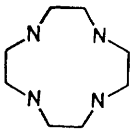
Thermodynamic and Kinetic Effects of 13-Membered Macrocycles. Polarographic Studies of 1,4,7,10-Tetra-azacyclotridecanecopper(II) [1]

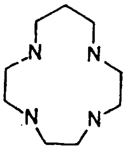
By **Mutsuo Kodama**, Department of Chemistry, College of General Education, Hirosaki University, Bunkyo, Hirosaki, Japan
Eiichi Kimura,* Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, Kasumi, Hiroshima, Japan

Thermodynamics and kinetics of complex formation between Cu^{2+} and 1,4,7,10-tetra-azacyclotridecane(L^2) in acetate-buffered solution have been studied polarographically. The stability constant (log K 29.1 at 25 °C) for the 1 : 1 complex with 5,5,5,6-membered chelate rings is *ca.* 10^5- and 10^9-fold greater than those for the corresponding open-chain tetra-amine complexes with 5,6,5- and 5,5,5-membered chelate rings, respectively. The enhanced stability with the 13-membered cyclic ligand is largely due to a more favourable entropy change, as found for 12-membered macrocycles. However, there is a significant, although small, contribution from the enthalpy term. These trends may link the differences between the 12- and 14-membered macrocyclic effects. The rate law ($pH < 4$, 25 °C) is $d[(CuL^2)^{2+}]/dt = k_5[Cu(O_2CMe)^+][(HL^2)^+] + k_6[Cu(O_2CMe)^+][(H_2L^2)^{2+}]$, where $k_5 = (5.6 \pm 0.5) \times 10^6\ dm^3\ mol^{-1}\ s^{-1}$ and $k_6 = 10.1 \pm 1\ dm^3\ mol^{-1}\ s^{-1}$. The activation parameters for $[HL^2]^+$ reaction are $\Delta H^{\ddagger} = 16.1$ kcal mol^{-1} and $\Delta S^{\ddagger} = +26.9$ cal $K^{-1}\ mol^{-1}$, and for $[H_2L^2]^{2+}$ reaction are $\Delta H^{\ddagger} = 11.6$ kcal mol^{-1} and $\Delta S^{\ddagger} = -15.1$ cal $K^{-1}\ mol^{-1}$. The strikingly different activation parameters between $[HL^2]^+$ and $[H_2L^2]^{2+}$ reactions suggest a shift of the reaction mechanism from dissociative to associative. The kinetic behaviours indicate that the 13-membered macrocycles have intermediate properties between 12-membered cyclic and open-chain tetra-amines.

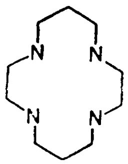
RECENTLY we reported [2,3] that the macrocyclic effect used to explain the enhanced stabilities of metal complexes containing 14-membered cyclic tetra-amines compared with the corresponding linear ligands [4-6] also occurs for a 12-membered ligand, 1,4,7,10-tetra-azacyclododecane (L^1). However, the thermodynamic parameter contributing to each macrocyclic effect is surprisingly different for the structurally similar ligands; the enhancement for the complex of L^1 is due to a favourable change in ΔS, whereas for 1,4,8,11-tetra-azacyclotetradecane (L^3 or cyclam) it is due to the ΔH term.[5,6] The latter result was explained in that the free macrocycle is less solvated due to steric hindrance and hence less enthalpic energy must be expended for desolvation before the complex formation. It was further supposed that the more favourable configurational entropy built into the cyclic ligands, which seems to account for the effect of 12-membered macrocycles,[2,3] should tend to be offset by less water being released from the solvated 14-membered ligand.



L^1



L^2



L^3

The effect of the ligand cyclization on the kinetics appears most notably at the dissociation steps for both the 12- [2,3] and 14-membered ligands.[7] Also noteworthy is the fact that the formation rate constants, especially with the diprotonated cyclic ligand species,[3,8] are much smaller than would be expected according to dissociative substitution mechanisms. It was therefore suggested that the rate-determining step shifts to an associative process, presumably involving proton loss from the rigid cyclic tetra-amine structures.

In order to find the origin of the thermodynamic differences between the 12- and 14-membered cyclic ligands on complex formation, and also to investigate the mechanism of the cyclic ligand substitution, we have undertaken polarographic studies of the complex formation of an intermediate macrocyclic tetra-amine, 1,4,7,10-tetra-azacyclotridecane (L^2), with copper(II).

EXPERIMENTAL

Reagents.—The ligand, L^2, was prepared by the method of Martin *et al.*[9] The tetrahydrochloride was purified by recrystallization from aqueous 6N HCl (Found: C, 26.8; H, 14.1; N, 7.9. Calc. for $L^2 \cdot 4HCl \cdot 4H_2O$: C, 26.9; H, 13.9; N, 7.4%). Copper(II) nitrate solution was prepared by dissolving a known amount of metallic copper (99.999% pure) in dilute nitric acid and by removing the excess of nitric acid by distillation under reduced pressure. All the other chemicals were of analytical reagent grade and were used without further purification.

Apparatus and Procedures.—All the polarograms and the current–time curves were obtained with a Yanagimoto P-8 pen-recording polarograph or a manual polarograph similar to that of Kolthoff and Lingane.[10] The dropping mercury electrode (d.m.e.) had the open-circuit characteristics $m = 0.897$ mg s^{-1} and $t_d = 4.76$ s in an air-free 0.1 mol dm^{-3} $Na[ClO_4]$ solution at a column height of 60.0 cm at 25 °C. A saturated calomel electrode (s.c.e.) of large area was used as a reference and was connected to the cell solution through a Hume and Harris type salt bridge.[11] The pH of the solution was measured with a glass-electrode

---

[1] Preliminary report, *J.C.S. Chem. Comm.*, 1975 891.

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

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

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

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

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

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

[8] T. Kaden, *Helv. Chim. Acta*, 1970, **53**, 617.

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

[10] I. M. Kolthoff and J. J. Lingane, 'Polarography,' Interscience, New York, 1952, vol. 1, p. 297.

[11] D. N. Hume and W. E. Harris, *Ind. and Eng. Chem. Analyt. Edn.*, 1943, **15**, 465.

pH meter (Hitachi-Hariba model F-7). A water-jacketed beaker cell with a rubber top, which was thermostatted to ±0.1 °C, was used for all the experiments. In the present study, all the measurements were in solutions of 0.2 mol dm^{-3} ionic strength, which was adjusted by adding appropriate amounts of sodium perchlorate. The oxygen dissolved in sample solutions was removed by bubbling with pure nitrogen gas. In the range pH 3.40—5.60 acetate buffer was employed.

The reaction was initiated by adding within 1 s a known amount of deaerated macrocycle solution to the deaerated reaction mixture with the aid of a 1 ml syringe. The resulting solution was thoroughly stirred for 5 s with a magnetic stirring bar driven by a synchronous motor. With this procedure, reproducible current–time curves were obtained 15 s after the initiation of the reactions. The rate of the complex formation was determined by measuring the change in the diffusion current of the cathodic wave of Cu^{2+} with time. Mixed protonation constants of L^2 were determined by potentiometric acid–base titration of its tetrahydrochloride (0.02 mol dm^{-3}) with carbonate-free sodium hydroxide by using sample solutions of ionic strength 0.20 mol dm^{-3} (Na[ClO$_4$]) (pK_1 11.1 ± 0.1, pK_2 10.1 ± 0.1, and pK_3 *ca.* 1.7 at 25 °C). Titrations were made on oxygen-free sample solutions in a beaker-type cell with a thermostatted water jacket. A value of pK_4 was estimated as *ca.* 1 from the initial pH value of $L^2\cdot 4HCl$ solution, using the pK_3 value.

RESULTS

Equilibrium Studies.—The L^2 complex of Cu^{II} in an acetate buffer solution ($4.3 < pH < 5.2$) gave a well defined single wave of the diffusion-controlled nature at the d.m.e. There was no concentration effect of acetate ion ($0.06 < [MeCO_2^-] < 0.2$ mol dm^{-3} at $[Cu^{2+}]_T = 0.2 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 3.33 \times 10^{-3}$ mol dm^{-3}, pH 4.72, and $I = 0.20$ mol dm^{-3}) on the polarographic behaviour of the [Cu^{II}L^2] complex, which was interpreted in that no mixed-ligand complex involving acetate ions was formed under the experimental conditions. Plots of $\log[i/(i_d - i)]$ against the d.c. potential were invariably linear with reciprocal gradient of *ca.* −36 mV, corresponding to a reversible two-electron reduction at the d.m.e. The half-wave potential of the [Cu^{II}L^2] complex, $(E_{\frac{1}{2}})_{CuL^2}$, shifted linearly to more negative potentials on increasing the logarithm of the concentration of free L^2, $[L^2]_F$, and pH, according to relations (1) and (2) (Table 1).

$$\Delta(E_{\frac{1}{2}})_{CuL^2}/\Delta\log[L^2]_F = -30\text{ mV} \qquad (1)$$

$$\Delta(E_{\frac{1}{2}})_{CuL^2}/\Delta pH = -60\text{ mV} \qquad (2)$$

TABLE 1

Effects of the concentration of L^2 and pH on the half-wave potentials at $I = 0.20$ mol dm^{-3} and 25 °C

(*a*) Concentration effect

$[Cu^{2+}]_T = 0.20 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.10$ mol dm^{-3}, pH 4.88

$\frac{10^3[L^2]_F}{\text{mol dm}^{-3}}$	$\frac{E_{\frac{1}{2}}}{\text{V against s.c.e}}$	$\Delta E_{\frac{1}{2}}$/mV obs.	$\Delta E_{\frac{1}{2}}$/mV calc.
2.00	-0.418_0	0	0
3.33	-0.424_5	−6.6	−6.6
4.66	-0.429_2	−10.2	−10.8

(*b*) pH Effect

$[Cu^{2+}]_T = 0.20 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 3.33 \times 10^{-3}$ mol dm^{-3}, and $[MeCO_2^-] = 0.06$ mol dm^{-3}

pH	$\frac{E_{\frac{1}{2}}}{\text{V against s.c.e.}}$	$\Delta E_{\frac{1}{2}}$/mV obs.	$\Delta E_{\frac{1}{2}}$/mV calc.
4.28	-0.396_0	0	0
4.43	-0.407_0	−9.0	−8.9
4.72	-0.418_0	−22.0	−26.0
5.01	-0.437_1	−41.0	−43.1
5.20	-0.449_0	−53.0	−53.3

TABLE 2

Effect of temperature on stability constants at $[Cu^{2+}]_T = 0.32 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 4.66 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.10$ mol dm^{-3}, $I = 0.20$ mol dm^{-3}, and pH 4.88

$\frac{\theta_c}{°C}$	$\frac{2.303RT/nF}{\text{mV}}$	$E_{\frac{1}{2}}$/V against s.c.e. $(E_{\frac{1}{2}})_{CuL^2}$	$E_{\frac{1}{2}}$/V against s.c.e. $(E_{\frac{1}{2}})_{Cu^{2+}}$	$\log K_{CuL^2}$*
7.0	27.8	−0.4464	+0.0225	30.61
16.0	28.7	−0.4372	+0.0252	29.87
25.0	29.6	−0.4246	+0.0279	29.07
33.0	33.0	−0.4211	+0.0303	28.67

* Calculated with the aid of equation (4).

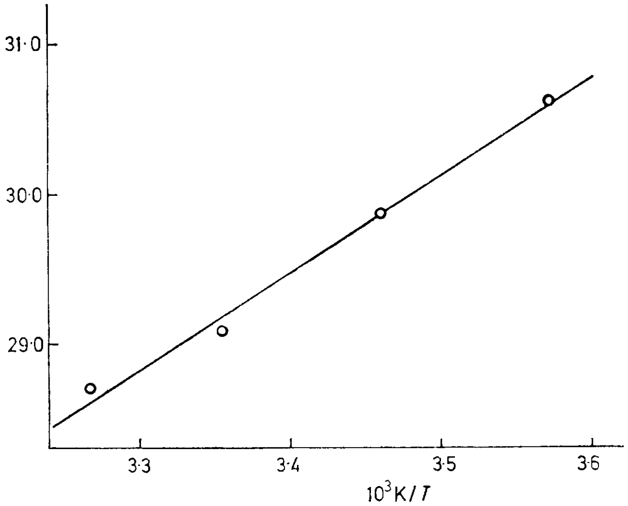


FIGURE 1 Determination of the thermodynamic functions for the formation of the complex of L^2 with Cu^{2+} at $[Cu^{2+}]_T = 0.32 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 4.66 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.10$ mol dm^{-3}, pH 4.88, and $I = 0.20$ mol dm^{-3}

Hence, as for formation of [Cu^{II}L^1],[3] we conclude that Cu^{2+} forms only a 1 : 1 complex with L^2 and that the electrode reaction mechanism for reduction of the complex is expressed by equation (3). Therefore, the shift of the

$$[CuL^2]^{2+} + 2e^- + Hg \rightleftharpoons Cu(Hg) + L^2 \qquad (3)$$

half-wave potential due to complex formation, $\Delta(E_{\frac{1}{2}})$, is given by equation (4), where $1/(\alpha_H)_{L^2}$ is the fraction of L^2

$$\Delta(E_{\frac{1}{2}}) = (E_{\frac{1}{2}})_{Cu^{2+}} - (E_{\frac{1}{2}})_{CuL^2} = 0.0296\left\{\log K_{CuL^2}\frac{[L^2]_F}{(\alpha_H)_{L^2}} + \log\frac{k_{CuL^2}}{k_{Cu^{2+}}}\right\} \qquad (4)$$

in the free-base form and $(\alpha_H)_{L^2}$ is defined as $1 + ([H^+]/K_1) + ([H^+]^2/K_1K_2) + ([H^+]^3/K_1K_2K_3) + ([H^+]^4/K_1K_2K_3K_4) \approx ([H^+]^2/K_1K_2)$ in the pH region under study (K_i is the equilibrium constant for $H_iL^{i+} \rightleftharpoons H_{i-1}L^{(i-1)+} + H^+$) and k is the diffusion current constant ($k_{CuL^2}/k_{Cu^{2+}} = 0.80$, as established experimentally).

Thus, the stability constant, $K_{CuL^2} = 10^{29.1}$ (at 25 °C and $I = 0.20$ mol dm^{-3}) was determined from equation (4). Table 1 includes the calculated $\Delta(E_{\frac{1}{2}})$ values derived from (4) and $\log K_{CuL^2}$ of 29.1, which show good agreement with

TABLE 3

Comparison of stability constants and enthalpy and entropy of formation of tetra-amine complexes at 25 °C

Complex	$\log K_{ML}$	ΔH / kcal mol^{-1}	ΔS / cal K^{-1} mol^{-1}
$[CuL^2]^{2+}$ [a]	29.1 ± 0.2	−29.2 ± 0.3	33.7 ± 2
$[CuL^1]^{2+}$ [b]	24.8	−18.3	51.4
$[CuL^5]^{2+}$ [c]	23.9	−27.7	16.5
$[CuL^4]^{2+}$ [c]	20.2	−21.6	19.5
$[NiL^3]^{2+}$ [d]	22.2	−31.0	−2
$[NiL^5]^{2+}$ [d]	15.8	−19.4	7.2
$[NiL^4]^{2+}$ [d]	13.8	−14.0	16.0

[a] This work, $I = 0.20$ mol dm^{-3}. Uncertainties are the standard deviations. [b] Refs. 2 and 3, $I = 0.20$ mol dm^{-3}. [c] Ref. 13, $I = 0.1$ mol dm^{-3}. [d] Refs. 5 and 6, $I = 0.1$ mol dm^{-3}.

the experimental values. The stability constants were measured at various temperatures (Table 2) to obtain thermodynamic parameters for the complex formation (Figure 1). These values are compared with the corresponding values for various tetra-amines in Table 3.

Kinetic Studies.—The formation of the L^2 complex with Cu^{2+} proceeded at a measurable rate in acetate buffer solutions (pH <4.0). Second-order plots of $\log[(a - x)/(b - x)]$ against t invariably gave straight lines with an intercept of $\log(a/b)$, where a and b are, respectively, the initial concentrations of L^2 and Cu^{II}, and x is the decrease in the concentration of a reactant in a given time. An addition of the $[Cu^{II}L^2]$ complex had virtually no effect on the gradient of the above linear relation, provided that the other conditions were kept constant. Together with the fact that the apparent equilibrium constant, $K_{app.}\{= [CuL^{2+}]/[L^2]_F[Cu^{2+}]_{0,app.} = K_{CuL^2}/(\alpha_H)_{L^2}\beta_{O_2CMe}\}$, is larger than 10^{13} under the present conditions, these observations indicate that the rate of the dissociation reaction is negligibly small compared with that of the formation reaction. Therefore, the apparent formation rate constant, k_f, can be determined from the gradient of the linear relation shown in Figure 2. Thus determined, k_f showed satisfactory agreement with a value determined from the initial gradient, $(-\Delta[Cu^{2+}]_{0,app.}/\Delta t)$, divided by $[Cu^{2+}]_{0,app.}[L]_F$, where $[Cu^{2+}]_{0,app.}$ is the initial concentration of Cu^{2+}.

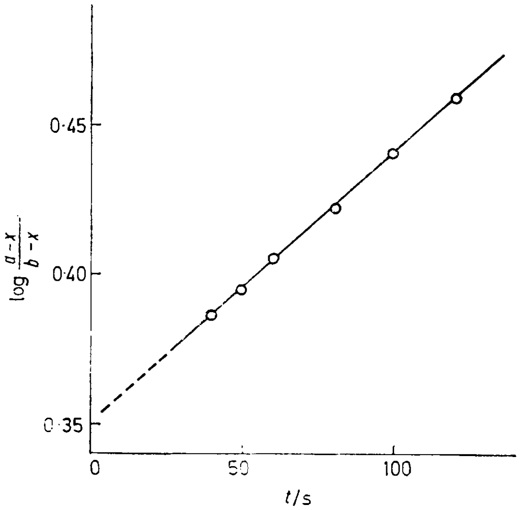


FIGURE 2 Plot of $\log[(a - x)/(b - x)]$ against t at $[Cu^{2+}]_{0,app.} = 0.192 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 0.440 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.096$ mol dm^{-3}, pH 3.54, and $I = 0.20$ mol dm^{-3}

In determining the formation rate constant, the following were found: (*i*) the ratio of the log-plot gradient and $(a - b)$ was independent of the $(a - b)$ values at given concentrations of $MeCO_2^-$ and H^+ (Table 4); (*ii*) at given concentrations of H^+, Cu^{2+}, and L, a plot of the log-plot gradient multiplied by β_{O_2CMe} against $[MeCO_2^-]$ gave a straight line passing through the origin, where β_{O_2CMe} is defined as $1 + K_{Cu(O_2CMe)}[MeCO_2^-] + K_{Cu(O_2CMe)}K_{Cu(O_2CMe)_2}[MeCO_2^-]^2$ (Figure 3);[12] (*iii*) at given concentrations

TABLE 4

Determination of the initial rate constant at 25 °C and $I = 0.20$ mol dm^{-3}

(*a*) $[L^2]_F = 0.44 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.096$ mol dm^{-3}, and pH 3.52

$10^3[Cu^{2+}]_{0,app.}$ / mol dm^{-3}	10^3 Log-plot gradient / s^{-1}	Gradient/$(a - b)$ / dm^3 mol^{-1} s^{-1}
0.081	1.55	4.30
0.192	1.08	4.35
0.384	0.25	4.10

(*b*) $[Cu^{2+}]_{0,app.} = 0.192 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.096$ mol dm^{-3}, and pH 3.52

$10^3[L^2]_F$ / mol dm^{-3}	10^3 Log-plot gradient / s^{-1}	Gradient/$(a - b)$ / dm^3 mol^{-1} s^{-1}
0.44	1.08	4.35
0.88	3.00	4.35
1.32	4.88	4.32

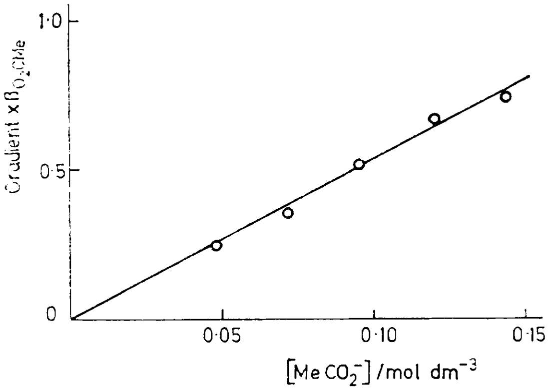


FIGURE 3 Plot of the gradient $\times \beta_{O_2CMe}$ against $[MeCO_2^-]$ at $[Cu^{2+}]_{0,app.} = 0.192 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 0.366 \times 10^{-3}$ mol dm^{-3}, pH 3.52, 25 °C, and $I = 0.20$ mol dm^{-3}

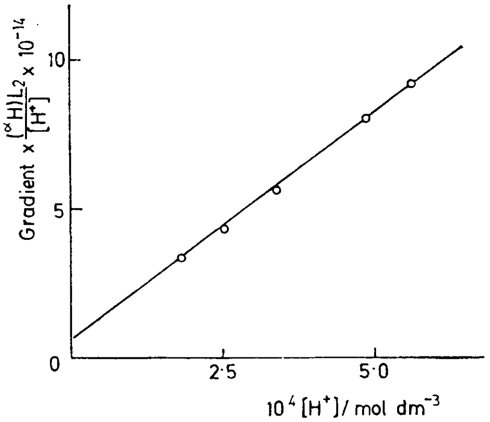
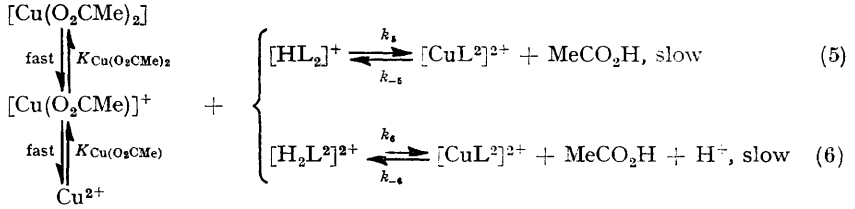


FIGURE 4 Plot of gradient $\times \{(\alpha_H)_{L^2}/[H^+]\} \times 10^{-14}$ against $[H^+]$ at $[Cu^{2+}]_{0,app.} = 0.192 \times 10^{-3}$ mol dm^{-3}, $[L^2]_F = 0.476 \times 10^{-3}$ mol dm^{-3}, $[MeCO_2^-] = 0.096$ mol dm^{-3}, 25 °C, and $I = 0.20$ mol dm^{-3}

[12] N. Tanaka and K. Kato, *Bull. Chem. Soc. Japan*, 1960, **33**, 417, 1412.

of Cu^{2+}, $MeCO_2^-$, and L, a plot of (log-plot gradient)-$(\alpha_H)_{L^2}/[H^+]$ against $[H^+]$ was linear with a finite intercept (Figure 4). These findings indicate that the L^2 complex formation involves a 1 : 1 copper(II)–acetate species $[Cu(O_2CMe)]^+$, and mono- ($[HL^2]^+$) and di-protonated L^2 ($[H_2L^2]^{2+}$) in the slow step, as found for the L^1 reaction.[2,3] Thus, for the reactions in equations (5) and (6), the rate expression, $k_5[Cu(O_2CMe)^+][(HL^2)^+] + k_6[Cu(O_2CMe)^+][(H_2L^2)^{2+}]$, is given in (7). The resolved formation rate constants, k_5 and k_6, were obtained respectively from the intercept and gradient of the linear relation in Figure 4.



$$[Cu(O_2CMe)_2] \underset{\text{fast}}{\overset{K_{Cu(O_2CMe)_2}}{\rightleftharpoons}} [Cu(O_2CMe)]^+ \underset{\text{fast}}{\overset{K_{Cu(O_2CMe)}}{\rightleftharpoons}} Cu^{2+}$$

$$[Cu(O_2CMe)]^+ + [HL_2]^+ \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} [CuL^2]^{2+} + MeCO_2H, \text{ slow} \quad (5)$$

$$[Cu(O_2CMe)]^+ + [H_2L^2]^{2+} \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} [CuL^2]^{2+} + MeCO_2H + H^+, \text{ slow} \quad (6)$$

$$\frac{-d[Cu^{2+}]_{0,app.}}{dt} = \frac{dx}{dt} = k_f[Cu^{2+}]_{0,app.}[L^2]_F = k_f(a - x)(b - x) =$$
$$\frac{K_{Cu(O_2CMe)}[MeCO_2^-]\,[Cu^{2+}]_{0,app.}}{\beta_{O_2CMe}} \cdot \frac{[L^2]_F}{(\alpha_H)_{L^2}} \left(k_5\frac{[H^+]}{K_1} + k_6\frac{[H^+]^2}{K_1K_2}\right) \quad (7)$$

TABLE 5

Summary of rate constants and associated activation parameters for the formation of copper(II) complexes of macrocycles at 25 °C and $I = 0.20$ mol dm^{-3}

Reaction system		k [a] dm^3 mol^{-1} s^{-1}	$\Delta H^\ddagger$ [a] kcal mol^{-1}	$\Delta S^\ddagger$ [a] cal K^{-1} mol^{-1}
$[Cu(O_2CMe)]^+$	+ $[HL^2]^+$ [b]	$(5.6 \pm 0.5) \times 10^6$	16.1 ± 0.3	26.9 ± 1
	+ $[H_2L^2]^{2+}$ [b]	10.1 ± 1	11.6 ± 0.3	-15.1 ± 1
Cu^{2+}(aq)	+ $[HL^2]^+$ [c]	$(1.7 \pm 0.2) \times 10^7$	16.8 ± 0.3	31.0 ± 1
	+ $[H_2L^2]^{2+}$ [c]	$(1.4 \pm 0.1) \times 10^{-1}$	11.0 ± 0.3	-25.2 ± 1
$[Cu(O_2CMe)]^+$	+ $[HL^1]^+$ [b]	$(1.8 \pm 0.2) \times 10^6$	16.9 ± 0.3	26.8 ± 1
	+ $[H_2L^1]^{2+}$ [b]	$(1.8 \pm 0.2) \times 10^{-1}$	12.5 ± 0.3	-19.9 ± 1

[a] Uncertainties are the standard deviations. [b] In acetate buffer medium (pH <4). [c] In acid medium (1.2 < pH < 2.0).

The activation parameters were determined from the variation of the rate constants with temperature (Figure 5).

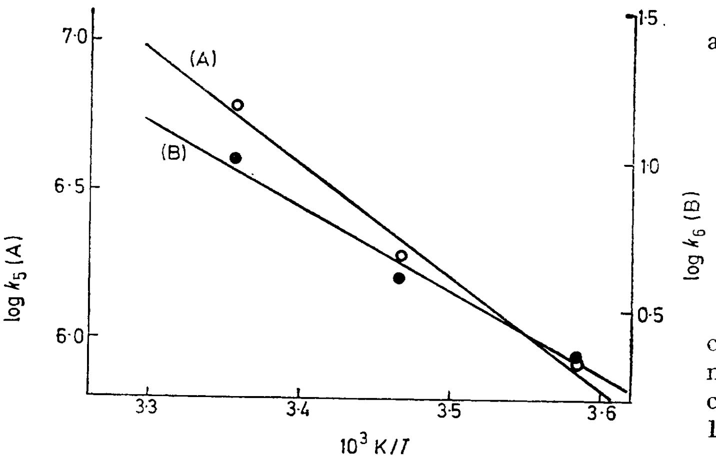


FIGURE 5 Determination of kinetic activation parameters for the formation of the complex $[CuL^2]^{2+}$

For comparison, those for the reaction of L^1 with $[Cu(O_2CMe)]^+$ were also determined. Since the acetate ion was shown to affect the reaction rate, the kinetics were also examined in more acidic media (1.2 < pH < 2.0) where no acetate buffer was used. The rate law was found to be of the same form as above: $d[(CuL^2)^{2+}]/dt = k_5'[Cu^{2+}][(HL^2)^+] + k_6'[Cu^{2+}][(H_2L^2)^{2+}]$. All the resulting data are summarized in Table 5.

DISCUSSION

Thermodynamic Comparisons with Similar Reactions.— A comparison of the first and second mixed-mode protonation constants of the cyclic tetra-amine ligands (pK_a in Table 6) shows a trend of increasing proton affinities as a methylene group is inserted into the ring, which reflects decreasing steric constraints in the protonated ring conformations.[13]

The 13-membered ring macrocyclic ligand, L^2, forms a 1 : 1 copper(II) complex composed of 5,5,5,6-membered chelate rings.† The stability constant of $10^{29.1}$ is more than 10^5 and 10^9 times greater than those for complexes of the linear tetra-amines 3,7-diazanonane-1,9-diamine (L^5 or 2,3,2-tet) with 5,6,5- and 3,6-diaza-

TABLE 6

Comparison of mixed-mode protonation constants for cyclic tetra-amines

	L^1 [a]	L^2 [b]	L^3 [b]
pK_1	10.7	11.1	11.5
pK_2	9.7	10.1	10.2
pK_3	*ca.* 1.5—2	*ca.* 1.7	*ca.* 1.7
pK_4		*ca.* 1.0	*ca.* 1.0

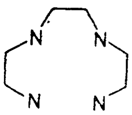
[a] Refs. 2 and 3. [b] This work.

---

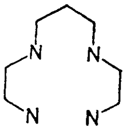
† We observed no sign of the presence of two isomeric complexes, such as the 'blue' and 'red' species of the copper(II) complex of tet *a*.[4] However, the polarogram of the copper(II) complex of L^3 gives a two-step reduction wave suggesting the existence of two isomeric species (M. Kodama and E. Kimura, unpublished work).

[13] The crystal structure of $[H_2L^3][ClO_4]_2$ has been reported; C. Nave and M. R. Truter, *J.C.S. Dalton*, 1974, 2351.

octane-1,8-diamine (L^4 or trien) with 5,5,5-membered chelate rings, respectively.[14] It is 10^4 times as stable as the 12-membered counterpart,[2,3] and is of similar stability to the copper(II) complex of 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradecane (tet *a*) measured by Cabbiness and Margerum[4] (log K_{CuL} 28 at 25 °C and $I = 0.1$ mol dm^{-3}).



L^4



L^5

A comparison of the thermodynamic parameters with those for the complex of L^5 clearly shows that the enhanced stability of the macrocyclic complex is due mostly to the entropic contribution as in the case of the L^1 complex.[2,3] However, there is a significant contribution from the enthalpic term, unlike the macrocyclic effect exerted by L^1. Normally, introduction of an ethylenic chain into tetra-amines causes steric strain in the existing five-membered chelate rings, leading to a decrease in the heat of complex formation.[14] The increase in the enthalpy term for L^2 against L^5 complex formation, therefore, may indicate another contributing factor such as the ligand solvation effect proposed by Hinz and Margerum.[5,6] The greater stability for the complex of the 13-membered macrocycle compared with the 12-membered macrocycle is due entirely to the enthalpy contribution which outweighs the less favourable entropy term. Obviously less steric strain and probably less ligand solvation[5,6] will contribute to the greater ΔH term.

Kinetic Comparisons.—The kinetic studies showed that steps (5) and (6) are applicable to the reactions of the 13- and the 12-membered tetra-amines.[2,3] The forward rate constant decreases abruptly on going from $[HL]^+$ to $[H_2L]^{2+}$ reactions. Previously this behaviour was ascribed to either a shift in the rate-determining step[3] or a drastic change in the conformation of the protonated ligands.[1] The activation parameters obtained in the current studies for L^2, as well as those for complex formations of L^1, provide more information on the reaction mechanism. For reaction (5), the relatively high $\Delta H^‡$, the large positive $\Delta S^‡$, and the small dependence of the rate constant, k_5, on ligands with differing formation constants suggest the occurrence of the rate-determining step at an early stage of the reaction path, *i.e.* a dissociative mechanism.[15] On the other hand, for reaction (6), the relatively small $\Delta H^‡$, the large negative $\Delta S^‡$, and a considerable dependence of the rate constant, k_6, on the ligands in parallel with the equilibrium constants suggest that the rate-determining step occurs at a later stage of the reaction path, *i.e.* an associative mechanism. Such a large difference [$\Delta(\Delta S^‡) \approx 40$ cal K^{-1} mol^{-1}] * in the activation entropy between reactions (5) and (6) cannot be rationalized merely on the basis of electrostatic effects which predict *ca.* 10 cal K^{-1} mol^{-1} for ionic reactions.[16] This lends support to a shift in the rate-determining step between the two reactions.

Inclusion of acetate ions as a buffer in the reaction mixture caused an increase in the rate of reaction of di-protonated L^2. Electrostatic repulsion between the reactants would be significantly reduced with $[Cu(O_2CMe)]^+$ compared with $Cu^{2+}(aq)$, which explains the more favourable $\Delta S^‡$ term found for the former reaction. With a reaction intermediate such as $[Cu(H_2L)(O_2CMe)]^{3+}$, internal proton transfer from a nitrogen atom to a carboxylate oxygen would also be easier. The fact that the rate constant of reaction (5), k_5, is little affected by the presence of acetate ions may also support a ligand-independent dissociative mechanism for (5).

The dissociation rate constants, k_{-5} and k_{-6}, were calculated from the forward reaction rates and the formation constants, which are compared with those for the reactions of L^1 in Table 7. The relatively faster dissociation rates for the L^2 system suggest that the 13-membered cyclic tetra-amine is more flexible than the 12-membered analogue, a trend which may link 12-membered cyclic and non-cyclic tetra-amine ligands.[17]

TABLE 7

Comparison of dissociation rate constants for L^1 and L^2 systems at 25 °C and $I = 0.20$ mol dm^{-3}

Ligand	log k_{-5}	Relative log k_{-5}	log k_{-6}	Relative log k_{-6}
L^2 [a]	−14.2	2.0 [b]	−9.9	3.6 [b]
L^1 [c]	−10.9	0	−8.2	0

[a] This work. [b] Relative $k_{-i} = \frac{(k_{-i})\ (\text{for } L^2)}{(k_{-i})\ (\text{for } L^1)} \cdot \frac{K_{CuL^1}}{K_{CuL^2}}$. [c] Refs. 2 and 3.

[5/2543 *Received, 30th December* 1975]

---

* 1 cal = 4.184 J.

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

[15] D. R. Stranks in ' Modern Coordination Chemistry,' eds. J. Lewis and R. G. Wilins, Interscience, New York, 1960; C. M. Frey and J. Stuehr in ' Metal Ions in Biological Systems,' ed. H. Sigel, Marcel Dekker, New York, 1974, vol. 1, p. 66.

[16] A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism,' 2nd edn., Wiley, New York, 1961, p. 145.

[17] D. B. Moss, C. Lin, and D. B. Rorabacher, *J. Amer. Chem. Soc.*, 1973, **95**, 5179 and refs. therein.