Elimination–addition with alkylidineoxophosphorane (phosphene) intermediates in nucleophilic substitution at P=O centres: fluoren-9-ylphosphonamidic chlorides with amine nucleophiles[1]

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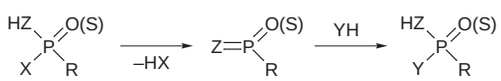
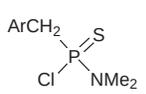
Compared with $Me_2CHP(O)(NEt_2)Cl$, the fluorenyl compound $R_2CHP(O)(NEt_2)Cl$ (R_2CH = fluoren-9-yl) shows remarkably high reactivity in nucleophilic substitution with Et_2NH. Substitution is catalysed by base {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)} and shows little discrimination between competing Me_2NH and Et_2NH. These characteristics point to an elimination–addition (EA) mechanism with a reactive phosphene intermediate [$R_2C{=}P(O)NEt_2$]. When Et_2ND is the nucleophile, H–D exchange at the α carbon atom occurs much more quickly than substitution. This suggests that the elimination stage of the EA mechanism is reversible E1cB.

Phosphoryl transfer is an essential part of many biological processes and the entire spectrum of nucleophilic substitution at a P=O (or P=S) centre is important in chemistry as a whole.[2] Not surprisingly, much effort has gone into uncovering the pathways by which P=O (and P=S) compounds can react with nucleophiles.[3] Substitution generally proceeds by an associative $S_N2(P)$ mechanism, with a five-coordinate phosphorane intermediate (or transition state), but when the substrate has a ligand HZ with an acidic hydrogen atom, a dissociative elimination–addition (EA) mechanism is also possible (Scheme 1; X = leaving group, YH = nucleophile).[3] The intermediate now will be a reactive three-coordinate P^V species,[4] but elimination–addition (EA) seems to be the preferred pathway when HZ is strongly acidic, *i.e.* when Z is oxygen[5] or sulfur,[6] and sometimes when it is only moderately acidic, *i.e.* when Z is nitrogen.[7]



Scheme 1

For compounds in which Z is just a saturated carbon atom, the EA mechanism is largely unknown. It seems to be important in the reactions of the thiophosphonyl substrate **1**



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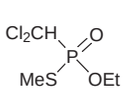

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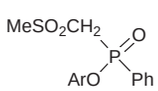

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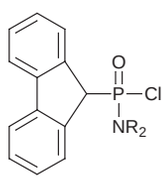
($Ar = 4\text{-}NO_2C_6H_4$ or $4\text{-}NCC_6H_4$) with amines but that, to date, is unique.[8] The possibility of the ester **2** reacting with methoxide by elimination–addition has been considered, but not established,[9] and for other cases of substitution at a P=O centre an EA mechanism has been firmly ruled out.[10,11] The alkaline hydrolysis of the ester **3**, for example, shows no signs of departure from the normal associative $S_N2(P)$ mechanism, in spite of the acidity of the C_α–H bonds and the strongly basic nature of the nucleophile.[10]

On two counts it seemed that fluoren-9-ylphosphonamidic chloride **4** might afford clear evidence of substitution at a P=O centre by an EA mechanism. First, the conjugate base of **4** will be stabilised because of its aromatic character, so the C_α–H bond could be acidic enough to make elimination of HCl, and formation of the alkylidineoxophosphorane (phosphene) intermediate **5**, a reasonably favourable process. Some idea of



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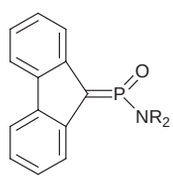

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how the fluorenyl group may enhance the acidity of **4** can be gained from the following pK_a values (in DMSO; R_2CH = fluoren-9-yl):[12]

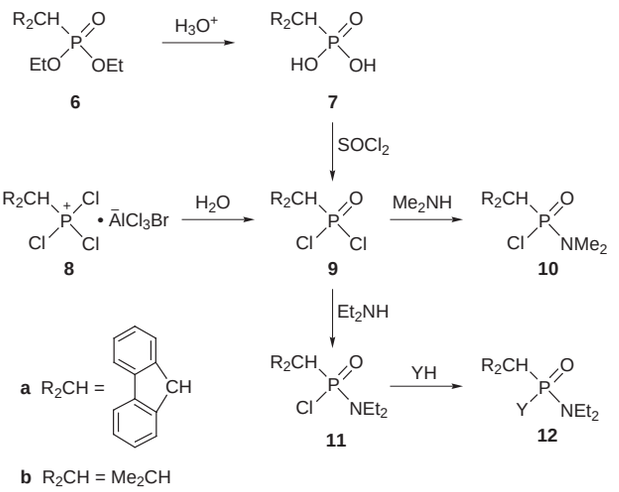
	$PhCH_2CN$	Ph_2CHCN	$4\text{-}NO_2C_6H_4CH_2CN$	R_2CHCN
pK_a	21.9	17.5	12.3	8.3

Second, the fluorenyl and NR_2 groups in **4** are both quite bulky and the latter is also a π donor, so the normal associative $S_N2(P)$ pathway could in this case be rather unfavourable. An indication of how reluctant **4** may be to react by $S_N2(P)$ is the reported failure of the related isopropyl compound $Me_2CHP(O)(NEt_2)Cl$ to undergo substitution with Et_2NH.[13] In the substitution reactions of the fluorenyl compound **4**, therefore, we felt that an EA mechanism might compete effectively with $S_N2(P)$.

Results and discussion

Substrates and products

Two contrasting approaches to fluoren-9-ylphosphonic dichloride **9a** were explored (Scheme 2). Phosphonate ester **6a** has previously been prepared by the copper-catalysed reaction of 9-diazafluorene with diethyl phosphite,[14] but we found the Arbuzov reaction of commercially-available 9-bromofluorene with triethyl phosphite to be both convenient and efficient. Heating the ester **6a** with concentrated hydrobromic acid gave the phosphonic acid **7a**, and this was converted into the dichloride **9a** with boiling thionyl chloride (DMF catalyst). Alternatively, the complex **8a** (not isolated) formed readily when 9-bromofluorene was treated with PCl_3–$AlCl_3$, and this on controlled hydrolysis gave the phosphonic dichloride **9a** directly. Although the product from the direct route was spectroscopically pure (^1H and ^{31}P NMR) its chemical behaviour pointed to the presence of some contamination (possibly aluminium salts). Analytically pure material could be obtained by distillation, followed by crystallisation, but unfortunately this resulted in considerable loss of product (decomposition and/or



Scheme 2

hydrolysis). On balance there is probably not much to choose between the two methods of preparation. The ^{1}H NMR spectrum of the dichloride **9a** showed coupling of the phosphorus atom not only to H–9 (2 bond; J_{PH} 23 Hz) but also to H–1 (and H–8) (4 bond; J_{PH} 3 Hz) and, more surprisingly, to H–2 (and H–7) (5 bond; J_{PH} 2.5 Hz) as well.

The phosphonic dichloride **9a** (δ_P 48.2) in CH_2Cl_2 reacted rapidly with Me_2NH (2 equiv.) to give the phosphonamidic chloride **10a** (δ_P 44.2), and more slowly with Et_2NH to give **11a** (δ_P 42.5). In both cases the product was a stable, crystalline solid. Chirality at phosphorus removes the equivalence of the benzene rings in the fluorenyl group, and this was evident in the ^{1}H NMR spectra, *e.g.* the protons H–1, H–4, H–5 and H–8 in **11a** gave rise to four distinct 1H doublets (J_{HH} 7) at δ_H 8.04, 7.98, 7.81 and 7.79. Unlike the dichloride, coupling to phosphorus was not significant for any of the aromatic protons, although for H–1 it was notably large (J_{PH} 29–30 Hz).

The known isopropylphosphonamide chlorides **10b** and **11b** were also prepared[13,15] from the phosphonic dichloride **9b**. These are unlikely to react by an EA mechanism, because the C_α–H bonds are not especially acidic, but they are useful as standards against which the behaviour of the fluorenyl compounds can be assessed.

On treatment with an excess of Me_2NH or Et_2NH in $CHCl_3$ or CH_2Cl_2, the phosphonamidic chlorides gave the expected phosphonic diamides, *e.g.* **11a** gave **12a** (Y = Me_2N) (δ_P 35.1) with Me_2NH and **12a** (Y = Et_2N) (δ_P 34.3) with Et_2NH. In the case of the isopropyl compound **11b** and Et_2NH, which previously failed to give any of the substitution product,[13] use of the neat amine at 110 °C (sealed tube) afforded the diamide **12b** (Y = Et_2N) in quite good yield (85% by ^{31}P NMR).

Reactivity

Rates of reaction were examined using ^{31}P NMR spectroscopy to follow the conversion of substrate into product. In general a large excess of the amine (Me_2NH or Et_2NH) was employed as a 1.2 mol dm^{-3} solution in $CHCl_3$ at 31 °C, and the time for 50% conversion ($t_{\frac{1}{2}}$) was deduced from the spectroscopic data. The choice of $CHCl_3$ as solvent was influenced by the fact that CH_2Cl_2 can react with secondary amines,[16] although in the event only some reactions of the isopropyl substrate **11b** were so slow that this would have presented problems. Concerning reactivity, our more significant observations are described below.

1. The isopropylphosphonic dichloride **9b** reacted rapidly with Et_2NH to form the phosphonamidic chloride **11b** ($t_{\frac{1}{2}}$ 2–3 min), but reaction of the phosphonamidic chloride **11b** with Et_2NH was extremely slow; only *ca.* 4% had been converted into the diamide **12b** (Y = Et_2N) after 6 days. The fluorenylphosphonic dichloride **9a** likewise formed the phosphonamidic chloride **11a** rapidly with Et_2NH ($t_{\frac{1}{2}}$ 2–3 min) but in this case, reaction of the phosphonamidic chloride with Et_2NH to give the diamide **12a** (Y = Et_2N) was not especially slow ($t_{\frac{1}{2}}$ 2.2 h). The reactivity of the fluorenylphosphonamidic chloride **11a** towards Et_2NH is thus notable in two respects: it is only about 50 times less than the reactivity of the fluorenylphosphonic dichloride (the corresponding difference for the isopropyl compounds is >10^4), and it is at least 500 times greater than the reactivity of the isopropylphosphonamidic chloride **11b**. A reasonable explanation is that the isopropyl compound is constrained to react by $S_N2(P)$ but the fluorenyl compound can switch to an alternative, non-associative, mechanism when $S_N2(P)$ is unfavourable.

2. Compared with Et_2NH, the amidine 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) is a much stronger base (pK_{BH^+} 24.3 in MeCN)[17] but not a more powerful nucleophile. When a small part (one fifteenth) of the Et_2NH was replaced by DBU, the effect on the reaction of the isopropylphosphonamidic chloride **11b** was minimal, as would be expected for an $S_N2(P)$ mechanism, but the effect on the reaction of the fluorenylphosphonamidic chloride **11a** was dramatic: the product was still the diamide **12a** (Y = Et_2N) but it was formed *ca.* 100 times more quickly ($t_{\frac{1}{2}}$ 1–1.5 min). The implication is surely clear: substitution proceeds by rate-limiting base-induced elimination, generating an intermediate, presumably the phosphene **5** (R = Et), which is then trapped by rapid addition of the nucleophile (Et_2NH) to give the diamide product.†

3. Base-induced β-elimination reactions frequently display substantial primary deuterium kinetic isotope effects. The 9-deuterio analogue of the fluorenylphosphonamidic chloride **10a** (~90 atom %D) was prepared (from deuteriated **6a**), with a view to measuring the isotope effect for its reaction with Et_2NH. However, preliminary studies (0.8 mol dm^{-3} Et_2NH; GLC monitoring) showed there to be no significant difference in the rate of substitution for the deuteriated and undeuteriated substrates. The absence of a kinetic isotope effect obviously does not add to the evidence for an EA mechanism but it does not necessarily detract from it either; the deuterium may be lost from the substrate, by rapid exchange with Et_2NH, before it undergoes substitution (see below).

4. For steric reasons, Me_2NH is usually a more effective nucleophile than Et_2NH. In the case of the isopropylphosphonamidic chloride **11b**, changing the nucleophile from Et_2NH to Me_2NH increased the rate at least 200-fold [85% conversion into **12b** (Y = Me_2N) in 11 h with 1.2 mol dm^{-3} Me_2NH]. Such a large effect is not unreasonable for $S_N2(P)$ attack at a tetrahedral P=O centre, leading to a sterically-congested five-coordinate phosphorane intermediate. For the fluorenyl substrate **11a**, by contrast, the rate with Me_2NH ($t_{\frac{1}{2}}$ 33 min) was only 4 times greater than with Et_2NH. This comparatively small difference accords with a mechanism in which the amine acts as a base in the rate-limiting step, not as a nucleophile, since removal of a proton from the α carbon atom should be relatively insensitive to steric effects.

5. The accessibility of the P=O centre in a phosphonamidic chloride will be influenced by the bulk of the amino group (NR_2) on the phosphorus atom. Even for $S_N2(P)$, however, the effect seems to be relatively small: with Me_2NH, for example, the isopropyl substrate **11b** (NEt_2 on P) was only about 10 times

† A referee has pointed out that unequivocal evidence for an intermediate should be available from experiments with DBU, if at a constant DBU concentration the rate were found to be independent of the concentration of Et_2NH while the product was still 100% derived from Et_2NH. Unfortunately, DBU can act as a nucleophile (L. Ma and D. Dolphin, *J. Chem. Soc., Chem. Commun.*, 1995, 2251 and references cited therein) and is probably not much less nucleophilic than Et_2NH. Only by using a large excess of Et_2NH (mol. ratio Et_2NH:DBU ≥ 14:1) could the amount of a product δ_P 37.4, believed to result from DBU acting as the nucleophile instead of Et_2NH, be kept to insignificant levels.

less reactive than **10b** (NMe_2 on P). The fact that the fluorenylphosphonamidic chlorides **11a** (NEt_2 on P) and **10a** (NMe_2 on P) differed little in their reactivity towards Et_2NH is therefore not really evidence against S_N2(P), even though it accords well with an EA mechanism.

Competing nucleophiles

To learn more about how the products are formed, the reactions of the phosphonamidic chlorides **11a** and **11b** were carried out using an equimolar mixture of Me_2NH and Et_2NH (20-fold excess; 1.2 mol dm^{-3} total concentration) in place of the single amines. With the isopropyl substrate **11b** only the NMe_2 product **12b** (Y = Me_2N) was observed [≤0.5% **12b** (Y = Et_2N) by GLC] but with the fluorenyl substrate **11a** both products **12a** (Y = Me_2N) and **12a** (Y = Et_2N) were formed, in a ratio of 4.7 : 1 (Me_2N : Et_2N). Clearly there is much less discrimination between the competing amines in the reaction of the fluorenyl compound. A trigonal three-coordinate phosphene such as **5** (R = Et), the intermediate on an EA pathway, will be both highly reactive and sterically accessible; if it is the product-forming species, a comparative lack of selectivity is only to be expected. The EA pathway may actually be even less discriminating than our product ratio (82 : 18) implies, if an appreciable part of the substrate reacts by an S_N2(P) mechanism (product ratio >99 : 1 Me_2N : Et_2N) rather than by EA. The competition experiment was therefore repeated with DBU present. If there are competing EA and S_N2(P) pathways, added base should shift the balance in favour of elimination–addition. The product ratio (4.5 : 1) was unchanged, however. This is important in two ways. First, it shows that EA is totally dominant for the fluorenyl substrate **11a**; even with Me_2NH available to act as the nucleophile, competition from S_N2(P) does not seem to be significant. Second, it shows that a three-coordinate P^V species such as the phosphene **5** can discriminate appreciably between competing nucleophiles, in spite of its high reactivity.

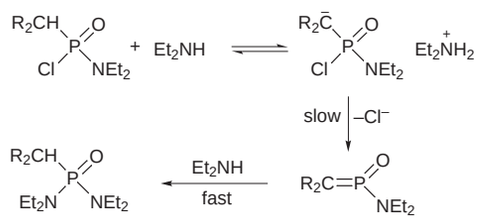
Deuterium incorporation

Potentially conclusive evidence that substitution proceeds *via* a phosphene intermediate, and not by S_N2(P), would be the presence of deuterium at the α carbon of the product when Et_2ND is employed as the nucleophile. This will depend, however, on the substrate itself being unaffected by H–D exchange before it undergoes substitution.

The behaviour of the fluorenylphosphonamidic chloride **11a** with Et_2ND (0.2 mol dm^{-3}) in $CDCl_3$ was examined using ^1H NMR spectroscopy. Within 45 min the integral for the H on the α carbon atom had declined to 0.25 H (0.75 D), notwithstanding the very low concentration of amine. Since the initial substrate : Et_2ND ratio was only 20 : 80, and the Et_2ND was not 100 atom% D, this represents practically complete equilibration. At very low amine concentrations (and T < 31 °C) the substitution reaction is so slow that product formation was minimal after 45 min. The implication is clear: the H on the α carbon atom exchanges with Et_2ND much faster than the substrate undergoes substitution, so the product of substitution will contain deuterium regardless of how it is formed. Nonetheless, the rapid exchange at the α carbon is mechanistically very revealing. Not only does it establish that the proton can be removed easily enough for EA to be the favoured pathway, it also shows that the conjugate base of the substrate reprotonates much more quickly that it eliminates chloride to form the phosphene. Indirectly, then, it not only supports an EA mechanism but it also points to a reversible E1cB mechanism (Scheme 3), rather than E2 or irreversible E1cB, for the elimination step. Of course, it also explains the absence of a kinetic isotope effect in the reaction of deuteriated **10a** with Et_2NH.

Salt effects

Although the goal of our rate studies was just an approximate (but reliable) measure of relative reactivity, the key reactions of the fluorenylphosphonamidic chloride **11a** were examined in more detail. With both Me_2NH and Et_2NH the first-order plots (amine in large excess) deviated somewhat from linearity, at least in the early stages of reaction (0–30% completion), suggesting that the amine hydrochloride by-product accelerates substitution. For confirmation of this, the reaction with Et_2NH was repeated in $CHCl_3$ containing $Et_2NH_2^+$ Cl^- (1 equiv. relative to substrate). The first-order plot was now linear throughout and the reaction appreciably faster [$t_{\frac{1}{2}}$ 1.3 h *versus* 2.2 h (average value) with no added salt]. To assess the importance of hydrogen bonding (acid catalysis) by the salt, $Et_2NH_2^+$ Cl^- was replaced by Et_4N^+ Cl^-. This, surprisingly, accelerated the reaction much more ($t_{\frac{1}{2}}$ ~ 0.25 h). The difference between the two salts may be mechanistically significant. Any positive general effect of the salt, such as its influence on the polarity of the medium, might be partially cancelled out by some negative specific effect.‡ If, as suggested, the elimination stage of the EA mechanism is reversible E1cB (Scheme 3), $Et_2NH_2^+$ will promote reprotonation of the conjugate base at the expense of phosphene formation. That is not the case with Et_4N^+, of course. Indeed, to the extent that it can displace $Et_2NH_2^+$ from the initial ion pair formed when Et_2NH deprotonates the substrate, it will tend to suppress reprotonation and encourage phosphene formation.



Scheme 3

Conclusion

The high reactivity of the fluorenyl substrate **11a** relative to the isopropyl compound **11b**, and the small difference in its reactivity towards Me_2NH and Et_2NH, point to an EA mechanism for its substitution reactions. The modest level of discrimination between competing Me_2NH and Et_2NH accords with a phosphene as the product-forming species. Rapid H–D exchange at the α carbon atom when **11a** reacts with Et_2ND is consistent with an EA mechanism in which the elimination stage is reversible E1cB, and the influence of the salts $Et_2NH_2^+$ Cl^- and Et_4N^+ Cl^- can be rationalised in terms of reversible E1cB. We find this evidence compelling: nucleophilic substitution at a P=O centre can proceed by an EA mechanism, with a phosphene intermediate, in preference to S_N2(P). Phosphenes have previously been postulated as intermediates in other types of reaction, notably oxidation,[18] fragmentation[19] and rearrangement;[20] now it seems they can also be formed in nucleophilic substitution reactions. The system we have examined is particularly well-suited to elimination–addition, but even in less favoured cases it may be possible for an EA pathway to compete with S_N2(P).

Experimental

Mps were determined using a Kofler hot-stage apparatus and

‡ More pronounced deviations from linearity were seen in the first-order plots for the isopropylphosphonamidic chlorides **10b** and **11b** with Me_2NH (reactions with Et_2NH are too slow for detailed examination) and curvature was apparent to ≥80% completion [k in later stages of reaction 2–3 times greater than in the early stages]. Here too the amine hydrochloride by-product is doubtless responsible [increasing the polarity of the reaction medium and/or catalysis (hydrogen bonding) by $R_2NH_2^+$].

are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM 390 spectrometer or at 250 MHz on a Bruker ARX 250 spectrometer (Me_4Si internal standard; coupling constants J given in Hz) and ^{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 on a Kratos Concept spectrometer. GLC analyses were performed using a Philips PU 4500 chromatograph (flame-ionisation detector) fitted with an OV 1701 wide-bore capillary column (1 μm film; 15 m × 0.53 mm) (He carrier gas, flow-rate 19 ml min^{-1}). Amines were dried over KOH. Chloroform was passed through a column of alumina and dried over molecular sieves. Ether refers to diethyl ether and light petroleum to the fraction bp 60–80 °C. Isopropylphosphonic dichloride (δ_P 62.0) was prepared by a published procedure.[21]

Fluoren-9-ylphosphonic acid 7a

A mixture of 9-bromofluorene (9.8 g, 40 mmol) and triethyl phosphite (8.3 g, 50 mmol) was stirred vigorously in a flask fitted with an air condenser and a nitrogen bubbler. The flask was placed in an oil bath preheated to 110 °C and the temperature was raised to 155 °C. Heating was continued for a further 2 h, giving *diethyl fluoren-9-ylphosphonate* **6a**, $\delta_P(CDCl_3)$ 24.5; $\delta_H(CDCl_3$, 90 MHz) 7.9–7.5 (4 H, m), 7.5–7.2 (4 H, m), 4.48 (1 H, d, J_{PH} 31), 3.86 (4 H, dq, $J_{PH} \sim J_{HH} \sim 7$) and 1.06 (6 H, t, J_{HH} 7). The crude phosphonate was stirred with 48% hydrobromic acid (30 ml) at 110–120 °C (bath temp.) until the ^{1}H NMR spectrum of the insoluble material showed hydrolysis to be complete (no P-OCH_2CH$_3$ signal) (2.5–4.5 h). The mixture was then diluted with water (20 ml) and cooled in ice. The solid was collected by suction filtration, washed repeatedly with ice-cold water, sucked as dry as possible, and dried *in vacuo* to give *fluoren-9-ylphosphonic acid* **7a** (6.7 g, 81%); $\delta_P(CDCl_3$–$CD_3OD)$ 23.9; $\delta_H(CDCl_3$–CD_3OD, 90 MHz) 7.85–7.65 (4 H, m), 7.4–7.2 (4 H, m) and 4.37 (1 H, d, J_{PH} 31). This material was used without further purification [a recrystallised sample had mp 254–257 °C (lit.,[22] 255–259 °C)].

Fluoren-9-ylphosphonic dichloride 9a

Method (a). A solution of 9-bromofluorene (4.90 g, 20 mmol) in CH_2Cl_2 (8 ml) was added dropwise over 20 min to a stirred mixture of PCl_3 (12.4 g, 90 mmol) and $AlCl_3$ (5.3 g, 40 mmol). After a further 1 h the mixture was diluted with CH_2Cl_2 (100 ml) and cooled to −20 °C by addition of solid CO_2. Concentrated (37%) hydrochloric acid (*ca.* 12 ml) was then added in small portions, with constant swirling and further additions of solid CO_2 ($T \leqslant -20$ °C), until the aluminium salts coagulated. The mixture was filtered and the filtrate was concentrated leaving crude *fluoren-9-ylphosphonic dichloride* **9a** (4.69 g, 82%) as a yellow solid; $\delta_P(CDCl_3)$ 48.7; $\delta_H(CDCl_3$, 250 MHz) 7.94 (2 H, dd, J_{PH} 3, J_{HH} 7), 7.85 (2 H, d, J_{HH} 7), 7.54 (2 H, ddd, J_{PH} 2.5, J_{HH} 7, 7), 7.42 (2 H, dd, J_{HH} 7, 7) and 5.11 (1 H, d, J_{PH} 23). No appreciable impurities were apparent in the NMR spectra but subsequent behaviour suggested a contaminant (possibly aluminium salts). Distillation (oven temp. 170 °C at 0.2 mmHg) gave the pure, colourless dichloride **9a**, mp 112–114 °C (from ether containing a little CH_2Cl_2), but with considerable loss of product (decomposition and/or hydrolysis); *m/z* 286, 284, 282 (M^+, 15%) and 165 (100) (Found: C, 55.05; H, 3.0. $C_{13}H_9Cl_2OP$ requires C, 55.15; H, 3.2%).

Method (b). Fluoren-9-ylphosphonic acid **7a** (1.65 g, 6.7 mmol) was heated (bath temp. 100 °C) with $SOCl_2$ (10 ml) containing a catalytic quantity of DMF (0.03 equiv., 23 μl) until the ^{31}P NMR spectrum of the reaction mixture contained just a single peak (δ_P 48) (≥2 h). Volatile material was completely evaporated and the residue was dissolved in a little CH_2Cl_2; dilution of the solution with light petroleum precipated the *phosphonic dichloride* **9a** having spectra (^{31}P and ^{1}H NMR) as in (a) above.

[9-^{2}H]Fluoren-9-ylphosphonic dichloride

Deuterium was introduced into diethyl fluoren-9-ylphosphonate **6a** by repeated washing of a CH_2Cl_2 solution with D_2O made basic by addition of Bu^{t}OK. The deuteriated ester was then hydrolysed by heating with 48% hydrobromic acid (*cf.* preparation of **7a** above) and the resulting acid was treated with $SOCl_2$ (DMF catalyst) as in method (b) above. Distillation gave [9-^{2}H]*fluoren-9-ylphosphonic dichloride*, bp 180 °C (oven temp.) at 0.2 mmHg; in the ^{1}H NMR spectrum ($CDCl_3$) the H–9 signal [δ_H 5.11 (d, J_{PH} 23)] integrated for ≤0.1 H.

Phosphonamidic chlorides

(a) Preparation of phosphonamidic chloride 10a. Dimethylamine (233 mg, 5.2 mmol) in CH_2Cl_2 (5 ml) was added dropwise with stirring to an ice-cold solution of fluoren-9-ylphosphonic dichloride **9a** (735 mg, 2.6 mmol) in CH_2Cl_2 (8 ml). The mixture was allowed to warm to room temperature and volatile material was removed by evaporation. The residue, dissolved in CH_2Cl_2 (10 ml), was washed with water (5 ml) containing a trace of HCl (to neutralise any remaining amine) and then with water (2 × 5 ml). The solution was dried and concentrated to an oil which solidified on addition of ether. The solid was collected, washed with ether, and dried (60 °C at 0.2 mmHg) to give N,N-*dimethyl*-P-(*fluoren-9-yl*)*phosphonamidic chloride* **10a** (630 mg, 83%); $\delta_P(CDCl_3)$ 44.0; $\delta_H(CDCl_3$, 250 MHz) 7.99 (1 H, d, J_{HH} 7), 7.87 (1 H, d, J_{HH} 7), 7.79 (2 H, d, J_{HH} 7), 7.46 (2 H, dd, J_{HH} 7, 7), 7.35 (2 H, dd, J_{HH} 7, 7), 4.89 (1 H, d, J_{PH} 29) and 2.26 (6 H, d, J_{PH} 12); ν_{max}(Nujol)/cm^{-1} 1240 (P=O); *m/z* 293, 291 (M^+, 20%) and 165 (100). A sample crystallised from light petroleum containing a trace of CH_2Cl_2 had mp 115–116 °C (softens at 111 °C) (Found: C, 61.9; H, 5.2; N, 4.6. $C_{15}H_{15}ClNOP$ requires C, 61.75; H, 5.2; N, 4.8%).

(b) Preparation of the 9-deuterio analogue of 10a. A mixture of [9-^{2}H]fluoren-9-ylphosphonic dichloride (20 mg, 0.07 mmol) and $Me_2ND_2^+$ Cl^- (8 mg, 0.10 mmol) was dried thoroughly (65 °C at 0.1 mmHg for 1 h). It was then dissolved in $CDCl_3$ (0.35 ml) and Et_3N (14 mg, 0.14 mmol) was added. When consumption of the substrate was complete (^{31}P NMR spectroscopy) the mixture was diluted with CH_2Cl_2, washed with D_2O [made slightly acidic by addition of a drop of $(COCl)_2$], and concentrated to give *deuteriated product* **10a**, $\delta_P(CDCl_3)$ 44.1 (slightly broadened by coupling to D); the ^{1}H NMR spectrum ($CDCl_3$) was as for the undeuteriated material except that the 9–H signal (δ_H 4.89, d, J_{PH} 29) was much reduced (integration 0.08 H).

(c) Preparation of phosphonamidic chloride 11a. Diethylamine (380 mg, 5.2 mmol) in CH_2Cl_2 (3 ml) was added to a solution of fluoren-9-ylphosphonic dichloride **9a** (735 mg, 2.6 mmol) in CH_2Cl_2 (5 ml). After 3 h the volatile material was evaporated and the residue, dissolved in CH_2Cl_2, was washed with water containing a trace of HCl, then repeatedly with water. The solvent was evaporated and the product was extracted from the residue with ether. Dilution of the ether solution with light petroleum gave N,N-*diethyl*-P-(*fluoren-9-yl*)*phosphonamidic chloride* **11a** (638 mg, 77%) after drying *in vacuo* at 60 °C, mp 114–115 °C; $\delta_P(CDCl_3)$ 42.6; $\delta_H(CDCl_3$, 250 MHz) 8.04 (1 H, d, J_{HH} 7), 7.98 (1 H, d, J_{HH} 7), 7.81 (1 H, d, J_{HH} 7), 7.79 (1 H, d, J_{HH} 7), 7.47 (2 H, m), 7.36 (2 H, dd, J_{HH} 7, 7), 4.89 (1 H, d, J_{PH} 30), 2.72 and 2.50 (both 2 H, ddq, $J_{PH} \sim J_{gem} \sim 14$, J_{HH} 7) and 0.57 (6 H, t, J_{HH} 7); ν_{max}(Nujol)/cm^{-1} 1240 (P=O); *m/z* 321, 319 (M^+, 20%) and 165 (100) (Found: C, 63.9; H, 5.9; N, 4.4. $C_{17}H_{19}ClNOP$ requires C, 63.85; H, 6.0; N, 4.4%).

(d) Preparation of phosphonamidic chlorides 10b and 11b. The known isopropylphosphonamidic chlorides were prepared[13,15] by dropwise addition of Me_2NH or Et_2NH (2 equiv.) to a stirred, ice-cold solution of isopropylphosphonic dichloride **9b** in ether or CH_2Cl_2. The product was isolated by extraction into ether ($R_2NH_2^+$ Cl^- removed by filtration) and distillation under reduced pressure. For **10b**, $\delta_P(CDCl_3)$ 60.4; $\delta_H(CDCl_3$, 90 MHz) 2.70 (6 H, d, J_{PH} 14), 2.35 (1 H, d septet, J_{PH} 12, J_{HH} 7), 1.36 and

1.25 (both 3 H, dd, J_{PH} 21, J_{HH} 7); for **11b**, $\delta_P(CDCl_3)$ 58.4; $\delta_H(CDCl_3$, 250 MHz) 3.16 (4 H, dq, J_{PH} 14, J_{HH} 7), 2.32 (1 H, d septet, J_{PH} 12, J_{HH} 7), 1.36 and 1.25 (both 3 H, dd, J_{PH} 22, J_{HH} 7) and 1.18 (6 H, t, J_{HH} 7).

Phosphonic diamides

(a) The crude product from the rate study of **10a** or **11a** with Me_2NH or Et_2NH was washed with water and chromatographed on silica. Elution with light petroleum–ethyl acetate (3:1) gave the diamides detailed below.

N,N,N′,N′-*Tetramethyl*-P-(*fluoren*-9-*yl*)*phosphonic diamide*. Precipitated from ether by dilution with light petroleum, mp 98–100 °C (softens at 95 °C); $\delta_P(CDCl_3)$ 34.9; $\delta_H(CDCl_3$, 250 MHz) 7.88 (2 H, d, J_{HH} 7.5), 7.80 (2 H, d, J_{HH} 7.5), 7.42 (2 H, dd, J_{HH} 7.5, 7.5), 7.32 (2 H, dd, J_{HH} 7.5, 7.5), 4.92 (1 H, d, J_{PH} 25) and 2.35 (12 H, d, J_{PH} 10); ν_{max}(Nujol)/cm^{-1} 1205 (P=O); *m*/*z* 300 (M^+, 12%), 165 (25) and 135 (100) (Found: M^+, 300.1392. $C_{17}H_{21}N_2OP$ requires *M*, 300.1392).

N,N-*Diethyl*-N′,N′-*dimethyl*-P-(*fluoren*-9-*yl*)*phosphonic diamide* 12a (Y = Me_2N). Bp 190 °C (oven temp.) at 0.1 mmHg, non-crystalline glass; $\delta_P(CDCl_3)$ 35.2; $\delta_H(CDCl_3$, 250 MHz) 7.99 (1 H, d, J_{HH} 7), 7.78 (3 H, m), 7.41 (2 H, dd, J_{HH} 7.5, 7.5), 7.33 (1 H, dd, J_{HH} 7.5, 7.5), 7.31 (1 H, dd, J_{HH} 7.5, 7.5), 4.89 (1 H, d, J_{PH} 26), 2.72 (4 H, m), 2.56 (6 H, d, J_{PH} 10.5) and 0.64 (6 H, t, J_{HH} 7); ν_{max}(film)/cm^{-1} 1215, 1190 (P=O); *m*/*z* 328 (M^+, 6%), 165 (25) and 163 (100) (Found: M^+, 328.1705. $C_{19}H_{25}N_2OP$ requires *M*, 328.1704).

N,N,N′,N′-*Tetraethyl*-P-(*fluoren*-9-*yl*)*phosphonic diamide* 12a (Y = Et_2N). Bp 200 °C (oven temp.) at 0.1 mmHg; $\delta_P(CDCl_3)$ 34.5; $\delta_H(CDCl_3$, 250 MHz) 7.87 (2H, d, J_{HH} 7.5), 7.76 (2 H, d, J_{HH} 7.5), 7.38 (2 H, dd, J_{HH} 7.5, 7.5), 7.29 (2 H, dd, J_{HH} 7.5, 7.5), 4.85 (1 H, d, J_{PH} 26.5), 2.86 (8 H, dq, J_{PH} 10, J_{HH} 7) and 0.81 (12 H, t, J_{HH} 7); ν_{max}(film)/cm^{-1} 1220, 1185 (P=O); *m*/*z* 356 (M^+, 3%), 191 (100) and 165 (25) (Found: M^+, 356.2017. Calc. for $C_{21}H_{29}N_2OP$: *M*, 356.2018). This compound was obtained as a non-crystalline glass but, made in a different way, is reported to be crystalline (mp 158 °C).[23]

(b) The crude product from the rate study of **10b** or **11b** with Me_2NH was extracted into ether. The extract was concentrated and distilled to give N,N,N′,N′-*tetramethyl*-P-*isopropylphosphonic diamide*, bp 120 °C (oven temp.) at 6 mmHg (lit.,[13] 74–76 °C at 0.15 mmHg); $\delta_P(CDCl_3)$ 42.7; $\delta_H(CDCl_3$, 250 MHz) 2.64 (12 H, d, J_{PH} 9), 2.24 (1 H, d septet, J_{PH} 12.5, J_{HH} 7) and 1.17 (6 H, dd, J_{PH} 16.5, J_{HH} 7); ν_{max}(film)/cm^{-1} 1200 (P=O); *m*/*z* 178 (M^+, 30%), 135 (100) and 92 (65), or N,N-*diethyl*-N′,N′-*dimethyl*-P-*isopropylphosphonic diamide* **12b** (Y = Me_2N), bp 130 °C (oven temp.) at 10 mmHg (lit.,[13] 83–85 °C at 0.15 mmHg); $\delta_P(CDCl_3)$ 42.3; $\delta_H(CDCl_3$, 250 MHz) 3.03 (4 H, m), 2.64 (6 H, d, J_{PH} 9), 2.15 (1 H, d septet, J_{PH} 12, J_{HH} 7), 1.14 and 1.13 (both 3 H, dd, J_{PH} 16, J_{HH} 7) and 1.09 (6 H, t, J_{HH} 7); ν_{max}(film)/cm^{-1} 1210, 1195 (P=O); *m*/*z* 206 (M^+, 35%) and 163 (100).

(c) Substrate **11b** was heated with an excess of Et_2NH in a sealed tube at 110 °C for 20 h, giving one major product (δ_P 41.3) (85%) and two minor products (δ_P 33.5 and 33.0). Extraction into ether and distillation afforded N,N,N′,N′-*tetraethyl*-P-*isopropylphosphonic diamide* **12b** (Y = Et_2N), bp 150 °C (oven temp.) at 10 mmHg; $\delta_P(CDCl_3)$ 42.0; $\delta_H(CDCl_3$, 250 MHz) 3.02 (8 H, m), 2.07 (1 H, d septet, J_{PH} 12, J_{HH} 7.5), 1.11 (6 H, dd, J_{PH} 15, J_{HH} 7.5) and 1.08 (12 H, t, J_{HH} 7); ν_{max}(film)/cm^{-1} 1210, 1190 (P=O); *m*/*z* 234 (M^+, 25%), 191 (70), 162 (40) and 120 (100) (Found: M^+, 234.1861. $C_{11}H_{27}N_2OP$ requires *M*, 234.1861). The less volatile products were probably the diastereoisomers of the phosphonamidic anhydride $[Pr^iP(O)NEt_2]_2O$, *m*/*z* 340 (M^+, 15%), 297 (20), 268 (20), 226 (85) and 72 (100), resulting from reaction of **11b** with traces of moisture.

Rate studies

(a) For the *N*,*N*-diethylphosphonamidic chlorides **11a** and **11b**, the substrate (0.07 mmol) was mixed with a solution of Me_2NH or Et_2NH (1.15 mmol) in $CHCl_3$ to give a reaction mixture having an initial amine concentration of 1.20 mol dm^{-3}. The mixture was maintained at 31 °C and the ^{31}P NMR spectrum was recorded at regular intervals. With one exception (see below), at least nine spectra were recorded as the reaction proceeded to ⩾80% completion. For each spectrum the fraction of unchanged substrate ($a - x$) was deduced from the relative areas of the substrate and product peaks, and for each reaction log ($a - x$) was plotted against time:

Substrate **11a** + Me_2NH (δ_P 42.5→35.1): plot linear from 25% completion; k 1.28 h^{-1}.

Substrate **11a** + Et_2NH (δ_P 42.5→34.4): plot linear from 30% completion; k 0.33 h^{-1}.

Substrate **11b** + Me_2NH (δ_P 58.3→42.3): curved plot throughout; k 0.086 h^{-1} in early stages (0–30% completion) increasing to 0.26 h^{-1} in later stages (65–85% completion); 85% complete at t = 11 h.

Substrate **11b** + Et_2NH (δ_P 58.3→41.7): very slow; at t = 6 days (sealed tube) a mixture of unchanged substrate (80%), diamide product (3%) and by-products (δ_P 38–28) (17%) (probably caused by traces of moisture).

(b) Modified versions of reactions in (a) above gave the following results:

Substrate **11a** + $Et_2NH_2^+$ Cl^- (1 equiv.) + Et_2NH (1.2 mol dm^{-3}): plot linear throughout; k 0.52 h^{-1}.

Substrate **11a** + Et_4N^+ Cl^- (1 equiv.) + Et_2NH (1.2 mol dm^{-3}): fast (only three spectra recorded); k ~ 2.7 h^{-1}.

Substrate **11a** + DBU (0.08 mol dm^{-3}) + Et_2NH (1.12 mol dm^{-3}): very fast; 78% completion at t = 3.2 min, 88% at t = 5.1 min. [A similar experiment with substrate **11b** showed no significant change from the reaction in (a) without DBU.]

(c) For other reactions an approximate rate was measured as in (a) or as indicated:

Substrate **10a** + Me_2NH (δ_P 44.0→35.0): k ~ 9.0 h^{-1} with 0.8 mol dm^{-3} amine.

Substrate **10b** + Me_2NH (δ_P 60.2→43.0): some curvature of plot; k ~ 0.7 h^{-1} in early stages increasing to ~1.8 h^{-1} in later stages, with 0.8 mol dm^{-3} amine.

Substrate **10a** and [9-^{2}H]-**10a** + Et_2NH (0.8 mol dm^{-3}): GLC analysis showed the peak for substrate (t_R 3.0 min at 225 °C) declining, and for the product (t_R 4.8 min) growing, at practically the same rate in both cases ($t_{\frac{1}{2}}$ ~ 1.3 h).

Dichloride **9a** + Et_2NH (δ_P 48.4→42.5): 62% conversion into **11a** at t = 4 min, 82% at t = 6 min, with 1.2 mol dm^{-3} amine.

Dichloride **9b** + Et_2NH (δ_P 61.8→58.4): 72% conversion into **11b** at t = 5 min, 84% at t = 7 min, with 1.2 mol dm^{-3} amine.

Dichlorides **9a** and **9b** + Me_2NH (δ_P 48.4, 61.8→44.2, 60.5): reactions too fast to follow. Limited amounts of Me_2NH (⩽1 equiv.) added to an equimolar mixture of **9a** and **9b** caused each to be converted (into **10a** or **10b**) to essentially the same extent.

Competition experiments

The *N*,*N*-diethylphosphonamidic chloride **11a** or **11b** (0.06 mmol) was added to an equimolar mixture of Me_2NH and Et_2NH in $CHCl_3$ (1.2 mol dm^{-3} total amine concentration) (1.1 ml) maintained at 31 °C. When reaction was complete (40 h for **11a**; 76 h for **11b**) the product was analysed by GLC and ^{31}P NMR spectroscopy. For **11a** the product was a mixture of the diamides **12a** (Y = Me_2N) and **12a** (Y = Et_2N), t_R 5.0 and 6.2 min at 225 °C, δ_P 35.1 and 34.4, in a ratio of 4.7:1. For **11b** the product was **12b** (Y = Me_2N), t_R 4.4 min at 130 °C, δ_P 42.3; a trace of **12b** (Y = Et_2N), t_R 7.7 min, δ_P 41.7 may have been present but the product ratio was ⩾200:1. In both cases the product was isolated and its composition confirmed by ^1H NMR spectroscopy. The experiment was repeated for **11a** with DBU (1 equiv.) added; the composition of the product (GLC) was the same as it had been with no DBU present.

Deuterium incorporation

The fluorenylphosphonamidic chloride **11a** (8 mg, 0.025 mmol) was dissolved in $CDCl_3$ (0.55 ml) containing Et_2ND (≥90 atom%D)[8] (~0.1 mmol). After 45 min, the ^{31}P NMR spectrum showed that no significant amount of substitution had occurred and the ^1H NMR spectrum showed that the integral for 9–H in the substrate had decreased to 0.25 H (0.75 D) as a result of H–D exchange.

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