

[CONTRIBUTION OF THE BERSWORTH RESEARCH LABORATORIES, AND OF THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

Interaction of Divalent Metal Ions with N-Hydroxyethylethylenediaminetriacetic Acid

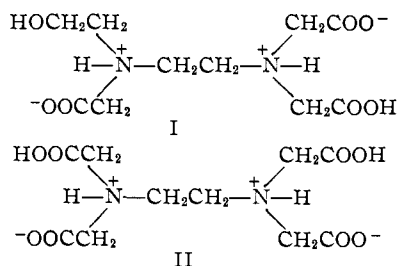
By S. CHABEREK, JR., AND ARTHUR E. MARTELL

RECEIVED JUNE 29, 1954

The formation of 1:1 metal chelates between N-hydroxyethylethylenediaminetriacetic acid (HEDTA) with Cu(II), Ni(II), Co(II), Zn(II), Cd(II), Mn(II), Fe(II) and Ca(II) ions was studied potentiometrically. The corresponding chelate formation constants and the acid dissociation constants are reported. On comparison with the corresponding constants of ethylenediaminetetraacetic acid, it is seen that the replacement of an acetate by a hydroxyethyl group decreases the basicity of the amino acid anion, and correspondingly reduces the chelate formation constants by 0.9–3.4 log K units. The influence of pH on the chelating tendencies of HEDTA is reported and the effects of metal hydrolysis and interference of oxalate and carbonate are described.

A recent investigation¹ has shown that interaction of this complexing agent with ferric ions produces a 1:1 ferric chelate which is considerably more stable against hydrolysis in alkaline medium than the corresponding ferric complex of ethylenediaminetetraacetic acid (EDTA). While this property is of considerable importance, general utility of this chelating agent is also conditioned by its performance in the presence of the divalent heavy metal and alkaline earth ions. This paper reports a study of this property for Ca(II), Zn(II), Cd(II) and metal ions of the first transition series.

The structural similarity of the N-hydroxyethylethylenediaminetriacetic and ethylenediaminetetraacetic acids is demonstrated clearly by a comparison of formulas I and II.



Since recent studies with hydroxyethyl amino acids derived from ammonia have indicated that the ethanolic group is involved in chelate formation^{2,3} the corresponding substitution of a hydroxyethyl group for an acetate linkage in these ethylenediamine derivatives still retains the potentially hexadentate chelating structure. The effect of such substitution upon chelation has not been extended previously to the polycarboxylic acids derived from ethylenediamine.

Experimental

Materials.—The monosodium salt of N-hydroxyethylethylenediaminetriacetic acid was prepared from the commercial trisodium salt by the usual ion-exchange methods, employing the acid form of Dowex-50 resin. An aqueous solution was standardized by potentiometric titration and by a second titration in the presence of nickel ions. Sufficient hydrochloric acid was added to convert the monosodium salt to the free amino acid. A number of check titrations were run using a sample of pure, recrystallized amino acid donated by Dr. A. E. Frost.

(1) S. Chaberek, "Ferric Iron Chelates of Some Tetra- and Hexadentate Chelating Agents," Bersworth Chemical Company, October 15, 1952.

(2) S. Chaberek, R. C. Courtney and A. E. Martell, *THIS JOURNAL*, **74**, 5057 (1952).

(3) S. Chaberek, R. C. Courtney and A. E. Martell, *ibid.*, **75**, 2185 (1953).

The metal ion solutions were prepared from J. T. Baker Analyzed Reagents and were standardized by the method of Jones and Martell. Carbonate-free potassium hydroxide was prepared by the procedure described by Schwarzenbach and Biedermann.⁴

Apparatus and Procedure.—The experimental method used in this investigation is similar to that described in a recent publication.⁵ The temperature was $29.6 \pm 0.05^\circ$, and the ionic strength was maintained at 0.10 with KCl. The amino acid concentration was maintained at approximately $2 \times 10^{-3} M$, so that its conversion to other ionic species during the course of the titration would have only a negligible effect upon the ionic strength. The titration was carried out with carbonate-free potassium hydroxide in a nitrogen atmosphere. Although the pH was recorded by a Beckman model G pH meter, the values corresponded to hydrogen ion activities determined by the hydrogen-silver-silver chloride cell, since the pH meter-glass electrode-calomel electrode system was calibrated periodically against the potential of the former cell with the experimental solution as the electrolyte.

Experimental Data.—The potentiometric titration data for HEDTA in the absence and in the presence of an equimolar concentration of metal ions are presented in graphic form in Fig. 2. The ordinate represents pH measurements corrected as described above and the abscissa, "a," denotes the moles of base added per mole of amino acid.

Calculations.—The acid dissociation constants, k_1 , k_2 , k_3 of HEDTA were calculated by both the algebraic and modified Bjerrum methods which have been described previously.⁵ The calculation of the chelate stability constant, K , was described in detail for ethylenediamine-N,N'-diacetic acid.⁶ The final form of the equation used may be written as

$$K = \frac{C_A - \beta(\text{AOH}^{-3})}{(\text{AOH}^{-3})[C_M + \beta(\text{AOH}^{-3}) - C_A]} \quad (1)$$

where $C_A + C_M$ are the total molar concentrations of amino acid and metal ions, respectively, and AOH^{-3} represents the completely ionized amino acid, HEDTA

$$\beta = \frac{(\text{H}^+)^3}{k_1 k_2 k_3} + \frac{(\text{H}^+)^2}{k_2 k_3} + \frac{(\text{H}^+)}{k_3} + 1$$

$$K = \frac{(\text{MA}^-)}{(\text{M}^{+2})(\text{AOH}^{-3})}$$

$$(\text{AOH}^{-3}) = \frac{(3-a)C_A - (\text{H}^+) + (\text{OH}^-)}{\frac{3(\text{H}^+)^3}{k_1 k_2 k_3} + \frac{2(\text{H}^+)^2}{k_2 k_3} + \frac{(\text{H}^+)}{k_3}} \quad (2)$$

The values of "a" chosen for calculation purposes corresponded as closely as possible to a Bjerrum \bar{n} value of 0.5. The degree of chelation, \bar{n} , may be determined readily by the use of the following relation

$$\bar{n} = \frac{C_A - \beta(\text{AOH}^{-3})}{C_M} \quad (3)$$

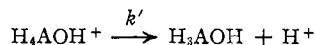
The stability constants were corrected for possible

(4) G. Schwarzenbach and W. Biedermann, *Helv. Chim. Acta*, **31**, 339 (1948).

(5) S. Chaberek and A. E. Martell, *THIS JOURNAL*, **74**, 5052 (1952).

(6) S. Chaberek and A. E. Martell, *ibid.*, **74**, 6228 (1952).

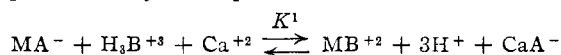
H_4A^+ formation, assuming that the acid dissociation constant, k' , for the reaction



was equal to 1×10^{-2} .

The pM - pH data given in Fig. 4 were calculated in a manner described in a paper to be submitted soon.⁷

In the case of Cu(II), Ni(II), Co(II) and Zn(II) ions, the degree of association with the amino acid is so great that it was not possible to calculate the formation constants by equations 1 and 2. The experimental methods employed for these ions was that of Ackermann and Schwarzenbach.⁸ The basis of this method is the introduction of a second chelating agent, triaminotriethylamine trihydrochloride, and a second metal ion, Ca(II) ion, which is strongly bound by the amino acid but not by the polyamine salt. The resulting equilibrium may be represented by the equation



The chelate stability constant K may be calculated from the relationship

$$K = \frac{k_1 k_2 k_3 K_{MB} K_{CaA}}{K^1}$$

where k_1 , k_2 , and k_3 are the acid dissociation constants of H_3B^{+3} , and K_{MB} and K_{CaA} are the chelate formation constants of the amino acid with Ca(II) ion and of the amine with M(II) ions. Potentiomet-

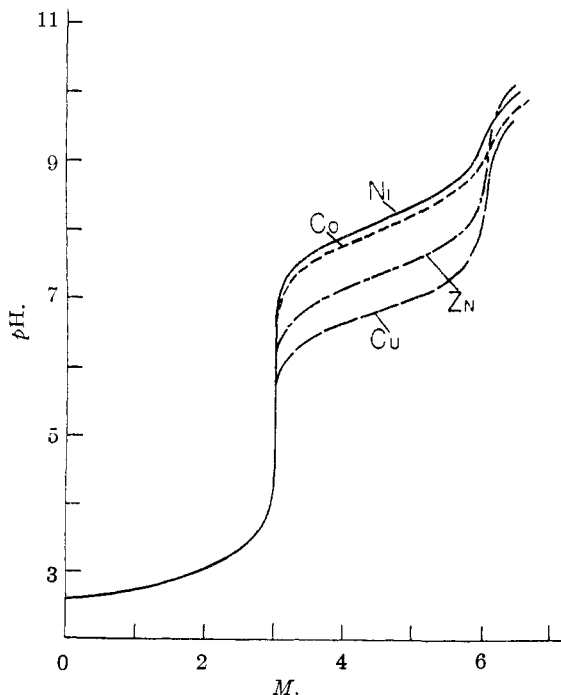


Fig. 1.—Values of pH vs. M , moles of KOH added per mole of transition metal ion, in a system containing equimolar amounts of metal chelate of N-hydroxyethylethylenediaminetriacetic acid, triaminotriethylamine trihydrochloride and calcium ion; $t = 25^\circ$, $\mu = 0.1$.

(7) S. Chaberek, F. C. Bersworth and A. E. Martell, in preparation.

(8) H. Ackermann and G. Schwarzenbach, *Helv. Chim. Acta*, **32**, 1545 (1949).

ric titration with standard base of the equilibrium mixture containing the metal chelate, the tetramine hydrochloride and calcium ion led to the formation of well-defined buffer regions in the pH range 6–8.5, from which the stability of the metal chelate was readily calculated. The corresponding titration curves, corresponding to displacement of the transition metal by calcium ion, are given in Fig. 1.

Discussion of Results

Titration Curves.—The free acid curve of Fig. 2 has two inflections at “ a ” values of 1 and 2, corresponding to the formation of the mono- and dialkali metal salts. A third inflection, corresponding to the formation of the tripotassium salt is absent, probably because of extensive hydrolysis of the trivalent anion. It is interesting to note that both acid buffer regions in the “ a ” interval of 1 to 3 lie at a lower pH level than those of the symmetrical ethylenediaminediacetic acid. Hence the zwitterion protons of HEDTA are more acidic than are those of the unsubstituted diacetic acid.

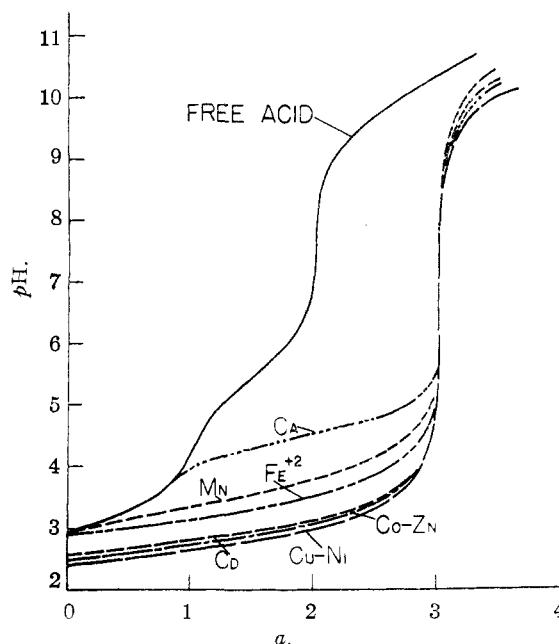
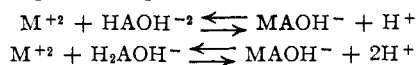
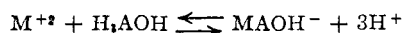


Fig. 2.—Values of pH vs. a , moles of KOH added per mole of N-hydroxyethylethylenediaminetriacetic acid: HEDTA curve in the absence of, and metal curves in the presence of 1:1 molar ratios of metal chlorides; $t = 25^\circ$, $\mu = 0.1$, HEDTA $C_A/C_M = 1$.

The addition of divalent heavy metal ions to solutions of the N-hydroxyethylethylenediaminetriacetic acid results in a great lowering of the second and third acid buffer regions to lower pH values, corresponding to the equilibria



The heavy metal chelates are apparently sufficiently stable so that appreciable interaction occurs with the undissociated acid species, according to the reaction



The formation of the 1:1 chelates is complete at a *pH* of approximately 6.0 for all the metals investigated.

The calcium-HEDTA titration curve shows a weak inflection at *a* = 1. The absence of an acidification effect in the range of *a* = 0 to *a* = 1, indicates that little interaction, if any, occurs between the undissociated acid species and metal ions. Hence, the chelation of calcium involves only the mono- and divalent anions of HEDTA.

Equilibrium Constants.—The acid dissociation and metal chelate formation constants of N-hydroxyethylethylenediaminetriacetic acid are listed in Table I, together with the corresponding values for EDTA⁹ and the symmetrical ethylenediaminediacetic acid (EDDA).

The substitution of a β -hydroxyethyl group for an acetate group in the ethylenediamine tetraacetate structure increases the acidity of both ammonium protons. Since the chelating ligand anion may be considered a Lewis base, this decrease in hydrogen ion affinity, resulting from the strong inductive effect of the ethanolic group, should influence the affinity of the amino acid for metal ions. This is indeed the case, and the log *K* values of EDTA with these metal ions are seen to be approximately 1–3 log *K* units higher than those of HEDTA. It is interesting, however, that the formation constants for the triacetic acid chelates are considerably greater than those of the corresponding metal-EDDA chelates. Since the latter amino acid is a tetradentate chelating agent, it is quite likely that N-hydroxyethylethylenediaminetriacetic acid acts at least as a pentadentate chelating agent in the presence of the octahedral metal ions. In view of the fact that acetate groups are stronger chelating linkages than are β -hydroxyethyl groups, the formation of the fourth chelate ring probably involves the former grouping. It is not possible to establish, on the basis of these data, the coordination of the β -hydroxyethyl group.

The metal chelate formation constants listed in Table I represent the results of two opposing tendencies. The decreased basicity of the ligand anion tends to decrease the metal ion affinity, while the

formation of additional chelate rings tends to increase the stability of the metal complex.

In addition to the difference in stability constants described above, HEDTA and EDTA show an interesting similarity in the correlation of chelate stability constants with the second ionization potential of the metals of the first transition series. In Fig. 3, the formation constants of the transition metal chelates and the corresponding values of the second ionization potential (dotted line) are plotted *vs.* the atomic number. Furthermore, the correlation of the stability constants of ethylenediamine, previously described by Irving and Williams,¹⁰ is also shown. It is apparent that the stabilities of the M-HEDTA chelates are lower than for the corresponding M-EDTA chelates. The difference in the behavior of these chelating agents, compared to ethylenediamine, indicates the strong influence of the acetate groups upon the resulting metal ion affinity.

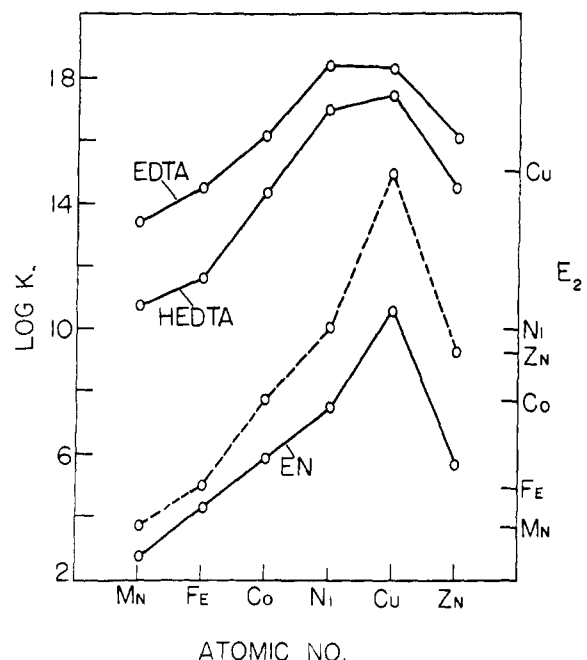


Fig. 3.—Correlation of log *K* with corresponding atomic numbers of the transition metals.

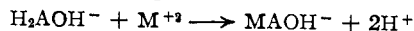
TABLE I
EQUILIBRIUM CONSTANTS
T = 29.6°, μ = 0.1, γ_{H^+} = 0.78

M ⁺⁺	EDDA	HEDTA	EDTA ^a	$\frac{\log K_{EDTA}}{\log K_{HEDTA}}$
(H ⁺) <i>p</i> k ₁	6.42	2.64	2.0	
<i>p</i> k ₂	9.46	5.33	2.67	
<i>p</i> k ₃	...	9.73	6.13	
<i>p</i> k ₄	10.26	
Cu ⁺⁺	16.2	17.4	18.3	0.9
Ni ⁺⁺	13.5	17.0	18.4	1.4
Co ⁺⁺	11.2	14.4	16.1	1.7
Zn ⁺⁺	11.1	14.5	16.1	1.6
Cd ⁺⁺	8.8	13.0	16.4	3.4
Fe ⁺⁺	...	11.6	14.5	2.9
Mn ⁺⁺	...	10.7	13.4	2.7
Ca ⁺⁺	...	8.0	10.6	2.6

^a G. Schwarzenbach and E. Freitag,⁹ *T* = 20°, μ = 0.1.

(9) G. Schwarzenbach and E. Freitag, *Helv. Chim. Acta*, **34**, 1503 (1951).

Comparison of *pM*–*pH* Functions for HEDTA and EDTA.—Sample *pZn* and *pNi* functions for HEDTA (solid lines) have been plotted in Fig. 4, along with corresponding EDTA values (dotted lines). In general, the HEDTA *pM*–*pH* plots are similar in shape to the corresponding EDTA relations. The *pH* range of 3 to 5 exhibits a slope of 2, corresponding to the interaction of the monovalent acid species according to the reaction



while in the *pH* interval of 5 to approximately 8.5, one proton is released. Interaction in this *pH* range may be expressed by the reaction



It is readily apparent from curves in Fig. 4 that the affinity of HEDTA for these divalent metal

(10) H. Irving and R. Williams, *Nature*, **162**, 746 (1948).

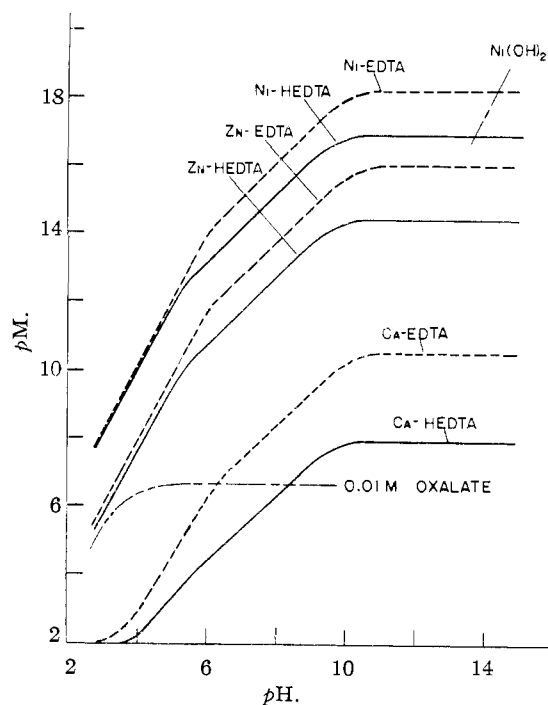
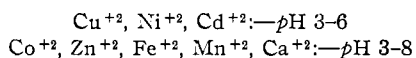


Fig. 4.—Regulation of zinc(II) and nickel(II) ion concentrations by ethylenediaminetetraacetic acid and N-hydroxyethylethylenediaminetriacetic acid when molar ratio of chelating agent to metal ion is 2/1. In the regions below metal hydroxide and oxalate curves, precipitation of hydroxide and oxalate occur, respectively, at equilibrium.

ions, compared to that of EDTA, is pH dependent, and compares favorably with the latter in the acid pH range. From similar plots for other metals, it can be shown that the pH intervals in which the metal ion affinities of EDTA and HEDTA compare favorably may be subdivided into two general groups



In pH ranges exceeding those cited above, EDTA is more effective in reducing the free metal ion concentration.

Figure 4 illustrates the general displacement of the HEDTA pM - pH curves to lower pM values. The relatively great displacement to the flat buffer region at pH values of 9 or greater is especially significant, since it is indicative of the relative effects of competing anions upon the chelates of the triacetic acid and EDTA. The plots of the Ni^{+2} - $\text{Ni}(\text{OH})_2$ and Zn^{+2} - $\text{Zn}(\text{OH})_2$ systems intersect the pM - pH plots of the HEDTA chelates at lower pH values than for the corresponding EDTA chelates. Hence, the former are more susceptible to hydrolysis effects. Similarly the more basic anions, such as carbonate, will exert a stronger precipitation tendency upon the HEDTA chelates at high pH .

The intersections in Fig. 4 of the Ca EDTA and Ca HEDTA curves with the oxalate curve indicate the pH values below which calcium oxalate will precipitate in the presence of 0.01 M oxalate ion concentration. It is seen that under these conditions the difference in the effectiveness of EDTA and HEDTA is greatly magnified. This is a consequence of the fact that in general the difference in metal ion affinity of EDTA over HEDTA is greater for the less basic ions investigated.

Although it is apparent that the affinity of HEDTA for divalent metal ions compares favorably with EDTA in the acid pH range, the metal chelates of the former are considerably more susceptible to metal hydrolysis and other interferences in alkaline solutions. When one considers its high affinity for iron(III) ions in alkaline solution, and its high aqueous solubility at all pH values, it is apparent that this new amino acid is a valuable addition to the list of metal chelating agents.

Acknowledgment.—The authors are indebted to Dr. F. C. Bersworth for support of this work and for many valuable suggestions. Thanks are due to Dr. Albert E. Frost of Versenes, Inc., for providing a sample of pure, crystalline N-hydroxyethylethylenediaminetriacetic acid used in checking some of the results of this investigation, and also to N. J. Bicknell for performing a number of check titrations.

FRAMINGHAM, MASS.
WORCESTER, MASS.