An Alkylphosphonyl Nucleophilic Substitution Reaction that proceeds by an Elimination–Addition Mechanism with an Alkylidineoxophosphorane (Phosphene) Intermediate

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For the phosphonamidic chloride $R_2CHP(O)(NEt_2)Cl$ having R_2CH = 9-fluorenyl, substitution at phosphorus is unexpectedly fast with Et_2NH as the nucleophile, and discriminates less than is usual between competing Me_2NH and Et_2NH nucleophiles; such behaviour is consistent with an elimination-addition mechanism and a fluorenylidineoxophosphorane intermediate **8**.

Phosphoryl (P=O) and thiophosphoryl (P=S) compounds generally undergo nucleophilic substitution by an associative addition-elimination (AE) mechanism, with a five coordinate intermediate (or transition state).[1] However, when the phosphorus centre in the substrate **1** (X = leaving group) carries a ligand HZ with an acidic hydrogen atom, an alternative dissociative elimination-addition (EA) mechanism is possible. This pathway, which proceeds *via* a three-coordinate P^V intermediate **2**, is often preferred when the ligand HZ is strongly acidic, *i.e.* when Z is oxygen[2] or sulphur,[3] and sometimes when it is only moderately acidic, *i.e.* when Z is nitrogen.[4]

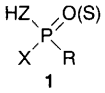
For substrates in which Z is just a saturated carbon atom, there is only one report of an alkylthiophosphonyl compound undergoing substitution by elimination–addition,[5] and none at all of an alkylphosphonyl compound doing so. Methyleneoxophosphorane (phosphene) intermediates such as $H_2C{=}P(O)Ph$ have been generated in other types of reaction, notably oxidation,[6] fragmentation[7] and rearrangement,[8] but not in nucleophilic substitution, at least if one excludes the special case of the substrates **3** (Ar = 4-hydroxyphenyl) which can eliminate HCl using the proton of the phenolic HO group.[9] Even recent attempts using phosphonyl substrates particularly well suited to elimination–addition have not succeeded in diverting reaction away from the normal associative AE pathway.[10] Against that background, the behaviour of the alkylphosphinoyl compound **5b** is, we think, significant.

Controlled hydrolysis of the complex formed by treating 9-bromofluorene with PCl_3–$AlCl_3$ (in CH_2Cl_2 at room temperature) gave the fluorenylphosphonic dichloride **4b**, mp 112–114 °C, δ_P 48.7, δ_H ($CDCl_3$) 5.11 (1 H, d, J_{PH} 23, R_2CH).† This, with Et_2NH (2 equiv.) in CH_2Cl_2, afforded the fluorenylphosphonamidic chloride **5b**, mp 111–113 °C, *m/z* 319, 321 (M^+, 20%), δ_P 42.6, δ_H ($CDCl_3$) 4.89 (1 H, d, J_{PH} 30, R_2CH). Likewise, isopropylphosphonic dichloride **4a** and Et_2NH gave the simple alkylphosphonamidic chloride **5a** (a known compound[11]), δ_P 58.4, δ_H ($CDCl_3$) 2.31 (1 H, d x septet, J_{PH} 12, J_{HH} 7, R_2CH). The rates of reaction of the two phosphonic dichlorides were practically identical; with 1.2 mol dm^{-3} Et_2NH (large excess) in $CHCl_3$ the half-lives for conversion of **4a** into **5a** and **4b** into **5b** were both 2–3 min at 31 °C.

Under the same conditions (1.2 mol dm^{-3} Et_2NH in $CHCl_3$; 31 °C) further reaction of the isopropylphosphonamidic chloride **5a** with Et_2NH was extremely slow; after 6 days only *ca.* 4% had been converted into the phosphonic diamide **6a** (^{31}P NMR).‡ Only by heating **5a** with neat Et_2NH (sealed tube) was a useful sample of the diamide **6a** obtained: bp 150 °C (oven temp.) at 10 mmHg, *m/z* 234 (M^+, 25%), δ_P 42.0, δ_H ($CDCl_3$) 2.07 (1 H, d x septet, J_{PH} 12, J_{HH} 7.5, R_2CH). That this substitution should be so slow is not really surprising; the electronic (π donor) and steric effects of the NEt_2 group will inevitably much reduce the susceptibility of the P=O group to nucleophilic attack, especially with a nucleophile (Et_2NH) that is also quite bulky.

More surprising was the relatively high reactivity of the fluorenylphosphonamidic chloride **5b**: with 1.2 mol dm^{-3} Et_2NH (large excess) in $CHCl_3$ this has a half-life of only *ca* 2.2 h at 31 °C for formation of the diamide **6b**: bp 190 °C (oven temp.) at 0.1 mmHg, *m/z* 356 (M^+, 2.5%), δ_P 34.5, δ_H ($CDCl_3$) 4.85 (1 H, d, J_{PH} 26.5, R_2CH). The fluorenyl compound is thus several hundred times more reactive than its simple isopropyl analogue. A difference of this magnitude clearly suggests a difference in mechanism. In the case of the fluorenyl compound the proton on the α-carbon atom must be quite acidic. With normal associative (AE) attack at phosphorus being greatly hindered this, we think, is enough to divert reaction to the dissociative EA pathway. The NEt_2 group on the phosphorus atom in the substrate will then have relatively little effect, since the rate-limiting step is formation of the methyleneoxophosphorane **8**, *i.e.* the Et_2NH acts as a base, attacking at the proton on the α-carbon atom, not as a nucleophile attacking at phosphorus. Only in the subsequent (fast) reaction of the three-coordinate intermediate **8** does Et_2NH act as a nucleophile and form a bond to the phosphorus atom.

Several additional observations seem also to accord with a dissociative EA mechanism for the reaction of **5b** with Et_2NH. First, when a small part (one fifteenth) of the Et_2NH was replaced by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (more basic; not more nucleophilic), the effect for the isopropyl substrate **5a** was insignificant but for the fluorenyl substrate **5b** it was dramatic: the product was still the diamide **6b** but the rate of reaction was 100 times greater. Second, when Et_2NH was replaced by Me_2NH [more nucleophilic; not more basic] the rate of reaction of the isopropyl substrate **5a** (to give **7a**; δ_P 42.3) increased more than 100-fold (85% conversion in 11 h using 1.2 mol dm^{-3} Me_2NH in $CHCl_3$ at 31 °C) whereas that of the



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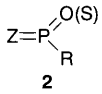

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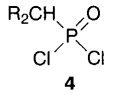

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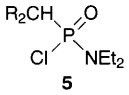

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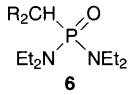

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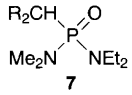

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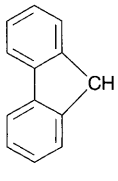
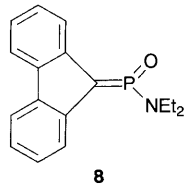
a $R_2CH = Me_2CH$

b $R_2CH =$ 



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fluorenyl substrate **5b** (to give **7b**; δ_P 35.2) increased only 4-fold ($t_{\frac{1}{2}}$ 33 min). Third, using an equimolar Me_2NH–Et_2NH mixture (large excess), the isopropyl substrate **5a** gave only the product **7a** derived from Me_2NH (GLC: ≤0.5% of **6a**) but the fluorenyl substrate **5b** gave a mixture containing a substantial amount (18%) of the product **6b** derived from Et_2NH (ratio **7b**:**6b** = 4.7:1). An associative (AE) substitution would be expected to discriminate strongly in favour of the more nucleophilic (less hindered) amine, whereas a dissociative (EA) substitution, with a reactive and sterically-accessible three coordinate P^V intermediate such as **8**, is likely to be much less selective.

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Footnotes

† All compounds were fully characterised by spectroscopy and, for new compounds, accurate mass measurement and/or elemental analysis.

‡ About 20% of the phosphonamidic chloride **5a** had actually been consumed after 6 days, but only a small part of this had gone to the amide **6a** (δ_P 41.7 in the reaction mixture); several other products (δ_P 28–38) were formed in small amounts, most probably by reactions involving **5a** and traces of moisture. Unchanged **5a** was isolated and its identity confirmed (^1H NMR, IR, GLC).

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