Our data allow the evaluation of this equilibrium constant for the reductant, $Ru(NH_3)_5OH_2^{2+}$, and the oxidant, $Cr(H_2O)_5Cl^{2+}$. From our value of the equilibrium constant for the process

$$Ru(NH_3)_5Cl^{2+} + Cr(H_2O)_6^{2+} \rightleftharpoons (NH_3)_5Ru^{II}ClCr^{III}(H_2O)_5^{4+} \quad (6)$$

literature values for the electrode potential of the couple, $Ru(NH_3)_5H_2O^{2+,3+}$,[53] and the affinity of $Cr(H_2O)_6^{3+}$[54] and $Ru(NH_3)_5H_2O^{3+}$[34] for chloride ion, we have calculated the equilibrium constant for the process

$$Ru(NH_3)_5H_2O^{2+} + Cr(H_2O)_5Cl^{2+} \rightleftharpoons (NH_3)_5RuClCr(H_2O)_5^{4+} + H_2O \quad (7)$$

to be 4×10^{-5} M^{-1}. The small value of this equilibrium constant indicates that direct kinetic observations of such a preequilibrium step in chloride bridged reactions will not be feasible except at high concentrations.

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Steric Factors in the Kinetics of Ligand Exchange with Copper(II)–Triglycine ($CuH_{-2}L^-$)

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Abstract: The reaction of $CuH_{-2}L^-$ (where L^- is the triglycinate ion and two protons are ionized from the peptide nitrogens) with multidentate ligands proceeds by two general mechanisms. (1) In a general acid catalysis mechanism a proton is transferred to a peptide nitrogen to assist the dissociation of the triglycine. The conjugate acid of the multidentate ligand may be a reactant in this mechanism. (2) In a nucleophilic mechanism the displacing ligand coordinates to copper and speeds the breaking of the copper–peptide nitrogen bonds. The peptide nitrogens add protons only after the rate-determining step. Polyamines and aminocarboxylates in which a nitrogen donor can coordinate to copper react much faster in the second mechanism than in the first. However, steric effects are very important and the structure of the multidentate ligand can easily block the nucleophilic mechanism. Triethylenetetramine and ethylenediaminediacetate ion react by the second mechanism while N,N′,N″,N‴-tetramethyltriethylenetetramine, ethylenediaminetetraacetate ion, and nitrilotriacetate ion do not.

In a previous report it was shown that the reaction of ethylenediaminetetraacetate ion (EDTA) with $CuH_{-2}L^-$ (see Figure 1) is general acid catalyzed[3] with EDTA reacting only after a proton had been transferred to $CuH_{-2}L^-$. On the other hand, the reaction is catalyzed by triethylenetetramine (trien) which greatly speeds the conversion of copper–triglycine to copper–EDTA.[4]

In the present work, the kinetics of the direct reaction of trien with $CuH_{-2}L^-$ is studied. Trien reacts as a nucleophile in a completely different type of mechanism than the EDTA reaction. Other ligands are tested and also follow either the acid-catalyzed or nucleophilic mechanism depending on the structure of the ligand.

Experimental Section

The copper(II)–triglycine complex was prepared from twice-recrystallized copper perchlorate and from triglycine (chromatographically homogeneous, Mann Research Laboratories, N. Y.). The copper peptide solutions were freshly prepared before each series of reactions. Boric acid or sodium tetraborate solutions were used as buffering agents (total borate was 6.0×10^{-3} M). Ionic strength was maintained at 0.10 M with $NaClO_4$. The hydrogen ion concentrations were calculated from pH measurements by the relationship $-\log [H^+] = pH - 0.11$.[5] In the pH range used (7.5–9.3) the predominant copper–triglycine species present is $CuH_{-2}L^-$.[6-8]

Trien solutions were prepared from the twice-recrystallized sulfate salt (Baker Analyzed Reagent). Solutions of ethylenediaminediacetate ion (EDDA) were freshly prepared from basic solution in order to avoid cyclization of the ligand.[9] The N,N′,N″,N‴-tetramethyltriethylenetetramine was obtained from the Ames Laboratories, Inc., Milford, Conn. All exchanging ligands were standardized either by acid–base titration or by a mole-ratio method using a standard copper solution and an acetate buffer.

Kinetic runs were followed spectrophotometrically at 235 mμ using a modified Durrum–Gibson stopped-flow, Durrum Instrument Corporation, Palo Alto, Calif. Data were recorded on Polaroid film. A typical kinetic run had a $CuH_{-2}L^-$ concentration of 4×10^{-5} M and a displacing ligand concentration equal to or greater than this concentration. Each rate constant is the average of at least four kinetic runs at 25.0°. Individual rate constants, under first-order or second-order (unequal concentrations) condi-

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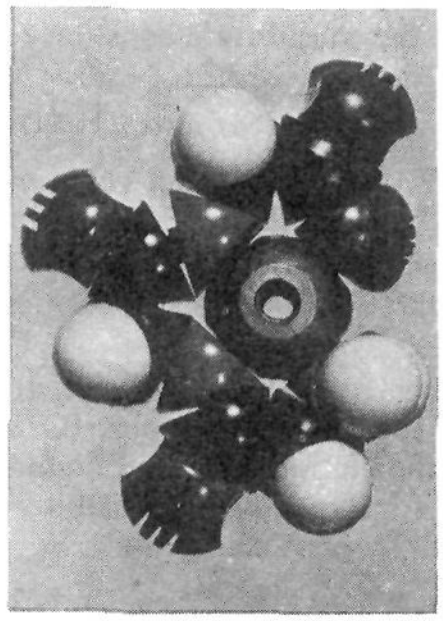

Figure 1. Structure of $CuH_{-2}L^-$. (The atoms coordinated to Cu are from the primary amine, the two deprotonated-peptide nitrogens and the carboxylate oxygen.)

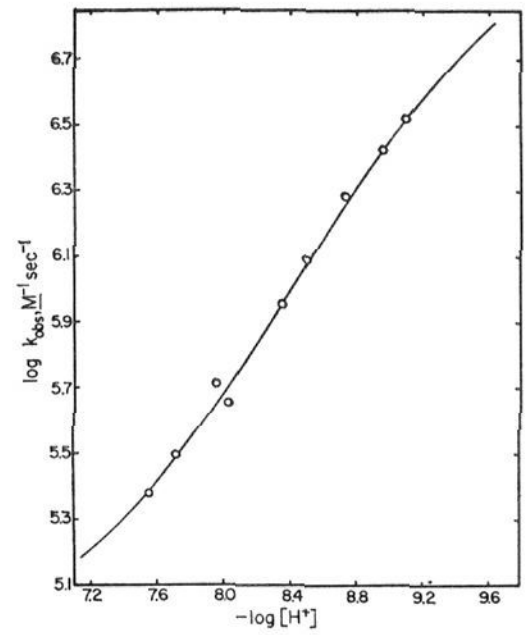

Figure 2. Hydrogen ion dependence of the second-order rate constant for the reaction of $CuH_{-2}L^-$ (2.46×10^{-5} M) with $trien_T$ (3.2×10^{-5} M) at 25.0°, $\mu = 0.10$ M ($NaClO_4$).

tions were calculated by computer using a least-squares line-fitting program. The resolved trien rate constants were calculated using a weighted regression analysis computer program (WRAP).

Results

Trien. The reaction studied is given in eq 1 where L^- is glycylglycylglycinate. The stability constants for the various species show the products to be strongly

$$\left[\begin{array}{l}\text{trien}\\ \uparrow\downarrow\\ \text{Htrien}^+\\ \uparrow\downarrow\\ \text{H}_2\text{trien}^{2+}\end{array}\right] + CuH_{-2}L^- \longrightarrow Cutrien^{2+} + \left[\begin{array}{c}L^-\\ \uparrow\downarrow\\ HL\end{array}\right] \quad (1)$$

favored for the reaction. Equimolar concentrations (2×10^{-3} M) of Cu(II), triglycine, and trien were titrated potentiometrically from pH 3.4 to 10.1 and gave titration curves identical with that expected for the products in eq 1. Therefore there are no stable mixed complexes at equilibrium. The kinetic behavior also shows no detectable intermediate species and the rate expression is given by

$$\frac{-d[CuH_{-2}L^-]}{dt} = k_{obsd}[CuH_{-2}L^-][trien_T] \quad (2)$$

where

$$[trien_T] = [trien] + [Htrien^+] + [H_2trien^{2+}] + [H_3trien^{3+}] \quad (3)$$

The reactions were very fast and the best data were obtained under second-order rather than pseudo-first-order conditions with excess trien. Nevertheless using various trien concentrations at pH 8.42–8.45 establishes that the reaction is first order in each reactant. These data are given in the first runs in Table I, which had the pH adjusted with 15% mannitol. The mannitol caused some mixing problems and although the reaction order was proved, the rate constants in this solvent mixture appeared slightly different from those in the remaining experiments in which mannitol was omitted. The pH dependence and resolution of the trien rate constants are based on experiments without mannitol.

The hydrogen ion dependence of the trien reaction is shown in Figure 2 where the points are experimental and the curve is calculated from the resolved rate constants in Table II using eq 4 and 5. At the lowest pH

$$k_{obsd}[trien_T] = k_{trien}[trien] + k_{Htrien}[Htrien^+] + k_{H_2trien}[H_2trien^{2+}] \quad (4)$$

$$Z = k_{obsd}(1 + \beta_1[H^+] + \beta_2[H^+]^2 + \beta_3[H^+]^3) = k_{trien} + k_{Htrien}\beta_1[H^+] + k_{H_2trien}\beta_2[H^+]^2 \quad (5)$$

value a small amount of H_3trien^{3+} is present but it is not considered to be a kinetically reactive species. The protonation constants used in eq 5 are $\log \beta_1 = 9.81$, $\log \beta_2 = 18.90$, and $\log \beta_3 = 25.46$,[10] and the rate constants are calculated from eq 5 using a weighting factor of $1/Z^2$ in the WRAP program.[11] The weighting

Table I. Rate Constants for the Reaction of Triethylenetetramine with Copper(II)–Triglycine[a]

10^5-$[CuH_{-2}L^-]$, M	10^5[trien], M	pH	$10^6 k_{obsd}$, M^{-1} sec^{-1}
4.92	5.05	8.45	1.45 ± 0.06[b]
	10.1	8.43	1.37 ± 0.08[b]
	24.1	8.42	1.18 ± 0.09[b]
2.46	2.55	8.45	1.06 ± 0.05[b]
	4.01	8.44	1.10 ± 0.03[b]
	3.21	8.12	0.45 ± 0.05
		8.60	1.23 ± 0.12
		8.83	1.92 ± 0.11
		9.06	2.68 ± 0.13
		9.20	3.31 ± 0.27
	3.26	8.45	0.891 ± 0.087
		8.05	0.518 ± 0.037
		7.82	0.313 ± 0.024
		7.66	0.236 ± 0.005

[a] Temperature, 25.0°; $\mu = 0.10$ M $NaClO_4$. [b] pH adjusted with 15% mannitol.

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Table II. Rate Constants for Trien Species Reaction with $CuH_{-2}L^-$ [a]

Species	k, M^{-1} sec^{-1}
trien	$1.1 \pm 0.4 \times 10^7$
$H \cdot trien^+$	$5.1 \pm 0.5 \times 10^6$
$H_2 \cdot trien^{2+}$	$1.2 \pm 0.3 \times 10^5$

[a] Temperature, 25.0°; μ = 0.10 M $NaClO_4$.

is based on a constant standard deviation for the rate constants over this pH range.

If trien reacted by the general acid catalysis mechanism (found with the EDTA reactions) the pH dependence would be the opposite to that observed in Figure 2. Furthermore even H_3trien^{3+} is such a weak acid that its predicted rate constant as an acid would be only 700 M^{-1} sec^{-1} which means that its kinetic contribution in these studies would be less than 0.1% of that observed. Because the unprotonated trien reacts the fastest of the trien species it is clear that the rate-determining step must be before or during the rupture of the first copper–peptide nitrogen bond. Once the peptide nitrogen is free from the copper it will rapidly add a proton, yet this proton is not required in the observed kinetics. Trien is reacting as a nucleophile and can coordinate to the copper–triglycine before the copper–peptide nitrogen bond dissociation. It must greatly accelerate this bond cleavage.

EDDA. In order to narrow the limits of which ligands can react directly with $CuH_{-2}L^-$, ethylenediaminediacetate ion (EDDA) was tested for comparison with the distinctly different mechanisms found for EDTA and for trien. The reaction of EDDA with $CuH_{-2}L^-$ is slower than the reaction with trien and could be studied under pseudo-first-order conditions. The dependence of the observed first-order rate constant on EDDA concentrations is shown in Table III. The value for the second-order rate constant, k' is 3.65×10^4 M^{-1} sec^{-1}, where $-d[CuH_{-2}L^-]/dt = k'[EDDA_T] \cdot [CuH_{-2}L^-]$ and $EDDA_T = EDDA^{2-} + H(EDDA)^-$.

EDTA, NTA, and TMT. Above pH 8 the reaction of EDTA with $CuH_{-2}L^-$ was shown earlier[3] to proceed largely by a first-order dissociation of $CuH_{-2}L^-$ (k_0(sec^{-1}) = $0.12 + 4.9 \times 10^6[H^+]$) independent of EDTA. Table IV lists the experimental conditions for reactions with EDTA, nitrilotriacetate ion (NTA), and N,N′,N″,N‴-tetramethyltriethylenetetramine (TMT). First-order reactions were observed with rate constants equal to or less than that expected from the proton-transfer mechanism. Although these ligands are capable of forming strong copper complexes they do not act in the nucleophilic mechanism of trien and EDDA.

NH_3. Ammonia will not easily displace $CuH_{-2}L^-$ from copper so it was tested as a catalyst for the EDTA reaction. The conditions and results are given in Table V.

Table III. Pseudo-First-Order Rate Constants for the Reaction of $CuH_{-2}L^-$ with EDDA[a]

$[CuH_{-2}L^-]$ $\times 10^5$ M	$[EDDA_T]$ $\times 10^4$ M	k_{obsd}, sec^{-1}
1.97	4.63	17.1
	3.71	13.4
	2.78	10.0

[a] pH 8.41, 25.0°, μ = 0.10 M $NaClO_4$.

Table IV. Rate Constants for $CuH_{-2}L^-$ Dissociation in the Presence of EDTA, NTA, and TMT[a]

Ligand	[Ligand] $\times 10^4$ M	$[CuH_{-2}L^-]$ $\times 10^4$ M	pH	k, sec^{-1}
EDTA	5.00	1.97	8.14	0.19
TMT	5.20	1.97	8.11	0.18
NTA	4.86	0.49	8.38	0.09

[a] 25.0°; μ = 0.10 M $NaClO_4$.

Table V. Ammonia Catalysis of the EDTA Reaction with $CuH_{-2}L^-$ [a]

$10^3[NH_3]$	k_{obsd}, sec^{-1}
1.08	0.158 ± 0.005
2.16	0.168 ± 0.006
4.32	0.230 ± 0.004
8.64	0.367 ± 0.008
k_{NH_3} = 29 ± 2 M^{-1} sec^{-1}	

[a] $[CuH_{-2}L^-] = 3.94 \times 10^{-5}$ M, $[EDTA] = 1.00 \times 10^{-4}$ M, pH 10.0, 25.0°.

Discussion

The failure of EDTA, NTA, and TMT to speed the dissociation of triglycine from copper means that coordination of either a carboxylate group or an amine group to the axial position in the structure of Figure 1 is not sufficient for the nucleophilic mechanism because all three ligands could coordinate in this manner. Copper(II) complexes in aqueous solution are well known to have square-planar or tetragonally distorted octahedral coordination and therefore axial coordination is expected to be weak.

The next most likely position for an entering ligand to coordinate is that initially occupied by the carboxylate group which should be rapidly displaced. Using models, Figure 3 shows that ammonia could coordinate in this planar position. However, Figure 4 shows that with $(CH_3)_3N$ (used to depict steric hindrance of a tertiary amine) the coordination at this position appears to be sterically blocked. Use of the criterion that the nucleophilic mechanism requires nitrogen coordination in the planar (or equatorial) position separates the ligands into two groups. Those with tertiary nitrogens (EDTA and NTA) are sterically blocked while those with primary or secondary nitrogens (trien and EDDA) can react.

On the other hand the tremendous acceleration of triglycine displacement by trien compared to the small effect of NH_3 indicates that chelation also is very important. Studies with ethylenediamine confirm this.[12] The failure of TMT to act as an effective nucleophile can be understood due to steric blocking if it needs to act as a chelate.

Therefore, we conclude that for the nucleophilic mechanism nitrogen coordination is needed in the equatorial position and that the ability to form a chelate is very important. Ligands which can react in this manner will labilize the dissociation of the deprotonated triglycine.

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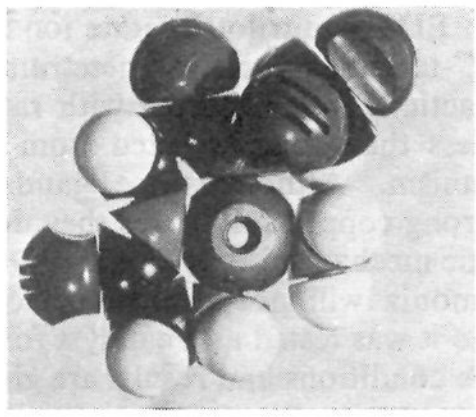

Figure 3. Proposed coordination of NH_3 to $CuH_{-2}L^-$ replacing the carboxylate group in an equatorial position.

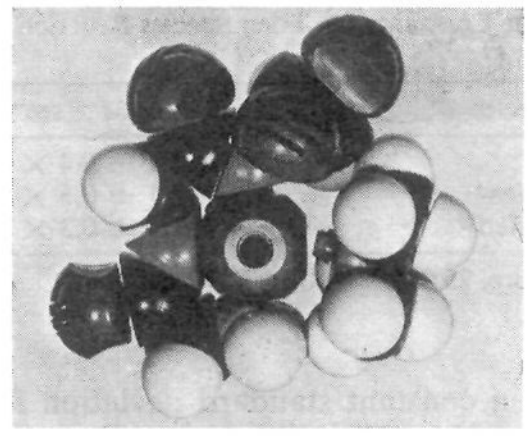

Figure 4. Proposed steric blocking of $(CH_3)_3N$ in the equatorial position.

The speed of the trien replacement of triglycine from copper is remarkable considering the number of coordinate groups which must be dissociated and replaced. Trien also reacts very rapidly with copper–EDTA[13] and this is one of the chain-propagating steps in several coordination chain reaction systems.[14,15] However, trien reacts with $CuH_{-2}L^-$ 26 times faster than it does with $CuEDTA^{2-}$. In the EDTA replacement at least half the EDTA ion must be unwrapped and three bonds to trien formed before the rate-determining step. In the triglycine replacement by free trien the rate-determining step appears to occur with the first copper–peptide nitrogen bond breakage. The number of coordination sites occupied by trien is uncertain but at least one chelate ring must be involved. Comparing $CuH_{-2}L^-$ to $CuEDTA^{2-}$ the ratio of rate constants for trien, $Htrien^+$, and H_2trien^{2+} are 26, 145, and 570, respectively. The relative increase in reactivity of the protonated species could result if less than three coordination positions were needed by trien in the rate-determining step with $CuH_{-2}L^-$. However, it is also possible that a protonated trien acts both as a nucleophile and as an acid to assist the dissociation of triglycine.

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