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Phosphonyl transfer by the elimination-addition mechanism: accelerated formation of an alkylidineoxophosphorane (phosphene) intermediate when a P–O single bond is replaced by P–S

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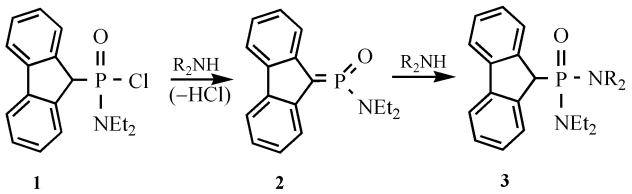
The phosphonochloridate $R_2CHP(O)(YEt)Cl$ (R_2CH = fluoren-9-yl, Y = O or S) reacts with Pr^i_2NH largely or exclusively by an elimination-addition mechanism; the three-coordinate phosphene intermediate $R_2C{=}P(O)YEt$ is formed *ca.* 10^3 times more easily when Y = S than when Y = O.

Phosphoryl transfer is an essential part of many biological processes[1] and investigation of its chemical detail has been boosted by the emergence of RNA enzymes (ribozymes) as an area of major importance.[2] Phosphate analogues (especially thiophosphates[3]) and phosphate mimics (notably phosphonates[4]) are important for probing the mechanisms of biological phosphorylation reactions and also for influencing metabolic processes.

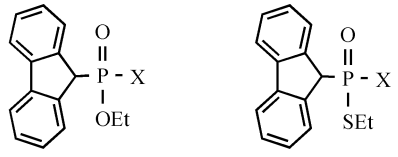
Phosphoryl and phosphonyl transfer reactions are usually associative $S_N2(P)$ processes in which direct attack of the acceptor (nucleophile) on the donor leads to a five-coordinate intermediate or transition state.[5] When the donor P=O group has an acidic ligand (HO, RNH, *etc.*) a dissociative pathway may become competitive, with elimination of HX (X = leaving group) generating a reactive three-coordinate P^V intermediate (*e.g.* monomeric metaphosphate) to which the acceptor subsequently adds.[5,6] Competition from the elimination-addition pathway is more likely if the P=O group is replaced by P=S, in part because the $S_N2(P)$ process is slower[7] and in part because a three-coordinate P^V entity with a P=S group is more stable than its P=O counterpart, or at least is formed more readily.[8] Our present concern is still with the effect of replacing oxygen by sulfur, but in a bridging (single bond) position of the donor rather than in the phosphoryl group. Is the formation of a three-coordinate P^V intermediate still accelerated and is the effect large enough to be of practical and mechanistic significance?

We have previously observed that the fluoren-9-ylphosphonamidic chloride **1** reacts with amines to give the diamide **3** by a dissociative elimination-addition (EA) mechanism, an alkylidineoxophosphorane (phosphene) **2** being the product-forming intermediate (Scheme 1).[9] It therefore seemed possible that the related fluorenylphosphonochloridates **4** (X = Cl) and **5** (X = Cl) would provide information of the kind now sought.



1 **2** **3**

Scheme 1



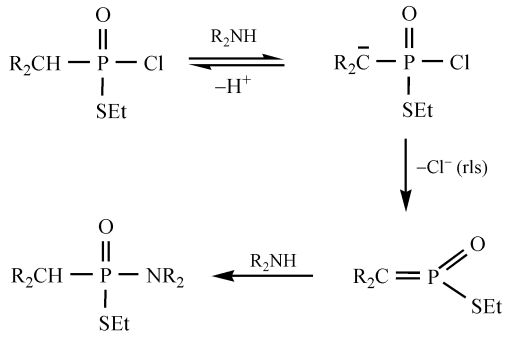
4 **5**

The ethyl phosphonate **4** (X = OH) (δ_P 27.0, mp 174–175 °C) was prepared by partial dealkylation (LiCl in DMF, 80 °C) of diethyl fluoren-9-ylphosphonate[9] and the ethyl thiophosphonate **5** (X = OH) [δ_P 58.2, mp 153–155 °C (decomp.)] by *S*-alkylation (EtI) of the salt obtained by hydrolysis ($H_2O + Et_3N$ in acetone) of fluoren-9-ylphosphonothioic dichloride.[10] These half esters were then subjected to DMF-catalysed reaction with oxalyl chloride, giving the chloridates **4** (X = Cl) (δ_P 38.5) and **5** (X = Cl) (δ_P 66.3) as moisture sensitive solids.†

The reactions of the chloridates with amines were examined by ^{31}P NMR spectroscopy, using an excess of the amine (8 mol equiv.) as a 1.2 mol dm^{-3} solution in $CDCl_3$ at 31 °C (the conditions previously employed in studies with **1**).[9,10] The chosen amines Et_2NH, $EtNHPr^i$ and Pr^i_2NH have similar basicities but for steric reasons they will differ greatly in their nucleophilicity towards a tetrahedral phosphonyl centre.

For the thio substrate **5** (X = Cl) the expected phosphonamidothioate **5** (X = NEt_2, δ_P 50.3 or $NEtPr^i$, δ_P 49.9 or NPr^i_2, δ_P 48.4) was the only significant product (≥97%) and its isolation simply required separation from amine hydrochloride.‡ The reactions were all fast, having half lives of approximately 1.5 min with Et_2NH (96% complete at t = 7 min), 2.5 min with $EtNHPr^i$ (90% complete at t = 8 min) and 5.5 min with Pr^i_2NH (68% complete at t = 8 min) (*cf.* $t_{½} \sim 2.2$ h for **1** with Et_2NH). Clearly the nucleophilicity (bulk) of the amine has only a small influence on the rate of reaction and that is not compatible with an associative mechanism involving nucleophilic attack at the P=O centre in the rate-limiting step [contrast EtP(O)(OEt)Cl: reaction with $EtNHPr^i$ > 100 times faster than with Pr^i_2NH].

Low sensitivity to steric effects is, however, consistent with a dissociative elimination-addition mechanism in which the amine acts initially as a base, not as a nucleophile, and the rate limiting step is unimolecular collapse of the conjugate base of the substrate (Scheme 2; R_2CH = fluoren-9-yl). Support for a reactive and sterically accessible three-coordinate phosphene intermediate came from competition experiments; with both Et_2NH–$EtNHPr^i$ and $EtNHPr^i$–Pr^i_2NH (1 : 1 mixtures, total amine 1.2 mol dm^{-3}) there was only a 2 : 1 preference for the product formed from the less hindered amine.



Scheme 2

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For the OEt substrate **4** (X = Cl) the reaction with Et_2NH was again fast, having a half life of ~3.5 min, and clean, giving the phosphonamidate **4** (X = NEt_2, δ_P 28.3) as the only product. With the more hindered amines, however, the reactions were much slower, by factors of 52 and 1450 with $EtNHPr^i$ and $Pr^i{}_2NH$ respectively (substrate half consumed in 3 h or 85 h). They also gave the phosphonamidate products **4** (X = $NEtPr^i$, δ_P 28.5; X = $NPr^i{}_2$, δ_P 27.6) less cleanly and formed substantial amounts of the pyrophosphonate hydrolysis product [δ_P 16.4 and 16.1, diastereoisomers; *m/z* (ES) 531 $(M + H)^+$] (8% or 18% of total ^{31}P NMR spectrum integral) in spite of strenuous efforts to exclude moisture.§ Such a high dependence of rate on the bulk of the amine nucleophile points to an associative $S_N2(P)$ mechanism, as does the emergence of side reactions when the amine is only feebly nucleophilic. With this substrate the Et_2NH–$EtNHPr^i$ competition experiment showed a very strong 99 : 1 preference for the less hindered amine and the $EtNHPr^i$–$Pr^i{}_2NH$ experiment a 97 : 3 preference. The slightly lesser discrimination in the latter case suggests a small contribution from the EA mechanism; when $EtNHPr^i$ is not present and only $Pr^i{}_2NH$ is available, $S_N2(P)$ will contribute (much) less and elimination-addition will surely predominate. Also, the decline in rate in going from $EtNHPr^i$ to $Pr^i{}_2NH$ – a factor of 28 – is less than would be expected unless the reaction with $Pr^i{}_2NH$ is largely elimination-addition [with EtP(O)(OEt)Cl the decline is > 100-fold]. It therefore seems likely that the observed 900-fold greater reactivity of the SEt substrate **5** (X = Cl) relative to **4** (X = Cl) with $Pr^i{}_2NH$ is close to the difference in the ease with which the two types of substrate form three-coordinate P^V intermediates. Formation of the conjugate base is not difficult in either case – with $Pr^i{}_2ND$ (0.1 mol dm^{-3}) there is rapid H/D exchange at the α carbon atom – but elimination of chloride from the conjugate base is apparently much faster when sulfur is present.

We conclude that it is about 10^3 times easier for an EtS-substituted phosphene intermediate to be formed from **5** (X = Cl) (Scheme 2) than it is for the corresponding EtO-substituted intermediate to be formed from **4** (X = Cl). This single-bond thio effect is not as great as the double-bond thio effect ($k_s/k_o \geqslant 10^4$) seen in the EA reactions of the phosphonamidic chloride **1** and its P=S counterpart[10] but it is large enough to have a profound influence on mechanistic preference, especially as $S_N2(P)$ reactivity with an amine seems to be reduced somewhat by an EtS ligand. Thus the reaction with unhindered Me_2NH is largely $S_N2(P)$ even for the EtS substrate [high selectivity (93 : 7) in a Me_2NH–Et_2NH competition experiment] and is now 2–3 times slower than the corresponding reaction of the EtO substrate (0.1 mol dm^{-3} Me_2NH; reactions too fast to follow by NMR at higher concentrations). If the behaviour of our phosphonochloridates is reasonably representative, an important single-bond thio effect may also be expected for other types of reaction and other kinds of three-coordinate P^V intermediate.

Notes and references

† To minimise self-condensation (pyrophosphonate formation) the half esters were added slowly to dilute solutions of oxalyl chloride (4 equiv.) and DMF (0.03 equiv.) in $CHCl_3$ (55 °C for **4**, 25 °C for **5**). The chloridate products were not easily recrystallised (MeOBu^t at low T) because of their sensitivity to moisture but it was important to ensure that no DMF (a potential nucleophilic catalyst) remained in case it interfered with the assessment of intrinsic reactivity in nucleophilic substitution.

‡ Substrates and products characterised by NMR (^1H, ^{13}C and ^{31}P) and IR spectroscopy and MS (including accurate M^+ determination). Because of chirality at P [**4** (X = OH) is exceptional] the methylene protons in OEt, SEt and NEt groups show non-equivalence (^1H NMR) as do the methyl groups in NPr^i moieties (^1H and ^{13}C NMR). Noteworthy is the difference in the C-9 signal for the compounds **4** (OEt on P) and **5** (SEt on P): X = OH: **4**, δ_C 47.0 (J_{PC} 139); **5**, δ_C 53.4 (J_{PC} 99). X = Cl: **4**, δ_C 52.1 (J_{PC} 119); **5**, δ_C 58.8 (J_{PC} 74). X = NR_2: **4**, δ_C 50.2 ± 0.6 (J_{PC} 124); **5**, δ_C 55.9 ± 0.6 (J_{PC} 85).

§ With $EtNHPr^i$ the byproduct (δ_P 22.9) is apparently **4** (X = $NHPr^i$) (6%) resulting from the presence of some Pr^iNH_2 in the amine. It amounted only to 1% (^{13}C NMR) but because it is much more nucleophilic (less hindered) than $EtNHPr^i$ it has a disproportionate effect when a large excess of amine is used. With $Pr^i{}_2NH$ there were several unidentified byproducts and they seemed to become relatively more important in the later stages of reaction. In this case attack at the tetrahedral P=O centre is so hindered that dealkylation (attack at the methylene carbon of the OEt group) and/or condensation (nucleophilic attack by product on substrate) may begin to compete.

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