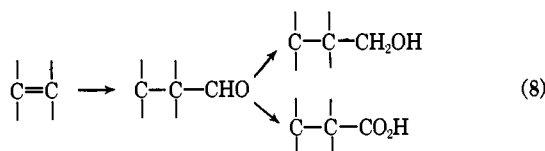


A disadvantage of this procedure is that only one of the three alkyl groups of the organoborane is converted into the aldehyde. Fortunately, we have found a means of circumventing this difficulty.⁶ However, it is apparent that this reaction is so simple and clean that it promises to provide a major new synthesis of aldehydes, readily converted into the corresponding methylol or carboxylic acid derivatives (8).



(6) Research in progress with E. Knights.

Herbert C. Brown, Randolph A. Coleman
Michael W. Rathke

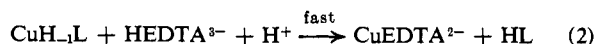
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Proton-Transfer Reactions with Copper(II)-Triglycine (CuH_2L^-)

Sir:

The copper(II)-triglycine complex is known to ionize peptide protons to form CuH_1L (or CuA) and CuH_2L^- (or CuB^-) with the loss of one and two protons, respectively ($\text{p}K_a = 5.4$ and 6.6).^{1,2} We have measured the kinetics of the proton-transfer reactions between acids and CuH_2L^- using a variety of techniques including temperature-jump relaxation, pH-jump relaxation,³ and ligand-exchange reactions by stopped flow. The latter reactions using EDTA or CyDTA (cyclohexylenediaminetetraacetate ion) are general acid (HX) catalyzed with eq 1 as the rate-determining step. The subsequent substitution reactions included in eq 2 are rapid by comparison.



The rate of conversion of CuH_2L^- to CuEDTA^{2-} was followed spectrophotometrically by observing the disappearance of CuH_2L^- at 235 or 555 $\text{m}\mu$. We observed that the rate was responsive to diprotonated EDTA rather than to the monoprotonated species, although the latter is a much better nucleophilic agent. Tests with CyDTA, which because of steric hindrance is very poor as a ligand displacing agent, showed similar behavior. The exchange reaction with EDTA also was catalyzed by buffers where the base form has little or no complexing ability (e.g., borate ion and 2,6-lutidine). The reaction rate responded to the concentration and strength of the acid form of the buffer. Finally, the values measured for k_{HX} with $\text{HX} = \text{H}_3\text{O}^+$ were in agreement with our temperature-jump and pH-jump measurements. Hence, the EDTA exchange

(1) H. Dobbie and W. D. Kermack, *Biochem. J.*, **59**, 257 (1955).

(2) M. K. Kim and A. E. Martell, *J. Am. Chem. Soc.*, **88**, 914 (1966).

(3) In this technique stopped-flow mixing permits a small change in pH to be imposed on the equilibrium between CuH_2L^- and CuH_1L . The relaxation of the system to the new equilibrium position is followed with low concentrations of indicators.

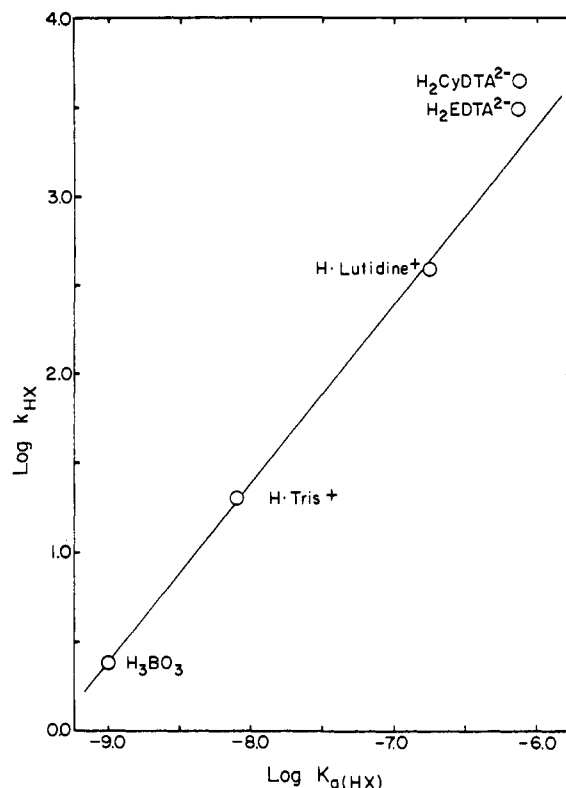


Figure 1. Brønsted plot for the reaction of acids with CuH_2L^- . The slope, α , is equal to unity which fits proton-transfer reactions far removed from the diffusion-controlled limit. The $\Delta\text{p}K$ is zero at $\log K_{a(\text{HX})} = -6.6$. The k_{HX} values are determined from the EDTA exchange reactions, at 25.0° , $\mu = 0.10$ (NaClO_4), $[\text{CuH}_2\text{L}^-] = (2.5\text{--}20) \times 10^{-4} \text{ M}$, $[\text{HX}]$ and $[\text{EDTA}] = (5\text{--}20) \times 10^{-3} \text{ M}$. Tris is tris(hydroxymethyl)aminomethane, lutidine is 2,6-dimethylpyridine, and CyDTA⁴⁻ and EDTA⁴⁻ are *trans*-cyclohexylenediaminetetraacetate ion and ethylenediaminetetraacetate ion.

reaction provides a convenient way to measure proton-transfer rate constants between acids and CuH_2L^- .

The experimentally observed first-order rate constant, k_0 , is the sum of the contributions of all acid species to reaction 1.

$$k_0 = \sum_{\text{HX}} k_{\text{HX}}[\text{HX}]$$

The k_0 values were resolved by varying the pH (6.1–8.6) and the concentrations of each acid. The rate constant for H_3O^+ and CuH_2L^- is only $6.6 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$, which is much smaller than typical diffusion-controlled rate constants. However, it is similar to the value of $1.2 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$ for the H_3O^+ reaction with the acetylacetonate anion to give the keto product.⁴

The rate constants for the other acids tested are shown in Figure 1 to follow a Brønsted general acid catalysis, and $\log k_{\text{HX}}$ against $\log K_{a(\text{HX})}$ gives a linear relationship with a slope (α) of unity. The decrease of k_{HX} with decrease in the acidity of HX is to be expected when the $\Delta\text{p}K$ ($\text{p}K_{\text{acceptor}} - \text{p}K_{\text{donor}}$) is near or less than zero.⁴ However, the fact that $\alpha = 1$ when $\Delta\text{p}K = 0$ and that the H_3O^+ reaction is four orders of magnitude less than the limiting diffusion-controlled reaction indicates that the proton addition to CuH_2L^- is associated with a charge displacement and structural modification of the complex.⁴ The addition of the proton to the

(4) M. Eigen, *Angew. Chem.*, **75**, 489 (1963).

peptide nitrogen forces it to be tetrahedral and undoubtedly changes the conformation of the chelate rings and the copper–nitrogen bond distance.

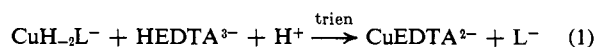
Acknowledgment. This investigation was supported by Public Health Service Research Grant No. GM-12152 from the National Institute of General Medical Sciences.

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Triethylenetetramine-Catalyzed Ligand Exchange between Copper(II)–Triglycine (CuH_2L^-) and Ethylenediaminetetraacetate Ion¹

Sir:

The exchange reaction in eq 1 is catalyzed by small concentrations of trien. Thus, when a $2.6 \times 10^{-4} M$ solution of CuH_2L^- is allowed to react with a $2.5 \times$



$10^{-3} M$ solution of EDTA in the presence of $1.20 \times 10^{-5} M$ trien at pH 8.5, the reaction velocity is four times larger than when no trien is present. In the

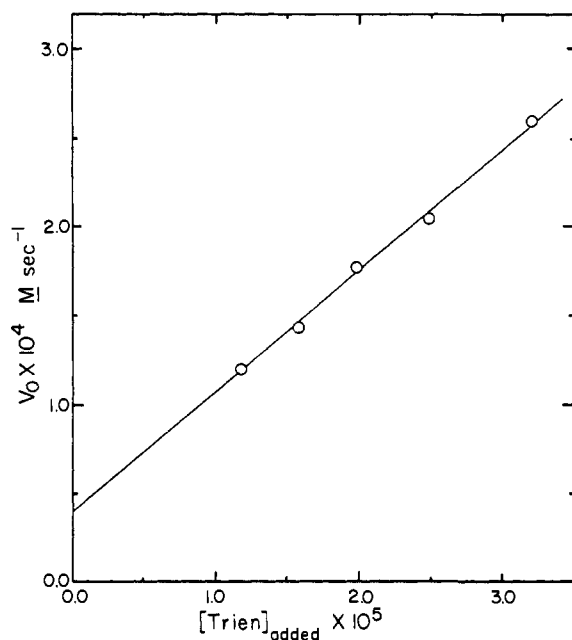


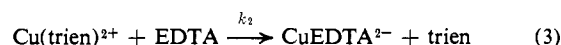
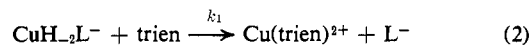
Figure 1. Trien catalysis of the exchange reaction between CuH_2L^- and EDTA. V_0 is the initial velocity of formation of CuEDTA^{2-} with $[\text{CuH}_2\text{L}^-]_{\text{initial}} = 2.46 \times 10^{-4} M$, $[\text{EDTA}] = 2.50 \times 10^{-3} M$, boric acid–borate buffer (0.013 M), pH 8.50, 25.0°, 0.10 M NaClO_4 .

absence of trien the reaction is first order in CuH_2L^- , while in its presence the reaction approaches zero-order dependence. Spectra of the products indicate that CuEDTA^{2-} is formed in both cases. All reactions are studied by stopped-flow techniques.

(1) In this paper trien stands for triethylenetetramine, EDTA for ethylenediaminetetraacetate ion, and CuH_2L^- for the copper complex with triglycine(glycylglycylglycine) which has undergone ionization of two peptide protons.

Although reaction 1 is subject to general acid catalysis,² the effect of trien cannot be attributed to this because of the high pK_a values for Htrien^+ and $\text{H}_2\text{trien}^{2+}$ and the low concentration of added trien in these experiments. The reaction of CuH_2L^- with trien was investigated separately at pH 8.5. It proceeds with a first-order dependence in each reactant ($k_1 = 1.2 \times 10^3 M^{-1} \text{sec}^{-1}$) and gives copper–trien and triglycine as products.

The mechanism proposed for reaction 1 is given by



where reaction 3 is the rate-determining step. The pH dependence of eq 2 is under study and therefore protons are omitted from the trien. The trien added is converted rapidly to Cu(trien)^{2+} , and this concentration is kept constant by the trien released in reaction 3. Therefore when EDTA is in large excess, the rate of formation of CuEDTA^{2-} is a constant (zero-order behavior).

In addition to the trien-catalyzed path, there is a contribution from water and the boric acid buffer to the general acid catalyzed path.² Therefore the reaction velocity is

$$\frac{d[\text{CuEDTA}^{2-}]}{dt} = V_0 = \left(\sum_{\text{HX}} k_{\text{HX}}[\text{HX}][\text{CuH}_2\text{L}^-] + k_0[\text{trien}]_{\text{added}} \right) \quad (4)$$

where V_0 is the observed initial velocity, and the first term on the right-hand side is the summation of all species, HX, which contribute to the general acid catalysis. Figure 1 shows the dependence of V_0 on the added trien concentration. The slope gives k_0 which in turn has been shown to depend on the EDTA concentration; $k_0 = k_2[\text{EDTA}]$. The value found for k_2 at pH 8.5 is $2.6 \times 10^3 M^{-1} \text{sec}^{-1}$, which is in good agreement with the value predicted from the reverse rate constant, $k_{\text{trien}}^{\text{CuEDTA}}$, and the corresponding conditional stability constant at this pH.³

This system is an example of one ligand catalyzing the exchange reaction between another ligand and a complex. This could be a general phenomenon, and it complements previous examples of (1) metal ion catalysis of the exchange between a metal ion and a complex⁴ and (2) ligand catalysis of complex–complex exchange (coordination chain reactions).⁵ The specific reasons for the difference in reactivity of trien and EDTA in this case are under investigation.

Acknowledgments. This investigation was supported by Public Health Service Research Grant No. GM-12152 from the National Institute of General Medical Sciences and by a David Ross Grant (G. K. P.) from Purdue Research Foundation.

(2) G. K. Pagenkopf and D. W. Margerum, *J. Am. Chem. Soc.*, **90**, 501 (1968).

(3) J. D. Carr, R. A. Libby, and D. W. Margerum, *Inorg. Chem.*, **6**, 1083 (1967).

(4) D. W. Margerum and T. J. Bydalek, *ibid.*, **1**, 852 (1962).

(5) D. C. Olson and D. W. Margerum, *J. Am. Chem. Soc.*, **85**, 297 (1963).

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