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Intramolecular Hydrogen-Bond Participation in Phosphonylammonium Salt Formation

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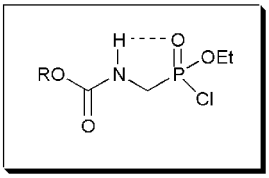
ABSTRACT

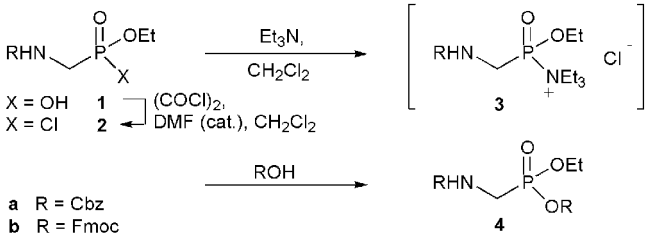


A series of phosphonochloridates and phosphonyl dichlorides were prepared, and their reactivity with triethylamine has been investigated using ^{31}P NMR spectroscopy. Taken together these studies provide evidence that an intramolecular hydrogen-bond is required for phosphonylammonium salt formation to render the phosphorus more electron-deficient.

Phosphonate esters are privileged surrogates for the unstable, high energy tetrahedral transition states found in many chemical reactions, including enzyme-catalyzed reactions.[1−3] Effective phosphorylation procedures are, therefore, of importance in the design and synthesis of, on one hand, inhibitors of proteolytic enzymes and, on the other, haptens for the generation of catalytic antibodies.[4] These protocols are also of great interest for the preparation of analogues of phospho-ester-containing natural products.[5]

The preparation of mixed phosphonate esters generally relies on the reaction between phosphonochloridates or phosphonyl dichlorides with alcohols.[6] Efforts have also been made to develop more reactive phosphonylating agents [e.g., bis(benzotriazolyl)-phosphonates].[7] During the course of our work on hapten synthesis, we reported a new method for the phosphonylation of alcohols.[8] This protocol calls for treatment of phosphonochloridates **2a**,**b** with triethylamine to afford a new species, the phosphonyl triethylammonium salts (**3a**,**b**; Scheme 1). The reactivity of these phosphonylating agents toward alcohols and amines was found to be high, often providing superior yields of phosphonate esters

Scheme 1



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(1) Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659−667.

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(4) For example, see: (a) Pratt, R. F. *Science* **1989**, *246*, 917−919. (b) Bartlett, P. A.; Giangiordano, M. A. *J. Org. Chem.* **1996**, *61*, 3433−3438. (c) Chen, S.; Lin, C.-H.; Kwon, D. S.; Walsh, C. T.; Coward, J. K. *J. Med. Chem.* **1997**, *40*, 3842−3850.

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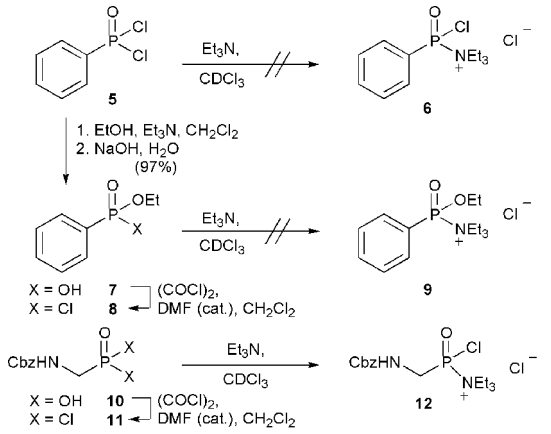
(**4a**,**b**) or phosphonamides when compared with the reaction of the corresponding phosphonochloridates. In addition to improved yields and reaction rates, **3a**,**b**, obtained by the sequential addition of triethylamine to the phosphonochloridates, also displayed a greater affinity for alcohols over amines.[8b]

Recently, we became interested in applying this method to phosphonyl dichloride **5**. Unexpectedly, no phosphonylammonium salt was formed when **5** was treated with triethylamine in deuterated chloroform (Scheme 2). According to ^{31}P NMR spectroscopy, the starting material remained unchanged.

Scheme 2

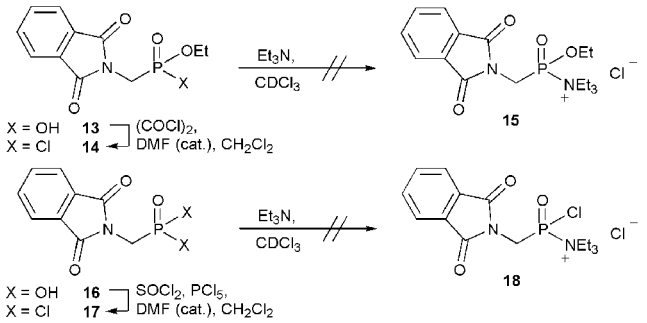


Intrigued that this result could arise from the structural differences between compounds **2** and **5**, we examined in more detail the structural features of phosphonochloridates that are suitable precursors of phosphonylammonium salts. For example, monochloride **8** was examined to determine whether the presence of an alkoxy group, more electronegative than chlorine, but having a greater π donor ability compared to Cl is required. Toward this end, conversion of dichloride **5** to the corresponding symmetrical diester followed by alkaline hydrolysis furnished **7** in 97% yield (Scheme 2). Monochloride **8**,[9] obtained by treatment of compound **7** with oxalyl chloride, however, failed upon addition of triethylamine (same conditions as for **2**) to generate phosphonylammonium salt **9**. The reverse experiment, using phosphonyl dichloride **11** having the same alkyl side-chain as **2a**, was then explored. Conversion of phosphonic acid **10**[10] to the corresponding dichloride **11** and treatment with triethylamine resulted in a downfield shift of the ^{31}P NMR resonance (from 44.0 to 54.0), characteristic for phosphonylammonium salt formation.[8]

These examples clearly demonstrate that both mono- and dichlorides can be converted into phosphonylammonium salts. The difference in reactivity between **2a** and **8** (or **11** and **5**) must therefore derive from the (*N*-benzyloxycarbonyl)aminomethyl vs phenyl side chain. The presence of an α-alkyl substituent on compound **2a** had already been demonstrated to be compatible with phosphonylammonium salt formation,[8b] indicating that an electronic factor, rather than steric, most likely accounts for the difference.

Following this reasoning, replacement of the Cbz-carbamate by another electron-withdrawing substituent like a phthalimide was expected to result in similar reactivity. Phthalimides **13**[11] and **16**[12] were converted, respectively, to the corresponding monochloride **14** and dichloride **17**, and then treated with triethylamine (Scheme 3). Both **14** and **17**

Scheme 3



failed to form the corresponding phosphonylammonium salt (e.g., ^{31}P NMR), implying that the carbamate group of **2** and **11**, absent in **14** and **17**, promotes phosphonylammonium salt formation by some mechanism other than a simple inductive effect.

This observation suggested that the acidic carbamate hydrogen might be the distinctive feature. Formation of an intramolecular hydrogen bond between the carbamate NH and the phosphonyl oxygen would increase the polarization of the P−O bond, rendering the phosphorus more electron-deficient, and therefore more susceptible to attack by the nucleophilic tertiary amine (Figure 1). The importance of

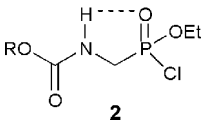


Figure 1. Electrophilic activation of phosphorus via an intramolecular hydrogen-bond.

intramolecular participation of a hydrogen-bond in the base-catalyzed hydrolysis of phosphonate esters has been re-

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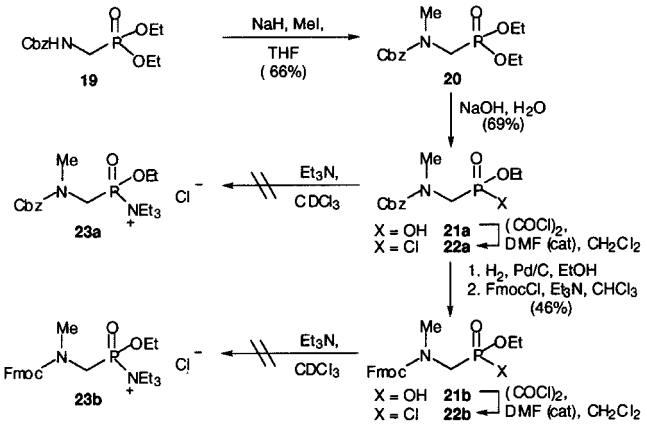
(9) The mono- and dichlorides described in this report were prepared in situ at 0 °C, concentrated in vacuo in the presence of toluene and used without further purification.

ported.[13] We propose here that in similar fashion, a five-membered-ring intramolecular hydrogen-bond activates the phosphorus atom in **2a** and **2b** and is thereby responsible for formation of the phosphonylammonium salts (Figure 1).

Infrared and ^{1}H NMR spectroscopy indicate that compound **2a** indeed forms an intramolecular hydrogen-bond. The IR spectra of compound **2a** in chloroform displayed two NH stretches; a broad peak at 3340 cm^{-1} derives from hydrogen-bonded conformers, whereas the sharp peak at 3445 cm^{-1} arises from non-hydrogen-bonded conformers.[14,15] The spectra are essentially identical over the concentration range studied (5×10^{-2} to 1×10^{-3} M), indicating that the hydrogen-bond is intra- and not intermolecular. Likewise, variable concentration ^{1}H NMR spectroscopy between 5×10^{-2} to 1×10^{-3} M revealed only a small concentration dependence of the NH chemical shift (0.25 ppm), consistent with the presence of an intramolecular hydrogen-bond.[14]

Additional support for electrophilic phosphorus activation arises from the *N*-methylated analogues of compounds **2a**,**b** (Scheme 4). Treatment of diethyl phosphonate **19**[8] with

Scheme 4



methyl iodide in the presence of sodium hydride furnished the *N*-methylated phosphonate **20**; basic hydrolysis then gave **21a** in 69% yield. The corresponding Fmoc analogue **21b** was obtained by hydrogenation of **21a**, followed by reprotection of the amine with FmocCl. Conversion of **21a** and **21b** to the corresponding monochlorides **22a** and **22b**, followed by treatment with triethylamine, did not result in phosphonylammonium salt formation, strongly supporting the hydrogen-bond hypothesis.

This result was confirmed by carrying out the same experiment on a 1:1 mixture of monochlorides **2a** and **22a**. Addition of triethylamine (3-fold excess) resulted in the complete conversion of **2a** into the corresponding phosphonylammonium salt **3a**, whereas the *N*-methylated derivative **21a** remained unmodified (Figure 2). The ^{31}P NMR spectra

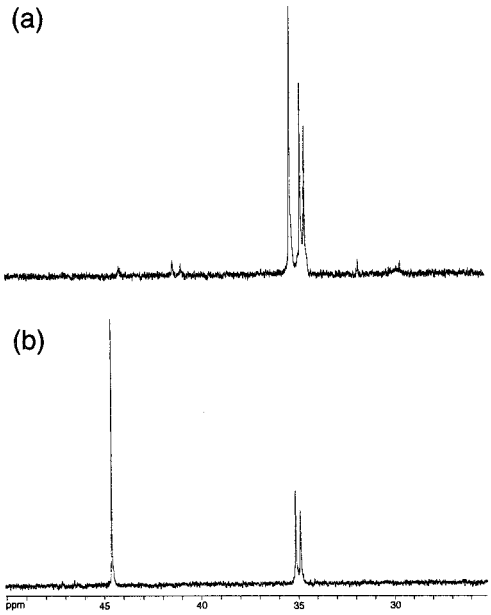


Figure 2. ^{31}P NMR spectra: (a) monochlorides **2a** and **22a** (1:1 mixture); (b) phosphonylammonium salt **3a** and monochloride **22a**, derived by reaction of sample a with 3 equiv of triethylamine.

of compounds **20**, **21a**, and **22a** displayed two resonances[16] which were assigned to carbamate rotamers on the basis of temperature-dependent ^{31}P NMR studies with compounds **20** and **22a** (coalescence observed at 325 K).

To explore further the scope of this reaction, we synthesized an analogue of monochloride **8** containing an ortho-substituted *N*-acetyl group which was anticipated to form via a six-membered ring, an intramolecular hydrogen bond with the phosphonyl (see **25**, Scheme 5). This experiment was anticipated to determine whether aromatic phosphonochloridates react with tertiary amines, providing the phosphonyl oxygen is hydrogen-bonded. To this end, hydrogenation of **24**[17] followed in turn by acetylation and hydrolysis of the derived phosphonate **25** furnished monoester **26**. Unfortunately, conversion to the corresponding monochloride proved impossible. Realizing that this difficulty was likely due to nucleophilic addition of the acetyl group to the phosphonochloridate, we targeted cyclic carbamate **31**.

Toward this end, reduction of **27**[18] with sodium borohydride and zinc chloride,[19] followed by formation of the cyclic carbamate and cross-coupling of the resulting aryl iodide with diethyl phosphite, afforded phosphonate **28**.[20] Treatment of

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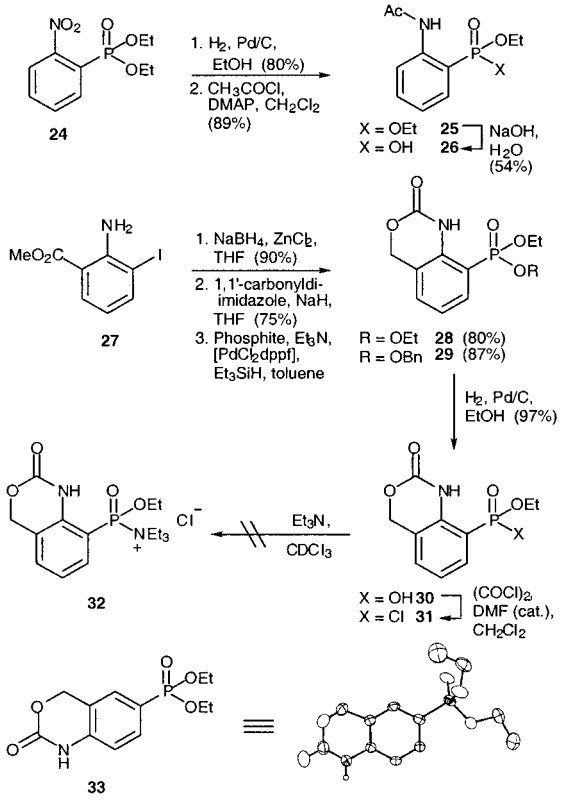
(17) Cadogan, J. I. G.; Sears, D. J.; Smith, D. M. *J. Chem. Soc.* **1969**, 1314−1318.

Scheme 5



28 with NaOH in water to hydrolyze the phosphonate unfortunately resulted in the cleavage of the cyclic carbamate. This problem was circumvented by preparing ethyl benzyl phosphonate **29** using ethyl benzyl phosphite.[21] Hydrogenolysis removed the benzyl group in **29** to furnish **30** in 97% yield. Conversion of **30** to the corresponding monochloride **31** was accomplished using oxalyl chloride with catalytic DMF. The presence of an intramolecular hydrogen-bond was verified via variable concentration IR spectroscopy[14,15] in $CHCl_3$ (concentration range 0.05 to 0.0025 M), as well as variable concentration ^{1}H NMR spectroscopy (0.0025 to 0.00010 M). In the IR experiment, the only observable NH stretch was at 3285 cm^{-1}, indicating the hydrogen-bonding was intramolecular. Likewise, during the ^{1}H NMR experiment, the NH resonance at 9.42 ppm did not vary across the concentration range studied, again suggesting the hydrogen-bonding is intramolecular. This observation is in marked contrast to **33**, obtained through a similar route from 5-iodo-2-nitrobenzoic acid.[21] The X-ray crystal structure of phosphonate **33** illustrates that no internal hydrogen-bond is possible, but the IR spectra showed a non-hydrogen-bonded NH stretch at 3422 cm^{-1} (5×10^{-2} to 2.5×10^{-3} M in $CHCl_3$), and at high concentration (above 10^{-2} M), a weak intermolecularly hydrogen-bonded NH stretch at 3240 cm^{-1}.

Treating a solution of **31** in $CDCl_3$ with triethylamine did not, however, result in the formation of phosphonylammonium salt **32** (as observed by ^{31}P NMR spectroscopy). Presumably, the aromatic ring deactivates the phosphorus atom by resonance so that, despite the presence of a hydrogen-bond, no reaction with triethylamine occurs.

In summary, we have obtained evidence that phosphorus activation via the participation of an intramolecular hydrogen-bond accounts for the formation of phosphonylammonium salts **3a**,**b** and **12**. Accordingly, phosphono mono- and dichloridates **5**, **8**, **14**, **17**, and **22a**,**b** that lack the ability to form an intramolecular hydrogen-bond remain unmodified upon triethylamine addition. We have also demonstrated that aromatic phosphonochloridates, regardless of the presence of an intramolecular hydrogen-bond (see **5**, **8**, and **31**), are not sufficiently reactive to form phosphonylammonium salts.

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Supporting Information Available: Spectroscopic and analytical data for **7**, **20**, **21a**−**b**, **25**, **26**, **28**, **29**, **30**, and **33** as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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