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Intramolecular nucleophilic displacement of halogen by phosphinate and thiophosphinate anions: relative rates of formation of five- and six-membered rings[1]

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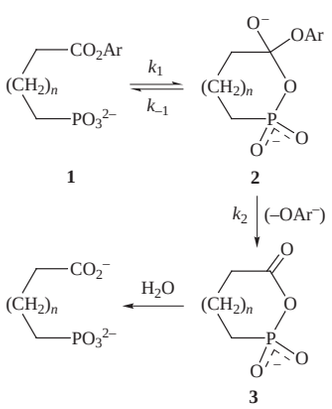
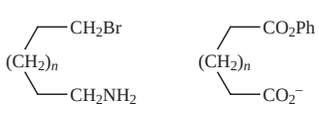
Intramolecular nucleophilic substitution transforms the phosphinate anions $XCH_2CH_2(CH_2)_nCH_2(Ph)P(O)O^-$ ($n = 0$, 1; X = Br, Cl) (Et_3NH^+ salts; CH_2Cl_2 solution) into cyclic phosphinate esters **14** ($n = 0$, 1); unusually the five-membered ring product ($n = 0$) is formed only 4.3 (X = Br) or 5.7 (X = Cl) times faster than the six ($n = 1$). The analogous cyclisation of the thiophosphinate anions $ClCH_2CH_2(CH_2)_nCH_2(Ph)P(S)O^-$ ($n = 0$, 1) gives the products **16** ($n = 0$, 1) with the sulfur atom in the ring; the five-membered ring is now formed 30 times faster than the six, still a rather modest rate advantage.

The carboxylate anion (RCO_2^-) is one of the most important and most studied functional groups in reactions involving neighbouring group participation[2] or intramolecular catalysis.[3] By contrast little is known about the phosphorus analogue, the phosphinate anion ($R_2PO_2^-$). Phosphinate is less basic than carboxylate (*e.g.* Et_2PO_2H, pK_a 3.29),[4] and presumably less nucleophilic,[5] but even the phosphonate dianion (RPO_3^{2-}) (*e.g.* $EtPO_3H_2$, pK_{a1} 2.45; pK_{a2} 7.85)[6] has not been studied extensively. That the dianion can provide catalysis seems clear since the phosphono-substituted carboxylic ester **1** ($n = 0$ or 1; Ar = *p*-nitrophenyl) is hydrolysed much faster than unsubstituted CH_3CO_2Ar.[7,8] The mechanism (Scheme 1) is thought to involve



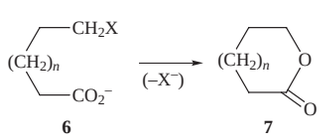
Scheme 1

the neighbouring phosphonate dianion acting as a nucleophile and forming a cyclic anhydride intermediate **3** with a five ($n = 0$) or six ($n = 1$) membered ring. As a rule cyclisations involving functional groups separated by a saturated alkyl chain form five-membered rings more quickly than six by a factor of around 10^2.[9–13] Typical examples are the intramolecular S_N2 reaction of the aminoalkyl bromide **4**, which forms the cyclic



ammonium salt 100 times faster when $n = 0$ than when $n = 1$, and the hydrolysis of the ester **5** ($n = 0$ or 1), which is 140 times faster when the cyclic anhydride intermediate is five membered rather than six.[14] It is remarkable, then, that in the hydrolysis of **1** (Scheme 1) the rate with $n = 0$ is only 1.5 times greater than with $n = 1$.[8] Phosphonate, it seems, may be an exception to the rule. On the other hand, it could be that the hydrolysis of **1** is inappropriate as a basis for generalisation. The case for the phosphonate group acting as a nucleophile rather than a base is persuasive, albeit that the anhydride **3** has not been detected;[7,8] less certain is whether the measured rate (release of *p*-nitrophenoxide) is a reliable indicator of the rate of cyclisation (k_1). If return of the tetrahedral intermediate **2** (k_{-1}) were (much) faster with $n = 0$, relative to the rate-limiting breakdown to anhydride **3** (k_2), then the actual cyclisation (k_1) might also be (much) faster when $n = 0$ even though the release of *p*-nitrophenoxide is not.

Generalisation ideally requires a reaction in which the product of cyclisation can be observed directly and its formation is the rate determining step. Also, to allow better comparison with carboxylate, it would be preferable to have phosphinate anion as the nucleophile instead of phosphonate dianion. Intramolecular alkylation (S_N2) should be ideal, especially as the corresponding cyclisation of halogeno carboxylates **6** to lactones **7** is well known (Scheme 2).[15] With phosphinate, however,



Scheme 2

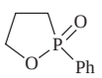
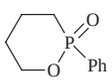
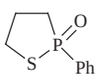
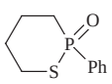
there is little encouragement to be had from intermolecular reactions. Phosphinate and related monoanions have been alkylated, using reactive alkyl halides ($PhCH_2X$, MeX) and silver salts or crown ether catalysis,[16] but the reverse is more often encountered, *i.e.* dealkylation (especially demethylation) of P^V esters by S_N2 attack of halide ion.[17] It was therefore with some uncertainty that we decided to explore the cyclisation of halogeno phosphinates and, for comparison, thiophosphinates.

Results and discussion

Preparation of substrates

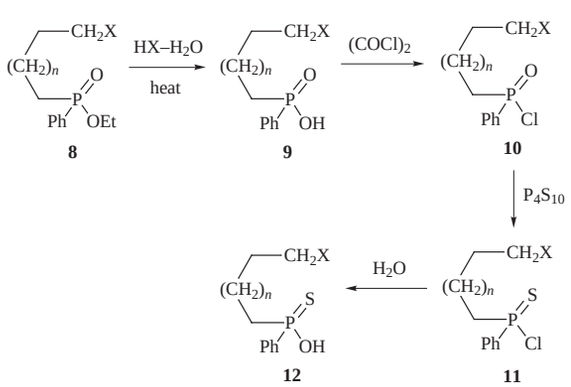
Following literature precedent the 3-bromopropylphosphinate ester **8** ($n = 0$, X = Br) was prepared by heating $PhP(OEt)_2$ with 1,3-dibromopropane (Arbusov reaction).[18] The same method using 1,4-dibromobutane proved equally satisfactory for the 4-bromobutyl ester **8** ($n = 1$, X = Br). With a five-fold excess of

Table 1 ^{13}C NMR spectra ($CDCl_3$, 75.5 MHz)

	δ_C (J_{PC}/Hz)					
	Alkyl			Phenyl		
	ω-C	β-C + γ-C	α-C	C-1	C-2 + C-3[a]	C-4
$Br(CH_2)_3P(O)(Ph)OH$	33.7 (18.5)	25.3 (2)	29.2 (100)	131.4 (132)	131.0 (10) 128.4 (13)	132.1
$Br(CH_2)_4P(O)(Ph)OH$	32.7	20.5 (3) 33.2 (15.5)	29.4 (99)	131.7 (133)	130.9 (10) 128.3 (13)	131.9
$Cl(CH_2)_3P(O)(Ph)OH$	45.0 (18)	25.2 (3)	27.9 (95)	131.5 (132)	131.0 (10) 128.4 (13)	132.1 (3)
$Cl(CH_2)_4P(O)(Ph)OH$	44.1	19.3 (3.5) 33.1 (13.5)	29.6 (100)	131.9 (131)	131.0 (10) 128.3 (13)	132.0 (2.5)
$Cl(CH_2)_3P(S)(Ph)OH$	44.7 (19.5)	25.8	34.4 (77)	133.4 (103)	130.5 (11.5) 128.4 (13)	132.1
$Cl(CH_2)_4P(S)(Ph)OH$	44.0	20.0 (2.5) 32.8 (17)	36.2 (76)	133.6 (103)	130.6 (11) 128.4 (13)	132.1 (3)
	70.4 (5)	24.3	25.6 (82)	130.7 (133)	131.2 (11) 128.4 (13)	132.4 (3)
	66.7 (6)	26.5 (6) 20.0 (8)	26.3 (89)	130.9 (134)	130.7 (10) 128.3 (13)	132.2 (2.5)
	36.6 (5.5)	27.5 (2)	36.2 (65)	133.3 (103)	131.5 (11) 128.5 (13)	132.2 (2.5)
	27.6 (2.5)[b]	27.3 (5)[b] 21.9 (7)	31.6 (71)	132.7 (102)	130.4 (10) 128.5 (12.5)	132.4 (3)

[a] Which signal is due to C-2 and which to C-3 is not known. [b] The assignments of the signals δ_C 27.6 and 27.3 should possibly be reversed.

the dibromoalkane there were no obvious signs of further reaction between the products **8** and $PhP(OEt)_2$. The esters **8** were not distilled (decomposition[18]) but the phosphinic acids **9** obtained on hydrolysis (48% HBr at 80–85 °C) (Scheme 3) were



8 **9** **10** **11** **12**

Scheme 3

crystalline and quite easy to purify. The chloroalkyl esters **8** ($n = 0$, 1; X = Cl) were prepared in the same way from $PhP(OEt)_2$ and $ClCH_2CH_2(CH_2)_nCH_2Br$ and were hydrolysed (37% HCl at 120 °C) to give the phosphinic acids **9** (X = Cl). In principle the alternative esters **8** (X = Br) could have been formed in the Arbusov reaction, by displacement of chlorine rather than bromine, but in practise this was not a problem.

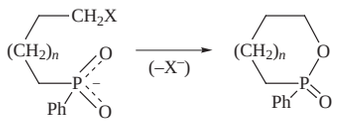
Obtaining the phosphinothioic *O*-acids **12** (X = Cl, Br) presents something of a challenge. Sulfur obviously has to be introduced but, because of the high nucleophilicity of thioate anions, it must be done in a way that produces the free acid, not its conjugate base, if the risk of premature cyclisation is to be averted. The phosphinic acids **9** were therefore converted into the phosphinic chlorides **10** (X = Cl, Br) (Scheme 3) and the P=O groups transformed into P=S by exchange with P_4S_{10} (dioxane solution; DMF catalyst; reflux). The phosphinothioic chlorides **11** were then hydrolysed in the absence of base. Thiophosphinyl compounds are much less reactive than their phosphinyl counterparts[19] and hydrolysis (5% H_2O in acetone) required several hours to reach completion (^{31}P NMR spectroscopy). The phosphinothioic acids were obtained as oils that were difficult to purify. The chloro compounds **12** (X = Cl) were sufficiently pure ($n = 0$, 90%; $n = 1$, >95%) for full spectroscopic characterisation but the identity of the more reactive of the bromo compounds ($n = 0$) could only be inferred from its subsequent behaviour.

Two details in the ^{13}C NMR spectra of the phosphinic acids **9** and phosphinothioic *O*-acids **12** are noteworthy (Table 1): $^1J_{PC}$ is ~25% smaller for the P=S compounds [sp^3 C, 75 Hz (P=S) *cf.* 100 Hz (P=O); sp^2 C, 100 Hz (P=S) *cf.* 130 Hz (P=O)] and for both types $^2J_{PC}$ (0–3.5 Hz) is much smaller than $^3J_{PC}$ (13.5–17 Hz). Similar features have been noted in the spectra of Bu_3PO and Bu_3PS.[20]

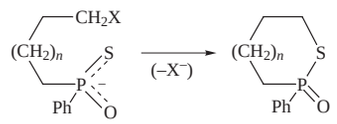
Cyclisation reactions

The bromo phosphinic acids ($\delta_P \sim 44$) in CH_2Cl_2 were converted with Et_3N into the phosphinate anions **13** ($n = 0$, 1; X = Br) ($\delta_P \sim 27$) and these passed slowly, but cleanly and completely, to

a product δ_P 57 ($n = 0$) or 37 ($n = 1$). Relative to the acyclic phosphinate ester **8** ($\delta_P \sim 44$) the product chemical shift is 13 ppm downfield ($n = 0$) or 7 ppm upfield ($n = 1$). Such a difference is reasonable for the five- or six-membered cyclic phosphinate **14** ($n = 0$ or 1) (Scheme 4), given that a comparable



13 **14**

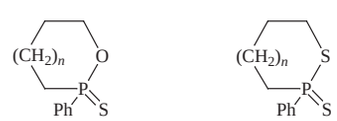


15 **16**

Scheme 4

dependence of δ_P on ring size (bond angle) is seen with cyclic phosphate esters.[21] The products were isolated and purified and their structures **14** ($n = 0$) and **14** ($n = 1$) confirmed spectroscopically. They are both known compounds having been obtained previously in other ways.[18,22]

The chloro phosphinothioic acids ($\delta_P \sim 86$) were similarly transformed into the thiophosphinate anions **15** ($n = 0$, 1; X = Cl) ($\delta_P \sim 63$) and thence into products having δ_P 72 ($n = 0$) or 39 ($n = 1$). In principle a thiophosphinate anion can act as a nucleophile through the O or the S atom although in intermolecular reactions with alkyl halides (S_N2) it is the S atom that is always alkylated.[23] The chemical shift of the product δ_P 39 is too small for a P=S compound **17** so by implication it must be



17 **18**

the cyclic P=O compound **16** ($n = 1$) (Scheme 4) with endocyclic sulfur. This was confirmed by the spectra of the isolated material, notably $\nu_{max} = 1190$ cm^{-1} (P=O) and δ_H 3.38 and 2.89 (diastereotopic CH_2S protons). The value of δ_P 72 for the other product is less clear cut: it is larger than we would anticipate for a P=O compound, even a five-membered cyclic one [contrast δ_P 57 for **14** ($n = 0$)], but small for a P=S group in a five-membered ring. From other features [$\nu_{max} = 1190$ cm^{-1} and δ_H 3.53 and 3.29 (CH_2S)], however, it is clear that this too is a P=O compound **16** ($n = 0$) with sulfur in the ring. Why δ_P should be so large, and so different from the value for the six-membered ring ($\Delta\delta_P = 33$ ppm), is not clear; superficially it points to an even greater contraction of the bond angle at phosphorus than is usual for a five-membered ring and is present in **14** ($n = 0$).† For the cyclic esters **14** and **16**, $^1J_{PC}$ is still 20% smaller for the sulfur-containing compounds (Table 1) even though there is now a defined P=O group and just a single bond to sulfur.

Whereas **16** ($n = 1$) was the only product obtained from the thiophosphinate **15** ($n = 1$, X = Cl), several minor products (2–3% each) accompanied **16** ($n = 0$). Given that the substrate **12** ($n = 0$, X = Cl) was only 90% pure, however, it seems probable that these were a consequence of the impurities rather than byproducts of the cyclisation. One of the minor products had a mass spectrum (M^+ 214) suggestive of the cyclic ester **18** ($n = 0$) having both a P=S group and sulfur in the ring. This points to a potential problem in our method of making the phosphinothioic *O*-acids (Scheme 3). If the phosphinothioic chloride **11** is not adequately purified before hydrolysis any traces of P_4S_{10} (or $P_4S_{10-n}O_n$) will generate H_2S which can react with **11** to give the dithiophosphinic acid (**12** with SH in place of OH).

Table 2 Rates of cyclisation of halogeno phosphinates **13** and thiophosphinates **15** in CH_2Cl_2 at 35 °C

	$k/10^{-6}$ s^{-1}		
Ring size	**13** (X = Br)	**13** (X = Cl)	**15** (X = Cl)
5 ($n = 0$)	178	2.5	230
6 ($n = 1$)	41	0.44	7.8

Rates of cyclisation

The cyclisations of the bromo phosphinates **13** (X = Br) and chloro thiophosphinates **15** (X = Cl) (Scheme 4) in CH_2Cl_2 at 35 °C were monitored by ^{31}P NMR spectroscopy.‡ In each case nine or ten spectra were recorded at regular intervals extending to 85–90% completion (3–72 h). The chloro phosphinates **13** (X = Cl) were examined in the same way except that in one case ($n = 1$) reaction was so slow it was followed only to 75% completion (40 days). From the relative peak areas of substrate and product in each spectrum first order plots [log ($a - x$) *vs.* t] were constructed. These were approximately linear and the slopes of the lines afforded values of the rate constant k (±8%) (Table 2). The bromo thiophosphinates **15** (X = Br) were not included in the study because of the very high reactivity of one of them ($n = 0$) and our inability to obtain the acid reasonably pure (>75%). Nonetheless, it was apparent from preliminary experiments that they cyclise with half-lives of about 1 min and 40 min at 25 °C, and at 35 °C they will presumably react about twice as quickly. Three aspects of the results (Table 2) require comment.

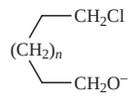
Leaving group. For the phosphinates **13** (oxygen nucleophile) the bromo compounds cyclise faster than the chloro compounds by a factor approaching 10^2 [Br/Cl rate ratio: 71 for five-ring formation ($n = 0$); 93 for six-ring formation ($n = 1$)]. For the thiophosphinates **15** (sulfur nucleophile) the picture is broadly similar although without better data for the bromo compounds a precise comparison is not possible. Differences in reactivity of this magnitude are much as expected for alkyl bromides and chlorides undergoing S_N2 reaction with anionic nucleophiles.[24]

Ring size. With oxygen as the nucleophile the rate ratio for formation of the five- and six-membered rings (k^5/k^6) is 4.3 for the bromo phosphinates and 5.7 for the chloro compounds. With sulfur as the nucleophile this ratio (k^5/k^6) is 30 for the chloro thiophosphinates (and seemingly not dissimilar for the bromo compounds). A 30-fold preference for the five-membered ring is possibly not anomalous although it is certainly at the low end of expectation. The five-fold preference seen with the phosphinates undoubtedly is anomalous however, especially when compared with the corresponding cyclisation of the carboxylates **6** (X = Br); there the k^5/k^6 ratio is 100 (Na^+

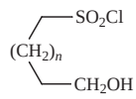
† We are grateful to a referee for pointing out that δ_P 72 is not an unreasonable chemical shift for the five-membered cyclic compound **16** ($n = 0$). It is within 20 ppm of the value of δ_P for the acyclic analogue PhEtP(O)SEt (δ_P 53.3; M. Mikolajczyk and J. Luczak, *J. Org. Chem.*, 1978, **43**, 2132) and a downfield shift of 15–20 ppm for a five-membered ring is not uncommon. Also, it is within 35 ppm of the value of δ_P for the six-membered cyclic analogue **16** ($n = 1$) (δ_P 39) and an upfield shift of 5–15 ppm, relative to the acyclic case, is not uncommon for a six-membered ring.

‡ The anions **13** and **15** were generated from the corresponding acids using 1.33 equiv. Et_3N. The ^{31}P chemical shifts suggest that the phosphinic acids are ~95% ionised under these conditions and the phosphinothioic acids 100% (see Experimental). No allowance has been made for incomplete ionisation in deducing the values of the rate constant k (Table 2).

salts in 99% DMSO).[15] Of possible significance in these cyclisations is the setting of the nucleophilic O atom, a tetrahedral centre in a phosphinate but a trigonal centre in a carboxylate. However, the alkoxides **19**, like the phosphinates, have the



19



20

nucleophilic oxygen attached to a tetrahedral centre and for them[25] the k^5/k^6 ratio of 200 is even larger than for the carboxylates.

Nucleophile. As would be expected for an S_N2 process, the thiophosphinates, with sulfur as the nucleophile, cyclise faster than the phosphinates, with oxygen.[26] For the chloro compounds the S/O rate ratio (k^S/k^O) is 92 for five-membered ring formation and 18 for six (with the bromo compounds the picture seems rather similar). Intuitively the larger value may be thought normal, given that oxygen does not compete with sulfur in the reactions of thiophosphinate anions with alkyl halides.[23] Model reactions suggest otherwise, however. The intermolecular alkylation of $Ph_2P(S)O^-$ with 1-bromopropane occurs exclusively at the S atom [≤1% $Ph_2P(S)OPr$] as expected, but it is only *ca*. 22 times faster than the alkylation of $Ph_2P(O)O^-$ [$t_{1/2}$ 8.3 h and 185 h respectively at 35 °C for Et_3NH^+ salts with 1.0 mol dm^{-3} PrBr in CH_2Cl_2]. It seems, therefore, that the smaller k^S/k^O ratio for the six-membered ring formation is actually normal and that the value for five-membered ring formation is anomalously large. The anomaly could result from an unusually large value for k^S but an unusually small k^O seems more likely.

Conclusion

Two anomalies become apparent when the rates of cyclisation of the halogeno phosphinates **13** and thiophosphinates **15** are analysed: the ratio $k^{O\text{-}5}/k^{O\text{-}6}$ is unusually small and $k^{S\text{-}5}/k^{O\text{-}5}$ is unusually large. The common factor in these is $k^{O\text{-}5}$ and both of the anomalies would disappear if $k^{O\text{-}5}$ were larger. The conclusion seems clear: intramolecular nucleophilic attack by a phosphinate anion is less favourable than expected when the product is a five-membered ring. To a lesser extent the same may be true for thiophosphinate (we have no data for thiocarboxylate with which to make comparison) but the problem is certainly less pronounced when the five-membered cyclic transition state contains sulfur in place of oxygen. Longer bonds (P–S and S–C) and a more accommodating bond angle (P–S–C) apparently relieve the transition state of some strain.[27] That there is strain in the O-5 transition state seems certain,[28] and the exceptionally high reactivity (P–O bond cleavage) of five-membered cyclic phosphonate (and phosphate) esters is most likely due in large part to ring strain.[29] Interestingly, King and Rathore have also found an anomalously small $k^{O\text{-}5}/k^{O\text{-}6}$ ratio (2.2) for the spontaneous hydrolysis of the hydroxy sulfonyl chlorides **20** ($n = 0$, 1).[30] Here, of course, the sulfonyl group is not the nucleophile but again the five-membered cyclic product (a sultone) shows exceptionally high reactivity attributable to ring strain.[31] The anomalies observed with the halogeno phosphinates are not large but they are significant, in part because they reinforce the conclusions drawn from the study of intramolecular nucleophilic catalysis by phosphonate dianion and in part because intramolecular S_N2 is a fundamentally important class of reaction.

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM 390 spectrometer or at 250 or 300 MHz on Bruker ARX 250 or AM 300 instruments (Me_4Si internal standard; coupling constants J given in Hz); ^{13}C NMR spectra were recorded on the AM 300 at 75.5 MHz. ^{31}P NMR spectra (^{1}H decoupled) were recorded at 36.2 MHz on a JEOL JNM-FX90Q spectrometer (positive chemical shifts downfield from 85% H_3PO_4). Mass spectra were obtained in EI mode unless otherwise indicated on a Kratos Concept spectrometer. CH_2Cl_2 was distilled from CaH_2. Light petroleum refers to the fraction bp 60–80 °C and ether to diethyl ether. Diethyl phenylphosphonite was prepared from $PhPCl_2$ by reaction with EtOH–pyridine in light petroleum and was purified by distillation, bp 60–62 °C at 0.05 mmHg.

Chloroalkyl(phenyl)phosphinic acids 9 (X = Cl)

(a) 1-Bromo-3-chloropropane (23.6 g, 150 mmol) was stirred vigorously at 150 °C (bath temp.) in a N_2 atmosphere and diethyl phenylphosphonite (5.94 g, 30 mmol) was added dropwise during 0.5 h. Heating was continued until ^{31}P NMR spectroscopy showed that the phosphonite (δ_P 158.5) had all been consumed (0.8 h). Volatile material was removed under reduced pressure and the residue was distilled to give ethyl 3-chloropropyl(phenyl)phosphinate **8** ($n = 0$, X = Cl) (5.46 g, 74%), bp 120 °C (oven temp.) at 0.2 mmHg, $\delta_P(CH_2Cl_2)$ 42.7, still contaminated with some of the low-boiling byproduct (δ_P 45.3; 5%). This material was used in (b). A sample purified by redistillation had $\delta_P(CDCl_3)$ 43.6; $\delta_H(CDCl_3$, 90 MHz) 7.9–7.5 (5 H, m), 3.95 (2 H, m, OCH_2Me), 3.51 (2 H, br t, J_{HH} 6, $ClCH_2$), 2.3–1.8 (4 H, m) and 1.33 (3 H, t, J_{HH} 7, OCH_2CH_3); ν_{max}(film)/cm^{-1} 1220 (P=O); *m*/*z* 248, 246 (M^+, 4%) and 141 ($M^+ - C_2H_4 - C_3H_6Cl$, 100) (Found: M^+, 246.0576. $C_{11}H_{16}{}^{35}ClO_2P$ requires *M*, 246.0576).

The same method starting from 1-bromo-4-chlorobutane afforded ethyl 4-chlorobutyl(phenyl)phosphinate **8** ($n = 1$, X = Cl) (70%), bp 125 °C (oven temp.) at 0.05 mmHg; $\delta_P(CDCl_3)$ 44.2; $\delta_H(CDCl_3$, 90 MHz) 7.9–7.4 (5 H, m), 3.95 (2 H, m), 3.47 (2 H, br t, J_{HH} 6), 2.25–1.5 (6 H, m) and 1.31 (3 H, t, J_{HH} 7); ν_{max}(film)/cm^{-1} 1215 (P=O); *m*/*z* 262, 260 (M^+, 1%), 225 ($M^+ - Cl$, 100) and 141 ($M^+ - C_2H_4 - C_4H_8Cl$, 60) (Found: M^+, 260.0733. $C_{12}H_{18}{}^{35}ClO_2P$ requires *M*, 260.0733).

(b) Ethyl 3-chloropropyl(phenyl)phosphinate **8** ($n = 0$, X = Cl) (5.4 g, 21.9 mmol) was stirred and heated (bath temp. 120 °C) with concentrated (37%) hydrochloric acid (50 ml) for 4.5 h. When cool the aqueous layer was decanted from the oil and was extracted with CH_2Cl_2; the extract was combined with the oil and the resulting solution was washed with water, dried ($MgSO_4$) and concentrated to a solid. Crystallisation twice from EtOAc–light petroleum afforded 3-chloropropyl(phenyl)-phosphinic acid **9** ($n = 0$, X = Cl) (2.11 g, 44%), mp 82–83 °C; $\delta_P(CDCl_3)$ 42.9; $\delta_H(CDCl_3$, 250 MHz) 12.53 (1 H, s), 7.8–7.35 (5 H, m), 3.45 (2 H, t, J_{HH} 6, $ClCH_2$) and 2.05–1.85 (4 H, m); ν_{max}(Nujol)/cm^{-1} 2620, 2200 and 1710 (all br, OH); *m*/*z* (CI) 221, 219 ($M + H^+$, 10%) and 183 ($M + H^+ - HCl$, 100) (Found: C, 49.4; H, 5.5. $C_9H_{12}ClO_2P$ requires C, 49.4; H, 5.3%).

In the same way ethyl 4-chlorobutyl(phenyl)phosphinate **8** ($n = 1$, X = Cl) gave 4-chlorobutyl(phenyl)phosphinic acid (31%), mp 52–53 °C; $\delta_P(CDCl_3)$ 43.7; $\delta_H(CDCl_3$, 250 MHz) 12.60 (1 H, s), 7.8–7.35 (5 H, m), 3.41 (2 H, t, J_{HH} 6.5) and 1.9–1.5 (6 H, m); *m*/*z* (CI) 235, 233 ($M + H^+$, 75%) and 197 ($M + H^+ - HCl$, 100) (Found: C, 50.9; H, 5.95. $C_{10}H_{14}ClO_2P$ requires C, 51.6; H, 6.1%. Found: M^+, 232.0420. $C_{10}H_{14}{}^{35}ClO_2P$ requires *M*, 232.0420).

Bromoalkyl(phenyl)phosphinic acids 9 (X = Br)

Ethyl bromoalkyl(phenyl)phosphinates **8** (X = Br) were prepared from 1,3-dibromopropane and 1,4-dibromobutane with $PhP(OEt)_2$ as in (a) above but the crude products were not distilled (decomposition[18]); rather, they were hydrolysed as in (b)

above, but with concentrated (48%) hydrobromic acid [4.5 h at 80–85 °C (bath temp.)], to give the phosphinic acids:

3-Bromopropyl(phenyl)phosphinic acid **9** ($n = 0$, X = Br), crystallised from aqueous MeOH then from EtOAc–light petroleum, mp 79–80 °C; $\delta_P(CDCl_3)$ 42.6; $\delta_H(CDCl_3$, 300 MHz) 13.05 (1 H, s), 7.85–7.4 (5 H, m), 3.34 (2 H, br t, J_{HH} 6, $BrCH_2$) and 2.1–1.9 (4 H, m); ν_{max}(Nujol)/cm^{-1} 2650, 2300 and 1710 (all br, OH); *m/z* (−FAB) 263, 261 [$(M - H)^-$, 15%] and 81, 79 (Br^-, 100) (Found: C, 41.1; H, 4.6. $C_9H_{12}BrO_2P$ requires C, 41.4; H, 4.4%).

4-Bromobutyl(phenyl)phosphinic acid **9** ($n = 1$, X = Br), crystallised from aqueous EtOH then from EtOAc–light petroleum, mp 78–80 °C (lit.,[32] 76–77 °C); $\delta_P(CDCl_3)$ 43.8; $\delta_H(CDCl_3$, 300 MHz) 13.3 (1 H, s), 7.85–7.35 (5 H, m), 3.28 (2 H, t, J_{HH} 6.5), 1.9–1.7 (4 H, m) and 1.7–1.5 (2 H, m); *m/z* (−FAB) 277, 275 [$(M - H)^-$, 15%] and 81, 79 (Br^-, 100).

Chloroalkyl(phenyl)phosphinothioic *O*-acids 12 (X = Cl)

Oxalyl chloride (0.76 g, 6.0 mmol) was added in portions to a stirred solution of 4-chlorobutyl(phenyl)phosphinic acid **9** ($n = 1$, X = Cl) (0.70 g, 3.0 mmol) in CH_2Cl_2 (7 ml). After 0.5 h the phosphinic chloride **10** ($n = 1$, X = Cl) (δ_P 57.1) was isolated by evaporation of volatile material and was dissolved in dioxane (4.5 ml). The solution was stirred with P_4S_{10} (333 mg, 0.75 mmol) and a catalytic amount of DMF (3 mg) at 120 °C (bath temp.) for 2 h, when ^{31}P NMR spectroscopy showed reaction (O/S exchange) to be complete. The solvent was evaporated and the residue was pumped *in vacuo*. Extraction of the residue with CH_2Cl_2 afforded 4-chlorobutyl(phenyl)phosphinothioic chloride **11** ($n = 1$, X = Cl), $\delta_P(CDCl_3)$ 89.9; $\delta_H(CDCl_3$, 90 MHz) 8.2–7.3 (5 H, m), 3.51 (2 H, br t, J_{HH} 6), 2.7–2.3 (2 H, m) and 2.1–1.5 (4 H, m); *m/z* 270, 268, 266 (M^+, 50%), 233, 231 ($M^+ - Cl$, 85), 178, 176 ($M^+ - C_4H_7Cl$, 100), 177, 175 ($M^+ - C_4H_8Cl$, 40) and 145, 143 ($M^+ - C_4H_8Cl - S$, 70). This was dissolved in acetone (10 ml) containing water (540 mg, 30 mmol) and hydrolysis (δ_P 91.2→81.2) was allowed to continue overnight (60% complete in 2.3 h at 28 °C). Volatile material was evaporated. The crude product was purified by extraction from ether (8 ml) into ice-cold aqueous NaOH (5 mmol in 9 ml H_2O), immediate acidification of the extract (7 mmol HCl in 3.5 ml H_2O), and back-extraction into ether (10 ml, 2 × 5 ml), giving 4-chlorobutyl(phenyl)phosphinothioic *O*-acid **12** ($n = 1$, X = Cl) (0.66 g, 88%) as an oil, $\delta_P(CDCl_3)$ 86.2; $\delta_H(CDCl_3$, 300 MHz) 7.95–7.8 (2 H, m), 7.6–7.4 (4 H, m; includes OH), 3.49 (2 H, t, J_{HH} 6.5), 2.25–2.05 (2 H, m) and 1.85–1.6 (4 H, m); ν_{max}(film)/cm^{-1} 1110 and 915; *m/z* 250, 248 (M^+, 30%), 213 ($M^+ - Cl$, 100), 158 ($M^+ - C_4H_7Cl$, 45), 157 ($M^+ - C_4H_8Cl$, 50) and 125 ($M^+ - C_4H_8Cl - S$, 60) (Found: M^+, 248.0191. $C_{10}H_{14}{}^{35}ClOPS$ requires *M*, 248.0192).

In the same way 3-chloropropyl(phenyl)phosphinic acid **9** ($n = 0$, X = Cl) was converted into 3-chloropropyl(phenyl)-phosphinothioic *O*-acid **12** ($n = 0$, X = Cl), a waxy solid, $\delta_P(CDCl_3)$ 85.5 [impurity δ_P 90 (broad), 10%]; $\delta_H(CDCl_3$, 300 MHz) 8.13 (1 H, s, OH), 7.9–7.8 (2 H, m), 7.6–7.4 (3 H, m), 3.53 (2 H, t, J_{HH} 6.5), 2.4–2.15 (2 H, m) and 2.15–1.9 (2 H, m); ν_{max}(Nujol)/cm^{-1} 1110 and 910; *m/z* 236, 234 (M^+, 15%), 199 ($M^+ - Cl$, 20), 198 ($M^+ - HCl$, 75) and 157 ($M^+ - C_3H_6Cl$, 100) (Found: M^+, 234.0035. $C_9H_{12}{}^{35}ClOPS$ requires *M*, 234.0035).

Bromoalkyl(phenyl)phosphinothioic *O*-acids 12 (X = Br)

Using the same method as for the chloro compounds the bromo phosphinic acids **9** ($n = 1$, 2; X = Br) were converted into the bromo phosphinothioic acids **12** ($n = 1$, 2; X = Br). The high reactivity of the anions (cyclisation) precluded purification by extraction into aqueous NaOH and the acids (especially $n = 0$) were not obtained in a sufficiently pure state for proper characterisation. The crude acids were cyclised by addition of base (Bu^tNH_2) to solutions in CH_2Cl_2.

Cyclisation reactions

(a) A mixture of 4-bromobutyl(phenyl)phosphinic acid **9** ($n = 1$, X = Br) (111 mg, 0.40 mmol) and Et_3N (54 mg, 0.53 mmol) in CH_2Cl_2 (1.6 ml) maintained at 35 °C for 41 h gave a single product (δ_P 37.0). The solvent was evaporated and the product was separated from Et_3NHBr by repeated extraction of the residue with ether. Distillation gave 2-phenyl-1,2-oxaphosphinane 2-oxide **14** ($n = 1$) (75 mg, 95%), bp 150 °C (oven temp.) at 0.2 mmHg, as an oil that solidified; crystallised from ether, mp 84–85 °C (lit.,[22] 86 °C); $\delta_P(CDCl_3)$ 37.0; $\delta_H(CDCl_3$, 300 MHz) 7.85–7.75 (2 H, m), 7.55–7.40 (3 H, m), 4.54 and 4.19 (both 1 H, m; CH_2O) and 2.3–1.75 (6 H, m); ν_{max}(Nujol)/cm^{-1} 1220 (P=O); *m/z* 196 (M^+, 100%), 195 (25), 142 ($M^+ - C_4H_6$, 90), 141 ($M^+ - C_4H_7$, 35) and 77 (35).

The corresponding reaction of 3-bromopropyl(phenyl)-phosphinic acid **9** ($n = 0$, X = Br), reaction time 16 h, gave a single product (δ_P 57.0) which was isolated in the same way. Distillation gave 2-phenyl-1,2-oxaphospholane 2-oxide **14** ($n = 0$), bp 150 °C (oven temp.) at 0.3 mmHg (lit.,[18] 157 °C at 0.7 mmHg); $\delta_P(CDCl_3)$ 58.0; $\delta_H(CDCl_3$, 300 MHz) 7.80–7.70 (2 H, m), 7.60–7.45 (3 H, m), 4.56 and 4.31 (both 1 H, m; CH_2O) and 2.5–1.9 (4 H, m); ν_{max}(film)/cm^{-1} 1215 (P=O); *m/z* 182 (M^+, 60%), 181 (25), 141 ($M^+ - C_3H_5$, 100) and 77 (40).

(b) A mixture of 4-chlorobutyl(phenyl)phosphinothioic *O*-acid **12** ($n = 1$, X = Cl) (103 mg, 0.42 mmol) and Et_3N (54 mg, 0.53 mmol) in CH_2Cl_2 (1.6 ml) was sealed in a glass ampoule. After 8 days at *ca.* 37 °C the solution contained a single substantial product (δ_P 39.0) (97%). The solvent was evaporated and the residue was extracted repeatedly with ether and was then partitioned between CH_2Cl_2 and water. The combined organic portions were chromatographed on silica gel (column: 30 mm × 9 mm), eluting with ether then with EtOAc. The later fractions afforded 2-phenyl-1,2-thiaphosphinane 2-oxide **16** ($n = 1$) (68 mg, 77%), bp 150 °C (oven temp.) at 0.1 mmHg, which slowly solidified; $\delta_P(CDCl_3)$ 40.5; $\delta_H(CDCl_3$, 250 MHz) 7.95–7.8 (2 H, m), 7.6–7.45 (3 H, m), 3.38 and 2.89 (both 1 H, m; CH_2S) and 2.5–1.8 (6 H, m); ν_{max}(Nujol)/cm^{-1} 1190 (P=O); *m/z* 212 (M^+, 100%), 184 (20), 179 (15), 158 ($M^+ - C_4H_6$, 40), 157 ($M^+ - C_4H_7$, 40), 125 ($M^+ - C_4H_7S$, 50) and 77 (20). A sample crystallised from ether had mp 74–75 °C (Found: C, 56.3; H, 5.9; M^+, 212.0425. $C_{10}H_{13}OPS$ requires C, 56.6; H, 6.2%; *M*, 212.0425).

The corresponding reaction of 3-chloropropyl(phenyl)-phosphinothioic *O*-acid **12** ($n = 0$, X = Cl) (90% pure), reaction time 8 h at 35 °C and overnight at room temperature, gave one principal product (δ_P 71.7) (~90%) and several minor products (δ_P 85.6, 84.5, 83.6, 63.0; each 2–3%). The principal product was isolated by extraction into ether and chromatography on silica gel (elution with EtOAc; some minor products eluted first using ether); it was identified as 2-phenyl-1,2-thiaphospholane 2-oxide **16** ($n = 0$), bp 150 °C (oven temp.) at 0.1 mmHg; $\delta_P(CDCl_3)$ 73.4; $\delta_H(CDCl_3$, 300 MHz) 8.0–7.85 (2 H, m), 7.6–7.45 (3 H, m), 3.53 and 3.29 (both 1 H, m; CH_2S) and 2.6–2.1 (4 H, m); *m/z* 198 (M^+, 95%), 157 ($M^+ - C_3H_5$, 100) and 77 (40) (Found: M^+, 198.0268. $C_9H_{11}OPS$ requires *M*, 198.0268). The oil did not solidify but when dissolved in ether crystals mp 102–103.5 °C were formed, ν_{max}(Nujol)/cm^{-1} 1190 (P=O).

One of the minor products was obtained pure (GLC) by TLC (silica gel; R_f 0.3 with 1:1 ether–light petroleum); the mass spectrum suggested 2-phenyl-1,2-thiaphospholane 2-sulfide **18** ($n = 0$), *m/z* 214 (M^+, 100%), 173 ($M^+ - C_3H_5$, 50), 105 ($M^+ - S - Ph$, 35) and 63 (40).

Rate studies

The cyclisation reactions of the phosphinic acids **9** ($n = 0$, 1; X = Br, Cl) and phosphinothioic *O*-acids **12** ($n = 0$, 1; X = Cl) (0.075 mmol) in CH_2Cl_2 (0.3 ml) containing Et_3N (0.10 mmol) were carried out in sealed 5 mm NMR tubes supported in 10 mm tubes containing D_2O (NMR lock). The probe of the

NMR spectrometer was maintained at 35 °C. Except for the faster reactions the sample was removed from the probe and placed in a water bath maintained at 35 °C between spectra. As detailed in Results and discussion, ^{31}P NMR spectra (^{1}H decoupled) were recorded at regular intervals and the information so obtained was used to deduce the values of the rate constant k for cyclisation (Table 2).

The extent to which the acids were ionised under the conditions of reaction was deduced as follows. For each of the phosphinic acids **9** the ^{31}P chemical shift was monitored as Et_3N was added in portions [5 or 6 × 0.35 equiv. then 3–5 × 0.7 equiv.] to a CH_2Cl_2 solution. Relative to the free acid the shift to higher field (*ca.* δ_P 44→26) was 17.5–17.8 ppm with 3–4 equiv. Et_3N (100% ionisation) and no further change occurred with additional Et_3N. Under the conditions used in the rate study (1.33 equiv. Et_3N) the shift to higher field (16.8–17.4 ppm) was *ca.* 95% of the maximum, indicating *ca.* 95% ionisation initially. In general there was a small further shift (≤1 ppm) to higher field as reaction progressed and the excess of the amine (relative to the remaining substrate) became greater. Exceptionally in the very slow reaction of **9** ($n = 1$, X = Cl) there was a gradual shift to lower field (1 ppm at $t = 28$ days), probably because reaction between the solvent (CH_2Cl_2) and Et_3N gradually reduced the excess of the amine. For the phosphinothioic *O*-acids **12** the shift to higher field (*ca.* δ_P 86→63) was 23.3–23.4 ppm and this maximum was achieved even with 1.33 equiv. Et_3N, indicating 100% ionisation under the conditions of reaction.

Model reactions

Diphenylphosphinothioic *O*-acid (7 mg, 0.03 mmol) was dissolved in a 1.0 mol dm^{-3} solution of 1-bromopropane in CH_2Cl_2 (0.5 ml), Et_3N (0.04 mmol) was added, and the solution was maintained at 35 °C. Examination by ^{31}P NMR spectroscopy showed reaction (δ_P 54.8→41.5) to be 27% complete at $t = 3.85$ h and 39% at $t = 5.9$ h ($t_{1/2} \sim 8.3$ h). When complete (72 h) the product was isolated and characterised as *S*-propyl diphenylphosphinothioate, $\delta_P(CDCl_3)$ 43.4; $\delta_H(CDCl_3$, 300 MHz) 7.95–7.83 (4 H, m), 7.60–7.43 (6 H, m), 2.78 (2 H, dt, J_{PH} 11, J_{HH} 7.5), 1.66 (2 H, sextet, J_{HH} 7.5) and 0.94 (3 H, t, J_{HH} 7.5); ν_{max}(film)/cm^{-1} 1200 (P=O); *m/z* 276 (M^+, 30%), 234 ($M^+ - C_3H_6$, 40), 202 ($M^+ - SC_3H_6$, 100) and 201 ($M^+ - SC_3H_7$, 100). No product δ_P 60–110 was observed (≤1%) indicating that no $Ph_2P(S)OPr$ was formed.

A similar experiment with diphenylphosphinic acid showed reaction (δ_P 17.9→29.9) to be 25% complete at $t = 70$ h, 48% at $t = 178$ h ($t_{1/2} \sim 185$ h). The product was isolated and confirmed to be propyl diphenylphosphinate, $\delta_P(CDCl_3)$ 31.3; $\delta_H(CDCl_3$, 250 MHz) 7.9–7.8 (4 H, m), 7.6–7.4 (6 H, m), 3.99 (2 H, dt, $J_{PH} \sim J_{HH} \sim 7$), 1.75 (2 H, sextet, J_{HH} 7) and 0.98 (3 H, t, J_{HH} 7); ν_{max}(melt)/cm^{-1} 1220 (P=O); *m/z* 260 (M^+, 20%), 219 ($M^+ - C_3H_5$, 100), 217 ($M^+ - C_3H_7$, 45) and 201 (40).

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