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Nucleophilic Displacement Reactions of Bis(triglycinato)cuprate(II) and Bis(glycinamide)copper(II)

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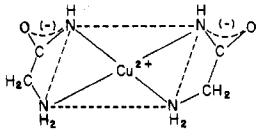
Bis(glycinamide)copper(II), $Cu(H_{-1}Ga)_2$, undergoes direct nucleophilic attack by triethylenetetramine (trien) with a rate constant of 1.4×10^4 M^{-1} s^{-1} at 25.0 °C. The trien reactivity with mono(triglycinato)cuprate(II), $Cu(H_{-2}G_3)^-$, is 3 orders of magnitude greater, but it is at least 2 orders of magnitude less with bis(triglycinato)cuprate(II), $Cu(H_{-1}G_3)_2^{2-}$, than with $Cu(H_{-1}Ga)_2$. Axial coordination of the carboxylate groups in $Cu(H_{-1}G_3)_2^{2-}$ is proposed. The reaction of *trans*-cyclohexanediaminetetraacetate, CyDTA, with $Cu(H_{-1}G_3)_2^{2-}$ proceeds by prior protonation of one peptide group to give $Cu(H_{-1}G_3)(G_3)^-$ followed by the formation of a ternary complex, $Cu(H_{-1}G_3)$CyDTA, with the displacement of one G_3^-. A similar path occurs with EDTA, but due to increased steric contraints CyDTA is 6×10^3 less effective as a nucleophile. The formation of $Cu(H_{-1}G_3)$CyDTA and the displacement of the second G_3^- to form $CuCyDTA^{2-}$ both contribute to the rate-limiting steps.

Introduction

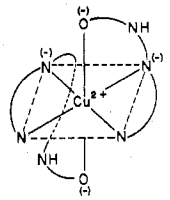
The rates of ligand-exchange reactions of the doubly deprotonated tripeptide complexes of copper(II), $Cu(H_{-2}$tripeptide$)^-$, are very sensitive to steric factors in both the attacking nucleophile[1-3a] and the tripeptide.[3b] The planarity of the coordinated deprotonated-peptide groups causes substantial hindrance to the equatorial coordination of incoming ligands. As a result nucleophiles such as EDTA which contain tertiary amine groups are not very reactive. On the other hand, triglycine (G_3^-) catalyzes[3] the exchange reaction between $Cu(H_{-2}G_3)^-$ and EDTA by forming bis(triglycinato)cuprate(II), $Cu(H_{-1}G_3)_2^{2-}$. While EDTA appears to react more rapidly with $Cu(H_{-1}G_3)_2^{2-}$ than it does with $Cu(H_{-2}G_3)^-$, just the reverse is true for trien, a nucleophile with primary amine groups.

In the present work the kinetics and mechanism of the reaction of CyDTA (*trans*-1,2-diaminocyclohexanetetraacetate) with $Cu(H_{-1}G_3)_2^{2-}$ and of trien with bis(glycinamide)copper(II), $Cu(H_{-1}Ga)_2$, are reported. The CyDTA study helps to confirm the mechanism proposed for the EDTA reaction,[3] in which $[Cu(H_{-1}G_3)G_3]^-$ is the reactive species. Greater steric hindrance for CyDTA compared to EDTA greatly decreases its rate of attack on $[Cu(H_{-1}G_3)G_3]^-$ and hence shifts the rate-determining steps to later stages in the mechanism than is the case for EDTA. The $Cu(H_{-1}G_3)_2^{2-}$ complex itself is not very reactive toward any nucleophiles. By contrast trien reacts quite rapidly with $Cu(H_{-1}Ga)_2$. The bis(glycinamide) complex of copper(II) is known to be doubly deprotonated[4-6] and has the spectral characteristics of square-planar copper complexes.[6] Raman data suggest the cis geometry shown in structure I.[2] The bis(triglycine) complex also appears to prefer a cis configuration and a coordination geometry similar to that in structure I was proposed earlier.[2] However, the large difference in the trien



I

reactivity with $Cu(H_{-1}Ga)_2$ and with $Cu(H_{-1}G_3)_2^{2-}$ leads to the proposal that the carboxylate groups in the bis(triglycine) complex are axially coordinated as shown in structure II.



II

Other physical properties provide some supporting evidence for the proposed axial coordination.

Experimental Section

Chromatographically homogeneous triglycine and glycinamide hydrochloride (Ga·HCl) were used without further purification. *trans*-1,2-Diaminocyclohexanetetraacetic acid was recrystallized as the monosodium salt and triethylenetetramine disulfate was twice recrystallized from ethanol–water. A stock 0.101 M $Cu(ClO_4)_2$ solution was prepared from the twice recrystallized salt and standardized with EDTA (murexide indicator).[7] The CyDTA and trien solutions were standardized by the mole ratio method against the Cu(II) solution and the copper(II)–triglycine and glycinamide solutions were freshly prepared prior to each day's experiments. The ionic strength was maintained at 0.20 M with $NaClO_4$. Hydrogen ion concentrations were calculated from the measured pH using the relationship $-\log [H^+] = pH - 0.14$.[8]

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Table I. Protonation and Equilibrium Constants for the Ligands and Copper(II) Complexes, 25.0 °C

protonated species or equilibrium reaction	log K	μ	ref
$HG_3^{\pm}$	7.88	0.1	12
HGa^+	7.95	0.1	6
$Htrien^+$	10.09	0.1	13
H_2trien^{2+}	9.31	0.1	13
H_3trien^{3+}	6.75	0.1	13
HCy^{3-}	9.25[a]	0.2	this work
$Cu(H_{-2}G_3)^- + H^+ \rightleftarrows Cu(H_{-1}G_3)$	6.68	0.1	12
$Cu(H_{-2}G_3)^- + G_3^- \rightleftarrows Cu(H_{-1}G_3)_2^{2-}$	2.24	0.1	2
$Cu(H_{-1}G_3)_2^{2-} + H^+ \rightleftarrows Cu(H_{-1}G_3)(G_3)^-$	7.95	1.0	14
$Cu(H_{-1}Ga)_2 + H^+ \rightleftarrows Cu(H_{-1}Ga)(Ga)^+$	8.12	0.1	6

[a] This is the apparent protonation constant in 0.2 M $NaClO_4$ where most of the unprotonated CyDTA species is $NaCyDTA^{3-}$.

Table II. Observed Rate Constants for the Reaction of $Cu(H_{-1}Ga)_2$ with trien[a]

$-\log [H^+]$	$10^2[Ga]_T$, M	$10^3[trien]_T$, M	k_{obsd}, s^{-1}
8.48	5.84	1.50	14.1 ± 0.7
8.49	5.84	3.01	16 ± 1
8.47	5.84	4.51	17.7 ± 0.9
8.75	5.37	3.01	17.2 ± 0.7
8.76	5.37	6.02	23.1 ± 0.9
8.75	5.37	9.02	26.3 ± 0.9
8.99	5.24	1.05	12.9 ± 0.3
9.00	5.24	4.51	21.6 ± 0.9
9.00	5.24	10.5	35 ± 1
9.49	5.24	1.05	16.1 ± 0.7
9.49	5.24	4.51	34 ± 2
9.51	5.24	10.5	64 ± 5
9.83	5.37	0.902	17.0 ± 0.5
9.83	5.37	3.01	31 ± 1
9.82	5.37	6.02	54 ± 2
9.83	5.37	9.02	76 ± 3
10.25	5.24	1.05	21.2 ± 0.9
10.23	5.24	4.51	58 ± 5
10.25	5.24	10.5	120 ± 20

[a] $[Cu(II)]_T = 4.04 \times 10^{-5}$ M, $\mu = 0.20$ ($NaClO_4$ + NaCl), 25.0 °C.

The reactions were monitored spectrophotometrically by following the appearance of $CuCyDTA^{2-}$ and $Cu(trien)^{2+}$ at 290 and 260 nm, respectively, using a Durrum stopped-flow spectrophotometer with a 2.0-cm observation cell thermostated at 25.0 °C. Absorbance data were collected and analyzed by means of an on-line digital computer.[9] All reactions were run under pseudo-first-order conditions and each observed rate constant is the mean of at least four kinetic runs. Further resolution of the data was accomplished by using appropriate linear or nonlinear least-squares computer programs which weighted the data as the reciprocal of the square of the observed standard deviations.

For $HCyDTA^{3-}$ the protonation constant was spectrophotometrically determined at 230 nm in 0.20 M $NaClO_4$ from repetitive scans of the UV spectrum (250–210 nm) using a Cary Model 14 spectrophotometer thermostated at 25.0 °C. The total CyDTA concentration was 7.74×10^{-4} M and the apparent protonation constant, K_{HCy}, was evaluated by means of a nonlinear regression fit to the equation: $A_i = (A_{HCy}K_{HCy}[H^+]_i + A_{Cy})/(1 + K_{HCy}[H^+]_i)$. Since CyDTA strongly complexes the sodium ion ($K_{NaCy} = 2.5 \times 10^4$ M^{-1}),[10] $NaCyDTA^{3-}$ is the predominant form of the unprotonated species in solution and the apparent protonation constant is much lower than in the absence of sodium ion.[10,11]

Table I lists the protonation and equilibrium constants for the ligands and complexes used in this study.

Results and Discussion

Reaction of $Cu(H_{-1}Ga)_2$ and $Cu(H_{-1}G_3)_2^{2-}$ with trien. The observed reactions for the bis(glycinamide) complex are first order in the $Cu(H_{-1}Ga)_2$ concentration and the rate increases with increasing trien concentration as well as with increasing pH (Table II). An absorbance change at 260 nm, which is proportional to the concentration of the $Cu(H_{-1}Ga)Ga^+$ species, occurs within the mixing time due to the rapid conversion of this species to $Cu(trien)^{2+}$. The amount of the $Cu(H_{-1}Ga)Ga^+$ species present is always less than 30% of the total copper(II) and the percent decreases as the pH increases. The rate of reaction of $Cu(H_{-1}Ga)_2$ is given by eq 1 and 2 where $k_d^{Cu(H_{-1}Ga)_2}$ is a solvent-dissociation rate constant (independent of trien). The trien-dependent rate constant, $k_{trien_T}^{Cu(H_{-1}Ga)_2}$, depends upon the pH because $[trien]_T = [trien] + [Htrien^+] + [H_2trien^{2+}]$ and the reactivity follows the sequence trien > $Htrien^+$ ≫ H_2trien^{2+} in accord with trien acting as a nucleophile. The proposed mechanism which accounts for the observed kinetics is given in eq 3–5.

$$\frac{d[Cu(trien)^{2+}]}{dt} = k_{obsd}[Cu(H_{-1}Ga)_2] \quad (1)$$

$$k_{obsd} = k_d^{Cu(H_{-1}Ga)_2} + k_{trien_T}^{Cu(H_{-1}Ga)_2}[trien]_T \quad (2)$$

$$Cu(H_{-1}Ga)_2 + trien_T \xrightarrow{k_{trien_T}^{Cu(H_{-1}Ga)_2}} Cu(trien)^{2+} + 2Ga \quad (3)$$

$$Cu(H_{-1}Ga)_2 + H_2O \xrightarrow{k_d^{Cu(H_{-1}Ga)_2}} Cu(H_{-1}Ga)Ga^+ + OH^- \quad (4)$$

$$Cu(H_{-1}Ga)Ga^+ + trien_T \xrightarrow{rapid} Cu(trien)^{2+} + 2Ga \quad (5)$$

Equation 6 is used to resolve the rate constants for the individual trien species. The resulting rate constants are summarized in Table III and are compared to the rate constants for trien reactions with other copper(II)–peptide complexes. The mono(triglycine) complex, $Cu(H_{-2}G_3)^-$, is almost 3 orders of magnitude more reactive with trien than is $Cu(H_{-1}Ga)_2$, whereas the tetraglycine complex, $Cu(H_{-3}G_4)^{2-}$, is about 30 times less reactive. The bis(triglycinato)cuprate(II) complex, $Cu(H_{-1}G_3)_2^{2-}$, fails to show direct attack by trien, but prefers a pathway in which the monotriglycine complex is formed first.[2] The data indicate that direct attack of trien on $Cu(H_{-1}G_3)_2^{2-}$ has a rate constant less than 10^2 M^{-1} s^{-1}.

$$k_{trien_T}^{Cu(H_{-1}Ga)_2}[trien]_T = k_{trien}[trien] + k_{Htrien}[Htrien^+] + k_{H_2trien}[H_2trien^{2+}] \quad (6)$$

Table III. Rate Constants for the Reactions of $Cu(H_{-1}Ga)_2$ and Other Copper(II)–Peptide Complexes, 25.0 °C

	$Cu(H_{-1}Ga)_2$[a]
k_d	11 ± 3 s^{-1}
k_{trien}	$(1.4 \pm 0.1) \times 10^4$ M^{-1} s^{-1}
k_{Htrien}	$(5.3 \pm 0.7) \times 10^3$ M^{-1} s^{-1}
k_{H_2trien}	$(5 \pm 3) \times 10^2$ M^{-1} s^{-1}
	$Cu(H_{-1}G_3)_2^{2-}$ [a]
k_{trien}	$<10^2$ M^{-1} s^{-1}
	$Cu(H_{-2}G_3)^-$ [b]
k_{trien}	1.1×10^7 M^{-1} s^{-1}
	$Cu(H_{-3}G_4)^{2-}$ [c]
k_{trien}	494 M^{-1} s^{-1}

[a] This work. [b] G. K. Pagenkopf and D. W. Margerum, *J. Am. Chem. Soc.*, **90**, 6963 (1968). [c] M. P. Youngblood, C. E. Bannister, K. L. Chellappa, and D. W. Margerum, to be submitted for publication.

Figure 1 shows a rough correlation between the rate constant for trien attack and the energy of the visible absorption maximum, ν_{max} (kK), for the copper(II)–peptide complexes. The values of ν_{max} are proportional to the degree of CFSE (crystal field stabilization energy).[15,16] Thus, the greater the CFSE due to strong donors from the peptide ligand, the slower the trien attack. The k_{trien} value with $Cu(H_{-1}Ga)_2$ (λ_{max} 540 nm)[6] is between that observed for $Cu(H_{-3}G_4)^{2-}$ (λ_{max} 520 nm)[6] and $Cu(H_{-2}G_3)^-$ (λ_{max} 555 nm).[17] On the basis of the CFSE

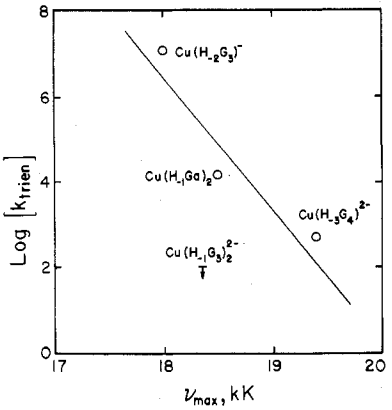

Figure 1. Correlation of the position of the visible absorption maximum with the second-order rate constant for the reaction of trien with several deprotonated-peptide complexes of copper(II).

correlation in Figure 1, a rate constant of 10^5 M^{-1} s^{-1} for trien with $Cu(H_{-1}G_3)_2^{2-}$ (λ_{max} 545 nm) would be expected, but in fact the experimental data show that the rate constant has to be less than 10^2 M^{-1} s^{-1}. The lack of a direct nucleophilic reaction with the $Cu(H_{-1}G_3)_2^{2-}$ species is attributed to the effective blocking of the axial coordination sites of the Cu^{2+} ion by the triglycine carboxylate groups (structure II). In the $Cu(H_{-1}Ga)_2$ complex (structure I), the axial Cu^{2+} sites are not blocked and therefore, this complex is susceptible to attack by trien.

The postulate that axial coordination is occurring in the $Cu(H_{-1}G_3)_2^{2-}$ complex is supported by a number of related observations. First, the visible absorption maximum for $Cu(H_{-1}G_3)_2^{2-}$ is shifted to a slightly longer wavelength than that of $Cu(H_{-1}Ga)_2$. This would be expected for axial coordination.[16] Second, the presence of a circular dichroism spectrum at long wavelengths for the analogous bis(glycylglycyl-L-alanine) (GGA) complex is also consistent with the proposed axial coordination. Circular dichroism in the complex is a consequence of the vicinal interaction of the copper chromophoric center and the carbon atom asymmetric center in the peptide residue. Under conditions favoring the formation of the $Cu(H_{-1}GGA)_2^{2-}$ complex the CD spectrum shows a large negative Cotton effect ($\Delta\epsilon^{600nm} \simeq -0.35$).[2] This suggests that the carboxylate ends of the L-alanine residues are axially coordinated, although intramolecular hydrogen-bonding interactions also could contribute to the CD signal.[18] Third, the reactions of the Cu(II) complexes of oligopeptides containing L-histidine as the third amino acid residue also indicate the presence of axial coordination by carboxylate groups.[19,20] In the case of (glycylglycyl-L-histidylglycinato)cuprate(II) the terminal carboxylate group, which can form an eight-membered chelate ring similar to the structure proposed for $Cu(H_{-1}G_3)_2^{2-}$, has a value of 93 for the equilibrium ratio of its axially coordinated form to its uncoordinated form.[20]

Reaction of $Cu(H_{-2}G_3)^-$ and $Cu(H_{-1}G_3)_2^{2-}$ with CyDTA. The rate of transfer of copper from triglycine to EDTA is faster for bis(triglycinato)cuprate(II), $Cu(H_{-1}G_3)^-$, than it is for mono(triglycinato)cuprate(II),[3] $Cu(H_{-2}G_3)^-$. Although CyDTA is more sterically hindered in mixed complex formation than is EDTA and is much slower to react, it also shows a kinetic preference for the bis(triglycine) complex compared to the mono(triglycine) complex.

The observed pseudo-first-order rate constant, k_{obsd}', is defined by eq 7 and 8. The value of k_{obsd}' is directly pro-

$$-d[CuL_n]_T/dt = k_{obsd}'[CuL_n]_T \quad (7)$$

$$[CuL_n]_T = [Cu(H_{-2}G_3)^-] + [Cu(H_{-1}G_3)_2^{2-}] + [Cu(H_{-1}G_3)G_3^-] \quad (8)$$

portional to the CyDTA concentration (Figure 2) and decreases with increasing pH (Table IV). The presence of excess G_3 over Cu(II) gives larger values of k_{obsd}', but as the excess G_3 increases the k_{obsd}' values decrease (Table IV).

A reaction mechanism analogous to that proposed for the triglycine autocatalysis[3] of the exchange reaction between $Cu(H_{-2}G_3)^-$ and EDTA is proposed for the reaction of CyDTA with $Cu(H_{-2}G_3)_2^{2-}$. The mechanism is given in eq 9–12, where

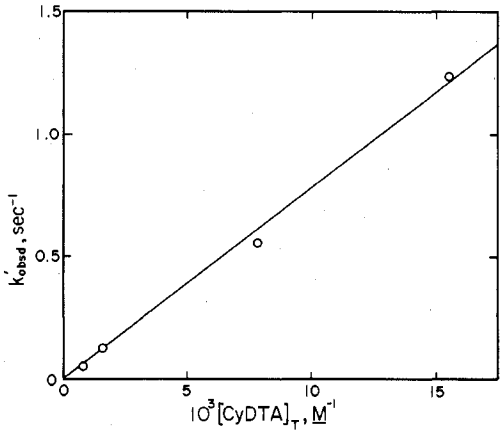

Figure 2. Effect of CyDTA on the observed rate constant for its reaction with $Cu(H_{-1}G_3)_2^{2-}$ at $-\log [H^+] = 9.42$: $[Cu(II)]_T = 4.04 \times 10^{-5}$ M, $[G_3^-]_T = 2.10 \times 10^{-2}$ M, $\mu = 0.20$ ($NaClO_4$), 25.0 °C.

Table IV. Effect of pH and Triglycine Concentration on the Rate of Transfer of Copper(II) from Triglycine to CyDTA[a]

$-\log [H^+]$	$10^2[G_3]_T$, M	$10^4[CyDTA]_T$, M	$10^2k_{obsd}'$,[b] s^{-1}
8.45	[c]	7.76	11.0 ± 0.8
8.45	2.01	7.76	75 ± 1
8.47	4.02	7.76	61 ± 2
8.47	6.02	7.76	52.4 ± 0.3
8.46	10.0	7.76	41.5 ± 0.2
8.97	[c]	3.88	7.07 ± 0.04
8.98	[c]	7.76	8.48 ± 0.09
8.97	[c]	15.5	11.0 ± 0.8
8.94	2.00	15.5	50.2 ± 0.5
8.97	3.16	15.5	44.6 ± 0.1
8.95	4.21	15.5	38.8 ± 0.1
8.94	5.02	15.5	36.8 ± 1.2
8.98	7.36	15.5	27.7 ± 0.2
8.97	9.47	15.5	24.7 ± 0.2
8.95	10.0	15.5	23.6 ± 0.4
9.40	[c]	15.5	8.0 ± 0.1
9.39	1.05	15.5	20.4 ± 0.8
9.41	2.10	15.5	12.7 ± 0.2
9.42	3.14	15.5	12.3 ± 0
9.41	4.19	15.5	10.3 ± 0.1
9.44	5.24	15.5	7.8 ± 0.2
9.42	8.03	15.5	5.89 ± 0.06
9.44	10.5	15.5	5.24 ± 0.08
9.91	[c]	77.6	12.6 ± 0.1
9.86	3.06	77.6	20.1 ± 0.2
9.90	4.02	77.6	12.6 ± 0.2
9.88	4.09	77.6	18.4 ± 0.1
9.89	6.02	77.6	10.1 ± 0.1
9.91	6.13	77.6	11.6 ± 0.1
9.90	10.0	77.6	7.4 ± 0.3
9.89	10.2	77.6	7.4 ± 0.1
10.51	[c]	77.6	8.3 ± 0.2
10.51	0.614	77.6	8.95 ± 0.07
10.50	1.02	77.6	6.8 ± 0.1
10.48	3.07	77.6	4.13 ± 0.07
10.45	6.14	77.6	2.87 ± 0.09
10.51	10.2	77.6	1.66 ± 0.02

[a] $[Cu(II)]_T = 4.04 \times 10^{-5}$ M, $\mu = 0.20$ ($NaClO_4$), 25.0 °C. [b] Error limit is 1σ for at least four replicates. [c] Reaction of CyDTA with the $Cu(H_{-2}G_3)^-$ species. $[G_3]_T = 4.10 \times 10^{-5}$ M.

$$Cu(H_{-2}G_3)^- + G_3^- + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} OH^- + Cu(H_{-1}G_3)_2^{2-} \quad (9)$$

$$Cu(H_{-1}G_3)_2^{2-} + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} OH^- + Cu(H_{-1}G_3)G_3^- \quad (10)$$

$$Cu(H_{-1}G_3)G_3^- + Cy_T \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Cu(H_{-1}G_3)Cy + G_3^- \quad (11)$$

$$Cu(H_{-1}G_3)Cy + H_2O \xrightarrow{k_4} CuCy^{2-} + G_3^- + OH^- \quad (12)$$

Cy_T is the sum of the concentrations equal to $[HCyDTA^{3-}] + [NaCyDTA^{3-}] + [CyDTA^{4-}]$. The charge of the mixed complex, $Cu(H_{-1}G_3)Cy$, is omitted because CyDTA may or may not be protonated. Any of the four steps in eq 9–12 could contribute to the rate-limiting process for EDTA depending on the conditions. However, with CyDTA the value of the k_3 rate constant is more than 3 orders of magnitude smaller than for EDTA. Hence the first two steps can establish rapid preequilibria among the various copper triglycine species. It should be noted that the species which is reactive with CyDTA (or with EDTA) is $Cu(H_{-1}G_3)G_3^-$ and not $Cu(H_{-1}G_3)_2^{2-}$.

The relatively small value of k_3 for CyDTA permits a rate contribution from the mono(triglycine) complex. This is not due to direct attack of CyDTA on $Cu(H_{-2}G_3)^-$ (eq 13) but

$$Cu(H_{-2}G_3)^- + Cy_T \xrightarrow{k_5} CuCy^{2-} + G_3^- \quad (13)$$

is from the aqueous dissociation pathway of the mono complex (eq 14 and 15).

$$Cu(H_{-2}G_3)^- + H_2O \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} Cu(H_{-1}G_3) + OH^- \quad (14)$$

$$Cu(H_{-1}G_3) + Cy_T \xrightarrow{k_7} CuCy^{2-} + G_3^- + OH^- \quad (15)$$

The data in Table IV for the reactions where $Cu(H_{-2}G_3)^-$ is the main reactant (i.e., using low G_3^- concentrations) can be used to evaluate $k_6 = 0.13\ s^{-1}$ and $k_7 = 9 \times 10^4\ M^{-1}\ s^{-1}$ at $-\log [H^+] = 8.97$. The k_6 rate constant has been determined in several other systems[3,21] and similar values have been found for this water dissociation rate constant (usually specified as k_d). The k_{obsd}' value at pH 10.5 with $[CyDTA] = 7.76 \times 10^{-3}$ M and low $[G_3^-]$ is only $0.083\ s^{-1}$, which is smaller than k_d because of hydroxide ion suppression in eq 14. This shows that the contribution from $k_5[Cy]_T$ at this pH must also be very small and that the value of k_5 must be less than $1\ M^{-1}\ s^{-1}$.

The combined expression for the observed rate constant using the reactions in eq 9–12 and 14 and 15 is given in eq 16 where $K_1 = k_1/k_{-1}$, $K_2 = k_2/k_{-2}$ and the steady-state

$$k_{obsd}' = \left[\frac{k_6k_7[Cy]_T}{(k_{-6}[OH^-] + k_7[Cy]_T)} + \frac{K_1K_2k_3k_4[G_3^-][Cy]_T}{[OH^-](k_{-3}[G_3^-] + k_4)} \right] \frac{[Cu(H_{-2}G_3)^-]}{[CuL_n]_T} \quad (16)$$

approximation is used for the species $Cu(H_{-1}G_3)$ and $Cu(H_{-1}G_3)Cy$.

As the concentration of G_3^- increases the contribution to the rate from the mono(triglycine) complex diminishes and it is convenient to define a corrected rate constant in terms of eq 17. Using the protonation constant for G_3^-, K_{HL}, the

$$k_{obsd}^{cor} = k_{obsd}' - \left(\frac{k_6k_7[Cy]_T}{k_{-6}[OH^-] + k_7[Cy]_T} \right) \frac{[Cu(H_{-2}G_3)^-]}{[CuL_n]_T} \quad (17)$$

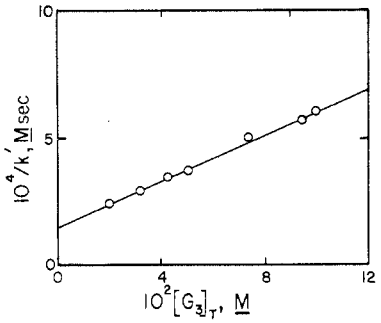

Figure 3. Resolution of the CyDTA rate constants, k_3 and k_4/k_{-3}, at $-\log [H^+] = 8.96$ from a plot of the left-hand side of eq 18 ($1/k'$) vs. $[G_3]_T$.

Table V. Comparison of Rate Constants for the Transfer of Copper(II) from Mono- and Bis(triglycine) Complexes to Polydentate Nucleophiles

	nucleophile			
constant	trien[a]	$EDTA^{4-}$ [b]	NaCy-DTA^{3-} [b]	HCy-DTA^{3-} [b]
k_d (or k_6), s^{-1}		0.12[c]	0.13	0.13
k_1, $M^{-2}\ s^{-1}$		1.26×10^7 [e]		
k_{-1}, $M^{-1}\ s^{-1}$		8.76×10^4 [e]		
k_2, s^{-1}	17.5[e]	16.7[d]		
k_{-2}, $M^{-1}\ s^{-1}$	$\sim 1 \times 10^7$ [f]	$\sim 1 \times 10^7$ [f]		
k_3, $M^{-1}\ s^{-1}$		5×10^7 [g]	8×10^5	6×10^3
k_4/k_{-3}, M		6.6×10^{-4} [d]	7.5×10^{-3}	9.4×10^{-2}
k_5, $M^{-1}\ s^{-1}$	1.1×10^7 [i]	6×10^2 [d]	(<0.1)[h]	

[a] $\mu = 0.10$ ($NaClO_4$), 25.0 °C. [b] $\mu = 0.20$ ($NaClO_4$), 25.0 °C. [c] G. K. Pagenkopf and D. W. Margerum, *J. Am. Chem. Soc.*, **90**, 6963 (1968). [d] Reference 3a. [e] Reference 2. [f] Estimated from k_2 and $\log K_2 = 7.95$.[14] [g] Estimated from $k_3/k_{-2} = 4.76$[3] and k_{-2}. [h] Estimated from comparison of k_3 for EDTA and CyDTA. [i] G. K. Pagenkopf and D. W. Margerum, *J. Am. Chem. Soc.*, **92**, 2683 (1970).

concentration of $[G_3^-]$ is $[G_3]_T/(1 + K_{HL}[H^+])$ and eq 16 and 17 can be rearranged to eq 18. Values for the left-hand side

$$\frac{[Cu(H_{-2}G_3)^-][G_3]_TK_1K_2}{[CuL_n]_T[OH^-]k_{obsd}^{cor}} = \frac{k_{-3}[G_3]_T}{k_3k_4} + \frac{(1 + K_{HL}[H^+])}{k_3} \quad (18)$$

of eq 18 at a constant log $[H^+]$ value of -8.97 (given as $1/k'$) are plotted against the concentration of free triglycine ($[G_3]_T$) in Figure 3. The values of k_3 and k_4/k_{-3} at each pH are obtained from the intercept and slope, respectively. This permits an additional resolution into the rate constants due to $HCyDTA^{3-}$ and to the unprotonated ligand (mainly $NaCyDTA^{3-}$). The resolved constants are given in Table V together with those for the analogous EDTA and trien reactions. As pointed out earlier the Na^+ complex is relatively strong[10] and $NaCyDTA^{3-}$ is the predominant unprotonated species present in these solutions.

Because the $Cu(H_{-1}G_3)_2^{2-}$ complex can be rapidly converted to the more reactive $Cu(H_{-1}G_3)(G_3)^-$ complex (Figure 4, species C), sterically constrained nucleophiles appear to react more rapidly with $Cu(H_{-1}G_3)_2^{2-}$ than with $Cu(H_{-2}G_3)^-$.[2] In fact, none of the nucleophiles tested (trien, EDTA, and CyDTA) react directly with the $Cu(H_{-1}G_3)_2^{2-}$ species, apparently because the axial coordination sites of this complex are effectively blocked by the carboxylate groups of the bound triglycinate ions. In each case the dissociation of one of the Cu(II)–N(peptide) bonds is a prerequisite for the nucleophilic reaction.

Although the $Cu(H_{-1}G_3)(G_3)^-$ species provides a more readily accessible equatorial site for nucleophilic attack than does the $Cu(H_{-2}G_3)^-$ species, a large degree of steric selectivity

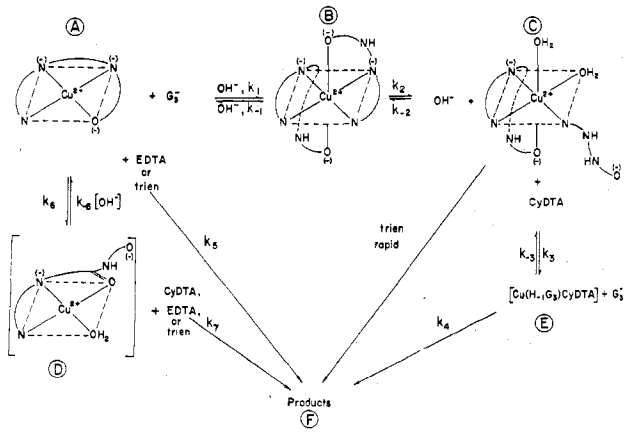

Figure 4. General reaction scheme for the transfer of copper(II) from mono- and bis(triglycine) complexes to polydentate nucleophiles. Species D and E are kinetic intermediates, not present in appreciable concentrations under the conditions used.

is still exhibited. A comparison of the k_3 values shows that CyDTA is 6×10^3 times less effective in its reaction with $Cu(H_{-1}G_3)(G_3)^-$ than is EDTA. Because of the sluggishness of the CyDTA reaction, the rate-contributing steps occur at a later stage in the reaction sequence and the interconversions of the mono- and bis(triglycine)copper complexes in eq 9 and 10 can be treated as rapid preequilibria, while for EDTA this was not possible.[3] As a consequence, a first-order dependence is observed for the CyDTA reaction, while under similar conditions there is no simple EDTA dependence. On the other hand, the k_4/k_{-3} ratio is larger for CyDTA than for EDTA because of steric hindrance in the attack of G_3^- on $Cu(H_{-1}G_3)$CyDTA (reverse reaction in eq 11). Hence for CyDTA the k_3 rate constant makes a larger contribution to the rate-limiting process than in the case with EDTA.

The general reaction scheme for the transfer of copper(II) from triglycine to polydentate nucleophiles is given in Figure 4. The direct transfer of copper(II) from triglycine (Figure 4, path A → F) is the preferred pathway for an unhindered ligand such as trien. A more sterically hindered nucleophile such as EDTA reacts only slowly by this route and this path for CyDTA was not detected. Instead, CyDTA and EDTA preferentially react via the bis complex $Cu(H_{-1}G_3)_2^{2-}$, which dissociates more rapidly (Figure 4, path B → C). However, at high pH and low nucleophile concentrations, trien also reacts primarily by this route.[2] At pH 10, the trien and EDTA reactions proceed at very similar rates because the dissociation of the $Cu(H_{-1}G_3)_2^{2-}$ species (Figure 4, path B → C) is the rate-determining step in both cases. Under the same conditions, however, the reaction with CyDTA is slower since the increased steric constraints experienced by CyDTA shift the rate-determining step to a latter stage (Figure 4, path C → E → F) in the reaction.

Conclusions

(1) Rate constants for the nucleophilic attack by trien on copper(II)–peptide complexes follow the order $Cu(H_{-2}G_3)^- \gg Cu(H_{-1}Ga)_2 \gg Cu(H_{-3}G_4)^{2-}$. This parallels the increasing degree of ligand field stabilization observed with the change in donor groups where the relative donor strength is N^- (peptide) or N^- (amide) > $-NH_2$ > $-COO^-$. By contrast the reactivity of the bis(triglycine) complex $Cu(H_{-1}G_3)_2$ is much less than expected.

(2) It is proposed that axial coordination by the carboxylate groups of the triglycinate ions in the $Cu(H_{-1}G_3)_2^{2-}$ complex prevents direct nucleophilic exchange reactions with trien, EDTA, and CyDTA. Rearrangement to the $Cu(H_{-1}G_3)(G_3)^-$ complex, which contains only one deprotonated peptide nitrogen, or loss of G_3 to form the $Cu(H_{-2}G_3)^-$ complex is a prerequisite to reaction.

(3) The reaction of CyDTA with $Cu(H_{-1}G_3)(G_3)^-$ is 6×10^3 times slower than the EDTA reaction, which in turn is much slower than the trien reaction.

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Registry No. $Cu(H_{-1}Ga)_2$, 37298-00-3; $Cu(H_{-2}G_3)^-$, 34803-37-7; $Cu(H_{-1}G_3)_2^{2-}$, 66842-51-1; trien, 4097-89-6; CyDTA, 13291-61-7.

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