Ring-size Effects of Macrocyclic Ligands on Complex Formation: the Copper(II) Complex of the 15-Membered Cyclic Tetra-amine 1,4,8,12-Tetra-azacyclopentadecane

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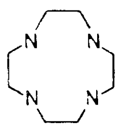
The thermodynamics and kinetics of complex formation between Cu^{II} and 1,4,8,12-tetra-azacyclopentadecane (L^4) have been studied polarographically. The stability constant of $10^{24.4\pm0.2}$ (I = 0.20 mol dm^{-3}, 25 °C) for the 1 : 1 complex containing 5,6,6,6-membered chelates is 10^7- and 10^3-fold greater than those for complexes of the corresponding open-chain tetra-amines 4,8-diazaundecane-1,11-diamine (L^5) containing 6,6,6-chelates and 4,7-diazadecane-1,10-diamine (L^6) containing 5,6,6-chelates, respectively. Depending on the choice of the reference complexes, either the ΔH term (*cf.* the L^5 complex) or the ΔS term (*cf.* the L^6 complex) makes a major contribution to the macrocyclic effects. A significant effect of the macrocyclic ring expansion is a facile protonation of the complexed ligand in acetate buffer solution, $K_{Cu(HL)}{}^{H} = [CuL^{2+}][H^+]/[Cu(HL)^{3+}] = (3.0 \pm 0.2) \times 10^{-6}$ mol dm^{-3}. The rate law for the formation of the complex of L^4 in acetate buffer is of the form $d[Cu(HL)^{3+}]/dt = k_5[Cu(O_2CMe)^+][HL^+]$, where $k_5 = (4.0 \pm 0.5) \times 10^8$ dm^3 mol^{-1} s^{-1} at 25 °C and the activation parameters are $\Delta H^\ddagger = 13.7 \pm 0.3$ kcal mol^{-1} and $\Delta S^\ddagger = 26.7 \pm 1.0$ cal K^{-1} mol^{-1}. The larger formation and dissociation rate constants suggest that the 15-membered macrocycle is more flexible relative to the smaller analogues.

In the preceding thermodynamic and kinetic studies of the complex formation between Cu^{II} and macrocyclic tetra-amine ligands we have disclosed the cyclic ring-size effects of 12 - (1,4,7,10-tetra-azacyclododecane, L^1) [1,2] and 13-membered ligands (1,4,7,10-tetra-azacyclotridecane, L^2).[3,4] Both complexes showed a *ca.* 10^5-fold stability enhancement relative to the corresponding complexes of the linear tetra-amines. However, their stability increases do not seem to stem from the same sources; for L^1 a large positive ΔS term, reflecting a favourable ligand configuration, outweighs a smaller $-\Delta H$ value (probably due to the unfavourable steric constraint), and for L^2 the increase in ΔS is smaller, but is compensated for by a considerable ΔH contribution.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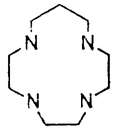
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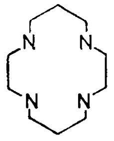
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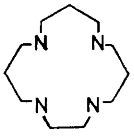
L^4

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[1] M. Kodama and E. Kimura, *J.C.S. Chem. Comm.*, 1975, 326.

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

[3] M. Kodama and E. Kimura, *J.C.S. Chem. Comm.*, 1975, 891.

[4] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, in the press.

An unusually large ΔH value was first reported for the stability of the nickel(II) complex of 1,4,8,11-tetra-azacyclotetradecane(L^3).[5-7] The effects of the ligand cyclization on the kinetics are most notable in the dissociation rates which are retarded to a much greater extent than the formation rates.[1,2] As the ring size increases, however, the steric rigidity diminishes and the dissociation rates tend to increase.[3,4]

In order to cast more light on the thermodynamic and kinetic macrocyclic ring-size effects, we have now studied the reaction of a 15-membered cyclic tetra-amine, 1,4,8,12-tetra-azacyclopentadecane (L^4) with Cu^{II}. A similar study of 12- to 18-membered cyclic tetrathiaethers was recently reported.[8]

EXPERIMENTAL

Reagents.—1,4,8,12-Tetra-azacyclopentadecane (L^4) was prepared by the method of Martin *et al.*[9] Its tetrahydrochloride was purified by two recrystallizations from aqueous 6N HCl, m.p. 240—245 °C (decomp.) (Found: N, 12.9. Calc. for $L^4\cdot 4HCl\cdot 4H_2O$: N, 13.0%). D,L-Valine was recrystallized twice from aqueous solution by adding hydrochloric acid and ethanol. The preparation of other solutions was described earlier.[2,4]

TABLE 1

Effects of ligand, Cu^{II}, pH, and valine in alkaline media on the half-wave potentials at $I = 0.20$ mol dm^{-3} and 25 °C

$10^3[L^4]$	$10^3[Cu^{II}]$	[valine]	pH	log $(\alpha_H)_L$	$(E_{\frac{1}{2}})_{\mathrm{CuL}}$	$\Delta(E_{\frac{1}{2}})_{\mathrm{CuL}}$/mV	
	mol dm^{-3}				V *versus* s.c.e.	calc.	obs.
Ligand concentration effect							
3.88	0.10	0.10	8.70		−0.524	0 [a]	0
1.94	0.10	0.10	8.70		−0.151	8.9 [a]	9
0.97	0.10	0.10	8.70		−0.507	17.8 [a]	17
pH Effect							
0.97	0.10	0.10	8.70	3.918	−0.507	0 [b]	0
0.97	0.10	0.10	9.30	2.763	−0.542	−34.2 [b]	−35
0.97	0.10	0.10	9.60	2.210	−0.556	−50.5 [b]	−49
Valine concentration effect							
0.97	0.10	0.05	8.70		−0.506		
0.97	0.10	0.10	8.70		−0.507		
0.97	0.10	0.20	8.70		−0.506		
Copper(II) concentration effect							
1.94	0.10	0.10	8.70		−0.515		
1.94	0.20	0.10	8.70		−0.514		

[a] Using equation (1). [b] Using equation (2).

Apparatus and Procedures.—All the apparatus and the procedures employed in this study were the same as those described previously.[2,4] As in the cases of L^1,[2] L^2,[4] and L^3,[4] mixed-mode protonation constants of L^4 were determined by potentiometric acid–base titration: pK_1 11.2 ± 0.1, pK_2 10.1 ± 0.1, and pK_3 and pK_4 *ca.* 2.0 at $I = 0.20$ mol dm^{-3} and 25 °C. In the present study, acetate ($3.4 < \mathrm{pH} < 5.4$) and valinate ($8.7 < \mathrm{pH} < 9.8$) buffers were used.

RESULTS

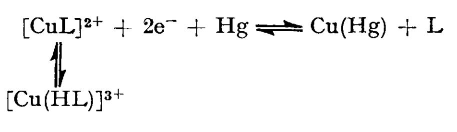
Equilibrium Studies.—The complex of Cu^{II} with L^4 in both acetate and valinate buffer solutions gave a well defined single wave of the diffusion-controlled nature at the dropping mercury electrode (d.m.e.). The polarographic behaviour of the complex was independent both of acetate and valinate concentrations from 0.05 to 0.2 mol dm^{-3}, showing that no mixed-ligand complex involving acetate or valinate anions was formed under the present conditions. Plots of $\log[i/(i_d - i)]$ against d.c. potential, E, were straight lines with a reciprocal gradient of *ca.* −32 mV, a value corresponding to a reversible two-electron reduction at the d.m.e. The half-wave potential of the complex $[Cu^{II}L^4]$, $(E_{\frac{1}{2}})_{\mathrm{CuL}}$, shifted to more negative potentials on increasing the logarithm of the concentration of free L^4, $[L]_f$, in either basic or acidic conditions [relation (1)]. Moreover, in basic solutions $(E_{\frac{1}{2}})_{\mathrm{CuL}}$ shifted linearly to more negative potentials with increasing pH, according to relation (2).*

$$\Delta(E_{\frac{1}{2}})_{\mathrm{CuL}}/\Delta \log\,[L]_f = -30\ \mathrm{mV} \qquad (1)$$

$$\Delta(E_{\frac{1}{2}})_{\mathrm{CuL}}/\Delta \log\,(\alpha_H)_L = 30\ \mathrm{mV} \qquad (2)$$

A typical result obtained in valinate buffer is given in Table 1. On the other hand, in acidic solution, relation (2) did not hold, but a plot of antilog$\{[(E_{\frac{1}{2}})_{Cu^{2+}} - (E_{\frac{1}{2}})_{\mathrm{CuL}}]/0.0296 + \log(k_{Cu^{2+}}/k_{\mathrm{CuL}}) - \log[[L]_f/(\alpha_H)_L]\}$ against $[H^+]$ was linear with an intercept (Figure).

These results, and a finding that variation of $[Cu^{2+}]$ had no effect on $(E_{\frac{1}{2}})_{\mathrm{CuL}}$ (see Table 1), indicate that Cu^{2+} forms a complex $[CuL]^{2+}$ in alkaline solution and an additional complex $[Cu(HL)]^{3+}$ in acidic solution. The electrode reaction mechanism for the reduction of the complexes is then expressed by (3). The shift in the half-wave potential



$$\begin{array}{l} [CuL]^{2+} + 2e^- + Hg \rightleftharpoons Cu(Hg) + L \\ \Big\updownarrow \\ [Cu(HL)]^{3+} \end{array} \qquad (3)$$

due to complex formation, $\Delta(E_{\frac{1}{2}})$, is given by the general

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* All the symbols used were, unless otherwise noted, defined elsewhere.[4]

[5] F. P. Hinz and D. W. Margerum, *J. Amer. Chem. Soc.*, 1974, **96**, 4993.

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[7] G. F. Smith and D. W. Margerum, *J.C.S. Chem. Comm.*, 1975, 807.

[8] T. E. Jones, L. L. Zimmer, L. L. Diaddario, D. B. Rorabacher, and L. A. Ochrymowycz, *J. Amer. Chem. Soc.*, 1975, **97**, 7163.

[9] L. Martin, L. J. DeHayes, L. J. Zompa, and D. H. Busch, *J. Amer. Chem. Soc.*, 1974, **96**, 4046.

equation (4). Here, $k_{\mathrm{CuL}}/k_{\mathrm{Cu^{2+}}} = 0.80$ (as experimentally established) and $K_{\mathrm{Cu(HL)}}{}^{\mathrm{H}} = [\mathrm{CuL}^{2+}][\mathrm{H}^+]/[\mathrm{Cu(HL)}^{3+}]$.

$$\Delta(E_{\frac{1}{2}}) = (E_{\frac{1}{2}})_{\mathrm{Cu^{2+}}} - (E_{\frac{1}{2}})_{\mathrm{CuL}} = 0.0296\left\{\log K_{\mathrm{CuL}}(1 + [\mathrm{H}^+]/K_{\mathrm{Cu(HL)}}{}^{\mathrm{H}}) \cdot \frac{[\mathrm{L}]_{\mathrm{f}}}{(\alpha_{\mathrm{H}})_{\mathrm{L}}} + \log \frac{k_{\mathrm{CuL}}}{k_{\mathrm{Cu^{2+}}}}\right\} \quad (4)$$

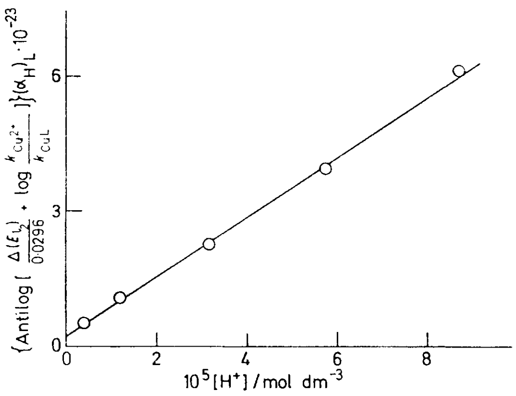
Under the alkaline conditions, the term $(1 + [\mathrm{H}^+]/K_{\mathrm{Cu(HL)}}{}^{\mathrm{H}})$ in equation (4) can be approximated to 1, thus affording the relations (1) and (2).

TABLE 2

Comparison of the stability constant, enthalpy, and entropy of formation of tetra-amine complexes at 25 °C

Complex	$\log K_{\mathrm{ML}}$	$-\Delta H$ / kcal mol^{-1}	ΔS / cal K^{-1} mol^{-1}	I / mol dm^{-3}	Ref.
$[\mathrm{CuL}^4]^{2+}$	24.4 ± 0.2	26.5 ± 0.3	22.7 ± 2	0.2	*
$[\mathrm{CuL}^2]^{2+}$	29.1	29.2	33.7	0.2	3, 4
$[\mathrm{CuL}^1]^{2+}$	24.8	18.3	51.4	0.2	1, 2
$[\mathrm{CuL}^5]^{2+}$	17.3	19.5	12.8	0.1	10, 11
$[\mathrm{CuL}^6]^{2+}$	21.8	25.9	13.1	0.5	12
$[\mathrm{CuL}^7]^{2+}$	23.9	27.7	16.5	0.5	13
$[\mathrm{CuL}^8]^{2+}$	20.2	21.6	19.5	0.1	11
$[\mathrm{NiL}^3]^{2+}$	22.2	31.0	−2	0.1	5, 6
$[\mathrm{NiL}^7]^{2+}$	15.8	19.4	7.2	0.1	13
$[\mathrm{NiL}^8]^{2+}$	13.8	14.0	16.0	0.1	13

* This work. Uncertainties are standard deviations.



Determination of K_{CuL} and $K_{\mathrm{Cu(HL)}}{}^{\mathrm{H}}$. Plot of equation (4) at $[\mathrm{Cu}^{2+}] = 0.20 \times 10^{-3}$ mol dm^{-3}, $[\mathrm{L}^4]_{\mathrm{f}} = 5.96 \times 10^{-3}$ mol dm^{-3}, $[\mathrm{MeCO_2}^-] = 0.05$ mol dm^{-3}, $I = 0.20$ mol dm^{-3}, and 25 °C

The stability constant, K_{CuL}, determined from $\Delta(E_{\frac{1}{2}})$ in alkaline media, was $10^{24.4\pm0.2}$ at 25 °C, which, together with the values of $10^{25.1}$ and $10^{23.7}$ dm^3 mol^{-1} at 15 and 35 °C, respectively, gives thermodynamic parameters for the complex formation (Table 2). The values of pK_1 used at 15 and 35 °C were 11.4 and 11.0, respectively, and pK_2 was 10.3 and 9.9, obtained experimentally. The value of $K_{\mathrm{CuL}} = 10^{24.5}$ dm^3 mol^{-1} determined independently from the intercept in the Figure is in very good agreement with the above value. The value of $K_{\mathrm{Cu(HL)}}{}^{\mathrm{H}} = (3.0 \pm 0.2) \times 10^{-6}$ mol dm^{-3} was also estimated from the intercept/gradient of the Figure.*

Kinetic Studies.—The formation of the complex of $\mathrm{Cu^{II}}$ with L^4 proceeded at a measurable rate in acetate buffer solutions (pH <4.0). As in the case of L^1,[2] the observed formation rate constant, k_{F}, was determined from the initial gradient. In analysing the kinetic data, the following results were found (Table 3); (*i*) at constant pH and $[\mathrm{MeCO_2}^-]$, k_{F} was independent of the initial concentrations of copper and L^4; (*ii*) at given pH and concentrations of copper and L^4, the values of k_{F} multiplied by $\beta_{\mathrm{O_2CMe}}/K_{\mathrm{Cu(O_2CMe)}}[\mathrm{MeCO_2}^-]$ were independent of $[\mathrm{MeCO_2}^-]$; (*iii*) at constant concentrations of copper, L^4, and acetate ion, the values of k_{F} multiplied by $(\alpha_{\mathrm{H}})_{\mathrm{L}}/[\mathrm{H}^+]$ were independent of $[\mathrm{H}^+]$.

TABLE 3

Rate data for reactions of $\mathrm{Cu^{II}}$ and L^4 at $I = 0.20$ mol dm^{-3} and 10 °C

(*a*) Dependence on initial concentrations of $\mathrm{Cu^{II}}$ and L^4 [a]

$10^3[\mathrm{Cu^{II}}]_{0,\mathrm{app.}}$ / mol dm^{-3}	$10^3[\mathrm{L}]_{\mathrm{f}}$ / mol dm^{-3}	k_{F} / dm^3 mol^{-1} s^{-1}
0.05	0.20	29.8
0.10	0.20	29.6
0.10	0.40	29.8
0.20	0.40	30.0
0.10	0.80	29.6

(*b*) Dependence on acetate concentration [b]

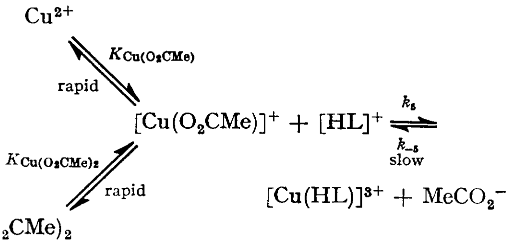
$[\mathrm{MeCO_2}^-]$ / mol dm^{-3}	$K_{\mathrm{Cu(O_2CMe)}}[\mathrm{MeCO_2}^-]/\beta_{\mathrm{O_2CMe}}$	k_{F} / dm^3 mol^{-1} s^{-1}	$k_{\mathrm{F}}\beta_{\mathrm{O_2CMe}}/K_{\mathrm{Cu(O_2CMe)}}[\mathrm{MeCO_2}^-]$
0.05	0.577	29.6	51.4
0.10	0.582	30.2	52.0
0.20	0.475	25.2	53.0

(*c*) Dependence on pH [c]

pH	$10^{-17}(\alpha_{\mathrm{H}})_{\mathrm{L}}/[\mathrm{H}^+]$	k_{F} / dm^3 mol^{-1} s^{-1}	$10^{-18}k_{\mathrm{F}}(\alpha_{\mathrm{H}})_{\mathrm{L}}/[\mathrm{H}^+]$
3.97	2.14	44.7	9.57
3.78	2.31	29.6	9.80
3.54	5.75	16.8	9.66
3.39	8.14	11.8	9.55

[a] At $[\mathrm{MeCO_2}^-] = 0.05$ mol dm^{-3} and pH 3.78. [b] At $[\mathrm{Cu^{II}}]_{0,\mathrm{app.}} = 0.10 \times 10^{-3}$ mol dm^{-3}, $[\mathrm{L}]_{\mathrm{f}} = 0.20 \times 10^{-3}$ mol dm^{-3}, and pH 3.78. [c] At $[\mathrm{Cu^{II}}]_{0,\mathrm{app.}} = 0.10 \times 10^{-3}$, $[\mathrm{L}]_{\mathrm{f}} = 0.20 \times 10^{-3}$, and $[\mathrm{MeCO_2}^-] = 0.05$ mol dm^{-3}.

The kinetic results in conjunction with the equilibrium study establish that the reaction occurs predominantly between a monoprotonated ligand, $[\mathrm{HL}]^+$, and a 1 : 1 copper(II)–acetate species, $[\mathrm{Cu(O_2CMe)}]^+$, to give a monoprotonated complex, $[\mathrm{Cu(HL)}]^{3+}$, as displayed in (5), where



(5)

the second-order rate constant in the rate law $\mathrm{d}[\mathrm{Cu(HL)}^{3+}]/\mathrm{d}t = k_5[\mathrm{Cu(O_2CMe)}^+][\mathrm{HL}^+]$ is derived from equation (6).

$$\frac{-\mathrm{d}[\mathrm{Cu}^{2+}]_{0,\mathrm{app.}}}{\mathrm{d}t} = k_{\mathrm{F}}[\mathrm{Cu}^{2+}]_{0,\mathrm{app.}}[\mathrm{L}]_{\mathrm{f}} = k_5 \cdot \frac{K_{\mathrm{Cu(O_2CMe)}}[\mathrm{MeCO_2}^-]}{\beta_{\mathrm{O_2CMe}}}[\mathrm{Cu}^{2+}]_{0,\mathrm{app.}} \cdot \frac{[\mathrm{H}^+]}{(\alpha_{\mathrm{H}})_{\mathrm{L}}K_1}[\mathrm{L}]_{\mathrm{f}} \quad (6)$$

The rate constants (k_5) of 1.1×10^8, 2.2×10^8, and 4.0×10^8 dm^3 mol^{-1} s^{-1} at 10, 17, and 25 °C, respectively, gave the activation parameters in Table 4 which are compared with values for other macrocyclic systems.

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* The $K_{\mathrm{Cu(HL)}}{}^{\mathrm{H}}$ values were virtually temperature independent (15—35 °C).

TABLE 4

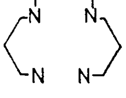
Summary of the rate constants and associated activation parameters for the reaction of $[Cu(O_2CMe)]^+$ with macrocyclic tetra-amine ligands at 25 °C and $I = 0.20$ mol dm^{-3}

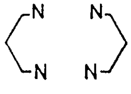
Reacting form of the ligand	Forward rate constant dm^3 mol^{-1} s^{-1}	$\Delta H^\ddagger$ kcal mol^{-1}	$\Delta S^\ddagger$ cal K^{-1} mol
$[HL^1]^+$ [a]	$(1.8 \pm 0.2) \times 10^6$	16.9 ± 0.3	27.3 ± 1
$[HL^2]^+$ [b]	$(5.6 \pm 0.5) \times 10^6$	16.1 ± 0.3	26.9 ± 1
$[HL^4]^+$ [c]	$(4.0 \pm 0.5) \times 10^8$	13.7 ± 0.3	26.7 ± 1

[a] Refs. 2 and 4. [b] Ref. 4. [c] This work.

DISCUSSION

The 15-membered cyclic tetra-amine in valinate buffer solutions forms a 1 : 1 complex with Cu^{II} composed of 5,6,6,6-membered chelate rings. Its stability constant is *ca.* 10^7, 10^3 times greater than those for complexes of the related linear tetra-amines 4,8-diazaundecane-1,11-diamine (L^5) and 4,7-diazadecane-1,10-diamine (L^6), respectively (see Table 1).[10-13] Compared with other macrocyclic systems the complex is as stable as that with L^1,[1,2] but four orders of magnitude less stable than those with L^2 (refs. 3 and 4) and L^3.[6,14] It is of interest that, despite having similar protonation constants pK_1 and pK_2 (11.1 and 10.1 for L^2),[4] the ligands L^2 and L^4 form copper(II) complexes with widely differing stability constants. The diminished stability of the 15-membered complex results from less favourable enthalpy as well as entropy changes. Apparently, a square-planar conformation of the 15-membered ring[9] should be more sensitive to internal steric and entropic factors than a protonated conformation.


L^5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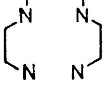
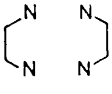

L^9


L^8

A comparison of the thermodynamic parameters for the reactions of Cu^{II} with L^4 and L^5 (ref. 10) may reveal that effect of the 15-membered macrocycle is primarily due to an enthalpy contribution [$\Delta(\Delta H)$ —7 kcal mol^{-1}] together with a minor entropy effect [$\Delta(\Delta S)$ 10 cal K^{-1} mol^{-1}].* However, we prefer to define the effect by considering similarities or differences between the geometries of the macrocyclic and linear ligands in the complexes. A large enthalpy contribution to the macrocyclic effect [$\Delta(\Delta H)$ —12 kcal mol^{-1}], however, was previously reported for Ni^{II} reacting with L^3, where a decreased ligand solvation of the macrocycle was invoked.[5-7] When the comparison is made with the L^6 complex,[12] the enthalpy contribution becomes small [$\Delta(\Delta H)$ —1 kcal mol^{-1}] with the entropy term [$\Delta(\Delta S)$ 10 cal K^{-1} mol^{-1}] emerging as the major term. According to this choice of reference complexes, the macrocyclic effect for L^4 is interpreted in terms of the entropy term, as for L^1.[1,2] Obviously, compared with the 12-membered ring, the more flexible 15-membered ring suffers more restriction of freedom on complex formation, leading to the observed smaller entropy contribution [$\Delta(\Delta S)$ 10 compared with 32 cal K^{-1} mol^{-1}]. The similar ΔH values for L^4 and L^6 systems may reflect the analogous complex geometries and strengths of the Cu–N bonds.[15,16]

The most striking manifestation of the expansion of the macrocyclic ring is the easy access of a proton to one of the nitrogen atoms in the complex, $pK_{Cu(HL)}^{H}$ being 5.5.† Mechanical constraint and conformational strain caused by the longer methylene chains results in a weaker metal–donor atom interaction, thus making available a nitrogen lone pair for the protonation. By contrast, no such protonation was detected for tetra-amine complexes having smaller ring sizes under the same (acetate-buffered) conditions.

The kinetic studies in acetate buffer solutions show that complex formation occurs between $[Cu(O_2CMe)]^+$ and the monoprotonated ligand. Although there was a significant contribution of the diprotonated ligand to the rate of the reactions[1-4] of L^1 and L^2, this term is negligible in the present instance due to an increased rate constant (k_5) of the monoprotonated species. Of further significance is the fact that the rate of reaction of $[HL^4]^+$ is close to those of linear polyamines,[17,18] suggesting the blocking effects of a nearby proton, and of steric constraint, on the donor sites are also small with the 15-membered ring.

Regarding the activation parameters for the macrocyclic systems Table 4 shows that for the 12-, 13-, and 15-membered series the $\Delta S^\ddagger$ term is *ca.* 27 cal K^{-1} mol^{-1} while $\Delta H^\ddagger$ gradually decreases as the ring expands. The transition state should involve loss of water molecules bound to the metal ion, thus resulting in the same positive $\Delta S^\ddagger$ value regardless of the macrocyclic ring size. The more facile ligand–metal outer-sphere interaction or easier water dissociation due to less steric hindrance may be responsible for the more favourable $\Delta H^\ddagger$ term for the larger macrocycle. These results are consistent with the usual dissociative reaction mechanism as proposed earlier.[4] A comparison with the reactions of linear polyamines[18] supports the notion that generally negative $\Delta S^\ddagger$ terms for linear systems are indicative of unfavourable ligand configurations which

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* 1 cal = 4.184 J.

† A similar protonation was reported for the related linear copper(II) complex of L^6, $pK_{Cu(HL)}^{H}$ 3.6.[12]

[10] R. Barbucci, L. Fabbrizzi, and P. Paoletti, *J.C.S. Dalton*, 1972, 745.

[11] R. Barbucci, L. Fabbrizzi, and P. Paoletti, *Co-ordination Chem. Rev.*, 1972, **8**.

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outweigh the positive $\Delta S^{\ddagger}$ of the water loss, and that generally higher $\Delta H^{\ddagger}$ values for the macrocyclic systems represent larger energies required for the loss of water attached to Cu^{2+}.

The dissociation rate constant (k_{-5}) is estimated to be 3.8×10^{-9} dm^3 mol^{-1} s^{-1} from equation (7). When

$$\frac{k_5}{k_{-5}} = \frac{[Cu(HL)^{3+}][MeCO_2^-]}{[Cu(O_2CMe)^+][HL^+]} = \frac{K_{CuL}K_1}{K_{Cu(HL)}{}^{H}K_{Cu(O_2CMe)}} \qquad (7)$$

reaction (8) is considered as was the case for L^1 (refs. 1 and 2) and L^2,[3,4] the dissociation rate constant, k_{-5}', is

$$[Cu(O_2CMe)]^+ + [HL]^+ \underset{k_{-5}'}{\rightleftharpoons} [CuL]^{2+} + MeCO_2H \qquad (8)$$

calculated to be $10^{-7.65}$ dm^3 mol^{-1} s^{-1} from $k_5/k_{-5}' = K_{CuL}K_1/K_{Cu(O_2CMe)}K_{MeCO_2H}$. A comparison with the L^1 and L^2 systems shows that the dissociation rate is definitely faster for the present L^4 system, indicating again the relief of the steric rigidity due to the cyclic geometry.

In the macrocyclic series, the correlation between the forward reaction rate and equilibrium constants of complex formation (including their parameters) is very poor. Provided that all the macrocycles follow the same reaction path, this leads to the conclusion that the differing thermodynamic functions arise from processes occurring after the formation of the transition state. For example, the difference, if any, in the macrocyclic effects of the 12—15-membered systems should occur after the formation of the first bond.

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