# Metal-Ion Catalysis of the Hydrolysis of Some Amino Acid Ester N,N-Diacetic Acids

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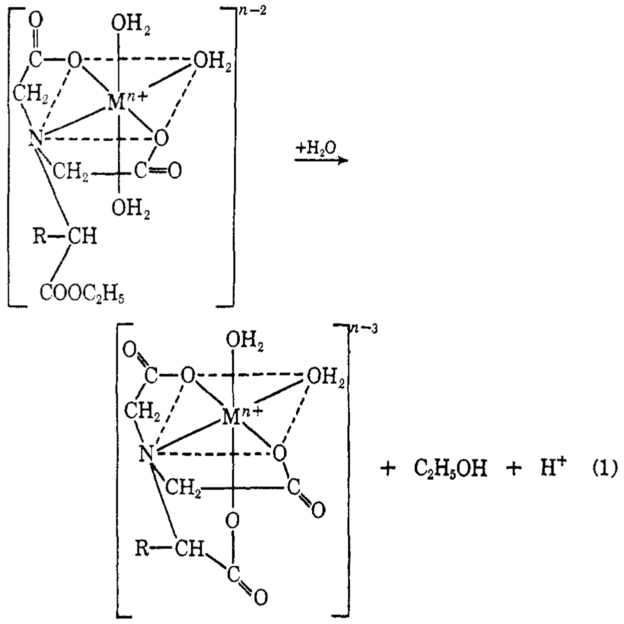
**Abstract:** The N,N-diacetic acids derived from the amino acid esters ethyl glycinate, butyl glycinate, ethyl alaninate, ethyl valinate, ethyl β-alaninate, and ethyl 4-aminobutyrate were prepared and identified by their nmr spectra. These ligands coordinate strongly with a number of metal ions. The rate of hydrolysis of the metal ion complexes in the pH range 5.0–8.0 depends more on the number of carbon atoms in the N-$COOC_2H_5$ linkage than on the substituent, R, of the amino acid ester $NH_2CHRCOOC_2H_5$, with the exception of valine and leucine ethyl esters. The rates of hydrolysis of ethyl glycinate-N,N-diacetic acid (EGDA) complexed with the metal ions Cd(II), Ni(II), Mn(II), Co(II), Fe(II), Zn(II), La(III), Cu(II), Pb(II), Nd(III), Gd(III), Sm(III), Dy(III), Er(III), Yb(III), and Lu(III) were studied and found to increase in the order listed. Temperature-dependence studies of the rates of hydrolysis were made for the metal ions Cu(II), Pb(II), Ni(II), Sm(III), and Lu(III) and were interpreted in terms of a mechanism consistent with the observed rate law, rate = $k[M(EGDA)][OH^-]$, in which an hydroxide ion attacks the carbonyl carbon of the ester which has coordinated to the metal ion in a rapid prior equilibrium.

Transition metals have long been known to promote the hydrolysis of α-amino acid esters and their derivatives.[1,2] We have continued our kinetic investigations of amino acid ester N,N-diacetic acids which coordinate strongly to many metal ions and thereby reduce the number of prior equilibria to be considered in the reaction mechanism. The present investigation includes transition and nontransition metal ions and utilizes a number of amino acid ester N,N-diacetic acids to determine the effects upon the rate of hydrolysis of variations of the ester and the metal ion. The amino acid ester N,N-diacetic acid is hydrolyzed to the corresponding substituted nitrilotriacetic acid (NTA) complex according to eq 1.[2]



(1)

## Experimental Section

**Materials.** Doubly distilled water and analytical grade $Cu(NO_3)_2 \cdot 3H_2O$, $CoCl_2 \cdot 6H_2O$, $MnCl_2 \cdot 4H_2O$, $Pb(NO_3)_2$, $ZnCl_2$, $NiCl_2 \cdot 6H_2O$, $Fe(NO_3)_2$, $CdCl_2 \cdot 2.5H_2O$, $Al(NO_3)_3 \cdot 9H_2O$, $UO_2(NO_3)_2 \cdot 6H_2O$, $VOCl_2$, $AgNO_3$, $Hg(NO_3)_2$, $Fe(NO_3)_3 \cdot 9H_2O$, $MgCl_2 \cdot 6H_2O$, $Sc(NO_3)_3$, and $SnCl_2 \cdot 2H_2O$ were used to prepared metal ion solutions. Lanthanide nitrate solutions and $HfI_4$ were gifts of Professors Jack Powell and John Corbett, Ames Laboratory, Iowa State University. DL-Valine and DL-alanine were supplied by Mann Research Laboratories, Inc., glycine butyl ester hydrochloride and glycine ethyl ester hydrochloride by Eastman, and β-alanine and 4-aminobutyric acid by Matheson Coleman and Bell. Iodoacetic acid was reagent grade. The solvent used in obtaining ir and nmr spectra was 99.5% $D_2O$.

**Preparation of Amino Acid Ester.** Amino acid esters were prepared from the parent amino acid by bubbling HCl gas through an ethanol–amino acid solution according to standard techniques.[3]

**Preparation of N,N-Diacetic Acids.** The ester ligands were prepared from the reaction of the desired amino acid ester with iodoacetic acid according to published procedures.[1] The nmr spectra of the N,N-diacetic acid derivatives of ethyl glycinate,[1] butyl glycinate,[1] ethyl valinate,[2] and ethyl leucinate[2] have been reported previously. The nmr spectra of the following salts or complexes were obtained at a pD of 5–7 on a Varian Associates Model A-60 spectrometer using 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard (chemical shift = 0.0). Chemical shifts, δ (ppm), are given for the respective alphabetic assignments (Table I). To improve the solubility of the ligands, they were examined as their sodium or zinc salts as discussed elsewhere.[2]

**Table I.** Chemical Shifts, δ (ppm)

| |
|---|
| Ethyl Alaninate-N,N-diacetic Acid (EADA) |
| $CH_3$–$CH_2$–OOC–$CH(CH_3)$–$N(CH_2COO)_2$ Ba<br>A B C D E |
| $\delta_A$ 1.23, $\delta_B$ 4.24, $\delta_C$ 3.56, $\delta_D$ 1.40, $\delta_E$ 3.38 |
| Ethyl β-Alaninate-N,N-diacetic Acid (EβADA) |
| $CH_3$–$CH_2OOCCH_2$–$CH_2$–$N(CH_2COO)_2$ Zn<br>A B C D E |
| $\delta_A$ 1.25, $\delta_B$ 4.24, $\delta_C$ ~3.08, $\delta_D$ ~2.79, $\delta_E$ 3.34 |
| Ethyl 4-Aminobutyrate-N,N-diacetic Acid (EABDA) |
| $CH_3$–$CH_2$–$OOCCH_2$–$CH_2$–$CH_2$–N–$(CH_2COO)_2Na_2$<br>A B C D E F |
| $\delta_A$ 1.25, $\delta_B$ 4.17, $\delta_C$ 3.22, $\delta_D$ 2.0, $\delta_E$ 2.50, $\delta_F$ 3.72 |

**Kinetic Measurements.** Rates of reaction were determined with a Radiometer titrator and titrigraph using pH-Stat techniques.[1] The pH was maintained at the desired value by addition of 0.0187

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(1) R. J. Angelici and B. E. Leach, *J. Am. Chem. Soc.*, **89**, 4605 (1967).

(2) R. J. Angelici and B. E. Leach, **90**, 2499 (1968), and references cited therein.

(3) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961.

*N* NaOH. Nitrogen was bubbled into the reaction vessel (10-ml volume) to exclude air. The reaction vessel was thermostated to ±0.05° of the temperature stated. Details of the treatment of the kinetic data have been given previously.[1] Hydrogen ion activity is measured by the pH meter. This has been converted into hydroxide ion concentration by estimating activity coefficients from the Guggenheim equation,[4] $\log \gamma_\pm = -[A|Z_1Z_2|I^{1/2}/(1 + I^{1/2})] + BI$; where $A = 0.507$ and $B = 0.1$. Thus hydroxide ion concentrations were calculated from the expression $\log [OH^-] = \log K_w + pH - \log \gamma_\pm$. The second-order rate constants are obtained by dividing $k_{obsd}$ by the hydroxide ion concentration. A general nonlinear least-squares program[5] was used to calculate the second-order rate constant, $k$, and also the enthalpy and entropy of activation from the temperature-dependence data. The error limits given in the tables are one standard deviation.

Infrared spectra were taken of some metal ethyl glycinate-N,N-diacetic acid (EGDA) complexes in $D_2O$ using a Beckman IR-12 grating spectrophotometer.

## Results

The rates of ester hydrolysis of ethyl glycinate-N,N-diacetic acid with the metal ions cadmium(II), nickel(II), manganese(II), cobalt(II), iron(II), zinc(II), lanthanum(III), copper(II), lead(II), neodymium(III), gadolinium(III), samarium(III), dysprosium(III), erbium(III), ytterbium(III), and lutetium(III) have been measured in the pH range 4.4–8.0 and found to obey the rate law: rate = $k[M(EGDA)][OH^-]$. The pseudo-first-order rate constants, $k_{obsd}$, for the hydrolysis reaction at 25.0° are given in Table II. 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 give a straight line of slope 1.00. Slopes obtained for all metal ions and esters studied were 1.00 ± 0.05. Table III gives the nonlinear least-squares evaluation of the second-order rate constant, $k$ ($M^{-1}$ sec$^{-1}$), and the standard deviation for each of the 16 metal ions studied. The following metal ions were not observed to catalyze the ester hydrolysis: Al(III), Fe(III), Mg(II), Sc(III), $HfO^{2+}$, $VO^{2+}$, and $UO_2^{2+}$; the following gave precipitates of the diacetic acids: Sn(II), Ag(I), and Hg(II). The metal ions which did not catalyze the ester hydrolysis form only very weak complexes or undergo extensive hydroxo complex formation at low pH values. Ethyl glycinate-N,N-diacetic acid itself has been found to undergo immeasurably slow ester hydrolysis in the 4.5–7.5 pH range, but near pH 8 hydrolysis becomes significant.

Copper(II) and samarium(III) complexes of the N,N-diacetic acids derived from butyl glycinate (BGDA), ethyl valinate (EVDA), ethyl leucinate (ELDA), ethyl β-alaninate (EβADA), ethyl alaninate (EADA), and ethyl 4-aminobutyrate (EABDA) were prepared and their rates of hydrolysis followed using the same techniques. The identical rate law was found; however, the rate of reaction was observed to vary with the amino acid ester derivative as shown in Table IV.

Temperature dependence data are given in Table VI for the hydrolysis of EGDA complexed with the metal ions Ni(II), Cu(II), Pb(II), Sm(III), and Lu(III). The data for methyl betaine ethyl ester, $[(CH_3)_3NCH_2COOC_2H_5]Cl$, and the parameters determined by Gustafson[6] for ethyl glycinate are included for comparison. Correction has been made for the change in $K_w$ with temperature in the calculation of hydroxide ion concentrations.[7]

The infrared spectra of a number of metal EGDA complexes in $D_2O$ are tabulated in Table VIII. If coordination of the ester carbonyl oxygen occurs, the stretching frequency of the carboxyl group should be lowered 50–100 cm$^{-1}$ from the free ester value.[8,9] No

**Table II.** Rates of Metal-Ion-Catalyzed Hydrolysis of EGDA at 25.0°[a]

| Metal ion | pH | $10^4k_{obsd}$, sec$^{-1}$ | pH | $10^4k_{obsd}$, sec$^{-1}$ |
|---|---|---|---|---|
| Cd(II) | 7.40 | 0.655 | 8.00 | 2.54 |
| | 7.70 | 1.45 | | |
| Ni(II) | 6.80 | 0.382 | 7.60 | 1.64 |
| | 7.20 | 0.780 | 7.70 | 2.39 |
| | 7.40 | 1.28 | 7.80 | 3.10 |
| Mn(II) | 7.00 | 0.575 | 7.50 | 1.62 |
| | 7.30 | 1.04 | 7.90 | 4.04 |
| Co(II) | 6.80 | 0.718 | 7.50 | 3.74 |
| | 7.10 | 1.52 | 7.70 | 6.45 |
| | 7.30 | 2.44 | 7.80 | 7.57 |
| Fe(II) | 6.10 | 0.573 | 6.40 | 1.21 |
| | 6.20 | 0.758 | | |
| Zn(II) | 5.80 | 0.567 | 6.60 | 3.51 |
| | 6.00 | 0.971 | 6.80 | 5.72 |
| | 6.20 | 1.33 | 7.00 | 8.62 |
| | 6.40 | 2.31 | 7.20 | 12.1 |
| | 6.50 | 2.61 | | |
| Pb(II) | 6.00 | 3.15 | 6.40 | 7.82 |
| | 6.10 | 3.56 | 6.50 | 9.45 |
| | 6.20 | 4.75 | 6.60 | 14.0 |
| | 6.30 | 6.34 | 6.80 | 23.2 |
| La(III) | 6.30 | 2.33 | 6.60 | 5.43 |
| | 6.60 | 5.52 | 6.90 | 11.3 |
| Nd(III) | 5.50 | 1.47 | 6.50 | 12.8 |
| | 5.90 | 3.54 | 6.80 | 27.0 |
| | 6.20 | 6.70 | | |
| Gd(III) | 5.30 | 0.889 | 6.10 | 6.10 |
| | 5.50 | 1.41 | 6.30 | 11.3 |
| | 5.70 | 2.21 | 6.50 | 13.1 |
| | 5.90 | 2.96 | 6.70 | 22.9 |
| Dy(III) | 5.60 | 4.76 | 6.30 | 21.3 |
| | 6.00 | 10.7 | | |
| Er(III) | 4.80 | 1.88 | 5.70 | 11.6 |
| | 5.10 | 3.29 | 6.00 | 23.3 |
| | 5.40 | 6.15 | | |
| Yb(III) | 5.00 | 4.21 | 5.50 | 13.3 |
| | 5.20 | 6.70 | 5.70 | 21.1 |
| Lu(III) | 4.40 | 0.901 | 5.30 | 7.14 |
| | 4.60 | 1.50 | 5.50 | 11.3 |
| | 4.80 | 2.20 | 5.70 | 17.9 |
| | 5.00 | 4.17 | 6.00 | 44.7 |

[a] $[M^{n+}] = [EGDA] = 0.00067\ M$; $[KNO_3] = 0.050\ M$.

**Table III.** Rates Constants for the Metal-Ion-Catalyzed Hydrolysis of EGDA at 25.0°[a]

| Metal ion | $10^{-2}k$, $M^{-1}$ sec$^{-1}$ | Metal ion | $10^{-2}k$, $M^{-1}$ sec$^{-1}$ |
|---|---|---|---|
| Cd(II) | 2.14 ± 0.09 | La(III) | 115 ± 3 |
| Ni(II) | 3.89 ± 0.13 | Nd(III) | 347 ± 5 |
| Mn(II) | 4.18 ± 0.05 | Sm(III) | 447 ± 21 |
| Co(II) | 10.1 ± 0.2 | Gd(III) | 376 ± 16 |
| Fe(II) | 38.6 ± 1.0 | Dy(III) | 877 ± 2 |
| Zn(II) | 66.2 ± 2.0 | Er(III) | 1920 ± 30 |
| Cu(II) | 218 ± 7 | Yb(III) | 3460 ± 100 |
| Pb(II) | 283 ± 11 | Lu(III) | 3450 ± 230 |

[a] $[M^{n+}] = [EGDA] = 0.00067\ M$; $[KNO_3] = 0.050\ M$.

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(4) E. A. Guggenheim, *Phil. Mag.*, 22, 322 (1936).

(5) R. H. Moore, based on a report from Los Alamos Scientific Laboratory, LA 2367, plus addenda. We thank Dr. J. P. Birk for modification of this program.

(6) C. Gustafson, *Ann. Acad. Sci. Fennicae*, 15 (1945); *Chem. Abstr.*, 41, 903*h* (1947).

(7) "Stability Constants," Special Publication No. 17, The Chemical Society, London, 1964.

(8) M. P. Springer and C. Curran, *Inorg. Chem.*, 2, 1270 (1963).

(9) M. D. Alexander and D. H. Busch, *J. Am. Chem. Soc.*, **88**, 1130 (1966).

**Table IV.** Rates of Hydrolysis of Amino Acid Ester N,N-Diacetic Acids with Cu(II) and Sm(III) at 25.0° [a]

| pH | $10^4k_{obsd}$, $sec^{-1}$ | pH | $10^4k_{obsd}$, $sec^{-1}$ |
|---|---|---|---|
| $[Sm(BGDA)]^+$ | | Cu(EβADA) | |
| 5.90 | 3.26 | 7.00 | 0.583 |
| 6.30 | 7.50 | 7.50 | 1.88 |
| 6.60 | 18.6 | 8.00 | 5.85 |
| Cu(EADA) | | $[Sm(EβADA)]^+$ | |
| 6.00 | 1.99 | 6.00 | 4.76 |
| 6.30 | 4.08 | 6.50 | 14.9 |
| 6.50 | 6.38 | 6.90 | 37.6 |
| 6.70 | 8.11 | $[Lu(EβADA)]^+$ | |
| 6.80 | 11.9 | 5.40 | 1.38 |
| 7.00 | 15.7 | Pb(EβADA) | |
| 7.10 | 19.8 | 6.40 | 1.52 |
| $[Sm(EADA)]^+$ | | | |
| 6.40 | 5.59 | Cu(II), Sm(III), Lu(III) (EABDA) | |
| 6.60 | 8.63 | 4–8 | No reaction |

[a] $[M^{n+}]$ = [ester] = 0.00067 *M*; $[KNO_3]$ = 0.050 *M*.

**Table V.** Rates of Hydrolysis of Amino Acid Ester N,N-Diacetic Acids with Cu(II) and Sm(III) at 25.0° [a]

| Ester | Cu(II) $10^{-2}k$, $M^{-1}$ $sec^{-1}$ | Sm(III) $10^{-2}k$, $M^{-1}$ $sec^{-1}$ |
|---|---|---|
| EGDA | 218 | 447 |
| BGDA | 97.5 | 326 |
| EADA | 134 | 180 |
| EVDA[b] | 2.1 | 4.7 |
| ELDA[b] | 22.5 | 26 |
| EβADA[c] | 4.83 | 381 |
| EABDA | No reaction | No reaction |

[a] $[M^{n+}]$ = [ester] = 0.00067 *M*; $[KNO_3]$ = 0.050 *M*. [b] Reference 2. [c] Lu(III), 4.50 × $10^5$ $M^{-1}$ $sec^{-1}$; Pb, 4.93 × $10^3$ $M^{-1}$ $sec^{-1}$.

**Table VI.** Temperature Dependence of the Rate of Metal-Ion-Catalyzed Hydrolysis of EGDA[a]

| Temp, °C | *k*, $M^{-1}$ $sec^{-1}$ | Temp, °C | $10^{-2}k$, $M^{-1}$ $sec^{-1}$ |
|---|---|---|---|
| Betaine ethyl ester (no metal ion present) | | Pb(EGDA) | |
| 40.0 | 97.7, 93.3 | 40.0 | 427 |
| 30.0 | 51.7, 52.9 | 30.0 | 348 |
| 25.0 | 39.4, 41.0 | 25.0 | 278 |
| 20.0 | 32.8, 33.0 | 17.0 | 245, 237 |
| 13.5 | 21.2 | $[Sm(EGDA)]^+$ | |
| Ni(EGDA) | | 40.0 | 976, 937 |
| | $10^{-2}k$, $M^{-1}$ $sec^{-1}$ | 30.0 | 512, 512 |
| 40.0 | 6.87, 7.15 | 25.0 | 447 |
| 35.0 | 5.82, 5.75 | 20.0 | 283, 284 |
| 30.0 | 4.97, 4.77 | 14.5 | 221, 197 |
| 25.0 | 3.89 | 8.5 | 147 |
| Cu(EGDA) | | $[Lu(EGDA)]^+$ | |
| 40.0 | 366 | 12.5 | 1530, 1560 |
| 30.0 | 252 | 20.0 | 2410, 2490 |
| 25.0 | 218 | 25.0 | 3700, 3520 |
| 20.0 | 194 | 30.0 | 4530 |
| 14.5 | 178 | | |

[a] $[M^{n+}]$ = [ester] = 0.00067 *M*; $[KNO_3]$ = 0.050 *M*.

evidence of ester carbonyl oxygen coordination is observed although the infrared peaks are quite broad and are inconclusive. No correlation of the rate of hydrolysis, *k*, is found with the stretching frequency of the carbonyl ester oxygen. Table VIII lists the metal ions in order of increasing values of the second-order rate constant, *k*. The difference in the stretching frequency the carboxylate group and the carbonyl ester, Δ, shows some correlation with the rate of ester hydrolysis although the rates are better paralleled by formation constants of hydroxo complexes of the metal ions as will be discussed in the following section.

**Table VII.** Enthalpies and Entropies of Activation for Ester Hydrolysis Reactions[a]

| Ester | Δ*H**, kcal/mole | Δ*S**, eu |
|---|---|---|
| Ethyl glycinate[b] | 10.6 ± 0.5 | −21.7 ± 1.0 |
| Betaine ethyl ester | 9.7 ± 0.3 | −18.5 ± 1.1 |
| Cu(EGDA) | 5.0 ± 0.5 | −21.9 ± 1.5 |
| Ni(EGDA) | 6.7 ± 0.4 | −24.2 ± 1.2 |
| Pb(EGDA) | 4.4 ± 0.6 | −23.5 ± 2.1 |
| $[Sm(EGDA)]^+$ | 10.0 ± 0.4 | −4.0 ± 1.2 |
| $[Lu(EGDA)]^+$ | 10.2 ± 0.6 | +0.8 ± 2.0 |

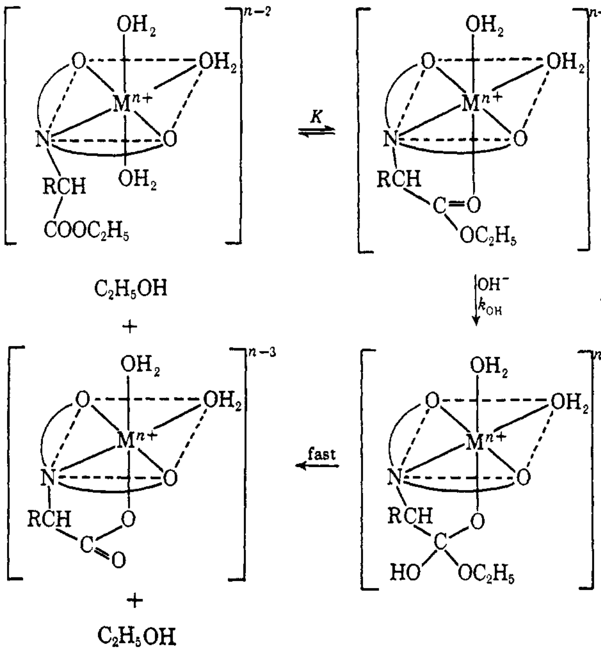
[a] $[KNO_3]$ = 0.050 *M*. [b] Reference 6.

**Table VIII.** Infrared Stretching Frequencies of Metal Ion EGDA Complexes in $D_2O$

| Metal ion | Carbonyl ester, $cm^{-1}$ | Carboxylate group, $cm^{-1}$ | Δ, $cm^{-1}$ |
|---|---|---|---|
| Ba(II) | 1722 | 1595 | 127 |
| Cd(II) | 1713 | 1615 | 98 |
| Mn(II) | 1710 | 1608 | 102 |
| Ni(II) | 1738 | 1625 | 113 |
| Co(II) | 1696 | 1607 | 87 |
| Zn(II) | 1686 | 1600 | 86 |
| Cu(II) | 1722 | 1636 | 86 |
| Pb(II) | 1703 | 1612 | 91 |
| Gd(III) | 1710 | 1623 | 87 |

## Discussion

On the basis of detailed studies[2] of Cu(EVDA), it was concluded that this complex underwent ester hydrolysis by way of $OH^-$ attack on the ester carbonyl group which was simultaneously bonded to the metal through the carbonyl oxygen atom. This same mechanism (eq 2) is assumed to be operative for the ester complexes discussed in this paper as well.



(2)

The experimental second-order rate constant, $k$, is $Kk_{OH}$ in terms of this mechanism. The value of $K$ is probably small as inferred from formation constant studies of EVDA with Cu(II), Pb(II), Ni(II), Co(II), and Sm(III).[2] Experimentally it has not been possible to determine $K$. In a previous publication,[2] hydroxo-complex formation was discussed with respect to the assumed mechanism. If [M(ester)] $\cong$ $[\text{M(ester)}]_{\text{total}}$, then $k = k_e$. This condition is satisfied if the concentration of [M(ester)(OH)] is small, which is the case for the pH range studied, except for the EVDA and ELDA metal-catalyzed hydrolysis.

The rate of ester hydrolysis of EGDA metal complexes increases with the metal ion in the following order: Cd(II) < Ni(II) < Mn(II) < Co(II) < Fe(II) < Zn(II) < La(III) < Cu(II) < Pb(II) < Nd(III) < Gd(III) < Sm(III) < Dy(III) < Er(III) < Yb(III) < Lu(III). In general the 3+ lanthanides are somewhat better catalysts. Within the lanthanide group, the relative catalytic properties increase with increasing atomic number except for the decrease at Gd(III) (Figure 1). Numerous properties of the lanthanides follow a similar trend. One example is the trend in formation constants, $K_f$, of these ions with the iminodiacetate ion (IMDA): $L^{3+} + \text{IMDA}^{2-} = [\text{L(IMDA)}]^+$ (Figure 1).

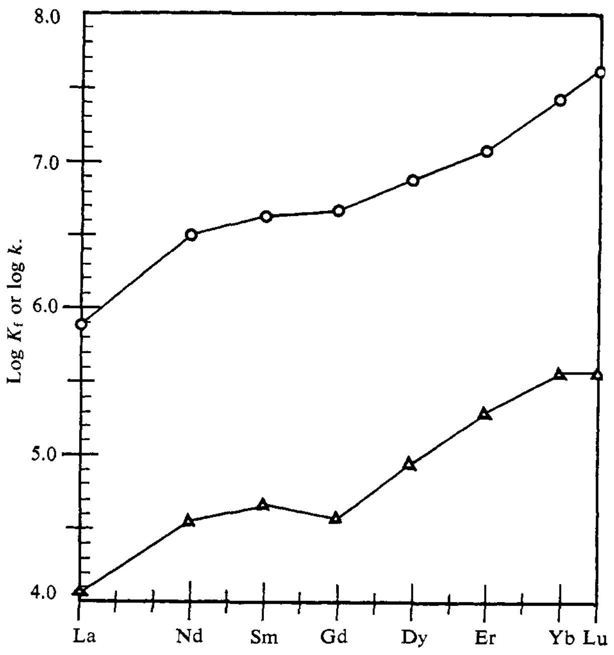


Figure 1. Plot of atomic number of lanthanides *vs.* log $K_f$ for M(III) + IMDA (○). Plot of atomic number of lanthanides *vs.* log $k$ for $[\text{M(EGDA)}]^+$ ester hydrolysis (△).

The catalytic properties of the 2+ ions show no such correlation with $K_f$ for complex formation with IMDA. There does, however, appear to be a limited correlation with the hydroxo formation constant for $\text{M(OH)}^+$ as pointed out earlier by Hix and Jones.[10] They found that metal ions were increasingly active in the hydroxide-catalyzed hydrolysis of ethyl glycinate in the order Ni(II) < Co(II) < Zn(II) << Cu(II). Although this is also the order of increasing hydroxo-complex stability,[10,11] it is uncertain what this limited correlation means since the observed general nucleophilic catalysis[2] of the hydrolysis of Cu(EVDA) minimized the importance of hydroxo complexes. Currently the limited and approximate correlation between the catalytic ability and the hydroxo formation constants of these four metal ions appears to be a fortuitous relationship. It should be noted that while the hydroxo formation constants for $[\text{M(EVDA)(OH)}]^-$ from M(EVDA) increase in the order Ni(II) < Co(II) < Cu(II), the constant for Pb(II) is much lower than would be expected from its observed catalytic properties.[2]

The enthalpy of activation of the hydroxide catalysis of ethyl glycinate[6] is 10.6 kcal/mole. For $(CH_3)_3N^+CH_2COOC_2H_5$ the activation energy is slightly lower at 9.7 kcal/mole. The $\Delta H^*$ of the 2+ metal catalyzed hydrolyses of EGDA are lower than that of ethyl glycinate and decrease in the order Ni(EGDA) > Cu(EGDA) > Pb(EGDA). The entropies of activation for ethyl glycinate and the EGDA complexes are all $-22.5 \pm 1$ eu. Thus the increased rate of ester hydrolysis of the EGDA complexes is a result of substantial lowering of $\Delta H^*$; $\Delta S^*$ remains virtually unchanged. On the other hand, the 3+ metal-ion-catalyzed reactions have virtually the same $\Delta H^*$ as for ethyl glycinate, but the $\Delta S^*$ increases drastically from $-21.7$ eu for ethyl glycinate to $-4.0$ eu for $[\text{Sm(EGDA)}]^+$ and $+0.8$ for $[\text{Lu(EGDA)}]^+$. Hence, the catalytic effect of the lanthanides results from an increase in $\Delta S^*$ with $\Delta H^*$ remaining essentially unchanged. The increase in $\Delta S^*$ is not unexpected when one considers that a positive $[\text{Sm(EGDA)}]^+$ and negative $OH^-$ are reacting in the rate-determining step to give a neutral and considerably less solvated activated complex. That $\Delta H^*$ remains unchanged suggests that the energy required to remove the water of solvation from the charged ions in going to the transition state is roughly the same as that gained by coordinating the ester to the lanthanide. It is presumably this difference in charge in the M(EGDA) and $[\text{M(EGDA)}]^+$ complexes which causes the characteristic differences in $\Delta H^*$ and $\Delta S^*$ for the 2+ and 3+ metal ions.

Altering the ester ligand also affects the rate of hydrolysis. Thus changing from an ethyl to a butyl ester as in the EGDA and BGDA slows the rate by a small factor, 1.4–2.2.

The R group in the ester ligand, $C_2H_5OOCCH(R)N(CH_2COOH)_2$, affects the rates, depending on its nature. Thus the rates are very similar for R = H or $CH_3$ for either the Cu(II) or Sm(III) complexes, but for R = $-CH_2CH(CH_3)_2$[12] or $-CH(CH_3)_2$,[13] the rates are considerably slower as observed for the nonmetal-catalyzed reactions and discussed in terms of Newman's "Rule of Six,"[14] which is an empirical rule which states that in reactions involving addition to an unsaturated function containing a double bond, the greater the number of atoms in the sixth position the greater will be the steric effect.

The number of methylene groups separating the N atom and the ester group is very important in determining the amount of catalysis exerted by the metal. The

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greatest catalysis is observed in complexes of the ligands $C_2H_5OOC(CH_2)_nN(CH_2COOH)_2$, when $n = 1$. Increasing $n$ to a value of 2 decreases the rate for the Cu(II) complex by a factor of 45 but only by a factor of 5.7 for Pb(II). For Sm(III) such a change decreases the rate only by a factor of 1.2, while the rate actually increases for Lu(III) by a factor of 1.3 in going from $n = 1$ to $n = 2$. While the relative catalytic abilities of different metal ions in the $n = 2$ series are not understood, the larger ions appear to be able to more effectively catalyze esters containing longer linkages between the N atom and the ester group. Extending the chain to $n = 3$ yields complexes of Cu(II), Sm(III), and Lu(III) which undergo no measurable hydrolysis up to pH 8. Models of these complexes show that it is very difficult for the ester carbonyl group to coordinate to the metal ion.

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# Equilibrium and Stereochemical Studies of the Interactions of Amino Acids and Their Esters with Divalent Metal Nitrilotriacetate Complexes

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**Abstract:** The formation constants of glycine ($K_{fGly}$) with a series of divalent metal nitrilotriacetates ($[M(NTA)]^-$) to form $[M(NTA)(Gly)]^{2-}$ follow the Irving–Williams order, Mn < Co < Ni < Cu > Zn. The formation constants of ethyl valinate ($K_{fEtVal}$), a representative $\alpha$-amino acid ester which hydrolyzes negligibly during the potentiometric titrations, were also measured with the $[M(NTA)]^-$ complexes. The latter constants show a significantly different trend to that exhibited by the constants for glycine complexation. The parameter $K_{fGly}/K_{fEtVal}$ increases from about unity to 800 along the series Mn $\lesssim$ Pb $\ll$ Co < Zn < Cu < Ni, suggesting that extensive coordination to both the amino and ester groups occurs only in the complexes of manganese and lead; these metal ions are the best oxygen acceptors in the series. On the other hand, $\alpha$-amino acid esters are probably monodentate in their complexes with copper and nickel nitrilotriacetates. The complexes of *l*-valine and its ethyl ester with $[Co(NTA)]^-$ exhibited Cotton effects which indicate a small extent of ester chelation, probably about 15%. This is consistent with the formation constant data. The absorption spectra of a series of $[Cu(NTA)]^-$ complexes with various ligands show that large tetragonal distortions only occur with chelating ligands such as $\alpha$-amino acids or ethylenediamine. Monodentate ligands form complexes of approximate cubic symmetry. Histidine and its methyl ester have very similar donor properties toward $[Cu(NTA)]^-$. They act as monodentate ligands at low pH bonding through the imino nitrogen, then chelate at higher pH through the imino and amino nitrogen atoms. The formation constants of a series of bidentate $\alpha$-amino acids, $NH_2CH(R)CO_2H$, or of their esters with $[Cu(NTA)]^-$ are relatively invariant.

Since the discovery of the metal-ion-catalyzed hydrolysis of amino acid esters in 1952,[1] these reactions have been studied by a number of research groups with hopes of elucidating the role of metal ions in biological systems.[2-4] The generally accepted mechanism of ester catalysis is one in which the carbonyl carbon atom is activated toward nucleophilic attack by the polarizing effect of the metal ion. This can occur by induction through the coordinated amino group or by interaction of the carbonyl oxygen atom with the metal. The former is proposed for the hydrolysis of copper(II) complexes of the potentially tridentate histidine esters in which carbonyl group interaction with the metal is less favorable.[5] The latter is postulated for the hydrolysis of metal complexes of potentially bidentate esters of $\alpha$-amino acids such as glycine.[6] In this case transient coordination of the carbonyl oxygen prior to nucleophilic attack is postulated for labile metal ions such as copper(II). Such ester carbonyl coordination has not, however, been conclusively established for amino acid ester–metal complexes in aqueous solution,[7] although it is present in some complexes in the solid state.[8,9] In solution the extent of ester coordination is probably very small, but Alexander and Busch[10] have demonstrated that it is necessary for a large rate enhancement for ethyl glycinate hydrolysis in the complex $[Co(en)_2EtGly]^{3+}$.

Current studies in this laboratory are concerned with the interaction of complexes of divalent metal ions and quadridentate ligands with amino acid esters. Re-

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