Thermodynamics of the Formation of Metal Complexes of 1,4,10-Trioxa-7,13-diazacyclopentadecane-*N,N'*-diacetic acid and of 1,4,10,13-Tetraoxa-7,16-diazacyclo-octadecane-*N,N'*-diacetic acid†

Rita Delgado, João J. R. Fraústo da Silva,* and Maria Cândida T. A. Vaz
Centro de Química Estrutural, Instituto Superior Técnico, Lisbon, Portugal
Piero Paoletti and Mauro Micheloni
Dipartimento di Chimica, Università degli Studi di Firenze, Florence, Italy

---

Thermodynamic functions for the formation of the alkaline-earth and some transition-metal complexes of the ligands L^1 (1,4,10-trioxa-7,13-diazacyclopentadecane-*N,N'*-diacetic acid) and L^2 (1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane-*N,N'*-diacetic acid) were determined by direct batch microcalorimetry. The ligand L^1 gives more stable transition-metal complexes than L^2 due to more favourable heats of reaction. The reverse situation is found for complexes of the alkaline-earth metals, although the differences in stability of the complexes of these metals with the two ligands are small due to less favourable entropy changes in the case of L^2. The two macrocyclic ligands behave similarly to their non-cyclic analogues L^3 and L^4 (3-oxapentane-1,5-diamine- and 3,6-dioxaoctane-1,8-diamine-*N,N,N',N'*-tetra-acetic acid) but form less stable complexes due to less favourable heats of reaction. The transition-metal complexes of L^1 do not follow the Irving–Williams order of stability, contrary to the situation with complexes of L^2. The reason for the inversion of the stability order is discussed in terms of the changes in crystal field stabilization energies when the octahedrally co-ordinated aqueous ions form complexes of a different structure, either five-co-ordinated or tetrahedral.

In a previous paper,[1] we presented accurate stability constant data for the formation of complexes of several transition and non-transition metal ions, including the alkali and alkaline-earth metals, with the ligand L^1 (1,4,10-trioxa-7,13-diazacyclopentadecane-*N,N'*-diacetic acid), see Figure 1, a diacetate derivative of Kryptofix 21.

We have shown that this ligand forms considerably more stable complexes with the transition metals than the analogous crown ether ligand L^2 (1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane-*N,N'*-diacetic acid), but that complexes of both ligands with alkaline-earth metals are of the same order of stability. We have also shown that the Irving–Williams order of stability is not followed for complexes of L^1 with the first series transition-metal ions, since the cobalt and iron complexes are more stable than that of nickel, contrary to the situation with complexes of L^2.

Since stability constants provide only limited information on the factors governing the formation of the metal complexes and their relative stability, we decided to undertake a more detailed study of these two ligands and their reactions and here we report the results of the determination of all the thermodynamic functions (free energy, enthalpy, and entropy changes) for the formation of complexes with metal ions which include the alkaline-earth metals and the first series transition-metal ions from Mn^{2+} to Zn^{2+}.

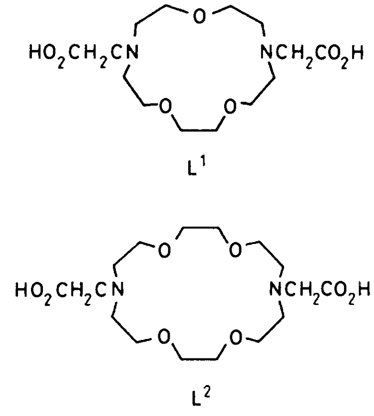


Figure 1. Molecular formulae of the ligands L^1 and L^2

Experimental

Reagents and Standard Solutions.—The ligand L^1 was synthesized as described previously;[1] L^2 was prepared by the method proposed by Chang and Rowland.[2] The ligands thus produced were recrystallized from water–ethanol (1 : 1) mixtures and their purity checked by titration with strong base-($[NMe_4]OH$), elemental analysis, and n.m.r. spectra.

Metal nitrates of analytical reagent grade were used and solutions were prepared in demineralized water and standardized by edta (ethylenediamine-*N,N,N',N'*-tetra-acetic acid) titrations. The ionic strength was adjusted with a solution of tetramethylammonium nitrate, $[NMe_4]NO_3$, prepared from $[NMe_4]OH$ and HNO_3 and recrystallized from 80% ethanol.

Carbonate-free solutions of the titrant were prepared according to the method of Schwarzenbach and Biederman,[3] by treating freshly prepared Ag_2O with tetramethylammonium iodide solution, under nitrogen, and in appropriate glass apparatus. The solutions were standardized by titration with 0.010 mol dm^{-3} hydrochloric acid and the absence of carbonate was tested regularly by inspection of Gran plots; the solutions were discarded when the concentration of carbonate reached 0.5% of the concentration of hydroxide.

---

† *Non-S.I. unit employed:* cal = 4.184 J.

Potentiometric Titrations.—The experimental apparatus has been described previously;[1] a Crison Digilab 517 measuring instrument was used together with an Ingold U1330 glass electrode and a U1335 saturated calomel reference electrode, with a Wilhelm-type salt bridge containing 0.10 mol dm^{-3} $[NMe_4]NO_3$ solution. The ionic strength of the titrated solutions was kept at 0.10 mol dm^{-3} using $[NMe_4]NO_3$ and the temperature was controlled at 25.0 ± 0.1 °C by circulating thermostatted water through the jacketed titration cell. The e.m.f. of the cell is given by $E = E^{\circ} + Q\log[H^+] + E_j$ and both E° and Q were determined by titrating a solution of known hydrogen-ion concentration at the same ionic strength. The liquid junction potential, E_j, was found to be negligible under the experimental conditions used. The ionic product of water, K_w, was determined in the alkaline region of the titrations, and the value obtained was 1.68×10^{-14} mol^2 dm^{-6}.

Calorimetric Determinations.—The calorimetric measurements were made on an LKB Batch model 2107 microcalorimeter. The ionic strength of the solutions of the metal nitrate and of the deprotonated ligands (with a slight excess of base, pH > 10.8) was adjusted to 0.10 mol dm^{-3} with $[NMe_4]NO_3$ and the distribution of the species present before and after mixing was calculated at equilibrium for the actual conditions in the calorimeter; these were such that only the ML complex and the free non-protonated form of the ligand were present. Corrections for the enthalpy of dilution of the ligand were made for each experiment.

Table 1. Ionization constants (p*K*) of $L^1\cdot 2HCl$ and $L^2\cdot 2HCl$ {T = 25.0 ± 0.1 °C; I = 0.10 mol dm^{-3} ($[NMe_4]NO_3$ or $[NMe_4]Cl$)}

	$L^1\cdot 2HCl$		$L^2\cdot 2HCl$	
	Ref. 1	Ref. 6*	This work	Ref. 2*
pK_1	< 1		< 1	
pK_2	1.75 ± 0.04	2.95 ± 0.06	2.50 ± 0.04	2.90 ± 0.1
pK_3	8.544 ± 0.009	8.79 ± 0.03	8.01 ± 0.01	7.80 ± 0.02
pK_4	9.067 ± 0.005	9.02 ± 0.05	8.926 ± 0.008	8.45 ± 0.02

* I = 0.1 mol dm^{-3}, $[NMe_4]Cl$.

Calculation of the Stability Constants.—The stability constants of the various species formed were obtained from the experimental titration data with the aid of the SUPERQUAD program,[4] using an IBM XT model 286 personal computer. The results obtained correspond to a minimum of two titrations for which the c_M/c_L ratios were 1:1 and 2:1. The errors quoted are calculated by propagation rules from the standard deviations (σ) of the overall constants obtained for about 50 readings in each set of titrations given by the program, and do not represent the total experimental errors, which can be estimated to be 0.25—0.45 log units for work of this nature.[5]

Results and Discussion

Stability Constants for the Metal Complexes.—Reliable stability constants for the complexes of L^1 have been determined by us[1] and by Chang and Ochaya[6] and previously reported.

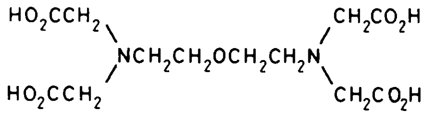
The ligand L^2 has also been studied by other authors[2,7] but we found it necessary to repeat part of that work to ensure comparability of results.

Tables 1 and 2 summarize the values that we have determined and compare our data with those of others (primarily Chang and co-workers) who have worked in almost identical operative conditions (same temperature and same ionic strength, maintained with a tetramethylammonium salt). Agreement between the two sets of data is generally satisfactory for complexes of L^1 but the differences in the values of the stability constants for complexes of L^2 are sometimes considerable, reaching up to 1 log unit. These differences are partly explained by the lower value for the proton ionization constants of L^2 obtained previously,[2] but also from the fact that the authors have used an ionic medium slightly more complexing towards the transition metals (chloride instead of nitrate), and particularly towards Cu^{2+} for which the differences are more relevant. It should also be noted that for the alkaline-earth

Table 2. Stability constants (log β) of metal complexes of L^1 and L^2 {T = 25.0 ± 0.1 °C; I = 0.10 mol dm^{-3} ($[NMe_4]NO_3$ or $[NMe_4]Cl$)}

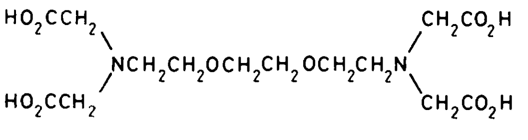
		L^1		L^2	
Metal ion	Species	Ref. 1[a]	Ref. 6[b]	This work[a]	Ref. 2[b]
Li^+	ML	2.139 ± 0.007			
Na^+	ML	2.72 ± 0.01			
K^+	ML	1.69 ± 0.03			3.9 ± 0.3
Mg^{2+}	ML	7.534 ± 0.004	7.42 ± 0.09	< 2[c]	
Ca^{2+}	ML	8.680 ± 0.003	8.74 ± 0.04	8.707 ± 0.003	8.39 ± 0.06
Sr^{2+}	ML	8.023 ± 0.004	7.91 ± 0.04		8.29 ± 0.07
Ba^{2+}	ML	7.412 ± 0.003	7.31 ± 0.04		7.63 ± 0.02
Mn^{2+}	ML	12.111 ± 0.006		8.657 ± 0.004	
Fe^{2+}	ML	*ca.* 13.0		7.88 ± 0.01	
Co^{2+}	ML	13.72 ± 0.01		7.983 ± 0.008	
	M_2L	16.37 ± 0.05		10.28 ± 0.08	
Ni^{2+}	ML	12.374 ± 0.008	12.23 ± 0.1	8.564 ± 0.005	7.39 ± 0.03
	M_2L	14.3 ± 0.1		10.5 ± 0.1	
Cu^{2+}	ML	17.79 ± 0.02	16.02 ± 0.5	15.36 ± 0.03	14.49 ± 0.03
	M_2L	22.79 ± 0.01		17.88 ± 0.08	
Zn^{2+}	ML	14.442 ± 0.007	14.08 ± 0.2	8.96 ± 0.01	8.42 ± 0.09
	M_2L	17.35 ± 0.02		11.1 ± 0.1	
Cd^{2+}	ML	13.432 ± 0.005	12.95 ± 0.04		11.07 ± 0.03
	M_2L	15.62 ± 0.05			
Pb^{2+}	ML	13.255 ± 0.005	12.91 ± 0.1		13.55 ± 0.06
	M_2L	15.69 ± 0.03			

[a] I = 0.1 mol dm^{-3}, $[NMe_4]NO_3$. [b] I = 0.1 mol dm^{-3}, $[NMe_4]Cl$. [c] From ref. 7; I = 0.1 mol dm^{-3}, KNO_3.



$(HO_2CCH_2)_2NCH_2CH_2OCH_2CH_2N(CH_2CO_2H)_2$

L^3



$(HO_2CCH_2)_2NCH_2CH_2OCH_2CH_2OCH_2CH_2N(CH_2CO_2H)_2$

L^4

Figure 2. Molecular formulae of the ligands L^3 and L^4

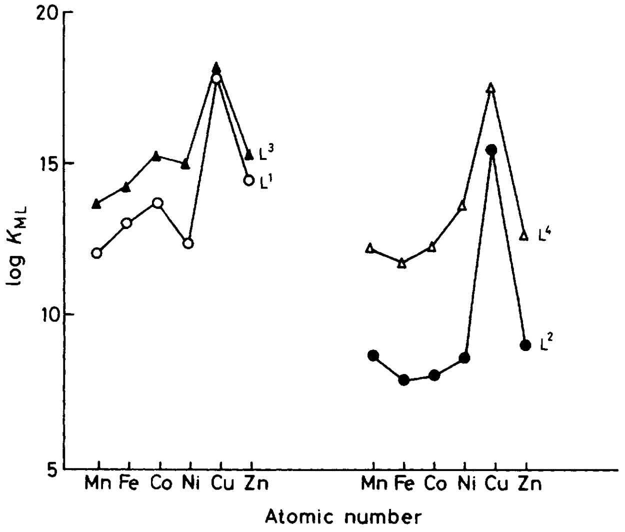


Figure 3. Variation of the stability constants of the complexes, for the pairs of ligands L^1/L^3 and L^2/L^4, with atomic number of the metals

metals the differences are small and entirely due to the differences in the proton ionization constants.

The values for the stability constants of the complexes of the alkaline-earth ions (and of Pb^{2+}) with the two cyclic ligands are almost equal, except in the case of Mg^{2+}, and at first sight this might imply that the co-ordination of these ions should be identical in both cases, *i.e.* it should involve the same set of donor atoms in the two ligands.

For the transition metals, however, the difference in stability between complexes of the same metal with the two different ligands are very large resulting in the conclusion that a different set of donor atoms and a different co-ordination geometry are probably involved in each case. It is curious, although not unexpected, that the variations of the stability constants for transition-metal complexes of L^1 and L^2 are similar to those for the complexes of L^3 (3-oxapentane-1,5-diamine-*N,N,N′,N′*-tetra-acetic acid) and L^4 (3,6-dioxaoctane-1,8-diamine-*N,N,N′,N′*-tetra-acetic acid) respectively (see Figures 2 and 3).

The trends shown in Figure 3 imply that the cyclic ligands behave like their non-cyclic counterparts, *i.e.* L^1 is similar to L^3 and L^2 is similar to L^4 but in both cases the stability of the complexes with the cyclic ligands is lower, particularly for L^2 when the drop in log K_{ML} may reach 5 units. For the complexes of the alkaline-earth metals of this ligand, the decrease in stability when compared with L^4 is much smaller (Mg^{2+} excepted) and is almost negligible for the Sr^{2+} complex. This may result from an optimal match of the ionic radius of Sr^{2+} (1.26 Å) to that of the internal cavity of the ligand (1.40 Å) or from a less distorted configuration of this cavity upon co-ordinating to the metal.

Thermodynamic Functions: ΔH *and* ΔS.—To help in understanding these differences in stability constants we have determined the enthalpy changes for the complexation of the alkaline-earth and some transition-metal ions with L^1 and L^2 by batch microcalorimetry. From these ΔH values and free energy data, ΔG, the entropy changes ΔS for the reactions were calculated ($\Delta G = \Delta H - T\Delta S$). The results are summarized in Table 3, along with the corresponding data for the complexes of L^3 and L^4, to allow comparisons between the various sets of values.

It is apparent that the alkaline-earth metal complexes of L^1 and L^2 are stabilized by both favourable enthalpy and entropy changes, except in the case of the small magnesium ion for which the enthalpy change is unfavourable. If one compares the results for the two ligands it can be seen that the entropy changes, albeit favourable, are considerably smaller for the alkaline-earth complexes of L^2 but that the enthalpy changes for the same complexes are more favourable than for L^1. We interpret these results as a more effective interaction of these ions with the donor atoms in L^2 than in L^1, but at the expense of greater loss of configurational entropy for L^2, which is also more flexible. If, however, one looks at the entropy changes for the formation of the corresponding complexes of L^3 and L^4, which are similar to each other and close to the values obtained for complexes of L^1, it seems that it is not just a matter of flexibility, which is even higher for the non-cyclic ligands. Hence, we must admit that in the alkaline-earth complexes of L^2 the metals can interact with a larger number of donor atoms than in the other cases.

It is also curious that a lower than expected ΔS value for the Ba^{2+} complex of L^4 is accompanied by a more negative ΔH value, and the same is observed for the Sr^{2+} complex of L^3. All this seems to imply that with these types of metal, which form complexes mainly by electrostatic interactions and have no strict stereochemical demands for the co-ordination geometry, the fluxional character of the metal–ligand bonds allows a closer adjustment of the ligand to match the size of each ion, and this leads to more favourable heats of reaction but to higher losses in configurational entropy of the ligands, subject to the degree of flexibility of the ligand concerned. Therefore, the values of ΔH and ΔS represent the best compromise between more effective bonding interactions and the acceptable distortion of bond angles in the structure of the ligand. In the case of L^1, which is more rigid, that compromise was reached with weaker interactions (lower ΔH values) but less distortion of the ligand (higher ΔS values).

If we now look at the transition metals (excluding Mn^{2+} and Fe^{2+} for the moment) it is interesting to see that the entropy changes upon complex formation are now closer for each ion. Thus all these metal ions behave similarly. However, since the stability of their complexes with the two cyclic ligands is so widely different, there is no question of adjustment of the ligands to the metals that might be reflected in the values of ΔH and ΔS. These complexes form mainly by covalent interactions, hence there are strict requirements for specific co-ordination geometries to allow effective overlap of the bonding orbitals involved, which is reflected in the heats of formation of these complexes, *i.e.* in the enthalpy changes ΔH, but the ΔS values remain essentially constant.

From the values presented in Table 3 and Figure 4, it is

Table 3. Thermodynamic functions for the formation of some metal complexes of L^1 and L^2 $\{T = 25.0 \pm 0.1$ °C; $I = 0.10$ mol dm^{-3} ([NMe_4]NO_3); ΔH/kcal mol^{-1}; ΔS/cal K^{-1} mol$^{-1}\}$

	$L^{1\,a}$		$L^{2\,a}$		$L^{3\,b}$		$L^{4\,b}$	
Metal ion	ΔH	ΔS	ΔH	ΔS	ΔH	ΔS	ΔH	ΔS
Mg^{2+}	+3.8	47			+3.5	50	+5.0	41
Ca^{2+}	−3.6	28	−8.3	11	−6.9	23	−8.1	23
Sr^{2+}	−5.8	17	−9.0	9	−8.1	15	−6.0	18
Ba^{2+}	−5.9	14	−10.3	1	−6.5	15	−8.9	8
Mn^{2+}	(−3.0)[c]	(45)[c]	(−1.6)[c]	(16)[c]	−5.9	43	−8.2	28
Fe^{2+}	(−3.5)[c]	(47)[c]	(+0.1)[c]	(36)[c]	−6.4	44	−5.2	37
Co^{2+}	−3.6	51	+2.6	45	−6.4	48	−2.8	47
Ni^{2+}	0.0	57	+1.6	45	−4.7	53	−3.8	50
Cu^{2+}	−9.2	50	−5.8	51	−9.8	49	−11.2	44
Zn^{2+}	−5.1	49	+1.7	47	−6.0	50	−4.3	43

The average standard deviation of the ΔH values is 0.1 kcal mol^{-1}. [a] This work. [b] A. Martell and R. Smith, 'Critical Stability Constants,' Plenum Press, New York, 1974, vol. 1. [c] Estimated value.

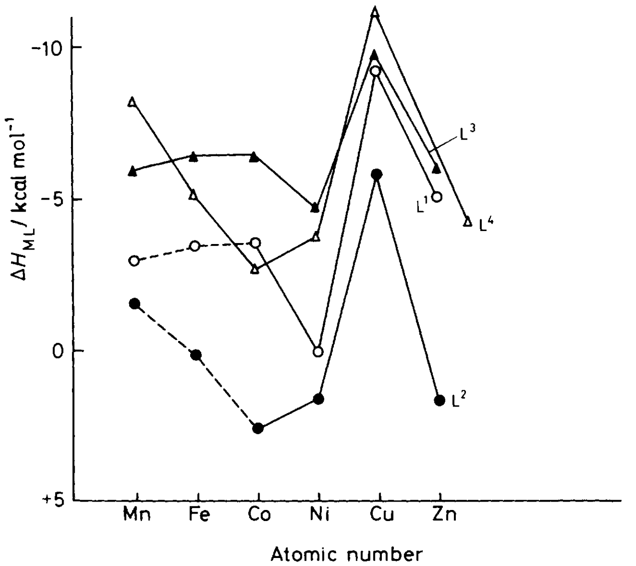


Figure 4. Variation of the values of ΔH with atomic number of the metals for complexes of L^1—L^4

obvious that the non-cyclic ligands L^3 and L^4, being more flexible, are less limited in satisfying the co-ordination requirements of the transition-metal ions; consequently they form more stable complexes than their cyclic counterparts due to more favourable enthalpy changes. The same must be true for the ligand L^1 compared with L^2, since its transition-metal complexes are more stable than those of L^2 and the corresponding ΔH values, naturally, are more negative.

The main conclusions to extract from the above observations are as follows. (*a*) For metal-ion complexes involving mostly electrostatic interactions, *i.e.*, alkali, alkaline-earth, and lanthanide ions, the ligands have a large degree of fluxionality on their surfaces and the free energy changes result from a tendency to maximize the enthalpy changes at the expense of entropy changes. (*b*) For metal-ion complexes involving mainly covalent interactions, *e.g.* the transition metals considered and zinc, loss of configurational entropy may not be of use in achieving the required co-ordination geometry, hence the ΔS values will be dominated by the metal-ion dehydration terms (almost constant for these ions), and the ΔH values regulate both the overall stability of the complexes and the order of their relative stability within each series and oxidation state.

For the Mn^{2+} and Fe^{2+} complexes we have not determined the enthalpy changes. It is known that these ions have little affinity for aliphatic nitrogen atoms and tend to behave more like the alkaline-earth metals in their complexes with the polyaminocarboxylate ligands, particularly Mn^{2+}, which very much resembles Ca^{2+}. The values presented in Table 3 are reasonable estimations based on the trends of variation of ΔH represented in Figure 4 and taking into account the differences in ΔS values for the alkaline-earth complexes of the pairs L^3/L^1 and L^4/L^2, together with the values of the entropy changes on formation of the Mn^{2+} and Fe^{2+} complexes of L^3 and L^4.

Inversion of the Irving–Williams Order of Stability.—Our final considerations concern the inversion of the order of relative stability of iron and cobalt relative to nickel complexes of L^1, which contradicts the Irving–Williams order. Inversion of the relative stabilities of the nickel and zinc complexes is not considered, as stated in a recent paper,[2,8] since the location of zinc in the order varies considerably with the type of ligand.[9] The Irving–Williams order of stability, $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$, is valid for high-spin octahedral complexes of a great variety of ligands, but inversions result when these conditions are not fulfilled. The variation in ΔH values with atomic number shown in Figure 4 bears a striking resemblance to that obtained for those complexes of ligands, such as tris(2-dimethylaminoethyl)amine $\{N[CH_2CH_2N(CH_3)_2]_3\}$[10] or bis(2-dimethylaminoethyl)methylamine $\{NCH_3[CH_2CH_2N(CH_3)_2]_2\}$,[11] which are known to have distorted square-pyramidal structures.

If a structure of this type occurs in the transition-metal complexes of L^1 then the reason for the inversion of the order of stability of iron and cobalt complexes relative to nickel is clear. Indeed, the Irving–Williams stability order is a consequence of the fact that in octahedral complexes, nitrogen and sulphur ligands favour Fe^{2+}, Ni^{2+}, and Cu^{2+} over the other first-series transition metals and zinc. This is due to the larger crystal field stabilization energies (c.f.s.e.s) to which must be added the effect of the tetragonal Jahn–Teller elongation in the case of Cu^{2+}. Carboxylate, phosphate, and sulphate donors on their own are much less effective and the differences in stability are smaller since the ligand-field strength of such ligands is close to that of water (they are neighbours in the spectrochemical series). When, however, the symmetry of the complexes varies from the octahedral aqueous ions to a tetrahedral, square-pyramidal or trigonal-bipyramidal structure in a complex, the situation changes because $Fe^{2+}(d^6)$ and $Co^{2+}(d^7)$ will then be more favoured in terms of c.f.s.e. relative to $Ni^{2+}(d^8)$. In such cases the expected 'normal' increase in stability of the complex with increasing atomic number may not compensate for the loss of this stabilization energy for Ni^{2+} and inversion of the Irving–Williams order is observed.

There are other examples of inversion of the order of stability resulting from symmetry changes besides those already referred to. One is that of the tetrachloro and tetrabromo complexes of the transition metals that have a tetrahedral structure which again favours d^6 and d^7 ions relative to d^8.[10,11] Kryptofix 21, the amine from which L^1 is derived, also shows the cobalt/nickel inversion,[1,8,12] and the same effect may be found in complexes of some biological ligands, *e.g.*, zinc enzymes with distorted tetrahedral sites in which the zinc can be replaced by transition-metal ions, but cobalt is taken up in preference to nickel.[13]

In the case of the complexes of L^1 the co-ordination geometry is not obvious, even from electronic spectra, and until good evidence from *X*-ray diffraction studies is obtained, it can only be suggested that the geometry is square pyramidal on the basis of the similarity of the variation in ΔH with that for the complexes of other ligands which apparently have that structure.

Acknowledgements

The authors thank the Instituto Nacional de Investigaçäo Cientifica (I.N.I.C.), Portugal, for financial assistance.

References

1 R. Delgado, J. J. R. Fraústo da Silva, and M. Cândida T. A. Vaz, *Polyhedron*, 1987, **6**, 29.
2 C. A. Chang and M. E. Rowland, *Inorg. Chem.*, 1983, **22**, 3866.
3 G. Schwarzenbach and W. Biederman, *Helv. Chim. Acta*, 1948, **31**, 331.
4 P. Gans, A. Sabatini, and A. Vacca, *J. Chem. Soc., Dalton Trans.*, 1985, 1195.
5 P. A. Overvoll and W. Lund, *Anal. Chim. Acta*, 1982, **143**, 153.
6 C. A. Chang and Ven O. Ochaya, *Inorg. Chem.*, 1986, **25**, 355.
7 M. Tazaki, K. Nita, M. Takagi, and K. Ueno, *Chem. Lett. (Jpn.)*, 1982, 571.
8 E. Luboch, A. Cygan, and J. F. Biernat, *Inorg. Chim. Acta*, 1983, **68**, 201.
9 H. Irving and R. J. P. Williams, *J. Chem. Soc.*, 1953, 3192.
10 P. Paoletti and M. Ciampolini, *Inorg. Chem.*, 1967, **6**, 64.
11 A. Bianchi and P. Paoletti, *Inorg. Chim. Acta*, 1985, **96**, 137.
12 F. Arnaud-Neu, B. Spiess, and M. J. Schwing-Weill, *Helv. Chim. Acta*, 1977, **60**, 2633.
13 R. J. P. Williams, *J. Mol. Catal.*, 1985, **30**, 1.

Received 25th *January* 1988; *Paper* 8/00373D