Alkaline Hydrolysis of Cyclic Phosphoramidates

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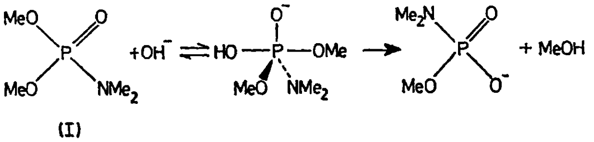
Summary The results of kinetic and product studies on the alkaline hydrolysis of cyclic phosphoramidates are rationalised in terms of trigonal bypyramidal intermediates which in the case of compounds with sufficient basic nitrogen atoms can exist in conformations involving apical nitrogen.

The classic work of Westheimer[1] showing that the acid-catalysed hydrolysis of cyclic phosphates produces both cyclic and *exo*-cyclic P–O fission led to the hypothesis of pseudo-rotation in intermediate oxyphosphoranes. We report here similar behaviour in the alkaline hydrolysis of cyclic phosphoramidates, which argues strongly in favour of pseudorotation in an intermediate generated in alkaline solution.



(1)

(I)

Whereas acyclic phosphoramidates are hydrolysed in alkaline solution with the exclusive release of the corresponding alcohol,† *e.g.* equation (1), the cyclic *N*-alkyl phosphoramidates (II) and (III) react *ca.* 2×10^6 times faster in alkaline solution with considerable P–N fission (Table 1). It is very remarkable that the extent of P–N bond breaking is almost the same with the amino group in the cyclic and *exo*-cyclic positions. In contrast no release of methanol from (II) was observed. The reactions are strictly first order with respect to hydroxide ion over a wide concentration range (usually 0·01—0·5N). At higher concentrations the rate constants decrease presumably owing to changes in activity coefficients.

Table 1. Products of alkaline hydrolysis of phosphoramidates[a]

		% Bond fission[b]	
	P–N	P–O cyclic	P–O acyclic
(I)[c]	0	—	100
(II)	40	60	0
(III)	30	20 (P–O′) 50 (P–O)	—
(IV)	0	100	0
(VII)	5	4	91 92(u.v.)

[a] Obtained by ^{31}P F.T. n.m.r. analysis. Accuracy *ca.* ± 1%. [b] Measured at 25°, unless otherwise stated, in 50% aqueous dioxan (ca. 0·75 M reactants). [c] Measured at 80°.

The *N*-phenyl phosphoramidate (IV), corresponding to (II), however, reacts under similar conditions with exclusive fission of the cyclic P–O bond, equation (2). This is to be

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† This reaction was shown by ^{18}O-tracer studies to proceed *via* 85% C–O bond fission and 15% P–O bond fission, at 80°.

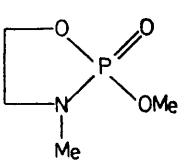
Table 2. Hydrolysis rates of cyclic and acyclic phosphoramidates at 25° in water.

Ester	k/l mol^{-1} s^{-1}	Ester	k/l mol^{-1} s^{-1}
(VII)	$1{\cdot}20 \times 10^{-1}$	$Me_2N(MeO)P(O)OPh$	$6{\cdot}85 \times 10^{-6}$
(II)	$0{\cdot}8 \times 10^{-1}$	$Me_2N(MeO)P(O)OMe$[a]	$2{\cdot}37 \times 10^{-7}$ (extrapolated)

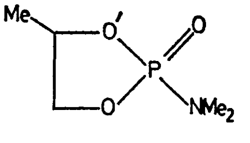
[a] 15% P–O fission.

expected in view of the low apicophilicity[2] of nitrogen compared to oxygen.‡ In view of the increased leaving-group tendency of an aromatic amine compared with an aliphatic amine, in line with their relative acidities, the ready release of amine from (II) and (III) indicates some form of acid catalysis during the hydrolysis. The highly electronegative quaternary ammonium group thus formed presumably has a very strong tendency to adopt an apical position. The acid-catalysed hydrolysis of phosphoramidates is extremely rapid, with the exclusive release of amine, showing the quaternary ammonium group to be very labile in contrast to the unprotonated amino-group.

These considerations lead to a reaction mechanism involving the formation of a zwitterionic intermediate (VI) as the result of proton transfer in concentrated alkaline solution (Scheme).



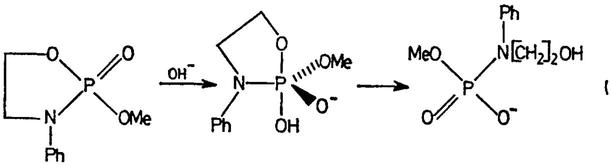
(II)



(III)

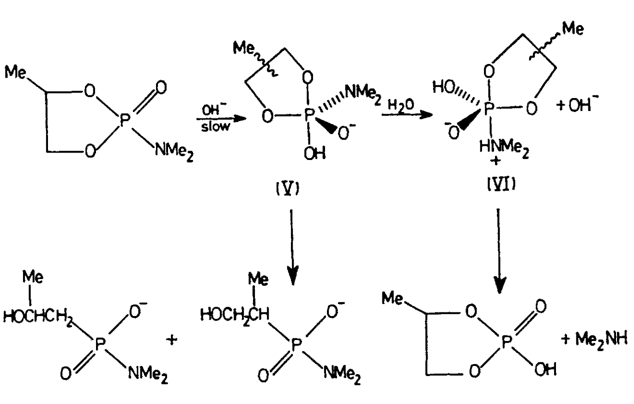
If formation of (VI) competes favourably with P–O bond cleavage in (V), extensive P–N bond cleavage should occur.

Reaction of (II) with sodium methoxide in methanol gave 100% P–N fission. This remarkable result is tentatively attributed to increased electrostatic attraction in the zwitterion in the solvent of reduced polarity.



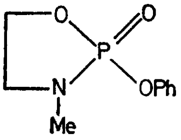
(IV) (2)

It remains to consider the extensive P–N fission of the cyclic compounds and negligible P–N fission of the acyclic analogue. The difference probably lies in the relative stability of the five-co-ordinate species.



Scheme

In the case of the cyclic analogue, the release of angle strain leads to the formation of a relatively stable oxyphosphorane. The life-time is sufficient to allow pseudorotation in the initial intermediate to occur after protonation to give (VI). The acyclic intermediate, with a smaller lifetime, decomposes with breaking of the cyclic P–O bond, before protonation and pseudorotation can occur (equation 1).



(VII)

In this connection we find that aliphatic and aromatic esters [*e.g.* (VII)] of the cyclic acid react at similar rates, whereas the acyclic aromatic ester undergoes alkaline P–O fission *ca.* 200 times more rapidly than the aliphatic analogue, in agreement with the increased leaving group tendency of phenol (Table 2). These data suggest that a pre-equilibrium is formed in the hydrolysis of the acyclic aliphatic ester, whereas in the hydrolysis of the cyclic esters (aliphatic and aromatic) and the acyclic aromatic ester, the first stage of the reaction is essentially irreversible (equation 2).

We thank Professor F. H. Westheimer for helpful discussions, and for informing us of his unpublished results in this field.

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‡ Relative apicophilicities may vary with the nature and charge on the substrate, but at the present time we have to assume a relatively low value for nitrogen compared with oxygen. This assumption may have to be revised when more information has been obtained in this field.

[1] F. H. Westheimer, *Accounts Chem. Res.*, 1968, 1, 70.
[2] R. K. Oram and S. Trippett, *J.C.S. Perkin I*, 1973, 1300.