Nucleophilic substitution reactions of benzyl- and diphenylmethylphosphonamidic chlorides with amines: competition between the usual $S_N2(P)$ mechanism and elimination–addition with an alkylideneoxophosphorane (phosphene) intermediate

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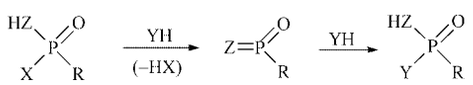
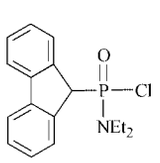
The substitution reaction of $PhCH_2P(O)(NMe_2)Cl$ with Me_2NH or Et_2NH in $CHCl_3$ is very sensitive to the bulk of the nucleophile (≥ 200 times slower with Et_2NH), affords only the product derived from Me_2NH in competition experiments, and gives largely undeuterated product with Et_2ND; these features are in accord with an $S_N2(P)$ mechanism. The corresponding reaction of $Ph_2CHP(O)(NMe_2)Cl$ is relatively insensitive to the bulk of the nucleophile (5 times slower with Et_2NH), gives some of the product derived from Et_2NH in competition experiments, and gives extensively deuterated product with Et_2ND; these features point to an elimination–addition (EA) mechanism with an alkylideneoxophosphorane intermediate [$Ph_2C{=}P(O)NMe_2$]. There is only a modest (13–19 fold) increase in the rate of substitution on going to $ArPhCHP(O)(NMe_2)Cl$ (Ar = 4-$NO_2C_6H_4$) but with R_2ND there is now very rapid H/D exchange at the α carbon atom. This suggests that the elimination stage of the EA mechanism comprises rapid reversible formation of the conjugate base followed by rate-limiting expulsion of chloride ion.

Nucleophilic substitution at phosphoryl (P=O) centres is important in many areas of chemistry and makes possible the phosphoryl transfer reactions on which biological systems depend.[1] The mechanism is generally associative [$S_N2(P)$], with a five-coordinate intermediate or transition state.[2] An alternative dissociative pathway is available to substrates that have an acidic ligand HZ (Scheme 1; X = leaving group), involving



Scheme 1

elimination–addition and a transient three-coordinate P^V intermediate.[2,3] This alternative mechanism is often important when Z is oxygen,[4] sulfur[5] or nitrogen[6] but not, it seems, when Z is just a carbon atom.[7] The fluoren-9-ylphosphonamidic chloride **1** is a rare exception, undergoing substitution reactions with amines by elimination–addition with an alkylideneoxophosphorane (phosphene) intermediate **2**.[8] This is an extreme case, however, since the C_α–H bond in **1** will be exceptionally acidic because of the aromaticity of the fluorenyl anion. In contrast are the many quite ordinary acyl and sulfonyl substrates that produce ketenes[9] or sulfenes[10] in their reactions with basic reagents. Is it *only* in extreme cases that phosphenes are formed as intermediates in the nucleophilic substitution reactions of P=O compounds? That question has prompted the present investigation.



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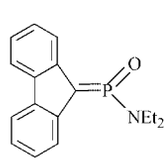
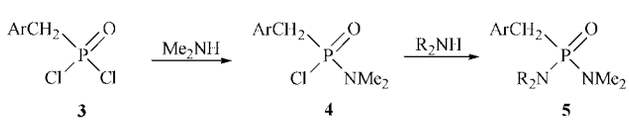


2

Results and discussion

Benzylphosphonic acid derivatives

The benzylphosphonamidic chloride **4a** and its 4-nitro analogue **4b** were prepared by controlled reaction of the phosphonic dichlorides **3a** and **3b** with Me_2NH (generated *in situ* from $Me_2NH_2^+Cl^-$ and Et_3N) (Scheme 2). Both could be purified by crystallisation but they hydrolyse quite readily and vacuum distillation proved more satisfactory for the relatively volatile and low melting compound **4a**.



3 **4** **5**

a Ar = Ph; **b** Ar = 4–$NO_2C_6H_4$

Scheme 2

With Et_2NH in $CHCl_3$, and moisture carefully excluded, the phosphonamidic chlorides formed the phosphonic diamides **5a** and **5b** (R = Et) (Scheme 2) over several hours at room temperature. The reactions were monitored by ^{31}P NMR spectroscopy (δ_P 46.9 or 44.0→33.9 or 32.0) using a large excess of a 2.0 mol dm^{-3} solution of Et_2NH in $CHCl_3$ at 30 °C and the pseudo-first-order rate constants k were deduced (Table 1).† These equate to half lives of 39 and 34 min for **4a** and **4b** respectively.

† In substitution reactions of phosphonamidic chlorides with amines the amine hydrochloride by-product can accelerate the reaction slightly, causing deviations from linearity in the first-order rate plots (ref. 8). In the present study a small amount of the appropriate amine hydrochloride (Et_2NH_2Cl or Me_2NH_2Cl) (0.1 mol dm^{-3}) was included in each reaction mixture and the rate plots showed little if any curvature.

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Table 1 Pseudo-first-order rate constants (k) for reactions of phosphonamidic chlorides with 2.0 mol dm^{-3} amines in $CHCl_3$ at 30 °C

Substrate	10^5k/s^{-1}	
	Me_2NH	Et_2NH
4a	~10[4] [a]	29.7
4b	~10[4] [a]	34.4
10a	1.04	0.21 [b]
10b	13.8	3.87

[a] Very approximate (based on 75–80% substitution in 15 s and by implication $t_{\frac{1}{2}} \sim 7$ s). [b] Some 10% of substrate formed by-products (hydrolysis); value of k is for overall consumption of substrate.

The corresponding reactions with Me_2NH were too fast to follow so they were quenched after just 15 s (aqueous HCl) and the resulting mixtures were analysed by ^{31}P NMR spectroscopy. In both cases the diamide product **5** (R = Me) (δ_P 34.2 or 33.2) accounted for 75–80%, unchanged substrate 5–10%, and by-products (most likely stemming from hydrolysis on quenching) 10–20%. This suggests half lives of *ca*. 7 s for the substitution reactions of **4a** and **4b** with Me_2NH and implies at least a 200-fold difference in reactivity between Et_2NH and Me_2NH.

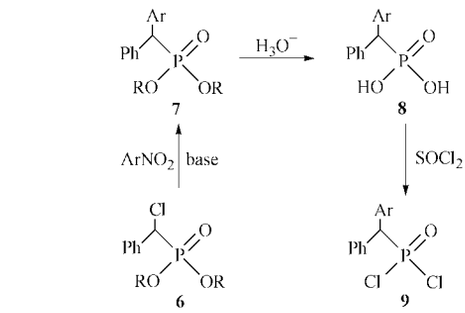
High sensitivity to the bulk of the nucleophile is not unreasonable for an $S_N2(P)$ mechanism, in which the four-coordinate phosphorus atom of the substrate becomes five-coordinate in the transition state, and it has often been noted before.[11] With PhP(O)(NMe_2)Cl, for example, where elimination–addition (EA) is not possible, Pr^iNH_2 reacts 120 times faster than the more bulky Bu^tNH_2,[12] and with $Pr^iP(O)(NEt_2)Cl$ the reactivity of Me_2NH is ≥ 200 times greater than Et_2NH.[8] For an EA mechanism, however, a large steric effect would not be expected given that the amine acts as a base in the rate-limiting elimination stage, not as a nucleophile, and attacks the substrate by abstraction of a proton from the α carbon atom. Indeed, in the corresponding reactions of the benzylic P=S substrate $ArCH_2P(S)(NMe_2)Cl$ (Ar = 4-$NO_2C_6H_4$), which are believed to proceed by elimination–addition, there is a mere 1.5 fold difference in reactivity between Et_2NH and Me_2NH.[13]

The influence of the 4-nitro substituent in the substrate **4** is also reasonable for $S_N2(P)$ but improbable for an EA mechanism. The acidity of the C_α–H bond should be greatly increased by the NO_2 group and so should the rate-limiting formation of the phosphene intermediate, at least if it occurs by an ElcB mechanism. In fact the nitro-substituted substrate **4b** is only marginally more reactive than **4a** (Table 1). The situation with the P=S substrate $ArCH_2P(S)(NMe_2)Cl$ is dramatically different: a 4-nitro substituent increases the observed reactivity towards Et_2NH by a factor of 2500, even though the unsubstituted compound reacts predominantly by $S_N2(P)$;[13] for the EA pathway alone, the effect of the NO_2 group must be to increase the rate by a factor >10^4.

There are two ways in which a benzylphosphonic acid derivative might become more susceptible to substitution by an EA mechanism: increased acidity of the C_α–H bond, encouraging elimination–addition, and steric hindrance of attack at the phosphorus atom, discouraging competition from $S_N2(P)$. On both counts replacing one of the benzylic hydrogen atoms by a phenyl group could have a profound effect.

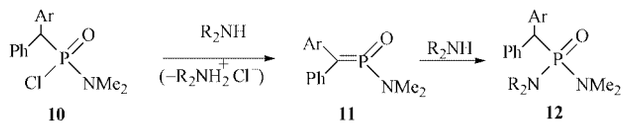
Diphenylmethylphosphonic acid derivatives

Diphenylmethylphosphonic acid **8a** and the related acid **8b** having a 4-nitro substituent in one of the phenyl groups were obtained by hydrolysis (48% HBr; 130 °C) of the phosphonate esters **7a** (R = Et) and **7b** (R = Me) (Scheme 3). The first of these esters was prepared directly, by the Arbusov reaction of $(EtO)_3P$ with Ph_2CHBr, but the second was obtained by an indirect route, making use of Makosza and Goliński's vicarious substitution.[14] This entailed reaction of the α-chlorobenzylphosphonate **6** (R = Me) with nitrobenzene in liquid NH_3 containing NaOH. The key steps are nucleophilic attack of the phosphonate anion at the *para* position of nitrobenzene and, subsequently, a 1,2 shift of hydride from that position with displacement of the chlorine from the α carbon atom.



a Ar = Ph; **b** Ar = 4–$NO_2C_6H_4$

Scheme 3



a Ar = Ph; **b** Ar = 4–$NO_2C_6H_4$

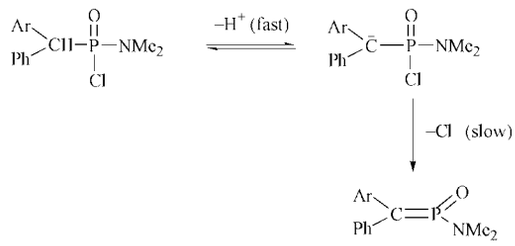
Scheme 4

The phosphonic acids were converted into the dichlorides **9** by heating with $SOCl_2$ (DMF catalyst) and these on controlled reaction with Me_2NH gave the phosphonamidic chlorides **10**. The two phenyl groups in the unsubstituted compound **10a** are diastereotopic, by virtue of chirality at the phosphorus atom, and that is reflected in a difference in the chemical shifts of the *ortho* hydrogens: δ_H 7.62 and 7.53 (both 2 H, d, J_{HH} 7.5). The nitro-substituted compound **10b** is chiral at carbon as well as phosphorus and was obtained as a mixture of diastereoisomers, δ_P 44.6 and 44.35. The NMe_2 groups of the two diastereoisomers give distinct ^{1}H NMR signals, δ_H 2.68 and 2.66 (both d, J_{PH} 12.5).

The phosphonamidic chlorides **10a** and **10b** gave the expected diamides **12** with Me_2NH and Et_2NH (Scheme 4). Of these **12a** (R = Me) is achiral [equivalent NMe_2 groups, δ_H 2.40 (12 H, d, J_{PH} 9)], **12b** (R = Me) is chiral at carbon [diastereotopic NMe_2 groups, δ_H 2.435 and 2.40 (both 6 H, d, J_{PH} 9)], **12a** (R = Et) is chiral at phosphorus [diastereotopic Ph groups; *ortho* protons δ_H 7.66 and 7.63 (both 2 H, d, J_{HH} 8)], and **12b** (R = Et) is chiral at both carbon and phosphorus and exists as diastereoisomers, δ_P 30.4 and 30.3 [NMe_2 groups δ_H 2.425 and 2.39 (both d, J_{PH} 8.5)].

Reactivity in substitution reactions with Me_2NH and Et_2NH. Rates of reaction were examined as before, using 2.0 mol dm^{-3} amine in $CHCl_3$ at 30 °C. Even the fastest reaction (**10b** + Me_2NH) was now slow enough to be followed by ^{31}P NMR spectroscopy (85% complete in 4 h) while the slowest (**10a** + Et_2NH) took 10 days to reach 85% completion. The values of the pseudo-first-order rate constant k are shown in Table 1 and correspond to half lives of 18.5 and 90 h for the unsubstituted substrate **10a**, and 1.4 and 5.0 h for the nitro compound **10b**, with Me_2NH and Et_2NH respectively.

As expected the reactions of both substrates are slower with Et_2NH (k^E) than with Me_2NH (k^M) but only by a factor of about five. The difference in amine reactivity is therefore much smaller than for the benzyl compounds **4** (k^M/k^E ≥ 200) and much less than would be expected for $S_N2(P)$. On the other hand it is similar to the value observed with the



Scheme 5

fluorenyl substrate **1** ($k^M/k^E = 4$) which reacts with amines by an EA mechanism.[8] The somewhat larger difference seen for **10a** ($k^M/k^E = 5.0$) than for **10b** ($k^M/k^E = 3.6$) may indicate that only the latter (nitro-substituted) substrate reacts entirely by elimination–addition. Competition from $S_N2(P)$ will be more important with the less acidic substrate **10a** and with the more nucleophilic (less hindered) amine, so the observed value of k^M for **10a** with Me_2NH may well be rather greater than the value for the EA pathway alone.

A contribution from $S_N2(P)$ in the case of Me_2NH and **10a** may also explain why introduction of a NO_2 group into the substrate (as in **10b**) has rather less impact on the observed rate of reaction with Me_2NH (13-fold increase) than with Et_2NH (19-fold increase). More important, however, is the fact that the NO_2 group effect is so modest, regardless of the amine. It is no longer marginal, as it was for the benzyl substrate **4**, but it is still nowhere near as great as for the EA pathway in the case of the P=S substrate $ArCH_2P(S)(NMe_2)Cl$ (>10^4-fold).[13] That being so, an EA mechanism in which removal of the proton from the α carbon atom is rate-limiting seems untenable for the substrates **10**. If they do react by an EA mechanism, the elimination stage must surely be E2, or reversible E1cB with formation of the conjugate base faster (or much faster) than its collapse (Scheme 5).

Reactions with Me_2ND and Et_2ND. The reactions of the phosphonamidic chlorides **10** were repeated using amine in which 80–85% of the NH group was replaced by ND (^{1}H NMR), looking particularly for H/D exchange at the α carbon atom of the substrate. The amine concentration was kept at *ca*. 2 mol dm^{-3} but the solvent was changed to $CDCl_3$ so that the reactions could be monitored by ^{1}H NMR spectroscopy. Ideally the signal for the methine group [CH(D)] of the substrate would have been compared with that for the NMe_2 group but this was often obscured by signals from the amine. The comparison therefore had to be with the aromatic signals of the substrate, using the ^{31}P NMR spectrum of the reaction mixture to ascertain the extent of reaction and hence the proportion of the total aromatic integral attributable to the substrate. The results in Table 2 are inevitably only approximate but they are instructive nonetheless.

With both Me_2ND and Et_2ND the nitro-substituted substrate **10b** exchanged so rapidly that the integral for the methine group had fallen close to its equilibrium value [0.15–0.2 H; R_2ND (large excess) contained 15–20% R_2NH] by the time the first spectrum had been recorded, but still before any appreciable conversion into product had occurred. The unsubstituted compound **10a** exchanges much less quickly, as expected, but still faster than its conversion into product or at least as fast. It follows that substitution could proceed by an EA mechanism in which rapid reversible formation of the conjugate base of the substrate is followed by rate-limiting expulsion of chloride ion and liberation of the phosphene intermediate (Scheme 5). It does not follow that this is the mechanism, however: unless collapse of the conjugate base is sufficiently fast the preferred route to product will still be bimolecular nucleophilic attack [$S_N2(P)$] on the substrate itself. That, indeed, is what prevails with the nitro-substituted benzyl substrate **4b**. Little if any of its substitution reaction with

Table 2 Exchange (H/D) during reactions of phosphonamidic chlorides with 2 mol dm^{-3} R_2ND (80–85 atom% D) in $CDCl_3$ at 30 °C

		Substrate	
Reaction	Time/h	Amount (%)	CH(D) Integral
10a + Me_2ND	0.4	>95	0.9 H
	1.0	>95	0.75 H
	2.5	95	0.5 H
	9.5	80	0.2 H
10b + Me_2ND	0.15[a]	>95	0.15 H
10a + Et_2ND	20	86	0.8 H
	37	78	0.6 H
	87	52	0.35 H
10b + Et_2ND	0.2	>95	0.2 H

[a] T = 18 °C in this case.

Et_2NH proceeds by elimination–addition, yet with Et_2ND we observed extensive H/D exchange in the methylene group of the substrate. With the unsubstituted benzyl substrate **4a** there was not much exchange and only a small part of the product (<10%) contained any deuterium (EI MS).

While exchange between the substrate and R_2ND is not necessarily indicative of an EA mechanism for substitution, incorporation of deuterium into the product in the course of the substitution process itself would surely point to a phosphene intermediate. It is significant, therefore, that in the reaction of **10a** with Et_2ND (80–85 atom% D) the methine group of the product was 80% deuteriated (0.2 H/0.8 D by ^{1}H NMR) at 50% completion. At that time the methine group of the substrate was 65% deuteriated (0.35 H/0.65 D) and most of the product would have been derived from substrate that was less extensively deuteriated (exchanged). So for some of the substitution, and probably for all of it, the product must have been formed by an EA mechanism. Then a H atom could be removed in the elimination stage (phosphene formation) and a D atom acquired in the addition (phosphene + Et_2ND).‡ The other substitution reactions (**10a** + Me_2ND; **10b** + Et_2ND or Me_2ND) also gave highly deuteriated products but in those cases H/D exchange in the substrate was so fast, relative to substitution, that we could not actually demonstrate that they were formed from less highly deuteriated starting materials.

It was not possible to compare the rates of H/D exchange with the different amines in the case of the nitro-substituted substrate **10b**—they were too fast to follow—but for **10a** it could be seen that exchange with Et_2ND is some 20 times slower than with Me_2ND (Table 2). This in spite of the fact that Et_2NH is a stronger base than Me_2NH. The difference in basicity is small for aqueous solutions [pK_a 10.68 (Me_2NH); 11.02 (Et_2NH)][15] but it is quite large in the gas phase [$R_2NH + NH_4^+ \rightleftharpoons R_2NH_2^+ + NH_3$; $\Delta G°$ −64.9 (Me_2NH); −84.6 (Et_2NH) kJ mol^{-1}][16] and might be in $CHCl_3$ solution as well.§ That being so, the relatively low kinetic basicity of Et_2NH seen here must be a consequence of steric hindrance. Some steric effect is to be expected, even for abstraction of a proton, but we had supposed it would be small. In fact it seems quite large, reflecting, presumably, a crowded environment for the methine hydrogen in the $Ph_2CHP(O)$ group.

Competition experiments with Me_2NH and Et_2NH. Additional evidence for the involvement of phosphene intermediates was sought from Me_2NH–Et_2NH competition experiments.

‡ A control reaction showed H/D exchange between the product **12a** (R = Et) and Et_2ND to be insignificant under the conditions of reaction (no change in ^{1}H NMR or MS during 113 h).

§ There is, however, only a small difference between Me_2NH and Et_2NH in ion-pair formation with 2,4-dinitrophenol in $CHCl_3$ (R. G. Pearson and D. C. Vogelsong, *J. Am. Chem. Soc.*, 1958, **80**, 1038).

The phosphonamidic chlorides were treated with a large excess of an equimolar mixture of the amines (each 2.0 mol dm^{-3}) in $CHCl_3$ and the ratio of the NMe_2 and NEt_2 products was determined by ^{31}P NMR spectroscopy. Whereas the benzyl substrates **4a** and **4b** gave only the products derived from Me_2NH (≥99%), in accord with an associative [$S_N2(P)$] mechanism in which formation of the five-coordinate transition state is highly sensitive to steric effects, the diphenylmethyl substrates **10a** and **10b** gave substantial amounts of the products derived from Et_2NH. This is easily understood in terms of an EA mechanism since the product would then arise by nucleophilic attack on a reactive and sterically accessible three-coordinate phosphene intermediate and relatively little discrimination between the amines would be expected. The NMe_2 : NEt_2 product ratio was actually 3.1 : 1 for the nitro compound **10b** but 6.4 : 1 for **10a**. It is possible that the phosphene intermediate from **10a** reacts more selectively but much of the difference probably originates elsewhere. The EA mechanism is slower for **10a** than for **10b** so $S_N2(P)$ has more chance to compete, and any of the substrate that does react by $S_N2(P)$ will give entirely the product derived from Me_2NH. When the experiments were repeated with a small amount of the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) included in the reaction mixture (5 mol% of total amine) the NMe_2 : NEt_2 product ratio was practically unchanged for **10b** (3.2 : 1). For **10a**, however, it was reduced to 3.05 : 1, presumably because $S_N2(P)$ cannot now compete effectively with the DBU-assisted EA mechanism. The rate measurements hinted at some contribution from $S_N2(P)$ in the reaction of **10a** with Me_2NH and that is now confirmed by the outcome of the competition experiments.

Conclusion

The simple benzylphosphonamidic chloride **4a** reacts with Me_2NH and Et_2NH by the normal associative [$S_N2(P)$] mechanism; there is no evidence of any appreciable competition from elimination–addition, even when the acidity of the C_α–H bonds is greatly increased by the presence of a 4-nitro substituent, as in **4b**. The nitro-substituted substrate is much less reactive towards Et_2NH than is the corresponding P=S compound [$ArCH_2P(S)(NMe_2)Cl$] for which an EA mechanism has previously been established (P=O: $t_{\frac{1}{2}}$ 34 min with 2.0 mol dm^{-3} Et_2NH; P=S: $t_{\frac{1}{2}}$ 0.6 min with 0.8 mol dm^{-3} Et_2NH). If the EA mechanism were as fast for the P=O compound it would, in fact, be the preferred pathway, notwithstanding the relatively high $S_N2(P)$ reactivity. The C_α–H bonds may be less acidic in the P=O compound,[17] but most evidence suggests that any difference will be marginal[18] and in any case the rapid H/D exchange seen in the reaction of **4b** with Et_2ND implies that the conjugate base is formed readily. Rather, it seems that elimination of chloride from the conjugate base is more difficult for the P=O compound, to form a phosphene, than for the P=S compound, forming a thiophosphene.

For the diphenylmethylphosphonamidic chloride **10a** the reaction with Me_2NH is in part elimination–addition and in part $S_N2(P)$. However, the EA mechanism is dominant with Et_2NH [steric hindrance; $S_N2(P)$ suppressed] and for both amines in the case of the 4-nitro substituted substrate **10b** (enhanced C_α–H acidity; EA promoted). The importance of elimination–addition here, but not with the benzyl substrates **4**, is obviously a consequence of the extra phenyl group; it will increase the thermodynamic acidity of the C_α–H bond, and probably also the kinetic acidity, and it will hinder nucleophilic attack on the phosphorus atom. It is not possible to assess the effect of the extra phenyl group on acidity from our results (H/D exchange is not competitive with substitution for **4a** and is too fast to measure for **4b**) but its hindrance of $S_N2(P)$ is clearly very severe: even though the observed rate for **10a** + Me_2NH is boosted by a substantial contribution from the EA pathway it is still 10^4 times less than the rate of the $S_N2(P)$ reaction of **4a** with Me_2NH.

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker ARX 250 or DPX 300 spectrometer (Me_4Si internal standard; coupling constants J given in Hz) and ^{31}P NMR spectra (^1H decoupled) were recorded on the same instruments at 101.3 or 122.0 MHz (positive chemical shifts downfield from 85% H_3PO_4). Mass spectra were recorded in EI mode unless otherwise indicated on a Kratos Concept spectrometer. Amines were distilled from KOH and amine hydrochlorides were dried at 0.2 mmHg over P_2O_5. Dichloromethane was distilled from CaH_2 and chloroform was dried over 5 Å molecular sieves. Light petroleum refers to the fraction bp 60–80 °C and ether to diethyl ether. The solutions used in rate studies were made up using dried materials and were stored over 3 Å molecular sieves at 4 °C for 15–24 h before use.

Diphenylmethylphosphonic acid 8a

A mixture of Ph_2CHBr (24.7 g, 0.10 mol) and $(EtO)_3P$ (22.6 g, 0.135 mol) was stirred vigorously under a gentle stream of nitrogen. The flask was placed in an oil bath preheated to 100 °C and the temperature was raised rapidly to *ca.* 165 °C. Heating was continued until all the Ph_2CHBr had been consumed [2–3 h; δ_H 6.26 (s) replaced by 4.38 (d, J_{PH} 25)]. The crude *diethyl phosphonate* **7a** (R = Et)[19] (δ_P 25.2) was hydrolysed by stirring efficiently with 48% hydrobromic acid (6 equiv.) at 130 °C until ^1H NMR spectroscopy showed no P–OEt signal (5 h). After cooling the solid was filtered off, washed thoroughly with water, and crystallised from aqueous MeOH to give *diphenylmethylphosphonic acid* **8a** (22.8 g, 92%), mp 229–231 °C (lit.,[20] 227–228 °C); *m/z* (−ES) 247 [$(M - H)^-$, 100%]; $\delta_P(CDCl_3$–MeOH, 9 : 1) 25.5; $\delta_H(CDCl_3$–MeOH, 9 : 1; 250 MHz) 7.5–7.1 (10 H, m) and 4.39 (1 H, d, J_{PH} 26).

4-Nitrophenyl(phenyl)methylphosphonic acid 8b

1-Chloro-1-phenylmethylphosphonic dichloride [$\delta_P(CDCl_3)$ 40.3] was prepared from PhCHO and PCl_3 (sealed tube; 200 °C for 8 h) as previously described[21] and was added as a CH_2Cl_2 solution to MeOH (large excess) containing Et_3N; evaporation of volatile material and extraction of the residue with ether afforded *dimethyl 1-chloro-1-phenylmethylphosphonate*[22] **6** (R = Me) (74%), $\delta_P(CDCl_3)$ 19.7; $\delta_H(CDCl_3$; 90 MHz) 7.6–7.2 (5 H, m), 4.88 (1 H, d, J_{PH} 15), 3.76 (3 H, d, J_{PH} 11) and 3.52 (3 H, d, J_{PH} 11). Following the published procedure[14] the phosphonate **6** (R = Me) was allowed to react with nitrobenzene and NaOH in liquid NH_3 to give *dimethyl 4-nitrophenyl(phenyl)-methylphosphonate* **7b** (R = Me) (77%), $\delta_P(CDCl_3)$ 25.9; $\delta_H(CDCl_3$; 90 MHz) 8.13 (2 H, d, J_{HH} 9), 7.66 (2 H, dd, J_{PH} 2, J_{HH} 9), 7.6–7.2 (5 H, m), 4.51 (1 H, d, J_{PH} 26), 3.51 (3 H, d, J_{PH} 11) and 3.49 (3 H, d, J_{PH} 11). The crude phosphonate **7b** (R = Me) (6.1 g, 19.0 mmol) was hydrolysed by stirring with 48% hydrobromic acid (6 equiv.) at 130 °C until reaction was complete (3 h) (δ_P 24.7). The mixture was diluted with water (50 ml) and refrigerated overnight, and the precipitated solid was collected. It could not be crystallised satisfactorily (other than from water) but dissolution in moist ether and gradual addition of light petroleum (bp 40–60 °C) afforded pure *4-nitrophenyl(phenyl)methylphosphonic acid* **8b** as the hemihydrate (4.3 g, 75%), mp 77–80 °C; *m/z* (−ES) 292 [$(M - H)^-$, 100%]; $\delta_P(CDCl_3)$ 27.0 br; $\delta_H(CDCl_3$; 250 MHz) 8.1 br (3 H; OH + 0.5 H_2O), 8.04 (2 H, d, J_{HH} 6), 7.41 (2 H, d, J_{HH} 6), 7.25 (5 H, m) and 4.39 (1 H, d, J_{PH} 25); ν_{max}(Nujol)/cm^{-1} 1520 and 1355 (NO_2) (Found: C, 52.3; H, 4.3; N, 4.4. $C_{13}H_{12}NO_5P \cdot 0.5H_2O$ requires C, 51.7; H, 4.3; N, 4.6%). Prolonged drying over P_2O_5 at 0.2 mmHg and 50 °C gave practically anhydrous acid.

Phosphonic dichlorides

(a) Benzylphosphonic dichloride **3a** and 4-nitrobenzylphosphonic dichloride **3b** were prepared by literature methods.[23,24]

(b) The phosphonic acid **8a** or **8b** was converted into the dichloride by stirring with $SOCl_2$ (12 equiv.) and DMF (catalyst; 0.03 equiv.) at 100 °C (bath temp.) until the ^{31}P NMR spectrum of the solution consisted of a single peak ($\delta_P \sim 45$) (1.5–3 h). Volatile material was evaporated and the residue was pumped at 0.2 mmHg. The following were obtained:

Diphenylmethylphosphonic dichloride 9a. Mp ~ 85 °C; *m*/*z* 288, 286, 284 (M^+, 1%) and 167 (Ph_2CH^+, 100); *m*/*z* (CI) 306, 304, 302 [$(M + NH_4)^+$, 50%]; $\delta_P(CDCl_3)$ 46.0; $\delta_H(CDCl_3$; 250 MHz) 7.60 (4 H, m), 7.4–7.3 (6 H, m) and 4.88 (1 H, d, J_{PH} 20); ν_{max}(Nujol)/cm^{-1} 1260 (P=O).

4-Nitrophenyl(phenyl)methylphosphonic dichloride 9b. Obtained as a foam, *m*/*z* 333, 331, 329 (M^+, 1%) and 212 ($ArPhCH^+$, 100); $\delta_P(CDCl_3)$ 43.5; $\delta_H(CDCl_3$; 250 MHz) 8.26 (2 H, d, J_{HH} 8), 7.82 (2 H, dd, J_{PH} 2.5, J_{HH} 8), 7.59 (2 H, m), 7.43 (3 H, m) and 5.00 (1 H, d, J_{PH} 20), which was used without purification.

Phosphonamidic chlorides

A solution of the phosphonic dichloride **3** or **9** (2.0 mmol) and $Me_2NH_2^+Cl^-$ (2.4 mmol) in CH_2Cl_2 (5 ml) was stirred and cooled in ice while Et_3N (4.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise. In the case of **9b** the phosphonic dichloride contained impurities (HCl, $SOCl_2$) that consumed some of the amine and additional reagent was required to complete the conversion (δ_P 44→46). After stirring at room temperature for 0.3 h the mixture was concentrated and the residue, dissolved in fresh CH_2Cl_2, was washed with iced water. The solvent was evaporated and the crude product was distilled (Kugelrohr) (**4a**) or crystallised from CH_2Cl_2–light petroleum. The following were prepared:

***N*,*N*-Dimethyl-*P*-benzylphosphonamidic chloride 4a.** Bp 140 °C (oven temp.) at 0.3 mmHg, mp 52–55 °C; *m*/*z* 219, 217 (M^+, 40%), 128, 126 ($M^+ - PhCH_2$, 50) and 91 (100); $\delta_P(CDCl_3)$ 46.4; $\delta_H(CDCl_3$; 250 MHz) 7.4–7.3 (5 H, m), 3.57 (2 H, ABP, δ_A 3.59, δ_B 3.55, J_{AB} 15, J_{AP} 20, J_{BP} 17) and 2.69 (6 H, d, J_{PH} 14); ν_{max}(Nujol)/cm^{-1} 1240 (P=O) (Found: C, 49.4; H, 6.1; N, 6.5. $C_9H_{13}ClNOP$ requires C, 49.7; H, 6.0; N, 6.4%).

***N*,*N*-Dimethyl-*P*-(4-nitrobenzyl)phosphonamidic chloride 4b.** (Yield 78%.) Recrystallised from Bu^{t}OMe, mp 93–95 °C; *m*/*z* 264, 262 (M^+, 13%) and 128, 126 ($M^+ - ArCH_2$, 100); $\delta_P(CDCl_3)$ 43.3; $\delta_H(CDCl_3$; 250 MHz) 8.22 (2 H, d, J_{HH} 8.5), 7.52 (2 H, dd, J_{PH} 3, J_{HH} 8.5), 3.66 (2 H, ABP, δ_A 3.68, δ_B 3.64, J_{AB} 14.5, J_{AP} 20, J_{BP} 18) and 2.73 (6 H, d, J_{PH} 14); ν_{max}(Nujol)/cm^{-1} 1515 and 1350 (NO_2), 1240 and 1230 (P=O) (Found: C, 41.1; H, 4.7; N, 10.4. $C_9H_{12}ClN_2O_3P$ requires C, 41.15; H, 4.6; N, 10.7%).

***N*,*N*-Dimethyl-*P*-(diphenylmethyl)phosphonamidic chloride 10a.** (Yield 88%.) Mp 180–182 °C (from CH_2Cl_2–ether); *m*/*z* 295, 293 (M^+, 2%) and 167 (Ph_2CH^+, 100); $\delta_P(CDCl_3)$ 46.9; $\delta_H(CDCl_3$; 250 MHz) 7.62 (2 H, d, J_{HH} 7.5), 7.53 (2 H, d, J_{HH} 7.5), 7.4–7.2 (6 H, m), 4.68 (1 H, d, J_{PH} 18.5) and 2.65 (6 H, d, J_{PH} 13); ν_{max}(Nujol)/cm^{-1} 1230 (P=O) (Found: C, 61.2; H, 5.8; N, 4.75. $C_{15}H_{17}ClNOP$ requires C, 61.3; H, 5.8; N, 4.8%).

***N*,*N*-Dimethyl-*P*-[4-nitrophenyl(phenyl)methyl]phosphonamidic chloride 10b.** (Yield 90%.) Mixture of diastereoisomers, mp 159–160 °C; *m*/*z* 340, 338 (M^+, 2%), 294, 292 ($M^+ - NO_2$, 5) and 212 ($ArPhCH^+$, 100); $\delta_P(CDCl_3)$ 44.6 (major) and 44.35; $\delta_H(CDCl_3$; 250 MHz) 8.19 (2 H, d, J_{HH} 8.5), 7.82 and 7.73 (major) (total 2 H; both dd, J_{PH} 2, J_{HH} 8.5), 7.65–7.25 (5 H, m), 4.79 and 4.78 (major) (total 1 H; both d, J_{PH} 18), 2.68 (major) and 2.66 (total 6 H; both d, J_{PH} 12.5); ν_{max}(Nujol)/cm^{-1} 1525 and 1360 (NO_2), 1240 (P=O) (Found: C, 52.85; H, 4.7; N, 7.9. $C_{15}H_{16}ClN_2O_3P$ requires C, 53.2; H, 4.8; N, 8.3%).

Phosphonamidic chloride rate studies

All materials and glassware were dried and moisture was excluded as completely as possible. The reaction medium was a 2.0 mol dm^{-3} solution of R_2NH (R = Me or Et) in $CHCl_3$ containing $R_2NH_2^+$ Cl^- (0.1 mol dm^{-3}). The substrate (10–15 μmol) was dissolved in the reaction medium (240 μl) and the solution was transferred to a 4 mm NMR tube housed in a 5 mm tube containing D_2O (NMR lock). Faster reactions were conducted in the probe of the NMR spectrometer at 30 °C. Slower reactions (sealed tubes) were maintained at 30 °C (block heater) and transferred to the spectrometer periodically. The reactions of **4a** and **4b** with Me_2NH were complete within 10 min but in other cases the ^{31}P NMR spectrum (^1H decoupled) was recorded at regular intervals so that ≥9 spectra were obtained as reaction progressed to 88% completion. For each spectrum the relative amounts of substrate and product were deduced from the integral. Minor by-products (hydrolysis) were seen in some of the Et_2NH reactions but in total they amounted to ≤10%. First-order plots were linear, or practically so, and the values of *k* (± 6%) were deduced from the slopes of the lines (Table 1).

When reaction was complete the volatile material was evaporated and the residue was dissolved in CH_2Cl_2. The solution was washed with water and the product was isolated and characterised spectroscopically (see below).

The very fast reactions of **4a** and **4b** with Me_2NH were repeated with quenching after just 15 s by addition to an excess of 1.0 mol dm^{-3} hydrochloric acid. The organic layer was separated, dried over anhydrous Na_2CO_3, and examined by ^{31}P NMR spectroscopy. The diamide product accounted for 75–80% of the total spectrum, implying that *ca*. two half lives had elapsed before quenching. (Only 6–8% substrate remained but the substantial by-products were supposed to be a consequence of quenching as they were not present in reactions allowed to proceed to completion.)

Phosphonamidic chloride deuterium incorporation experiments

The salts $R_2ND_2^+Cl^-$ (R = Me or Et) were prepared by dissolving $R_2NH_2^+Cl^-$ in D_2O (2 equiv.) and evaporating to dryness, and repeating four more times.

A solution of Me_2ND in $CDCl_3$ was obtained by adding NaOD (6 mmol) in D_2O (0.2 ml) to a stirred solution of $Me_2ND_2^+Cl^-$ (0.42 g, 5 mmol) in $CDCl_3$ (1.9 ml) at 0 °C. The organic layer was separated, shaken with solid NaCl, and dried over anhydrous K_2CO_3 and then over a little 3 Å molecular sieve. A sample was examined by ^1H NMR spectroscopy to assess the deuterium content of the amine (NH integral 0.2 H) and its concentration (Me_2N integral relative to added CH_2Cl_2; 1.9 mol dm^{-3}).¶

A solution of Et_2ND in $CDCl_3$ was obtained by shaking Et_2NH (1.1 g, 15 mmol) in $CDCl_3$ (5 ml) with D_2O (20 mmol) containing a little NaCl. The organic layer was collected and the process was repeated four more times. The resulting solution was dried and analysed as above (NH integral 0.15 H; amine concentration 2.5 mol dm^{-3} but 2.0 mol dm^{-3} after dilution with more $CDCl_3$).¶

The behaviour of the phosphonamidic chlorides **4** and **10** (12–16 μmol) with R_2ND (R = Me or Et) in $CDCl_3$ (containing 0.1 mol dm^{-3} $R_2ND_2^+Cl^-$) was examined using the solutions obtained above (65 μl portions) in capillary NMR tubes. At

¶ The deuterium content was not as high as expected, apparently because some D/H exchange occurred with the molecular sieve.

intervals the ^{31}P and ^{1}H NMR spectra were recorded and from them the extent of reaction and the deuterium content of the substrate (and sometimes the product) were estimated (see Results and discussion). The temperature was generally maintained at *ca.* 30 °C (or 18 °C for **10b** + Me_2ND) but no attempt was made to obtain precise rate data. Selected results are shown in Table 2.

Phosphonamidic chloride competition experiments

The phosphonamidic chloride **4** or **10** (10–15 μmol) was added to an equimolar mixture of Me_2NH and Et_2NH (each 2.0 mol dm^{-3}) in $CHCl_3$ (containing $Me_2NH_2^+Cl^-$ and $Et_2NH_2^+Cl^-$, each 0.05 mol dm^{-3}) (150–250 μl) at *ca.* 30 °C. After several hours (days for **10a**; reaction conducted in sealed ampoule) volatile material was evaporated and the residue was dissolved in $CDCl_3$. The NMe_2 : NEt_2 product ratio was determined by ^{31}P NMR spectroscopy. The experiments with **10a** and **10b** were also carried out with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.2 mol dm^{-3}) present in the reaction medium (amine hydrochloride omitted).

Phosphonamidic chloride reaction products

The identities of the phosphonic diamide products **5** and **12** from the rate studies were confirmed as detailed below (crystallised from CH_2Cl_2–light petroleum unless indicated otherwise).

From **4a** and Me_2NH, *product* **5a** (R = Me), mp 78–80 °C (lit.,[25] 79.5–80.5 °C); *m*/*z* 226 (M^+, 20%) and 135 ($M^+ - CH_2Ph$, 100); $\delta_P(CDCl_3)$ 34.2; $\delta_H(CDCl_3$; 250 MHz) 7.4–7.2 (5 H, m), 3.21 (2 H, d, J_{PH} 17) and 2.54 (12 H, d, J_{PH} 9.5); ν_{max}(melt)/cm^{-1} 1210 and 1190 (P=O).

From **4a** and Et_2NH, *product* **5a** (R = Et), bp 150 °C (oven temp.) at 0.2 mmHg, solidifies at room temperature; *m*/*z* 254 (M^+, 11%) and 163 ($M^+ - CH_2Ph$, 100); $\delta_P(CDCl_3)$ 33.3; $\delta_H(CDCl_3$, 250 MHz) 7.4–7.15 (5 H, m), 3.18 (2 H, d, J_{PH} 16.5), 2.97 (4 H, m), 2.54 (6 H, d, J_{PH} 9.5) and 1.00 (6 H, t, J_{HH} 7); ν_{max}(melt)/cm^{-1} 1220 (P=O) (Found: M^+, 254.1548; $C_{13}H_{23}N_2OP$ requires *M*, 254.1548).

From **4b** and Me_2NH, *product* **5b** (R = Me), mp 132–134 °C; *m*/*z* 271 (M^+, 13%), 151 (14) and 135 ($M^+ - ArCH_2$, 100); $\delta_P(CDCl_3)$ 32.3; $\delta_H(CDCl_3$; 250 MHz) 8.17 (2 H, d, J_{HH} 8.5), 7.50 (2 H, dd, J_{PH} 2, J_{HH} 8.5), 3.30 (2 H, d, J_{PH} 17) and 2.57 (12 H, d, J_{PH} 10); ν_{max}(Nujol)/cm^{-1} 1520 and 1350 (NO_2), 1210 and 1190 (P=O) (Found: M^+, 271.1085. $C_{11}H_{18}N_3O_3P$ requires *M*, 271.1086).

From **4b** and Et_2NH, *product* **5b** (R = Et), mp 114–116 °C (from ether); *m*/*z* 299 (M^+, 15%) and 163 ($M^+ - ArCH_2$, 100); $\delta_P(CDCl_3)$ 31.4; $\delta_H(CDCl_3$; 250 MHz) 8.18 (2 H, d, J_{HH} 8.5), 7.53 (2 H, dd, J_{PH} 2, J_{HH} 8.5), 3.28 (2 H, d, J_{PH} 17), 2.97 (4 H, m), 2.58 (6 H, d, J_{PH} 9.5) and 1.03 (6 H, t, J_{HH} 7); ν_{max}(Nujol)/cm^{-1} 1515 and 1350 (NO_2), 1215 and 1200 (P=O) (Found: M^+, 299.1398. $C_{13}H_{22}N_3O_3P$ requires *M*, 299.1399).

From **10a** and Me_2NH, *product* **12a** (R = Me), mp 182–184 °C; *m*/*z* 302 (M^+, 7%) and 135 ($M^+ - Ph_2CH$, 100); $\delta_P(CDCl_3)$ 32.2; $\delta_H(CDCl_3$; 250 MHz) 7.64 (4 H, d, J_{HH} 7), 7.35–7.15 (6 H, m), 4.345 (1 H, d, J_{PH} 15) and 2.40 (12 H, d, J_{PH} 9); ν_{max}(Nujol)/cm^{-1} 1200 and 1185 (P=O) (Found: M^+, 302.1548. $C_{17}H_{23}N_2OP$ requires *M*, 302.1548).

From **10a** and Et_2NH, *product* **12a** (R = Et), mp 152–154 °C; *m*/*z* 330 (M^+, 8%) and 163 ($M^+ - Ph_2CH$, 100); $\delta_P(CDCl_3)$ 31.7; $\delta_H(CDCl_3$; 250 MHz) 7.66 (2 H, d, J_{HH} 8), 7.63 (2 H, d, J_{HH} 8), 7.3–7.15 (6 H, m), 4.33 (1 H, d, J_{PH} 16), 2.86 (4 H, m), 2.39 (6 H, d, J_{PH} 9) and 0.86 (6 H, t, J_{HH} 7); ν_{max}(Nujol)/cm^{-1} 1185 (P=O) (Found: M^+, 330.1861. $C_{19}H_{27}N_2OP$ requires *M*, 330.1861).

From **10b** and Me_2NH, *product* **12b** (R = Me), mp *ca.* 190 °C (softens at 180 °C); *m*/*z* 347 (M^+, 11%), 196 (65), 166 (50), 165 (40) and 135 ($M^+ - ArPhCH$, 100); $\delta_P(CDCl_3)$ 31.0; $\delta_H(CDCl_3$; 250 MHz) 8.15 (2 H, d, J_{HH} 9), 7.86 (2 H, d, J_{HH} 9), 7.61 (2 H, d, J_{HH} 7), 7.35–7.2 (3 H, m), 4.47 (1 H, d, J_{PH} 15), 2.435 (6 H, d, J_{PH} 9) and 2.40 (6 H, d, J_{PH} 9); ν_{max}(Nujol)/cm^{-1} 1520 and 1355 (NO_2), 1180 (P=O) (Found: M^+, 347.1398. $C_{17}H_{22}N_3O_3P$ requires *M*, 347.1399).

From **10b** and Et_2NH, *product* **12b** (R = Et), mixture of diastereoisomers (melts 153–166 °C); *m*/*z* 375 (M^+, 8%), 212 (15), 196 (55), 179 (25) and 163 ($M^+ - ArPhCH$, 100); $\delta_P(CDCl_3)$ 30.4 and 30.3 (ratio 1.2 : 1); $\delta_H(CDCl_3$; 250 MHz) 8.15 (2 H, d, J_{HH} 9), 7.88 (major) and 7.85 (total 2 H; both d, J_{HH} 9), 7.60 and 7.59 (major) (total 2 H; both d, J_{HH} 7), 7.35–7.2 (3 H, m), 4.46 and 4.45 (major) (total 1 H; both d, J_{PH} 15), 2.88 (4 H, m), 2.425 and 2.39 (major) (total 6 H; both d, J_{PH} 8.5), 0.90 (major) and 0.87 (total 6 H; both t, J_{HH} 7); ν_{max}(Nujol)/cm^{-1} 1515 and 1350 (NO_2), 1170 (P=O) (Found: M^+, 375.1712. $C_{19}H_{26}N_3O_3P$ requires *M*, 375.1712). Prior to crystallisation the highfield ^{31}P NMR diastereoisomer was in excess (ratio *ca.* 1 : 2).

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