384. *Metal Complexes of Bis-[3-di(carboxymethyl)aminopropyl] Ether. The Computation of Stability Constants with the Aid of a High-speed Digital Computor.*

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Values valid for 20° C and $\mu = 0{\cdot}1$M-KCl are reported for the stability constants of 1 : 1 metal complexes, ML, and protonated complexes, MHL, formed by bis-[3-di(carboxymethyl)aminopropyl] ether, H_4L, with a number of bivalent ions (Mg, Ca, Sr, Ba, Zn, Cd, and Hg).

Problems which arise in computing the " best " values for stability constants from titration data when mixtures of metal complexes, ML_j ($j = 1,2,\ldots.N$), and a protonated complex, MHL, occur are discussed, and a programme for a high-speed digital computor to overcome the difficulties is described.

COMPLEXES of strontium with organic reagents are generally much weaker than those of calcium with the same ligand.[1] With ethylenediaminetetra-acetic acid (I; $n = 2$) (H_4Y) the stability constants are $K_{CaY} = 10^{10{\cdot}7}$ and $K_{SrY} = 10^{8{\cdot}63}$, respectively, so that the calcium complex is the more stable by about one hundred times. The removal of ingested strontium-90 would be simplified if a reagent, H_nZ, could be synthesised for which the ratio K_{CaZ}/K_{SrZ} was small (and ideally less than unity) while the complex-forming power for strontium remained high.

(I) $A_2N{\cdot}[CH_2]_n{\cdot}NA_2$ $\quad$ $A_2N{\cdot}[CH_2]_n{\cdot}X{\cdot}[CH_2]_n{\cdot}NA_2$ (II) $\quad$ $A = CH_2{\cdot}CO_2H$

Schwarzenbach has published data for a number of analogues of EDTA (I; n = 2) in which the chain separating the two chelating groups, NA_2, is extended either (*a*) by additional methylene groups (I; $n = 3$—8), or (*b*) by additional methylene groups joined through a symmetrically placed donor atom (II; X = O, $n = 2$, 3, or 4; or X = S, S–S, or NMe, $n = 2$).[2] In the first group, the increase in the size of the chelate ring produces the expected decrease in stability of both the calcium and the strontium complex,[3] but the relative stability for complexes of, *e.g.*, trimethylenediaminetetra-acetic acid (I; $n = 3$), *viz.*, $K_{CaY}/K_{SrY} = 10^{7{\cdot}12}/10^{5{\cdot}18}$ is still about 100 : 1. On the other hand, with the triamine (II; X = NMe, $n = 2$) the stability of the strontium complex had increased relative to that of the calcium complex for now $K_{CaY}/K_{SrY} = 10^{9{\cdot}55}/10^{8{\cdot}35} = 16$. The effect was even more striking with the hexadentate ligand (II; X = O, $n = 2$) for which $K_{CaY}/K_{SrY} = 10^{10{\cdot}0}/10^{9{\cdot}34} = 4{\cdot}6$. Unfortunately, studies with analogues of (II) were limited to measurements of the stabilities of the calcium (and sometimes the cadmium and mercury) complexes. In the present paper we extend the range of data for the complexone (II; X = O, $n = 3$) by reporting values for the stabilities of its complexes with magnesium, calcium, strontium, barium, zinc, cadmium, and mercury.

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[1] Irving, *Chem. Soc. Spec. Publ.*, No. 13, 1959, p. 13.

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

[3] Irving, Williams, Ferrett, and Williams, *J.*, 1954, **3494**.

EXPERIMENTAL

Bis-[3-*di*(*carboxymethyl*)*aminopropyl*] *Ether* (II; X = O; *n* = 3).—The sample used in earlier measurements [2] was made available to us by Professor Schwarzenbach. It had remained reasonably pure (*M*, by titration, 411. Calc. for $C_{14}H_{24}O_9N_2,2H_2O$: *M*, 400·4) and after being recrystallised from water a redetermination of its acid dissociation constants gave values ($pK_1 = 2{\cdot}0$, $pK_2 = 2{\cdot}74$, $pK_3 = 9{\cdot}64$, $pK_4 = 10{\cdot}14$) in good agreement with those reported by Schwarzenbach, Senn, and Anderegg,[2] *viz.*, 2·1, 2·7, 9·67, and 10·17, respectively. The values found for the stability constants of its calcium complexes CaY and CaHY (Table) (concentration constants valid for 20° and a constant ionic strength of 0·1M-potassium chloride) were identical with those previously reported [2] under the same conditions.

Potentiometric titrations were carried out with a glass electrode (Beckman Type H) in a double-walled vessel maintained at 20·0° with water pumped from a thermostat bath. Magnetic stirring was used. The saturated calomel reference electrode (also at 20°) was connected through a bridge of 0·1M-potassium chloride. The pH-meter (Radiometer PHM4) was calibrated with 0·05M-potassium hydrogen phthalate, and the slope for the glass electrode was checked at intervals by comparison with a hydrogen electrode. Carbonate-free potassium hydroxide [4] and all metal solutions were made up to an ionic strength of 0·1M with potassium chloride. The concentration, C_M, of stock solutions of metal salts ("AnalaR") was determined by titration against standard EDTA. The initial total volume was always 100 ml. and the concentration of ligand acid, C_A, was $1{\cdot}07 \times 10^{-3}$M. The results of typical titrations are tabulated.

(a) *Reagent alone.* $C_A = 0{\cdot}001070$M.

a	0·000	0·194	0·388	0·582	0·776	0·970	1·164	1·357	1·560	1·746	2·150	2·520
pH ...	2·794	2·814	2·895	2·955	3·026	3·108	3·207	3·333	3·503	3·780	8·733	9·443
a	2·325	2·720	2·910	3·105	3·300	3·495	3·690	3·880	3·980	4·160	4·355	4·580
pH ...	9·183	9·626	9·778	9·914	10·040	10·158	10·280	10·401	10·456	10·573	10·684	10·781

(b) *Reagent,* $C_A = 0{\cdot}001070$, *and various metals.*

C_M/C_A	Mg = 2	Ca = 1·7	Sr = 2	Ba = 2	Zn = 1	Cd = 1
a	pH	pH	pH	pH	pH	pH
0·970	3·110	3·103	3·102	3·094	3·044	3·108
1·164	3·213	3·203	—	—	3·118	3·205
1·357	—	—	3·323	3·317	3·204	3·327
1·560	3·504	3·502	3·496	3·487	3·300	3·492
1·746	3·777	3·784	3·766	3·760	3·415	3·726
2·150	7·605	7·316	8·171	8·348	3·737	4·417
2·325	8·110	7·755	8·590	8·769	3·968	4·638
2·520	8·460	8·044	8·841	9·013	4·298	4·798
2·720	8·714	8·260	9·021	9·187	4·820	4·944
2·910	8·930	8·446	9·172	9·342	5·636	5·084
3·105	9·130	8·621	9·309	9·466	6·282	5·231
3·300	9·315	8·794	9·450	9·596	6·692	5·394
3·495	9·502	8·977	9·592	9·735	7·056	5·602
3·690	9·695	9·188	9·753	9·880	7·567	5·916
3·880	9·905	9·453	9·933	10·052	8·890	7·912
3·980	10·013	9·621	10·042	10·148	9·607	9·450
4·160	10·200	10·015	10·272	10·343	10·110	10·028
4·270	10·350	10·192	—	10·435	—	—
4·355	10·448	—	10·484	—	10·456	10·397
4·550	10·613	—	10·648	—	—	—
4·460	—	10·486	—	10·610	10·567	10·515

Values of pH for $a < 0{\cdot}97$, not used in the calculations, have been omitted.

The Stability of the Mercuric Complex.—Solutions of mercuric nitrate and ligand acid contained in stoppered Pyrex test-tubes (50 ml.) were made up to a total ionic strength of 0·1M with sodium nitrate, and the pH was adjusted to different values between 3 and 6 by the addition of drops of 0·1M-potassium hydroxide or -nitric acid. A drop of mercury was added to each tube, the stoppers were inserted, and after being thoroughly shaken the tubes were transferred to a thermostat. Each tube had a stout platinum wire sealed through the bottom, and the progress of equilibration was followed at intervals by measuring $pHg = -\log_{10} [Hg^{2+}]$. The test-tube was removed from the thermostat bath, contact was made through a pool of

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[4] Schwarzenbach and Biedermann, *Helv. Chim. Acta*, 1948, **30**, 331.

mercury to the internal mercury electrode, and the circuit completed through a bridge of 0·1M-sodium nitrate and a saturated calomel electrode. A precision potentiometer (Messrs. Cambridge Instrument Co.) was used and the pH of the solution was measured simultaneously with a glass electrode. The details of procedure have been fully described by Schwarzenbach and Anderegg.[5] Typical results are tabulated. The average value of log K(I) (=log $K_{HgY} - pK_3 - pK_4$) is 1·89 ± 0·05, whence log K_{HgY} = 21·67 ± 0·05.

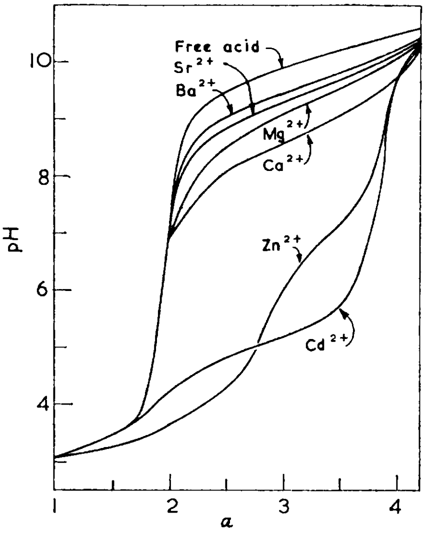
10^4C_A	8·73	8·73	11·23	11·23	15·68	15·68	15·68	15·68
10^4C_M	3·07	3·07	6·14	6·14	5·86	5·86	5·86	5·86
pH	4·93	4·02	3·92	3·70	4·81	4·03	4·60	3·82
log K(I)	1·86	1·96	(2·01)	1·86	1·96	1·86	1·90	1·86

The acidity constant of the protonated complex HgHY was determined by titrating a solution of the mercury complex of the ether-acid (II; X = O; n = 3) with 0·1M-potassium hydroxide at 20° and μ = 0·1M-sodium nitrate. The curve near the end-point did not conform exactly to the theoretical shape and only the approximate value $K^{H}_{HgHY} = 3 \cdot 5 \pm 0 \cdot 2$ was obtained, whence log K^{Hg}_{HgHY} = log K^{H}_{HgHy} + log $K_{HgY} - pK_4$ = 15·0 ± 0·2.

The Cadmium Complex.—In addition to the determination of the stability constant of the cadmium complex, K_{CdY}, by potentiometric determination, its value was also determined with the mercury electrode,[5] with the following results:

10^4C_{Cd}	10^4C_{Hg}	10^4C_L	pH	pHg	log K(II)
10·40	6·25	13·71	4·21	10·186	(−6·50)
10·40	6·25	13·71	4·56	10·722	−7·07
10·40	6·25	13·71	4·75	10·949	−7·32
12·25	6·13	13·45	4·72	10·864	−7·45
12·25	6·13	13·45	4·76	10·911	−7·50
14·00	6·00	13·20	4·76	10·836	−7·56

From the average value we have log K(II) = log K_{HgY} − log K_{CdY} = 7·38 ± 0·19, whence log K_{CdY} = 14·29 ± 0·20.



Titration curves for acid (II; X = O, n = 3).

COMPUTATION OF RESULTS

The titration curves (see Figure) show that complex formation with the alkaline-earth metals begins when the third buffer region is reached, where the ligand is present mainly as HY^{3-}. It thus becomes necessary to consider the occurrence of both the normal 1 : 1 complex MY^{2-} (where M is a bivalent cation) and the protonated complex MHY^-. Higher complexes (*e.g.*, MY_2^{6-}) and polynuclear complexes (*e.g.*, M_2Y, M_2HY^+) should not occur under the experimental conditions used. This assumption is supported by the results of Schwarzenbach

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[5] Schwarzenbach and Anderegg, *Helv. Chim. Acta*, 1957, **40**, 1773.

et al.[2] for analogous complexones (obtained by using a metal : ligand ratio of 1 : 10) for which values of log $K^{\mathrm{M}}_{\mathrm{M_2Y}}$ only reach 2—3 units when a chelate ring greater than seven-membered would otherwise be formed: in other cases it was too small to be measureable.

From the equations for mass-balance and electroneutrality, *viz.*,

$$C_{\mathrm{A}} = [\mathrm{H_4Y}] + [\mathrm{H_3Y^-}] + [\mathrm{H_2Y^{2-}}] + [\mathrm{Y^{4-}}] + [\mathrm{MY^{2-}}] + [\mathrm{MHY^-}] \quad . \; . \quad (1)$$

$$C_{\mathrm{M}} = [\mathrm{M^{2+}}] + [\mathrm{MY^{2-}}] + [\mathrm{MHY^-}] \quad . \; . \; . \; . \; . \; . \quad (2)$$

$$[\mathrm{K^+}] + [\mathrm{H^+}] + 2[\mathrm{M^{2+}}] = [\mathrm{H_3Y^-}] + 2[\mathrm{H_2Y^{2-}}] + 3[\mathrm{HY^{3-}}] + 4[\mathrm{Y^{4-}}] + 2[\mathrm{MY^{2-}}] + [\mathrm{MHY^-}] + [\mathrm{X^-}] + [\mathrm{OH^-}] \quad . \; . \; . \; . \; . \quad (3)$$

where $[\mathrm{K^+}] = aC_{\mathrm{A}}$ is the concentration of potassium ions introduced during the titration and $[\mathrm{X^-}] = 2C_{\mathrm{M}}$ is the concentration of univalent anion arising from the salt of the bivalent metal M, we obtain:

$$(4 - a)C_{\mathrm{A}} - [\mathrm{H^+}] + [\mathrm{OH^-}] = 4[\mathrm{H_4Y}] + 3[\mathrm{H_3Y^-}] + 2[\mathrm{H_2Y^{2-}}] + [\mathrm{HY^{3-}}] + [\mathrm{MHY^{2-}}] \quad (4)$$

$$[\mathrm{M^{2+}}] = C_{\mathrm{M}} - C_{\mathrm{A}} + \alpha_{\mathrm{H}}[\mathrm{Y^{4-}}] \quad . \; . \; . \; . \; . \; . \; . \quad (5)$$

$$[\mathrm{Y^{4-}}] = \frac{(4 - a)C_{\mathrm{A}} + [\mathrm{H^+}] - [\mathrm{OH^-}]}{\beta_{\mathrm{H}} + ([\mathrm{M^{2+}}][\mathrm{H^+}]K_{\mathrm{MHY}}/K_4)} \quad . \; . \; . \; . \; . \; . \; . \quad (6)$$

where

$$\alpha_{\mathrm{H}} = \frac{[\mathrm{H^+}]^4}{K_1K_2K_3K_4} + \frac{[\mathrm{H^+}]^3}{K_2K_3K_4} + \frac{[\mathrm{H^+}]^2}{K_3K_4} + \frac{[\mathrm{H^+}]}{K_4} + 1$$

$$\beta_{\mathrm{H}} = \frac{4[\mathrm{H^+}]^4}{K_1K_2K_3K_4} + \frac{3[\mathrm{H^+}]^3}{K_2K_3K_4} + \frac{2[\mathrm{H^+}]^2}{K_3K_4} + \frac{[\mathrm{H^+}]}{K_4}$$

$$K_{\mathrm{MY}} = [\mathrm{MY^{2-}}]/[\mathrm{M^{2+}}][\mathrm{Y^{4-}}]; \quad K_{\mathrm{MHY}} = [\mathrm{MHY^-}]/[\mathrm{M^{2+}}][\mathrm{HY^{3-}}];$$

and

$$K_n = [\mathrm{H^+}][\mathrm{H}_{4-n}\mathrm{Y}^{n-}]/[\mathrm{H}_{5-n}\mathrm{Y}^{1-n}]$$

The degree of formation of the metal complexes is defined by

$$\bar{n} = ([\mathrm{MY^{2-}}] + [\mathrm{MHY^-}])/([\mathrm{M^{2+}}] + [\mathrm{MY^{2-}}] + [\mathrm{MHY^-}])$$

$$= (C_{\mathrm{A}} - \alpha_{\mathrm{H}}[\mathrm{Y^{4-}}])/C_{\mathrm{M}} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (7)$$

whence

$$\bar{n} + (\bar{n} - 1)[\mathrm{H^+}][\mathrm{Y^{4-}}]K_{\mathrm{MHY}}/K_4 + (n - 1)[\mathrm{Y^{4-}}]K_{\mathrm{MY}} = 0 \quad . \; . \; . \; . \quad (8)$$

The evaluation of the constants K_{MY} and K_{MHY} proceeds from the solution of a series of equations of the form (8) which relate values of $\bar{n}$, $[\mathrm{Y^{4-}}]$, and $[\mathrm{H^+}]$ for each point on the experimental titration curve. It will be appreciated that the computation of $[\mathrm{Y^{4-}}]$ (and thence that of $\bar{n}$) by equations (6) and (7) involves a foreknowledge of the value of K_{MHY}. The computation is started by assuming $K_{\mathrm{MHY}} = 0$ as a first approximation. Values of $[\mathrm{Y^{4-}}]$ and $\bar{n}$ for each experimental value of $[\mathrm{H^+}]$ and the corresponding degree of neutralisation, a, are then computed from equations (6) and (7) and substituted into equation (8). The sets of simultaneous equations are then solved to give approximate values for the constants K_{MY} and K_{MHY}. By using an average value of K_{MHY} obtained in this way better values of $[\mathrm{Y^{4-}}]$ and $\bar{n}$ can now be calculated from equations (6) and (7) and substituted into equation (8). The new sets of simultaneous equations are then solved to give improved values for the two stability constants, and the process of successive approximation continued until no further improvement occurs. When an electrical desk calculating machine is used, the time occupied by the calculations for a single metal–ligand system may be as long as 80 hr.

USE OF A HIGH-SPEED DIGITAL COMPUTOR

We have therefore developed for use with this University's high-speed digital computor " Mercury " a programme which can deal with these calculations or indeed with the complex problem of a metal ion in equilibrium with a 1 : 1 complex ML, its protonated complex, MHL, and a series of higher complexes $\mathrm{ML_2}$, $\mathrm{ML_3}$, $\cdots \mathrm{ML}_N$. (For simplicity we shall now omit charges on the various species.) For a polybasic ligand acid, H_BL, the fundamental equations become:

$$[M] = (C_M - C_A + \alpha_H[L])/\{1 - (\beta_2[L]^2 + 2\beta_3[L]^3 + \cdots + (n-1)\beta_n[L]^n)\} \qquad (9)$$

$$[L] = \{(B - a)C_A - [H] + [OH]\}/\{\beta_H + ([M][H]K_{MHL}/K_B)\} \quad . \quad . \quad . \quad . \qquad (10)$$

$$\bar{n} = \frac{([H][L]K_{MHL}/K_B) + \beta_1[L] + 2\beta_2[L]^2 + \cdots + n\beta_n[L]^n}{1 + ([H][L]H_{MHL}/K_B) + \beta_1[L] + \beta_2[L]^2 + \cdots + \beta_n[L]^n} \quad . \quad . \quad . \qquad (11)$$

$$= (C_A - \alpha_H[L])/C_M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \qquad (12)$$

$$\bar{n} + \{(\bar{n} - 1)[H][L]K_{MHL}/K_B\} + (\bar{n} - 1)\beta_1[L] + (\bar{n} - 2)\beta_2[L]^2 + (\bar{n} - n)\beta_n[L]^n = 0 \qquad (13)$$

where $\alpha_H = 1 + ([H]/K_B) + ([H]^2/K_{B-1}K_B) + \cdots + ([H]^B/K_1K_2 \cdots K_B)$;

$$\beta_H = ([H]/K_B) + 2([H]^2/K_{B-1}K_B) + \cdots + B([H]^B/K_1K_2 \cdots K_B);$$

$$K_{MHL} = [MHL]/[M][HL]; \quad \beta_n = [ML_n]/[M][L]^n; \quad \text{and}$$

$$K_n = [H][H_{B-n}Y]/[H_{B+1-n}Y].$$

As already stated, the calculation of [L] requires a foreknowledge of K_{MHL} and as a first approximation this is set equal to zero. Values of [L] are then calculated from equation (10), and values of $\bar{n}$ from equation (11). Equations of the form (13) are now set up, using the experimental values of [H] and these approximate values of [L] and $\bar{n}$. The complete set of simultaneous equations is then solved by the method of least squares (for which a standard sub-routine is available in the computor programme) to give the best values for K_{MHL} and for each of the overall constants β_1 ($= K_{ML}$), β_2 ($= K_{ML}K_{ML_2}$), $\cdots$ and β_n ($= K_{ML}K_{ML_2} \cdots K_{ML_n}$). Being given a first approximation to the value of K_{MHL}, calculated values of [L] could then be improved in the following way. The value of [L] obtained from equation (10) depends on that of [M]; but this itself is a function of [L] [cf. equation (9)]. If the term [M] were to be eliminated from equations (9) and (10) there would result a polynomial in [L] of the second or higher degree for which no simple formula is available for evaluation of its real root. Advantage could be taken here of the speed of the electronic computor to find a value for [L] to satisfy both equations (9) and (10) by an iterative method.

A value of [M] computed from equation (9) (by using values of $\beta_2, \cdots \beta_n$ previously computed together with the value of [L] calculated for the approximation $K_{MHL} = 0$) is inserted into equation (10), and the value of [L] is computed by using the approximate value of K_{MHL} found as described above. This new value of [L] is used to calculate [M] from equation (9), and the iterative process is continued until successive values of [L] differs by less than 0·5%. This precision could not always be attained for certain values of pH, especially if the term $[M][H]K_{MHL}/K_B \geqslant \beta_H$, and at a later stage in the development of the programme a machine instruction was included to prevent more than 100 iterations being performed for any point on the titration curve. If this provision was not included the computor might " stick " at this stage in the calculations.

When consistent values of [L] and $\bar{n}$ have been obtained for each value of a and [H], the sets of simultaneous equations of the form (13) are set up and solved as before by a least-squares method, to give improved values of K_{MHL} and for β_1, β_2, $\cdots$ β_n. With this second approximation to the value of K_{MHL} and the other stability constants the whole cycle of calculations is repeated automatically.

A difficult point of procedure was the inclusion of a satisfactory criterion for terminating the operations of the computor. Although we do not now believe it to be the best solution, the following procedure formed a chapter in the programme we used. Values of $\bar{n}$ were first computed from equation (11) by using experimental values of [H], the sets of constants K_{MHL}, β_1, β_n to be tested, and the corresponding corrected values of [L]. Thence theoretical values of $[L]_{calc.}$ were computed from equation (12) and substituted into equation (10) after this had been rearranged in the form

$$a_{calc.} = [B]C_A - [H] + [OH] - [L]_{calc.}\{\beta_H + ([M][H]K_{MHL}/K_B)\}]/C_A \quad . \qquad (10a)$$

The values of the differences between calculated and observed degrees of neutralisation are then found and the machine was instructed to print out the root-mean-square deviation

$$d = \sqrt{(a_{calc.} - a_{obs.})^2/(\text{no. of observations} - 1)}$$

after each successive set of constants, K_{MHL}, $\beta_1, \cdots \beta_n$, had been computed. As the fit of the calculated curve to that of the experimental curve improved, the value of d decreased to a constant value which generally lay between 0·05 and 0·01. The number of iterations needed to compute the values finally adopted varied from three (when $K_{ML} \gg K_{MHL}$) to twelve (when $K_{MHL} \approx K_{ML}$). The accuracy of the final constants will depend on the relative magnitudes of the terms in equation (13). Thus the relative accuracy of determination of K_{MHL} and K_{ML} depends on the ratio ($[H]K_{MHL}/K_B$) : $K_{ML} = [H]K^H_{MHL}$, where K^H_{MHL} is the equilibrium constant for the process $ML + H \rightleftharpoons MHL$ and is a measure of the tendency of the 1 : 1 complex to take up a proton. If the ratio $[MHL]/[ML] = [H]K^H_{MHL}$ is less than unity, the value of K_{ML} can be determined with high accuracy and that of K_{MHL} to lower accuracy. This is the case with the complexes of our ether-acid (II; X = O, n = 3) with cadmium, but not with the alkaline-earth metals for which $[H]K^H_{MHL} > 1$ until pH > 9, *i.e.*, until the degree of neutralisation is over 2·7 (with Ba^{2+}) or 3·3 (with Ca^{2+}). In some cases, therefore, it may be found that the computed values of K_{MHL} vary considerably between successive iterations although values for the metal stability constants have remained stationary.

The absence of complexes higher than ML (or ML_2, etc.) is generally revealed by the production of negative values for β_2 (or β_3, etc.). In such cases it is expedient to repeat the calculations with the appropriate lower value for N, the maximum co-ordination number: the simplification is shown to be justified if there is a concomitant reduction in the computed root-mean-square deviation, d. Such a decision is confirmed (and can indeed be anticipated) by plotting the formation curve ($\bar{n}$ against $pL = -\log_{10} [L]$, a procedure which is facilitated by arranging for values of $\bar{n}$ and pL to be printed out during the course of the programme.

In computations of results from neutralisation data of polybasic acids, alone or in the presence of metals, it is obvious that every observation will not be of equal weight. In the range between the buffer regions (usually at integral a-values) the value of pH may change very rapidly for small changes in the volume of titrant added (see Fig.). From the form of equation (13) the greatest percentage errors in individual terms of the equation occur when $\bar{n}$ approaches an integral value. For this reason it has always been customary to make a judicious selection from experimental data before starting any calculations. It would clearly be desirable, and relatively easy, to include in the computor programme some provision for weighting experimental observations according to some pre-arranged assessment of their precision. We have not solved this problem to our satisfaction. An independent approach to the whole problem of computing stability constants has been described recently by Sullivan, Rydberg, and Miller who discuss several possible ways of weighting the experimental data.[6]

DISCUSSION

The annexed Table summarises values for the acid dissociation constants for the homologous complexones (II; X = O, n = 2 and 3) and values for the metal stability constants K_{MY}, $K_{MHY} = [MHY]/[M][HY]$, and $K^H_{MHY} = [MHY]/[H][MY]$.

Increase in the size of two chelate rings of MY^{2-} from five- to six-membered has produced the expected decrease in stability,[3] but the order Hg ≫ Cd ≫ Ca > Sr > Mg > Ba has now become Hg ≫ Cd > Zn ≫ Ca > Mg > Sr > Ba, *i.e.*, the smaller magnesium ion is now favoured. A similar effect is seen in the order of values for K^M_{MHY}. It is noteworthy that whole-ring expansion lowers the stability of alkaline-earth complexes, MY^{2-}, by 3·5—5·2 log units (4·8—7·1 kcal. mole^{-1}); those of cadmium and zinc are only lowered by 1·5—2·0 log units (2·0—2·7 kcal. mole^{-1}). The stability of the calcium complex has been decreased less than that of the strontium complex so that the complexone (II; X = O, n = 3) is less selective for strontium as well as being a far less powerful chelating agent.

Of other complexones of similar structure and proton affinity the closest comparison can be made to the tetradentate methoxyethyliminodiacetic acid, $MeO{\cdot}C_2H_4{\cdot}N(CH_2{\cdot}CO_2H)_2$ (cf. Table of stability constants). Although data for the alkaline earths are restricted to 1 : 1 complexes, values of log K_2 ranging from 1·5 to 2·0 would not be unreasonable: these would lead to values of log β_2 of a similar order to those found for complexes of (II;

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[6] Sullivan, Rydberg, and Miller, *Acta Chem. Scand.*, 1959, **13**, 2023.

X = O, $n = 3$). The 1 : 2 complexes formed by methoxyethyliminodiacetic acid with zinc and cadmium are comparable in stability with those of (II; X = O, $n = 3$) but the increased stability associated with its five-membered rings does not compensate for the smaller "chelate effect"[7] associated with complex formation by a tetradentate ligand in comparison with the much larger decrease in free energy found with the potentially hexadentate ligand (II). The abnormally low stability of the mercury complex of methoxyethyliminodiacetic acid ($\log \beta_2 = 10{\cdot}03$) compared with that of the complexone (II; X = O, $n = 3$), *viz.*, 21·67, is very difficult to understand.

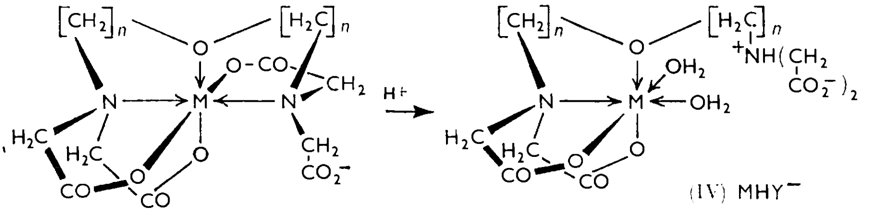
Stability constants of metal complexes of acids (II; X = O, n = 2 and 3).
Valid for 20° *and* $\mu = 0{\cdot}1$M-KCl.

pK values for	H_4Y	H_3Y^-	H_2Y^{2-}	HY^{3-}
$n = 2$	1·8 [a]	2·76	8·84	9·47
$n = 3$	2·0 [b]	2·74	9·64	10·14
	2·1 [c]	2·7	9·67	10·17

	Mg	Ca	Sr	Ba	Zn	Cd	Hg
$\log K_{\mathrm{MY}}$ $n = 2$ ...	8·32	10·0	9·34	8·15	—	16·27	23·09
$\log K_{\mathrm{MY}}$ $n = 3$ ...	4·8	5·38 5·39 [c]	4·15	3·77	13·53	14·22 14·29 [d]	21·67
$\log K^{\mathrm{M}}_{\mathrm{MHY}}$ $n = 2$ ...	3·8	4·9	4·6	4·0	—	9·90	16·14
$\log K^{\mathrm{M}}_{\mathrm{MHY}}$ $n = 3$	3·92	4·04 4·0 [c]	3·06	2·69	9·19	8·20	15·0
$\log K^{\mathrm{H}}_{\mathrm{MHY}}$ $n = 2$ ...	4·95	4·4	4·7	5·3	—	3·1	2·5
$\log K^{\mathrm{H}}_{\mathrm{MHY}}$ $n = 3$ ...	9·3	8·9 8·8 [c]	9·1	9·2	5·9	4·2	3·6
Cf. methoxyethyliminodiacetic acid							
$\log K_{\mathrm{ML}}$	3·31	4·53	3·84	3·56	8·43	7·53	5·94
$\log \beta_2$	—	—	—	—	12·85	13·18	10·03

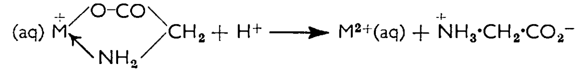
[a] All data for acid (II; X = O, $n = 2$) are from Schwarzenbach, Senn, and Anderegg.[2] [b] Data for acid (II; X = O, $n = 3$) are from the present paper. [c] Cf. ref. 2. [d] Values obtained by using the mercury electrode, $\mu = 0{\cdot}1$M-NaNO$_3$. [e] For methoxyethyliminodiacetic acid, $MeO{\cdot}C_2H_4{\cdot}N(CH_2{\cdot}CO_2H)_2$, p$K$ of $H_2L = 2{\cdot}1$ and of $HL^- = 8{\cdot}91$.

Values of $K^{\mathrm{H}}_{\mathrm{MHY}}$ in the Table show that increase in the chain length of the ligand causes an increase in the basicity of the 1 : 1 complex MY^{2-}. With the alkaline earths the average value of 4·8 ± 0·4 ($n = 2$) increases to 9·1 ± 0·2 for the higher homologue ($n = 3$). If the proton in MHY^- is attached to a nitrogen atom (rather than to an oxygen atom of a carboxylate ion) this will become incapable of co-ordinating to a metal and two chelate rings must be broken in the transition $H^+ + MY^{2-} \longrightarrow MHY^-$, (III $\longrightarrow$ IV).



(III) MY^{2-} (IV) MHY^-

The protonation of MY^{2-} to MHY^- may be compared with the protonation of a 1 : 1 complex of a bivalent ion with an amino-acid to form the zwitterion HZ±, *viz.*:



$$(aq)\ \overset{+}{M}\langle{}^{O-CO}_{NH_2}\rangle CH_2 + H^+ \longrightarrow M^{2+}(aq) + \overset{+}{N}H_3{\cdot}CH_2{\cdot}CO_2^-$$

Ceteris paribus, the change in free energy (III $\longrightarrow$ IV) measured by $\log K^{\mathrm{H}}_{\mathrm{MHY}}$ should be comparable to that in the latter reaction as measured by $pK_{HZ\pm} - \log K_1$ (metal glycine). For calcium and glycine $\log K_1 \approx 1{\cdot}2$, whence $\log K^{\mathrm{H}}_{\mathrm{CaHY}} = 10{\cdot}2 - 1{\cdot}2 =$

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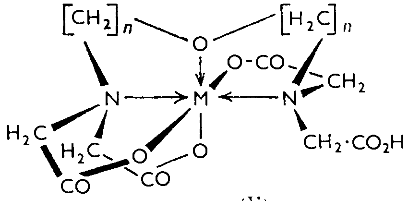
[7] Schwarzenbach, *Helv. Chim. Acta*, 1952, **35**, 2344.

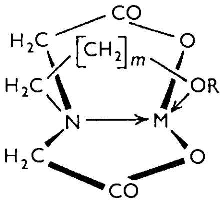
9·0 (found 8·9) and log $K^{\rm H}_{\rm ZnHY} = 10{\cdot}2 - 5 = 5{\cdot}2$ (found 5·9). Although the agreement is certainly fortuitous, the chelate effect [7] must favour the formation of MY^{2-} from MHY^- and the value of $K^{\rm H}_{\rm MHY}$ should therefore become larger as the size of the chelate ring increases from five- to six-membered. This is found experimentally (Table).

The structure (V) for MHY^- is inadmissible, for log $K^{\rm H}_{\rm MHY}$ would not then be much greater than ~2·2, the value for the dissociation of the first proton from glycine.[8] If the proton is assumed to be attached to a nitrogen atom in the species MHY^- derived from the acid (II; X = O, $n = 3$), the free energy of formation of a complex (IV; $n = 3$) from HY^{3-} and M^{2+} (which is measured by the stability constant $K^{\rm M}_{\rm MHY}$) may be compared with the values for 1 : 1 complexes of the same metals with the anion, Y^{2-}, of methoxyethyliminodiacetic acid. Naturally the values will be somewhat lower since a six-membered ring has replaced a five-membered one. The agreement is good for the alkaline earths Ca, Sr, and Ba, but with the more strongly polarising ions of magnesium, zinc, and cadmium the protonated complexes formed by the acid (II; X = O, $n = 3$) are the stronger by 0·6—0·8 log unit: the difference for the mercury complex is again anomalously high (~9 log units) and raises some doubts concerning the validity of the stability data for the mercury complexes of methoxyethyliminodiacetic acid.

The Table of stability constants shows that the protonated complex, MHY^-, of zinc is more stable than that of cadmium, although the 1 : 1 complex, MY^{2-}, of cadmium is more stable than that of zinc. This accounts for the crossing of the titration curves shown in the Figure. A similar anomaly is shown by complexes of methoxyethyliminodiacetic acid (Table) where the 1 : 1 complex with zinc is more stable than that of cadmium although its overall stability is less. The same behaviour characterises a number of other tetradentate ligands.[8] With ethylenediamine K_1 and K_2 are greater for zinc than for cadmium, but the third molecule of ligand is attached more firmly to cadmium than to zinc.[8] These peculiarities may be connected with the tendency of the smaller zinc ion to favour a tetrahedral structure. Thus a tetrahedral structure (as VI) may result with the tetradentate ligands formed by the ion HY^{3-} of the complexone (II; X = O, $n = 3$) when forming the protonated complex MHY^-, or with the anion, Y^{2-}, of methoxyethyliminodiacetic acid or its analogues. Here the stability order will be Zn > Cd. With the hexadentate ion, Y^{4-}, from an acid (II; X = O, $n = 3$), or with two molecules of methoxyethyliminodiacetic acid (or with three molecules of ethylenediamine) octahedral co-ordination will be easier for the larger ion (as III), so that stabilities will be in the order Cd > Zn.



(V)



(VI) $m = 1$, R = Me
$m = 2$, R = $C_3H_6\cdot\overset{+}{N}H(CH_2\cdot CO_2^-)_2$

The stability ($K_{\rm HgY} = 10^{21\cdot64}$) of the mercury complex of acid (II; X = O, $n = 3$) ($pK_{\rm HY} = 10{\cdot}23$) which has a chain of seven atoms ($-C_3H_6\cdot O\cdot C_3H_6-$) between the two linearly co-ordinated nitrogen atoms would not be expected to differ greatly from that of an analogue of acid (I; $n = 7$) of similar proton affinity, provided the oxygen atom did not participate in co-ordination. From the values $pK_{\rm HY^-} = 10{\cdot}7$ and log $K_{\rm MY} = 21{\cdot}6$ interpolated from data [2] for the complexones (I; $n = 6$ and 8), a value of log $K_{\rm HgY} < 21{\cdot}6$ would be predicted for a ligand of $pK_{\rm HY} = 10{\cdot}23$ that forms a ten-membered chelate

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[8] "Tables of Stability Constants," *Chem. Soc. Spec. Publ.*, No. 7, Part I, 1957.

ring. The experimental value for the mercury complex of (II; $X = O$, $n = 3$) is $10^{21 \cdot 7}$, which shows that the oxygen atom does co-ordinate to mercury though far less effectively than sulphur or nitrogen does, as would be expected from the character of this element.[1,2]

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