Copper(II) and Samarium(III) Catalysis of the Hydrolysis of Ethyl Glycinate-N,N-diacetic Acid

Robert J. Angelici and Bruce E. Leach

Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa 50010. *Received March 30, 1967*

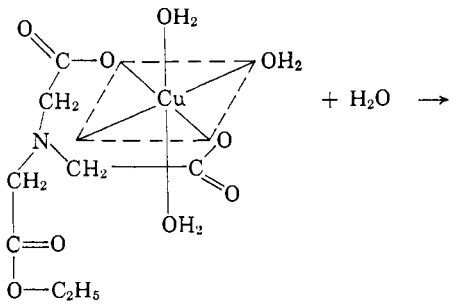
Abstract: Ethyl glycinate-N,N-diacetic acid (EGDA) was prepared by the reaction of iodoacetic acid and glycine ethyl ester in basic solution and was identified by elemental analysis, nmr, and infrared spectra. Butyl glycinate-N,N-diacetic acid (BGDA) was prepared analogously and identified by nmr. These ligands coordinate strongly with copper(II) and samarium(III), but the extent of ester carbonyl coordination to the metal is uncertain. The rate of hydrolysis of the complexes to form metal nitrilotriacetic acid (NTA) complexes in the pH range 5.0–7.0 was studied and found to obey the following rate law: rate = k[M(EGDA][OH$^-$]. These kinetic results suggest mechanisms in which a hydroxide ion attacks the carbonyl carbon of the ester which has to some extent coordinated to the copper(II) or samarium(III) in a prior equilibrium. The most probable mechanisms consistent with ionic strength dependence studies and hydroxyl complex formation constants are discussed.

Transition metal ions have long been known to promote the hydrolysis of α-amino acid esters.[1] The nature of the hydrolytic process is important because of the possible relationships to biological systems. Several mechanisms have been proposed.[1-6] Most explain the promoted hydrolysis by the assumption that polarization of the carbonyl group by the metal ion makes the carbonyl carbon more susceptible to nucleophilic attack. However, most of these studies do not indicate whether coordination of the ester in fact occurs through only the amino group or through both the amino group and the carbonyl oxygen. There is also uncertainty as to the identity of the nucleophile. Evidence for water and hydroxide attack as well as general base catalysis has been presented.

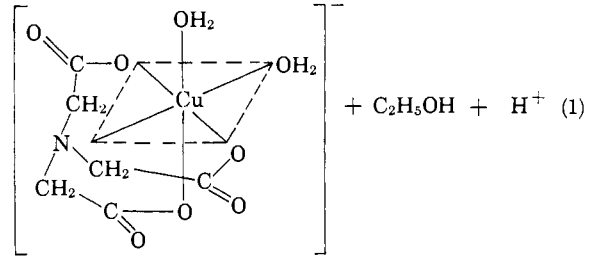
Determinations of a mechanism and treatment of the kinetics have been difficult because of the many labile complexes which result when an α-amino acid ester and a metal ion are placed in aqueous solution and the pH is varied. In general, one or two ester ligands may coordinate and these may form hydroxo complexes as well so that determination of the reactive species and their concentrations is difficult. In the presence of so many species it is nearly impossible to rule out contributions to the observed rate from species other than the mono-α-amino acid ester–metal complex.

A solution to the problem is to use relatively inert metal complexes[5] or to simplify the aqueous system under survey by minimizing prior ester equilibria.

With the latter in mind, a study of substituted iminodiacetic acids was begun. Iminodiacetic acid (IMDA) itself has a high first formation constant (log K_1 = 10.55)[7] with copper(II) and a relatively low second formation constant (log K_2 = 5.65). These values maximize the amount of Cu(IMDA) formed in near-neutral solutions. The present investigation utilizes the copper(II) and samarium(III) complexes of ethyl glycinate-N,N-diacetic acid and butyl glycinate-N,N-diacetic acid to elucidate the kinetics and mechanism of the hydrolysis of an amino acid ester derivative. The product of the reaction is the well-known metal complex of nitrilotriacetic acid (NTA).



complex I



Experimental Section

Materials. Doubly distilled water and reagent grade $Cu(NO_3)_2 \cdot 3H_2O$ and KNO_3 were used in the kinetic studies. Samarium nitrate was a gift of Professor Jack Powell, Ames Laboratory. The concentration of Cu(II) in standard $Cu(NO_3)_2$ solutions was determined by thiosulfate titration of the iodine liberated from the reaction of KI with Cu(II). Samarium(III) was determined by titration with Na_2HEDTA using xylene orange indicator.[8,9] For the infrared spectral studies in D_2O, $Cu(NO_3)_2 \cdot 3D_2O$ was prepared by dissolving $Cu(NO_3)_2 \cdot 3H_2O$ in 99.5% D_2O and evaporating to dryness under vacuum. IMDA, methyliminodiacetic acid (Me-IMDA), and NTA used in nmr studies were reagent grade.

Preparation of $C_2H_5OOCCH_2N(CH_2COO)_2Ba$. Ethyl glycinate-N,N-diacetic acid was prepared by a modification of the general procedure given by Schwarzenbach[7] for substituted iminodiacetic acids.

(1) H. Kroll, *J. Am. Chem. Soc.*, 74, 2036 (1952).
(2) M. L. Bender and B. W. Turnquest, *ibid.*, 79, 1889 (1957).
(3) H. L. Conley, Jr., and R. B. Martin, *J. Phys. Chem.*, 69, 2914 (1965).
(4) W. A. Conner, M. M. Jones, and D. L. Tuleen, *Inorg. Chem.*, 4, 1129 (1965).
(5) M. D. Alexander and D. H. Busch, *J. Am. Chem. Soc.*, 88, 1130 (1966).
(6) R. W. Hay and P. J. Morris, *Chem. Commun.*, 23 (1967).
(7) G. Schwarzenbach, G. Anderegg, W. Schneider, and H. Senn, *Helv. Chim. Acta*, 38, 1147 (1955).
(8) J. Korbl and R. Pribil, *Chemist-Analyst*, 45, 102 (1956).
(9) J. Kinnunen and B. Wennerstand, *ibid.*, 46, 92 (1957).

A 46.5-g portion (0.25 mole) of iodoacetic acid was dissolved in a minimum amount (~15 ml) of H_2O and chilled in an ice bath. Several drops of phenolphthalein indicator was added and a solution of NaOH added slowly with stirring. The temperature was kept below 30°. When the neutralization was complete, a solution of 17.6 g (0.125 mole) of glycine ethyl ester hydrochloride was added slowly. The pH was maintained at approximately 9 during the addition of the ester by addition of NaOH. After stirring the solution for 30 min at room temperature the product was precipitated by adding 31.8 g (0.26 mole) of $BaCl_2 \cdot 2H_2O$. The precipitate was filtered, washed with hot water, and dried.

For identification by nmr it was necessary to convert the barium salt which was only slightly soluble in water into the sodium salt. This was accomplished by adding Na_2SO_4, filtering the $BaSO_4$, and evaporating the resulting solution to dryness at room temperature under vacuum. The nmr spectrum was obtained on a Varian Associates Model HR-60 spectrometer in D_2O using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard (chemical shift = 0.0). As will be discussed later the chemical shifts of the ligands are dependent upon the pH of the solution (see Table I).

Table I. Nmr of $CH_3(A)-CH_2(B)-O-\overset{O}{\overset{\|}{C}}-CH_2N(CH_2COONa)_2$ (C, D)

pD 5.90 δ, ppm	Rel intensity	Multiplicity	Assignment
1.28	3	Triplet (J_{H-H} = 6.8 cps)	A
4.30	2	Quartet (J_{H-H} = 6.8 cps)	B
3.86	2	Singlet	C
3.78	4	Singlet	D
3.47		Singlet	NTA

The nmr spectrum clearly identifies ethyl glycinate-N,N-diacetic acid, but the weak singlet at δ 3.47 indicates a small amount of NTA. Integration showed that 9% of the sample was NTA, the remaining 91% being the desired EGDA. Consistent with the purity was the observation that 89% of the sample undergoes ester hydrolysis. The presence of some NTA in the sample is not unexpected since at pH 9 of the preparation, EGDA was observed to undergo slow hydrolysis to NTA.

On the basis of the nmr results, the elemental composition was calculated for a mixture of 90 mole % ($C_2H_5OOCCH_2N(CH_2COO)_2Ba \cdot H_2O$) and 10 mole % ($HN(CH_2COO)_3Ba \cdot H_2O$). *Anal.* Calcd: C, 25.40; H, 3.42; N, 3.80; Ba, 37.13. Found: C, 25.45; H, 3.93; N, 3.99; Ba, 36.70.

The infrared spectrum of the mixture in a KBr pellet showed characteristic absorptions at 3440 (H_2O), 2960 (C–H), 1740 (ester C=O), 1570 and 1408 (salt of carboxylic acid), and 1210 and 1142 cm^{-1} (ester).

Preparation of $C_4H_9OOCCH_2N(CH_2COO)_2Ba$. Butyl glycinate-N,N-diacetic acid was prepared analogously using glycine butyl ester instead of glycine ethyl ester. Lanthanum nitrate was added to the barium salt of BGDA to form the lanthanum complex. The results of the nmr taken in D_2O are given in Table II.

Table II. Nmr of $[CH_3(A)-CH_2(B)-CH_2(C)OOCCH_2N(CH_2COO)_2La(D,E)]^-$

pD 4 δ, ppm	Multiplicity	Assignment
0.90	Triplet	A
1.3–1.7	Multiplet	B
4.30	Triplet	C
3.82	Singlet	D
3.55	Singlet	E
3.47	Singlet	NTA

Kinetic Measurements. Rates of reaction were determined with a Radiometer TTTlc titrator and SBR2c titrigraph. The titrigraph plotted per cent volume of an SBUla syringe buret. The titrator was set for pH-stat work and the pH was maintained at the desired value by the addition of 0.0187 *N* NaOH. The standard 10-ml Radiometer thermostated reaction vessel was maintained at 25.0 ± 0.05°, and nitrogen was bubbled into the reaction vessel to exclude air. Radiometer electrodes and the standard stirrer were used.

A standard solution was prepared by adding 0.1480 g of the barium salt of EGDA to 62.5 ml of H_2O to make a 0.0067 *M* solution. For each kinetic run, 1.0 ml of 0.0067 *M* EGDA, 1.0 ml of 0.0067 *M* $Cu(NO_3)_2$, 2.5 ml of 0.2 *M* KNO_3, and 5.5 ml of H_2O were placed in the reaction vessel and thermostated for 15 min. The pH was raised to the desired value and the reaction followed automatically by the addition of NaOH solution while maintaining the given pH. One thus obtains a plot of the per cent of the total syringe capacity of NaOH solution delivered *vs.* time. Since the per cent at the end of the reaction (% end) minus the per cent at any time *t* (%*t*) is proportional to the concentration of unreacted EGDA, the slope of first-order plots of ln (% end − %*t*) *vs.* time, which are linear to at least 90% completion of reaction, yielded pseudo-first-order rate constants, k_{obsd}. Experimental and calculated % end values were identical if the known 90% purity of the ester was used and the pH was below the region of formation of appreciable amounts of hydroxo complexes. This is due to a difference in formation constants for Cu(EGDA)(OH) and Cu(NTA)(OH) or for the samarium analogs. Rate constants were almost always reproducible within ±10%. A general nonlinear least-squares computer program[10] was used to calculate the second-order rate constant, *k*, from the k_{obsd} and pH (*i.e.*, $-\log [a_{H^+}]$) data.

Rate Constants. The slope of a plot of ln (% end − %*t*) *vs.* time yields k_{obsd} from which the second-order rate constant, *k*, is obtained in activity units. All rate constants have been converted to molarity units by division by the appropriate factor (1.22 for 0.05 *M* ionic strength) calculated in the following manner:[11] pH* − pH = log *y*, where pH* = $-\log [H^+]$ and pH = $-\log a_{H^+}$; log *y* is given by $\log y = [-AZ_1Z_2I^{1/2}/(1 + I^{1/2})] + BI$, where *I* is the ionic strength and *B* is 0.1 for KNO_3.

Hydroxo-Complex Formation Constants. Hydroxo-complex formation constants, K_f, were determined at 25.0° for the MeIMDA and NTA complexes of Cu(II) and Sm(III) by titrating automatically with a Radiometer TTTlc titrator using 0.210 *N* NaOH and 0.05 *M* KNO_3 with a correction for NaOH consumed in a blank titration. The pH at the half-neutralization point was determined. Since the hydroxide activities, a_{OH^-}, were converted to concentrations, $[OH^-]$, the K_f values are expressed in units of molarity. The calculated titration curve using the value of K_f, the hydroxo-complex formation constant, fits the experimental curve to within 10%.

Infrared Spectra. The infrared spectra obtained in 99.5% D_2O were made in 0.10-mm cells with Irtran-2 windows using a Beckman IR-12 grating spectrophotometer.

Results

The barium salt of ethyl glycinate-N,N-diacetic acid, $[C_2H_5OOCCH_2N(CH_2COO)_2Ba]$, has been prepared and found to undergo immeasurably slow ester hydrolysis in the 4.5–7.5 pH range even in the presence of added Ba(II), but near pH 8 hydrolysis becomes significant. The pseudo-first-order rate constant, k_{obsd}, for hydrolysis at pH 9.5 is 2.0×10^{-4} sec^{-1}. Undoubtedly this includes contributions from several mechanisms of ester hydrolysis, probably including internal attack by $-COO^-$.[12] In the presence of copper(II) or samarium(III), however, hydrolysis is measurable in the 5.0–7.0 pH range. At higher pH values the rate of hydrolysis becomes too fast to measure by pH-Stat techniques.

From the known chelating tendencies of substituted iminodiacetic acids.[6] it is certain EGDA is strongly coordinated to Cu(II) or Sm(III) through the iminodiacetic acid group to give complex I probably having a

(10) R. H. Moore, based on a report from Los Alamos Scientific Laboratory, LA 2367, plus addenda. We thank Mr. J. P. Birk for modification of this program for use on the present problem and computer facilities.

(11) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp 521–526.

(12) For a review on ester hydrolysis, see M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

Table III. Summary of Chemical Shifts (cps) for MeIMDA and EGDA

I. MeIMDA, $CH_3N(CH_2COOH)_2$			La^{+3} + $CH_3N(CH_2COOH)_2$		
	A B			A B	
pD	A	B	pD	A	B
2.40	181	240	3.00	179	233
3.05	179	232	4.50	177	228
4.05	177	227	5.58	170	222
7.00	177	227	6.70	152	205
8.35	176	225			
9.12	173	222			
12	134	183			

II. EGDA, $CH_3CH_2OOCCH_2N(CH_2COOH)_2$					$[La(CH_3CH_2OOCCH_2N(CH_2COO)_2)]^+$				
	A	B	C	D		A	B	C	D
pD	A	B	C	D	pD	A	B	C	D
4.00	77	259	234	228	5	77	259	224	211
5.90	77	259	232	227	5[a]	77	260	225	210
7.40	76	255	227	217					
9.50	74	259	209	195					

[a] Using sodium acetate buffer solution at pD 5.

structure as shown in eq 1. In this structure, the three donor atoms are shown to occupy meridional positions. While this configuration has been shown not to be preferred for cobalt(III) iminodiacetic acid complexes,[13] it is very probably adopted by Cu(II) which has a tendency to form square-planar complexes.

Of particular importance for the catalysis of the hydrolysis of EGDA is whether the ester carbonyl group is coordinated to the metal or not. In an attempt to clarify the situation, nmr studies were undertaken using a Varian Associates Model A-60 spectrometer. Attention was focused on the methylene in the $-NCH_2-COOC_2H_5$ grouping. The chemical shifts of the uncoordinated ligand were studied as a function of pD to determine the pD range for the species $[C_2H_5OOCCH_2N(H)(CH_2COO)_2]^-$ which has the same charge as $[CH_3N(H)(CH_2COO)_2]^-$, methyliminodiacetic acid (MeIMDA), the model compound which was selected for comparison with EGDA. The methylene of EGDA ($-NCH_2COOC_2H_5$) would be expected to show a downfield shift (provided the ester carbonyl oxygen is coordinated) upon coordination to a metal relative to the change in chemical shift of the methyl group in MeIMDA upon the coordination of MeIMDA to the same metal. Chemical shift parameters in cps were obtained for EGDA and MeIMDA both as free ligand and complexes with La(III). These results are given in Table III.

Lanthanum(III) was used because it forms the most soluble complexes of diamagnetic metal ions which catalyze the hydrolysis of EGDA. Considering the use of D_2O, a more valid measure of the acidity of the sample solutions was obtained by making use of an equation given by Mikkelson and Nielson:[14] pD = meter reading + 0.40.

One must first account for the change in chemical shifts with pD. If there are more than one species in solution, the nmr spectrum gives the time average of these species. To ensure that only one species is present, the pD must not be near the value of a pK_a. This is seen in Table III for MeIMDA. pD values of 2.40 and 3.05 are too near the pK_a of the acid protons (pK_a = 2.12) and the chemical shift values contain contributions from $[CH_3N(H)(CH_2COOH)(CH_2COO)]$ as well as $[CH_3N(H)(CH_2COO)_2]^-$. The chemical shift values were relatively constant for MeIMDA in the pD 4–7 range, and this was taken to indicate a single species in solution. Titrations had previously established the presence of $(CH_3N(H)(CH_2COO)_2]^-$ in this pH range.[7] The values of the chemical shifts in this pD range were therefore taken for use in the comparison. At higher pD values (8–12) the hydrogen on the nitrogen is removed (pK_a = 9.65) and an upfield shift was observed with increasing pD. Similarly for EGDA, the chemical shift values are relatively constant between pD 4 and 6, and this was evidence for a single species in solution. The pK_a of the amino group in amino acid esters is about 2 pK_a units lower than that for amino acids,[15] and consequently it was observed that at a lower pD value (7.40) the chemical shifts due to the EGDA were already showing effects of proton removal from the nitrogen.

La(III) does not complex with MeIMDA at pD 3–4.5, and the chemical shifts were those expected due to free MeIMDA. The addition of excess La(III) at pK = 6.70 had no effect on the chemical shifts which implied that complexation was complete. Hence these values of chemical shifts due to $[La(MeIMDA)]^+$ were used in the comparison.

Utilizing the values in Table III for the particular pD at which the desired species exist, a comparison was made between the difference in chemical shift values of free and coordinated EGDA and the difference in chemical shift values between free and coordinated MeIMDA. For $[CH_3N(H)(CH_2COO)_2]^-$ chemical shifts of 177 and 227 cps for the methyl and methylene groups, respectively, were utilized. Upon coordination to form $La[CH_3N(CH_2COO)_2]^+$, the chemical shifts were 152 and 205 cps from the methyl and methylene groups, respectively. The upfield shift with coordination is due to the fact that La(III) is apparently not as strong an acid as H^+ in this system. EGDA values of chemical shifts are 77, 259, 232, and 227 from A, B, C, and D, respectively, for the species

$$\underset{A\ \ B}{[CH_3CH_2OOCCH_2N(H)(CH_2COO)_2]^-} \quad \underset{C\qquad D}{\text{(pH 4–6)}}$$

(13) D. W. Cooke, *Inorg. Chem.*, **5**, 1141 (1966).
(14) K. Mikkelson and S. O. Nielson, *J. Phys. Chem.*, **64**, 632 (1960).
(15) R. W. Hay, L. J. Porter, and P. J. Morris, *Australian J. Chem.*, **19**, 1197 (1966).

and, for the coordinated species (LaEGDA)$^+$ with corresponding assignments, the chemical shifts were 77, 259, 224, and 211 for the respective assignments A, B, C, and D.

It is to be noted that the chemical shifts of the methyl and methylene hydrogens of the ester function do not change on coordination. The $-N(CH_2COO^-)_2$ methylene protons of MeIMDA shift 21 cps upfield upon coordination, while the analogous protons in EGDA undergo a slightly smaller upfield shift (16 cps). Coordination with La(III) also produces upfield shifts in the CH_3 protons of MeIMDA (25 cps) and the $-NCH_2COOC_2H_5$ methylene protons of EGDA (8 cps). If the $-COOC_2H_5$ group did not coordinate to the La(III), it would be expected that the $-NCH_2COOC_2H_5$ methylene protons would shift upfield by roughly the same amount as observed for the CH_3 protons of MeIMDA. That the $-NCH_2COOC_2H_5$ protons do not shift as far upfield suggests that the ester group is losing electron density to La(III). While this interpretation of the shifts is not unambiguous, it does imply that some ester to La(III) bonding occurs.

In a further attempt to clarify the possibility of ester carbonyl coordination, the infrared stretching frequency in D_2O of the Cu(EGDA) complex was investigated. It has been established from solid-state infrared spectra of some amino acid ester complexes of Cu(II) that carbonyl coordination to Cu(II) lowers the carbonyl stretching frequency by about 100 cm^{-1}.[16] In the present study in the absence of $Cu(NO_3)_2$ and at a pD of about 7 the ester carbonyl absorption occurred at 1723 cm^{-1}, and the $-COO^-$ groups absorbed at 1603 cm^{-1}. Both frequencies are usual for the respective groups.[17] Upon addition of $Cu(NO_3)_2$ to the solution, the pD dropped to about 5 and the $-COO^-$ absorption shifted to 1636 cm^{-1} as expected for this group when coordinated to Cu(II).[17] The ester carbonyl absorption, however, broadens and its frequency shifts insignificantly to 1725 cm^{-1}. These results suggest that the predominant form of the complex present in solution before hydrolysis occurs is the metal complex of EGDA in which the ester group is not coordinated to the Cu(II) (structure I, eq 1). Because of the broadness of the ester carbonyl absorption of the La(III) complex of EGDA, it was impossible to determine any carbonyl stretching shift, although this broadness may itself suggest the presence of two absorptions corresponding to uncoordinated and coordinated ester. In general, however, the nmr and infrared spectral results do not allow us to unambiguously determine the amount of ester–metal coordination.

The product of the hydrolytic reaction is the metal complex of NTA. This was supported by the reaction stoichiometry and by noting that the ultraviolet–visible spectrum of the reaction solution using Cu(II) as the metal ion at infinite time was identical with that of a solution prepared from Cu(II) and NTA. The ester was also hydrolyzed in the presence of Zn(II), and the proton nmr gave a singlet at δ 3.65 ppm which was in good agreement with that found for a D_2O solution prepared from Zn(II) and NTA directly.

The pseudo-first-order rate constants, k_{obsd}, for reaction 1 at various pH values at 25.0° are given in Tables IV and V for Cu(II) and Sm(III), respectively. If k_{obsd} depends on the hydroxide ion concentration in the following manner, $k_{obsd} = k[OH^-]$, a plot of log k_{obsd} *vs.* pH will yield a straight line with a slope of 1.00. This was observed and the over-all rate of hydrolysis is then given by the expression

$$\text{rate} = k[\text{complex I}][OH^-]$$

where complex I is the Cu(II) complex of EGDA as shown in eq 1 or where Sm(III) is substituted for Cu(II) or BGDA for EGDA. The nonlinear least-squares evaluation of k yields a value of 2.18×10^4 M^{-1} sec^{-1} with a standard deviation of 0.07×10^4 M^{-1} sec^{-1} for Cu(II) and EGDA. The rates of hydrolysis of BGDA according to eq 1 at 25.0° with [Cu(II)] = [BGDA] = 0.00067 M and $[KNO_3]$ = 0.05 M were determined at pH 6.30, 6.50, and 6.70 with values of 10^4k_{obsd} (sec^{-1}) of 1.98, 2.90, and 4.97, respectively. The nonlinear least-squares evaluation of k yields a value of 9.75×10^3 M^{-1} sec^{-1} with a standard deviation of 0.03×10^3 M^{-1} sec^{-1}. For Sm(III) and EGDA the evaluation of k yields a value of 4.47×10^4 M^{-1} sec^{-1} with a standard deviation of 0.28×10^4 M^{-1} sec^{-1}.

The dependence of the rate of hydrolysis on the ionic strength of the medium was determined at pH 6.30 for the hydrolysis reaction involving Cu(II) and EGDA. Concentrations of KNO_3 of 0.025, 0.050, and 0.0100 M were used to give values of ionic strength, I (KNO_3 + Ba(II) from BaEGDA), of 0.028, 0.053, and 0.103 M. Values of 10^4k_{obsd} (sec^{-1}) at these respective ionic strengths were 3.86, 3.90, and 3.78, which are the same within experimental error. Replacement of KNO_3 with KCl has no effect. The corresponding study with Sm(III) and EGDA with values of ionic strength of 0.003, 0.028, 0.053, 0.103 and 0.203 M gave values of $10^4{}_{obsd}$ (sec^{-1}) of 10.9, 8.90, 9.81, 7.20, and 5.84, respectively. A plot of log k_{obsd} *vs.* $\sqrt{I}/(1 + \sqrt{I})$ gave a straight line of slope 1.04.

A medium of high dielectric constant stabilizes charged species, and the effects can be predicted by considering the following reaction.

$$[M^{+n}(EGDA)]^{n-2} + OH^- \rightleftharpoons [M^{+n}(EGDA)(OH)]^{n-3} \quad (2)$$

Table IV. Rates of Cu(II)-Catalyzed Hydrolysis of EGDA According to Eq 1[a]

pH	10^4k_{obsd}, sec^{-1}	pH	10^4k_{obsd}, sec^{-1}
5.50	0.684	6.50	6.15
5.80	1.21	6.60	8.78
6.10	2.48	6.80	12.3
6.30	3.91	7.00	23.2
6.40	4.92		

[a] At 25.0°, [Cu(II)] = [EGDA] = 0.00067 M; $[KNO_3]$ = 0.050 M.

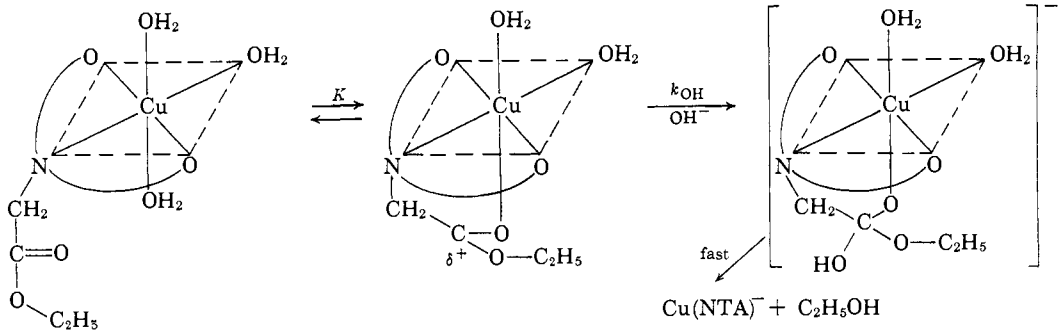
Table V. Rates of Sm(III)-Catalyzed Hydrolysis of EGDA According to Eq 1[a]

pH	10^4k_{obsd}, sec^{-1}	pH	10^4k_{obsd}, sec^{-1}
5.50	1.82	6.30	9.84
5.80	3.26	6.50	13.4
6.00	4.66	7.10	54.5

[a] At 25.0°, [Sm(III)] = [EGDA] = 0.00067 M; $[KNO_3]$ = 0.05 M.

(16) M. P. Springer and C. Curran, *Inorg. Chem.*, **2**, 1270 (1963).
(17) Y. Tomita and K. Uneo, *Bull. Chem. Soc. Japan*, **36**, 1069 (1963).

Mechanism A[18]



Equation 2 corresponds to formation of a hydroxo complex or an intermediate. For Cu(II) and EGDA, the Cu(EGDA) complex is neutral and the left side of eq 2 contains a singly charged particle (OH^-). The right side of eq 2 also bears a single charge, so that neither side of the equation is favored by changing the ionic strength, and indeed no effect was observed. For Sm(III) there are two unit charged species on the left and a neutral species on the right side of eq 2, and therefore the charged species should be stabilized by increasing ionic strength and the observed rate constant k_{obsd} should decrease as was observed. Quantitatively $\log k_1/k_0 = -A\Delta(Z)^2\sqrt{I}/(1 + \sqrt{I})$, where $A = 0.507$ for aqueous solutions and $\Delta(Z)^2$ is defined as usual as the charges on products minus reactants (*i.e.*, $(n - 3)^2 - (1)^2 - (n - 2)^2$ for eq 2).[11]

Excess Cu(II) ion had no effect on the rate of hydrolysis. With a concentration of 0.00067 *M* EGDA and increasing the concentration of Cu(II) from 0.00067 to 0.0011 to 0.0015 *M*, the pseudo-first-order rate constants (3.90, 3.68, and 3.65 $\times 10^{-4}$ sec^{-1}, respectively) remained, within experimental error (<10%), unchanged. Also adding Sm(III) up to a 1:1:1 ratio of Cu:EGDA:Sm had no effect on the copper-catalyzed rate constant consistent with the higher formation constants of Cu(II) with the model compounds (IMDA or NTA). The addition of excess Sm(III) to the Sm(III)-catalyzed hydrolysis reaction of EGDA had no effect within the limits of experimental error on the rate even for [Sm(III)] = 0.00134 *M* and [EGDA] = 0.00067 *M*. Using a deficiency of metal the rate of hydrolysis was that expected for the particular concentration of complex I. However, after the complexed ester had hydrolyzed, the reaction continues at a much slower rate until all the ester had been hydrolyzed. The slow terminal hydrolysis was presumably a result of some complexation with excess EGDA instead of NTA by the metal ion. Addition of other chelating groups such as glycine to a solution of Cu(EGDA) slowed the rate of hydrolysis presumably by complexation.

The formation constants of hydroxo complexes of Sm(III) and Cu(II) with MeIMDA and NTA were determined. EGDA itself hydrolyzed in the pH range where hydroxo complexes form, and no accurate formation constants could be obtained. However, it would be expected that the hydroxo formation constants of metal EGDA complexes would be bounded by the values of the hydroxo complex formation constants for MeIMDA and NTA, depending on the extent of the ester carbonyl oxygen coordination. Values of $K_f = [M(L)(OH)]/[ML][OH^-]$ for L = MeIMDA or NTA were as follows (±5%): Cu(MeIMDA)(OH), $K_f = 6.4 \times 10^5$; Cu(NTA)(OH), $K_f = 8.2 \times 10^4$; Sm(MeIMDA)(OH), $K_f = 6.4 \times 10^6$; Sm(NTA)(OH), $K_f = 2.0 \times 10^6$.

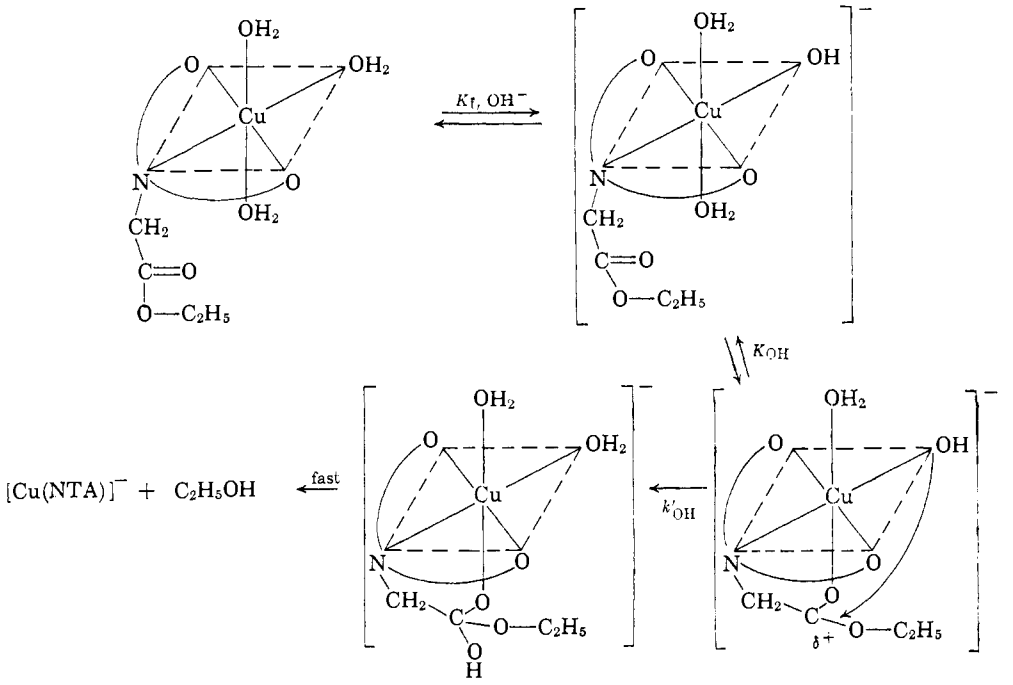
Discussion

The kinetic study of reaction 1 shows that the rate of reaction depends on the concentration of complex I and hydroxide ion. It is very likely that complex I, however, may not be the reactive form of the ester, but rather a complex in which the carbonyl oxygen of the ester is coordinated with Cu(II) or Sm(III). The existence of such an intermediate is supported by the work of Alexander and Busch.[5] They found that an amino acid ester which is coordinated to Co(III) only through the amino group hydrolyzes very slowly, but, when coordinated through both the amino group and the carbonyl oxygen, hydrolysis proceeds quite rapidly. The absence of the detection of such an intermediate in the current work does not eliminate the possibility of such an intermediate being present in very low concentrations. Alexander and Busch also observed general nucleophilic catalysis, and external nucleophilic attack on the carbonyl carbon was postulated. A similar mechanism written for Cu(II) catalysis of the hydrolysis of EGDA is Mechanism A which involves rate-determining hydroxide ion attack on the carbonyl carbon which has been polarized by coordination to the metal ion in a rapid prior equilibrium to yield NTA metal complex and ethyl alcohol. This mechanism gives the rate law: rate = Kk_{OH}[complex I][OH^-] and is consistent with the observed rate law and ionic strength dependence. *K*, the equilibrium constant for coordinated carbonyl ester oxygen, is probably small but indeterminable. An infrared study in D_2O of Cu(II) and ethyl glycinate showed no evidence for ester carbonyl oxygen coordination to Cu(II) so that an indeterminable constant *K* is involved for Cu(II)-catalyzed hydrolysis of ethyl glycinate as well.[2-4]

There is, however, another mechanism which is kinetically indistinguishable in which the hydroxo complex [Sm(EGDA)(OH)] or the copper analog is the reactive species (Mechanism B). Formation constants of hydroxo complexes are large enough so that appreciable concentrations (approximately 0.01–20%) of Sm(EGDA)(OH) or Cu(EGDA)$(OH)^-$ exist in solution in the pH range 5.0–7.0. The hydroxide ion in the complex is in a position which makes possible an attack of hydroxide ion perpendicular to the plane of the carbonyl and ester bond as postulated by Bender.[12] The formation constants of hydroxo complexes of metal

(18) Catalysis by Sm(III) would involve eight- or nine-coordination rather than octahedral as shown for Cu(II).

Mechanism B [18]



ions have been found to parallel the order found for hydrolytic rate constants for metal–ethyl glycinate complexes,[19] and preliminary work with other metal complexes of EGDA indicates this generalization may be applied in the present situation. This mechanism need not involve full coordination of the ester carbonyl to the metal, as suggested by the drawing. It is also possible that there is weak or no direct interaction between the carbonyl group and the metal. In any case, mechanism B gives a rate law of the form

$$\text{rate} = K_{OH}K_f k'_{OH}[\text{complex I}][OH^-]$$

No second-order hydroxide ion term was detected even at pH 7.0 so that hydroxide ion attack on an hydroxo complex may be eliminated. Water attack on a negatively charged or neutral species $Cu(EGDA)(OH)^-$ or Sm(EGDA)(OH) would seem unlikely since no water attack is observed for the neutral and positively charged complexes, Cu(EGDA) or $Sm(EGDA)^+$.

The problems of interpretation due to the unknown values of K and K_{OH}, the equilibrium constants for ester carbonyl oxygen coordination, and the possibility of either external or internal hydroxide ion attack are common to metal-catalyzed hydrolysis of amino acid esters and their derivative unless coordination of the ester carbonyl can be proven and the absence of hydroxo complexes established. Literature values for the rates of hydroxide ion catalyzed hydrolysis of various amino acid esters and their metal complexes are tabulated in Table VI. The rate constants for $Cu(EGDA)^0$ and $Cu(NH_2CH_2COOEt)^{+2}$ are surprisingly similar in view of the formal charges of zero and +2 on the respective complexes.

Table VI. Rate Constants for Hydroxide Ion Catalyzed Hydrolysis Reactions of Amino Acid Esters and Derivatives at 25°

Ester	k_1, M^{-1} sec^{-1}	Ref
NH_2CH_2COOEt	0.635	15 (I = 0.1)
$^+NH_3CH_2COOEt$	24	3 (I = 0.16)
$(C_2H_5)_3N^+CH_2COOEt$	20.8	15
$Cu(NH_2CH_2COOEt)^{+2}$	7.6×10^{-4}	3
Cu(EGDA)	2.18×10^{-4}	This work
Sm(EGDA)	4.47×10^{-3}	This work
Cu(BGDA)	9.75×10^{-3}	This work

The decrease in the rate of hydrolysis of the butyl ester (BGDA) by a factor of 2.2 compared to the ethyl ester (EGDA) is somewhat larger than that observed for basic hydrolysis of organic acetates (1.18)[20] but is in good agreement with the rate of hydrolysis of butyl glycinate (0.305 M^{-1} sec^{-1})[21] compared to that of ethyl glycinate (0.635).[15]

Acknowledgment. We gratefully acknowledge support of this research by the U. S. Public Health Service through Grant No. GM-12626.

(19) J. E. Hix and M. M. Jones, *Inorg. Chem.*, 5, 1863 (1966).

(20) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 220.

(21) D. Hopgood, unpublished results.