THE REACTION OF HYDROGEN S-n-PROPYL METHYLPHOSPHONOTHIOIC ACID WITH ACETALDEHYDE

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Summary: The reaction provides a new phosphonylation procedure for simple alcohols.
Results obtained in inert solvents are consistent with the intermediacy of a phosphorus hemi-
acetal.

Some organophosphorus insecticides that contain P - OEt groups are reported to undergo
metabolic oxidative dealkylation[1,2] presumably by α-hydroxylation of the ethyl group to give
hemiacetals which break down to the phosphorus acid and acetaldehyde, viz.

$$CH_3CH_2OP(O)R_2 \longrightarrow CH_3CH(OH)OP(O)R_2 \longrightarrow CH_3CHO + HOP(O)R_2$$
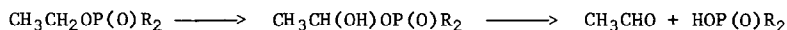
The α-hydroxylated intermediates have not been isolated or synthesised and their intermediacy
in metabolic processes has been assumed from the products isolated.[2] It was therefore
pertinent to examine the behaviour of organophosphorus monoacids with acetaldehyde to
establish if these compounds are in equilibrium with detectable quantities of the hemiacetal
or whether such an equilibrium can be inferred from the resulting products. The experimental
approach chosen was to mix organophosphorus monoacids with acetaldehyde and to monitor changes
in the mixture by ^{31}P n.m.r. Preliminary experiments with monoacids from some organo-
phosphorus insecticides gave complex reaction patterns which have not yet been completely
interpreted. However, although no hemiacetal could be detected when acetaldehyde and
S-n-propyl methylphosphonothioic acid were mixed, the results reported below and illustrated
in Scheme 2 were relatively simple and consistent with such an intermediate.

Experiments were carried out in dry THF solution and were directly monitored by ^{31}P
n.m.r. (spectra quoted are ^{1}H decoupled). The acid (1) gives a single peak at -56.6 ppm
(relative to H_3PO_4). Addition of an excess of acetaldehyde leads to the appearance of a
number of other signals: (A) A singlet at -31 ppm due to methylphosphonic acid (6), (B) A
singlet at -20 ppm due to methylphosphonic anhydride (5), and (C) A pair of doublets,
-47.6 ppm and -22.3 ppm (J_{PP} = 30 Hz) consistent with the spectrum expected for the mixed
anhydride (4). (The doublet at -47.6 ppm being that expected from the thiophosphonate
phosphorus and that at -22.3 ppm from the phosphonic acid phosphorus. The ^{1}H coupled ^{31}P
spectra exhibited a multiplet centred at -47.6 ppm and doublet of quartets at -22.3 ppm
(J_{PH} 18 Hz)). The ^{31}P n.m.r. spectrum as a function of time is outlined in Scheme 1. As the
starting acid (1) disappears peaks (A) and (B) increase in intensity but peaks (C) remain
approximately constant. After all of (1) has reacted then peaks (C) also disappear.
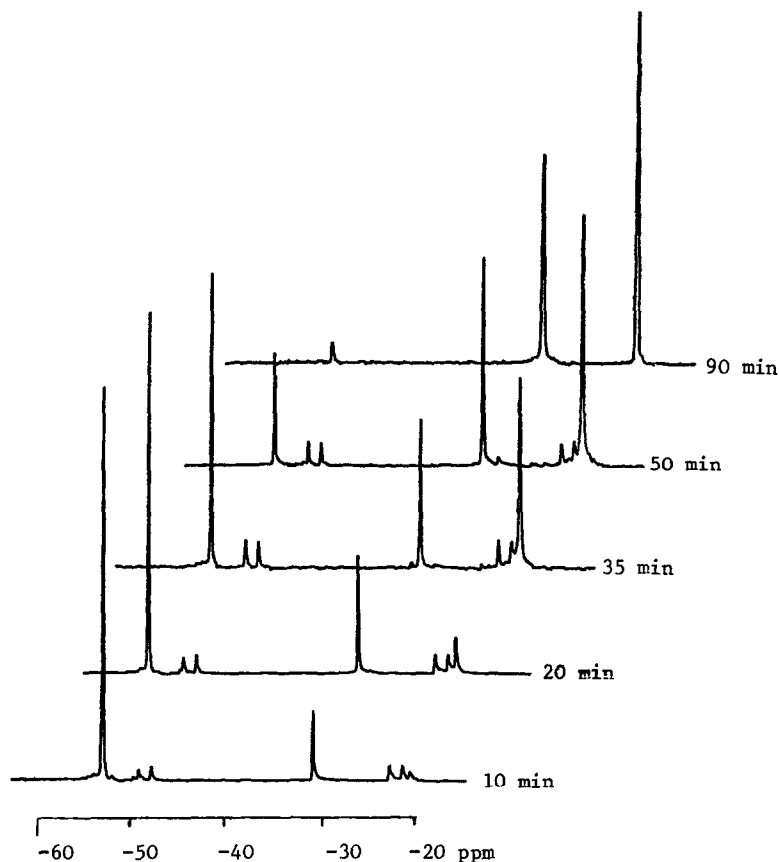
Scheme 1. ^{31}P n.m.r. spectrum of a typical reaction mixture as a function of time

A possible reaction sequence is outlined in Scheme 2. An equilibrium established between the acid (1) and acetaldehyde generates the hemi-acetal (2). Unlike (1), (2) is prone to nucleophilic attack at phosphorus. This may be explained either by simple electron density arguments or possibly by neighbouring group participation of the hemi-acetal OH group. Attack by water yields methylphosphonic acid (6) whilst attack by another molecule of the acid (1) gives the anhydride (3) and n-propane thiol. Acetaldehyde and the anhydride (4) are in equilibrium with (3). Hydrolysis of (4) by attack of water at the thiolate phosphorus gives the observed methylphosphonic anhydride (5) and more thiol. Hydrolysis of (3), (4) or (5) could also generate (6). An alternative, although perhaps less likely, route to (5) would involve attack of methylphosphonic acid (6) at phosphorus in (2) or (3).
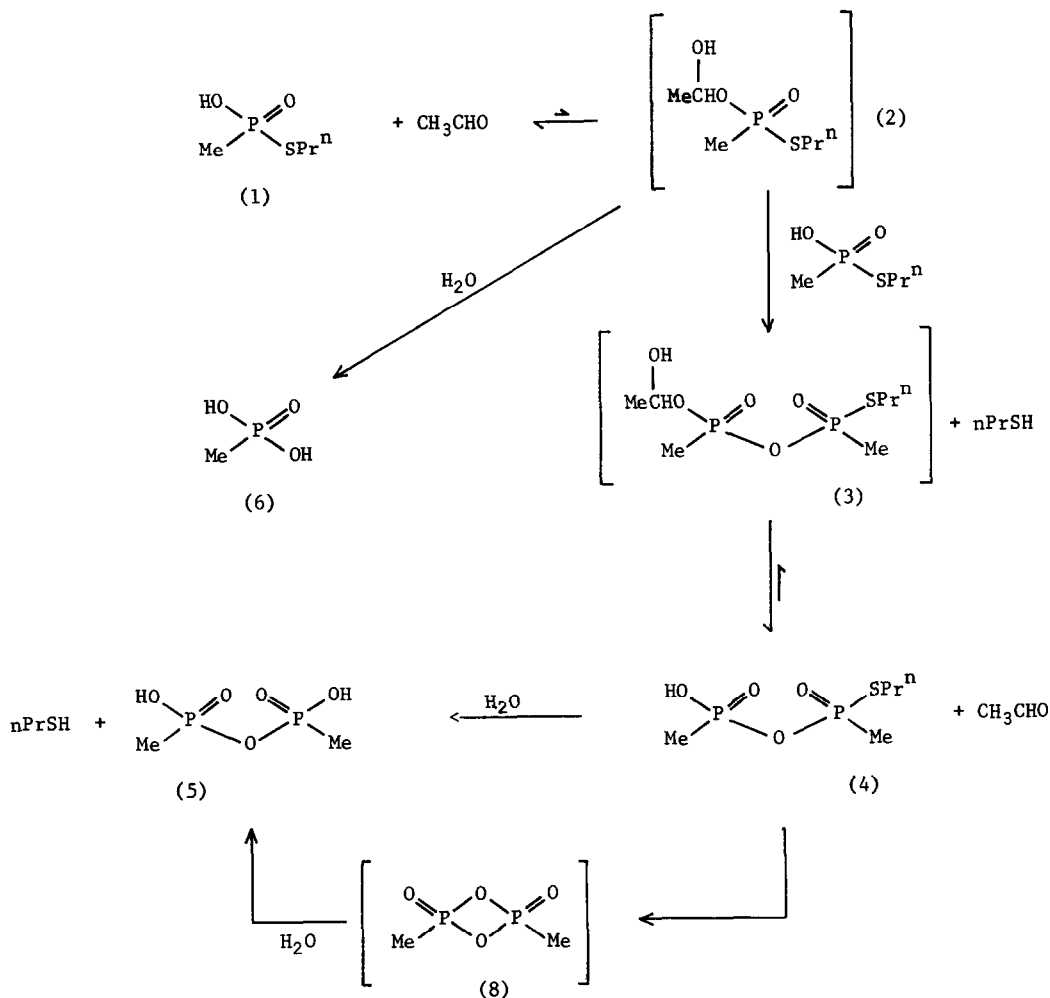
Scheme 2

The water required by Scheme 2 is generated by the reaction of the displaced n-propane thiol with excess of acetaldehyde to give the dithioacetal (7), a good yield of which can be isolated by distillation of the crude reaction mixture (Scheme 3). That the acid (1) can
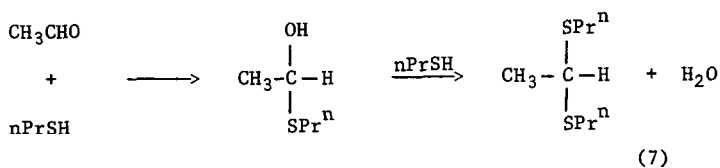
Scheme 3

compete with water as a nucleophile at (2) is a reflection of the limited amount of water generated. When the reaction was carried out in damp THF solution the only product was (6). No intermediate peaks were observed. (1) was unchanged by aqueous THF after several hours.

Because hydrolysis of (4) may be expected to result in displacement of the more acidic phosphonate group rather than $-SPr^n$, the possibility that a cyclic anhydride such as (8) may be involved in the reaction (Scheme 2) was investigated. (8) was synthesised from methyl-phosphonic dichloride and water.[3] The product is almost certainly a mixture of polymers of the general formula $[MeP(O)O]_n$. The major peak in its ^{31}P spectrum (-21 ppm in THF) is very close to that observed for (5) (-20 ppm) and is probably due to (8). Very short exposure of (8) to air results in complete conversion into (5). (It is probable that the quoted[3] infra red spectrum of (8) is in fact due to a mixture of (8) ν_{max} 1275, 1000 (broad), 905, 805 and 673 cm^{-1} and (5) ν_{max} 1210, 1120, 1010, 945, 890, 810 and 776 cm^{-1}). Methyl-phosphonic anhydride (5) generated by both routes gives an identical $X_3AA'X_3'$ pattern for the coupled ^{31}P and ^1H n.m.r. spectra. No peak at -21 ppm corresponding to (8) could be detected in the (1) - acetaldehyde reaction mixture.

Replacement of (1) by S-methyl methylphosphonothioic acid or of acetaldehyde by formaldehyde does not change the course of the reaction. Use of benzaldehyde reduced the reaction rate considerably.

To establish whether or not acetaldehyde catalyses the phosphonylation of alcohols by phosphorus mono acids, the acid (1) in methanol or ethanol was treated with an excess of acetaldehyde. A quantitative yield of alkyl methylphosphonic acid was obtained and no intermediate ^{31}P n.m.r. peaks were observed. With isopropanol as solvent some methyl-phosphonic acid was formed in addition to isopropyl methylphosphonic acid, presumably due to the small amount of water formed by the reaction competing as a nucleophile with the iso-propanol. Acetaldehyde did not promote phosphonylation of more complex alcohols such as benzyl 2,3,4-tri-O-benzyl glucopyranoside.

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