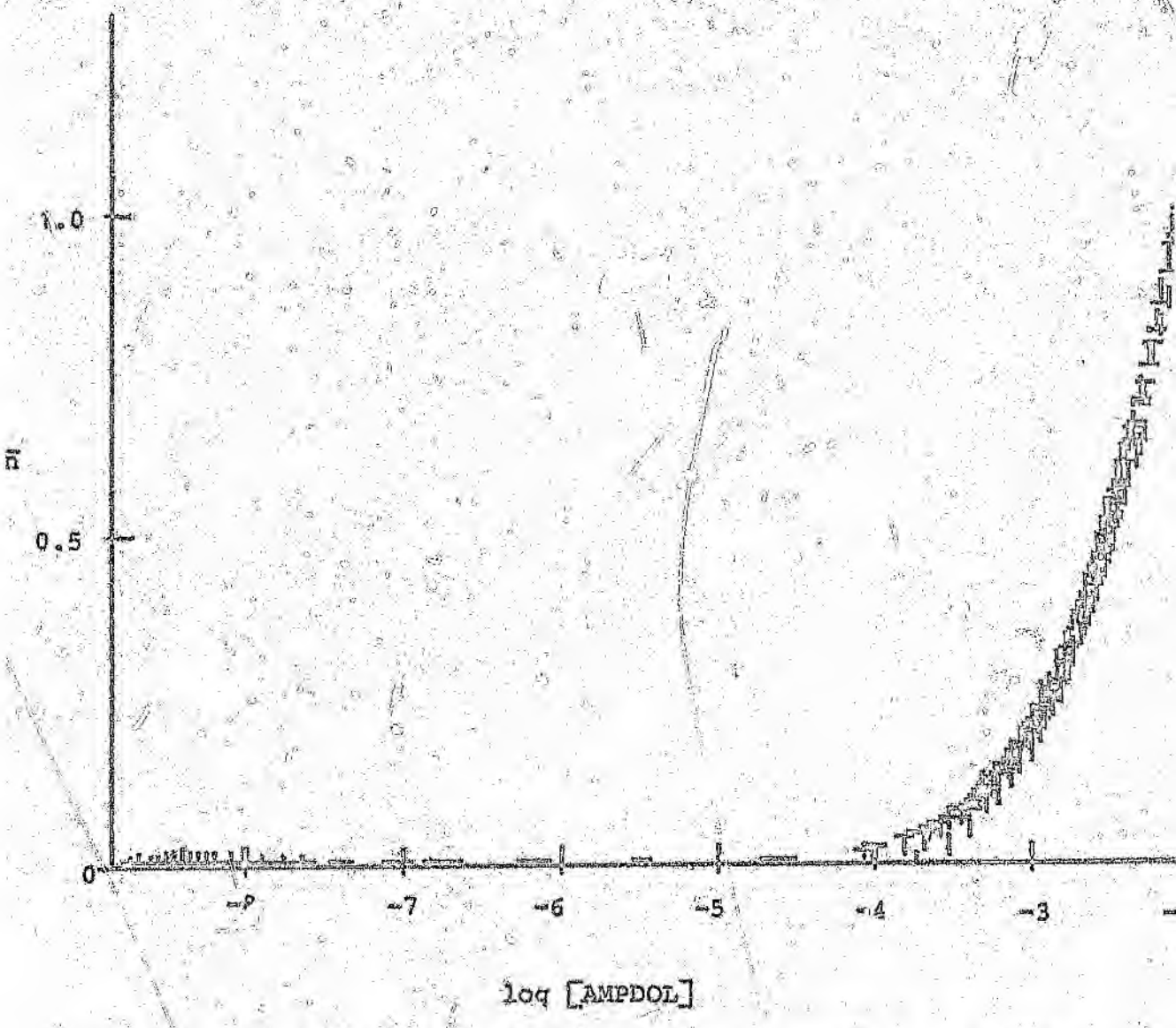


Figure A5 : A plot of n̄ versus log [free AMPDOL] for Ni (II). | = Experimental n̄ calculated from potentiometric results. -- = theoretical n̄ calculated on refinement of stability constants. Both calculations assumed that no deprotonation occurred.

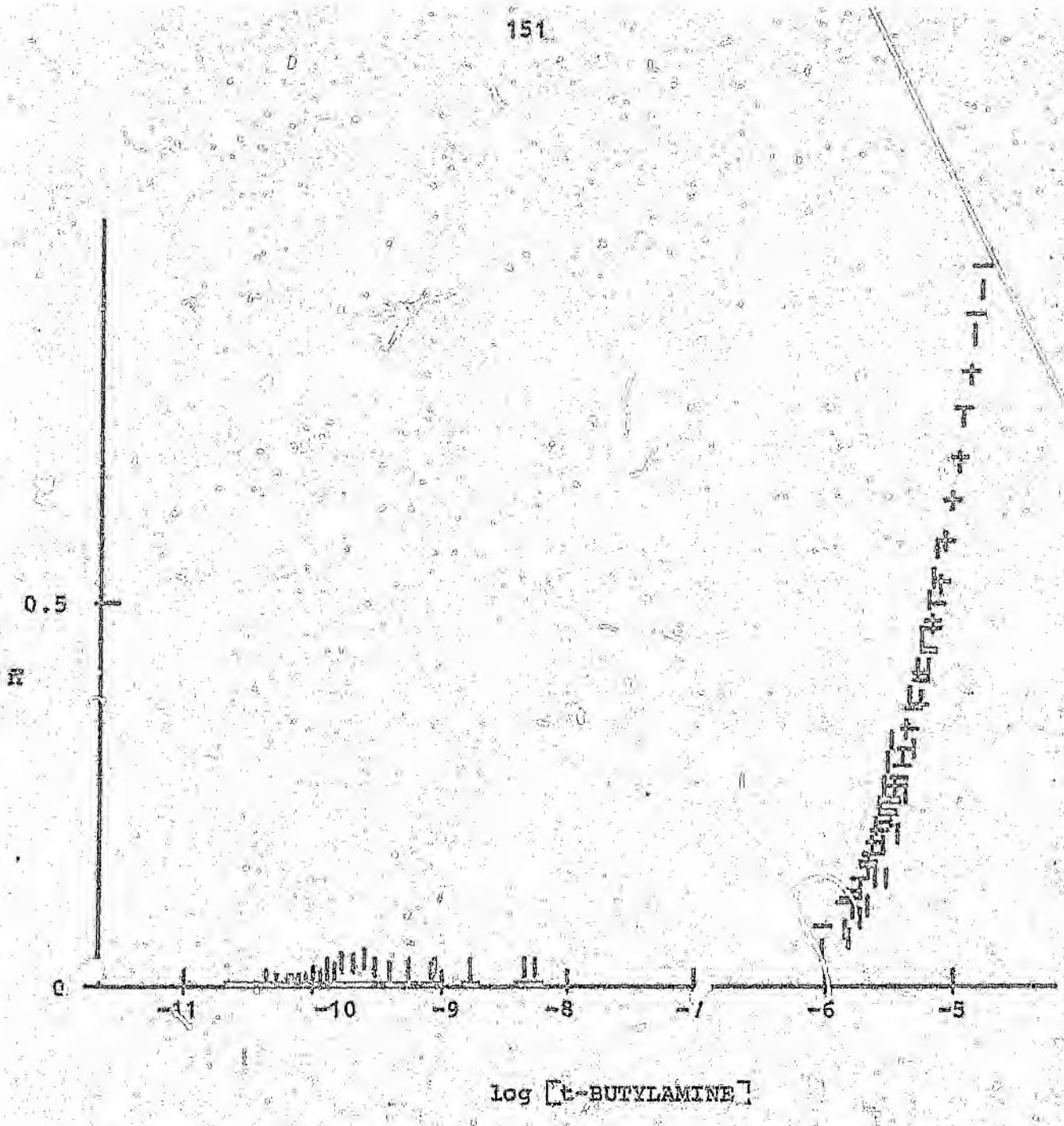


Figure A6 : A plot of n̄ versus log [free t-BUTYLAMINE] for Pb (II). | = Experimental n̄ calculated from potentiometric results. — = theoretical n̄ calculated on refinement of stability constants. Both calculations assumed that no deprotonation occurred.

APPENDIX B Statistics from computer analysis of results

Statistics (R-factors) generated from the use of the program MINIQUAD to refine stability constants from the potentiometric results

TABLE B1 : R-factors from the refinement of the CY_2-K2?, t-Butylamine, AMPOL and AMPDOL metal stability constants.

Metal Ion	R-factors			
	CY_2-K2?	t-Butylamine	AMPOL	AMPDOL
Cu^{2+}	0.020	a	0.003	0.001
Ni^{2+}	a	0.003	0.001	0.001
Zn^{2+}	a	a	0.001	0.002
Cd^{2+}	0.012	0.003	0.005	0.002
Pb^{2+}	0.009	0.002	0.006	0.003
Ba^{2+}	0.009	-	-	-
Ca^{2+}	0.007	-	-	-
La^{3+}	0.020	-	-	-
Sr^{2+}	0.011	-	-	-

[a] Metal hydrolysis prevented stability constant determinations

TABLE B2 :R-factors from the refinement of the THAM, A_2POL, AP_2OL and BHEAC metal stability constants

Metal Ion	R-factors			
	THAM	A_2POL	AP_2OL	BHEAC
Cu^{2+}	0.001	0.001	0.003	0.009
Ni^{2+}	0.001	0.002	0.002	0.007
Zn^{2+}	0.002	a	a	0.009
Cd^{2+}	0.004	0.001	0.002	0.001
Pb^{2+}	0.002	0.002	0.003	0.001

[a] Refined by the EQUILIBRIA program. Stability constants reported are estimates since low n-bar values were obtained.

Author: Croft Graeme John Bruce.
Name of thesis: The Selective Complexation Of Metal Ions By Ligands Bearing Cyclohexyl Substituents.

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