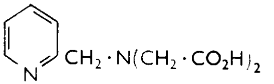
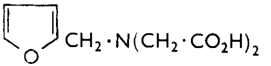
211. *Complexones containing Heterocyclic Donor Oxygen Atoms.*

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

N-2-Furfuryliminodiacetic acid and *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid have been prepared, and the stabilities of their proton and metal complexes measured at 20° in a medium of constant ionic strength $\mu = 0{\cdot}1\text{M}$-KNO_3. The former complexone forms weaker, and the latter stronger, complexes than the analogous *N*-(methoxyethyl)iminodiacetic acid. The order of stability for 1 : 1 complexes is $Na^+ < Li^+ < Ba^{2+} < Mg^{2+} < Sr^{2+} < Tl^+ < Ag^+ < Ca^{2+} < Mn^{2+} < Fe^{2+} < Cd^{2+} < Co^{2+} < Zn^{2+} < Pb^{2+}$. The stabilities of complexes of *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid are compared with those of *N*-(2-pyridylmethyl)iminodiacetic acid, and reasons are discussed for the stronger bonding by the latter ligand.

In a previous paper[1] we noted some unusual properties of a polyaminocarboxylic acid (" complexone "), *viz.*, *N*-(2-pyridylmethyl)iminodiacetic acid (I) in which a donor nitrogen atom formed part of a heterocyclic ring. In the present paper we describe the preparation and reactions of two new complexones in which donor oxygen atoms are incorporated in a heterocyclic ring in either an aromatic (II) or aliphatic (III) environment. The new ligands, *N*-(2-furfurylimino)diacetic acid (II) and *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid were synthesised from the corresponding amines by condensation with chloroacetic acid under alkaline conditions. Their acid dissociation constants and the stabilities of their metal complexes were measured by potentiometric titrations and computed as described previously.[1,2]


(I)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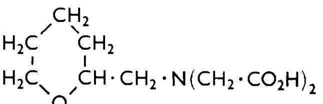
(III)

$$H_3C{\cdot}O{\cdot}[CH_2]_2{\cdot}N(CH_2{\cdot}CO_2H)_2 \qquad (IV)$$

EXPERIMENTAL

Preparation of N-*Furfuryliminodiacetic Acid.*—The hydrochloride of furfurylamine was obtained from a commercial sample of the amine and recrystallised twice from ethanol as light yellow platelets, m. p. 143—144°. Furfurylamine hydrochloride (6·4 g., 0·05 mol.) was neutralised with 5M-sodium hydroxide and condensed with chloroacetic acid (9·5 g., 0·1 mol.) under alkaline conditions as described for *N*-(2-pyridylmethyl)iminodiacetic acid.[1] The mixture was cooled to room temperature, acidified with concentrated hydrochloric acid (15 ml.), and set aside. The crude acid separated very slowly, contaminated by much inorganic material. An aqueous solution was passed slowly through a column of ZeoKarb 225 in the hydrogen-ion form, and the eluant concentrated to a viscous liquid which was taken up in a large volume of acetone in which the complexone is sparingly soluble (~0·3 g./l.). On spontaneous evaporation the solution deposited N-*furfuryliminodiacetic acid* as a white powder, m. p. 165—167°, which was further recrystallised from acetone [Found: C, 50·7; H, 5·2; N, 6·3%; *M* (by titration), 214. $C_9H_{11}NO_5$ requires C, 50·7; H, 5·2; N, 6·6%; *M*, 213].

Preparation of N-(*Tetrahydropyran-2-ylmethyl*)*iminodiacetic Acid.*—2-Aminomethyltetrahydropyran (11·5 g., 0·1 mol.) in water (25 ml.) was condensed with chloroacetic acid (18·9 g., 0·2 mol.) in alkaline conditions as previously described.[1] The mixture was cooled and made strongly acid, but no precipitation occurred. The solution was concentrated to a thick syrup during which process several batches of precipitated sodium chloride were removed. An excess

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[1] Irving and da Silva, *J.*, 1963, 945.
[2] Irving and da Silva, *J.*, 1963, 448.

of barium carbonate was then added; the barium salt of the desired complexone slowly separated. This was collected, washed with water, alcohol, and acetone, and digested with the amount of sulphuric acid equivalent to the barium content (as determined on a small sample). The solution was heated to coagulate the barium sulphate which was collected after 24 hr. A white powder obtained by concentrating the filtrate was dissolved in a little water and passed through a cation-exchange resin in the hydrogen-ion form. The eluate was taken to dryness on a water-bath, and the product washed with distilled water. On titration it behaved as a tribasic acid and was found to be the *hydrochloride* of the desired complexone. It was too soluble in water and ethanol to be recrystallised successfully from these solvents [Found: C, 41·8; H, 7·0; N, 4·8%; *M* (by titration), 287. $C_{10}H_{17}NO_5,HCl,H_2O$ requires C, 42·0; H, 7·0; N, 4·9%; *M*, 285·7]. Attempts to prepare the free *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid by removing the hydrochloric acid were initially unsuccessful and only a viscous product was obtained. If, however, a solution was exactly neutralised with sodium hydroxide and taken to dryness, absolute ethanol extracted the desired pure ligand *acid* in 97% yield [Found: *M* (by titration), 231. $C_{10}H_{17}NO_5$ requires *M*, 231·2].

Acid dissociation constants of *N*-furfuryliminodiacetic acid.

$C_L = 1\cdot000 \times 10^{-3}$M; $C_B = 9\cdot524 \times 10^{-2}$M-KOH; $\mu = 0\cdot1$M-KNO_3.

a	0·095	0·190	0·285	0·380	0·476	0·571	0·666	0·761	0·856	0·952	1·047
pH	3·165	3·213	3·270	3·334	3·410	3·499	3·611	3·767	4·000	4·539	6·935
a	1·142	1·237	1·332	1·428	1·523	1·618	1·713	1·808	1·904	2·000	
pH	7·589	7·889	8·101	8·281	8·441	8·600	8·770	8·959	9·173	9·444	

Titration of *N*-furfuryliminodiacetic acid with metal ions.

$C_L = 9\cdot048 \times 10^{-4}$M; $C_B = 9\cdot524 \times 10^{-2}$M; $\mu = 0\cdot1$M-KNO_3.

	pH					
a	Ag$^+$	Tl$^+$	Mg^{++}	Ca^{++}	Sr^{++}	Ba^{++}
1·000	5·610	5·790	6·063	5·720	5·906	5·708
1·105	6·560	7·101	7·238	6·860	7·230	7·277
1·210	6·967	7·510	7·631	7·248	7·630	7·661
1·315	7·273	7·779	7·880	7·520	7·890	7·920
1·420	7·500	7·991	8·092	8·850	8·100	8·130
1·525	7·750	8·195	8·290	7·965	8·291	8·320
1·630	8·003	8·396	8·482	8·181	8·486	8·509
1·735	8·270	8·610	8·690	8·420	8·696	8·711
1·840	8·592	8·868	8·940	8·710	8·940	8·950
1·945	8·980	9·203	9·260	9·110	9·252	9·250
2·050	9·450	9·589	9·614	9·571	9·610	9·551
C_M	0·010	0·010	0·0108	0·010	0·010	0·010

Acid dissociation constants of *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid hydrochloride.

$C_L = 1\cdot000 \times 10^{-3}$M; $C_B = 9\cdot524 \times 10^{-2}$M-KOH; $\mu = 0\cdot1$M-KNO_3.

a	0·000	0·476	0·952	1·047	1·142	1·237	1·332	1·428	1·523	1·618	1·713	1·808
pH	2·769	2·905	3·070	3·111	3·160	3·212	3·272	3·341	3·422	3·525	3·659	3·840
a	1·904	2·000	2·095	2·190	2·285	2·380	2·476	2·571	2·666	2·761	2·856	2·952
pH	4·186	6·050	7·990	8·384	8·630	8·828	8·988	9·140	9·280	9·420	9·569	9·706

Titration of *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid with metal ions.*

(*A*) $C_L = 9\cdot714 \times 10^{-4}$M; $C_B = 9\cdot524 \times 10^{-2}$M-KOH; $\mu = 0\cdot1$M-KNO_3.

	pH		
a	Ag$^+$	Tl$^+$	Fe^{++}
1·098	6·320	6·849	4·112
1·196	6·861	7·420	4·332
1·294	7·194	7·740	4·564
1·392	7·460	7·992	4·801
1·490	7·700	8·212	5·039
1·588	7·938	8·422	5·281
1·686	8·190	8·630	5·542
1·784	8·452	8·840	5·825
1·882	8·750	9·075	6·136
1·980	9·092	9·325	6·520
2·078	9·440	9·580	6·950
C_M	$9\cdot8 \times 10^{-3}$	0·010	0·010

* This ligand was studied as its hydrochloride except for titrations under (*A*), for which the free acid was used.

(*B*) $C_L = 1{\cdot}000 \times 10^{-3}$M; $C_B = 9{\cdot}524 \times 10^{-2}$M-KOH; $\mu = 0{\cdot}1$M-KNO$_3$.

	pH					
a	Mg^{++}	Ca^{++}	Sr^{++}	Ba^{++}	Li^{+}	Na^{+}
2·000	5·970	5·355	5·529	5·735	5·630	5·660
2·095	7·292	6·337	7·090	7·383	7·730	7·710
2·190	7·711	6·730	7·531	7·801	8·200	8·148
2·285	7·982	7·005	7·812	8·079	8·464	8·407
2·380	8·210	7·250	8·050	8·292	8·666	8·600
2·476	8·401	7·481	8·251	8·488	8·830	8·703
2·571	8·590	7·715	8·450	8·670	8·988	8·911
2·666	8·774	7·970	8·650	8·841	9·131	9·059
2·761	8·967	8·250	8·859	9·030	9·278	9·210
2·856	9·170	8·580	9·080	9·220	9·427	9·356
2·952	9·382	8·970	9·320	9·420	9·580	9·510
C_M	0·0108	0·010	0·010	0·010	0·100	1·200

(*C*) $C_L = 1{\cdot}000 \times 10^{-3}$M; $C_B = 9{\cdot}52 \times 10^{-2}$M; $C_M = 0{\cdot}005$M; $\mu = 0{\cdot}1$M-KNO$_3$.

	pH					pH			
a	Mn^{++}	Zn^{++}	Co^{++}	Cd^{++}	*a*	Mn^{++}	Zn^{++}	Co^{++}	Cd^{++}
2·475	7·190	4·726	5·170	5·402	2·808	8·510	8·373	8·354	6·945
2·571	7·450	—	6·270	5·700	2·850	8·674	8·548	8·530	7·170
2·618	7·719	7·180	7·270	6·005	2·897	8·829	8·700	8·701	7·435
2·666	7·955	7·660	7·671	6·260	2·952	8·980	8·859	8·870	7·742
2·713	8·161	7·957	7·945	6·491	3·000	9·125	9·008	9·040	8·125
2·761	8·341	8·185	8·169	6·711					

Determination of the acid dissociation constants of the two ligand acids, and of the stability constants of their metal complexes, was carried out as described previously.[1,3]

RESULTS AND DISCUSSION

The stoicheiometric acid dissociation constants for the new ligands are summarised in Table 1 together with values for *N*-(2-pyridylmethyl)iminodiacetic acid (I). The values of pK_1 refer in each case to the dissociation of a proton from a carboxylic acid, and values of pK_2 correspond to the dissociation of an ammonium ion. The ligand (III) was studied as its hydrochloride but the dissociation constant of the species H$_3$L$^+$ was too low to be measurable: it would correspond, of course, to the dissociation of a carboxylic proton.

TABLE 1.

Acid dissociation constants valid for 20° and $\mu = 0{\cdot}1$M-KNO$_3$.

Complexone	pK_1	pK_2
N-(2-Pyridylmethyl)iminodiacetic acid (I)	2·85 ± 0·02 *	8·25 ± 0·01 *
N-Furfuryliminodiacetic acid (II)	2·17 ± 0·04	8·41 ± 0·01
N-(Tetrahydropyran-2-ylmethyl)iminodiacetic acid (III)	1·88 ± 0·02	9·04 ± 0·02

* Ref. 1.

Titration curves for the two ligands in the absence and in the presence of various metal ions are shown in Figs. 1 and 2, and stability constants derived from them [3] are summarised in Table 2, together with values for *N*-(2-pyridylmethyl)iminodiacetic acid (I) and *N*-(2-methoxyethyl)iminodiacetic acid (IV).

It is apparent that *N*-furfuryliminodiacetic acid is a poor co-ordinating agent. The values found for the stabilities of its metal complexes are lower than those expected on the grounds of basicity alone for a tetradentate ligand of p$K = 8{\cdot}41$ (cf. Fig. 6 of ref. 1). This cannot be a consequence of steric hindrance which is equally not shown in acid (III);

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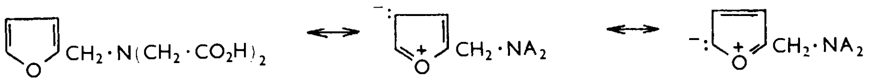
[3] Irving, Shelton, and (in part) Evans, *J.*, 1958, 3540.

it probably arises from a decrease in donor character of the oxygen atoms in the furan ring, which becomes more positive owing to contributions from other canonical forms (as shown)



(II)

(A = $-CH_2·CO_2H$)

Comparison (Table 2) of the stability constants for complexes of *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid (III; pK_2 = 9·04) with those of *N*-(2-methoxyethyl)iminodiacetic acid (IV; pK_2 = 8·96) shows that the former ligand forms slightly stronger

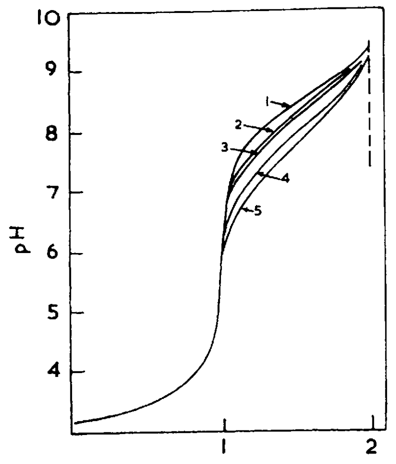


FIG. 1. Titration curves for *N*-furfuryliminodiacetic acid at 20°.

(1) Ligand alone in 0·1M-KNO_3. (2) Mg^{2+} (1 : 1). (3) Tl^+ (1 : 1). (4) Ca^{2+} (1 : 1). (5) Ag^+ (1 : 1).

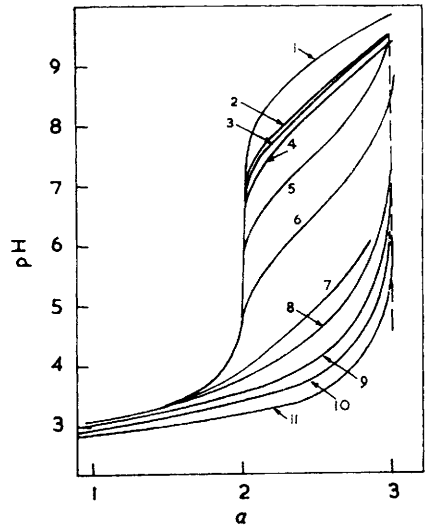


FIG. 2. Titration curves for *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid at 20°.

(1) Ligand alone in 0·1M-KNO_3. (2) Ba^{2+}. (3) Mg^{2+}. (4) Sr^{2+}. (5) Ca^{2+} and Ag^+. (6) Mn^{2+}. (7) Fe^{2+}. (8) Cd^{2+}. (9) Co^{2+}. (10) Zn^{2+}. (11) Pb^{2+}.

TABLE 2.

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

	Acid (I) *		Acid (II) †		Acid (III) †		Acid (IV) ‡	
	log K_{ML}	log K_{ML_2}	log K_{ML}	log K_{MHL}	log K_{ML}	log K_{ML_2}	log K_{ML}	log K_{ML_2}
Li^+	1·71 ± 0·01	—	—	—	1·74 ± 0·1	—	—	—
Na^+	0·85 ± 0·03	—	—	—	0·85 ± 0·04	—	—	—
Tl^+	3·84 ± 0·01	—	3·11 ± 0·03	—	4·06 ± 0·01	—	—	—
Ag^+	6·09 ± 0·01	—	3·92 ± 0·03	—	4·83 ± 0·03	—	—	—
Mg^{2+}	3·90 ± 0·01	—	2·78 ± 0·03	—	3·70 ± 0·01	—	3·31	—
Ca^{2+}	4·92 ± 0·02	—	3·58 ± 0·01	—	4·86 ± 0·01	—	4·53	—
Sr^{2+}	3·65 ± 0·01	—	2·79 ± 0·02	—	3·97 ± 0·01	—	3·84	—
Ba^{2+}	3·40 ± 0·01	—	2·68 ± 0·02	—	3·61 ± 0·01	—	3·56	—
Mn^{2+}	6·97 ± 0·01	3·63 ± 0·01	—	—	5·89 ± 0·03	4·35 ± 0·02	5·53	4·09
Fe^{2+}	8·94 ± 0·01	—	—	—	7·40 ± 0·01	—	6·81	3·92
Co^{2+}	10·16 ± 0·05	3·18 ± 0·05	—	2·60 ± 0·02	8·51 ± 0·01	4·54 ± 0·9	7·96	4·94
Zn^{2+}	10·87 ± 0·03	—	—	2·75 ± 0·02	9·06 ± 0·01	4·52 ± 0·05	8·43	4·42
Cd^{2+}	9·45 ± 0·02	5·29 ± 0·01	—	1·47 ± 0·02	7·93 ± 0·01	6·06 ± 0·02	7·53	5·65
Pb^{2+}	10·31 ± 0·04	—	—	5·16 ± 0·03	10·30 ± 0·02	—	3·49	3·75

* Ref. 1. † Present work. ‡ Schwarzenbach, Anderegg, Schneider, and Senn, *Helv. Chim. Acta*, 1955, **38**, 1147.

complexes. This may well be due to a less favourable structure in (IV) than in the cyclic analogue (III) where the adjacent carbon atoms are " tied back " into the tetrahydropyran ring. A similar situation is encountered in comparison of complexes of quinuclidine and trimethylamine.

In Fig. 3 the logarithms of the stability constants for complexes of *N*-(2-pyridylmethyl)iminodiacetic acid (I) are compared with corresponding values for the complexes of *N*-(tetrahydropyran-2-ylmethyl)iminodiacetic acid (III). The points fall roughly on two straight lines passing through the origin. The lower line is of unit slope and embraces points for cations that cannot form π-bonds. The upper line (of slope 1·2) includes cations that could form π-bonds, although this correlation alone is not sufficient grounds for postulating that they do so. Had the two ligands been strictly comparable in their co-ordinating characteristics the line of unit slope (for metals forming essentially only σ-bonds) would have been expected to pass through the point for hydrogen,[4] *i.e.*, to have an intercept $\Delta pK = 0{\cdot}79$. This theoretical line is shown broken in Fig. 3. Clearly some additional stabilisation, ~1 kcal. mole^{-1}, assists the complex formation with the alkali and alkaline-earth metals, and an even greater effect occurs with the cations whose electronic structure terminates with a filled or partly filled *d*-shell. Apart from considerations of possible donor π-bonding (which we shall discuss in detail in a later paper), these effects reflect the greater polarisability of nitrogen than of oxygen atoms and the greater polarising power of the cations derived from the B subgroups.

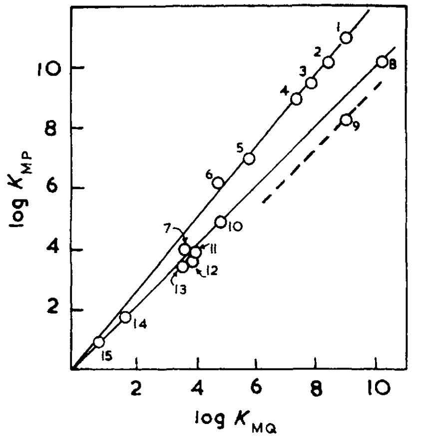


FIG. 3. A comparison of the stabilities of 1 : 1 complexes of *N*-(2-pyridylmethyl)iminodiacetic acid (HP) with those of *N*-(tetrahydrofuran-2-ylmethyl)iminodiacetic acid (HQ). Data for 20° and $\mu = 0{\cdot}1M\text{-}KNO_3$.

(1) Zn^{2+}. (2) Co^{2+}. (3) Cd^{2+}. (4) Fe^{2+}. (5) Mn^{2+}. (6) Ag^{+}. (7) Mg^{2+}. (8) Pb^{2+}. (9) H^{+}. (10) Ca^{2+}. (11) Tl^{+}. (12) Sr^{2+}. (13) Ba^{2+}. (14) Li^{+}. (15) Na^{+}.

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THE DEPARTMENT OF INORGANIC AND STRUCTURAL CHEMISTRY, THE UNIVERSITY OF LEEDS.
[Present address (J. J. R. F. da S.): INSTITUTO SUPERIOR TECHNICO,
LISBON, PORTUGAL.]
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