Associative and Dissociative Mechanisms for the Reactions of *N*-t-Butyl-*P*-phenylphosphonamidic Chloride with Isopropylamine and t-Butylamine: Competitive, Kinetic, and Stereochemical Studies

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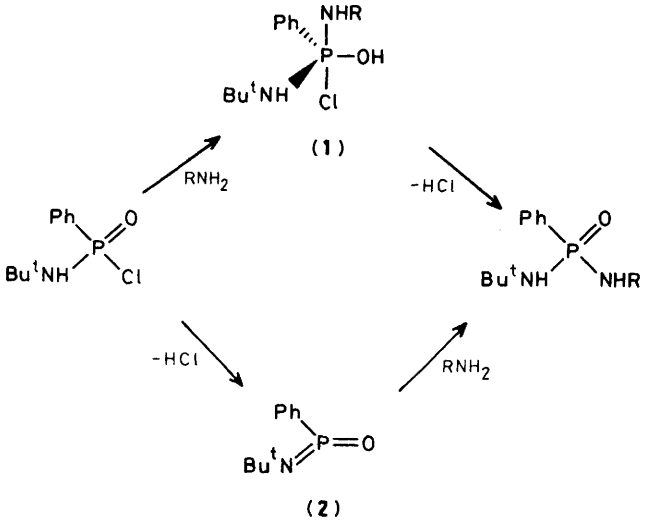
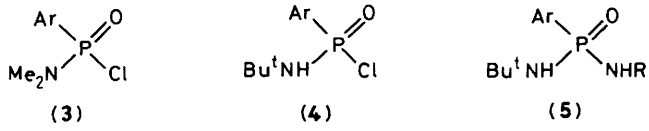
The substitution reactions of *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) with isopropylamine and t-butylamine (or t-pentylamine in stereochemical experiments) in MeCN at 0 °C can apparently proceed by one associative and two dissociative mechanisms *viz:* $S_N2(P)$ [first-order in amine (nucleophile); high selectivity for Pr^iNH_2 in Pr^iNH_2–Bu^tNH_2 competitive experiments; complete stereospecificity]; simple elimination–addition with a free (symmetrically solvated) metaphosphonimidate intermediate [first-order in amine (base); low selectivity; practically complete racemisation]; preassociation elimination–addition [second-order in amine (nucleophile and base); low selectivity; extensive but not complete racemisation].

There are in principle two types of mechanism by which a phosphonamidic chloride containing an NH group can undergo nucleophilic substitution. One is the normal associative $S_N2(P)$ mechanism, with a five-co-ordinate phosphorane intermediate [*e.g.* (**1**) in Scheme 1].[1] The other is a dissociative elimination–addition mechanism (EA), with a three-co-ordinate metaphosphonimidate intermediate [*e.g.* (**2**) in Scheme 1] analogous to monomeric metaphosphate.[2–4] A dissociative mechanism of this kind is now generally accepted [2,3] for the alkaline hydrolysis of some phosphoric acid derivatives.[5] For phosphonamidic chlorides there is relatively little information † but it does seem that the EA mechanism can compete with $S_N2(P)$, and may become dominant, even in aprotic media.[6,7] Thus, for example, a recent study revealed marked differences between the NHBu^t phosphonamidic chlorides (**4**) and the corresponding NMe_2 compounds (**3**) in their reactions with isopropylamine and t-butylamine.[7] The NMe_2 compounds, which cannot react by elimination–addition, displayed the sort of features expected for



Scheme 1.

† Phosphonamidic chlorides are distinguished from the better known phosphoramidic chlorides by the presence of a C–P bond.



a; Ar = phenyl **b**; Ar = *o*-tolyl **c**; Ar = mesityl

reaction by $S_N2(P)$ *e.g.* they became progressively less reactive as the *P*-aryl group became more sterically restricting (Ar = phenyl, *o*-tolyl, mesityl, 2,4,6-tri-isopropylphenyl) and they reacted much faster with isopropylamine than with the more hindered t-butylamine. The NHBu^t compounds, by contrast, were not retarded by steric crowding—in fact they showed pronounced steric acceleration—and did not discriminate much between isopropylamine and t-butylamine. In that study the reactions were all carried out using an excess of the amine as a 1.0M solution in acetonitrile at 0 °C. This new investigation has been prompted by the discovery that at lower concentrations of amine some of the NHBu^t compounds become quite strongly discriminating between isopropylamine and t-butylamine. It has resulted in a better understanding of the nature of the EA mechanism.

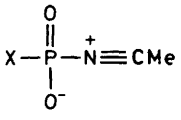
Results and Discussion

Competitive Experiments.—Competitive reactions were carried out by adding the phosphonamidic chlorides (**4**) to mixtures of Pr^iNH_2 and Bu^tNH_2 in MeCN at 0 °C. Various concentrations of amine were used but the Pr^iNH_2/Bu^tNH_2 ratio was always 1:1 and each amine was always in 10-fold excess with respect to the substrate. The ratios of the products (**5**; R = Pr^i) and (**5**; R = Bu^t) (n^i/n^t) were measured by ^{31}P n.m.r. spectroscopy (Table 1) and checked by g.l.c.

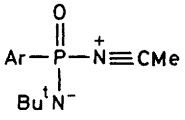
Table 1. Competitive reactions of ArP(O)(Cl)NHBu^t with Pr^iNH_2–Bu^tNH_2 (1:1) in MeCN at 0 °C. Dependence of NHPr^i/NHBu^t product ratio (n^i/n^t) on amine concentration

Each amine (M)	Phenyl n^i/n^t	*o*-Tolyl n^i/n^t	Mesityl n^i/n^t
2.0	1.75		
1.0	2.2	2.0	1.7
0.5	3.2	3.2	1.65
0.25	5.1	4.6	1.75
0.125	10.5	7.5	1.8

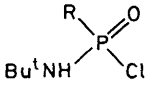
In a solution 2M in each amine the *P*-phenyl substrate (**4a**) shows only a small preference for reaction with Pr^iNH_2 (n^i/n^t = 1.75). This points to an EA mechanism with the products being formed by rapid nucleophilic attack of the amines on a reactive and sterically accessible three-co-ordinate metaphosphonimidate intermediate. Given that the NMe_2 compound (**3a**) shows a very large preference for reaction with Pr^iNH_2 ($n^i/n^t \geqslant 100$)[7] it seems that $S_N2(P)$ can be making little contribution to the overall reaction of (**4a**) under these conditions. As the concentration of amine is reduced the selectivity for Pr^iNH_2 increases quite dramatically (Table 1). The *P*-*o*-tolyl substrate (**4b**) shows similar behaviour although the change in selectivity is not quite as marked. These results imply either that the EA mechanism becomes increasingly selective at lower amine concentrations or that a different and more selective mechanism—presumably $S_N2(P)$—becomes increasingly important. Concerning the first of these possibilities, there have been suggestions that monomeric metaphosphate anion[8] and methyl metaphosphate[9] are stabilised in MeCN by forming complexes (**6**; X = O^- or OMe) with the solvent. It could be that metaphosphonimidate intermediates form similar complexes (**7**) and that these relatively stable species have a relatively high preference for reaction with Pr^iNH_2. At lower



(**6**)



(**7**)



(**8**)

amine concentrations a greater proportion of the metaphosphonimidate would react *via* the complex, rather than directly with the amines, and a greater selectivity would therefore be observed. While we do not discount the possibility of such complexation, there are two reasons for believing it is not the primary cause of the observed changes in selectivity. The first concerns the behaviour of the *P*-*o*-tolyl substrate (**4b**) when CH_2Cl_2 was used as solvent in place of MeCN. It is difficult to imagine any substantial stabilisation of the metaphosphonimidate by co-ordination with CH_2Cl_2 yet the selectivity of the reaction still increased substantially when the concentration of amine was reduced:

Each amine (M)	0.5	0.25	0.125
n^i/n^t in CH_2Cl_2	2.6	4.1	5.1

The second reason concerns the behaviour of the *P*-mesityl substrate (**4c**). Like the phenyl and *o*-tolyl compounds it shows rather little selectivity at high amine concentrations (Table 1). In this instance however the small preference for Pr^iNH_2 remains essentially unchanged (n^i/n^t = 1.7 ± 0.1) when the concentration of amine is reduced. There seems no reason why complexation of the metaphosphonimidate should be much less significant in the reactions of the mesityl compound in which case it can hardly be responsible for the changes in the selectivity observed with the other substrates. In contrast to complexation the extent to which $S_N2(P)$ competes with the EA mechanism certainly will be very different in the case of the mesityl compound. The two *ortho* methyl substituents will not only reduce its $S_N2(P)$ reactivity (steric hindrance) but will also increase its EA reactivity (steric acceleration). The retardation of $S_N2(P)$ is possibly quite small [*cf.* the NMe_2 substrates (**3**)[7]] but the acceleration of EA is not; in our earlier study the mesityl substrate was found to react with Bu^tNH_2 50—100 times faster than the phenyl or *o*-tolyl compounds.[7] It is therefore perfectly reasonable to envisage $S_N2(P)$ playing an important part in the reactions of the phenyl and *o*-tolyl compounds but being of no significance (at the concentrations of amine employed) in the reactions of the mesityl substrate. To find support for this idea we have looked again at the reactions of the *P*-alkylphosphonamidic chlorides (**8**)[6] with Pr^iNH_2–Bu^tNH_2 (1:1) to see which if any of them also exhibit increased selectivity at low amine concentrations. In MeCN at 0 °C the product ratios (n^i/n^t) as measured by ^{31}P n.m.r. spectroscopy were as follows:

R in RP(O)(Cl)NHBu^t	Me	Et	Pr^i	Bu^t
Each amine 1.0M; n^i/n^t	3.3	2.3	1.4	1.35
Each amine 0.125M; n^i/n^t	25	14	1.6	1.4

Clearly there is a large increase in selectivity for the unhindered methyl and ethyl substrates but little or none at all for the more crowded isopropyl and t-butyl compounds. This is precisely what would be expected if increased selectivity is a consequence of increased competition from $S_N2(P)$.

The problem now is to find a satisfactory explanation for the reduced importance of the EA mechanism relative to $S_N2(P)$ at lower concentrations of amine. The mechanisms shown in Scheme 1 should both be first-order in amine, albeit that in one the amine acts initially as a nucleophile, in the other as a base. Yet to account for the observed changes in selectivity it is necessary to postulate that the EA mechanism is of a higher order in amine than is $S_N2(P)$. Evidence on this point was sought by examining the influence of amine concentration on the rates of the reactions.

Kinetic Studies.—The rates of the reactions of the *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) with Pr^iNH_2 and Bu^tNH_2 in MeCN at 0 °C were measured using different concentrations of amine. In each experiment the amine was present initially in 10-fold excess with respect to the substrate so that its concentration remained practically constant throughout the reaction. Lacking a satisfactory method for continuous monitoring, the progress of reaction had to be followed by removing samples, quenching them, and analysing. Quenching was accomplished by mixing the sample with a large excess of MeOH (40 mol/mol amine). Control experiments showed that when the substrate was added directly to a mixture of the amine and MeOH (large excess) in MeCN it was converted entirely into the methyl phosphonamidate PhP(O)(OMe)NHBu^t; none of the phosphonic diamide (**5a**) was formed by reaction with the amine. It follows that the quenching procedure is efficient in stopping diamide formation and that the amount of methyl phosphonamidate in a quenched sample corresponds to the amount of substrate remaining at the time of quenching. Analysis of the quenched samples was accomplished by g.l.c. This allowed both the phosphonamidate and the phosphonic diamide to be determined. To assist in the analysis a small amount of *trans*-stilbene was included in each reaction mixture as an internal g.l.c. standard. The areas of the peaks representing the methyl phosphonamidate (corresponding to starting material) (A^S) and the phosphonic diamide (product) (A^P) were measured relative to the area of the standard peak. In each case

Table 2. Observed rate constants for reactions of PhP(O)(Cl)NHBu^t with Pr^iNH_2 (k^i_{obs}) or Bu^tNH_2 (k^t_{obs}) at different concentrations in MeCN at 0 °C[a]

$[RNH_2]$/M	$10^4k^i_{obs}/s^{-1}$	$10^4k^t_{obs}/s^{-1}$
1.0	348 ± 8	107 ± 4
0.5	153 ± 4	28.5 ± 1.2
0.25	69 ± 1.5	8.4 ± 0.3
0.125	31.5 ± 1	2.7 ± 0.15

[a] RNH_2 10-fold molar excess with respect to substrate.

Table 3. Rate constants k_1 and k_2 derived from slopes of lines in Figure 1

Pr^iNH_2	$k_1^i = 23 \times 10^{-3}$ s^{-1} M^{-1}	$k_2^i = 11 \times 10^{-3}$ s^{-1} M^{-2}
Bu^tNH_2	$k_1^t = 1.0 \times 10^{-3}$ s^{-1} M^{-1}	$k_2^t = 9.5 \times 10^{-3}$ s^{-1} M^{-2}

5—8 samples were examined during the time taken for the reaction to reach 90—95% completion (1—140 min). For disappearance of starting material first-order plots of log A^S *vs.* time were linear, and from the slopes of the lines the values of the observed rate constant (k_{obs}) shown in Table 2 were deduced. For appearance of product plots of log $(A^P_\infty - A^P)$ were also reasonably linear but produced values of k_{obs} up to 20% smaller. Two factors—relatively serious irreversible adsorption of phosphonic diamides on the g.l.c. column and the need to use empirical infinity values—make these values of k_{obs} less reliable and no quantitative use was made of them.*

The values of k_{obs} in Table 2 show that the rate of reaction is more sensitive to the concentration of the amine with Bu^tNH_2 than with Pr^iNH_2 (40-fold and 11-fold changes respectively for an 8-fold change in amine concentration), and that for both reactions the observed order is between one and two with respect to the amine. This suggests that reaction occurs by parallel pathways having first- and second-order dependencies on amine, so that the observed rate is given by equation (1).

$$\text{Rate} = k_1[\text{PhP(O)(Cl)NHBu}^t][\text{RNH}_2] + k_2[\text{PhP(O)(Cl)NHBu}^t][\text{RNH}_2]^2 \quad (1)$$

Since in each experiment the amine was in excess and its concentration remained (approximately) constant throughout, k_{obs} can be represented by equation (2).

$$k_{obs} = k_1[\text{RNH}_2] + k_2[\text{RNH}_2]^2 \quad (2)$$

The equations (3) and (4), expressed in the form y = mx + c, follow directly.

$$k_{obs}[\text{RNH}_2]^{-1} = k_2[\text{RNH}_2] + k_1 \quad (3)$$

$$k_{obs}[\text{RNH}_2]^{-2} = k_1[\text{RNH}_2]^{-1} + k_2 \quad (4)$$

Using the data in Table 2, plots of these equations were constructed for each amine; they are shown in Figure 1(a) and (b). The slopes of the lines in (a) and (b) give, respectively, the values of k_2 and k_1; these are shown in Table 3. The values of k_2 and k_1 are also given by the intercepts in (b) and (a) respectively.

If k_1 relates to the $S_N2(P)$ mechanism it should be much larger for Pr^iNH_2 than for Bu^tNH_2. This is seen to be the case, albeit that the difference ($k_1^i \sim 23k_1^t$) is not as great as might have been expected. In the competitive experiments, the part of the substrate that reacts by $S_N2(P)$ will give the products derived from the two amines in a ratio equal to the ratio of the k_1 values, *i.e.* with high selectivity. The pathway associated with k_1 will be considered in more detail later; of immediate concern is the pathway corresponding to k_2.

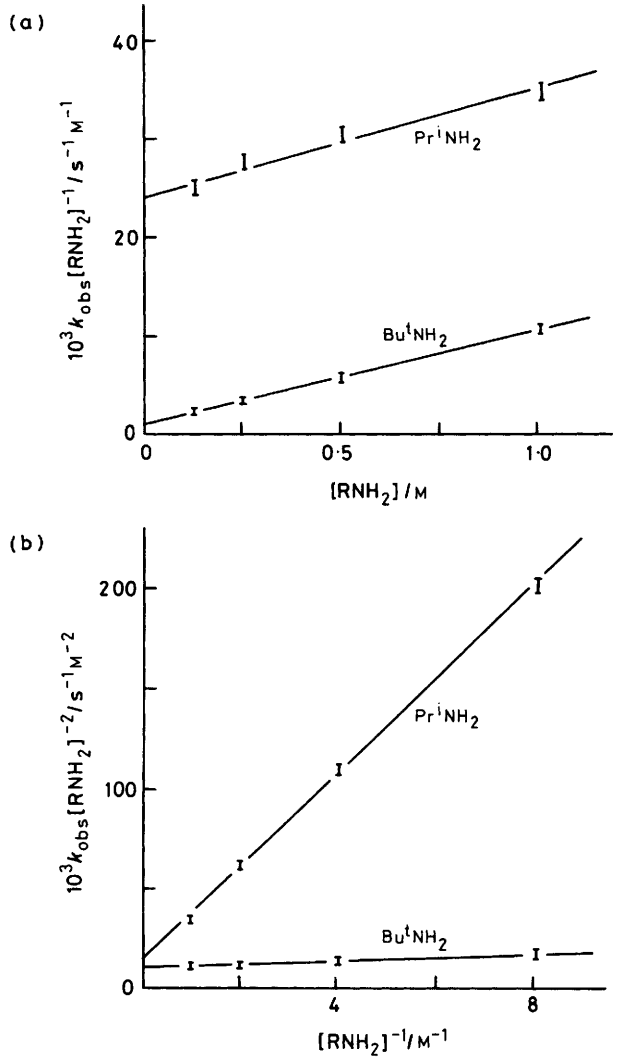
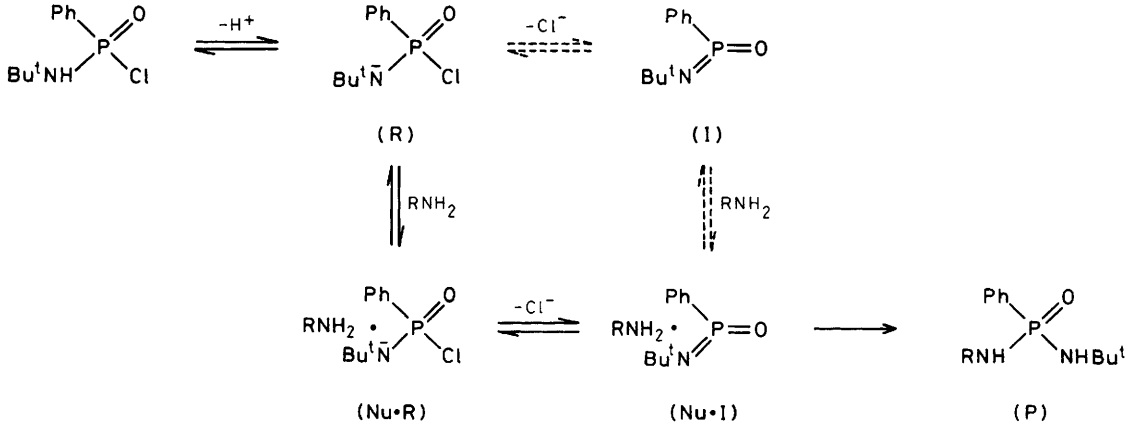


Figure 1. Reactions of PhP(O)(Cl)NHBu^t with Pr^iNH_2 and Bu^tNH_2 in MeCN at 0 °C. Dependence of k_{obs} on amine concentration expressed in the form (a) $k_{obs}[RNH_2]^{-1} = k_2[RNH_2] + k_1$; (b) $k_{obs}[RNH_2]^{-2} = k_1[RNH_2]^{-1} + k_2$

Pathway having a Second-order Dependence on Amine.—The second-order in amine term (k_2) must correspond to the low-selectivity pathway revealed by the competitive experiments. If it were a simple EA mechanism (Scheme 1) there would probably be no appreciable difference in rate for Pr^iNH_2 and Bu^tNH_2 since their basicities, at least in water (10.63 and 10.45 respectively [10]), are so similar. The values of k_2 shown in Table 3 are certainly similar—sufficiently so that the difference could be accommodated by the experimental uncertainty—but the probability is that they really are not the same. That being so, the slightly greater reactivity of Pr^iNH_2 may be of mechanistic significance. In any case, the very fact that this pathway is second-order in amine indicates that it cannot be a simple EA mechanism. Rather, it must involve the amine, in a kinetically significant way, not only as a base but also as a nucleophile. This nucleophilic involvement of the amine in the EA mechanism is of great importance; it reveals much about the nature of the mechanism and the reactivity of the metaphosphonimidate intermediate.

Jencks [11] has explained most clearly how the choice of a reaction mechanism depends on the lifetimes of the intermediates that may be formed. The comments below, and

* Some of the discrepancies between the values of k_{obs} deduced from disappearance of starting material and appearance of product seem too large to be dismissed as experimental error, especially as the discrepancies are all in the same direction. It could be that this is of some chemical significance but at present we do not know what. The mechanistic analysis is based entirely on the values of k_{obs} deduced from disappearance of starting material, although essentially the same conclusions are reached if it is based entirely on the values deduced from appearance of product.



Scheme 2.†

the mechanism shown in Scheme 2, summarise our attempts to apply his general insights to the particular case of the EA reactions of the phosphonamidic chlorides (**4**). For convenience the elimination of HCl is considered to be a stepwise process rather than concerted; the starting material for metaphosphonimidate formation is then in effect the conjugate base of the substrate (Reactant R).

(i) The metaphosphonimidate is not stable enough to diffuse out of the solvent cage in which it is formed; if it were the reaction would proceed *via* the free metaphosphonimidate (Intermediate I) and the nucleophile would not be involved until after the rate-limiting step.

(ii) Because it is too unstable to diffuse into the bulk of the solvent the metaphosphonimidate will simply revert to starting material (Reactant R) if the nucleophile is not already present when it is formed.

(iii) To form product (P) the EA reaction must proceed by a preassociation mechanism, *i.e.* the starting material and amine (Nucleophile Nu) must be assembled into an encounter complex (Nu•R) before the leaving group (Cl) is expelled in the rate-limiting step.†

(iv) The preassociation EA mechanism may be stepwise or concerted. As depicted in Scheme 2 it is stepwise, *i.e.* the encounter complex forms product non-concertedly *via* a metaphosphonimidate intermediate generated in the presence of the nucleophile. In reality non-concertedness is possible only if the metaphosphonimidate has a significant lifetime. If its lifetime is less than *ca.* 10^{-13} s (the time taken for a bond vibration) the preassociation EA mechanism is necessarily concerted *i.e.* the encounter complex forms product *via* a single transition state in which there is some bonding of phosphorus to both the incoming amine and the departing chlorine. Provided the transition state has much metaphosphonimidate character—bond breaking far advanced, bond making barely begun—this mechanism will still show only a slight dependence on the nucleophilicity of the amine, as required by the results of the competitive experiments and the similarity of the values of k_2^{i} and k_2^{t}. Our results do not allow distinction to be made between the concerted and stepwise preassociation mechanisms for the EA reaction.

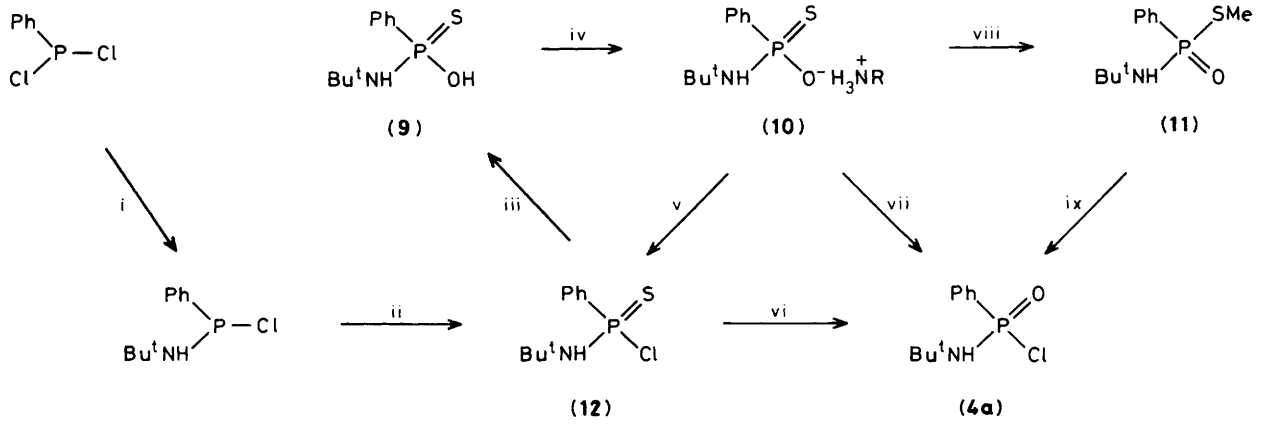
Pathway having a First-order Dependence on Amine.—For isopropylamine a substantial part of the reaction with the *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) proceeds by the pathway that is first-order in amine ($k_1^{i} \sim 2k_2^{i}$). At low amine concentrations, where this pathway is dominant, the Pr^iNH_2–Bu^tNH_2 competitive experiments reveal quite high selectivity towards the less sterically demanding Pr^iNH_2 (Table 1). It is therefore perfectly reasonable to postulate that with Pr^iNH_2 the first-order term corresponds to the $S_N2(P)$ mechanism. As noted earlier, however, the value of k_1 for Bu^tNH_2 is only 23 times less than for Pr^iNH_2. This difference is not as great as might be expected for $S_N2(P)$ [Pr^iNH_2 reacts *ca.* 100 times faster than Bu^tNH_2 with $PhP(O)(Cl)NMe_2$[7] and $Ph_2P(O)Cl$[6]] and it suggests that with Bu^tNH_2 the (small) first-order term may include a substantial contribution from a mechanism other than $S_N2(P)$. With this in mind some competitive reactions were carried out using di-isopropylamine and t-butylamine. Di-isopropylamine was chosen because it is even less nucleophilic than t-butylamine, *e.g.* with $Ph_2P(O)Cl$ it reacts at least 100 times more slowly [$S_N2(P)$ mechanism].[12] When the phosphonamidic chloride (**4a**) was allowed to react with dilute equimolar mixtures of Pr^i_2NH and Bu^tNH_2 in MeCN at 0 °C the product ratios (^{31}P n.m.r. spectroscopy) observed at various concentrations of amine were as follows:

[Each amine]/M	0.5	0.125	0.05
Product ratio $NHBu^t/NPr^i_2$	11	11	8.5

The kinetic data for Bu^tNH_2 ($k_2^{t} = 9.5k_1^{t}$) imply that at the highest of these concentrations the substrate reacts predominantly (>80%) by the pathway (preassociation EA) that is second-order in amine. Perhaps not surprisingly, even this dissociative mechanism shows considerable discrimination against the highly hindered Pr^i_2NH. At lower concentrations a greater proportion of the substrate will follow the pathway that is first-order in amine. To the extent that this is $S_N2(P)$ it will give only the product derived from Bu^tNH_2. However, the observed $NHBu^t/NPr^i_2$ ratio does not increase; if anything it decreases. It would be wrong to attach great significance to results obtained with amines that differ in type (primary *vs.* secondary) but the implication is surely that much of the first-order term for Bu^tNH_2 corresponds to a mechanism other than $S_N2(P)$. An interesting possibility is that it is the simple (non-preassociation) EA mechanism with a free metaphosphonimidate intermediate [Scheme 2, top pathway (– – – →)]. Further evidence on this point will be presented later.

Relation between Results of Kinetic Studies and Competitive Experiments.—By making certain assumptions it is possible to estimate theoretical product ratios for the Pr^iNH_2–Bu^tNH_2 competitive reactions of *N*-t-butyl-*P*-phenylphosphonamidic

† In Scheme 2 the formation of the complex (Nu•R) is depicted as combination of the conjugate base of the substrate (Reactant R) with the nucleophile (Nu). As pointed out by a referee, this complex may well be formed by association of the neutral substrate with the nucleophile before the base removes the proton.



Scheme 3. *Reagents:* i, 2Bu^{t}NH$_2$ (– Bu^{t}NH$_3$Cl); ii, S (PhH, 80 °C); iii, HO$^-$–H$_2$O then H$_3$O$^+$; iv, (*S*)-PhCHMeNH$_2$; v, (COCl)$_2$; vi, O$_3$ (–78 °C); vii, COCl$_2$; viii, MeI; ix, SO$_2$Cl$_2$ or Cl$_2$

chloride (**4a**) in terms of the experimental rate constants k_1 and k_2. Each product can be formed by three mechanisms: preassociation EA (first-order in the appropriate nucleophile and first-order in base); simple EA with a free metaphosphonimidate intermediate (first-order in base); $S_N2(P)$ (first-order in the appropriate nucleophile). The first of these mechanisms is associated with k_2, the other two together with k_1. Let $k_{1'}$ be the part of k_1 corresponding to simple EA [and $(k_1 - k_{1'})$ the part corresponding to $S_N2(P)$]. Assuming that the two amines can act with equal efficiency as the base in the preassociation EA mechanism and that the free metaphosphonimidate is trapped equally well by the two amines, then because the concentrations of Pr^{i}NH$_2$ and Bu^{t}NH$_2$ are equal the rates of formation of the NHPr^i and NHBu^t products in the competitive experiments are as shown in equations (5) and (6), where [RNH$_2$] is the total amine concentration.

$$\text{Rate}^{\text{NHPr}^i} = k_2^i[\text{Pr}^i\text{NH}_2][\text{RNH}_2] + 0.5\{k_{1'}^i[\text{Pr}^i\text{NH}_2] + k_{1'}^t[\text{Bu}^t\text{NH}_2]\} + (k_1^i - k_{1'}^i)[\text{Pr}^i\text{NH}_2] \quad (5)$$

$$\text{Rate}^{\text{NHBu}^t} = k_2^t[\text{Bu}^t\text{NH}_2][\text{RNH}_2] + 0.5\{k_{1'}^i[\text{Pr}^i\text{NH}_2] + k_{1'}^t[\text{Bu}^t\text{NH}_1]\} + (k_1^t - k_{1'}^t)[\text{Bu}^t\text{NH}_2] \quad (6)$$

Since [Pr^{i}NH$_2$] = [Bu^{t}NH$_2$] the NHPr^i/NHBu^t product ratio is therefore given by the expression (7).

$$\frac{\text{NHPr}^i}{\text{NHBu}^t} = \frac{k_2^i[\text{RNH}_2] + 0.5(k_{1'}^t - k_{1'}^i) + k_1^i}{k_2^t[\text{RNH}_2] + 0.5(k_{1'}^i - k_{1'}^t) + k_1^t} \quad (7)$$

With the further assumption that the two amines are equally effective (as bases) in bringing about reaction by the simple EA mechanism, *i.e.* that $k_{1'}^i = k_{1'}^t$, this simplifes to the expression (8).

$$\frac{\text{NHPr}^i}{\text{NHBu}^t} = \frac{k_2^i[\text{RNH}_2] + k_1^i}{k_2^t[\text{RNH}_2] + k_1^t} \quad (8)$$

The competitive experiments employed concentrations of each amine of 2.0, 1.0, 0.5, 0.25, and 0.125M, *i.e.* total amine concentrations [RNH$_2$] of 4.0, 2.0, 1.0, 0.5, and 0.25M. Substituting the values of the rate constants from Table 3 into equation (8) the theoretical product ratios at the appropriate concentrations become NHPr^i/NHBu^t = 1.7, 2.3, 3.2, 5.0, and 7.6. The agreement between these values and the product ratios measured in the competitive experiments (Table 1) is generally very good. To some extent this may be fortuitous, but it does suggest that the values of k_1 and k_2 used in calculating the theoretical product ratios [and the assumptions on which the simple relationship (8) depends] are essentially correct.

Stereochemical Studies.—Knowledge of the stereochemistry of the substitution reactions of phosphonamidic chlorides would be useful for confirming (or refuting) the mechanistic picture developed above. More important, it could give valuable insight into the nature of the elimination–addition process. To obtain this knowledge it was necessary to prepare an optically active sample of *N*-t-butyl-*P*-phenylphosphonamidic chloride.

Several optically active phosphoric and phosphonic acid chlorides are reported in the literature but none of them contain an NH group attached to the phosphorus atom.[13] Some difficulty must be expected in obtaining optically active phosphonamidic chlorides because chlorine is such a good leaving group; even EtP(O)(Cl)OEt, which cannot react by elimination–addition, racemises rapidly in the presence of chloride ion.[14]

The key compound in our attempts to prepare the optically active phosphonamidic chloride was the phosphonamidothioic acid (**9**). This was obtained in good yield from phenylphosphonous dichloride (Scheme 3) and was converted into diastereoisomeric salts (**10**; R = CHMePh) with (*S*)-α-methylbenzylamine. The salt that crystallised out from ether was an 89:11 mixture of diastereoisomers (^{1}H n.m.r.); all attempts to increase the diastereoisomeric purity were thwarted by decomposition (P–N bond rupture). The salt (**10**) could be converted into the phosphonamidic dichloride (**4a**) by way of either the phosphonamidothioic chloride (**12**) or the *S*-methyl phosphonamidothioate (**11**) but the product in both cases turned out to be totally racemic. Treatment of the salt with phosgene[14] proved somewhat more successful; it gave the phosphonamidic chloride directly, with an enantiomer ratio 57:43 (^{1}H n.m.r.; see below). The enantiomeric excess could be increased greatly by recrystallisation but unfortunately the enrichment occurred in the mother liquor (the crystals were racemic) where impurities, probably hydrolysis products, also began to accumulate. Since impurities could give rise to false results in the stereochemical studies, it seemed prudent to settle for material of modest enantiomeric excess (64:36 enantiomer ratio) but good chemical purity.

Ideally the stereochemical investigation should have employed the same amines as were used in the competitive experiments and kinetic studies. For Pr^{i}NH$_2$ there was no problem but with Bu^{t}NH$_2$ the diamide product (**5a**; R = Bu^t) lacks chirality. A replacement for Bu^{t}NH$_2$ was obviously

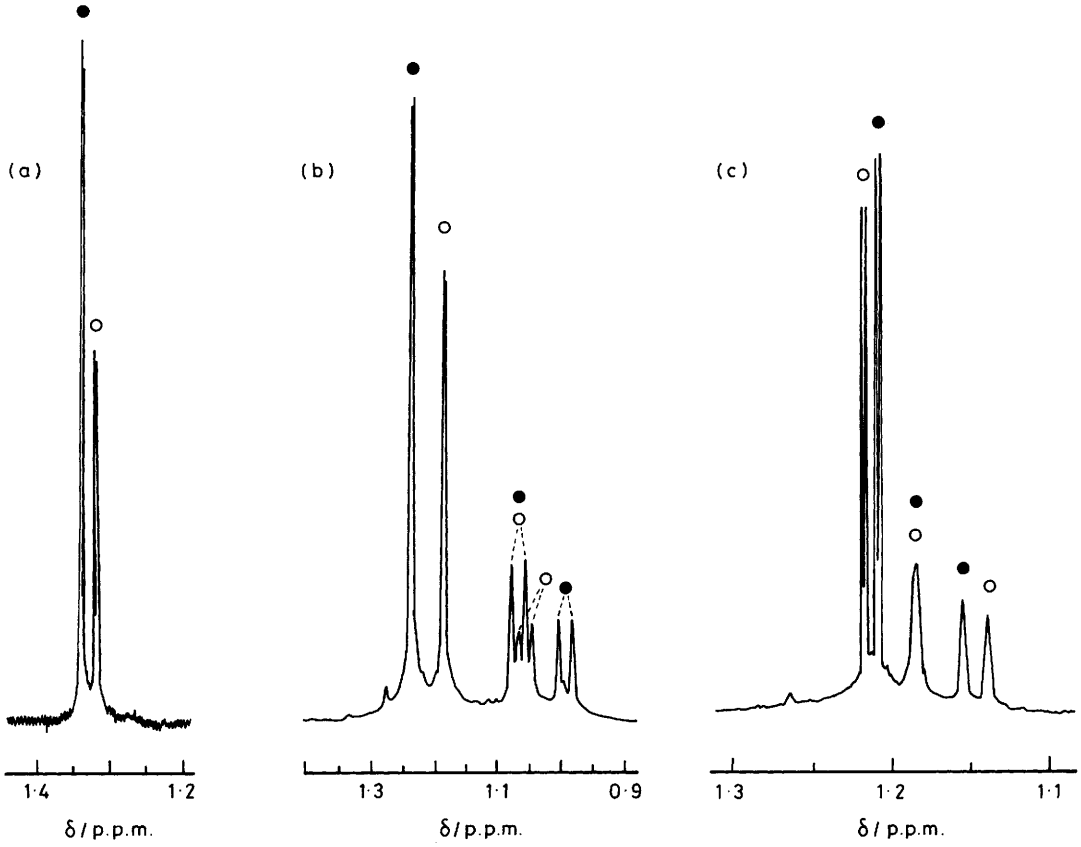
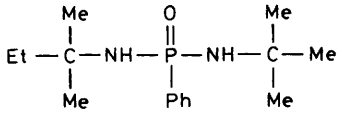


Figure 2. ^{1}H N.m.r. spectra ($CDCl_3$; 300 MHz) in the presence of (−)-(*S*)-PhMeP(S)OH [2 equiv. in (a) and (b); 3 equiv. in (c)]: (a) PhP(O)(Cl)-NH*Bu*^{t} (64:36 enantiomer ratio); (b) PhP(O)(NHCH*Me*$_2$)NH*Bu*^{t} (58.5:41.5 enantiomer ratio); (c) PhP(O)(NHC*Me*$_2$Et)NH*Bu*^{t} (53:47 enantiomer ratio). Peaks assigned to major (●) and minor (○) enantiomers as indicated

needed. We chose to work with t-pentylamine ($EtMe_2CNH_2$) because its basicity and steric demands should be quite similar and the kinetic results obtained for Bu^tNH_2 should be more or less valid for this amine as well.

Enantiomer ratios were measured by ^{1}H n.m.r. spectroscopy. For the phosphonamidic chloride the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) induced separation of the *N*-t-butyl signals of the enantiomers but line broadening (slight at 90 MHz; severe at 300 MHz) reduced the precision of the measurements. The chiral complexing (hydrogen bonding) agent (−)-(*S*)-methylphenylphosphinothioic acid [PhMeP(S)OH][15] proved more satisfactory: when 2 equiv. was added to a solution of the phosphonamidic chloride in $CDCl_3$ the *N*-t-butyl signals of the enantiomers were seen to be sharp (both d, J_{PH} 0.8 Hz) and well separated (Δδ 0.020 p.p.m. at 300 MHz) and to have intensities in the ratio 64:36 (major enantiomer at lower field) [Figure 2(a)]. Optically active PhMeP(S)OH also induced ^{1}H n.m.r. non-equivalence of the enantiomers of the phosphonic diamide products (**5**; R = Pr^i) [*N*-t-butyl and one methyl in *N*-isopropyl; Figure 2(b)] and (**5**; R = $EtMe_2C$). In the latter case the phosphorus atom is chiral only by virtue of the fact that



one of the amide groups has an ethyl group on the carbon atom next to nitrogen where the other has a methyl group. Nonetheless, the spectrum obtained in the presence of the optically active acid (3 equiv.) showed clear separation of the signals for the *N*-t-butyl groups of the two enantiomers (Δδ 0.010 p.p.m. at 300 MHz; both d, J_{PH} 0.5 Hz) and also for one of the methyls in the *N*-t-pentyl group (Δδ 0.017 p.p.m.; both broadened s) [Figure 2(c)].

Having found a reliable method for the determination of enantiomeric excesses with reasonable precision (±2%) the partially resolved phosphonamidic chloride (**4a**) (enantiomer ratio 64:36) was treated with Pr^{i}NH$_2$ and t-pentylamine in MeCN over a wide range of concentrations. With both amines the same enantiomer was the major product at all concentrations, and the ratios of the enantiomers were as shown in Table 4.

For Pr^{i}NH$_2$ the kinetic results indicate that at 0.125M the mechanism that is first-order in amine is dominant (>90%). At this low amine concentration the reaction is now seen to proceed stereospecifically, *i.e.* the enantiomer ratio of the product is the same (within experimental error) as that of the reactant. For acyclic substrates with good leaving groups the stereochemical outcome of the associative $S_N2(P)$ mechanism is generally stereospecific inversion of configuration at phosphorus.[16] While we have no proof that the configuration has been inverted, the stereospecificity agrees with the inference from the competitive experiments *viz.* the pathway having a first-order dependence on amine is predominantly $S_N2(P)$ in the case of Pr^{i}NH$_2$. For t-pentylamine by contrast, the product formed at low concentrations of amine was found to be close to racemic. To exclude the possibility that this was simply due to rapid racemisation of the substrate (chloride exchange) under the conditions of the reaction a control experiment was carried out. This employed a low concentration of amine (0.25M) in MeCN

Table 4. Stereochemistry of reaction of PhP(O)(Cl)NHBu^t (enantiomer ratio 64:36) with isopropylamine or t-pentylamine in MeCN at 0 °C. Enantiomer ratio (^{1}H n.m.r.) of the diamide product formed at different concentrations of amine[a]

$[RNH_2]$/M	Isopropylamine Enantiomer ratio[b]	t-Pentylamine Enantiomer ratio[c]
0.05		51:49[d]
0.125	65:35	
0.25		52:48
0.5		52.5:47.5
1.0	61:39	53:47
2.0	58.5:41.5	
4.0	58.5:41.5	56.5:43.5
8.0	60.5:39.5	59.5:40.5
Neat	61:39	

[a] Amine in 10-fold molar excess with respect to substrate. [b] Major enantiomer gives low-field *N*-t-butyl signal with (−)-(*S*)-PhMeP(S)OH. [c] Major enantiomer gives high-field *N*-t-butyl signal with (−)-(*S*)-PhMeP(S)OH. [d] Some unidentified by-products were formed in this high-dilution experiment. They did not interfere with the ^{1}H n.m.r. analysis but their presence inevitably reduces confidence in the result.

at 0 °C, conditions under which the product with t-pentylamine was substantially racemic (Table 4). As information on the stereochemistry of the product was not required here Bu^{t}NH$_2$ was employed as the amine. When the reaction with Bu^{t}NH$_2$ was *ca.* 40% complete the stereochemistry of the remaining substrate was examined. To this end the solution was concentrated (0 °C) and a large excess of neat t-pentylamine was added. The reaction mixture was then *ca.* 8M in t-pentylamine. When the reaction with t-pentylamine was complete the enantiomer ratio of the *N*-t-butyl-*N'*-t-pentyl-*P*-phenylphosphonic diamide product was measured (^{1}H n.m.r.). It was found to be 59:41, the same (±0.5%) as the ratio observed in the original reaction of the optically active substrate with 8M-t-pentylamine (Table 4). This implies that no significant racemisation of the substrate occurred during the first part of the experiment, *i.e.* that the substrate is configurationally stable under the initial reaction conditions (0.25M-amine in MeCN). With this established the stereochemistry of the product formed with t-pentylamine can be taken as a true representation of the stereochemical course of the substitution reaction. At the lowest concentrations of t-pentylamine the product is almost completely racemic even though a substantial part of it will have been formed by the pathway that is first-order in amine (*ca.* 30% at 0.25M and 67% at 0.05M, based on the values of k_1 and k_2 for Bu^{t}NH$_2$). The principal first-order reaction cannot therefore be stereospecific S_N2(P). On the other hand it may well be completely non-stereospecific, as required if a free (symmetrically solvated) planar metaphosphonimidate intermediate is involved. This stereochemical result therefore adds credence to the suggestion that in the case of Bu^{t}NH$_2$ the reaction that is first-order in amine is simple (non-preassociation) elimination–addition.

The reaction that is second-order in amine (preassociation EA) assumes increasing importance at higher amine concentrations, so it should be possible to learn something of its stereochemistry from the remaining results in Table 4. There is, however, an important limitation. With 2M-Pr^{i}NH$_2$ the molar ratio of solvent (MeCN) to amine has already fallen to *ca.* 8:1 and with t-pentylamine it is even less. At high amine concentrations, therefore, it is probably no longer reasonable to think in terms of the substrate (or its conjugate base) undergoing reaction in a cage of solvent containing at most one molecule of nucleophile. That being so, the stereochemical results at high amine concentrations may be of little immediate mechanistic relevance.

For t-pentylamine it does seem clear that the second-order-in-amine reaction (dominant at 1.0M based on the values of k_1 and k_2 for Bu^{t}NH$_2$) proceeds with extensive racemisation. Likewise for Pr^{i}NH$_2$: given that the stereospecific S_N2(P) mechanism still makes substantial contributions at 1.0 and 2.0M-amine the stereochemistry of the product (Table 4) implies that the remaining reaction—preassociation EA—proceeds with a high degree of racemisation. Because of the modest enantiomeric excess of the substrate it is not possible to be more precise.

Extensive racemisation may seem surprising for a substitution involving preassociation of the reactants, especially as preassociation has been considered a possible reason for the inversion of configuration observed in some dissociative phosphoryl-transfer reactions.[17] However, monomeric metaphosphate is probably intrinsically more reactive (less long-lived) than a monomeric metaphosphonimidate, and in any case the reactions that gave inversion were carried out in hydroxylic media under solvolytic conditions—the nucleophile was the solvent—and are not really comparable. If the conjugate base of the phosphonamidic chloride reacts by a stepwise preassociation mechanism the nucleophile (amine) does not bond to phosphorus until the leaving group (chlorine) has become detached, so it should not be constrained to occupy any particular position relative to the leaving group in the preassociation complex. The proximity of the leaving group will presumably make one face of the metaphosphonimidate rather less accessible than the other, thus favouring somewhat inversion of configuration, but extensive racemisation is still an entirely reasonable result. In fact the lack of stereospecificity does not necessarily exclude even a concerted preassociation mechanism: as Jencks has pointed out,[11] if the transition state is open ('exploded') there may be no necessity for the nucleophile to attack opposite the leaving group.

Conclusions

The substitution reactions of *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) with aliphatic amines can proceed by both associative and dissociative pathways. The associative pathway displays the characteristics expected of an S_N2(P) mechanism, *i.e.* it is first-order in amine (nucleophile), it discriminates strongly against bulky amines (Bu^{t}NH$_2$), and it proceeds with complete stereospecificity. The dissociative pathway is less straightforward and seems to embrace two mechanisms, both of which involve elimination–addition. Both discriminate rather poorly between competing amines (Pr^{i}NH$_2$ and Bu^{t}NH$_2$) and form the substitution product non-stereospecifically, but they have different kinetic characteristics. One of the EA mechanisms is first-order in amine (base) and tends to be overshadowed by the S_N2(P) reaction; being of the same order in amine it cannot be made more visible merely by changes in concentration. With more hindered (less nucleophilic) amines (Bu^{t}NH$_2$, EtMe$_2$CNH$_2$) however, steric hindrance makes the S_N2(P) reaction less favourable and the EA mechanism becomes revealed more clearly. It is then seen to proceed with practically complete racemisation. This is consistent with a simple EA mechanism in which the substitution product is derived from the free, symmetrically solvated, metaphosphonamidate intermediate. The other EA mechanism is second-order in amine (nucleophile and base) and is therefore favoured relative to the competing mechanisms by high concentrations of amine. It involves preassociation of the nucleophile with the conjugate base of the substrate and is important because the metaphosphonimidate is short-lived: in the absence of the nucleophile the usual fate of the meta-

phosphonimidate is simply (stereospecific) reversion to its precursor by recombination with the chloride ion; only rarely does it manage to diffuse into the bulk and become free. This preassociation mechanism is probably not completely non-stereospecific, but it does seem to proceed with extensive racemisation. Apparently there is not much constraint on the nucleophile as regards its position relative to the leaving group in the preassociation complex.

Although our detailed investigation has been confined to one substrate and one type of nucleophile it is reasonable to expect that a similar spectrum of mechanistic possibilities will be open to other phosphonamidic (and phosphoramidic) acid derivatives undergoing reaction with other nucleophiles. A number of factors will determine the balance between the various mechanisms, with the extent of steric crowding in the substrate and the basicity of the reagent relative to its nucleophilicity being generally the most influential.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 298 instrument. G.l.c. and ^{31}P n.m.r. analyses were carried out as previously described.[6] ^1H N.m.r. spectra were recorded using Varian EM 390 (90 MHz) or Bruker AM 300 (300 MHz) spectrometers, tetramethylsilane as internal standard. Mass spectra were obtained with a V.G. Micromass 16B instrument. The chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$] was obtained commercially; the single enantiomers of (−)-(*S*)-PhMeP(S)OH and (+)-(*R*)-PhBu^{t}P(S)OH were prepared as previously described.[15] Amines were dried over and distilled from potassium hydroxide. Acetonitrile was refluxed over and distilled from calcium hydride. Light petroleum refers to the fraction b.p. 60—80 °C unless otherwise indicated.

Phosphonamidic Chlorides.—The *P*-aryl and *P*-alkyl *N*-t-butylphosphonamidic chlorides (**4**) and (**8**) were as previously described.[6,7] The sample of (**4a**) enriched in one enantiomer was obtained as detailed below.

Racemic N-t-Butyl-P-phenylphosphonamidothioic Chloride (**12**).—Air was removed from the benzene used as solvent in this preparation by ultrasonic irradiation. A solution of phenylphosphonous dichloride (2.50 g, 14.0 mmol) in dry benzene (12 ml) was stirred and cooled at 0—5 °C while a solution of t-butylamine (2.04 g, 28.0 mmol) in benzene (12 ml) was added during 0.3 h. Stirring was continued for a further 0.5 h at 0—5 °C and 0.5 h at room temperature. A single product [PhP(Cl)NHBu^t] was observed by ^{31}P n.m.r. spectroscopy (δ_P 116.6). Sulphur (3.58 g, 8 mol equiv.) was added to the reaction mixture which was then heated (sealed vessel) at 80—85 °C (oven temp.) for 23 h. Insoluble material (Bu^{t}NH$_3$Cl, sulphur) was filtered off and the filtrate was evaporated. The residue was extracted with hot light petroleum (b.p. 40—60 °C) and the extract was evaporated to give crude racemic *N-t-butyl-P-phenylphosphonamidothioic chloride* (**12**) (2.82 g, 81%) as a colourless oil that eventually solidified. A portion was purified by Kugelrohr distillation, b.p. 130 °C (oven temp.) at 0.15 mmHg, and crystallisation from light petroleum (b.p. 40—60 °C), m.p. 40—41 ° C; *m/z* 249, 247 (M^+, 22, 66%) and 234, 232 (M^+ − Me, 25, 75); $\nu_{max.}$(Nujol) 3 240 (NH) and 1 020 cm^{-1}; δ_H(CDCl$_3$) 8.15—7.8 (2 H, m), 7.55—7.3 (3 H, m), 3.35 (br s, NH), and 1.35 (9 H, s); δ_P(CDCl$_3$) 72.2 (Found: C, 48.5; H, 6.1; N, 5.6. $C_{10}H_{15}ClNPS$ requires C, 48.5; H, 6.1; N, 5.65%).

Racemic N-t-Butyl-P-phenylphosphonamidothioic Acid (**9**).—Crude racemic phosphonamidothioic chloride (**12**) (from 0.17 mol PhPCl$_2$) was hydrolysed by mixing with sodium hydroxide solution (2M; 210 ml). The resulting solution was washed with ether (2 × 100 ml) and then, while cooling, was made just strongly acidic with 2M-hydrochloric acid. Extraction with ether (300 ml) and evaporation of the extract (no heat) afforded racemic *N-t-butyl-P-phenylphosphonamidothioic acid* (**9**) (27.1 g, 71%); $\nu_{max.}$(Nujol) 3 300 (NH) and ~3 000br cm^{-1} (OH/SH). A sample was purified by dissolution in ether (no heat) and immediate precipitation with light petroleum (b.p. 40—60 °C); m.p. 81.5—82.5 °C (Found: C, 52.45; H, 7.1; N, 6.0. $C_{10}H_{16}NOPS$ requires C, 52.4; H, 7.0; N, 6.1%). This acid was unstable (P–N bond rupture) in CDCl$_3$ ($t_{\frac{1}{2}}$ *ca.* 5 min at room temperature) or C_6D_6. It formed a stable *salt with t-butylamine* (**10**; R = Bu^t), m.p. 114—117 °C; $\nu_{max.}$(Nujol) 3 340 (NHBu^t) and ~3 100—2 500 cm^{-1} (RNH_3^+); δ_H(CDCl$_3$–CD$_3$OD) 8.0—7.65 (2 H, m), 7.35—7.15 (3 H, m), 1.31 (9 H, s), and 1.08 (9 H, s) (Found: C, 55.9; H, 9.0; N, 9.1. $C_{14}H_{27}N_2OPS$ requires C, 55.6; H, 9.0; N, 9.3%).

(S)-α-*Methylbenzylamine Salt of* N-*t-Butyl*-P-*phenylphosphonamidothioic Acid.*—(*S*)-α-Methylbenzylamine (13.8 g, 0.114 mol) in ether (300 ml) was added to racemic *N*-t-butyl-*P*-phenylphosphonamidothioic acid (26.1 g, 0.114 mol) to give a clear solution which gradually deposited crystals. After 2 h filtration afforded the salt (**10**; R = CHMePh) (10.3 g, 0.029 mol, 26%) as an 89:11 mixture of diastereoisomers, m.p. 90—92 °C; $\nu_{max.}$(Nujol) 3 300 (NHBu^t) and ~3 200—2 000 cm^{-1} (RNH_3^+); δ_H (CDCl$_3$; 300 MHz) 7.9—7.8 (2 H, m), 7.35—7.2 (11 H, m), 4.20 (1 H, q, J_{HH} 6.9 Hz), 1.46 (3 H, d, J_{HH} 6.9 Hz), and 1.05 and 1.03 (both d, J_{PH} 0.3 Hz; ratio 11:89; total 9 H). This salt had only limited stability in CDCl$_3$ solution (P–N bond rupture). Attempts to increase the diastereoisomeric purity by recrystallisation were unsuccessful (decomposition).

Attempts to obtain N-*t-Butyl*-P-*phenylphosphonamidic Chloride* (**4a**) *Enriched in One Enantiomer.*—(a) via S-*Methyl* N-*t-butyl*-P-*phenylphosphonamidothioate* (**11**). The salt (**10**; R = CHMePh) (diastereoisomer ratio 3:2) was treated with methyl iodide (1.5 mol equiv.) in dichloromethane to give the S-*methyl phosphonamidothioate* (**11**) (64%), b.p. 130 °C (oven temp.) at 0.05 mmHg, m.p. 75.5—77.5 °C (from light petroleum); *m/z* 243 (M^+, 14%) and 228 (100); $\nu_{max.}$(Nujol) 3 180 (NH) and 1 185 cm^{-1} (P=O); δ_H(CDCl$_3$) 8.0—7.2 (5 H, m), 2.9 (1 H, d, J_{PH} 9 Hz, NH), 2.13 (3 H, d, J_{PH} 13 Hz, SMe), and 1.29 (9 H, s); δ_P(CH_2Cl_2) 36.5 (Found: C, 54.5; H, 7.5; N, 5.75. $C_{11}H_{18}NOPS$ requires C, 54.3; H, 7.5; N, 5.8%). When the ^1H n.m.r. spectrum was recorded in the presence of the optically active complexing agent (*R*)-phenyl-t-butylphosphinothioic acid[15] (~1 mol equiv.) the SMe groups of the two enantiomers gave rise to separate signals, δ_H (CDCl$_3$; 300 MHz) 2.16 (d, J_{PH} 13.2 Hz) and 2.13 (d, J_{PH} 13.3 Hz), in a 3:2 ratio. This material was converted into *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) by treatment with either sulphuryl chloride (1 mol equiv. in benzene or CCl_4) or chlorine (1 mol equiv. in CCl_4) at room temperature, but in both cases the product was completely racemic [^1H n.m.r. spectroscopy; Eu(tfc)$_3$ shift reagent; *N*-t-butyl signals].

(b) via N-*t-butyl*-P-*phenylphosphonamidothioic chloride* (**12**). The salt (**10**; R = CHMePh) (89:11 diastereoisomer ratio) was treated with oxalyl chloride (3 mol equiv.) in ether to give, after flash chromatography [silica; eluant light petroleum–ethyl acetate (20:1)], the phosphonamidothioic chloride (**12**) (57%). Attempts to determine the enantiomer ratio by ^1H n.m.r. spectroscopy [with Eu(tfc)$_3$ or (*R*)-PhBu^{t}P(S)OH] were unsuccessful. This material was dissolved in dichloromethane, the solution was cooled to −78 °C, and ozone was bubbled through for 15 min. The mixture was allowed to stand at room temperature for 1 h and was then concentrated to a gum. The

phosphonamidic chloride (**4a**) (40%) was extracted with ether, but ^{1}H n.m.r. spectroscopy [with Eu(tfc)$_3$] showed it to be racemic.

(c) *Directly*. The salt (**10**; R = CHMePh) (89:11 diastereoisomer ratio) (0.91 g, 2.6 mmol) was added to a stirred solution of phosgene (0.52 g, 5.2 mmol) in a mixture of toluene (4 ml) and dichloromethane (5 ml). After 0.5 h the solid (RNH_3Cl) was filtered off and the filtrate was evaporated. The residue was extracted with ether (2 × 10 ml). Concentration of the extract and addition of light petroleum precipitated pure *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) (0.48 g, 80%), $\delta_P(CDCl_3)$ 29.5, having an enantiomer ratio of 57:43 (^{1}H n.m.r.). Crystallisation from light petroleum–ether (1:1) gave crystals that were racemic; concentration of the mother liquor afforded a solid that was enriched in the major enantiomer. The ^{1}H n.m.r. spectrum of this material in the presence of (−)-(*S*)-PhMeP(S)OH (2 mol equiv.) included separate *N*-t-butyl signals for the two enantiomers, δ_H ($CDCl_3$; 300 MHz) 1.34 (d, J_{PH} 0.8 Hz) and 1.32 (d, J_{PH} 0.8 Hz), in a 64:36 ratio. Varying the conditions (solvent, concentration, temperature, added LiCl) of the phosgene reaction did not significantly improve the initial 57:43 enantiomer ratio.

Phosphonic Diamide Products.—Samples of all except one of these compounds were available from earlier work.[6,7] The diamide (**5a**; R = CMe_2Et) was prepared by treating a solution of the phosphonamidic chloride (**4a**) in CH_2Cl_2 with t-pentylamine (4 mol equiv.). The product was washed with water and crystallised from light petroleun–toluene to give N-*t-butyl*-N′-*t-pentyl*-P-*phenylphosphonic diamide* (76%), m.p. 154.5—155.5 °C; *m/z* 267 (M^+ − Me, 15%) and 253 (M^+ − Et, 100) (M^+ not observed); $\nu_{max.}$(Nujol) 3 240 cm^{-1} (NH); δ_H ($CDCl_3$; 300 MHz) 7.9—7.8 (2 H, m), 7.45—7.35 (3 H, m), 2.39 (1 H, br d, J_{PH} 10 Hz, NH), 2.32 (1 H, br d, J_{PH} 10 Hz, NH), 1.54 (2 H, q, J_{HH} 7.5 Hz), 1.28 (9 H, d, J_{PH} 0.5 Hz), 1.26 (3 H, s), 1.22 (3 H, s), and 0.86 (3 H, t, J_{HH} 7.5 Hz); $\delta_P(CDCl_3)$ 15.1 (Found: C, 64.3; H, 9.5; N, 10.0. $C_{15}H_{27}N_2OP$ requires C, 63.8; H, 9.6; N, 9.9%).

Competitive Experiments.—The *N*-t-butyl-*P*-arylphosphonamidic chloride (**4**) (*ca.* 70 mg) in MeCN was added at 0 °C to an equimolar mixture of Pr^iNH_2 and Bu^tNH_2 in MeCN to give a reaction mixture containing each amine in 10-fold molar excess (with respect to substrate) and of the required concentration (Table 1). When reaction was complete the mixture was concentrated and examined by ^{31}P n.m.r. spectroscopy with the aid of pure samples of both possible diamide products. The $NHPr^i/NHBu^t$ product ratio (n^i/n^t) was deduced directly from the relative areas of the peaks, *i.e.* it was assumed that because of their structural similarity the two products did not differ significantly in their ^{31}P n.m.r. response. The results are shown in Table 1. The conclusions from the n.m.r. measurements were checked by g.l.c.

Other competitive experiments (see Results and Discussion) were carried out in exactly the same way but with the *N*-t-butyl-*P*-alkylphosphonamidic chlorides (**8**; R = Me, Et, Pr^i, or Bu^t) as substrates, or with CH_2Cl_2 as solvent instead of MeCN.

Kinetic Studies.—A solution of *N*-t-butyl-*P*-phenylphosphonamidic chloride (**4a**) (*ca.* 10 mg) in MeCN [containing *trans*-stilbene (*ca.* 2.5 mg) as g.l.c. standard] was mixed at 0 °C with an equal volume of a solution of Pr^iNH_2 or Bu^tNH_2 in MeCN to give a reaction mixture containing the amine in 10-fold molar excess (with respect to substrate) and at the required concentration (Table 2). Samples were withdrawn at intervals (0.25—30 min) and added to MeOH (40 mol/mol amine) to halt formation of the phosphonic diamide product (**5a**) and convert the remaining phosphonamidic chloride into methyl *N*-t-butyl-*P*-phenylphosphonamidate. The samples were then examined by g.l.c. (3% OV 225 at 196 °C) and the area (A^P) of the amidate peak (R_t 3.0 min) (corresponding to unchanged starting material at the time MeOH was added) in each was measured relative to the area of the internal standard peak. In each case 5—8 samples were examined over a period of 3—4 half-lives. Plots of log A^P *vs.* time were linear ($r \geqslant 0.998$) and from them the rate constants k_{obs} shown in Table 2 were deduced. The area (A^P) of the diamide product [R_t 5.7 min (R = Pr^i); 4.7 min (R = Bu^t)] in each sample was also measured, together with the infinity value for the reaction. Values of k_{obs} were obtained from plots of log ($A^P_\infty - A^P$) *vs.* time but these were considered to be less reliable than those obtained above (see Results and Discussion) and they were not used.

Stereochemical Studies.—*N*-t-Butyl-*P*-phenylphosphonamidic chloride (**4a**) (enantiomer ratio 64:36) (*ca.* 16 mg) was treated at 0 °C with a solution of isopropylamine or t-pentylamine (10 mol equiv.) of the required concentration (Table 4) in MeCN. The reaction was allowed to proceed to completion. Volatile matter was evaporated off and the residue was dissolved in CH_2Cl_2 (1.5 ml). The solution was washed with water (2 × 0.8 ml) (to remove RNH_3Cl), dried ($MgSO_4$), and evaporated to dryness. The product was then examined by ^{1}H n.m.r. spectroscopy at 300 MHz. This showed the phosphonic diamide (**5a**; R = Me_2CH or Me_2CEt) to have been formed cleanly except in the experiment with [Me_2EtCNH_2] = 0.05M where some unidentified by-products were also formed. So that the enantiomer ratio could be determined, (−)-(*S*)-methylphenylphosphinothioic acid [$\delta(CDCl_3) \sim 2.0$ (3 H, d, J_{PH} 14 Hz, Me)] was added and the spectrum was re-examined.

For (**5a**; R = Me_2CH): δ_H ($CDCl_3$; 300 MHz) 7.9—7.35 (5 H, m), 3.44 (1 H, m), 2.43 (NH), 2.23 (NH), 1.28 (9 H, d, J_{PH} <0.5 Hz, $NHCMe_3$), and 1.15 and 1.05 (both 3 H, d, J_{HH} 6.5 Hz, $NHCHMe_2$). On addition of (−)-(*S*)-PhMeP(S)OH (2 mol equiv.) the $NHCMe_3$ signal became separated into two parts, δ 1.24 (major) and 1.19 (minor) (one of the $NHCHMe_2$ signals also became separated).

For (**5a**; R = Me_2CEt): δ_H ($CDCl_3$; 300 MHz) 7.9—7.35 (5 H, m), 2.40 (1 H, d, J_{PH} 8 Hz, NH), 2.30 (1 H, d, J_{PH} 8 Hz, NH), 1.54 (2 H, q, J_{HH} 7.5 Hz, $NHCMe_2Et$), 1.28 (9 H, d, J_{PH} 0.5 Hz, $NHCMe_3$), 1.26 and 1.22 (both 3 H, broadened s, $NHCMe_2Et$), and 0.86 (3 H, t, J_{HH} 7.5 Hz, $NHCMe_2Et$). On addition of (−)-(*S*)-PhMeP(S)OH (3 mol equiv.). the $NHCMe_3$ signal became separated into two parts, δ 1.22 (minor) and 1.21 (major) and one of the $NHCMe_2Et$ signals became separated into two parts, δ 1.16 (major) and 1.14 (minor).

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