722. *The Heats of Ionization of Ethylenediaminetetra-acetic Acid and its Dissociation as an Ammonium-ion Acid.*

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The four heats of ionization of ethylenediaminetetra-acetic acid (EDTA) have been measured calorimetrically at 20° and in solutions of ionic strength 0·1. By pH determinations with a hydrogen electrode during titration of a solution of the dipotassium salt of EDTA with acid, it has been shown that the ion H_5Y^+ exists in sufficiently acid solution, where H_4Y^0 is the neutral molecule of EDTA. p*K* for the stage $H_5Y^+ \longrightarrow H_4Y^0 + H^+$ has been estimated to be $1{\cdot}55 \pm 0{\cdot}13$, and a rough value for the associated heat content change has also been obtained. Possible structures for the various ionic species formed by EDTA are considered.

In recent work in this laboratory[1] on the heat of formation of complexes of EDTA (ethylenediamine-*NNN'N'*-tetra-acetic acid) with metal ions, it has been necessary to know the heat content changes ΔH_3 and ΔH_4 for the ionization of the last two ionizable protons. Values of ΔH_3 and ΔH_4 have been given by Carini and Martell[2] from a careful study of the corresponding dissociation constants over a range of temperature and ionic strengths. It seemed desirable to check these values of ΔH_3 and ΔH_4 by direct calorimetric measurement. Since there is relatively little thermochemical information on polybasic acids, and in view of the interest attaching to EDTA in particular, it seemed worth while also to measure ΔH_1 and ΔH_2, *i.e.*, the heat content changes on the successive ionizaton of the first two ionizable protons, which have not yet been even indirectly determined.

These experiments involved preparing solutions of known composition and of constant ionic strength. By measuring the pH and using existing data on the four ionization constants of EDTA, the concentration of each ion in any one solution could be calculated, and it was then possible to examine the mutual consistency of all the experimental quantities involved by an electroneutrality check. So long as the pH was not too low, this check was always satisfactory, but in the experiments designed to determine ΔH_1 and ΔH_2 some of the solutions were of pH of about 2 or less, and for these there were apparently consistent departures from electroneutrality. There appeared to be an excess of negative charge amounting to as much as 4%, which could not be attributed to experimental errors. The most likely explanation of this discrepancy was that in solutions of EDTA of low pH there exist ions of the type H_5Y^+ and perhaps even H_6Y^{++} (where

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[1] Care and Staveley, *J.*, 1956, 4571.

[2] Carini and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4810.

H_4Y^0 represents the neutral molecule of EDTA). To investigate this possibility, pH measurements were made on solutions of the dipotassium salt of EDTA during titration with a strong acid. Analysis of the results gave definite evidence of the existence of the ion H_5Y^+, and the ionization constant at 20° for the reaction $H_5Y^+ \longrightarrow H_4Y^0 + H^+$ was evaluated. A rough value for the associated heat-content change ΔH_0 was also obtained.

EXPERIMENTAL

EDTA was purified by dissolving it in aqueous potassium hydroxide and reprecipitating it by dilute nitric acid. After two repetitions of this process, the dry product was analyzed by titration against calcium solution, and proved to be 100·0% pure. Carbonate-free, approximately M-potassium hydroxide was prepared from silver oxide and potassium chloride. This solution, after dilution, was analyzed by titration with 0·1N-hydrochloric acid which had been standardized against a sodium carbonate solution, with which the strength of the hydrochloric acid used in the calorimetric work was also estimated.

From the solid EDTA and the ~M-potassium hydroxide, three solutions were prepared, such that the EDTA existed principally as the ions Y^{4-}, HY^{3-}, and H_2Y^{2-} respectively. The potassium content of each solution was known from the amount of potassium hydroxide used, and the total EDTA content, which was ~0·2M, was checked by titration, after dilution, against standard calcium solution. 50 ml. of one of these solutions were added to a fixed quantity (~1 l.) of a dilute solution of potassium chloride contained in the calorimeter described by Davies, Singer, and Staveley.[3] The calorimetric experiment consisted in adding to this solution, now ~0·01M in EDTA, ~20 ml. of a suitable solution of hydrochloric acid, previously contained in a double-stoppered vessel within the calorimeter, and measuring the heat change. The amount of potassium chloride present was such that the ionic strength of the solution, after addition of the acid, was 0·1. The pH of the final mixture was measured with a Cambridge pH meter after its removal from the calorimeter. (All calorimetric experiments and pH measurements were carried out at 20°.) When the EDTA was introduced essentially as K_4Y or K_3HY, the hydrochloric acid was ~0·5N. In the first case, therefore, the chief reaction occurring in the calorimeter was $Y^{4-} + H^+ \longrightarrow HY^{3-}$, and in the second $HY^{3-} + H^+ \longrightarrow H_2Y^{2-}$. With the solution of K_2H_2Y, three sets of experiments were performed, in which ~1, 2, and 3 equivalent proportions of hydrochloric acid were added, the last two necessitating the use of ~N and ~1·5N acid respectively. The relatively acid solutions resulting from these last experiments were supersaturated with respect to EDTA and sooner or later deposited it. This could readily be detected in the calorimeter from the thermal effects accompanying precipitation, but usually there was ample time to follow the " after-drift " before separation of solid occurred. (Solubility limitations made it impracticable to carry out experiments starting with K_3HY.)

Corresponding to each experiment of the type described, it was also necessary to measure the heat change when the same amount of hydrochloric acid was added to a solution of potassium chloride only, to give the same final volume (and an ionic strength of 0·1) as in the experiment with EDTA. Combination of the heat changes on dilution and reaction gave the heat change which would have been observed if the reaction had been carried out with the acid already diluted. Finally, it was necessary to prepare a replica of each ~0·01M-EDTA solution used in the calorimeter, at the concentration and ionic strength prevailing before the addition of acid, and measure its pH at 20°.

Determination of the Dissociation Constant of EDTA as an Ammonium-ion Acid.—Schwarzenbach and Ackermann[4] determined the four dissociation constants of EDTA by making pH measurements during the titration of ~0·001M-EDTA with alkali, starting at pH ~2·8. To examine the possibility of the existence of H_5Y^+ and perhaps H_6Y^{++}, at low pH values, we titrated a solution of K_2H_2Y with standard hydrochloric acid and measured the pH with a hydrogen electrode. Ideally, to correspond with the calorimetric work, the total EDTA concentration should have been ~0·01M, but precipitation would have interfered. However, three sets of experiments were carried out where EDTA concentrations were respectively ~0·001, 0·003, and 0·004M. With the most dilute solution pH values as low as 1·5 could be reached. The apparatus used had been constructed by Mr. R. Shelton and was kindly made available to us by Dr. H. M. Irving. The electrodes were platinised platinum over which

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[3] Davies, Singer, and Staveley, *J.*, 1954, 2304.

[4] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798.

bubbled high-purity hydrogen pre-saturated with the vapour of the solution, and a silver–silver chloride electrode. To maintain a constant chloride-ion concentration, the EDTA was 0·1M in potassium chloride, and the acid (added from a microburette) was 0·1N. E.M.F. measurements were made to 0·1 mv, and pH values were calculated from the equation pH = $(E - E_0)/0{\cdot}05818$. E_0 was determined before each experiment by titrating 0·1M-potassium chloride with 0·1N-hydrochloric acid. The reliability of the electrode system was checked by frequently measuring the E.M.F. of the cell formed by immersing the hydrogen electrode in 0·1N-hydrochloric acid. This was constant at 0·3526 ± 0·0003 v throughout the work (cf. the value of 0·3525 derived from Harned and Ehlers's very careful study[5] of this system). In the EDTA titrations, the E.M.F. values recorded for a given amount of hydrochloric acid added could be reproduced from run to run to within 0·1 mv.

RESULTS

Ionization of EDTA as an Ammonium-ion Acid.—It was first assumed that both the ions H_5Y^+ and H_6Y^{++} exist at low pH values at concentrations determined by the equations

$$K_0 = [H^+][H_4Y^0]/[H_5Y^+] \quad . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

$$K_{00} = [H^+][H_5Y^+]/[H_6Y^{++}] \quad . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

K_0 and K_{00} are " concentration constants " at 20° with a constant salt background of 0·1N-potassium chloride. K_0 and K_{00} were evaluated from the pH titration data by a method similar to that employed by Schwarzenbach, Willi, and Bach.[6] At the low pH values concerned here the concentrations of the ions HY^{3-} and Y^{4-} are negligible, and the only relevant equilibria are those controlled by K_1, K_2, K_0, and K_{00}, where

$$K_1 = [H^+][H_3Y^-]/[H_4Y^0] \quad . \; . \; . \; . \; . \; . \; . \; . \quad (3)$$

$$K_2 = [H^+][H_3Y^{2-}]/[H_3Y^-] \quad . \; . \; . \; . \; . \; . \; . \; . \quad (4)$$

The following two relations must also hold:

$$[Y] = [H_2Y^{2-}] + [H_3Y^-] + [H_4Y^0] + [H_5Y^+] + [H_6Y^{++}] \quad . \; . \; . \quad (5)$$

$$[H^+] + [K^+] + [H_5Y^+] + 2[H_6Y^{++}] = [Cl^-] + 2[H_2Y^{2-}] + [H_3Y^-] \quad . \quad (6)$$

[Eqn. (6) is the electroneutrality requirement.] [Y] is the total concentration of EDTA, $[K^+]$ the concentration of potassium ion associated with the EDTA, and $[Cl^-]$ the concentration of the chloride ion due to the added hydrochloric acid. [Y], $[K^+]$, and $[Cl^-]$ are all known. From eqns. (1)—(6) it follows that

$$K_0 = P(1/K_{00}) + Q \quad . \; . \; . \; . \; . \; . \; . \; . \quad (7)$$

where $$P = [H^+]^2([H^+] + [K^+] - [Cl^-] + 2[Y])/D$$

and $$Q = [H^+]([H^+] + [K^+] - [Cl^-] + [Y])/D$$

with $$D = [Y]\left(\frac{2K_1K_2}{[H^+]^2} + \frac{K_1}{[H^+]}\right) - ([H^+] + K^+] - [Cl^-])\left(\frac{K_1K_2}{[H^+]^2} + \frac{K_1}{[H^+]} + 1\right)$$

From any one pH value, P and Q can be evaluated, and for these values of P and Q and for various arbitrary values of say, $1/K_{00}$, corresponding values of K_0 can be obtained, which give a straight line when plotted against $1/K_{00}$. Ideally, these lines (one for each of the experimental pH values) should meet at a point, the co-ordinates of which give the actual values of K_0 and $1/K_{00}$. The points of intersection, however, fell randomly on either side of the K_0 axis, implying that $1/K_{00}$ was zero and K_{00} infinite, *i.e.*, that in the pH range studied the ion H_6Y^{++} does not exist in significant amounts. On the other hand, all lines made approximately the same intercept [the Q of eqn. (7)] on the K_0 axis, and the mean value of Q was taken to be K_0. From seventeen values of Q taken from three sets of experiments, it was found that $K_0 = 2{\cdot}80 \pm 0{\cdot}75 \times 10^{-2}$, whence $pK_0 = 1{\cdot}55 \pm 0{\cdot}13$. With this value of K_0, the electroneutrality discrepancy which had prompted the investigation was removed. This is shown in Table 1, which relates to one of the runs carried out with ~0·003M-EDTA. It will be seen that without the introduction of

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[5] Harned and Ehlers, *J. Amer. Chem. Soc.*, 1932, **54**, 1350.

[6] Schwarzenbach, Willi, and Bach, *Helv. Chim. Acta*, 1947, **30**, 1303.

the ion H_5Y^+ there is a persistent discrepancy between the apparent total positive and negative charges, but that with the above value of K_0 the discrepancy becomes random and small.

TABLE 1. *Specimen electroneutrality check.* $10^{-3}A = [H^+] + [K^+]$; $10^{-3}B = [Cl^-] + 2[H_2Y^{2-}] + [H_3Y^-]$; $10^{-3}C = [H^+] + [K^+] + [H_5Y^+]$. (Concns. in g.-ions/l.)

	Without H_5Y^+		With H_5Y^+			Without H_5Y^+		With H_5Y^+	
pH	$A(+)$	$B(-)$	$C(+)$	$B(-)$	pH	$A(+)$	$B(-)$	$C(+)$	$B(-)$
2·011	14·84	15·44	15·18	15·22	1·678	25·40	26·43	26·12	26·16
1·908	17·28	18·02	17·73	17·76	1·629	27·72	28·74	28·49	28·48
1·807	20·34	21·08	20·91	20·82	1·592	29·73	30·92	30·52	30·67
1·731	23·13	23·98	23·79	23·71					

Heats of Ionization.—The experimental results are shown in Table 2 with the change in ionic composition in each experiment, since these changes are relevant to a consideration of the relative accuracies of the individual heat of ionization values. Each value for the heat evolved is the mean of two concordant figures, and should be accurate to ±0·5 cal. A substantial contribution to the heat change in the first experiment comes from the neutralization of hydroxyl ions, for which process a heat content change of −13,800 cal./g.-ion was taken.[7] The hydroxyl-ion concentration of the solution before the addition of acid was calculated by using a K_w value of $1{\cdot}02 \times 10^{-14}$, which was determined by experiments at 20° on standard potassium hydroxide solutions ($\sim 10^{-3}$M) of the appropriate ionic strength, with the same glass electrode as was employed in the pH measurements in the calorimetric work.

Each of the five measured heat quantities recorded in Table 2 can be expressed in terms of two or more of the heat content changes ΔH_0 to ΔH_4. Thus, the heat evolved in reaction 1 (Table 2) can be expressed in terms of ΔH_3 and ΔH_4, that in reaction 2 in terms of ΔH_2, ΔH_3, and ΔH_4, and so on.

TABLE 2. *Amounts of the various ionic species in* 10^{-3} *g.-ions in the calorimeter before and after the addition of acid, and the mean value in calories of the heat evolved on the addition of acid.* Temp., 20°; final ionic strength, 0·1; total EDTA concn., $\sim 10^{-2}$M; 1 cal. = 4·1840 abs. joules.

Approx. reaction		OH^-	Y^{4-}	HY^{3-}	H_2Y^{2-}	H_3Y^-	H_4Y^0	H_5Y^+	Heat evolved
1) $K_4Y + HCl$	Before	1·33	7·75	1·32	—	—	—	—	—
	After	—	0·01	8·58	0·47	—	—	—	+64·44
(2) $K_3HY + HCl$ ...	Before	—	0·12	9·34	0·05	—	—	—	—
	After	—	—	0·24	9·17	0·10	—	—	+41·03
(3) $K_2H_2Y + HCl$...	Before	—	—	0·56	8·75	0·04	—	—	—
	After	—	—	—	3·81	4·37	1·07	0·10	−5·64
(4) $K_2H_2Y + 2HCl$	Before	—	—	0·64	8·69	0·04	—	—	—
	After	—	—	—	1·37	4·35	2·94	0·71	−9·55
(5) $K_2H_2Y + 3HCl$	Before	—	—	0·56	8·75	0·04	—	—	—
	After	—	—	—	0·53	3·13	3·93	1·76	−11·92

The five heat content changes ΔH_0 to ΔH_4 were thus calculated from the results of Table 2 by solving the five simultaneous equations. It will be clear that the relative accuracies of these quantities vary widely. The most accurate are, of course, ΔH_3 and ΔH_4. Experiment 2 (Table 2), in particular, depends more nearly than any other on one process only, namely $H^+ + HY^{3-} \longrightarrow H_2Y^{2-}$, and so should give a good value for ΔH_3. ΔH_3 and ΔH_4 should be accurate within ~1%. The only values for comparison are those derived by Carini and Martell [2] from the temperature variation of K_3 and K_4, which are $\Delta H_3 = 3690$ and $\Delta H_4 = 5340$ cal./g.-ion. With regard to the discrepancies between our values and theirs, it is recognized that heat content changes derived, as were Carini and Martell's, by the temperature-coefficient method can seldom be as accurate as those measured directly (see, *e.g.*, Rowlinson [8]). In experiment 3 (Table 2), about half of the EDTA has undergone the conversion $H^+ + H_2Y^{2-} \longrightarrow H_3Y^-$, and though some H_4Y^0 has been formed, ΔH_1 is undoubtedly small and so most of the observed heat change is due to the formation of H_3Y^- from H_2Y^{2-}. The resulting value for

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[7] Harned and Owen, " Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corpn., New York, 2nd Edn., 1950, p. 494.

[8] Rowlinson, *Discuss. Faraday Soc.*, 1957, **24**, 121.

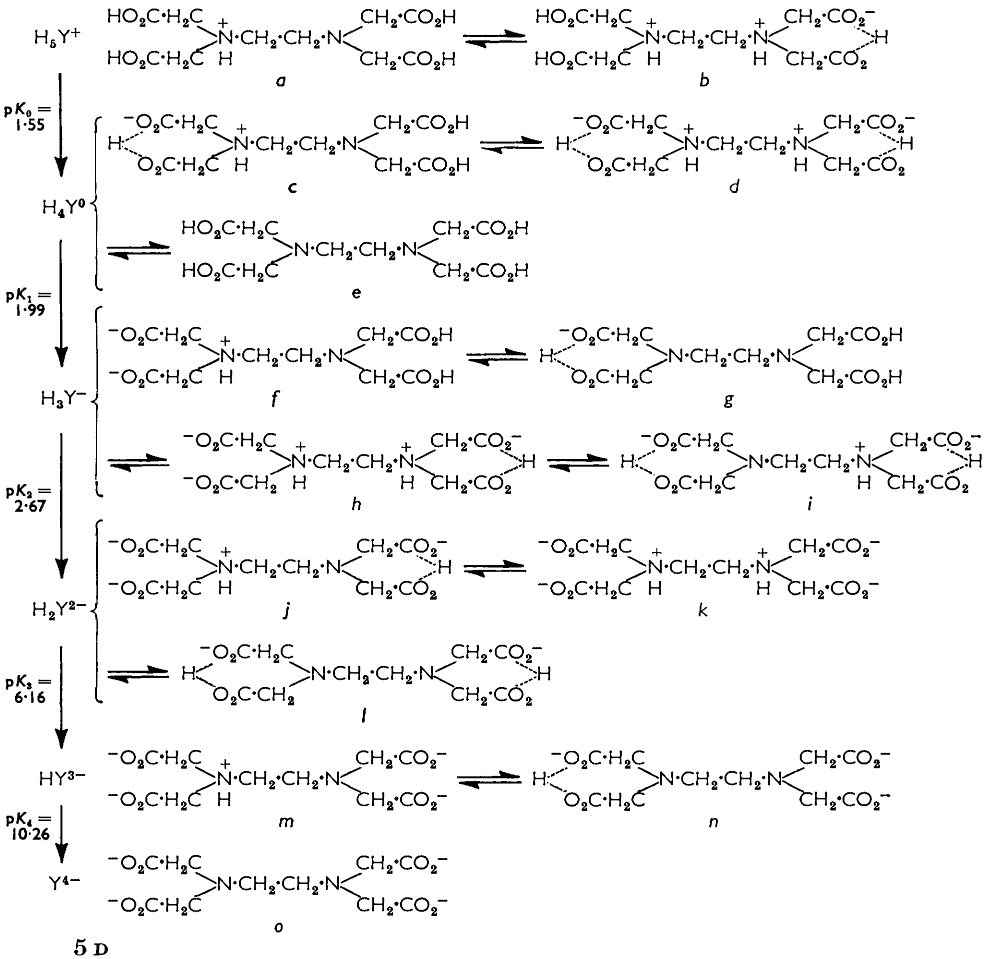
ΔH_2 should therefore be fairly reliable. Least accurate of all are ΔH_0 and ΔH_1, and perhaps it would be unwise to claim more for the values presented than that they show that these two quantities are numerically small and do not differ much from each other.

DISCUSSION

The values of ΔG, ΔH, and ΔS for the five ionization processes are recorded in Table 3. The values of pK_1 to pK_4 are those given by Schwarzenbach and Ackermann.[4] Although information on ΔH for simpler polycarboxylic acids and amino-acids is rather meagre, the thermodynamic parameters of Table 3 should throw some light on the structures of the various ions formed by EDTA. The various possibilities for these structures are shown in the annexed ionization scheme.

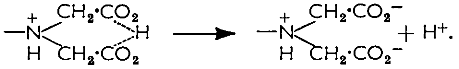
TABLE 3. *Thermodynamic parameters for the various ionization stages of* EDTA *at* 20°. *ΔG and ΔH in cal./mole, ΔS in cal./mole deg.*

Reaction	pK	ΔG	ΔH	ΔS
$H_5Y^+ \longrightarrow H_4Y^0 + H^+$	1·55	2,080	−490	−8·8
$H_4Y^0 \longrightarrow H_3Y^- + H^+$	1·99	2,680	−180	−9·8
$H_3Y^- \longrightarrow H_2Y^{2-} + H^+$	2·67	3,580	−1,430	−17·1
$H_2Y^{2-} \longrightarrow HY^{3-} + H^+$	6·16	8,260	+4,390	−13·2
$HY^{3-} \longrightarrow Y^{4-} + H^+$	10·26	13,760	+5,690	−27·5



In attempting to decide which structures are the most probable, the following points should be noted: (1) It is highly likely that for some ions, at least, there is tautomeric equilibrium between two or more structures. If equilibrium prevails between two tautomers HA and HB, the apparent ionization constant will fall between the values for the two separate structures. (2) From a study of the infrared spectrum of the disodium salt of EDTA, Chapman[9] concluded that, in the solid salt at least, the ion H_2Y^{2-} does not have the double zwitterion structure in which both nitrogen atoms are linked to protons. In view of this and of our own finding that the value of K_{00} (eqn. 2) seems to be effectively zero, it is unlikely that structures such as *b*, *d*, and *h* are important. Chapman's work, however, does not seem to be inconsistent with the possibility of the existence of single betaine structures, and our demonstration of the probable existence of H^5Y^+ requires that, in solution at least, such structures must be considered in any ionization scheme. (3) As Chapman pointed out, structures such as *c* and *j* which contain the group $-\dot{N}<^{CH_2\cdot CO_2^-}_{CH_2\cdot CO_2H}$ should be somewhat stabilized by internal hydrogen-bond formation between the OH and CO_2^- groups. This stabilization no doubt results primarily from favourable entropy factors.[10]

With these considerations in mind, *a* and *c* seem the most probable structures for the species H_5Y^+ and H_4Y^0 respectively. We should expect pK_0 to be appreciably less than the corresponding figure of 2·35 for the protonated form of glycine, just as pK_1 for glutaric acid is less than p*K* for acetic acid. It might appear that the next proton is lost from the carboxyl group adjacent to the carboxylate ion, *i.e.*, from the charged rather than the uncharged end of the molecule, since the pK_1 of 1·996 is not far from the value of 2·12 for methyliminodiacetic acid. However, for the ion H_3Y^-, the structure *i* rather than *f* may be dominant, for the following reason. Schwarzenbach and Ackermann[11] found that pK_2 is almost unaffected by increasing the number of methylene groups between the two nitrogen atoms. With a sufficient number of such groups, there is no reason why the double zwitterion structure should not be preferred, and both the first and the second ionization stage (starting from H_4Y^0) will then be as follows:



In view of the constancy of pK_2, it is likely that this mode of ionization holds for EDTA itself, so that the most important structure for H_3Y^- is probably *i*, formed by loss of a proton from a carboxyl group of *c*. This leads to *j* as the favoured structure for H_2Y^{2-}, which seems consistent with Chapman's spectroscopic work and is supported by the value of pK_3, which is not very different from pK_1 (= 5·58) for the acid $H_2N\cdot CH_2\cdot CH_2\cdot N(CH_2\cdot CO_2H)_2$. This last substance in its uncharged form should exist as a zwitterion with the charges as widely separated as possible,[12] *i.e.*, as $H_3\overset{+}{N}\cdot CH_2\cdot CH_2\cdot N<^{CH_2\cdot CO_2^-}_{CH_2\cdot CO_2}>H$ (cf. structure *j*), and on losing a proton should produce an ion $H_3\overset{+}{N}\cdot CH_2\cdot CH_2\cdot N<^{CH_2\cdot CO_2^-}_{CH_2\cdot CO_2^-}$ (cf. *m*). It should be noted that, in contrast to pK_2, pK_3 increases markedly with the number of methylene groups separating the nitrogen atoms, reaching 9·94 for octamethylenediaminetetra-acetic acid. This is no doubt due to the increasing importance of structures such as *k* for the analogues of the ion H_2Y^{2-}, so that for the higher homologues the third and the fourth ionization stage become essentially identical.

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[9] Chapman, *J.*, 1955, 1766.
[10] Jaffe, *J. Amer. Chem. Soc.*, 1957, **79**, 2373.
[11] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1948, **31**, 1029.
[12] Cohn and Edsall, "Proteins, Amino-acids, and Peptides," Reinhold Publ. Corpn., New York, 1943, p. 103.

As regards the last ionization stage, ΔH for the second ionization of a simple mono-amino-monocarboxylic acid is usually between 10,000 and 11,000 cal., while for the tri-methylammonium ion ΔH is 8500 cal. ΔH_4 for EDTA is considerably smaller than these figures. Moreover, ΔS_4 differs considerably from the value of ~ -8 e.u. associated with the second ionization stage of an acid like glycine. It is therefore difficult to believe that the fourth ionization stage is simply represented by $m \longrightarrow o$. Rather would it appear that a significant proportion of the ions HY^{3-} have the structure *n*. If *m* and *n* compete on comparable terms, the possible participation of structures such as *l* and *g* cannot be disregarded.

We are grateful to Imperial Chemical Industries Limited for financial assistance.

THE INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, April 9th,* 1958.]