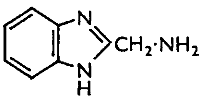
510. *Metal Complexes of 2-Aminomethylbenzimidazole.*

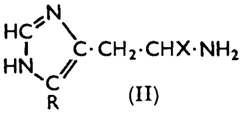
By H. Irving and O. A. Weber.

2-Aminomethylbenzimidazole is a diacid base with pK_1 = 3·46 and pK_2 = 7·96 at μ = 1(KCl). With bivalent cations it forms 1 : 1 and 1 : 2 (but not higher) complexes which are less stable than those formed by histamine or histidine. The order of increasing stability is: Alkaline earths $\ll$ Fe < Cd < Zn < Co < Ni < Cu. The absorption spectra of the copper complexes have been studied.

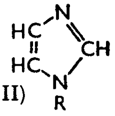
When, in 1938, Hughes and Lions prepared 2-aminomethylbenzimidazole (I) they suggested that it might be a useful reagent for metals,[1] but it appears never to have been examined from this point of view. Should it react as a bidentate ligand, co-ordination to metal must involve the secondary 1-nitrogen atom or the tertiary 3-nitrogen atom. In either case the base may be regarded as an *N*-substituted ethylenediamine and, as such, likely to give metal complexes weaker than those of ethylenediamine,[2] especially as benzimidazole is itself a weak base. Any novel or useful analytical features would therefore have to be a consequence of incorporating a benzimidazole residue in the chelating ligand. Since the benzimidazole nucleus appears in several metal complexes of biological importance (*e.g.* vitamin B_{12}, " Factor III "), a quantitative study of the stabilities of the metal complexes of 2-aminomethylbenzimidazole was undertaken.



(I ; ambi)



(II)



(III)

Histamine, X = H. Histidine, X = CO_2H.

The dihydrochloride of 2-aminomethylbenzimidazole (I; ambi) was synthesised by condensing *o*-phenylenediamine with hippuric acid [1] or (more conveniently) with ethyl aminoacetate hydrochloride.[3]

---

[1] Hughes and Lions, *Proc. Roy. Soc. N.S. Wales*, 1938, **71**, 209.
[2] Irving and Griffiths, *J.*, 1954, 213.
[3] Lane, *J.*, 1957, 3313.

The dissociation constants of the conjugate acids of ambi, defined by $K_1 = [H^+][H\ ambi^+]/[H_2\ ambi^{2+}]$ and $K_2 = [H^+][ambi]/[H\ ambi^+]$, were determined potentiometrically at 20° in a salt-background of 0·1M-potassium chloride. The stabilities of the various metal complexes were measured in the same medium by techniques previously described.[4] Alkaline-earth metals did not appear to form complexes, but formation curves for typical bivalent ions are shown in Fig. 1 which gives the experimental points and the formation curves calculated from the stability constants (Table 1) which most closely represent the experimental data.[5]

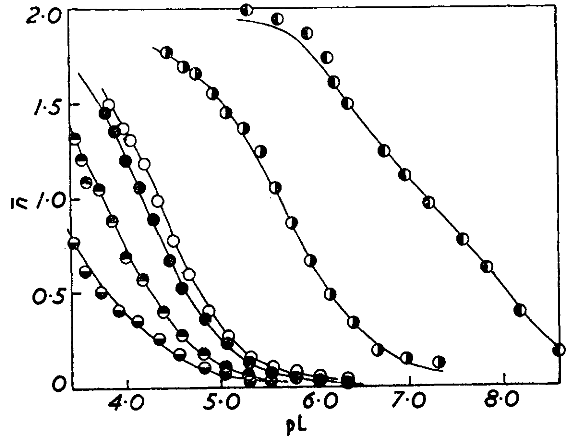


FIG. 1. *Formation curves of metal complexes of 2-aminomethylbenzimidazole.*

◐ Cu^{2+}. ◑ Ni^{2+}. ○ Co^{2+}. ● Zn^{2+}. ◓ Cd^{2+}. ◒ Fe^{2+}.

From its acid dissociation constants (Table 1), it is clear that ambi is a much weaker base than *N*-methylethylenediamine for which $pK_1 = 7{\cdot}42$ and $pK_2 = 10{\cdot}36$ at 25° (M-KCl).[6] Other things being equal, its metal complexes would be expected to be less stable, and this is shown to be the case in Fig. 2. A closer comparison can be made with histamine (II; X = H) which, like ambi, contains an imidazole ring. Histamine is a stronger base than ambi, and values of $\log K_1$ for the chelation of the first molecule of ligand are uniformly higher (Table 1) despite the fact that it can form only a six-membered ring whereas ambi can form a five-membered ring on chelation. On the other hand, values of $\log K_2$ for complexes of the two ligands are very similar, so that while the overall stabilities of the histamine complexes (as measured by $\log \beta_2 = \log K_1K_2$) are uniformly higher than those of corresponding complexes of ambi, the values of $\log (K_1/K_2)$ are lower for the complexes formed by 2-aminomethylbenzimidazole. This suggests that there is little steric hindrance to co-ordination from the 4 (or 7) position of ambi and that there is an enhanced stability in the systems containing two aromatic rings, possibly through π-bonding. It is particularly interesting that imidazole itself (III; R = H), which is a monodentate ligand and somewhat less basic than ambi (the p*K*'s of HL^+ are 4·09 and 7·69 respectively), forms complexes of comparable stability, as may be seen by comparing corresponding values of $\log K_1K_2$ (or $\log K_3K_4$) for the co-ordination of two (or four) molecules of imidazole with those of $\log K_1$ (or $\log K_2$) for ambi (Table 1). Here again the greater difficulty of co-ordinating the second pair of imidazole molecules (as shown by values of $\log(K_1K_2/K_3K_4)$) than of co-ordinating the second molecule of ambi is very striking. The absence of any marked chelate effect [7,8] is surprising; measurements with benzimidazole itself, now in progress, may help to explain these anomalies.

Although copper will take up only two molecules of histamine (or histidine), nickel forms a definite 1 : 3 complex (Table 1), and in the cobalt system $\bar{n}$ certainly rises above 2.

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

[5] Irving and Rossotti, *J.*, 1953, 3397.

[6] Basolo and Murmann, *J. Amer. Chem. Soc.*, 1952, **74**, 5243.

[7] Schwarzenbach, *Helv. Chim. Acta*, 1952, **35**, 2344.

[8] Irving and Williams, *J.*, 1953, 3192.

TABLE 1. *Stability of metal complexes formed by derivatives of imidazole.*

	Fe	Co	Ni	Cu	Zn	Cd
2-*Aminomethylbenziminazole* (I) (pK of H_2L^{2+} = 3·46; pK of HL^+ = 7·69) [a]						
log K_1	3·8	4·51	6·00	8·00	4·44	4·07
log K_2	2·5	4·11	5·21	6·42	3·91	3·42
log β_2	6·3	8·62	11·21	14·42	8·35	7·46
log (K_1/K_2)	1·3	0·40	0·79	1·58	0·53	0·65
Histamine (II; X = H) (pK of H_2L^{2+} = 6·22; pK of HL^+ = 9·92) [b]						
log K_1	—	5·28	6·94	9·65	—	—
log K_2	—	3·70	5·07	6·55	—	—
log β_2	—	8·98 [b, c]	12·01 [b, c]	16·20 [b, c]	8·7 [d]	—
log (K_1/K_2)	—	1·58	1·87	3·10	—	—
log K_3	—	2·04	3·12	—	—	—
Histidine (II; X = CO_2H) (pK of H_3L^{2+} = 1·82; pK of H_2L^+ = 6·0; pK of HL = 9·20) [e]						
log β_2	—	13·86 [e]	15·9 [e]	18·33 [e]	12·88 [e]	—
	—	—	15·84 [f]	19·40 [f]	11·78 [g]	11·1 [g]
Imidazole (III; R = H) (pK of HL^+ = 4·09) [b]						
log K_1K_2	—	4·37 [h]	5·49 [b]	7·82 [b, i]	5·01 [j]	5·0 [k]
log K_3K_4	—	2·78	3·33	4·93	4·25	2·7
log (K_1K_2/K_3K_4) ...	—	1·59	2·16	2·89	0·78	2·3

[a] Present work. Valid for 20° and μ = 0·1M(KCl). No correction has been made for the effect of competitive complex-formation by chloride ions in the case of cadmium and zinc.

[b] Calc. for 20° and μ = 0·135M(KCl) by interpolation from data for 0° and 25° (Michel and Andrews, *J. Amer. Chem. Soc.*, 1955, **77**, 323, 5291). Extrapolation of data for 30° and 50° (Hares, Diss. Pennsylvania State College, 1952) gives the following values for μ = 0·1M(KNO_3) and 20°: Nickel, 7·03, 5·06, and 3·21 [log β_2 = 12·09; log (K_1/K_2) = 1·97]; cobalt, 5·47, 4·00, and 2·06 [log β_2 = 9·47; log (K_1/K_2) = 1·47]; zinc, 6·06, 4·86 [log β_2 = 10·32; log (K_1/K_2) = 1·20].

[c] Albert (*Biochem. J.*, 1952, **50**, 690) reports the following values for log β_2 at 20° and μ = 0·015: cobalt, 8·7; nickel, 11·7; copper, 16·2.

[d] Albert (*loc. cit.*).

[e] Data for 20° and μ = 0·01 from Albert (*loc. cit.*).

[f] Data for 25° and μ = 0·15 (KNO_3) from Li, Doody, and White (*J. Amer. Chem. Soc.*, 1957, **79**, 5859).

[g] Data for 25° and μ = 0·15(KNO_3) from Li and Manning (*ibid.*, 1955, **77**, 5285).

[h] Data for 25° and μ = 0·16 from Martin and Edsall (*ibid.*, 1958, **80**, 5033), who also report log β_2 = 2·90 for manganese.

[i] Values for copper at 20° calculated from potentiometric data for 4·5° and 22·5° by Edsall, Felsenfeld, Goodman, and Gurd (*J. Amer. Chem. Soc.*, 1954, **76**, 3054) are 7·99, 4·97, and 3·02.

[j] Calculated values for 20° from data at 4·5° and 24·0° by Edsall *et al.* (*loc. cit.*).

[k] Calculated value for 20° and μ = 0·15M(KNO_3) from data at 15°, 25°, and 35° (Tanford and Wagner, *J. Amer. Chem. Soc.*, 1953, **75**, 434). Li, White, and Doody (*loc. cit.*) report log K_1K_2 = 5·07 and log K_3K_4 = 2·41 from polarographic measurements at 25°, whence log (K_1K_2/K_3K_4) = 2·66.

However, no evidence for complexes higher than 1 : 2 was found with ambi. It has been suggested that high values of log (K_1/K_2) for complexes of histamine with copper (3·10), compared with those for cobalt (1·58) or nickel (0·87), reflect the steric resistance to adoption of a square-planar configuration.[9] A similar maximum can be seen among complexes of ambi and imidazole (Table 1). However, such maxima are not necessarily due to steric factors: for, since the stability of metal complexes of the ligands referred to in this paper, and indeed, with few and predictable exceptions, all other ligands follow the Irving–Williams order,[8] numerical values of K_n reach their greatest value with copper, and differences between successive step-constants are also, in general, largest when the constants are themselves large. This point is exemplified in the cadmium–imidazole system (Table 1) where the ratio log (K_1K_2/K_3K_4) = 2·3 (or 2·66) is comparable with that of copper (2·89 or 3·02) although there is no question of a square-planar arrangement in this case. Ratios between numerical values of step constants are very sensitive to the precision of the individual values as shown by the various data for histamine and imidazole in Table 1 (notes *b*, *i*, and *k*), and much circumspection is needed in their interpretation in the absence of reliable values for the entropy and enthalpy of complex formation.

By reason of the formation of an additional and five-membered ring, complexes of

---

[9] Michel and Andersen, *J. Amer. Chem. Soc.*, 1955, **71**, 5291.

histidine (II; X = CO_2H) are appreciably more stable than those of histamine (II; X = H) although the proton affinities of the two ligands are almost identical. Chelation must, for steric reasons, involve the pyridine rather than the remoter pyrrole nitrogen atom although Li, Doody, and White advanced additional reasons based on a study of the stability of metal complexes of histidine methyl ester.[10] The five-membered chelate rings formed by ambi could engage a heterocyclic nitrogen atom in either position 1 or position 3. That (in the absence of tautomerism) the pyridine nitrogen atom is most probably involved follows from the observation that copper complexes of imidazole (III; R = H; pK = 7·1) and 1-methylimidazole (III; R = Me, pK = 7·2) are of almost identical stability (log β_4 = 12·72 and 12·68 respectively).[11] Had co-ordination involved the pyrrole nitrogen atom, steric hindrance to co-ordination caused by the methyl group would surely have lowered the stability.

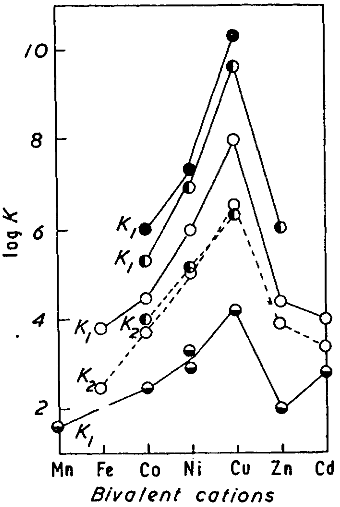


FIG. 2. *Comparison of the stability constants of 2-aminomethylbenziminazole* (○) *with those of imidazole* (◒), *histamine* (◐), *and* N-*methylethylenediamine* (●).

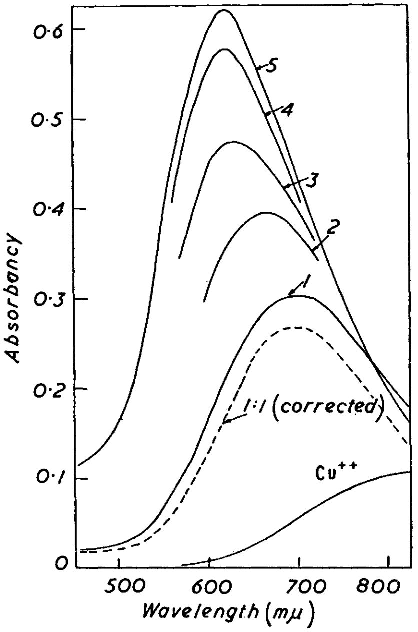


FIG. 3. *Absorption spectra of cupric complexes of 2-aminomethylbenzimidazole.*

Fig. 3 shows the absorption spectra of blue solutions formed by mixtures of 0·002M-cupric sulphate containing various proportions of ambi at pH 4·5. When the ratio [ambi] : [Cu^{2+}] is increased from 10 : 1 to 12 : 1 no further change occurs in the absorption spectrum which is that of the complex ion $Cu(ambi)_2^{2+}$ and for which ε = 78 at $\lambda_{max.}$ 620 mμ. The gradual displacement of the maximum to longer wavelengths, and the decrease in intensity shown in curves 4, 3, 2, and 1 are due to progressive displacement of $Cu(ambi)_2^{2+}$ by $Cu(ambi)^{2+}$ and Cu^{2+}. For equimolar quantities of the components (Fig. 3, curve 1), calculations from the stability constants given in Table 1 and the parameters $C_{ambi} = C_{Cu^{2+}}$ = 0·002M, and pH = 4·5, lead to the values pL = 3·40 and $\bar{n}$ = 0·800, showing that this absorption curve is that of a mixture of 8·3% of the 2 : 1 complex, 65·2% of the 1 : 1 complex, and 26·5% of Cu^{2+}. Subtracting the contributions due to $Cu(ambi)_2^{2+}$ and Cu^{2+} gave the curve shown by the broken line in Fig. 3, whence for the 1 : 1 complex ε = 52 at $\lambda_{max.}$ 702 mμ. Regularities in the spectra of copper complexes of ammonia,[12]

---

[10] Li, Doody, and White, *J. Amer. Chem. Soc.*, 1957, **79**, 5859.

[11] Li, White, and Doody, *ibid.*, 1954, **76**, 6219.

[12] Bjerrum, Ballhausen, and Jørgensen, *Acta Chem. Scand.*, 1954, **8**, 1275.

ethylenediamine (en),[12] 2-aminomethylbenzimidazole (ambi), and *NN'*-dimethylethylenediamine (dimen)[2] are shown in Table 2.

TABLE 2. *Absorption spectra of some copper–amine complexes.*

	$2NH_3$ (*cis*)	en	ambi	dimen
$\varepsilon_{max.}$	30	37·5	52	54·3
$\lambda_{max.}$	680	670	702	700
	$4NH_3$	2en	2ambi	2dimen
$\varepsilon_{max.}$	54	63	78	107
$\lambda_{max.}$	590	550	620	575

EXPERIMENTAL

Reagents.—2-Aminomethylbenzimidazole (I) was prepared as its dihydrochloride [1,3] which was purified by repeated recrystallisation from boiling alcohol in which it is sparingly soluble. It formed colourless needles, m. p. 253° (decomp.) [Found: C, 43·55; H, 5·1; N, 19·1; Cl, 32·1%; *M* (titration), 219·8. Calc. for $C_8H_9N_3,2HCl$: C, 43·65; H, 5·0; N, 19·1; Cl, 32·2%; *M*, 220·1].

TABLE 3.

(i) *Reagent alone.* *C* (for ambi,2HCl) = $1·5 \times 10^{-3}$. Initial vol., 50 ml.

KOH (ml.)	pH	KOH (ml.)	pH	KOH (ml.)	pH	KOH (ml.)	pH
0·02	3·34	0·08	3·62	0·22	7·20	0·28	7·85
0·03	3·38	0·09	3·70	0·23	7·32	0·29	7·94
0·04	3·42	0·10	3·77	0·24	7·43	0·30	8·02
0·05	3·46	0·11	3·86	0·25	7·55	0·31	8·12
0·06	3·52	0·12	3·97	0·26	7·65	0·32	8·24
0·07	3·57	0·20	6·81	0·27	7·75	0·33	8·35

The initial volume in all titrations with metals was 50 ml. and the concentrations of metal and ligand (ambi,2HCl) were 0·00075M and 0·0015M respectively.

$\bar{n}$	pL	$\bar{n}$	pL	$\bar{n}$	pL	$\bar{n}$	pL
			(ii) *Copper.*				
0·184	8·59	0·964	7·23	1·488	6·37	1·865	5·94
0·390	8·18	1·110	6·97	1·609	6·23	1·909	5·86
0·614	7·84	1·234	6·75	1·743	6·16	1·921	5·82
0·768	7·51	1·358	6·54	1·805	6·05	1·949	5·63
			(iii) *Nickel.*				
0·138	7·32	0·481	6·17	1·241	5·44	1·659	4·75
0·152	6·97	0·669	5·96	1·365	5·27	1·691	4·62
0·188	6·66	0·860	5·77	1·449	5·08	1·773	4·54
0·338	6·41	1·050	5·60	1·548	4·93		
			(iv) *Cobalt.*				
0·044	6·34	0·157	5·31	0·772	4·49	1·377	3·98
0·063	6·06	0·271	5·08	0·986	4·33	1·495	3·83
0·086	5·80	0·409	4·87	1·186	4·20		
0·110	5·55	0·598	4·67	1·309	4·05		
			(v) *Zinc.*				
0·040	6·34	0·157	5·31	0·678	4·46	1·354	3·89
0·042	6·06	0·248	5·08	0·890	4·29	1·457	3·79
0·065	5·80	0·364	4·85	1·060	4·14		
0·088	5·54	0·529	4·58	1·200	3·99		
			(vi) *Cadmium.*				
0·044	5·53	0·276	4·58	0·873	3·84	1·207	3·53
0·067	5·29	0·398	4·38	1·046	3·72	1·314	3·46
0·113	5·05	0·577	4·18	1·084	3·57		
0·182	4·81	0·682	3·99				
			(vii) *Iron* (*ferrous*).				
0·059	5·29	0·188	4·56	0·404	3·91	0·633	3·56
0·103	5·04	0·266	4·34	0·502	3·72	0·780	3·44
0·105	4·80	0·359	4·12				

" AnalaR " specimens of metal salts were used and de-ionised water was employed in making up all solutions.

Titration Procedure.—Solutions of the dihydrochloride with added acid and/or metal cations of initial known concentrations C_B, C_A, and C_M were made up in a total volume of 50 or 100 ml. with the addition of sufficient potassium chloride to give an ionic strength of 0·1M. Titrations at 20·0° (thermostat) were carried out potentiometrically with a solution of 0·424M-potassium hydroxide (carbonate-free) in 0·1M-potassium chloride, with a hydrogen electrode and a silver/silver chloride reference electrode. Details of the procedure have already been given.[4] Measurements with metals were made (also at 20·0° and μ = 0·1M-potassium chloride) with a glass electrode and a calomel reference electrode. A redetermination of the dissociation constants of the two ligand acids H_2B^{2+} and HB^+ by means of this system agreed exactly with the values previously obtained. Values of K_1 and K_2 were calculated from the expressions:

$$1/K_1 = \{(1 - R)/R[H^+]\} + \{(2 - R)K_2/R[H^+]^2\}$$

and

$$K_2 = \{(R - 1)[H^+]/(2 - R)\} + \{R[H^+]^2/(2 - R)K_1\}$$

by successive approximations, where $R = \{[H^+] + [K^+] + [OH^-]\}/C$ (for ambi,2HCl).

The degree of formation, $\bar{n}$, of the metal–ligand systems at various free-ligand concentrations defined by $pL = -\log_{10}[\text{ambi}]_{\text{free}}$ was calculated from the relevant titration curves by the usual procedure.[5] The results of typical titrations are tabulated.

Absorption Spectra of Copper Complexes.—Stock solutions of 0·02M-copper sulphate and 0·1M-ambi were mixed to give solutions in which $[Cu^{2+}]$ = 0·002M and the ratio $[Cu^{2+}]$: [ambi] was 1 : 0, 1 : 1, 1 : 3, 1 : 5, 1 : 10, and 1 : 12 respectively. The pH was adjusted to 4·5. Absorption curves (Fig. 3) were measured between 450 and 900 mμ with a Unicam, S.P. 500 spectrophotometer with matched 4 cm. cells.

One of us (O. A. W.) is indebted to the World Health Organisation and to the Medical Research Council for generous financial assistance.

INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

[*Received, February* 16*th*, 1959.]