The Enhanced Reactivity of a Cyclic Phosphoramidite

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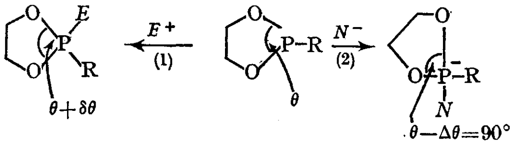
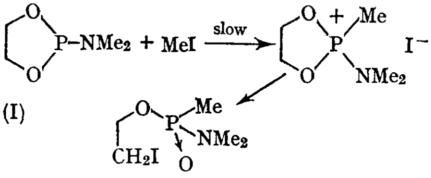
THE high rate of hydrolysis of cyclic phosphates has been explained, in an elegant manner by Westheimer and his colleagues,[1] by the release of ring strain on formation of the transition state or pentacovalent intermediate with a cyclic O–P–O angle of 90°. We have used this principle to interpret the reactivity of tervalent phosphorus compounds. Thus nucleophilic interaction of phosphorus should lead to a slight increase in bond angles since the transition state involves phosphorus in the sp^3 hybridised state. On the other hand, nucleophilic attack on phosphorus leads to sp^3d hybridisation of the phosphorus atom and a large decrease in the cyclic bond angle.



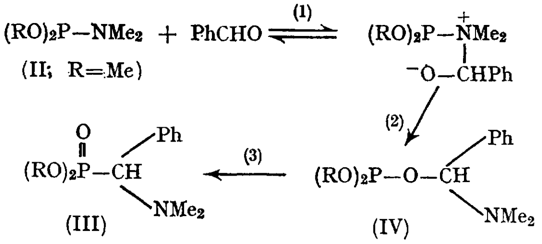
E^+ = electrophile; N^- = nucleophile.

Comparison of the reactivities of cyclic and analogous acyclic P^{III} compounds should enable the rôle of the phosphorus in these reactions to be deduced. The rates of reaction of 2-dimethylamino-1,3,2-dioxaphospholan (I) and dimethyl *NN*-dimethylphosphoramidite (II) with methyl iodide, benzaldehyde, and phenyl isocyanate are compared in the Table. The rate constants for the reactions of (I) and (II) with methyl iodide are similar, in agreement with the nucleophilic action (1) of the phosphorus atom. The cyclic compound (I) is considerably more reactive than (II) in the other reactions indicating that these are of the second kind (2).

All the reactions were followed by proton n.m.r. at 34° with nitrobenzene as solvent. The reaction with methyl iodide, carried out under first order conditions, was characterised by a downfield shift of the $N(CH_3)_2$ and $O{\cdot}CH_3$ signals and the appearance of $P{\cdot}CH_3$ signals (at τ 8·56; J 13·5 c./sec). The product gave a ratio of 1 : 2 : 1 for these differently bound protons, and was further identified by the ^{31}P absorption of (I) at −27·5 p.p.m. [*cf.* the ^{31}P absorption of (I) at 137 p.p.m.]. These observations show that quaternisation occurs exclusively on the phosphorus atom according to the reaction:



The reactions with benzaldehyde and phenyl isocyanate were carried out with equimolecular mixtures of the reactants, and followed by the change in intensity of the doublets, centred at τ 7·34 and 7·45 for (I) and (II) respectively, due to the P–NMe$_2$ protons, which collapsed to singlets. Reaction of (I) with benzaldehyde led to a single product, assigned[2] structure (III), which may be formed by the general mechanism involving a cyclic transition state postulated previously,[3] in which the P–N bond is broken in the rate-determining step (2). This involves nucleophilic attack at the phosphorus atom, which accounts for the enhanced reactivity of the cyclic compound.



The reactions of (I) and (II) with phenyl isocyanate gave single products, each with a singlet peak (NMe$_2$) with the same Me$_2$N : MeO

Reactions of (I) *and* (II) *in nitrobenzene at* 34° *with methyl iodide, benzaldehyde, and phenyl isocyanate*

Reactant	(I)	(II)	$k_{(I)}/k_{(II)}$
Methyl iodide	0·03 min.$^{-1}$	0·097 min.$^{-1}$	0·33
Benzaldehyde	$0{\cdot}97 \times 10^{-4}$ l.M^{-1} min.$^{-1}$	0·11/l.M^{-1} min.$^{-1}$	1156
Phenyl isocyanate	$1{\cdot}12 \times 10^{-3}$ l.M^{-1} min.$^{-1}$	0·38/l.M^{-1} min.$^{-1}$	339

ratio as for the starting materials, and the ^{31}P spectra showed peaks at 127 and 128 p.p.m. These observations and the absence of a characteristic P=O peak, suggest that the products are in the P^{III} form [*cf.* structure (IV)].

On the other hand, the quaternisation of the cyclic ester is three times slower than that of (II), and a similar rate difference is found for the analogous reactions of trimethyl phosphite and 2-methoxy-1,3,2-dioxaphospholan with ethyl iodide.[4] In view of the reduced steric hindrance of the cyclic ester, this significant rate reduction is probably caused by a small increase in the cyclic O–P–O bond angle on formation of the transition state.

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