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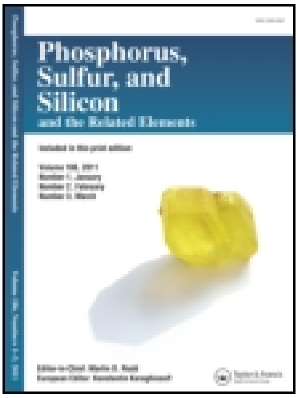

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Nucleophilic Displacements in Alkylphosphonates: P-O Versus P-C Bond Cleavage. A Combined DFT and Experimental Study

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NUCLEOPHILIC DISPLACEMENTS IN ALKYLPHOSPHONATES: P–O VERSUS P–C BOND CLEAVAGE. A COMBINED DFT AND EXPERIMENTAL STUDY

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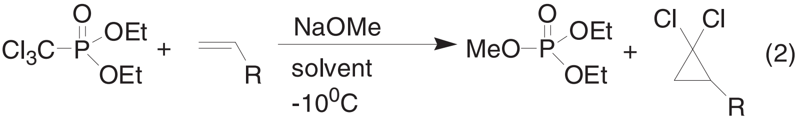
GRAPHICAL ABSTRACT



Abstract *Potential energy surfaces for the nucleophilic displacements at phosphorus in dimethyl methyl, chloromethyl, dichloromethyl, and trichloromethyl phosphonates have been computed by DFT methods. The results reveal that sequential introduction of chlorine substituents at the methyl group in methyl phosphonates increases the stability of transition states and intermediates, which facilitates P–C bond cleavage. While nonsubstituted dimethyl methylphosphonate may undergo exclusive P–O bond cleavage, the trichlorinated analogue reacts exclusively via P–C bond dissociation to form dichlorocarbene, which was trapped by various olefins to form the corresponding gem-dichlorocyclopropanes.*

Keywords Alkylphosphonates; DFT; potential energy surface; dichlorocarbene; gem-dichlorocyclopropanes

Processes involving a nucleophilic attack at the phosphorus center of alkylphosphonic acid derivatives (i.e., esters, amides, thio esters, halides, etc.), followed by P-ligand bond cleavage (P–O, P–N, P–S, P-Halogen, etc.), are well documented in the literature.[1] In contrast, the analogous P–C bond scission is rare. As the P–C bond is polarized with a negative charge on the carbon, these compounds might be useful in organic transformations (e.g., transmetallation), being a potential source for carbanions activated alkylphosphonates are known to react as carbanions only with carbonyl compounds in the Horner-Wadsworth-Emmons reaction, via a different mechanism: nucleophilic attack of phosphoryl-stabilized carbanion on carbonylic carbon.[1] To the best of our knowledge for nonactivated alkylphosphonic acid derivatives (e.g., dialkyl methylphosphonates), P–C bond dissociation, which evolves from nucleophilic displacement at the phosphorus, has never been described. Some unique examples of P–C bond fission in activated systems are the $-CF_3$ elimination from

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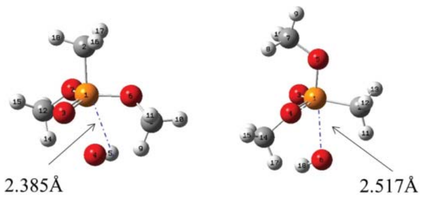


∠C(2)-P-O(4)=171.6°

1-TS1

∠O(5)-P-O(6)=167°

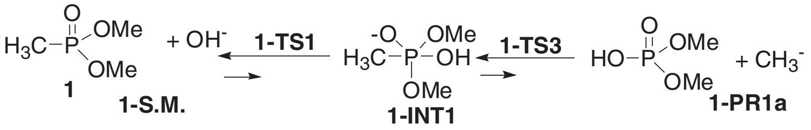
1-TS2

Figure 1 Transition states structures for the attack of OH– on 1. (Color figure available online).

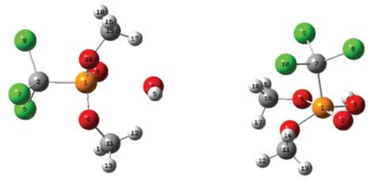
tris(trifluoromethyl)phosphine oxide,[2] P–CCl_3 cleavage under nucleophilic conditions both in phosphonates[3] and in phosphinates,[4] α-hydroxyphosphonate-phosphate rearrangement,[5] and dephosphonylation of β-ketophosphonic acids presumably via nucleophilic addition of water to the phosphorus.[6] Elimination of CX_3^- moieties are of particular interest as these reactions can be considered as the phosphorus equivalent of the Haloform reaction, therefore, as dihalocarbenes source.[7] Surprisingly, we found only few examples where these commercially available compounds were used as precursors for carbenes.[7] The ability to accurately elucidate reaction mechanisms involving nucleophilic transformations of P(V) compounds using ab intio and DFT methods, both in the gas phase and in solution, has been demonstrated many times during the last decade.[8,9] Therefore, we believed that by using this methodology and conducting a thorough study of the potential energy surfaces (PES), we could gain a better understanding of the structure and the reactivity of alkylphosphonates and their nucleophilic transformations. This insight may unveil some of the terms and conditions that dictate the reaction course and consequently the ability to obtain carbanions and\or carbenes via P–C bond cleavage. To address this issue, the PES for the nucleophilic displacements at phosphorus in the model compounds—dimethyl methyl, chloromethyl, dichloromethyl, and trichloromethyl phosphonates—have been computed at the B3LYP/6–31+G* level of theory using IEF-PCM to account for the solvent effect.[9h]

For dimethyl methylphosphonate (**1**), two different modes of attack were found: (a) OH^- approach from the opposite side to the CH_3^- group via the transition state **1-TS1** (Figure 1) to form the distorted trigonal bipyramid (TBP) intermediate **1-INT1** and (b) Attack opposite to the $^-$OMe substituent (**1-TS2**, Figure 1) to form the corresponding pentacoordinated TBP intermediate **1-INT2**. Kinetically, the latter is favored as the required free energy of activation is $\Delta G^\ddagger = 20.5$ kcal/mol (in accordance with the experimental value of 21.1 kcal/mol)[10] and lower by 8.7 kcal/mole compared to the energy needed to obtain **1-TS1**.

Furthermore, cleaving the P–C bond in **1-INT1** via the proper TS (**1-TS3**) demands an activation free energy of 32.5 kcal/mol. Thus, making this step the rate determining one and yields the initial products **1-PR1a**, which are 33.9 kcal/mol higher in energy than the starting materials. Therefore, this reaction would be strongly shifted toward the starting materials (Equation 1), as indicated in the literature for analogous phosphoric acid derivatives.[11]



(1)



Trigonal bipyramid Square pyramid

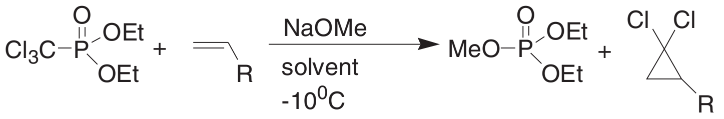
4-TS1 **4-TS2**

Figure 2 Transition states structures for the attack of OH– on 4. (Color figure available online).

Consequently, according to our calculations, the P–CH_3 bond in phosphonic acid derivatives, such as **1**, is indeed inert.

Adding chlorine substituents to the methyl group bonded to phosphorus, such as in dimethyl chloromethyl and dichloromethyl phosphonate (**2** and **3**, respectively) reveals some remarkable differences. Both paths (P–O or P–C cleavage) are less energy demanding following the sequential addition of chlorines, although fission of the P–O bond is still preferred. The activation barriers found for both systems are in excellent agreement with previously reported experimental values.[12] However, for all processes the initial step, attack of the nucleophile on the phosphorus center of **2** or **3**, is the rate determining step. Therefore, for suitable systems (e.g., chloromethyl or dichloromethyl dialkyl or diaryl phosphine oxides) a P–C cleavage of the halomethyl group should be feasible.

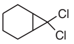
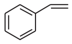
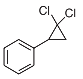
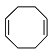
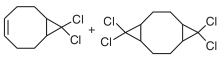
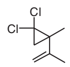
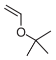
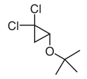
The calculated profiles for the reaction of dimethyl trichloromethyl phosphonate (**4**) with OH^- in water unveil totally different results, both structurally (Figure 2) and energetically, from those obtained for the previous systems. When the nucleophile approaches from the opposite side to the OMe moiety, the first stationary point found was the transition state **4-TS2**, which possesses square pyramid geometry in which the CCl_3 fragment is in the apical position (Figure 2), rather than the expected TBP. The formation of this transition state requires free energy of activation of 15.7 kcal/mol and leads to the formation of an intermediate, which is already lower in energy than the starting materials (ca. –4.2 kcal/mol). Intrinsic reaction coordinate (IRC) calculations confirmed that indeed **4-TS2** connects the two minima of the starting materials and this intermediate, from which only 0.9 kcal/mol is required in order to dissociate the CCl_3 fragment. Attack from the opposite side to the CCl_3 ligand is also possible as $\Delta G^{\ddagger}_{\mathbf{4\text{-}TS1}} = 16.7$ kcal/mol, only 1.0 kcal/mol higher than the required energy for **4-TS2**. Moreover, once such an attack takes place, the rest of the process is down hill in energy as the formation of the following intermediate releases 19.5 kcal/mol. These calculations imply that the nucleophilic displacement process in **4** would follow a S_N2(P) type mechanism, as could be anticipated,[13] in contrast to addition-elimination mechanism, which was observed for systems **1–3**.



(2)

Combining the facts that P–C cleavage is the sole process observed theoretically for **4** and that trihalomethyl anions spontaneously dissociate to dihalocarbenes, we tested the ability of a commercially available analogue, diethyl trichloromethyl phosphonate to act as dichlorocarbene precursor. Indeed, trapping the later with various olefins formed the corresponding gem-dichlorocyclopropanes.[14] These manipulations were carried out in organic

Table 1 Summary of the reactions and products

Run	Olefin	Product	Solvent	Reference
1			Cyclohexane	7a, 15
2			THF	15b
3			THF	16
4			Acetonitrile	17
5			THF	18

solutions (in contrast to the common biphasic or the phase-transfer catalyzed reactions),[14] using both acyclic and cyclic olefins and methoxide as the attacking nucleophile (Equation 2 and Table 1). The spectral data of the products were identical to those previously reported in the literature.

In conclusion, our calculations show that the P–C cleavage in alkylphosphonates can be achieved only if the alkyl is substituted by electronegative substituents (e.g., halogens). This substitution increases the apicophilicity of the alkyl fragment and in turn enhances the kinetic stability of key transition states and intermediates. These electronic properties obviously have also a profound thermodynamic effect regarding the leaving group properties of this fragment. Therefore, P–O cleavage is always preferred. Only for trichloromethyl phosphonic diesters, a dramatic change is observed. In such systems, P–C bond dissociation becomes the dominant process. In this case, the reaction is similar to the Haloform reaction in carbonyls. Hence, these compounds are a useful source for trichloromethyl anion and consequently as dichlorocarbene precursor.

REFERENCES

1. (a) Ando, K. *J. Org. Chem.* **1999,** 64, 6815-6821 and ref. 8 therein. (b) This reaction is normally feasible only for activated alkylphosphonates. See: Maryanoff, B. E.; Raitz, A. B. *Chem. Rev.* **1989,** 89, 863-927.
2. (a) Paul, R. M. *J. Chem. Soc.* **1955,** 574-584. (b) Burg, A. B.; Sarkis, A. J. *J. Am. Chem. Soc.* **1965,** 87, 238-242.
3. Hall, C. R.; Inch, T. D.; Peacock, G.; Pottage, C.; Williams, N. E. *J. Chem. Soc. Perkin Trans. 1* **1984,** 669-674.
4. Hammond, P. S.; Kirchner, M. B.; Lieske, C. N. *J. Org. Chem.* **1990,** 55, 6049-6051.
5. (a) Hammerschmidt, F. *Monatsh. Chem.* **1993,** 124, 1063-1069 (b) Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem.* **2000,** 2239-2245.
6. Hawkins, M. J.; Powell, E. T.; Leo, G. C.; Gauthier, D. A.; Greco, M. N.; Marynoff, B. *Org. Lett.* **2006,** 8, 3429-3431.

7. (a) Berry, J. P.; Arnold, J. R.; Isbell, A. F. *J. Org. Chem.* **1968,** 33, 1664-1665. (b) Perlikowska, W.; Modro, A. M.; Modro, T. A.; Mphahlele, M. J. *J. Chem. Soc. Perkin Trans. 2* **1996,** 2611-2613. (c) Zafrani, Y.; Sod-Moriah, G.; Segall, Y. *Tetrahedron* **2009,** 65, 5278-5283.
8. (a) Dejaegere, A.; Karplus, M. *J. Am. Chem. Soc.* **1993,** 115, 5316-5317. (b) Dejaegere, A.; Liang, X.; Karplus, M. *J. Chem. Soc. Faraday Trans.* **1994,** 90, 1763-1770. (c) Chang, N.-Y.; Lim, C. *J. Phys. Chem. A* **1997,** 101, 8706-8713. (d) Chang, N.-Y.; Lim, C. *J. Am. Chem. Soc.* **1998,** 120, 2156-2167. (e) Florian, J.; Warshel, A. *J. Phys. Chem. B.* **1998,** 102, 719-734. (f) Hu, C.-H.; Brinck, T. *J. Phys. Chem. A* **1999,** 103, 5379-5386. (g) Lopez, X.; Dejaegere, A.; Karplus, M. *J. Am. Chem. Soc.* **2001,** 123, 11755-11763. (h) Menegon, G.; Loos, M.; Chaimovich, H. *J. Phys. Chem. A* **2002,** 106, 9078-9084. (i) Arantes, G. M.; Chaimovich, H. *J. Phys. Chem. A* **2005,** 109, 5625-5635. (j) López, C. S.; Faza, O. N.; de Lera, A. R.; York, D. M. *Chem. Eur. J.* **2005,** 11, 2081-2093. (k) Iché-Tarrat, N.; Barthelat, J.-C.; Rinaldi, D.; Vigroux, A. *J. Phys. Chem. B.* **2005,** 109, 22570-22580. (l) Lopez, X.; Dejaegere, A.; Leclerc, F.; York, D. M.; Karplus, M. *J. Phys. Chem. B.* **2006,** 110, 11525-11539.
9. (a) Thatcher, G. R. J.; Campbell, A. S. *J. Org. Chem.* **1993,** 58, 2272-2281. (b) Zheng, F.; Zhan, C.-G.; Ornstein, R. L. *J. Chem. Soc. Perkin Trans. 2* **2001,** 2355-2363. (c) Bell, A. J.; Citra, A.; Dyke, J. M.; Ferrante, F.; Gagliardi, L.; Watts, P. *Phys. Chem. Chem. Phys.* **2004,** 6, 1213-1218. (d) Barbosa, A. C. P.; Borges Jr, I.; Lin, W. O. *J. Mol. Struct. (THEOCHEM)* **2004,** 712, 187-195. (e) Doskocz, M.; Roszak, S.; Majumbar, D.; Doskocz, J.; Gancarz, R.; Leszczynski, J. *J. Phys. Chem. A* **2008,** 112, 2077-2081. (f) McAnoy, A. M.; Paine, M. R. L.; Blanksby, S. J. *Org. Biomol. Chem.* **2008,** 6, 2316-2326. (g) McAnoy, A. M.; Williams, J.; Paine, M. R. L.; Rogers, M. L.; Blanksby, S. J. *J. Org. Chem.* **2009,** 74, 9319-9327. (h) Ashkenazi, N.; Segall, Y.; Chen, R.; Sod-Moriah, G.; Fattal, E. *J. Org. Chem.* **2010,** 75, 1917-1926.
10. Kluger, R.; Taylor, S. D. *J. Am. Chem. Soc.* **1990,** 112, 6669-6671.
11. (a) Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999,** 55, 13109-13320. (b) Ashkenazi, N.; Karton, Y.; Segall, Y. *Tetrahedron Lett.* **2004,** 45, 8003-8006. (c) Ashkenazi, N.; Zade, S. S.; Segall, Y.; Karton, Y.; Bendikov, M. *Chem. Commun.* **2005,** 5879-5881.
12. (a) Aksnes, G.; Songstad, J. *Acta Chem. Scand.* **1965,** 19, 893-897. (b) Aksnes, G.; Gierstae, R.; Wulvik, E. A. *Phosphorus and Sulfur and the Relat. Elem.* **1988,** 39, 141-152.
13. (a) van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. *J. Am. Chem. Soc.* **2006,** 128, 10738-10744. (b) van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. *Chem. Phys. Chem.* **2007,** 8, 2452-2463. (c) van Bochove, M. A.; Bickelhaupt, F. M. *Eur. J. Org. Chem.* **2008,** 649-654.
14. Fedoryński, M. *Chem. Rev.* **2003,** 103, 1099-1132.
15. (a) Parham, W. E.; Schweizer, E. E. *J. Org. Chem.* **1959,** 24, 1733-1735. (b) Regen, S. L.; Singh, A. *J. Org. Chem.* **1982,** 47, 1587-1588.
16. (a) Basil, S. F.; Gilbert, E. E. *J. Chem. Eng. Data* **1962,** 7, 568-569. (b) Chien, C.-T.; Tasi, C.-H.; Chang, T.-Y.; Tsai, P.-K.; Wang, Y.-C.; Yan, T.-H. *J. Org. Chem.* **2006,** 71, 4324-4327.
17. DeWeese, F. T.; Minter, D. E.; Nosovitch, J. T.; Michael, G. R. *Tetrahedron* **1986,** 42, 239-244.
18. Ledwith, A.; Woods, H. J. *J. Chem. Soc. B* **1967,** 10, 973-976.