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Reactive species formed from *N*-benzyloxycarbonyl α-aminophosphonochloridates and triethylamine: probable identity and implications for synthesis†

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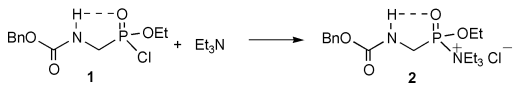
The sterically congested phosphonochloridate BnOCONHCMe$_2$P(O)(OMe)Cl reacts rapidly with Et$_3$N to give what is thought to be an oxazaphospholine oxide 7 (and Et$_3$NHCl); unhindered BnOCONHCH$_2$P(O)(OMe)Cl seems to react in the same way, in which case the product is not a phosphonylammonium salt as has been suggested.

As phosphonopeptides have become important synthetic targets so coupling reactions involving α-aminophosphonic acid derivatives have attracted attention.[1–3] Hirschmann, Smith *et al*.[3] have examined the reactivity of the N-protected α-aminophosphonochloridate **1** in phosphonylation (alcohols and amines), with emphasis on the formation of a new and more reactive phosphonylating agent with Et$_3$N and its reliance on intramolecular catalysis by the carbamate group.[4]

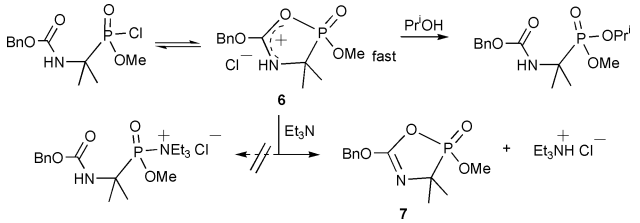
The reaction of **1** with Et$_3$N is accompanied by a rather dramatic downfield shift of the ^{31}P NMR signal (δ_P 35.6 → 44.7 in $CDCl_3$).[3] This, and also the change in selectivity for O *vs*. N nucleophiles, was attributed to the formation of a phosphonylammonium salt **2**.[3] The remarkable ability of chloridate **1** to form the salt was rationalised in terms of *electrophilic* catalysis by the carbamate group, *i.e*. activation of the P=O group by hydrogen bonding with the acidic carbamate NH moiety.[4] That, however, would require formation of a five-membered ring (Scheme 1) and intramolecular hydrogen bonding is generally rather weak in a ring so small.[5] Since intramolecular *nucleophilic* catalysis seems to be responsible for the high reactivity of the α-amidophosphonate ester **3** towards hydrolysis (acid or base)[6] we felt there might be an alternative explanation. That possibility has now been explored using the *N*-benzyloxycarbonyl α-aminophosphonochloridates **4** and **5** (X = Cl).‡



1 **2**

Scheme 1

Evidence was first sought for nucleophilic participation by the carbamate group in the absence of base by examination of the reactions of the chloridates **4** and **5** (X = Cl) with Pr^{i}OH (0.08 mol dm^{-3}) in $CDCl_3$. The expected esters (X = OPr^i) were formed rapidly (≥90% completion in 6 min at rt), with rate enhancements of 10^3–10^4 (for **4**) or ~10^6 (for **5**) relative to analogous substrates lacking the carbamate group [**4** and **5** (X = Cl) with BnOCONH replaced by Cl]. The fact that the sterically congested α,α-dimethyl substrate **5** (X = Cl) is as reactive as its unalkylated counterpart **4** (X = Cl) is mechanistically very significant. If the BnOCONH group were providing electrophilic catalysis of substitution (activation of P=O) the rate-limiting step would involve nucleophilic attack at phosphorus and would be subject to steric hindrance. If there is intramolecular nucleophilic catalysis, however, a reactive cyclic intermediate will be formed in the rate-limiting step and the sterically-sensitive intermolecular nucleophilic attack at phosphorus will occur only in a subsequent fast step (Scheme 2).

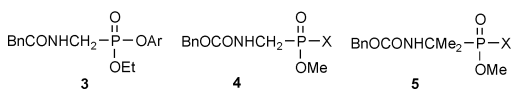


6 **7**

Scheme 2

Our chloridate **4** (X = Cl) differs from **1**, the substrate studied by Hirschmann, Smith *et al*.,[3] only in the identity of the 'spectator' alkoxy group on phosphorus (OMe in place of OEt) so it was predictable that it too would react with Et$_3$N and that the ^{31}P chemical shift would also change quite dramatically (δ_P 37.3 → 45.2 in $CDCl_3$) (product **A**).† By contrast the chemical shift of the sterically congested chloridate **5** (X = Cl) changed little with Et$_3$N (δ_P 47.5 → 48.3). It might be thought that no reaction occurs here because of steric hindrance, and that the small change in δ_P is merely a medium effect. When less than one equivalent of Et$_3$N was used, however, two discrete species (δ_P 47.4 and 48.2) were clearly present. For the reasons outlined below we are certain that the new species (product **B**) is not in this case a phosphonylammonium salt; rather we think it is probably a cyclic oxazaphospholine oxide **7** resulting from nucleophilic participation by the carbamate group (Scheme 2);† an ammonium salt is formed but only as the by-product (Et$_3$NHCl). Hirschmann, Smith *et al*.[3] considered a similar structure for the new phosphonylating agent formed from **1** and Et$_3$N but rejected it as being inconsistent with their data. It is indeed difficult to see how the formation of such a cyclic species could be reliant on intramolecular *electrophilic* catalysis by the NH of the carbamate group.[4]

Our reasons for thinking that product **B** has the structure **7** are as follows. (i) When < 1 equiv. Et$_3$N is used (in $CDCl_3$) and **5** (X = Cl) is only partially converted into **B** the only NMR signal in the region δ_H 2.0–3.8 is a doublet of quartets (δ_H 3.11, dq, *J* 4 and 7, NC*H*$_2$Me). The doublet splitting (4 Hz) does not collapse when the P nucleus is irradiated, implying that the N atom of Et$_3$N has not formed a bond to phosphorus but has simply acquired a proton (NH, δ 11.4). (When > 1 equiv. Et$_3$N is used the detail of the ^{1}H NMR signal is obscured by line broadening, presumably because of exchange between Et$_3$NH$^+$ and Et$_3$N.) (ii) In the ^{13}C NMR spectra of the acyclic compounds **4** and **5**, regardless of the nature of the substituent on phosphorus (X = OH, Cl, OMe, OPr^i), the carbamate carbonyl C atom (δ_C 155.8 ± 1.1) shows only a small three-bond coupling to phosphorus (J_{PC} 0–11 Hz). For product **B**, however, the corresponding signal (δ_C 152.9) displays a rather large coupling (J_{PC} 36 Hz), implying a fundamental change of structure (although we do not know what value of J_{PC} would be



3 **4** **5**

† Electronic supplementary information (ESI) available: NMR data for compounds **4** and **5** (X = Cl) and the products formed by them with Et$_3$N. See http://www.rsc.org/suppdata/cc/b1/b109231f/

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expected for structure **7**). There is also a substantial change in J_{PC} for the α carbon atom, from 152 Hz in **5** (X = OMe) and 134 Hz in **5** (X = Cl) to 107 Hz in **B**. (iii) In the IR spectrum ($CDCl_3$) of **5** (X = Cl) the carbamate C=O gives a strong absorption at 1735 cm^{-1}. When Et_3N is added and product **B** is formed that absorption is replaced by a comparably strong one at 1660 cm^{-1} attributable to a C=N bond (the N–H peak at 3420 cm^{-1} disappears as well). (iv) The chloridate **5** (X = Cl) also reacts with Et_3N (slight excess) in C_6D_6 (δ_P 46.9 → 47.5); a solid (Et_3NHCl) precipitates and the ^1H NMR spectrum shows that product **B** is present in solution. However, the NCH_2Me signal for the solution (δ_H 2.25) is only about a tenth as strong (integral) as it would be if **B** contained an $^+NEt_3$ group and represents little more than the slight excess of the amine.

Taken as a whole the spectroscopic evidence rules out the possibility that product **B** is a phosphonylammonium salt; it is not so conclusive as evidence for a cyclic oxazaphospholine oxide structure **7** but that would be the expected outcome of nucleophilic participation by the carbamate group in the presence of a base if nucleophilic attack at phosphorus is impaired by steric hindrance (Scheme 2). With an unhindered chloridate like **1** or **4** (X = Cl) it is possible to envisage participation being followed by rapid nucleophilic attack and formation of a phosphonylammonium salt. Our attempts to obtain spectroscopic confirmation have been hampered by the relative instability (reactivity) of the lowfield species (product **A**) (δ_P 45.2) formed from **4** (X = Cl) and Et_3N but the following seem to us significant. (i) The 'carbonyl' C atom (δ_C 155.1) in product **A** has a coupling to phosphorus (J_{PC} 42 Hz) as large as that of the imine C atom in **B** and the coupling of C_α (J_{PC} 104 Hz) is again substantially reduced relative to the acyclic compounds **4** (X = OMe or Cl) (J_{PC} 158 or 142 Hz). (ii) The IR spectrum of product **A** shows a strong absorption at 1670 cm^{-1}; a moderately strong peak at 1730 cm^{-1} (C=O) was also present in our spectrum but that could well have resulted from partial hydrolytic regeneration of the carbamate group (a substantial amount of the pyrophosphonate was evident in the ^{31}P NMR spectrum of the solution). (iii) In C_6D_6 the addition of Et_3N (slight excess) again produced a lowfield species (δ_P 46.2), presumably product **A**, but also a precipitate of Et_3NHCl. The ^1H NMR spectrum of the solution was poor because of the insoluble material but the integrals of the NCH_2CH_3 signals (δ_H 2.4 and 0.95) were clearly only about a fifth of what they should be for a compound having an $^+NEt_3$ group.

Rather than confirming product **A** as a phosphonylammonium salt these observations actually suggest (but do not prove) a structure analogous to that of product **B**, *i.e.* an oxazaphospholine oxide **7** with H atoms in place of the Me groups at C_α. Moreover the *N*-methyl derivative of **4** (X = Cl) shows no sign of reaction with Et_3N in the time taken for the parent compound to react completely (< 10 min); since the *N*-methyl derivative is no less reactive in substitution with Pr^iOH (no base) it would be surprising if the reaction of **4** (X = Cl) with Et_3N were formation of a phosphonylammonium salt. Smith, Hirschmann *et al.*[4] likewise noted the failure of the *N*-methyl derivative of their chloridate **1** to react with Et_3N. They supposed the reason to be the lack of activation of the P=O group by intramolecular hydrogen bonding and a consequent loss of the ability to form the phosphonylammonium salt. We think the carbamate group actually acts as a nucleophile, and that where possible (**4** and **5**) the resulting cyclic intermediate is deprotonated by Et_3N (**6** → **7** in Scheme 2) (*cf.* oxazolone formation from activated acylamino acids in peptide synthesis). Where deprotonation is not possible (*N*-methyl derivatives), the cyclic intermediate simply returns to the chloridate.

Two other observations of Smith, Hirschmann *et al.*[4] are now more easily understood. One is the reaction of chloridate **1** with Pr^i_2NEt (Hünig's base): it proceeds in the same way as with Et_3N even though nucleophilic attack at phosphorus now seems most unlikely on steric grounds. The other is the failure of their β-aminophosphonochloridate derivative (structure **31** in ref. 4) to react with Et_3N: it has a fixed conformation about the CO–NH bond that ensures efficient hydrogen bonding between the carbamate NH and the P=O group but which precludes nucleophilic attack at phosphorus by the carbamate C=O group.

Reinterpretation of the observations of Hirschmann, Smith *et al.*[3] need not detract from the value of their procedure and treatment of an α-amidophosphonochloridate with Et_3N *before* the nucleophile is introduced may become the method of choice. Our analysis does suggest some limitations however, at least with sterically hindered chloridates such as **5** (X = Cl). Intramolecular nucleophilic attack[7] is not retarded by the Me groups on C_α but the product-forming intermolecular reaction of the resulting cyclic species potentially is. That will be of little consequence when the intermediate is protonated (as in **6**) because then it is extremely reactive, but when deprotonated (as in **7**) it will be less reactive and product formation may be the slow step. In that case some of the benefit to be had from participation of the neighbouring carbamate group will have been wasted. Thus, for example, the rapid reaction of **5** (X = Cl) with Pr^iOH is at least an order of magnitude slower if the chloridate is pretreated with Et_3N (≥1 equiv). The competing reaction with traces of moisture tends also to be more serious when Et_3N is used because the less reactive (deprotonated) intermediate **7** discriminates more strongly against the less nucleophilic (more hindered) OH group of Pr^iOH.§ If moisture is rigorously excluded, however, enhanced selectivity could be a real advantage with phosphonate acceptors containing two or more competing nucleophilic groups.

Notes and references

‡ The phosphonochloridates **4** and **5** (X = Cl) were prepared from the corresponding dimethyl phosphonates (X = OMe) by partial hydrolysis (2 mol dm^{-3} NaOH, rt, 40 min) (for **4**) or demethylation (2 mol dm^{-3} NaI in acetone, 55 °C, 18 h) (for **5**) and treatment of the resulting monoesters (X = OH) with $SOCl_2$. Compounds **4** and **5** (X = OMe, OH, Cl, OPr^i) were characterised by NMR (^1H, ^{13}C, ^{31}P) and IR spectroscopy and except for the chloridates (X = Cl) by mass spectrometry (including accurate mass measurement for new compounds). The chloridates were obtained as crystalline solids but they were extremely sensitive to moisture and any manipulation (in the absence of $SOCl_2$) generally introduced some of the anhydride (pyrophosphonate) [^{31}P NMR: 2 peaks (diastereoisomers) at *ca.* 17 or 23 ppm].

§ With a 10:1 mixture of Pr^iOH and MeOH the chloridate **5** (X = Cl) gives similar amounts of the two possible esters (X = OPr^i or OMe) in the absence of base but if the chloridate is pretreated with Et_3N the reaction becomes more selective and hardly any of the isopropyl ester (< 1%) is formed.

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