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The Mechanism of Nucleophilic Displacements at Phosphorus in Chloro-Substituted Methylphosphonate Esters: P−O vs P−C Bond Cleavage: A DFT Study

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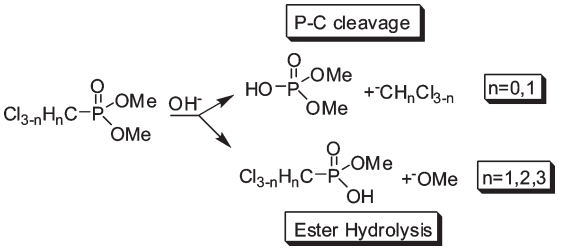

Potential energy surfaces for the nucleophilic displacements at phosphorus in dimethyl methyl-, chloromethyl-, dichloromethyl-, and trichloromethylphosphonates have been computed at the B3LYP/6-31+G* level of theory, using IEF-PCM to account for the solvent effect. The results reveal that sequential addition of chlorine substituents on the methyl phosphonates increases the stability of transition states and intermediates which facilitate P−C bond cleavage. Thus, while nonsubstituted dimethyl methylphosphonate and dimethyl chloromethylphosphonate may undergo exclusive P−O bond cleavage, the trichlorinated analogue exclusively undergoes P−C bond dissociation. Dichloromethylphosphonic acid derivatives were found to be borderline cases: while P−O fission is the preferred process, P−C scission might also be feasible. The increase in stability of the corresponding transition states and intermediates can account for the enhancement in the apicophilicity of the methyl ligand upon substitution with chlorine atoms.

Introduction

Alkylphosphonic acid derivatives (i.e., esters, amides, thio esters, halides, etc.) have been studied for decades both in respect to organic transformations and for their biological activities.[1] Although many processes involving nucleophilic attacks at the phosphorus center in P(V) compounds followed by P−ligand bond cleavage are known (P−O, P−N, P−S, P−halogen, etc.), the analogous P−C bond scission is rare.[1b] As the P−C bond is formally polarized and the carbon is negatively charged, it might be a potential carbanion source in organic transformations (e.g., transmetalation).[2] To the best of our knowledge for non-activated alkylphosphonic acid derivatives (e.g., dialkyl methylphosphonates) P−C bond dissociation, which evolves from nucleophilic displacement at the phosphorus, has never been described. The inertness of this bond might be explained by using the "preference rules" and the pseudorotation hypothesis.[3] Hence, under nucleophilic conditions other bonds are cleaved more readily (e.g., phosphonic acid diesters would undergo a P−O bond dissociation since the alkyl substituent occupies an equatorial position and the O-alkyl is

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(2) Alkyl phosphonates 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), see: Ando K. *J. Org. Chem.* **1999**, *64*, 6815 and ref 8 therein. This reaction is normally feasible only for activated alkylphosphonates. See: Maryanoff, B. E.; Raitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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placed at an apical position in the pentacoordinated intermediate). This is also supported by the fact that thermodynamically P−O cleavage is preferred as the resulting alkoxide is a much better leaving group than a carbanion. Other possible contributions to the unique stabilization effects of the adjacent phosphorus, mainly on carbanions but also on neutral CH_3 substituent, have been shown recently.[4] Some unique examples of P−C bond fission in activated systems are the $-CF_3$ elimination from tris-(trifluoromethyl)phosphine oxide,[5] P−CCl_3 cleavage under nucleophilic conditions both in phosphonates[6] and in phosphinates,[7] α-hydroxyphosphonate−phosphate rearrangement,[8] and a recent example of dephosphonylation of β-ketophosphonic acid presumably via nucleophilic addition of water to the phosphorus.[9] Elimination of CX_3^- moieties should be of particular interest as these reactions can be considered as the phosphorus equivalent of the Haloform reaction, therefore, a source for dihalocarbenes.[10] Surprisingly, we found only a few examples where the commercially available compound diethyl (trichloromethyl)phosphonate was used as a precursor for dichlorocarbene.[10a,b]

A major interest in the stability of the P−C bond stems from the use of phosphonates as agrochemicals, and the need to monitor any possible toxic degradation products and metabolites. One of us has studied in recent years the mechanism by which the plant growth regulator ethephon (2-chloroethylphosphonic acid) acts as a phosphorylation agent via P−C bond cleavage.[11]

Other aspects involving phosphonates are the decontamination of chemical warfare agents and the destruction of pesticides which had also been discussed extensively in the literature.[12]

As far as we know, this inertness of the P−C bond in unsubstituted alkylphosphonates, compared to its high reactivity in perhalomethyl analogues,[13] has never been studied in depth.

The ability to accurately elucidate reaction mechanisms involving nucleophilic transformations of P(V) compounds (mainly phosphates) with use of ab intio and DFT methods, both in the gas phase and in solution, has been demonstrated many times during the past decade.[14,15] Therefore, we believed that by using this methodology and conducting a thorough mechanistic study 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 which dictate the reaction course and consequently the ability to obtain carbanions and/or carbenes via P−C bond cleavage.

As a model we studied the reaction pathways which may evolve from nucleophilic attacks of hydroxide anion on dimethyl methylphosphonate (DMMP) [**1**] and its chlorinated analogues dimethyl chloromethylphosphonate (**2**), dimethyl dichloromethylphosphonate (**3**), and dimethyl trichloromethylphosphonate (**4**). Progressive halogenation at the methyl−phosphonate increases the C−P bond polarization, its apicophilicity, and hence its capability as a leaving group. Comparing P−C to P−O dissociations would be a representative test case as the methyl ester substituents at the phosphorus atom are less readily cleaved compared to other groups (i.e., halogens or thioesters), due to their lower apicophilicity.[16] It should also be noted that attack at the ester carbon is also hypothetically possible, as it was shown to occur for several phosphate triesters in the gas phase.[14c,g,h,17] Nevertheless, we[18] and others[15e,19] showed that in solution only attack at the phosphorus takes place,

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TABLE 1. Calculated Relative Free Energies and Selected Bond Lengths and Angle for the Species Involved in the Reaction of 1 with OH^- in the Aqueous Phase

	ΔG (kcal/mol)[a]	P−apical ligand bond length (Å)	$\angle L_{ap}-P-L_{ap}$ (deg)
1-TS1	29.2 [28.0]	2.385 (P−O), 1.846 (P−C)	171.6
1-TS2	20.5 [18.3]	2.517 (P−OH), 1.679 (P−OMe)	167.0
1-TS3	54.0 [53.9]	3.044 (P−C), 1.658 (P−O)	168.6
1-TS4	20.4	2.516 (P−OMe), 1.680 (P−OH)	166.9
1-TS5	11.5	2.271, 1.695 (P−OMe)	161.4
1-TS6	29.4	1.715 (P−O),[b] 1.874 (P−C)[b]	151.6[b]
1-TS7	24.8	1.716 (P−OH),[b] 1.719 (P−OMe)[b]	138.5[b]
1-TS8	44.2	2.548 (P−C), 1.683 (P−O)	167.2
1-TS9	17.9	2.125 (P−O), 1.857 (P−C)	163.8
1-INT1	21.5 [19.3]	1.774(P−OH), 1.887 (P−C)	165.5
1-INT2	13.6	1.809 (P−OH), 1.795 (P−OMe)	169.0
1-INT3	10.0	1.870, 1.775 (P−OMe)	165.1
1-INT4	21.2	1.770 (P−O), 1.902 (P−C)	163.4

[a]All energies are relative to the starting materials which were determined as 0.0 kcal/mol. Values in square brackets were obtained at MP2/6-31+G(d)//B3LYP/6-31+G(d). [b]Square pyramid geometry.

TABLE 2. Calculated Relative Free Energies and Selected Bond Lengths and Angle for the Species Involved in the Reaction of 2 with OH^- in the Aqueous Phase

	ΔG (kcal/mol)[a]	P−apical ligand bond length (Å)	$\angle L_{ap}-P-L_{ap}$ (deg)
2-TS1	23.2 [21.3]	2.543 (P−O), 1.861 (P−C)	168.9
2-TS2	17.0 [15.7]	2.781 (P−OH), 1.633 (P−OMe)	163.8
2-TS3	29.5	2.902 (P−C), 1.638 (P−OH)	172.7
2-TS4	15.7	2.706 (P−OMe), 1.645 (P−OH)	159.5
2-TS5	7.9	2.266, 1.682 (P−O)	160.8
2-TS6	29.4	1.718 (P−O),[b] 1.923 (P−C)[b]	151.2[b]
2-TS7	19.9	1.723 (P−OH),[b] 1.713 (P−OMe)[b]	145.2[b]
2-TS8	24.7	2.591 (P−C), 1.660 (P−O)	171.4
2-TS9	10.1	2.228 (P−O), 1.874 (P−C)	162.7
2-INT1	11.5	1.758 (P−OH), 1.924 (P−C)	168.2
2-INT2	8.2	1.786 (P−OH), 1.783 (P−OMe)	167.4
2-INT3	5.0	1.835, 1.767 (P−OMe)	164.5
2-INT4	10.9	1.747 (P−O), 1.945 (P−C)	163.7

[a]All energies are relative to the starting materials which were determined as 0.0 kcal/mol. Values in square brackets were obtained at MP2/6-31+G(d)//B3LYP/6-31+G(d). [b]Square pyramid geometry.

as expected from a hard nucleophile such as hydroxide.[20] Therefore, processes comprising addition of the nucleophiles to atoms other than P were neglected.

Computational Methods

Optimized geometries and harmonic frequencies for all the reported species (starting material, transition states, intermediates, and products) were obtained by density functional calculations with use of B3LYP hybrid functional and 6-31+G* basis set (corrected for unscaled ZPVE).[21] Gas phase optimized structures were used as input for the calculations in solution which were reoptimized at the same level of theory with the integral equation formalism polarized continuum solvation model (IEF-PCM).[22] Although continuum models may not be the best in analyzing hydrolysis or esterolysis reactions they have been shown to yield accurate results.[23] Moreover, it was shown in the past that water does not participate in the alkaline hydrolysis of phosphate triesters, and the reaction rates are not much affected by solvent changes.[24] Therefore, and keeping in mind that phosphonates (including the transition states and intermediates derived from their reactions) are more hydrophobic than the corresponding phosphates, we trust this model to account for the effect of water as the solvent for the reactions in hand. Energies from these calculations were converted to thermodynamic data based on the frequency calculations. All transition states were verified by calculating the intrinsic reaction coordinates (IRC) and/or by examining the imaginary frequency's normal mode.[25] DFT methods, including B3LYP/6-31+G*, were previously shown to yield accurate results in theoretical studies of analogous nucleophilic attacks on various phosphates and phosphonates.[14f,g,j−l,15c,15g,18a] Most importantly, the calculated energies in this work are in good agreement with kinetic experimental results, vide infra. Nonetheless, to further establish the validity of these methods in our studies we performed single-point MP2 calculations for all species involved in the rate determining steps. Only a slight and consistent decrease (1−2 kcal/mol) in the calculated free energies of

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TABLE 3. Calculated Relative Free Energies and Selected Bond Lengths and Angle for the Species Involved in the Reaction of 3 with OH^- in the Aqueous Phase

	ΔG (kcal/mol)[a]	P−apical ligand bond length (Å)	$\angle L_{ap}-P-L_{ap}$ (deg)
3-TS1	19.4 [17.2]	2.650 (P−O), 1.889 (P−C)	170.1
3-TS2	14.9 [13.7]	2.563 (P−OH), 1.646 (P−OMe)	163.8
3-TS3	14.0	2.603 (P−C), 1.656 (P−OH)	176.4
3-TS4	12.1	2.565 (P−OMe), 1.656 (P−OH)	165.3
3-TS5	4.9	2.281, 1.661 (P−O)	169.0
3-TS6	16.2	1.704 (P−O),[b] 1.966 (P−C)[b]	145.6[b]
3-TS7	18.6	1.712 (P−OH),[b] 1.708 (P−OMe)[b]	149.7[b]
3-TS8	10.2	2.550 (P−C), 1.661 (P−O)	173.2
3-TS9	6.0	2.244 (P−O), 1.908 (P−C)	161.5
3-INT1	4.4	1.744 (P−OH), 1.984 (P−C)	170.2
3-INT2	5.7	1.781 (P−OH), 1.736 (P-OMe)	161.8
3-INT3	2.2	1.837, 1.728 (P−OMe)	162.0
3-INT4	2.8	1.724 (P−O), 2.003 (P−C)	168.1

[a]All energies are relative to the starting materials which were determined as 0.0 kcal/mol. Values in square brackets were obtained at MP2/6-31G*//B3LYP/6-31+G(d). [b]Square pyramid geometry.

TABLE 4. Calculated Relative Free Energies and Selected Bond Lengths and Angle for the Species Involved in the Reaction of 4 with OH^- in the Aqueous Phase

	ΔG (kcal/mol)[a]	P−apical ligand bond length (Å)	$\angle L_{ap}-P-L_{ap}$ (deg)
4-TS1	16.7 [14.1]	2.780 (P−O), 1.923 (P−C)	172.0
4-TS2	15.7 [13.3]	1.695 (P−OH),[b] 1.697 (P−OMe),[b] 1.987 (P−C)[b]	142.3
4-TS3	−3.4	2.417 (P−C), 1.676 (P−OH)	175.2
4-TS4	−3.3	1.675 (P−OMe), 2.369 (P−C)	169.6
4-TS5	1.8	2.256 (P−OMe), 1.950 (P−C)	163.0
4-INT1	−2.8	1.721 (P−OH), 2.090 (P−C)	172.8
4-INT2	−4.2	1.699 (P−OMe), 2.149 (P−C)	168.3

[a]All energies are relative to the starting materials which were determined as 0.0 kcal/mol. Values in square brackets were obtained at MP2/3-21G*//B3LYP/6-31+G(d). [b]Square pyramid geometry.

activation was obtained by MP2 calculations when compared to the corresponding B3LYP results (see Tables 1−4). Thus, we feel confident in using these methods to study the problem at hand.

Results and Disscusion

To carefully evaluate all plausible reaction pathways which may evolve from initial attack of the hydroxide nucleophile at the P center, all species involved (starting material, transition states, intermediates, and products) were fully optimized in solution and their thermodynamic data were obtained from frequency calculations (in all cases water was chosen, and in addition the reaction pathways for **4** were also computed in Et_2O as an adequate solvent for carbene chemistry).

Calculated Reaction of Dimethyl Methylphosphonate (1) with Hydroxide Anion. All possible pathways involving attack of OH^- at the phosphorus atom of **1** resulting in either P−O or P−C bond fissions are presented in Scheme 1 (**X** = **1**). The calculated transition states and intermediates are shown in Figure 1. The potential energy surfaces, for these pathways, are shown in Figure 2. 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** to form the distorted trigonal bipyramid (TBP) intermediate **1-INT1** (Scheme 1, path 1) and (b) attack opposite to the MeO^- substituent (**1-TS2**) to form the pentacoordinated TBP **1-INT2** (Scheme 1, path 2). Kinetically, path 2 is favored as the required free energy of activation is lower by 8.7 kcal/mol (9.7 kcal/mol with the MP2 approximation method, see Figure 2 and Table 1).

Aksnes et al. measured the activation parameters for alkaline hydrolysis of diethyl methylphosphonate (the diethyl ester analogue of **1**) in H_2O to be $\Delta G^{\ddagger} = 23.6$ kcal/mol and $\Delta S^{\ddagger} = -33.7$ eu at 303 K,[26,27] which corresponds well with those calculated for the formation of **1-TS2** ($\Delta G^{\ddagger} = 20.5$ kcal/mol and $\Delta S^{\ddagger} = -34.0$ eu). The "preference rules"[3] are also well emphasized in this case as **1-INT2**, in which the apical positions are occupied by the OH and OMe groups, is 7.9 kcal/mol lower in energy than **1-INT1**, in which the CH_3 moiety is apical.[28] Intermediate **1-INT2** further undergoes P−O bond dissociation via **1-TS4** to form methyl methylphosphonic acid and methoxide anion (**1-PR2a**), which would react further spontaneously to form the corresponding phosphonic acid anion and methanol (**1-PR2**). The total free energy of **1-PR2** is 35.7 kcal/mol lower than that of **1-S.M.** therefore the net reaction is obviously exothermic. Alternatively, **1-INT2** may undergo pseudorotation via **1-TS7** (a square pyramid intermediate, see Figure 1) to form **1-INT4** (IRC calculations confirmed that this TS connects the two intermediates) and then undergoes P−O bond scission leading to **1-PR2** (Scheme 1, path 2b). However, this path is disfavored as **1-INT4**, comprising a CH_3 group in the apical position, is 7.6 kcal/mol higher in energy than its precursor **1-INT2**. Therefore, the pseudorotation between **1-INT2** and **1-INT4** is disfavored or may be regarded as an equilibrium that is strongly shifted toward the former. Two intermediates were found to possess the CH_3 group in the apical position and therefore might lead to P−C bond dissociation: **1-INT1** and **1-INT4** (Figure 1). Cleaving the bond in the former, via **1-TS3**

(26) (a) Aksnes, G.; Songstad, J. *Acta Chem. Scand.* **1965**, *19*, 893. (b) Aksnes, G.; Gierstae, R.; Wulvik, E. A. *Phosphorus Sulfur Relat. Elem.* **1988**, *39*, 141.

(27) Note that the leaving group in ref 26 is EtO^- while in the calculations it is MeO^-.

(28) Bone, S. A.; Trippett, S.; Whittle, P. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 437.

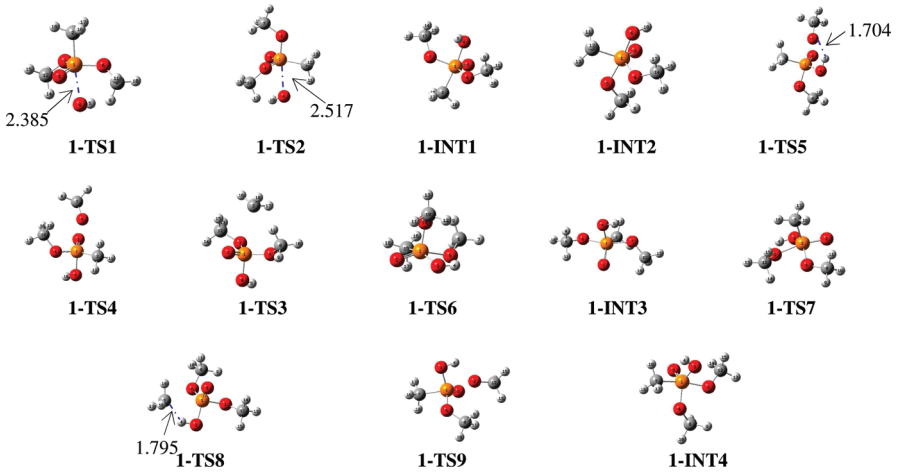
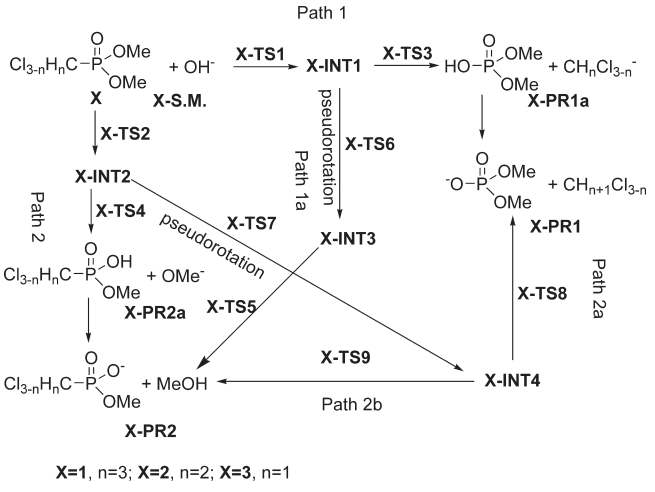


FIGURE 1. Calculated transition states and intermediates in the reaction of DMMP (**1**) with OH^- (orange = phosphorus, red = oxygen, gray = carbon).

SCHEME 1. Calculated Pathways for the Reaction of OH^- with 1, 2, and 3



(path 1), demands an activation free energy of 32.5 kcal/mol (Figure 2 and Table 1), thus making this step the rate determining one and forming the initial products **1-PR1a**, which are 33.9 kcal/mol higher in energy than the starting materials. Therefore, path 1 is also strongly shifted toward the starting materials. Moreover, **1-INT1**, if formed, would preferably pseudorotate to form **1-INT3** (an intermediate in which both ester groups are apical, therefore more stable by 11.5 kcal/mol) via the distorted square pyramid intermediate **1-TS6** (this TS was also confirmed by IRC calculation to connect these two minima). **1-INT3** can only undergo P−O cleavage via **1-TS5** (path 1a). The calculated structure for this transition state (Figure 1) reveals that there is substantial hydrogen bonding between the leaving group and the equatorial OH (the distance O7−H5 is calculated to be 1.704 Å), hence yielding directly the final products **1-PR2**. Hydrogen bonds of this type were also observed in the TS of dissociation processes in the hydrolysis of phosphate esters.[14a] Cleaving the P−C bond in **1-INT4** via **1-TS8** (path 2a) demands free energy of 23.0 kcal/mol (Figure 2 and Table 1), which makes this step the rate determining one. Therefore, this intermediate would preferably undergo a spontaneous P−O fission via **1-TS9** (path 2b). Moreover, the reverse sequence of path 1 (i.e., reaction of phosphate esters with CH_3 anion) is known to yield methylphosphonates.[29] Reviewing all the possible pathways, presented in Scheme 1, it is clear that the kinetically favored process is hydrolysis of the ester, which evolves from the sequence: **1-S.M.** → **1-TS2** → **1-INT2** → **1-TS4** → **1-PR2a** → **1-PR2** (path 2). Any route that can theoretically lead to P−C cleavage demands higher activation energy and the rate determining step shifts from the addition to the elimination. In addition, from the thermodynamic point of view P−O dissociation was always found to be an exothermic process: −3.2 and −35.7 kcal/mol in the formation of **1-PR2a** and **1-PR2**, respectively. On the other hand, P−C cleavage that results in the formation of CH_3 anion is highly endothermic, as shown in path 1 ($\Delta G_{\text{1-PR1a-1-S.M.}}$ = 33.9 kcal/mol). Only in the formation of CH_4 and dimethyl phosphate anion (**1-PR1**), either from **1-PR1a** or directly via **1-TS8** (the distance H4−C7 was calculated to be only 1.795 Å in this transition state), does the reaction become exothermic with total release of 46.3 kcal/mol. Therefore, according to our calculations, indeed the P−CH_3 bond in phosphonic acid derivatives, such as **1**, is inert.

Calculated Reaction of Dimethyl Chloromethylphosphonate (2) with Hydroxide Anion. Substituting one proton on the methyl in phosphonic acid derivatives by a halogen atom (e.g., chlorine) should, in principle, facilitate the P−C bond cleavage. For example, chloromethylphosphonyl dichloride underwent P−C scission upon reaction with PCl_5 to form $POCl_3$.[30] Albeit, by identifying other products, it was concluded that the bond cleaved only after further chlorination at both the carbon and the phosphorus atoms. To establish whether a single chlorine substitution on the methylphosphonate moiety is sufficient to facilitate P−C bond dissociation, we ran another series of calculations to study the possible outcomes of nucleophilic attacks at the phosphorus atom of **2** (Scheme 1, **X** = **2**). The structures of all transition states and intermediates which may be involved in these transformations are presented in Figure 3, and the relative

(29) (a) For a review see: Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 13109. (b) Ashkenazi, N.; Karton, Y.; Segall, Y. *Tetrahedron Lett.* **2004**, *45*, 8003.

(30) Frank, A. W. *Can. J. Chem.* **1968**, *46*, 3573.

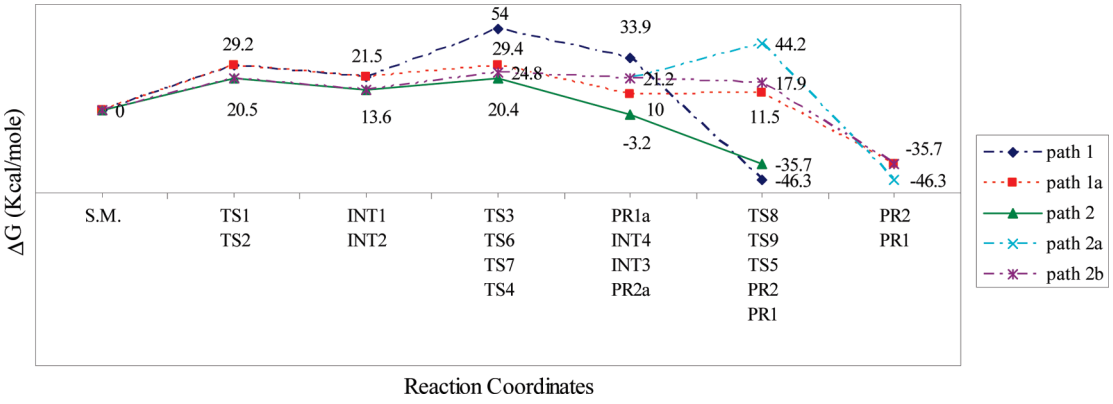


FIGURE 2. Potential energy surface in the reaction of DMMP (**1**) with hydroxide anion in the aqueous phase.

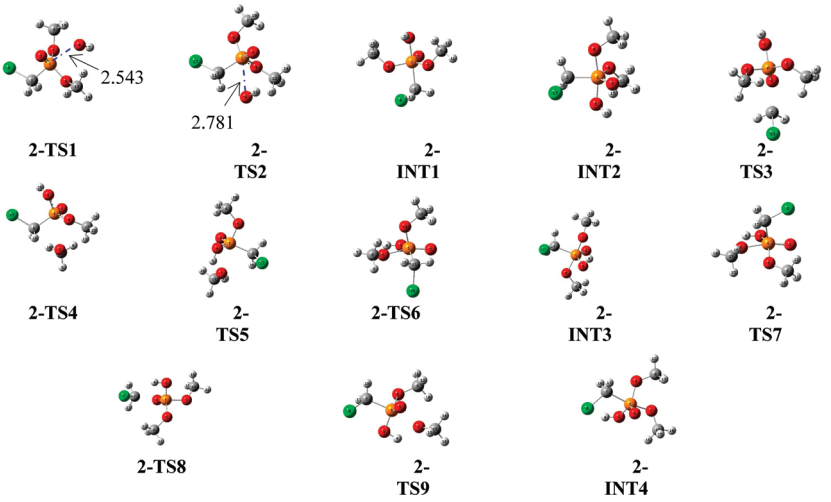


FIGURE 3. Calculated transition states and intermediates in the reaction of **2** with OH^- (orange = phosphorus, red = oxygen, gray = carbon, green = chlorine).

free energies of these species are given in Figure 4 and Table 2. According to our calculations the kinetically preferred process is still path 2, namely, attack from the opposite side to the ester, rather than the chloromethyl moiety, to form **2-INT2**, which further undergoes P−O bond dissociation via **2-TS4** to give initially **2-PR2a** and finally **2-PR2**. Nevertheless, there are some distinctive differences in the respective potential energy surfaces of **1** (Figure 2) and **2** (Figure 4). The activation free energy for path 2 (Scheme 1), namely the formation of **2-TS2**, is decreased by 3.5 kcal/mol (2.6 kcal/mol by single-point MP2 calculations) compared to the formation of **1-TS2**. A slightly smaller decrease of 1.6 kcal/mol was obtained experimentally[26] in the alkaline hydrolysis of the diethyl ester analogues ($\Delta G^{\ddagger}$ = 22.0 kcal/mol and $\Delta S^{\ddagger}$ = −31.9 eu at 303 K for diethyl chloromethylphosphonate, compared to calculated $\Delta G^{\ddagger}$ = 17.0 kcal/mol and $\Delta S^{\ddagger}$ = −35.0 eu for the formation of **2-TS2**).[27] A more significant decrease of 6.0 kcal/mol (6.7 kcal/mol with the MP2 level) was found for the formation of **2-TS1**, via attack of the OH^- from the opposite side to the CH_2Cl group, compared to **1-TS1**. Moreover, examining path 1 it becomes obvious that the rate determining step is switched to the addition of the nucleophile rather than the elimination of the leaving group. Albeit, the formation of **2-TS1** still requires 6.2 kcal/mol more than that of **2-TS2**. The calculated distance P−OH in **2-TS1** and **2-TS2** is 2.543 and 2.781 Å, respectively (Figure 3 and Table 2), while in **1-TS1** and **1-TS2** they are 2.385 and 2.517 Å (Figure 1 and Table 1). Therefore, the transition states for attack on **2** are somewhat earlier. This may also explain the decrease in the activation free energy for the attack on **2**. A similar decrease is also observed in the relative energies of the intermediates which possess hydroxy/alkoxy groups in the apical positions (**2-INT2** and **2-INT3**) and those with an apical CH_2Cl ligand (**2-INT1** and **2-INT4**), as reflected from Figure 4 and Table 2. This observation implies that although a single chlorination does not yet shift the kinetically preferred process from ester hydrolysis to dealkylation, substitution by chlorine considerably increases the apicophilicity of the alkyl group.[31]

These effects are also observed thermodynamically as the formation **1-PR1a** is considerably more exothermic (33.9 kcal/mol, Figure 2 and Table 1) than the formation of **2-PR1a** (8.9 kcal/mol, Figure 4 and Table 2).

Calculated Reaction of Dimethyl Dichloromethylphosphonate (3) with Hydroxide Anion. The reaction profiles calculated for **3** (Scheme 1, **X** = **3**) were identical to those found

(31) By increasing the elecetronegativity and/or the steric bulk of the ligand. See: (a) Trippett, S. *Pure Appl. Chem.* **1974**, *40*, 595. (b) Trippett, S. *Phosphorus Sulfur Relat. Elem.* **1976**, *1*, 89.

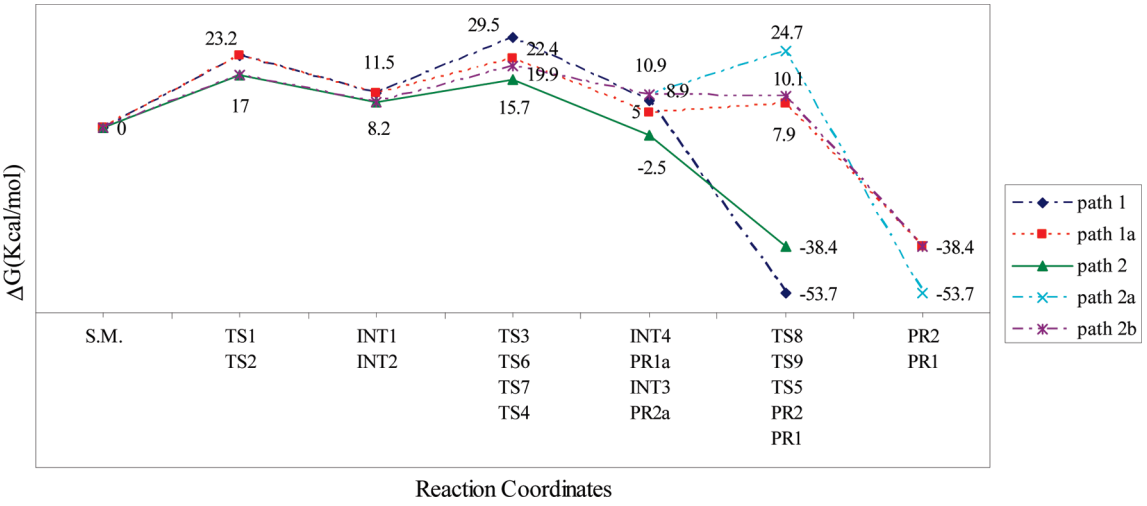


FIGURE 4. Potential energy surface in the reaction of **2** with hydroxide anion in the aqueous phase.

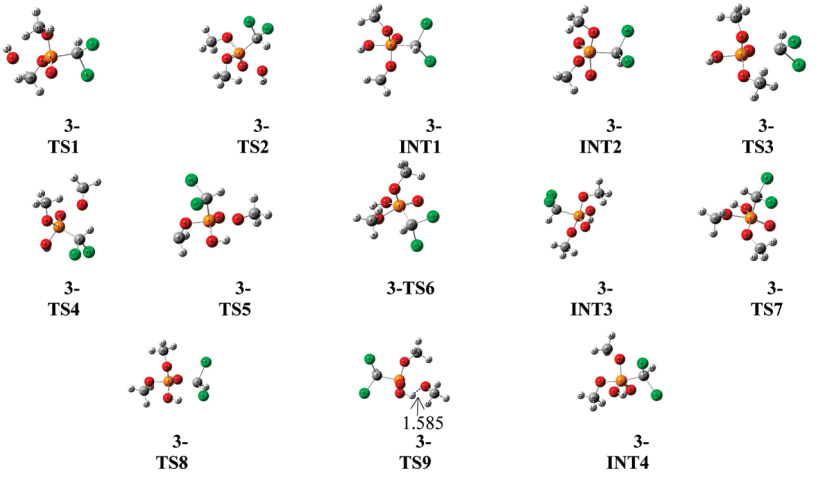


FIGURE 5. Calculated transition states and intermediates in the reaction of **3** with OH^- (orange = phosphorus, red = oxygen, gray = carbon, green = chlorine).

for **1** and **2**. Albeit, the energetic properties of the species involved (Figure 5) were considerably different (Figure 6 and Table 3). A second chlorine atom substitutent at the methylphosphonate moiety further reduces the activation free energy for both the attack opposite to the OMe ligand (path 2, $\Delta G^{\ddagger}_{\mathbf{3\text{-}TS2}}$ = 14.9 kcal/mol) and the attack opposite to the $CHCl_2$ (path 1, $\Delta G^{\ddagger}_{\mathbf{3\text{-}TS1}}$ = 19.4 kcal/mol). Thus, the former is still the kinetically preferred process, although the energy difference is reduced to ca. 4.5 kcal/mol (3.5 kcal/mol single-point MP2). Also noteworthy is the fact that the stable intermediates formed from these two transition states (i.e., **3-INT2** and **3-INT1**, respectively), which possess some substantial geometrical differences (Figure 5 and Table 3), are very similar energetically (the free energy difference is only 1.3 kcal/mol in favor of the latter). Furthermore, according to our calculations the apicophilicity of a $CHCl_2$ group is similar to that of the OMe, as deduced from the relative energies of intermediates **3-INT1**, **3-INT2**, **3-INT3**, and **3-INT4**.[31] The intermediate **3-INT2** undergoes elimination of the apical methoxy ligand to form initially **3-PR2a**, which further reacts to give **3-PR2**. This route involves the formation of **3-TS4**, which requires 6.4 kcal/mol. Alternatively, **3-INT2** can pseudorotate to **3-INT4**, which is 2.9 kcal/mol lower in energy, via the formation of the square pyramid transition state **3-TS7**, which requires 12.9 kcal/mol. **3-INT4**, having both OMe and $CHCl_2$ as apical ligands, may undergo either P−O (path 2b) or P−C cleavage (path 2a). The former proceeds via the formation of **3-TS9**, which possesses a considerable hydrogen bonding between the leaving group and the equatorial OH ligand (the distance O2−H4 is calculated to be 1.585 Å, see Figure 5), to form directly the final product **3-PR2**. Path 2a proceeds via transition state **3-TS8**, which is 4.2 kcal/mol higher in energy than **3-TS9**, to form methylene chloride and dimethyl phosphate anion (**3-PR1**).

Therefore, P−O dissociation is still the kinetically preferred process although in other dichloromethylphosphonate systems, which possess ligands that bind stronger to the phosphorus atoms than OMe, P−C scission may be feasible. Such may be the case for dichloromethylphosphonic acid that has no other leaving group but the $CHCl_2$. Thermodynamically all products are exothermic (Figure 6 and Table 3): **3-PR1a** by 6.9 kcal/mol, **3-PR1** by 53.0 kcal/mol, **3-PR2a** by 2.9 kcal/mol, and **3-PR2** by 43.2 kcal/mol. These

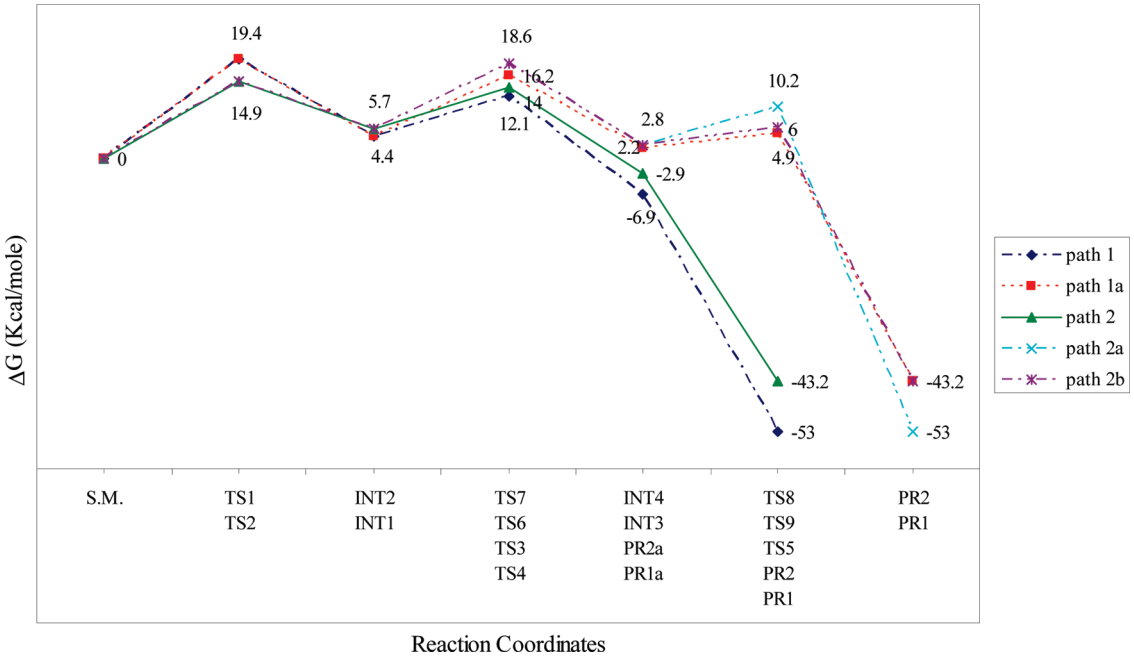
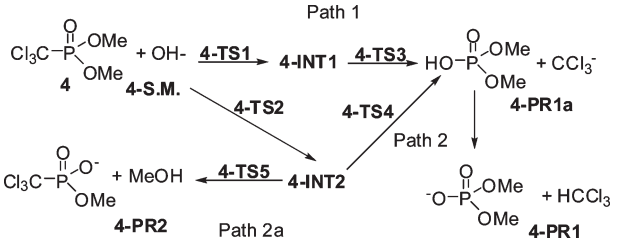


FIGURE 6. Potential energy surface in the reaction of **3** with hydroxide anion in the aqueous phase.

SCHEME 2. Calculated Pathways for the Reaction of OH^- and 4



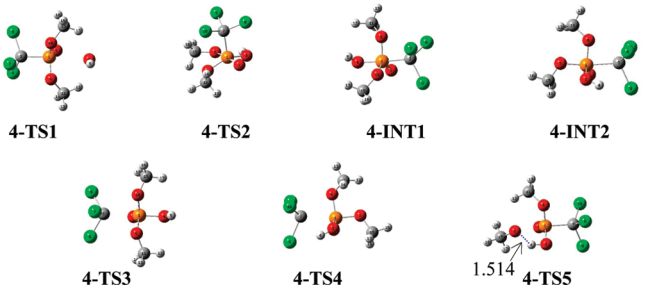


FIGURE 7. Calculated transition states and intermediates in the reaction of **4** with OH^- (orange = phosphorus, red = oxygen, gray = carbon, green = chlorine).

results emphasize the fact that substituting two protons on the methyl moiety by two chlorine atoms increases its ability to act as a leaving group.

Calculated Reaction of Dimethyl Trichloromethylphosphonate (4) with Hydroxide Anion in Water. The calculated profiles for the reaction of **4** with OH^- in water (Scheme 2) reveal totally different results, both structurally (Figure 7) and energetically (Figure 8 and Table 4), from those obtained for the systems **1**−**3**. When the nucleophile approaches from the opposite side to the OMe moiety (path 2) the first stationary point found was the transition state **4-TS2**, which possesses a square pyramid geometry in which the CCl_3 fragment is in the apical position (Figure 7), 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 **4-INT2**, which is already lower in energy than the starting materials (ca. −4.2 kcal/mol). IRC calculations confirmed that indeed **4-TS2** connects the two minima of the starting materials and this intermediate. From **4-INT2** only 0.9 kcal/mol is required in order to dissociate the CCl_3 fragment via **4-TS4**. Alternatively P−O cleavage, via path 2a, demands 6.0 kcal/mol to form **4-TS5**. This TS also possesses a considerable hydrogen bonding (the distance O2−H4 is calculated to be 1.514 Å, see Figure 7). Attack from the opposite side to the CCl_3 ligand (path 1) 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 path 2. Moreover, once such an attack takes place, the rest of the process is down hill in energy as the formation of **4-INT1** releases 19.5 kcal/mol and the following transition state (**4-TS3**) is 0.6 kcal/mol lower in energy than the previous intermediate.

Thus, path 1 is essentially a classical S_N2 type mechanism, where no stable intermediates are formed. Bickelhaupt and co-workers recently concluded that the existence of stable intermediates during nucleophilic substitution at phosphorus is determined by steric bulk around the phosphorus and that electronic effects modulate the barrier height.[32] Clearly, in our case CCl_3 is both the bulkiest and the most electronegative substituent (vide infra).

These kinetic results obviously suggest that in **4** the most favorable process is P−C bond cleavage, as observed in the past for the analogous diethyl trichloromethylphosphonate.[26] Notably, this process can be regarded as an analogue to the cleavage step in the Haloform reaction of carbonyl

(32) (a) van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. *J. Am. Chem. Soc.* **2006**, *128*, 10738. (b) van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. *ChemPhysChem* **2007**, *8*, 2452. (c) van Bochove, M. A.; Bickelhaupt, F. M. *Eur. J. Org. Chem.* **2008**, 649.

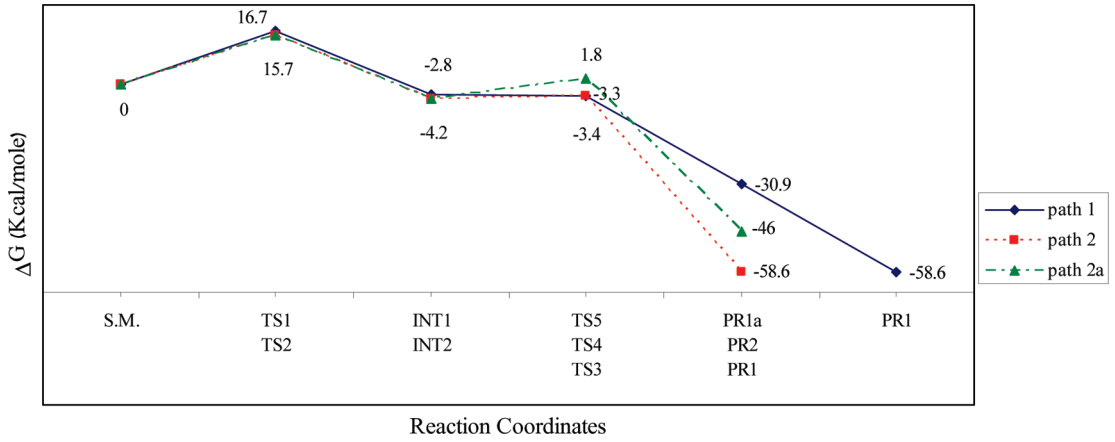


FIGURE 8. Potential energy surface in the reaction of **4** with hydroxide anion in the aqueous phase.

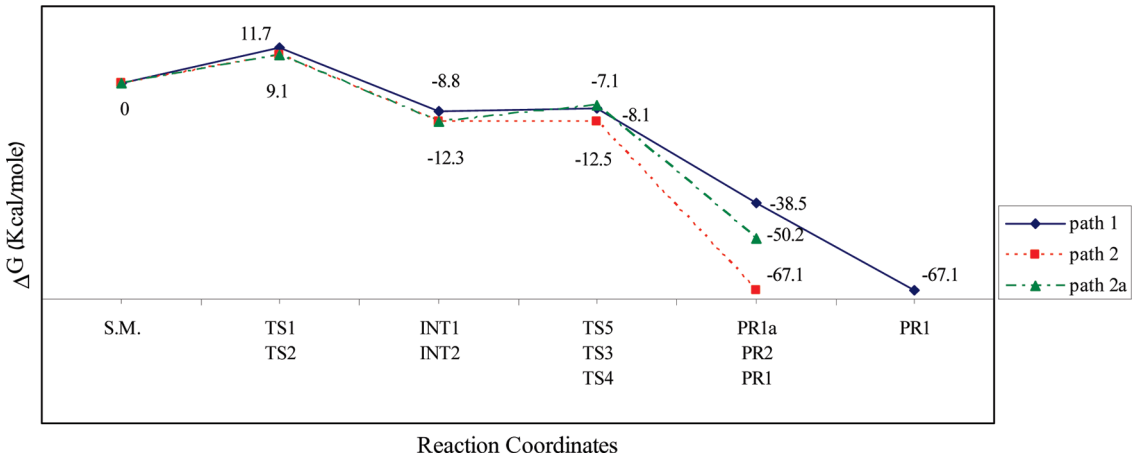


FIGURE 9. Potential energy surface in the reaction of **4** with hydroxide anion in Et_2O.

compounds, which also proceeds via addition−elimination type mechanism.[33] The P−C scission in **4-INT1** and **4-INT2** is in analogy to the C−CCl_3 bond fission in 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethanol.[34]

The formation of the products **4-PR1a** has some obvious synthetic utilities as $^{-}CCl_3$ is a precursor to dichlorocarbene.[35] Yet, water or acid such as dimethyl phosphoric acid, which is produced together with the trichloromethyl anion, can readily quench the anion to form chloroform. The latter is exothermic by 27.7 kcal/mol, as presented in Figure 8. Therefore, in practice the formation of dichlorobarbene from $^{-}CCl_3$ is carried out under phase transfer catalyst conditions or in aprotic media.[10]

Calculated Reaction of Dimethyl Trichloromethylphosphonate (4) with Hydroxide Anion in Ether. To study the feasibility of obtaining $^{-}CCl_3$, and consequently dichlorocarbene, directly from **4** under more practical conditions (i.e., aprotic media), we recalculated the pathways presented in Scheme 2 in Et_2O using the same solvent model. For consistency reasons the nucleophile of choice remained ^{-}OH, although practically other soluble nucleophiles (alkoxides, aryloxides, etc.) should be more appropriate. The reaction profiles obtained in this solvent are presented in Figure 9 and Table S4 (Supporting Information). Geometrically all transition states and intermediates were almost identical with those calculated in water. Switching from H_2O to Et_2O makes the reactions more favorable kinetically and thermodynamically. The free energy of activation for both path 1 and path 2 is reduced by 5.0−6.7 kcal/mol although the preference of path 2 is more pronounced ($\Delta\Delta G^{\ddagger}_{\text{4-TS1-4-TS2}}$ = 2.6 kcal/mol). Evidently, path 2 in Et_2O proceeds without the formation of a stable intermediate (**4-TS4** is ca. 0.2 kcal/mol lower in energy than **4-INT2**), although the latter is more stable than the starting materials by 12.5 kcal/mol. These results clearly support the assumption that the trichloromethylphosphonate system can serve as a dichlorocarbene precursor in aprotic media.[10]

Effect of the Ligand Charge on the Stability of the Intermediates. It was established in the past[3,31] that the relative stability of the TBP species is derived from the apicophilicity of the ligands binding to the phosphorus center. Trippett[31] pointed out some factors primarily responsible for the relative stability of these five-coordinated intermediates. Among which, those relevant to our discussion are the charge of ligands and changes in steric strain. As charge properties can be readily obtained by computational methods,

(33) Zucco, C.; Lima, C. F.; Rezende, M. C.; Vianna, J. F.; Nome, F. *J. Org. Chem.* **1987**, *52*, 5356.
(34) (a) Nome, F.; Schwingel, E. W.; Ionesco, L. G. *J. Org. Chem.* **1980**, *45*, 705. (b) Nome, F.; Erbs, W.; Correia, V. R. *J. Org. Chem.* **1981**, *46*, 3802.
(35) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099.

TABLE 5. Calculated Natural Charges of the Reaction Intermediates at B3LYP/6-31+G(d)

	P	CH_nCl_{3-n}	OMe	OH	(O)
1-INT1	2.135	−0.264	−0.554	−0.557	−1.203
1-INT2	2.366	−0.287	−0.643 (ap), −0.568 (eq)	−0.625	−1.245
1-INT3	2.251	−0.265	−0.643	−0.501	−1.205
1-INT4	2.390	−0.373	−0.621 (ap), −0.578 (eq)	−0.563	−1.257
2-INT1	2.419	−0.449	−0.568	−0.591	−1.241
2-INT2	2.381	−0.364	−0.625 (ap), −0.554 (eq)	−0.610	−1.227
2-INT3	2.386	−0.372	−0.641	−0.513	−1.218
2-INT4	2.424	−0.469	−0.611 (ap), −0.557 (eq)	−0.550	−1.239
3-INT1	2.462	−0.539	−0.555	−0.596	−1.227
3-INT2	2.428	−0.460	−0.605 (ap), −0.544 (eq)	−0.585	−1.233
3-INT3	2.410	−0.458	−0.622	−0.507	−1.210
3-INT4	2.471	−0.574	−0.599 (ap), −0.544 (eq)	−0.534	−1.220
4-INT1	2.506	−0.634	−0.539	−0.576	−1.209
4-INT2	2.515	−0.686	−0.587 (ap), −0.528 (eq)	−0.517	−1.196

we performed full NBO analyses,[36] from which the ligand charges were derived (Table 5). Some general characteristics regarding the effect of the sequential addition of chlorine substituents on the methyl ligands emerge: (a) a consistent increase in the positive charge of the P center and (b) a consistent increase of the negative charge on the alkyl ligand.

Most interesting is the comparison of the charge distribution in the intermediates which possess OMe and CH_nCl_{3-n} ligands in the apical positions (**1-INT4**, **2-INT4**, **3-INT4**, and **4-INT2**). As *n* decreases so does the negative charge of the OMe ligand, while the electronegativity of the alkyl ligand increases. In **3-INT4** the electronegativity of the two ligands is almost equal (supporting our estimation that P−C cleavage in this system may be feasible, vide supra), and in **4-INT2** the CCl_3 ligand is clearly the more electronegative one. This effect of charge correlates very well with the relative energies of these intermediates and the following TS for the respective bond cleavage (Figures 2,4,6, and 8). Examining **1-INT1**, **2-INT1**, and **3-INT1** it becomes clear why these intermediates, if formed, are the most unstable. The more electronegative ligands (OMe) occupy the equatorial positions (which is in contradiction with the "preference rules")[3] and therefore are expected to undergo pseudorotation. This is again less pronounced in the case of **3** as the negative charge on the alkyl ligand increases. In the intermediates **1-INT2**, **2-INT2**, **3-INT2**, and **4-INT1** the most negatively charged ligand is already occupying an apical position, therefore, the corresponding bond can be readily cleaved. Notably, for the first three intermediates this is the ester bond while for the latter it is the P−CCl_3 bond.

(36) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, Version 3.1, Theoretical Chemistry Institute, University of Wisconsin, Madison WI, 2001.

Conclusion

According to our calculations the main factor governing whether P−C cleavage in methylphosphonates can be achieved is the apicophilicity of the substituted methyl fragment. Higher electronegativity and/or larger steric bulk increases its apicophilicity, and in turn enhances the kinetic stability of key transition states and intermediates. This may be obtained by multiple chlorination of the methyl ligand, consequently increasing the ability of this bond to be cleaved. These electronic properties obviously also have a profound thermodynamic effect regarding the leaving group properties of this fragment. Indeed, we find that in the nonsubstituted methylphosphonate, the apicophilicity of CH_3 is considerably poorer than that of OMe. Therefore, P−C fission cannot occur as this process is an equilibrium that is predominantly shifted toward the binded species. The rate determining step in this case would be the bond dissociation rather than the attack of the nucleophile. This should sustain for all analogous systems regardless of any other bonds which may be more susceptible to hydrolysis. The same should also stand for a single chloro-substitution on the methyl moiety although it changes the rate determining step to the initial addition. Adding a second chlorine substituent largely increases the ability of the dichloromethyl group to leave but when competing with ester hydrolysis the latter would still be preferred. Nonetheless, it might be suggested that in some systems, such as dichloromethylphosphonic acid, P−C cleavage may be obtained. For trichlomethylphosphonic diesters a dramatic change is observed. In such systems P−C bond dissociation becomes the dominant one as the apicophilicity of the CCl_3 is the highest (this ligand is both the more electronegative and the bulkiest). In this case the reaction is similar to the Haloform reaction in carbonyls, which also proceeds via an addition−elimination-type mechanism. Albeit, in carbonyls the transition states should be tetrahedral while in the phosphoryl analogues they possess a trigonal-bipyramid geometry, from which the apical $-CCl_3$ ligand leaves. Hence, these compounds can be a useful source for trichloromethyl anion and consequently as dichlorocarbene precursor. These utilities are currently studied in our lab.

Supporting Information Available: Optimized geometries, summary of NBO analyses, calculated absolute energies, and the number of imaginary frequencies of all stationary points mentioned in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.