A Stereochemical Study of the Dissociative Substitution Reactions of *N*-(*S*)-α-Phenylethyl-*P*-t-butylphosphonamidic Chloride with t-Butylamine and Isopropylamine[1]

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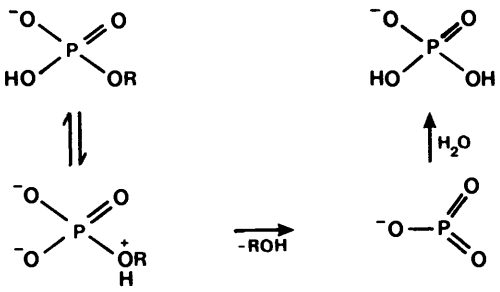
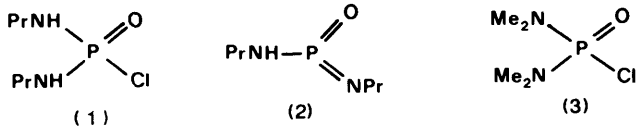
The diastereoisomers of the title phosphonamidic chloride (**8**) have been separated and their substitution reactions with Bu^tNH_2 and Pr^iNH_2 (MeCN solvent) have been examined. The reactions are entirely dissociative in nature, any contribution from $S_N2(P)$ being insignificant. At very low concentrations of amine, reaction occurs mainly by simple elimination–addition with a free monomeric metaphosphonimidate intermediate (**13**). This mechanism is first-order in amine (base) and gives the phosphonic diamide product (**14**) with complete non-stereospecificity. As the concentration of amine is increased, preassociation elimination–addition becomes increasingly important. This mechanism is second-order in amine (base and nucleophile) and has variable stereochemistry. The degree of stereospecificity is very small at first, but it increases with the concentration of the amine. Even with neat amine, however, the preassociation elimination–addition mechanism is still substantially non-stereospecific. For both elimination–addition mechanisms, there is only weak discrimination between Pr^iNH_2 and Bu^tNH_2 under competitive conditions.

Evidence in support of an elimination–addition mechanism for phosphoric monoester hydrolysis (Scheme 1) has accumulated

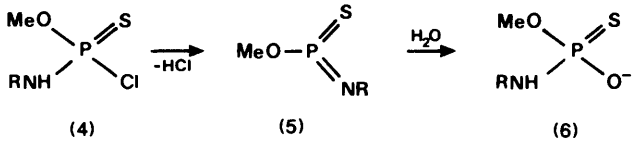


Scheme 1.

steadily[2] since the original proposals[3] in 1955. The dissociative nature of the reaction has become generally accepted, albeit that now it seems probable that the three-co-ordinate monomeric metaphosphate intermediate is too unstable (short-lived) to exist as a fully liberated species in water and most other hydroxylic solvents,[4,5] t-butyl alcohol being a notable exception.[6,7] An important factor in the gradual acceptance of monomeric metaphosphate as an intermediate has been the need to postulate analogous three-co-ordinate P^V intermediates in related substitution reactions.[2,3] Consider, for example, the alkaline hydrolyses of the phosphoramidic chlorides (**1**) and (**3**). These two reactions differ in rate by a factor in excess of a million.[8] The much greater reactivity of compound (**1**) can reasonably be explained only in terms of an elimination–addition mechanism with a three-co-ordinate metaphosphorimidate intermediate (**2**). Compound (**3**), being fully alkylated at nitrogen, cannot form a metaphosphorimidate and has to react by the 'normal' associative [$S_N2(P)$] mechanism.



The general acceptance of metaphosphate-like species as intermediates in nucleophilic substitution owes much to the stereochemical investigation of Gerrard and Hamer, reported in 1968.[9] Using optically active samples of the phosphoramidothioic chloride (**4**), they found that hydrolysis under basic conditions in aqueous dimethoxyethane proceeded with almost complete racemisation. Not surprisingly this has come to be seen as compelling evidence for the intermediacy of a free (symmetrically solvated), planar, three-co-ordinate P^V species (**5**) (Scheme 2). Viewed as a whole, however, the stereochemical



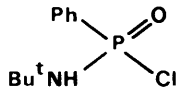
Scheme 2. R = cyclohexyl

results were not entirely clear cut; in aqueous methanol (1:1) the hydrolysis of chloride (**4**) proceeded with only partial racemisation, 62% at 30 °C, 21% at 0.7 °C.[9,10] Arguably this incomplete racemisation does not always receive the attention it should in discussions of Gerrard and Hamer's work.

An obvious limitation of Gerrard and Hamer's study was its use of a thiophosphoryl chloride as substrate. There were good preparative and analytical reasons for working with a P=S compound but the fact remains that it is the chemistry of P=O compounds that is of more general concern. There is no justification for assuming that they will behave in the same way, and in fact Gerrard and Hamer[10] have noted significant differences in the solvolytic behaviour of their phosphoramidothioic chloride and its P=O analogue. Unfortunately, no stereochemical information is available for the P=O compound.†

† In the original literature (ref. 10) the structure of the phosphoramidothioic chloride (**4**) is erroneously shown with a P=O instead of a P=S group. Unfortunately this error has found its way into a major textbook where the P=O compound is shown undergoing base hydrolysis with partial racemisation (J. Emsley and D. Hall, 'The Chemistry of Phosphorus,' Harper and Row, 1976, p. 317). In fact no stereochemical investigation of the P=O compound has ever been reported.

Recently we attempted a stereochemical study as part of our investigation of the reactivity of the phosphonamidic chloride (7), but it was not an unqualified success.[11] A rather low enantiomer excess for the substrate combined with a tendency to react associatively prevented us from obtaining definitive stereochemical data for dissociative nucleophilic substitution. We have therefore undertaken a study designed specifically to give reliable and precise information on the stereochemistry of dissociative substitution in a phosphonamidic chloride.



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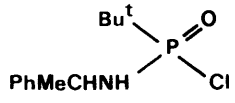

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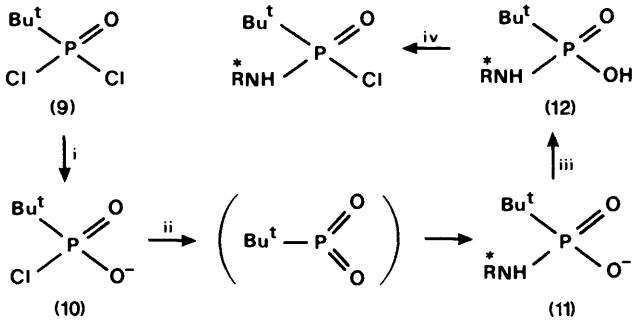
Results and Discussion

No compound containing the –P(O)(Cl)NH– structural unit has previously been obtained in the form of pure stereoisomers differing in configuration at phosphorus. We chose to work with the phosphonamidic chloride (**8**) for two reasons. (i) By having a chiral alkyl group of defined configuration on the N atom, the phosphonamidic chloride (**8**) will exist as two diastereoisomers (not enantiomers) that can, in principle, be separated.* This is important because the strategy adopted by Gerrard and Hamer[9] to obtain their optically active samples of the phosphoramidothioic chloride (**4**)—resolution of the phosphoramidothioic acid (**6**),[12] then treatment of the separate enantiomers with PCl_5—is not applicable to a phosphoramidic chloride; in contrast to its P=S counterpart, the P atom in a phosphoramidic acid cannot be chiral and the acid cannot be resolved. (ii) By having a bulky t-butyl group on the P atom, nucleophilic attack [S_N2(P)] will be sterically hindered. This is important because P=O compounds are more reactive than P=S compounds towards nucleophiles,[13] so the risk of the stereochemical integrity of a phosphonamidic chloride being compromised by traces of chloride ion is very real. Indeed, without steric shielding of the P atom, it is unlikely that such an intrinsically reactive system could survive attempts to separate the stereoisomers. Also, a bulky *P*-alkyl group is important in that it increases the likelihood of nucleophilic substitution proceeding entirely by elimination–addition, without interference from the associative S_N2(P) mechanism.[14]

Preparative Experiments.—Although an advantage in the long term, the bulky *P*-alkyl group proved troublesome in the short term. Because of steric hindrance *P*-t-butylphosphonic dichloride (**9**) would not react with α-methylbenzylamine under mild conditions, and selective replacement of just one of the Cl atoms was not possible. An indirect route to the phosphonamidic chloride (**8**) was therefore attempted (Scheme 3). The free phosphonamidic acid (**12**) [$\delta_P(CH_2Cl_2)$ 42.6] was obtained pure and in reasonable yield (39% overall), and treatment with oxalyl chloride then afforded the required phosphonamidic chloride as a 3:2 mixture of diastereoisomers, $\delta_P(CDCl_3)$ 59.3 (major) and 59.6 (minor). Crystallisation gave analytically pure material but did not effect any useful separation of the diastereoisomers. However, the phosphonamidic chloride could be flash chromatographed[15] [silica gel; eluant light petroleum–ethyl acetate (7:3)] without any serious loss through decomposition and this, followed by crystallisation, led to pure



Scheme 3. *RNH = (*S*)-PhMeCHNH. *Reagents:* i, H_2O, *RNH_2; ii, *RNH_2; iii, CF_3CO_2H; iv, $(COCl)_2$

samples of the individual diastereoisomers of the chloride (**8**): R_F 0.35; $\delta_H(CDCl_3)$ 1.62 (3 H, d, J_{HH} 7 Hz, Me) and 1.26 (9 H, d, J_{PH} 20 Hz, PBu^t) (major diastereoisomer); and R_F 0.27; $\delta_H(CDCl_3)$ 1.55 (3 H, d, J_{HH} 7 Hz, Me) and 1.28 (9 H, d, J_{PH} 20 Hz, PBu^t) (minor diastereoisomer).

Stereochemical Studies.—Both diastereoisomers of the phosphonamidic chloride (**8**) reacted smoothly with an excess of a 1M solution of t-butylamine in acetonitrile at 27 °C ($t_{\frac{1}{2}}$ *ca.* 1 h) and gave cleanly the phosphonic diamide (**14**; R=Bu^t). The diastereoisomers of the diamide could be resolved by g.l.c. (25 m medium polarity bonded phase capillary at 240 °C) and distinguished by ^{1}H n.m.r. spectroscopy: R_t 7.4 min; $\delta_H(CDCl_3)$ 1.48 (d, J_{HH} 7 Hz, Me), 1.17 (s, NBu^t), and 1.12 (d, J_{PH} 15 Hz, PBu^t); and R_t 7.8 min; $\delta_H(CDCl_3)$ 1.51 (d, J_{HH} 7 Hz, Me), 1.35 (s, NBu^t), and 0.98 (d, J_{PH} 15 Hz, PBu^t). Using one pure diastereoisomer of (**8**) (R_F 0.35), the g.l.c. ratio of diastereoisomers in the product was 57:43, and using the other pure diastereoisomer (R_F 0.27), it was 53:47. The same diastereoisomer of (**14**; R = Bu^t) (R_t 7.4 min) was the major product in both cases. The possibility of the observed non-stereospecificity being merely a consequence of epimerisation of the substrate (or the product) was eliminated by control experiments.†

The use of acetonitrile as the solvent in our experiments might be a cause for concern. Acetonitrile was chosen because its high polarity (ε 37.5)[16] should eliminate any risk of preferential

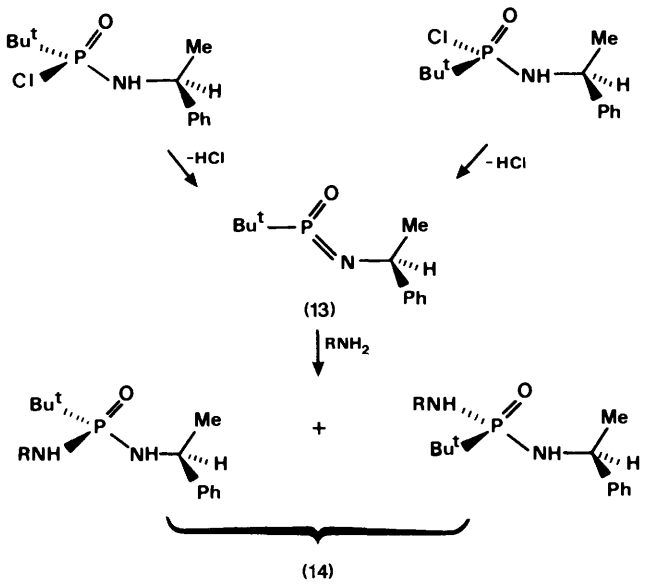
* The (*S*)-enantiomer of α-methylbenzylamine was used for the preparation of the phosphonamidic chloride (**8**) so that it, and its substitution products, would be obtained as just two stereoisomers. In principle, however, all the work described in the present paper could have been carried out equally well using racemic α-methylbenzylamine.

† In control experiments where ^{1}H n.m.r. spectroscopy was used to examine the configurational stability of the substrate, the extent of the reaction was deliberately kept small. In this way the remaining substrate dominated the spectrum of the reaction mixture and its diastereoisomer composition could be measured with the greatest precision and confidence. Even at such low conversions the diastereoisomer composition of the product could be measured accurately using g.l.c. With these experiments, it was possible to show that epimerisation of the substrate was not to any appreciable extent responsible for the observed non-stereospecificity of the substitution. They thus fulfilled their objective satisfactorily. It would, nonetheless, be of interest to know whether any epimerisation of the substrate does occur, even if it is only in the later stages of reaction that it becomes appreciable. Since the completion of the main investigation we have found g.l.c. conditions that allow the diastereoisomers of the phosphonamidic chloride (**8**) to be resolved (25 m OV 101 capillary at 196 °C; R_t 7.9 and 8.1 min). When the reaction of either diastereoisomer of (**8**) with 0.25M Bu^{t}NH$_2$ in MeCN was examined at *ca.* 80% completion the remaining substrate was seen to contain *ca.* 20% of the other diastereoisomer. Some epimerisation seems to occur when samples of the reaction mixture are injected into the chromatograph but we think some also occurs under the conditions of the reaction. Of course it remains the case that epimerisation of the substrate would not have any appreciable effect on the stereochemistry of the product in the early stages of reaction. At higher concentrations of amine the importance of epimerisation relative to product formation is probably even less.

solvation of the polar substrate by the amine nucleophiles (ε 5.45 for Pr^iNH_2; presumably even less for Bu^tNH_2).[16] However, a number of authors have speculated on the possibility of monomeric metaphosphate, a powerful electrophile, forming a complex with MeCN.[2,17,18] In the present experiments the monomeric metaphosphonimidate might conceivably form a similar type of complex (**15**). It could then be the case that the initial nucleophilic attack (by MeCN) in fact proceeds stereospecifically with inversion, and that the observed non-stereospecificity is merely a consequence of repeated transfer of the metaphosphonimidate between molecules of solvent prior to its reaction with the amine. We therefore repeated the reaction of chloride (**8**) (R_F 0.35) with 1M t-butylamine, but with dichloromethane as solvent. The reaction was *ca.* four times slower than in acetonitrile ($t_{\frac{1}{2}}$ *ca.* 4 h) but the diastereoisomer ratio of the product (57:43 by g.l.c.) was exactly the same. As there is no real likelihood of complex formation with CH_2Cl_2, there is no reason to suppose that the non-stereospecificity of the reactions in acetonitrile is a consequence of complexation.

The product diastereoisomer ratios observed with 1M t-butylamine in acetonitrile imply that a completely non-stereospecific ('racemisation') reaction should result in a 55:45 ratio, whichever diastereoisomer of the phosphonamidic chloride is used. When the reactions were repeated at higher dilution (0.25M Bu^tNH_2) that is essentially what was observed, at 30% conversion as well as near completion.* As measured the product diastereoisomer ratios are not quite identical (Table), but the difference can be accommodated by the experimental uncertainty (±0.5% in each diastereoisomer). It is therefore reasonable to conclude that reaction is now completely non-stereospecific. The fact that the limiting diastereoisomer ratio is 55:45 rather than 50:50 must be a consequence of asymmetric induction; the reactions are devoid of stereospecificity at high dilution, but do display a small degree of stereoselectivity.

The lack of stereospecificity at high dilution is surely compelling evidence for a mechanism involving a free monomeric metaphosphonimidate intermediate (**13**) (Scheme 4)—free in as much as it has a significant lifetime independent of the leaving group and the nucleophile, and attains stereochemical equilibrium with its surroundings (corresponding to symmetrical solvation for an achiral species) before passing on to product. It is in complete contrast to the results obtained by Buchwald and Knowles[19] in their stereochemical investigation of some substitution reactions that (by other criteria) proceed through monomeric metaphosphate. Using [^{16}O,^{17}O,^{18}O]-labelled substrates, and ^{31}P n.m.r. spectroscopic analysis, they observed stereospecific inversion of configuration. However, their experiments were carried out under solvolysis conditions (very high nucleophile concentration) in nucleophilic protic media, where the metaphosphate intermediate is least likely to exist as a fully liberated species. More appropriate comparison can be made with the more recent results of Friedman and Knowles[17] and of Cullis and Rous.[20] Working with dilute solutions in aprotic solvents (MeCN or CH_2Cl_2), they have observed extensive racemisation in metaphosphate-like phosphoryl transfers to alcohol acceptors. Our results for the metaphosphonimidate (**13**) are therefore broadly in line with these later results for monomeric metaphosphate.



Scheme 4.

Table. Diastereoisomer ratios of the products (**14**; R = Bu^t or Pr^i) formed by reaction of the separate diastereoisomers of the phosphonamidic chloride (**8**) with Bu^tNH_2 or Pr^iNH_2 at different concentrations in MeCN (T = 25—27 °C)[a]

$[RNH_2]$/M	(**8**) (R_F 0.35) + Bu^tNH_2	(**8**) (R_F 0.27) + Bu^tNH_2	(**8**) (R_F 0.35) + Pr^iNH_2[b]
0.25	55.5/44.5	54.5/45.5	55.5/44.5
1.0	57/43	53/47	57/43
2.0	59·5/40.5	51.5/48.5	63/37
4.0	65/35	47.5/52.5	67/33
8.0	79/21	35.5/64.5	80/20
Neat	87/13	31/69	88.5/11.5

[a] Estimated uncertainty ±0.5% in each diastereoisomer (assuming same g.l.c. detector response for both diastereoisomers). [b] Ratio 55.5:44.5 with 0.125M Pr^iNH_2; 56:44 with 0.5M Pr^iNH_2.

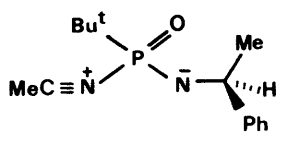
At higher concentrations of t-butylamine, the reactions of the diastereoisomers of the phosphonamidic chloride (**8**) became progressively more stereospecific (Table). For (**8**) (R_F 0.35) the product diastereoisomer ratio increased to 87:13 in neat amine while for (**8**) (R_F 0.27) it reversed and reached 31:69 in the opposite sense.†

The simplest explanation for the increasing stereospecificity at higher amine concentrations is that $S_N2(P)$ is playing an increasingly important part, notwithstanding our hope that the bulky *P*-t-butyl group would block associative reactions; it is known that nucleophilic displacement of a good leaving group from an acyclic P=O compound generally proceeds stereospecifically with inversion of configuration.[21] Our results would, of course, require that the $S_N2(P)$ mechanism be kinetically of a higher order in amine than the simple elimination–addition (EA) mechanism, but that is not impossible. Presumably simple

* In our preliminary communication the concentration of Bu^tNH_2 in the high dilution experiments is incorrectly given as 0.125M; it should be 0.25M. (With Pr^iNH_2 the concentration of amine was taken down to 0.125M.)

† The fact that the diastereoisomeric substrates give products having diastereoisomer compositions that differ greatly from one another (and that remain constant during the course of reaction) at high amine concentrations is testimony to the configurational stability of the products under these reaction conditions. Also, the fact that the composition of the product obtained from (**8**) (R_F 0.35) and neat amine (87:13 diastereoisomer ratio) did not change perceptibly in 3.75 h when the crude product (still containing Bu^tNH_2 and Bu^tNH_3Cl) was dissolved in MeCN (to simulate the 1M amine reaction conditions) provides confirmation of the configurational stability of the product under lower amine concentration reaction conditions.

EA is first-order in amine, since it is only as a base that the amine participates in the rate-limiting formation of the metaphosphonimidate. For $S_N2(P)$, however, the rate-limiting attack of the amine nucleophile could be assisted by a second molecule of amine acting as a base. There is ample precedent for this in the base-catalysed aminolysis reactions of carboxylic esters[22] while in phosphorus chemistry the displacement of *p*-nitrophenoxide from $Ph_2P(O)OAr$ by Bu^nNH_2 in acetonitrile is reported to be second-order in amine.[23] It was with this in mind that we extended the stereochemical study of the phosphonamidic chloride (**8**) to include its reaction with isopropylamine. For steric reasons Pr^iNH_2 is a much more effective nucleophile than Bu^tNH_2; with the phosphonamidic chloride (**16**), for



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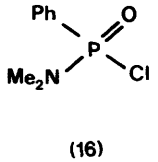


(16)

example, where EA is not possible, it reacts >100 times faster than Bu^tNH_2.[24] If $S_N2(P)$ competes with EA to any significant extent in the Bu^tNH_2 reactions, it will be of overwhelming importance in reactions with Pr^iNH_2. As can be seen from the Table, however, the stereochemical results are actually rather similar. At low amine concentrations the ratio of the diastereoisomers of the diamide product is the same as with Bu^tNH_2, and at higher concentrations the drift towards stereospecificity is not much more pronounced. Even with $MeNH_2$, where steric interactions will be minimised and $S_N2(P)$ most favoured, reaction is still far from stereospecific at high amine concentrations [product diastereoisomer ratios 73:27 and 39:61 for reactions of (**8**) (R_F 0.35) and (**8**) (R_F 0.27) with ~9M $MeNH_2$ in CH_2Cl_2]. There seems no way in which the drift towards stereospecificity with Bu^tNH_2 (or with Pr^iNH_2) can possibly be ascribed to competition from $S_N2(P)$.

Competitive and Rate Studies.—In an attempt to define more clearly the nature of the mechanism that competes with simple EA, we examined the behaviour of the phosphonamidic chloride (**8**) in competitive experiments. Using a large excess of an equimolar mixture of Pr^iNH_2 and Bu^tNH_2 at various concentrations in acetonitrile (T = 25—26 °C), the $NHPr^i$:$NHBu^t$ product ratios [(**14**; R = Pr^i): (**14**; R = Bu^t)], as measured by ^{31}P n.m.r. spectroscopy, were as follows:

[Total amine]/M	0.5	1.0	2.0	4.0	8.0
Ratio $NHPr^i$:$NHBu^t$	1.32	1.30	1.25	1.33	1.30

The above product ratios should be set against values >50 found in similar experiments with compound (**16**), a phosphonamidic chloride that cannot react by an EA mechanism.[11] The mechanism that competes with the free metaphosphonimidate pathway at higher concentrations may be more stereospecific, but clearly it is not any more discriminating with regard to competing nucleophiles.

A better understanding of the competing mechanism requires knowledge of its stereochemistry in isolation; we need to know, for example, whether the small overall shift towards stereospecificity observed with 1M amine is the result of a small incursion by a mechanism having a high degree of stereospecificity or a large incursion by a mechanism having a low degree of stereospecificity. For clarification it was necessary to look at the kinetics. The reactions of the phosphonamidic chloride (**8**) (1:1 mixture of diastereoisomers) were examined using concentrations of Bu^tNH_2 of 0.5, 1.0, and 2.0M in acetonitrile at 25.8 °C, the amine being initially in 20-fold excess with respect to the substrate (pseudo-first-order conditions). Samples were removed at intervals and added to a very large excess of MeOH (≥40 mol/mol amine). This effectively quenched the reaction with Bu^tNH_2 by converting all of the remaining phosphonamidic chloride into the corresponding methyl ester (**17**). The samples were then analysed by g.l.c. The amounts of the methyl ester (corresponding to substrate) and the diamide product in each were measured, and the fraction of the substrate remaining at the time of quenching [$(a - x)$] was deduced. In each experiment 9—13 samples were examined over a period of 3.5—5 half-lives. Plots of $\log(a - x)$ *vs.* time were linear (rate = $k_{obs.}$[substrate]) and the slopes of the lines yielded the following values of the observed rate constant:

$[Bu^tNH_2]$/M	0.5	1.0	2.0
$10^5k_{obs.}/s^{-1}$	6.7 ± 0.2	20.2 ± 0.2	68.4 ± 0.8

The 10-fold increase in $k_{obs.}$ for a 4-fold increase in $[Bu^tNH_2]$ indicates an overall order between 1 and 2 in amine. This suggests parallel pathways that are first- and second-order in Bu^tNH_2, so that the observed rate is given by equation (1). In

$$\text{Rate} = k_1[\text{substrate}][Bu^tNH_2] + k_2[\text{substrate}][Bu^tNH_2]^2 \quad (1)$$

each experiment the amine was present in large excess and its concentration remained practically constant throughout that particular experiment; $k_{obs.}$ can therefore be expressed in the form of equation (2). A plot of $k_{obs.}[Bu^tNH_2]^{-1}$ *vs.* $[Bu^tNH_2]$

$$k_{obs.} = k_1[Bu^tNH_2] + k_2[Bu^tNH_2]^2 \quad (2)$$

gave a line of slope $k_2 = 14.0 \pm 0.5 \times 10^{-5}\ s^{-1}\ M^{-2}$ and a plot of $k_{obs.}[Bu^tNH_2]^{-2}$ *vs.* $[Bu^tNH_2]^{-1}$ gave a line of slope $k_1 = 6.5 \pm 0.6 \times 10^{-5}\ s^{-1}\ M^{-1}$ (Figure). Here k_1 corresponds to the simple EA mechanism (first-order in amine) and k_2 corresponds to the competing mechanism (second-order in amine) that is responsible for the drift towards stereospecificity.

Mechanistic Deductions.—The value of k_2 relative to k_1 implies that with 1M Bu^tNH_2 some two-thirds of the total reaction goes *via* the alternative (k_2) mechanism. Since the observed product diastereoisomer ratios with 1M Bu^tNH_2 were 57:43 and 53:47 using the two diastereoisomers of the substrate, and the limiting diastereoisomer ratio (for completely non-stereospecific simple EA) is 55:45, it follows that the alternative mechanism alone gives ratios of *ca.* 58:42 and 52:48. Thus with 1M amine it seems there is in fact a large incursion (65—70%) by a mechanism that has a low degree of stereospecificity. Even with 0.25M Bu^tNH_2, the values of k_2 and k_1 imply that about one-third of the total reaction goes by the alternative (k_2) mechanism. That being so, complete non-stereospecificity should not be observed with 0.25M amine; the numbers above lead to the prediction of product diastereoisomer ratios of 56:44 and 54:46. The ratios actually observed (Table) were midway between these predicted values and the limiting value of 55:45; it was the experimental uncertainty (±0.5%) which, although small, allowed us to interpret the results in terms of completely non-stereospecific reaction. That same uncertainty now allows a different interpretation *viz.* there is a substantial contribution (30—35%) from a mechanism having a very low degree of stereospecificity; this interpretation now seems more likely to be correct. As to the identity of this mechanism that is second-order in amine, shows the same lack of any substantial discrimination between competing Pr^iNH_2 and Bu^tNH_2 as simple EA, and is only a little more stereospecific than simple EA, we think the answer must be preassociation elimination–addition.[11,25]

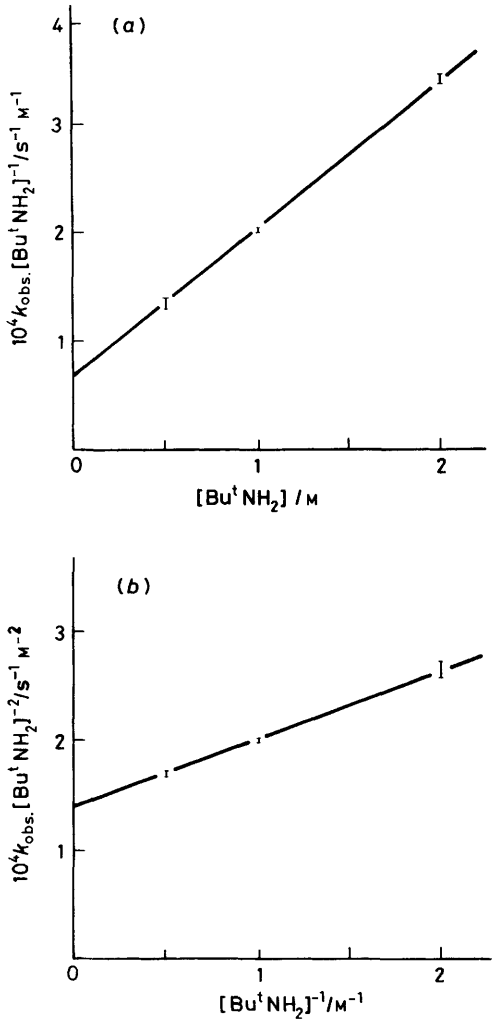
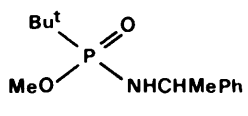
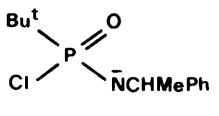


Figure. Reaction of Bu^{t}P(O)(Cl)NHCHMePh with Bu^{t}NH$_2$ in MeCN at 25.8 °C. Dependence of $k_{obs.}$ on amine concentration expressed in the form: (*a*) $k_{obs.}[Bu^tNH_2]^{-1} = k_2[Bu^tNH_2] + k_1$ and (*b*) $k_{obs.}[Bu^tNH_2]^{-2} = k_1[Bu^tNH_2]^{-1} + k_2$

The conjugate base (**18**) of the substrate can eliminate the leaving group (Cl) within a cage of solvent from which the nucleophile (RNH_2) is excluded. The resulting metaphosphonimidate will then react with the nucleophile to form the product, rather than merely recombining with the leaving group, only if it is sufficiently stable (long-lived) to diffuse into the bulk of the solution. For the metaphosphonimidate (**13**) we think it is, so that the reaction occurs (in part) by a simple EA mechanism with a fully liberated metaphosphonimidate intermediate. This pathway is first-order in amine (base) and completely non-stereospecific.



(17)



(18)

Alternatively, the substrate (or its conjugate base) can form a preassociation complex with the nucleophile before the leaving group is eliminated; now the nucleophile is already present when the metaphosphonimidate is formed, and diffusion is not a prerequisite of product formation. This preassociation EA pathway, which may be concerted or stepwise,[25] is in competition with simple EA; it is second-order in amine (nucleophile as well as base) and assumes increasing importance as the concentration of the amine increases. In the pre-association EA mechanism the monomeric metaphosphonimidate intermediate is not fully liberated, and the stereochemical course is not a fixed quantity. At low concentrations of nucleophile the degree of stereospecificity is small but never negligible, and at higher concentrations it increases markedly. Nonetheless, the preassociation mechanism remains substantially non-stereospecific, even with the highest possible concentration of nucleophile. It is, perhaps, the definition of this variable preassociation stereochemistry that is the most important aspect of the present work.

The picture of dissociative substitution that has emerged from this new investigation is similar to that tentatively put forward earlier,[11] but in detail it is very much clearer. To achieve that clarity, it has been necessary to work with a substrate having an exceptionally bulky substituent on phosphorus; the *P*-phenyl compound used in the earlier investigation was undoubtedly a more typical substrate. Thus the new investigation complements the old; it does not make it redundant.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 298 instrument and mass spectra with a V.G. Micromass 16B instrument. Routine n.m.r. spectra were obtained using a Varian EM390 spectrometer (^{1}H, 90 MHz) or a JEOL JNM-FX60 spectrometer (^{31}P, 24.3 MHz; positive chemical shifts downfield from external 85% H_3PO_4). High resolution n.m.r. spectra were recorded with a Bruker AM-300 instrument (^{1}H, 300 MHz; ^{31}P, 121.5 MHz). G.l.c. analyses were carried out using either a 25 m × 0.22 mm i.d. fused silica capillary column containing a 0.25 μ film of medium polarity bonded phase (SGE BP 10) (He carrier gas; Pye Unicam PU4500 chromatograph; split injection) or a 1.5 m × 4 mm i.d. glass column packed with 3% OV 225 coated on silanised 100—120 mesh diatomite C 'Q' (N_2 carrier gas; Pye 104 chromatogaph; on-column injection). Peak areas were measured with a Spectra-Physics SP4270 integrator. 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. t-Butylphosphonic dichloride was prepared by a literature method.[26]

N-(S)-α-*Phenylethyl*-P-*t-butylphosphonamidic Acid* (**12**).—A mixture of t-butylphosphonic dichloride (6.61 g, 0.038 mol), water (1.02 g, 0.057 mol), and (*S*)-α-phenylethylamine (28.5 g, 0.236 mol) was stirred at room temperature overnight. Ether was added and the insoluble amine hydrochloride was filtered off. Volatile material was evaporated from the filtrate and the residual gum was dissolved in dichloromethane (200 ml). The solution was washed first with water (150 ml) containing trifluoroacetic acid (14.2 g, 0.125 mol), then with water (100 ml). It was concentrated (to *ca.* 100 ml) and on dilution with ether deposited N-(S)-α-*phenylethyl*-P-*t-butylphosphonamidic acid* (**12**) (3.56 g, 39%), m.p. 181—182.5 °C (from dichloromethane–toluene); $\nu_{max.}$(Nujol) 3 260 (NH), 2 640, 2 130, and 1 630 (all br, OH), and 1 165 cm^{-1}; $\delta_H(CDCl_3)$ 7.4—7.1 (5 H, m), 5.35br (2 H, NH and OH), 4.48 (1 H, dq, $J_{PH} \sim J_{HH} \sim 7$ Hz), 1.47 (3 H, d, J_{HH} 7 Hz), and 1.07 (9 H, d, J_{PH} 15 Hz); $\delta_P(CH_2Cl_2)$ 42.6 (Found: C, 59.7; H, 8.3; N, 5.8. $C_{12}H_{20}NO_2P$ requires C, 59.7; H, 8.4; N, 5.8%).

N-(S)-α-*Phenylethyl*-P-*t-butylphosphonamidic Chloride* (**8**).—Oxalyl chloride (2.60 g, 20.5 mmol) was added to a stirred solution of *N*-(*S*)-α-phenylethyl-*P*-t-butylphosphonamidic acid (1.65 g, 6.83 mmol) in dichloromethane (30 ml) at room temperature. After 1 h volatile material was evaporated off and a mixture of ether–light petroleum (1:2) was added to precipitate N-(S)-α-*phenylethyl*-P-*t-butylphosphonamidic chloride* (**8**) (1.26 g, 71%) as a mixture of diastereoisomers (3:2 after crystallisation from toluene–light petroleum), m.p. 126—128 °C; *m/z* 261, 259 (M^+; 0.5, 1.5%), 246, 244 (M^+ − Me; 5, 15%), 120 (55), and 105 (100); $\nu_{max.}$(Nujol) 3 210 (NH), 1 230, and 1 200 cm^{-1}; δ_H($CDCl_3$; 300 MHz) includes 1.62 (d, J_{HH} 7 Hz) and 1.26 (d, J_{PH} 20 Hz) (major diastereoisomer); 1.55 (d, J_{HH} 7 Hz) and 1.28 (d, J_{PH} 20 Hz) (minor diastereoisomer); δ_P($CDCl_3$) 59.3 (major) and 59.6 (minor) (Found: C, 55.5; H, 7.4; Cl, *ca.* 14.0; N, 5.4. $C_{12}H_{19}ClNOP$ requires C, 55.5; H, 7.4; Cl, 13.65; N, 5.4%).

A portion (0.35 g) of the diastereoisomer mixture was flash chromatographed on a column of silica (60 μm; 15 × 2 cm). The column was eluted with light petroleum (b.p. 40—60 °C)–ethyl acetate (7:3) and 10 ml fractions were collected. Fractions 9—15 were combined and crystallised from ether–light petroleum to give the major diastereoisomer of (**8**) (0.17 g), R_F 0.35, m.p. 125—126 °C; δ_H($CDCl_3$; 300 MHz) 7.4—7.2 (5 H, m), 4.83 (1 H, m), 3.15 (1 H, NH), 1.62 (3 H, d, J_{HH} 7 Hz), and 1.26 (9 H, d, J_{PH} 20 Hz). Fractions 22—33 similarly afforded the minor diastereoisomer of (**8**) (0.07 g), R_F 0.27, m.p. 122—123 °C; δ_H($CDCl_3$, 300 MHz) 7.45—7.25 (5 H, m), 4.72 (1 H, m), 3.15 (1 H, NH), 1.55 (3 H, d, J_{HH} 7 Hz), and 1.28 (9 H, d, J_{PH} 20 Hz).

N-(S)-α-*Phenylethyl*-N′,P-*di-t-butylphosphonic Diamide* (**14**; R = Bu^t).—The phosphonamidic chloride (**8**) (mixture of diastereoisomers) (60 mg, 0.23 mmol) was heated with t-butylamine (0.76 g, 10.5 mmol) in dichloromethane (4 ml) for 3.5 h. The reaction mixture was filtered and the filtrate was washed with water (2 × 1 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the crude phosphonic diamide (56 mg, 83%) as a 1:1 mixture of diastereoisomers (^1H and ^{31}P n.m.r.). Crystallisation from light petroleum afforded pure N-(S)-α-*phenylethyl*-N′,P-*di-t-butylphosphonic diamide* (**14**; R = Bu^t) as a 3:2 diastereoisomer mixture, R_t 7.4 (minor) and 7.8 min (major) (BP 10, 240 °C), m.p. 140—145 °C; *m/z* 296 (M^+, 7%), 281 (M^+ − Me, 45), 120 (50), and 105 (100); $\nu_{max.}$(Nujol) 3 390, 3 285 (NH), and 1 175 cm^{-1}; δ_H($CDCl_3$; 300 MHz) 7.4—7.2 (5 H, m), 4.55 (1 H, m), 2.45 (1 H, m, NH), 2.00 (1 H, NH), 1.51 (major diastereoisomer) and 1.48 (minor diastereoisomer) (total 3 H; both d, J_{HH} 7 Hz), 1.35 (major) and 1.17 (minor) (total 9 H; both s, NBu^t), and 1.12 (minor) and 0.98 (major) (total 9 H; both d, J_{PH} 15 Hz, PBu^t); δ_P(CH_2Cl_2) 33.3 (major) and 34.1 (minor) (Found: C, 64.9; H, 9.8; N, 9.4. $C_{16}H_{29}N_2OP$ requires C, 64.8; H, 9.9; N, 9.45%).

N-*Isopropyl*-N′-(S)-α-*phenylethyl*-P-*t-butylphosphonic Diamide* (**14**; R = Pr^i).—Treatment of the phosphonamidic chloride (**8**) with isopropylamine as above (reaction time 12 h at room temperature) gave the *phosphonic diamide* (**14**; R = Pr^i) (81%) as a 1:1 diastereoisomer mixture, R_t 7.4 and 7.9 min (BP 10, 240 °C), m.p. 98—104 °C; *m/z* 282 (M^+, 7%), 267 (M^+ − Me, 25), 120 (50), and 105 (100); $\nu_{max.}$(Nujol) 3 395, 3 240 (NH), and 1 175 cm^{-1}; δ_H($CDCl_3$; 300 MHz) 7.4—7.2 (5 H, m), 4.53 (1 H, m), 3.6—3.3 (1 H, m), 2.45 (1 H, NH), 1.92 and 1.57 (total 1 H; NH), 1.50 and 1.48 (total 3 H; both d, J_{HH} 7 Hz), 1.21, 1.07, 1.02, and 1.00 (total 6 H, all d, J_{HH} 6.5 Hz, NPr^i), and 1.14 and 1.06 (total 9 H; both d, J_{PH} 15 Hz, PBu^t); δ_P(MeCN) 34.7 and 35.3 (Found: C, 63.7; H, 9.55; N, 9.9. $C_{15}H_{27}N_2OP$ requires C, 63.8; H, 9.6; N, 9.9%).

N-Methyl-N′-(S)-α-*phenylethyl*-P-*t-butylphosphonic Diamide* (**14**; R = Me).—Treatment of the phosphonamidic chloride (**8**) with methylamine as above (reaction time 40 min at room temperature) gave the *phosphonic diamide* (**14**; R = Me) (86%) as a 3:2 mixture of diastereoisomers (crystallised from toluene–light petroleum), R_t 8.5 (major) and 9.1 min (minor) (BP 10, 240 °C), m.p. 117—125 °C; *m/z* 254 (M^+, 9%), 239 (M^+ − Me, 40), and 105 (100); $\nu_{max.}$(Nujol) 3 300, 3 200 (NH), and 1 155 cm^{-1}; δ_H($CDCl_3$; 300 MHz) 7.4—7.2 (5 H, m), 4.5 (1 H, m), 2.58 (minor) and 2.50 (major) (total 3 H; both dd, J_{PH} 11, J_{HH} 5.5 Hz, NMe), 2.48 (1 H, NH), 2.19 and 1.88 (total 1 H, NH), 1.51 (3 H, d, J_{HH} 7 Hz), and 1.16 (major) and 1.10 (minor) (total 9 H; both d, J_{PH} 15 Hz, PBu^t); δ_P(CH_2Cl_2) 38.1 (minor) and 38.3 (major) (Found: C, 61.6; H, 9.1; N, 11.0. $C_{13}H_{23}N_2OP$ requires C, 61.4; H, 9.1; N, 11.0%).

Stereochemical Study of Reactions of N-(S)-α-*Phenylethyl*-P-*t-butylphosphonamidic Chloride* (**8**).—The single diastereoisomers of the phosphonamidic chloride (**8**) (R_F 0.35 or 0.27) were treated with t-butylamine (10 mol equiv.) as a solution in acetonitrile (or CH_2Cl_2) of the required concentration (Table). The reaction vessel was securely stoppered to minimise evaporation (Bu^tNH_2, b.p. 46 °C) and was maintained at 25—27 °C until the reaction was complete. Both the progress of reaction and the diastereoisomer composition of the product were monitored by g.l.c. (BP 10, 240 °C): phosphonamidic chloride, R_t 6.6 min (diastereoisomers not resolved); phosphonic diamide (**14**; R = Bu^t) diastereoisomers, R_t 7.4 and 7.8 min. The values of the product diastereoisomer ratio shown in the Table relate to measurements made at (or close to) completion, but they were the same (within experimental error) at all stages of reaction. Reactions with neat amine were also examined.

Experiments with isopropylamine (b.p. 33—34 °C) were carried out in the same way except that, because of the volatility of the amine, sealed tubes were generally used. These reactions were examined by g.l.c. only at (or close to) completion: phosphonic diamide (**14**; R = Pr^i) diastereoisomers, R_t 7.4 and 7.9 min.

Reactions with methylamine were examined under only one set of conditions, *i.e.* using an approx. 9M (25% w/w) solution in dichloromethane; phosphonic diamide (**14**; R = Me) diastereoisomers, R_t 8.5 and 9.1 min.

For the substrate (**8**) (R_F 0.35), the short R_t diastereoisomer of the phosphonic diamide (**14**) was the major product with all three amines at all concentrations; for the substrate (**8**) (R_F 0.27), the long R_t diastereoisomer of the diamide (**14**) became the major product at high amine concentrations.

The configurational stability of the phosphonamidic chloride (**8**) under the conditions of the substitution reactions was examined as follows. The phosphonamidic chloride (**8**) (R_F 0.35) (9.8 mg, 0.038 mmol) was dissolved in a 1M solution of isopropylamine (0.38 mmol) in acetonitrile. After 20 min at 26 °C, the volatile material was removed and the residue was examined by ^1H n.m.r. spectroscopy ($CDCl_3$; 300 MHz). Signals for the product (**14**; R = Pr^i) (20%) included δ 1.48 (d, J_{HH} 7 Hz, Me) and 1.14 (d, J_{PH} 15 Hz, PBu^t) (major diastereoisomer), and δ 1.50 (d, J_{HH} 7 Hz, Me) and 1.07 (d, J_{PH} 15 Hz, PBu^t) (minor diastereoisomer), ratio 55:45. Signals for the remaining phosphonamidic chloride (**8**) (80%) included δ 1.63 (d, J_{HH} 7 Hz, Me) and 1.26 (d, J_{PH} 20 Hz, PBu^t); the other diastereoisomer of (**8**) (R_F 0.27) [δ 1.56 (d, J_{HH} 7 Hz, Me)] amounted to <2%. For a similar experiment using t-butylamine the signals for the product (**14**; R = Bu^t) (17%) included δ 1.17 (s, NBu^t) and 1.12 (d, J_{PH} 15 Hz, PBu^t) (major diastereoisomer), and δ 1.35 (s, NBu^t) and 0.98 (d, J_{PH} 15 Hz, PBu^t) (minor diastereoisomer), ratio 57:43. The signals for the remaining phosphonamidic chloride (83%) were exactly as above. Similar results were obtained using dichloromethane as solvent, except that reaction was only 8% complete after 50 min.

Reactions of N-(S)-α-*Phenylethyl*-P-*t-butylphosphonamidic Chloride* (**8**) *Under Competitive Conditions.*—The phosphonamidic chloride (**8**) (mixture of diastereoisomers) (30—40 mg) was added to an acetonitrile solution of an equimolar mixture of isopropylamine and t-butylamine (20 mol equiv.) of the required concentration (total amine 0.5, 1.0, 2.0, 4.0, or 8.0M). The mixture was maintained at 25—26 °C in a tightly stoppered vessel until reaction was complete (g.l.c.). After concentration or dilution where appropriate, the mixture was examined (in duplicate) by ^{31}P n.m.r. spectroscopy. The molar ratio ($NHPr^i$:$NHBu^t$) of the phosphonic diamide products (**14**; R = Pr^i) [δ_P(MeCN) 35.3 and 34.7 (diastereoisomers)] and (**14**; R = Bu^t) [δ_P(MeCN) 33.9 and 33.5 (diastereoisomers)] was deduced from the relative intensities of the peaks in the spectrum. Assuming an equal spectrometer response for the different products, the $NHPr^i$:$NHBu^t$ ratio was 1.30 ± 0.05 at all amine concentrations.

Rate Study of Reactions of N-(S)-α-*Phenylethyl*-P-*t-butylphosphonamidic Chloride* (**8**).—The phosphonamidic chloride (**8**) (*ca.* 1:1 mixture of diastereoisomers) (10 μmol) in acetonitrile was mixed with t-butylamine (200 μmol) in acetonitrile to give a reaction mixture having [Bu^tNH_2] = 0.50, 1.00, or 2.00M. Portions of the reaction mixture (each containing ~0.7 μmol of substrate) were quickly transferred to capillary tubes (*ca.* 14) which were sealed and placed in a thermostat bath at 25.8 °C. At regular intervals a tube was removed and a large excess of methanol (≥40 molar excess with respect to Bu^tNH_2) immediately added. Control experiments showed that the reaction with Bu^tNH_2 was effectively quenched in this way, the remaining phosphonamidic chloride being converted entirely into the methyl phosphonamidate (**17**). When sufficient time had elapsed to ensure completion of the quenching reaction (20 h for reaction with 2.0M amine, 40 h otherwise), the contents of the tubes were examined by g.l.c. (3% OV 225, 207 °C): methyl phosphonamidate (**17**), R_t 3.3 min (diastereoisomers not resolved); phosphonic diamide product (**14**; R = Bu^t), R_t 5.6 and 6.3 min (diastereoisomers). The peak areas were measured and, making allowance for the different detector responses [(**17**):(**14**; R = Bu^t) = 1.4:1], the amounts (mol %) of product (**14**; R = Bu^t) and phosphonamidate (**17**) (corresponding to unchanged substrate at time of quenching) in each tube were deduced. For each concentration of Bu^tNH_2, the pseudo-first-order rate constant ($k_{obs.}$) was determined (see Results and Discussion) using data from 9—13 tubes quenched over a period of 3.5--5 × $t_{\frac{1}{2}}$.

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