Mechanism of Hydrolysis of Phosphonium Salts and Ylides

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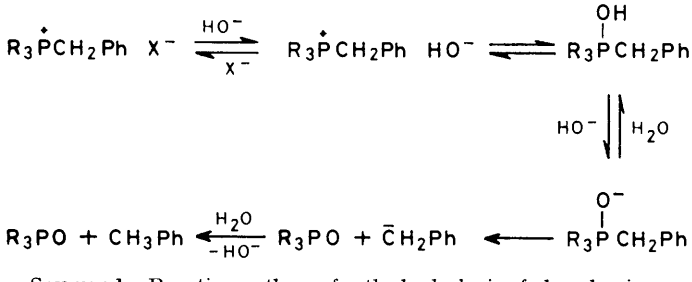
Hydrolysis of (+)-benzylethylmethylphenylphosphonium iodide *via* the corresponding ylide in a low polarity medium gives (±)-ethylmethylphenylphosphine oxide. This racemisation is in contrast to the inversion of configuration that accompanies alkaline hydrolysis of the salt in highly aqueous media. The stereochemical difference must be due to the change in medium because the mechanisms are basically the same. It is concluded that the decrease in the polarity of the medium increases the lifetimes of the five-co-ordinate intermediate phosphoranes, permitting extensive pseudorotation. Furthermore, the inversion in the hydrolyses in highly aqueous media can be seen to be due to the short lifetimes of the intermediate phosphoranes, which inhibits pseudorotation, and blocks the reaction pathways leading to products with retention of configuration.

ALKALINE hydrolyses of phosphonium salts have been studied extensively,[1,2] and there is general agreement that the reactions occur by the pathway shown in Scheme 1. The stereochemistry of nucleophilic substitution at



SCHEME 1 Reaction pathway for the hydrolysis of phosphonium salts and ylides

phosphonium centres is generally rationalised by making the assumptions (*a*) that the nucleophile attacks phosphorus to become a substituent in the apical position of the resultant trigonal bipyramidal intermediate and that the leaving group departs from an apical position; and (*b*) that the nucleophile can attack opposite any phosphorus substituent to give four possible intermediates each of which can pseudorotate in three ways.

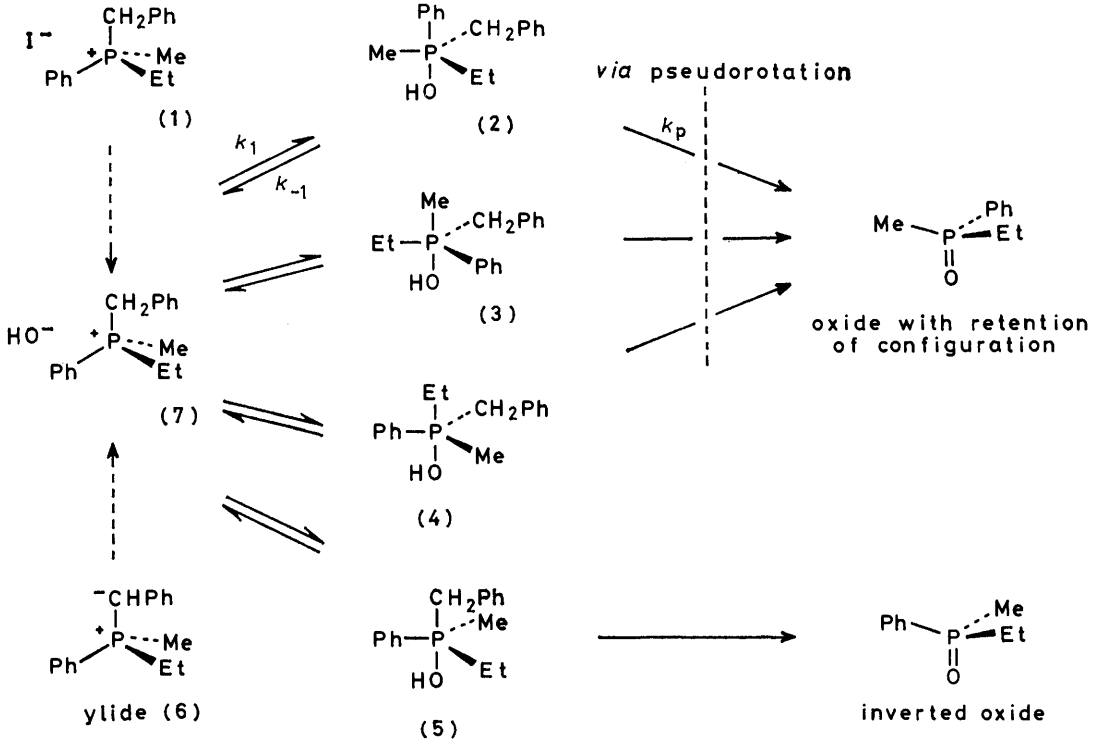
The alkaline hydrolysis of acyclic benzylphosphonium salts has been shown to occur with inversion of configuration at phosphorus, the rate usually being third-order overall (second-order with respect to hydroxide ion).[1]

[1] K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1959, **81**, 3805; G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 1929, 2342; L. Horner, H. Hoffmann, H. G. Wippel, and G. Hassel, *Chem. Ber.*, 1958, **91**, 52; M. Zanger, C. A. VanderWerf, and W. E. McEwen, *J. Amer. Chem. Soc.*, 1959, **81**, 3806; H. Hoffmann, *Annalen*, 1960, **634**, 1; G. Aksnes and J. Songstad, *Acta Chem. Scand.*, 1962, **16**, 1426; R. F. Hudson and M. Green, *Angew. Chem. Internat. Edn.*, 1963, **2**, 11; W. E. McEwen, *Topics Phosphorus Chem.*, 1965, **2**, 1; R. Luckenbach, *Phosphorus*, 1972, **1**, 223.

[2] W. E. McEwen, K. F. Kumli, A. Blade-Font, M. Zanger, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1964, **86**, 2378.

When bulky groups [3] (or small rings) [4] are bound to phosphorus the stereochemical path changes to one of retention of configuration. This is attributed to faster attack of the hydroxide ion opposite the bulky group (or one of the ring ligands) followed by minimal pseudorotation to place the benzyl group in an apical leaving position. Molecular models of the intermediates produced by attack at alternative sites reveal destabilising steric effects. However, steric effects are not the only factors controlling the stereochemistry: the alkaline hydrolyses of non-hindered acyclic phosphonium salts occur with inversion of configuration, although there appear to be no large steric differences amongst the four possible intermediates. Thus benzylethylmethylphenylphosphonium iodide (1) may give any of the four hydroxyphosphorane intermediates (2)—(5) shown in Scheme 2. The configurations (2)—(4), which arise from attack of hydroxide ion opposite non-benzylic groups, all give retention of configuration if the benzyl group attains an apical leaving position by the shortest pathway. Only attack opposite the benzyl group gives the inverted oxide. More extensive pseudorotation of the intermediates would lead to racemisation. There are two possible explanations to be considered: (*A*) that the benzyl group is considerably more apicophilic than the other organic groups, resulting in a corresponding extra stability of the intermediate (5) as compared with intermediates (2)—(4); and (*B*) that all four possible intermediates are formed in similar amounts but that their lifetimes are too short to allow pseudorotation, with the consequence that only the intermediate (5), with an apical benzyl group, can decompose to products, the others reverting to the phosphonium hydroxide.

A variable-temperature ^{19}F n.m.r. study [5] of the hexafluoroacetone adducts of a series of 1-substituted phosphetans showed that the apicophilicities of the methyl, isopropyl, 2-methylbut-1-enyl, and phenyl groups are in the inverse order of their electronegativities. This is attributed to increased back-bonding into phosphorus *d* orbitals which favours occupation of the radial positions. Although such back-bonding should be minimal for the benzyl group, the increase in electronegativity of the methylene group induced by the benzene ring would not be expected to be sufficient to induce exceptional stability in the hydroxyphosphorane intermediate (5). Since the order of the reaction shows that the hydrolysis is not concerted, there appears to be no way in which the excellent carbanion-stabilising properties of the benzyl group can determine the stereochemistry. Thus although the reaction probably occurs *via* mechanism (*B*), more evidence is desirable.



SCHEME 2 Stereochemical pathways for the hydrolysis of phosphonium salts and ylides

We have previously shown [6] that the hydrolysis of benzylidenetriphenylphosphorane follows the same reaction pathway as the alkaline hydrolysis of the corresponding phosphonium salt, and that the much greater

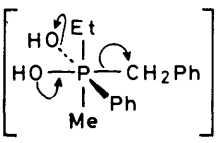
[3] N. J. De'Ath and S. Trippett, *Chem. Comm.*, 1969, 172.
[4] W. Hawes and S. Trippett, *Chem. Comm.*, 1968, 295; K. L. Marsi, *ibid.*, p. 1968, 846; R. L. Burwell and R. G. Pearson, *J. Phys. Chem.*, 1966, **70**, 300.
[5] R. K. Oram and S. Trippett, *J.C.S. Chem. Comm.*, 1972, 554; *J.C.S. Perkin I*, 1973, 1300.
[6] A. Schnell and J. C. Tebby, *J.C.S. Chem. Comm.*, 1975, 134; A. Schnell, J. G. Dawber, and J. C. Tebby, *J.C.S. Perkin II*, 1976, 633.

rate of hydrolysis of the ylide than of the salt is due to the low polarity of the medium in which ylides must be prepared. The main cause of the rate increase is attributed to the stabilisation of the five-co-ordinate intermediates and a destabilisation of the salt in the low polarity media.[6,7] Since the configuration at phosphorus is unaltered upon conversion into the ylide,[2] the results of hydrolysis of an ylide derived from an optically active phosphonium salt could provide evidence on the mechanism, and make possible a choice amongst the above possible explanations for the inversion of configuration. This test is based on the assumptions that the relative apicophilic properties of the organic groups are not appreciably altered by the change in medium, but that the lifetimes of the intermediates are increased considerably when the polarity is greatly reduced.

Benzylidene-ethylmethylphenylphosphorane (6) was generated in anhydrous tetrahydrofuran from the (+)-salt, m.p. 166—167°, $[\alpha]_D$ +21° (*c* 1.17 in MeOH),[8] and the orange solution was mixed rapidly with an equal volume of tetrahydrofuran containing 2% water. Evaporation gave completely racemic ethylmethylphenylphosphine oxide. On the other hand, alkaline hydrolysis of the (+)-salt in 3 : 2 water–tetrahydrofuran gave the inverted oxide, $[\alpha]_D$ −17.6°. There can be little doubt that the racemisation arises from extensive pseudorotation of the intermediate five-co-ordinate phosphoranes, and that this is due to their extended lifetimes in low polarity media. It follows that the phosphorane intermediates generated in highly aqueous media are not sufficiently long-lived to undergo pseudorotation with or without oxyanion generation. Thus the phosphonium hydroxide (7) is favoured over the five-co-ordinate intermediates (2)—(5) to such an extent in aqueous media that the solvent-dependent equilibrium rate constant, k_{-1} (see Scheme 2) is much larger than the solvent-independent rate constant for pseudorotation, k_p. Consequently the inability of the phosphorane intermediates to pseudorotate in aqueous media (*a*) prevents racemisation and (*b*) blocks the pathways which lead to oxides with retention of configuration. Thus the main forward pathway involves the decomposition of the initial intermediate, *e.g.* (5), which already has the leaving group in an apical orientation, and this is the pathway which leads to inverted oxide.

With regard to the base-catalysed expulsion of the leaving group, it is recognised that when the initial hydroxide ion attacks opposite a non-leaving group, generation of the oxyanion, assists the movement of the oxygen function to a radial position, allowing the leaving group to attain an apical position. However there is no such advantage for the decomposition of intermediates such as (5), and their base-catalysed decomposition may well occur in a concerted manner.

These results are also evidence against an interesting mechanism which has been put forward for discussion.[9] In this mechanism a second hydroxide anion attacks the phosphorane (5) to give the six-co-ordinate intermediates (8)—(10). The anions (8)—(10) can also be formed from



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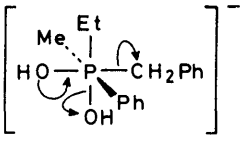

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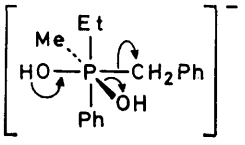

(10)

the phosphoranes (2)—(4), and to ensure the formation of inverted oxide only *trans*-elimination of hydrocarbon across the octahedral intermediates, with simultaneous ejection of the other hydroxide group, can be allowed. Thus pseudorotation is avoided completely and, unless there is a change in the mechanism, it cannot account for the loss of stereospecificity upon decreasing the polarity of the medium.

EXPERIMENTAL

Benzylethylmethylphenylphosphonium Iodide (1).—The racemic salt was prepared by reduction of dibenzylmethylphenylphosphonium iodide with lithium aluminium hydride in tetrahydrofuran.[10] Quaternisation of the resulting benzylmethylphenylphosphine with ethyl iodide and recrystallisation from hot water gave the pure iodide (1), m.p. 166—167° (lit.,[10] 165—166°).

Resolution of the (±)-*Iodide* (1).—This was carried out according to the method of McEwen *et al.*[2,8,11,12] Silver hydrogen (−)-di-*O*-benzoyltartrate (18.6 g, 0.04 mol) and the racemic iodide (1) (14.8 g, 0.04 mol) gave a salt which after four recrystallisations produced needles (1.45 g), m.p. 138—139° (decomp.), $[\alpha]_D$ −56° (*c* 0.908 in MeOH) {lit. for (+)-benzylethylmethylphenylphosphonium hydrogen (−)-di-*O*-benzoyltartrate, m.p. 142—143° (decomp.),[11] 138—139° (decomp.);[12] $[\alpha]_D$ −56°,[8] −57°,[12] −54°[11]}. Decomposition of the phosphonium tartrate by ammonium iodide gave, after extraction with acetone, (+)-benzylethylmethylphosphonium iodide (1) (0.43 g), m.p. 166—167°, $[\alpha]_D$ +21° (*c* 1.17 in MeOH) {lit.,[8] m.p. 165.5—166.5°, $[\alpha]_D$ +24°}. Complete evaporation of the acetone extract gave further (+)-iodide (0.25 g), $[\alpha]_D$ +21° (overall yield 76% from the dibenzoyltartrate; 4.6% from the racemic iodide).

(+)-*Benzylidene-ethylmethylphenylphosphorane* (6).—Anhydrous tetrahydrofuran (20 cm³) was distilled, under nitrogen, from a large excess of lithium aluminium hydride directly into a flask containing finely ground, vacuum dried (+)-benzylethylmethylphenylphosphonium iodide (1) (0.25 g, 0.675 mmol). After the addition of an excess of powdered sodium hydride (0.03 g, 1.25 mmol), the mixture was stirred

[7] F. Y. Khalil and G. Aksnes, *Acta Chem. Scand.*, 1973, **27**, 3832.
[8] R. G. Barnhardt, Ph.D. Thesis, University of Massachusetts, 1965.
[9] G. Wittig, *Bull. Soc. chim. France*, 1966, 1162.
[10] W. J. Bailey, S. A. Buckler, and F. Marktscheffel, *J. Org. Chem.*, 1960, **25**, 1996.
[11] K. F. Kumli, Ph.D. Thesis, University of Kansas, 1959.
[12] A. Blade-Font, Ph.D. Thesis, University of Kansas, 1960.

for 22 h at room temperature, then allowed to settle overnight. The clear orange solution was then decanted, under positive nitrogen pressure in all-glass apparatus, into a dry 25 cm^3 graduated flask.[6]

Hydrolysis of the Ylide (6).—The ylide solution (*ca.* 0.03 mol dm^{-3}) prepared as described above was introduced into a sample reservoir of an SF1A stopped-flow apparatus through a glass tube, under positive nitrogen pressure. Water–tetrahydrofuran (2 : 98) was placed in the adjacent sample reservoir, and equal volumes of the two reactant solutions were rapidly mixed under nitrogen in a dry receiving flask. After the rapid disappearance of the ylide colouration (<10 s), the solvent was removed under reduced pressure at 40 °C. The pale yellow oil was dried in a vacuum oven for 72 h at 40 °C. The resulting ethylmethylphenylphosphine oxide (0.117 g), an extremely hygroscopic semisolid, was taken up in anhydrous methanol (5 cm^3). This solution showed no optical rotation. Evaporation of the methanol left ethylmethylphenylphosphine oxide as a pale yellow oil; $\nu_{max.}$ (film) 3 060, 2 970, 1 620, 1 482, 1 460, 1 440s, 1 410, 1 300, 1 265, 1 235, 1 155s, 1 100, 1 068, 1 030, 965, 886, 800, 740, 708, and 690 cm^{-1}; τ ($CDCl_3$) 0.64—0.94 (5 H, m, aromatic), 6.48—6.8 (2 H, m, CH_2), 6.95 [3 H, d, J (P,CH_3) 13.5 Hz, *P*-Me], and 7.38—7.74 (3 H, d of overlapping, t, $CH_3{\cdot}CH_2$).

Hydrolysis of the (+)-*Iodide* (1).—The (+)-iodide (1) was unchanged after treatment for 24 h at room temperature with an equimolar amount of sodium hydroxide in 3 : 2 water–tetrahydrofuran. Hydrolysis was achieved by refluxing the salt (0.239 g, 0.646 mmol) in a solution of sodium hydroxide (0.5 g, 12.5 mmol) in 3 : 2 water–tetrahydrofuran (20 cm^3) for 16 h. The two-phase mixture was allowed to cool and the tetrahydrofuran layer was collected and evaporated under reduced pressure at 40 °C. The pale yellow oil was dried in a vacuum oven at 40 °C for 72 h. The semisolid oxide (0.0425 g, 0.25 mmol), dissolved in anhydrous methanol (5.0 cm^3), showed $[\alpha]_D$ −17.6° (*c* 0.85) {lit.,[2] $[\alpha]_D$ −22.8° for (−)-ethylmethylphenylphosphine oxide}.

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