CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
PURDUE UNIVERSITY, LAFAYETTE, INDIANA 47907

Multidentate Ligand Kinetics. XV. Tetraethylenepentamine Reaction with Copper(II) Complexes

BY REX E. SHEPHERD,[1a] GERALD M. HODGSON,[1b] AND DALE W. MARGERUM*[2]

Received October 21, 1970

The kinetics of formation of Cu–tetren are first order in tetren (tetraethylenepentamine) and first order in aquocopper(II) ion or in copper complex concentrations. With $\mathrm{Cu_{aquo}}^{2+}$ the rate-determining step corresponds to the first copper–nitrogen bond formation and the reactivity order is $\mathrm{H_2tetren^{2+}} > \mathrm{H_3tetren^{3+}} > \mathrm{H_4tetren^{4+}}$ for pH 4–6.5. The rate constant–pH profiles are determined for five aminocarboxylate complexes. Several of these complexes reach a maximum rate about pH 10 and $\mathrm{Htetren^{+}}$ is the most reactive species. The reactivities of the aminocarboxylate complexes vary inversely with their copper stability constants. The rate-determining step corresponds to the coordination of three nitrogen donor groups from tetren and an appropriate degree of unwrapping of the aminocarboxylate ligand from copper. At pH 5–7 $\mathrm{CuNTA^-}$ [NTA = $\mathrm{N(CH_2COO)_3{}^{3-}}$] reacts faster with tetren than does $\mathrm{Cu_{aquo}}^{2+}$ despite the replacement of the strongly coordinated NTA group during the reaction.

Introduction

Ligand–ligand replacement rates are measured for the reaction of tetraethylenepentamine (tetren) with copper complexes of aminocarboxylate ligands according to eq 1 (written with proton assignments

$$\mathrm{CuL}^{2-z} + \text{tetren} \xrightarrow{k} \mathrm{Cu(tetren)}^{2+} + \mathrm{L}^{z-} \qquad (1)$$

omitted). The effects of the structure, dentate number, and charge of L^{z-} on the magnitude and pH dependence of the reaction rate constants are studied using tetren (and its protonated forms) as the replacement ligand. This work complements an earlier study in which polyamines were varied in their reactions with copper–EDTA.[3] The reactions are fast, requiring stopped-flow methods. The variations in L^{z-} give 5×10^4-fold variation in the observed second-order rate constants. The rate constants are highly pH dependent, increasing with pH as the degree of protonation of tetren decreases. The significance of the rate constant–pH profiles is considered in terms of reaction mechanisms with mixed-ligand intermediates and the assignment of protons to both the entering and leaving ligands.

In order to understand better the ligand-exchange reactions the formation of $\mathrm{Cu(tetren)}^{2+}$ from the aquocopper ion and highly protonated forms of tetren also was studied. The mechanism proposed for this reaction is consistent with that for the aquonickel ion in which the first polyamine–metal coordination is the rate-determining step.[4]

Experimental Section

Table I shows the structures of the ligands studied and summarizes the protonation and copper stability constants used.

The ligands were recrystallized twice before use. NTA (Aldrich Chemical Co.) and DTPA (LaMont Laboratories) were recrystallized as their acids from boiling water. EDDA (K & K Laboratories) also was obtained as the acid by first boiling it in 1 *M* NaOH to eliminate cyclic contaminants,[5] then adjusting the solution to pH 5–7, and precipitating EDDA by rapid addition of 2-propanol. HEEDTA was recrystallized as the trisodium salt from water–ethanol. tetren (Aldrich Chemical Co.) was prepared as $\text{tetren}\cdot2.5\mathrm{H_2SO_4}$. Solutions of tetren, NTA, DTPA, EDDA, and HEEDTA were standardized by a spectrophotometric mole ratio method using copper nitrate solutions prepared from electrolytic copper wire.

Copper–HEEDTA and copper–EDDA solutions were prepared by adding 10% excess copper ion to the standardized ligand solution followed by precipitation of the uncomplexed copper at pH 10. Copper–DTPA was obtained by stoichiometric addition in order to avoid the formation of the 2:1 complex[6] and the absence of the 2:1 complex was confirmed spectrophotometrically. Copper–NTA was similarly prepared from equimolar quantities of copper nitrate and NTA. The pH of the final solution was adjusted to pH 4.3 to avoid formation of the $\mathrm{Cu(NTA)_2{}^{4-}}$ complex.[7]

Constant ionic strength was maintained at 0.1 *M* adjusted with KCl for solutions involving EDDA, HEEDTA, and DTPA. Doubly recrystallized $\mathrm{NaClO_4}$ (G. F. Smith Chemical Co.) was used for the aquocopper and NTA studies. Buffers used were sodium borate–boric acid (0.005–0.01 *M*) for pH 8–10, boric acid (0.01 *M*) with mannitol added for pH 6.5–8, 2,6-lutidine (0.005–0.04 *M*) for pH 6–6.5, or sodium acetate–acetic acid (0.002–0.05 *M*) for pH 4–5.2. Measurements of pH were taken at 25° with a Beckman Research or Instrumentation Laboratory Inc. Model 245 pH meter.

Stopped-flow measurements for the HEEDTA and DTPA systems were obtained with a 0.20-cm cell path instrument attached to a Beckman DU spectrophotometer.[8] For the other reactions a Durrum-Gibson instrument with a 2.0-cm cell path was used. Temperature was controlled at 25.0 ± 0.1°. Reactions were followed at 560 or 580 nm and at 263 or 265 nm for concentrations lower than 10^{-4} *M* by measuring the increase in absorbance due to the formation of $\mathrm{Cu(tetren)}^{2+}$. With excess tetren first-order plots of $-\ln(A_\infty - A)$ *vs.* time were used. Second-order plots at equal concentration of $(A - A_i)/(A_\infty - A)$ *vs.* time were used, where A_i, A and A_∞ are the initial observed, and final absorbances, respectively. For second-order unequal concentration $\ln[a(b-x)/b(a-x)]/(b-a)$ *vs.* time was used where a, b, and x are the concentrations of tetren, copper species, and $\mathrm{Cu(tetren)}^{2+}$, respectively.

The molar absorptivities ($M^{-1}\ \mathrm{cm}^{-1}$) at the wavelengths employed are 2900 at 265 nm and 33.8 at 560 nm for CuEDDA, 3220 at 265 nm and 20.2 at 560 nm for $\mathrm{CuHEEDTA^-}$, 3310 at 265 nm and 51.6 at 560 nm for $\mathrm{CuDTPA^{3-}}$, 2230 at 263 nm and 7.1 at 580 nm for $\mathrm{CuNTA^-}$, 4800 at 236 nm, 4510 at 265 nm, 107 at 560 nm, and 156 at 580 nm for $\mathrm{Cu(tetren)}^{2+}$.

Results

Copper–DTPA and tetren.—This exchange reaction is thermodynamically favorable except at low pH. The log of the conditional equilibrium constant, $K' = ([\mathrm{DTPA}]_{\mathrm{total}}[\mathrm{Cu(tetren)}]_{\mathrm{total}})/([\mathrm{CuDTPA}]_{\mathrm{total}}\cdot$

---

[1] (a) National Science Fountation Undergraduate Research Participant, 1966. (b) National Institutes of Health Fellow, 1968–1970.

[2] Address correspondence to this author.

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

[4] D. W. Margerum, D. B. Rorabacher, and J. F. G. Clarke, Jr., *ibid.*, **2**, 667 (1963).

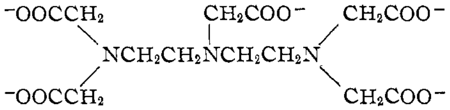
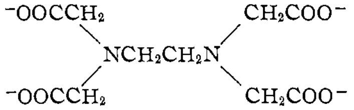
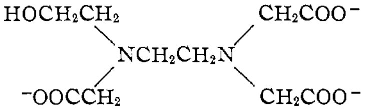
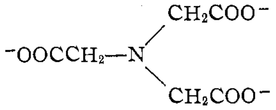
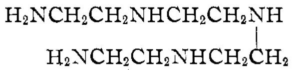
[5] R. B. LeBlanc, *Anal. Chem.*, **31**, 1840 (1959).

[6] R. E. Sievers and J. C. Bailar, Jr., *Inorg. Chem.*, **1**, 174 (1962).

[7] T. J. Bydalek and M. L. Blomster, *ibid.*, **3**, 667 (1964).

[8] D. W. Margerum and J. D. Carr, *J. Amer. Chem. Soc.*, **88**, 1639 (1966).

TABLE I
LIGANDS AND STABILITY CONSTANTS

		Log K_{CuL}	Log (protonation constants)^a				
			K_1	K_2	K_3	K_4	K_5
DTPA		21.1	10.55	8.60	4.26	2.41	2.08
EDTA		18.8	10.26	6.16	2.67	1.99	
HEEDTA		17.4	9.93	5.37	2.39		
EDDA	$^{-}OOCCH_2NHCH_2CH_2NHCH_2COO^{-}$	16.2	9.57	6.48			
NTA		13.0	9.73	2.49	1.89		
OAc	CH_3COO^{-}	1.72 (K_2 = 0.25)	4.53				
tetren	 $H_2NCH_2CH_2NHCH_2CH_2NH$ / $H_2NCH_2CH_2NHCH_2CH_2$	22.8	9.68	9.10	8.08	4.72	2.98

^{a} Constants taken from L. G. Sillén and A. E. Martell, "Stability Constants of Metal Ion Complexes," The Chemical Society, London, 1964. The tetren constants are from P. Paoletti and A. Vacca, *J. Chem. Soc.*, 5051 (1964). The acetate constants are from N. Tanaka and K. Kato, *Bull. Chem. Soc. Jap.*, **33**, 417 (1960).

$[\mathrm{tetren}]_{\mathrm{total}}$), varies from 0.2 (pH 6.5) to 2.2 (pH 10) and 1.7 (pH 12) for the reaction. Using the method of initial slopes at pH 8.6 with [tetren] = 2.42×10^{-3} *M* showed a first-order dependence in [$CuDTPA^{3-}$] (initial concentrations (0.12–1.8) $\times 10^{-3}$ *M*). A first-order dependence in [tetren] also was found using $[CuDTPA^{3-}]_i = 1.21 \times 10^{-3}$ *M* and a tetren concentration range of (1.21–9.07) $\times 10^{-3}$ *M*. The rate expression is given in eq 2 where $[\mathrm{tetren}]_{\mathrm{total}}$ refers to

$$\frac{d[\mathrm{Cu(tetren)}^{2+}]}{dt} = k^{\mathrm{CuDTPA}}{}_{\mathrm{tetren}}[\mathrm{CuDTPA}^{3-}][\mathrm{tetren}]_{\mathrm{total}} \qquad (2)$$

all forms of free tetren, protonated and unprotonated. Pseudo-first-order conditions ($[\mathrm{tetren}]_i = 1.10 \times 10^{-2}$ *M* and $[\mathrm{CuDTPA}]_i = 6.05 \times 10^{-4}$ *M*) were used to establish the pH profile shown in Figure 1.

Copper–HEEDTA and tetren.—The log *K'* value for this exchange reaction varies from 0.04 at pH 6 to 5.50 at pH 12. The reaction is much faster than with DTPA at high pH so that above pH 7.2 it was necessary to use low and equal concentrations (9.85×10^{-5} *M*) of reactants. The fastest reactions had half-lives of 25 msec. At lower pH excess tetren (9.04×10^{-3} *M* tetren and 6.02×10^{-4} *M* $CuHEEDTA^{-}$) was used as well as equimolar conditions. The reaction is first order in each reactant as in eq 2 and the $k^{\mathrm{CuHEEDTA}}{}_{\mathrm{tetren}}$ values are given in Figure 1.

A study of the influence of buffers was made with the CuHEEDTA–tetren system using 0.012 *M* lutidine and HCl in the range of pH 6–6.4, mannitol and 0.01 *M* sodium borate–boric acid pH 6.7–7.8, 0.005 *M* lutidine and 0.005 borate–boric acid pH 7, and 0.01 *M* borate–boric acid plus HCl or NaOH from pH 8.8 to 11.7. No effect on the rate constant was observed that is attributable to the buffer.

Copper–EDDA and tetren.—The log *K'* value varies from 2.8 at pH 6 to 7.8 at pH 10. The reactions were very fast so that equal concentrations were used (1.50×10^{-4} *M*) and second-order kinetics were observed. The pH profile (Figure 1) was studied only between pH 6.5 and 8 because the reactions were too fast for the stopped-flow apparatus at higher pH and lutidine buffer could not be used in the ultraviolet analysis so that pH control below pH 6.5 was difficult without introducing possible complexing agents.

Copper–NTA and tetren.—The log *K'* value for this exchange varies from 4.4 at pH 4 to 8.5 at pH 12. Since the reaction is very fast, equal concentrations were used (1.47×10^{-4} *M*) for pH >6. Second-order kinetics were observed in all cases. Below pH 5 excess tetren (1.78×10^{-4} *M* tetren and 1.01×10^{-5} *M* $CuNTA^{-}$) was used. First-order dependence in tetren was found using $[CuNTA^{-}]_i = 1.01 \times 10^{-5}$ *M* and a tetren concentration range of (1.28–2.66) $\times 10^{-4}$ *M*. No effect on the rate of reaction can be attributed to either lutidine or acetate buffers. The spectra of the product solution corresponded to that of copper–tetren and showed no evidence of a mixed complex with NTA^{3-}.

The reaction products at pH 6 and below contain appreciable concentrations of $\mathrm{Cu(tetrenH)}^{3+}$ (log $K_{\mathrm{Cu(tetrenH)}}$ = 18.3) and below pH 5 they contain appreciable amounts of $\mathrm{Cu(tetrenH_2)}^{4+}$ (log $K_{\mathrm{Cu(tetrenH_2)}}$ = 13.0).[9] A distribution curve has been given for the various tetren and copper(II)–tetren complexes.[10]

The reaction was also studied using an indicator, methyl red (p*K* = 4.95), to observe the change in pH. The reaction was monitored at 520 nm. For one set of experiments where $[\mathrm{CuNTA}]_i = 2.0 \times 10^{-5}$ *M* (pH_i

---

[9] P. Paoletti and A. Vacca, *J. Chem. Soc.*, 5051 (1964).

[10] D. Gattegno, A. M. Guiliani, and M. R. Imperatori, *J. Electroanal. Chem.*, **24**, 435 (1970).

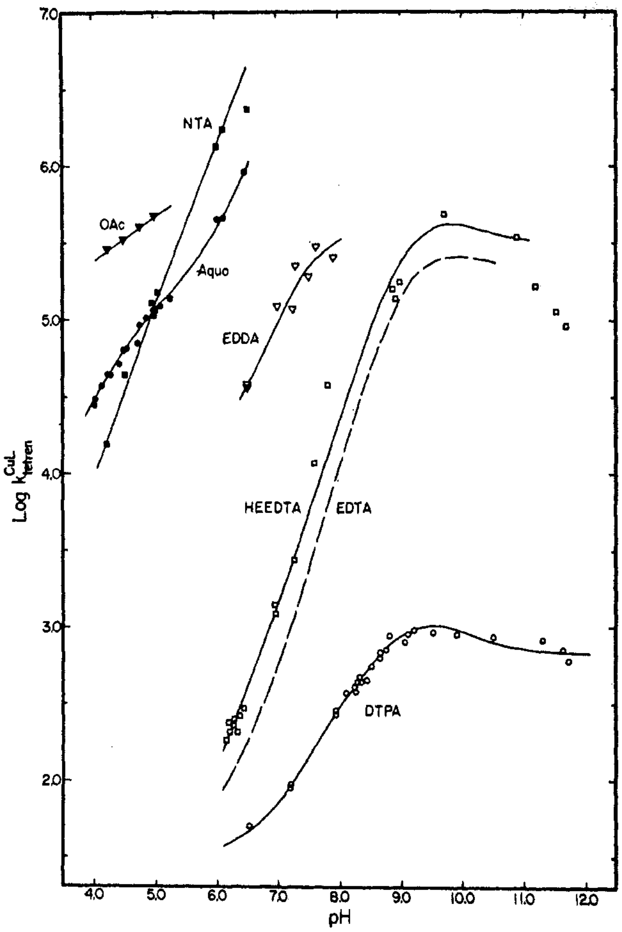


Figure 1.—Second-order rate constant–pH profile for the reaction of tetren with copper complex at 25.0° and μ = 0.10: ○, DTPA; □, HEEDTA; ▽, EDDA; ●, aquo; ■, NTA; ▼, OAc. Curves (up to pH 11) are calculated from the resolved second-order rate constants (M^{-1} sec^{-1}) in Table V except for OAc and EDDA.

4.97) and $[\text{tetren}]_i = 1.1 \times 10^{-4}$ M (pH$_i$ 4.94) the final pH was 4.60. The indicator (5.8×10^{-6} M) was initially dissolved in the tetren solution. In a second set of experiments where $[\text{CuNTA}]_i = 4.9 \times 10^{-4}$ M (pH$_i$ 4.95), $[\text{tetren}]_i = 5.5 \times 10^{-4}$ M (pH$_i$ 4.90), and [methyl red] = 9.7×10^{-6} M the final pH was 4.09. Only one reaction was observed in all experiments and the rates were essentially the same as for reactions run under buffered conditions. No further pH change was found once the reactants were mixed. The initial and final absorbances checked with calculated values within experimental error.

Aquocopper and tetren.—This formation reaction is very rapid and was studied under both pseudo-first-order conditions where either copper or tetren was in excess and second-order unequal conditions ($[\text{Cu}^{2+}]_i = 5.03 \times 10^{-6}$ to 1.06×10^{-4} M and $[\text{tetren}]_i = 1.02 \times 10^{-5}$ to 1.98×10^{-4} M). Acetate was employed to buffer the solutions. All results indicated overall second-order behavior. Some results run using excess tetren as the buffer ($[\text{Cu}^{2+}]_i = 2.51 \times 10^{-5}$ M and $[\text{tetren}]_i = 8.89 \times 10^{-4}$ M) were used to help give the rate constant–pH profile (Figure 1) for the reaction between pH 4.0 and 5.3. There was a small change in the pH during the reaction and therefore these results were confirmed using acetate buffer. Rates for the reaction above pH 6 were obtained under second-order equal conditions (1.51×10^{-4} M) with 2,6-lutidine as the buffer.

KCl, which was used initially to maintain the ionic strength, caused curvature of first-order rate plots. When $NaClO_4$ was employed, the curvature was eliminated and all results reported are with $NaClO_4$. Acetate, used as a buffer, also complicated the results by accelerating the rate of formation.

The effect of acetate ion on the Cu–tetren formation rate was studied at different pH values and by varying the acetate concentration. The experimental conditions and results are shown in Table II. For comparison, results also have been included where no acetate was present. The stability constants for the copper acetate complexes favor the 1:1 complex which resulted in approximately 10% copper acetate in solution except at the highest acetate levels where as much as 70% of the copper was in an acetate complex. The $Cu(OAc)_2$ complex concentration was negligible under the conditions used. The expression in eq 3 gave linear plots of k_{obsd} against $[OAc^-]$ at the various pH values and the intercepts agreed with values determined in the absence of acetate buffer with excess tetren. The

$$(1 + K_{CuOAc}[OAc^-])k_{obsd} = k^{Cu}{}_{tetren} + k^{CuOAc}{}_{tetren}K_{CuOAc}[OAc^-] \quad (3)$$

points for $k^{CuOAc}{}_{tetren}$ in Figure 1 were determined by use of eq 3 and the data from Table II.

TABLE II

SECOND-ORDER RATE CONSTANTS FOR THE tetren REACTION WITH AQUOCOPPER(II) IN ACETATE BUFFER MEDIA

$10^3[\text{Ac}]_{tot}$ M	$10^5[\text{Cu}^{2+}]_{tot}$ M	$10^5[\text{tetren}]_{tot}$, M	pH	$10^{-5}k$,[a] M^{-1} sec^{-1}
...	2.51	88.9	4.13[b]	0.38 ± 0.02
...	2.51	88.9	4.26[b]	0.44 ± 0.02
...	2.51	88.9	4.54[b]	0.66 ± 0.03
...	2.51	88.9	5.0[b]	1.25 ± 0.05
2.0	2.51	5.10	4.96	1.43 ± 0.06
4.0	2.51	5.10	4.98	1.65 ± 0.12
5.0	10.6	1.02	4.01	0.28 ± 0.02
5.0	106	2.04	4.02	0.31 ± 0.02
5.0	2.51	5.10	4.24	0.68 ± 0.06
5.0	2.51	5.10	4.50	1.02 ± 0.06
5.0	2.51	5.10	4.76	1.53 ± 0.07
5.0	2.51	5.10	4.99	1.89 ± 0.12
10	2.51	5.10	5.00	2.32 ± 0.18
25	2.51	5.10	4.98	3.08 ± 0.13
50	2.51	5.10	4.99	4.1 ± 0.7

[a] Average of three or more experiments. Error limits are average deviations. [b] No acetate present. The pH is the average value for the reaction.

Resolution of the aquocopper data was accomplished by a linear regression analysis which fit the pH profile using eq 4 where K_3, K_4, and K_5 refer to the protonation constants of tetren. This procedure used a weighted

$$k^{Cu}{}_{tetren}\left[1 + \frac{[H^+]}{K_3} + \frac{[H^+]^2}{K_3K_4} + \frac{[H^+]^3}{K_3K_4K_5}\right] = k^{Cu}{}_{H_2tetren} + k^{Cu}{}_{H_3tetren}\frac{[H^+]}{K_3} + k^{Cu}{}_{H_4tetren}\frac{[H^+]^2}{K_3K_4} \quad (4)$$

regression analysis program carried out on a CDC 6500 computer.[8] The hydrogen ion concentrations were calculated from pH measurements by the relationship $-\log [H^+] = pH - 0.10$. Results are shown in Table III along with the corresponding rates for the nickel(II) reaction.[4] The curve through the experi-

TABLE III

COMPARISON OF COPPER AND NICKEL FORMATION RATE CONSTANTS WITH tetren AT 25.0° AND $\mu = 0.10$

tetren species	Formn rate constants, M^{-1} sec^{-1} Cu(II)	Ni(II)	Rate ratio Cu/Ni
$H_2tetren^{2+}$	$(4.2 \pm 0.2) \times 10^7$	3.2×10^2	1.3×10^5
$H_3tetren^{3+}$	$(1.55 \pm 0.03) \times 10^5$	3.5	4.4×10^4
$H_4tetren^{4+}$	$(1.4 \pm 0.1) \times 10^4$	...	

mental points in Figure 1 is calculated using the resolved rate constants.

The same procedure was used to resolve the rates and to construct the curves in Figure 1 for $CuNTA^-$, $CuHEEDTA^-$, and $CuDTPA^{3-}$. For $CuHEEDTA^-$ only experimental points obtained up to pH 11 were used in the regression analysis.

Discussion

Aquocopper.—The substitution reactions of copper(II) are extremely rapid and the value for the characteristic water-exchange rate constant of the aquo ion is estimated to be 2 × 10^9 sec^{-1}. This constant is from the studies of Stuehr, *et al.*,[11,12] using copper(II) glycinate and copper(II) α-alanate. It is in fair agreement with the revised sound absorption data of Maass for Cu(II) and acetate ion.[13] The characteristic water-exchange rate constant for aquonickel at 25° is 2.8 × 10^4 sec^{-1}.[14] Therefore, the relative rate of initial substitution for Cu(II)/Ni(II) is approximately 7 × 10^4. Table III shows that the relative rates of the reaction of these metal ions with $H_2tetren^{2+}$ and with $H_3tetren^{3+}$ fall within a factor of 2 of this estimate. An analysis of the reaction of polyamine species with nickel(II) indicated that the rate-determining step is the first coordinate bond formation.[4] The close parallel with the relative water-substitution rate constants indicates that the first coordinate bond formation also is the rate-determining step for the copper(II) reactions with $H_2tetren^{2+}$ and $H_3tetren^{3+}$. The rate constants, although large, are less than the diffusion-controlled values even after correction for electrostatic repulsion.[15]

Cu(II) also reacts with $H_4tetren^{4+}$; the kinetic pH profile could not be resolved without including a rate term for $H_4tetren^{4+}$. Comparison with Ni(II) is not available because the nickel complex is not very stable below pH 5. The rate constant for the $Cu^{2+}{}_{aquo}$ reaction with $H_4tetren^{4+}$ is only a factor of 11 less than with $H_3tetren^{3+}$ but this is consistent with the relative electrostatic repulsion of the ions when the size of the polyamine and the distribution of the charge over the ion is considered. Clearly the rate-determining step cannot be after the loss of a proton because then $H_4tetren^{4+}$ would not be the reactant. It is less clear, however, whether or not the proton-transfer step itself might not help to limit the rate. The first two steps in the reaction sequence are given in eq 5 and 6. A steady-state approximation gives the rate expression in eq 7 where B is any proton acceptor. If B is H_2O, the magnitude of k_2 normally would depend on the

$$Cu^{2+} + H_4tetren^{4+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu(tetrenH_4)^{6+} \quad (5)$$

$$Cu(tetrenH_4)_6{}^+ + B \xrightarrow{k_2} Cu(tetrenH_3)^{5+} + HB^+ \quad (6)$$

$$\text{rate} = \frac{k_1k_2[Cu^{2+}][H_4tetren^{4+}][B]}{k_{-1} + k_2[B]} \quad (7)$$

acidity of the proton which is to be transferred from $Cu(tetrenH_4)^{6+}$. For example, if the pK_a value were 3 (the same as that of $H_5tetren^{5+}$), then the maximum possible value for k_2[B] would be ~10^7 sec^{-1} (based on a diffusion-controlled rate of 10^{10} M^{-1} sec^{-1} for the reverse process). Therefore if k_{-1} is 10^6 sec^{-1} or larger, the proton-transfer rate could become important. Electrostatic repulsion in $Cu(tetrenH_4)^{6+}$ must make k_{-1} much larger than 10^4 sec^{-1}, which is the estimated rate constant for the dissociation of the $CuNH_3^{2+}$ complex. (The dissociation rate constant is estimated from the characteristic water-exchange constant, the outer-sphere association constant of NH_3 found with nickel, and the equilibrium constant of $CuNH_3^{2+}$.) It is not known if k_{-1} approaches a value of 10^7 sec^{-1}. However, the rate constant found for the formation of products from Cu^{2+} and $H_4tetren^{4+}$ is sufficiently large that it is extremely unlikely that k_{-1} is significantly larger than k_2[B].

All the reactions of aquocopper ion with tetren showed good second-order kinetics with no evidence of appreciable concentrations of reaction intermediates. Depending on the acidity the final product may be a mixture of $Cu(tetren)^{2+}$, $Cu(tetrenH)^{3+}$, and $Cu(tetrenH_2)^{4+}$, however.

Effect of Acetate.—Inclusion of acetate as a buffer in the reaction mixtures caused an increase in the rate of the tetren reaction with copper as shown in Table II. The effect might be attributed to OAc^- acting as B in eq 6 and 7, thus removing a proton-transfer limiting step by making $k_2[B] \gg k_{-1}$. However, the increase (4 times faster at pH 5) is too large for this to be the case and the preferred explanation is that given by eq 3 where $CuOAc^+$ is a faster reactant with the highly protonated tetren species. Electrostatic repulsion would be significantly reduced with $CuOAc^+$ and this accounts for its greater reactivity. With the reaction intermediate, $AcOCu(tetrenH_4)^{5+}$, an internal proton transfer from a nitrogen to a carboxylate oxygen would tend to remove any difficulty with the proton-transfer step. However, the kinetic–pH profile of $CuOAc^+$ is subject to considerable error and the difference in its slope and that of $Cu_{aquo}{}^{2+}$ between pH 4 and 5 may not be significant.

Aminocarboxylate Ligand Exchange.—The kinetic–pH profile for the reaction of tetren with copper–EDTA shown in Figure 1 is taken from an earlier study.[3] The rate of ligand exchange increases in the order $CuDTPA^{3-} < CuEDTA^{2-} < CuHEEDTA^- < CuEDDA < CuNTA^-$ which corresponds to the decreasing stability of the CuL^{2-z} complexes. The rate-determining step must take place after the displacement of major segments of DTPA, EDTA, HEEDTA, and EDDA in order to account for the differences in their reactivities. The rate constants can all be compared at pH 6.5 and are given in Table IV relative to the EDTA reaction. In the reaction of $CuEDTA^{2-}$ with polyamines it was shown that three nitrogens from the polyamine are bonded to copper in the rate-determining

---

[11] A. F. Pearlmutter and J. Stuehr, *J. Amer. Chem. Soc.*, **90**, 858 (1968).

[12] W. B. Makinen, A. F. Pearlmutter, and J. E. Stuehr, *ibid.*, **91**, 4083 (1969).

[13] G. Maass, *Z. Phys. Chem. (Frankfurt am Main)*, **60**, 138 (1968).

[14] D. W. Margerum and H. Rosen, *J. Amer. Chem. Soc.*, **89**, 1088 (1967).

[15] E. F. Caldin, "Fast Reactions in Solution," Wiley, New York, N. Y., 1964, p 12.

TABLE IV
COMPARISON OF tetren RATE CONSTANTS (M^{-1} SEC^{-1}) AT pH 6.5

CuL^{2-z}	k^{CuL}_{tetren} (pH 6.5)	Ratio to Cu-$EDTA^{2-}$	CuL^{2-z}	k^{CuL}_{tetren} (pH 6.5)	Ratio to Cu-$EDTA^{2-}$
$CuNTA^-$	2.35×10^5	1.3×10^4	$CuEDTA^{2-}$	1.78×10^2	1.0
CuEDDA	3.70×10^4	2.1×10^2	$CuDTPA^{3-}$	0.50×10^2	0.28
$CuHEEDTA^-$	3.39×10^2	1.9			

step. This requires that at least an iminodiacetate segment of EDTA be displaced from the metal. If the aminocarboxylate ligands all reacted by a parallel mechanism with the cleavage of the last nitrogen of L as the rate-determining step, then the rate constants in Table IV might be expected to vary by 10^8 (log K_{CuDTPA} − log K_{CuNTA}) rather than 10^5. However, this neglects the very important effect of protonation of the leaving ligand as well as electrostatic effects. Nevertheless, Figure 2 shows that at pH 6.5 the relative k^{CuL}_{tetren} values are approximately proportional to $(K_{CuL})^{-1}$ for NTA, EDDA, HEEDTA, and EDTA. At pH 8 a similar proportionality is seen for EDDA, HEEDTA, EDTA, and DTPA. The effect of the differences in the charges of the various CuL^{2-z} complexes would be to decrease the slope of the line shown in Figure 2. No attempt has been made to correct for this electrostatic effect.

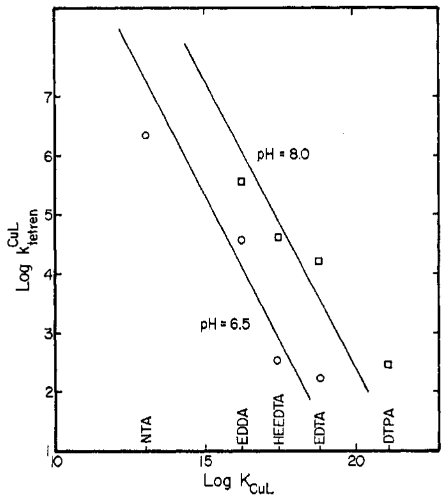
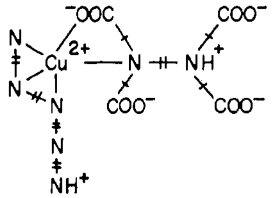
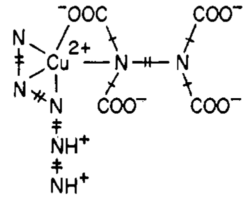


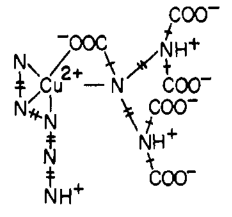
Figure 2.—Plot showing the inverse relationship between the second-order reaction rate constant (M^{-1} sec^{-1}) and the stability of the copper aminocarboxylate at pH 6.5 (○) and pH 8 (□). The slope of the line is −1.0.

Some general observations can be made concerning the effect of pH on the exchange rate constants. (1) The fact that the k^{CuL}_{tetren} values increase in all cases from pH 4 to 9 supports the argument that more than one tetren nitrogen is coordinated before the rate-determining step. If this were not the case electrostatic attraction of $H_n tetren^{n+}$ for the negative CuL^{2-z} complexes would have the opposite effect on the pH profile. (2) The large decrease in k^{CuL}_{tetren} between pH 9 and 6 corresponds to the addition of a third proton to the polyamine to give $H_3tetren^{3+}$, which is much less reactive kinetically. (3) The differences in the slopes of the pH profiles and the appearance of maxima show that protonation of the leaving group also is important.

Table V gives the resolved rate constants in terms of the reactant species. In the reaction intermediates the same number of protons as given in the reactants must be present before the rate-determining step but the protons can be distributed between the entering and leaving ligand. This distribution will depend on the relative basicity of the sites and on the kinetic effect of the proton on that site (*i.e.*, hindering an incoming group or assisting a leaving group). Thus, in the reaction of $H_2tetren^{2+}$ with $CuEDTA^{2-}$ if the polyamine has three nitrogens coordinated before the rate-determining step, the proton distribution in structure I would be much more favorable than that in structure II. Addition of a third proton to structure I would tend to place two protons on the polyamine and make its three-nitrogen coordination structure much more difficult. This corresponds to the much smaller reactivity of $H_3tetren^{3+}$ with $CuEDTA^{2-}$. On the other hand, $H_3tetren^{3+}$ is just as reactive with $CuDTPA^{3-}$ as it is with $CuEDTA^{2-}$, although the DTPA complex is kinetically more difficult to displace with $H_2tetren^{2+}$ or $Htetren^+$. This is possible because the leaving DTPA group can accept additional protons and suggests structure III as a possible reaction intermediate. The presence of this intermediate species would also explain why DTPA does not fit the pattern shown by the other ligands at pH 6.5 in Figure 2.


I


II


III

There is a much larger difference in the reactivity of $H_2tetren^{2+}$ and $H_3tetren^{3+}$ with $CuNTA^-$ (a factor

TABLE V
RESOLVED RATE CONSTANTS (M^{-1} SEC^{-1}) FOR THE VARIOUS PRONTONATED FORMS OF tetren ON CuL^{2-z}

L^{z-}	$H_4tetren^{4+}$	$H_3tetren^{3+}$	$H_2tetren^{2+}$	$Htetren^+$	tetren
$DTPA^{5-}$	. . .	(34 ± 5)	$(6.6 \pm 0.3) \times 10^2$	$(1.43 \pm 0.12) \times 10^3$	$(6.8 \pm 0.4) \times 10^2$
$EDTA^{4-}$	. . .	34	6.7×10^3	3.7×10^5	2.2×10^5
$HEEDTA^{3-}$	. . .	. . .	$(1.9 \pm 0.3) \times 10^4$	$(6.4 \pm 1.3) \times 10^5$	$(3.2 \pm 1.1) \times 10^5$
NTA^{3-}	. . .	$(6.1 \pm 0.1) \times 10^4$	$(2.1 \pm 0.4) \times 10^8$	. . .	. . .
Aquo	$(1.4 \pm 0.1) \times 10^4$	$(1.55 \pm 0.03) \times 10^5$	$(4.2 \pm 0.2) \times 10^7$	. . .	. . .

of 3.4×10^3) than with the other aminocarboxylate complexes. This too is understandable because NTA^{3-} as a leaving group has only weakly basic carboxylate sites free before cleavage of the copper–nitrogen bond in $CuNTA^-$.

In the three instances (Table V) where it was possible to measure the relative reactivity of tetren and $Htetren^+$ the latter was found to be about twice as reactive. The electrostatic attraction between CuL^{2-z} and $Htetren^+$ will assist the reaction, and if the proton remains on the tetren, it will be sufficiently distant from the tetren nitrogens coordinated to copper (see structure I) to prevent its disruption of this coordination. Also, transfer of the proton to the nitrogen of the aminocarboxylate may kinetically assist the cleavage of the aminocarboxylate copper bonding.

Only two systems were studied at high pH. For $CuDTPA^{3-}$ the same resolved rate constants were obtained regardless of the data employed. However with $CuHEEDTA^-$ it was not possible to fit the maximum point to the curve shown in Figure 1 unless the points above pH 11 were disregarded. There is no apparent reason for the large decrease above pH 11 since unprotonated tetren is the major reactant species in solution throughout this pH range. Similar unexplained results have been obtained for the reactions of diethylenetriamine with the copper(II)–cyclohexylenediaminetetraacetate complex.[3]

Comparison of Cu_{aquo}^{2+} and $CuNTA^-$.—It can be shown from the stability constant of $CuNTA^-$ and its kinetic behavior[16] that the dissociation rate of $CuNTA^-$ is slow at pH 5–6 ($k_d \approx 10^{-5}$ sec^{-1}), yet $CuNTA^-$ reacts faster with tetren in this pH range than does Cu_{aquo}^{2+}. The reaction of $H_2tetren^{2+}$ is a factor of 5 larger for the NTA complex. Electrostatic factors become quite important in comparing the reaction of 2+ and 2+ ions to that of 1− and 2+ ions. The electrostatic advantage with $CuNTA^-$ must overcome the disadvantage that its rate-determining step with $H_2tetren^{2+}$ is not the first bond formation as it is with Cu_{aquo}^{2+}. The difference in the position of the rate-determining step explains the crossover in the relative rate constants at pH 5. Additional protonation has a more adverse effect on the $CuNTA^-$ reaction because more of the tetren nitrogens need to coordinate to copper before the limiting step is reached in NTA^{3-} displacement and there are fewer basic sites on the leaving ligand to accept these protons. The experiments with methyl red show that NTA^{3-} is released in the rate-determining step and that the reaction is not a fast addition of tetren followed by a slow release of NTA^{3-}.

In general when a polyamine displaces an aminocarboxylate from a metal complex the rate is inversely proportional to the stability of the aminocarboxylate–metal complex. This rate is altered by the number of basic sites available for protons transferred from the polyamine to the leaving ligand. However there is no evidence that this transfer step limits the rate of the reaction with copper. Unlike the formation of the metal–polyamine complex from the hydrated metal ion, where the rate-determining step is the formation of the first metal–nitrogen bond, the transition state in the ligand-exchange mechanism involves at least three polyamine nitrogens bonded to the metal leaving only a single metal–nitrogen bond for the aminocarboxylate. Electrostatic effects are also important when comparing ligand-exchange reactions with formation reactions. When one reactant is a highly protonated polyamine, a ligand-exchange reaction may become more rapid than the rate of formation of the same polyamine–metal complex since the metal–aminocarboxylate complex has a reduced positive charge compared with the hydrated metal ion.

Acknowledgments.—This work was supported by National Institutes of Health Grant GM-12152 and by National Institutes of Health Fellowship No. 5-FO1-GM-39,286.

[16] N. Tanaka and M. Kimura, *Bull. Chem. Soc. Jap.*, **41**, 2375 (1968).

CONTRIBUTION FROM THE BROWN CHEMICAL LABORATORY,
UNIVERSITY OF DELAWARE, NEWARK, DELAWARE 19711

The Zinc(II)-Catalyzed Reaction of Malononitrile with Ethyl Alcohol

BY JOEL L. SILVER, MONTHER Y. AL-JANABI, ROBERT M. JOHNSON, AND JOHN L. BURMEISTER*[1]

Received August 11, 1970

Malononitrile reacts with ethyl alcohol in the presence of zinc(II) halides to form a substituted pyridine (2,4-diamino-5-cyano-6-ethoxypyridine = L), which coordinates to the metal ion, forming the complex ZnL_2X_2 (X = Cl, Br, I). The complex and the free pyridine (isolated by hydrolysis of the complex) were characterized by chemical analysis and infrared, nuclear magnetic, visible–uv, conductance, and mass spectral measurements. A possible mechanism of formation is presented involving the condensation of two molecules of malononitrile and a molecule of ethyl alcohol followed by cyclization in the presence of the zinc(II) salt. When cadmium(II) chloride or bromide was employed, a mixture of CdL_2X_2 and a trimer of malononitrile was produced. With cadmium(II) iodide, only the trimer was obtained. No reaction took place in the presence of the mercury(II) halides.

Introduction

Metal complexes of alkyl and aryl nitriles, wherein bonding to the metal atom occurs *via* the nitrogen atom, are quite common and have been known for some time.[2] Recently, complexes of alkyl dinitriles[3,4] and

[1] To whom correspondence should be addressed.

[2] R. A. Walton, *Quart. Rev., Chem. Soc.*, **19**, 126 (1965).

[3] M. F. Farona and N. J. Bremer, *J. Amer. Chem. Soc.*, **88**, 3735 (1966).

[4] M. F. Farona and K. F. Kraus, *Inorg. Chem.*, **9**, 1700 (1970).