A Microcalorimetric Study of the Macrocyclic Effect. Enthalpies of Formation of Copper(II) and Zinc(II) Complexes with Some Tetra-aza Macrocyclic Ligands in Aqueous Solution

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Enthalpies of formation of copper(II) and zinc(II) complexes with three tetra-aza macrocyclic ligands of differing ring size have been determined directly by microcalorimetry. The values for the copper(II) complexes, which reach a maximum with the ligand 1,4,8,11-tetra-azacyclotetradecane, have been correlated with the calculated ideal size of the aperture in the macrocyclic ligand required to maintain the ligand in a minimum-strain conformation. The macrocyclic effect has been interpreted as being due to a favourable entropy term and to a normally favourable enthalpy term, the magnitude of which is critically dependent on matching the size of the metal ion to that of the aperture in the macrocyclic ligand.

THE current interest in metal complexes containing simple cyclic nitrogen donor ligands can be partly attributed to the fact that these complexes can be regarded as simple models for naturally occurring metal–macrocycle centres found in proteins.

Cyclisation of a linear polyamine ligand produces striking changes in the properties of the metal complexes, when compared to the equivalent complexes of the linear ligands. Typical properties of macrocyclic complexes include: (*a*) a marked kinetic inertness both towards the formation of the complex from an aqueous metal ion and ligand and towards decomposition;[1] (*b*) strong metal–nitrogen interactions which are reflected in the spectrochemical parameters (Dq);[2] (*c*) the possibility of stabilisation of high oxidation states for the metal ion;[3] and (*d*) high thermodynamic stability, reflected in the stability constants which can be several orders of magnitude larger than for the corresponding complexes of linear ligands.[4]

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[1] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1970, **92**, 2151.

[2] D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperati, and N. Tokel, *Adv. Chem. Ser.*, 1971, **100**, 44.

[3] D. C. Olson and J. Vasilevskis, *Inorg. Chem.*, 1969, **8**, 1611; 1971, **10**, 463, 1228.

[4] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540.

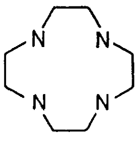
The purpose of the present work is to investigate further the origin of the high thermodynamic stability, which has hitherto remained controversial, to see whether the role of particular metal ions in some proteins can be explained in thermodynamic terms.

In order to emphasize the greater stability of macrocyclic complexes over similar complexes of non-cyclic ligands, the term ' macrocyclic effect ' was put forward [4] in 1969 to account for the much higher stability constant found for the copper(II) complex of *meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetra-azacyclotetradecane, compared to that with the similar non-cyclic ligand 3,7-diazanonane-1,9-diamine in which the chelate rings have the same sequence. Since then, the enhanced stability of other macrocyclic complexes, of different ligands and different metal ions, has been well established.

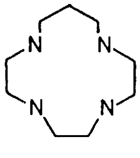
The macrocyclic effect is a Gibbs energy term, referring

$$\underset{\text{(non-cyclic)}}{[\mathrm{ML}]^{n+}} + \underset{\text{(macrocyclic)}}{\mathrm{L}'} \longrightarrow \underset{\text{(macrocyclic)}}{[\mathrm{ML}']^{n+}} + \underset{\text{(non-cyclic)}}{\mathrm{L}} \quad (1)$$

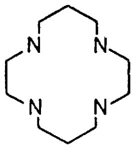
to the metathetical reaction (1), and the enhanced stability of the macrocyclic complex may have its origins in both enthalpy and entropy terms. The first attempts to separate the effect into these components led to opposing conclusions. Using the temperature dependence of equilibrium data for the system $\mathrm{Ni^{II}}$-$\mathrm{L^3}$, Hinz and Margerum [5] concluded that the macrocyclic effect was due entirely to an enthalpy term, but Kodama and Kimura [6] reached the opposite conclusion for $\mathrm{Cu^{II}}$–$\mathrm{L^1}$, that an entropy term was solely responsible. The method employed by these workers for determining $\Delta H^\ominus$, from the temperature dependence of equilibrium data, is, at best, only approximate, since a very small error in the equilibrium constants can result in a large error in $\Delta H^\ominus$, particularly if a limited number of constants are used over a narrow temperature range. The direct calorimetric determination of the enthalpies of formation of macrocyclic complexes had previously appeared impossible for several reasons. Both formation and destruction (with $\mathrm{H^+}$ or $[\mathrm{CN}]^-$) of macrocyclic complexes are extremely slow and could not be followed in conventional calorimeters; the low solubility of many macrocyclic ligands in water would have necessitated the use of extremely dilute solutions, making the measurement of the thermal output for a given reaction impossible by isoperibolic calorimetry; the strong proton affinity of most tetra-aza macrocyclic ligands ($\mathrm{p}K_1$ and $\mathrm{p}K_2 \approx$ 11—12) meant that, in aqueous solutions of the ligand, significant amounts of protonated species would have been present.



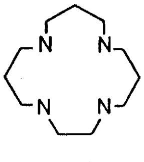
$\mathrm{L^1}$



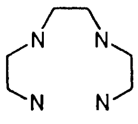
$\mathrm{L^2}$



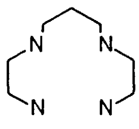
$\mathrm{L^3}$



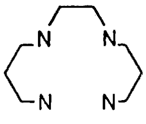
$\mathrm{L^4}$



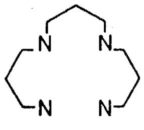
$\mathrm{L^5}$



$\mathrm{L^6}$



$\mathrm{L^7}$



$\mathrm{L^8}$

In this work, we have overcome these experimental difficulties by devising an experimental procedure which ensures the rapid incorporation of the metal ion into the macrocyclic ligand. All the reactions were carried out at pH 14 in 1 mol $\mathrm{dm^{-3}}$ Na[OH], the high pH also eliminating the problem of the protonated ligand species. The small heat output was measured with extremely sensitive microcalorimeters. Two different experimental procedures, one based on flow microcalorimetry [7] and the other on batch microcalorimetry,[8] were used for the first system studied and gave the same enthalpy values within experimental error. We report directly measured enthalpies for complexes of both $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$ with the series of macrocyclic ligands $\mathrm{L^1}$, $\mathrm{L^3}$, and $\mathrm{L^4}$ of different ring size, enabling the enthalpic contribution to the macrocyclic effect to be assessed. The preliminary results of this work have been reported previously.[9,10]

EXPERIMENTAL

Reagents.—Compound $\mathrm{L^3}$ was obtained commercially (Strem Chemicals) and purified by double recrystallisation from acetonitrile, and $\mathrm{L^4}$ from the same source was purified as the tetrahydrochloride by bubbling HCl through an ethanolic solution of the ligand and recrystallising from aqueous ethanol. Pure $\mathrm{L^1{\cdot}4HCl}$ was a gift from Professor Kimura (Hiroshima University, School of Medicine) and was used without further purification. The ligands $\mathrm{L^5}$ and $\mathrm{L^6}$ (Eastman–Kodak) were purified as the tetrahydrochlorides in the same manner as for $\mathrm{L^4}$. Elemental analyses (%) for these ligands are given below.

	Found			Calc.		
	C	H	N	C	H	N
$\mathrm{L^5{\cdot}4HCl}$	24.8	7.3	19.8	24.7	7.6	19.2
$\mathrm{L^6{\cdot}4HCl}$	28.0	7.5	18.1	27.7	7.3	18.4
$\mathrm{L^1{\cdot}4HCl}$	29.0	8.1	17.7	30.2	7.6	17.6
$\mathrm{L^3}$	60.1	12.7	28.1	60.0	12.1	28.0
$\mathrm{L^4{\cdot}4HCl}$	35.6	8.8	15.0	36.7	8.4	15.6

Standard aqueous solutions of $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$ were analysed by conventional gravimetric methods and were used to prepare solutions of the appropriate concentrations in 1 mol $\mathrm{dm^{-3}}$ Na[OH]. Solutions of the metal complexes were prepared from the solid complex perchlorates $[\mathrm{ML}][\mathrm{ClO_4}]_2$ ($\mathrm{M} = \mathrm{Cu^{II}}$ or $\mathrm{Zn^{II}}$, $\mathrm{L} = \mathrm{L^3}$ or $\mathrm{L^4}$) obtained by mixing equimolar amounts of $\mathrm{M[ClO_4]_2{\cdot}6H_2O}$ and ligand in butanol, and recrystallising the product from ethanol. For $\mathrm{L^1}$, because of the limited quantity of ligand available, solutions of the complexes were prepared by mixing equimolar amounts of metal perchlorate and ligand hydrochloride and subsequently deprotonating with standard Na[OH]. The

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[5] F. P. Hinz and D. W. Margerum, *Inorg. Chem.*, 1974, **13**, 2941.

[6] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 116.

[7] P. Monk and I. Wadsö, *Acta Chem. Scand.*, 1968, **22**, 1842.

[8] I. Wadsö, *Acta Chem. Scand.*, 1968, **22**, 927.

[9] A. Anichini, L. Fabbrizzi, P. Paoletti, and R. M. Clay, *J.C.S. Chem. Comm.*, 1977, 244.

[10] A. Anichini, L. Fabbrizzi, P. Paoletti, and R. M. Clay, *Inorg. Chim. Acta Letters*, 1977, **22**, L25.

1 mol dm^{-3} Na[OH] solution was prepared by adding Na[OH] (Erba RP) to carbon dioxide-free twice-distilled water.

Apparatus.—For the calorimetric measurements, LKB BATCH (10 700—2) and FLOW (10 700—1) microcalorimeters were used. The thermal output of both instruments was amplified by a Keithley 150B microvolt amplifier and recorded as a trace on a potentiometric recorder. For the BATCH measurements the heat output was determined by comparison of the area under the heat curve with a similar area produced by electrical calibration. The areas were determined as the mean from six measurements made with an accurate planimeter. The reaction cells were glass, and in order to prevent the reactants from ' creeping ' over the partition wall and causing prereaction the inside of the reaction cell was coated with a thin layer of paraffin wax. Solutions were introduced into the cells by weight by means of hypodermic syringes and the total volume of the reactants was between 3.0 and 4.0 cm^3. The reference cell was empty throughout all the measurements.

For the FLOW instrument, the amplified voltage, which is proportional to the heat flow, was recorded numerically on a printer at predetermined time intervals and the value at each steady state was calculated as the mean of many printed values. The reactants were passed through the flow cell by means of two high-precision automatic burettes (METTLER DV-10) equipped with 50 cm^3 cylinders. The flow rate of each burette was regulated by a resistance box and could be accurately varied from 3×10^{-6}—8×10^{-6} dm^3 s^{-1}. Once the reactant solutions had been introduced into the burettes and the calorimetric system was stable, a series of experiments was performed by varying the flow rates of each reactant but keeping the sum constant.

Both calorimeters were checked for absolute accuracy by determining the enthalpy of formation of water [11] (FLOW, $\Delta H^{\ominus} = -13.4$; BATCH, $\Delta H^{\ominus} = -13.2$ kcal mol^{-1}).* Visible spectra of the complexes were recorded on a Beckman DK2 spectrophotometer equipped with 1-cm quartz cells.

Calorimetric Procedure.—The tetra-aza macrocyclic ligands are strong bases, and an aqueous solution of the ligand contains mainly the diprotonated species $[H_2L]^{2+}$. The reaction between a metal ion and a macrocyclic ligand in aqueous solution is very slow, presumably because of the short-range electrostatic repulsions.[12] However, by deprotonating the ligand in a strongly basic solution, the formation reaction becomes sufficiently fast to enable the enthalpy to be determined calorimetrically. Thus all the calorimetric measurements were made with solutions of the ligand in 1 mol dm^{-3} Na[OH] at pH 14. This has the added advantage that no corrections need be made for protonated ligand species. (pK_1 and pK_2 values for the ligands are as follows: L^1, 10.7, 9.7;[6] L^3, 11.59, 10.62;[13] L^4, 11.08, 10.38.[13]) The key calorimetric measurement was therefore the direct formation of the macrocyclic complex in aqueous solution at pH 14, and two separate procedures were employed.

BATCH technique. In order to obtain the enthalpy change, $\Delta H_1^{\ominus}$, for reaction (1) between the aqueous metal ion and the aqueous ligand the following thermochemical cycle was employed:

$$\begin{tikzcd}
M^{2+}(aq) + L(aq) \arrow[r, "(1)"] \arrow[d, "(2)"] & {[ML]^{2+}(aq)} \arrow[d, "(4)"] \\
M^{2+}(aq) + L(1\,mol\,dm^{-3}\,Na[OH]) \arrow[r, "(3)"] & {[ML]^{2+}(1\,mol\,dm^{-3}\,Na[OH])}
\end{tikzcd}$$

CYCLE 1

$\Delta H_3^{\ominus}$ was obtained by mixing an aqueous solution of MCl_2 (0.4 cm^3, 0.05 mol dm^{-3}) with an alkaline solution of the ligand (3.0 cm^3, 0.01 mol dm^{-3}) using a *ca.* 50% excess of ligand. A comparatively small volume of metal solution was used in order to minimise the endothermic enthalpy of dilution of the Na[OH]. The last quantity was determined separately (0.4 cm^3 of H_2O + 3.0 cm^3 of mol dm^{-3} 1 Na[OH]) and used to correct the heat output, giving $\Delta H_3^{\ominus}$. This correction is *ca.* 7% of the heat output from the reaction. $\Delta H_4^{\ominus}$ was determined by adding an aqueous solution of the metal complex (0.4 cm^3) to 1 mol dm^{-3} Na[OH] (3.0 cm^3) and correcting for dilution as above. $\Delta H_2^{\ominus}$ cannot be determined due to the impossibility of forming an aqueous solution containing solely the pure unprotonated species L. It has been taken as zero throughout, and thus all the enthalpies of formation are calculated with reference to the pure ligand in aqueous solution at pH 14. The assumption that $\Delta H_2^{\ominus}$ is zero was tested by determining the enthalpy of formation, $\Delta H^{\ominus}$, of $[CuL^5]^{2+}$ by the above cycle (-21.4 kcal mol^{-1}) and comparing it with the value previously determined by isoperibolic calorimetry (-21.6 kcal mol^{-1}),[14] the small difference being within the limits of experimental error.

FLOW technique. $\Delta H_1^{\ominus}$ was determined from Cycle 2.

$$\begin{tikzcd}
M^{2+}(aq) \arrow[d, "(5)"] & + L(aq) \arrow[r, "(1)"] \arrow[d, "(2)"] & {[ML]^{2+}(aq)} \arrow[d, "(4)"] \\
M^{2+}(1\,mol\,dm^{-3}\,Na[OH]) & + L(1\,mol\,dm^{-3}\,Na[OH]) \arrow[r, "(6)"] & {[ML]^{2+}(1\,mol\,dm^{-3}\,Na[OH])}
\end{tikzcd}$$

CYCLE 2

The key measurement, that of $\Delta H_6^{\ominus}$, was made in the flow calorimeter by passing solutions of the metal ion and the ligand in 1 mol dm^{-3} Na[OH] simultaneously through the mixing cell. For determinations with Cu^{II}, the solutions were 10^{-4} mol dm^{-3}, the limiting factor being the solubility of copper(II) hydroxide in Na[OH]. The solubility of zinc(II) hydroxide is much higher, and for the zinc(II) determinations 10^{-2} mol dm^{-3} metal and ligand solutions were used.

The flow rates of the two burettes were changed in such a way that the total flow rate remained constant, while the L : M ratio was varied from 0.6 to 1.7 : 1. For L^3 and L^4 $\Delta H_6^{\ominus}$ was independent of the L : M ratio; however, for L^1, both with Cu^{II} and Zn^{II}, although $\Delta H_6^{\ominus}$ was independent of this ratio below L : M = 1 : 1 it increased rapidly above this value, becoming constant again when L : M $\geqslant$ 1.5 : 1. This suggests that a further polymeric species is formed with the smallest macrocycle ligand, possibly $[M_2L^1{}_3]^{4+}$. Therefore, for L^1, $\Delta H_6^{\ominus}$ was determined for a mean of steady states obtained with L : M < 1 : 1 and based on the ligand as the limiting reagent. For the other two ligands, $\Delta H_6^{\ominus}$

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* Throughout this paper: 1 cal = 4.184 J.

[11] J. D. Hall, R. M. Izatt, and J. J. Christensen, *J. Phys. Chem.*, 1963, **67**, 2605; C. E. Vanderzee and J. A. Swanson, *ibid.*, p. 2608.

[12] C. Lin, D. B. Rorabacher, G. C. Cayley, and D. W. Margerum, *Inorg. Chem.*, 1975, **14**, 919.

[13] M. Micheloni and A. Vacca, unpublished work.

[14] L. Sacconi, P. Paoletti, and M. Ciampolini, *J. Chem. Soc.*, 1961, 5115.

was determined with L : M > 1 : 1 and based on the metal ion as the limiting reagent.

$\Delta H_2^\ominus$ and $\Delta H_4^\ominus$ have already been discussed in connection with the BATCH technique. In order to make the measurements compatible with those from the BATCH technique and to remove the uncertainty arising from the nature of the species present in strongly alkaline solutions of $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$, $\Delta H_5^\ominus$ was determined as follows. For $\mathrm{Zn^{II}}$ it was measured directly by adding a solution of $\mathrm{ZnCl_2}$ (0.4 cm^3, 0.05 mol dm^{-3}) to Na[OH] (3.0 cm^3, 1 mol dm^{-3}) in the BATCH calorimeter, and making an appropriate correction for dilution. For $\mathrm{Cu^{II}}$, due to the limited solubility, this was not possible and the system $\mathrm{Cu^{II}}$–$\mathrm{L^6}$ was studied by means of Cycle 2, and $\Delta H_1^\ominus$, which had been determined previously,[15] was inserted thereby indirectly giving $\Delta H_5^\ominus$. This procedure is justified by the good agreement between values for $\Delta H_1^\ominus$ obtained for the $\mathrm{Cu^{II}}$–$\mathrm{L^3}$ system by Cycles 1 and 2, since the value obtained *via* Cycle 1 does not depend on $\Delta H_5^\ominus$.

TABLE 1

Experimental results (kcal mol^{-1}) at 25 °C

System	$\Delta H_3^\ominus$	$\Delta H_4^\ominus$	$\Delta H_5^\ominus$	$\Delta H_6^\ominus$	$\Delta H_1^\ominus$		
					Cycle 1	Cycle 2	Other literature values
$\mathrm{Cu^{II}}$–$\mathrm{L^5}$	-21.4 ± 0.3	0.0 ± 0.1	-10.9 ± 0.1 [a]	-10.6 ± 0.2	-21.4 ± 0.4	-21.5 ± 0.3	-21.6 [14]
$\mathrm{Cu^{II}}$–$\mathrm{L^6}$			-10.9 ± 0.1 [a]	-16.8 ± 0.2			-27.7 [15]
$\mathrm{Cu^{II}}$–$\mathrm{L^1}$		0.0 ± 0.1	-10.9 ± 0.1 [a]	-11.8 ± 0.2		-22.7 [illegible] 0.3	-18.3 [16]
$\mathrm{Cu^{II}}$–$\mathrm{L^3}$	-32.2 ± 0.3	0.0 ± 0.1	-10.9 ± 0.1 [a]	-21.6 ± 0.2	-32.2 ± 0.4	-32.5 ± 0.3	
$\mathrm{Cu^{II}}$–$\mathrm{L^4}$		0.0 ± 0.1	-10.9 ± 0.1 [a]	-15.6 ± 0.2		-26.5 ± 0.3	-26.5 [16]
$\mathrm{Zn^{II}}$–$\mathrm{L^1}$		1.2 ± 0.1	-7.7 ± 0.2 [b]	-8.2 ± 0.1		-14.5 ± 0.3	
$\mathrm{Zn^{II}}$–$\mathrm{L^3}$	-15.6 ± 0.2	0.9 ± 0.1	-7.7 ± 0.2 [b]	-8.3 ± 0.1	-14.7 ± 0.3	-14.9 ± 0.3	
$\mathrm{Zn^{II}}$–$\mathrm{L^4}$		0.3 ± 0.1	-7.7 ± 0.2 [b]	-9.3 ± 0.1		-16.5 ± 0.3	

[a] Calculated by inserting the value [15] of $\Delta H_1^\ominus$ for $\mathrm{Cu^{II}}$–$\mathrm{L^6}$ into Cycle 2. [b] Measured directly on the BATCH instrument.

FLOW versus *BATCH Techniques*.—The FLOW technique has the decided advantage over the BATCH in that, once the correct experimental conditions have been found, a series of measurements can be made in a single session, simply by varying the flow rates. In comparison, the procedures involved with the BATCH technique are extremely laborious, requiring the complete emptying, cleaning, and refilling of the cell, and the consequent delay in waiting for thermal equilibrium to be attained before the next measurement can be made. On the other hand, it is not possible to mix solutions of significantly differing densities in the FLOW calorimeter, and the BATCH instrument must be used for determining $\Delta H_4^\ominus$ and $\Delta H_5^\ominus$. The two instruments are therefore essentially complementary. We have used Cycle 1 (based entirely on BATCH measurements) for the systems M–$\mathrm{L^3}$ (M = $\mathrm{Cu^{II}}$ or $\mathrm{Zn^{II}}$) to confirm the reliability of the experimentally easier Cycle 2 (in which the key measurement is made on the FLOW instrument). Thereafter we used Cycle 2 to determine the enthalpies of formation.

RESULTS AND DISCUSSION

The experimental results are given in Table 1. Data for $\Delta H_3^\ominus$, $\Delta H_4^\ominus$, and $\Delta H_5^\ominus$ (for $\mathrm{Zn^{II}}$) from the BATCH calorimeter are given as the mean from 2—4 separate measurements, and for $\Delta H_6^\ominus$ from the FLOW calorimeter as the means of at least five steady-state values. $\Delta H_5^\ominus$ (-10.9 kcal mol^{-1}) has been obtained by inserting the previously determined [15] value of $\Delta H_1^\ominus$ for $\mathrm{Cu^{II}}$–$\mathrm{L^6}$ into Cycle 1. The consistency of the two methods can be seen in the excellent agreement between $\Delta H_1^\ominus$ obtained *via* Cycle 1 and Cycle 2 for the $\mathrm{L^3}$ complexes of both $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$. The accuracy is demonstrated by the agreement between our $\Delta H_1^\ominus$ values for $\mathrm{Cu^{II}}$–$\mathrm{L^5}$, obtained from both cycles (-21.4 and -21.5 kcal mol^{-1}), and the previously determined literature value (-21.6 kcal mol^{-1}).[14]

Previously determined enthalpy values for the systems $\mathrm{Cu^{II}}$–$\mathrm{L^1}$ and –$\mathrm{L^4}$ have been reported by Kodama and Kimura,[6,16] who made polarographic determinations of the stability constants at different temperatures between 10 and 35 °C. Our results agree extremely well for $\mathrm{L^4}$ but differ by 4.4 kcal mol^{-1} for $\mathrm{L^1}$. For the system $\mathrm{Cu^{II}}$–$\mathrm{L^1}$ several criticisms of the polarographic results can be made. First the previous workers reported only the formation of a 1 : 1 complex. Secondly, they did not correct their calculations of the stability constants at different temperatures for the temperature dependence of pK_1 and pK_2. Thirdly, the reversibility of the electrode process is not satisfactorily established since the log plot gives a gradient (-36 to -40 mV) considerably different from that required by a reversible two-electron process (-29.6 mV). For $\mathrm{L^4}$ these criticisms are not as serious. Only a 1 : 1 complex is formed, the pK_1 and pK_2 values were corrected for temperature dependence, and the gradient of the log plot (-32 mV) is much closer to the theoretical value. We therefore believe that our calorimetric value for $\mathrm{Cu^{II}}$–$\mathrm{L^1}$ is the more reliable and we have recalculated the entropy change on complex formation using the log K_{ML} value obtained by Kodama and Kimura [16] and our own $\Delta H^\ominus$ value. While this log K_{ML} value must still remain doubtful, the $\Delta S^\ominus$ value of 36 cal K^{-1} mol^{-1} seems much more reasonable than the 51 cal K^{-1} mol^{-1} originally reported, when compared to the other tetra-aza macrocyclic ligands, and the $\Delta S^\ominus$ values now diminish steadily with increasing size and decreasing rigidity of the macrocyclic ligands (Figure 1). This suggests that the greater error is manifest in $\Delta H^\ominus$, and emphasizes the unreliability of determining $\Delta H^\ominus$ by this method, particularly if the stability constants themselves are doubtful.

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[15] L. Fabbrizzi, R. Barbucci, and P. Paoletti, *J.C.S. Dalton*, 1972, 1529.

[16] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 2341.

The best available thermodynamic parameters for complexes of Cu^{II} and Zn^{II} with macrocyclic and associated non-cyclic ligands are given in Table 2, together with their origins and the estimated uncertainties in the $\Delta H^{\ominus}$ values.

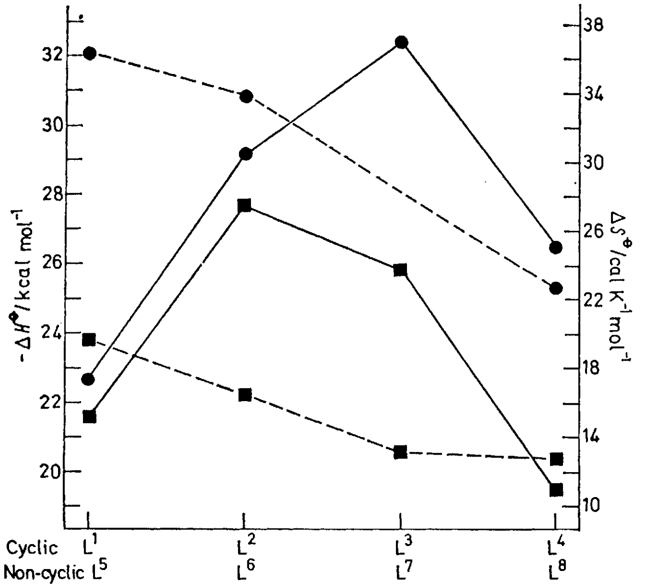

FIGURE 1 Enthalpies (——) and entropies (- - - -) of formation for cyclic (●) and non-cyclic (■) polyamine copper complexes

Copper(II) *Complexes*.—Of the ligands studied, L^3 reacts most exothermically with Cu^{II}. It has previously been demonstrated [17] that the ideal M–N distance for this ligand to adopt its strain-free conformation with all the four nitrogens coplanar is 2.07 Å. The Cu–N bond distance found in tetragonal polyamine complexes ranges from 2.03 to 2.10 Å,[18] and the Cu^{2+} ion is therefore tailor-made to form a strain-free complex with L^3. This is reflected in the large $\Delta H^{\ominus}$ value. Furthermore, the complex $[CuL^3]^{2+}$ contains a system of fused alternating 5,6,5,6 membered chelate rings, an arrangement which has previously been found to favour the greatest exothermicity in complexes of non-cyclic tetra- and triamines.[19]

TABLE 2

Thermodynamic parameters for macrocyclic and non-cyclic tetra-aza ligand complexes of Cu^{II} and Zn^{II}

	Cu^{II}			Zn^{II}
Ligand	$\Delta H^{\ominus}$/ kcal mol⁻¹	log K_{ML}	$\Delta S^{\ominus}$/ cal K⁻¹ mol⁻¹	($\Delta H^{\ominus}$/ kcal mol⁻¹)
L^1	-22.7 [a] ± 0.3	24.8	36.2 [b]	-14.5 [a] ± 0.3
L^2	-29.2 [c]	29.1 [c]	33.7 [c]	
L^3	-32.4 ± 0.3 [a,d]			-14.8 [a,d] ± 0.3
L^4	-26.5 [a] ± 0.3	24.4 [e]	$+22.7$ [e]	-16.5 [a] ± 0.3
L^5	-21.6 [f]	20.2	$+19.5$	-8.9
L^6	-27.7 [f]	23.9	$+16.5$	-11.9
L^7	-25.9 [f]	21.8	$+13.1$	-10.6
L^8	-19.5 [f]	17.3	$+12.8$	-7.4

[a] This work. [b] Ref. 6; calculated using $\Delta H^{\ominus}$ from this work. [c] Ref. 23. [d] Mean of Cycle 1 and Cycle 2 determinations. [e] Ref. 16. [f] Ref. 19 and reference therein.

For L^4 the Cu–N distance is now smaller than the ideal [17] (M–N 2.22 Å) required to maintain the minimum strain energy in planar co-ordination, and less strong metal–donor interactions will result, which are reflected in the lower $\Delta H^{\ominus}$. Similarly, L^1 is too small (ideal M–N 1.83 Å) to accommodate the metal ion in square co-ordination, and in this case, where the mismatch is largest, a distortion from square co-ordination may result. This could take the form of ligand folding to form a *cis*-octahedral structure, rings folding to form a trigonal-bipyramidal structure, or the removal of the metal ion from the nitrogen plane to give a square-pyramidal structure. Examples of all these distortions are known with other metal ions and macrocyclic ligands.[20-22] In any case the strong in-plane Cu–N interaction will be reduced resulting in a lower $\Delta H^{\ominus}$, as confirmed by our calorimetric results. A similar situation exists for L^2, for which $\Delta H^{\ominus}$ has been determined by Kodama and Kimura,[23] but the distortion would not be expected to be so severe as for L^1 and $\Delta H^{\ominus}$ will consequently be higher. The experimental $\Delta H^{\ominus}$ values are plotted in Figure 2

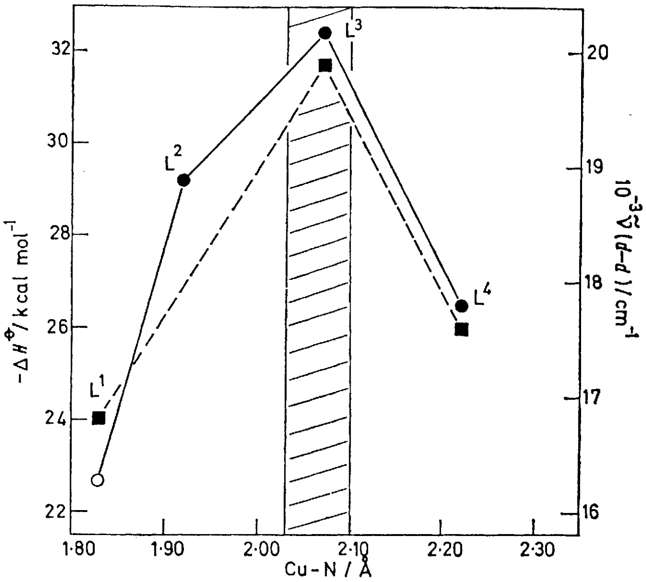

FIGURE 2 Enthalpies of formation (●) and energies of the *d–d* band (■) plotted against the Cu–N distance calculated for minimum strain energy, in an ideal square co-ordination for aqueous macrocyclic complexes. The hatched area indicates the normal range of Cu–N distances in polyamine complexes

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against the M–N ideal distance[17] for the ligand to minimise its strain energy in planar co-ordination.

The maximum in the enthalpies is also paralleled by the energies of the *d–d* bands in the visible spectra (Figure 2). Previously, a linear relation had been found between $\Delta H^{\ominus}$ and ν(*d–d*) for over 30 copper(II) complexes of non-cyclic amines[24] and, interestingly, of the three macrocyclic complexes studied only that of L^3 fits this relation. It therefore appears that the adherance to this relation may be a sensitive test for complexes containing a CuN_4 planar geometry, with Cu–N bond distances in the normal range (2.03—2.10 Å). The other significant exceptions to this relation were tripod-like ligands such as tris(2-aminoethyl)amine in which the four nitrogen donors cannot co-ordinate in a plane. We can surmise at this point that significant distortions from square planarity will occur in $[CuL]^{2+}$ ($L = L^1$ or L^2), that $[CuL^3]^{2+}$ is almost certainly planar, and $[CuL^4]^{2+}$ is probably planar, with a lengthened Cu–N bond and consequently reduced $\Delta H^{\ominus}$ and ν(*d–d*) values. Any distortion or bond lengthening has a more significant effect in ν(*d–d*) than on $\Delta H^{\ominus}$, since for the complexes with both L^1 and L^4 the experimental $\Delta H^{\ominus}$ is well in excess of the value calculated from the linear relation.

Zinc(II) *Complexes*.—The enthalpies do not show a peak like the copper(II) system, but decrease slowly along the series L^4, L^3, L^1. The Zn^{2+} ion is larger than Cu^{2+} and this will favour the larger macrocyclic ligand. On the other hand zinc is known to have a preference for tetrahedral co-ordination of polyamines and this stereochemistry can be most easily achieved by the largest macrocycle. However, with no reliable structural evidence it would be dangerous to draw firm conclusions.

The Macrocyclic Effect.—The origin of the term 'macrocyclic effect' is described in the Introduction. Both enthalpy and entropy contributions are possible to the added stability of the macrocyclic complex and it is the relative importance of these two contributions which has for some time been controversial.[5,6] Unfortunately, the choice of the appropriate non-cyclic reference ligand is not easy. For copper(II) complexes the enthalpies of the non-cyclic tetramine ligands also go through a maximum while the entropy changes on complexation decrease slowly with the size of the ligand (Figure 1). The highest $\Delta H^{\ominus}$ for a non-cyclic complex occurs with an alternating 5,6,5 chelate-ring sequence, and the lower enthalpies of the other complexes are due to internal strain energies associated with the introduction of bridgeheads between either two five- or two six-membered chelate rings. In order to correctly assess the macrocyclic enthalpy, $\Delta H^{\ominus}$ for the macrocyclic complex should be compared to $\Delta H^{\ominus}$ for a complex containing the same degree of internal strain, the remaining difference between these two enthalpies being associated with ring closure. A proper estimate can therefore only reastically be made for the complexes with L^1 and L^3 which can be compared to the complexes with L^5 and L^6 respectively, maintaining the same ring sequence between cyclic and non-cyclic ligands. The macrocyclic enthalpies are given in Table 3.

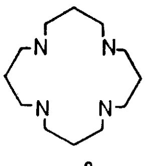
TABLE 3

Macrocyclic enthalpies

Ring sequence	Reaction	$\Delta H^{\ominus}_{\text{macrocyclic}}$ kcal mol^{-1}
All five-membered	$[CuL^5]^{2+} + L^1$	−1.1
	$[ZnL^5]^{2+} + L^1$	−5.6
Alternating five and six membered	$[CuL^6]^{2+} + L^3$	−4.7
	$[ZnL^6]^{2+} + L^3$	−2.9

For these two systems accurate entropy data are unfortunately not available for any of the cyclic compounds. However, an estimate of $\Delta S^{\ominus}$ for the complex $[CuL^1]^{2+}$ has already been made using Kodama and Kimura's $\Delta G^{\ominus}$ value[6] and our own value of $\Delta H^{\ominus}$. $\Delta S^{\ominus}$ for $[CuL^3]^{2+}$ can be estimated from Figure 1 as 29 cal K^{-1} mol^{-1} probably to within ±2 cal K^{-1} mol^{-1}, since the entropy changes on complex formation for the cyclic ligands parallel their non-cyclic counterparts by decreasing slowly down the series. Thus $\Delta S^{\ominus}$ (macrocyclic) can be estimated for the two metathetical copper systems with L^1 and L^3 as 17 and 13 cal K^{-1} mol^{-1} respectively. While these values are very tentative, they reinforce our belief that there will always be a positive and therefore favourable entropy contribution to the macrocyclic effect. This arises from the fact that the macrocyclic ligand, before co-ordination, is already rigid and pre-orientated, unlike its non-cyclic counterpart, and will therefore not lose configurational entropy after co-ordination to nearly the same extent. In fact, all the reported entropy values for macrocyclic complexes are in excess of the equivalent non-cyclic complexes with the exception of some nickel(II) complexes[5] including $[NiL^3]^{2+}$. It is extremely desirable to have a calorimetric value of $\Delta H^{\ominus}$ for this complex, since much of the original thermodynamic interpretation of the macrocyclic effect has been based on the original work of Hinz and Margerum,[5] who found that the macrocyclic effect was solely due to an enthalpy term and that the macrocyclic entropy change was negative (−16 cal K^{-1} mol^{-1}).

In the examples studied in this work it is clear that a macrocyclic enthalpy is present, the magnitude of which depends on both the matching of the metal-ion size to the size of the aperture in the macrocyclic ligand in its strain-free conformation and on the stereochemical preference of the metal ion. We would therefore expect the macrocyclic enthalpy to vary considerably for different systems. Because of the importance of matching the size of metal ion to the size of the ligand aperture, very large macrocyclic enthalpies can be



L^9

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expected when the match is good. However, in cases of extreme mismatch the macrocyclic enthalpy may well become unfavourable, and, for example, we would predict, by extrapolating the enthalpy data in Figure 2 to the complex with L^9, for which the ideal M–N distance is 2.38 Å,[17] that $\Delta H^{\ominus}$ for $[CuL^9]^{2+}$ will probably be less than -20 kcal mol^{-1}, or in other words less than that for any of the non-cyclic tetramines. The macrocyclic entropy, however, should always remain positive and favourable, its magnitude changing only slightly from ligand to ligand.

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