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AN ELIMINATION-ADDITION MECHANISM FOR SOME PHOSPHONAMIDIC CHLORIDE-AMINE REACTIONS

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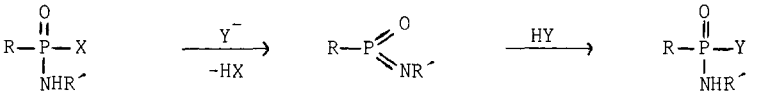
For the reactions of RP(O)(NHBu^t)Cl with Pr^{i}NH$_2$ and Bu^{t}NH$_2$ in CH$_2$Cl$_2$, relative rates and product ratios suggest an elimination-addition mechanism with a reactive (monomeric) metaphosphonimidate intermediate.

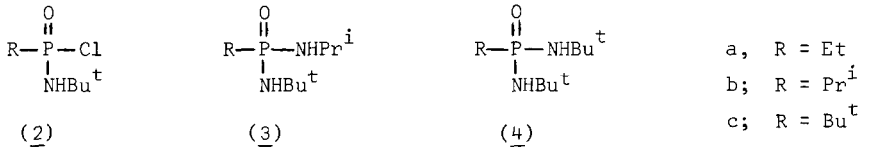
Nucleophilic substitution at a phosphoryl centre usually proceeds by an associative mechanism, with a five-coordinate transition state or intermediate. When the phosphorus atom is bonded to an NH group an elimination-addition (EA) pathway, with a three-coordinate intermediate (1), is in principle also possible.[1]



(1)

Species such as (1) are of particular interest because of their formal resemblance to the highly reactive monomeric metaphosphate,[2] and they are thought to be intermediates in the alkaline hydrolysis of some phosphoric acid derivatives such as (RNH)$_2$P(O)Cl.[3] Our concern is with the possible involvement of monomeric metaphosphonimidates (1, R = alkyl) in the substitution reactions of phosphonic acid derivatives, especially in non-hydroxylic solvents with nucleophiles less basic than hydroxide.

The phosphonamidic chlorides (2a) and (2b) were prepared by addition of Bu^{t}NH$_2$ (2 equiv.) to the appropriate phosphonic dichloride. Compound (2c) could not be obtained in this way from Bu^{t}P(O)Cl$_2$; it was therefore prepared by oxidation (SO_2Cl_2) of the product formed by treating Bu^{t}PCl$_2$ with Bu^{t}NH$_2$ (2 equiv.).[4]



(2) (3) (4)

a, R = Et
b; R = Pr^i
c; R = Bu^t

The phosphonamidic chlorides (2, a-c) gave the expected phosphonic diamides (3) or (4) with Pr^{i}NH$_2$ or Bu^{t}NH$_2$ in CH_2Cl_2. Monitoring of the reactions by g.l.c. enabled approximate pseudo-first-order rate constants at 23.0 °C, [amine] = 1.33M, to be deduced:

Substrate	2a (R = Et)	2b (R = Pr^i)	2c (R = Bu^t)
10^3 k s^{-1} with Pr^iNH_2	2.5	0.60	0.38
10^3 k s^{-1} with Bu^tNH_2	1.1	0.40	0.25

With both amines there is only a modest decrease in rate as the bulk of the P-alkyl group increases Et → Pr^i → Bu^t. Such behaviour is in marked contrast to that usually found for substitution at phosphorus; for example, $EtP(O)Cl_2$ hydrolyses 26 and >10^5 times faster than $Pr^iP(O)Cl_2$ and $Bu^tP(O)Cl_2$ respectively.[5] Moreover, the phosphonamidic chlorides (2) react almost as quickly with Bu^tNH_2 as with the less hindered Pr^iNH_2, whereas $(Pr^iO)_2P(O)Cl$ reacts with Bu^tNH_2 60 times less quickly than with Bu^sNH_2.[6]

The low sensitivity of our reactions to steric effects seems incompatible with an associative mechanism involving rate-limiting nucleophilic attack at phosphorus. At the same time, the fact that the substrates (2) react much less readily with aniline implies that the nature of the amine is important. We therefore suggest an EA mechanism, with Pr^iNH_2 or Bu^tNH_2 acting as a base to convert the substrate into a metaphosphonimidate, and as a nucleophile to trap the metaphosphonimidate in a subsequent fast step.

The results of competitive experiments are consistent with a reactive intermediate that discriminates only poorly between different nucleophiles. Thus in CH_2Cl_2 containing a large excess of an equimolar mixture of Pr^iNH_2 and Bu^tNH_2, the phosphonamidic chlorides (2) give substantial amounts of the product (4) derived from the more hindered amine; by contrast, $Ph_2P(O)Cl$ gives exclusively $Ph_2P(O)NHPr^i$ under similar conditions. The product ratio (3):(4) at 0 °C is 1.4:1 (by g.l.c.) for both (2b) and (2c) and 2.4:1 for (2a). In the case of (2a), which is relatively uncrowded, it may be that direct nucleophilic attack by Pr^iNH_2 competes with the EA mechanism.

The ability of a phosphonamidic chloride to react by a non-associative mechanism may have important practical consequences. Thus, for example, it enables (2c) to react >300 times faster than $Bu^tP(O)Cl_2$ with Bu^tNH_2, even though it is sterically more crowded. It is for this reason that (2c) could not be prepared by the method that was used for (2a) and (2b).

References and Footnotes

1. J. Emsley and D. Hall, The Chemistry of Phosphorus, Harper and Row, Chap. 8.
2. A.C. Satterthwait and F.H. Westheimer, J. Am. Chem. Soc., 1981, 103, 1177 and references therein; P. Haake and G.W. Allen, Biorganic Chem., 1980, 9, 325.
3. P.S. Traylor and F.H. Westheimer, J. Am. Chem. Soc., 1965, 87, 553; E.W. Crunden and R.F. Hudson, J. Chem. Soc., 1962, 3591.
4. The phosphonamidic chlorides (2) and their reaction products were stable, crystalline compounds. They were characterised spectroscopically and by elemental analysis.
5. A.A. Neimysheva and I.L. Knunyants, J. Gen. Chem. U.S.S.R., 1968, 38, 575; 1972, 42, 2415.
6. I. Dostrovsky and M. Halmann, J. Chem. Soc., 1953, 511. With MeP(O)(OEt)Cl Bu^tNH_2 is only ca. 4.5 times less reactive than Bu^sNH_2 (L. Keay, J. Org. Chem., 1963, 28, 329) but this unhindered substrate seems less appropriate for comparison with the phosphonamidic chlorides (2).

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