Effects of Cyclization and Ring Size on Complex Formation Between Penta-amine Ligands and Copper(II)

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Equilibria and kinetics of complex formation between Cu^{II} and the macrocyclic penta-amines 1,4,7,10,13-penta-azacyclopentadecane (L^1), 1,4,7,10,13-penta-azacyclohexadecane (L^2), and 1,4,7,11,14-penta-azacycloheptadecane (L^3) have been investigated. Thermodynamic functions for formation of the 1 : 1 complex have been determined polarographically: for L^1, L^2, and L^3, respectively, log K_{CuL} 28.3, 27.1, and 23.8, $-\Delta H$ 32.9, 32.7, and 27.2 kcal mol^{-1}, and ΔS 22, 14, and 18 cal K^{-1} mol^{-1} (at *I* 0.2 mol dm^{-3} and 25 °C). The large stability enhancements caused by the cyclization of penta-amines are due to a favourable enthalpy factor, in contrast to the entropy-favoured macrocyclic effects of tetra-amines. Kinetic studies have established the rate laws for the complex formation in acetate buffer as $d[CuL]/dt = k_{2H}[Cu(O_2CMe)^+][H_2L^{2+}] + k_{3H}[Cu(O_2CMe)^+][H_3L^{3+}]$, and in unbuffered acid solution as $d[CuL]/dt = k_{2H}'[Cu^{2+}][H_2L^{2+}] + k_{3H}'[Cu^{2+}][H_3L^{3+}]$. (The macrocyclic complexes formed are a mixture of $[CuL]^{2+}$ and $[Cu(HL)]^{3+}$ depending on the acidity.) The rate constant k_{2H}' for the diprotonated ligand species increases from 10^5 to 10^7 dm^3 mol^{-1} s^{-1} as the macrocyclic ring opens, approaching the value found for 3,6,9-triazaundecane-1,11-diamine (L^4). The rate constant k_{3H}' for the triprotonated species increases similarly from zero to 10^2 dm^3 mol^{-1} s^{-1}, although falling below the corresponding value for L^4. The presence of acetate anions as a buffer significantly accelerates the reactions involving proton-congested species. The implications for substitution reactions of protonated macrocyclic ligands are discussed.

As a continuation of our investigation into the cyclization effects of polyamine ligands on complex formation [1-8] we now present a study of the behaviour of cyclic penta-amines towards copper(II) ion. The ligands investigated, 1,4,7,10,13-penta-azacyclopentadecane (L^1), 1,4,7,10,13-penta-azacyclohexadecane (L^2), and 1,4,7,11,14-penta-azacycloheptadecane (L^3), comprise 15- to 17-membered ring macrocycles in which the size of the N_5 hole cavity and the conformational flexibility are gradually increased. The behaviour of the larger macrocycles was expected to be intermediate between that of a typical linear ligand 3,6,9-triazaundecane-1,11-diamine (L^4) and the least flexible macrocycle L^1. The study should provide more information on the effects of penta-amine cyclization on complex formation with Cu^{II}.

EXPERIMENTAL

The macrocyclic penta-amines L^1, L^2, and L^3 were synthesized from suitable linear tetra-amine tetrakis-(toluene-*p*-sulphonates) and *NN*-bis(2-bromoethyl)toluene-*p*-sulphonamide by methods used [9,10] in the preparation of a

[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, 1720.
[5] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 2335.
[6] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 2341.
[7] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1977, 1473.
[8] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1977, 2269.
[9] J. E. Richman and J. J. Atkins, *J. Amer. Chem. Soc.*, 1974, **96**, 2268.
[10] L. Y. Martin, L. J. DeHayes, L. J. Zompa, and D. H. Busch, *J. Amer. Chem. Soc.*, 1974, **96**, 4046.

related series of cyclic polyamine ligands: $L^1 \cdot 5HCl$ (recrystallized from an aqueous solution of 6N HCl and dried *in vacuo* at 50—60 °C) (Found: N, 17.1. Calc. for $C_{10}H_{25}N_5 \cdot 5HCl$: N, 17.6%; *m/e* 215); $L^2 \cdot 5HBr$ (recrystallized from acetic acid and dried *in vacuo* at 50—60 °C) (Found: N, 10.8. Calc. for $C_{11}H_{27}N_5 \cdot 5HBr$: N, 11.0%; *m/e* 229); and $L^3 \cdot 5HBr$ (recrystallized from $MeCO_2H$ and dried *in vacuo* at 50—60 °C) (Found: N, 10.1. Calc. for $C_{12}H_{29}N_5 \cdot 5HBr$: N, 10.7%; *m/e* 243). The preparation of other reagents and solutions was described previously.[2,4,6] The mixed ionization constants were determined by a pH-titration method, as for tetra-amines,[4,8] at 15, 25, and 35 °C (Table 1).

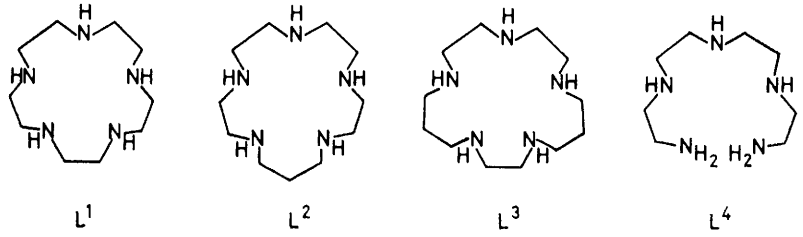

TABLE 1

Mixed ionization constants * of macrocyclic penta-amine ligands at I 0.20 mol dm^{-3} and several temperatures

Ligand	θ_c/°C	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}	pK_{a5}
L^1	15	11.07	9.81	6.22		
	25	10.85	9.65	6.00	1.74	1.16
	35	10.72	9.45	5.81		
L^2	15	10.86	9.71	7.50		
	25	10.64	9.49	7.28	1.71	1.45
	35	10.42	9.27	7.06		
L^3	15	10.55	9.85	7.58		
	25	10.32	9.62	7.36	4.10	2.38
	35	10.10	9.38	7.13		

* K_{ai} refers to the mixed ionization constant of $[H_iL]^{i+}$.

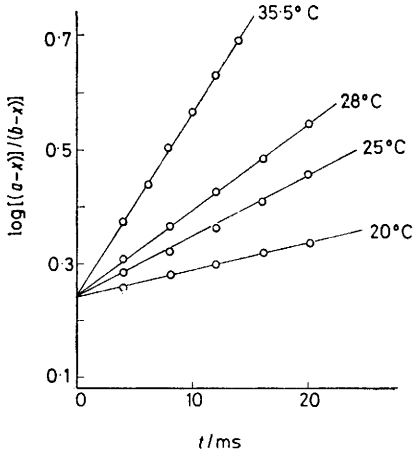

FIGURE 1 Second-order plots for the reaction of Cu^{II} with L^1. $[Cu]_0 = 5.00 \times 10^{-3}$, $[L^1]_0 = 0.35 \times 10^{-3}$, $[MeCO_2^-] = 0.10$ mol dm^{-3}, pH = 3.81, and $I = 0.20$ mol dm^{-3}

The polarographic techniques for the equilibrium studies were as used previously.[2,4,6] The kinetics of $[CuL]^{2+}$ complex formation in acetate buffers were studied by a stopped-flow method, using a Union Giken RA-401 stopped-flow spectrophotometer. The formation of the complex was followed at 585 (L^1), 560 (L^2), and 583 nm (L^3), where the 1 : 1 $[CuL]^{2+}$ complex (as polarographically established) has an absorption maximum. The apparent formation rate constants, k_f, were determined from gradients of linear second-order plots of $\log[(a - x)/(b - x)]$ against time, where a and b are, respectively, the initial concentrations of L and Cu^{II}, and x is the decrease in concentration of a reactant in a given time (Figure 1). The dissociation rates were neglected since the apparent equilibrium constant $[= K_{CuL}/(\alpha_H)_L\beta_{MeCO_2}]$ under the experimental conditions is calculated to be greater than 10^{13} (L^1), 10^{12} (L^2), and 10^8 dm^3 mol^{-1} (L^3) and addition of the $[CuL]^{2+}$ complex had no effect on the gradients of the second-order plots. The kinetics at lower pH (1.8—2.5, unbuffered) were determined polarographically by the initial-gradient method as described earlier.[4,7]

RESULTS

Equilibrium Study.—The copper complexes of L^1, L^2, and L^3 in valinate buffer solutions ($8.5 < pH < 10$) gave a well defined diffusion-controlled single wave at the dropping mercury electrode (d.m.e.). The polarographic behaviour of the complexes was unaffected by the valine concentration (0.05—0.2 mol dm^{-3}) indicating little formation of mixed-ligand complexes in this range. Plots of $\log [i/(i_d - i)]$ against d.c. potential, E, were linear for all the complexes and gave reciprocal gradients of −30 to −32 mV, which correspond to a reversible two-electron reduction at the d.m.e. The half-wave potential of the complexes, $(E_{\frac{1}{2}})_{CuL}$, shifted with changes in the ligand concentration and pH according to equation (1) (see Table 2) where $[L]_F =$

$$(E_{\frac{1}{2}})_{Cu} - (E_{\frac{1}{2}})_{CuL} = 0.0296\left\{\log \frac{K_{CuL}[L]_F}{(\alpha_H)_L} - \log \frac{(i_d)_{Cu}}{(i_d)_{CuL}}\right\} \quad (1)$$

concentration of uncomplexed L, protonated and unprotonated, [L] = concentration of unprotonated L, $(\alpha_H)_L$ is given by equation (2), and $\log [(i_d)_{Cu}/(i_d)_{CuL}]$ = log of the ratio of the diffusion-current constant for Cu^{2+} and CuL^{2+}

$$(\alpha_H)_L = \frac{[L]_F}{[L]} = 1 + \frac{[H^+]}{K_{a1}} + \frac{[H^+]^2}{K_{a1}K_{a2}} + \cdots\cdots\cdots + \frac{[H^+]^5}{K_{a1}K_{a2}K_{a3}K_{a4}K_{a5}} \quad (2)$$

(determined experimentally as 0.07 for L^1, L^2, and L^3). From relation (1) we obtained the complex stability constants, K_{CuL}, for L^1—L^3 at 15, 25, and 35 °C. The thermodynamic parameters were estimated from the linear relation between $\log K_{CuL}$ and T^{-1}. In the case of L^3, a small decrease in pH (*ca.* 0.03) was seen after the polarographic measurement (this is not the case with the other ligands). Using this final pH reading, slightly different K_{CuL} values were obtained at 15 and 35 °C. All the resulting data are summarized and compared with other polyamine complexes in Table 3.

TABLE 2

Effects of ligand, copper, and valine (or acetate) concentrations and pH on the half-wave potentials of macrocyclic penta-amine complexes of Cu^{II} at I 0.2 mol dm^{-3} and 25 °C

$10^3[L]_F$ / mol dm^{-3}	$10^3[Cu^{II}]$ / mol dm^{-3}	[Valine] / mol dm^{-3}	pH	$E_{\frac{1}{2}}$ / V *versus* s.c.e.	$\Delta E_{\frac{1}{2}}$/mV calc.*	$\Delta E_{\frac{1}{2}}$/mV obs.
L = L^1						
1.80	0.144	0.05	8.52	-0.623_0	0	0
3.60	0.144	0.05	8.52	-0.632_0	−8.9	$-9._0$
5.40	0.144	0.05	8.52	-0.640_3	−17.8	$-17._3$
3.60	0.072	0.05	8.52	-0.622_7		
3.60	0.288	0.05	8.52	-0.622_3		
1.80	0.144	0.10	8.52	-0.623_0		
1.80	0.144	0.20	8.52	-0.622_3		
1.80	0.144	0.05	9.06	-0.648_5	−26.0	$-25._5$
1.80	0.144	0.05	9.51	-0.678_5	−58.4	$-55._5$
1.80	0.144	0.05	9.96	-0.701_0	−82.5	$-78._0$
L = L^2						
1.0	0.10	0.20	9.52	-0.640_1	0	0
2.0	0.10	0.20	9.52	-0.649_1	8.9	$9._0$
4.0	0.10	0.20	9.52	-0.656_6	17.8	$16._5$
8.0	0.10	0.20	9.52	-0.667_6	26.7	$27._5$
10.0	0.10	0.20	9.52	-0.671_1	29.6	$31._0$
8.0	0.30	0.20	9.52	-0.668_0		
8.0	0.60	0.20	9.52	-0.667_2		
2.0	0.10	0.05	9.52	-0.650_0		
2.0	0.10	0.10	9.52	-0.649_5		
2.0	0.10	0.05	8.38	-0.590_0	59.2	$59._1$
2.0	0.10	0.05	8.90	-0.617_9	30.3	$31._2$
2.0	0.10	0.05	9.52	-0.649_1	0	0
2.0	0.10	0.05	10.11	-0.670_7	−20.4	−21.5
L = L^3						
1.9	0.20	0.06	9.00	-0.532_9	8.9	$9._0$
3.8	0.20	0.06	9.00	-0.541_9	0	0
5.7	0.20	0.06	9.00	-0.551_0	−8.9	$-9._1$
9.5	0.20	0.06	9.00	-0.553_9	−11.8	$-12._0$
15.2	0.20	0.06	9.00	-0.559_5	−17.8	$-17._6$
5.7	0.10	0.06	9.00	-0.551_1		
5.7	0.30	0.06	9.00	-0.551_2		
5.7	0.50	0.06	9.00	-0.550_9		
3.8	0.20	0.03	9.00	-0.542_0		
3.8	0.20	0.12	9.00	-0.541_5		
3.8	0.20	0.20	9.00	-0.542_1		
3.8	0.20	0.06	8.40	-0.494_8	30.5	$31._0$
3.8	0.20	0.06	8.68	-0.525_8	0	0
3.8	0.20	0.06	9.00	-0.541_9	−16.7	$-16._1$
3.8	0.20	0.06	9.56	-0.574_0	−45.0	$-48._2$
3.8	0.20	0.06	10.01	-0.593_3	−61.0	$-67._5$
L = L^1		[$MeCO_2^-$]				
1.56	0.12	0.10	4.21	-0.329_5	101.6	$87._5$
1.56	0.12	0.10	4.46	-0.344_0	79.4	$73._0$
1.56	0.12	0.10	4.57	-0.351_1	69.7	$65._9$
1.56	0.12	0.10	4.90	-0.376_2	40.9	$40._8$
1.56	0.12	0.10	5.38	-0.417_0	0	0
L = L^3		[$MeCO_2^-$]				
2.14	0.20	0.20	4.60	-0.199_2	0	0
2.14	0.20	0.20	4.25	-0.179_0	35.0	$20._0$
2.14	0.20	0.20	4.02	-0.149_0	58.7	$50._2$
2.14	0.20	0.20	3.86	-0.135_0	75.7	$64._2$

* Using equation (1) (in valine buffer) or (3) (in acetate buffer).

In acetate buffers the copper complexes of L^1 and L^3 gave reversible polarograms, while that of L^2 gave an irreversible polarogram; *i.e.* plots of $\log [i/(i_d - i)]$ against E afforded a reciprocal gradient of −50 mV. The polarograms of the complexes of L^1 and L^3 were unaffected by the acetate concentration (0.03—0.2 mol dm^{-3}), indicating no mixed-ligand complex with acetate ion. The variation of $(E_{\frac{1}{2}})_{CuL}$ with changes in ligand concentration and pH conforms to equation (3) (see Table 2), where K_{aCuHL} refers to the

$$(E_{\frac{1}{2}})_{Cu} - (E_{\frac{1}{2}})_{CuL} = 0.0296\left\{\log \frac{K_{CuL}(K_{aCuHL} + [H^+])}{K_{aCuHL}} + \log \frac{[L]_F}{(\alpha_H)_L} - \log \frac{(i_d)_{Cu}}{(i_d)_{CuL}}\right\} \quad (3)$$

ionization $[Cu(HL)]^{3+} \rightleftharpoons [CuL]^{2+} + H^+$. This indicates that the electrode reaction mechanism is as in equation (4).[11,12] For the complex of L^1, the plots in Figure 2 give

$$\begin{array}{ccc} [CuL]^{2+} & & L \\ \Big\Uparrow\Big\Downarrow & + 2e^- + Hg \rightleftharpoons Cu(Hg) + & \Big\Uparrow\Big\Downarrow \\ [Cu(HL)]^{3+} & & [HL]^+ \end{array} \quad (4)$$

log $K_{CuL} = 28.3$ (from intercept) and $K_{aCuHL} = 4.6 \times 10^{-5}$ mol dm^{-3} (from intercept/gradient). Similar plots for

[11] M. Kodama and Y. Tominaga, *Bull. Chem. Soc. Japan*, 1969, **42**, 394.

[12] M. Kodama and Y. Tominaga, *Bull. Chem. Soc. Japan*, 1969, **42**, 724.

the L^3 complex give log $K_{CuL} = 23.9$ and $K_{aCuHL} = 2.0 \times 10^{-5}$ mol dm^{-3}. The agreement between the K_{CuL} values derived under alkaline and acidic conditions is thus excellent. The K_{aCuHL} value for the complex L^2 is predicted to be $>10^{-5}$ mol dm^{-3}, although the irreversible polarograms prevented an exact determination.

TABLE 3

Comparison of stability constants, enthalpies, and entropies of copper(II)–polyamine complex formation at I 0.2 mol dm^{-3} and 25 °C

Ligand	log K_{CuL}	$-\Delta H$ / kcal mol^{-1}	ΔS / cal K^{-1} mol^{-1}
L^1 [a]	28.3 ± 0.2	32.9 ± 0.3	22 ± 2
L^2 [a]	27.1 ± 0.2	32.7 ± 0.3	14 ± 2
L^3 [a]	23.8 ± 0.2	27.2 ± 0.3	18 ± 2
	(23.8 ± 0.2) [b]	(28.8 ± 0.3)	(12 ± 2)
L^4 [c]	22.8	25.0	20.5
L^5 [d]	24.8	18.3	51.4
L^6 [e]	20.2	21.6	19.5

[a] This work. Uncertainties are the standard deviations. 1 cal = 4.184 J. [b] pH change accounted for (see text). [c] Ref. 14, $I = 0.1$ mol dm^{-3}. [d] Refs. 1 and 2. L^5 = 1,4,7,10-Tetra-azacyclododecane. [e] L. Sacconi, P. Paoletti, and M. Ciampolini, *J. Chem. Soc.*, 1961, 5115. $I = 0.1$ mol dm^{-3}. L^6 = 3,6-Diazaoctane-1,8-diamine.

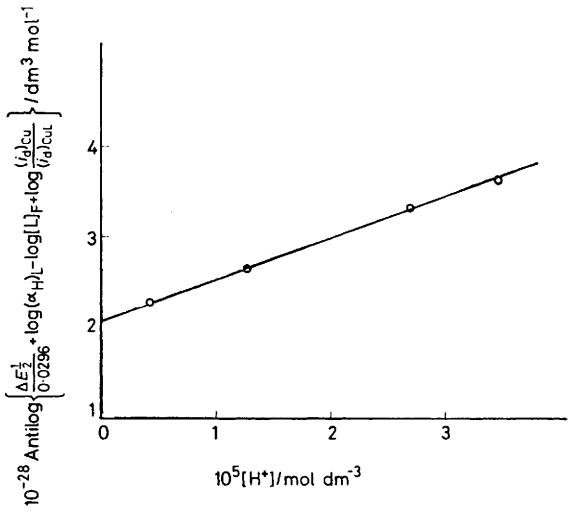

FIGURE 2 Determination of K_{CuL} and K_{aCuHL} for L^1. Plot of equation (3) at $[Cu^{II}] = 0.12 \times 10^{-3}$, $[L^1]_H = 1.56 \times 10^{-3}$, $[MeCO_2^-] = 0.10$ mol dm^{-3}, $I = 0.20$ mol dm^{-3}, and 25 °C

TABLE 4

Experimental rate data for copper(II)-macrocyclic penta-amine complex formation at I 0.20 mol dm^{-3} and 25 °C

$10^3[L]_0$ / mol dm^{-3}	$10^3[Cu]_0$ / mol dm^{-3}	$[MeCO_2^-]$ / mol dm^{-3}	$10^{-2}k_f$ / dm^3 mol^{-1} s^{-1}	$k_f\beta_{MeCO_2}/K_{Cu(O_2CMe)}[MeCO_2^-]$ / dm^3 mol^{-1} s^{-1}
L = L^1 (pH 4.11)				
8.35	7.50	0.10	140	
8.35	5.00	0.10	140	1.6×10^4
8.35	2.50	0.10	130	
12.53	5.00	0.10	140	
8.35	5.00	0.05	120	1.6×10^4
8.35	5.00	0.20	150	1.6×10^4
L = L^2 (pH 4.11)				
4.0	2.0	0.05	5.2	
4.0	3.0	0.05	5.3	7.7×10^2
5.0	2.0	0.05	5.3	
5.0	3.0	0.05	5.3	
8.0	4.0	0.05	5.3	
10.0	5.0	0.05	5.3	
4.0	3.0	0.025	4.3	7.7×10^2
4.0	3.0	0.075	5.5	7.7×10^2
4.0	3.0	0.10	5.7	7.8×10^2
L = L^3 (pH 4.05)				
4.0	2.0	0.05	39	
4.0	3.0	0.05	39	5.6×10^3
6.0	3.0	0.05	39	
8.0	3.0	0.05	38	
8.0	4.0	0.05	39	
4.0	3.0	0.025	32	5.8×10^3
4.0	3.0	0.075	40	5.6×10^3
4.0	3.0	0.10	41	5.6×10^3

Kinetic Study.—The reaction of Cu^{II} with L was second order in the presence of acetate buffers. The polyamine L is rapidly protonated in the pH region investigated (*ca.* 3.5 < pH < *ca.* 4.5) to $[HL]^+$, $[H_2L]^{2+}$, $[H_3L]^{3+}$, *etc.*, and the Cu^{II} is present as Cu^{2+}(aq), $[Cu(O_2CMe)]^+$, and $[Cu(O_2CMe)_2]$ in a rapid equilibrium.[13] The fact that at a given pH, the observed rate constant, k_f, is proportional to $K_{Cu(O_2CMe)}[O_2CMe^-]/\beta_{MeCO_2}$ (see Table 4) indicates that $[Cu(O_2CMe)]^+$ is the reactive species of Cu^{II}. Expressions (5) and (6) are applicable. Assuming that the protonated forms of L react with $[Cu(O_2CMe)]^+$, it can be easily shown that the rate law is as in (7) where k_{iH} is the rate constant

$$\beta_{MeCO_2} = [Cu^{2+}]_F/[Cu^{2+}(aq)] = 1 + K_{Cu(O_2CMe)}[MeCO_2^-] + K_{Cu(O_2CMe)}K_{Cu(O_2CMe)_2}[MeCO_2^-]^2 \quad (5)$$

$$[Cu^{2+}]_F = [Cu^{2+}(aq)^+] + [Cu(O_2CMe)^+] + [Cu(O_2CMe)_2] \quad (6)$$

$$\text{Rate} = k_f[Cu^{2+}]_F[L]_F = k_{1H}[HL^+][Cu(O_2CMe)^+] + k_{2H}[H_2L^{2+}][Cu(O_2CMe)^+] + k_{3H}[H_3L^{3+}][Cu(O_2CMe)^+], \text{ etc.}$$

$$= \frac{K_{Cu(O_2CMe)}[MeCO_2^-]}{\beta_{MeCO_2}(\alpha_H)_L} \times \left(\frac{k_{1H}[H^+]}{K_{a1}} + \frac{k_{2H}[H^+]^2}{K_{a1}K_{a2}} + \frac{k_{3H}[H^+]^3}{K_{a1}K_{a2}K_{a3}}, \text{ etc.}\right)[Cu^{2+}]_F[L]_F \quad (7)$$

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

for the ith protonated species. Hence, by examining the variation of k_f with pH at a given $[MeCO_2^-]$ it is possible to assess the contributions of the various protonated forms of the ligand to the rate. Plots of $k_f(\alpha_H)_L/[H^+]$ against $[H^+]$ for L^1 were linear passing through the origin (Figure 3, inclusive of a constant β term), indicating that the di-protonated form is the reactive species of L^1. Plots of $k_f(\alpha_H)_L/[H^+]^2$ against $[H^+]$ for L^2 (Figure 4) and L^3 were linear with finite intercepts, indicating the participation of di- and tri-protonated ligand species. The resolved rate constants were thus determined graphically.

The reactions in acid solutions ($1.8 < pH < 2.5$, unbuffered) were similarly treated and were found to follow the common rate equation (8). The rate constants for the

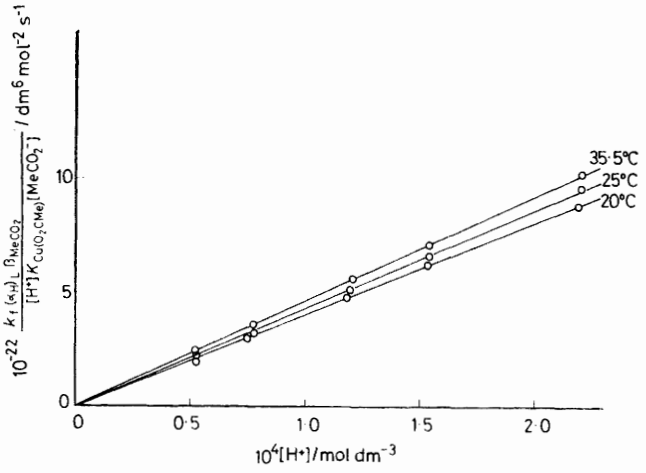

FIGURE 3 Plot of $10^{-22}k_f(\alpha_H)_L\beta_{MeCO_2}([H^+][MeCO_2^-]K_{Cu(O_2CMe)})^{-1}$ against $10^4[H^+]$ for reaction of Cu^{2+} with L^1 in acetate buffer. $[Cu^{2+}]_0 = 5.0 \times 10^{-3}$, $[L^1]_0 = 8.35 \times 10^{-3}$, $[MeCO_2^-] = 0.10$ mol dm^{-3}, and I 0.2 mol dm^{-3}

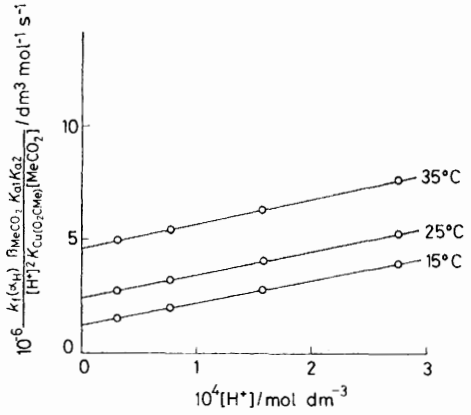

FIGURE 4 Plot of $10^{-6}k_f(\alpha_H)_L\beta_{MeCO_2}([H^+]^2[MeCO_2^-]K_{Cu(O_2CMe)})^{-1}K_{a1}K_{a2}$ against $10^4[H^+]$ for reaction of Cu^{2+} with L^2 in acetate buffer. $[Cu^{2+}]_0 = 4.0 \times 10^{-3}$, $[L^2]_0 = 3.0 \times 10^{-3}$, $[MeCO_2^-] = 0.05$ mol dm^{-3}, and I 0.2 mol dm^{-3}

reaction of $Cu^{2+}(aq)$ with $[H_2L]^{2+}$ (k_{2H}') and $[H_3L]^{3+}$ (k_{3H}') were estimated graphically. Typical plots for L^3 are shown in Figure 5.

$$k_f(\alpha_H)_L = \frac{k_{2H}'[H^+]^2}{K_{a1}K_{a2}} + \frac{k_{3H}'[H^+]^3}{K_{a1}K_{a2}K_{a3}} \quad (8)$$

The activation parameters for the reactions in acetate buffers were estimated from Arrhenius plots. All the results are summarized in Table 5.

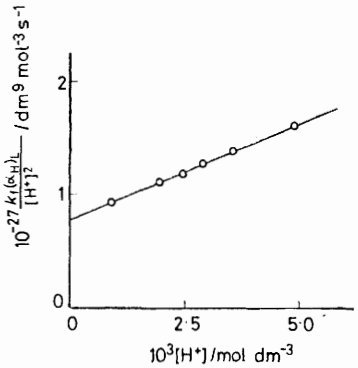

FIGURE 5 Plot of $10^{-27}k_f(\alpha_H)_L/[H^+]^2$ against $10^3[H^+]$ for the reaction of L^3 in unbuffered solution. $[Cu^{2+}]_0 = 0.2 \times 10^{-3}$, $[L^3]_0 = 0.346 \times 10^{-3}$ mol dm^{-3}, and I 0.2 mol dm^{-3}

TABLE 5

Summary of rate constants and associated activation parameters for copper(II)-macrocyclic penta-amine complex formation at I 0.2 mol dm^{-3} and 25 °C

Rate constant (dm³ mol⁻¹ s⁻¹)	$\Delta H^\ddagger$ (kcal mol⁻¹)	$\Delta S^\ddagger$ (cal K⁻¹ mol⁻¹)
L = L^1		
$k_{2H} = (1.4 \pm 0.2) \times 10^6$	13.0 ± 0.3	13 ± 1
$k_{2H}' = (9.7 \pm 0.2) \times 10^4$		
L = L^2		
$k_{2H} = (2.4 \pm 0.2) \times 10^6$	10.9 ± 0.3	7 ± 1
$k_{3H} = (5.6 \pm 0.2) \times 10^2$	9.4 ± 0.3	−14 ± 1
$k_{2H}' = (3.1 \pm 0.2) \times 10^6$		
$k_{3H}' = ca.\ 1$ *		
L = L^3		
$k_{2H} = (4.9 \pm 0.2) \times 10^6$	10.0 ± 0.3	5 ± 1
$k_{3H} = (8.7 \pm 0.2) \times 10^3$	7.3 ± 0.3	−15 ± 1
$k_{2H}' = (8.6 \pm 0.2) \times 10^6$		
$k_{3H}' = (8.1 \pm 0.2) \times 10$		

* Cannot be measured accurately.

DISCUSSION

Equilibrium Study.—A glance at the pK_a values of L^1—L^3 (Table 1) and of L^4 [9.68, 9.10, 8.08, 4.72, and 2.98;[14] 10.36, 9.65, 8.50, 4.70, and 2.40 (ref. 15)] immediately shows the effects of ligand cyclization. Considering L^1 as a typical example of the macrocycles, the first nitrogen atom is rendered more basic, while the last three nitrogens become less basic. The first trend is due to favourable hydrogen bonding stabilizing the conjugate acid in the cavity surrounded by nitrogen lone pairs. The latter trend is due to the close proximity of the N^+H groups to each other thus destabilizing the conjugate acid. Similar trends in the nitrogen basicities occur in macrocyclic tetra-[4,6] and tri-amines.[16] These cyclization effects diminish with ring expansion to those of 16 and 17 members. Thus, the pK_a values of L^3 are closest to those of L^4. It was expected that, among the macrocyclic penta-amines, L^1 would behave least and L^3 most like L^4 towards metal ions.

[14] P. Paoletti and A. Vacca, *J. Chem. Soc.*, 1964, 5051.
[15] D. B. Moss, C. Lin, and D. B. Rorabacher, *J. Amer. Chem. Soc.*, 1973, **95**, 5179.
[16] R. Yang and L. J. Zompa, *Inorg. Chem.*, 1976, **15**, 1499.

The macrocyclic penta-amines co-ordinate to Cu^{II}, most likely with four nitrogen atoms in the quadratic equatorial plane and one nitrogen at an axial position, to form stable 1 : 1 complexes in valinate buffers. However, one of the nitrogen atoms (*e.g.* the axial N) will be bound less tightly, favouring protonation in acetate buffers. Protonation of the complexes containing tetra- and tri-amine macrocycles does not occur, except for a 15-membered tetra-amine having a large ring cavity.[6] Amongst complexes of macrocyclic and linear penta-amines, there is no significant difference between the first pK_{aCuHL} value (4.3 for L^1 and 4.7 for L^3 as against 5.2 for L^4),[14] but a characteristic of the macrocyclic complexes is the absence of additional protonation under the same buffered conditions (*cf.* the second pK_a of 3.8 for L^4).[14]

Of the penta-amine macrocycles, L^1 forms the most stable complex with Cu^{II}, followed by L^2 and L^3. The entropy term for complex formation neither varies significantly with the ring size nor contributes much to the stability of each complex, which is in contrast to the corresponding macrocyclic tetra-amine series.[2,4,6,7] For complexes of macrocyclic tetra-amines, values of $-\Delta H$ vary depending on the ring size, and this has been rationalized in terms of the matching of the ring cavity to the metal ion (*i.e.* the Cu–N bond strength), as supported by a linear correlation with the *d–d* electronic spectrum.[7,17,18] It is uncertain whether a similar argument can be applied to the variation in enthalpy values of the penta-amine complexes since the correlation with the *d–d* band is not linear: $\nu(d\text{–}d)$ at 17 100, 17 800, and 17 100 cm^{-1} for L^1, L^2, and L^3, respectively.

The complexes of macrocycles L^1 and L^2 are 10^4—10^5 times more stable than the related (complex of) linear L^4.[14] A comparable stability enhancement by the ligand cyclization (' macrocyclic effect ') [19] was observed for tetra-amines.[2,4] However, the cause of the macrocyclic effect is dramatically different for the penta-amines and tetra-amines. For the former, it is the enthalpy term, and for the latter it is the entropy term (although the contribution of the ΔH term is not insignificant with large rings). At present we cannot specify the reason(s) why the ΔH term plays such an important role in the penta-amine macrocyclic effect. It is of interest that L^3, having the most similar nitrogen basicities among the macrocyclic penta-amines to L^4, also shows the most similar K_{CuL} and ΔH values.

Kinetic Study of the Macrocyclic Complex Formation.—The general rate expressions for macrocyclic penta-amine complex formation are rate $= k_{2H}[Cu(O_2CMe)^+][H_2L^{2+}] + k_{3H}[Cu(O_2CMe)^+][H_3L^{3+}]$ (in acetate buffer) and $k_{2H}'[Cu^{2+}(aq)][H_2L^{2+}] + k_{3H}'[Cu^{2+}(aq)][H_3L^{3+}]$ (in unbuffered acid solution). However, rate terms can also be formulated in terms of the different reactants, *e.g.* that involving $[Cu(O_2CMe)]^+$ or $Cu^{2+}(aq)$ and $[H_2L]^{2+}$ can also be expressed in terms of $[Cu(O_2CMe)(OH)]$ or $[Cu(OH)]^+$ reacting with $[H_3L]^{3+}$. Since the pK_a of Cu^{II} is *ca.* 8 {the pK_a of $[Cu(O_2CMe)]^+$ would be larger}, the kinetic contribution of the hydroxo-species appears to be significant only at pH values greater than those investigated. Although these and some other possible combinations are not totally discarded, the following discussion is based exclusively on the above formulations.

A major reactive species of the penta-amine ligands is found to be the diprotonated form $[H_2L]^{2+}$ at $1.8 < pH < 4.5$ where species having greater degrees of protonation are more abundant. Some analogies may be drawn between the reactions of tetra- and tri-amine macrocycles, in which the monoprotonated species is the major reactant despite diprotonated species being more abundant at *ca.* $2 < pH <$ *ca.* 5.[2,4,6,7] Particularly noteworthy in the present kinetic results is the fact that, as the ring expands, the contribution of the triprotonated reactant becomes increasingly significant, accompanying an increase in the rate constant for the diprotonated ligands: the rate constants for the reaction of $Cu^{2+}(aq)$ with $[H_3L]^{3+}$ for L^1, L^2, and L^3, respectively, are 0, *ca.* 1, and $10^{1.9}$, and those with $[H_2L]^{2+}$ are $10^{5.0}$, $10^{6.5}$, and $10^{6.9}$ dm^3 mol^{-1} s^{-1}. The effects of the ring expansion on the kinetics are not so pronounced in the tetra-amine system, except for one 15-membered ligand which exhibited faster complex formation than 12- to 14-membered analogues.[6,7] Moreover, a comparison of the rate constants with the linear L^4 (values for log k_{2H}', k_{3H}', and k_{4H}' respectively, are 7.6, 5.2, and 4.1 dm^3 mol^{-1} s^{-1} at I 0.1 mol dm^{-3} and 25 °C) [20] suggests that as the ring size increases the macrocycle tends to behave kinetically more like a linear ligand.

The reactions of the various protonated forms of L^4 with Cu^{II} are generally supposed to occur *via* a normal dissociative mechanism.[15,20] The dissociative mechanism might govern the reactions of fewer protonated species of larger macrocyclic penta-amines, whose rate constants, as a result, are nearly comparable to that for L^4 species. For the reactions of monoprotonated macrocyclic tetra-amines with several bivalent metal ions such as Cu^{II}, Zn^{II}, Pb^{II}, or Cd^{II} we proposed dissociative mechanisms based mainly on the close parallel of the rate constants for complex formation and those for the water-exchange reaction.[4,6–8] As the ring size becomes smaller or the number of protons attached to the penta-amine increases, the conformational flexibility or the influence of the protons would become more pronounced, resulting in unusually slow rates or no kinetic contribution of these species. An example is the rate-determining proton loss from protonated species, proposed for the reaction of Cu^{II} with diprotonated macrocyclic tetra-amines.[4,6,7]

The effects of acetate anions gives further mechanistic information. For macrocyclic tetra-amines the acetate anion {also in the form of $[Cu(O_2CMe)]^+$} has little effect

[17] L. Fabbrizzi, P. Paoletti, and A. B. P. Lever, *Inorg. Chem.*, 1976, **15**, 1502.
[18] A. Anichini, L. Fabbrizzi, and P. Paoletti, *J.C.S. Chem. Comm.*, 1977, 244.
[19] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540.
[20] R. E. Shepherd, G. M. Hodgson, and D. W. Margerum, *Inorg. Chem.*, 1971, **10**, 989.

on the reactions of the monoprotonated ligands, suggesting that dissociation of acetate ions is not involved in the rate-limiting step.[4,7] The same observation may be made for the diprotonated penta-amine species. The ligand L^1, where k_{2H} is 10 times k_{2H}', is exceptional. For the reaction of $[H_3L]^{3+}$ species, the presence of acetate anions enhances the rate by factors of 2—3. A similar accelerating effect of $[MeCO_2]^-$ occurs with diprotonated tetra-amine macrocycles.[4,7] The Lewis base may help to remove H^+ from the highly proton-congested reactive centre, thus facilitating the metal–amine interaction.

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