stoppered 125-ml. erlenmeyer flask and the flask thoroughly swirled. Precipitation began within a minute. After the appropriate time elapsed, the mixture was filtered through a tared sintered glass funnel containing a layer of glass wool to aid in rapid filtration. The reaction flask and the precipitate were washed with 50 cc. of anhydrous benzene and 25 cc. of anhydrous ether, the last traces of the precipitate being removed from the flask during this operation. The funnel and salt were then dried at 50° under vacuum to constant weight and the amount of salt determined by weighing. Direct determination of the solubility of the salt in each of the reactants showed it to be negligible in comparison to the total weight, when benzene was used. In acetone, however, the weight of the salt was corrected for the solubility (0.027 g./50 cc.).

In order to compare the rates of reaction of various substituted phenacyl bromides under approximately equivalent conditions three determinations at the half-reaction time were carried out for each substituent in benzene solution, assuming the reaction to be second order in each case.

EVANSTON, ILLINOIS

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY]

Stability of Metal Chelates. IV. N,N'-Ethylenediaminediacetic Acid and N,N'-Ethylenediaminediacetic-N,N'-dipropionic Acid

BY S. CHABEREK, JR.,[1] AND A. E. MARTELL

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Acid dissociation constants and chelate stability constants of N,N'-ethylenediaminediacetic acid and of ethylenediamine-N,N'-diacetic-N,N'-dipropionic acid are reported for Cu^{+2}, Ni^{+2}, Co^{+2}, Zn^{+2}, Pb^{+2}, Cd^{+2} and Mg^{+2} ions. The results are compared with the stabilities of the corresponding ethylenediaminetetraacetate chelates, and the relative values for these three chelating agents are interpreted in the light of the corresponding structural differences.

The sequestering properties of ethylenediaminetetraacetic acid have been well known for some time. Extensive equilibrium studies of this complexing agent with both alkaline earth and transition metal ions have been made by Schwarzenbach and co-workers,[2,3] who found that this α-amino acid formed unusually strong complexes with these metal ions. Although there has been considerable speculation regarding the reasons for this unusually strong metal ion affinity, especially with the alkaline earth metals, very few additional quantitative data have been obtained. The ethylenediaminetetraacetate anion has been considered to supply from four to six donor groups to the metal ion, and various workers in this field have disagreed as to the probable structures of the corresponding chelates, the proposed formulas varying from tetradentate to hexadentate in nature. There is no doubt but that in the case of copper at least, the ligand possesses more coördinating groups than are actually required for complete chelation of the metal. This is not true of other first-row transition metals, however. No definite information is available regarding the function of the acetate groups and their effect upon the stability of the chelate.

In order to obtain additional information on the relation between ligand structure and chelation, metal stability constants of two amino acids related structurally to ethylenediaminetetraacetic acid have been measured. These are N,N'-ethylenediaminediacetic acid and N,N'-ethylendiaminediacetic-N,N'-dipropionic acid.

Both compounds retain at least a portion of the basic structure necessary for chelation, namely, two nitrogen atoms and two acetic acid groups, but differ in the additional substituents on the nitrogen atoms. It is interesting to note, also, that while complex formation involving ethylenediaminetetraacetic acid results in the formation of five-membered chelate rings, chelation with the corresponding dipropionic-diacetic acid derivative can involve the formation of five-membered rings with the acetic acid groups *or* six-membered rings with the propionic acid groups. The effect of these substituents upon complex formation has not been determined previously.

Experimental

The experimental method used in this investigation is the same as that described in detail in the first paper of this series.[4] The N,N'-ethylenediaminediacetic-N,N'-dipropionic acid and N,N'-ethylenediaminediacetic acid were synthesized by a method to be described in a subsequent publication.[5]

Calculations.—The potentiometric titration data for N,N'-ethylenediaminediacetic acid and N,N'-ethylenediaminediacetic-N,N'-dipropionic acid in the presence and in the absence of an equivalent concentration of metal ion are given in graphic form in Figs. 1 and 2. It is apparent from these curves that both reagents produce 1:1 metal chelates, as in the case of ethylenediaminetetraacetic acid.

The acid dissociation constants of the symmetrical diacetic acid were calculated both by the algebraic and modified Bjerrum methods described previously.[4] The stability constants were calculated by the algebraic method, only. The acid dissociation constants of N,N'-ethylenediaminediacetic-N,N'-dipropionic acid were calculated by the method of Schwarzenbach and Ackermann.[2b]

The calculation of the metal stability constants for the ethylenediaminediaceticdipropionic acid was accomplished in the following way: The acid dissociation equilibria may be described by the relations.

$$H_4A \overset{k_1}{\rightleftharpoons} H_3A^- + H^+ \quad k_1 = (H_3A^-)(H^+)/(H_4A) \tag{1}$$

$$H_3A^- \overset{k_2}{\rightleftharpoons} H_2A^{-2} + H^+ \quad k_2 = (H^+)(H_2A^{-2})/(H_3A^-) \tag{2}$$

$$H_2A^{-2} \overset{k_3}{\rightleftharpoons} HA^{-3} + H^+ \quad k_3 = (H^+)(HA^{-3})/(H_2A^{-2}) \tag{3}$$

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(1) Bersworth Postdoctoral Fellow, Clark University.

(2) (a) G. Schwarzenbach and H. Ackermann, *Helv. Chim. Acta*, **30**, 1798 (1947); (b) G. Schwarzenbach and H. Ackermann, *ibid.*, **31**, 1029 (1948).

(3) G. Schwarzenbach and E. Freitag, *ibid.*, **34**, 1503 (1951).

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

(5) S. Chaberek, Jr., F. C. Bersworth and A. E. Martell, unpublished results.

$$\mathrm{HA^{-3}} \underset{}{\overset{k_4}{\rightleftarrows}} \mathrm{A^{-4}} + \mathrm{H^+} \qquad k_4 = (\mathrm{H^+})(\mathrm{A^{-4}})/(\mathrm{HA^{-3}}) \quad (4)$$

$$\mathrm{M^{+2}} + \mathrm{A^{-4}} \overset{K}{\rightleftarrows} \mathrm{MA^{-2}} \quad K = (\mathrm{MA^{-2}})/(\mathrm{M^{+2}})(\mathrm{A^{-4}}) \quad (5)$$

where H_4A represents ethylenediaminediaceticdipropionic acid and parentheses indicate molar concentration. Also

$$C_A = (\mathrm{H_4A}) + (\mathrm{H_3A^-}) + (\mathrm{H_2A^{-2}}) + (\mathrm{HA^{-3}}) + (\mathrm{A^{-4}}) + (\mathrm{MA^{-2}}) \quad (6)$$

$$C_M = (\mathrm{M^{+2}}) + (\mathrm{MA^{-2}}) \quad (7)$$

where C_A and C_M = total molar concentrations of acid species and metal species, respectively. From electroneutrality considerations it follows that

$$aC_A + (\mathrm{H^+}) - (\mathrm{OH^-}) = (\mathrm{H_3A^-}) + 2(\mathrm{H_2A^{-2}}) + 3(\mathrm{HA^{-3}}) + 4(\mathrm{A^{-4}}) + 4(\mathrm{MA^{-2}}) \quad (8)$$

Calculation of (A^{-4}).—By elimination of (MA^{-2}) from equations (8) and (6) and substitution for H_4A, H_3A^-, H_2A^{-2}, HA^{-3} the corresponding equations (1)-(4), the following relationship is obtained

$$(\mathrm{A^{-4}}) = \frac{(4-a)C_A - \mathrm{H^+} + \mathrm{OH^-}}{\frac{4(\mathrm{H^+})^4}{k_1k_2k_3k_4} + \frac{3(\mathrm{H^+})^3}{k_2k_3k_4} + \frac{2(\mathrm{H^+})^2}{k_3k_4} + \frac{(\mathrm{H^+})}{k_4}} \quad (9)$$

Calculation of K.—The following equation was obtained by the elimination of (M^{+2}) and (MA^{-2}) from equation (5) by the use of equations (7) and (6), respectively, and substitution of equations (1)-(4) for (H_4A), (H_3A^{-1}), (H_2A^{-2}) and (HA^{-3})

$$K = \frac{C_A - y(\mathrm{A^{-4}})}{(\mathrm{A^{-4}})[C_M + y(\mathrm{A^{-4}}) - C_A]} \quad (10)$$

where

$$y = \frac{(\mathrm{H^+})^4}{k_1k_2k_3k_4} + \frac{(\mathrm{H^+})^3}{k_2k_3k_4} + \frac{(\mathrm{H^+})^2}{k_2k_4} + \frac{(\mathrm{H^+})}{k_4} + 1 \quad (11)$$

K may be calculated from equations (9), (10) and (11). The final expression is very similar to that derived for a dicarboxylic acid.[4] In the case of strong metal ion–amino acid interaction, which results in strong acidification, the terms containing the $(H^+)^4$ and $(H^+)^3$ functions are not negligible in magnitude and cannot be ignored. However, in cases where interaction results in the establishment of buffer regions at a pH of 5.5 or higher, these terms are negligible and may be eliminated.

Discussion of Results

Titration Curves.—The titration curve of N,N′-ethylenediaminediacetic acid (Fig. 1) has a buffer region at about pH 6.5 followed by a weak inflection point at one equivalent of base per mole of amino acid. Thus the free acid and the monovalent anion exist as relatively pure entities in solution; whereas the dialkali metal salt is extensively hydrolyzed. In the case of N,N′-ethylenediaminediacetic-N,N′-dipropionic acid, the titration curve shown in Fig. 2 indicates that the free acid and the di- and trialkali metal salts are well-defined substances in solution. The overlapping of the first two neutralization steps indicates a disproportionation of the monoalkali metal salt, and the tetraalkali metal salt is apparently extensively hydrolyzed in solution. It is interesting to note that the second half of the titration curve of the propionic acid derivative is quite similar to that of N,N′-ethylenediaminediacetic acid, with the exception that the intermediate buffer region is somewhat lower.

The titration curves in the presence of metal ions, shown in Figs. 1 and 2, indiate strong chelate formation with all metals investigated, with the possible exception of magnesium and N,N′-ethylenediaminediacetic acid. The relative order of chelation tendencies is apparent from the curves, the

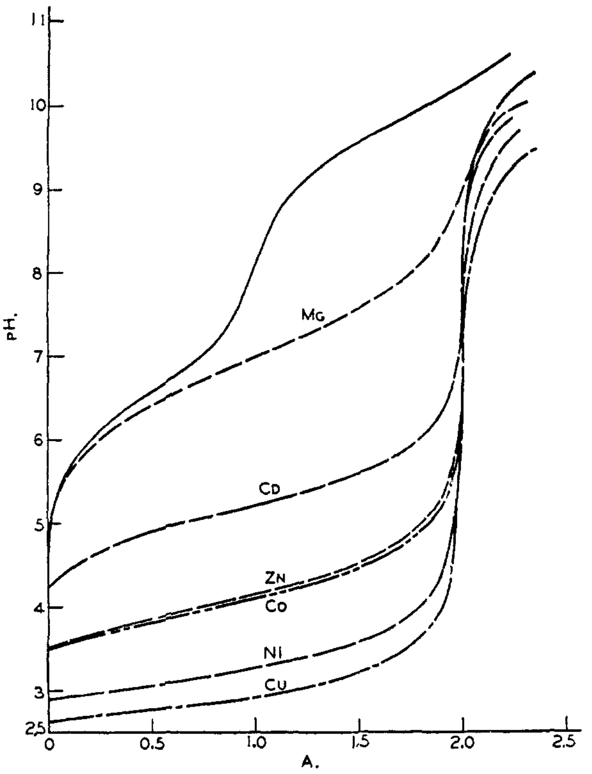


Fig. 1.—Titration curves of N,N′-ethylenediaminediacetic acid; A = moles of base added per mole of acid.

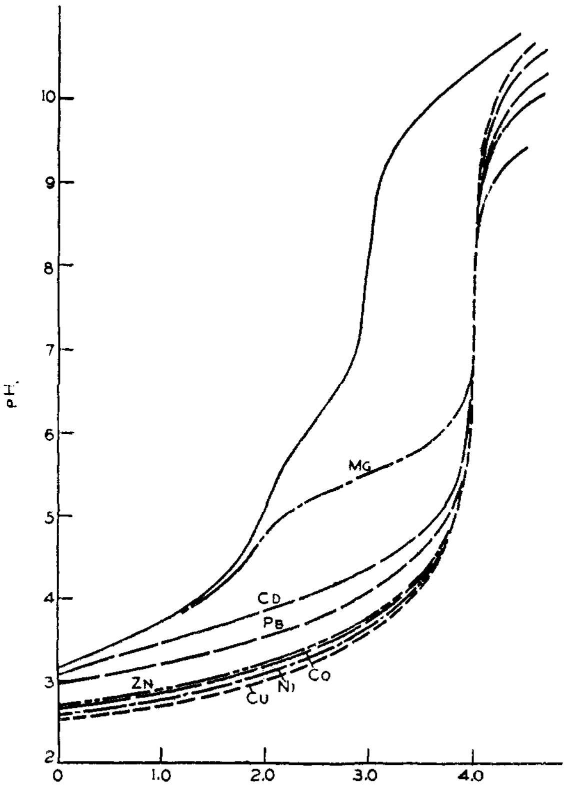


Fig. 2.—Titration curves of N,N′-ethylenediaminediacetic-N,N′-dipropionic acid; A = moles of base per mole of acid.

lower the pH of the initial buffer region, the greater the stability of the metal chelate. Qualitative comparison of the two figures also indicates that the stabilities of the metal chelates of the propionic acid derivative are probably somewhat greater. For both chelating agents, the affinities for metal ions are sufficiently great that, with the exception of magnesium ion, extensive interaction takes place at pH values so low that the free acid is the principal species of the complexing agent in the solution.

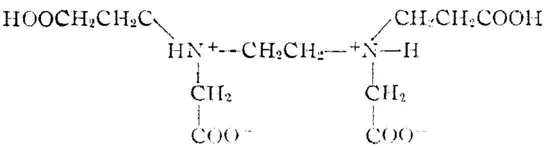
Acid Dissociation Constants.—The first and second acid dissociation constants (pk_1 and pk_2) of ethylenediaminediaceticdipropionic acid, listed in Table I, are approximately one pk unit higher than the corresponding values for ethylenediaminetetraacetic acid. Comparison of the structures of these compounds (formulas I and II) indicates that the explanation lies in the greater inductive effect of the $\equiv\overset{+}{N}H$ on the carboxyl group in structure II. The differences between structures I and II with respect to both the first and second dissociation constants is approximately the same as the difference in pk_1 values for glycine and β-alanine.

Table I

Equilibrium Constants

	N,N'-Ethylene-diamine-diacetic acid[a]	N,N'-Ethylene-diamine-diacetic N,N'-dipropionic acid[a]	N,N'-Ethylene-diamine-tetraacetic acid[b]
	Dissociation constants		
pk_1	6.42	3.00	2.00
pk_2	9.46	3.79	2.67
pk_3		5.98	6.13
pk_4		9.83	10.26
	Chelate stability constants (log K_1 values)		
M^{+2}			
Cu^{+2}	16.2	16.3	18.3
Ni^{+2}	13.5	15.5	18.4
Co^{+2}	11.2	14.9	16.1
Zn^{+2}	11.1	14.5	16.1
Pb^{+2}		13.2	18.2
Cd^{+2}	8.8	11.8	16.4
Mg^{+2}	3.9	6.9	8.7[c]

[a] This investigation, 30°, $\mu = 0.1$, $\gamma_{H^+} = 0.78$. [b] From Schwarzenbach and Freitag,[2a] 20°, $\mu = 0.1$. [c] From Schwarzenbach and Ackermann,[2b] 20°, $\mu = 0.1$.



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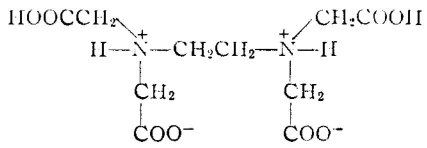
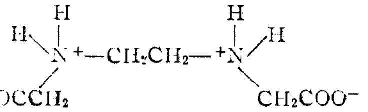
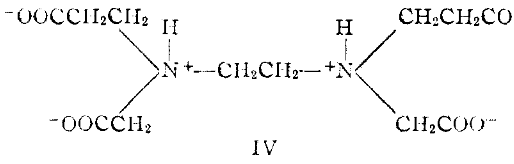


II

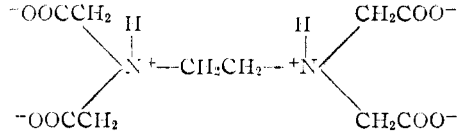
Comparison of pk_1 of ethylenediaminediacetic acid with pk_3 of ethylenediaminediaceticdipropionic and ethylenediaminetetraacetic acid indicates that they are roughly equivalent, the total spread being about 0.4 pk unit. This seems reasonable on the basis of the similarity of structure of the molecules and ions which dissociate (formulas III, IV and V). In all three compounds the dissociation reaction is influenced primarily by the positive charge of the adjacent ammonium group.



III



IV



V

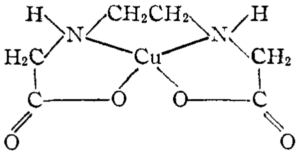
The relative acidities of the last proton to dissociate from III, IV and V may be explained from the relative electrostatic effects in these anions. The most basic ion is the tetravalent anion of ethylenediaminetetraacetic acid, in which the large negative charge probably helps to develop the maximum basicity of the nitrogen. The same may be said for the tetravalent anion of IV, except that two of the negative charges are spaced farther from the nitrogens and hence there is some reduction of the effect. With two of the negative carboxylate ions removed, we have the divalent anion of III which is still less basic than the corresponding anion of IV.

It is of interest to note that the difference in pk values of the two amino nitrogens in III is about equal to that in ethylenediamine ($\sim$3.0 pk units), and is the accepted value for the electrostatic effect of a positive charge spaced two carbon atoms away from a substituted ammonium ion. On this basis the differences for IV and V are over one pk unit too large. It is this phenomenon that led Schwarzenbach to suggest a hydrogen bridge between the two basic nitrogens in the trialkali metal salt of ethylenediaminetetraacetic acid.

The relative stabilities of the 1:1 metal complexes are the same for both acids investigated and are in agreement with those found for other chelating agents, namely, $Cu^{+2} > Ni^{+2} > Co^{+2}$, $Zn^{+2} > Cd^{+2} > Mg^{+2}$. In general, the values reported in Table I are reliable within 0.15–0.2 log K unit for constants in the range of 10^{13}–10^{16}, while with values of 10^{12} and lower, the error is probably less than 0.1 log K unit.

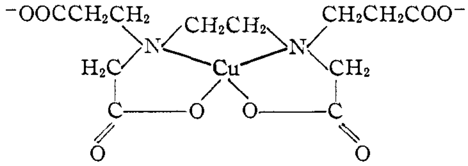
In the calculation of the chelate stability constants, the possible interference of species of the type MHA^- and MH_2A, where H_4A represents ethylenediaminetetrapropionic acid, was neglected. It was not possible to evaluate proton complexing from the potentiometric data at low pH, and additional experimental work, probably along spectrophotometric lines, is needed to obtain such information. By assuming reasonable dissociation constants of MHA^- and MH_2A, the authors have calculated the interference of these substances with the postulated equilibria to be small.

The stability constants of the copper complexes of both acids are equivalent within experimental error. This is not surprising in view of the fact that these complexes have a square planar arrangement of donor groups about the copper atom. Since only four coördination positions are required, it is quite probable that chelation of copper with both ligands involves the nitrogen atoms and acetic acid groups, and the resulting chelate structures would be the same.



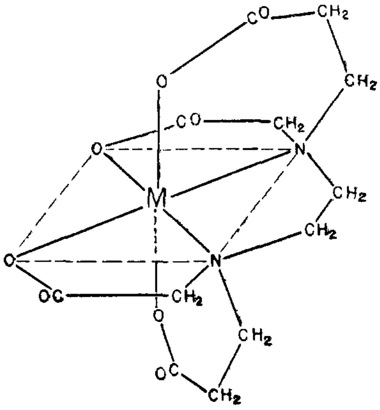
and

VI



VII

On the other hand, the stability constants of those metals having a coördination number of 6 are increased considerably (10^2–10^3) by the substitution of the propionic acid groups for the hydrogen atoms on the nitrogens of ethylenediaminediacetic acid. It is quite probable, therefore, that these additional coördinating groups do take part in the chelation process, and consequently increase the stability of the complex. The probable structure of the chelate compounds formed between the ethylenediaminediacetatedipropionate anion and hexacovalent metals such as Ni^{+2}, Co^{+2}, Pb^{+2}, and Cd^{+2} is indicated by formula VIII. Although Zn^{+2} and Mg^{+2} are usually considered to have coördination number of 4, the large increase in stability of the corresponding chelates of ethylenediaminedipropionicdiacetic acid over those of ethylenediaminediacetic probably indicates indirect involvement of the propionate groups in the stability of these chelate compounds.



VIII

From the comparison of the chelation tendencies of ethylenediaminediacetic, ethylenediaminediaceticdipropionic and ethylenediaminetetraacetic acids given in Table I, it is seen that the stabilities of the copper complexes of the ethylenediaminediacetic acid and ethylenediaminediaceticdipropionic acid are roughly equivalent, while the corresponding copper complex of ethylenediaminetetraacetic acid is 10^2 times greater. This difference cannot be due to a difference in structure, since all three complexes are square planar. It is possible that the increased stability is in part an entropy effect, resulting from an increase in the ethylenediaminetetraacetate ion of the probability of attaining a spatial orientation required for chelation with the cupric ion. Also, it seems that the inductive effect of the two additional negative carboxylate ions increases considerably the donor power of the amino nitrogen atoms.

The remaining metal ions may be divided into two groups on the basis of the relative behaviors with the tetravalent anions of ethylenediaminedipropionicdiacetic acid and of ethylenediaminetetraacetic acids: 1, those which show a stability difference of 10^2–10^3, including Ni^{+2}, Co^{+2}, Zn^{+2} and Mg^{+2}; and 2, Pb^{+2} and Cd^{+2}, which show a stability difference of 10^5. It is not apparent why the ethylenediaminetetraacetate anion should be relatively so much more effective as a complexing agent for the latter pair of ions. Regardless of the relative effects, however, it is clear that the acetate groups form more stable chelate structures than do β-propionate groups for all the metals listed in Table I.

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WORCESTER, MASS.