



The Reaction of Chlorophosphates with Strong Bases: Synthesis and Characterization of the Phosphonate Salts

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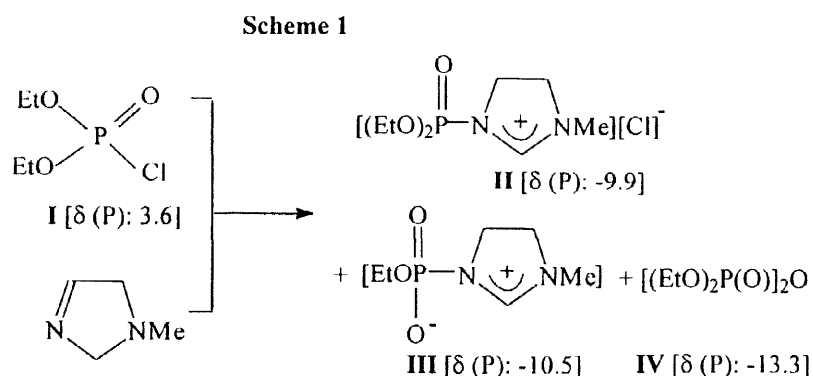
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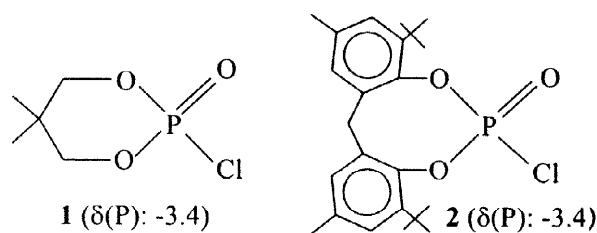
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Abstract: The reaction of $(\text{OCH}_2\text{CMe}_2\text{CH}_2\text{O})\text{P}(\text{O})\text{Cl}$ (**1**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the phosphonate salt $[(\text{OCH}_2\text{CMe}_2\text{CH}_2\text{O})\text{P}(\text{O})(\text{DBU})]^+[\text{Cl}]^-$ (**3**); the X ray structure of this compound as a hydrate shows that the C-6 (labeled as C1 in Fig.1) of the DBU is connected to the phosphorus. In an analogous manner the eight-membered ring compound $\{\text{CH}_2(4\text{-Me-2-}t\text{-Bu-C}_6\text{H}_2\text{O})_2\}\text{P}(\text{O})\text{Cl}$ (**2**) also afforded a phosphonate salt along with the pyrophosphate $[\{\text{CH}_2(4\text{-Me-2-}t\text{-Bu-C}_6\text{H}_2\text{O})_2\}\text{P}(\text{O})]_2\text{O}$ (**5**). By contrast, in the reaction of **1** with 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methyl imidazole or 4-dimethylaminopyridine no phosphonate salt was observed; the pyrophosphate was found to be the end product and could be isolated. © 1998 Elsevier Science Ltd. All rights reserved.

In the reaction of diethyl chlorophosphate (**I**) with N-methyl imidazole, Corriu and coworkers have identified the ionic intermediate **II**, which is a phosphate-base complex [Scheme 1].^{1,2} Reactions such as these may have relevance in the synthesis of biophosphate esters by the reaction of a chlorophosphate and an



alcohol in the presence of a base.³ Compounds analogous to **II** have also been isolated in a) the reaction of $(\text{Me}_3\text{SiO})\text{P}(\text{O})\text{Ph}(\text{H})$ with 4-dimethylaminopyridine/ CCl_4 ,⁴ b) $(\text{MeO})\text{P}(\text{O})\text{Cl}_2$ with 4-dimethylaminopyridine^{4,5} and c) $\{(\text{Ph})(\text{Br})\text{CH}\}_2\text{P}(\text{O})\text{Cl}_2$ with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).⁶ Although it is said that these compounds (eg. **II**) may not be important in the nucleophilic catalysis of the nucleophilic substitution reactions at phosphorus,¹ they can be valuable intermediates as precursors for dioxaphosphoranes.⁷ We are interested in studying the reaction chemistry of species of the type **II** and have chosen the readily synthesized substrates **1** and **2**.



Interestingly, in the reaction of **1** with DBU, we observed the P-C bonded *phosphonate* salt $[(\text{OCH}_2\text{CMe}_2\text{CH}_2\text{O})\text{P}(\text{O})(\text{DBU})]^+[\text{Cl}]^-$ (**3**) (Fig. 1) as the major product.⁸ This type of P-C bonded product is different from the P-N bonded compounds mentioned above or the ones reported by Bertrand and coworkers in the reaction of $(\text{R}_2\text{N})_2\text{PCl}$ with DBU.⁹ Although it is known that DBU can be lithiated at C-6 position (labeled as C1 in Fig. 1) by *n*-butyl lithium,¹⁰ P-C bond formation in the reaction of chlorophosphates with phenylethylamine/ DBU has not been inferred before.¹¹ Formation of **3** may involve a salt analogous to **II** which undergoes 1,3-proton shift from C-6 to N-1 to give an enamine (see structure of **4** for numbering sequence); this could reorganize to **3** via a cyclic 4-membered transition state involving C-6, C-7, N-8 and P.

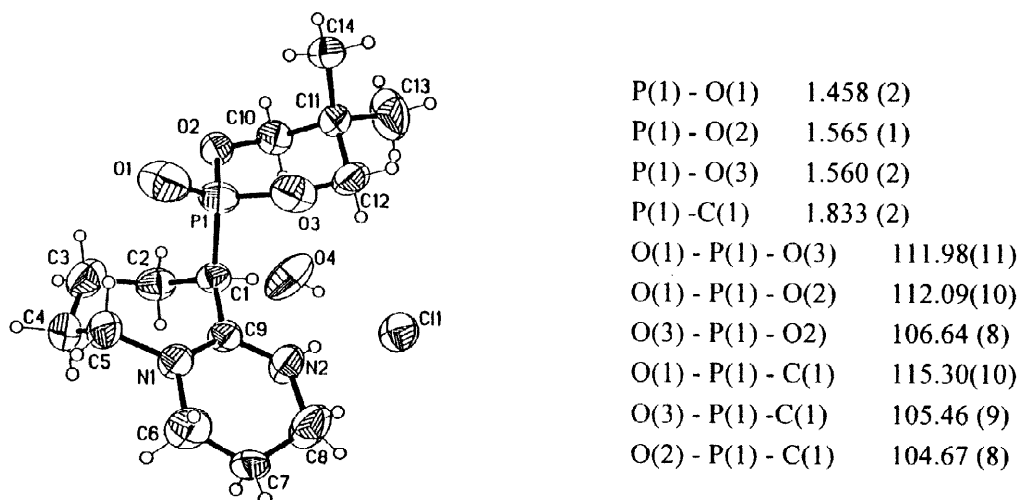
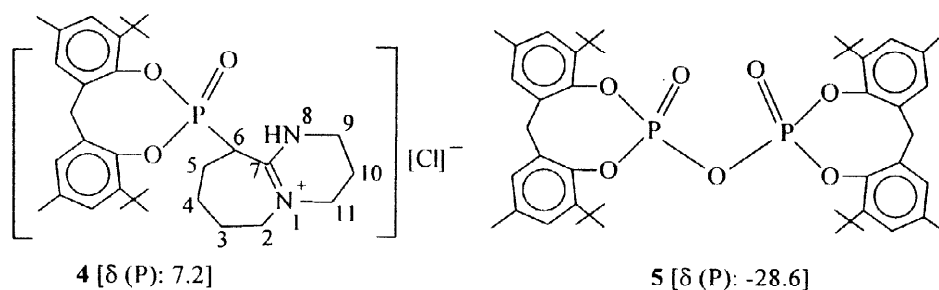


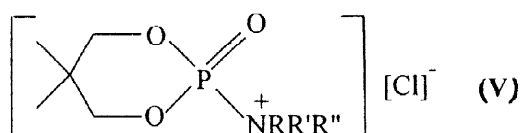
Fig. 1 An ORTEP picture of **3**.H₂O; also shown are selected bond parameters around phosphorus.

Reaction of the eight membered ring compound **2** with DBU also gave a phosphonate salt, **4**, along with the pyrophosphate $[\{\text{CH}_2(4\text{-Me-2-}i\text{-Bu-C}_6\text{H}_2\text{O})_2\}\text{P}(\text{O})_2]$ (**5**) (X-ray).¹²



In contrast to the above, when **1** was allowed to react with 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), we could not detect a P-C bonded compound (*vide infra*); in the reaction of **1** with N-methyl imidazole,

imidazole and 4-dimethylaminopyridine, although intermediates are found, the pyrophosphate $[(\text{OCH}_2\text{CMe}_2\text{CH}_2\text{O})\text{P}(\text{O})]_2\text{O}$ (**6**)¹³ is the end product and is the only one that could be isolated in a pure state. This latter result is analogous to that reported by Corriu and coworkers (*cf* compound **IV**).¹ Similar pyrophosphates are also obtained in the reactions of the eight-membered ring compounds $\{\text{CH}_2(4\text{-Me-2-}t\text{-Bu-C}_6\text{H}_2\text{O})_2\}\text{P}(\text{O})\text{Cl}$ (**2**) and $\{\text{CH}_2(2,4\text{-}(t\text{-Bu})_2\text{-C}_6\text{H}_2\text{O})_2\}\text{P}(\text{O})\text{Cl}$ (**7**) with these bases.¹⁴ We believe that these pyrophosphates are formed *via* betaines of the type **V** and adventitious moisture.¹⁵ We observe signals attributable to these; for example in the reaction of **1** with DBN two ³¹P NMR signals at -6.7 and -12.0 which are different from those for a phosphonate (*cf* compound **3**) or for the pyrophosphate **6** [$\delta(\text{P})$: -21.9] are seen. However, full characterization of these products has eluded us so far because of the extreme sensitivity of the intermediates in our hands.



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8. Preparation of **3**: To a solution of **1** (0.77g, 4.21 mmol) in toluene (10 mL) a solution of DBU (0.64g, 4.21mmol) in toluene (10 mL) was added over a period of 10 min at 25°C and the mixture stirred overnight. The solid obtained (³¹P NMR: single peak at 10.67 ppm) was filtered and washed with cold toluene (2 x 5 mL). Recrystallization was done from hot toluene to obtain **3**. Yield: 1.21g (84%). M. p. 184°C. ¹H NMR: 0.95 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.64-2.17 (m, 8H, CH₂), 3.00-3.10 (d, ²J ≈ 12 Hz, PCH), 3.41 - 3.92 (m, 6H, NCH₂), 4.67 (d, ²J = 11.1Hz, OCH_AH_B), 4.78-4.97 (m, 2H, OCH₂), 5.34 (d, OCH_AH_B), 11.48 (br s, 1H, NH⁺). ¹³C NMR: 19.52, 19.97, 22.26, 23.55, 23.63, 24.35, 26.25, 32.83, 32.99, 38.37, 39.38 (¹J(P-C) = 126.5Hz), 49.96, 53.25, 78.59, 161.40. ³¹P NMR: 10.67. Anal. calcd (**3** with one molecule of water that probably has entered during the process of crystallization) for C₁₄H₃₀ClN₂O₄P: C, 47.13; H, 8.41; N, 7.85. Found: C, 47.88; H, 8.09; N, 8.60. The filtrate showed a small quantity of the pyrophosphate **6** also (*ca* 0.05g). *Crystal data for 3.H₂O* Formula: C₁₄H₂₈CN₂O₄P; M = 354.80; Monoclinic; Space group : C2/c; Diffractometer: Siemens SMART CCD. *a* = 20.7477(3), *b* = 9.6621(1), *c* = 18.1810 (3)Å, β = 95.733 (1)⁰. *V* = 3626.41 (8)

\AA^3 . $Z = 8$. $D_c : 1.300 \text{ g cm}^{-3}$. θ range: 1.97 - 29.14. $\mu (\text{Mo-K}\alpha) = 0.317 \text{ mm}^{-1}$. Indep. reflections [R(int) = 0.0189]: 4347; Absorption correction: SADABS (Sheldrick, 1996). Max. and min. transmission: 0.945 and 0.830. Data/restraints/parameters: 4347/ 6/ 220. GooF: 1.032. $R_1(I > 2\sigma(I))$ 0.0483, $wR2 = 0.1173$ (SHELXTL, Version 5.03). Two orientations were found for C(7); only one of these is shown in the Fig. 1

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11. See, for example, Merckling, F. A.; Ruedi, P. *Tetrahedron Lett.* **1996**, *37*, 2217.
12. To a solution of **2** (0.328 g, 0.78 mmol), prepared by reacting 0.012 mol each of POCl_3 , diol and triethylamine in benzene [60%. M. p. 162-164°C. $^1\text{H NMR}$: 1.44 (s, 18H, *t*-BuH), 2.31 (s, 6H, CH_3), 3.85-4.20 (AB qrt, 2H, ArCH_2), 7.07-7.10 (m, 4H, *Ar-H*). $^{31}\text{P NMR}$: -3.4], in toluene (10 mL) a solution of DBU (0.118g, 0.78 mmol) in toluene (10 mL) was added dropwise at 25°C and the mixture was stirred overnight. Upon concentration to *ca* 10 mL compound **4** came out (0.2 g, 45%). The residue upon further concentration afforded **5** as a crystalline solid (0.15 g, 33 %). Compound **4**: M. p. 220°C (dec.). $^1\text{H NMR}$: 1.38 (s, 9H, *t*-BuH), 1.42 (s, 9H, *t*-BuH), 1.80-2.30 (m, 8H, CH_2), 3.20 (br, 2H, CH_2), 3.45- 3.60, m, 6H, NCH_2), 4.90 (d, 1H, $\text{Ar-CH}_A\text{H}_B$), 5.50 (d, 1H, $\text{Ar-CH}_A\text{H}_B$), 7.00-7.25 (m, 4H, *Ar-H*), 11.48 (br, 1H, NH^+). An additional peak at 12.0 ppm was also observed. $^{31}\text{P NMR}$: 7.21 (s). Note that this $\delta(^{31}\text{P})$ value is in the range of our other phosphonates with phosphorus as a part of a 1,3,2-dioxaphosphorinane ring: Kumaraswamy, S.; Selvi, R. S.; Kumara Swamy, K. C. *Synthesis* **1997**, 207. Compound **5**: M. p. 276°C. $^1\text{H NMR}$: 1.44 (s, 18H, *t*-BuH), 2.31 (s, 6H, CH_3), 3.70 (d, $^2J = 15 \text{ Hz}$, $\text{Ar-CH}_A\text{H}_B$), 4.31 (d, $^2J = 15 \text{ Hz}$, 1H, $\text{Ar-CH}_A\text{H}_B$), 7.21- 7.24 (m, 4H, *Ar-H*). $^{13}\text{C NMR}$: 20.94, 34.55, 34.99, 127.66, 129.41, 131.43, 135.21, 141.32, 146.0. $^{31}\text{P NMR}$: -28.6. X-ray data for **5**: Empirical formula: $\text{C}_{23}\text{H}_{30}\text{O}_{3.5}\text{P}$; Formula weight: 393.44; Tetragonal; Space group: P4, Diffractometer: Enraf Nonius MACH3. $a = 15.996(2)$, $c = 9.3227(7)\text{\AA}$. $V = 2385.4(5) \text{\AA}^3$. $Z = 4$. $D_c: 1.096 \text{ g cm}^{-3}$. θ range : 2- 22.5. $\mu (\text{Mo-K}\alpha) = 0.135 \text{ mm}^{-1}$. Indep. reflections [R(int) = 0.0569]: 1680. Data/restraints/parameters: 1680/ 0/ 249. GooF: 1.573. $R_1(I > 2\sigma(I)) = 0.0698$; $wR2 = 0.1811$ (SHELXL-97). More details including the ORTEPs are available from the authors.
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14. Compound **7** [$\delta(\text{P})$: -2.4] was prepared in a manner analogous to that for **2**. Physical data for the pyrophosphate [$\{\text{CH}_2(2,4-(t\text{-Bu})_2\text{-C}_6\text{H}_2\text{O})_2\}\text{P}(\text{O})_2\text{O}$] (**8**): M. p. 276°C. $^1\text{H NMR}$: 1.30 (s, 18H, *t*-BuH), 1.45 (s, 18H, *t*-BuH), 3.75 (d, $^2J = 11.9 \text{ Hz}$, $\text{Ar-CH}_A\text{H}_B$), 4.41 (d, $^2J = 11.9 \text{ Hz}$, $\text{Ar-CH}_A\text{H}_B$), 7.20 and 7.30 (s each, 4H, *Ar-H*). $^{31}\text{P NMR}$: -28.50. Anal. calcd for $\text{C}_{58}\text{H}_{84}\text{O}_7\text{P}_2$: C, 72.95, H, 8.86. Found: C, 72.77, H, 9.36.
15. A second possibility for the formation of pyrophosphates is *via* the reaction of the phosphate salts of the type $[(\text{RO})_2\text{PO}_2] [\text{Base}]^+$ formed by hydrolysis *in situ* with the starting chlorophosphate. We did isolate such a salt in the reaction of **7** with DBU [X-ray]. However, when we treated the phosphate $(\text{OCH}_2\text{CMe}_2\text{CH}_2\text{O})\text{P}(\text{O})(\text{OH})$ with DBN (or DBU) in an NMR tube experiment the $^{31}\text{P NMR}$ peak for the mixture [-4.2 ppm in the reaction with DBN] was different from any of the two peaks [-6.8, -12.0] observed in the reaction of **1** with DBN. This, in conjunction with the fact that the concentration of the pyrophosphate increases over a period of time in the reaction of **1** with N-methylimidazole or imidazole or 4-dimethylaminopyridine, suggests the involvement of the betaines of type **III**. This aspect is currently under investigation.