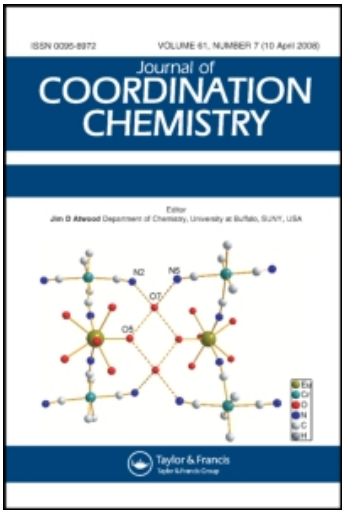

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LIGAND EXCHANGE REACTIONS. THE KINETICS OF THE REACTION OF [14]aneN$_4$, [15]aneN$_4$ AND [16]aneN$_4$ WITH COPPER(II) GLYCYLGLYCINATE

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LIGAND EXCHANGE REACTIONS. THE KINETICS OF THE REACTION OF [14]aneN$_4$, [15]aneN$_4$ AND [16]aneN$_4$ WITH COPPER(II) GLYCYLGLYCINATE

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The kinetics of the reaction of the 14-, 15- and 16-membered tetra-aza macrocycles (1–3) with Cu(II)-glycylglycinate have been studied at 25°C by stopped-flow techniques. A biphasic reaction was observed in all the reactions at λ_{max} for the Cu(II) macrocycle (470–550 nm). The initial fast step is associated with an absorbance decrease and the slower reaction to an absorbance increase. The latter reaction is assigned to the metal exchange step and is first order in both the total ligand and Cu(II)-glycylglycinate concentrations. All kinetic measurements were carried out under *pseudo* first-order conditions in the pH range 7.5 to 9.0 with Cu(II)-glycylglycinate in at least a ten-fold excess. Specific rate constants have been obtained for the reactions

$$[CuG_2H_{-1}(OH_2)] + HL^+ \rightarrow [CuL]^{2+} + G_2;\ k_1$$

$$[CuG_2H_{-1}(OH)]^- + HL^+ \rightarrow [CuL]^{2+} + G_2;\ k_2$$

where HL^+ is the monoprotonated form of the tetra-aza macrocycle and G_2 is the anion of glyclyglycine. Thus for the reaction with [14]aneN$_4$, $k_1 = 3.0 \times 10^3$ dm^3 mol^{-1} s^{-1} and $k_2 = 1.3 \times 10^5$ dm^3 mol^{-1} s^{-1} at 25°C and I = 0.15 mol dm^{-3} (NaCl). The mechanism of the reaction is discussed in detail.

KEYWORDS: copper(II), glyclyglycine, macrocycles, exchange kinetics.

INTRODUCTION

Ligand exchange reactions of the general type $ML_1^{n+} + L_2 \rightarrow ML_2^{n+} + L_1$ are of considerable interest from a mechanistic viewpoint and because of their importance in biological processes. In general, these reactions proceed through intermediates in which the incoming ligand is partially coordinated and the leaving ligand is partially dissociated. It has been observed in some systems that there is an inverse relationship between the thermodynamic stability of the reactant complex and its reactivity. Such a relationship has been found for open-chain ligands[1] and for cyclic polyamines.[2]

Wu and Kaden[3] have studied the kinetics of the reaction of cyclam (1,4,8,11-tetra-azacyclotetradecane = [14]aneN$_4$) with a series of Cu(II) complexes CuL for

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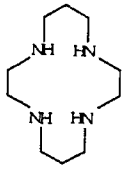
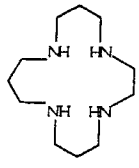
which the formation constants span some fifteen orders of magnitude. For complexes with formation constants greater than 2.3×10^{10} mol dm^{-3} there is an inverse relationship between K_{CuL} and its reactivity towards cyclam. However, for complexes of lower thermodynamic stability the rates are quite similar with k for the exchange process falling within the range 5×10^6 to 5×10^7 dm^3 mol^{-1} s^{-1} at 25°C.

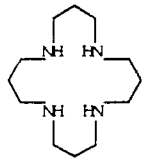
There are a large number of metalloproteins and metalloenzymes. The apoprotein or apoenzyme is normally prepared by reaction of a suitable chelating agent such as 1,10-phenanthroline with the metalloprotein or enzyme. The macrocyclic ligands [14]aneN$_4$, [15]aneN$_4$ and [16]aneN$_4$ (1–3) form very thermodynamically stable



(1)
[14]aneN$_4$

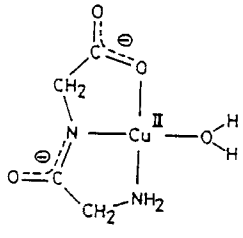


(2)
[15]aneN$_4$



(3)
[16]aneN$_4$

complexes with such biologically important metal ions as Cu(II) and Zn(II). For example, the formation constants for the Cu(II) complexes of the macrocycles are logK = 26.50 ([14]aneN$_4$); logK = 24.20 ([15]aneN$_4$) and logK = 18.92 ([16]aneN$_4$) at 25°C.[4] For this reason we have been interested in studying the ligand exchange kinetics for the reaction of tetra-aza macrocycles with model peptide complexes. The present paper deals with reaction of the macrocycles with the Cu(II) complex of glyclyglycine (4).



(4)
[CuG$_2$H$_{-1}$(OH$_2$)]

EXPERIMENTAL

Materials

Glyclyglycine, cyclam, ([14]aneN$_4$) and [15]aneN$_4$ were obtained from Aldrich. The ligand [16]aneN$_4$ was prepared as previously described.[7] Solutions of the macro-

cycles were standardized by potentiometric titration against Cu(II) in ammonia buffer pH 10, using a copper electrode.

The Cu(II) dipeptide complex $[CuG_2H_{-1}]$ was prepared in solution by slow addition of sodium hydroxide solution to a solution of Cu(II) chloride and the dipeptide (1:2 mole ratio) in 0.02 mol dm^{-3} HEPES buffer until a pH in the range 7.5 to 10.5 was obtained. A colour change from blue to violet took place on amide deprotonation (pH > 6). The Cu(II) dipeptide solutions were freshly prepared for each set of kinetic measurements. The ionic strength was maintained at 0.15 mol dm^{-3} with NaCl.

Methods

pH measurements were made using an Orion Research Ionanalyser type 901 in the pH mode. The pH meter was provided with an Orion glass electrode (91–01) and a calomel (90–05–00) electrode. The electrode system was calibrated before use with two NBS buffers (pH 9.00 and 6.87) at 25°C.

The reaction of the macrocycles with the Cu(II) dipeptide was studied under first order conditions using a Union Giken stopped-flow system type RA-401. The initial concentration of the macrocycle was 1×10^{-4} mol dm^{-3} and the Cu(II) dipeptide concentration was varied between 1×10^{-3} and 6×10^{-3} mol dm^{-3}. The reaction monitored is shown in equation (1).

$$\text{Cu(II)-dipeptide} + L_T \rightarrow CuL_T + \text{dipeptide} \quad (1)$$

where L_T represents the total ligand concentration and Cu(II)-dipeptide is the total Cu(II)-dipeptide concentration. The kinetics could be fitted to the rate expression

$$\text{Rate} = k_f[CuG_2H_{-1}][L_T] + k_d[L_T]$$

where k_f and k_d are the rate constants for complex formation and solvolytic dissociation, respectively. For each of the systems studied a series of kinetic runs were carried out at several pH values under conditions where [Cu-peptide] $\gg$ $[L_T]$ to give the first order expression

$$d[CuL_T]/dt = k_{obs}[L_T]$$

for which the observed first order rate constants k_{obs} could be obtained from the integrated form

$$\ln[CuL_T]/([CuL_T]_e - [CuL_T]_t) = 1nA_e/(A_e - A_t) = k_{obs}t$$

which can be analyzed directly. In this expression, $[CuL_T]_t$ represents the total concentration of the copper complex and $[CuL_T]_e$ the equilibrium concentration; A_t and A_e are the corresponding values of the absorbance due to the copper complex measured at λ_{max} (in the range 470–550 nm) and t is the elapsed time for each measurement of A_t.

The kinetics at each pH were measured at a minimum of four copper concentrations. At each concentration an average of six kinetic runs were carried out and the rate constants k_{obs} statistically averaged.

Protonation Constants

Stock solutions of the macrocyclic amines were standardized potentiometrically by

titration against Cu(II) using a Cu(II) selectrode in ammonia buffer pH 10. The Cu(II) solutions were prepared from the perchlorate salt (Aldrich, twice recrystallized from water) and standardized potentiometrically against EDTA. Potassium nitrate (Aldrich A.R.) was used to maintain the ionic strength at I = 0.4 mol dm^{-3}. Carbonate free solutions of sodium hydroxide (0.4 mol dm^{-3}), standardized against potassium hydrogen phthalate) were prepared from CONVOLS ampoules and degassed. All solutions were prepared with distilled CO_2-free water.

The pH titrations were carried out with a Metrohm Titro-processor (Model 670) equipped with a Metrohm glass electrode and calomel electrode. The titration cell was thermostated at 25°C using a Julabo circulator. Metrohm buffer solutions (pH 4.00, 7.00 and 9.00) were used for electrode calibration. Direct pH meter readings were used for calculation of the protonation constants. The constants determined are mixed constants (also known as Brønsted or practical constants) which involve the hydrogen ion activity and the concentration of the other species. Titration data were processed using the SUPERQUAD program.

Potentiometric Titrations

Potentiometric titrations of 1:1 mixtures of glycylglycine and (II) chloride both 3.0×10^{-3} mol dm^{-3} at I = 0.15 mol dm^{-3} (NaCl) were carried out using a Radiometer Titralab system interfaced with an Elonex PC. The titrating base was 0.098 mol dm^{-3} sodium hydroxide. Potentiometric data were processed using the SUPERQUAD program.[5]

RESULTS AND DISCUSSION

In the titration curve of a 1:1 mole ratio of Cu(II) and glyclyglycine (both 3×10^{-3} mol dm^{-3}) with sodium hycdroxide, the first end point which occurs above pH 6 is due to the formation of $[CuG_2H_{-1}(OH_2)]$ (4) with the loss of two protons from the amino group and the amide nitrogen. A second, relatively flat buffer region is followed by a weak inflection after addition of a further equivalent of base due to deprotonation of the coordinated water molecule

$$[CuG_2H_{-1}(OH_2)] \rightleftharpoons [CuG_2H_{-1}(OH)]^- + H^+ \; ; \; K \qquad (2)$$

The pK for this ionization is 9.39 at I = 0.15 mol dm^{-3} at 25°C in good agreement with the reported value of 9.31 at I = 1.0 mol dm^{-3} ($NaClO_4$).[6] In addition the dimerization equilibrium (3) can also occur in solution

$$2[CuG_2H_{-1}(OH_2)] \underset{\rightleftharpoons}{K_D} [G_2H_{-1}Cu{-}\underset{H}{O}{-}CuG_2H_{-1}]^- + H^+ + H_2O \qquad (3)$$

The value of pK_D obtained from the potentiometric data was 5.01 at I = 0.15 mol dm^{-3} in excellent agreement with a recently reported value of 5.06 at I = 1.0 mol dm^{-3} and 25°C.[6]

For the three macrocyclic ligands studied the protonation equilibria of the macrocycle (L) can be represented by the equations,

$$L + H^+ \rightleftharpoons LH^+ \; ; \; K_1$$
$$LH^+ + H^+ \rightleftharpoons LH_2^{2+} \; ; \; K_2$$

$$LH_2^{2+} + H^+ \rightleftharpoons LH_3^{3+} ; K_3$$
$$LH_3^{3+} + H^+ \rightleftharpoons LH_4^{4+} ; K_4$$

for this work it was most appropriate to use practical constants thus $K_1 = [LH^+]/a_H[L]$ where a_H is the activity of the hydrogen ion. The constants obtained for the three macrocycles are summarized in Table 1. Values of log K_3 and log K_4 are markedly dependent on the size of the macrocyclic ring, whereas log K_2 and log K_1 are relatively insensitive to the ring size. As the ring becomes smaller formation of the species LH_3^{3+} and LH_4^{4+} is increasingly difficult due to electrostatic repulsive effects.

Table 1 Protonation constants for the macrocyclic tetraamines at 25°C and I = 0.4 mol dm^{-3} (KNO_3).

Amine	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$
[14]aneN$_4$	11.050(0.003)	10.311(0.010)	<2	<2
[15]aneN$_4$	11.180(0.010)	10.310(0.010)	5.210(0.020)	3.550(0.020)
[16]aneN$_4$	10.630(0.020)	9.570(0.030)	7.480(0.040)	5.780(0.040)

Standard deviations are given in parenthesis.

Kinetics

Reaction of the tetra-aza macrocycles (L) with $[CuG_2H_{-1}]$ to give $[CuL]^{2+}$ was studied at 25°C and I = 0.15 mol dm^{-3} (NaCl). In the pH range of the measurements (8.40 to 9.0) the predominant ligand species is LH_2^{2+}. Speciation curves for [15]aneN$_4$ and [16]aneN$_4$ are shown in Fig. 1. Within this pH range Cu(II)-glycylglycinate exists as a mixture of $[CuG_2H_{-1}(OH_2)]$ and $[CuG_2H_{-1}(OH)]^-$, Fig. 2. Under the conditions used in the measurements the concentration of the Cu(II) dimer was quite small (<5%) and its contribution to the reaction was neglected.

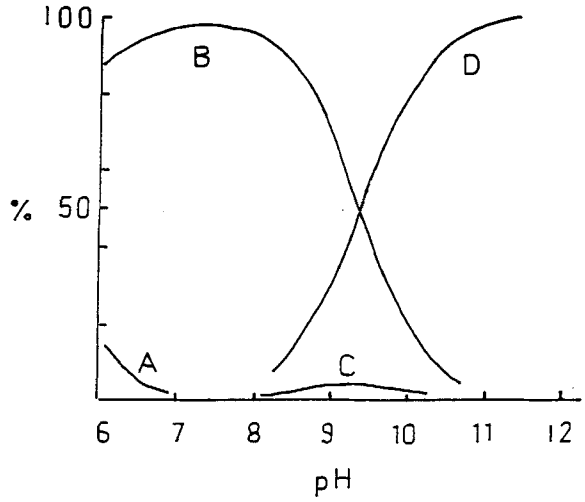


Figure 1 Speciation curves for the Cu(II)-glycylglycine system, A = free Cu(II); B = $[CuG_2H_{-1}(OH_2)]$; C = the hydroxo-bridged dimer; D = $[CuG_2H_{-1}(OH)]^-$.

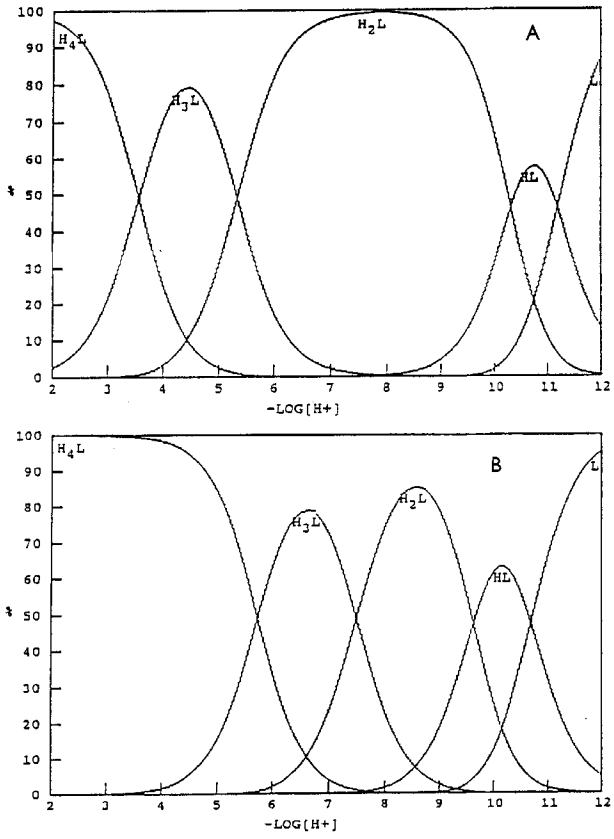


Figure 2 Speciation curves for protonation of (A) [15]aneN$_4$ and (B) [16]aneN$_4$, both 0.01 mol dm^{-3} at 25°C and I = 0.4 mol dm^{-3} (KNO_3).

The Cu(II) peptide was in at least a ten-fold excess, so that first order kinetics were observed. The reaction was monitored by stopped-flow methods at λ_{max} for the Cu(II) macrocycle (470–550 nm). At this wavelength two kinetic steps were observed. The first reaction was fast and was associated with a decrease in absorbance. This reaction was followed by a slower reaction involving an increase in absorbance. The fast step was in the 20–50 ms time range and was independent of pH or concentration of Cu(II)-glycylglycinate. The subsequent slow step was dependent on both the pH and the concentration of Cu(II)-glycylglycinate. On completion of the slow step there was an induction period of 10 to 15 s, which was followed by two or more subsequent steps with a decrease in absorbance. Only the slow step was considered in this work. The subsequent steps are probably associated with inversions of chiral *sec*-NH centers in the macrocyclic complex, which would be expected to occur in basic solution, to give the most thermodynamically stable ligand configuration.

Values of k_{obs} for the three macrocycles are summarized in Table 2. Plots of k_{obs}

Table 2 Values of k_{obs} for the reaction of tetra-azamacrocycles with Cu(II)-glycylglycinate at 25°C and I = 0.15 mol dm^{-3}

pH	$10^3[CuG_2H_{-1}]$ (mol dm^{-3})	k_{obs} (s^{-1})	pH	$10^3[CuG_2H_{-1}]$ (mol dm^{-3})	k_{obs} (s^{-1})
L = [14]aneN$_4$					
8.40	0.50	0.20	8.75	3.00	1.49
8.40	1.50	0.33	8.90	0.05	0.73
8.40	2.50	0.45	8.90	1.50	1.53
8.40	3.00	0.50	8.90	3.00	2.42
8.57	0.50	0.36	9.08	0.50	1.46
8.57	1.50	0.65	9.08	1.00	2.15
8.57	3.00	1.10	9.08	1.50	3.39
8.75	0.50	0.45	9.08	3.00	5.88
8.75	1.50	0.94			
8.75	2.50	1.28			
L = [15]aneN$_4$					
7.80	0.50	0.34	8.29	0.50	0.70
7.80	1.25	0.52	8.29	2.00	2.25
7.80	2.25	0.75	8.29	3.00	3.42
7.80	3.00	0.96	8.44	0.50	1.10
8.11	0.50	0.40	8.44	1.25	2.70
8.11	1.00	0.63	8.44	2.25	4.10
8.11	2.00	1.10	8.44	3.00	5.20
8.11	3.00	1.65	8.50	0.50	1.57
8.23	0.50	0.60	8.50	1.25	3.40
8.23	1.50	1.34	8.50	2.25	5.60
8.23	3.00	2.70	8.50	3.00	7.25
L = [16]aneN$_4$					
8.40	0.50	0.13	8.80	1.75	1.40
8.40	1.13	0.21	8.80	2.38	1.95
8.40	1.75	0.35	8.80	3.00	2.50
8.40	2.38	0.44	8.93	0.50	0.70
8.40	3.00	0.61	8.93	1.25	1.40
8.60	0.50	0.24	8.93	1.75	2.30
8.60	1.13	0.46	8.93	2.38	3.10
8.60	1.75	0.70	8.93	3.00	3.70
8.60	2.38	0.89	9.07	0.50	1.30
8.60	3.00	1.07	9.07	1.13	2.50
8.80	0.50	0.39	9.07	1.75	4.60
8.80	1.13	0.93	9.07	2.38	6.00

vs. the total concentration of Cu(II)-glycylglycinate, $[CuG_2H_{-1}]_T$ are linear (Fig. 3) with slope k_f and intercept k_d so that

$$k_{obs} = k_d + k_f[CuG_2H_{-1}]_T \quad (4)$$

The rate constant k_d relates to the spontaneous dissociation of the Cu(II) complex. The second order rate constant k_f was obtained from the relationship

$$k_f = (k_{obs} - k_d)/[CuG_2H_{-1}]_T \quad (5)$$

Plots of k_f *vs.* the hydroxide ion concentration indicate a second order dependence on $[OH^-]$, Fig. 4. This is confirmed by the results listed in Table 3 for the ligand [14]aneN$_4$. Values of $k_f/[OH^-]^2$ are essentially constant with an average value of 7.9×10^{12} M^{-3} s^{-1} at 25°C and I = 0.15 mol dm^{-3}.

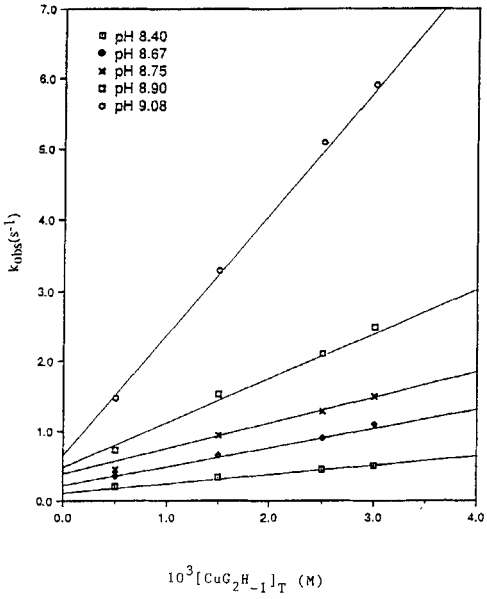


Figure 3 Plots of k_{obs} *vs.* the total concentration of Cu(II)-glycylglycinate for reaction with [14]aneN$_4$ at 25°C and I = 0.15 mol dm^{-3}. The concentration of [14]aneN$_4$ was 5×10^{-5} mol dm^{-3}.

Table 3 Hydroxide ion dependence of the reaction of [14]aneN$_4$ with Cu(II)-glycylglycinate.

pH	$10^6[OH^-]$ (mol dm^{-3})	k_2 ($M^{-1}s^{-1}$)	$k_2/[OH^-]^2$ $M^{-3}s^{-1}$)
8.40	2.51	120	1.87×10^{13}
8.57	3.72	293	2.11×10^{13}
8.75	5.62	397	1.26×10^{13}
8.90	7.93	657	1.04×10^{13}
9.0	12.00	1807	1.25×10^{13}

Measurements were made at a total Cu(II)-glycylglycinate concentration ($[CuG_2H_{-1}]_T$) of 3×10^{-3} mol dm^{-3}. The rate constant $k_2 = k_f/[CuG_2H_{-1}]_T$

If it is assumed that reaction of the species LH_2^{2+} and L with copper-glycylglycinate are not kinetically significant within the pH range used in the measurements, the kinetically important reactions are

$$LH^+ + [CuG_2(OH_2)] \xrightarrow{k_1} \text{products}$$

$$LH^+ + [CuG_2(OH)]^- \xrightarrow{k_2} \text{products}$$

In the pH range 8 to 9.5 the total ligand concentrations $L_T \sim [LH_2^{2+}]$ and

$$[L_T] = [LH_2^{2+}] = [LH^+] \cdot a_H \cdot K_2$$

The total concentration of Cu(II) glycylglycinate is given by

$$[CuG_2H_{-1}]_T = [CuG_2H_{-1}(OH_2)] + [CuG_2(OH)^-] \quad (6)$$

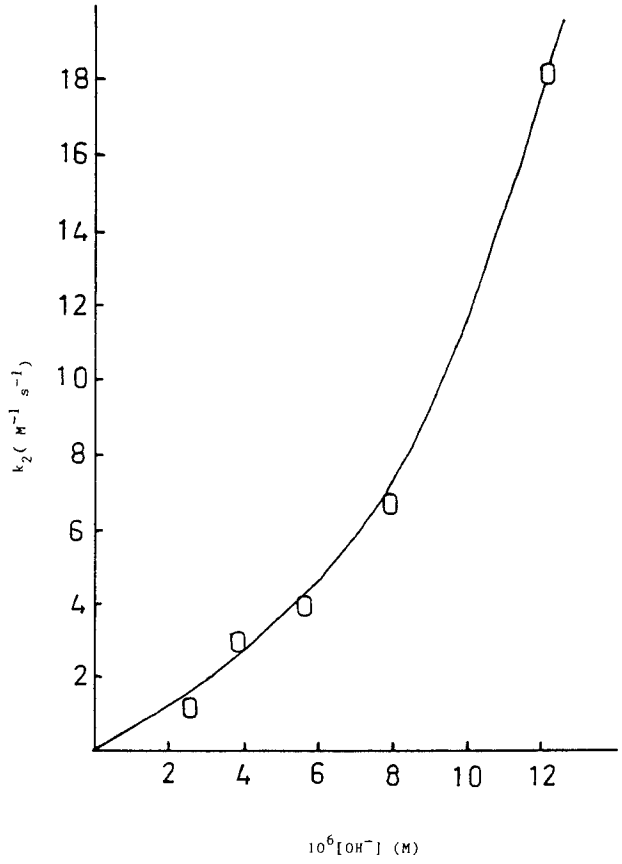


Figure 4 Plots of k_2 *vs.* the hydroxide ion concentration for reaction of Cu(II)-glycylglycinate with [14]aneN$_4$ at 25°C and I = 0.15 mol dm^{-3}. The total concentration of Cu(II)-glycylglycinate was 3×10^{-3} mol dm^{-3}. The rate constant $k_2 = k_f/[CuG_2H_{-1}]_T$.

By appropriate substitution in equation (6) it can be readily shown that

$$k_f K_2(a_H + K) = k_1 + (k_2 K/a_H) \quad (7)$$

so that a plot of $k_f K_2(a_H + K)$ *vs.* $1/a_H$ should be linear with slope k_2K and intercept k_1. The equilibrium constant K relates to ionization of the coordinated water molecule in Cu(II)-glycylglycinate and has the value 4.02×10^{-10} mol dm^{-3} at 25°C and I = 0.15 mol dm^{-3}. The constant K_2 is the second protonation constant of the ligand. A typical plot of this type for [14]aneN$_4$ is shown in Fig. 5, giving $k_1 = 3.0 \times 10^3$ dm^3 mol^{-1} s^{-1} and $k_2 = 1.3 \times 10^5$ dm^3 mol^{-1} at 25°C and I = 0.15 mol dm^{-3}.

Rate constants k_1 and k_2 for the three macrocycles are summarized in Table 4. As predicted from electrostatic considerations, reaction of the monoprotonated

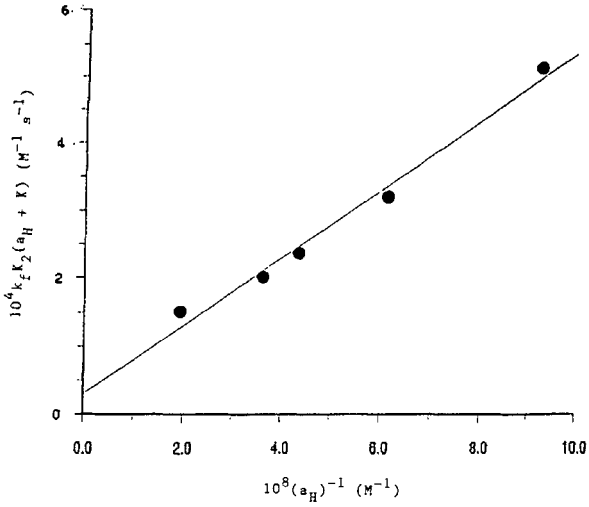


Figure 5 Plot of equation (7) to give the resolved rate constants k_1 and k_2 at 25°C and I = 0.15 mol dm^{-3}.

Table 4 Rate constants for the reaction of monoprotonated macrocycles with Cu(II)-glycylglycinate

Ligand	k_1 ($M^{-1}s^{-1}$)	k_2 ($M^{-1}s^{-1}$)	k_2/k_1
[14]aneN$_4$	3.0×10^3	1.3×10^5	41
[15]aneN$_4$	7.1×10^4	1.1×10^6	15
[16]aneN$_4$	1.8×10^3	2.5×10^4	14

macrocycles with the negatively charged hydroxo-complex $[CuG_2H_{-1}(OH)]^-$ is considerably faster than with the neutral complex $[CuG_2H_{-1}(OH_2)]$. The rate constant ratio k_2/k_1 falls within the range 14 to 41 with the effect being most marked with [14]aneN$_4$.

Wu and Kaden[3] have studied the reaction of the LH^+ species of cyclam with a number of Cu(II)-aminocarboxylate complexes. For the series of complexes $[Cu(H_2O)_6]^{2+}$, $[Cu(Gly)]^+$, [Cu(IDA)] and $[Cu(NTA)]^-$ the rate constants are 2.4×10^6, 5.2×10^6, 3.7×10^6 and 8.5×10^4 dm^3 mol^{-1} s^{-1} respectively at 25°C and I = 0.5 mol dm^{-3} (KNO_3). Limited electrostatic effects occur in moving from positively charged to negatively charged complexes. For reaction of LH^+ with $[Cu(dien)]^{2+}$ in which the nitrogen donors occupy three coordination sites k = 4.5×10^2 dm^3 mol^{-1} s^{-1} which is some ten times slower than the analogous reaction of LH^+ with $[CuG_2H_{-1}(OH_2)]$. This rate difference can be rationalized both in terms of electrostatic effects and the previously made observation[3] that a carboxylate group on Cu(II) is more easily displaced than an amino group as the latter is a stronger donor.

Displacement of glycylglycine from the Cu(II) complexes studied likely involves initial coordination of the macrocycle at the site occupied by the aquo or hydroxo ligand. This reaction is followed by displacement of the adjacent carboxylate donor.

CONCLUSIONS

Wu and Kaden[3] have shown that Cu(II) complexes which are not very thermodynamically stable react at similar rates with the monoprotonated form of [14]aneN$_4$. However, with more thermodynamically stable complexes, such as those with dipn, dien and HEDTA the more stable complexes react more slowly. The results can be fitted to an equation of the form

$$\log k = \log[k_0/(1 + K_{CuL}/K_0)]$$

where k is the experimentally determined rate constant, k_0 is the limiting rate constant observed with complexes of low stability (*ca.* 10^7 M^{-1} s^{-1}) and K_0 is the critical value of the stability constant above which the rate of ligand exchange declines (k_0 *ca.* 2.3×10^{10} M^{-1}). The present results are consistent with this pattern. For reaction of the monoprotonated LH^+ species of [14]aneN$_4$ with [$CuG_2H_{-1}(OH_2)$] k = 3.0×10^3 M^{-1} s^{-1} which is very much less than the limiting rate value at 25°C of 10^7 M^{-1} s^{-1} due to the high stability constant of the [$CuG_2H_{-1}(OH_2)$] complex. Metalloproteins with stability constants greater than 10^{10} M^{-1} are therefore expected to react relatively slowly with the monoprotonated form of [14]aneN$_4$ and the other tetra-aza macrocycles.

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