70. *The Stabilities of Complexes of Uramildiacetic Acid and Its Homologues.*

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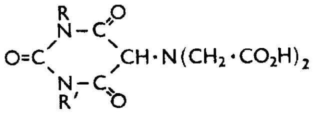
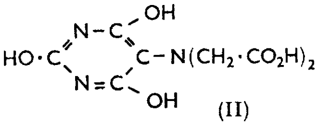
The synthesis of 1-methyl- and 1,3-dimethyl-uramil-*NN*-diacetic acid is described. The acid dissociation constants for these reagents and values for the stability constants of metal complexes with Li^+, Na^+, K^+, Tl^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} valid for 20° and $\mu = 0{\cdot}1$M (tetramethylammonium nitrate) are reported. The results are discussed in relation to values for uramildiacetic acid itself and for other polyamino-carboxylic acids.

In a previous paper[1] we have shown that uramildiacetic acid (H_3Ur) (I; R = R′ = H) forms quite strong complexes with thallium(I) and lithium, and that complexes of appreciable strength result even with sodium and potassium, despite unfavourable (negative) entropies of reaction. The facts remained unexplained that these complexes and that formed by beryllium(II) are more stable than those of the same cations with ethylenediaminetetra-acetic acid (EDTA), whereas the position is reversed for the alkaline earths and other bivalent ions. In particular, we could not be sure to what extent the unique behaviour of uramildiacetic acid might be connected with the possibility of its tautomerising to give an effectively aromatic ring (as II and anions derived from it). To investigate this point and to extend our knowledge of complexes of univalent ions, we have prepared two homologues of uramildiacetic acid in which such tautomerism is progressively restricted.

(I: R = R′ = H)
(Ia: R = Me, R′ = H)
(Ib: R = R′ = Me)





(II)

1-Methyluramildiacetic acid (Ia) and 1,3-dimethyluramildiacetic acid (Ib) were synthesised by condensation, under alkaline conditions, of chloroacetic acid and the substituted uramils resulting from reduction of the nitrosobarbiturates formed from diethyl malonate and *N*-methyl- and *NN*′-dimethyl-urea, respectively.

In view of the tendency of the alkali metals to form strong complexes with uramildiacetic acid,[1] measurements with these ions could not be carried out by using potassium hydroxide as titrant or potassium nitrate to provide the constant salt background. Acid dissociation constants of the complexones and the stability constants of their complexes with alkali metals were therefore determined potentiometrically at 20° by using a glass electrode–calomel reference electrode with carbonate-free tetramethylammonium hydroxide as titrant and a salt background of 0·1M-tetramethylammonium nitrate. The experimental procedure and methods of calculation have been previously described.[1,2]

Experimental

1-*Methyluramil*-NN-*diacetic Acid* (Ia).—Sodium 1-methylbarbiturate (8·2 g.), prepared in 60% yield by the condensation of methylurea and diethyl malonate with an ethanolic solution of sodium ethoxide,[3] was dissolved in water (200 ml.) and treated with concentrated sulphuric acid (2·6 ml.). Sodium nitrite (3·8 g.) was then added and the resultant deep purple solution of 1-methylvioluric acid was heated to the b. p. and reduced[4] by addition of sodium dithionite

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[1] Irving and da Silva, *J.*, 1963, 448.
[2] Irving and Shelton, *J.*, 1958, 3540.
[3] Stein, Gregor, and Spoerri, *J. Amer. Chem. Soc.*, 1956, **78**, 6185.
[4] Davidson and Epstein, *J. Org. Chem.*, 1936, **1**, 305.

(30 g.) in water (150 ml.) and aqueous ammonia (50 ml.; *d* 0·880); immediate decolorisation ensued. After being boiled for 1 hr. the solution was cooled to 0°; 1-methyluramil (50%, 4 g.), m. p. 260° (decomp.) (lit.,[3] 253—256°, 272° with decomp.), separated.

Monochloroacetic acid (5 g., 0·05 mole), previously neutralised with 5M-sodium hydroxide, was added to 1-methyluramil (3·1 g., 0·02 mole) dissolved in 5M-sodium hydroxide (4 ml., 0·02 mole), and to the boiling, pale red mixture 5M-sodium hydroxide was added dropwise at such a rate that the pH remained between 8 and 10 (30 min.). The reaction was rapid during the first 15 min.; when all the base had been added the resulting yellow solution showed no change in alkalinity after being boiled for a further 10 min. The mixture was cooled and acidified with concentrated hydrochloric acid (6 ml.). The white solid which separated overnight was collected, dissolved in water, and passed through a column of Zeo-Karb 225 cation-exchange resin in the hydrogen-ion form. The eluant was concentrated; 1-*methyluramil*-NN-*diacetic acid* separated as a white powder that had m. p. 203° (decomp.) after recrystallisation from water (yield 50%, 2·7 g.) [Found: C, 39·7; H, 4·3; N, 15·3%; *M* (by titration as a tribasic acid), 273. $C_9H_{11}O_7N_3$ requires C, 39·6; H, 4·0; N, 15·4%; *M*, 273·2]. The synthesis of a monohydrate of this acid has been previously reported.[3]

1,3-*Dimethyluramil*-NN-*diacetic Acid*.—1,3-Dimethylbarbituric acid (7·8 g.; m. p. 124°), prepared quantitatively by condensation of diethyl malonate (8 g.) and dimethylurea (4·4 g.) in ethanolic sodium ethoxide, was heated to the b. p. with a solution of sodium nitrite (3·8 g.) in water (350 ml.). The deep purple solution of 1,3-dimethylvioluric acid was then reduced by sodium dithionite (30 g.) in water (150 ml.), followed by aqueous ammonia (50 ml.; *d* 0·880).

TABLE 1.

Titrations with uramil-*NN*-diacetic acid. Metal stability constants for bivalent ions.

(i) $C_L = 9{\cdot}838 \times 10^{-4}$M; $C_B = 9{\cdot}524 \times 10^{-2}$M.

	pH				
a	Be^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
0	2·730				
0·484	2·815				
0·968	2·920				
1·065	2·943				
1·162	2·969				
1·259	2·993				
1·356	3·022				
1·452	3·051				
1·549	3·085				
1·646	3·120				
1·743	3·160				
1·840	3·200	3·729	3·711		
1·936	3·241	3·842	3·829	4·310	4·510
2·033	3·291	3·979	3·959	4·742	5·370
2·130	3·349	4·127	4·100	5·111	5·871
2·227	3·408	4·285	4·261	5·400	6·187
2·324	3·479	4·458	4·440	5·647	6·441
2·420	3·563	4·645	4·630	5·880	6·680
2·517	3·662	4·852	4·850	6·122	6·919
2·614	3·799	5·098	5·099	6·373	7·170
2·711	3·970	5·381	5·401	6·670	7·457
2·808	4·234	5·750	5·801	7·041	7·810
2·905	4·744	6·289	6·400	7·589	8·280
3·002	6·146	7·800	7·880	8·600	8·940
C_M	0·010	0·0108	0·010	0·010	0·010

(ii) $C_L = 1{\cdot}0 \times 10^{-3}$M; $C_B = 0{\cdot}100$M; $C_M = 0{\cdot}005$.

	pH			
a	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
2·500	7·591	6·448	7·774	8·106
2·600	8·661	7·310	8·402	8·671
2·650	8·875	—	—	8·865
2·700	9·035	7·795	8·788	9·020
2·750	9·165	—	—	9·175

	pH			
a	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
2·800	9·302	8·290	9·090	9·295
2·850	9·410	—	—	9·415
2·900	9·540	8·875	9·380	9·540
3·000	9·750	9·395	9·658	9·770

TABLE 2.

Titrations with 1-methyluramildiacetic acid (Ia).

(a) Acid dissociation constants.

$C_L = 9{\cdot}619 \times 10^{-4}$M; $C_B = 9{\cdot}524 \times 10^{-2}$M.

a	pH	*a*	pH	*a*	pH	*a*	pH	*a*	pH
0·000	2·871	0·990	3·188	1·683	3·719	2·277	9·334	2·673	9·881
0·198	2·920	1·089	3·287	1·881	4·180	2·376	9·511	2·772	9·980
0·396	2·974	1·287	3·348	2·079	8·590	2·475	9·651	2·871	10·071
0·594	3·033	1·485	3·495	2·178	9·080	2·574	9·775	2·970	10·153
0·792	3·105								

(b) Metal stability constants for univalent cations.

$C_L = 9{\cdot}619 \times 10^{-4}$M; $C_B = 9{\cdot}524 \times 10^{-2}$M.

	pH			
a	Tl$^+$ *	Li$^+$ *	Na$^+$	K$^+$
2·079	6·032	6·909	7·870	8·040
2·178	6·508	7·430	8·430	8·696
2·277	6·820	7·741	8·709	8·990
2·375	7·081	8·000	8·909	9·196
2·475	7·330	8·230	9·075	9·360
2·574	7·572	8·465	9·226	9·502
2·673	7·840	8·701	9·364	9·634
2·772	8·142	8·950	9·501	9·760
2·871	8·511	9·202	9·634	9·880
2·970	8·975	9·456	9·769	9·991
3·069	9·450	9·689	9·900	10·050
C_M	0·010	0·010	0·100	1·200

* In 0·1M-tetramethylammonium nitrate.

(c) Metal stability constants for bivalent ions.

(i) $C_L = 9{\cdot}619 \times 10^{-4}$M; $C_B = 9{\cdot}524 \times 10^{-2}$M.

	pH				
a	Be^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
0	2·750				
0·495	2·837				
0·990	2·949				
1·089	2·970				
1·188	2·997				
1·287	3·024				
1·386	3·057				
1·485	3·090				
1·584	3·121				
1·683	3·160				
1·782	3·201	3·710	3·710		
1·881	3·244	3·830	3·834	4·101	
1·980	3·296	3·967	3·981	4·560	4·765
2·079	3·351	4·121	4·150	5·130	5·799
2·178	3·410	4·292	4·330	5·510	6·251
2·277	3·481	4·480	4·521	5·789	6·557
2·376	3·569	4·676	4·721	6·035	6·811
2·475	3·670	4·888	4·941	6·270	7·050
2·574	3·800	5·114	5·180	6·514	7·295
2·673	3·972	5·380	5·460	6·780	7·557
2·772	4·220	5·695	5·799	7·100	7·859
2·871	4·732	6·122	6·250	7·522	8·239
2·970	5·602	6·897	7·065	8·205	8·741
3·069	—	9·225	9·220	9·275	9·324
C_M	0·010	0·0108	0·010	0·010	0·010

(ii) $C_L = 1{\cdot}000 \times 10^{-3}$M; $C_B = 9{\cdot}524 \times 10^{-2}$M; $C_M = 0{\cdot}005$M.

	pH				pH		
a	Ca^{2+}	Sr^{2+}	Ba^{2+}	*a*	Ca^{2+}	Sr^{2+}	Ba^{2+}
2·478	6·291	7·358	7·930	2·761	8·150	9·085	9·267
2·524	6·768	7·775	8·211	2·809	8·387	9·230	9·391
2·571	7·145	8·210	8·501	2·856	8·625	9·361	9·506
2·619	7·440	8·515	8·755	2·904	8·881	9·486	9·610
2·666	7·686	8·740	8·960	2·952	9·131	9·605	9·707
2·714	7·920	8·924	9·130	3·000	9·370	9·717	9·800

TABLE 3.

Titrations with 1,3-dimethyluramildiacetic acid (Ib).

(a) Acid dissociation constants.

$C_L = 1·000 \times 10^{-3}$M; $C_B = 9·524 \times 10^{-2}$M.

a	pH	*a*	pH	*a*	pH	*a*	pH	*a*	pH
0·000	2·871	0·990	3·188	1·683	3·719	2·277	9·334	2·673	9·881
0·198	2·920	1·089	3·287	1·881	4·180	2·376	9·511	2·772	9·980
0·396	2·974	1·287	3·348	2·079	8·590	2·475	9·651	2·871	10·071
0·594	3·033	1·485	3·495	2·178	9·080	2·574	9·775	2·970	10·153
0·792	3·105								

(b) Metal stability constants for univalent ions.

$C_L = 9·619 \times 10^{-4}$M; $C_B = 9·524 \times 10^{-2}$M.

	pH			
a	Tl^+ *	Li^+ *	Na^+	K^+
2·000	5·720	5·815	6·072	6·630
2·095	6·548	7·330	8·401	8·740
2·190	6·937	7·739	8·805	9·140
2·285	7·220	8·029	9·050	9·371
2·380	7·470	8·270	9·231	9·550
2·476	7·711	8·500	9·386	9·690
2·571	7·955	8·725	9·520	9·810
2·666	8·228	8·954	9·642	9·924
2·761	8·538	9·185	9·760	10·025
2·858	8·903	9·411	9·870	10·120
2·952	9·303	9·633	9·979	10·210
3·047	9·655	9·830	10·080	10·290
C_M	0·010	0·010	0·100	1·200

* In 0·1M-tetramethylammonium nitrate.

(c) Metal stability constants for bivalent ions.

(i) $C_L = 9·619 \times 10^{-4}$M; $C_B = 9·524 \times 10^{-2}$M.

	pH				
a	Be^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
0	2·750				
0·476	2·835				
0·952	2·939				
1·047	2·962				
1·142	2·990				
1·237	3·015				
1·332	3·044				
1·428	3·074	3·420	3·430		
1·523	3·109	3·497	3·503		
1·618	3·131	3·581	3·598		
1·713	3·181	3·685	3·710		
1·808	3·220	3·805	3·848	3·830	3·839
1·904	3·265	3·950	4·019	4·150	4·189
2·000	3·314	4·118	4·220	4·876	5·420
2·095	3·370	4·300	4·433	5·545	6·291
2·190	3·430	4·495	4·660	5·869	6·671
2·285	3·501	4·692	4·880	6·140	6·952
2·380	3·588	4·900	5·100	6·386	7·202
2·476	3·689	5·121	5·336	6·620	7·440
2·571	3·811	5·360	5·586	6·865	7·685
2·666	3·980	5·635	5·885	7·142	7·956
2·761	4·220	5·984	6·250	7·485	8·274
2·856	4·650	6·452	6·790	7·935	8·647
2·952	5·350	7·370	7·780	8·618	9·088
3·000	—	9·340	9·348	9·340	9·492
C_M	0·010	0·0108	0·010	0·010	0·010

(ii) $C_L = 1·000 \times 10^{-3}$M; $C_B = 9·524 \times 10^{-2}$M; $C_M = 0·005$M.

	pH					pH			
a	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	*a*	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
2·524	6·566	6·921	8·038	8·560	2·809	9·585	8·641	9·420	9·592
2·571	7·800	7·390	8·455	8·825	2·856	9·693	8·845	9·540	9·691
2·619	8·750	7·725	8·725	9·050	2·904	9·789	9·049	9·646	9·780
2·666	9·091	7·989	8·969	9·221	2·952	9·870	9·240	9·743	9·862
2·714	9·300	8·220	9·145	9·357	3·000	9·949	9·420	9·833	9·938
2·761	9·459	8·431	9·291	9·481					

The colourless solution so formed was boiled vigorously for 1 hr. and then chilled to 0°. 1,3-Dimethyluramil separated as almost colourless crystals (7 g., 82%), m. p. 200° (decomp.) [lit.,[4] 200° (decomp.)]. 1,3-Dimethyluramil was condensed with chloroacetic acid under alkaline conditions as described above. When the mixture had been acidified with concentrated hydrochloric acid (7·5 ml.) white crystals separated overnight. These were collected, washed with a little water, and dried. On titration the product behaved as a dibasic acid with a molecular weight of 330 and it was probably the acid sodium salt NaH_2Y,H_2O. After two recrystallisations from 3M-perchloric acid followed by one from de-ionised water the monohydrate of 1,3-dimethyluramil-*NN*-diacetic acid was obtained as colourless needles (4 g., 53%), m. p. 198° (decomp.). The molecular weight by titration as a tribasic acid was 305 (theory 305·2) and the loss of weight on drying *in vacuo* at 100° for 10 hr. was 5·85% (calc. for H_3Y,H_2O, 5·9%). The anhydrous *acid* was analysed (Found: C, 41·6; H, 4·7; N, 14·5%; *M*, 288. $C_{10}H_{13}O_7N_3$ requires C, 41·8; H, 4·5; N, 14·6%; *M*, 287·2). The anhydrous acid was very hygroscopic and this may account for the slightly high value for hydrogen and the low values for carbon and nitrogen. The monohydrate was also obtained from the sodium salt by passing its solution through a cation-exchange resin in the hydrogen-ion form; since this salt is not very soluble in water, recrystallisation from perchloric acid proved preferable.

Titrations with Uramildiacetic Acids.—The pH corresponding to various degrees of neutralisation, *a*, was recorded when the ligand acid (concn. C_L) was titrated at 20° by tetramethylammonium hydroxide (concentration C_M). The ionic strength was maintained at 0·1M by the addition of tetramethylammonium nitrate or potassium nitrate (bivalent metals).

The results are shown in Tables 1—3, as are those of titrations in presence of metals.

DISCUSSION

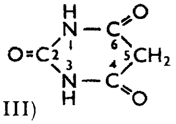
The stoicheiometric acid dissociation constants for uramildiacetic acid (I) and its methyl homologues (Ia and b) are summarised in Table 4.

TABLE 4.

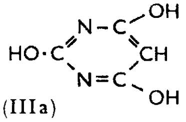
Acid dissociation constants of uramildiacetic acid and its homologues at 20° and μ = 0·1M.

Acid	pK_1	pK_2	pK_3
Uramildiacetic (I)	1·7 ± 0·3	2·67 ± 0·02	9·63 ± 0·03
1-Methyluramildiacetic (Ia)	1·85 ± 0·05	2·67 ± 0·02	9·81 ± 0·01
1,3-Dimethyluramildiacetic (Ib)	2·05 ± 0·05	2·67 ± 0·02	10·12 ± 0·01

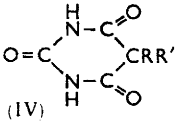
The values of pK_1 and pK_2 correspond to the ionisation of protons from carboxylic acids, while that of pK_3 must be attributed to the ionisation of an ammonium ion. The constancy of pK_2 for different complexones is interesting, while the regular gradation for values of pK_1 and pK_3 is certainly due to the inductive effect of a suitably placed methyl group. Noller pointed out [5] that barbituric acid (III) could be stabilised in its enolic form (IIIa) by resonance of the pyrimidine ring; the electron-attracting properties of the two nitrogen atoms greatly increase the acidity of the intermediate >C(OH) group, so that barbituric acid (p*K* 4·0) is even stronger than acetic acid (p*K* 4·7). He further noted that the introduction of two 5-alkyl substituents (as IV) would prevent the ring from becoming fully aromatic, with a consequent reduction of acidity (cf. Table 5).



(III)



(IIIa)



(IV)

This explanation cannot be regarded as satisfactory since the dissociation constants of 1-methyl- and 1,3-dimethyl-barbituric acid differ only slightly from that of barbituric acid, although resonance due to an aromatic pyrimidine ring is clearly impossible.

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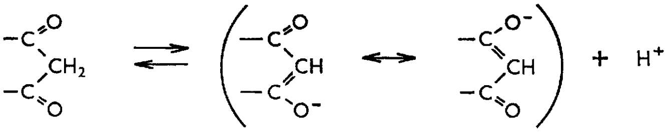
[5] Noller, " Chemistry of Organic Compounds," Sanders & Co., London, 1955, p. 603.

TABLE 5.

Dissociation constants of barbituric acid and its homologues.[6] Data for 25° and $\mu = 0$.

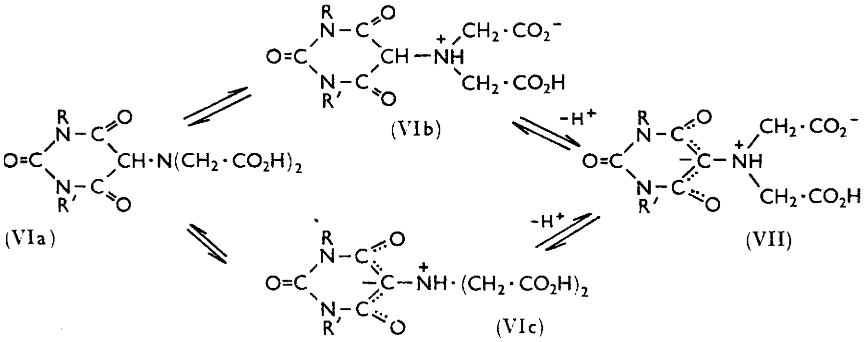
Substituent	p*K*	Substituent	p*K*
None (as III)	4·035	5,5-Diethyl	7·97
1-Methyl	4·348	5-Methyl-5-phenyl	7·73
1,3-Dimethyl	4·679	5-Ethyl-5-phenyl	7·45
5-Isopropyl	4·94		

It seems possible rather that the higher acidity of barbituric acid is related to the possibility of resonance in the base conjugate to the 1,3-diketone moiety, *viz.*:



which would not be affected greatly by a single substituent in position 1, 3, or 5 or by alkyl groups in both positions 1 and 3. The proton that ionises in the more weakly acidic 5,5-dialkylbarbituric acids cannot originate from the 5-position and must come from one or other of the imino-groups. Indeed it is a little surprising that this ionisation is not also observed in barbituric acid as a second stage at high alkalinities.

Similar considerations apply to the ionisation of uramil-*NN*-diacetic acid and its homologues. If the presence of the acidifying iminodiacetic acid group increases the tendency of a proton to dissociate from the 5-position to a value comparable with that for a carboxylic acid the mechanism of the first stage of ionisation may well be composite. The structure of the parent acid could be formulated as several alternatives (VIa, b, or c) (where the broken lines indicate partial double-bond character in a resonance hybrid), and the loss of the first proton would give (VII).



The next stages of ionisation are certainly the loss of a proton from the remaining carboxyl group and the ionisation of the resulting ammonium ion. Although this seems unambiguous it is difficult to see why pK_3 is so high when the value for phenyliminodiacetic acid is only 4·96, unless this is due solely to the formal negative charge on the adjacent aromatic part of the ring.

Titration curves for 1,3-dimethyluramil-*NN*-diacetic acid (Ib) in the presence of various cations are shown in Fig. 1, as examples. They show that metal complexes of appreciable stability are formed even with potassium ions, and that the order of increasing stability for univalent ions is $K^+ < Na^+ < Li^+ < Tl^+$. For bivalent ions the order is $Ba^{2+} < Sr^{2+} < Ca^{2+}$, $Mg^{2+} < Be^{2+}$ for 1 : 1 complexes. Increasing methyl substitution

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[6] Kortüm, Vogel, and Andrussow, " Dissociation Constants of Organic Acids in Aqueous Solutions," Butterworths Scientific Publns., London, 1961.

has little influence on the stability of lithium complexes, but produces a slight decrease in the stabilities of complexes with other univalent ions and with calcium, strontium, and barium: with beryllium and magnesium the opposite is observed and the stability order $Mg^{2+} < Ca^{2+}$ for uramildiacetic acid becomes reversed for its 1,3-dimethyl homologue. The stabilities of the 1 : 2 complexes of the alkaline earths increase in the order $Ba^{2+} < Sr^{2+} < Mg^{2+} < Ca^{2+}$ and are little affected by alkyl substitution.

Table 6 summarises the calculated values for stability constants and includes data for nitrilotriacetic acid (NITA) and ethylenediaminetetra-acetic acid (EDTA), together with data for uramildiacetic acid (I) from ref. 1 and new results for its complexes with alkaline-earth metals.

TABLE 6.

Values of log K for the species ML, MHL, and ML_2 for complexes of metals with uramildiacetic acid (H_3Ur) (I) and its homologues (Ia and b) and for NITA and EDTA. Results valid for 20° and $\mu = 0{\cdot}1$M.

Ion	Species	(I)	(Ia)	(Ib)	NITA	EDTA
Li^+	ML	4·90 ± 0·02 *	4·86 ± 0·01	4·91 ± 0·01	2·51 ± 0·01 ‡	2·79 †
Na^+	ML	2·72 ± 0·01 *	2·67 ± 0·01	2·53 ± 0·01	1·22 ± 0·02 ‡	1·66 †
K^+	ML	1·23 ± 0·03 *	1·11 ± 0·02	0·94 ± 0·01	—	—
Tl^+	ML	5·99 ± 0·02 *	5·79 ± 0·01	5·73 ± 0·01	4·74 ± 0·01 ‡	6·55 ± 0·01 ‡
	MHL	—	—	—	—	2·06 ± 0·02 ‡
Be^{2+}	ML	10·36 ± 0·02	10·42 ± 0·02	10·54 ± 0·02	7·11 §	9·27 §
	MHL	3·44	3·32	3·54		
Mg^{2+}	ML	8·19 ± 0·02	8·23 ± 0·01	8·29 ± 0·01	5·41 †	8·69 †
	ML_2	3·62 ± 0·05	3·72 ± 0·06	3·78 ± 0·02		
Ca^{2+}	ML	8·31 ± 0·01	8·22 ± 0·01	8·13 ± 0·01	6·41 †	10·70 †
	ML_2	5·27 ± 0·02	5·38 ± 0·01	5·40 ± 0·02		
Sr^{2+}	ML	6·93 ± 0·02	6·83 ± 0·02	6·82 ± 0·02	4·98 †	8·63 †
	ML_2	4·06 ± 0·10	4·19 ± 0·02	4·27 ± 0·10		
Ba^{2+}	ML	6·13 ± 0·02	6·06 ± 0·01	6·00 ± 0·01	4·82 †	7·76 †
	ML_2	3·68 ± 0·10	3·85 ± 0·05	3·88 ± 0·10		

* Ref. (1). † Data from ref. 7, valid for $\mu = 0{\cdot}1$M-KCl. ‡ Irving and da Silva, unpublished observations. § Starý, personal communication; to be published in *Analyt. Chim. Acta.* All other results from the present work. Values for Li^+, Na^+, and Tl^+, $\mu = 0{\cdot}1$M-tetramethylammonium nitrate; all other data valid for $\mu = 0{\cdot}1$M-KNO_3. Values of Na^+ determined with $C_M/C_L = 10$; values for K^+ with $C_M/C_L = 100$.

The complexes of univalent ions with uramildiacetic acid have been shown[1] to be stabilised by their favourable enthalpy of formation which dominates the unfavourable negative entropies of reaction (the entropies decrease from approximately zero with Li^+ to —25 and —35 cal. per degree for Tl^+ and K^+). In view of the relatively small changes in stabilities seen to be produced by methyl substitution in uramildiacetic acid it seems likely that the same considerations apply to these compounds.

From an examination of Fig. 2 it will be seen that, except with beryllium, uramildiacetic acid forms weaker complexes than does ethylenediaminetetra-acetic acid (EDTA) with bivalent metals. This is not surprising since EDTA is potentially sexidentate, whereas uramildiacetic acid could at most act as quinquedentate ligand if both the 4- and the 6-oxygen atom co-operated with the terdentate grouping, $N(CH_2{\cdot}CO_2H)_2$. However, inspection of scale models shows that this is impossible, for the " plane " of the pyrimidine ring can only be accommodated relative to the grouping $N(CH_2{\cdot}CO_2H)$ in such a way that at most one of the adjacent oxygen atoms can participate in co-ordination. That nitrilotriacetic acid (NITA), $N(CH_2{\cdot}CO_2H)_3$ ($pK_{HL} = 9{\cdot}73$), can form more stable complexes than iminodiacetic acid (IMDA), $HN(CH_2{\cdot}CO_2H)_2$ ($pK_{HL} = 9{\cdot}38$), is expected from the change from potentially terdentate to quadridentate character (Fig. 2), assisted by the slight increase in basic character of the nitrogen atom. What is so surprising is that the anion of uramildiacetic acid (I) ($pK_{HL} = 9{\cdot}63$), though of comparable basicity, should

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[7] Bjerrum *et al.*, " Stability Constants," *Chem. Soc. Spec. Publ.* No. 6, Part I, 1957.

form so much more stable complexes than either (Fig. 2), approaching in this respect EDTA itself. On these grounds alone, at least quadridentate character should be ascribed to uramildiacetic acid.

Since the introduction of methyl groups in positions 1 and 3 has so little effect on the stabilities of any metal complex we can infer that full resonance in the pyrimidine ring system (as II) is not a significant factor. However, if a mesomeric structure (as in VIc or VII) plays an important role such that the atoms C-4, C-5, and C-6 are coplanar and suitably orientated with respect to the terdentate system $N(CH_2{\cdot}CO_2H)_2$, then, as an examination of scale models shows, a sterically favoured conformation results which could form a cage-like structure to accommodate small ions and one which would appear specially to favour a tetrahedral environment. The adjacent negative charge on the mesomeric ion (as in VIc and VII) would favour complex formation by an inductive effect, and possibly by reducing the dielectric constant in the neighbourhood of the metal ion.

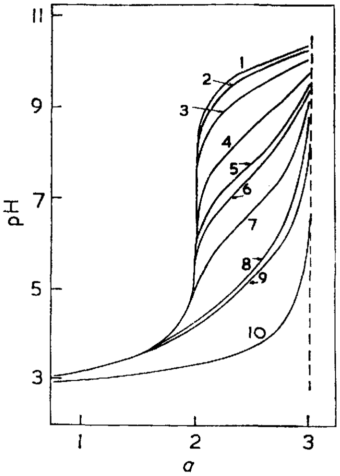

Fig. 1. Titration curves for 1,3-dimethyluramil-*NN*-diacetic acid (10^{-3}M) with tetramethylammonium hydroxide in the absence and in the presence of various cations. Almost identical curves are found for 1-methyluramil-*NN*-diacetic acid.

1, NMe_4NO_3. 2, K^+ (100 : 1). 3, Na^+ (10 : 1). 4, Li^+ (1 : 1). 5, Tl^+. 6, Ba^{2+}. 7, Sr^{2+}. 8, Ca^{2+}. 9, Mg^{2+}. 10, Be^{2+}.

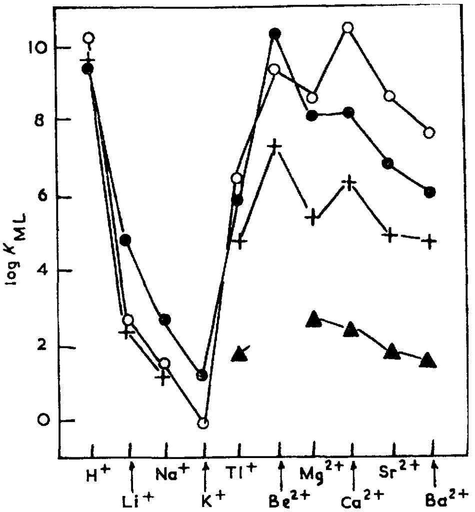

Fig. 2. Values of log K_{ML} for the stabilities of 1 : 1 complexes at 20° and μ = 0·1M. Data for uramildiacetic acid (filled circles) from present paper and ref. 1. Data for ethylenediaminetetra-acetic acid (EDTA; open circles), nitrilotriacetic acid (NITA; crosses), and iminodiacetic acid (triangles) from ref. 7.

The fact that uramildiacetic acid forms stronger complexes than does EDTA with univalent ions is probably due, not to some abnormality in bonding by the former, but to the inability of the latter to act as a sexidentate ligand. Owing to the small affinity of alkali-metal ions for nitrogen ligands it is likely that only the more strongly basic of the two nitrogen atoms is effectively co-ordinated and that the ligand is then no longer able to exhibit its full potentialities, behaving more like nitrilotriacetic acid.

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[*Received, July* 30*th*, 1962.]