The Effect of Potassium Chloride on the Equilibrium between Ethylenediaminetetraacetate and Calcium Ions[1]

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The various ionization constants of ethylenediaminetetraacetic acid, and the stability constant of the calcium-ethylenediaminetetraacetate anion are reported at various potassium chloride concentrations. The data are extrapolated graphically to infinite dilution to give the corresponding thermodynamic constants.

Introduction

Schwarzenbach and Ackermann[2] have determined the apparent ionization constants of ethylenediaminetetraacetic acid and the chelate stability constant of the calcium ion with its tetranegative anion, at 20°, in 0.100 M KCl. The present investigation was undertaken to determine the effect of neutral salt (KCl) concentration on the dissociation and complex formation equilibria. In view of the high degree of interaction of simple dipolar ions with various basic metal ions, a large effect would be expected for dissociation of the various species of ethylenediaminetetraacetic acid. Further, since the stability of the complex is usually expressed in terms of the tetranegative anion of the complexing agent, the equilibrium constant involving the metal ion should show a large salt effect. Potassium chloride was chosen as the neutral salt since the potassium ion has been shown by Schwarzenbach[2] not to interact with the ethylenediaminetetraacetate anion, and since the chloride ion makes it possible to employ a silver–silver chloride reference electrode.

Ethylenediaminetetraacetic acid (I) contains two dipolar groups and would be expected to interact more strongly with neutral salts than do simple dipolar ions such as glycine. The next higher ionic species which is well-defined in solution is the divalent anion (II) which contains two carboxylate ions in addition to the two dipolar ions. The monovalent anion (not shown) probably also exists as an intermediate in solution. The trinegative anion is illustrated with a hydrogen bridge of the type suggested by Schwarzenbach[2] to account for the abnormally large difference between the third and fourth dissociation constants. Although there are theoretical reasons for doubting the stability of a bridge of this type, it is certain that additional interaction of some kind must take place. Possibly the carboxylate ions are also involved in the hydrogen bridging, and the hydrogen ion is complexed to some extent in the same manner as are the more basic metal ions. The tetranegative anion (IV) is usually used as the reference ion for expressing the stability constant of the metal complex. The structure now generally accepted for the calcium complex, in which the calcium ion is hexacoördinate, is illustrated by formula V. The use of molecular models indicates that this structure may be achieved approximately with little strain in the organic molecule.

I

II

III

IV
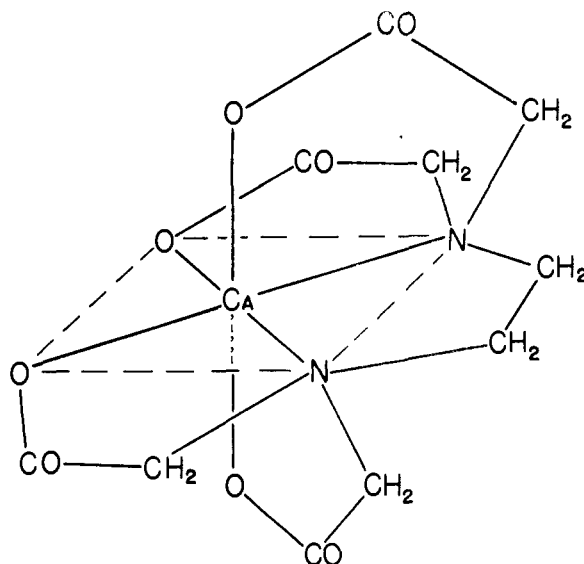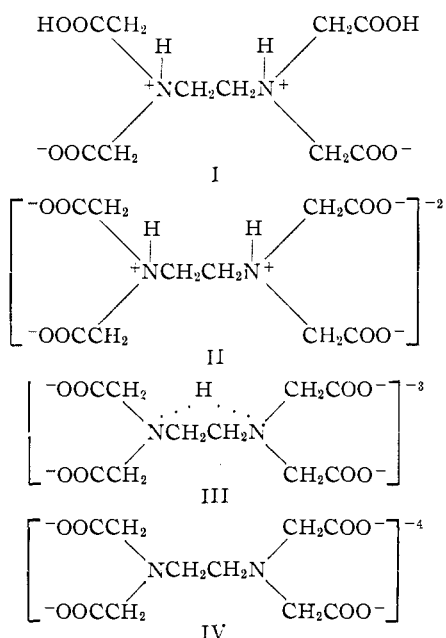
V, Calcium chelate of ethylenediaminetetraacetate ion

Experimental

Apparatus.—The titration vessel consisted of a 250-ml. flask fitted with seven necks to accommodate a mercury-seal stirrer, acid and base microburets, and platinum, silver–silver chloride, saturated calomel, and glass electrodes. A 5-inch shielded glass electrode (Beckman No. 1190-75) and a saturated calomel electrode (Beckman No. 1170) were

(1) Abstracted from a thesis submitted by Francis F. Carini to the Faculty of Clark University, in partial fulfillment of the requirements for the degree of Master of Arts, June, 1951.

(2) G. Schwarzenbach and H. Ackermann, Helv. Chim. Acta, 31, 1793 (1947).

used with a Beckman model G pH meter. The hydrogen electrodes were platinized by the method outlined in Weissberger,[3] and the method described by Shedlovsky and MacInnes[4] was employed in preparing the silver–silver chloride electrodes. The e.m.f. of the hydrogen silver–silver chloride cell was determined with the help of a Leeds and Northrup type K potentiometer. The temperature was maintained at 25.03 ± 0.01°.

Materials.—The analytical-reagent grade ethylenediaminetetraacetic acid, kindly donated by the Bersworth Chemical Company, was twice stirred with hot water for 10 hours and decanted. The remaining solid was twice recrystallized from hot water. Carbonate-free KOH was prepared according to the method outlined by Schwarzenbach.[5] A stock solution of the disodium salt of ethylenediaminetetraacetic acid was made by weighing out approximately 0.0100 mole of acid, adding slightly more than 0.0200 mole of KOH, and diluting to one liter.

Measurements.—The calibration of the Beckman glass electrode-calomel electrode system was carried out at 0.01, 0.1 and 1.0 M KCl concentrations by comparing the pH reading with the pH calculated from the measured e.m.f. of the cell

$$\text{Pt, } H_{2(f)}, \text{ } H^+_{(a)}, \text{ } Cl^-_{(a)}, \text{ } AgCl - Ag$$
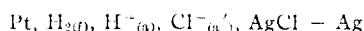
The readings of the two cells were taken simultaneously and under the same conditions that were employed for the potentiometric titrations (i.e., with the complexing agent present). In the calibration runs at least two hydrogen electrodes and at least two silver–silver chloride electrodes were employed. Equilibrium was obtained for the hydrogen electrodes within a few minutes on a buffered solution, but 20 to 30 minutes were required in non-buffered regions of the titration curve. The pH of the solution was calculated from the equation

$$pH = \frac{E_{cell} - (E_0 + \frac{RT}{F} \ln m_{Cl^-} \gamma_\pm)}{RT/F}$$

where

E_{cell} = measured potential

E_0 = potential of Ag-AgCl electrode, −0.2224 volt

$\gamma_\pm$ = mean ionic activity coefficient of KCl, obtained from the work of Harned and Cook[6]

m_{Cl^-} = molality of chloride ion
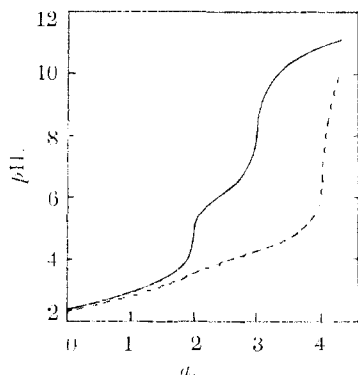
Other symbols have their usual meaning.

Fig. 1.—Titration of 0.001 M ethylenediaminetetraacetic acid in 0.1 M KCl with and without 0.001 M Ca⁺²: ——, EDTA; — — — —, EDTA + Ca⁺²; a = moles of KOH per mole of EDTA.

Titration of the amino acid at other salt concentrations was carried out in a manner analogous to the procedure outlined above, but readings were taken on the pH meter only. The solutions employed for the determination of the calcium complex constants were made up and titrated in the same manner, except that sufficient CaCl₂ solution was added to make its molarity approximately equal to that of the complexing agent.

Calculations.—The conditions employed in the titration and the method employed in calculating the various equilibrium constants differ from previously published reports and so are briefly described here. The symbols and terms are defined as

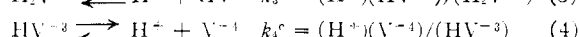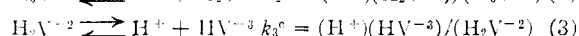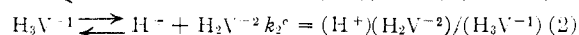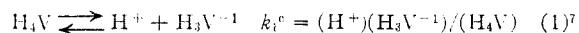C_s = total concentration of complexing agent species in solution

C_m = total concentration of metal ion species present

( ) = molar concentration of species indicated

a = moles of base added per mole of complexing agent present. H_4V, H_3V^{-1}, H_2V^{-2}, HV^{-3}, V^{-4} represent forms of ethylenediaminetetraacetic acid and its dissociation products

CaV^{-2} represents the calcium complex

Other terms have their usual meaning. The acid equilibria and the corresponding apparent ionization constants may be represented by

$$H_4V \rightleftharpoons H^+ + H_3V^{-1} \quad k_1^c = (H^+)(H_3V^{-1})/(H_4V) \quad (1)^{[7]}$$

$$H_3V^{-1} \rightleftharpoons H^+ + H_2V^{-2} \quad k_2^c = (H^+)(H_2V^{-2})/(H_3V^{-1}) \quad (2)$$

$$H_2V^{-2} \rightleftharpoons H^+ + HV^{-3} \quad k_3^c = (H^+)(HV^{-3})/(H_2V^{-2}) \quad (3)$$

$$HV^{-3} \rightleftharpoons H^+ + V^{-4} \quad k_4^c = (H^+)(V^{-4})/(HV^{-3}) \quad (4)$$

where K_n^c is the equilibrium constant at a definite concentration of KCl. In the absence of calcium ions, the following relationship holds

$$C_s = (H_4V) + (H_3V^{-1}) + (H_2V^{-2}) + (HV^{-3}) + (V^{-4}) (5)$$

From electroneutrality requirements it is seen that

$$aC_s + (H^+) = (OH^-) + (H_3V^{-1}) + \\ 2(H_2V^{-2}) + 3(HV^{-3}) + 4(HV^{-4}) \quad (6)$$

The first two ionization constants may be combined to give

$$k_1^c k_2^c = (H^+)^2(H_2V^{-2})/(H_4V) = k_{12}^c \quad (7)$$

It may be seen from the shape of the titration curve of the amino acid (curve A, Fig. 1) that in the region between $a = 0$ and $a = 2$, (HV^{-3}) and (V^{-4}) may be neglected. At the point on the titration curve where $a = 1$, $C_{H^+} = (H_2V^{-2}) - (H_4V)$. Assuming that the ratio k_1/k_2 has the statistical value of 8/3, the above equations may be combined to give the relationships

$$4/3C_{H_3V} - 4(C_s - 1/3C_{H^+})C_{H_3V} + (C_s - C_{H^+})^2 = 0 \quad (8)$$

$$4/3C_{H_3V} - 2 - 4(C_s + 1/3C_{H^+})C_{H_2V} - 2 + (C_s + \\ C_{H^+})^2 = 0 \quad (9)$$

The values of $C_{H_2V} - 2$ and C_{H_3V} calculated from equations (8) and (9) are used in equation (7) for the determination of k_{12}^c. The individual constants k_1^c and k_2^c were not calculated since they are subject to much larger errors than is the combined constant k_{12}^c. The statistical ratio of 8/3 was chosen for k_1^c/k_2^c since it gave the best agreement for values of k_{12}^c calculated from different titrations.

The third dissociation constant, k_3^c, is very simply calculated from the pH of curve A, Fig. 1, at $a = 2.5$. At this point $(HV^{-3}) = (H_2V^{-2})$ and

$$k_3^c = (H^+)(HV^{-3})/(H_2V^{-2}) = (H^+) \quad (10)$$

The fourth ionization constant was determined from the pH at $a = 4$. Since hydrolysis of the tetranegative anion occurs, $C_{HV^-} = C_{OH}$, at $a = 4.0$ the pH is considerably above the neutral point, and the ionization of water may be neglected. Also, at this high pH the concentrations of H_4V, H_3V^{-1}, and H_2V^{-2} may be dropped from equation (5). As a result the expression for k_4^c reduces to

$$k_4^c = (H^+)(V^{-4})/(HV^{-3}) = (H^+)(C_s - C_{OH})/C_{OH^-} \quad (11)$$

(3) A. Weissberger, "Physical Methods of Organic Chemistry," 2nd edition, Vol. II, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1722.

(4) T. Shedlovsky and D. A. MacInnes, THIS JOURNAL, 58, 1970 (1936).

(5) G. Schwarzenbach and W. W. Biedermann, Helv. Chim. Acta, 31, 331 (1948).

(6) H. S. Harned and M. A. Cook, THIS JOURNAL, 59, 1290 (1937).

(7) In the case of hydrogen ions parentheses signify activity, since this was assumed to be measured by the hydrogen–silver–silver chloride cell. In stoichiometric relationships such as (5) and (6), it was necessary to obtain approximate concentrations of H⁺ and OH⁻ by comparison with HCl–NaOH titration curves.

The equilibria for complex formation may be expressed by the relationships

$$Ca^{+2} + V^{-4} \longrightarrow CaV^{-2} \qquad K_{Ca}^{\circ} = (CaV^{-2})/(Ca^{+2})(V^{-4}) \tag{12}$$
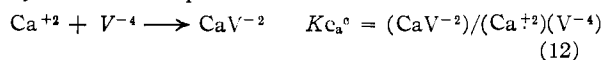
The possibility of intermediate complexes of the CaHV^{-1} type is neglected since it has been shown by Schwarzenbach[2] that in the case of ethylenediaminetetraacetic acid this is a relatively unstable intermediate. Also, the conditions of the present investigation did not allow calculation of the concentration of this substance since the bivalent metal ion concentration was not maintained constant. It was not feasible to do this (by using a large excess of calcium ions) since it was necessary to make up solutions of known and relatively low ionic strength.

In the presence of calcium ions, equations (5) and (6) must be modified to include the metal complex species. In the region between $a = 3.5$ and $a = 3.8$, it is possible to effect a simplification by neglecting H_4V and H_3V^{-1}, the concentrations of which are very low. Thus (5) becomes

$$C_a = (H_2V^{-2}) + (HV^{-3}) + (V^{-4}) + (CaV^{-2}) \tag{13}$$

Also, equation (6) is converted to

$$(a - 2)C_a + (H^+) =$$
$$(OH^-) + (HV^{-3}) + 2(V^{-4}) + 2(CaV^{-4}) \tag{14}$$

Combination of (3), (4), (13) and (14) yields

$$(a - 3)C_a + (H^+) - (OH^-) = 1 -$$
$$\frac{(H^+)^2}{k_3 k_4} C_{V^{-4}} + C_{CaV^{-2}} \tag{15}$$

Equation (15) is solved simultaneously by the use of two different "a" values.

For the purpose of calculating the equilibrium constant, the experimental data were plotted on a large scale graph, the ml. of HCl or KOH added being first converted to a moles of base added per mole of complexing agent present, with the pure acid as the reference point, at which $a = 0$. Smooth curves were drawn through the points of corrected pH vs. a, and values from the graph were taken to solve the equations for apparent dissociation constants and apparent chelate formation constants. Curves A and B of Fig. 1 are typical of the plots obtained for titration of the acid in the absence of and in the presence of calcium ions.

Discussion of Results

The results, together with some of the quantities from which they were calculated, are listed in Table I. The product of the first two ionization constants, k_{12}^c, was found to be the least reliable of the equilibrium constants; but, as already noted, it is more satisfactory in this respect than either of the first two constants taken separately. The third ionization constant, k_3^c, is the most reliable, since it is calculated from the hydrogen ion activity, which is directly determined. Since the positions of the inflection points are obtained from the graph, the estimation of k_3^c is not subject to errors in standardization of the solutions and to the presence of small amounts of impurities. The fourth ionization constant, k_4^c, depends on the value assumed for the ionization constant of water, K_w, which is not readily found either experimentally or theoretically. The value of 1.008×10^{-14} reported by Harned and Owen for 25°, was used in this paper. Since Schwarzenbach used 1.14×10^{-14} as the value of K_w, his value of k_4^c differs somewhat from that calculated in the present investigation.

Calculation of the formation constant, K_{Ca}^c, depends on the value of K_w chosen. The small difference (0.13×10^{-14}) in the ion-product constants of water given above results in a difference of 0.2 log K_{Ca}^c unit in the calculated chelate stability constant.

TABLE I

a^a	$10^3 m_{EDTA}$	m_{KCl}	pH	$m_{CaCl_2} \times 10^3$
1	5.03	0.0536	2.84	
1	4.70	.02575	2.78	
1	5.63	.543	2.72	
1	5.11	.496	2.75	
1	6.17	.975	2.71	
2.5	5.86	0.00987	6.35	
2.5	4.95	.0528	6.29	
2.5	5.49	.0879	6.24	
2.5	5.84	.3000	6.14	
2.5	5.86	.546	6.22	
2.5	5.04	.781	6.28	
4.0	5.26	0.00887	10.80	
4.0	4.32	.0464	10.65	
4.0	5.01	.0800	10.72	
4.0	5.66	.496	10.61	
4.0	4.64	.720	10.39	
3.5	4.46	0.0176	4.61	4.63
3.5	4.48	.0473	4.65	4.66
3.5	4.49	.0856	4.66	4.67
3.5	5.49	.523	4.81	4.71
3.5	4.46	.744	4.94	4.63

[a] Only sample data are given here. Constants were actually determined from a spread of "a" values.

The apparent ionization and stability constants listed in Table I are plotted as a function of the square root of the ionic strength in Figs. 2 and 3. The considerable variation in the equilibrium constants with ionic strength which is observed may be interpreted in the following manner:

Since the measured pH may be considered equivalent to the reciprocal of the hydrogen ion activity, the apparent ionization constants may be formulated as

$$k_n^{\circ} = a_{H^+} c_{A^-} / c_{HA} \tag{16}$$

where a and c represent activity and molar concentration, respectively, and HA represents the species which ionizes. The thermodynamic equilibrium constant may therefore be written as

$$k_n = \frac{a_{H^+} \gamma_{A^-} c_{A^-}}{\gamma_{HA} c_{HA}} = k_n^{\circ} \frac{\gamma_{A^-}}{\gamma_{HA}}$$

or

$$pk_n^{\circ} = pk + \log \frac{\gamma_{A^-}}{\gamma_{HA}} \tag{17}$$

The values of the thermodynamic equilibrium constants were determined by extrapolating the curves in Figs. 2 and 3 to infinite dilution. The results listed in Table II are accurate to the nearest tenth of a unit except in the case of pK_3 for which the values are somewhat better. From these values it is possible to determine the ratio of the activity coefficients of the ions in the reactions involved.

TABLE II
THERMODYNAMIC DISSOCIATION CONSTANTS, CALCIUM CHELATE STABILITY CONSTANT, AND CORRESPONDING FREE ENERGY CHANGES

	pK_{12}	pK_3	pK_4	log K_{Ca}
Equilibrium constants	5.8	6.47	10.1	11.1
Free energy changes, kcal. mole^{-1}	7.9	8.82	13.8	−15.2

The fourth ionization constant involves the ratio $\gamma_{V^{-4}}/\gamma_{HV^{-3}}$. The negative slope of Fig. 2
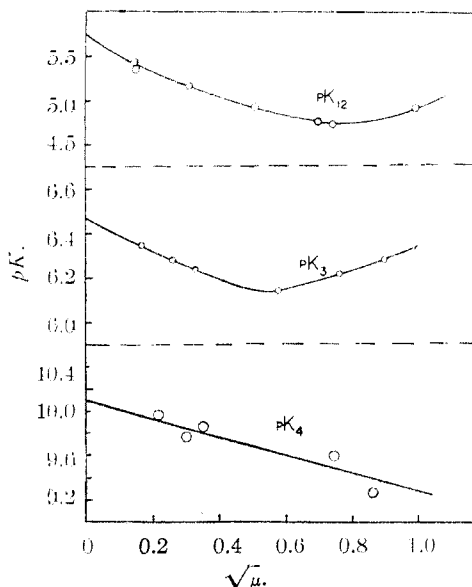
Fig. 2.—Variation of the dissociation constants of ethyl-enediaminetetraacetic acid with ionic strength: K_{12} = product of the first and second dissociation constants; K_3 and K_4 represent the third and fourth dissociation constants, respectively.
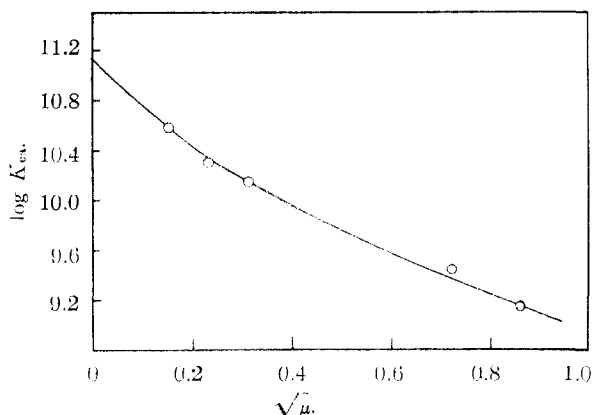

Fig. 3.—Variation of stability constant of the calcium-ethylenediaminetetraacetate anion with ionic strength.

indicates that this ratio decreases with increasing ionic strength. Therefore the reasonable conclusion may be drawn that the activity coefficient of the more highly charged ion is decreased to a greater extent. The pK_4^c values listed in Table I

are not exact since K_w at infinite dilution was used in the calculation by equation 13. However, since the activity of water is not available for dilute salt solutions, it was not possible to further refine the calculations.

Figure 2 indicates that k_{12}^c and k_3^c also vary in the same manner at low ionic strength. Kirkwood[8] has shown that extensive interaction takes place between dipolar ions and simple ions. On this basis a considerable decrease in activity coefficient of H_4V with increasing ionic strength would be predicted. However, further increasing the number of charged groups in the amino acid should result in even greater interaction. It is to be expected, therefore, that the values of k_{12}^c and k_3^c decrease with increasing ionic strength. However, the situation here seems to be somewhat more complicated in view of the fact that the constants increase again at high ionic strength. This effect is suggestive of the use of higher terms in the Kirkwood and Debye–Hückel relationships, although these idealized equations would not be expected to apply to the present system.

The chelate stability constant, K_{Ca}^c, is an even more striking example of the effect of ionic strength. This involves the ratio $\gamma_{Ca^{-2}}\gamma_{V^{-4}}/\gamma_{CaV^{-2}}$. One would expect a much greater change in K_{Ca}^c with ionic strength than has been noted for the acid dissociation constants, since the numerator contains a bivalent and tetravalent ion, while the denominator contains only a bivalent ion. The fact that the negative slope of Fig. 3 is much larger than those of Fig. 2 is in agreement with this concept.

Comparison of the results of this investigation with published work on the salt effect of glycine and other simple amino acids indicates that the variation with ionic strength of the equilibrium constants involving ethylenediaminetetraacetic acid is much greater than that observed for ordinary dipolar ions. This is probably due to (1) the larger number of charges and polar groups in ethylenediaminetetraacetic acid and (2) extensive deviation of the structure of this amino acid from approximately spherical structural models used for the simple dipolar ions.

(8) J. G. Kirkwood, J. Chem. Phys., 2, 351 (1934).