

712. Steric Hindrance in Analytical Chemistry. Part IV.* Some Sterically Hindered Complexones.

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Steric factors and other preparative difficulties have prevented the isolation of pure homologues of ethylenediaminetetra-acetic acid with $-\text{CHMe}\cdot\text{CO}_2\text{H}$ in place of $-\text{CH}_2\cdot\text{CO}_2\text{H}$, or homologues of ethylenediamine-tetrapropionic acid with $-\text{CH}_2\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$ in place of $-\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, although the nitriles, di-(2-cyanopropyl)ethylenediamine and *NNN'N'*-tetra-(2-cyanopropyl)ethylenediamine, were obtained.

Ethylenediamine-*NN'*-di- α -propionic acid was prepared from ethylenediamine and α -chloropropionic acid and from ethylenediamine, potassium cyanide, and acetaldehyde. The stabilities of its metal complexes increase in the order $\text{Ba} < \text{Ca} < \text{Mg} < \text{Cd} < \text{Zn} < \text{Co} < \text{Ni} < \text{Cu}$, but owing to steric factors they are uniformly lower than corresponding complexes of the stronger acid ethylenediamine-*NN'*-diacetic acid.

Attempts to prepare a homologue of anthranilic acid-*NN'*-diacetic acid gave only α -*o*-carboxyanilinopropionic acid whose metal complexes were even weaker than those of *N*-substituted glycines.

PREVIOUS papers from this laboratory have considered the effect on the stability of the corresponding proton- and metal-complexes of introducing alkyl groups into bidentate ligands such as ethylenediamine,¹ 8-hydroxyquinoline and its various aza-substituted analogues,² 1 : 10-phenanthroline,³ and analogues of 2 : 2'-dipyridyl.^{4,5} These studies have since been extended to ter- and multi-dentate ligands and in particular to the aminopolycarboxylic acids (complexones) of analytical importance which may formally be considered as being derived from ammonia, amines, or polyamines, by replacing two or more hydrogen atoms by carboxyalkyl residues. The effect of alkyl- or aryl-substitution on the nitrogen atoms in such complexones has been considered by Schwarzenbach and his colleagues^{6,7} but hitherto no attempt has been made to examine complexones substituted (*a*) in the carboxyalkyl residues, or (*b*) in the carbon chain linking the nitrogen atoms of the parent polyamine. The first alternative forms the subject of the present paper.

Synthetic Work.—An increase in the size of a chelate ring resulting from the replacement of $-\text{CH}_2\cdot\text{CO}_2\text{H}$ by $-\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ in a complexone is known to produce less stable metal complexes.⁸ We proposed to replace $-\text{CH}_2\cdot\text{CO}_2\text{H}$ in typical complexones by $-\text{CHMe}\cdot\text{CO}_2\text{H}$ and thence to study the effect of alkyl-substitution while retaining the five-membered chelate rings. The inductive effect of the methyl group would be expected to produce its customary acid-weakening effect in the ligand so that, other factors remaining equal, an increase in the stability of the corresponding metal complexes should result.⁵ However, an examination of molecular models indicated that the replacement of hydrogen by methyl could introduce considerable steric hindrance to co-ordination, especially around a small cation: the net effect of the proposed substitution could not therefore be predicted.

Although ethylenediamine-*NNN'N'*-tetra-acetic acid (I; R = H) and ethylenediamine-*NNN'N'*-tetra- β -propionic acid can readily be prepared by condensing ethylenedi-

* Part III, *J.*, 1955, 430.

¹ Irving and Griffiths, *J.*, 1954, 213.

² Irving and Rossotti, *J.*, 1954, 2910.

³ Irving, Cabell, and Mellor, *J.*, 1953, 3417.

⁴ Irving and Williams, *Analyst*, 1952, 77, 813.

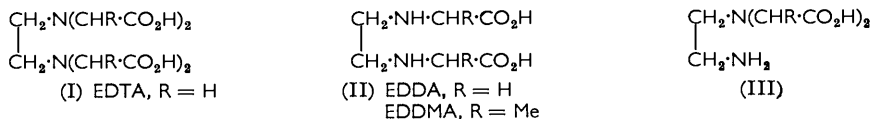
⁵ Irving and Rossotti, *Acta Chem. Scand.*, 1956, 10, 72.

⁶ Schwarzenbach, Ackermann, and Ruckstuhl, *Helv. Chim. Acta*, 1949, 32, 1175.

⁷ Schwarzenbach, Willi, and Bach, *ibid.*, 1947, 30, 1303.

⁸ Irving, Williams, Ferrett, and Williams, *J.*, 1954, 3494.

amine with chloroacetic and β -chloropropionic acid respectively in aqueous alkali, attempts to prepare ethylenediamine-*NNN'*-tetra- α -propionic acid (I; R = Me) from ethylenediamine and α -chloropropionic acid under similar conditions gave only a dibasic acid, $C_8H_{16}O_4N_2$, shown later to be ethylenediamine-*NN'*-di- α -propionic acid (II; R = Me), even when an excess of the chloropropionic acid was employed. No evidence for the formation of any of the desired tetra-acid, $C_{14}H_{24}O_8N_2$, could be obtained from the titration curve of the mother-liquors, and when these liquors were taken to dryness and esterified with methyl alcohol with dry hydrogen chloride as catalyst, methyl α -chloropropionate was the sole identifiable product. In case the desired tetra-acid had been formed initially to any extent but had subsequently been partly decarboxylated at the pH (10) employed for the condensation, this was repeated with calcium carbonate in place of aqueous sodium hydroxide: the yield of ethylenediamine-*NN'*-di- α -propionic acid was reduced and no tetra-acid could be isolated.



Ulrich and Ploetz⁹ obtained high yields of ethylenediamine-*NNN'*-tetra-acetonitrile by condensing ethylenediamine with formaldehyde and hydrogen cyanide. Hydrolysis to the tetra-acid (I; R = H) presented some difficulties but a detailed study of the optimum conditions for its synthesis (using alkali cyanide in place of hydrogen cyanide¹⁰) permitted the yield to be raised to 96%. The condensation of ethylenediamine with acetaldehyde and potassium cyanide appeared, therefore, to be a promising route to the desired tetra-acid (I; R = Me). Unfortunately, acetaldehyde is extremely prone to condensation under alkaline conditions, but by carrying out the reaction over an extended period (76 hr.) at a low temperature (below 5°) and removing ammonia and water at intervals by vacuum-distillation (to minimise undesirable side-reactions), a fair yield of ethylenediamine-*NN'*-di- α -propionic acid was obtained. Again it appears that steric hindrance had prevented the formation of the desired tetra-acid (I; R = Me). On the assumption that this steric hindrance occurs principally when the third and the last imino-hydrogen atoms of the acid (II; R = Me) should undergo replacement by bulky groups, a more promising route appeared to be the condensation of ethylene dibromide with iminodi- α -propionitrile, $\text{NH}(\text{CHMe}\cdot\text{CN})_2$, which is readily accessible,¹¹ although the subsequent hydrolysis might be sterically hindered or accompanied by partial decarboxylation. We have not succeeded in bringing about this condensation although a wide range of temperatures and experimental conditions have been tried, with ether, carbon tetrachloride, and toluene as media, with calcium carbonate to take up any hydrogen bromide liberated. Condensation in water under the conditions used to prepare "nitrogen mustards"¹² or *NN'*-di- or *NNN'*-tetra-alkylated ethylenediamines¹³ were also unsuccessful.

That the acid, $C_8H_{16}O_4N_2$, should be formulated as the symmetrical ethylenediamine-*NN'*-di- α -propionic acid (II; R = Me) rather than as the unsymmetrical ethylenediamine-*NN'*-di- α -propionic acid (III; R = Me) follows from the shape of its titration curve (Fig. 1) and a comparison of its proton dissociation constants with those of symmetrical and unsymmetrical ethylenediaminediacetic acids (Table 1). There is a quite remarkable agreement with the values for ethylenediamine-*NN'*-diacetic acid and ethylenediamine-*NN'*-di- β -propionic acid (despite the small difference in the temperature of measurement)

⁹ Ulrich and Ploetz, U.S.P., 2,205,995/1940.

¹⁰ Smith, Bullock, Bersworth, and Martell, *J. Org. Chem.*, 1949, 355.

¹¹ Dubsky, *Ber.*, 1916, 49, 1045.

¹² Ken and Roberts, *J.*, 1950, 979.

¹³ Basolo, Murmann, and Yun Ti Chen, *J. Amer. Chem. Soc.*, 1953, 75, 1478.

and marked divergence from the values for the unsymmetrical ethylenediamine-*NN*-diacetic acid (cf. Table 1), for iminodiacetic acid, $\text{NH}(\text{CH}_2\cdot\text{CO}_2\text{H})_2$ ($\text{p}K_1 = 2.65$, $\text{p}K_2 = 9.38$; ref. 14), for methylimino-*NN*-diacetic acid, $\text{CH}_3\cdot\text{N}(\text{CH}_2\cdot\text{CO}_2\text{H})_2$ ($\text{p}K_1 = 2.12$, $\text{p}K_2 = 9.65$; ref. 15), or for hydrazine-*NN*-diacetic acid, $\text{NH}_2\cdot\text{N}(\text{CH}_2\cdot\text{CO}_2\text{H})_2$, ($\text{p}K_1 = 2.54$, $\text{p}K_2 = 9.30$; ref. 16).

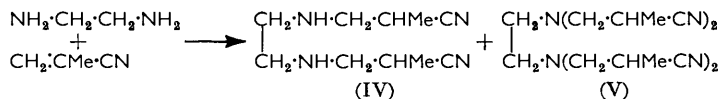
Failure to prepare the tetramethyl homologue (I; $\text{R} = \text{Me}$) of EDTA or to condense iminodi- β -propionitrile with dibromoethane could well be a consequence of overcrowding round the nitrogen atoms. To test this an attempt was made to prepare a homologue of

TABLE 1. Values of stability constants at $\mu = 0.1$.

Ion (M)	Ligand:	EDDA ^a	EDDMA ^b	EDDP ^c	EDDA (unsymm.) ^d
	Temp.:	30°	20°	30°	20°
		Values of $\log K_{ML}$			
H^+ {	$\text{p}K_1$	6.42	6.69 ± 0.02	6.87	5.58
	$\text{p}K_2$	9.46	9.58 ± 0.02	9.60	11.05
Mg^{++}		3.9	2.8 ± 0.1	1.6	4.53
Mn^{++}		—	—	3.4	7.71
Co^{++}		11.2	10.2 ± 0.1	7.3	11.78
Ni^{++}		13.5	12.2 ± 0.1	9.3	13.73
Cu^{++}		16.2	15.2 ± 0.2	15.1	15.9
Zn^{++}		11.1	10.1 ± 0.1	7.6	11.93
Cd^{++}		8.8	8.1 ± 0.1 ^e	5.6	10.58
Ca^{++}		—	~ 1	—	4.63
La^{+++}		—	5.8 ± 0.1	—	—

^a Ethylenediamine-*NN*-diacetic acid (Chabarek and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 6228). ^b Present work. ^c Ethylenediamine-*NN'*-di- β -propionic acid (Courtney, Chabarek, and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4814). ^d Ethylenediamine-*NN*-diacetic acid (ref. 15). ^e Data given by Chabarek *et al.* (*loc. cit.*) do not take into account the formation of chloro-complexes; when allowance is made for complex-formation between cadmium ions and the 0.1M-KCl salt background, the true stability constant for this complex would be 8.8.

ethylenediamine-*NNN'N'*-tetra- β -propionic acid (which can itself be readily prepared) with methyl groups remote from the nitrogen atoms. To this end ethylenediamine was condensed with an excess of α -methylacrylonitrile, sodium ethoxide being used as catalyst. *NN'*-Di-(2-cyanopropyl)ethylenediamine (IV) and *NNN'N'*-tetra-(2-cyanopropyl)ethylenediamine (V) were obtained in yields of 30% and 11.5% respectively. Acid-hydrolysis of the dinitrile (IV) gave a small amount of an acid, which appeared to form a complex



with calcium ions: but attempts to obtain the material analytically pure failed. Alkaline hydrolysis of the dinitrile (IV) gave an uncrystallisable syrup and attempts to isolate the desired acid as its dipotassium or potassium hydrogen salt gave white crystalline materials which decomposed in a few hours. The same instability characterised products obtained by hydrolysis of the tetranitrile (V) under a variety of experimental conditions.

Schwarzenbach *et al.*⁷ described a number of complexones (VI; $\text{R} = \text{R}' = \text{H}$) derived from aromatic amines, that from anthranilic acid forming the most stable metal complexes. Our attempts to prepare a homologue with $-\text{CHMe}\cdot\text{CO}_2\text{H}$ in place of $-\text{CH}_2\cdot\text{CO}_2\text{H}$ gave only α -*o*-carboxyanilinopropionic acid (VII), again demonstrating the difficulty of replacing



both hydrogen atoms of a primary amine by the grouping $-\text{CHMe}\cdot\text{CO}_2\text{H}$. When the complexone (VII) was treated with sodium chloroacetate under alkaline conditions a

¹⁴ "Stability Constants," Part I, Chem. Soc. Special Publ., No. 6, 1957.

¹⁵ Schwarzenbach, Anderegg, Schneider, and Senn, *Helv. Chim. Acta*, 1955, **38**, 1147.

¹⁶ Vickery, *J.*, 1954, 385.

crystalline acid resulted in 45% yield. This was doubtless the fully substituted complexone (VI; R = H, R' = Me). It was, however, very unstable and on each successive crystallisation the melting-point range increased. Similar instability characterised *N*-methylanilinoacetic acid, for although its methyl ester, C₆H₅·NMe·CH₂·CO₂Me, was prepared from *N*-methylaniline and methyl bromoacetate, hydrolysis gave a product which readily lost carbon dioxide and could not be obtained analytically pure. We also failed to obtain complexones pure enough for physicochemical measurements by reaction of aniline with α-bromopropionic ester, or from α- or β-naphthylamine or *o*- and *p*-arsanilic acid with chloroacetic acid or methyl bromoacetate, although crystalline products were obtained in some cases, notably when using β-naphthylamine.

Measurements of Proton- and Metal-Ligand Association Constants.—Ethylenediamine-*NN'*-di-α-propionic acid (EDDMA) (II; R = Me) and α-*o*-carboxyanilinopropionic acid (VII) were titrated potentiometrically against carbonate-free potassium hydroxide at 20.0° by means of a hydrogen electrode, a silver-silver chloride reference electrode, and a constant salt background of 0.1M-potassium chloride. Their acid dissociation constants, defined by $K_1 = \frac{[H^+][HL^-]}{[H_2L]}$ and $K_2 = \frac{[H^+][L^{2-}]}{[HL^-]}$, were calculated from the known total amount of acid taken, C_A, the hydrogen-ion concentration, [H⁺], and the degree of neutralisation, *a*, the following expression being used:

$$[H^+]^2\{aC_A + [H^+] - [OH^-]\} = K_1[H^+]\{(1 - a)C_A - [H^+] + [OH^-]\} + K_1K_2\{(2 - a)C_A - [H^+] + [OH^-]\} \quad (1)$$

Successive approximations were unnecessary with EDDMA since its two dissociation constants were well separated.

Similar titrations were carried out in the presence of various concentrations, C_M, of metal ions. A glass electrode and calomel reference electrode were used for titrations with copper. Calculations of stability constants, defined by $K_{ML} = \frac{[ML]}{[M^{2+}][L^{2-}]}$, were carried out by means of the equations:

$$C_A = [H_2L] + [HL^-] + [L^{2-}] + [ML] + 2[ML_2^{2-}] \quad \dots \quad (2)$$

$$C_M = [M^{2+}] + [ML] + [ML_2^{2-}] \quad \dots \quad (3)$$

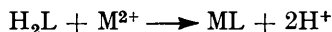
$$aC_A + [H^+] - [OH^-] = [HL^-] + 2[L^{2-}] + 2[ML] + 4[ML_2^{2-}] \quad \dots \quad (4)$$

Under the conditions employed the 1 : 2 complex did not occur to a measurable extent and the expressions could be simplified by omitting the term [ML₂²⁻].

RESULTS AND DISCUSSION

The titration curve of ethylenediamine-*NN'*-di-α-propionic acid (EDDMA) reproduced in Fig. 1 shows two well-separated buffer regions and corresponds to the titration of a dibasic acid with pK₁ = 6.69 and pK₂ = 9.58. It closely resembles those for ethylenediamine-*NN'*-diacetic acid¹⁷ and ethylenediamine-*NN'*-di-β-propionic acid.¹⁸ The methyl groups have produced the expected acid-weakening effect (cf. glycine with pK₂ = 9.78 and β-alanine with pK₂ = 9.87) and the acid strengths increase in the order EDDP < EDDMA < EDDA.

The titration curves (Fig. 1) show that the formation of complexes with the transition metals Cu²⁺, Ni²⁺, Co²⁺, with Zn²⁺, and to some extent with Cd²⁺ takes place according to the reaction:



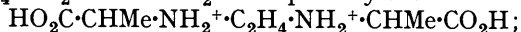
Complex formation with La³⁺ is small until the buffer region where the ion HL⁻ occurs. With Mg²⁺ there is only slight complex-formation even in the buffer region where L²⁻ predominates. Titration curves for EDDMA in the presence of excess Li⁺, Sr²⁺, and Ba²⁺ are indistinguishable from that of the reagent alone, showing that these ions do not form

¹⁷ Chaberek and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 6228.

¹⁸ Courtney, Chaberek, and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4814.

complexes of appreciable stability. Measurements with Ca^{2+} indicated slight complex-formation with $K < 1$.

In strongly acid solutions EDDMA could take up protons to form the cationic species $\text{HO}_2\text{C}\cdot\text{CHMe}\cdot\text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2^+\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$ and possibly even



this can be established by titrating it with concentrated hydrochloric acid. Since copper

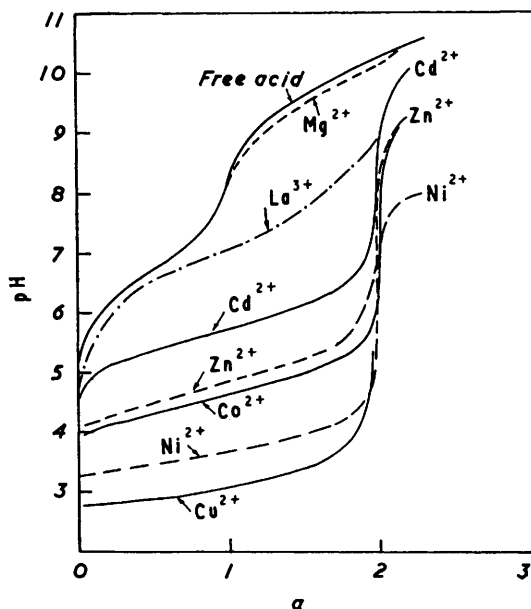


FIG. 1. Titration curves for ethylenediamine-*NN'*-*di-α*-propionic acid and its metal complexes at 20° and $\mu = 0.1\text{M}$ (KCl).

FIG. 2. Correlation between the stabilities of corresponding complexes of ethylenediamine-*NN'*-*diacetic* acid (EDDA) and ethylenediamine-*NN'*-*di-α*-propionic acid (EDDMA). The broken line is that predicted theoretically for measurements all at 30°.

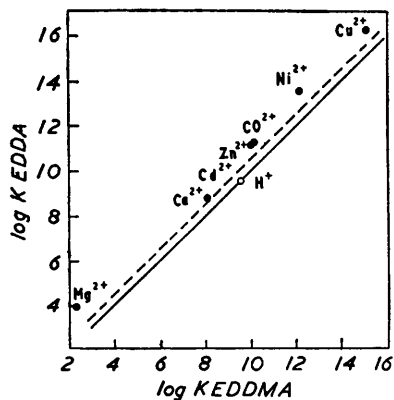
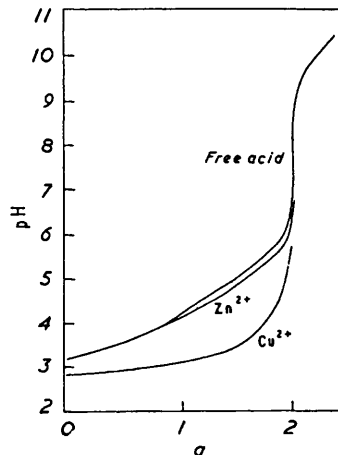


FIG. 3. Titration curves for α -*o*-carboxyanilino-propionic acid and its metal complexes at 20.0° and $\mu = 0.1\text{M}$ (KCl).



begins to form a complex with EDDMA even below pH 3, the dissociation constants of the species H_3L^+ (and possibly H_4L^{2+}) should be taken into account when calculating the stability constant of CuL . Preliminary measurements suggest that the value $K_{\text{CuL}} = 15.2$ will not be altered significantly by such refinements.

Plots of the degree of formation, \bar{n} , against pL confirm the titration curves (Fig. 1) in showing that only 1 : 1 complexes are formed, even when excess of the ligand is used. EDDMA acts throughout as a quadridentate ligand.

Stability constants for the metal complexes of EDDMA are collected in Table I and compared with values for EDDA, EDDP, and the unsymmetrical complexone (III; R = H). The stabilities of its complexes with bivalent ions are in the order Ba < Ca < Mg < Co < Ni < Cu > Zn > Cd, thus providing another example of the Irving-Williams order¹⁹ and the correlation of stability with the second ionisation potential.^{19, 20}

Since EDDMA is a weaker acid than EDDA, it would be expected to form more stable metal complexes: that the reverse is true indicates that some other factors, *e.g.*, steric effects, are operative. (The still lower stabilities of the metal complexes formed by the even weaker acid EDDP are, of course, due primarily to the increase in the size of the chelate rings.⁸) It has been shown⁵ that if two very similar ligands P and Q form complexes MP and MQ with a series of metals such that the size, the number, and the geometry of the chelated rings is essentially the same, a plot of $\log K_{MP}$ against $\log K_{MQ}$ should be a straight line of unit slope and intercept ($pK_{HQ} - pK_{HP}$). For the pair of complexones ethylenediaminetetra-acetic acid and 1 : 2-diaminocyclohexanetetra-acetic acid this has been shown to hold for some two dozen cations and stability constants ranging from 10^8 to 10^{24} .

Fig. 2 shows points for metal complexes of EDDA and EDDMA together with the line of unit slope (solid line) passing through the point (9.46, 9.58) and hence of the theoretical intercept. All the experimental points lie to the left of this line, showing that steric factors have weakened the metal complexes of EDDMA relatively to those of EDDA. In fact, the discrepancies become even larger than at first sight when differences in the temperatures of measurement are taken into account. Thermodynamic data for complexones and for their metal complexes are still scanty, but an increase of temperature from 20° to 30° is known to decrease pK_3 of 2-carboxyethyliminodiacetic acid, $HO_2C \cdot C_2H_4 \cdot N(CH_2 \cdot CO_2H)_2$, by 0.3 log unit, and pK_4 of EDTA (I; R = H) by about 0.5 log unit.¹⁴ Applying the same correction to EDDMA and adopting an upper limit of $pK_2 = 9.08$ at 30° we obtain the "theoretical" line for 30° shown (broken) in Fig. 2. Increase of temperature also reduces the strength of metal-ligand complexes to varying extents. For the change from 20° to 30° the stability of the zinc complex of 2-carboxyethyliminodiacetic acid decreases by 0.27 log unit, but that of the Mg^{2+} complex by only 0.8 log unit (ref. 14, page 57). With EDTA (ref. 14, page 76) the decreases for bivalent ions of Mg, Ca, Sr, Ba, Co, Ni, Cu, Zn, and Pb are 0.4, 0.13, 0.10, 0.9, 1.1, 1.0, 1.0, and 1.2 log units respectively, and hence all points in Fig. 2 should be displaced horizontally to the left. Unfortunately it is impossible to do more than guess the extent of the correction needed although it is likely to be very small indeed for magnesium and not more than 0.5 for the transition metals. In view of these uncertainties it is impossible to infer to what extent the steric effect is related to the ionic radius of the ion which has become the centre of the complex.

The titration curve for α -*o*-carboxyanilino-propionic acid (VII) shows a very weak inflection on the addition of one equivalent of base and a sharp rise in pH when $a = 2$, corresponding to the behaviour of a dibasic acid with $pK_1 = 3.12$ and $pK_2 = 5.01$, the first proton detached probably being that of the aliphatic carboxyl group. Titrations were only carried out with zinc, copper, calcium, and cadmium (Fig. 3) since it was quickly obvious that this complexone had no analytical value and that the low values of stability constants would be of little service for comparative purposes. In every case only 1 : 1 complexes were formed and the stability constants $\log K_{CuL} = 6.6 \pm 0.2$ and $\log K_{ZnL} = 2.85 \pm 0.1$ are well below the corresponding values for *o*-carboxyphenyliminodiacetic acid ($\log K_{ZnL} = 7.7$) or even for dimethylaminoacetic acid ($\log K_{CuL} = 7.3$).

¹⁹ Irving and Williams, *J.*, 1953, 3192.

²⁰ *Idem*, *Nature*, 1948, 162, 746.

EXPERIMENTAL

The titration vessel of 250 ml. capacity was constructed like a vacuum flask with double walls, and water from a thermostat at $20.0^\circ \pm 0.05^\circ$ was circulated through the jacket. A tightly fitting rubber stopper carried a hydrogen electrode of the Hildebrand type, a thermometer, a mechanical stirrer, a gas-inlet tube, a silver-silver chloride electrode, and a hole for a 3 ml. microburette. The reference electrode was contained in a blackened glass tube drawn to a narrow orifice which dipped into the solution. Operation of a small rubber bulb allowed the liquid surrounding the reference electrode to be forced out and replaced by fresh titration mixture. In this way hydrogen was prevented from coming into contact with the silver electrode, and junction potentials were avoided. At the same time the arrangement provided possibilities for differential titration and gave useful indications of approaching rapid changes in the slope of titration curves.

The microburette was mounted on a rack-and-pinion device which enabled the tip to be withdrawn except when alkali was actually being delivered. This device added greatly to the precision of the measurements by preventing drifts of potential due to the slow diffusion of titrant, especially at those stages where small additions of alkali produced marked changes in hydrogen-ion concentration. The gas outlet was fitted with a soda-lime tube to prevent the back-diffusion of carbon dioxide. Hydrogen gas, freed from oxygen by means of a "De-oxo" platinum catalyst, passed through a pre-saturator (in a thermostat) containing 0.1M-potassium chloride and then through a pressure-regulator before it entered the hydrogen electrode. Potential measurements were made to 0.1 mv with a Pye "Universal" slide wire potentiometer in conjunction with a Pye "Scalamp" galvanometer. Hydrogen and silver-silver chloride electrodes were checked before and after each titration by determining the E.M.F. of the cell Ag-AgCl(s), 0.1M-HCl, H₂(Pt), and results were rejected if this differed by more than 0.2 mv from the published value.²²

A solution of carbonate-free potassium hydroxide in potassium chloride was prepared from silver oxide and potassium chloride²³ and diluted until exactly 0.1M with respect to potassium chloride. It was stored in a vessel from which it could be transferred by hydrogen to the microburette without contact with carbon dioxide. All chemicals were of "AnalaR" grade. Doubly distilled water, tested with dithizone for freedom from traces of heavy metals, was used throughout. All metal solutions (usually 0.002M), perchloric acid (0.001M), and 0.002M-solutions of the complexones were made up in 0.1M-potassium chloride. 50 ml. of the complexone acid, x ml. of metal solution, and (50 - x) ml. of 0.1M-potassium chloride were taken for each titration so that the ionic strength remained throughout at 0.1M.

Hydrogen-ion concentrations were calculated from the equation $E = E^0 + 0.05818[\text{H}^+]$. The value of E^0 was determined from the results of titrating a standard solution of perchloric acid (0.0009676M in 0.1M-KCl) against carbonate-free potassium hydroxide (0.09950M in 0.1M-KCl) which had been standardised potentiometrically against potassium hydrogen phthalate and recrystallised ethylenediaminetetra-acetic acid. In this and in all other neutralisations Gran's method was used to locate the exact end-point.²¹ E^0 was determined daily and whenever either electrode was changed. It varied slightly with barometric pressure, the maximum variation being 2 mv.

The apparatus was tested by determining the dissociation constants of a very pure specimen of ethylenediaminetetra-acetic acid. The calculated dissociation constants, *viz.*, $pK_1 = 1.994$, $pK_2 = 2.674$, $pK_3 = 6.170$, and $pK_4 = 10.260$ agreed excellently with those reported by Schwarzenbach *et al.*,²⁴ *viz.*, 1.996, 2.672, 6.161, and 10.262. The results of typical titrations are tabulated.

Titrations with calcium ($C_{Ca} = 2C_A$) gave no evidence of complex-formation. The titrations with cadmium gave evidence of complex-formation after $a = 1$, but the curves were not reproducible, suggesting that the formation of hydroxy-complexes or polymeric species was also occurring to extents dependent on both pH and the time allowed between successive measurements of the E.M.F.

Preparation of Ethylenediamine-NN'-di- α -propionic Acid (II; R = Me).—(a) From α -chloropropionic acid and ethylenediamine. α -Chloropropionic acid (54 g., 0.5 mole) was exactly

²¹ Gran, *Acta Chim. Scand.*, 1950, **4**, 559.

²² Harned and Ehlers, *J. Amer. Chem. Soc.*, 1932, **54**, 1350.

²³ Schwarzenbach and Biedermann, *Helv. Chim. Acta*, 1948, **30**, 331.

²⁴ Schwarzenbach and Ackermann, *Helv. Chim. Acta.*, 1947, **30**, 1798.

(a) *Titrations with ethylenediamine-NN'-di- α -propionic acid (contd.).*(ix) Lanthanum. $C_A = 0.0010M$, $C_{La} = 0.000705M$.

<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH
0.000	4.655	0.394	6.310	0.985	6.958	1.380	7.413	1.774	8.264
0.099	5.552	0.591	6.548	1.182	7.165	1.577	7.773	1.970	8.674
0.197	5.873	0.788	6.742						

(b) *Titrations with α -O-carboxyanilinopropionic acid.*(i) Reagent alone. $C_A = 0.001M$.

<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH
0.000	3.229	0.697	3.778	1.154	4.488	1.692	5.389	2.010	8.561
0.0398	3.248	0.796	3.903	1.194	4.551	1.792	5.623	2.030	9.056
0.0995	3.288	0.896	4.055	1.254	4.652	1.891	5.964	2.070	9.401
0.199	3.352	0.936	4.112	1.333	4.780	1.930	6.210	2.110	9.649
0.298	3.412	0.995	4.222	1.393	4.879	1.951	6.580	2.189	9.982
0.398	3.487	1.0054	4.321	1.493	5.036	1.971	6.703	2.288	10.22
0.498	3.572	1.095	4.390	1.593	5.199	1.990	7.302	2.385	10.39
0.597	3.666								

(ii) Zinc. $C_A = C_{Zn} = 0.001M$.

<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH
0.000	3.237	0.597	3.654	1.294	4.547	1.692	5.177	1.971	6.372
0.099	3.295	0.796	3.875	1.393	4.690	1.792	5.405	1.990	6.682
0.199	3.358	0.995	4.112	1.493	4.839	1.891	5.769	2.010	6.855
0.398	3.499	1.095	4.261	1.593	5.008	1.951	6.176	2.030	6.855

(iii) Copper. $C_A = C_{Cu} = 0.001M$.

<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH	<i>a</i>	pH
0.000	2.770	0.597	2.934	1.194	3.205	1.593	3.580	1.891	4.500
0.199	2.820	0.796	3.005	1.393	3.360	1.792	4.020	1.951	5.180
0.398	2.870	0.995	3.100						

neutralised with sodium hydroxide, and after the addition of ethylenediamine (6.0 g., 0.1 mole) the mixture was diluted to 165 ml. and maintained at 80–100° while an almost saturated solution of sodium hydroxide (20.0 g., 0.5 mole) was added at such a rate that the pH remained between the change-points of phenolphthalein and thymolphthalein. Towards the end of the reaction the solution was allowed to become more strongly alkaline and it was held at 80–100° for 30 min. after all the alkali had been added, then cooled and acidified to pH 2. A white solid separated which was collected, washed with distilled water (4×500 ml.) to remove sodium chloride, recrystallised three times from distilled water, and dried in vacuum for 3 days. *Ethylenediamine-NN'-di- α -propionic acid* forms needles, m. p. 260–265° (decomp.) [Found: C, 47.1; H, 7.8; N, 13.5%; *M* (by titration), 203.5, 305. $C_8H_{16}O_4N_2$ requires C, 47.0; H, 7.9; N, 13.7%; *M*, 204.2. Calc. for $C_{14}H_{24}O_8N_2$ (the corresponding tetra-acid): C, 48.3; H, 6.9; N, 8.0%; *M*, 348.5].

The yield was not improved by heating at 100° for 6 hr. after the addition of alkali or by conducting the condensation under the conditions used for the preparation of ethylenediamine-*NNN'N'*-tetra- β -propionic acid.

(b) *From acetaldehyde, potassium cyanide, and ethylenediamine.* By means of a dropping funnel fitted with a very fine air leak, a solution of freshly distilled acetaldehyde (14.7 g., 0.33 mole) in distilled water (200 ml.) was added continuously during 24 hr. to a stirred solution of 60% ethylenediamine (33.3 g., 0.33 mole), potassium cyanide (110 g., 1.66 mole), and sodium hydroxide (7.0 g.) diluted to 200 ml. with water and kept below 0°. Stirring was continued for some hours after addition of aldehyde, the temperature was then slowly raised to 60°, and the solution distilled under vacuum until 200 ml. of distillate had collected. The temperature was then reduced and a further 100 ml. of aqueous acetaldehyde (0.166 mole) were added during the next 12 hr. to the mixture kept at 0° and stirred as before. After removal

of 100 ml. of distillate in vacuum the sequence of operations was repeated, as shown in the following Table, until a total of 1.33 moles of acetaldehyde had been added.

Reaction time (hr.)	20	12	12	10	8	8	6
Acetaldehyde added (mole)	0.333	0.166	0.166	0.166	0.166	0.166	0.166
Temp.	-2°	0°	0°	0°	5°	5°	10°
Water removed (ml.)	200	100	100	100	100	100	200

The final red-brown solution was diluted to 1 l. and stirred while 6*N*-sulphuric acid was added slowly to bring the pH to 2. After a further 2 hours' stirring, the yellow precipitate was collected, washed free from potassium salts with water (4 × 500 ml.), and recrystallised 3 times from metal-free water [yield 3 g.; m. p. 262—265° (decomp.)] (Found: C, 47.3; H, 7.8; N, 13.6%; *M*, 204.8).

Preparation of α-o-Carboxyanilinopropionic Acid (VII).—Solutions of anthranilic acid (13.7 g., 0.1 mole) and α-chloropropionic acid (54 g., 0.45 mole) were separately neutralised with sodium carbonate, mixed, diluted to 450 ml., and heated under reflux while sodium hydroxide (8.0 g.) in water (100 ml.) was added dropwise (48 hr.), and then for a further 4 hr. After being cooled, the mixture was acidified to pH 5. α-*o*-Carboxyanilinopropionic acid separated as a yellow solid (5.3 g.) which after being decolorised (charcoal) and recrystallised three times from boiling water formed very pale yellow crystals, m. p. 178—180° (decomp.) [Found: C, 57.8; H, 5.3; N, 6.75%; *M* (by titration), 209.5. C₁₀H₁₁O₄N requires C, 57.4; H, 5.3; N, 6.7%; *M*, 209.2].

Methyl N-Methylanilinoacetate (With R. EVANS).—Redistilled *N*-methylaniline (21.4 g., 0.2 mole), methyl bromoacetate (46 g., 0.3 mole), anhydrous potassium carbonate (45 g.), and dry ether (150 ml.) were heated under reflux for 2 weeks. After removal of the solvent and excess of bromo-ester the main product was *methyl N-methylanilinoacetate*, b. p. 100—102°/1 mm. (19.5 g., 55%) (Found: C, 66.9; H, 7.4. C₁₀H₁₃O₂N requires C, 67.0; H, 7.3%). The ester was obtained pure after several distillations in a vacuum but it darkened rapidly in air and was best preserved under nitrogen.

Condensation of Methacrylonitrile with Ethylenediamine.—Methacrylonitrile (200 g., 3 moles) was added dropwise (1 hr.) to freshly distilled ethylenediamine (30 g., 0.5 mole) containing as catalyst a solution of sodium (0.57 g., 0.025 mole) dissolved in the minimum amount of alcohol. After being heated under reflux for 18 hr. the mixture was left for 1 week, excess of methacrylonitrile was removed by distillation at atmospheric pressure, and the residue fractionated under reduced pressure in small portions (5 ml.). The main products were NNN'-*tetra*-(2-cyanopropyl)ethylenediamine (V) (19 g., 11.5%), b. p. 160—170°/1 mm. (Found: C, 65.7; H, 8.5. C₁₈H₂₈N₆ requires C, 65.8; H, 8.6%), and (?) NN'-*di*-(2-cyanopropyl)ethylenediamine (IV) (34.5 g., 35.5%), b. p. 103—104°/1 mm. (Found: C, 60.0; H, 9.5; N, 28.4. C₁₀H₁₈N₄ requires C, 61.8; H, 9.3; N, 28.8%).