Intramolecular Nucleophilic Substitution by Phosphinate and Thiophosphinate Anions: Relative Rates of Formation of Five- and Six-membered Rings

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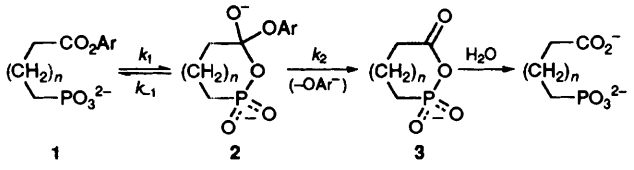
In CH_2Cl_2 solution the phosphinate anion $BrCH_2CH_2(CH_2)_nCH_2(Ph)P(O)O^-$ cyclises only 4.3 times faster when n = 0 (five-membered ring product) than when n = 1; for the thiophosphinate anion $ClCH_2CH_2(CH_2)_nCH_2(Ph)P(S)O^-$ cyclisation (*via* sulfur) is still only 30 times faster when n = 0 than when n = 1.

Byers and coworkers have shown that the neighbouring dianionic phosphonate group in the ester **1** (Ar = *p*-nitrophenyl) greatly increases the rate of hydrolysis (release of *p*-nitrophenoxide) when n = 0 or 1 (Scheme 1).[1] Surprisingly, however, the hydrolysis is only 1.5 times faster when n = 0 and the intermediate anhydride **3** is a five-membered ring, than it is when n = 1.[1] By contrast, intramolecular nucleophilic catalysis by the carboxylate anion (Scheme 1, CO_2^- in place of PO_3^{2-}, Ar = Ph) is *ca.* 140 times more effective when the cyclic intermediate is five-membered rather than six.[2] A large difference is actually quite normal; most intramolecular reactions involving functional groups separated by a saturated chain form the five-membered ring some 10^2 times faster than the six.[3–6] It is important to know whether intramolecular nucleophilic attack by the anion of a phosphorus(V) acid is generally an exception to the rule.

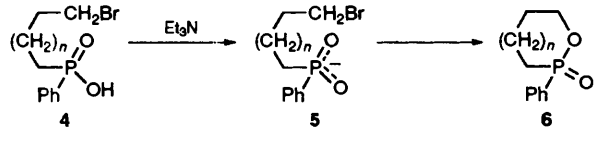
As a basis for generalisation the ester hydrolysis in Scheme 1 is not ideal. There is no reason to doubt that the phosphonate dianion acts as a nucleophile and forms the anhydride, albeit that this is unproven; of more concern is the identity of the rate-determining step. If, as seems likely,[1] this is the breakdown of the initial tetrahedral intermediate **2** (k_2) rather than its formation (k_1), then similar rates of hydrolysis (release of *p*-nitrophenoxide) when n = 0 or 1 are not necessarily indicative of similar rates of cyclisation: the actual cyclisation step (**1** → **2**; k_1) could be (much) faster when n = 0 if reversion of the tetrahedral intermediate (**2** → **1**; k_{-1}) were (much) faster too. We have therefore examined a reaction in which there can be no real doubt that the rate observed is the rate of cyclisation, and also where the nucleophile is a monoanion so that it is more strictly comparable with carboxylate.

The bromoalkylphosphinic acids **4** (n = 0), mp 79–80 °C, δ_H ($CDCl_3$) 3.34 (2 H, t, J_{HH} 6.8, CH_2Br)† and **4** (n = 1), mp 78–80 °C (lit.[7] 76.5–77 °C), δ_H ($CDCl_3$) 3.28 (2 H, t, J_{HH} 6.5, CH_2Br) were prepared by acid-catalysed hydrolysis of the ethyl esters obtained by heating $Br(CH_2)_3Br$ or $Br(CH_2)_4Br$ with $PhP(OEt)_2$ (Arbuzov reaction). In CH_2Cl_2 the acids (δ_P 43.5 or 44.4) were converted into their anions **5** (δ_P 26.4 or 27.7) with Et_3N (1.33 mol equiv.)‡ and these then gradually formed the cyclic phosphonates **6** by intramolecular nucleophilic substitution (Scheme 2); **6** (n = 0), δ_P 56.9, δ_H ($CDCl_3$) 4.56 and 4.31 (both 1 H, m; OCH_2) (an oil);[8] **6** (n = 1), δ_P 36.9, δ_H ($CDCl_3$) 4.54 and 4.19 (both 1 H, m; OCH_2), mp 84–85 °C (lit.[9] 86 °C). Monitoring of the reactions by ^{31}P NMR spectroscopy revealed that cyclisation was clean (no detectable intermediates or byproducts) and went to completion, following approximately first-order kinetics.§ The halflife for **5** (n = 0) was 1.1 h at 35 °C and for **5** (n = 1), 4.7 h. The rates of five- and six-membered ring formation thus differ by a factor of 4.3. This is somewhat greater than the difference inferred from the hydrolysis reactions in Scheme 1, but it is still remarkably small. In particular, it is much less than is the case when either carboxylate (O^- on trigonal C)[10] or alkoxide (O^- on tetrahedral C)[11] is the nucleophile; the cyclisations of **7** (in 99% Me_2SO) and **8** (in H_2O) form the five-membered ring faster than the six by factors of *ca.* 100 and 200 respectively. For quantitative comparison with the cyclisation of phosphonate **1** and its carboxylate analogue it would obviously have been more appropriate to work in an aqueous medium. However, we were anxious to suppress ring-opening of the initial cyclisation products, and therefore chose a non-nucleophilic aprotic solvent (CH_2Cl_2). Our phosphinate anions would presumably be more heavily solvated in an aqueous environment; the extent to which this might affect their relative rates of cyclisation is at present unknown.

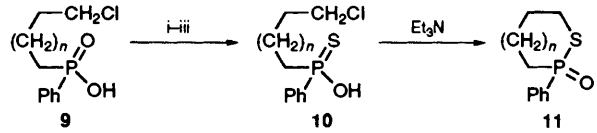
To assess the possible importance of ring strain we turned to the thiophosphinic [>P(S)OH] analogues of the substrates **4**. These would be expected to cyclise *via* sulfur rather than oxygen, and a five-membered ring is known to be less strained, relative to the six-membered ring, when it contains sulfur in place of oxygen.[12] Attempts to convert the bromoalkyl phosphinic acids **4** into their thiophosphinic counterparts were complicated by side reactions (especially when n = 0) but it was possible to obtain reasonably pure samples of the less reactive chloroalkyl thiophosphinic acids **10** from **9** (Scheme 3): **10** (n = 0), δ_P 86.2 (*ca.* 90% pure), δ_H ($CDCl_3$) 3.53 (2 H, t, J_{HH} 6.3, CH_2Cl); **10** (n = 1), δ_P 86.8 (>95% pure), δ_H ($CDCl_3$) 3.49 (2 H, t, J_{HH} 6.4, CH_2Cl). In CH_2Cl_2 the anions, δ_P 62.9 (n = 0) and δ_P 63.5 (n = 1), cyclised with halflives of 0.83 and 24.6 h respectively at 35 °C.§ The products, as expected, had the S atom in the ring: **11** (n = 0), δ_P 71.7, δ_H ($CDCl_3$) 3.53 and 3.29 (both 1 H, m; SCH_2), ν_{max} 1190 cm^{-1} (P=O), mp 102–103.5 °C; **11** (n = 1), δ_P 39.0, δ_H ($CDCl_3$) 3.38 and 2.89 (both 1 H, m; SCH_2), ν_{max} 1190 cm^{-1} (P=O), mp 74–75 °C. The difference in rate for five- and six-membered ring formation—a



Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions*: i, $(COCl)_2$; ii, P_2S_5 ($HCONMe_2$ catalyst, dioxane, heat); iii, H_2O (aq. acetone)

factor of 30—is clearly greater now that thiophosphinate is the nucleophile, but it is still modest enough to suggest that something other than ring strain contributes to the behaviour of the phosphinates **5**.

Whatever the explanation, the conclusion from this work and that of Byers seems clear: large differences in rate for the formation of five- and six-membered rings should not be expected when the cyclisation involves nucleophilic attack by the oxygen anion of a phosphorus(V) acid.

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Footnotes

† The new compounds **4** (n = 0) and **9–11** (n = 0,1) were fully characterised by spectroscopy and elemental analysis or accurate mass measurement.

‡ The change in δ_P (relative to the change using a large excess of Et_3N) suggests *ca.* 95% ionisation for the phosphinic acids **4** (n = 0,1) and 100% ionisation for the thiophosphinic acids **10** (n = 0,1) with 1.33 mol equiv. Et_3N in CH_2Cl_2.

§ For each cyclisation nine or ten spectra were recorded at regular intervals up to 85–90% completion. The Et_3NH cation doubtless has some influence on the absolute rates of cyclisation [association (hydrogen bonding) with phosphinate or thiophosphinate nucleophile and bromide or chloride leaving group], but it would not be expected to affect significantly the relative rates of cyclisation of the anions of **4** (n = 0) and **4** (n = 1) or of **10** (n = 0) and **10** (n = 1).

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