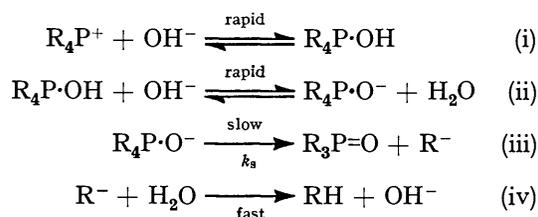


The Chemistry of Heteroarylphosphorus Compounds. Part II.¹ The Importance of Inductive Effects on Pre-equilibria in the Alkaline Hydrolysis of Heteroarylphosphonium Salts; Phosphorus-31 Nuclear Magnetic Resonance Studies

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The alkaline hydrolysis of the heteroarylphosphonium salts, tri-(2-furyl)methylphosphonium iodide (III; R = Me, X = I) and benzyltri-(2-furyl)phosphonium bromide (III; R = PhCH₂, X = Br) results in cleavage of a phosphorus-furan bond to produce di-(2-furyl)methylphosphine oxide (IV; R = Me) and benzyl-di-(2-furyl)phosphine oxide (IV; R = PhCH₂), respectively. Preliminary rate studies show that these reactions proceed *ca.* 10²–10³ times faster than the hydrolysis of the corresponding tri-(2-thienyl)phosphonium salts, which have been shown previously to undergo hydrolysis *ca.* 10⁸ times faster than the phenyl analogues. The greater rate of hydrolysis of the heteroarylphosphonium salts compared to the phenyl analogues is attributed to the greater electron-withdrawing character of the heteroaryl substituent, which increases from 2-thienyl to 2-furyl. Evidence for this has been adduced from a comparison of *pK_a* data for the analogous carboxylic acids, and also from a study of ³¹P n.m.r. chemical shifts of the phosphonium salts and a related series of phosphonate esters. The electron-withdrawing heterocyclic ring systems cause increases in the equilibrium constants of the pre-equilibria involved in the hydrolysis reactions; in addition, the heteroaryl carbanions eliminated in the rate-determining step are more stable than the phenyl carbanion. The question of 3*d* orbital stabilisation of the 2-thienyl carbanion is discussed. The equilibria between a series of phosphonium salts (V) and methoxide ion, in absolute methanol, to form the methoxyphosphoranes (VI) have been studied by ³¹P n.m.r. techniques. The position of equilibrium has been shown to depend on the electron-withdrawing character of the groups attached to phosphorus.

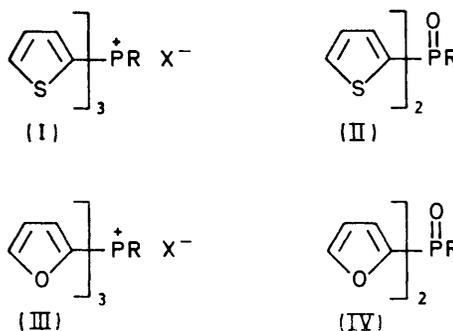
THE mechanism of the alkaline hydrolysis of phosphonium salts to give a phosphine oxide and a hydrocarbon is thought to involve steps (i)–(iv). As required by this



mechanistic scheme, kinetic studies have established that a third-order rate law ($\text{rate} = k_{\text{obs}}[\text{R}_4\text{P}^+][\text{OH}^-]^2$) is followed. The relative ease of departure of the R group in the rate-determining step (iii) parallels its stability as a carbanion, and is also influenced by the nature of the non-departing groups.²⁻⁴ Thus the presence of electron-withdrawing substituents accelerates the reaction, whereas electron-donating substituents tend to retard it.

Recently, we have shown that, under the same conditions, the alkaline hydrolysis of methyltri-(2-thienyl)phosphonium iodide (I; R = Me, X = I) to give methyl-di-(2-thienyl)phosphine oxide (II; R = Me) and thiophen, proceeds *ca.* 10⁸ times more rapidly than the analogous reaction of methyltriphenylphosphonium iodide (giving methyl-diphenylphosphine oxide and benzene).¹ It was suggested that the very rapid rate of hydrolysis of the thienylphosphonium salt could be attributed to the electron-withdrawing (inductive) effect of the 2-thienyl group and the stability of the 2-thienyl carbanion; the effects of *d*_π-*p*_π bonding between the π-electrons of the heterocyclic ring and the phosphorus 3*d* orbitals appeared to be of little consequence in influenc-

ing the rate of the reaction. The factors promoting stabilisation of the 2-thienyl carbanion were also briefly considered; either inductive stabilisation due to the electronegative sulphur atom, and/or overlap of the *sp*² orbital of the carbanion with a 3*d* orbital of sulphur may occur.



In order to shed further light on the possible role of *d* orbitals of the heteroatom of the heterocyclic ring in influencing the stability of the carbanion and hence the rate of the reaction, the alkaline hydrolysis of the analogous alkyltri-(2-furyl)phosphonium salts (III; R = Me, X = I) and (III; R = PhCH₂, X = Br) has been studied. The salt (III; R = Me, X = I) undergoes hydrolysis with loss of furan to give di-(2-furyl)methylphosphine oxide (IV; R = Me); loss of furan also occurs on hydrolysis of the salt (III; R = PhCH₂, X = Br) to give the oxide (IV; R = PhCH₂). As with the hydrolysis of benzyltri-(2-thienyl)phosphonium bromide (I; R = PhCH₂, X = Br), the course of the hydrolysis of the furyl salts contrasts with that of benzyltriphenylphosphonium bromide, which proceeds with loss of the

¹ W. E. McEwen, G. Axelrad, M. Zanger, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1965, **87**, 3948.

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

⁴ M. Zanger, C. A. VanderWerf, and W. E. McEwen, *J. Amer. Chem. Soc.*, 1959, **81**, 3806.

benzyl group (as toluene) to give triphenylphosphine oxide. The preferential cleavage of furan or thiophen from the benzyltri(heteroaryl)phosphonium salts would suggest that the heteroaryl carbanions are more stable than the benzyl carbanion.

Preliminary rate studies of the hydrolysis of the salts (III) show that the reactions are extremely rapid, and proceed considerably faster than the hydrolysis of the analogous salts (I). It was found that the reactions proceed essentially to completion in 10 s at 5°. Under the same conditions, the half-life of methyltri-(2-thienyl)-phosphonium iodide is 94 s, and that of benzyltri-(2-thienyl)phosphonium bromide is 540 s.

Assuming that the reactions go essentially to completion after the passage of ten half-lives, an estimate of 1 s for the half-life for the hydrolysis of the salts (III)

due to the increased electron-withdrawing nature of the phosphorus substituents, would be reflected in an overall rate increase of *ca.* 10⁸ for the reaction.

Simple heterocyclic systems such as furan and thiophen appear to function as electron-withdrawing species, owing to the influence of the electronegative heteroatom, when the electronic interactions between the ring system and the reaction site do not directly involve the π -electron system. Thus, a comparison of the pK_a data for furan-2-carboxylic acid (pK_a 3.2), furan-3-carboxylic acid (4.0), thiophen-2-carboxylic acid (3.5), thiophen-3-carboxylic acid (4.1), and benzoic acid (4.2) reveals that the heteroarene-carboxylic acids are all stronger than benzoic acid. In addition, the furancarboxylic acids are stronger than the corresponding thiophen compounds, in keeping with the greater electronegativity of oxygen.⁵

TABLE 1

³¹P Chemical shifts (relative to 85% H₃PO₄) of phosphonium salts in trifluoroacetic acid

Salt			
δ /p.p.m.	-18.8	-2.25	+15.4
Salt			
δ /p.p.m.	-19.9	-3.9	+12.8

enables the third-order rate constants to be crudely estimated at 10⁸ l² mol⁻² min⁻¹. Comparison with the rate data for the salts (I; R = Me; X = I) ($k_{obs} = 1.13 \times 10^6$ l² mol⁻² min⁻¹) and (I; R = PhCH₂, X = Br) ($k_{obs} = 1.61 \times 10^5$ l² mol⁻² min⁻¹) reveals that the hydrolysis of the analogous tri-(2-furyl)phosphonium salts proceeds *ca.* 10²–10³ times faster.

The overall rate constant, k_{obs} , for the hydrolysis of a phosphonium salt, although governed by the slow step (iii), is composite, and can be expressed as the product of the equilibrium constants of steps (i) and (ii), K_1 and K_2 respectively, and the rate constant of step (iii), k_s . Thus, rate of slow step (iii) = $k_s[R_4P \cdot O^-]$. Now $[R_4P \cdot O^-] = K_2[R_4P \cdot OH][OH^-]$ and $[R_4P \cdot OH] = K_1[R_4P^+][OH^-]$. Hence rate = $k_s K_1 K_2 [R_4P^+][OH^-]^2$, *i.e.* rate = $k_{obs} [R_4P^+][OH^-]^2$ where $k_{obs} = k_s K_1 K_2$.

A referee for our earlier paper¹ commented that rate increases of *ca.* 10⁸, observed for the hydrolysis of the heteroaryl salts relative to the phenyl analogues, are rather large to be accounted for by 'inductive effects'. In a footnote to the paper, the composite nature of k_{obs} was briefly indicated; consequently, moderate increases of *ca.* 10²–10³ in the individual constants, k_s , K_1 , and K_2

Further evidence of the electron-withdrawing nature of these heterocyclic systems has been adduced from the ³¹P n.m.r. spectra of the salts (I) and (III). The ³¹P chemical shifts of the heteroarylphosphonium salts, together with those of their phenyl analogues, are given in Table 1.

Recent studies of the ³¹P n.m.r. spectra of a series of substituted phenylphosphonic acids have shown that the chemical shifts are affected by the substituents on the phenyl ring in a direction opposite to that expected from the electron-withdrawing ability of the substituent. For the phenylphosphonic acids, the more electron-withdrawing the substituent, the more shielded is the phosphorus.⁶ While such behaviour would appear to be anomalous in comparison with the trends observed in ¹H and ¹⁹F n.m.r. spectra, it has been shown that it follows directly from quantum mechanical theory.⁷ A study of the data is Table 1 reveals a trend to a greater shielding of the phosphorus on passing from phenyl, to 2-thienyl, to 2-furyl substituents, indicating the increasing electron-withdrawing character of the heteroaryl ring as the electronegativity of the heteroatom increases.

We have also observed a similar trend in the ³¹P

⁵ A. Albert, 'Heterocyclic Chemistry,' Athlone Press, London, 1968.

⁶ C. C. Mitsch, L. D. Freedman, and C. G. Moreland, *J. Magnetic Resonance*, 1970, **3**, 446.

⁷ J. R. Van Wazer and J. H. Letcher, '³¹P Nuclear Magnetic Resonance,' 'Topics in Phosphorus Chemistry Series,' eds. M. Grayson and E. J. Griffith, Interscience, New York, 1967, vol. 5, p. 179.

above experiments resulted in the evolution of considerable heat, and a marked change in the ^{31}P n.m.r. spectrum, which exhibited a single peak at $\delta -9.9$ p.p.m. characteristic of di-(2-furyl)methylphosphine oxide (IV; R = Me), the product of aqueous alkaline hydrolysis of methyltri-(2-furyl)phosphonium iodide (III; R = Me, X = I); the oxide (IV; R = Me) was subsequently isolated from the solution.

We have also investigated the temperature dependence of the equilibrium between the furylphosphonium salt and methoxide ion. On progressively cooling a solution of the salt (1 mol. equiv.) and sodium methoxide (0.5 mol. equiv.) in absolute methanol, to -70° , the ^{31}P resonance (at $\delta +48.5$ p.p.m.) gradually broadened until, at -75° , it could no longer be observed. At -80° , two new signals, at $\delta 16$, due to the phosphonium ion (V; R = 2-furyl), and $+97$ p.p.m., presumably due to the phosphorane (VI; R = 2-furyl), were observed. (Pentacovalent phosphoranes are known to have considerably more positive ^{31}P chemical shifts than other classes of organophosphorus compounds.^{7,15}) On further cooling to -90° , the signals intensified; on allowing the sample to warm to room temperature, the original signal at $\delta +48.5$ p.p.m. reappeared and those due to the phosphonium ion and the phosphorane disappeared.

Integration of the ^{31}P resonance signals due to the phosphonium ion (V; R = 2-furyl) and the phosphorane (VI; R = 2-furyl), at -83° , enabled the equilibrium constant for the reaction to be evaluated as 11.05 l mol^{-1} . Clearly, in this case, the position of the equilibrium lies well to the right, whereas for the corresponding 2-thienyl- and, particularly, the phenyl-phosphonium salts, it lies very much over to the left. Our suggestion of the contribution to the overall rate constant of moderate increases of *ca.* 10^2 – 10^3 in the equilibrium constants of steps (i) and (ii) in the mechanism of the hydrolysis of phosphonium salts, due to variation in the nature of the groups bound to phosphorus, would therefore seem reasonable.

Studies of the chemistry of heteroarylphosphorus compounds are continuing, with a view to establishing the electronic properties of heterocyclic systems, and their influence on the rate of reactions at phosphorus.

EXPERIMENTAL

^1H N.m.r. spectra were recorded at 60 MHz on a JEOL spectrometer. ^{31}P N.m.r. spectra were recorded at 24 MHz on the same instrument, with phosphoric acid (85%) as external standard. G.l.c. analyses were carried out with a Pye series 104 chromatograph equipped with a 25 ft column of 10% silicone oil on Celite, and a flame ionisation detector. M.p.s were determined with a Kofler hot-stage apparatus.

Preparation of Phosphonium Salts.—*n*-Butyl-lithium (0.2 mol) in light petroleum (b.p. 40 – 60°) (200 ml) was added dropwise, with stirring, under nitrogen, to furan (20 g, >0.2 mol) in ether (100 ml), during 20 min. The resulting solution was left for 1 h before being cooled in ice. Phosphorus trichloride (5.5 g, 0.04 mol) in benzene (50 ml) was then added slowly. The mixture was then heated under

reflux for 1 h, cooled in ice, and hydrolysed with ammonium chloride solution (10% w/v; 100 ml). The organic layer was then separated, dried (Na_2SO_4), and evaporated; the residue was distilled to give tri-(2-furyl)phosphine (6.5 g, 42%), b.p. 114° at 0.6 mmHg (lit.¹⁶ 136 at 4 mmHg). The phosphine, in benzene, with methyl iodide gave *tri*-(2-furyl)methylphosphonium iodide, m.p. 112 – 113° (Found: C, 41.4; H, 3.45. $\text{C}_{13}\text{H}_{12}\text{IO}_3\text{P}$ requires C, 41.7; H, 3.25%); τ (CDCl_3) 1.9 (3H, m), 2.12 (3H, m), 3.17 (3H, m), and 6.85 (3H, d, $^2J_{\text{POCH}}$ 14.55 Hz); δ ^{31}P ($\text{CF}_3\cdot\text{CO}_2\text{H}$) $+15.4$ p.p.m.

The phosphine, in benzene, with benzyl bromide gave *benzyltri*-(2-furyl)phosphonium bromide, m.p. 216 – 217° (Found: C, 56.4; H, 3.85. $\text{C}_{19}\text{H}_{18}\text{BrO}_3\text{P}$ requires C, 56.6; H, 4.0%; τ (CDCl_3) 2.0 (6H, m), 2.83 (5H, s), 3.24 (3H, m), and 4.75 (2H, d, $^2J_{\text{POCH}}$ 14.8 Hz); δ ^{31}P ($\text{CF}_3\cdot\text{CO}_2\text{H}$) $+12.8$ p.p.m.

Alkaline Hydrolysis of Furylphosphonium Salts.—(a) *Tri*-(2-furyl)methylphosphonium iodide. To the salt (0.2 g, 1 mol. equiv.) dissolved in aqueous ethanol (50% v/v; 25 ml) was added 0.02M-sodium hydroxide solution in aqueous ethanol (50% v/v) (25 ml, 1 mol. equiv.). After 2 h, the solution was evaporated and the residue was extracted with water (10 ml) and chloroform (2×10 ml). The chloroform layer was dried (Na_2SO_4) and evaporated to give *di*-(2-furyl)methylphosphine oxide, m.p. 78 – 80° (Found: C, 55.1; H, 4.4. $\text{C}_9\text{H}_9\text{O}_3\text{P}$ requires C, 55.1; H, 4.6%); τ (CDCl_3) 2.31 (2H, m), 2.94 (2H, m), 3.50 (2H, m), and 7.98 (3H, d, $^2J_{\text{POCH}}$ 14.25 Hz); δ ^{31}P -9.9 p.p.m. The presence of furan in the reaction mixture was confirmed by g.l.c.

(b) *Benzyltri*-(2-furyl)phosphonium bromide. The salt was treated in the same manner as in (a) to give *benzyl*di-(2-furyl)phosphine oxide, m.p. 93° (Found: C, 66.0; H, 5.15. $\text{C}_{15}\text{H}_{13}\text{O}_3\text{P}$ requires C, 66.2; H, 4.8%) τ (CDCl_3) 2.3 (2H, m), 2.85 (5H, s), 2.96 (2H, m), 3.52 (2H, m), and 6.31 (2H, d, $^2J_{\text{POCH}}$ 15.6 Hz). The presence of furan in the reaction mixture was confirmed by g.l.c.

Kinetic Studies.—The hydrolyses were carried out at 5° in aqueous 50% (v/v) ethanol, at equal initial concentrations (0.001M) of phosphonium salt and sodium hydroxide in a thermostatted bath controlled to $\pm 0.1^\circ$, and were followed by measurement of the decrease in conductance of the solution as the reaction proceeded, using a Lock conductance bridge as described earlier.¹ The hydrolyses proceeded very rapidly, the reactions reaching completion after *ca.* 10 s, as indicated by the conductance of the solution reaching that of a 0.001M-solution of the appropriate sodium halide in the above solvent. Attempts to follow the rate by carrying out the reactions in water (increasing the polarity of the solvent is known to retard the hydrolysis of phosphonium salts¹⁴) were also unsuccessful, no noticeable difference in rate being observed. Significant reduction in the concentration of the reactants below 0.001M was impracticable, owing to the very low conductance of the solutions.

^{31}P N.m.r. Studies of the Reaction between *Tri*-(2-furyl)methylphosphonium Iodide and Sodium Methoxide.—To the salt (0.374 g, 1 mol. equiv.) in dry methanol (1.5 ml) was added methanolic sodium methoxide (0.25 ml, 0.5 mol. equiv.) [from sodium (0.23 g) in dry methanol (5 ml)]. The ^{31}P n.m.r. spectrum of the resulting solution was then recorded. Further sodium methoxide solution (0.25 ml, 0.5 mol. equiv.) was added, and the ^{31}P spectrum was re-

¹⁵ D. Hellwinkel, *Chem. Ber.*, 1969, **102**, 528.

¹⁶ E. Niwa, H. Aoki, H. Tanaka, and K. Munakata, *Chem. Ber.*, 1966, **99**, 712.

corded after each addition. To the resulting solution was added water (0.1 ml) and the solution was mixed, resulting in considerable evolution of heat and a marked change in the position of the ^{31}P resonance. The solution was poured into water and extracted with chloroform (10 ml). The extract was dried (Na_2SO_4) and evaporated to give di-(2-furyl)-methylphosphine oxide, m.p. 78–80°, identical with the product of aqueous alkaline hydrolysis of the phosphonium salt.

Preparation of Phosphonate Esters.—Diethyl phenylphosphonate was prepared by the reaction of phenylphosphonic dichloride with absolute ethanol (3 mol. equiv.) in dry benzene, in the presence of pyridine (2 mol. equiv.), according to the general procedure described by Kosolapoff,¹⁷ and had b.p. 114° at 0.2 mmHg (lit.,¹⁷ 117–118 at 1.5 mmHg); τ (CDCl_3) 2.25–3.0 (5H, m) 6.1 (4H, q), and 8.78 (6H, t); δ ^{31}P (CDCl_3) –16.7 p.p.m.

Diethyl (2-thienyl)phosphonate. 2-Thienylmagnesium bromide (0.1 mol) in ether was added dropwise, with constant stirring, under nitrogen, to a refluxing solution of diethyl phosphorochloridate (0.1 mol) in ether. The resulting solution was heated under reflux for 2 h, and then hydrolysed by the addition of dilute hydrochloric acid. The ether layer was separated, and the aqueous phase extracted

¹⁷ G. M. Kosolapoff, 'Organophosphorus Compounds,' Wiley, New York, 1950, p. 139.

¹⁸ P. Tavs, *Chem. Ber.*, 1970, **103**, 2428.

with a further portion of ether. The combined ether layers were dried (Na_2SO_4) and evaporated. The residue was then distilled to give the ester, b.p. 118° at 1.5 mmHg (lit.,¹⁸ b.p. 103–104 at 0.1 mmHg) (22.0 g, 80%) (Found: C, 43.3; H, 6.1. Calc. for $\text{C}_8\text{H}_{13}\text{O}_3\text{PS}$: C, 43.6; H, 5.9%); τ (CDCl_3) 2.2–2.6 (2H, m), 3.02 (1H, m), 6.0 (4H, q), and 8.5 (6H, t); δ ^{31}P (CDCl_3) –10.9 p.p.m.

Diethyl (2-furyl)phosphonate. 2-Furyl-lithium (0.1 mol) in ether [prepared¹⁹ from furan (0.2 mol) and n-butyl-lithium (0.1 mol)] was added to a stirred, refluxing solution of diethyl phosphorochloridate (0.1 mol) in ether, and the resulting solution was heated under reflux for 2 h, cooled, and hydrolysed by the addition of ammonium chloride solution (10% w/v; 100 ml). The organic layer was separated, the aqueous layer was extracted with ether, and the combined organic layers were dried (Na_2SO_4). The solvent was evaporated off and the residue was distilled to give the crude ester, b.p. 98–108° at 0.8 mmHg. Further purification was effected by preparative g.l.c., (Apiezon L stationary phase at 190°; nitrogen flow rate 50 ml min⁻¹) (Found: C, 46.9; H, 6.75. $\text{C}_8\text{H}_{13}\text{O}_4\text{P}$ requires C, 47.05; H, 6.35%), τ (CDCl_3) 2.55 (1H, m), 3.05 (1H, m), 3.73 (1H, m), 6.0 (4H, q), and 8.72 (6H, t); δ ^{31}P (CDCl_3) –3.9 p.p.m.

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¹⁹ C. H. Heathcock, L. G. Gulick, and T. Dehlinger, *J. Heterocyclic Chem.*, 1969, **6**, 141.