1349. *Thermodynamics of Ion Association. Part XII.*[1] *EGTA Complexes with Divalent Metal Ions*

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Equilibrium constants for the dissociation reactions $H_2L^{2-} \rightleftharpoons H^+ + HL^{3-}$ and $HL^{3-} \rightleftharpoons H^+ + L^{4-}$, where H_4L represents di(2-aminoethoxy)-ethanetetra-acetic acid (EGTA) have been determined by a potentiometric method at 5, 15, 25, and 35°, and at an ionic strength of 0·1M. Calorimetric measurements have been made of the heats of formation of 1 : 1 complexes of EGTA with the metal ions, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, and Cd^{2+}, and the data have been combined with known stability constants to give the corresponding entropy changes. The thermodynamic functions for the formation of the alkaline-earth complexes are discussed and compared with similar data for other aminocarboxylate complexes.

The great interest in the aminocarboxylate ions lies in their ability to form very stable complexes with a wide variety of metal ions. This has resulted in their frequent use as analytical reagents for the determination of metal ions in solution and, for successful application, a ligand should show a large difference in stability of its complexes with a series of closely similar cations. Much of the work, stimulated by the application of the ligand-field theory, has been done with the transition metal complexes, particularly with the EDTA molecule, whereas the alkaline-earth cations have received less attention. The latter form a particularly suitable series for study and, if the bonding were purely electrostatic, the order of stability would be expected to follow the inverse order of ionic radii, *viz.*, $K_{MgL} > K_{CaL} > K_{SrL} > K_{BaL}$. Although the last three members invariably conform to this sequence, the association constant for MgL is frequently considerably smaller than that predicted on the basis of simple ionic bonding. Thus, the stability constants of the 1 : 1 complexes of di-(2-aminoethoxy)-ethanetetra-acetic acid (EGTA) with Ca^{2+} ($\log K = 10{\cdot}93$), Sr^{2+} ($\log K = 8{\cdot}45$), and Ba^{2+} ($\log K = 8{\cdot}32$) ion [2] are similar to those of the EDTA complexes, whereas the value for Mg^{2+} ($\log K = 5{\cdot}29$) is smaller by a factor of 10^6 than that for Mg EDTA^{2-}. In order to be able to discuss the reasons for the observed orders of stability, it is desirable to know the heat and entropy as well as the free energy changes accompanying the association reactions. From a consideration of free energy data alone, the anomalous behaviour of magnesium chelates has often been attributed to the difficulty of a multidentate ligand to fold around the small cation sufficiently closely for all its donor atoms to be bound. This would result in fewer bonds being made to the magnesium ion, with the replacement of a smaller number of water molecules from its co-ordination shell. The relatively large and positive entropy changes for such reactions however, indicate that other factors may be important.

In order to discuss in more detail the important factors involved in the association reactions, precise calorimetric heat changes have been obtained for the association of the EGTA ion with the alkaline-earth and some other divalent metal ions.

Experimental

The Calorimeter.—The differential calorimeter was developed from that described in a previous Paper.[3] The Dewar vessels each had a capacity of 300 ml., and thermistors were used as the temperature-sensing devices in place of the thermopile. The solution container was closed by means of two rubber stoppers cemented to Perspex discs. The Nylon threads for opening the container and mixing the calorimeter contents were fastened to these discs. The usefulness of the calorimeter was enchanced by incorporating a mixing device and heating coil in each of the Dewar vessels, so that each side could be used, in turn, as the blank. The two thermistors

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[1] Part XI, J. R. Brannan, H. S. Dunsmore, and G. H. Nancollas, *J.*, 1964, 304.

[2] G. Schwarzenbach, H. Senn, and G. Anderegg, *Helv. Chim. Acta*, 1957, **40**, 1886.

[3] A. McAuley and G. H. Nancollas, *J.*, 1963, 989.

(resistance 100 Kohms; temperature coefficient of resistance 4% per degree; Standard Telephones and Cables, type F15) were incorporated in the arms of a Wheatstone bridge, and the other two arms of similar resistance were made up of high-quality Helipot. potentiometers. Capacity effects were balanced out by means of two 5—50 pF variable condensers in parallel with the Helipots. The bridge was energised by a stabilised 1v a.c. signal of frequency 800 c./sec. The out-of-balance signal was amplified by means of a high-gain amplifier incorporating a phase-conscious synchronous detector, and the output was fed to a d.c. amplifier coupled to a 1 mv, fast-response chart recorder (Honeywell Controls).

Tests showed that the recorded signal was proportional to the resistance difference between the two thermistors, and could therefore be used as a direct measure of the temperature difference between the calorimeters. The noise level was sufficiently low to enable temperature differences of about 10^{-5} degree, corresponding to 3 × 10^{-3} cal., to be detected. In a typical complex formation experiment, the measured heat change was 2—8 calories. Energy equivalents were obtained by use of the heating circuit and experimental procedure described previously.[3]

The calorimeters were tested by studying two reactions which have well-authenticated heat changes at concentrations such that the measured temperature differences (~0·02°) were approximately equal to those in the complex formation experiments. (i) The heat of solution of potassium chloride corrected to 1 mole of solid in 167 moles of water, 4·21 ± 0·05 kcal.mole^{-1}, was in good agreement with the value 4·184 ± 0·008 kcal.mole^{-1} obtained by Davies, Singer, and Staveley.[4] (ii) The heat of neutralisation corrected to infinite dilution of carbonate-free sodium hydroxide with perchloric acid, was found to be −13·33 ± 0·20 kcal.mole^{-1}, in excellent agreement with the value −13·33 ± 0·02 kcal.mole^{-1} obtained by a number of independent workers from measurements involving considerably greater heat changes.[5]

Potentiometric Measurements.—E.m.f. measurements were made at 25° with a glass/0·1N-calomel electrode system using a Pye potentiometer and Vibron electrometer (EIL. model 33B) as a null indicator. Readings were reproducible to 0·1 mv, and the electrodes were standardised with 0·01m-sodium borate (pH = 9·180 at 25°), 0·008695m-potassium dihydrogen phosphate + 0·03043m-disodium hydrogen phosphate (pH = 7·413 at 25°), and 0·025m-potassium dihydrogen phosphate + 0·025m-disodium hydrogen phosphate (pH = 6·865 at 25°).[6]

Solutions of EGTA (Judex Reagent) were analysed by titrating against standard calcium solutions using Eriochrome Black T [7] as indicator.

Heats of Complex Formation.—The procedure followed for the determination of the heats of complex formation was similar to that described by Care and Staveley for the corresponding EDTA complexes.[8] A relatively concentrated solution of the potassium salt of EGTA in 0·1M-potassium chloride (or nitrate) and containing a slight excess of potassium hydroxide was placed in the mixing device. The heats of mixing of identical volumes of this solution were determined with (i), 300 ml. of divalent metal chloride solution (the nitrate in the case of cadmium) in 0·1M-potassium chloride (or nitrate) with sufficient acid to give a suitable final pH, pH_C (heat change, Q_C cal.) and (ii), 300 ml. of a solution containing no complexing cation, but otherwise identical with solution (i) (heat change, Q_B; final pH, pH_B).

RESULTS AND DISCUSSION

Potentiometric measurements were made with mixtures of EGTA and carbonate-free potassium hydroxide solution with sufficient potassium chloride to maintain an ionic strength of 0·1M. Values of the dissociation constants, k_3, for

$$H_2L^{2-} \rightleftharpoons HL^{3-} + H^+ \qquad (1)$$

and k_4, for

$$HL^{3-} \rightleftharpoons L^{4-} + H^+ \qquad (2)$$

were obtained graphically from the equation

$$\alpha = \beta k_3 + k_3 k_4 \qquad (3)$$

where $\alpha = \{\gamma - 2\delta\}a_{H^+}{}^2/\{\gamma - 4\delta\}$, $\beta = \{\gamma - 3\delta\}{}^aH^+/\{\gamma - 4\delta\}$, $\gamma = [KOH] - [OH^-]$, and $\delta = [H_2L^{2-}] + [HL^{3-}] + [L^{4-}]$. The dissociation constants are composite values,

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[4] T. Davies, S. S. Singer, and L. A. K. Stavely, *J.*, 1954, 2304.

[5] J. D. Hale, R. M. Izatt, and J. J. Christensen, *J. Phys. Chem.*, 1963, **67**, 2605.

[6] R. G. Bates, " Determination of pH," Wiley, New York, 1964.

[7] A. I. Vogel, " Quantitative Inorganic Analysis," Longmans, London, 1962.

[8] R. A. Care and L. A. K. Staveley, *J.*, 1956, 4571.

incorporating the hydrogen ion activity, a_{H^+}; $k_3 = a_{H^+}[HL^{3-}]/[H_2L^{2-}]$ and $k_4 = {}^{a}H^{+}[L^{4-}]/[HL^{3-}]$. Equation (3) is of a similar form to the equation derived by Speakman for a dibasic acid.[9] The results at 5, 15, 25, and 35° are summarised in Table 1. The interpolated values at 20°, $k_3 = 11{\cdot}32 \times 10^{-10}$ and $k_4 = 2{\cdot}54 \times 10^{-10}$, are in good agreement with the values, $11{\cdot}28 \times 10^{-10}$ and $2{\cdot}78 \times 10^{-10}$, respectively, calculated from the concentration constants of Schwarzenbach, Senn, and Anderegg[2] by introducing a value for the activity coefficient of the hydrogen ion, $f_{H^+} = f\pm$ (HCl) $= 0{\cdot}799$ in 0·1M-hydrochloric acid.[10]

TABLE 1

Dissociation constants of EGTA

$T°$	5	15	25	35
$k_3 \times 10^{10}$	6·25	9·70	13·3	16·9
$k_4 \times 10^{10}$	1·13	2·06	2·93	4·14

The variation of k_3 and k_4 with temperature may be expressed, with an accuracy of better than 1% in k_3 and k_4, by the equation[11] $\log k = a + bT + cT^2$, and the derived thermodynamic functions for the dissociation reactions are $\Delta H_3 = 4{\cdot}88$, $\Delta H_4 = 6{\cdot}33$ kcal. mole^{-1}, $\Delta S_3 = -24{\cdot}2$ and $\Delta S_4 = -22{\cdot}4$ cal. deg.$^{-1}$ mole^{-1} at 25°. The values of ΔH at 20° to be compared with Anderegg's[12] calorimetric values of $\Delta H_3 = 5{\cdot}76$ and $\Delta H_4 = 5{\cdot}84$ kcal. mole^{-1} are 5·4 and 6·1 kcal. mole^{-1}, respectively. The agreement is good and, in addition, the present temperature coefficient data may be used to calculate an approximate value for the change in heat capacity for reaction (1). The value, $\Delta C_{p3} = -48 \pm 20$ cal. deg.$^{-1}$ mole^{-1}, is similar to that obtained for other weak acid dissociation reactions.[13]

In the calorimetric experiments, the difference between the measured heat changes $(Q_C - Q_B)$ gives the heat change for the process[8]

$$\begin{aligned} M^{2+} + H_B{}^{+} + OH_B{}^{-} + L_B{}^{4-} + HL_B{}^{3-} + H_2L_B{}^{2-} \longrightarrow \\ ML_C{}^{2-} + L_C{}^{4-} + HL_C{}^{3-} + H_C{}^{+} + OH_C{}^{-} + H_2L_C{}^{2-} \end{aligned} \qquad (4)$$

The concentration of all ionic species can be calculated from the measured pH_B and pH_C by using equations for the total metal concentration,

$$T_M = [M^{2+}] + [ML^{2-}];$$

the total EGTA concentration,

$$T_L = [ML^{2-}] + [H_2L^{2-}] + [HL^{3-}] + [L^{4-}];$$

electroneutrality,

$$2[M^{2+}] + [KOH] + [H^+] = [OH^-] + 4[L^{4-}] + 3[HL^{3-}] + 2[H_2L^{2-}] + 2[ML^{2-}] + 2T_M;$$

the association constant, $K_1 = [ML^{2-}]/[M^{2+}][L^{4-}]$; and the dissociation constants k_3 and k_4, where [KOH] is the total alkali added to prepare K_4L + excess. Values of K_1 at 20° (ref. 2) were corrected to 25° by using the Van't Hoff equation. The enthalpy change for the formation of complex in the reaction

$$M^{2+} + L^{4-} \rightleftharpoons ML^{2-} \qquad (5)$$

may be evaluated from $(Q_C - Q_B)$ by allowing for the heat changes due to the concomitant reactions (1), (2) and $H^+ + OH^- \rightleftharpoons H_2O$. The ΔH results given in Table 2 represent the mean values of at least five experiments with each metal ion. The recently published calorimetric values at 20° obtained by Anderegg[12] for Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+} are given in parentheses in Table 2, and the agreement with the present results is seen to be satisfactory.

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[9] J. C. Speakman, *J.*, 1940, 855.

[10] H. S. Harned and B. B. Owen, " The Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1958.

[11] A. McAuley and G. H. Nancollas, *J.*, 1961, 2215.

[12] G. Anderegg, *Helv. Chim. Acta*, 1964, **47**, 1801.

[13] E. L. King, *J. Phys. Chem.*, 1955, **59**, 1208.

TABLE 2

Thermodynamic functions at 25° for the formation of $MEGTA^{2-}$ complexes

Metal ion	$-\Delta G$ (kcal. mole^{-1})	ΔH (kcal. mole^{-1})	ΔS (cal. deg.$^{-1}$ mole^{-1})
Mg^{2+}	7·20	+5·49 ± 0·12 (5·18)	42·6
Ca^{2+}	14·86	−7·94 ± 0·07 (−8·38)	23·2
Sr^{2+}	11·50	−5·74 ± 0·15	19·3
Ba^{2+}	11·32	−8·99 ± 0·22	7·8
Zn^{2+}	17·55	−5·02 ± 0·10 (−4·28)	42·1
Cd^{2+}	22·55	−14·89 ± 0·20 (−14·8)	25·7

The entropy of association can be written

$$\Delta S = S^\circ(ML^{2-}) - S^\circ(M^{2+}) - S^\circ(L^{4-}) \tag{6}$$

where S° is the standard aqueous entropy of the species enclosed in parentheses. For the formation of 1 : 1 complexes between an anion and a series of cations, equation (6) may be conveniently rearranged to give

$$\Delta S + S^\circ(M^{2+}) = \underset{\text{(I)}}{[S_g(ML^{2-}) - S_g(L^{4-})]} + \underset{\text{(II)}}{[\Delta S_{\text{hyd}}(ML^{2-}) - \Delta S_{\text{hyd}}(L^{4-})]} \tag{7}$$

in which S_g and ΔS_{hyd} are the gas phase and hydration entropies, respectively. Values of $[\Delta S + S^\circ(M^{2+})]$ are given in Table 3, for EGTA at 25°, and for other aminocarboxylate ligands for which alkaline-earth data [14,15] are available at 20°. The difference in temperature will not affect the following arguments.

TABLE 3

Values of $\Delta S + S^\circ$ (M^{2+}) for 1 : 1 metal aminocarboxylate complexes

Metal ion	EDTA [a]	CDTA [b]	EGTA [c]	EEDTA [d]
Mg^{2+}	22·8	34·9	14·4	21·8
Ca^{2+}	13·4	34·3	10·0	9·2
Sr^{2+}	16·2	36·3	9·9	—
Ba^{2+}	21·7	43·9	10·8	—

[a] Ref. 14; [b] ref. 14, cyclohexanediaminetetra-acetic acid; [c] present work; [d] ref. 15, ethyletherdiaminetetra-acetic acid.

The right hand side of equation (7) contains terms in ML^{2-} and L^{4-}. Term (I) reflects the change in configurational and vibrational entropy of the ligand molecule when it enters into complex formation. The increase in translational entropy will be small, and, since the ligand loses freedom, this term will be negative. The negative hydration entropy of the ion L^{4-} will be greater than that of the lower-charged ML^{2-}, resulting in a positive term (II) in equation (7). The positive values of $[\Delta S + S^\circ(M^{2+})]$ in Table **3** indicate that term (II) represents the overriding factor for these metal ions.

Following Kroll and Gordon,[16] it is convenient to divide the polyamineacetic acid chelates into three groups: (i) those with the EDTA skeleton, including the carbocyclic cyclohexanediaminetetra-acetic acid, CDTA; (ii) those with an additional potential co-ordinating atom, X, in the central chain, having the general formula $(^-O_2CCH_2)_2N(CH_2)_2{\cdot}X{\cdot}(CH_2)_2N(CH_2CO_2^-)_2$ where X = O (EEDTA); $X = NCH_2CO_2^-$ (DTPA, diethylenetriaminepenta-acetic acid), etc.; (iii) those with two potential co-ordinating centres in the central chain, $(^-O_2CCH_2)_2N(CH_2)_2{\cdot}X{\cdot}(CH_2)_2{\cdot}X{\cdot}(CH_2)_2N(CH_2CO_2^-)_2$ where X = O (EGTA); $X = CH_3N$ {BDAM, bis-[(dicarboxymethyl)aminoethyl]methylamine}. The trends in the available ΔG, ΔH, and ΔS for the alkaline-earth cations are illustrated in the Figure. Unfortunately, ΔH and ΔS have not been determined for any strontium or barium complexes of group (ii) ligands, and it is possible to include only the calcium and magnesium values. For DTPA, the ΔG values are plotted for comparison.[2] The Figure illustrates a number of characteristic patterns of behaviour. In group (i),

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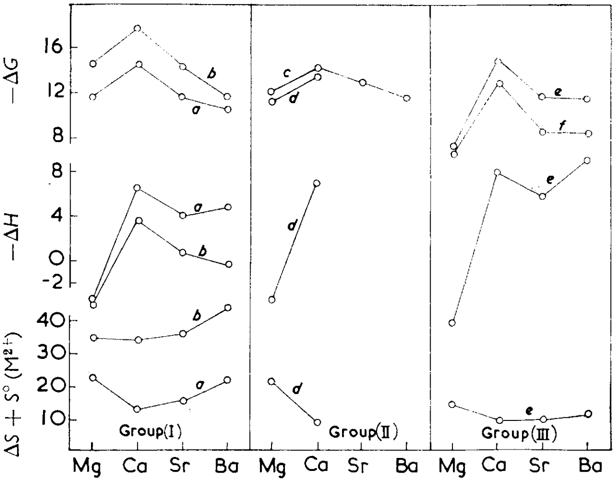
[14] G. Anderegg, *Helv. Chim. Acta*, 1963, **46**, 1833.

[15] G. Anderegg, *Helv. Chim. Acta*, 1964, **47**, 1992.

[16] H. Kroll and M. Gordon, *Ann. New York Acad. Sci.*, 1960, **88**, 341.

the greater stability of CDTA complexes as compared with those of EDTA is primarily the results of a much more favourable entropy term [$\Delta S + S^\circ(M^{2+})$] for the former, which outweighs the unfavourable ΔH difference. The explanation lies in the fact that in CDTA, the two nitrogen atoms are restricted in their movement by the carbocyclic chain, and so term (I) in equation (7) will be more positive than for EDTA. In addition, it has been suggested [14] that as the carboxyl groups are held more rigidly in CDTA than in EDTA, the resulting localisation of charge will lead to a more effective orientation of water molecules, making $-\Delta S_{\text{hyd}}(\text{CDTA}^{4-}) > -\Delta S_{\text{hyd}}(\text{EDTA}^{4-})$, and term (II) (equation 7) more positive for CDTA. The increased endothermicity accompanying the formation of CDTA complexes is a consequence of the steric hindrance imposed by the cyclohexyl ring.[14] The value of $\Delta G(\text{MgL}^{2-}) - \Delta G(\text{CaL}^{2-})$ is about the same for both EDTA and CDTA, but the heat and entropy trends are quite different. In going from calcium to magnesium, there is an appreciable increase in $\Delta S + S^\circ(M^{2+})$ for EDTA compared with that for CDTA, indicating a smaller positive contribution in term (II) (equation 7) for CDTA. It is possible that Mg CDTA^{2-} is more hydrated than Mg EDTA^{2-} since there is considerable strain involved in completing the co-ordination of the rigid CDTA^{4-} anion to the small magnesium ion. Some support for this suggestion is provided by the rather large drop in $-\Delta H$ in the Figure for the formation of Mg EDTA^{2-}.

Plots of thermodynamic properties for the formation of alkaline-earth aminocarboxylate complexes. Group (I) *a*, EDTA; *b*, CDTA; Group (II) *c*, DTPA; *d*, EEDTA; Group (III) *e*, EGTA; *f*, BDAM



There are very few thermodynamic properties available for the group (ii) ligands, although it is seen in the Figure that the general trends are similar to those in group (i), with a rather smaller difference in ΔG between the calcium and strontium chelates. Group (iii) has two members for which stability constants have been measured, and the results of the present work provide detailed thermodynamic data for one of them, EGTA. The complexes are characterised by a particularly large increase in stability in going from magnesium to calcium. $\Delta S + S^\circ(M^{2+})$ values for EGTA differ very little, indicating a similar structure for all the complexes in the series. The results of n.m.r. studies [17] lend support to this suggestion, and it appears that both ether-oxygen atoms in the central chain are involved in the bonding to the metal ion. The drop in stability at magnesium is clearly the result of the more endothermal ΔH reflecting the increased potential energy involved in the interaction between the small Mg^{2+} ion and the negatively charged EGTA^{4-} ion. Considerable strain is imposed in bringing the co-ordinating centres sufficiently close for stable electrostatic bonds to be formed.

The smaller $\Delta S + S^\circ(M^{2+})$ values for EGTA as compared with EDTA complexes may be caused by two factors: (i) The greater loss of configurational entropy of the larger

[17] A. Bryson and G. H. Nancollas, *Chem. and Ind.*, 1965, 654.

EGTA molecule when it interacts with the metal ions. (ii) The two carboxylate groups which remain free in the EGTA complexes and which will retain some solvent-ordering properties whilst not being able, through negative charge repulsion, to make full use of their mobility.

In order to be able to discuss the formation of aminocarboxylate complexes in solution, many more precise thermodynamic data are required, particularly for ligands in groups (ii) and (iii). As it is necessary to examine quite small differences in ΔH and ΔS, precise pH as well as calorimetric measurements are essential in order to make reliable corrections for the accompanying heats of protonation. A programme of work with this aim in view is under way.

Note Added in Proof.—Since this work was submitted for publication, D. C. Wright, J. H. Holloway, and C. N. Reilley (*Analyt. Chem.*, 1965, **37**, 884) have published calorimetric results for the formation of mono-EGTA complexes with Mg^{2+} ($\Delta H = 4{\cdot}4$ kcal. mole^{-1}), Ca^{2+} ($-8{\cdot}0$), Sr^{2+} ($-6{\cdot}4$), Ba^{2+} ($-8{\cdot}8$), Zn^{2+} ($-3{\cdot}8$), and Cd^{2+} ($-14{\cdot}1$). With the exception of magnesium, zinc, and cadmium, the agreement with the data in Table 2 is satisfactory. Their thermodynamic data for the two Group (II) ligands, DTPA and EEDTA, show trends, when plotted in the Figure, which are similar to those of the Group (I) ligands.

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