Kinetics of Ligand-displacement Reactions of Copper(II) Complexes of Deprotonated Linear and Macrocyclic Dioxotetra-amines. Comparative Studies with Glycylglycylglycine and Glycylglycylhistidine

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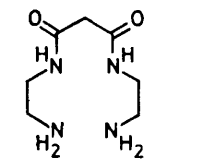
The kinetics of displacement of doubly deprotonated linear (X^1) and 13—15-membered macrocyclic dioxotetra-amines (X^2—X^4), compared with glycylglycylglycine (X^5) and glycylglycylhistidine (X^6), from their copper(II) complexes (all commonly expressed as $[CuH_{-2}X]$) have been studied with ligands of various degrees of nucleophilicity including a linear tetra-amine (L^1), macrocyclic tetra-amines (L^2 and L^3), or ethylenediaminetetra-acetate (edta) in borate (pH 8—9.5) or lutidine buffers (pH 6—7.5). The proposed mechanisms for X^1—X^4 are analogous to that reported for X^6, where proton assistance is needed to aid cleavage of the non-terminal copper–imide bonds and provide open sites for nucleophilic attack. The effects of cyclization of the X ligands and ring size on the relative stability of the $[CuH_{-2}X]$ complexes are well manifested in the ligand-replacement kinetics. Thus, the 14-membered X^3 which forms the most stable complex among X^1—X^6 is the most inert to the substitution reactions.

A LINEAR dioxotetra-amine (X^1) forms a stable complex with Cu^{II} in which both of the amide protons are ionized.[1-4] Ionization of the protons is virtually complete by pH 8 and the complex is designated by $[CuH_{-2}X]$.[1] Copper(II) also facilitates the ionization of amide protons from co-ordinated polypeptides.[5,6] As with X^1, the deprotonated complexes are generally formed by pH 8. Thus, tripeptides such as glycylglycylglycine X^5 (refs. 7 and 8) or glycylglycylhistidine X^6 (refs. 9 and 10) and X^1 have a similar mode of quadridentate co-ordination to copper through the two terminal donors and the two deprotonated amide nitrogens at pH 8. The complex stability constant $K_{CuH_{-2}X}$ (= $[CuH_{-2}X][H^+]^2/[Cu][X]$) for X^1 is $10^{-5.1}$ mol dm^{-3}, as compared with $10^{-6.5}$ for X^5 (ref. 7) and $10^{-2.1}$ mol dm^{-3} for X^6.[10]

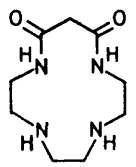
The stability of the deprotonated tripeptide complexes and the reaction mechanism for the displacement of the tripeptides from Cu^{II} [as shown generally by equation (1)] vary dramatically with the donor group in the third

$$[CuH_{-2}X] + L \longrightarrow [CuL] + X \qquad (1)$$

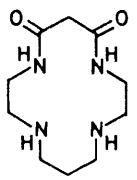
amino-acid residue. For X^5 having a carboxylate donor, the peptide is believed to unwrap stepwise from the metal starting with the carboxyl terminus.[11-13] When the third residue is replaced by histidine as in X^6 with the imidazole N taking over from a carboxyl donor, the complex stability is greatly enhanced,[9,10] and the reactivity pattern is altered to a proton-assisted mechanism that is initiated at a non-terminal position.[14,15] In a part of this paper we deal with the reaction mechanism for replacement of X^1 and compare it with those for replacement of the tripeptides.



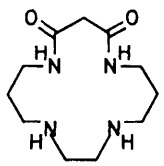
X^1
1,9-Diamino-3,7-diazanonane-4,6-dione



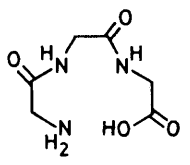
X^2
1,4,7,10-Tetra-azacyclotridecane-11,13-dione



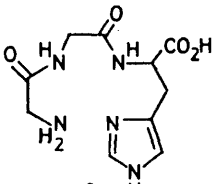
X^3
1,4,8,11-Tetra-azacyclotetradecane-12,14-dione



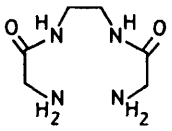
X^4
1,4,8,12-Tetra-azacyclopentadecane-9,11-dione



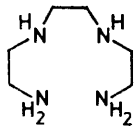
X^5
Glycylglycylglycine



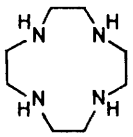
X^6
Glycylglycylhistidine



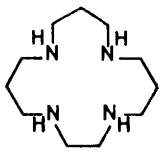
X^7
1,8-Diamino-3,6-diazaoctane-2,7-dione
(*NN'*-Diglycylethylenediamine)



L^1
3,6-Diazaoctane-1,8-diamine



L^2
1,4,7,10-Tetra-azacyclododecane



L^3
1,4,8,12-Tetra-azacyclopentadecane

The doubly deprotonated dioxotetra-amine complexes are stabilized by ligand cyclization as shown by X^2—X^4.[1] Of the 13—15-membered rings the 14-membered X^3 shows the most profound effect; the stability of the X^3 complex ($10^{1.0}$ mol dm^{-3}) surpasses that of X^6.[1] Cyclization also enhances the selectivity of the ligand for copper(II) ion in both a thermodynamic and kinetic sense, and results in a potential application as specific sequestering agents for this ion.[1] This outstanding stabilization and cation selectivity is ascribable to the good match of the metal ion with the ring cavities. Similar macrocyclic effects were reported for unsubstituted tetra-amine complexes.[16-22] In continuation of a series [23-25] of investigations of the kinetic aspects of macrocyclic and ring-size effects, we have now studied the ligand substitutions (1) of the dioxotetra-amine complexes. The entering ligands L studied are a linear tetra-amine (L^1), 12- (L^2) and 15-membered macrocyclic tetra-amine (L^3), and ethylenediaminetetra-acetate (edta). Their various degrees of nucleophilicity should help in understanding the substitution mechanisms. Very recently, the replacement of an X^1 analogue (X^7) by edta in a nickel(II) complex has been reported.[26]

EXPERIMENTAL

The dioxotetra-amines X^1·2HCl, X^2, X^3, and X^4 were prepared according to previous methods.[3,27,28] Their purity was checked by elemental analysis, n.m.r. spectrum, or m.p. Sources of other reagents used were as reported previously.[17,20,22,23] The protonation constants log K_1, K_2, K_3, and K_4 used were 10.09, 9.31, 6.75, and 3.39 for L^1,[29] 10.70, 9.70, 1.73, and 0.94 for L^2,[22] 11.20, 10.10, <2, and <2 for L^3,[22] and 9.80, 6.12, 2.56, and 1.98 for edta.[30] The complex formation constants used were log $K_{CuH_{-2}X} = -5.1$ (X^1), -2.2 (X^2), 1.0 (X^3), and -4.5 (X^4) (all ref. 1) and log $K_{CuL} = 20.2$ (L^1),[31] 24.8 (L^2),[17] 24.4 (L^3),[20] and 18.2 (edta).[30] Ionic strength was maintained at 0.2 mol dm^{-3} with Na[ClO_4]. All the work was at 25.0 ± 0.1 °C. Values of $-\log[H^+]$ were calculated by applying a correction of -0.13 unit to the pH meter reading.[32]

Solutions of [$CuH_{-2}X$] were prepared by reaction of dioxotetra-amines with standardized Cu[NO_3]$_2$ solutions in borate (*ca.* 5% excess of X over Cu) or lutidine buffers (40—60% excess of X over Cu). The reactions between [$CuH_{-2}X$] and L were followed at the wavelengths sensitive to the product complex formation: 630 (L^1), 645 (L^2), 630 (L^3), and 750 nm (edta). Kinetic runs were followed using a Union Giken stopped-flow instrument. The initial-gradient method or second-order (unequal concentrations) plots were used to obtain observed rate constants $k_{obs.}$. The presence of 40—60% excess of X in the reaction mixture did not appear to influence the rate of the reactions. Typical primary kinetic data are shown in Table 1.

RESULTS AND DISCUSSION

Replacement by Tetra-amines L^1—L^3.—In the pH range used (8—9.5) all the starting complexes are present as [$CuH_{-2}X$] (ref. 1) and most of the exchange reactions (1) are thermodynamically very favourable: the log of the conditional equilibrium constant $K' = [X]_T[CuL^2]_T/[CuH_{-2}X][L]_T$ at pH 9 is estimated as 6.2 (X^1, L^1), 3.1 (X^2, L^1), 5.7 (X^4, L^1), 9.9 (X^1, L^2), 9.7 (X^1, L^3), *etc.* The only exception is the reaction of the X^3 complex with L^1. Kinetically, the reactions (1) are feasible except for those involving X^3 replaced by L^1 or X^2—X replaced by L^2 or L^3, which were too slow in the borate buffers.

The kinetics indicated the direct appearance of the product [CuL] complexes with no intermediate formation. The concentration of borate ions in the buffers had little effect on the reaction kinetics. All the rates were first order in [$CuH_{-2}X$] and first order in $[L]_T$. A reaction scheme consistent with these observations is shown in equations (2)—(4).* The individual rate constants k_{iH}

$$[CuH_{-2}X] + [HL]^+ + H_2O \xrightarrow{k_H} [CuL]^{2+} + X + [OH]^- \quad (2)$$

$$[CuH_{-2}X] + [H_2L]^{2+} \xrightarrow{k_{2H}} [CuL]^{2+} + X \quad (3)$$

$$[CuH_{-2}X] + [H_3L]^{3+} \xrightarrow{k_{3H}} [CuL]^{2+} + X + H^+ \quad (4)$$

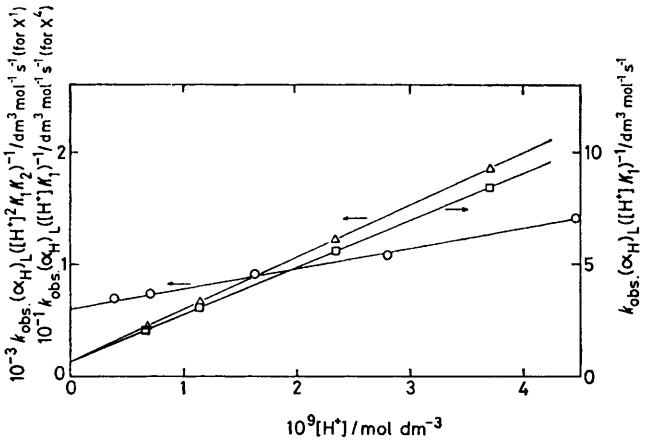


FIGURE 1 Plots of equation (5) for the reaction of the X^1 (○), X^2 (□), and X^4 (△) complexes with L^1. Conditions are: for X^1, [$CuH_{-2}X$] = 2.52×10^{-3}, [L] = 50×10^{-3}, and [borate] = 52.5×10^{-3} mol dm^{-3}; for X^2, [$CuH_{-2}X$] = 4.0×10^{-3}, [L] = 50×10^{-3}, and [borate] = 45.0×10^{-3} mol dm^{-3}; and for X^4, [$CuH_{-2}X$] = 4.8×10^{-3}, [L] = 50×10^{-3}, and [borate] = 37.5×10^{-3} mol dm^{-3}

in (2)—(4) were determined from the pH dependence of $k_{obs.}$ using equation (5). Figures 1 (X^1, X^2, and X^4

$$k_{obs.}(\alpha_H)_L = k_H[H^+]K_1 + k_{2H}[H^+]^2K_1K_2 + k_{3H}[H^+]^3K_1K_2K_3 \quad (5)$$

where

$$(\alpha_H)_L = [L]_T/[L] = 1 + [H^+]K_1 + [H^+]^2K_1K_2 + \ldots, \textit{etc.} \quad (6)$$

$$[L]_T = [L] + [HL]^+ + [H_2L^{2+}] + \ldots, \textit{etc.} \quad (7)$$

replacement by L^1) and 2 (X^1 replacement by L^2 and L^3) show the linear relations between $k_{obs.}(\alpha_H)_L/[H^+]K_1$ and $[H^+]$. The gradients represent $k_{2H}K_2$ and the intercepts

* As a referee has suggested, the pH dependence of $k_{obs.}$ may also be consistent with a mechanism involving a rapid protonation pre-equilibrium ([$CuH_{-2}X$] + $H^+ \rightleftharpoons$ [$CuH_{-1}X$], [$CuH_{-1}X$] + $H^+ \rightleftharpoons$ [CuX], *etc.*) followed by slow attack of L([$CuH_{-1}X$], *etc.* + L → [CuL] + X). However, since we were unable to determine the protonation constants of [$CuH_{-2}X$], [$CuH_{-1}X$], *etc.* (these species were not detected) [1] needed for the estimation of the rate constants we have adopted the present mechanism (2), (3), or (4).

TABLE 1

Typical rate data for the reaction of L with [$CuH_{-2}X$] at I 0.2 mol dm^{-3} and 25 °C

10[$CuH_{-2}X$] / mol dm^{-3}	10^3[L] / mol dm^{-3}	10^3[Buffer] / mol dm^{-3}	pH	$k_{obs.}$ / dm^3 mol^{-1} s^{-1}
X^1	L^1	Borate		
7.0	25.0	37.5	8.93	520
4.0	25.0	37.5	8.93	520
2.0	25.0	37.5	8.93	530
2.0	50.0	37.5	8.93	540
2.0	5.0	37.5	8.93	530
2.0	25.0	75.0	8.93	530
2.5	50.0	52.5	8.36	1 300
2.5	50.0	52.5	8.55	920
2.5	50.0	52.5	8.74	700
2.5	50.0	52.5	9.15	400
2.5	50.0	52.5	9.44	260
X^2	L^1	Borate		
4.0	25.0	45.0	8.95	1.0
4.0	50.0	45.0	8.95	1.0
4.0	100	45.0	8.95	1.0
2.0	50.0	45.0	8.95	1.0
8.0	50.0	45.0	8.95	1.0
4.0	50.0	90.0	8.95	1.0
4.0	50.0	45.0	8.43	1.0
4.0	50.0	45.0	8.63	1.0
4.0	50.0	45.0	9.18	0.86
X^4	L^1	Borate		
4.8	25.0	37.5	8.95	1.9
4.8	50.0	37.5	8.95	1.9
4.8	100	37.5	8.95	1.9
2.4	50.0	37.5	8.95	1.9
7.2	50.0	37.5	8.95	1.9
4.8	50.0	75.0	8.95	1.8
4.8	50.0	37.5	8.43	2.2
4.8	50.0	37.5	8.63	2.1
4.8	50.0	37.5	9.18	1.8
X^1	L^2	Borate		
2.0	3.0	45.0	9.12	2.1
2.0	5.0	45.0	9.12	2.1
2.0	10.0	45.0	9.12	2.1
6.0	10.0	45.0	9.12	2.0
6.0	15.0	45.0	9.12	2.1
2.0	5.0	30.0	9.12	2.0
2.0	5.0	90.0	9.12	2.1
3.0	5.0	48.8	8.27	2.9
3.0	5.0	48.8	8.57	2.8
3.0	5.0	48.8	8.97	2.4
3.0	5.0	48.8	9.12	2.1
3.0	5.0	48.8	9.43	2.0
X^1	L^3	Borate		
2.0	3.0	45.0	8.57	3.1
2.0	10.0	45.0	8.57	3.0
6.0	10.0	45.0	8.57	3.1
8.0	15.0	45.0	8.57	3.0
2.0	5.0	30.0	8.57	3.1
2.0	5.0	90.0	8.57	3.1
3.0	5.0	48.8	8.27	3.1
3.0	5.0	48.8	8.57	3.1
3.0	5.0	48.8	8.97	2.9
3.0	5.0	48.8	9.12	2.8
3.0	5.0	48.8	9.43	2.7
X^1	edta	Borate		
1.5	5.0	33.8	8.61	1 200
3.0	5.0	33.8	8.61	1 100
3.0	10.0	33.8	8.61	1 000
3.0	25.0	33.8	8.61	1 100
6.0	10.0	33.8	8.61	1 100
3.0	5.0	67.6	8.61	1 200
3.0	5.0	33.8	8.44	1 600
3.0	5.0	33.8	8.87	520
3.0	5.0	33.8	9.20	260
3.0	5.0	33.8	9.50	130

TABLE 1 (*Continued*)

10[$CuH_{-2}X$] / mol dm^{-3}	10^3[L] / mol dm^{-3}	10^3[Buffer] / mol dm^{-3}	pH	$k_{obs.}$ / dm^3 mol^{-1} s^{-1}
X^2	edta	Borate		
1.5	20.0	37.5	8.66	1.4
3.0	20.0	37.5	8.66	1.4
6.0	20.0	37.5	8.66	1.3
3.0	10.0	37.5	8.66	1.4
3.0	30.0	37.5	8.66	1.4
3.0	20.0	25.0	8.66	1.4
3.0	20.0	75.0	8.66	1.4
3.0	20.0	37.5	8.52	1.7
3.0	20.0	37.5	8.99	0.79
X^4	edta	Borate		
1.5	20.0	37.5	8.66	0.82
3.0	20.0	37.5	8.66	0.86
6.0	20.0	37.5	8.66	0.87
3.0	10.0	37.5	8.66	0.85
3.0	20.0	25.0	8.66	0.87
3.0	20.0	75.0	8.66	0.91
3.0	20.0	37.5	8.52	1.2
3.0	20.0	37.5	8.99	0.47
X^3	edta	Lutidine		
2.5	5.0	100	6.02	7.2×10^{-4}
2.5	10.0	100	6.02	10×10^{-4}
2.5	20.0	100	6.02	18×10^{-4}
2.5	5.0	100	6.20	5.4×10^{-4}
2.5	10.0	100	6.20	8.3×10^{-4}
2.5	20.0	100	6.20	14×10^{-4}
2.5	2.5	100	6.62	2.1×10^{-4}
2.5	5.0	100	6.62	2.8×10^{-4}
2.5	10.0	100	6.62	4.0×10^{-4}
2.5	20.0	100	6.62	6.4×10^{-4}
2.5	5.0	100	7.50	1.2×10^{-4}
2.5	10.0	100	7.50	1.5×10^{-4}
2.5	20.0	100	7.50	2.1×10^{-4}

k_H. In the case of replacement of X^1 by L^1, only a plot of $k_{obs.}(\alpha_H)_L/[H^+]^2K_1K_2$ against $[H^+]$ gave a straight line with an intercept. The resolved rate constants k_{2H} and k_{3H} were thus obtained graphically.

Replacement by edta.—Calculated values of log K' at pH 9 are 4.9 (X^1, edta), 1.8 (X^2, edta), and 4.4 (X^4, edta). In these reactions no intermediates were detected and

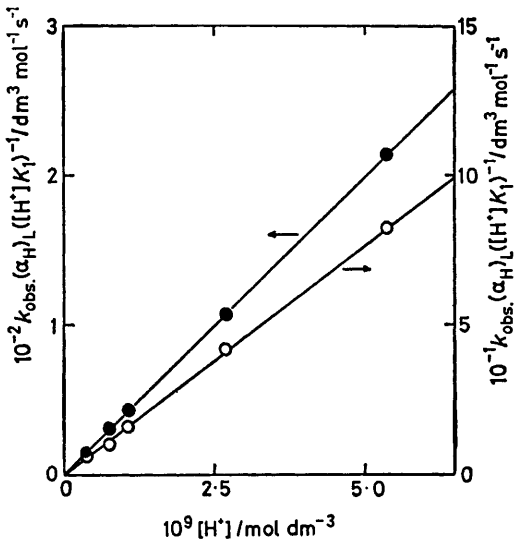


FIGURE 2 Plots of equation (5) for the reaction of the X^1 complex with L^2 (○) and L^3 (●). Conditions are [$CuH_{-2}X$] = 3.0×10^{-3}, [L] = 5.0×10^{-3}, and [borate] = 48.8×10^{-3} mol dm^{-3}

the rates of formation of the product edta complex were first order in $[CuH_{-2}X]$ and in $[edta]_T$. From the pH dependence of $k_{obs.}$ the individual rate constants k_H and k_{2H} in reactions (2) and (3) (L = edta) were determined graphically (Figure 3).

The replacement of X^3 by edta at pH 9 was kinetically as well as thermodynamically unfavourable. To drive reaction (1) to the right and raise the rate to a measurable level, the reaction pH was lowered while maintaining the starting concentration of $[CuH_{-2}X]$ complex. In the pH range 6—7.5 employed using lutidine buffers, the calculation indicates the deprotonated complex to be virtually undissociated: the degree of dissociation α is $6 \times 10^{-5}\%$ at $[Cu] = [X^3] = 2 \times 10^{-3}$ mol dm^{-3} and pH 6. The log K' value (1.9 at pH 7.5) increases with decrease in pH. The reaction rates were determined by the initial-gradient method. The concentration of the lutidine buffer had little effect on the reaction rates. The kinetics indicate that the three simultaneous pathways (8)—(10) lead to the product edta complex. The

$$[CuH_{-2}X] + H_2O \xrightarrow[\text{slow}]{k_0} Cu^{2+} \xrightarrow[\text{fast}]{\text{edta}} [Cu(edta)]^{2-} \quad (8)$$

$$[CuH_{-2}X] + H^+ \xrightarrow[\text{slow}]{k_{H^+}} Cu^{2+} \xrightarrow[\text{fast}]{\text{edta}} [Cu(edta)]^{2-} \quad (9)$$

$$[CuH_{-2}X] + \text{edta} \xrightarrow{k_{edta}} [Cu(edta)]^{2-} \quad (10)$$

overall rate is expressed as in equation (11). At constant

$$d[Cu(edta)^{2-}]/dt = [CuH_{-2}X](k_0 + k_{H^+}[H^+] + k_{edta}[edta]_T) \quad (11)$$

pH and $[CuH_{-2}X]_0$, plots of the initial rate/$[CuH_{-2}X]_0$ against $[edta]_0$ (= $[edta]_T$ at initial time) gave straight lines whose gradients correspond to k_{edta} and intercepts to $(k_0 + k_{H^+}[H^+])$. Further, plots of the intercept values against $[H^+]$ afforded a straight line (gradient = k_{H^+}) with an intercept (= k_0). The constant k_{edta} was further resolved by a plot of $k_{edta}(\alpha_H)_{edta}/[H^+]K_1$ against $[H^+]$ using equation (5) where $k_{obs.} = k_{edta}$; this gave a straight line passing through the origin with a gradient

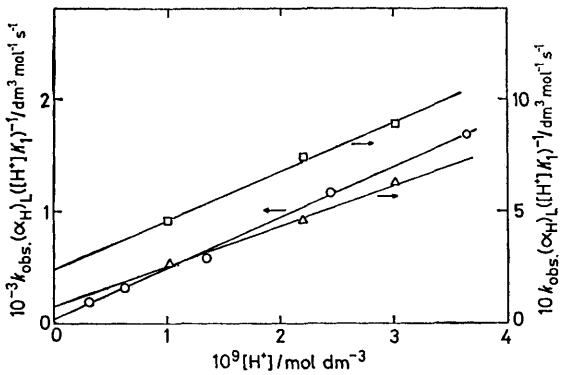


FIGURE 3 Plots of equation (5) for the reaction of X^1 (○), X^2 (□), and X^4 (△) complexes with edta in borate buffers. Conditions are: for X^1, $[CuH_{-2}X] = 3.0 \times 10^{-3}$, $[edta]_T = 5.0 \times 10^{-3}$, and [borate] = 33.8×10^{-3} mol dm^{-3}; for X^2 and X^4, $[CuH_{-2}X] = 3.0 \times 10^{-3}$, $[edta]_T = 20.0 \times 10^{-3}$, and [borate] = 37.5×10^{-3} mol dm^{-3}

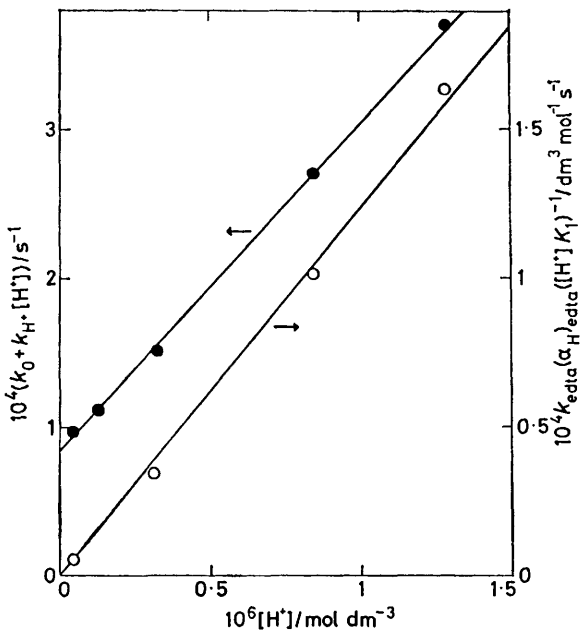


FIGURE 4 Resolution of k_{edta} [see, equation (11)] using a plot of equation (5) (○), and determination of k_0 and k_{H^+} (●) for the reaction of the X^3 complex with edta in lutidine buffer. Conditions are $[CuH_{-2}X] = 2.5 \times 10^{-3}$ and [lutidine] = 0.1 mol dm^{-3}

corresponding to $k_{H_2edta}K_2$ (where H_2edta represents diprotonated edta) (Figure 4).

For comparative purposes the replacement of X^2 by edta in the lutidine buffer ($6.4 < pH < 7.5$) was studied in a similar fashion. The reaction is more favourable kinetically and thermodynamically than in the borate buffer. In the low pH range the starting X^2 complex is still stable as $[CuH_{-2}X]$ with little ligand dissociation; the degree of dissociation α is estimated as 0.94% at [Cu] = $[X^2] = 2 \times 10^{-3}$ mol dm^{-3} and pH 6. The k_{H_2edta} value of 2.1×10^2 dm^3 mol^{-1} s^{-1} so obtained satisfactorily agrees with the value of 3.3×10^2 dm^3 mol^{-1} s^{-1} determined in the borate buffer. All the results are listed in Table 2 and compared with rate data for the tripeptides X^5 and X^6.*

Mechanistic Considerations.—Although the copper(II) complexes of the linear ligands X^1 and X^5 in aqueous solutions assume a more or less similar square-planar co-ordination,[3,5] their kinetic behaviours towards L^1 are significantly different: first, the observed second-order rate constant at a given pH is much larger with X^5; and secondly, while the replacement of X^5 becomes slower as

* The data for the reaction of $[H_3L]^{3+}$ with the X^1 complex or for the reaction of H_2edta with the X^1—X^4 complexes may be reinterpreted in terms of a combined proton and $[H_2L]^{2+}$ mechanism or a combined proton and Hedta mechanism. The latter mechanism was adopted for the reactions of L^1 or edta with the X^6 complex by Cooper and co-workers.[14,15] Both mechanisms emphasize the role of the protons in the nucleophilic attack. The rates for our reactions would also be equivalent to $k[H^+][H_2L^{2+}]$-$[CuH_{-2}X]$ or to $k[H^+][Hedta][CuH_{-2}X]$, where the third-order rate constants k are evaluated from the gradients of the linear plots in Figure 1 or 3. In Table 2, the data of Cooper for the X^6 complex have been recalculated based on our second-order mechanism, for the sake of comparison.

TABLE 2

Rate constants [a] for reactions of L with $[CuH_{-2}X]$

	X^1	X^2	X^3	X^4	X^5	X^6
log $K_{CuH_{-2}X}$	−5.1 [b]	−2.2 [b]	1.0 [b]	−4.5 [b]	−6.5 [c]	−2.2 [d]
L^1 Reaction						
k_H		0.7 ± 0.1		1.4 ± 0.2	5.1×10^6 [e]	*ca.* 0.5 [f]
k_{2H}	$(6.0 \pm 0.5) \times 10^2$	1.2 ± 0.1		2.3 ± 0.2	1.2×10^5 [e]	
k_{3H}	$(3.3 \pm 0.4) \times 10^4$					1.1×10^2
L^2 Reaction						
k_H					2.5×10^2 [g]	
k_{2H}	3.0 ± 0.3				2.7×10^2 [g]	
L^3 Reaction						
k_H					3.0×10^2 [g]	
k_{2H}	3.2 ± 0.3				1.4×10^2 [g]	
edta Reaction						
k_{Hedta}	$(7.5 \pm 0.8) \times 10^1$	0.49 ± 0.05		0.17 ● 0.02		
k_{H_2edta}	$(3.5 \pm 0.4) \times 10^5$	$(3.3 \pm 0.3) \times 10^2$ (2.1×10^2)	$(9.3 \pm 0.9) \times 10^1$	$(2.7 \pm 0.3) \times 10^2$	3.1×10^3 [h]	1.7×10^2
k_0		$(7.5 \pm 0.8) \times 10^{-2}$	$(8.3 \pm 0.8) \times 10^{-5}$		0.12 [h]	7.5×10^{-4}
k_{H^+}		$(1.0 \pm 0.1) \times 10^6$	$(2.2 \pm 0.2) \times 10^2$		4.9×10^6 [h]	1.8×10^5 [f]

[a] Units are all $dm^3\ mol^{-1}\ s^{-1}$ except for $k_0(s^{-1})$. Values are averages of three or four determinations; error limits are average deviations. [b] Ref. 1. [c] Ref. 7. [d] Ref. 10. [e] Ref. 12. [f] Refs. 14 and 15. [g] Ref. 25. [h] Ref. 11.

the solution pH decreases,[12] the opposite is true with X^1. The replacement of X^5 by L^1 is postulated [12] to start with the nucleophilic substitution of the equatorial carboxylate group, which facilitates the dissociation of the otherwise stable deprotonated X^5 complex. The rate-determining step is supposed to occur before or during the rupture of the Cu–N peptide bond. This nucleophilic mechanism accounts for the observed rate increase at higher pH or the resolved reactivity order among the L^1 reactants, *viz.* unprotonated L > $[HL]^+$ > $[H_2L]^{2+}$. In contrast, the observed opposite pH–rate profile (which implies a significant participation of the $[H_3L]^{3+}$ reactant) or the resolved reactivity order $[H_3L]^{3+} > [H_2L]^{2+}$ in the replacement of X^1 suggests that the L^1 co-ordination would require an intramolecular proton transfer to one of the deprotonated amide sites prior to or during the rate-determining step. A concerted process of this type would facilitate the breakage of a copper–imide bond and thus provide a path for L^1 to replace X^1. The reaction would then be initiated at the non-terminal position. The inert nature of the copper–amine bonding relative to the labile copper–carboxylate bonding would be responsible for the difference in the reaction mechanisms and hence in rates between the X^1 and X^5 replacements. A similar proton addition to a non-terminal imide has been demonstrated in the replacement of X^6 by L^1,[14,15] where an imidazole nitrogen occupying the terminus makes direct nucleophilic attack by L^1 very difficult.

The cyclic dioxotetra-amine X^2 and X^4 complexes also undergo ligand substitution by L^1, but the rates are much slower than that for the linear X^1 counterpart. The conformational inflexibility characteristic of the macrocyclic ligands would resist their unwrapping at the rate-determining stage. Another interesting finding is that the rates for X^2 and X^4 do not show great increases as does that for X^1 on lowering the pH from 9.2 to 8.4. This may be interpreted in that the reactive species towards the macrocyclic X^2 and X^4 complexes are $[HL]^+$ and $[H_2L]^{2+}$ with a significant contribution of the former reaction pathway (23% to the overall reaction at pH 9 for both X^2 and X^4), as compared with $[H_3L]^{3+}$ (23%) and $[H_2L]^{2+}$ (77%) in the X^1 substitution. It may also indicate that the nucleophilic L^1 species (*i.e.* $[HL^1]^+$) plays a relatively important role in loosening the rigid chelation of the macrocycles X^2 and X^4 as does the acidic $[H_3L]^{3+}$ with the flexible linear X^1.

The necessity for an entering ligand to have acidic properties is more evident in the reaction of the poor nucleophilies L^2 and L^3 with the X^1 complex. When L^2 or L^3 replaces labile H_2O or acetate ion in $Cu^{2+}(aq)$ or $[Cu(O_2CMe)]^+$ by the direct nucleophilic mechanism, most of the reactions proceed *via* $[HL]^+$ species {although $[H_2L]^{2+}$ are predominant at the pH employed (<6)}.[17,20] This should be compared with the present case where $[H_2L]^{2+}$ are the exclusive reactants (despite the higher pH). For labilization of the deprotonated X^1, the attacking L^2 or L^3 lacks sufficient nucleophilicity because of steric reasons, and thus has no choice but to act as the acid form. The reaction of X^1 is in contrast to that of X^5 (ref. 25), as revealed by a comparison of the k_{iH} values in Table 2. This fact is rationalized, as before, by the differing properties of the terminal donor atoms on X^1 and X^5.

In the exchange reaction of edta with the X^5 complex the poor nucleophile edta cannot expel X^5 by the direct nucleophilic mechanism, but it can do so with the aid of the protons attached to it.[11,12] A similar proton-assisted nucleophilic mechanism operates in the reaction with the X^1 complex, as evidenced by the fact that H_2edta is a much more effective reactant than Hedta (in the borate buffers). An inspection of the H_2edta reaction rates k_{H_2edta} for X^1 through X^6 shows that the X^3 complex is extremely inert to the substitution reaction.

Undoubtedly, this kinetic inertness is associated with the high thermodynamic stability of the complex which is derived from the ligand cyclization and the ring-size fitness (to the metal ion).[1] There seems to be an inverse relation between the stability constants $K_{CuH_{-2}X}$ and the displacement rates $k_{H,edta}$ but the correlation here is not as straightforward as in the direct nucleophilic substitution reaction of macrocyclic polyether (crown ether) complexes of Pb^{II} with L^2,[24] or of copper(II) aminocarboxylate complexes with a 13-membered macrocyclic tetra-amine homologue.[23]

In the reaction of the X^2 and X^3 complexes with edta in lutidine buffers ($6 < pH < 7.5$) additional pathways (8) and (9) other than (3) lead to the edta complex product. The rate constant k_0 in (8) is attributed to a solvent-assisted molecular rearrangement (or dissociation) of $[CuH_{-2}X]$ to a form that can react directly with edta, the rates being limited by the rearrangement. In the reaction of the X^5 complex, the rate-determining step is considered to involve breakage of a copper–imide bond.[26] The lowest k_0 value, with the macrocycle X^3, should be associated with the extremely difficult breakage of the copper–imide (or –amine) bonds which requires extensive rearrangement of the rigid square-planar 14-membered macrocyclic co-ordination. The relative k_0 values for X^2 and X^3 are inversely proportional to their $K_{CuH_{-2}X}$ values, indicating that the ease of Cu–N bond cleavage determines the rates. Protonation does not affect the relative kinetic inertness of the X^3 complex, as shown by its having the smallest k_{H^+} value.

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