614. *The Stabilities of Metal Complexes of Some Derivatives of Iminodiacetic Acid.*

By H. Irving and J. J. R. F. da Silva.

Cyclohexyl-, *o*-hydroxyphenyl-, *o*-methoxyphenyl-, and *o*-mercaptophenyl-iminodiacetic acid have been prepared, and values for their acid dissociation constants and the stability constants of their complexes with a variety of metals, valid for 20° and $\mu = 0{\cdot}1$M, are reported and compared with data for complexones of similar composition.

It is shown statistically that stability data for complexes of ten tetradentate ligands of the type $X{\cdot}N(CH_2{\cdot}CO_2H)_2$ (where X includes a donor oxygen atom) with the metals magnesium, calcium, strontium, barium, and zinc can be represented by a linear relation $\log K_{ML} = a \, . \, pK_{HL} + b$, and that the values of the slopes, a, are a linear function of the sum of the first and the second ionisation potentials. The equation is then used to examine complexes of other tetradentate ligands of similar character to see whether divergencies from stabilities predicted on the basis of their proton affinities are statistically significant. The abnormal behaviour of uramildiacetic acid and of *o*-carboxy- and *o*-sulpho-phenyliminodiacetic acid is confirmed and the effect of replacing a donor oxygen atom by nitrogen or sulphur is discussed.

ALTHOUGH molecular models show that uramildiacetic acid and its homologues (I; R = H or Me, A = $CH_2{\cdot}CO_2H$) can act as tetradentate ligands, the stabilities of their metal complexes are consistently higher than those of other typical tetradentate ligands of comparable basicity.[1,2] So far as complexes with thallium(I) and the alkali metals are concerned it has been shown that the principal stabilising factor is the favourable enthalpy of reaction and that the entropy changes are actually opposed to complex formation.[1] However, the marked tendency for uramildiacetic acid and its homologues to form complexes with the smaller ions (Be^{2+}, Mg^{2+}, and Li^{+}) confirms the hypothesis reached from an examination of scale models that an especially favourable tetrahedral disposition of the co-ordinating atoms may be the reason for the high stabilities observed.

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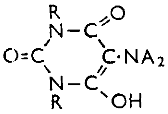
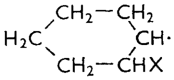
[1] Irving and da Silva, *J.*, **1963**, 448.
[2] Irving and da Silva, *J.*, **1963**, 458.

To throw further light on this problem we have examined a number of other ligands of related structures, *viz.*, cyclohexyliminodiacetic acid (II; X = H, A = $CH_2{\cdot}CO_2H$), 2-hydroxycyclohexyliminodiacetic acid (II; X = OH, A = $CH_2{\cdot}CO_2H$), *o*-carboxyphenyliminodiacetic acid (III), *o*-hydroxyphenyliminodiacetic acid (IV; X = OH), *o*-methoxyphenyliminodiacetic acid (IV; X = OMe), and 2-hydroxybenzyliminodiacetic acid (VI; A = $CH_2{\cdot}CO_2H$). For further comparison we have also studied *o*-mercaptophenyliminodiacetic acid (VII). Comparisons of these compounds were expected to show the extent to which the *o*-hydroxyl group participated in co-ordination, and the effect of replacing oxygen by sulphur.


(I)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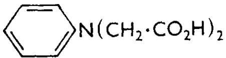
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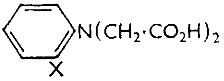
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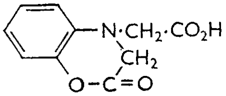
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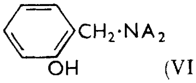
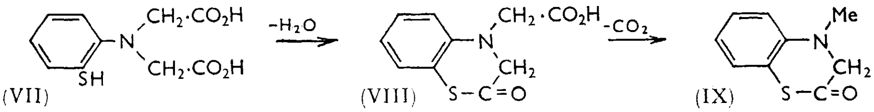

(VI)

(X = H, OH, or OMe ; A = $CH_2{\cdot}CO_2H$)

The complexones (II; X = OH), (III), and (VI) have been described previously[3-5] but few of the metal complexes of *o*-hydroxycyclohexyliminodiacetic acid (II; X = OH) have been examined.[3] Cyclohexyliminodiacetic acid (II; X = H) was prepared by condensing cyclohexylamine with chloroacetic acid under alkaline conditions. Condensation of chloroacetic acid with *o*-anisidine under alkaline conditions proceeded readily as far as *o*-methoxyphenylaminoacetic acid but, doubtless owing to the steric hindrance from the *o*-methoxy-group, preparation of the diacid (IV; X = OMe) required forcing conditions. Condensation of chloroacetic acid with *o*-aminophenol under alkaline conditions gave a δ-lactone[6] (V) which titrated as a simple monobasic acid. If, however, three equivalents of alkali were added, the lactone ring opened at once and three stages of neutralisation were obtained on back-titration with acid. The presence of a δ-lactone ring (γδ-unsaturated) in compound (V) was shown by the infrared absorption at **1760** cm.$^{-1}$ (Nujol mull): the identification of a normal carboxyl group frequency (**1715** cm.$^{-1}$) proved that the compound does not exist as a zwitterion.


(VII) (VIII) (IX)

o-Aminothiophenol with chloroacetic acid under alkaline conditions gave a variety of products. Under the usual conditions of this condensation at 100° the main product was 3,4-dihydro-4-methyl-1,4-benzothiazin-2-one (IX) which was shown to contain no free carboxyl group and to be a δ-thiolactone (γδ-unsaturated) ($\nu_{max.}$ 1640 cm.$^{-1}$). Doubtless it arose by decarboxylation of the acid (VIII) which was obtained by acidification of the reaction mixture containing an alkaline solution of the desired complexone (VII). The compound (VIII) is a thiolactone (γδ-unsaturated; $\nu_{max.}$ 1660 cm.$^{-1}$) and contains a free carboxyl group ($\nu_{max.}$ 1703 cm.$^{-1}$); it can be titrated with alkali whereby the molecular weight is established. Metal complexes of acids (IV; X = OH) and (VII) were studied by dissolving the compounds (V) and (VIII), respectively, in alkali whereby the lactone rings

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[3] Anderegg and Schwarzenbach, *Helv. Chim. Acta*, 1955, **38**, 1940.
[4] Schwarzenbach, Willi, and Bach, *Helv. Chim. Acta*, 1947, **30**, 1303.
[5] Schwarzenbach, Anderegg, and Sallmann, *Helv. Chim. Acta*, 1952, **35**, 1785.
[6] Freedman and Frost, *J. Org. Chem.*, 1958, **23**, 1292.

were opened: metal ions were then added and the solutions were back-titrated with standard acid.

Acid dissociation constants for the various ligands and stability constants of their metal complexes were obtained from the results of potentiometric titrations as described previously.[1]

EXPERIMENTAL

Cyclohexyliminodiacetic Acid (II; X = H) (with R. L. EVANS).—Cyclohexylamine (5 g., 0·05 mole) was condensed with chloroacetic acid (14·8 g., 0·15 mole) under alkaline conditions as previously described. On acidification of the mixture with concentrated hydrochloric acid (20 ml.) no complexone separated even after 24 hr. An aliquot portion was therefore treated with an excess of barium carbonate, and the insoluble barium salt was collected, washed, and digested with a slight excess of sulphuric acid. The excess of sulphuric acid was then removed by barium hydroxide solution and the barium sulphate coagulated by boiling and removed by centrifugation. Concentration of the mother-liquor gave crystals of the complexone which were used to seed the bulk; *cyclohexyliminodiacetic acid* then separated in colourless crystals as a hemihydrate, having m. p. 197—198° after recrystallisation from water (Found: C, 53·5; H, 8·3; N, 6·3. $C_{10}H_{17}O_4N,\frac{1}{2}H_2O$ requires C, 53·5; H, 8·1; N, 6·25%). The material was recrystallised twice more from 50% aqueous alcohol and then heated in a vacuum at 100° to obtain the anhydrous *complexone*, m. p. 194—196° (6 g.) [Found: C, 55·9; H, 8·2; N, 6·8%; *M*(by titration), 215. $C_{10}H_{17}O_4N$ requires C, 55·8; H, 8·0; N, 6·5%; *M*, 215·2]. The first preparation of this ligand,[7] on which a few measurements have been reported,[8] was found to be contaminated by a small proportion of the barium complex.

o-*Carboxyphenyliminodiacetic Acid* (III).—This was prepared by the procedure of Schwarzenbach *et al.*[4] in 40% yield and had m. p. 212—214° (lit., 212°) (Found: C, 52·1; H, 4·5; N, 5·4. Calc. for $C_{11}H_{11}NO_6$: C, 52·2; H, 4·4; N, 5·5%).

o-*Methoxyphenyliminodiacetic Acid* (IV; R = OMe).—Freshly distilled *o*-anisidine (12·3 g., 0·1 mole) in water (25 ml.) was heated under reflux with constant stirring with chloroacetic acid (40 g., 0·4 mole) previously neutralised with 5M-sodium hydroxide; 5M-sodium hydroxide (20 ml., 0·1 mole) was then added at such a rate (10 min.) that the pH remained between 8 and 10. Condensation with a further 20 ml. (0·1 mole) of sodium hydroxide under the same conditions was very slow (6 hr.). The reaction mixture was cooled below 0° and made strongly acid, whereupon a viscous material first separated but this redissolved in the excess of acid (20 ml.). Neutralisation with N-sodium hydroxide gave o-*methoxyphenyliminodiacetic acid* (IV; R = OMe) that, recrystallised from water, had m. p. 104—105° (2·4 g., 10%) [Found (on sample dried *in vacuo* over phosphorus pentoxide): C, 55·3; H, 5·4; N, 5·9%; *M* (by titration as a dibasic acid), 238. $C_{11}H_{13}NO_5$ requires C, 55·5; H, 5·3; N, 6·0%; *M*, 239·2].

By stopping the condensation when only one equivalent of alkali had been added o-*methoxyphenylaminoacetic acid* was isolated as needles, m. p. 143—144° (from aqueous alcohol) (Found: *M*, 181. $C_9H_{11}NO_3$ requires *M*, 181·2).

2,3-*Dihydro*-2-*oxobenzomorpholine*-4-*acetic Acid* (V).—*o*-Aminophenol (10 g.), freshly recrystallised from water, was heated under reflux with water (25 ml.) and chloroacetic acid (30 g.) (previously neutralised with 5M-sodium hydroxide). 5M-Sodium hydroxide (160 ml.) was then added at such a rate (4 hr.) that the pH remained between 8 and 10; the solid slowly dissolved. The solution was cooled below 0° and acidified strongly with concentrated hydrochloric acid (20 ml.), whereupon 2,3-dihydro-2-oxobenzomorpholine-4-acetic acid separated. It recrystallised from aqueous ethanol (charcoal) and finally water as leaflets, m. p. 178—179° (Found: C, 58·0; H, 4·4; N, 6·6. Calc. for $C_{10}H_9NO_4$: C, 58·0; H, 4·9; N, 6·8%). On titration with alkali it behaved as a monobasic acid with *M* 207 (Calc. for $C_{10}H_9NO_4$: *M*, 207·2).

The preparation of this compound (m. p. 180—182°) has been reported previously[6] and the infrared frequency given (1769 cm.$^{-1}$) agrees with our finding. The analytical figures reported are for $C_{16}H_{14}N_2O_4$ in obvious error for the compound immediately preceding it.[6]

When this was dissolved in 3 equiv. of alkali and back-titrated with perchloric acid a curve with three stages of neutralisation was obtained corresponding to a tribasic acid with *M* 225 (Calc. for $C_{10}H_{11}NO_5$: *M*, 225·2). The lactone ring is easily opened to give the dicarboxylic

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[7] R. L. Evans, D.Phil. Thesis, Oxford, 1958.

[8] Irving and Pettit, " Advances in Co-ordination Chemistry," McGraw-Hill, New York, 1960.

acid (IV; R = H) which changes the colour of a mixture of calcium ions and Eriochrome T from red to blue. At a sufficiently high pH the phenolic groups ionise.

o-*Mercaptophenyliminodiacetic acid* (VII).—*o*-Aminothiophenol (12·5 g., 0·1 mole) was dispersed in water (25 ml.) containing chloroacetic acid (30 g., ~0·3 mole) previously neutralised with concentrated aqueous sodium hydroxide. The mixture was heated to 50—60° and 5M-sodium hydroxide (60 ml., 0·3 mole) was added at such a rate (24 hr.) that the pH remained between 9 and 10. The mixture was then chilled below 0° and a precipitate of 3,4-*dihydro*-4-*methyl*-1,4-*benzothiazin*-2-*one* (IX) was collected and recrystallised from glacial acetic acid (Found: C, 60·3; H, 5·1; N, 7·3. C_9H_9NOS requires C, 60·3; H, 5·0; N, 7·3%).

The alkaline mother-liquors were acidified with concentrated hydrochloric acid (30 ml.), a white precipitate appearing after several hours. When recrystallised from aqueous alcohol (50% v/v) this gave a white powder (A), m. p. 69—71°, and colourless crystals (B), m. p. 143—145°, which separated slowly. The m. p. of product A rose gradually and reached 143° after 2 months. Both samples gave analytical results corresponding to 3,4-*dihydro*-2-*oxo*-1,4-*benzothiazine*-4-*acetic acid* (VIII) and they had identical infrared spectra with bands at 1660 (δ-thiolactone, $\gamma\delta$-unsaturated), and 1703 cm.$^{-1}$ (free carboxyl group) [Found: (sample A) C, 53·7; H, 4·1; N, 6·0%; *M* (by titration), 223. (Sample B) C, 53·8; H, 4·0; N, 6·5%; *M* (by titration), 223. $C_{10}H_9NO_3S$ requires C, 53·8; H, 4·0; N, 6·3%; *M*, 223·1]. Both samples behaved as monobasic acids on titration. The lactone ring opened on treatment with warm alkali (30 min. for A; 90 min. for B). When three equivalents of alkali were added and the solution was boiled, back-titration with perchloric acid then gave a curve with three stages of neutralisation. In preparations carried out under different conditions the yield of the lactone (IX) increased with the temperature and duration of the reaction.

Acid Dissociation Constants.—The acid dissociation constants of the various ligand acids and the stability constants of their metal complexes were measured potentiometrically as described previously, at 20·0° and are valid for μ = 0·1M. They are reported in the annexed Tables.

Acid dissociation constants of cyclohexyliminodiacetic acid (II).

$C_L = 1{\cdot}000 \times 10^{-3}$M; $C_B = 0{\cdot}100$M-KOH; $\mu = 0{\cdot}1$M-KNO_3.

a	0·000	0·100	0·200	0·300	0·400	0·500	0·600	0·700	0·800	0·900	1·000
pH	3·121	3·170	3·220	3·280	3·345	3·425	3·528	3·656	3·850	4·197	6·629
a	1·100	1·200	1·300	1·400	1·500	1·600	1·700	1·800	1·900	2·000	
pH	9·480	9·830	10·032	10·178	10·290	10·382	10·460	10·530	10·598	10·645	

Titrations of cyclohexyliminodiacetic acid (II).

(i) *With univalent ions.*

$C_L = 1{\cdot}000 \times 10^{-3}$M; C_B = 0·100M-tetramethylammonium hydroxide; μ = 0·1M-tetramethylammonium nitrate.

	pH			
a	Ag^+	Tl^+	Li^+	Na^+
1·000	6·045	6·150	6·665	6·150
1·100	8·041	9·160	8·950	9·350
1·200	8·460	9·560	9·320	9·709
1·300	8·750	9·787	9·540	9·918
1·400	8·990	9·957	9·701	10·064
1·500	9·205	10·089	9·831	10·187
1·600	9·413	10·198	9·940	10·275
1·700	9·611	10·290	10·035	10·351
1·800	9·791	10·374	10·120	10·421
1·900	9·961	10·450	10·195	10·481
2·000	10·110	10·515	10·540	10·645
C_M	0·010	0·010	1·200	1·200

(ii) *With bivalent ions.*

$C_L = 1{\cdot}000 \times 10^{-3}$M; $C_B = 0{\cdot}100$M-KOH; $\mu = 0{\cdot}1$M-KNO_3.

	pH				
a	Mg^{++}	Ca^{++}	Sr^{++}	Ba^{++}	Pb^{++}
1·000	6·238	6·695	6·270	6·000	4·484
1·100	8·460	9·299	9·140	9·180	4·881
1·200	8·830	9·600	9·499	9·570	5·202
1·300	9·067	9·816	9·709	9·791	5·471
1·400	9·248	9·980	9·870	9·950	5·720
1·500	9·400	10·109	9·992	10·079	5·970
1·600	9·540	10·218	10·100	10·182	6·231
1·700	9·670	10·310	10·194	10·270	6·546
1·800	9·796	10·390	10·280	10·350	6·920
1·900	9·914	10·461	10·352	10·420	7·458
2·000	10·022	10·522	10·421	10·485	8·082
C_M	0·100	0·010	0·100	0·100	0·010

Acid dissociation constants of *o*-carboxyphenyliminodiacetic acid (III).

$C_L = 1{\cdot}260 \times 10^{-3}$M; $C_B = 0{\cdot}111$M-tetramethylammonium hydroxide; $\mu = 0{\cdot}1$M-tetramethylammonium nitrate.

a	0·000	0·176	0·353	0·529	0·706	0·882	1·058	1·235	1·323	1·411
pH	2·888	2·933	2·985	3·040	3·105	3·175	3·259	3·358	3·423	3·482
a	1·499	1·588	1·676	1·764	1·852	1·940	2·029	2·117	2·205	2·293
pH	3·559	3·650	3·763	3·910	4·140	4·602	6·265	6·870	7·165	7·380
a	2·381	2·470	2·558	2·646	2·734	2·822	2·911	3·000	3·087	3·175
pH	7·546	7·704	7·854	8·011	8·183	8·385	8·655	9·053	9·530	9·861

Titrations with *o*-carboxyphenyliminodiacetic acid (III): with univalent ions.

		pH				pH			pH		pH
a	Tl^+	Li^+	Na^+	*a*	Tl^+	Li^+	Na^+	*a*	Ag^+	*a*	Ag^+
2·205	6·949	6·070	6·912	2·734	8·008	7·119	7·932	2·134	6·405	2·667	7·660
2·293	7·162	6·279	7·121	2·822	8·219	7·345	8·134	2·223	6·700	2·756	7·853
2·381	7·359	6·455	7·298	2·911	8·505	7·679	8·406	2·311	6·925	2·845	8·086
2·470	7·509	6·615	7·450	3·000	8·941	8·421	8·822	2·400	7·121	2·934	8·391
2·558	7·665	6·773	7·602					2·489	7·302		
2·646	7·824	6·939	7·760	C_M	0·010	1·200	1·200	2·578	7·477	C_M	0·0099

Acid dissociation constants of *o*-methoxyphenyliminodiacetic acid (IV; X = OMe).

$C_L = 1{\cdot}173 \times 10^{-3}$M; $C_B = 0{\cdot}111$M-KOH; $\mu = 0{\cdot}1$M-KNO_3.

a	0·000	0·095	0·189	0·284	0·379	0·474	0·568	0·663	0·758	0·852	0·947	1·042
pH	3·135	3·189	3·240	3·298	3·361	3·440	3·531	3·642	3·787	3·989	4·263	4·600
a	1·136	1·231	1·326	1·421	1·515	1·610	1·705	1·799	1·894	1·989	2·083	2·178
pH	4·880	5·095	5·277	5·446	5·607	5·775	5·961	6·190	6·531	7·620	9·519	9·917

Titrations of *o*-methoxyphenyliminodiacetic acid with metal ions.

For Ca^{2+} and Be^{2+} conditions as above.

With the other ions $C_L = 9{\cdot}375 \times 10^{-4}$M; $C_B = 0{\cdot}100$M-KOH; $\mu = 0{\cdot}1$M-KNO_3.

		pH			pH				pH			pH	
a	Ag^+	Tl^+	Sr^{2+}	*a*	Ca^{2+}	Be^{2+}	*a*	Ag^+	Tl^+	Sr^{2+}	*a*	Ca^{2+}	Be^{2+}
0·959	4·324	4·130	4·400	1·042	4·477	4·600	1·600	5·630	5·250	5·720	1·610	5·639	5·742
1·066	4·595	4·328	4·710	1·136	4·739	4·850	1·707	5·868	5·470	5·931	1·705	5·824	5·930
1·173	4·838	4·521	4·960	1·231	4·955	5·045	1·813	6·183	5·758	6·219	1·799	6·054	6·165
1·280	5·047	4·710	5·170	1·326	5·137	5·235	1·920	6·797	6·270	6·740	1·894	6·397	6·530
1·387	5·241	4·882	5·351	1·421	5·307	5·409	2·027	9·170	8·850	9·070	1·989	7·361	7·640
1·493	5·430	5·060	5·530	1·515	5·470	5·570	C_M	0·010	0·100	0·010	C_M	0·010	0·010

Titrations with *o*-hydroxyphenyliminodiacetic acid (II; X = OH).

For back-titrations with 0·100M-$HClO_4$ the equivalent amount of 0·105M-KOH was first added to solutions of the ligand acid prepared in the usual manner. The total volume corresponding to *a* = 0 was 125·85 and decreased by 0·1 ml. for each increase of 0·105 in *a*. Values of pK_1 and pK_3 were obtained by direct and that of pK_2 by reverse titration.

(i) *Acid dissociation constants.*

$C_L = 1{\cdot}00 \times 10^{-3}$M; $C_B = 0{\cdot}105$M; $\mu = 0{\cdot}1$M-KNO_3.

a	0·000	0·105	0·210	0·315	0·420	0·525	0·630	0·735	0·840	0·945
pH	3·258	3·310	3·376	3·444	3·527	3·621	3·740	3·886	4·078	4·337
a	1·050	1·110	1·215	1·320	1·425	1·530	1·635	1·740	1·845	1·950
pH	4·642	4·785	4·973	5·147	5·310	5·481	5·670	5·901	6·225	6·915
a	2·105	2·210	2·315	2·420	2·525	2·630	2·735	2·840	2·945	3·000
pH	9·550	9·971	10·152	10·300	10·411	10·501	10·580	10·641	10·700	10·727

(ii) *Titrations in the presence of metal ions* (conditions as above).

				pH			
a	Tl^+	Li^+	Na^+	Mg^{++}	Ca^{++}	Sr^{++}	Ba^{++}
1·000	4·448			4·433	4·271	4·335	4·381
1·100	4·660			4·653	4·457	4·544	4·610
1·200	4·858			4·851	4·640	4·759	4·810
1·300	5·030			5·025	4·810	4·955	5·000
1·400	5·201			5·190	4·976	5·120	5·109
1·500	5·370			5·350	5·147	5·291	5·346
1·600	5·551			5·510	5·330	5·489	5·530
1·700	5·750			5·688	5·540	5·677	5·740
1·800	6·011			5·887	5·800	5·925	5·995
1·900	6·401			6·116	6·146	6·222	6·325
2·000	7·450	7·960	7·770	6·370	6·606	6·781	7·050
2·100	8·497	8·812	9·398	6·631	7·130	8·411	8·780
2·200	8·880	9·179	9·781	6·900	7·471	8·961	9·248
2·300	9·128	9·410	10·011	7·140	7·725	9·239	9·518
2·400	9·336	9·585	10·171	7·379	7·950	9·456	9·709
2·500	9·515	9·735	10·291	7·625	8·170	9·634	9·870
2·600	9·681	9·856	10·380	7·887	8·391	9·790	10·009
2·700	9·825	9·970	10·465	8·185	8·641	9·931	10·121
2·800	9·971	10·069	10·533	8·550	8·935	10·058	10·231
2·900	10·094	10·152	10·594	9·000	9·270	10·178	10·326
3·000	10·210	10·230	10·649	9·435	9·602	10·290	10·405
C_M	0·010	1·200	1·200	0·010	0·010	0·010	0·010

Titrations with *o*-mercaptophenyliminodiacetic acid (VII).

Solutions were prepared by heating known weights of the lactone (VIII) with the equivalent amount of potassium hydroxide (2 hr.) and then diluting the solution to a concentration of ~0·1M. Perchloric acid (0·094M) was used for back-titrations; *a* = 0 corresponds to a total volume of 123·2 ml..

(i) *Acid dissociation constants.*

$C_L = 9{\cdot}964 \times 10^{-4}$M; $\mu = 0{\cdot}1$M-KNO_3.

a	0·005	0·099	0·193	0·288	0·382	0·476	0·571	0·665	0·754	0·854	0·948
pH	3·241	3·290	3·340	3·400	3·466	3·540	3·630	3·740	3·881	4·081	4·420
a	1·042	1·137	1·231	1·325	1·420	1·514	1·608	1·703	1·797	1·891	1·986
pH	5·019	5·510	5·790	6·000	6·150	6·285	6·470	6·669	6·880	7·142	7·647
a	2·080	2·174	2·269	2·363	2·457	2·552	2·646	2·740	2·835	2·929	3·023
pH	8·468	8·862	9·067	9·251	9·399	9·516	9·627	9·736	9·824	9·917	10·011

(ii) *Titrations with alkaline earths.*

C_M as specified; other conditions as above.

		pH	
a	Mg^{2+}	Ca^{2+}	Sr^{2+}
2·174	8·350	8·621	8·650
2·269	8·685	8·911	8·940
2·363	8·927	9·110	9·151
2·457	9·109	9·270	9·306
2·552	9·254	9·400	9·440
2·646	9·380	9·510	9·561
2·740	9·499	9·620	9·666
2·835	9·610	9·720	9·769
2·929	9·710	9·814	9·861
3·023	9·810	9·905	9·951
C_M	0·100	0·010	0·010

Titrations with 2-hydroxycyclohexyliminodiacetic acid (II; X = OH).

(i) *Acid dissociation constants.*

$C_L = 1{\cdot}000 \times 10^{-3}$M; $C_B = 0{\cdot}100$M; $\mu = 0{\cdot}1$M-KNO_3.

a	0·000	0·100	0·200	0·300	0·400	0·500	0·600	0·700	0·800	0·900	1·000
pH	3·140	3·182	3·232	3·292	3·362	3·448	3·550	3·687	3·885	4·239	5·805
a	1·100	1·200	1·300	1·400	1·500	1·600	1·700	1·800	1·900	2·000	
pH	8·455	8·898	9·151	9·340	9·498	9·641	9·770	9·892	10·010	10·125	

(ii) *Titrations with metal ions.*

C_M as specified; other conditions as above.

			pH		
a	Ag^+	Tl^+	Sr^{++}	Ba^{++}	Li^+
1·000	5·649	5·698	5·761	5·631	5·560
1·100	7·730	8·185	7·775	8·090	7·210
1·200	8·167	8·630	8·200	8·550	7·636
1·300	8·455	8·892	8·485	8·824	7·902
1·400	8·691	9·098	8·716	9·032	8·110
1·500	8·898	9·269	8·921	9·210	8·291
1·600	9·091	9·424	9·111	9·374	8·468
1·700	9·284	9·581	9·306	9·527	8·648
1·800	9·471	9·725	9·496	9·675	8·843
1·900	9·658	9·870	9·685	9·822	9·070
2·000	9·832	10·010	9·875	9·964	9·340
C_M	0·010	0·010	0·010	0·010	1·200

(iii) *Further titrations with alkali metal ions.*

Conditions as specified. The ionic strength could not be maintained at 0·1M.

a	Li^+	*a*	Li^+	*a*	Na^+	*a*	Na^+
1·075	7·942	1·827	9·671	1·068	8·070	1·747	9·649
1·182	8·518	1·935	9·830	1·165	8·620	1·844	9·761
1·290	8·800	2·042	9·985	1·262	8·896	1·941	9·876
1·397	9·011			1·359	9·091		
1·505	9·190	C_M	0·100	1·456	9·253	C_M	1·200
1·612	9·359	C_L	$9·300 \times 10^{-4}$	1·553	9·399	C_L	$9·810 \times 10^{-4}$
1·720	9·514	C_B	0·200	1·650	9·530	C_B	$9·524 \times 10^{-2}$

RESULTS AND DISCUSSION

The stoicheiometric dissociation constants of the various complexones are summarised in Table 1 together with values for certain related ligand acids, namely, 2-hydroxyethyliminodiacetic acid, $HO{\cdot}C_2H_4{\cdot}N(CH_2{\cdot}CO_2H)_2$, 2-methoxyethyliminodiacetic acid, and 2-carboxyethyliminodiacetic acid. The values for pK_1 correspond to the ionisation of a proton from a carboxyl group: these are lower for the aliphatic complexones than for those with aromatic groups in consequence of the negative inductive effect of the substituents in the latter. Comparison with results for phenyliminodiacetic acid shows the expected influence of *ortho*-substitution by OH, OMe, and CO_2H. Low values of the same order for pK_2 in the range 2·5—4·0 for uramildiacetic acid (I), *o*-carboxyphenyliminodiacetic acid (III) and 2-carboxyethyliminodiacetic acid clearly correspond to the ionisation of a second carboxyl group. Much higher values for pK_2 in the range 5·4—9·6 must, however, correspond to the removal of a proton from an ammonium-type ion. The lower values in this range (for *o*-hydroxy-, *o*-methoxy-, and *o*-mercapto-phenyliminodiacetic acid) are comparable with that for phenyliminodiacetic acid (IV; X = H) and will be a consequence of the participation of the nitrogen atom in the resonating system of the

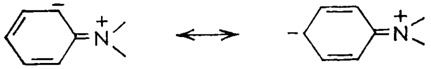
TABLE 1.

Dissociation constants of some aminopolycarboxylic acids. Data valid for 20° and $\mu = 0{\cdot}1\text{M-}KNO_3$ or -KCl.

Ligand acid	pK_1	pK_2	pK_3	Ref.
Uramildiacetic (I)	1·7 ± 0·3	2·67 ± 0·02	9·63 ± 0·02	1
Cyclohexyliminodiacetic (II; X = H)	2·15 ± 0·02	10·81 ± 0·01	—	*a*
2-Hydroxycyclohexyliminodiacetic (II; X = OH)	2·32 ± 0·01	9·57 ± 0·01	—	*a*
o-Carboxyphenyliminodiacetic (III)	2·33 ± 0·02	2·98 ± 0·01	7·75 ± 0·01	*a*
Phenyliminodiacetic (IV; X = H)	2·40	4·96	—	*b*
o-Hydroxyphenyliminodiacetic (IV; X = OH)	2·98 ± 0·01	5·43 ± 0·01	11·08 ± 0·03	*a*
o-Methoxyphenyliminodiacetic (IV; X = OMe)	2·69 ± 0·01	5·58 ± 0·01	—	*a*
2-Hydroxyethyliminodiacetic	2·2	8·73	—	*b*
2-Methoxyethyliminodiacetic	2·2	8·96	—	*b*
2-Carboxyethyliminodiacetic	2·06	3·69	9·66	*b*
2-Hydroxybenzyliminodiacetic (VI)	2·2	8·17	11·79	*b*
o-Mercaptophenyliminodiacetic (VII)	2·85 ± 0·01	6·30 ± 0·01	9·54 ± 0·02	*a*

References: (*a*) Present work, $\mu = 0{\cdot}1\text{M-}KNO_3$; other data refer to $\mu = 0{\cdot}1\text{M-KCl}$. (*b*) *Chem. Soc. Special Publ.* No. 6, Part I, 1957, and refs. therein.

benzene ring with a consequent decrease in its basicity due to the canonical forms in which it carries a formal positive charge:



Conjugation between the nitrogen and the aromatic ring is inhibited by the interposition of a methylene group in 2-hydroxybenzyliminodiacetic acid (VI) and its value for pK_2 (8·17) is comparable with those for the aliphatic ligands 2-hydroxy- and 2-methoxyethyliminodiacetic acid (8·73 and 8·96) and approaches that for 2-hydroxycyclohexyliminodiacetic acid (II; X = OH).

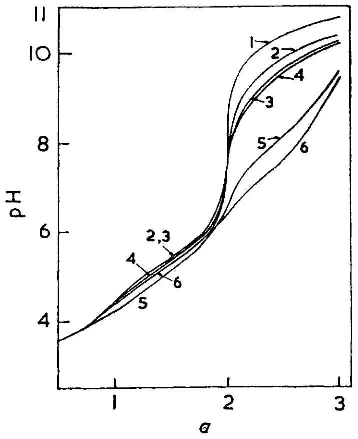


FIG. 1. Titration curves for *o*-hydroxyphenyliminodiacetic acid (IV; X = OH). (1) Ligand alone in 0·1M-potassium nitrate; (2) Ba^{2+}, 1 : 1; (3) Sr^{2+}, 1 : 1; (4) Tl^{+}, 1 : 1; (5) Ca^{2+}, 1 : 1; (6) Mg^{2+}, 1 : 1.

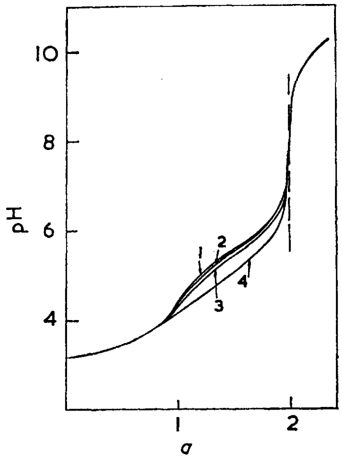


FIG. 2. Titration curves for *o*-methoxyphenyliminodiacetic acid (IV; X = OMe). (1) Ligand alone in 0·1M-potassium nitrate; (2) Sr^{2+} and Ba^{2+}, 1 : 1; (3) Ca^{2+} and Ag^{+}, 1 : 1; (4) Tl^{+}, 10 : 1.

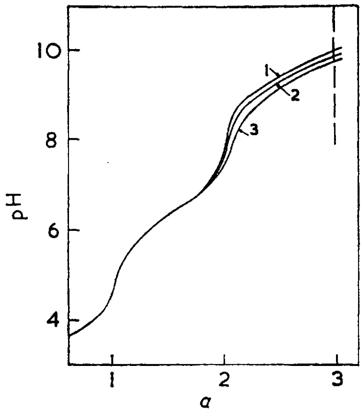


FIG. 3. Titration curves for *o*-mercaptophenyliminodiacetic acid (VII). (1) Ligand alone in 0·1M-potassium nitrate; (2) Ca^{2+} and Sr^{2+}, 1 : 1; (3) Mg^{2+}, 10 : 1.

The values reported for pK_3 for uramildiacetic acid (I), for *o*-carboxyphenyliminodiacetic acid (III) and for 2-carboxyethyliminodiacetic acid correspond to the removal of a proton from ammonium nitrogen. For the ligands (IV; X = OH), (VI), and (VII) the proton is removed from an *ortho*-substituent and the values reflect the increase in acidity of phenols relative to alcohols in consequence of their aromatic character. Values of pK_3 for the purely aliphatic 2-hydroxyethyliminodiacetic acid and for 2-hydroxycyclohexyliminodiacetic acid (II) are too high to be measurable by our procedures.

Figs. 1—3 show typical titration curves for mixtures of the ligands with various metals. Stability constants derived from such titrations are summarised in Table 2, together with results for other relevant ligands. For the alkaline-earth metals the stability order is invariably Ca > Sr > Ba but the position of magnesium is very variable: generally the stability of magnesium complexes lies between those of calcium and strontium, but with *o*-methoxyphenyliminodiacetic acid it is too small to be measured whereas with *o*-hydroxyphenyliminodiacetic acid it is appreciably greater than that for calcium. A comparison of results for the ligands (IV; X = OMe and OH) shows that complexes of the latter are stronger: since the two ligands are of similar basicity (pK_2 = 5·58 and 5·43, respectively) this confirms the view that the *o*-hydroxyl group takes part in the chelation. The extra stability increases with decreasing radius of the alkaline earth metal ion, *e.g.* (in log units), Ba^{2+} 2·2, Sr^{2+} 2·5, Ca^{2+} 3·5, and Mg^{2+} > 6·5, which suggests that the structure is geometrically favourable to the smaller ions. The effect of replacing the oxygen atom of *o*-hydroxyphenyliminodiacetic acid by sulphur, giving ligand (VII), is to decrease markedly its tendency to form complexes with the alkaline-earth cations, and the measurements with all metals were complicated by the marked tendency to give precipitates (which were not further examined). The introduction of a hydroxyl group into cyclohexyliminodiacetic acid lowers the value of pK_2 from 10·81 to 9·57; notwithstanding its

TABLE 2.

Metal stability constants valid for 20° and μ = 0·1M-KNO_3 or -KCl.

Ligand acid	Constant	Ag^+	Tl^+	Li^+	Na^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Ref.
Uramildiacetic (I)	log K_{ML}	Redn.	5·99	4·90	2·72	8·19	8·71	6·93	6·13	1, 2
Cyclohexyl-iminodiacetic (II; X = H)	log K_{ML}	4·94 ±0·02	3·40 ±0·01	1·74 ±0·02	0·90 ±0·03	3·46 ±0·02	3·34 ±0·02	2·55 ±0·01	2·37 ±0·02	*a*
2-Hydroxycyclohexyliminodiacetic (II; X = OH)	log K_{ML}	3·83 ±0·01	3·07 ±0·01	2·19 ±0·01	0·76 ±0·01	4·27 ^{d}	5·19 ^{d}	3·81 ±0·01	3·26 ±0·01	*a*
o-Carboxyphenyliminodiacetic (III)	log K_{ML}	3·54 ±0·01	2·93 ±0·01	2·05 ±0·01	0·89 ±0·01	3·91 ^{b}	5·06 ^{b}	3·91 ^{b}	3·57 ^{b}	*a*
				2·18	0·98					*c*
Phenyliminodiacetic (IV; X = H)	log K_{ML}	~1				1·15	~1·5			*a*
						1·15	1·50	~1	~1	*b*
o-Hydroxyphenyliminodiacetic (IV; X = OH)	log K^{M}_{MHL}	Redn.	2·34 ±0·02			2·67 ±0·02	3·21 ±0·01	2·67 ±0·02	2·50 ±0·04	*a*
	log K_{ML}	Redn.	4·79 ±0·03	2·20 ±0·02	1·0 ±0·1	6·86 ±0·01	6·27 ±0·03	4·65 ±0·01	4·27 ±0·01	*a*
	log K^{H}_{MHL}	Redn.	8·63			6·79	8·02	9·10	9·31	*a*
o-Methoxyphenyliminodiacetic (IV; X = OMe)	log K_{ML}	2·75 ±0·02	2·46 ±0·01	—	—	no ev. cpx.	2·75 ±0·01	2·13 ±0·02	2·08 ±0·02	*a*
2-Methoxyethyl-iminodiacetic	log K_{ML}					3·31	4·53	3·84	3·56	*b*
2-Hydroxyethyl-iminodiacetic	log K_{ML}					3·44	4·63	3·77	3·42	*b*
2-Carboxyethyl-iminodiacetic	log K_{ML}					5·28	5·04	3·87	3·40	*b*
2-Hydroxybenzyliminodiacetic (IV)	log K^{M}_{MHL}						3·0	2·25	1·96	*b*
	log K_{ML}					7·28	6·74	4·99	4·40	*b*
	log K^{M}_{MHL}						8·05	9·05	9·35	*b*
υ-Mercaptophenyliminodiacetic (VII)	log K_{ML}	Ppt.	No ev. cpx.			1·84 ±0·03	2·79 ±0·04	(2·6)	Ppt.	*a*

References: (*a*) Present work; results valid for μ = 0·1M-KNO_3 and 20°; other results valid for μ = 0·1M-KCl. (*b*) *Chem. Soc. Special Publ.* No. 6, Part I, 1957 and refs. therein. (*c*) A. Willi, Diss., Zurich, 1950. (*d*) Ref. 3.

lower basicity, 2-hydroxycyclohexyliminodiacetic acid (II; X = OH) forms stronger complexes with the alkaline-earth cations, thus confirming its behaviour as a tetradentate ligand. The values for silver and thallium suggest that the ligand may not be forming so many chelate rings.

Complexes of 2-hydroxybenzyliminodiacetic acid (VI) are all stronger by up to 0·4 log unit than corresponding complexes of *o*-hydroxyphenyliminodiacetic acid. At first sight this is unexpected since the chelate ring involving the phenolic group has increased from five- to six-membered. However, it must not be overlooked that the basic strength of the ligand as measured by pK_3 has increased still more—from 11·08 to 11·79. This raises the perennial difficulty of comparing two ligands of similar structure and chelating potentialities but of different basicities.

Many authors have noted a linear trend between values of log K_{ML} and log K_{HL} for complexes of a particular metal with a series of similar ligands.[9,11] Irving and (Mrs.) Rossotti have discussed the conditions under which a relationship of the form log $K_{ML} = a \,.\, pK_{HL} + b$ would be predictable on thermodynamic grounds.[10] Essentially the conditions are that the ligands should be as nearly identical as possible and that the bonds to the metal M should be identical in number and of the same nature. The first condition can only be met, even among compounds of the general composition $X{\cdot}N(CH_2{\cdot}CO_2H)_2$, by a careful choice of the components represented by X; the second is largely met by restricting comparisons to ions that do not favour π-bonding and to donor atoms of the first horizontal group in the Periodic Table that cannot act as π-acceptors.

To test whether there really is a linear relation of the form $y = a + bx$ between values of log K_{SrL} and pK_{HL} for a number of complexes of strontium with ligands of the type $X{\cdot}N(CH_2{\cdot}CO_2H)_2$, which can act as tetradentate ligands by virtue of a suitably situated oxygen atom in the group X, we have calculated the correlation coefficient defined by

$$r = \Sigma(x - \bar{x})(y - \bar{y})/\{\Sigma(x - \bar{x})^2\Sigma(y - \bar{y})^2\}^{\frac{1}{2}},$$

where $\bar{x}$ and $\bar{y}$ are the mean values of x and y. This has the characteristic that $r = +1$ if the data can be represented exactly by a straight line; if, on the other hand, $r = 0$ there is no relation between the variables. For the ten strontium complexes we find $r = 0{\cdot}983$. The calculated value of r for $10 - 2 = 8$ degrees of freedom is 0·872 at the 99·9% level of significance, implying that there is a still higher probability of a linear relation which, in the present case can be represented by the equation

$$\log K_{SrL} = 0{\cdot}44 pK_{HL} - 0{\cdot}25.$$

Fig. 4 shows the plot of the experimental values against a line drawn to this specification, together with the best straight lines calculated by a least-squares treatment for complexes of the same ligands with magnesium, calcium, barium, and zinc. The high values of the respective correlation coefficients are summarised in Table 3, together with the values of the parameters *a* and *b* for the best straight lines. Table 3 also contains values for *a**, the slopes of corresponding plots for three ligands only of the type $Y{\cdot}C_2H_4{\cdot}N(CH_2{\cdot}CO_2H)_2$ where Y = SO_3^- (Sim β), CO_2H (Cim β), and $PO(OH)_2^-$ (Pim β) taken from Fig. 1 of a publication by Schwarzenbach, Ackermann, and Ruckstuhl.[11] In this paper it is stated that one of the co-authors (H. A.) had noted that the slopes, *a**, " were proportional to the ionisation potential of the four metals." In Fig. 5 we show that this generalisation holds for all five metals and that it holds even better for the more extensive results now considered. An equally good relation holds with the first or with the second ionisation potential as with the sum of the first and second ionisation potentials used in Fig. 5: this follows from the almost linear relation between these ionisation potentials for zinc and all

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[9] Bjerrum, *Chem. Rev.*, 1950, **46**, 381.

[10] Irving and (Mrs.) Rossotti, *Acta Chem. Scand.*, 1956, **10**, 72.

[11] Schwarzenbach, Ackermann, and Ruckstuhl, *Helv. Chim. Acta*, 1949, **32**, 1175.

the alkaline-earth metals. For the alkaline-earth metals there is an excellent correlation with Allred–Rochow electronegativities but, as might be expected, this does not extend to the B sub-group metal zinc.

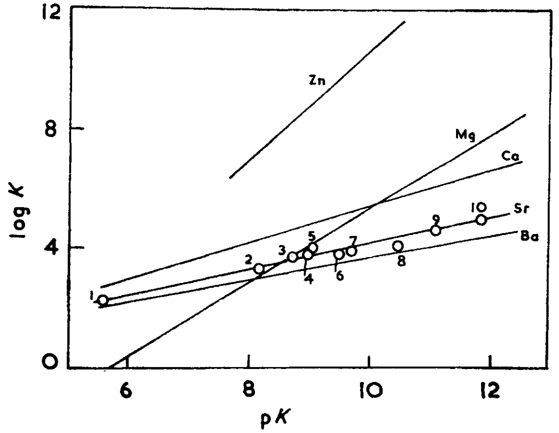

FIG. 4. The linear relation, log K_{ML} = a . pK_{HL} + b, between the stability constants of metal complexes, ML, of derivatives of iminodiacetic acid of the type $R{\cdot}N(CH_2{\cdot}CO_2H)_2$ and the dissociation constants, pK, of the acids HL. The best straight lines for Zn, Mg, Ca, Sr, and Ba have been plotted with the parameters a and b given in Table 3. The experimental points for Sr^{2+} refer to: (1) R = *o*-methoxyphenyl; (2) 2-sulphoethyl (Sim β); [11] 2-hydroxyethyl; (4) 2-methoxyethyl; (5) tetrahydropyran-2-ylmethyliminodiacetic acid; (6) 2-hydroxycyclohexyl (II; X = OH); (7) carboxyethyl (Cim β); [11] (8) 2-phosphoethyl (Pim β); [11] (9) *o*-hydroxyphenyl (IV; X = OH); (10) 2-hydroxybenzyl (VI).

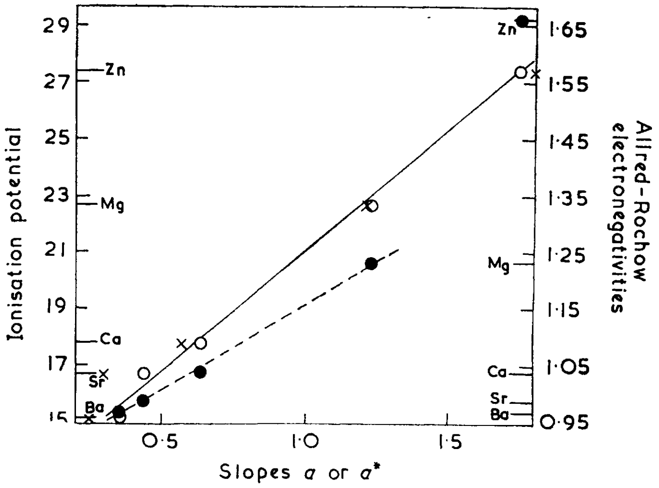

FIG. 5. The relation between the slopes, a^*, of the linear plots in Fig. 4 and ionisation potentials (○) and Allred–Rochow electronegativities (●). Corresponding data for slopes, a^*, calculated for the reagents Sim β, Cim β, and Pim β (×) are from ref. 11.

The second column of Table 3 gives the correlation coefficient, r. The third and fourth give values of the slopes and intercepts of the straight lines shown in Fig. 4. The column headed a^* gives the slopes of the lines plotted in Fig. 1 of ref. 10. The column headed

$\sigma_r t$ gives the residual variance about the regression line for 90% confidence limits and the appropriate number of degrees of freedom. The last three columns give the ionic radius, the Allred–Rochow electronegativities, and the sum of the first and second ionisation potential in electron-volts. Several tetradentate ligands were not used in calculating the parameters (Table 3) for the graphs in Fig. 4: (*a*) Uramildiacetic acid (I) certainly forms abnormally stable complexes and it cannot be established *a priori* whether it is acting as a purely tetradentate ligand;[1,2] (*b*) ligands with $X = CH_2{\cdot}CO_2H$ (nitrilotriacetic acid) and $X = CH_2{\cdot}PO(OH)_2$ are not geometrically comparable with the others; (*c*) the aromatic ligands with $X = o\text{-}C_6H_4{\cdot}CO_2H$ and $X = o\text{-}C_6H_4{\cdot}SO_3H$ form complexes of higher stability than the average. Possible reasons for this have been discussed by Martell and Calvin.[12] It remains to show whether these omissions were justified statistically.

TABLE 3.

Relations between the proton- and metal-ligand stability constants of some tetradentate ligands of the type $X{\cdot}N(CH_2{\cdot}CO_2H)_2$ where X contains an oxygen atom.

Ion	*r*	*a*	*b*	*a* *	$\sigma_r t$	Ionic radius	Electro-negativity	Ionisation potential †
Mg	0·980	1·23	−7·05	1·21	±0·84	0·65	1·23	22·67
Ca	0·989	0·64	−1·00	0·57	±0·35	0·99	1·04	17·98
Sr	0·983	0·44	−0·25	0·30	±0·28	1·13	0·99	16·73
Ba	0·953	0·36	+0·12	0·27	±0·38	1·35	0·97	15·23
Zn	0·979	1·75	−7·10	1·8	±0·60	0·74	1·66	27·36

* See Allred and Rochow, *J. Inorg. Nuclear Chem.*, 1958, **5**, 264. † See W. M. Latimer, "Oxidation States of the Elements and their Potentials in Aqueous Solution," Prentice-Hall Inc., New Jersey, 2nd edn., 1952.

TABLE 4.

Ligand acid	log K_{ML}	Mg	Ca	Sr	Ba	Zn
Uramildiacetic, pK_3 = 9·63	exp.	8·19	8·31	6·93	6·73	—
	calc.	4·80	5·16	3·99	3·59	9·75
	Δ	+3·39	+3·15	+2·94	+3·14	—
o-Carboxyphenyliminodiacetic, pK_3 = 7·75	exp.	3·91	5·06	3·91	3·57	—
	calc.	2·48	3·96	3·16	2·91	6·46
	Δ	+1·43	+1·10	+0·75	+0·66	—
o-Sulphophenyliminodiacetic, pK_3 = 6·29	exp.	2·68	4·57	3·50	3·48	—
	calc.	0·68	3·03	2·52	2·38	3·91
	Δ	+2·00	+1·54	+0·98	+1·10	—
Ethylenediamine-*NN*-diacetic, pK_2 = 11·05	exp.	4·53	4·63	3·55	3·19	11·93
	calc.	6·54	6·07	4·61	4·04	12·24
	Δ	−2·01	−1·44	−1·06	−0·85	(−0·31)
Methylthioethyliminodiacetic, pK_2 = 8·91	exp.	3·02	3·34	2·71	2·62	8·28
	calc.	3·91	4·70	2·67	3·33	8·49
	Δ	−0·89	−1·36	−0·96	−0·71	(−0·21)
Mercaptoethyliminodiacetic, pK_3 = 10·79	exp.	4·32	4·88	3·62	3·55	15·92
	calc.	6·22	5·91	4·50	4·00	11·78
	Δ	−1·90	−1·03	−0·88	−0·45	+4·14

For any other tetradentate ligand that behaves normally, *i.e.*, that conforms to the pattern set by the ten typical ligands used in calculating the parameters of Table 3, there will be a 90% chance that the difference between the experimental and calculated values of log K_{ML} will lie within the range $\pm\sigma_r t$. Any values substantially outside these limits must indicate some exceptional behaviour. In Table 4 we summarise the results of calculations on these lines where values along the rows labelled Δ represent log K_{ML} (calc.) — log K_{ML} (exp.).

All complexes of uramildiacetic acid are seen to be far more stable than calculated on

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[12] Martell and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall Inc., New York, 1952, p. 156.

the basis of their being formed by a tetradentate ligand analogous to, *e.g.*, 2-hydroxycyclohexyliminodiacetic acid, when due allowance is made for the differences in basicity by the method now proposed. Equally the two aromatic ligands produce complexes of exceptional stability.[11] It is noteworthy that the extra stabilisation is greatest for the magnesium complex in each case and then decreases with ionic radius, Mg > Ca > Sr ~ Ba.

When the chelate ring additional to those formed by the tridentate grouping $N(CH_2 \cdot CO_2H)_2$ includes a donor nitrogen or sulphur atom in place of oxygen the complexes with the alkaline-earth metals are less stable. With NH_2 and S^- as donors the destabilisation increases with ionic radius to a maximum with magnesium. With ethylenediamine-*NN*-diacetic acid and methylthioethyliminodiacetic acid the values of Δ for zinc lie well within the calculated range of $\sigma_r t = \pm 0{\cdot}60$, indicating that the chelate ring completed through nitrogen is here comparable in strength with that through oxygen. With mercaptoethyliminodiacetic acid the position is unambiguous, showing the tendency of ionised sulphur to form a strong bond to zinc. It must be emphasised that the above arguments involve the assumption that the values of p*K* used in constructing Fig. 3 always refer to combination between protons and ligands of the same structure as is encountered in the formation of the metal complexes ML. Schwarzenbach *et al.*[13] have considered the co-ordination tendencies of *N*-substituted iminodiacetic acids from a somewhat different viewpoint but there are no substantial differences between their conclusions and ours.

We are grateful to Dr. J. K. Aiken of Messrs. Geigy Co. for a gift of *o*-hydroxyphenyliminodiacetic acid. One of us (J. J. R. F. da S., present address: Department of Chemistry, Instituto Superior Tecnico, Lisbon) acknowledges generous financial assistance from the Instituto de Alta Cultura, Portugal.

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[*Received, November* 19*th*, **1962**.]

[13] Schwarzenbach, Anderegg, Schneider, and Senn, *Helv. Chim. Acta*, 1955, **38**, 1147.