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ALKYLATING PROPERTIES OF PHOSPHATE ESTERS. 3. REACTIVITY OF DIALKYL 2-(DIMETHYLAMINO)ETHYL PHOSPHATES

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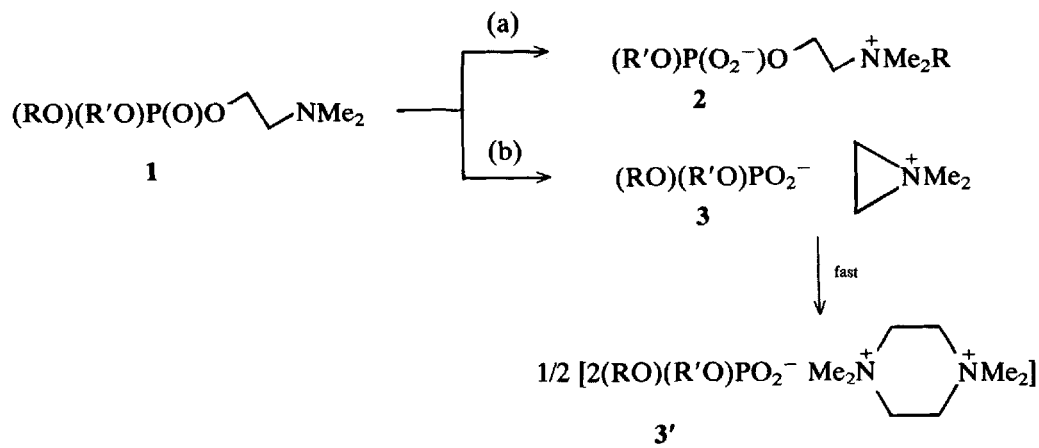
ABSTRACT

Reactivity of dialkyl 2-(dimethylamino)ethyl phosphates, $(RO)_2P(O)OCH_2CH_2NMe_2$ (R = Me, $PhCH_2$) was studied in aqueous solutions. Depending on the initial substrate's concentration, reaction can involve the unimolecular fragmentation to N,N-dimethylaziridinium dialkylphosphate, or the bimolecular isomerization to the zwitterionic derivative. The latter reaction proceeds via two consecutive S_N2 steps and involves the formation of two ionic intermediates which were synthesized independently and allowed to react to give the zwitterionic product. Rate constants for the isomerization of the dimethyl ester (R = Me), as well as rate constant for the reaction between the corresponding intermediates have been determined, and the reactivity of the dimethyl ester has been compared with that of the dibenzyl derivative.

Spontaneous decomposition of dialkyl 2-(dimethylamino)ethyl phosphates (**1**) can follow two pathways—isomerization to the zwitterionic product **2**, and fragmentation to the aziridinium dialkylphosphate **3**, which then undergoes fast dimerization to N,N,N′,N′-tetramethylpiperazinium bis-dialkyl phosphate, **3′** (Scheme 1).



Scheme 1

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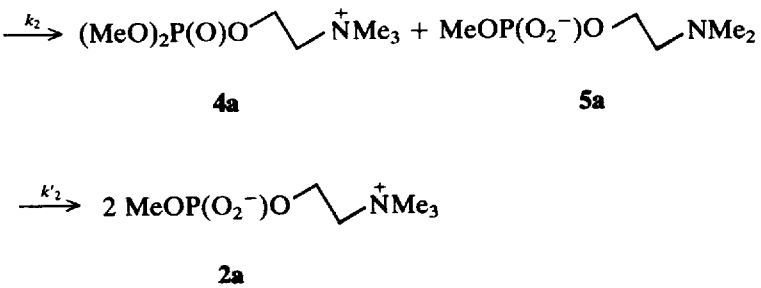
Lacey and Loew[1] employed the isomerization of methyl phosphates (**1**, R = Me) in the synthesis of phospholipids. Isomerization pathway (a) gives good results only when high concentrations of **1** (or neat **1**) are used; in dilute solutions fragmentation (b) prevails. Manninen[2] studied the reactions of dimethyl 2-(dimethylamino)ethyl phosphate **1a** (**1**, R = R′ = Me) and found that at concentrations about 1 M **1a** reacts according to pathway (a), which, as demonstrated by ^{1}H-NMR spectroscopy, involves transient formation of some intermediate products. On the basis of this observation Manninen proposed[2] for reaction (a) the bimolecular mechanism illustrated in equation (1).

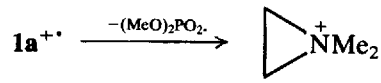


(1)

As a continuation of our interest[3] in the alkylating properties of organic phosphates, we decided to reinvestigate the reactivity of **1a** from the following points of view: (i) independent preparation of intermediates **4a** and **5a** in order to provide support for the bimolecular mechanism of isomerization; (ii) rate measurement of the isomerization **1a** → **2a**, and of the formation of **2a** from authentic **4a** and **5a** (k'_2, pathway a); (iii) extension of the isomerization to another system containing easily removable ester groups,[4] namely dibenzyl 2-(dimethylamino)ethyl phosphate **1b** (**1**, R = R′ = $PhCH_2$).

RESULTS AND DISCUSSION

1a can be easily prepared from dimethyl phosphorochloridate and sodium 2-(dimethylamino)ethanolate[2] and identified by ^{1}H-NMR spectroscopy. Because of the high and diverse reactivity of **1a**, its storage presents however a problem. As a neat compound (oil) at room temperature, **1a** soon changes to a transparent gel insoluble in organic solvents; ^{1}H-NMR spectrum (D_2O) revealed that the gel consists of a mixture of **1a**, **2a**, **4a** and **5a**, which, after *ca.* one week, is transformed completely into **2a**. The gel can be however stored in a refrigerator without any noticeable change, most likely because of the high viscosity preventing further reaction. **1a** cannot be stored as a dilute solution in polar solvents, as it undergoes complete fragmentation to **3** (Scheme 1, pathway b). This tendency for the unimolecular fragmentation involving the 1,3 attack of the amine nitrogen atom at the α-carbon atom rather than for the unimolecular isomerization was also confirmed under conditions of the electron—impact induced fragmentation. Mass spectrum of **1a** reveals that one of the major fragmentations involves expulsion of the dimethylphosphoryloxy radical and the formation of the N,N-dimethylaziridinium ion (rel. abundance 30%; equation (2)).



(2)

Substrate **1a** is however quite stable as a <1M solution in hexane at 5–10 °C. In this case the low polarity of the solvent slows down the formation of ionic products of reactions (a) and (b), but if the solution is cooled below 5 °C, **1a** separates out and undergoes fast isomerization.

Although zwitterion **2a** can be prepared by allowing neat **1a** to isomerize completely, it always contains some quantities of the intermediates **4a** and **5a**, complete conversion of which to **2a** is very slow because of the system's viscosity. Pure samples of **2a** could be obtained by the isomerization of **1a** catalysed by sodium iodide. In this case the iodide ion (a better nucleophile than amine nitrogen[5]) is responsible for the demethylation step, while iodomethane formed for the quaternization of the 2-dimethylamino group (equation (3)).

$$\mathbf{1a} + \text{NaI} \longrightarrow \mathbf{5a} \cdot \text{Na}^+ + \text{MeI} \longrightarrow \mathbf{2a} + \text{NaI} \qquad (3)$$

Under these conditions **2a** (a very hygroscopic substance) precipitates out from acetone solution as a stable, 1:1 complex with sodium iodide, and can be easily identified by ^{1}H-NMR spectroscopy.

The cationic intermediate **4a** can be prepared as its iodide salt by N-methylation of **1a** with iodomethane in *n*-hexane. The product contains however up to 10% of **2a**, formed by the subsequent O-demethylation by the iodide ion (equation (4)).

$$\mathbf{1a} + \text{MeI} \longrightarrow \mathbf{4a} \cdot \text{I}^- \longrightarrow \mathbf{2a} + \text{MeI} \qquad (4)$$

Pure **4a** can be prepared as a nitrate salt by carrying out reaction (4) at 0 °C in dry acetonitrile containing silver nitrate. The iodide ion is then removed immediately as a silver salt, and the nitrate counterion left in the solution is too weakly nucleophilic[5] to significantly demethylate **4a** to **2a**.

The anionic intermediate **5a** was prepared as a highly hygroscopic tetramethylammonium salt according to equation (5).

$$\mathbf{1a} + \text{NMe}_3(\text{excess}) \longrightarrow \text{NMe}_4^+ \cdot \mathbf{5a} \qquad (5)$$

Each of the compounds (**1a**, **2a**, **4a** and **5a**) present in the reaction mixture (D_2O) could be easily identified and determined in the presence of others due to the characteristic signals in the ^{1}H-NMR spectrum. For example, **1a** and **5a** can be distinguished by their NMe_2 group signals (s, δ 2·25 ± 0·02 and 2·35 ± 0·02, respectively); **2a** gives a characteristic signal of the trimethylammonio group (s, δ 3·22 ± 0·01), and the methyl ester group of **4a** gives rise to a signal at the lowest value of the magnetic field (d, δ 3·86) relative to the other methyl phosphate groups.

At 25 °C, the half-life of the 3·47 M solution of **1a** in D_2O is *ca.* 50 min. It was therefore possible to follow the course of the reaction by periodically monitoring the ^{1}H-NMR spectrum of the reaction mixture and determining the relative concentrations of all species present. Under these conditions only the isomerization reaction (Scheme 1, pathway a) is observed and the intermediate formation of ions **4a** and **5a** can be easily demonstrated. The plot of the concentrations of all species involved in reaction (a), typical for systems in which transient intermediates are formed, is presented in the Figure.

Disappearance of **1a** follows the second-order kinetic law and yields the rate constant, k_{obs} = 1·42 (±0·06) × 10^{-4} M^{-1} s^{-1}. We found no evidence for any contribution from the intramolecular isomerization of **1a**, and we believe that this system, like the previously studied dimethyl 2-pyridylmethyl phosphate,[3] isomerizes exclusively via the bimolecular mechanism involving a sequence of two S_N2 reactions. At very high concentrations of **1a** (e.g. 6·7 M) strong deviations from the second-order kinetics were observed and only the initial rate gave good agreement (k_{obs} = 1·44 × 10^{-4} M^{-1} s^{-1}) with the value obtained at lower substrate

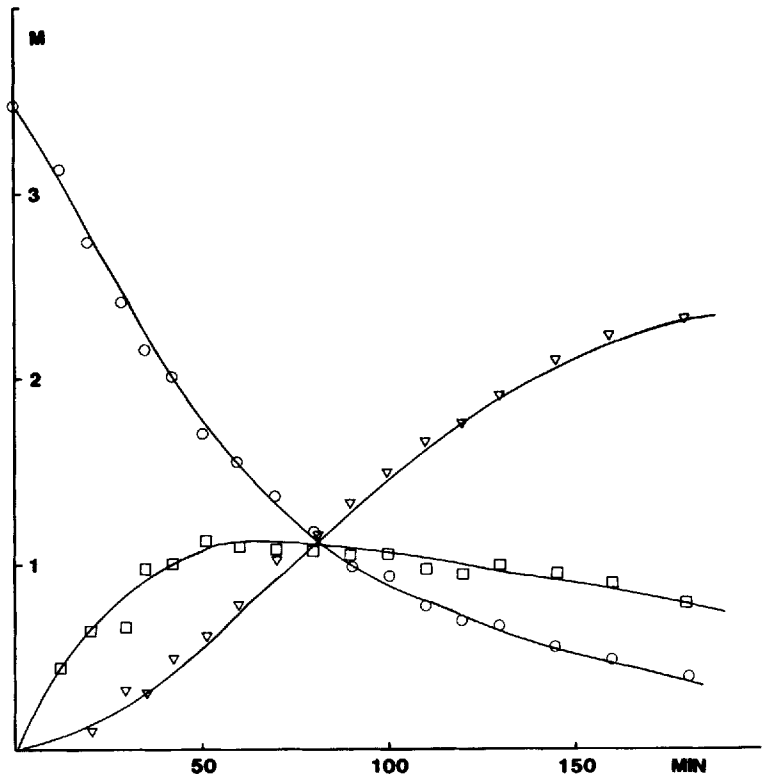
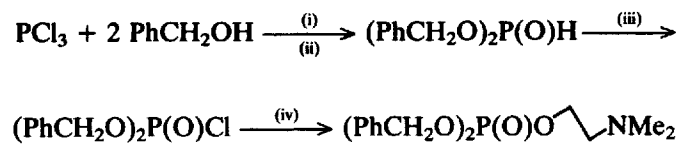


Figure. Reaction of **1a** in D_2O at 25 °C: composition of the mixture at different times. (○) **1a**; (□) **4a** + **5a**; (▽) **2a**

concentrations. It is worth noting that under such conditions the second step of isomerization (reaction between **4a** and **5a** to give **2a**) is very slow, and the full conversion could not be achieved even after 60 h. It seems most likely that in the highly viscous, ionic solution the conformational freedom of **4a** and **5a** is limited to a degree that hinders the proper orientation of the functional groups, necessary for the second substitution step. At lower concentrations the reaction between **4a** and **5a** followed the second-order kinetic law and gave, at 25 °C, the rate constant for the second step of equation (1), $k'_2 = 3{\cdot}20\ (\pm 0{\cdot}12) \times 10^{-4}\,M^{-1}\,s^{-1}$. The reaction between **4a** and **5a** is therefore *ca.* 2·2 times faster than is the disappearance of **1a**. The greater reactivity of **4a** and **5a** in the nucleophilic methyl group transfer relative to that of two molecules of **1a** results certainly from the ionic centres introduced in the first step and increasing both the nucleophilicity of **5a** and the alkylating ability of **4a**. The difference in the rates of these two S_N2 reactions, equation (1), is however not large and allows for a significant accumulation of the intermediates **4a** and **5a** in the reaction mixture.

Dibenzyl 2-(dimethylamino)ethyl phosphate (**1b**) was prepared according to Scheme 2. **1b** showed greater reactivity and lower selectivity than **1a**. When **1b** was heated as a neat oil or refluxed in acetone solution in the presence of sodium iodide, the zwitterionic product **2b** (**2**, R = R′ = $PhCH_2$) formed always contained piperazinium salt **3′b** (**3′**, R = R′ = $PhCH_2$). It is worth noting that in the mass spectrum of (**1b**) the N,N-dimethylaziridinium ion formed by the loss of the dibenzylphosphoryloxy radical from the molecular ion of (**1b**), cf. equation (2),



1b

(i): 2 $PhNMe_2$, C_6H_6, O °C; (ii): aq. NH_3;[6] (iii): SO_2Cl_2;[7]

(iv): Me_2N⌒⌣ONa, ether–hexane

Scheme 2

occurs as a base peak. The cationic and anionic intermediates, **4b** and **5b**, however were prepared easily from **1b** by N-benzylation with benzyl chloride and O-demethylation with trimethylamine, respectively. Examination of the ^{1}H-NMR spectra of the solutions of **1b** in D_2O/acetone-d_6 (1:1) produced analogous results as for **1a**, revealing the transient formation of intermediates **4b** and **5b**. We conclude that the bimolecular mechanism of isomerization is common for the dialkyl 2-(dimethylamino)ethyl phosphates.

Since the rate constant for the isomerization of **1b** could not be measured because of the parallel fragmentation, the reactivity of **1b** was determined relative to that of **1a**. Solutions of **1a** and **1b** in D_2O/acetone-d_6 (1:1) at concentrations at which both reactions (Scheme 1, pathways a and b) occur (e.g. 0·7 M), were incubated at 25 °C and the ^{1}H-NMR spectra of the solutions were periodically recorded. In this way the relative conversions, as well as relative proportions of the two products possible (**2** and **3'**) were determined for both substrates. Under identical conditions the ratio of the conversions of **1b** and **1a** to the corresponding products **2** and **3** is 1·5. The greater reactivity of **1b** is reflected in both the isomerization and the fragmentation reactions; the corresponding relative rates being 1·3 and 2·7, respectively. Rate acceleration in the bimolecular reaction results from the greater susceptibility of the benzyl group for nucleophilic displacement. The difference is however very small; although the average relative rate of benzyl and methyl substrates in S_N2 reactions is estimated as k_{rel} = 4, in some cases the two substrates show identical reactivity.[8] The greater reactivity of **1b** in the unimolecular fragmentation stems from the higher nucleofugality of the dibenzyl phosphate ion relative to the dimethyl phosphate ion, as indicated by the 0·54 pK_a unit difference[9] in the acidities of the corresponding dialkyl phosphates. In conclusion, it seems that reaction (a) (Scheme 1) may have no general application to the synthesis of the zwitterionic systems **2** because the competition from the fragmentation reaction is the function of not only the substrate's concentration, but also of the relative nucleofugalities of the phosphate ions involved in both reactions.

EXPERIMENTAL

NMR spectra were recorded on a superconducting FT Bruker AC300 spectrometer with sodium 3-(trimethylsilyl)-propanesulphonate as internal standard. Mass spectra were recorded on a VG Micromass 16F spectrometer. Dimethyl phosphorochloridate was prepared from PCl_3 and methanol.[10] Bp. 39–41 °C (5 mm). Dibenzyl phosphite was prepared from PCl_3 and

two mole-equivalents of benzyl alcohol in the presence of dimethylaniline, followed by hydrolysis with aq. ammonia.[6] ^{1}H-NMR ($CDCl_3$): δ 5·05 (4H, d, $J_{H—P}$ 9·6 Hz, 2 × CH_2); 6·93 (1H, d, $J_{H—P}$ 706·5 Hz, P—H); 7·20–7·50 (10H, m, 2 × Ph). Dibenzyl phosphorochloridate was prepared from freshly prepared dibenzyl phosphite by treatment with sulphuryl chloride in CCl_4 at 0 °C.[7] ^{1}H-NMR ($CDCl_3$): δ 5·18 (4H, d, $J_{H—P}$ 9·2 Hz, 2 × OCH_2); 7·35 (10H, bs, 2 × Ph). N,N-Dimethylethanolamine (Aldrich) was dried over KOH and distilled; bp. 40–42 °C (20 mm). All reagents and solvents were purified by conventional methods immediately before use.

Dimethyl 2-(N,N-dimethylamino)ethyl phosphate, 1a

Small pieces of clean sodium (0·16 g, 0·007 mol) were added to the solution of N,N-dimethylethanolamine (0·61 g, 0·007 mol) in anh. ether (10 ml), the mixture was stirred for 1 h and then heated under reflux for another hour. The solution was cooled to 0 °C, and the solution of freshly distilled dimethyl phosphorochloridate (1·0 g, 0·007 mol) in anh. ether (5 ml) was added dropwise within five min., and the mixture was stirred at 0 °C for 1 h. The solution was filtered through layers of sea sand and anh. magnesium sulphate and the ether was removed under reduced pressure. **1a** was obtained as a colourless oil, 1·15 g (85%). Anal. Found: C, 36·05; H, 8·53; N, 7·24%. Calcd. for $C_6H_{16}O_4NP$: C, 36·55; H, 8·20; N, 7·10%. ^{1}H-NMR ($CDCl_3$): δ 2·29 (6H, s, NMe_2); 2·61 (2H, d of t, $J_{H—H}$ 5·9 Hz, $J_{H—P}$ 0·7 Hz, NCH_2); 3·78 (6H, d, $J_{H—P}$ 11·3 Hz, 2 × OMe); 4·14 (2H, d of t, $J_{H—H}$ 5·9 Hz, $J_{H—P}$ 7·5 Hz, OCH_2). The reaction can be carried out in *n*-hexane and the 0·15 M solution of **1a** can be stored in a refrigerator without significant isomerization.

Dibenzyl 2-(N,N-dimethylamino)ethyl phosphate, 1b

This substrate was prepared as **1a**, using anh. ether/*n*-hexane (1:1) as a solvent. Colourless oil; 81%. Anal. Found: C, 60·00; H, 7·34; N, 4·12%. Calcd. for $C_{18}H_{24}O_4NP$: C, 61·87; H, 6·92; N, 4·00%. ^{1}H-NMR (D_2O/acetone-d_6; 1:1): δ 2·18 (6H, s, NMe_2); 2·49 (2H, d of t, $J_{H—H}$ 5·9 Hz, $J_{H—P}$ 0·9 Hz, NCH_2); 4·05 (2H, d of t, $J_{H—H}$ 5·9 Hz, $J_{H—P}$ 7·8 Hz, OCH_2CH_2); 5·06 (4H, d, $J_{H—P}$ 8·1 Hz, 2 × $PhCH_2$); 7·20–7·50 (10H, m, 2 × Ph). Solutions of **1b** in ether/*n*-hexane were stored in a refrigerator before further use.

Methyl 2-(N,N,N-trimethylammonio)ethyl phosphate, 2a

Dry sodium iodide (0·20 g, 0·0013 mol) is added to the solution of **1a** (0·108 g, 0·00055 mol) in anh. acetone (20 ml) and the solution is heated under reflux for 8 h. The white precipitate is filtered off, washed with anh. acetone and dried under reduced pressure, yielding almost quantitatively (0·188 g, 99%) the double salt, **2a** • NaI. ^{1}H-NMR (D_2O): δ 3·23 (9H, s, NMe_3^+); 3·60 (3H, d, $J_{H—P}$ 10·8 Hz, OMe); 3·61–3·73 (2H, m, NCH_2); 4·15–4·45 (2H, m, OCH_2).

Benzyl 2-(N,N-dimethyl-N-benzylammonio)ethyl phosphate, 2b

This product could be prepared as (**2a**) or by heating neat **1b**; in all cases zwitterionic compound **2b** contained some quantities (*ca.* 10%) of **3b**. ^{1}HNMR (D_2O/acetone-d_6, 1:1): δ

3·13 (6H, s, NMe_2^+); 3·50–3·70 (2H, m, $CH_2CH_2N^+$); 4·15–4·45 (2H, m, OCH_2CH_2); 4·60 (2H, s, $PhCH_2N^+$); 4·97 (2H, d, J_{H-P} 7·9 Hz, OCH_2Ph); 7·39–7·56 (1OH, m, 2 × Ph).

Trimethyl 2-(dimethylphosphoryloxy)ethylammonium nitrate, 4a • NO_3

1a (0·115 g, 0·00058 mol) was dissolved in anh. acetonitrile (15 ml), silver nitrate (0·15 g, 0·00088 mol) was added and the mixture stirred at 0 °C for a few minutes. Excess iodomethane (0·5 ml, 0·0080 mol) was added at once to the solution which was then stirred at room temperature for 1 h. The solution was filtered through layers of Celite and anh. magnesium sulphate, and the solvent was removed under reduced pressure, yielding **4a** • NO_3 as a transparent gel, 0·155 g, 97%. Anal. Found: C, 31·49; H, 6·68; N, 10·34%. Calcd. for $C_7H_{19}O_7PN_2$: C, 30·66; H, 6·98; N, 10·22%. ^{1}H-NMR (D_2O): δ 3·22 (9H, s, NMe_3^+); 3·71–3·87 (2H, m, NCH_2); 3·86 (6H, d, J_{H-P} 11·3 Hz, 2 × OMe); 4·45–4·71 (2H, m, OCH_2).

Dimethyl benzyl 2-(dibenzylphosphoryloxy)ethylammonium chloride, 4b • Cl

Benzyl chloride (0·20 g, 0·0079 mol) was added to a solution of **1b** (0·175 g, 0·00050 mol) in anh. acetonitrile (10 ml) and the solution was stirred at room temperature for 1 h. Solvent and excess of benzyl chloride were removed under reduced pressure and **4b** • Cl was obtained as a transparent, highly hygroscopic gel; 0·238 g, 100%. ^{1}H-NMR ((D_2O/acetone-d_6, 1:1): δ 3·17 (6H, s, NMe_2^+); 3·65–3·85 (2H, m, $CH_2CH_2N^+$); 4·55–4·70 (2H, m, OCH_2CH_2); 4·66 (2H, s, NCH_2Ph); 5·16 (4H, d, J_{H-P} 9·2 Hz, 2 × OCH_2Ph); 7·30–7·50 (10H, m, 2 × OCH_2Ph); 7·58 (5H, s, NCH_2Ph).

Tetramethylammonium methyl 2-(N,N-dimethylamino)ethyl phosphate, NMe_4^+• 5a

1a (0·39 g, 0·00198 mol) was dissolved in anh. acetonitrile (20 ml) containing trimethylamine (0·03 mol) and the solution was incubated at room temperature for 5 days. Solvent and excess of trimethylamine were removed under reduced pressure yielding NMe_4^+• **5a** as a white, highly hygroscopic crystalline substance, 0·505 g, 100%. Anal. Found: C, 32·84; H, 9·63; N, 8·00%. Calcd. for $C_9H_{25}O_4PN$ • $4H_2O$: C, 32·92; H, 10·13; N, 8·53%. ^{1}H-NMR (D_2O): δ 2·25 (6H, s, NMe_2); 2·61 (2H, t, J_{H-H}) 6·0 Hz, NCH_2); 3·16 (12H, s, NMe_4^+); 3·55 (3H, d, J_{H-P} 10·9 Hz, OMe); 3·92 (2H, d of t, J_{H-H} 6·0 Hz, J_{H-P} 6·1 Hz, OCH_2).

Benzyltrimethylammonium benzyl 2-(N,N-dimethylamino)ethyl phosphate, $PhCH_2NMe_3^+$• 5b

1b (0·337 g, 0·00114 mol) in anh. acetonitrile (2 ml) was added to a concentrated (1·88 M) solution of trimethylamine in acetonitrile (20 ml, 0·0376 mol Me_3N) and the solution was incubated at room temperature for 4 days. Solvent and excess of amine were removed under reduced pressure to give the product as white, highly hygroscopic crystalline material, 0·393 g, 100%. ^{1}H-NMR (D_2O/acetone-d_6, 1:1): δ 2·23 (6H, s, NMe_2); 2·52 (2H, t, J_{H-H} 5·8 Hz, CH_2NMe_2); 3·17 (9H, s, NMe_3^+); 3·94 (2H, d of t, J_{H-H} 5·8 Hz, J_{H-P} 5·9 Hz, OCH_2CH_2); 4·57 (2H, s, CH_2N^+); 4·94 (2H, d, J_{H-P} 6·5 Hz, OCH_2Ph); 7·58–7·59 (1OH, 2 × Ph).

N,N,N',N'-tetramethylpiperazinium dimethylphosphate, 3'a

This product of the dimerization of N,N-dimethylaziridinium dimethyl phosphate (**3**, R = R' = Me), produced by the unimolecular fragmentation of **1a** was prepared in solution, in order to identify signals characteristics of this compound in the ^{1}H-NMR spectra of the reaction mixtures. 0·010 M solution of **1a** in D_2O was incubated at room temperature and the ^{1}H-NMR spectrum of the solution was recorded periodically. After 93 h **1a** was absent in the reaction mixture which consisted of *ca.* 92% of **3'b** and 8% of **2a**. **3'b**: δ 3·40 (12H, s, 2 × NMe_2^+); 3·57 (12H, d, $J_{H—P}$ 10·5 Hz, 2 × $(MeO)_2PO_2^-$); 3·99 (8H, bs, 2 × CH_2CH_2).

Rate measurement

Second-order rate constant for the isomerization of **1a**, equation (1), was obtained by incubating the 3·47 M solution of **1a** in D_2O at 25·0 °C and monitoring the progress of reaction by ^{1}H-NMR spectroscopy. The value of k_2 was then determined from a slope of the plot of the term $x_t/a_o(a_o - x_t)$ vs. time (x_t corresponds to the total product concentration, i.e. [**4a**] + [**5a**] + [**2a**]). The required concentrations were calculated from the relative values of integrals for selected signals of the species involved, corrected to the number of hydrogen atoms responsible for a signal. For all four species involved in reaction (1), the most accurate results were obtained by following the changes in the relative intensities of the signals of the N-methyl groups (NMe_2 for **1a** and **5a**, and NMe_3^+ for **4a** and **2a**). The reaction was followed to *ca.* 80% conversion; duplicate runs gave the rate constant, k_{obs} = 1·42 (±0·06) × 10^{-4} M^{-1} s^{-1}; r = 0·991.

Second-order rate constant for the reaction between **4a** and **5a** to produce **2a** (second step of equation (1)) was determined in analogous manner, by incubating the D_2O solution of the equimolar quantities of **4a** and **5a** (total concentration 0·181 M) at 25·0 °C and periodically recording the ^{1}H-NMR spectrum of the reaction mixture. The reaction was followed to *ca.* 60% conversion; duplicate runs gave the rate constant, k'_2 = 3·20 (±0·12) × 10^{-4} M^{-1} s^{-1}; r = 0·995.

The relative reactivities of **1a** and **1b** were determined by incubating D_2O solutions of both substrates at identical concentrations (0·72 M) at 25·0 °C and recording the ^{1}H-NMR spectra of these solutions at identical time intervals, in order to determine the reaction progress and the relative proportions of products formed. The ratio of conversions, together with the ratio of the corresponding products of isomerization, **2a** and **2b** (Scheme 1, pathway a) and of fragmentation, **3'a** and **3'b** (Scheme 1, pathway b), gave the average relative (total) reactivity of **1b** and **1a**, k_{rel} = 1·5; for the isomerization and the fragmentation reactions the relative reactivities are 1.3 and 2.7, respectively.

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