Alkaline Hydrolysis of Cyclic Phosphonamidates

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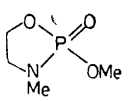
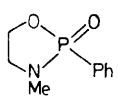
Summary Comparison of the rates of alkaline hydrolysis of cyclic phosphonamidates with those of their acyclic analogues, and analysis of the reaction products, indicate that the intermediates or transition states involved in the hydrolysis of the cyclic esters have square-pyramidal, rather than trigonal-bipyramidal geometry.

IN substitution reactions at phosphonyl phosphorus, the basic assumption of a bipyramidal transition state or intermediate, with electronegative groups preferentially occupying apical positions, is usually made.[1] This interpretation is strongly supported by structural investigations on penta-co-ordinated species,[2] and by studies on permutational isomerisation[1,3] which can elegantly explain the composition of substitution reaction products, particularly in the case of heterocyclic compounds.


(I)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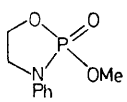
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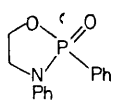

(IV)

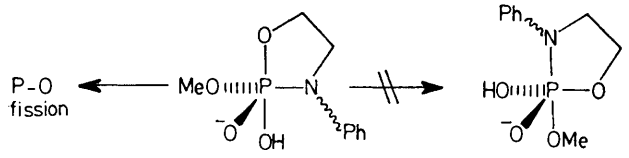
There is, however, no fundamental reason why a system of D_{3h} local symmetry should, in all cases, have a lower energy than one of C_{4v} or C_s local symmetry, since the nature of the ligands can markedly affect the structure of individual pentaco-ordinate compounds. Several quinquevalent phosphorus molecules are now known[4] with square-pyramidal (C_{4v}) structures, and it is therefore not unreasonable to suppose that such structures may be adopted by substitution reaction intermediates and/or transition states. Moreover, recent studies of oxygen exchange reactions of highly strained bicyclic phosphine oxides[5] show that substitution at phosphorus may proceed readily, even when any bipyramidal transition states must be highly distorted.

In this communication we describe some recent work on the hydrolysis of phosphonamidates which cannot be explained adequately in terms of bipyramidal intermediates or transition states alone.

We have shown that the ready† hydrolysis of compounds (I)—(IV) in 0·01—0·5 M NaOH follows strictly second-order kinetics, and have analysed the reaction products formed under kinetic control by a combination of ^{1}H, ^{13}C, and ^{31}P n.m.r. spectroscopy. The results of these experiments are summarised in the Table. We find that although the relative reactivities of (I) and (III), and of (II) and (IV) are virtually identical, and that the products of hydrolysis of (I) and of (II) are very similar, the esters (III) and (IV) give quite different products.

† In all cases the rate constants (k_c) for the cyclic compounds are *ca.* 10^6 greater than the rate constant (k_a) for the corresponding acyclic compounds.

The behaviour of (I) and (III) we have previously rationalised[6] in terms of bipyramidal intermediates, that derived from (I) being capable of pseudorotation following protonation of the nitrogen atom and so giving products from both P–O and P–N cleavage, but that from (III) being incapable of such pseudorotation and so giving exclusively the product resulting from P–O cleavage (Scheme).‡



SCHEME

However, although the analogous pseudorotation processes for the intermediate (V) derived from (IV) should be even less likely, since these would involve placing either the very poorly apicophilic phenyl group[7] or the (presumably) equally poorly apicophilic $-O^-$ group in an axial position, we observe 100% P–N cleavage in this case.

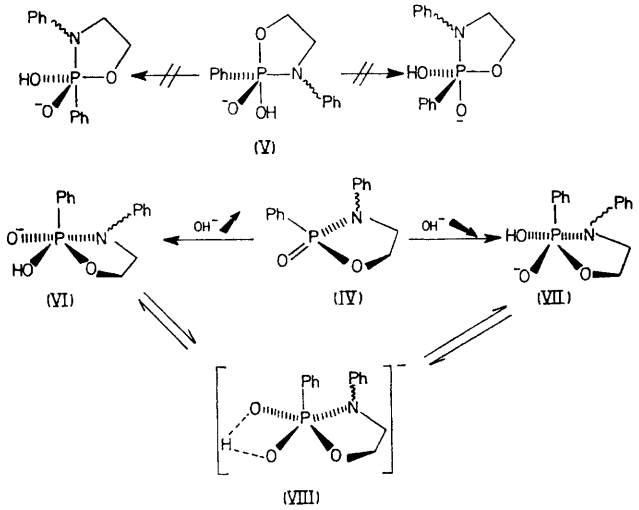
Since we can therefore rule out the intermediacy of trigonal-bipyramidal species, we suggest, as a possible explanation for the formation of P–N cleaved product from (IV), that a square-pyramidal intermediate or transition state is involved. This could arise from attack of the hydroxide ion on the P–O and/or P–N bonds along a line of approach at an angle significantly different from 180° to the axis of these bonds. Theoretical calculations[8] indicate that the inclusion of a directly bound carbon atom in pentacoordinated phosphorus species will significantly decrease the energy difference between trigonal-bipyramidal and square-pyramidal structures.

TABLE. Rate and product data

Compound	Bond fission/% P–O[a]	P–N	P–OMe	Rate constant $l\ mol^{-1}\ s^{-1}$ k_c
(I)	60	40	0	0·08
(II)	67	33	–	2·40
(III)	100	0	0	0·10
(IV)	0	100	–	3·10

[a] Endocyclic bond.

In structures such as (VI) and (VII) the axial bond is stronger than equivalent§ basal bonds, which are therefore potentially labile. Under these conditions P–N cleavage can now compete effectively with P–O cleavage. In the case of (IV) both bond-energy considerations and stabilisation of the incipient amide anion by the *N*-phenyl group will favour P–N cleavage, as observed. It should be noted that proton exchange will render the two exocyclic oxygen atoms equivalent in (VI) and (VII), whereas apical and equatorial oxygen atoms of a bipyramidal intermediate have different basicities. Symmetrically hydrogen bonded structures, *e.g.* (VIII), may be formed, and the orientation of attacking hydroxide ion and leaving group is therefore unimportant in this case. In the case of the *N*-methyl analogue (II), protonation of the nitrogen atom of the kind postulated by us in a previous communication[6] is necessary for P–N bond fission, and in this case P–O cleavage competes more effectively.



It should be noted that the cyclic N–P–O angle in such square-pyramidal structures should be $\leq 90°$, and hence strain in the reactant originally present is reduced, just as it is in trigonal-bipyramidal structures. This is entirely consistent with the large values of k_c/k_a observed for both (II) and (IV).

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‡ Products of P–N cleavage have also been observed by Inch *et al.*[9] from the reaction of methoxide ions with cyclic phosphoramidates analogous to (II).

§ It should be noted that the equivalence of the basal bonds means that decomposition of intermediates such as (VI) or (VII) can occur with retention of configuration without the intervention of isomerisation processes without violating the microscopic reversibility principle. We are further investigating the stereochemical consequences of this important point.

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