Strong Hydrogen Bonding between Imidazole and Trimethyl Phosphate

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A new crystalline 1 : 1 complex of imidazole and trimethyl phosphate has been prepared and its i.r. and n.m.r. spectra reveal the presence of strong asymmetrical N–H · · · O=P hydrogen bonds.

The hydrogen bonding properties of imidazole and its derivatives are of considerable importance in biochemistry. In recent years experimental evidence has been put forward to support the suggestions that hydrogen bonding of histidyl imidazoles in haemoglobins in both the proximal (to other protein residues) and distal (to bound dioxygen) positions plays an important role in determining the oxygen-binding properties of the proteins.[1–6] As part of our programme of research on hydrogen bonding in model biological systems[7] we have investigated the interactions of imidazoles with model oxygen-centred hydrogen-bond electron-donors. We report here a novel N–H . . . O=P hydrogen bond formed between imidazole and trimethyl phosphate. This bond is notable for its strength, high polarisibility, and its often unexpected effects on non-local sites within the complex.

Imidazole readily dissolves endothermically in dry trimethyl phosphate. The viscosity of a 50 mole % imidazole solution increases with time and crystallisation eventually occurs to produce a hygroscopic 1 : 1 imidazole–trimethyl phosphate complex.† This process can be speeded up by first warming and then cooling the solution suggesting that disruption of imidazole chains (which are themselves held together by strong hydrogen bonds) is the rate-determining step for complex formation. This is confirmed by n.m.r. and i.r. spectroscopic monitoring of the process although the details of this are beyond the scope of this preliminary article and will be published subsequently. The 1 : 1 complex can also be grown from a 1 : 1 mixture of the components in tetrahydrofuran.

The solid-state i.r. spectrum of the complex (Figure 1) reveals a very intense, broad N–H stretching vibration with

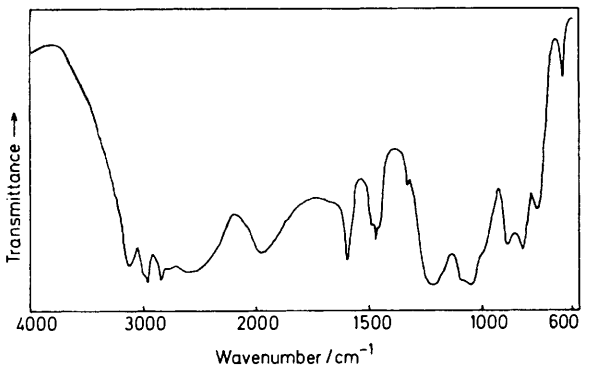
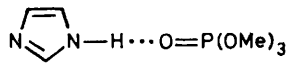


Figure 1. I.r. spectrum of the imidazole–trimethyl phosphate complex.

definite sub-maxima in the 3000—1600 cm^{-1} region. The spectrum differs from those of the parent molecules in several other regions, notably near 1200 cm^{-1} where the P=O stretching vibration of the phosphate is 55 cm^{-1} to lower energy than the corresponding band in the neat phosphate. The spectrum of the complex as a solution in $CHCl_3$ is very similar whereas that of a saturated solution in dimethyl sulphoxide shows an additional sub-maximum in the continuum at *ca.* 1850 cm^{-1} and the shift in the P=O stretch is reduced by *ca.* 15 cm^{-1}. These observations are consistent with a strong, asymmetric, easily polarisable hydrogen bond that interacts with its environment (**1**).[8] The sub-maxima in the continuum are probably due to Fermi resonance interactions of the stretching mode with other vibrations of the hydrogen bond.[9]

The n.m.r. spectra of the complex in perdeuteriodimethyl sulphoxide reveal a number of interesting and unexpected features (Table 1). The ^{13}C and ^{31}P n.m.r. spectra of the complex are very similar to those of the parents ($\Delta\delta_C$ and $\Delta\delta_P$ $\leqslant 2$ p.p.m.) whereas the ^{15}N n.m.r. spectra of the complex and of imidazole are quite different ($\Delta\delta_N$ *ca.* 40 p.p.m.). These results

† ^1H N.m.r. integration is consistent with a 1 : 1 complex containing residual water. Attempts to remove these last traces of water resulted in loss of imidazole (leaving Me_3PO_4) or in decomposition. The mass spectrum of the complex shows, in addition to the fragmentation pattern of imidazole, an unusually strong peak at m/z 126. This is presumably due to the formation of $(MeO)_2PO_2H$ on decomposition of the complex. Preliminary thermogravimetric and elemental analyses are consistent with these conclusions.



(1)

Table 1. N.m.r. chemical shifts[a] of the imidazole–trimethyl phosphate complex, imidazole, trimethyl phosphate, and the imidazole anion.

	Complex[b,c]	Imidazole[b]	Me_3PO_4[b]	Imidazole anion[b]
N-*H*	*ca.* 14 (s, br)	11.4 (s)	—	—
C(2)-*H*	8.9 (s)	7.8 (s)	—	7.1 (s)[d]
C(4,5)-*H*	7.6 (s)	7.1 (s)	—	6.7 (s)[d]
CH_3	3.4 (d)	—	3.8 (d)	—
C(2)	134 (d)	136 (d)	—	146 (d)[e]
C(4,5)	120 (d)	122 (d)	—	127 (d)[e]
CH_3	52 (d of q)	—	54 (d of q)	—
P	0.7 (s,br)	—	2.3 (s)	—
N(1,3)	210(s)[f]	170(s)	—	—

[a] P.p.m. with respect to Me_4Si (^1H, ^{13}C), H_3PO_4 (^{31}P), and 0.1M $MeNO_2$ in $CDCl_3$ (^{15}N). [b] Saturated dimethyl sulphoxide solutions unless stated otherwise. [c] The observed chemical shifts of the complex are somewhat dependent on the bulk medium. In particular, the C(2)-*H* and C(4,5)-*H* chemical shifts occur at δ 8.2 and 7.0 respectively in $CDCl_3$ although the Δδ(H) between these resonances is approximately medium independent. [d] S. Bradamante, G. Pagani, and A. Marchesini, *J. Chem. Soc., Perkin Trans.* 2, 1973, 568. [e] Saturated aqueous solutions of the potassium salt: R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.*, 1968, **90**, 4232. [f] Neat 1:1 imidazole–Me_3PO_4 solution (no signal was observed for the complex in Me_2SO).

along with the observed changes in the i.r. spectra are consistent with the concept of a highly localised hydrogen bond interaction with major changes in electron density distribution being contained within the three-atom (NHO) unit. The ^1H n.m.r. spectrum is quite unexpected, however, in that the imidazole CH proton resonances move downfield on complexation [Δδ(2-H) *ca.* 1.2, Δδ(4- and 5-H) *ca.* 0.5 p.p.m.]. This can be compared to the effect of deprotonation whereby the CH proton resonances experience a small upfield shift. We are not able to offer an explanation for these unusual observations at this stage.

We have shown that imidazole is capable of forming strong intermolecular hydrogen bonds with neutral oxygen-centred electron donors. It seems reasonable, therefore, to suggest that naturally occurring imidazoles may well be involved in strong, easily polarisable hydrogen bonding interactions in biological systems such as haemoglobins. Such a strong interaction between bound dioxygen and a distal histidyl imidazole in certain haemoglobins could explain a number of recent observations including the unusually large Fe–O–O bond angles in oxyhaemoglobin, oxymyoglobin, and 'picket fence' compounds.[4] The rapid autoxidation of the α-subunit in oxyhaemoglobin could also be explained in terms of a strong, easily polarisable O · · · H–N hydrogen bond.[4] Strong hydrogen bonding of oxygen centres in protein residues to proximal imidazoles producing imidazole anion character could also explain the apparent occurrence of five-co-ordinate haems in ferric horseradish peroxidase and cytochrome c'.[3]

Received, 22nd October 1982; Com. 1227

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