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Phosphoryl Compounds in Strong Acids. Stability of the P–N Bond and Alkyl–oxygen Cleavage of Phosphoramidates in Trifluoromethanesulphonic Acid

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Summary In trifluoromethanesulphonic acid (HTFMS) the P–N bond of $(RO)_2P(O)NMe_2$ is stable, but de-*O*-alkylation is observed; rates of the oxygen–alkyl cleavage of phosphoramidates and some other phosphoryl compounds in HTFMS have been determined.

ACID-CATALYSED solvolysis of phosphoric amides $X(Y)P(O)$-NR_2 involves the associative (*A*-2) mechanism.[1] Although the contribution of an *A*-1 pathway has been suggested,[2] the generality of the bimolecular, $S_N2(P)$ mechanism seems well established.[3] Such behaviour is due to the fact that phosphoryl compounds are reluctant to form phosphorylium ions $X(Y)PO^+$.[4] In consequence, nucleophilic assistance is required in the rate-determining step. Under conditions of high acidity but low nucleophilicity, reactions at centres other than phosphorus can occur; *e.g.*, *N*-alkyl bond cleavage.[5] Under acidic conditions the P–N bond in phosphoramidates is much less stable than the corresponding ester function;[1] this is explained by the greater basicity and better leaving ability of the (protonated) amino substituent.

We now report the high stability of the P–N bond in strongly acidic but poorly nucleophilic media such as trifluoromethanesulphonic acid (HTFMS). When the *NN*-dimethyl dimethyl-phosphoramidate (**1**) is dissolved in rigorously anhydrous HTFMS the n.m.r. signal of the NMe_2 group remains virtually unchanged for a period of *ca.* 70 h. Under these conditions however, slow demethylation takes place (reaction 1). Reaction (1) can be easily followed by

$$\underset{(\mathbf{1})}{(MeO)_2P(O)NMe_2} \xrightarrow{\text{HTFMS}} (HO)_2P(O)NMe_2 + 2\ \text{Me-TFMS} \quad (1)$$

^1H n.m.r. spectroscopy, since a doublet of MeO groups in (**1**) (65·4 Hz downfield from Me_2N, $J_{H,P}$ 12·0 Hz) is replaced by a singlet (61·4 Hz downfield from Me_2N).† The reaction follows pseudo first-order kinetics with the observed rate constant $k_\psi = 6{\cdot}55 \times 10^{-6}\ s^{-1}$ ($r = 0{\cdot}998$).‡ Kinetics were measured over more than two half-lives and no curvature was observed, which indicates that the first and second demethylation steps proceed with the same rate. When the *O*-demethylation is complete, more than 80% of the amide function remains unchanged. We believe that reaction (1) involves the unimolecular oxygen–alkyl cleavage in protonated (**1**). For the *NN*-dimethyl diethyl-phosphoramidate (**2**) the de-ethylation was faster; $k_\psi = 1{\cdot}7 \times 10^{-4}\ s^{-1}$ ($r = 0{\cdot}995$) [methyl of the EtO group in (**2**) t of d, $J_{H,H}$ 6·8 Hz; $J_{H,P}$ 1·6 Hz; after dealkylation t, $J_{H,H}$ 7·4 Hz; 2·4 Hz upfield from substrate]. Again, $<$ 10% of the P–N bond cleavage was observed. In the *NN*-dimethyl di-isopropyl-phosphoramidate (**3**) dealkylation was fast ($t_{\frac{1}{2}} < 60$ s) but the lower limit of the rate constant, $k_\psi > 10^{-2}\ s^{-1}$ could be established. This gives the relative rates of the

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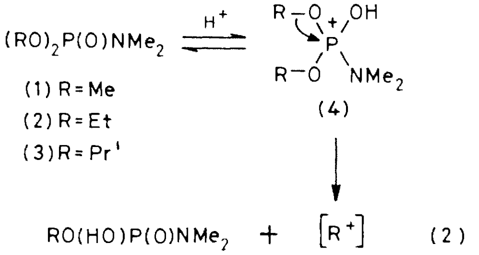
† Identified as methyl trifluoromethanesulphonate by addition of the authentic sample of Me-TFMS.

‡ ^1H n.m.r. spectra were recorded at 60 MHz on a Varian T-60 spectrometer at a probe temperature 33 ± 1 °C. Rate constants were determined by integration as described before (ref. 5), and are given per single alkyl group.

oxygen–alkyl fission in $(RO)_2P(O)NMe_2$: R = Me, $k_{rel} = 1$; R = Et, $k_{rel} = 26$; R = Pr^i, $k_{rel} > 1500$. Such an order clearly follows the order of the relative easiness of the carbonium ion formation by group R.§



Our results obviously suggest the *O*-protonation of a substrate, since only in such a form as (**4**) can the release of a carbonium ion result in the re-establishment of the phosphoryl function (reaction 2). Rate of dealkylation is dependent on the protonation equilibrium. *O*-Demethylation of (**1**) was also studied in FSO_3H; $k_{\psi} = 1{\cdot}05 \times 10^{-5}\ s^{-1}$ ($r = 0{\cdot}998$, and no P–N bond cleavage was observed), *i.e.*, $k_{\psi}(FSO_3H)/k_{\psi}(HTFMS) = 1{\cdot}6$. This ratio correlates well with the relative acidities of the acids; in anhydrous H_2SO_4 $K_a(FSO_3H)/K_a(HTFMS) = 2{\cdot}8$.[7]

Simple protonation followed by the C–O bond fission (reaction 2) does not, however, account for the dealkylation reaction. We have measured the rates of the O–Me fission in $(MeO)_2P(O)X$ (**5**) and found that rates vary drastically with substituent X. Dimethylphosphorofluoridate (**5a**, X = F) and phosphorochloridate (**5b**, X = Cl) undergo demethylation with measurable rates. For (**5a**) the reaction was followed over three half-lives (d, $J_{H,P}$ 12·2 Hz changing to s, 3·6 Hz upfield from substrate); $k_{\psi} = 1{\cdot}98 \times 10^{-7}\ s^{-1}$. Demethylation of (**5b**) (d, $J_{H,P}$ 14·2 Hz changing to s, 0·2 Hz lowfield) gave $k_{\psi} = 4{\cdot}36 \times 10^{-8}\ s^{-1}$ ($r = 0{\cdot}994$). Trimethyl phosphate (**5c**, X = OMe) proved to be remarkably resistant to the demethylation; the CH_3 signal (d, $J_{H,P}$ 11·6 Hz) remained unchanged for over hundred days (**5c** can therefore be used as a convenient standard for ^{31}P n.m.r. spectroscopy in strongly acidic media). The most cautious estimate for (**5c**) gives the upper limit as $k_{\psi} < 6 \times 10^{-9}\ s^{-1}$. The rate constants obtained allow compounds (**5**) to be arranged in an order of decreasing reactivity (Table). The effect of groups X upon dealkylation follows neither the electronegativity order, nor the usual electron-withdrawing effects at phosphorus.[8] The reactivity order indicates that the reaction may involve both the monoprotonated $(MeO)_2P(OH)X^+$ (**6**) and diprotonated $(MeO)_2P(OH)XH^{2+}$ (**7**) forms as reactive intermediates, second protonation depending strongly upon the nature of X. In view of this the extremely low reactivity of (**5c**) is especially intriguing. It is possible that the highly symmetrical, tetraoxysubstituted phosphonium ion (**6**, X = OMe) is particularly stable owing to significant charge delocalization to the four oxygen atoms.[9] It has been reported[9] that in FSO_3H (**5c**) is stable, but trimethyl phosphite, probably owing to less symmetrical charge distribution in the conjugate acid, undergoes slow demethylation.

$(MeO)_2P(O)X$ $(MeO)_2P(OH)X^+$
(**5**) **a**; X = F (**6**)
b; X = Cl $(MeO)_2P(OH)XH^{2+}$
c; X = OMe (**7**)

TABLE. Relative rates of demethylation of $(MeO)_2P(O)X$ in HTFMS at 33 ± 1 °C.

X	NMe_2	F	Cl	OMe
Relative rate	1	0·03	0·0066	< 0·0003

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§ In formic acid relative rates of solvolysis of RBr are: k_{rel}, (Me) 1; (Et) 1·7; (Pr^i) 43.[6] In HTFMS solvent nucleophilic assistance (if any) will be much less important than in formic acid.

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