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The elimination–addition mechanism of nucleophilic substitution at an alkylphosphonyl centre: stereospecificity, non-stereospecificity and the alkylidineoxophosphorane (phosphene) intermediate

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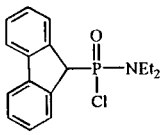
The substitution reactions of $R'_2CHP(O)(NMeR^*)Cl$ (R'_2CH = fluoren-9-yl; R* = CHMePh) with secondary amines (Me_2NH, Et_2NH, Pr^iNHEt) are largely stereospecific or non-stereospecific depending on the bulk of the amine and its concentration; two elimination–additon pathways, differing in whether or not the phosphene intermediate $R'_2C{=}P(O)NMeR^*$ becomes liberated, may be responsible.

Methyleneoxophosphoranes, or phosphenes, are the phosphorus analogs of sulfenes.[1] Like other three-coordinate P^V species they generally have only a fleeting existence in solution.[2] They have been generated in some oxidation,[3] fragmentation[4] and rearrangement[5] reactions, but unlike sulfenes they have not been implicated as intermediates in nucleophilic substitution.[6] A possible exception is the conversion of the fluorenylphosphonamidic chloride **1** into the phosphonic



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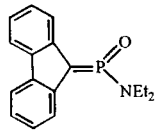

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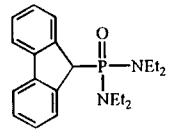

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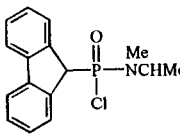

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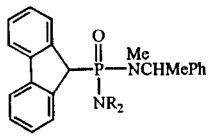

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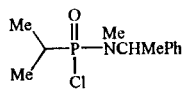

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diamide **3** with Et_2NH.[7] On steric grounds (substrate and nucleophile) this should proceed very slowly, at least by the normal associative $S_N2(P)$ mechanism,[8] but in fact it proceeds quite readily.[7] It may be that in this case the acidity of the C_α–H bond in the substrate makes a dissociative elimination–addition mechanism, with a phosphene intermediate **2**, more accessible than is usual. We hoped that a stereochemical study, using a substrate related to **1**, would help to clarify the role of phosphene intermediates in nucleophilic substitution.

The phosphonamidic chloride **4** was prepared by treating fluoren-9-ylphosphonic dichloride[7] with (S)-(−)-PhMeCHNHMe (2.5 equiv.) in CH_2Cl_2 (1 : 1 v/v amine–CH_2Cl_2). Chromatography (silica gel; 1 : 6 EtOAc–light petroleum) and crystallisation afforded pure (≥99%) samples of the individual diastereoisomers of **4**: sample **A**, mp 145–147 °C; $\delta_P(CDCl_3)$ 43·0; $\delta_H(CDCl_3)$ 4.99 (d, J_{PH} 29, >CH), 1.61 (d, J_{PH} 12.5, NMe) and 0.68 (d, J_{HH} 7, CH*Me*); sample **B**, mp 103.5–104.5 °C; $\delta_P(CDCl_3)$ 43.15; $\delta_H(CDCl_3)$ 4.98 (d, J_{PH} 30, >CH), 1.62 (d, J_{PH} 13, NMe) and 1.33 (d, J_{HH} 7, CHMe).†

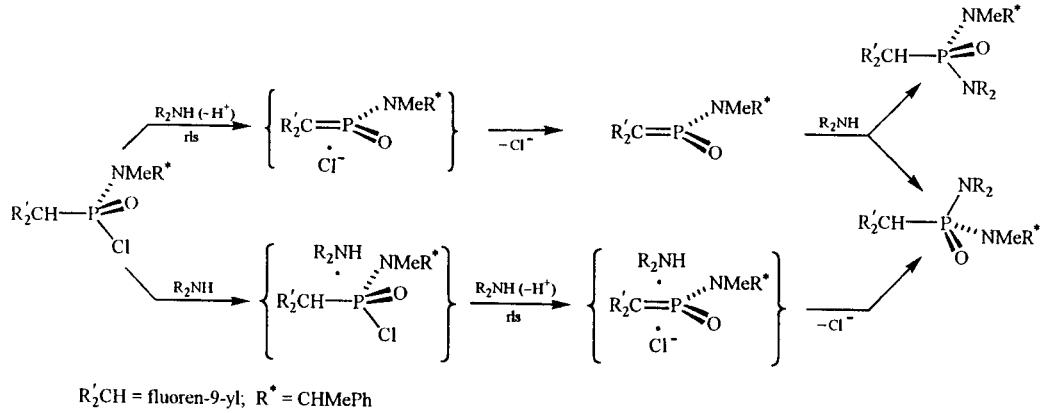
The two samples (**A** and **B**) of the substrate **4** were allowed to react with Et_2NH (large excess) as a 1.2 mol dm^{-3} solution in $CHCl_3$ at 31 °C. In both cases the phosphonic diamide **5** (R = Et), *m/z* 418 (M^+, 10%) and 253 ($M^+ - C_{13}H_9$, 100), was obtained as an unequal mixture of diastereoisomers: $\delta_P(CDCl_3)$ 34.25; $\delta_H(CDCl_3)$ 4.93 (d, J_{PH} 27, >CH), 2.18 (d, J_{PH} 9.5, NMe), 1.48 (d, J_{HH} 7, CH*Me*) and 0.80 (t, J_{HH} 7, NCH_2*Me*) (major from **A**); $\delta_P(CDCl_3)$ 34.65; $\delta_H(CDCl_3)$ 4.96 (d, J_{PH} 26, >CH), 1.82 (d, J_{PH} 9.5, NMe), 0.96 (t, J_{HH} 7, NCH_2*Me*) and 0.81 (d, J_{HH} 7, CH*Me*) (major from **B**). Monitoring the reactions by ^{31}P NMR spectroscopy showed that stereoisomerisation of the substrate was slight (≤3%) up to 50% completion (*t* = 9.5 h for **A**, 6 h for **B**) and the diastereoisomer ratio of the product did not change significantly as the reaction progressed. The observed product diastereoisomer ratios, 33 : 67 from **A** and 77 : 28 from **B**, can therefore be taken as a true indication of how the diastereoisomers of the substrate **4** react with Et_2NH.

The reactions clearly fall between the extremes of complete stereospecificity (product diastereoisomer ratios 0 : 100 and 100 : 0) and complete non-stereospecificity (ratios same; not necessarily 50 : 50). A likely explanation is that two mechanisms are operating in parallel, one stereospecific and the other non-stereospecific. The obvious candidates for these are $S_N2(P)$ and elimination–addition (EA). In the former the five-coordinate intermediate or transition state would be formed by attack of the nucleophile opposite the leaving group, resulting in inversion of configuration at phosphorus, while in the latter the trigonal three-coordinate phosphene intermediate would be susceptible to attack at either of its diastereotopic faces.

Consistent with that picture is the behaviour of **4** with other amines. Me_2NH differs little from Et_2NH in basicity but, for steric reasons, it is much more nucleophilic towards a tetrahedral P=O centre [≥100 times with $Pr^iP(O)(NEt_2)Cl$ as substrate[7]]. The $S_N2(P)$ pathway should therefore be more important with Me_2NH and increased stereospecificity was indeed observed; using 1.2 mol dm^{-3} Me_2NH in $CHCl_3$ the product **5** (R = Me) [$\delta_P(CDCl_3)$ 35.15 and 34.3] was formed with diastereoisomer ratios of 6 : 94 from **A** and 97 : 3 from **B**. Conversely, Pr^iNHEt is much less nucleophilic than Et_2NH and reduced stereospecificity was observed; with 1.2 mol dm^{-3} Pr^iNHEt the product diastereoisomer ratios were 42 : 58 and 52 : 48 [$\delta_P(CDCl_3)$ 34.3 and 34.2]. Nonetheless, there are two reasons why the competing $S_N2(P)$–EA picture seems unsustainable.

First, the reaction of the fluorenyl substrate **4** with Me_2NH is some 50 times *faster* than the corresponding reaction of the analogous isopropyl compound **6** [$\delta_P(CDCl_3)$ 58.75 and 58.45 (diastereoisomers); product $\delta_P(CDCl_3)$ 42.6 and 41.9].† We would not expect $S_N2(P)$ to be less sterically hindered when the alkyl group on phosphorus is fluorenyl rather than isopropyl, and some evidence supports that view: methanolysis of the phosphonamidic chlorides **4** and **6** under non-basic conditions (MeOH containing 0.2 mol dm^{-3} AgOTf) is 10–20 times *slower* for the fluorenyl compound ($t_{½}$ *ca.* 10 min for **6** but 3 h for **4** at 31 °C). The high reactivity of **4** with Me_2NH thus seems irreconcilable with a mechanism that is predominantly $S_N2(P)$, notwithstanding the high stereospecificity of the reaction.‡

Second, inclusion of a small amount of the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2 equiv.; 0.07 mol dm^{-3}) increases the rate of the reaction of the fluorenyl substrate **4** with Me_2NH (1.2 mol dm^{-3}) *ca.* 100-fold but does not accelerate the reaction [$S_N2(P)$] of the isopropyl analogue **6**. Crucially, the stereochemistry of the reaction of **4** is unaffected



Scheme 1

by the presence of DBU, *i.e.* the reaction is still largely stereospecific [product **5** (R = Me) diastereoisomer ratio 97 : 3 from **B**]. The implication is clear: the stereospecific pathway, like its nonstereospecific counterpart, is base-induced and is not $S_N2(P)$.

One further observation is pertinent. When the Et_2NH concentration was reduced to 0.2 mol dm^{-3} substrate **4** gave the product **5** (R = Et) with a diastereoisomer ratio of 42 : 58 from **A** and 55 : 45 from **B**. This reduced stereospecificity implies that the stereospecific pathway is kinetically of a higher order in amine.

As a whole the results point to two EA pathways, one first order in amine and nonstereospecific, the other second order in amine and stereospecific (or practically so). In the former (Scheme 1, top pathway) the amine acts only as a base in the rate-limiting elimination step, and the resulting phosphene intermediate recombines with the chloride ion, or diffuses away and becomes free before reacting with the nucleophile. In the latter (Scheme 1, bottom pathway) there is preassociation:[9] the nucleophile is already in place when elimination occurs, the phosphene is trapped before it can diffuse away, and the nucleophile becomes attached to that face of the phosphene which is not shielded by the chloride ion.§ Of the two pathways the one involving preassociation will be more sensitive to the bulk of the amine and its concentration. As the amine changes from Me_2NH to Et_2NH to Pr^iNHEt, or the concentration of amine decreases, the contribution of the stereospecific pathway declines; the free phosphene intermediate plays an increasingly important part and the overall reaction becomes increasingly nonstereospecific.

Notes and references

† The new compounds **4** and **6** and the products derived from them were fully characterised by NMR spectroscopy (^{31}P and ^{1}H), mass spectrometry, and elemental analysis and/or accurate mass measurement.

‡ The reaction of **4** with Me_2NH is of an order > 1 in amine; this may also point to a mechanism that is not $S_N2(P)$.

§ The elimination step of the EA mechanism probably involves rapid reversible removal of the C_α proton followed by rate-limiting elimination of chloride from the conjugate base (reversible ElcB) [in the reaction of the 9-deuterio analogue of substrate **1** with Et_2NH, D/H exchange is much faster than substitution (ref. 7)]; for simplicity this detail is omitted from Scheme 1.

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