560. *The Stability of Metal Complexes of 1,4-Piperazine-*
diacetic Acid

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1,4-Piperazinediacetic acid has been prepared and its acid dissociation constants have been measured at 20° and $\mu = 0.1\text{M-KCl}$. Values for the stability constants of its complexes with Mg, Ca, Sr, Ba, Ni, Cu(II), and Zn have been measured and are compared with corresponding data for 1-piperidine-acetic acid and other ligands of related structure. It is concluded that chelation involving both nitrogen atoms of the piperazine derivative does not occur with small ions.

ALKYL substitution in ammonia is known to reduce the thermodynamic stability of ammines, for increases in basicity are more than offset by concomitant increases in steric hindrance to co-ordination,[1,2] The same effects are shown with N-substituted derivatives

[1] Bjerrum, *Chem. Rev.*, 1950, **46**, 381.
[2] Irving and Griffiths, *J.*, 1954, 213.

of ethylenediamine [2,3] and there is an increasing tendency to form hydroxylated species. Thus the reaction between copper perchlorate and NNN'-triethylethylenediamine gives bistriethylethylenediamine-$\mu\mu'$-dihydroxydicupric perchlorate.[4] It was therefore surprising when Mann and Watson reported that $NNN'N'$-tetramethylethylenediamine, $Me_2N \cdot C_2H_4 \cdot NMe_2$, would form non-ionic chelate compounds of type (I) with bivalent palladium, platinum, and iridium, and even with cadmium and copper. Analogous compounds (as II) were formed by 1,4-dimethylpiperazine and evidence for the boat conformation of the co-ordinated ligand was obtained from infrared measurements.[5] The boat conformation in the palladous complex (II; M = Pd, X = Cl) has been established unequivocally by X-ray crystallography.[6]

M	X
Pt, Ir, Cd	Cl
Pd	Br
Cu(II)	CNS
	Picrate

(I)

M	X
Pt	Cl
Ir	Cl
Pd	Br

(II)
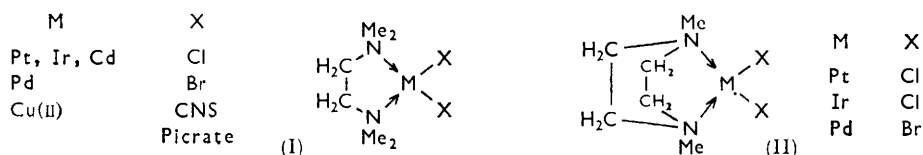
Although Mann and Watson were able to isolate solid chelates of types (I) and (II) with the larger cations, failure attended attempts to prepare stable co-ordination compounds of tetramethylethylenediamine with smaller cations such as Co^{3+}, Rh^{3+}, and Ni^{2+} or of 1,4-dimethylpiperazine with these ions and with Cu^{2+} and Cd^{2+}. The differences in behaviour were interpreted in terms of steric hindrance to co-ordination.[5] We have now attempted to throw further light on the co-ordinating ability of the piperazine residue by incorporating it into the structure of a complexone in the hope that the metal complexes might be soluble in water and thus permit determination of their thermodynamic stabilities. To this end we have synthesised 1,4-piperazinediacetic acid (III) by condensing piperazine with chloroacetic acid under alkaline conditions.

(III)   (IV)   (V)   (VI)
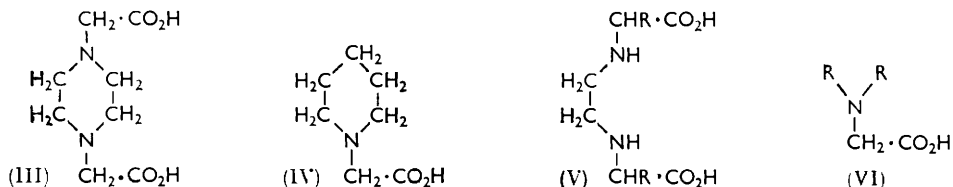
Measurements of the stability of its proton and metal complexes are discussed in relation to similar data for 1-piperidineacetic acid (IV), ethylenediamine-NN'-diacetic acid (V; R = H), ethylenediamine-NN'-di(methylacetic acid) (V; R = Me), and NN'dialkylglycines (VI; R = Me and Et).

EXPERIMENTAL

Materials.—Piperazine (8·6 g.) was condensed with a solution of chloroacetic acid (28 g.) in water (100 ml.) previously neutralised with concentrated sodium hydroxide, by heating the mixture to 90° and adding concentrated aqueous sodium hydroxide (3 mol.) at such a rate that the pH was maintained as long as possible between the change-points of phenolphthalein and thymolphthalein. Then heating was continued for 30 min. and the mixture next cooled and acidified with concentrated hydrochloric acid. *1,4-Piperazinediacetic acid monohydrochloride* which separated was collected and repeatedly recrystallised from water. It darkened at 245—250° and decomposed at 295—300° (Found: C, 40·4; H, 6·2; N, 11·8; Cl, 14·5.

³ Basolo and Murmann, *J. Amer. Chem. Soc.*, 1954, **76**, 211; Basolo, Chen, and Murmann, *ibid.*, p. 956.
⁴ Pfeiffer and Glaser, *J. prakt. Chem.*, 1938, **151**, 134.
⁵ Mann and Watson, *J.*, 1958, 2772.
⁶ Hassel and Pedersen, *Proc. Chem. Soc.*, 1959, 394.

$C_8H_{14}N_2O_4$,HCl requires C, 40·3; H, 6·3; N, 11·7; Cl, 14·85%). Van Dorp [7] prepared 1,4-piperazinediacetic acid through the dinitrile and reports the analysis of the hydrated dihydrochloride $C_8H_{14}N_2O_4$,2HCl,2H$_2$O.

1-Piperidineacetic acid was prepared by condensing piperidine with chloroacetic acid.[8] The free acid was obtained from its hydrochloride by treatment with freshly prepared silver oxide, and its monohydrate was prepared by recrystallisation from aqueous ethanol (yield, 30%). The anhydrous acid was obtained by drying the monohydrate *in vacuo* at 85° and formed colourless crystals, m. p. 214° (lit.,[9] 211—216°) (Kraut [8] reports a monohydrate) (Found: N, 9·6. Calc. for $C_7H_{13}NO_2$: N, 9·8%).

Dissociation Constants.—Acid dissociation constants for the ligand acids were determined in the apparatus described by Irving, Shelton, and Evans [10] in which changes in the potential

TABLE 1.

Titrations of 1,4-piperazinediacetic acid.

(*a*) $C_L = 0.00100$M. $C_M = 0.00100$M.   Total initial volume, 100 ml.   Strength of alkali used as titrant, 0·1013N.

	pH in the presence of the named cations					pH in the presence of the named cations		
a	None	Ca²⁺	Sr²⁺	Ba²⁺	*a*	None	Ca²⁺	Sr²⁺	Ba²⁺
0·00	2·937	2·950	2·954	2·958	2·07	7·788	7·570	7·711	7·758
0·20	3·059	3·059	3·047	3·064	2·17	8·078	7·919	7·994	8·035
0·40	3·180				2·27	8·291	8·163	8·219	8·262
0·60	3·326	3·317	3·319	3·341	2·37	8·487	8·371	8·417	8·446
0·80	3·535				2·47	8·663	8·560	8·580	8·639
0·99	3·765	3·740	3·760	3·770	2·57	8·836	8·728	8·754	8·814
1·19	4·036				2·67	9·037	8·912	8·932	9·005
1·39	4·345	4·305	4·330	4·326	2·77	9·242	9·125	9·220	9·223
1·58	4·648				2·87	9·529	9·349	9·419	9·505
1·78	5·091	5·033	5·091	5·093	2·96	9·793	9·639	9·715	9·797
1·88	5·530	5·506	5·519	5·511	3·06	10·04	9·916	9·979	10·04
1·98	6·981	6·645	6·963	7·007					

(*b*) $C_L = 0.00200$M. $C_M = 0.00200$M.   Total volume, 100 ml.   Strength of alkali, 0·1036N.

	pH in the presence of the named cation				pH in the presence of the named cation		
a	None	Zn²⁺	Ni²⁺	Cu²⁺	*a*	None	Zn²⁺	Ni²⁺	Cu²⁺
0·00	2·73	2·74	2·73	2·68	2·70	4·404	4·381	4·310	3·533
0·19	2·765				2·90	4·582	4·561	4·488	3·672
0·39	2·820				3·09	4·781	4·768	4·686	3·830
0·77	2·950	2·963		2·835	3·28	5·040	5·032	4·940	4·000
0·97	3·025	3·040	3·023	2·885	3·48	5·485	5·480	5·360	4·225
1·16	3·110			2·940	3·67	6·980	6·680	6·282	4·494
1·35	3·223	3·240		3·000	3·86	7·784	7·394	6·969	4·761
1·55	3·360	3·371		3·060	4·05	8·115	7·665	7·311	5·025
1·74	3·518	3·528		3·120	4·25	8·350	7·729 *	7·572	5·272
1·93	3·700	3·702	3·650	3·190	4·44	8·560		7·800	
2·13	3·882	3·878	3·818	3·270	4·63	8·755		8·040	
2·32	4·060	4·052	3·982	3·351	4·83	8·961		8·255	
2·51	4·230	4·215	4·153	3·448	5·02	9·209		8·470 *	

* Precipitation at this point.

of a hydrogen electrode–silver/silver chloride pair were followed. Stability constants of complexes with the alkaline-earth metals were obtained in the same way. Other measurements were carried out by following changes in the potentials of a glass electrode–calomel reference electrode with a Radiometer pH-meter, model PHM4b, as described elsewhere.[11] The pH-meter was calibrated by means of the hydrogen electrode to give values of hydrogen-ion concentration directly. Ionic strengths were maintained at 0·1M with potassium chloride, and

[7] van Dorp, *Rec. Trav. chim.*, 1909, **28**, 68.
[8] Kraut, *Annalen*, 1871, **157**, 66.
[9] Wedekind, *Ber.*, 1899, **32**, 722.
[10] Irving, Shelton, and Evans, *J.*, 1958, 3540.
[11] Irving and Pettit, *J.*, 1963, 1546.

all measurements refer to 20·0°. Carbonate-free potassium hydroxide was prepared by Schwarzenbach and Biedermann's method.[12] The experimental results are in Tables 1 and 2,

TABLE 2.

Titrations of 1-piperidineacetic acid.

$C_L = 0.0100$M. $C_M = 0.0050$M. $C_{HCl} = 0.0100$M. Total initial volume 20 ml. Strength of alkali, 0·914N.

a	0·000	0·046	0·091	0·137	0·183	0·229	0·274
pH,* HCl	2·27	2·29	2·31		2·36		2·42
Cu^{2+}	4·52	5·09	5·25	5·50	5·66	5·81	5·94 †
Ni^{2+}	5·08	7·20	7·90	8·12	8·27	8·38 †	
a	0·366	0·457	0·548	0·640	0·732	0·823	0·914
pH,* HCl	2·49	2·56	2·65	2·76	2·90	3·09	3·42
a	1·005	1·097	1·188	1·280	1·371	1·462	1·554
pH,* HCl	7·95	9·29	9·63	9·85	10·03	10·19	10·35
a	1·645	1·737	1·828				
pH,* HCl	10·50	10·66	10·83				

* This is the pH of solutions of the ligand containing hydrochloric acid, copper, or nickel as specified. † Precipitation took place.

where C_L is the original concentration of ligand, C_M that of the metal, and C_{HCl} that of the mineral acid present at the beginning of the titrations with 1-piperidineacetic acid. The degree of neutralisation of the ligand acid is denoted by a.

RESULTS AND DISCUSSION

The acid dissociation constants of 1,4-piperazinediacetic acid and 1-piperidineacetic acid and the stability of their metal complexes are summarised in Table 3, with comparable data for related compounds.

In 1,4-piperazinediacetic acid hydrochloride (H_2P,HCl) at least one of the nitrogen atoms must have accepted a proton and pK_1 must refer to the dissociation of a proton from a carboxylic acid adjacent to a positively charged ammonium ion; pK_2 would then refer to the dissociation of the second carboxyl group and pK_3 to the dissociation of the resulting piperazinium ion. It is, however, possible that the species H_2P forms a double betaine (as VII) in which the *trans*-chair conformation has been adopted to minimise repulsive forces. Should this have been the case, pK_2 would refer to the dissociation of one of the two piperazinium ions, the unusually low value of pK for an ammonium ion being a consequence of the proximity of the second positively charged ion. On account of hydrolysis it was impossible to measure pK_1 by titrating a 0·001M-solution. A value for pK_1 was, however, obtained from measurements with a 0·01M-solution and the values obtained for pK_2 and pK_3 from the two solutions were in good agreement (see Table 3).

It is interesting that the increase in acidity of piperazine caused by introduction of acetic acid residues ($\Delta pK = 1.0$) is about the same as that caused by a similar substitution in piperidine ($\Delta pK = 1.1$ units). The difference between pK_2 and pK_3 for 1,4-piperazine-diacetic acid (4·2 log units) is almost identical with the difference between pK_3 and pK_4 for ethylenediaminetetra-acetic acid (4·1 units). A similar situation must occur with the symmetrical di-acids (as V) if they too exist as double betaines in aqueous solution (as VIII). The values of ΔpK are, respectively, 2·89 (R = H) and 3·04 (R = Me). Protons attached to nitrogen atoms in 1,4-piperazinediacetic acid are clearly more labile than those occuring in comparable structures in ethylenediaminetetra-acetic acid or in the diacids (V) and (VIII). The increased acidity is that expected from the closer proximity of the nitrogen atoms since they are part of a cyclic system.

Precipitation of zinc hydroxide occurred in the titration by alkali of mixtures of 1-piperidineacetic acid and zinc ions before measurable proton displacement had taken

[12] Schwarzenbach and Biedermann, *Helv. Chim. Acta.* 1948, **31**, 331.

TABLE 3.

Acid dissociation constants and metal stability constants.

Ligand	(III)	(III)	(IV)	(VIa)	(VIb)	(Va)	(Vb)
Ionic strength	0·1M	0·1M	0·1M	0·2M	0·2M	0·1M	0·1M
Temp.	20°	20°	20°	25°	25°	30°	20°
Ref.	a	a	a	b	b	c	d
pK of H_3L^+	—	1·78ᵉ					
H_2L	4·46ᶠ	4·40	2·13	2·04	2·08	6·42	6·69
HL^-	8·70	8·68	10·25	10·47	9·80	9·46	9·58
log K_{ML} for							
Mg	1·5					3·9	2·8
Ca	2·5						1
Sr	2·2						n.m.
Ba	1·6						n.m.
Zn	3·05		Pptn.			11·1	10·1
Cu	7·37		6·33	6·88	7·30	16·2	15·2
Ni	3·64		3·7	4·21	4·82	13·5	12·2
log β_2 for							
Cu			~12	12·86	13·65		
Ni			~7		8·60		
log K_{CuHL}^{H}	5·41						
log K_{NiHL}^{H}	6·35						

a Present work. *b* Basolo and Chen, *J. Amer. Chem. Soc.*, 1954, **76**, 953. *c* Chaberek and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 6228. *d* Irving, Shelton, and Evans, *J.*, 1958, 3540. *e* $C_L =$ 0·010M. *f* $C_L = $ 0·001M. (III) is 1,4-piperazinediacetic acid. (IV) is 1-piperidineacetic acid. (Va) is ethylenediamine-*NN'*-diacetic acid. (Vb) is ethylenediamine-*NN'*-di(methylacetic acid). (VIa) is *NN*-diethylglycine. (VIb) is *NN*-dimethylglycine. $K_{ML} = [ML]/[M][L]$. $\beta_2 = [ML_2]/[M][L]^2$. $K_{MHL}^{H} = [MHL]/[ML][H]$. n.m. signifies not measurable.

place. Complex formation with alkaline-earth metals was too weak for quantitative treatment. However, stability constants were measurable for copper and nickel where both 1 : 1 and 1 : 2 complexes were shown to be formed. No similar difficulties were found in titrations with 1,4-piperazinediacetic acid. Here no evidence was obtained
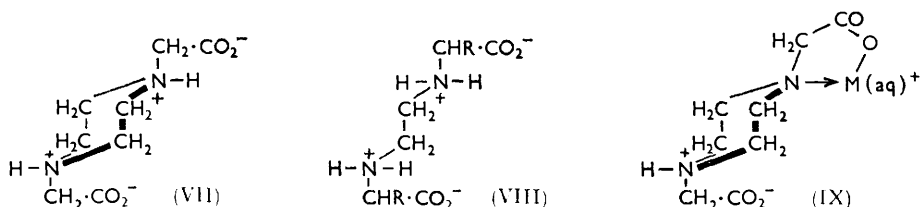
for complexes other than 1 : 1 with copper, even when titrations were carried out in which the molar ratio metal : ligand was varied from 2 : 1 to 1 : 5. On the other hand, there was clear indication of the formation of protonated complexes, and the calculation of stability constants was carried through with a programme designed for an electronic digital computor.[13] Although precipitation occurred with nickel just before $\bar{n} = 0.5$ a value for log K_{NiL} and for log K_{NiHL} was obtainable.

The values shown in Table 3 demonstrate that complexes of 1,4-piperazinediacetic acid (III) with the smaller bivalent ions (Cu^{2+}, Ni^{2+}, or Zn^{2+}) are substantially weaker than those formed by the formally analogous tetradentate ligands ethylenediamine-*NN'*-diacetic (or dimethylacetic) acid (as V). The same is true for the small magnesium ion. If we estimate the effect of *C*-methyl substitution in the acidic portion of ethylenediamine-*NN'*-diacetic acid as lowering values of log K_{ML} by about 1 log unit on the average, it appears that the stabilities of complexes of the larger alkaline-earth metals with 1,4-piperazinediacetic acid would not differ greatly from the corresponding values estimated for ethylenediamine-*NN'*-diacetic acid. The anomalously low stabilities are thus limited

[13] Irving and Stacey, *J.*, 1961, 2019.

to the smaller ions. The picture is much clearer when comparison is made with amino-acids that can only form a single chelate ring. The similarity in absolute values of log K_{CuL} and log K_{CuL_2} (or log K_{NiL} and log K_{NiL_2}) for 1-piperidineacetic acid (IV) and the structurally similar NN-dialkylaminoacetic (as VI), and the regular increase in stability (IV) < (VI; R = Et) < (VI; R = Me) are consistent with the very similar proton affinities of the three ligand anions and the decreasing steric hindrance to co-ordination. Had 1,4-piperazinediacetic acid behaved as a tetradentate ligand then, despite its lower basicity, a value of log K_{CuL} nearer the value of log K_{CuL_2} for these bidentate ligands (*i.e.*, ~12) would have been expected. The conclusion that the ligand behaves only as a bidentate amino-acid (as IX) is confirmed by the high values of $K_{\text{MHL}}^{\text{H}}$ which measures the proton-affinity of the monochelate species ML. For copper, log $K_{\text{CuHL}}^{\text{H}}$ is 5·4. Otherwise expressed, the species CuHL is a weak acid with a dissociation constant measured by $\text{p}K_{\text{CuHL}} = 5\cdot4$. This is seen to be somewhat larger than the value $\text{p}K = 4\cdot46$ for the dissociation of the first proton from the metal-free double betaine (VII) in consequence of the greater separation of the positive centres in (IX).

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