The Mechanism of Phosphonium Ylide Alcoholysis & Hydrolysis: Concerted Addition of the O-H Bond Across the P=C bond

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Abstract: The previous work on the hydrolysis and alcoholysis reactions of phosphonium ylides is summarized and reviewed in the context of their currently accepted mechanisms. Several experimental facts relating to ylide hydrolysis and to salt & ylide alcoholysis are shown to conflict with those mechanisms. In particular, we demonstrate that the pK_a values of water & alcohols are too high in organic media to bring about protonation of ylide. Therefore, we propose concerted addition of the water or alcohol O-H bond across the ylide P=C bond. In support of this, we provide NMR evidence for an equilibrium between ylide & aclohol that does not require the involvement of phosphonium hydroxide. We report the first *P*-alkoxyphosphorane to be characterised by NMR that does not undergo exchange on an NMR timescale. Two-dimensional NMR techniques have been applied to the characterisation to *P*-alkoxyphosphoranes for the first time.

Introduction

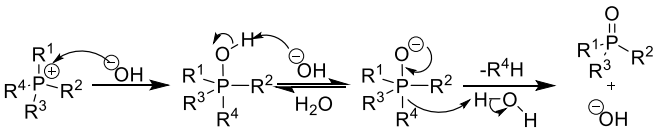
1. Phosphonium Salt and Ylide Hydrolysis

The alkaline hydrolysis of phosphonium salts is one of the prototypical reactions in phosphorus chemistry, having been reported on for the first time (to our knowledge) as early as 1857.[1] The reaction has been the subject of numerous mechanistic investigations over the course of many years.[2-17] Phosphorane (P^V) species are the only observable intermediates in phosphonium salt & ylide hydrolysis[18] & alcoholysis reactions (*vide infra*).[11], [19-21] The growth in the number and breadth of catalytic organophosphorus reactions that rely on the intervention of a phosphorane intermediate in recent years has been rapid.[22-26] Of particular relevance to the present study is a recent report on the use of an organocatalytic species formed by activation of CO_2 by phosphonium ylides in reactions with epoxides, alkynols and aziridines (to form cyclic carbonates & carbamates) in which a putative alkoxyphosphorane (or aminophosphorane) is a key catalytic intermediate.[27]

In addition to being of interest for historical and mechanistic reasons, phosphonium salt hydrolysis provides a very useful synthetic route to tertiary phosphine oxides,[28,29] often with control of stereochemistry that can be predicted based on the nature of the groups attached to phosphorus. Given the recent advent of methods for the facile reduction of phosphine oxides to phosphines & phosphine boranes, [30,31,32] phosphonium salt hydrolysis now has the potential to become a relatively straightforward and stereospecific route to access phosphines.

The mechanism of phosphonium salt hydrolysis is well-established,[2-7] and the steps are summarised in Scheme 1. Nucleophilic attack of hydroxide at phosphorus gives a *P*-hydroxytetraorganophosphorane (with apical oxygen). This is deprotonated by hydroxide to give an oxyanionic phosphorane, which expels a carbanion (probably protonated in the process of its expulsion) to give phosphine oxide and alkane or arene.[8] The leaving group (R^4) is invariably the most stable anion.[3,4,9-11] Reactions of phosphonium salts in which phosphorus is not involved in a ring appear to proceed stereospecifically with inversion at phosphorus.[12,13, 33] Consistent with the above mechanism, phosphonium salt hydrolyses are usually first-order in phosphonium salt, second-order in hydroxide, and therefore third-order overall.[2,3,4,14] Exceptional cases are known in which reactions show 1st order dependence on hydroxide concentration – e.g. the hydrolysis reactions of *para*-nitrobenzyltriphenylphosphonium bromide,[3,15] of methyltris(pentafluorophenyl)phosphonium fluorosulfonate,[15] and of phospholium iodides.[16]

In contrast, comparatively little work has been done on the mechanism of the closely related reaction, hydrolysis of phosphonium ylides. It has commonly been observed that phosphonium ylide hydrolysis results in the cleavage of the same (ultimately protonated) leaving group that would be expected in the hydrolysis of the corresponding phosphonium salt.[4,29,34,35] Thus, as identified by Johnson, "Largely on this basis it has been concluded that hydrolysis of ylides proceeds via initial protonation to a phosphonium salt, followed by hydrolysis of the salt to hydrocarbon and phosphine oxide".[5] In other words, the currently accepted mechanism for ylide hydrolysis is essentially the same as that shown in Scheme 1 for phosphonium salt hydrolysis, just involving an extra step (ylide protonation) at the start. Therefore, the two processes should have several common intermediates. Importantly, implicit in the above mechanism for ylide hydrolysis is that the hydroxyphosphorane intermediate is formed in a stepwise fashion via phosphonium hydroxide.



Scheme 1. The mechanism of alkaline hydrolysis of a phosphonium salt.

Although strong indirect evidence indicating the involvement of a pentavalent intermediate in phosphonium salt & ylide hydrolysis has existed for some time, and despite the fact that analogous hydroxyphosphoranes and related compounds with two or more cyclic *P*-alkoxy groups have been reported,[36,37] until

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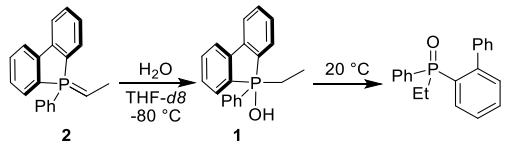
recently, no *P*-hydroxytetraorganophosporane (with four P-C bonds) had ever been detected experimentally. [38,39] However, very recently, we reported the spectroscopic observation and characterisation of *P*-hydroxytetraorganophosphorane **1** at low temperature (Scheme 2, obtained by addition of H_2O to the parent ylide **2**), finally confirming the involvement of such species in these reactions.[18]



Scheme 2. The production of *P*-hydroxyphosphorane **1** from ylide **2**.

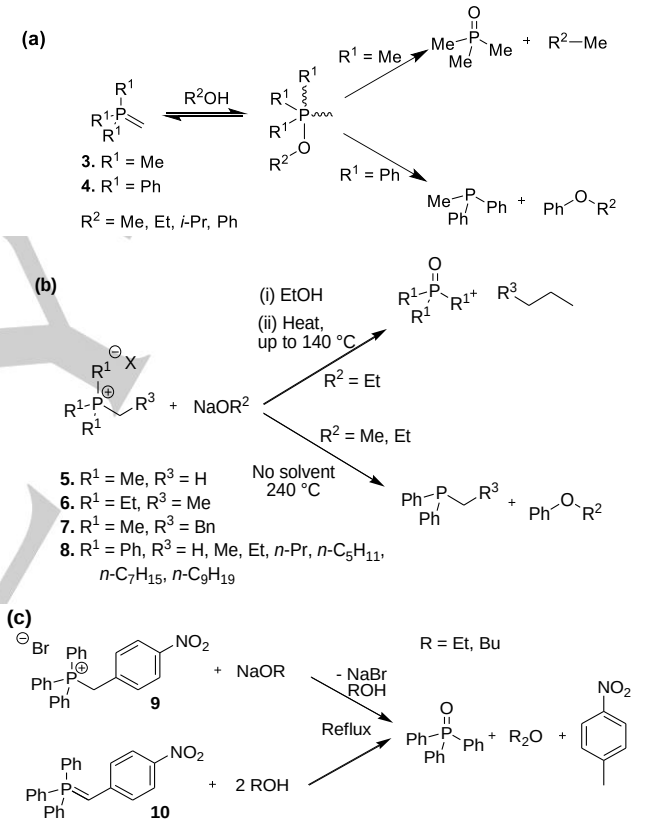
Finally, we note that a small number of differences have been observed between phosphonium salt and ylide hydrolysis. For example, hydrolysis of the enantiopure chiral ylide (*R*)-(benzylidene)ethylmethylphenylphosphorane (derived from the enantiopure parent salt) gives racemic ethylmethylphenylphosphine oxide[40] (whereas the hydrolysis of the enantiopure parent salt is stereospecific[12]). Ylide hydrolysis is faster than salt hydrolysis,[35] which has been ascribed to the low polarity of the medium in which the ylide must necessarily be prepared compared to the relatively high polarity of the aqueous organic media in which salt hydrolysis is usually conducted.[35] Additionally, we have reported one specific case where different products were obtained from hydrolysis of a salt and its derived ylide.[41]

2. Phosphonium Salt & Ylide Alcoholysis

The alcoholysis reactions of phosphonium salts & ylides are closely related to the hydrolysis reactions of the same species. A large and relatively complex body of data exists on these alcoholysis reactions, the details of which have never previously been fully summarised. Thus we collect together the most pertinent details below.

Several examples exist in which the alkoxyphosphorane intermediates of alcoholysis reactions have been observed spectroscopically.[11,19-21] For example, Schmidbaur & co-workers generated alkoxyphosphoranes by reacting ylides **3** & **4** with various alcohols[19] (see Scheme 3(a)) and ethene oxide,[19] and characterised them by ^{1}H, ^{13}C, and ^{31}P NMR. Alkoxyphosphoranes have also been proposed (although not observed) numerous times as intermediates in reactions of phosphonium salts or ylides with alcohols (*vide infra*).

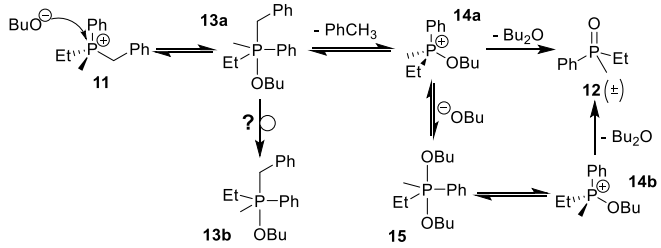
The nature of the products of these reactions seems to depend on the conditions. Heating of the alkoxytetralkylphosphoranes generated from ylide **3** (Scheme 3(a))[19] or of tetraalkylphosphonium alkoxide salts (**5**-**7**, generated by treatment of phosphonium halides with NaOEt in dry ethanol, Scheme 3(b))[10,42] in the absence of solvent gave phosphine oxide & alkane. In both the alcoholysis of **3** and that of **5**-**7**, the alkane formed was the product of C-C bond formation between the oxygen-bearing carbon of the alkoxy group and the phosphorus-bearing group of the phosphonium ylide or salt i.e. between groups initially attached to P and C, respectively.[43] Heating of alkoxymethyltriphenylphosphoranes (derived from **4**; see Scheme 3(a))[19] or of alkyltriphenylphosphonium halides (**8**) & solid soldium alkoxide (Scheme 3(b))[44,45,46] in the absence of solvent gave mainly *P*-alkyldiphenylphosphine and the phenyl ether derived from the alkyl group of the alkoxide/alcohol.[47] In the series of reactions of *n*-hexyltriphenylphosphonium bromide with NaOMe, NaOEt and NaO(*i*-Pr), progressively less of the phenyl alkyl ether was produced, and indeed none at all was produced if NaO(*t*-Bu) was employed (instead, products arising from elimination or hydrolysis were observed).[45] Eyles & Trippett concluded that the size of the larger alkoxides hindered or prevented altogether the formation of the phosphorane intermediate, resulting in the observed reduction in the trend of phenyl alkyl ether formation. The reaction of benzyltriphenylphosphonium bromide with solid NaOMe at 240 °C gave Ph_3P and stilbene (isomeric mixture).[45]



Scheme 3. Phosphonium salt and ylide alcoholysis reactions of (a) Schmidbaur;[19] (b) Hey & Ingold[10] and Eyles & Trippett[45] (c) Grayson and Keough.[49]

Grayson and Keough found that treatment of either *p*-nitrobenzyltriphenylphosphonium bromide (**9**) with sodium alkoxide in refluxing alcohol or of *p*-nitrobenzylidenetriphenylphosphorane (**10**) with refluxing alcohol gave the same products - Ph_3PO, *p*-nitrotoluene,[48] and the homo dialkyl ether derived from the alcohol (see Scheme 3(c)).[49,50,51] Entirely analogous products were observed by McEwen & co-workers in the reaction of enantioenriched benzyl phosphonium salt **11** with sodium *n*-butoxide in refluxing butanol - phosphine oxide **12**, toluene and Bu_2O (see Scheme 4).[52] Of particular significance is that alcoholysis of **11** led to racemisation of the phosphine oxide product (this phenomenon

was also observed in the alcoholysis of other benzyl phosphonium salts by Luckenbach,[53] and is similar to what is observed in the hydrolysis of the derived chiral ylide[40] – *vide supra*). The authors proposed that racemisation occurred as a consequence of the interconversion of enantiomeric butoxyphosphonium salts **14a** & **14b** via *meso*-dibutoxyphosphorane **15** (see Scheme 4).[54-57]



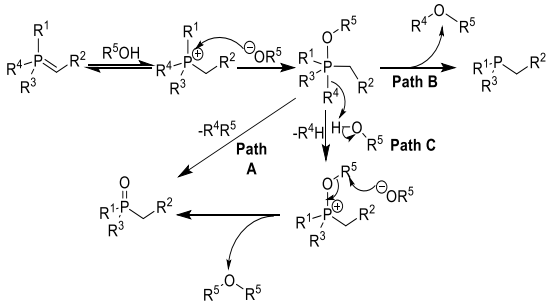
Scheme 4. Alcoholysis reaction of scalemic phosphonium salt **11** to give racemic phosphine oxide **12**.

Grayson & Keough found butyltriphenylphosphonium & tetrabutylphosphonium bromide to be inert to treatment with sodium alkoxide or in refluxing alcohol solvents.[49] All of the congeners of $[Me_nPh_mP]Br$ (n = 4 – m, m ≤ 3) have been shown to be inert to treatment with ethoxide in ethanol,[58] while $[MePh_3P]I$ has been observed not to react with NaOMe in methanol.[11] Thus, phosphonium salts that are closely related to those studied by Schmidbaur & co-workers and by Hey & Ingold do not undergo phosphorane formation or ether formation under the conditions of Grayson & Keough. *o*-Chlorophenyltriphenylphosphonium iodide underwent rapid alcoholysis when reacted with NaOMe in refluxing methanol, with the expulsion of chlorobenzene (this was deuterated in the 2-position if the reaction was conducted in MeOD).[59] Alkyltri(fur-2-yl)phosphonium and benzyltri(fur-2-yl)phosphonium salts (and their thiophen-2-yl analogues) expel a (protonated) heteroarene during hydrolysis and alcoholysis.[11]

Almost no examples of alcoholysis of stabilised ylides can be found in the literature; however there do exist two examples in which various alcohols are reacted with cyanomethylidene-trialkylphosphorane to give a proposed *P*-alkoxy-*P*-cyanomethylphosphorane intermediate.[60] The phosphorane is proposed to expel MeCN (the anion of which is protonated on expulsion) to give alkoxyphosphonium salt, which can be reacted with nucleophiles to give, for example, thioethers or amines.

3. The Mechanism of Ylide Alcoholysis

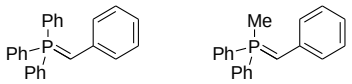
The existing consensus on the mechanism of phosphonium ylide alcoholysis[3,5,15,49,52,59] (Scheme 5) is that the first step is ylide protonation to form phosphonium hydroxide or alkoxide (exactly as for ylide hydrolysis). This is followed by nucleophilic attack of the alkoxide anion to give alkoxyphosphorane (direct displacement of the carbanion leaving group has also been suggested[49]). Decomposition of the alkoxyphosphorane gives different products depending on their structure and the reaction conditions (*vide supra*). In contrast, hydroxyphosphoranes (whether produced in the presence of excess base, as in phosphonium salt hydrolysis, or in its absence, as in ylide hydrolysis) decompose exclusively to phosphine oxide and protonated alkyl/aryl leaving group, with (to our knowledge) only one exception.[41] The alcoholysis reactions of the alkoxyphosphorane derived from **3** & **4**, and those of the phosphonium ethoxides (or possibly ylides[61]) derived from **5**-**8** were carried out in the absence of solvent or any external nucleophile at very high temperature, and in these reactions the alkyl group of the alcohol ends up attached to the carbanion leaving group in either an alkane (Scheme 5 path A) or via oxygen in a phenyl alkyl ether (path B).[62] Alcoholysis reactions of compounds **8**, **9**, **10** & **11** (and related benzylides) and cyano-stabilised ylides were carried out in refluxing alcohol[49,52] and propionitrile solvents,[60] respectively. In these reactions, the alkyl group of the alcohol ends up attached to an external nucleophile (as a thioether,[60] amine,[60] or homoether of the alcohol[49,52]), separate to the carbanion leaving group, which ends up as a protonated alkane or arene (see Scheme 5 path C). Despite the differences in the products formed – perhaps imposed by the differing reaction conditions – the two sets of reactions still share many common features: alkoxyphosphorane intermediates are almost certainly involved in all of these reactions; the P-C bond that is cleaved is that to the most stable carbanion;[5,11,49,52,59,60] and analogous phosphine & phosphine oxide products are formed in each case. Furthermore, the alcoholysis of **9** is 2nd order in alkoxide & 3rd overall,[3] similar to the order observed for phosphonium salt hydrolysis.[2,4,14] These common features are shared with phosphonium salt and ylide hydrolysis, and since analogous intermediates & products are formed in each process, there is a high likelihood that closely related mechanisms operate in each. Importantly, both hydrolysis of ylides and alcoholysis of phosphonium salts & ylides give racemic product from enantiopure starting material.



Scheme 5. The currently accepted mechanism(s) for alcoholysis of a phosphonium ylide.

Our first inkling that the mechanisms discussed above, or aspects thereof, for ylide hydrolysis and alcoholysis might not operate in aprotic organic solvents (or perhaps not at all for some types of ylide) came from the simple observation that the pK_a of water in DMSO is 31,[63] much higher than that of even the most basic ylides (e.g. pK_a = 22 for deprotonation of $MePh_3P^+$),[64] a situation which is likely to be replicated in other organic media such as (dry) THF or acetonitrile. Similar remarks apply to alcohols in organic solvents – for example, potassium *tert*-butoxide (pK_a in DMSO = 32[63]) is routinely used to irreversibly deprotonate phosphonium salts (even the most basic

ones) to give ylides for use in Wittig reactions,[65,66] while Wittig reactions of stabilised ylides can even be carried out in alcohol solvents.[67] Furthermore, subsequent to the work of Grayson and Keough, it has been established that the pK_a of ethanol in water is 15.9,[68] while that of the *p*-nitro phosphonium salt **9** used in their study is 11.0 in DMSO,[69] a value that is likely to be lower, if anything, in protic solvents.[70,71] Consequently, protonation of the benzylide (**10**) derived from the *p*-nitro salt may not be possible even in polar protic solvents. Indeed, in several of the studies cited above, the authors report the formation of coloured solutions that they attributed to the presence of ylide (the colour of which in some cases persisted for hours in refluxing alcohol, even as products formed).[15,49,72] Furthermore, the observation of Aksnes & Songstad that the hydrolysis of **9** is first order in each of phosphonium salt & hydroxide (cf. hydrolysis of **16** – 3rd order overall) may indicate that the reaction proceeds by initial formation of ylide, and hence occurs by a different mechanism to Scheme 1.[3,73]



16 **17**

Chart 1. Benylides **16** and **17**.

We have found in the course of this study that benzylides **16** & **17** (Chart 1) are protonated in dry CD_3OD solvent in dry methanol, but not by CD_3OD (or CH_3OH) in [D_8]THF solvent (*vide infra*). **16** has a pK_{aH} of 17.4 in DMSO,[64] substantially higher than that of the *p*-nitro ylide (**10**). Therefore in organic media containing only small amounts of water or alcohol, ylides cannot deprotonate water or alcohol to produce phosphonium hydroxide or alkoxide, respectively, and so the first step of the currently accepted mechanism of ylide hydrolysis/alcoholysis (ylide protonation) is an impossible process in aprotic organic solvents. Even in aqueous or alcohol solvents, the pK_a of at least some benzylides may be too low for protonation by alcohol (i.e. phosphonium alkoxide formation) to occur. Indeed, in our recent report on the observation & characterisation of a *P*-hydroxytetraorganophosphorane intermediate (**1**) in the hydrolysis of ylide **2**, it was notable that the phosphorane could be seen to co-exist with ylide and water, apparently in the absence of any phosphonium hydroxide.[18]

Results

In our previous investigations on the mechanism of the Wittig reaction,[74,75] we had devoted significant effort to the NMR observation of oxaphosphetanes (OPAs, see **18** in Chart 2). Given the structural similarity of OPAs to alkoxyphosphoranes (which differ from OPAs only in the absence of a "tether" between the ylide α-carbon and the alcohol hydroxyl carbon) & hydroxyphosphoranes, we became interested in the latter entities, as we supposed that spectroscopic observation of them might shed some light on the mechanisms of ylide alcoholysis and hydrolysis.[18]

1. Reactions of non-stabilised ylides with alcohols

After circumventing problems arising from the sensitivity of non-stabilised ylides (present over extended periods in an equilibrium) to oxidation & hydrolysis,[76,77] we were able to generate alkoxyphosphoranes **19**, **20** (from ylide **2**) and **21-24** (from ylide **25**), and characterise them by ^{1}H, ^{31}P, ^{13}C, gCOSY, gHSQC and gHMBC NMR spectroscopy. This is the first time that two dimensional NMR techniques have been applied to the study of these types of compounds. The use of NMR techniques that were previously not available in studies of alkoxyphosphoranes has allowed us to access information that is highly significant for the mechanism of ylide alcoholysis, and, by extension, for the closely related mechanism of ylide hydrolysis. Selected ^{31}P, ^{1}H & ^{13}C NMR chemical shifts and coupling constants that carry illustrative physical information about phosphoranes **19-24** are collected in Table 1.

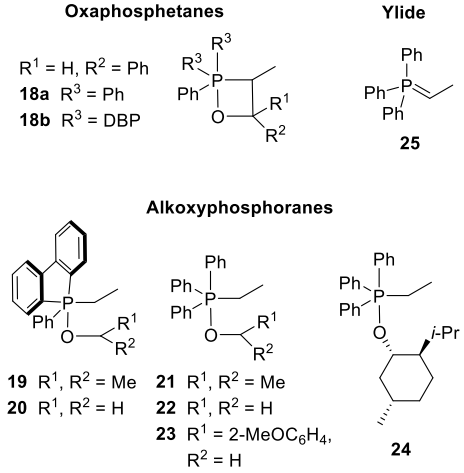


Chart 2. Oxaphosphetanes **18** (DBP: dibenzophosphole ring spanning axial & equatorial positions, *cf.* **1**, **2**, **19**, **20**), alkoxyphosphoranes **19-24**, and ylide **25**.

Table 1. Selected NMR data for phosphoranes **19-24**.

#	δ_P ppm (% by integration)	$\delta_C(PCH_2)$ ppm	$^1J_{PC}$ Hz	$\delta_H(PCCH_3)$ ppm	$^3J_{PH}$ Hz
19[a]	−72.8 (89%)	25.9	112	0.86	23.5
20	−68.6 (80%)[b]	-	-	-	-
21[a]	−52.6 (95%)	29.6	115	1.32	20.2
22[c]	−66 (93%) −51 (7%)	33.1	111	1.20	20.8
23[c]	−64 (85%) −43 (broad)	35.4	119	1.34	21.1
24[d]	8.7[e] 11.7[f]	-	-	1.56	19.3

[a] Reaction solvent: [D_8]THF.

[b] Reaction solvent THF. Alcohol = CH_3OD; ylide present in excess.

[c] Reaction solvent: [D_8]toluene.

[d] Reaction solvent: mixed THF/[D_8]THF.

[e] 2 equivalents of (−)-menthol used, broad signal.

[f] 1 equivalent of (−)-menthol used, broad signal.

The upfield ^{31}P chemical shifts found for each reaction are indicative of an electron-rich, pentacoordinate environment at phosphorus, consistent with the formation of alkoxyphosphorane. In the case of alkoxyphosphoranes **21-23** the signals are rather broad (width of *ca.* 5 ppm in the spectrometer used; see Figure 1(a) for the case of **21**).

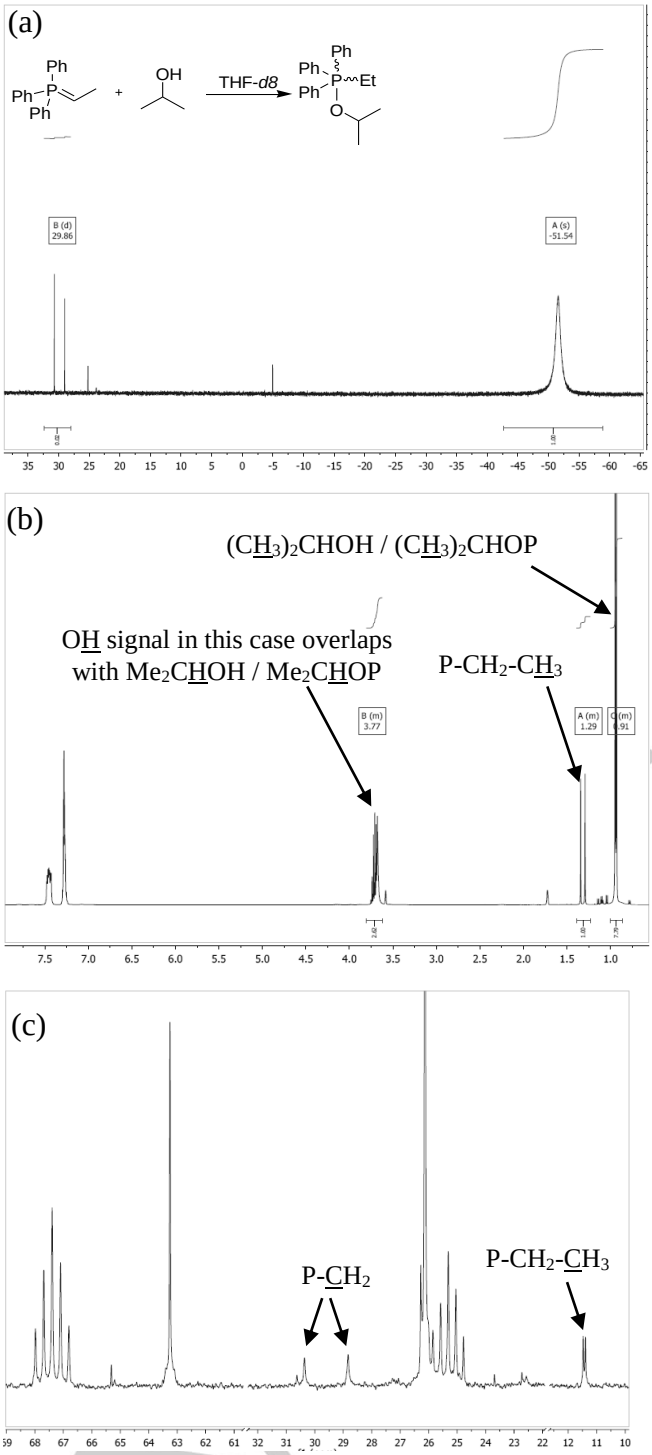


Figure 1. (a) ^{31}P NMR, (b) ^{1}H NMR, and (c) partial ^{13}C NMR spectra of isopropoxyphosphorane **21** from the reaction of isopropanol with ylide **25**.

The ^{1}H NMR spectra of **21-23** (see Table 1 for individual chemical shifts, and Figure 1(b) for the ^{1}H NMR of **21**) generally show one broad signal of variable chemical shift (the variability is even between different runs of a given reaction, and appears to be concentration dependent), which we attribute to the alcohol hydroxyl proton. The relative integration of this signal indicates that there is no contribution from the ylide PC*H* or phosphorane PCH_2, and thus that there is no signal present for these protons. The *P*-ethyl CH_3 signal is generally a sharp doublet (see Table 1 column 6 for coupling constants), showing only coupling to phosphorus (i.e. no ^{1}H-^{1}H coupling to this signal is observed in either the 1D spectrum or the gCOSY).[78] This signal collapses to a singlet under broadband decoupling from phosphorus.[79] The signals of the *P*-alkoxy group of each phosphorane appear to be coincident with those of the alcohol, which is typically present in excess. However, in the reaction of **25** with MeOH to give **22**, separate signals could be observed for the protons of the methanol CH_3 moiety and the methoxyphosphorane P-O-CH_3 moiety (separate ^{13}C signals could also be observed for these groups, *vide infra*).

In the ^{13}C NMR spectra of **21-23** (see Table 1 for individual chemical shifts, and Figure 1(c) for parts of the ^{13}C NMR of **21**), a doublet is generally observed in the neighbourhood of δ_C 30, with $^{1}J_{PC}$ between 110 & 120 Hz (see Table 1 column 4 for coupling constants). This signal shows no cross peaks in the gHSQC spectrum (see ESI), but couples to the P-C-CH_3 protons according to the gHMBC spectrum (see the gHMBC spectrum of **21** in Figure 2, and examples from other phosphoranes in the ESI). The magnitudes of the $^{1}J_{PC}$ values show clearly that the ethyl moiety in each of **21-23** resides primarily in an equatorial position in the phosphorus-centred trigonal bipyramid.[80] As in the ^{1}H NMR spectrum, the signals of the phosphorane *P*-alkoxy group and alcohol appear to be coincident. However, separate ^{13}C signals could be observed for the methyl carbons of methanol and methoxyphosphorane **22**.

The reaction of **25** with (−)-menthol in mixed THF/[D_8]THF gave a ^{31}P NMR that is somewhat different to those of **21-23**. A broad signal was observed at δ_P 11.7 after the addition of one equivalent of the alcohol. The addition of a second equivalent of the menthol solution caused the ^{31}P chemical shift to move to 8.7 ppm (compare figures 10(a) & 10(b) in ESI). The ^{1}H NMR, however, showed the same characteristics that are seen in the ^{1}H spectrum of **21-23**, i.e. a broad signal for the alcohol O*H*, a doublet only for the *P*-ethyl CH_3 at δ 1.56,[78] and no signals for ylide PC*H* or phosphorane PCH_2. No signal could be detected for the phosphorane PCH_2 carbon in the ^{13}C NMR of the reaction mixture. Neither could any signals indicating the presence of this moiety be observed in two-dimensional ^{1}H-^{13}C NMR experiments (ASAPHSQC and gHMBC). A broad and very small doublet at 7.5 ppm in the ^{13}C NMR which is shown by the gHMBC spectrum to couple to the *P*-ethyl CH_3 doublet may indicate the presence of ylide **25**.[81] The ^{31}P NMR chemical shift of the adduct of the reaction of **25** and (−)-menthol is not by itself directly indicative of a phosphorane species. However, based on the broadness of the ^{31}P NMR signal (similar to **21-23**), the difference in the chemical shift (*ca.* 12 ppm) compared to the ^{31}P shift of ylide **12** in the absence of (−)-menthol, and the similarity

of the features of the ^{1}H NMR to those of **21-23**, we conclude that there is menthoxyphosphorane, **24**, present in the reaction mixture.

Across the spectra of **21-24**, the broadness of the ^{31}P NMR signals, the absence of a discrete signal for the phosphorane α-protons in the ^{1}H NMR, the absence of coupling to the P-C*H*$_2$ protons in the ^{1}H NMR, gCOSY, gHSQC & gHMBC, and the absence of a two-bond coupling constant between phosphorus and the oxygen-bearing alkoxy carbon is consistent with the existence of an equilibrium in which the alkoxyphosphorane undergoes rapid exchange with ylide + alcohol. Similar exchange phenomena were observed by Schmidbaur & co-workers in their studies of alkoxyphosphoranes.[19] Reversion of the alkoxyphosphorane to ylide + alcohol can involve transfer of either of the α-protons to the departing alkoxide, hence both are subject to the rapid exchange process. Entry of the alcohol to the trigonal bipyramidal alkoxyphosphorane should occur along a trajectory to place the alkoxy group in an apical position.[82] In addition, the apicophilicity of the alkoxy oxygen is such that this group is highly likely to occupy an apical position in all stable (or meta-stable) phosphoranes,[82,83] since in general electronegative elements favour being positioned in apical sites in hypervalent compounds.[82-86] The fact that the *P*-ethyl group appears to be in an equatorial position in each alkoxyphosphorane means that it is ideally placed to swap protons with alcohol undergoing apical entry & departure from the trigonal bipyramidal species. In **24**, the steric bulk in the vicinity of the hydroxyl group of menthol may disfavour phosphorane formation with this alcohol compared with reactions of other alcohols, meaning that the ylide remains the predominant form in the equilibrium (as reflected by the relatively low field ^{31}P chemical shift). Indeed, the reaction mixture in question retains the vibrant red/orange colour of the ylide, which is dissipated in the reactions of the other alcohols detailed above. This interpretation is also consistent with the observations of Eyles & Trippett on the reactions of *n*-hexyltriphenylphosphonium bromide with alkoxides of varying steric bulk (*vide supra*).[45]

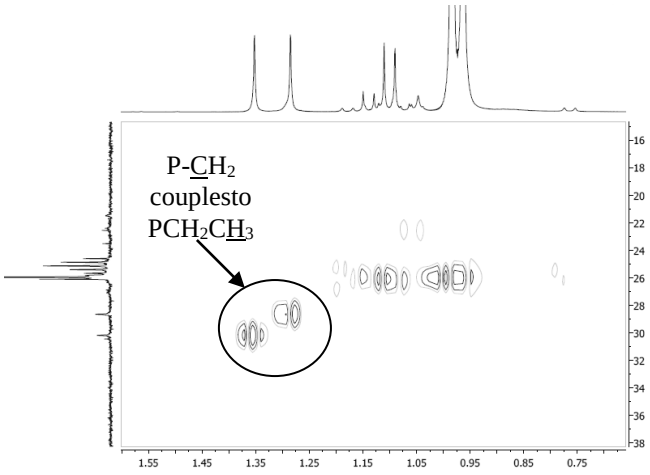


Figure 2. Close up on a region of the gHMBC spectrum of **21** showing the coupling between P-CH$_2$ and P-C-C*H*$_3$.

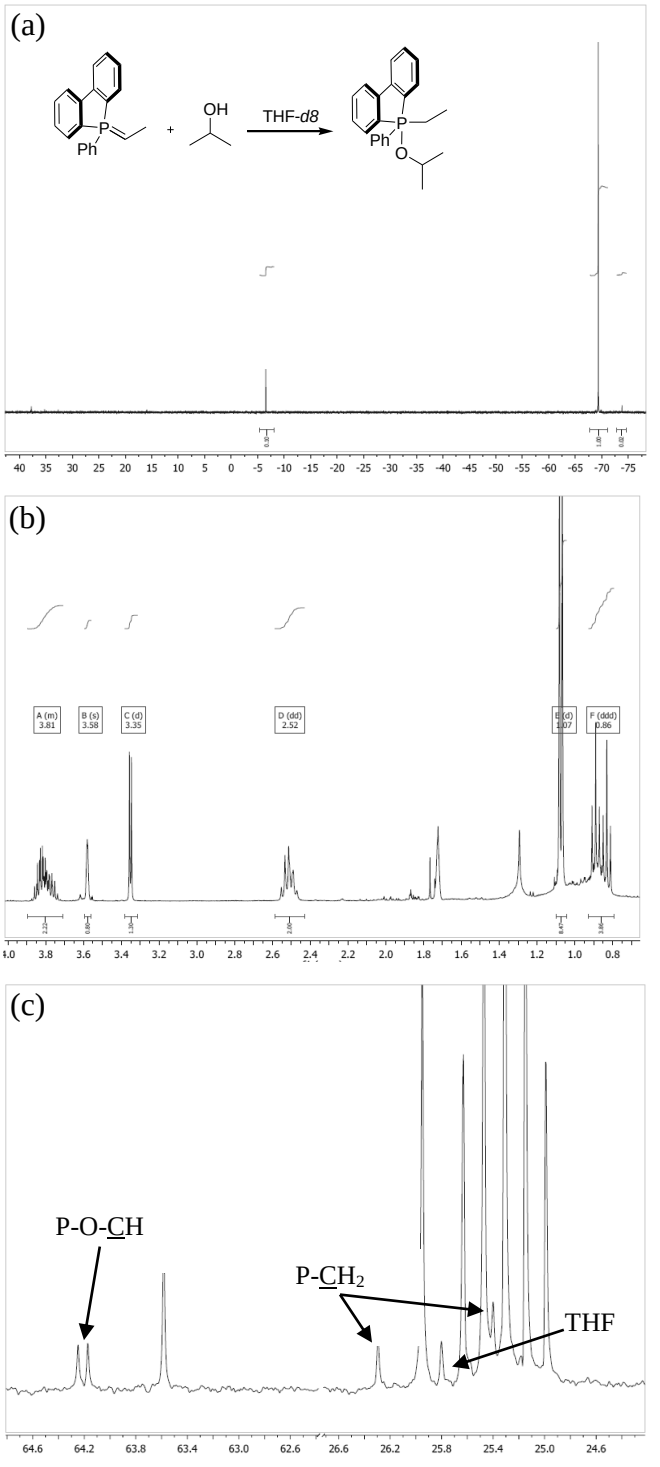


Figure 3. (a) ^{31}P NMR, (b) ^{1}H NMR, (c) partial ^{13}C NMR of phosphorane **19** from the reaction of isopropanol with ylide **2**, showing doublets for the *P*-isopropoxy *C*H (δ_C 64.2) and the P-CH$_2$ carbon (doublet centred at δ_P 25.9, partially obscured by [D$_8$]THF signal). Note: The small signal at δ 25.8 is due to non-deuterated THF.[87]

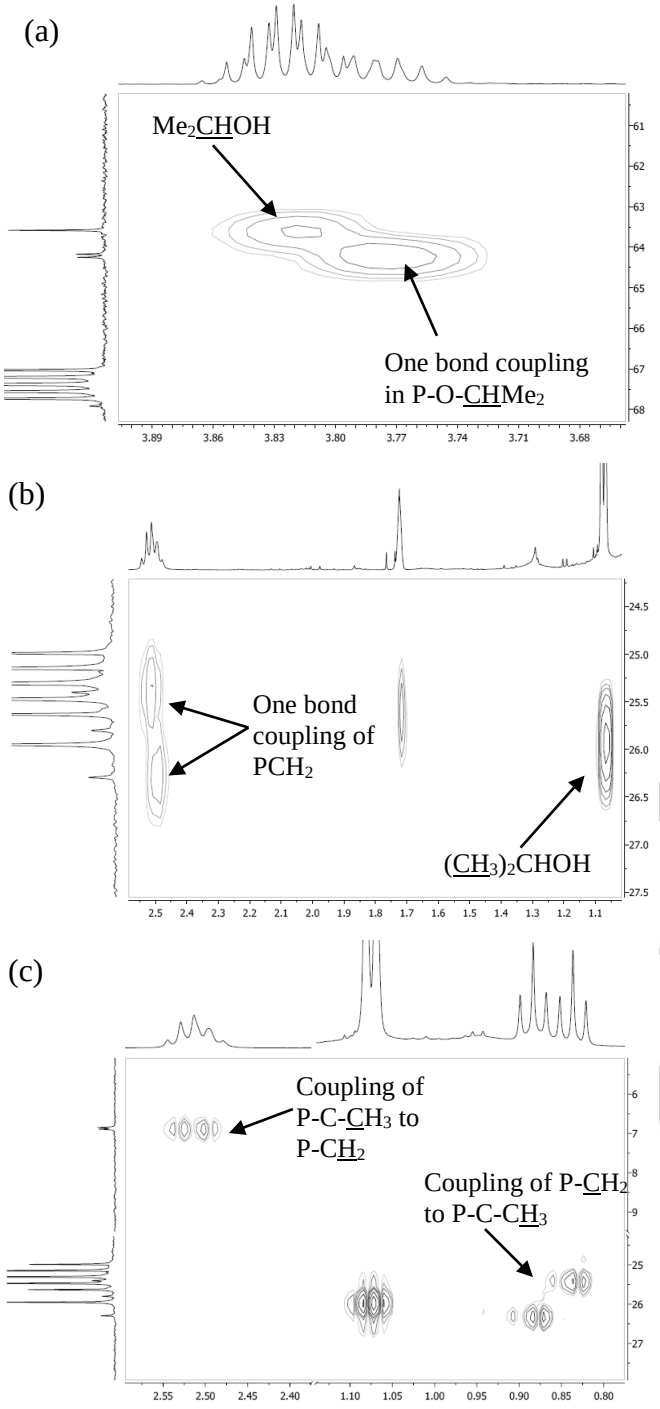


Figure 4. (a) Close-up of gHSQC spectrum of **19** showing one-bond coupling for P-O-CH_2 unit, (b) Close-up of gHSQC spectrum of **19** showing one-bond coupling for P-CH_2 unit, (c) Close-up of gHMBC spectrum of **19** showing the connectivity in the P-CH_2-CH_3 moiety.

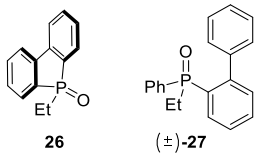
The ylide/phosphorane equilibration process leads to broadening or averaging of the P-CH_2 signals in the ^{31}P, ^{1}H and ^{13}C NMR spectra of **21-24**, meaning that discrete chemical shifts and coupling constants containing valuable physical information either could not be readily observed (e.g. $^{2}J_{PC}$ for the P-O-C moiety, $^{1}J_{PC}$ for the *P*-ethyl moiety (*vide infra*)) or simply did not exist (e.g. the *P*-ethyl group CH_2 signal in the ^{1}H NMR, and hence the value of $^{3}J_{HH}$ for that moiety). In an attempt to circumvent this limitation, we decided to generate alkoxyphosphoranes **19** & **20** from ylide **2** to investigate if this phosphorane would behave differently to unconstrained analogues **21-24** (see Table 1 row 1 for chemical shifts and coupling constants from the ^{31}P, ^{1}H and ^{13}C NMR spectra of **19**, and row 2 for ^{31}P NMR chemical shift of **20**). In doing so, we hoped to take advantage of the known effect by which constraining two of the phosphorus-substituents in a five-membered ring dramatically affects the rates of reactions of compounds containing pentacoordinate phosphorus.[67,74,82] Gratifyingly, one or more sharp peaks were observed in the high field region of the ^{31}P NMR spectra of each of **19** (δ_P −74.4, see Figure 3(a)) and **20** (two almost coincident peaks for separate pseudorotamers at δ_P −68.6). Since there is also a signal at δ_P −11.6 for the ylide (**2**), these phosphoranes undergo only slow or non-existent reversion to ylide + alcohol on the NMR timescale.

A discrete signal for the P-CH_2 protons of phosphorane **19** is present at δ 2.52, and the ^{1}H-^{1}H coupling of this group to the vicinal CH_3 protons is detected in the ^{1}H NMR ($^{3}J_{HH}$ = 7.7. Hz; see Figure 3(b)) and also in the COSY spectrum (see ESI Fig. S1(c)). In all the other examples given above (**21-24**), no discrete signal for the P-CH_2 is observed, and only ^{1}H-^{31}P coupling is observed for the P-C-CH_3 protons. Furthermore, the gHMBC spectrum of **19** indicates coupling between the methylene carbon and methyl protons, and between the methyl carbon and methylene protons (see Figure 3(c); these signals were identified using the gHQSC spectrum – see ESI). For phosphoranes **21-24** (*vide supra*), the gHMBC shows that no coupling exists to the *P*-methylene protons.

Phase-sensitive gHSQC allowed assignment of the ^{1}H and ^{13}C signals of the P-O-*i*-Pr (see Figure 4(a)) and P-CH_2CH_3 (see Figure 4(b)) moieties of **19** to be made. Hence, $^{2}J_{PC}$ for coupling between phosphorus and the secondary isopropoxy carbon was established as 9.5 Hz (see Figure 4(c)), establishing unequivocally that the structures produced in these reactions are indeed alkoxyphosphoranes, since there is clear physical evidence of bonding between the isopropoxy unit and the phosphorus. In addition, although the P-CH_2 signal in the ^{13}C NMR overlaps with one of the signals of the [D_8]THF solvent (see Figure 4(c)), this signal is also almost coincident with a signal of isopropanol), we can say with reasonable confidence based on the gHSQC spectrum (Figure 4(b)) that the value of $^{1}J_{PC}$ is *ca.* 112 Hz, indicating that the *P*-ethyl group of **19** occupies an equatorial position. The additional structural data obtained by spectroscopic study of **19**, which is simply not available from NMR studies of unconstrained phosphoranes such as **21**-**24**, is in complete agreement with our interpretation of the structure and behaviour of each of the phosphoranes **21**-**24**.

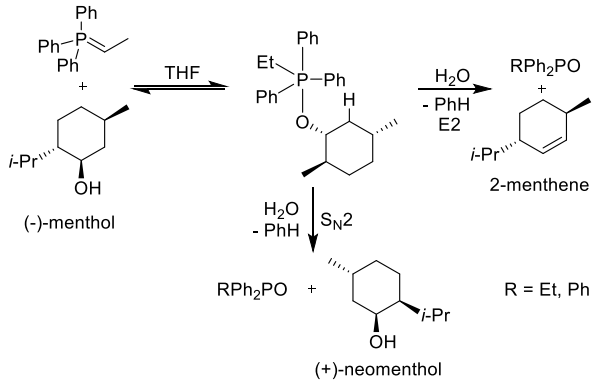
The alkoxyphosphoranes presented in Chart 2 appear to be stable indefinitely at 20 °C under an inert atmosphere based on repeated NMR observations of the samples that yielded the data

given above, with one exception: when the reaction of **25** and *i*-PrOH to give **21** was left to stand for two days at 20 °C, the phosphorane was observed to have disappeared (giving $EtPh_2PO$ and benzene), and a substantial amount of diisopropyl ether had been produced.[88] In this case, it is possible that phosphorane decomposition could occur by an S_N1-type process, ultimately resulting in ether formation. Such an occurrence would be highly unlikely for phosphoranes derived from primary alcohols (although an S_N2 process may occur at higher temperatures based on the work of Schmidbaur & co-workers[19]). We surmise that a similar occurrence (i.e. production of dimenthyl ether) does not occur at an appreciable rate in the reaction of **25** and (−)-menthol because the concentration of menthoxyphosphorane **24** is so low. That acyclic **21** undergoes decomposition comparatively quickly at 20 °C while **19** does not is not altogether surprising in light of the relative stability of analogous pentavalent dibenzophosphole-derived compounds such as **1** and **18b** compared to their unconstrained equivalents.[18,65,74]



26 (±)-**27**

Chart 3. Phosphine oxides **26** & **27**.



Scheme 6. Possible mechanisms for hydrolysis of menthoxyphosphorane (neither of which is observed; see the main text).

Addition of water to reaction mixtures containing **22-24** (derived from ylide **25**) yields $EtPh_2PO$ exclusively (or nearly so), the product expected in the hydrolysis of **25**. Addition of water to **19** yields two products, **26** & **27** (see Chart 3; formation of **27** predominates strongly, exactly as has been observed in the hydrolysis of ylide **2**[18]). Examination of the ^1H NMR of the crude hydrolysis product formed from the reaction of **25** and (−)-menthol shows that the alcohol product is (−)-menthol (δ_H 3.3[89]). This shows that the addition of water to the ylide/phosphorane mixture results in the hydrolysis of the ylide exclusively, whereas if the phosphorane (**24**) were hydrolysed, one would expect to see evidence of the formation of (+)-neomenthol (δ_H 4.10 in $CDCl_3$)[90] or 2-menthene (δ_H 5.52 in $CDCl_3$)[91] – see Scheme 6.[92] The starting alcohol is also the only observed non-phosphorus-containing product when water is added to reactions involving **19**, **22** & **23** (demonstrated by NMR and, in the case of **23**, GC), which we again interpret to be a consequence of hydrolysis of the starting ylide.

2. Reactions of semi-stabilised and stabilised ylides with alcohols

Having observed alkoxyphosphoranes by NMR that had been produced from non-stabilised ylides, we set about an attempt to determine if similar species are formed in reactions of semi-stabilised ylides, and if they could be observed spectroscopically. The results of Grayson and Keough[49] strongly indicate that an alkoxyphosphorane-type species is involved at some point on the reaction coordinate in the reactions of Scheme 6, but these species need not necessarily be stable intermediates in those reactions. We further hoped to establish if benzylphosphonium alkoxide salts are formed in the process of alcoholysis of semi-stabilised benzylides, as is suggested by the existing literature on the topic.[3,5,15,49,52,59]

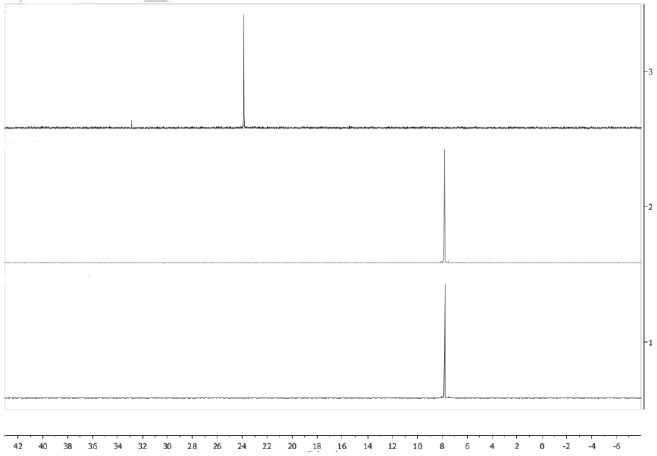


Figure 5. Stacked ^{31}P NMR spectra of experiments involving salt-free benzylide **16**. Bottom spectrum: ylide (δ_P 7.9) generated in $[D_8]$THF and diluted with CD_3CN, containing a very small amount of the parent phosphonium salt (δ_P 25.6; not visible in this figure; integrates for 1% of ylide signal). Middle spectrum: solution of ylide in $[D_8]$THF after addition of 1 equivalent of CD_3OD and subsequent dilution with CD_3CN, parent phosphonium salt is present & integrates for 1% of the ylide signal (i.e. identical to the control sample in the bottom spectrum). Top spectrum: Formation of parent phosphonium salt of **16** after addition of CD_3CN solution of **16** to excess dry CD_3OD. A very small signal phosphine oxide can be seen at the low field side of (c), formed by reaction of the ylide with adventitious water.

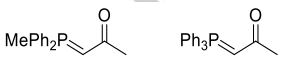
To these ends, salt-free benzylide **16** was generated in dry $[D_8]$THF under argon and characterised by ^1H and ^{31}P NMR (see Figure 5). One equivalent of dry CD_3OD was then added to the ylide solution (under argon). Since the parent phosphonium salt of **16** is almost completely insoluble in THF, the solution was diluted to 5 times its original volume with dry CD_3CN, in which the phosphonium salt is readily soluble. ^1H & ^{31}P NMR of the resulting solution indicated that the ylide was unchanged, i.e. neither alkoxyphosphorane formation nor deuteration of the ylide (see ^{31}P NMR - Figure 5 lower spectrum)[93] had occurred.

Identical results were obtained in similar experiments in which benzylides **16** and **17** were generated in dry CD_3CN under argon and treated with one equivalent of dry CD_3OD or methanol. This confirms that the pK_a of methanol is too high in aprotic organic media for a single equivalent to protonate semi-stabilised ylides.

Of course, many of the experiments reported in the literature for alcoholysis of benzylides (summarised in section 2 of the Introduction) were carried out not in polar aprotic solvents, but in alcohol solvents in which the pK_a of the hydroxyl hydrogen is much lower. Generation of salt-free benzylides **16** and **17** (in CD_3CN and THF, respectively) under an argon atmosphere and subsequent addition to a large excess of dry CD_3OD solvent resulted in immediate dissipation of the orange colour of the ylide. ^{1}H and ^{31}P NMR characterisation of the adducts indicated that the products were the parent benzylphosphonium trideuteromethoxide salts (parent phosphonium salt of **16** has δ_P 23.9 in CD_3OD, while the parent salt of **17** has δ_P 18.0 in CD_3OD).[94] We surmise that the pK_a of the hydroxyl hydrogen/deuterium of the alcohol becomes sufficiently low in alcohol solvent that protonation/deuteration of benzylides (and therefore, by implication, non-stabilised ylides) can occur. No alkoxyphosphorane was observed in any of these experiments, either in protic or aprotic media.

The solution of the phosphonium trideuteromethoxide salt derived from **17** in CD_3OD (plus a small amount of CD_3CN or THF) was heated in an oil bath (under nitrogen atmosphere, bath temperature 120 °C), resulting in the gradual formation of methyldiphenylphosphine oxide (δ_P 30.0),[95] according to ^{31}P NMR analysis of the reaction mixture. The formation of phosphine oxide under these conditions, which is consistent with the observations of Grayson and Keough,[49] presumably occurs through a transient alkoxyphosphorane or similar pentacoordinate species, which may not be a stationary point on the reaction coordinate.[83]

We also attempted to observe an alkoxyphosphorane derived from a stabilised ylide, **28** (see Chart 4), using the same method as was applied for benzylides **16** and **17** and non-stabilised ylide **25**. Neither the addition of one equivalent of CH_3OD nor of a large excess of the alcohol to a CD_3CN solution of **28** caused either protonation of this ylide or phosphorane formation – the spectra of the reaction mixture after alcohol addition merely indicated the continued presence of acetonylide.[96] The fact that **28** is not protonated by methanol is of little surprise given that Wittig reactions of stabilised ylides can be carried out in alcohol solvents,[67] and that the pK_a of related acetonylide **29** is 7.1.[64] To prove that the ylide was indeed still present in the above reaction mixture, benzaldehyde was added, resulting in the formation of 4-phenylbut-3-en-2-one and methyldiphenylphosphine oxide by Wittig reaction.

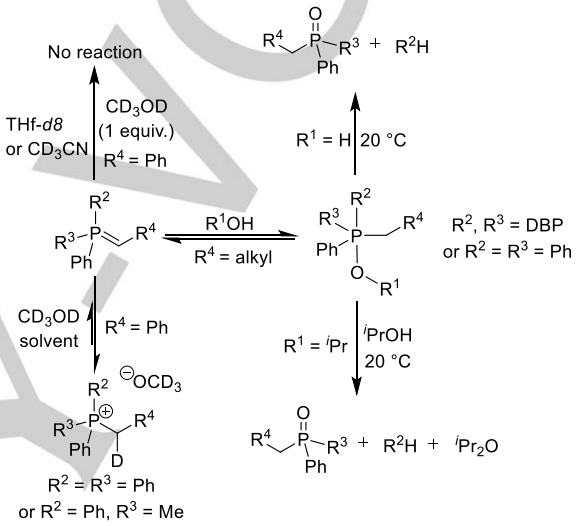


28 **29**

Chart 4. Stabilised ylides **28** and **29**.

Discussion

Protonation of benzylides **16** & **17** in solvent containing a high proportion of methanol or CD_3OD results in the production of phosphonium trideuteromethoxide (see Scheme 7). Thus, alcoholysis of alkylides and benzylides in *alcohol* solvent may occur, in at least some circumstances, by the existing mechanism involving phosphonium alkoxide as an intermediate (Scheme 5). By analogy, presumably benzylide hydrolysis in media in which the pK_a of water is lower than that of the benzylide (i.e. media containing a substantial amount of water or alcohol) proceeds through phosphonium hydroxide (mechanism of Scheme 1).



Scheme 7. Summary of results in ylide alcoholysis & hydrolysis. R^1 = H, Me, *i*-Pr, CH_2Ph.

However, based on the results presented above, we conclude that the pK_as of the hydroxyl groups of alcohols are too high in organic media for direct protonation of even the most basic phosphonium ylides (exemplified by **2** and **25)** to occur. We have also definitively established that protonation of benzylides **16** and **17** by alcohol does not occur in aprotic organic media (i.e. when *ca*. one equivalent of alcohol is used). Given that the pK_a of water is at least as high as that of alcohol in the same media, it is reasonable to conclude that water also cannot protonate phosphonium ylides in aprotic organic media.

Notwithstanding this impossible protonation, hydroxyphosphorane **1**[18] and alkoxyphosphoranes **19** and **20** are evidently formed in the reactions of ylide **2** with water, isopropanol and methanol, respectively ((see Scheme 7), while in the reactions of non-stabilised ylide **25** with alcohol, the ylide and alcohol are in rapid equilibrium with alkoxyphosphorane (**21-24**; see Figures 3 & 5 and associated discussion, and the work of Schmidbaur & co-workers for further examples).[19] Furthermore, each of **2**, **17** and **25** undergo exceedingly rapid hydrolysis when small amounts of water (2 equivalents or less) are added to solutions of these ylides in dry aprotic organic media.

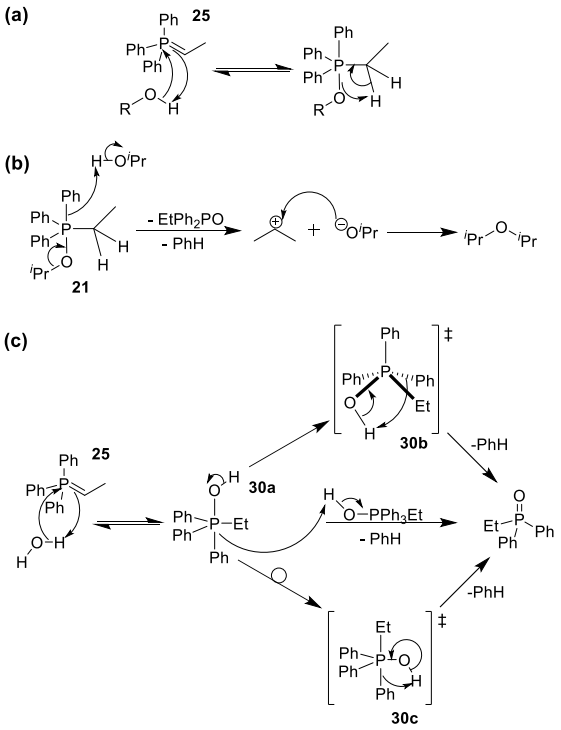
Phosphonium alkoxides/hydroxides are not necessary intermediates in the processes of formation of

alkoxyphosphoranes/hydroxyphosphoranes from phosphonium ylides + alkoxide/hydroxide. The available evidence indicates that protonation of ylides by alcohols or water in polar aprotic organic solvents does not occur. Therefore we propose an alternative explanation that accounts for the results shown here and for the observations described in the introduction which does not require the initial protonation of ylide by water or alcohol, but remains consistent with the other observations: The first step involves addition of an O-H bond of the water or alcohol across the ylide P=C bond in a concerted manner (see Scheme 8(a)), resembling in certain aspects the mechanisms of other concerted reactions such as the Alder-Ene reaction[97] and the Wittig reaction.[67,74,75] In this mechanism, the ylide carbon could be considered to be acting as an internal general base. In the trigonal bipyramidal alkoxyphosphorane or hydroxyphosphorane intermediate, the oxygen would occupy an apical position.[82,83,85,86] The ethyl moiety derived from the carbanion appears to be in an equatorial position, at least initially, based on the magnitudes of the observed one bond P-C coupling constants ($^1J_{PC}$ > *ca.* 100 Hz), and also by analogy with pentacoordinate spirophosphoranes.[98]

The pathway followed during decomposition of alkoxyphosphorane intermediates generally depends on the conditions employed (*vide supra* – section 2 of Introduction). Breakdown of isopropoxyphosphorane **21** appears to occur by an S_N1 mechanism at 20 °C (Scheme 8(b)) based on the formation of diisopropyl ether in this reaction & that phosphoranes **22** & **23** derived from primary alcohols are stable at room temperature under the same conditions (in the absence of water). Analogous decomposition products to those observed in the decomposition of **21** have been observed previously in reactions involving alkoxybenzylphosphoranes derived from primary alcohols conducted at high temperatures or in the presence of alkoxide at high temperatures (*vide supra*).[49-53] It is likely that in these cases, decomposition of alkoxyphosphoranes derived from primary alcohols occurs by an S_N2 mechanism.

It is unclear whether breakdown of the hydroxyphosphorane produced in ylide hydrolysis is intramolecular[99] or intermolecular. Assuming that equatorial departure of the *P*-phenyl group from a trigonal bipyramid cannot happen,[82, 100] intramolecular decomposition of hydroxyphosphorane can occur either (i) by concerted 4-centre apical-apical elimination of benzene from **30a** (Scheme 8(c)) – perhaps through a square pyramidal transition state, **30b**, with the phenyl & hydroxyl groups in basal positions (and *trans* relative to each other), reminiscent of the transition state in Berry pseudorotation – or (ii) by concerted 4-centre apical-equatorial elimination from pseudorotamer **30c**, which itself would probably be a transition state.[83] One way or another it seems unlikely that a second equivalent of water is necessary since no means of regenerating hydroxide is needed (cf. phosphonium salt hydrolysis).

As mentioned above, Schnell and Tebby observed that an enantiopure chiral benzylide is racemised during hydrolysis, while the parent benzyl phosphonium salt is hydrolysed stereospecifically.[40] McEwen & co-workers observed that chiral benzyl phosphonium salt **11** was racemised during alcoholysis (using *one equivalent* of butoxide).[52] In ylide hydrolysis & alcoholysis (and indeed in phosphonium salt alcoholysis reactions), once the phosphorane intermediate is produced, there is not necessarily any remaining external source of nucleophile or base (hydroxide or alkoxide). Thus, the lifetime of the phosphorane intermediate may be sufficiently long for pseudorotation to occur, giving rise to racemic product from chiral starting phosphonium ylide or salt.[101,102,103] The case is markedly different in phosphonium salt hydrolysis, in which at least a second equivalent of hydroxide is present. Racemisation could also occur via dialkoxyphosphorane or dihydroxyphosphorane intermediates, but we consider it to be unlikely that this is the case. In particular, in the case of ylide hydrolysis, racemisation via dihydroxyphosphorane would require the formation of hydroxyphosphonium salt in a non-acidic medium.

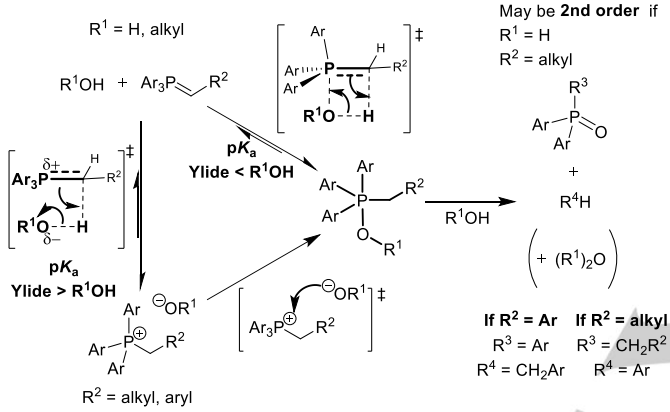


Scheme 8. (a) Mechanism for exchange process between alcohol + ylide and alkoxyphosphorane in aprotic organic media, (b) Possible mechanism for the breakdown of isopropoxyphosphorane **21**, (c) Possible mechanisms for hydrolysis of ylide **25**.

Conclusion

In summary, we have proposed and provided evidence for a new mechanism for the first step of phosphonium ylide alcoholysis and hydrolysis (see Scheme 9) which applies at least to reactions in aprotic organic media, but may also be applicable in all media to reactions of ylides derived from particularly acidic phosphonium salts (pK_a < 14) e.g. stabilised ylides and certain semi-stabilised ylides. In certain examples of phosphonium salt hydrolysis or alcoholysis involving particularly acidic phosphonium salts (e.g. *p*-nitrobenzyl salt **9**), it may even be the case that the generation of alkoxyphosphoranes from phosphonium salts and sodium alkoxide goes by deprotonation

of the salt to give ylide, which then undergoes concerted addition of the alcohol O-H bond across the P=C bond i.e. that this reaction goes from phosphonium salt to ylide and not the other way around! This may explain why no members of the $[R_nPh_mP]^+$ family (n = 4 – m, m ≤ 3) undergo alcoholysis in alcohol solvent,[11,49,58] since they cannot be deprotonated by alkoxide in this medium. The mechanisms of hydrolysis and alcoholysis of non-stabilised ylides and benzylides derived from relatively non-acidic phosphonium salts in polar protic media (solvents in which the pK_as of alcohols and water are as low as possible) are unaffected by these considerations and are as proposed previously.[4,49] Additional studies focusing on the reactivity and synthetic utility of the hydroxy and alkoxyphosphoranes discussed here are underway and will be reported presently.



Scheme 9. Summary of mechanisms of ylide alcoholysis & hydrolysis in different solvents. In aprotic organic media (in which the pK_a of the ylide is lower than that of water/alcohol), the first step is concerted addition of ylide & water/alcohol to give phosphorane. In solvents in which the pK_a of water/alcohol is lower than that of the ylide (generally protic media), phosphorane is formed in a stepwise fashion through phosphonium alkoxide or hydroxide.

Experimental Section

General Procedure for Ylide Alcoholysis

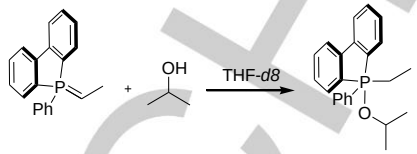
All glassware used for inert atmosphere operations was flame-dried and cooled under vacuum. Phosphonium salt (1.0 equivalent) and KHMDS (1.0 equivalent) were added to a flask in a glove box under an atmosphere of dry argon. [D_8]THF or [D_8]toluene-*d8* (1.0 ml) was added, and the resulting ylide solution was stirred for 15 minutes. Stirring was then stopped, and the KBr precipitate was allowed to settle. The (brightly coloured) supernatant solution was carefully withdrawn by syringe, and added to an NMR tube. The dry alcohol (2-4 equivalents) was then added by one of two methods:

(i) Direct addition by syringe in the glove box, or

(ii) The NMR tube was placed into a long Schlenk flask,[104] which was then sealed with a greased stopper, removed from the glove box and attached to a nitrogen supply through a nitrogen/vacuum manifold by the pump & fill technique. The alcohol could then be added to the NMR tube by syringe through a rubber septum.

In either case, the NMR tube was sealed with a rubber septum under inert atmosphere, and brought to the NMR spectrometer to record spectra.

Phosphorane 19 from ylide 17 + isopropanol



The ylide was generated from *P*-ethyl-*P*-phenyl-*5H*-dibenzophospholium bromide (31 mg, 0.080 mmol) & KHMDS (18 mg, 0.090 mmol) in [D_8]THF (0.8 ml). To this was added a 3 mol L^{-1} solution of isopropanol in [D_8]THF (0.1 ml, 0.3 mmol).

NMR signals assigned to alkoxyphosphorane **19**:

^{31}P NMR (121 MHz, [D_8]THF) δ = -11.6 (0.15P), -74.4 (1.0P), -78.9 (0.01P).
^{1}H NMR (500 MHz, [D_8]THF) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.48 – 7.39 (m, 3H), 7.34 – 7.25 (m, 2H), 7.25 – 7.12 (m, 3H), 3.89 – 3.71 (m, 3.3H, contains C*H*OH (2.3H) and C*H*OP (1H) signals), 2.58 – 2.43 (m, 2H, CH_2P), 0.86 (dt, *J* = 23.5, 7.7 Hz, 3H, CH_3CH$_2$P). Several signals were broadened to such an extent that unambiguous assignment and accurate integration were not possible. These signals were: δ 7.91 – 7.77 (m), 7.66 – 7.52 (m), 7.11 – 6.90, 1.20 – 0.90.
^{13}C NMR (101 MHz, [D_8]THF) δ 145.0 (d, *J* = 2.8 Hz), 143.9 (d, *J* = 3.8 Hz), 140.5 (d, *J* = 142.1 Hz), 133.6 (d, *J* = 20.5 Hz), 131.5 (d, *J* = 22.3 Hz), 130.2 (s), 129.7 (s), 129.7 (d, *J* = 7.8 Hz), 129.1 (d, *J* = 14.6 Hz), 128.6 (d, *J* = 7.3 Hz), 128.3 (d, *J* = 3.0 Hz), 125.9 (d, *J* = 9.4 Hz), 122.6 (s), 64.5 (d, *J* = 9.4 Hz, *C*H$_2$OP), 26.2 (s, (*C*H$_3$)$_2$CHOP, by [D_8]THF signal & identified from 2-dimensional spectra), 25.9 (d, PCH$_2$, obscured by [D_8]THF signal & identified from 2-dimensional spectra), 7.2 (d, *J* = 5.4 Hz).

NMR signals assigned to isopropanol:

^{1}H NMR (500 MHz, [D_8]THF) δ 3.89 – 3.71 (m, 3.3H, contains C*H*OH (2.3H) and C*H*OP (1H) signals), 3.36 (d, *J* = 4.2 Hz, 2.3H), 1.08 (t, *J* = 6.3 Hz, signal partially obscured by broad signal).
^{13}C NMR (101 MHz, [D_8]THF) δ 63.9 (s, (CH$_3$)$_2$*C*HOH), 26.3 (*C*HOH).

After obtaining NMR characterization for the phosphorane, H_2O (0.03 ml) was added to the reaction mixture in the NMR tube at 20 °C, resulting in formation of ylide hydrolysis products in a very similar ratio to that observed in the hydrolysis of ylide **2**.[18] Isopropanol (but no diisopropyl ether) was also observed to be present.

^{31}P NMR (121 MHz, [D_8]THF) δ 42.8 (0.04P, phosphine oxide EtDBPO, compound **26**, lit.[105] δ_P 46.11 ($CDCl_3$)), 33.2 (1P, phosphine oxide **27**, lit. δ_P ([D_8]THF) 32.2[18]), 30.7 (0.15P, PhDBPO from ylide oxidation, (lit. δ_P (dioxane-*d8*) 30.0;[106] δ_P ($CDCl_3$) 33.5[30])), two signals at 22.9 (cumulative 0.1P), -10.1 (PhDBP0, 0.1P, lit.[106] δ_P ([D_8]dioxane) -10.0).
^{1}H NMR (300 MHz, [D_8]THF) δ3.92-3.73 (m, 1H, Me$_2$C*H*OH), 1.10 (d, *J* = 6.2 Hz, (CH_3)$_2$CHOH).

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Keywords: Alkoxyphosphorane • hypervalent compounds • phosphonium ylides • concerted additions • reaction intermediates

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[51] An analogous set of products – phosphine oxide (n-Bu_3PO), benzoic anhydride and alkane (the alkane derived that would be expected from the hydrolysis of the ylide - the best leaving group attached to P) - was obtained from the reaction of a heavily conjugated stabilised ylide with benzoic acid in benzene; see Y. Kawamura, Y. Sato, T. Horle, M. Tsukayama, *Tetrahedron Lett.* **1997**, *38*, 7893 - 7896. Analogous results were not obtained with more typical stabilised ylides, e.g. $Ph_3P{=}C(Me)CO_2Me$.

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[61] These entities were prepared from the parent phosphonium halides by treatment with NaOEt in dry EtOH (see ref. [10]); although the pK_a of this base in EtOH is probably too low to deprotonate a phosphonium alkylide at room temperature, it is possible that at the high temperatures at which the reactions were carried out (and after the EtOH solvent had been distilled away) that the reacting entity was an ylide and not a phosphonium ethoxide.

[62] According to reference [85], the least-motion pathway for eliminations such as the one in path B, 3-centre apical-equatorial elimination, is forbidden based on the symmetry of the molecular orbital of the phosphorane (whether trigonal bipyramidal or square-based pyramidal)[84] that gives rise to the new σ-bond. On this basis, the process must occur by apical-apical or equatorial-equatorial elimination. Formally, this reaction is the reverse of biphilic additions of e.g. peroxides to phosphines (see reference [55]). The process of path A, if it is an intramolecular process, may occur by analogous 4-centre apical-apical or equatorial-equatorial elimination mechanisms, or perhaps through a trigonal bipyramidal transition state[83] in which the alkoxy group (undergoing dealkylation) is in an equatorial position. See however references [25] & [26].

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protonate non-stabilised ylides in alcohol solvents. However, the pK_{aH} values of semi-stabilised and stabilised ylides in alcohol solvents may be too low (and indeed may themselves be lowered in alcohol solvents) for protonation of ylide by alcohol to occur. For example, the pK_as of *P*-phenacyltriphenylphosphonium cation and *P*-acetonyltriphenylphosphonium cation are the same (or slightly lower) in mixed ethanol/water solvents[70] as in DMSO.[63]

[72] The experiments of Eyles & Trippett involved neat mixtures of phosphonium salt and sodium alkoxide.[45] To investigate the formation of ylide in their reactions, the authors reacted (α-deuteroisopropyl)triphenylphosphonium iodide and NaOMe under the above conditions and recovered substantial amounts of MeOD, indicating that phosphonium salt deprotonation by alkoxide to give ylide had indeed occurred. However, the other products obtained in this case were propene (with diminished deuterium-labelling vs. starting phosphonium salt) and Ph_3P i.e. reaction that led to scission of the phosphonium P-C bond was an elimination reaction, mediated either by ylide or methoxide, or perhaps by both.

[73] The possibility that benzyl phosphonium salt hydrolysis could occur via benzylide was suggested in reference **3**, but discounted on the basis that the hydrolysis of tetraphenylphosphonium bromide, which cannot form ylide, shows the same 2nd order dependence on hydroxide concentration that is exhibited by benzyl salt **17**. The authors concluded that the 1st order dependence on hydroxide concentration exhibited by **9** was due to a change in the rate determining step from phosphorane decomposition to phosphorane formation.

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[76] Even after alkoxyphosphorane formation had occurred, due to the existence of a phosphorane/ylide equilibrium, there was still ylide present, and standard Schlenk techniques proved insufficient to prevent this reactive species from undergoing oxidation and/or hydrolysis over the time course of our experiments. Most noticeably, the process of fitting a rubber septum (to facillitate addition of a reagent) to a Schlenk flask under a flow of nitrogen allowed a sufficient quantity of water and oxygen into the flask to cause hydrolysis and/or oxidation over time of significant quantities of the ylide in the ylide/alkoxyphosphorane mixture. Furthermore, the act of transferring the reaction mixture to an NMR tube (under nitrogen atmosphere in a long Schlenk flask) by cannula invariably led to some oxidation and hydrolysis of the ylide despite our best efforts.

[77] See ESI for description of air-sensitive ylide generation.

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[88] See figures S5(a)-(f) in the ESI.

[89] See Fig. 11(b) in the ESI.

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[92] An alternative possibility involves attack of water at phosphorus to give a species that is hexavalent at phosphorus (*cf.* reference [57]). Although we do not unequivocally rule out this possibility, we have seen no evidence in our ^{31}P NMR studies of meta-stable hydroxyphosphorane 1[18] or alkoxyphosphoranes **19** & **20** for the existence of such hexavalent species.

[93] Significantly, the red/orange colour of the reaction mixture remained after the addition of the CD_3OD.

[94] Identical results were obtained in separate experiments with ylide **17** (i) in the presence of KBr salt and (i) using non-deuterated dry methanol. In a further experiment conducted by the same procedure (ylide quenched with an excess of dry methanol) using dry CD_3CN as solvent, benzaldehyde was added after the addition of methanol. No alkene or phosphine oxide was formed by Wittig reaction, showing that the ylide was indeed no longer present.

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[96] The chemical shift of the composite signal of the two isomers that arise by restricted rotation about the alpha-beta bond of the ylide changed a little, from δ_P 8.0-7.5 in neat CD_3CN to δ_P 3.5-2.9 in CD_3CN with added methanol.

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[99] See the discussion in reference [85] on molecular orbital symmetry considerations in the elimination of H_2 from PH_5, which are certainly of relevance to this discussion.

[100] See however reference [25] (and discussion in note [62]) in which P^V to P^{III} reductive elimination appears highly likely to occur by an axial-equatorial elimination pathway.

[101] Compare with racemisation of chiral phosphine oxide in the presence of HCl,[102] and racemisation in alkaline hydrolysis of chiral dialkoxyphosphonium salts,[103] both of which are proposed to occur by pseudorotation of a pentavalent entity.

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[104] Standard Schlenk techniques could then be applied when using the long Schlenk flask without the occurrence of oxidation or hydrolysis. We found that diffusion of adventitious oxygen or water down into the NMR tube was extremely slow due to the narrow diameter of the tube and the fact that the solution in the NMR tube was not being stirred. Ylide hydrolysis and oxidation could also be avoided in reactions where NMR observation of the intermediate was not required by generating the ylide in the glove box (under dry argon) in a Schlenk flask fitted with a second tap. When the Schlenk flask was removed from the glove

box and fitted to the nitrogen supply, the second tap could be fitted with a septum and the region between the septum and tap then purged with nitrogen gas before opening the tap to permit addition of reagents. This prevented the entry of all but the tiniest quantities of oxygen and water to the reaction flask.

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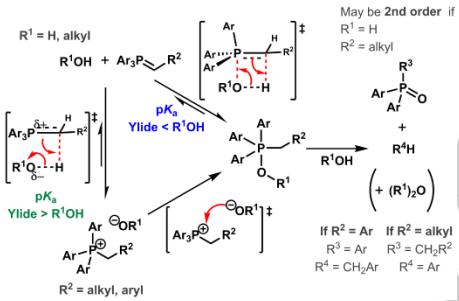
The existing mechanism for phosphonium ylide alcoholysis & hydrolysis is at odds with several experimental facts e.g. H_2O & ROH cannot protonate phosphonium ylide in aprotic organic solvents. We propose instead a concerted 4-centre addition of the O-H bond across the P=C bond. NMR characterisation of alkoxyphosphoranes shows them to be in equilibrium with ylide + alcohol in aprotic solvents.



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Page No. – Page No.

The Mechanism of Phosphonium Ylide Alcoholysis & Hydrolysis: Concerted addition of the O-H bond across the P=C bond

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Page No. – Page No.

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Text for Table of Contents