[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

Thermodynamic Dissociation Constants of Methylaminediacetic Acid and Dimethylethylenediaminediacetic Acid

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The potentials of hydrogen–silver–silver chloride cells were measured in buffer solutions of methylaminediacetic acid and dimethylethylenediaminediacetic acid. The e.m.f. data obtained were extrapolated to infinite dilution with aid of the Hückel extension of the Debye–Hückel equation. The thermodynamic equilibrium constants of the amino acids were determined and values of ΔF^0, ΔH^0 and ΔS^0 for the temperature range 0–40° were calculated for each dissociation step.

The purpose of this investigation was to determine the thermodynamic relationships associated with acid dissociation of methylaminediacetic acid and N,N′-dimethylethylenediaminediacetic acid. These thermodynamic values are needed for the determination by potentiometric means of the thermodynamic changes associated with the combination of the corresponding amino acid anions with various metal ions. It has been shown in a previous publication[2] that it is possible to calculate the thermodynamic stability constants of ethylenediaminetetraacetate chelates from potentiometric measurements. The present paper describes part of a series of similar investigations of a number of metal chelates of lower order.

Equilibrium constants previously reported for methylaminediacetic acid (MADA) and dimethylethylenediaminediacetic acid (DMEDDA) have been measured at only one temperature and one ionic strength. Measurements of the dissociation constants of MADA were made by Schwarzenbach and Ackermann[3] at 0.1 ionic strength and at 20°, while similar measurements on DMEDDA were reported by Chaberek and Martell,[4] also at 0.1 ionic strength but at 30°. Since these determinations were made at one ionic strength, no thermodynamic equilibrium constants could be calculated. In addition to usefulness in the study of complexing of metal ions, the heats and entropies of ionization of these acids are interesting in view of structural relationships which they bear to the well-known chelating agents, ethylenediaminetetraacetic acid (EDTA) and nitrilotriacetic acid (NTA).

Experimental

The method employed for the determination of thermodynamic constants consists of extrapolation to zero ionic strength of the e.m.f. of cells without liquid junction containing a buffer system made up of the appropriate amino acid anions.

Two general types of cells were employed

$$\text{Pt-H}_2,\ \text{H}_2\text{A}(m_1),\ \text{KHA}(m_2),\ \text{KCl}(m_3),\ \text{AgCl-Ag} \quad \text{(I)}$$

$$\text{Pt-H}_2,\ \text{KHA}(m_1),\ \text{K}_2\text{A}(m_2),\ \text{KCl}(m_3),\ \text{AgCl-Ag} \quad \text{(II)}$$

where H_2A represents the undissociated form of a diprotic acid.

The electromotive forces of cells I and II were measured from 0 to 40°. The values for 0° were evaluated by extrapolation of data taken at slightly higher temperatures.

Materials and Equipment.—The dimethylethylenediaminediacetic acid was obtained through the courtesy of Dr. A. Frost of Versenes, Inc., Framingham, Mass., and the methylaminediacetic acid was prepared by Mrs. Sonya J. Westerback of Clark University. The amino acids were further purified by successive recrystallizations from water. The buffer solutions employed in cells I and II were made up by adding to the pure acid the required amount of carbonate-free standard potassium hydroxide, prepared by the method of Schwarzenbach and Biedermann.[5] The amount of chloride present in the base was determined by the Volhard method. The potassium chloride used was freed of bromide contamination by recrystallization from water and 95% ethanol as outlined by Pinching and Bates.[6]

The silver–silver chloride electrodes were prepared by the method of Shedlovsky and MacInnes[7] and the platinum-

TABLE I

DIMETHYLETHYLENEDIAMINEDIACETIC ACID

m_3	E.m.f. measurements (mv.) 0°	10°	20°	30°	40°
	Cell I, $m_1:m_2:m_3 = 1:1:3.80$				
4.735×10^{-3}	704.76	709.62	713.37	716.45	718.09
6.892×10^{-3}	696.38	700.79	704.21	706.71	708.09
9.174×10^{-3}	690.20	694.36	697.84	699.96	701.30
1.137×10^{-2}	686.14	690.01	693.51	694 96	695.81
1.366×10^{-2}	681.90	685.60	687.80	690.36	691.42
	Cell II, $m_1:m_2:m_3 = 1:1:26$				
2.230×10^{-2}	889.15	895.79	901.55	910.93	911.07
3.007×10^{-2}	884.84	891.55	897.68	902.66	906.51
3.707×10^{-2}	897.47	886.21	892.28	897.94	901.95
4.379×10^{-2}	877.61	883.91	889.46	894.24	898.35
5.063×10^{-2}	870.16	876.50	882.18	887.33	890.82

TABLE II

METHYLAMINEDIACETIC ACID

m_3	E.m.f. measurements (mv.) 0°	10°	20°	30°	40°
	Cell I, $m_1:m_2:m_3 = 1:2:6$				
6.746×10^{-3}	533.81	537.97	541.86	545.42	548.05
9.034×10^{-3}	523.90	528.13	531.68	534.72	536.88
1.011×10^{-3}	519.99	523.88	527.41	530.34	532.82
1.179×10^{-2}	515.12	518.80	522.23	524.88	527.19
1.434×10^{-2}	508.01	511.91	514.97	517.46	519.47
1.769×10^{-2}	502.01	504.96	507.52	509.51	511.35
	Cell II, $m_1:m_2:m_3 = 1:1:16.2$				
1.629×10^{-2}	894.70	902.81	910.46	917.15	922.31
2.302×10^{-2}	882.55	894.39	898.25	905.15	910.75
3.027×10^{-2}	879.29	887.23	894.09	901.04	907.09
3.899×10^{-2}	873.12	880.60	887.66	894.37	900.03
4.366×10^{-2}	869.30	870.45	884.26	890.64	896.38

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[1] Abstracted from a thesis presented by Nelson E. Ockerbloom to the Faculty of Clark University in partial fulfillment of the requirements for the degree of Master of Arts.

[2] F. Carini and A. E. Martell, THIS JOURNAL, **76**, 2153 (1954).

[3] G. Schwarzenbach, H. Ackermann and P. Ruckstuhl, *Helv. Chim. Acta*, **32**, 1175 (1949).

[4] S. Chaberek and A. E. Martell, unpublished results.

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

[6] G. Pinching and R. Bates, *J. Research Natl. Bur. Standards*, **37**, 311 (1946).

[7] T. Shedlovsky and D. A. MacInnes, THIS JOURNAL, **58**, 1970 (1936).

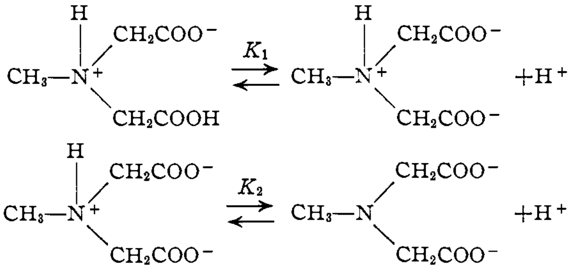
hydrogen electrodes were made according to directions outlined in Weissberger.[8]

The electromotive force measurements were made with the Leeds and Northrup type K potentiometer and a sensitive galvanometer. For each measurement at least two platinum electrodes and four silver–silver chloride electrodes were employed, and the electrodes which disagreed by more than 0.1 mv. were discarded. The temperature of the cell was maintained constant within ±0.02°. The glass vessel used in the measurements was described in a previous publication.[9]

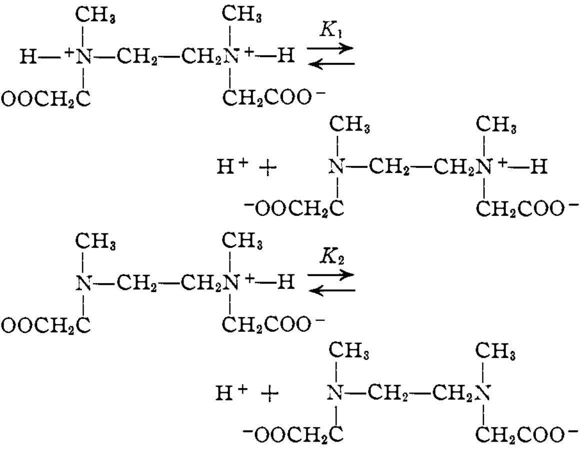
The measured e.m.f. values obtained for cells I and II at various temperatures and ion concentrations for both amino acids are presented in Tables I and II.

Calculations.—The equilibria under investigation may be presented as follows.

Methylaminediacetic acid:



Diamethylethylenediaminediacetic acid:



Although the structures and the nature of the groups dissociating differ somewhat, both amino acids may be considered diprotic acids, H_2A, which dissociate into two more basic forms, HA^- and $A^=$.

These dissociation steps have been shown to be sufficiently separated[3,4] for both amino acids, that each may be considered to have two independent buffer systems, involving the species H_2A, HA^- and HA^-, A^{-2}.

Both cells I and II, corrected to standard pressure in the usual way, are given in the general form

$$\text{Pt-H}_2(1\ \text{atm.}),\ \text{H}^+(a_{\text{H}^+}),\ \text{Cl}^-(a_{\text{Cl}^-}),\ \text{AgCl-Ag}$$

the electromotive force of the cell is given as

$$E = E^0 - \frac{RT}{F}\ln a_{\text{Cl}^-}\gamma_{\text{Cl}^-}m_{\text{Cl}^-} \qquad (1)$$

where m, γ and a represent molal concentration, activity coefficient and activity, respectively, and the other symbols employed have their usual meaning. For the first dissociation constant

$$\text{H}_2\text{A} \rightleftharpoons \text{HA}^- + \text{H}^+$$

$$K_1 = \frac{a_{\text{H}^+}a_{\text{HA}^-}}{a_{\text{H}_2\text{A}}} \qquad (2)$$

substitution of (2) into (1) and rearrangement gives

$$\frac{(E - E^\circ)F}{2.303RT} + \log m_{\text{Cl}^-} = -\log K_1 \frac{a_{\text{H}_2\text{A}}\gamma_{\text{Cl}^-}}{a_{\text{HA}^-}} \qquad (3)$$

By expressing the two left-hand terms as pwH according to usual practice and splitting the activity terms into molality and activity coefficient terms, equation 3 is converted to

$$p\text{wH} + \log \frac{m_{\text{H}_2\text{A}}}{m_{\text{HA}^-}} + \log \frac{\gamma_{\text{Cl}^-}\gamma_{\text{H}_2\text{A}}}{\text{HA}^-} = p\text{K} \qquad (4)$$

where the activity terms are expressed by the Hückel extension of the Debye–Hückel relationship

$$-\log \gamma_i = \frac{AZ_i^2\mu^{1/2}}{1 + Ba_i^*\mu^{1/2}} + \beta\mu \qquad (5)$$

The values of A and B have been given by Manov, Bates, Hammer and Acree.[10] The other terms have their usual meanings. This equation was employed to evaluate the activity coefficient term of equation 4 with exception of the parameter a^* for which various reasonable values were assumed. The sum of these terms was plotted as a function of ionic strength and extrapolated to infinite dilution to evaluate K_1.

The equilibrium constant K_2 is defined by the expression

$$\text{HA}^- \rightleftharpoons \text{H}^+ + \text{A}^{-2}$$

$$K_2 = \frac{a_{\text{H}^+}a_{\text{A}^{-2}}}{a_{\text{HA}^-}} \qquad (6)$$

The evaluation of this constant was carried out in a manner similar to that used for K_1. However, in this case it was necessary to take into account the hydrolysis of the A^{-2} ion. Hence it follows that $m_{\text{A}^{-2}} = m_{\text{K}_2\text{A}} - m_{\text{OH}^-}$ and $m_{\text{HA}^-} = m_{\text{KHA}} + m_{\text{OH}^-}$. The value of m_{OH^-} was evaluated by means of the expression $\log m_{\text{OH}^-} = \log K_w + p\text{wH}$ according to the method of Harned and Owen.[11]

The relationship analogous to equation 4 used in the determination of K_2 is

$$p\text{wH} + \log \frac{m_{\text{KHA}} + m_{\text{OH}^-}}{m_{\text{K}_2\text{A}} - m_{\text{OH}^-}} + \log \frac{\gamma_{\text{Cl}^-} - \gamma_{\text{HA}^-}}{\gamma_{\text{A}^{-2}}} = pK_2 \qquad (7)$$

The graphical extrapolations of equations 4 and 7 to give pK_1 and pK_2 are given in Fig. 1.

Discussion of Results

The values obtained for the thermodynamic quantities ΔF^0, ΔH^0 and ΔS^0 associated with the reactions investigated are listed in Tables III and IV.

Since this research constitutes the first attempt to measure thermodynamic dissociation constants for methylaminediacetic and dimethylethylenedi-

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[8] A. Weissberger, "Physical Methods of Organic Chemistry," 2nd Edition, Vol. II, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1722.

[9] F. F. Carini and A. E. Martell, THIS JOURNAL, **74**, 5745 (1952).

[10] G. Manov, R. Bates, W. Hammer and J. Acree, *ibid.*, **65**, 1765 (1943).

[11] H. Harned and B. Owen, "The Physical Chemistry of Electrolytic Solutions," Second Edition, Reinhold Publ. Corp., New York, N. Y., 1950, p. 485.

TABLE III

THERMODYNAMIC CHANGES FOR DISSOCIATION OF DIMETHYLETHYLENEDIAMINEDIACETIC ACID

t, °C.	pK_1	ΔF^0, kcal./mole	ΔH^0, kcal./mole	$-\Delta S^0$, e.u.
0	6.294	7.87	3.68	15.3
10	6.169	7.99	3.68	15.2
20	6.047	8.11	3.69	15.1
30	5.926	8.22	3.70	14.9
40	5.803	8.32	3.72	14.7
t, °C.	pK_2	ΔF^0, kcal./mole	ΔH^0, kcal./mole	$-\Delta S$, e.u.
0	10.446	13.08	6.78	23.1
10	10.268	13.30	6.82	22.9
20	10.068	13.51	6.83	22.8
30	9.882	13.71	6.85	22.6
40	9.684	13.88	6.88	22.3

TABLE IV

THERMODYNAMIC CHANGES FOR DISSOCIATION OF METHYLAMINEDIACETIC ACID

t, °C.	pK_1	ΔF^0, kcal./mole	t, °C.	pK_2	ΔF^0, kcal./mole
0	2.138	2.66	0	10.474	13.09
10	2.142	2.76	10	10.287	13.32
20	2.146	2.87	20	10.088	13.53
30	2.150	2.97	30	9.920	13.76
40	2.154	3.07	40	9.763	13.99

$\Delta H_1^0 \cong 0$ $\Delta S_1^0 = -9.5$ e.u.

$\Delta H_2^0 = 6.8$ $\Delta S_2^0 = -23$ e.u.

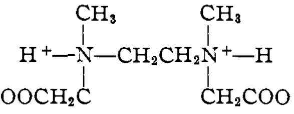
aminediacetic acid, a direct comparison with the results of other workers is not possible. The dissociation constants that have been reported for methylaminediacetic acid, $pK_1 = 2.1$ and $pK_2 = 9.65$ at 20°, and dimethylethylenediaminediacetic acid $pK_1 = 5.83$, $pK_2 = 9.73$ at 30°, are concentration constants which were measured at an ionic strength of 0.1. The constants reported in Tables III and IV are slightly higher than the constants reported at 0.1 ionic strength. This discrepancy is reasonable, since K and K^c, the thermodynamic and concentration constants are related to each other according to the relationship.

$$K_1 = K_1^c \frac{\gamma_{H^+}\gamma_{HA^-}}{\gamma_{H_2A}}, \text{ and } K_2 = K_2^c \frac{\gamma_{H^+}\gamma_{A^{-2}}}{\gamma_{HA^-}}$$

Since the activity coefficient quotients are always less than unity, the thermodynamic dissociation constants for substances of this type should always be less than the "concentration constants."

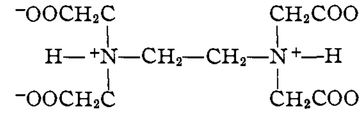
Over the temperature range employed, 0–40°, ΔH^0 of DMEDDA shows a rather uniform trend from 3.68 to 3.72 kcal./mole, while $-\Delta S^0$ decreased from 15.3 to 14.7 e.u. Although the tabulated results seem to indicate that these trends actually exist, the variation in these quantities probably do not exceed the limits of accuracy of the results, and hence cannot be considered significant.

The value of pK_1 of DMEDDA may be compared with the analogous dissociation constant, pK_3 of EDTA. The similarity of the corresponding structures is indicated by the formulas



$$\begin{array}{ccc} CH_3 & & CH_3 \\ | & & | \\ H^+{-}N{-} & CH_2CH_2 & {-}N^+{-}H \\ | & & | \\ {}^-OOCH_2C & & CH_2COO^- \end{array}$$

DMEDDA



$$\begin{array}{ccc} {}^-OOCH_2C & & CH_2COO^- \\ | & & | \\ H{-}{}^+N{-} & CH_2{-}CH_2 & {-}N^+{-}H \\ | & & | \\ {}^-OOCH_2C & & CH_2COO^- \end{array}$$

Divalent anion of EDTA

In both cases a hydrogen ion is dissociated from a substituted ammonium group which is separated by two carbon atoms from another positive nitrogen atom. Thus one would expect approximately the same dissociation constant for these two substances, and the comparisons in Table V indicate that this is the case. It has been pointed out by Carini and Martell[12] that the third dissociation constant of EDTA is unusually low for an ammonium proton. It is interesting that the dissociation constant of the analogous form of DMEDDA is even lower (about 0.3 pK unit at 30°). This further decrease in hydrogen ion affinity, or basicity, may be due to the fact that the substance undergoing dissociation is neutral in the case of DMEDDA and binegative for EDTA.

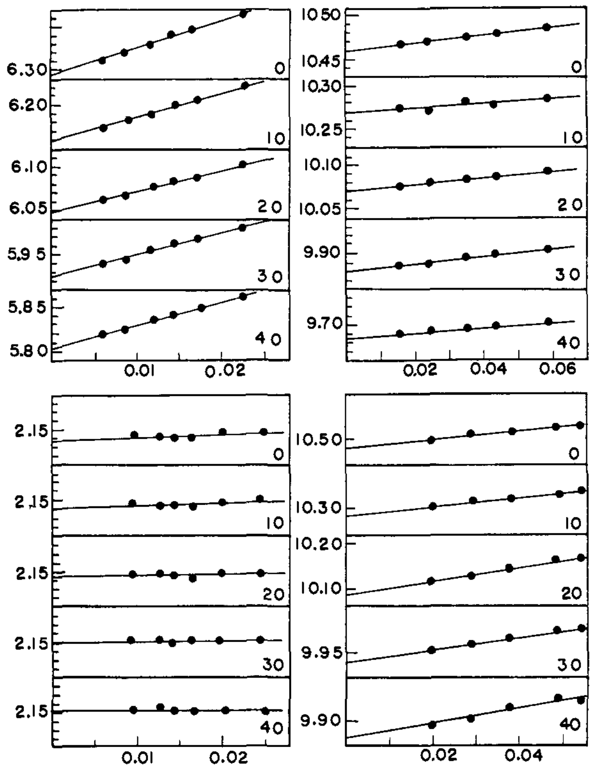


Fig. 1.—Determination of thermodynamic dissociation constants by extrapolation of equations 4 and 7 to infinite dilution; ordinate is pK_n' and abscissa is μ, ionic strength, in each case; upper left pK_1' of DMEDDA, upper right pK_2' of DMEDDA, lower left pK_1' of MADA, lower right pK_2' of MADA; scale divisions of lower left ordinate equivalent to 0.01 pK unit.

The difference in pK_1 for DMEDDA and MADA is attributable to the fact that the dissociation of a substituted ammonium group occurs in the former, while in the latter case, dissociation of a carboxyl group takes place. The value of pK_1 for MADA might be expected to be comparable to the value of

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[12] F. Carini and A. E. Martell, THIS JOURNAL, **75**, 4810 (1953).

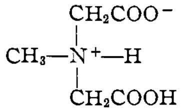
TABLE V

COMPARISON OF THERMODYNAMIC CONSTANTS ASSOCIATED WITH DISSOCIATION OF ANALOGOUS STRUCTURES (30°)

Amino acid	Dissociation step	pK_n	ΔH^0, kcal./mole	$-\Delta S^0$, e.u.
DMEDDA	K_1	5.926	3.7	15
EDTA	K_3	6.236	3.7	16
MADA	K_1	2.150	~0	9.5
NTA[a]	K_2	2.956	−0.8	16
DMEDDA	K_2	9.882	6.8	23
EDTA	K_4	10.883	5.3	32
MADA	K_2	9.920	6.8	22
NTA[a]	K_3	10.230	4.0	34

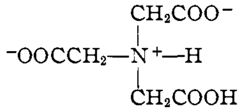
[a] V. Hughes and A. E. Martell, unpublished results; DMEDDA = dimethylethylenediaminetetraacetic acid; EDTA = ethylenediaminetetraacetic acid; MADA = methylaminediacetic acid; NTA = nitrilotriacetic acid.

pK_2 of nitrilotriacetic acid (NTA), since similar groups are involved in the dissociation. The analogy between these structures is illustrated by the formulas



$$\mathrm{CH_3{-}\overset{\overset{\textstyle CH_2COO^-}{|}}{\underset{\underset{\textstyle CH_2COOH}{|}}{N}}{}^+{-}H}$$

Acid form of MADA

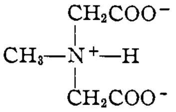


$$\mathrm{{}^-OOCCH_2{-}\overset{\overset{\textstyle CH_2COO^-}{|}}{\underset{\underset{\textstyle CH_2COOH}{|}}{N}}{}^+{-}H}$$

Mononegative anion of NTA

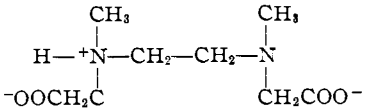
The corresponding dissociation constants are not as close as might be expected. The smaller value of the dissociation constant K_2 of NTA is probably due to the greater negative charge of this anion, and to a statistical factor resulting from the presence of a larger number of carboxylate anionic proton acceptors.

Since the second dissociation constants of DMEDDA and MADA corresponds to the last dissociation constant of the amino acid, they may be compared directly with the corresponding values of EDTA and NTA. The dissociation process is similar for all four substances, as is indicated by the graphic formulas



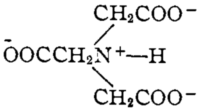
$$\mathrm{CH_3{-}\overset{\overset{\textstyle CH_2COO^-}{|}}{\underset{\underset{\textstyle CH_2COO^-}{|}}{N}}{}^+{-}H}$$

Mononegative anion of MADA

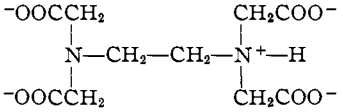


$$\mathrm{H{-}{}^+\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle {}^-OOCH_2C}{|}}{N}}{-}CH_2{-}CH_2{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_2COO^-}{|}}{N}}}$$

Mononegative anion of DMEDDA



Dinegative anion of NTA



$$\mathrm{\overset{\overset{\textstyle {}^-OOCCH_2}{|}}{\underset{\underset{\textstyle {}^-OOCCH_2}{|}}{N}}{-}CH_2{-}CH_2{-}\overset{\overset{\textstyle CH_2COO^-}{|}}{\underset{\underset{\textstyle CH_2COO^-}{|}}{N}}{}^+{-}H}$$

Trinegative anion of EDTA

It is seen from Table V that all the dissociation constants of the above compounds are quite small ($pK \geqq 9.9$), as would be expected of strongly basic amino groups. Also, it is interesting to note a secondary effect of the increasing number of negative acetate groups of the ion. As the charge increases, the basicity of the nitrogen increases, in the order of decreasing dissociation constants: DMEDDA, MADA > NTA > EDTA.

It is interesting to compare the extremely low values of ΔH° for the final ammonium proton dissociation obtained in this research with corresponding values observed for other compounds. Heats of dissociation of the last ammonium proton to dissociate from glycine, β-alanine, ethylenediamine, trimethylamine and dimethylamine are 10.6, 11.6, 13.1, 9.0 and 12.0 kcal./mole, respectively, while the corresponding entropy changes are −9.4, −8.3, −1.8, −14.3 and −9.0 e.u., respectively. The values observed for the final ammonium-type dissociation of DMEDDA and MADA are about one-half of what would be expected on the basis of the examples cited. The values of ΔS^0 for these dissociation steps of methylaminediacetic acid and dimethylethylenediaminediacetic acid are therefore negative and much greater in magnitude than would have been predicted. The entropy changes found for MADA and DMEDDA are not as negative as the value of ΔS^0 reported for EDTA by Carini and Martell.[12] The entropy change for the fourth dissociation of EDTA would be expected to be more negative because of the greater charge of the anions involved.

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