944. Complex-forming Agents Similar to 2,2′-Bipyridyl. Part I. Some Ligands containing Imidazole.

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A general study has been made of chelated complexes formed by 4-2′-pyridylimidazole and 2,2′-bi-imidazolyl. With neither ligand can stability constants of the metal complexes be evaluated conveniently by potentiometric titration. Two series of solid complexes are formed by each ligand, those from acid solution being in general similar to the corresponding compounds of bipyridyl, whereas those from alkaline solution are " inner complexes " formed by loss of the imidazole imino-hydrogen. The ferrous complex of bi-imidazolyl is yellow, not red.

2,2′-Bipyridyl is well known as an analytical reagent for ferrous iron and for a number of other metal ions in a lower valency state. Much less attention has been given to other bases of the type. Bailar and Busch,[1] and Stoufer and Busch,[2] studied compounds in which an imine structure was generally achieved by a –C=NR side chain at the position 2 of pyridine. Studies with compounds containing heterocyclic rings other than pyridine, however, have been very few. Breckenridge [3] published the absorption spectra of ferrous and cuprous complexes with ligands containing quinoline, isoquinoline, or thiazole. Harkins and Freiser [4] described in greater detail the reactions of pyridyl-benzimidazole and -imidazoline. We have studied a number of other examples of the type, chiefly containing imidazole or thiazole rings. Here we describe work with 4-2′-pyridylimidazole and 2,2′-bi-imidazolyl.

Experimental

Materials.—(i) *4-2′-Pyridylimidazole.* 2-Acetylpyridine oxime was obtained by addition of the ketone to aqueous hydroxylamine hydrochloride, being liberated by addition of solid potassium carbonate and recrystallised from ether. From it the 4-2′-pyridylimidazole was prepared essentially by the method of Clemo *et al.*[5] The toluene-*p*-sulphonate of the oxime was treated with potassium in dry ethanol. We found it essential to keep the mixture cool at this stage or much of the 2-aminoacetylpyridine was lost.

The ligand itself was obtained from the final reaction as a yellowish gum. Recrystallisation of this from ether–light petroleum (seeding) gave crystals, m. p. 111·5° (Found: C, 66·4; H, 4·9; N, 29·0. Calc. for $C_8H_7N_3$: C, 66·2; H, 4·8; N, 29·0%).

(ii) *2,2′-Bi-imidazolyl.* Debus [6] prepared this compound by condensing ammonia and glyoxal. We found the yield to be greatly increased by preparing the glyoxal *in situ* from concentrated ammonia solution and the sodium salt of glyoxal bisulphite. The precipitated compound was recrystallised from a large volume of water (Found: C, 53·8; H, 4·6; N, 41·6. Calc. for $C_6H_6N_4$: C, 53·7; H, 4·5; N, 41·8%).

(iii) " AnalaR " dioxan was purified as described by Weissberger and Proskauer.[7] Other reagents, where possible, were of " AnalaR " grade, or they were purified by appropriate methods.

Determinations.—Dissociation constants for the ligands were obtained by potentiometric titration at 25·0° ± 0·1°. 5·00 ml. of *ca.* 0·1N-perchloric acid, 10·00 ml. of 10^{-2}M-aqueous solution of the organic base, and 35·00 ml. of air-free water were titrated with carbonate-free 0·1000N-sodium hydroxide. Stirring was by means of nitrogen, purified and saturated with aqueous vapour at 25·0°.

Attempts were made to obtain stability constants for the metal complexes from the results of similar titrations performed in the presence of metal ions added as their perchlorates, the metal : ligand molar ratio generally being 1 : 3.

Potentiometric Titrations: Determinations of Dissociation Constants.—p*K*'s quoted are stoicheiometric and refer to ionic strength ~0·01M.

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[1] Bailar and Busch, *J. Amer. Chem. Soc.*, 1956, **78**, 1137.
[2] Stoufer and Busch, *J. Amer. Chem. Soc.*, 1956, **78**, 6016.
[3] Breckenridge, *Canad. J. Chem.*, 1954, **32**, 512, 641.
[4] Harkins and Freiser, *J. Amer. Chem. Soc.*, 1956, **78**, 1143.
[5] Clemo, Holmes, and Leitch, *J.*, 1938, 953.
[6] Debus, *Annalen*, 1859, **107**, 199.
[7] Weissberger and Proskauer, " Organic Solvents," Oxford Univ. Press.

4-2′-Pyridylimidazole. The p*K*′ of this compound under our conditions was 5·46. Up to a pH of 11·5 there was no evidence in the titration curve for dissociation of the imino-hydrogen atom. This is consistent with the known fact that it is difficult to remove this hydrogen and with the result obtained by Harkins and Freiser [4] in the titration of 2-2′-pyridylbenzimidazole and -imidazoline. 4-2′-Pyridylimidazole is thus similar to 2,2′-bipyridyl, which is also monobasic under these conditions.

2,2′-Bi-imidazolyl. This compound and its complexes were very insoluble in cold water; the titrations were carried out in 50% (v/v) dioxan–water. The pH correction for this medium was made as given by Van Uitert and Haas [8] and by Holmes and Crimmin.[9] The p*K*′ was 4·57. No other ionisation was found up to pH 11·5, so this compound also behaves as a mono-acidic base.

Potentiometric Titrations: Determination of Stability Constants.—With 4-2′-pyridylimidazole, complex formation began at quite low pH's, particularly with copper(II) and nickel(II), so that no great reliance could be placed on the results. When formation curves were plotted they were not symmetrical. For these reasons no stability constants were evaluated.

With 2,2′-bi-imidazolyl, chelation occurred at higher pH's but the formation curves were not completely symmetrical so that no stability constants are given.

The titration curves show that, in both cases, after neutralisation of all the acid present either as free acid or protonated base, continued titration is accompanied by further liberation of hydrogen ions. This could be due either to hydrolysis or to dissociation of the imino-hydrogen of the imidazole. It may well be due to the latter, as will be seen. It is not found when the ligand is titrated alone. It must be partly responsible for the dissymmetry in the upper part of the formation curves.

A more detailed study of the stability constants will be published later.

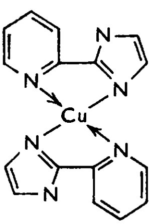
Solid Complexes of 4-2′-Pyridylimidazole.—Solid complexes were obtained by precipitation from an aqueous solution containing ligand and metal ion. They were identified by analysis and by conductance measurements. Metal analyses were by standard semimicro-gravimetric methods after destruction of the organic material by wet oxidation; water determinations were by loss of weight at 115° and, except for copper complexes, by Karl Fischer titration.

Copper complexes. Several compounds were obtained:

(1) Cupric ions and ligand in aqueous solution of pH <7 gave an intensely blue-green solution ($\lambda_{max.}$ 710 mμ), the coloured material not being extractable into pentyl alcohol. Addition of sodium chloride gave a bright green crystalline precipitate, insoluble in pentyl alcohol but soluble in hot water. The green *product* obtained after centrifugation, washing with cold water, and drying in a vacuum-desiccator and then at 115° was formulated as CuA_2Cl_2, where A = pyridylimidazole (Found: Cu, 15·0; C, 45·3; H, 2·8; N, 19·0; Cl, 16·9. $CuC_{16}H_{14}N_6Cl_2$ requires Cu, 15·0; C, 45·2; H, 3·3; N, 19·8; Cl, 16·7%). When dried *in vacuo*, it retained one molecule of water, which was removed on heating.

(2) A blue solid similarly obtained on addition of sodium perchlorate was the corresponding *perchlorate* [Found: Cu, 11·2; C, 35·3; H, 3·6; N, 15·8; ClO_4, 35·9. $CuC_{16}H_{14}N_6(ClO_4)_2$ requires Cu, 11·5; C, 34·8; H, 2·6; N, 15·2; ClO_4, 36·0%].

(3) When the aqueous suspension in (1) or (2) is warmed to dissolve the precipitate, and aqueous sodium hydroxide is added to pH 8—9, a blue, rather gelatinous precipitate is obtained. Centrifugation and washing with hot water (to remove cationic complex) gave a blue-green solid, insoluble in water but soluble in ethanol or pentyl alcohol (Found, in material dried at 105°: Cu, 17·8; C, 53·4; H, 3·7; N, 23·7; Cl or ClO_4, 0%). The analysis approximates to that required for CuR_2, where R represents pyridylimidazole less one hydrogen atom (Calc. for $CuC_{16}H_{12}N_6$: Cu, 18·1; C, 54·6; H, 3·4; N, 23·9%).



(I)

The complexes from acid solution are those expected, being similar to those of bipyridyl; that obtained from slightly alkaline solution may be represented as an " inner complex " (I).

Such formulæ are supported by conductance measurements. (*a*) The diperchlorate and the corresponding complex obtained from bipyridyl had almost identical values of Λ_∞ in nitrobenzene, and plots of conductance against the square root of concentration had similar slopes. Both ligands gave values acceptable for a uni-bivalent electrolyte. (*b*) Values of Λ_∞ obtained

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[8] Van Uitert and Haas, *J. Amer. Chem. Soc.*, 1953, **75**, 451.

[9] Holmes and Crimmin, *J.*, 1955, 3467.

with the dichloride were much lower, but so were those for (Cu bipy$_2$)Cl$_2$; and the slopes were similar. The chloride, unlike the more ionic perchlorate, may be partly co-ordinated when nitrobenzene is used as a solvent. (*c*) A solution of the inner complex in nitrobenzene had a conductance too low to be measured. Values of Λ_∞ in nitrobenzene were: [Cu (pyim)$_2$](ClO$_4$)$_2$ 60·0, [Cu (bipy)$_2$](ClO$_4$)$_2$ 60·0, [Cu (pyim)$_2$]Cl$_2$ 9·7, [Cu (bipy)$_2$]Cl$_2$ 8·5, Cu (pyim — H)$_2$ 0·0.

(4) 2,2′-Bipyridyl gives well-defined complexes with copper(I), so the previous preparations were repeated in the presence of reducing agents. If hydroxylamine hydrochloride was present at pH <7, the cationic complexes were once more obtained, as might be expected. If, however, it was added before the solution was made alkaline during the preparation of the inner complex, then a light green flocculent precipitate was formed, insoluble in ethanol and pentyl alcohol, and differing from the other compounds. Preliminary work showed it to be probably a hydroxy-complex; it is being further investigated.

Nickel. At pH 4 a pink *complex* was precipitated on addition of an excess of aqueous sodium iodide to a 1 : 3 molar ratio of nickel chloride and ligand. This became buff when dried *in vacuo*, and proved rather soluble in hot water (Found: Ni, 7·0; C, 35·0; H, 3·8; N, 15·1; I, 31·3; H$_2$O, 7·5. NiC$_{24}$H$_{21}$N$_9$I$_2$,4H$_2$O requires Ni, 7·2; C, 35·2; H, 3·6; N, 15·4; I, 31·0; H$_2$O, 8·8%).

Addition of aqueous sodium hydroxide to pH 8, after warming to dissolve the original precipitate, gave a pale green-blue precipitate. This *product* was analysed after drying *in vacuo* and is formulated as NiR$_2$,2H$_2$O (R as above) (Found: Ni, 15·5; C, 50·6; H, 4·4; N, 22·1; I, 0; H$_2$O, 7·7. NiC$_{16}$H$_{12}$N$_6$,2H$_2$O requires Ni, 15·3; C, 50·7; H, 4·2; N, 21·9; H$_2$O, 9·4%).

Cobalt. When an excess of aqueous sodium iodide was added to a solution of cobalt(II) chloride (1 mol.) and ligand (3 mols.) under conditions which prevented oxidation, a brown precipitate appeared which, after drying *in vacuo*, gave analyses corresponding to CoA$_3$I$_2$,4H$_2$O (Found: Co, 6·9; C, 33·9; H, 3·6; N, 15·8; I, 34·3; H$_2$O, 7·8. CoC$_{24}$H$_{21}$N$_9$I$_2$,4H$_2$O requires Co, 7·2; C, 35·1; H, 3·6; N, 15·4; I, 30·9; H$_2$O, 7·8%). Precipitation in aerobic conditions gave a precipitate of similar composition.

When this complex was dissolved by heating the solution and sodium hydroxide was then added, no inner complex was precipitated but the colour of the solution changed from pale buff to orange. The solution, on concentration, gave an orange deposit which, after drying and analysis, proved to be the cobalt(III) inner *complex* (Found; Co, 11·2; C, 58·6; H, 3·6; N, 25·9; halide, 0; sodium, 0. CoC$_{24}$H$_{21}$N$_9$ requires Co, 12·0; C, 58·7; H, 3·7; N, 25·7%).

If sodium hydroxide was added to a 1 : 2 (molar) mixture of cobalt(II) chloride and ligand, then at pH $\sim$8 the cobalt(II) inner *complex* was obtained as a brown precipitate (Found: Co, 16·3; C, 52·0; H, 3·5; N, 23·4; Cl, 0. CoC$_{16}$H$_{12}$N$_6$,H$_2$O requires Co, 16·1; C, 52·6; H, 3·9; N, 23·0%). When an attempt was made to wash this with ethanol it blackened. The complex was therefore heated with ethanol; an orange solution and a black precipitate of a hydrated cobalt oxide resulted. On evaporation, the orange solution gave the orange cobalt(III) inner complex once more.

Ferrous iron. Cationic *complexes* were prepared, as above. All were red, *e.g.*, FeA$_3$I$_2$,3H$_2$O (Found: Fe, 7·1; C, 35·4; H, 3·6; N, 16·3; I, 32·3; H$_2$O, 6·3. FeC$_{24}$H$_{21}$N$_9$I$_2$,3H$_2$O requires Fe, 7·0; C, 36·1; H, 2·9; N, 15·8; I, 31·8; H$_2$O, 5·8%).

When a 1 : 3 or a 1 : 2 molar ratio was used and the mixture made alkaline, a scarlet precipitate was first obtained which became brown when dry. It contained one molecule of ligand to each iron atom. This was a hydrolysed product which is being further investigated.

Ferric iron. A *complex*, FeA$_3$I$_3$,3H$_2$O, was prepared as a brown precipitate (Found: Fe, 6·0; C, 31·8; H, 2·7; N, 14·0; I, 39·6; H$_2$O, 5·9. FeC$_{24}$H$_{21}$N$_9$I$_3$,3H$_2$O requires Fe, 6·0; C, 31·1; H, 2·5; N, 13·6; I, 41·1; H$_2$O, 5·8%). Attempts to produce an inner complex resulted in precipitation of ferric hydroxide.

Molar conductances in nitrobenzene were negligible for all the inner complexes. Values for some of the others are given in Table 1.

Both of our iron complexes gave low values for Λ_∞ in nitrobenzene. In water, however, the figures were much nearer those expected and it must be assumed that some association had occurred in nitrobenzene.

Solid Complexes of 2,2′-Bi-imidazolyl.—Again two series of complexes were isolated but the methods were modified slightly because the ligand was very much less soluble in water, and the cationic complexes were rather less soluble in hot water.

Copper. Bi-imidazolyl (0·1—0·2 g.) was dissolved in 0·1M-hydrochloric acid (10 ml.), and

TABLE 1.

Values of Λ_∞ in nitrobenzene for some cationic complexes.

Complex	Λ_∞	Ref.	Complex	Λ_∞	Ref.
$Ni(bipy)_3(ClO_4)_2$	79·0	*a*	$Fe(py\text{-}im)_3I_2$	39·5	*a*
$Ni(bipy)_3Cl_2$	66·0	*a*	$Fe(py\text{-}im)_3I_3$	48·0	*a*
$Ni(py\text{-}im)_3I_2$	73·5	*a*	$Rh(bipy)_3(ClO_4)_3$	~120	*b*
$Co(bipy)_3(ClO_4)_2$	78·5	*a*	$Fe(bipy)_3I_2$	57·8	*c*
	~75	*b*	$Cu(phenan)_2(ClO_4)_2$	43·1	*d*
$Co(py\text{-}im)_3I_2$	65·0	*a*	$[Rh(bipy)_3Cl_2]ClO_4$	~32	*b*

(*a*) Present work, valid for 25·0°. (*b*) Estimated from the data of Martin and Waind (*J.*, 1958, 4284), valid for 25°. (*c*) Nyholm and Harris (*J.*, 1956, 4377), valid for $2·5 \times 10^{-4}$M and 20°. (*d*) *Idem, ibid.*, valid for $5·0 \times 10^{-4}$M and 25°.

cupric sulphate added so that the ligand : metal molar ratio was >2 : 1. Aqueous sodium hydroxide was added to pH 3·5, the solution becoming intensely green and a small amount of green crystals appearing. These were the cationic complex; they were redissolved by addition of water and warming. An excess of solid sodium chloride was added, giving a bright green crystalline *complex*; this was centrifuged off, recrystallised from dilute sodium chloride solution, and dried *in vacuo* (Found: Cu, 15·2; Cl, 17·1; H_2O, 4·6. $CuC_{12}H_{12}N_8,Cl_2H_2O$ requires Cu, 15·1; Cl, 16·9; H_2O, 4·3%).

The original solution containing hydrochloric acid was warmed and aqueous sodium hydroxide added to pH ~8. A pink precipitate of the inner *complex* appeared. This was centrifuged off while hot and the solid digested with hot water several times to remove unchanged ligand or cationic complex. The final residue was light brown (Found: Cu, 18·9; C, 45·0; H, 3·7; N, 34·0; Cl, 0. $CuC_{12}H_{10}N_8$ requires Cu, 19·3; C, 43·7; H, 3·1; N, 34·0%). Specimens which had not been washed thoroughly with hot water contained small amounts of chloride.

Complexes with other metals were prepared in the same way.

Nickel. The *complex sulphate* was pale blue (Found: Ni, 10·4; C, 39·3; H, 3·4; N, 29·9; SO_4, 17·4; H_2O, 0. $NiC_{18}H_{18}N_{12}\cdot SO_4$ requires Ni, 10·5; C, 38·8; H, 3·3; N, 30·2; SO_4, 17·2%).

Attempts to wash solid NiA_3Cl_2 to remove the excess of sodium chloride produced a colourless residue of ligand. All the chloride or iodide complexes of this ligand were very easily hydrolysed.

A *product*, NiR_2, formed a brown solid from slightly alkaline solution; when prepared from chloride solution it was light brown (Found: Ni, 17·9; C, 43·8; H, 3·0; N, 34·1. $NiC_{12}H_{10}N_8$ requires Ni, 18·1; C, 44·4; H, 3·1; N, 34·5%), but when prepared from sulphate, however, analyses for nickel were always high, and for ligand low, indicating hydrolysis; the solid was always much darker brown.

Cobalt. A *sulphate*, CoA_3SO_4, was pink (Found: Co, 10·4; C, 39·2; H, 3·3; N, 30·5; SO_4, 17·7. $CoC_{18}H_{18}N_{12}\cdot SO_4$ requires Co, 10·6; C, 38·8; H, 3·3; N, 30·2; SO_4, 17·2%).

A purple product, CoR_2, was obtained from alkaline solution but was impure (Found, for material prepared from sulphate: Co, 18·7; C, 42·7; H, 3·1; N, 33·2. Calc. for $CoC_{12}H_{10}N_8$: Co, 18·1; C, 44·3; H, 3·1; N, 34·5%). The remarks made for the nickel complex apply in this case also.

Ferrous iron. A yellow *product*, FeA_3SO_4, was precipitated from an almost colourless solution. It was easily hydrolysed and was washed with dilute sulphuric acid (unlike the other cation sulphates formed by this ligand) (Found: Fe, 9·9; C, 38·5; H, 3·4; N, 30·0; SO_4, 17·6. $FeC_{18}H_{18}N_{12}\cdot SO_4$ requires Fe, 10·1; C, 39·0; H, 3·3; N, 30·3; SO_4, 17·3%).

No neutral complex was isolated; although a pale green precipitate was obtained at pH 10 it became contaminated with ferric hydroxide in attempts to purify it.

No complex was obtained for ferric iron, any precipitate being ferric hydroxide.

DISCUSSION

Imidazole does not release a hydrogen ion when titrated with sodium hydroxide, nor does it in the presence of metal ions. This has been shown by Edsall *et al.*[10] to pH 8, and by Holmes and Morris-Jones [11] for a number of substituted imidazoles to much higher pH's. The lower p*K* of the conjugated ligands considered in this paper would make for easier

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[10] Edsall, Felsenfeld, Goodman, and Gurd, *J. Amer. Chem. Soc.*, 1954, **76**, 3054.

[11] Holmes and Morris Jones, unpublished information.

release of the imino-hydrogen but there is no evidence for this up to pH 11. In the presence of metal ions, however, the stability of the chelated system causes the p*K* of the imino-hydrogen to be lowered further and the hydrogen is released on titration with sodium hydroxide.

This results in the formation of two series of complexes, with both 4-2′-pyridylimidazole and 2,2′-bi-imidazolyl. Those from acid solution are the normal cationic complexes; those from slightly alkaline solution are inner complexes and non-electrolytes.

The cationic complexes formed by the pyridylimidazole resemble those of bipyridyl. Copper(II) forms a bis-complex; bivalent cobalt, nickel, and iron form tris-complexes. The last-named is deep red, like the corresponding bipyridyl complex, and has a molar extinction coefficient of almost 10^4 in aqueous solution. However, unlike in the bipyridyl case, heating the tris-complexes *in vacuo* at 140° causes no apparent change. Nor can copper(I) derivatives be made, directly or by simple reduction with hydrazine or hydroxylamine.

Similar complexes can, in general, be formed from 2,2′-bi-imidazolyl. However, although this ligand is about as basic as the pyridylimidazole its complexes are more easily hydrolysed. In particular, the halides proved difficult to purify. Approximate formation constants show that they are less stable, so this result is not unexpected. The iron(II) complex is not highly coloured and would probably be paramagnetic.

The systems will be discussed later in detail, together with other similar ones. The behaviour of the ligands now considered may give some support to Pauling's suggestion of imidazole ionisations in hæmoglobin; as has already been said, no such ionisation has been observed with complexes of imidazole itself [10] or with compounds such as histamine and related molecules with a second nitrogen atom which is aliphatic,[12] yet it becomes possible in the more highly conjugated systems discussed in this paper.

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[12] Holmes and Jones, *J.*, 1960, 2398.