Phosphoric Amides. Part 8. The Effect of the Ethylenimine Substituent on the Solvolytic Reactivity of Phosphate and Phosphoramidate Bonds

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Rates and products of the base-catalysed hydrolysis of some amidoesters of phosphoric acid have been determined. In the *N,N*-dimethyl derivative, the P–N bond is resistant, and the P–O bond deactivated towards hydrolysis, while in the *N*-methyl substrate, the reactivity of the ester link is similar to that in trimethyl phosphate. In the *N*-ethylene compound, both P–O and P–N bonds are strongly activated. The *N*-(β-chloroethyl) substrate reacts *via* fast, base-catalysed cyclization to the *N*-ethylene amidate.

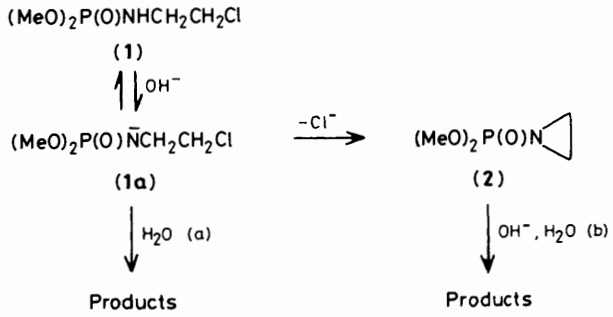
Because of the difference in the nucleofugality of the OR and NR_2 groups, the basic hydrolysis of di-*O*-alkyl *N,N*-dialkylphosphoramidates results in ester bond cleavage but not in any amide (P–N) bond cleavage,[1] equation (1). The only notable

$$(RO)_2P(O)NR^1{}_2 \xrightarrow{OH^-} RO(R^1{}_2N)PO_2^- + ROH \qquad (1)$$

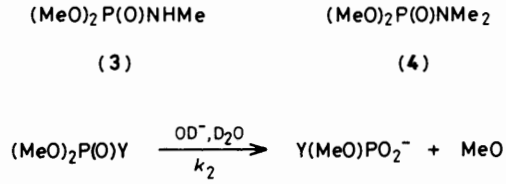
exceptions are phosphoramidates in which the nitrogen and one oxygen are constrained in a five-membered ring; in these systems P–N bond cleavage is known to compete with the cleavage of the P–O bond.[1,2] The R_2N group in a phosphoramidate molecule is not only resistant to nucleophilic substitution, it also strongly deactivates the remaining ester functions by donating electrons to the phosphoryl centre.[3] The deactivation caused by the nitrogen substituent is absent in secondary phosphoramidates because they are capable of reacting *via* the reactive conjugate base intermediate,[4] equation (2).

$$(RO)_2P(O)NHR^1 \underset{}{\overset{OH^-}{\rightleftharpoons}} (RO)_2P(O)NR^{1-} \longrightarrow \text{Products} \qquad (2)$$

Following our interest in the behaviour of *N*-(β-chloroethyl)-phosphoramidates and their conversion into *N*-phosphorylated ethylenimines,[5] we have investigated the alkaline hydrolysis of *O,O*-dimethyl *N*-(β-chloroethyl)phosphoramidate (**1**) and *N*-(dimethylphosphoryl)ethylenimine (**2**). The aim of this study was two-fold: firstly, we were interested in the hydrolysis of (**1**), which can proceed according to two independent pathways (Scheme 1), one of which (a) can be compared with the hydrolysis of *O,O*-dimethyl *N*-methylphosphoramidate (**3**); and secondly, we wanted to determine the reactivity of (**2**) and compare it with that of the *O,O*-dimethyl *N,N*-dimethylphosphoramidate (**4**), and thus evaluate the effect of the ethylenimine group on the nucleophilic displacement at phosphorus.



Scheme 1.



Scheme 2.

Results and Discussion

P–O Cleavage.—The rates of alkaline hydrolysis for some substrates of the general formula $(MeO)_2P(O)Y$ (Scheme 2) were determined and the results are given in the Table.

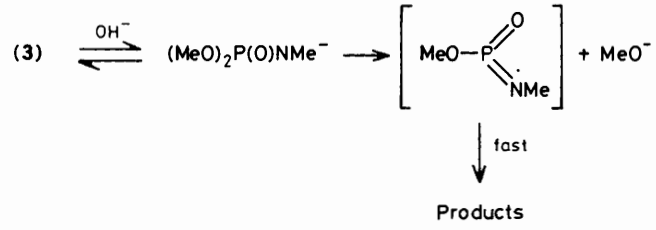
As reported previously, the dialkylamino group deactivates the phosphate bond towards nucleophilic cleavage; the 250-fold decrease in reactivity of (**4**) relative to (**5**) can be taken as a measure of the electron-releasing effect of the NMe_2 group relative to that of the OMe group in the triester molecule. The P–O bond in amide (**3**) is, however, cleaved with a rate comparable to that for the reference compound (**5**). The considerable difference in P–O reactivity observed for the tertiary and secondary amidates [k_{P-O} (**3**)/k_{P-O} (**4**) = 150] suggests the participation of the elimination–addition mechanism[4] in the hydrolysis of (**3**) (Scheme 3).

Comparison of the rates of the P–O bond cleavage in the two tertiary amidates (**4**) and (**2**) shows that a change from the *N,N*-dimethylamino to the *N*-ethylene group has a dramatic effect on

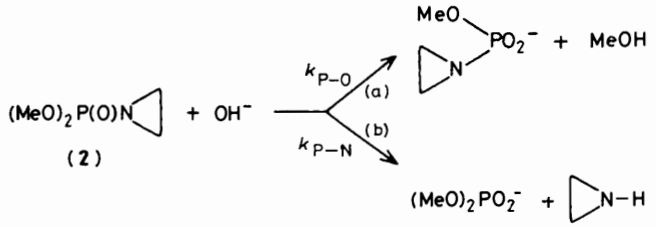
Table. Rates of alkaline hydrolysis of phosphoryl derivatives. [OD^-] = 1.68M; [substrate] *ca.* 0.31M

Substrate	Temperature, °C	Y	$10^4 \times k_2$ (M^{-1} s^{-1})[a]	k_{rel}
$(MeO)_3PO$, (**5**)	31	OMe	1.0[b]	1
(**4**)	31	NMe_2	0.0040[b]	4×10^{-3}
(**4**)	25	NMe_2	0.0027	
(**3**)	25	NHMe	0.40	0.60
(**2**)	31	NCH_2CH_2	2.9	2.9

[a] Corrected to the number of ester groups present. [b] Lit.,[3] k_2 = $1.1 \times 10^{-4}M^{-1}$ s^{-1} for (**5**) and $4.2 \times 10^{-7}M^{-1}$ s^{-1} for (**4**)



Scheme 3.

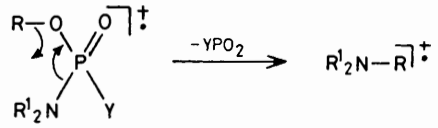


Scheme 4.

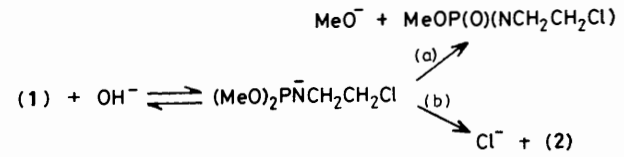
the reactivity of the adjacent phosphate ester linkage [k_{P-O} (**2**)/k_{P-O} (**4**) = 725]. The P–OMe bond in the ethylenimine derivative (**2**) is even more reactive than in (**5**), giving the order of decreasing reactivity in the series $(MeO)_2P(O)Y$ of Y = NC_2H_4 > MeO ≫ NMe_2. The observed order of reactivity parallels the order of electron-releasing effects of group Y, as measured by the resonance substituent constants σ_R° for the NC_2H_4, OMe, and NMe_2 groups (σ_R° = −0.38, −0.45, and −0.52, respectively).[6] Although the values for the k_{P-O} rate constants in (**5**), (**4**), and (**2**) do not correlate linearly with the corresponding σ_R° (Y) constants, the relative rates obtained confirm the unusually low electron-releasing effect of the ethylenimine substituent with respect to the phosphoryl centre.

P–N Cleavage.—Alkaline hydrolysis of (**4**) shows no detectable P–N cleavage. In 1.68M-NaOD the k_{P-O} for substrate (**4**) is $4 \times 10^{-7}M^{-1}$ s^{-1}; assuming that the contribution of the parallel P–N cleavage is less than 2%,* the upper limit of k_{P-N} for (**4**) can be estimated as $k_{P-N} \leqslant 8 \times 10^{-9}M^{-1}$ s^{-1}. The P–O *versus* P–N selectivity in (**4**) ($k_{P-O}/k_{P-N} > 50$) results from the difference in the leaving ability of the MeO^- and Me_2N^- groups in the product-determining step, *i.e.*, collapse of the pentavalent intermediate formed by the hydroxy attack at the phosphoryl substrate. The P–O/P–N selectivity observed for the hydrolysis of (**4**) is absent in the substrate (**2**); in this case P–N bond cleavage competes successfully with P–O bond fission (Scheme 4).

In 1.68M-NaOD solution, cleavage of the amide bond in (**2**) is in fact faster ($k_{P-N} = 3.3 \times 10^{-4}M^{-1}$ s^{-1}) than cleavage of the ester linkage ($k_{P-O} = 2.9 \times 10^{-4}M^{-1}$ s^{-1}). This is, to our knowledge, the first case of greater reactivity of the P–N *versus* the P–O bond in nucleophilic displacement occurring without prior activation of the P–N bond by means of acid catalysis.[7] Since the upper limit of k_{P-N} for *N,N*-dimethylamidate (**4**) has been estimated as $8 \times 10^{-9}M^{-1}$ s^{-1}, the P–N bond in (**2**) is hydrolysed faster than the P–N bond in (**4**) by a factor of at least 4×10^4. Thus the presence of the ethylenimine group in a phosphoramidate molecule has a profound effect on the reactivity of both the adjacent ester function and on the phosphorus–nitrogen bond itself. The difference in reactivity of the two tertiary phosphoramidates (**2**) and (**4**) indicates a large



Scheme 5.



Scheme 6.

difference in electron density at the nitrogen atoms in these substrates. In our study of the electron-impact-induced fragmentation behaviour of phosphoramidates[8] P–N bond cleavage accompanied by migration of an ester group R from oxygen to nitrogen was observed (Scheme 5).

It was postulated that the group R migrates with its bonding electrons to the electron-deficient nitrogen. In agreement with this, the O ⟶ N methyl migration (formation of the *N*-methylethylenimine radical ion) was observed in the m.s. of (**2**), but not for (**4**) (no trimethylamine radical ion was observed). It is also known[9] that there is an appreciable increase in the stretching vibration frequency for the carbonyl group in *N*-acetylethylenimine (ν_{CO} = 1 706 cm^{-1}) relative to that for *N,N*-dimethylacetamide (ν_{CO} = 1 652 cm^{-1}). The enhanced electronegativity of nitrogen in (**2**) should therefore be responsible for increasing the rates of both steps of substitution: the attack of OH^- at phosphorus (which accelerates both the P–O and P–N cleavage), and the collapse of the P^V intermediate with the ethylenimine as a good leaving group.† The P–O *versus* P–N selectivity in the hydrolysis of (**2**) is dependent on the hydroxide ion concentration. As [OD^-] was varied from 0.84 to 3.38M, the ratio k_{P-O}/k_{P-N} (statistically corrected) for the hydrolysis of (**2**) changed from 0.67 to 1.21. It seems that the base catalysis is less important for the amide bond cleavage in (**2**) than for the ester bond cleavage, consequently (**2**) hydrolyses slowly ($t_{\frac{1}{2}}$ = 85 h) in pure water,‡ but only *via* P–N bond cleavage. The observed variations in the regioselectivity in the hydrolysis of (**2**) may imply that in the product-determining step the ethylenimine group departure pathway has a higher requirement for electrophilic assistance by water than the cleavage of the P–O bond. On the other hand, the variations in the k_{P-O}/k_{P-N} ratio are rather small considering the range of hydroxide concentration involved, and may result from some changes in general solvation properties of the reaction medium affecting two product-determining steps in different ways.

Hydrolysis of (**1**).—According to Scheme 1, there are, in principle, two pathways available for the hydrolysis of (**1**), which depend on the ways of collapse of the conjugate base of (**1**) (Scheme 6). Pathway (a), analogous to that shown in Scheme 3, would result in P–O, but not P–N cleavage, while pathway (b), yielding (**2**), would be followed by the hydrolysis of this compound, described by Scheme 4. When (**1**) is dissolved in hydroxide solution, the ^1H n.m.r. spectrum shows fast formation of (**2**), followed by the formation of methanol and ethylenimine with rates very close to those obtained for the

* 2% Dimethylamine can be detected by ^1H n.m.r. in the presence of (**4**) and its hydrolysis products.

† pK_a Values for the conjugate acids of ethylenimine and dimethylamine are 8.01 and 10.73, respectively.

‡ Both (**4**) and (**5**) are indefinitely stable in water within the accuracy of ^1H n.m.r. spectroscopy.

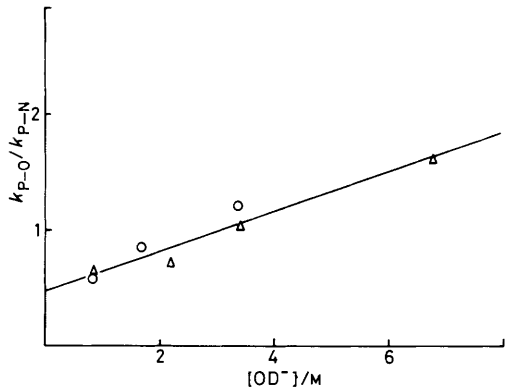
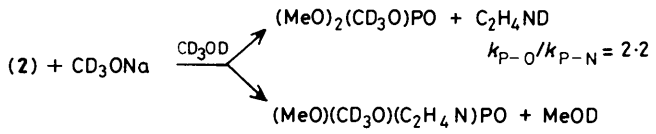


Figure. Variation of k_{P-O}/k_{P-N} for the hydrolysis of (1) (triangles) and (2) (circles) with OD^- concentration



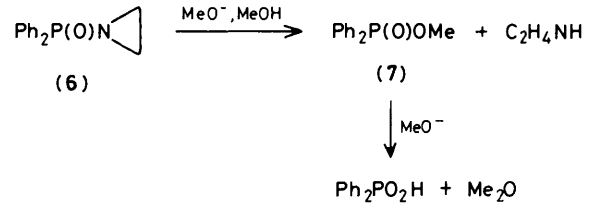
Scheme 7.

hydrolysis of (2) itself. The k_{P-O}/k_{P-N} ratio for (1), as measured by the product ratio of methanol to ethylenimine, shows similar dependence on hydroxide ion concentration as (2) (Figure).

It should be noted that any contribution by pathway (a) (Scheme 6) would increase the proportion of methanol relative to ethylenimine, but we find no indication for this to be the case. In aqueous alkaline solution (1) therefore behaves simply as a precursor of (2), which then reacts as previously described. This result shows that the nucleophilic nitrogen in the conjugate base of (1) preferentially attacks the β-carbon atom to give (2) and Cl^-, rather than donating its electrons to phosphorus, releasing methoxide ion and a metaphosphate-type species.*

Reactions with Other Nucleophiles.—The obvious difference between the reactivity of the tertiary phosphoramidates (2) and (4) was also confirmed with respect to the methoxide ion. At 25 °C (4) remains unchanged in methanolic solution containing an equimolar quantity of sodium methoxide for a period of at least 44 h. Under the same conditions, the ethylenimine derivative (2) reacts with both P–O and P–N bond cleavage (Scheme 7); after a period of 24 h a conversion of 20% was obtained.

Similarly, the phosphinamidate (6) reacts easily with the methoxide ion to give ethylenimine and methyl diphenylphosphinate (7); the latter product undergoes subsequent demethylation reaction (Scheme 8). At 25 °C the cleavage of the P–N bond in (6) is complete in 70 h. The observed behaviour of (6) contrasts with the low reactivity of its *N,N*-dimethyl analogue towards nucleophilic cleavage, reported by Koizumi and Haake.[10] As mentioned above, amide (2) solvolyses slowly in pure water with exclusive P–N cleavage, while (4) remains unchanged in this medium. The fluoride ion, which is known to catalyse nucleophilic displacement at phosphorus,[11] accelerates



Scheme 8.

the hydrolysis of both (4) and (2), the reactivity of (2) is again much higher than that of (4). At 31 °C (4), incubated in water containing an equimolar quantity of NaF, releases 8% dimethylamine after 7 days. Under the same conditions, the release of ethylenimine from (2) is complete after 41 h.†

Experimental

General.—Melting points are uncorrected. [$^2H_4$]Methanol (Wilmad Glass Co Inc., 99.5% D min.) and deuteriochloroform (Nuclear Magnetic Resonance Ltd., ≥99.8% D) were used as supplied. ^1H N.m.r. spectra were determined on a Varian EM 360A spectrometer using TMS or DDS as an internal standard. All solvents and reagents were AnalaR grade and were purified before use by conventional methods.

Substrates.—Substrates (1) and (2) were prepared as described before[5]; (3) and (4) were prepared from dimethyl phosphorochloridate and two equivalents of the corresponding amine in ether. (3): 40%, b.p. 95—96 °C at 0.5 mmHg (lit.,[12] b.p. 81 °C at 1 mmHg). (4): 62%, b.p. 46—48 °C at 0.5 mmHg (lit.,[13] b.p. 72—72.5 °C at 11 mmHg). (5): from Merck and distilled prior to use. (6) Was prepared from *N*-(β-chloroethyl)diphenylphosphinamidate by treatment with a slight excess of NaH in THF: 87%, m.p. 120—121.5 °C (from acetone–light petroleum) (lit.,[14] m.p. 119—119.4 °C); δ($CDCl_3$) 2.29 (4 H, d, *J* 15 Hz, NCH_2CH_2) and 7.36—7.65, 7.70—8.18 (10 H, m, 2 × Ph) (Found: C, 68.9; H, 5.75; N, 5.7. $C_{14}H_{14}NOP$ requires C, 69.1; H, 5.8; N, 5.8%). Methyl diphenylphosphinate was prepared from diphenylphosphinyl chloride and methanol.[15] ^1H N.m.r. (CD_3OD); δ 3.77 (3 H, d, *J* 11 Hz, OMe); 7.53—8.15 (10 H, m, 2 × Ph).

Product Determination and Rate Measurement.—Solutions of sodium deuterioxide were prepared by diluting a 40% solution of NaOD in D_2O (99.0% D, Wilmad Glass) with D_2O (99.75% D, Merck Uvasol) and standardising with aqueous HCl using Methyl Orange. The cleavage products were identified by addition of authentic samples of sodium dimethylphosphate [prepared from (5) and aqueous NaOH[16]], methanol, ethylenimine, dimethylammonium chloride, and by comparison with the ^1H n.m.r. spectra of mixtures of the relevant compounds. The following signals were used to identify reaction products and to follow kinetics of base-catalysed reactions [in all cases the P(O)–OMe signal appears as a doublet, *J* 11 Hz]. (2): δ 3.80 (d, OMe); 2.30 (d, *J* 14 Hz, NC_2H_4), P–O cleavage products: δ 3.64 (d, OMe); 1.98 (d, *J* 14 Hz, NC_2H_4); 3.31 (s, MeOD). P–N cleavage products: δ 3.58 [d, $(MeO)_2PO_2^-$]; 1.62 (s, C_2H_4ND). (3): δ 3.80 (d, OMe); 2.62 (d, *J* 12 Hz, NMe). P–O cleavage products: δ 3.60 (d, OMe); 2.50 (d, *J* 13 Hz, NMe); 3.38 (s, MeOD). (4): δ 3.67 (d, OMe); 2.67 (d, *J* 10 Hz, NMe_2). P–O cleavage products: δ 3.51 (d, OMe); 2.48 (d, *J* 10 Hz, NMe_2); 3.29 (s, MeOD). (5): δ 3.82 (d, OMe). P–O cleavage products: δ 3.58 [d, $(MeO)_2PO_2^-$]; 3.35 (s, MeOD).

* In the preparation of *N*-(diphenylphosphoryl)ethylenimine $(PhO)_2P(O)NC_2H_4$ *via* sodium hydride-promoted ring closure of diphenyl *N*-(β-chloroethyl)phosphoramidate we observed the formation of large quantities of phenol. This result indicates that, in the case of a better leaving group present (phenoxide), the conjugate base of the secondary phosphoramidate is capable of expelling one of the esters groups.

† In the presence of an equimolar quantity of $NaNO_3$, the half-life of (2) is 85 h, exactly the same as in pure water.

The substrate (20—30 mg) was introduced into an n.m.r. tube which was equilibrated in a water-bath at 31 ± 0.5 °C. The solution of NaOD in D_2O was added and the reaction was followed by recording the spectrum at 31 °C (probe temperature). Fast runs ($t_{\frac{1}{2}}$ < 30 min) were followed by placing the n.m.r. tube in the probe immediately after mixing and repeatedly recording the integration curve in the region of the spectrum containing the signals selected to monitor the reaction. Slower reactions were followed by periodically recording the spectrum of a sample thermostatted in a water-bath at the desired temperature. For all runs good first-order kinetics were obtained ($r > 0.99$); the kinetic runs were reproducible to ±5% and were followed to 85—90% completion. It was difficult to determine accurately rates of P–O and P–N bond cleavage for (**1**), because the initial ring closure reaction (see Scheme 6) results in the ^1H n.m.r. spectra of the reaction mixture being fairly complex. It was, however, possible to determine in each case the product ratio for the substrate.

Reactions with sodium methoxide were carried out by dissolving the required amount of sodium in [$^2H_4$]methanol with exclusion of moisture, adding the equimolar amount of substrate, and following the reaction by means of ^1H n.m.r. spectroscopy. For the cleavage of (**6**) (see Scheme 8) the initial products [ethylenimine and (**7**)] were identified by comparison of the ^1H n.m.r. spectra with those of the mixtures of authentic samples. Methyl diphenylphosphinate (**7**) is cleaved slowly in [$^2H_4$]methanol containing sodium methoxide yielding diphenylphosphinic acid (m.p. and mixed m.p. 196—197 °C) and [1,1,1-$^2H_3$]dimethyl ether (δ 3.38, s).

Acknowledgements

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