Stereochemistry of Reaction of a Phosphonamidic Chloride with t-Butylamine

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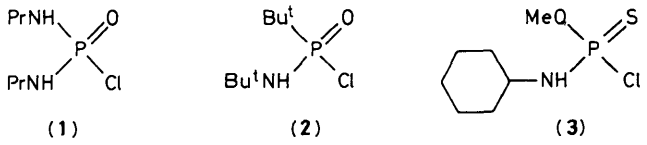
Both diastereoisomers of $Bu^tP(O)(Cl)NHR$ [RNH = (*S*)-PhMeCHNH] give the same mixture (55/45) of the diastereoisomers of $Bu^tP(O)(NHBu^t)NHR$ on reaction with Bu^tNH_2 in dilute MeCN solution, but some stereospecificity is seen at higher amine concentrations.

Nucleophilic substitution at a phosphoryl (P=O) centre usually proceeds by an associative [$S_N2(P)$] mechanism.[1] For acyclic substrates with good leaving groups, the stereochemical outcome is generally inversion of configuration at phosphorus.[2] Some phosphoryl halides having one or more NH groups attached to the P atom show unexpectedly high reactivity towards basic nucleophiles *e.g.* (**1**) with aqueous hydroxide,[3] (**2**) with t-butylamine.[4] In such cases substitution is thought to proceed by an elimination–addition (EA) mechanism with a 3-co-ordinate P^V intermediate [*e.g.* (**9**)] analogous to monomeric metaphosphate.[5] The only pertinent stereochemical study is that of Gerrard and Hamer.[6] Using optically active samples of the thiophosphoryl substrate (**3**) they found that hydrolytic replacement of chloride proceeds stereospecifically in neutral solution, but with extensive racemisation under basic conditions. Racemisation is in accord with a mechanism involving a planar 3-co-ordinate P^V intermediate. Important as this is, the fact that the substrate contains a P=S group necessarily limits its general significance. We have therefore prepared the P=O compound (**8**) and examined the stereochemistry of its reaction with t-butylamine.

t-Butylphosphonic dichloride (**4**) did not react with (*S*)-α-methylbenzylamine under normal conditions and the phosphonamidic chloride (**8**) could not be obtained directly. The dichloride was therefore converted into the salt (**6**) [presumably *via* (**5**)] by treatment with water (1.5 mol equiv.) in (*S*)-α-methylbenzylamine (6 mol equiv.) at room temperature overnight. Acidification (CF_3CO_2H) liberated the free phosphonamidic acid (**7**), m.p. 181—182.5 °C, which with oxalyl chloride gave (**8**) as an unequal mixture of diastereoisomers.† Flash chromatography [silica gel; eluant light petroleum–ethyl acetate (7 : 3)] and crystallisation afforded pure samples of the individual diastereoisomers of (**8**); R_f 0.35, δ($CDCl_3$) 1.62 (d, J_{HH} 7 Hz, Me) and 1.26 (d, J_{PH} 20 Hz, Bu^t) (major diastereoisomer); and R_f 0.27, δ($CDCl_3$) 1.55 (d, J_{HH} 7 Hz, Me) and 1.28 (d, J_{PH} 20 Hz, Bu^t).

The phosphonamidic chloride (**8**) reacted with an excess of a 1 M solution of t-butylamine in acetonitrile ($t_{0.5}$ *ca.* 1 h at 27 °C) to give the phosphonic diamide (**10**). The diastereoisomers of (**10**) could be resolved by g.l.c. (25 m bonded-phase capillary equivalent of OV-17 at 240 °C) and distinguished by

† A single enantiomer of α-methylbenzylamine was used so that both (**8**) and (**10**) were obtained as just two stereoisomers. For the work described in this communication, however, the racemic amine should be equally satisfactory. The new compounds (**7**), (**8**), and (**10**) were fully characterised by spectroscopy and elemental analysis.

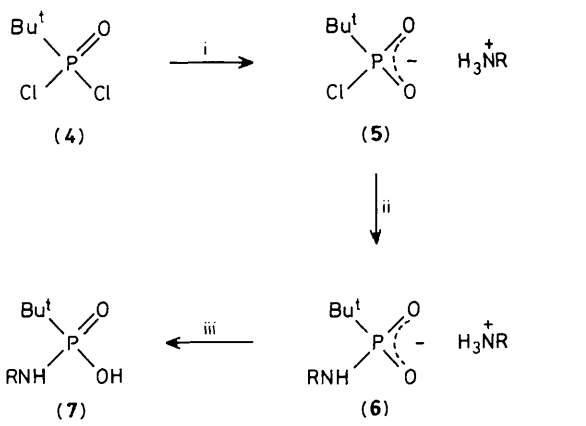


(1) (2) (3)

^{1}H n.m.r. spectroscopy; R_t 7.4 min, δ($CDCl_3$) 1.48 (d, J_{HH} 7 Hz, Me), 1.17 (s, NBu^t), and 1.12 (d, J_{PH} 15 Hz, PBu^t); R_t 7.8 min, δ($CDCl_3$) 1.50 (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 diastereoisomer (R_f 0.27) it was 53/47. The same diastereoisomer of (**10**) (R_t 7.4 min) was the major product in both cases. The significance of the results was established by means of a control experiment in which the reaction of (**8**) (R_f 0.35) was halted before completion. Analysis of the mixture by ^{1}H n.m.r. spectroscopy showed the product (**10**) (17%) to be present as a 57/43 mixture of diastereoisomers, and the unreacted phosphonamidic chloride to be still a single diastereoisomer. Since the phosphonamidic chloride is configurationally stable, the composition of the product can be taken as a true representation of the stereochemical course of substitution.

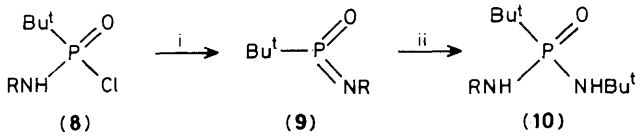
The product diastereoisomer ratios observed with 1 M t-butylamine imply that totally non-stereospecific reaction ('racemisation') should result in a 55/45 ratio, whichever diastereoisomer of (**8**) is used, and this was actually observed (±0.5%) when the reactions were repeated at higher dilution (0.125 M Bu^{t}NH$_2$). It therefore seems that (**8**) can undergo substitution by way of an intermediate monomeric metaphosphonimidate (**9**) that is free in as much as it has a significant existence independent of the nucleophile and leaving group. By contrast, stereospecific inversion of configuration has been observed for substitution reactions that (by other criteria) proceed *via* monomeric metaphosphate.[7] These experiments have, however, been conducted under solvolytic conditions (high nucleophile concentration) in protic media, where the metaphosphate intermediate is least likely to become free.[7]‡

At higher concentrations of amine the reactions of (**8**) (R_f 0.35) showed increasing stereospecificity, the product diastereoisomer ratio reaching 83/17 in neat-t-butylamine. It could be that an increasing proportion of the reaction now goes stereospecifically by the S_N2(P) mechanism (although we do not know that it is inversion of configuration that predominates), but the result of a competitive experiment seems to rule out that possibility. For steric reasons isopropylamine is much more reactive than t-butylamine in S_N2(P). Yet when (**8**) was allowed to react with a large excess of an equimolar Pr^{i}NH$_2$–Bu^{t}NH$_2$ mixture (neat or in MeCN), the same small NHPr^i/NHBu^t product ratio, 1.30 ± 0.05, was observed whatever the amine concentration.§ This implies that the



RNH = (*S*)-PhMeCHNH

Scheme 1. *Reagents:* i, H_2O, RNH_2; ii, RNH_2; iii, CF_3CO_2H.



RNH = (*S*)-PhMeCHNH

Scheme 2. *Reagents:* i, Bu^{t}NH$_2$ (−Bu^{t}NH$_3$Cl); ii, Bu^{t}NH$_2$.

S_N2(P) mechanism provides little (if any) competition to EA even when isopropylamine is present. When t-butylamine is the only available nucleophile the S_N2(P) mechanism can be of no significance. It therefore seems likely that (**8**) reacts with t-butylamine by an EA mechanism at all amine concentrations, but it is only at low concentrations that the metaphosphonimidate (**9**) becomes completely free. At higher concentrations some of the reaction follows a preassociation pathway in which the nucleophile is already in position when the metaphosphonimidate is formed.[8]

We thank the S.E.R.C. for a research studentship.

Received, 26th June 1985; Com. 901

References

1 J. Emsley and D. Hall, 'The Chemistry of Phosphorus,' Harper and Row, London, 1976, ch. 8.
2 C. R. Hall and T. D. Inch, *Tetrahedron*, 1980, **36**, 2059 (see p. 2079).
3 P. S. Traylor and F. H. Westheimer, *J. Am. Chem. Soc.*, 1965, **87**, 553.
4 M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2127.
5 F. H. Westheimer, *Chem. Rev.*, 1981, **81**, 313; M. Regitz and G. Maas, *Top. Curr. Chem.*, 1981, **97**, 71.
6 A. F. Gerrard and N. K. Hamer, *J. Chem. Soc (B)*, 1968, 539; 1969, 369.
7 S. L. Buchwald and J. R. Knowles, *J. Am. Chem. Soc.*, 1982, **104**, 1438; S. L. Buchwald, J. M. Friedman, and J. R. Knowles, *ibid.*, 1984, **106**, 4911.
8 W. P. Jencks, *Acc. Chem. Res.*, 1980, **13**, 161; *Chem. Soc. Rev.*, 1981, **10**, 345.

‡ *Added in proof*: It has been shown that the metaphosphate generated by the Conant–Swan fragmentation goes on to product with inversion of configuration at phosphorus, implying that even when formed by fragmentation the metaphosphate is not completely free (K. C. Calvo, *J. Am. Chem. Soc.*, 1985, **107**, 3690). On the other hand, some substitution reactions having metaphosphate character have been found to proceed with extensive racemisation when carried out using relatively low concentrations of nucleophile in aprotic solvents (P. M. Cullis and A. Rous, *J. Am. Chem. Soc.*, in the press; J. M. Friedman and J. R. Knowles, *ibid.*, in the press).

§ In contrast PhP(O)(Cl)NMe$_2$, which can not react by an EA mechanism, gives an NHPr^i/NHBu^t product ratio >50/1.