Kinetics of Replacement of Aminocarboxylates by Macrocyclic Polyamines in Copper(II) Complexes

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The rate constants have been determined for the reaction of macrocyclic polyamine ligands and their protonated forms with [Cu(ida)], [Cu(nta)]$^-$, [Cu(hedta)]$^-$, and [Cu(edta)]$^{2-}$ [ida = iminodiacetate, nta = nitrilotriacetate, hedta = *N*-(2-hydroxyethyl)ethylenediamine-*NN'N'*-triacetate, and edta = ethylenediaminetetra-acetate]. The macrocyclic ligands include 1,4,7,10-tetra-azacyclotridecane, 1,4,8,12-tetra-azacyclopentadecane, and 1,4,7,10,13-penta-azacyclopentadecane. These ligand-displacement reactions demonstrate the effects of protonation of macrocyclic polyamines having different ring sizes and denticities. The formation of the macrocyclic complex from [Cu(ida)] or [Cu(nta)] occurs as fast as (or sometimes even faster) from Cu^{2+}(aq), despite the fact that the former reactions require the replacement of strongly co-ordinated aminocarboxylate ligands. The reaction rates for the unprotonated or protonated macrocycles are inversely dependent on the stability constants of the aminocarboxylate complexes, suggesting that the rate-determining step is rupture of the ida segment of an aminocarboxylate from copper. Compared with the same replacement reactions with corresponding linear polyamines, the rate constants are consistently 10^3—10^4 times smaller, indicating a close parallel in the two reaction mechanisms.

In order to obtain a better understanding of reactions of macrocyclic polyamines with metal ions, we have examined the ligand–ligand replacement kinetics for reaction (1), where X = an aminocarboxylate ligand and L = a macrocyclic polyamine. (The degree of protonation is not indicated.) Table 1 shows the ligands studied and their abbreviations.

It is recognized that for reactions (1) where L = a linear polyamine such as 3,6-diazaoctane-1,8-diamine (L^4) or 3,6,9-triazaundecane-1,11-diamine (L^5) there are two distinct mechanisms: when X = H_2O,[1-3] the rate-determining step is dissociation of the inner-sphere water molecules ('normal' dissociative mechanism); and when X = aminocarboxylate such as nta, hedta, or

$$[CuX]^{(2-z)+} + L \xrightarrow{k} [CuL]^{2+} + X^{z-} \qquad (1)$$

edta [1,4] the transition state involves dissociation of the last aminocarboxylate nitrogen from the intermediate complex containing the partially co-ordinated polyamine ligand (ligand-exchange mechanism).

Earlier studies of the formation of macrocyclic polyamine complexes from Cu^{2+}(aq) or $[Cu(O_2CMe)]^+$ and a

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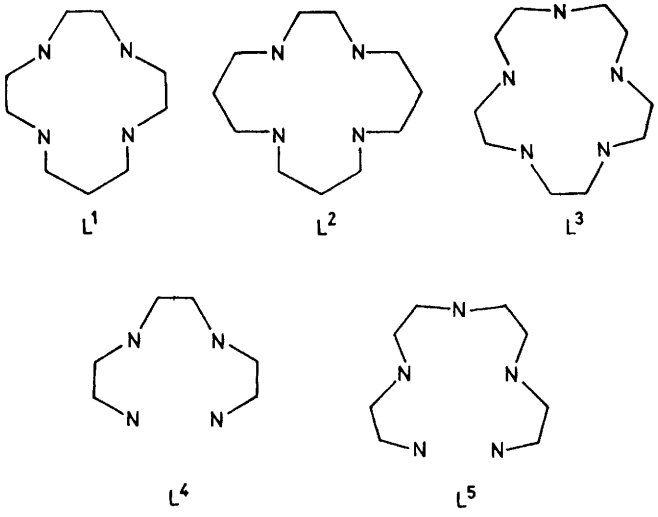
monoprotonated tetra-amine [5-16] or diprotonated penta-amine [17] showed that the reaction rates (which are the same in the presence or absence of acetate ion) are several orders slower than would be anticipated from a normal dissociative mechanism. However, the close parallel of the rate constants for the complex formation and those of water exchange for bivalent metal ions, Cu^{II}, Zn^{II}, Ni^{II}, Pb^{II}, Cd^{II}, *etc.*,[10-14] led us to propose a kind of dissociative mechanism wherein the rate deceleration may be explained by smaller values of K_0 and/or k_0 * presumably due to steric effects and conformational rigidity. Upon increased protonation of the ligand the formation of the macrocyclic complexes is drastically slowed; this cannot be explained by only electrostatic effects.[6-10] It was thought that the macrocyclic structure makes proton removal preceding metal–nitrogen interaction extremely difficult, resulting in a shift of the rate-determining step to the deprotonation stage.

TABLE 1

Ligands and their equilibrium constants * at I = 0.2 mol dm^{-3} and 25 °C

Ligand	Abbreviation	log K_{CuL} (log K_{CuL_2})	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}	pK_{a5}
Iminodiacetic acid	H_2ida	10.31 (5.65)	9.27	2.62			
Nitrilotriacetic acid	H_3nta	12.38 (3.50)	9.64	2.38	1.86		
N-(2-Hydroxyethyl)ethylenediamine-*NN'N'*-triacetic acid	H_3hedta	17.15	9.74	5.26	2.35		
Ethylenediaminetetra-acetic acid	H_4edta	18.2	9.80	6.12	2.56	1.96	
1,4,7,10-Tetra-azacyclotridecane	L^1	29.1	11.10	10.10	1.7	1.0	
1,4,8,12-Tetra-azacyclopentadecane	L^2	24.4	11.20	10.10	2>	2>	
1,4,7,10,13-Penta-azacyclopentadecane	L^3	28.3	10.85	9.65	6.00	1.74	1.16
3,6-Diazaoctane-1,8-diamine	L^4	20.4	10.09	9.31	6.75	3.39	
3,6,9-Triazaundecane-1,11-diamine	L^5	22.8	9.68	9.10	8.08	4.72	2.98

* Constants were taken from ' Stability Constants of Metal–Ion Complexes.' eds. L. G. Sillén and A. E. Martell, *Special Publ.*, The Chemical Society, London, 1964, No. 17. Values for L^1, L^2, and L^3 are from refs. 7, 8, and 17, respectively, for L^4 (I 0.1 mol dm^{-3}) from ref. 2, and for L^5 (I 0.1 mol dm^{-3}) from P. Paoletti and A. Vacca, *J. Chem. Soc.*, 1964, 5051.



Since restriction of conformational freedom would be more pronounced in the later stages of the polyamine chelation, it is of particular interest to see how the macrocyclic ligands affect the ligand-exchange mechanism, *i.e.* the final stage of the complex formation. We also hoped that use of the aminocarboxylates, by providing the metal with various charges that are opposite in sign to that of the protonated L, would help us to assess the effects of protonation on macrocyclic complex formation.[18]

EXPERIMENTAL

All of the aminocarboxylate ligands were highest quality commercial products. The macrocyclic ligands were prepared as described before: L^1,[7] L^2,[8] and L^3.[17] Table 1 summarizes the stability constants of their copper complexes, K_{CuL} and K_{CuL_2}, and the logarithms of the ionization constants, pK_a, together with those for L^4 and L^5. Copper(II) nitrate solution was prepared as previously described.[6] Other reagents were of analytical reagent grade and were used without further purification.

The displacements of ida (at acid pH) from its copper complex [Cu(ida)] were followed polarographically by measuring the decrease in the height of the wave due to the starting complex. All the other kinetic runs were followed by stopped-flow spectrophotometry employing a 0.20-cm pathlength and a Union Giken RA-401 spectrophotometer. The exchange reactions were followed by measuring the increase in absorbance due to the formation of the $[CuL]^{2+}$

* On the basis of the equation $k = K_0k_0$, where K_0 is the outer-sphere association constant and k_0 is the rate constant for breakdown of the outer-sphere complex to give an inner-sphere complex (M. Eigen and K. Tamm, *Z. Electrochem.*, 1962, **66**, 107).

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[17] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1978, 104.
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TABLE 2

Kinetic data for aminocarboxylate ligand-exchange reactions with macrocyclic polyamines on Cu^{II} at $I = 0.20$ mol dm^{-3} and 25 °C

$10^3[Cu^{II}]_T$	$10^3[X]_F$	$10^3[L]_T$	$[MeCO_2^-]$	pH	k	$k(1 + \{K_{CuX_2}[X]_F/(\alpha_H)_X\})$
	mol dm^{-3}				$dm^3\ mol^{-1}\ s^{-1}$	
	ida	L^1				
4.0	28	4.62		8.96	3.9×10^2	1.6×10^6
4.0	44	4.62		8.96	2.4×10^2	1.6×10^6
4.0	52	4.62		8.96	2.1×10^2	1.6×10^6
4.0	60	4.62		8.96	1.8×10^2	1.6×10^6
2.0	52	4.62		8.96	2.0×10^2	1.6×10^6
4.0	52	9.23		8.96	2.0×10^2	
8.0	52	9.23		8.96	2.1×10^2	
3.0	120	5.35	0.025	5.26	28	
3.0	120	5.35	0.05	5.26	28	
3.0	120	5.35	0.075	5.26	29	
3.0	120	5.35	0.10	5.26	28	
3.0	30	5.35	0.10	5.26	74	1.7×10^2
3.0	60	5.35	0.10	5.26	48	1.8×10^2
3.0	120	5.35	0.10	5.26	28	1.7×10^2
	nta	L^1				
4.0	23	4.62		9.63	3.5×10^3	1.3×10^5
4.0	46	4.62		9.63	1.8×10^3	1.3×10^5
4.0	69	4.62		9.63	1.2×10^3	1.3×10^5
2.0	46	4.62		9.63	1.8×10^3	
4.0	46	9.24		9.63	1.7×10^3	
4.0	10	5.0	0.025	5.25	3.4	
4.0	10	5.0	0.05	5.25	3.3	
4.0	10	5.0	0.10	5.25	3.3	3.3
4.0	10	5.0	0.20	5.25	3.3	
4.0	20	5.0	0.10	5.25	3.3	3.3
4.0	40	5.0	0.10	5.25	3.2	3.3
4.0	60	5.0	0.10	5.25	3.3	3.3
	hedta	L^1				
2.0	13	3.0		9.59	47	
2.0	26	3.0		9.59	46	
2.0	39	3.0		9.59	49	
2.0	26	6.0		9.59	44	
4.0	26	6.0		9.59	48	
4.0	26	10.0		9.59	46	
2.0	26	3.0		6.06	0.027	
2.0	52	3.0		6.06	0.028	
2.0	26	9.0		6.06	0.027	
4.0	26	9.0		6.06	0.027	
	edta	L^1				
4.0	10	5.0	0.05 [a]	9.66	5.0	
4.0	20	5.0	0.05 [a]	9.66	5.1	
4.0	40	5.0	0.05 [a]	9.66	5.0	
4.0	40	5.0	0.025 [a]	9.66	5.0	
2.0	20	5.0	0.05 [a]	9.66	5.2	
4.0	20	10.0	0.05 [a]	9.66	5.2	
4.0	20	5.0	0.04 [b]	7.53	0.012	
4.0	20	5.0	0.08 [b]	7.53	0.012	
4.0	40	5.0	0.04 [b]	7.53	0.013	
4.0	40	10.0	0.04 [b]	7.53	0.012	
2.0	40	5.0	0.04 [b]	7.53	0.012	
	edta	L^2				
4.0	25	5.0		10.34	5.5	
4.0	37.5	5.0		10.34	5.3	
4.0	50	5.0		10.34	5.5	
2.0	25	5.0		10.34	5.6	
6.0	25	10.0		10.34	5.5	
4.0	25	5.0		6.80	0.054	
4.0	37.5	5.0		6.80	0.054	
4.0	50	5.0		6.80	0.053	
2.0	25	5.0		6.80	0.055	
6.0	25	10.0		6.80	0.053	
	ida	L^3				
4.0	26	5.0		8.87	8.2×10^3	2.2×10^7
4.0	52	5.0		8.87	4.2×10^3	2.3×10^7
4.0	78	5.0		8.87	2.8×10^3	2.2×10^7
2.0	52	5.0		8.87	4.3×10^3	
4.0	52	10.0		8.87	4.2×10^3	
4.0	52	5.0	0.025	5.08	3.9×10^4	

TABLE 2 (*Continued*)

$10^3[Cu^{II}]_T$	$10^3[X]_F$	$10^3[L]_T$	$[MeCO_2^-]$	pH	k	$k(1 + \{K_{CuX_2}[X]_F/(\alpha_H)_X\})$
mol dm^{-3}					dm^3 mol^{-1} s^{-1}	
4.0	52	5.0	0.05	5.08	3.8×10^4	
4.0	52	5.0	0.10	5.08	3.9×10^4	9.8×10^4
4.0	52	5.0	0.20	5.08	4.0×10^4	
4.0	26	5.0	0.10	5.08	5.5×10^4	9.7×10^4
4.0	78	5.0	0.10	5.08	3.1×10^4	9.9×10^4
	nta	L[3]				
4.0	18	5.0		9.50	3.3×10^4	8.2×10^5
4.0	36	5.0		9.50	1.7×10^4	8.3×10^5
4.0	54	5.0		9.50	1.1×10^4	8.2×10^5
2.0	50	5.0		9.15	1.0×10^4	
4.0	50	5.0		9.15	1.1×10^4	
4.0	50	10.0		9.15	1.0×10^4	
4.0	50	5.0	0.025	4.60	3.2×10^3	
4.0	50	5.0	0.05	4.60	3.2×10^3	3.2×10^3
4.0	50	5.0	0.10	4.60	3.2×10^3	
4.0	25	5.0	0.05	4.60	3.3×10^3	3.3×10^3
4.0	75	5.0	0.05	4.60	3.3×10^3	3.3×10^3
	hedta	L[3]				
4.0	18	5.0		9.50	5.5×10^2	
4.0	36	5.0		9.50	5.5×10^2	
4.0	54	5.0		9.50	5.5×10^2	
2.0	26	3.0		9.87	7.5×10^2	
2.0	26	6.0		9.87	7.5×10^2	
4.0	26	6.0		9.87	7.4×10^2	
4.0	26	8.0		9.87	7.5×10^2	
	edta	L[3]				
2.0	13	3.0		9.85	2.0	
2.0	26	3.0		9.85	2.0	
2.0	52	3.0		9.85	2.0	
2.0	26	3.0		9.56	1.5	
2.0	26	6.0		9.56	1.5	
4.0	26	6.0		9.56	1.5	
4.0	26	8.0		9.56	1.5	
2.0	26	3.0		6.02	0.11	
2.0	26	9.0		6.02	0.11	
4.0	26	9.0		6.02	0.12	
4.0	26	6.0		6.02	0.11	
4.0	52	6.0		6.02	0.11	

[a] Glycinate buffer. [b] Phosphate buffer.

complex: with L = L[1] at 520 (X = ida), 525 (nta), 550 (hedta), and 540 nm (edta); L[2] at 540 nm (edta); and L[3] at 545 (ida), 550 (nta), 565 (hedta), and 570 nm (edta). The visible spectra or polarographic waves of the product solutions corresponded to those of $[CuL]^{2+}$ and showed no evidence of a mixed complex with X. Apparent formation rate constants, k, were determined from gradients of linear second-order plots of $\log[(a - x)/(b - x)]$ against time, where a and b are the initial concentrations of L and Cu^{II}, respectively, and x is the decrease in concentration of the reactant. The kinetic data are shown in Table 2. The ionic strength was maintained at 0.20 mol dm^{-3} with $Na[ClO_4]$. Acetate buffer was used for studies at pH 4—5.5. Since the aminocarboxylate ligands themselves have sufficient buffering capacity, no other reagent was added for reactions at pH 9—10. For edta–L[1] exchange at pH 9.7, glycine was used, and at pH 7.5, phosphate buffer was employed. The buffers had no effect on the rate constants observed. The temperature was maintained at 25.00 ± 0.05 °C.

RESULTS

The ligand-exchange reactions under the present experimental conditions are generally thermodynamically very favourable. The conditional equilibrium constant, K', was calculated using equation (3). Here $[Z]_F$ = the concentration of uncomplexed ligand (Z), protonated and unprotonated, [Z] = concentration of uncomplexed unprotonated Z, $[CuX]_T = [CuX] + [CuX_2]$, and $K_{CuX_2} = [CuX_2]/[CuX][X]$. Log K' (all at $[X]_F = 0.05$ mol dm^{-3})

$$\begin{array}{ccc} CuX + H_iL^{i+} & \underset{\text{slow}}{\overset{k}{\rightleftharpoons}} & [CuL]^{2+} + H_iX \\ & & \{+\ [Cu(HL)]^{3+}\}\ * \\ \Big\Updownarrow \text{rapid} & & \\ CuX_2 & & \end{array} \qquad (2)$$

* For L[2] (ref. 8) and L[3] (ref. 17).

$$K' = \frac{[CuL]_T[X]_F}{[CuX]_T[L]_F} = \frac{K_{CuL}/(\alpha_H)_L}{\frac{K_{CuX}}{(\alpha_H)_X}\left\{1 + \frac{K_{CuX_2}[X]_F}{(\alpha_H)_X}\right\}} \qquad (3)$$

where

$$(\alpha_H)_Z = \frac{[Z]_F}{[Z]} = 1 + \frac{[H^+]}{K_{1a}} + \frac{[H^+]^2}{K_{1a}K_{2a}} +, \textit{ etc.}$$

for L = L[1] is 11.6, 10.1, 5.4, and 4.7 at pH 5.0, and 11.8, 12.5, 9.4, and 8.5 at pH 9.0, for X = ida, nta, hedta, and edta, respectively; for L[2] it is 0 at pH 5.0 and 4.0 at pH 9.0 for X = edta; and for L[3] it is 10.5, 9.0, 4.3, and 3.5 at pH 5.0, and 11.0, 12.3, 9.2, and 8.3 at pH 9.0 for X = ida, nta, hedta, and edta, respectively. Other than treatment of the nta, hedta, and edta kinetics (at low pH) by the

initial-gradient method, no consideration was given to the reverse reaction of (2).

Second-order kinetics were observed in each case, as expressed by (4). By examining the variation of the observed rate constants with $[X]_F$ and pH, the contribution of the various reactive forms of copper and the macrocyclic ligand, unprotonated or protonated, were determined. In the presence of excess of $[X]_F$, which we employed to buffer the solution, the observed rate constants were independent of $[X]_F$ for X = hedta and edta at given $[Cu^{II}]_T$, $[L]_T$, and pH. Since hedta and edta form only 1 : 1 complexes, this fact indicates that the 1 : 1 complex species are the reactants. For X = ida and nta, the k values varied with $[X]_F$ in proportion to $\{1 + K_{CuX_2}[X]_F/(\alpha_H)_X\}^{-1}$ (see Table 2), indicating that the [CuX] complex in rapid equilibrium with $[CuX_2]$ is the sole reactive species.

$$d[CuL]_T/dt = k[CuX]_T[L]_F \quad (4)$$

Rate expression (4) may then be transformed into (5)

$$\text{Rate} = k_L[CuX][L] + k_{HL}[CuX][HL^+] + k_{H_2L}[CuX][H_2L^{2+}] +, \textit{etc.}$$
$$= \frac{[CuX]_T[L]_F}{\left\{1 + \frac{K_{CuX_2}[X]_F}{(\alpha_H)_X}\right\}(\alpha_H)_L}\left(k_L + \frac{[H^+]k_{HL}}{K_{a1}} + \frac{[H^+]^2k_{H_2L}}{K_{a1}K_{a2}} +, \textit{etc.}\right) \quad (5)$$

(where the term for CuX_2 is zero for the hedta and edta exchange reactions). The individual values of the rate constants k_L, k_{HL}, k_{H_2L}, *etc.* in (5) were resolved graphically.* A typical plot is contained in the Figure. At alkaline pH, the rate data [shown as (*b*) in the Figure] fit expression (6),

$$k(\alpha_H)_L\left(1 + \frac{K_{CuX_2}[X]_F}{(\alpha_H)_X}\right) = k_L + \frac{[H^+]k_{HL}}{K_{a1}} \quad (6)$$

* Expression (5) may represent a number of kinetically indistinguishable processes. The discussion followed assumes that only the reactants shown are involved.

TABLE 3

Resolved second-order rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for polyamine reactions with $[CuX]^{(2-z)+}$ at 25 °C and I = 0.2 mol dm^{-3}

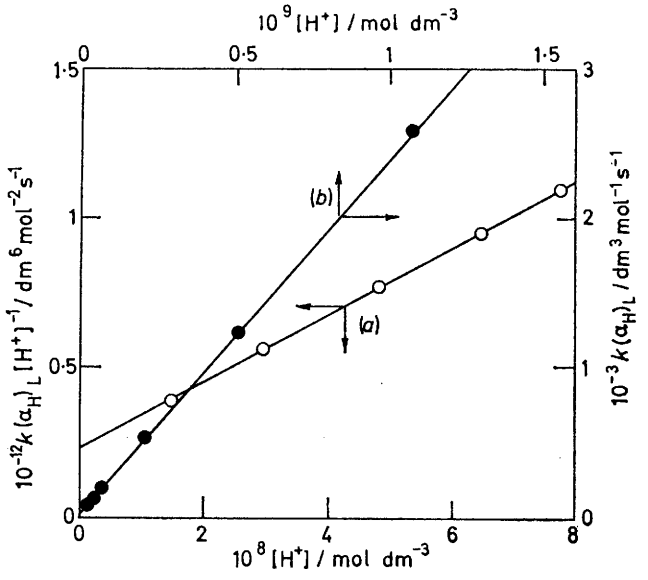
L	X^{z-}	k_L	k_{HL}	k_{H_2L}
L^1	ida^{2-}	$(7.2 \pm 0.7) \times 10^8$	$(1.9 \pm 0.2) \times 10^7$	$(2.0 \pm 0.2) \times 10$
	nta^{3-}	$(7.8 \pm 0.8) \times 10^6$	$(1.8 \pm 0.2) \times 10^5$	1.0 ± 0.1
	$hedta^{3-}$	$(1.5 \pm 0.2) \times 10^2$	$(1.4 \pm 0.2) \times 10^2$	$(8.6 \pm 0.9) \times 10^{-3}$
	$edta^{4-}$	31 ± 4	17 ± 3	$(7.4 \pm 0.7) \times 10^{-3}$
	$MeCO_2^-$ [a]		5.6×10^6	10
	H_2O [a]		1.7 ± 10^7	0.14
L^2	$edta^{4-}$	$(2.5 \pm 0.6) \times 10^2$	40 ± 8	$(3.4 \pm 0.7) \times 10^{-2}$
	$MeCO_2^-$ [b]		2.2×10^8	
	H_2O [c]		4.0×10^7	
L^4	$edta^{4-}$ [d]	4.3×10^5	3.5×10^4	2.1×10^2
	H_2O [e]			7.0×10^6
L^3	ida^{2-}		$(1.7 \pm 0.2) \times 10^8$	$(1.0 \pm 0.1) \times 10^6$
	nta^{3-}		$(1.9 \pm 0.2) \times 10^6$	$(7.9 \pm 0.8) \times 10^4$
	$hedta^{3-}$	$(2.0 \pm 0.3) \times 10^3$	$(1.2 \pm 0.2) \times 10^3$	21 ± 4
	$edta^{4-}$	$(4.0 \pm 0.5) \times 10^2$	$(3.3 \pm 0.4) \times 10^2$	2.0 ± 0.4
	$MeCO_2^-$			1.4×10^6
	H_2O [f]			9.7×10^4
L^5	nta^{3-} [g]			2.1×10^8
	$hedta^{3-}$ [g]	3.2×10^5	6.4×10^5	1.9×10^4
	$edta^{4-}$ [g]	2.2×10^5	3.7×10^5	6.7×10^3
	H_2O [g]			4.2×10^7

[a] Ref. 7. [b] Ref. 8. [c] Unpublished work. [d] Ref. 4. [e] Ref. 3. A value of k_{H_2L} *ca.* 2×10^3 was also obtained. [f] Ref. 17. [g] Ref. 1. The triprotonated species contributes to the nta (6.1×10^4) and water (1.55×10^5) displacement. The tetraprotonated species contributes only to water displacement (1.4×10^4).

of L, as expressed by (7). The data plotted as (*a*) in the

$$k(\alpha_H)_L\left(1 + \frac{K_{CuX_2}[X]_F}{(\alpha_H)_X}\right) = \frac{[H^+]}{K_{a1}}k_{HL} + \frac{[H^+]^2k_{H_2L}}{K_{a1}K_{a2}} \quad (7)$$

Figure give k_{HL} (from the intercept) and k_{H_2L} (from the gradient). The k_{HL} values obtained from the gradient of

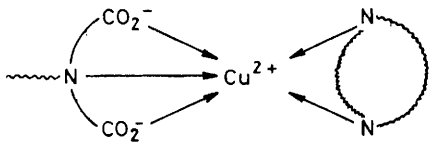


Plots of (*a*) equation (7) and (*b*) equation (6) (where $K_{CuX_2}[X]_F/(\alpha_H)_X = 0$ for the reaction of $[Cu(edta)]^{2-}$ with L^1

(*b*) and the intercept of (*a*) are in good agreement, within experimental error. All the results are shown in Table 3.

DISCUSSION

Comparison of Aminocarboxylate, Aqua-, and Acetate Ligands.—In general (see L^1 and L^3 reactions), the rates of ligand displacement increase in the order edta < hedta < nta < ida, which corresponds to the decreasing stability of the copper complexes. Moreover, the relative rate constants among the aminocarboxylates are approximately proportional to $(K_{CuX})^{-1}$. We tentatively adopt the same mechanism proposed for the displacement reactions of the linear polyamines L^4 or L^5,[1,4] which accounted for a similar proportionality in the rate among $[Cu(edta)]^{2-}$, $[Cu(hedta)]^-$, $[Cu(nta)]^-$, and other aminocarboxylate complexes.[1] In this mechanism the intermediate complexes (1) are chelated to the ida segment (from X) and several (but not all) of the nitrogen atoms of L before the rate-determining co-ordination of the remaining nitrogens of L at the site vacated by rupture of the ida nitrogen bond. [In (1),



(1)

it is not essential to the argument that the carboxylate groups are co-ordinated.] Thus, the nearly theoretical 10^8-fold variation of the rate [$\log K_{Cu(edta)} - \log K_{Cu(ida)}$] is observed for the reaction of unprotonated L^1. A difference in the position of the rate-determining steps in the aminocarboxylate and water (or acetate) displacements is also suggested from the fact that the formation of complexes of L^1 and L^3 from [Cu(ida)] occurs as fast as (or even faster than) from $Cu^{2+}(aq)$ or $[Cu(O_2CMe)]^+$ (*cf.* k_{HL} for L^1 and k_{H_2L} for L^3) despite the former reactions involving much slower dissociation of the aminocarboxylate chelates relative to water or acetate.[19]

Comparison with Reactions of Linear Polyamines.—The reaction rates for the macrocyclic (L^3) and linear (L^5) penta-amines with $[Cu(nta)]^-$, $[Cu(hedta)]^-$, and $[Cu(edta)]^{2-}$ are nearly parallel, those for the macrocyclic system being consistently slower by a factor of *ca.* 10^3. This is also true for the ratio of the rates of the reactions of tetra-amines L^1 to L^4 with $[Cu(edta)]^{2-}$. The rate retardation for the macrocyclic system may come from the unfavourable formation of the intermediate (1) and/or slower co-ordination of the final macrocycle nitrogen(s) (in the intermediate) due to the requirement of the drastic twisting and folding. Somewhat similar orders of deceleration of the macrocyclic ligand L^3 are seen for the reaction with $Cu^{2+}(aq)$.

Of considerable interest is a comparison of the rate constants for the displacement of edta by the unprotonated macrocyclic and linear polyamines. In previous reports,[18] it was suggested that the reason for the unusually slow rates of macrocyclic (relative to linear) complex formation with $M^{2+}(aq)$ may lie in the electrostatic effects characteristic of the protonated macrocyclic structure, rather than in conformational flexibility. In the reactions of the unprotonated forms there are no electrostatic effects due to protonation, and only the steric effects, including conformational change, are emphasized. The results clearly indicate that the unprotonated macrocycles are as unreactive (by a factor of *ca.* 10^4 relative to the linear homologues) as the mono- (by *ca.* 10^3) and di-protonated forms (by *ca.* 10^4). That is, steric effects are mainly responsible for the sluggish substitution of the aminocarboxylates by the macrocycles.

Comparison of the Resolved Rate Constants for Protonated Macrocyclic and Linear Polyamines.—Normally the addition of one more proton to a polyamine diminishes the rate constant for reaction owing to increased electrostatic repulsion and the requirement for available nitrogen-donor sites. This is the case for the reaction of monoprotonated L^1 with [Cu(ida)] or $[Cu(nta)]^-$ and for the reaction of mono- and di-protonated L^3 with nearly all the aminocarboxylate complexes tested. On the other hand, protonated polyamines may possess a greater affinity for highly negatively charged complexes which also aid in dispersion of protons from the attacking polyamines. This accounts for the fact that monoprotonated L^1 and L^3 give the same rate constants for reaction with $[Cu(edta)]^{2-}$ and $[Cu(hedta)]^-$. In the reaction of L^5 with these complexes, the rates are faster for mono- and for un-protonated ligand species.[1,4] For the same reasons, L^1 should show a smaller discrepancy in the reactivity of $[HL]^+$ and $[H_2L]^{2+}$ with $[Cu(hedta)]^-$ or $[Cu(edta)]^{2-}$ (by a factor of *ca.* 10^4) than with [Cu(ida)] (by a factor of *ca.* 10^6) or $[Cu(nta)]^-$ (a factor of *ca.* 10^5). (Here, addition of one more proton to the monoprotonated macrocyclic tetra-amine L^1 leaves two weakly-basic free nitrogens, causing a drastic decrease in the rate of complex formation.) Similarly rationalized was the greater rate for the reaction of $[H_2L]^{2+}$ with $[Cu(O_2CMe)]^+$ than with $Cu^{2+}(aq)$, while $[HL]^+$ reacts with these species at the same rates.[7,9] The ions $hedta^{3-}$ and nta^{3-} differ in their reactivity towards various protonated polyamines despite carrying the same negative charge, $hedta^{3-}$ behaving more like $edta^{4-}$ and nta^{3-} like ida^{2-}. This is because hedta (like edta) in the intermediate complex has a stronger basic site than does nta, an extra free nitrogen capable of accepting H^+.

Comparison of Macrocyclic Polyamines.—As anticipated from the number of available free nitrogen atoms, the reactivity pattern of the unprotonated and monoprotonated tetra-amine L^1 almost parallels that of the mono- and di-protonated penta-amine L^3. Some deviations found for highly charged reactants are explained by electrostatic repulsion or attraction. A comparison of the reactions of L^1, L^2, and L^3 with $[Cu(edta)]^{2-}$ involves the effects of ring size and denticity of macrocyclic polyamines with or without protons. In

[19] For instance, see A. F. Perlmutter and J. Stuehr, *J. Amer. Chem. Soc.*, 1968, **90**, 858; N. Tanaka and M. Kimura, *Bull. Chem. Soc. Japan*, 1968, **41**, 2375.

the reactions of unprotonated species free from the protonation effect, the ring size and/or conformational flexibility control the reaction rates, since the k_L value for the 15-membered tetra-amine L^2 is nearer to that for the 15-membered penta-amine L^3 than for the 13-membered tetra-amine L^1. In the reactions of protonated species, the number of unprotonated nitrogen atoms available for chelation is decisive, since the k_{HL} and k_{H_2L} values for L^2 are nearer to those for L^1 than for L^3.

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