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RESEARCH ARTICLE

GC-MS Study of Mono- and Bishaloethylphosphonates Related to Schedule 2.B.04 of the Chemical Weapons Convention: The Discovery of a New Intramolecular Halogen Transfer

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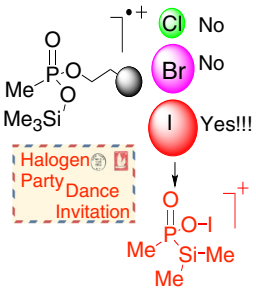

Abstract. A new class of compounds, mono- and bis-haloethylphosphonates (HAPs and bisHAPs, respectively), listed in Schedule 2.B.04 of the Chemical Weapons Convention (CWC), has been synthesized and studied by GC-MS with two aims. First, to improve the identification of this type of chemicals by the Organization for the Prohibition of Chemical Weapons, (OPCW). Second, to study the synergistic effect of halogen and silicon atoms in molecules undergoing mass spectrometry. Fragmentation patterns of trimethylsilyl derivatives of HAPs were found to depend on the nature of the halogen atom; this was in agreement with DFT-calculations. The data suggest that a novel intramolecular halogen transfer takes place during the fragmentation process.

Keywords: Iodine transfer, Haloethylphosphonates, Chemical weapons convention

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Introduction

Recent use of chemical warfare agents (CWAs) during the Syrian conflict has caused international apprehension [1]; in 1997, the CWC was created to protect the world from any CWA attack; it prohibits the development, production, acquisition, stockpiling, retention, transfer, or use of chemical weapons [2]. The OPCW, the compliance body for CWC, holds inspections that may include sampling and on-site or off-site analysis [3]. The chemicals subject to control by the OPCW are listed in an Annex of the CWC under various schedules relating to military and nonmilitary purposes, chemical nature, etc. To carry out the mandatory CWAs verifications, the OPCW maintains an analytical database, the Central Analytical Database (OCAD), which is a collection of gas chromatography retention indexes (GC(RI)), infrared (IR), mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectra for scheduled chemicals and related compounds [4]. The primary on-site analytical tool is gas chromatography/mass spectrometry (GC/MS). Therefore, GC(RI) and MS data in the OCAD are the primary analytical references [5]. Because these efforts are of critical international importance, a large number of scientific articles regarding GC/MS analysis of CWAs and related compounds has been reported [6–26].

The compounds of the present study belong to Schedule 2.B.04, which includes "all chemicals, except for those listed in

Dedicated to Professor Michael Hanack (University of Tübingen, Germany) on the occasion of his 85th birthday.

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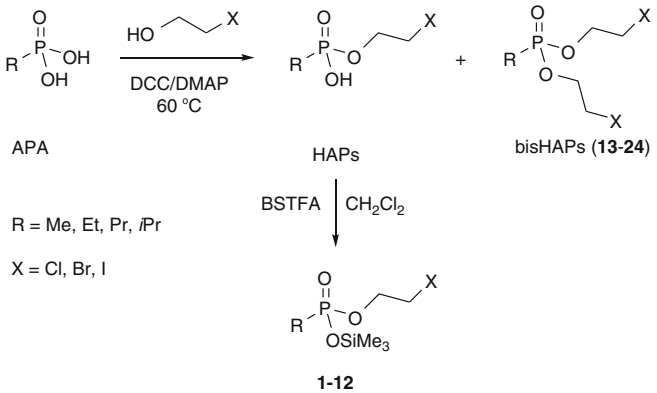


Scheme 1. Synthesis of HAPs, bisHAPs, and TMS derivatives investigated

Schedule 1, containing a phosphorus atom to which is bonded one methyl, ethyl, or propyl (normal or *iso*) group but no additional carbon atoms" [2]. Since the degradation of Scheduled 1 chemicals may lead to the formation of this kind of organophosphorous compounds, some of them are considered environmental markers of nerve agents [19, 24, 26]. Schedule 2.B.04 is open to many compounds. Therefore, an understanding of the different classes of compounds in 2.B.04 is of paramount importance. In this study, we report the EI-MS data for new bis-haloethylphosphonates (bisHAPs) and trimethylsilyl derivatives of monohaloethylphosphonic acids (HAPs). Through a combination of experimental and computational methods, we have discovered new, unprecedented fragmentation patterns of some of these compounds. Specifically, an iodine transfer may be of relevance in the spectral interpretation of compounds in the OCAD and related data bases.

Experimental

General

All the chemicals required for the synthesis of HAPS and bisHAPs as well as the solvents and derivatizing agent *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) are commercially available and were used without further purification.

Synthesis of bisHAPs and HAPs and Derivatization with BSTFA (Scheme 1)

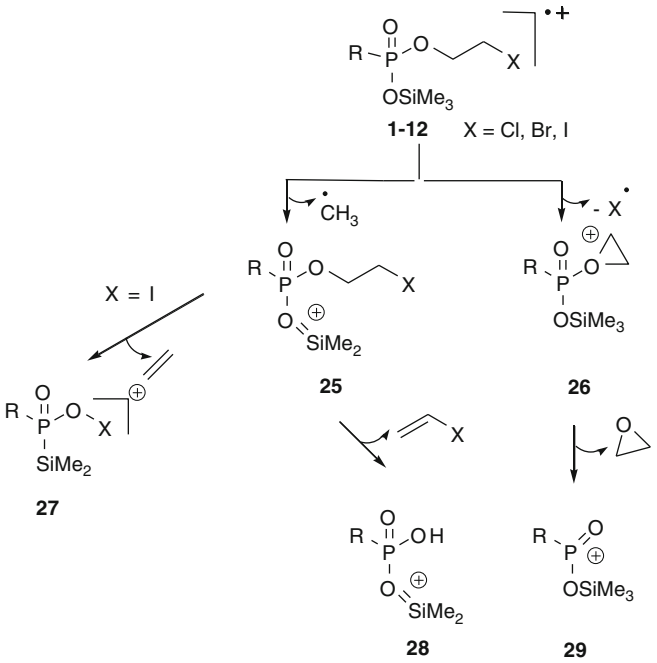
N,N-dicyclohexylcarbodiimide (DCC, 0.15 mmol) and 4-dimethylaminopyridine (DMAP, 0.04 mmol) were added to a solution of the corresponding alkylphosphonic acid (APA, 0.1 mmol) in dichloromethane (1 mL) at room temperature. The mixture was stirred at 60 °C for 1 h. Immediately following, the corresponding haloalcohol (0.44 mmol) was poured into the reaction and stirred at 60 °C for 3 h. Stock solutions were prepared by dilution to the desired concentration with dichloromethane and by derivatization with 200 μL of BSTFA at 60 °C for 30 min in 2 mL sealed glass vials when necessary. The corresponding bisHAPs and silylated HAPs were analyzed by GC/MS.

GC/MS(EI) Analysis

The GC/MS analyses were conducted in electron ionization (EI) mode (70 eV) using an Agilent 6890 gas chromatograph, equipped with a 5973 MSD model (Agilent Technologies, Palo Alto, CA, USA). An HP5 column (5% phenyl 95% methylpolysiloxane; 30 m length, 0.25 mm i.d., and 0.25 mm film thickness) was used at a temperature program of 40 °C (1 min),

Table 1. Significant Peaks **25**–**29** (*m/z*, Relative Peak Intensities) in the Mass Spectra of Monohalogenated TMS Derivatives **1**–**12**

Compound	R	X	**25**	**26**	**27**	**28**	**29**
1	Me	Cl	215 (30)	195(55)		153 (100)	151 (40)
$C_6H_{16}ClPO_3Si$							
2	Me	Br	259 (20)	195 (65)		153 (100)	151 (40)
$C_6H_{16}BrPO_3Si$							
3	Me	I	307 (<10)	195 (75)	279 (100)	153 (65)	151 (50)
$C_6H_{16}IPO_3Si$			306.9439	195.0446	278.8776	152.9995	151.0257
4	Et	Cl	229 (30)	209 (72)		167 (100)	165 (38)
$C_7H_{18}ClPO_3Si$							
5	Et	Br	275 (20)	209 (72)		167 (100)	165 (50)
$C_7H_{18}BrPO_3Si$							
6	Et	I	321 (<10)	209 (80)	293 (100)	167 (60)	165 (50)
$C_7H_{18}IPO_3Si$				209.0660	292.8932	167.0181	165.0417
7	Pr	Cl	243 (45)	223 (80)		181 (100)	
$C_8H_{20}ClPO_3Si$							
8	Pr	Br	287 (30)	223 (95)		181 (100)	179 (60)
$C_8H_{20}BrPO_3Si$							
9	Pr	I	335 (<10)	223 (100)	307 (98)	181 (50)	179 (70)
$C_8H_{20}IPO_3Si$				223.0793	306.9146		179.0565
10	*i*-Pr	Cl	243 (50)	223 (100)		181 (100)	
$C_8H_{20}ClPO_3Si$							
11	*i*-Pr	Br	287 (35)	223 (100)		181 (85)	179 (70)
$C_8H_{20}BrPO_3Si$							
12	*i*-Pr	I	335 (10)	223 (90)	307 (100)	181 (60)	179 (80)
$C_8H_{20}IPO_3Si$				223.9081	306.9513	181.0529	179.0773



Scheme 2. Proposed fragmentation pattern for TMS derivatives of (2-haloethyl)alkylphosphonates **1–12**

then raised at 10 °C/min to 280 °C, where it was held for 5 min. Helium was used as the carrier gas at a constant flow of 1 mL/min. The samples were injected in splitless mode at an injection temperature of 250 °C and 1 µL volume. The spectra were acquired at an EI source temperature of 230 °C and a quadrupole analyzer temperature of 150 °C, with unit mass resolution, scan range *m/z* 40–500 and a scan cycle of 3.15 scans/s. The GC/MS plots as well as the retention indexes (RIs) of the investigated compounds are included in the Supplementary Material. HRMS spectra were recorded using a TOF GCT Premier from Waters (Manchester, UK) Micromass coupled with a gas chromatograph 7890A from Agilent with continuous internal calibration, scan time of 0.9 s, and inter-scan delay of 0.1 s, and are included in the Supplementary Material.

GC/MS(CI) Analysis

The molecular mass of the compounds subject to this study was confirmed by GC/MS analysis conducted in chemical ionization (CI) mode using a Varian (Palo Alto, CA, USA) 3400 gas chromatograph, equipped with a Saturn 2000 ion trap. Chromatographic conditions were identical to those described for above. The spectra were acquired at a CI source temperature of 200 °C and acetonitrile as reactant gas, with unit mass resolution, scan range *m/z* 80–500 and a scan cycle of 2.5 scans/s.

Computational Details

All calculations were performed at the DFT level using the uB3LYP functional [27, 28] as implemented in Gaussian 09 [29]. Cl, Br, and I atoms were described using the lanl2dz pseudopotential [30]. The 6-31G** basis set was used for the H, C, N, and O atoms [31, 32]. All structures of the reactants, intermediates, transition states, and products were fully optimized in vacuo [31]. Transition states were identified by having one imaginary frequency in the Hessian matrix. It was

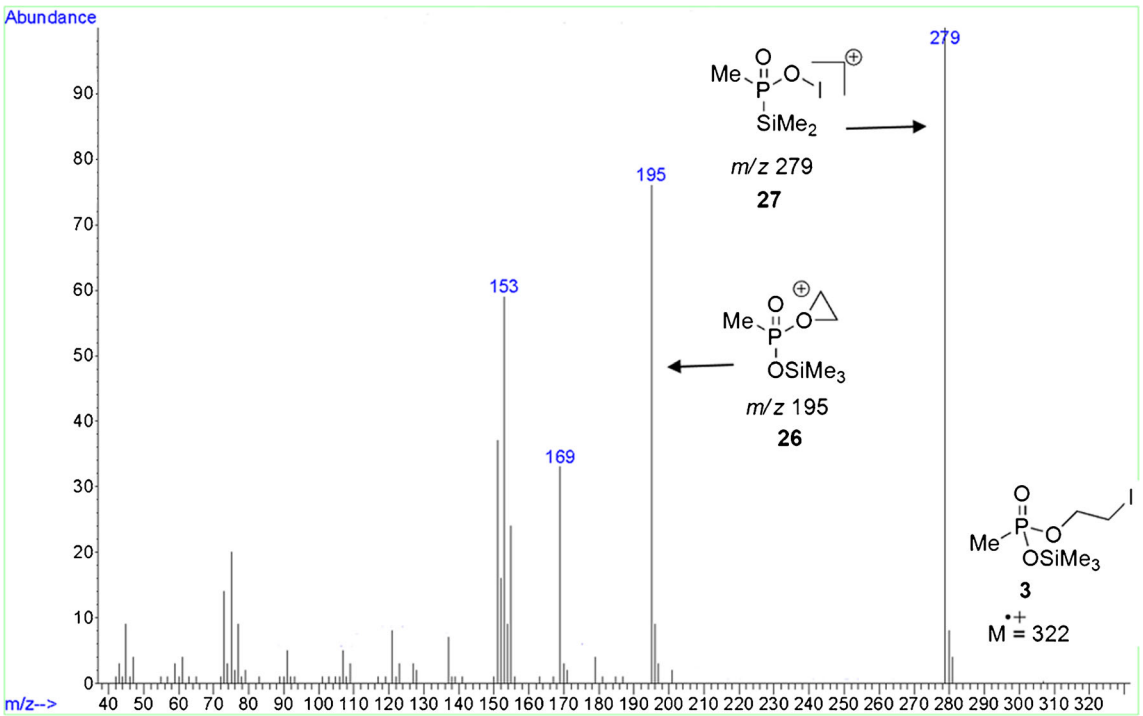


Figure 1. EI Mass spectrum of 2-iodoethyl trimethylsilyl methylphosphonate **3**

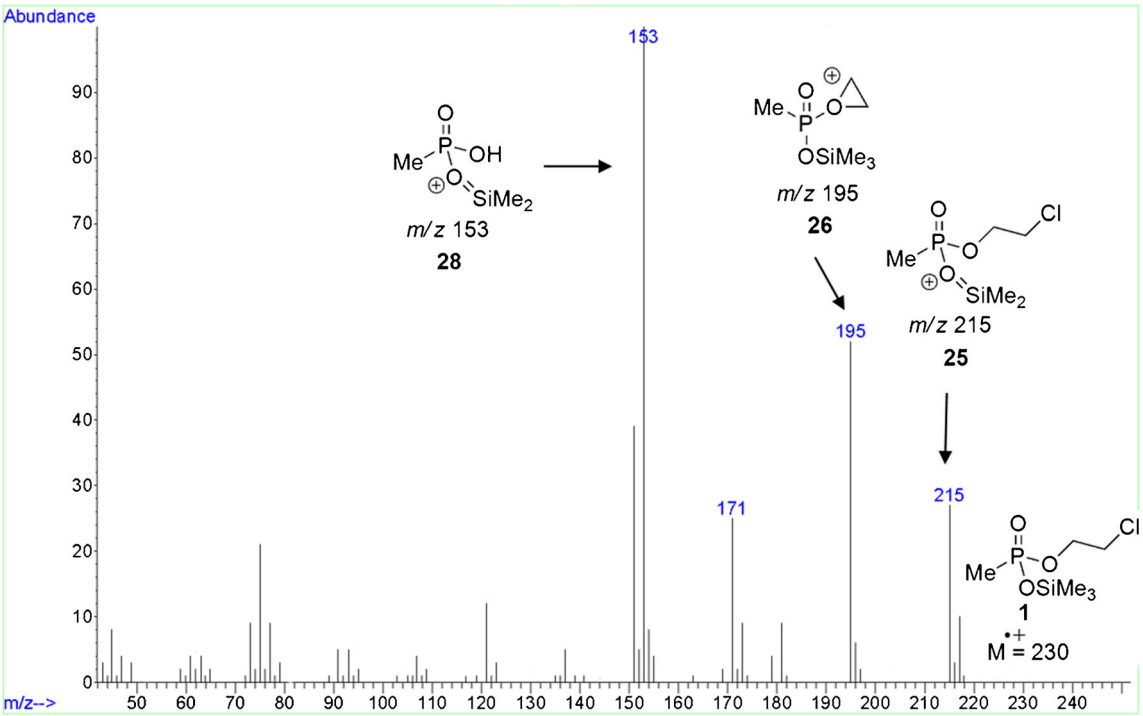
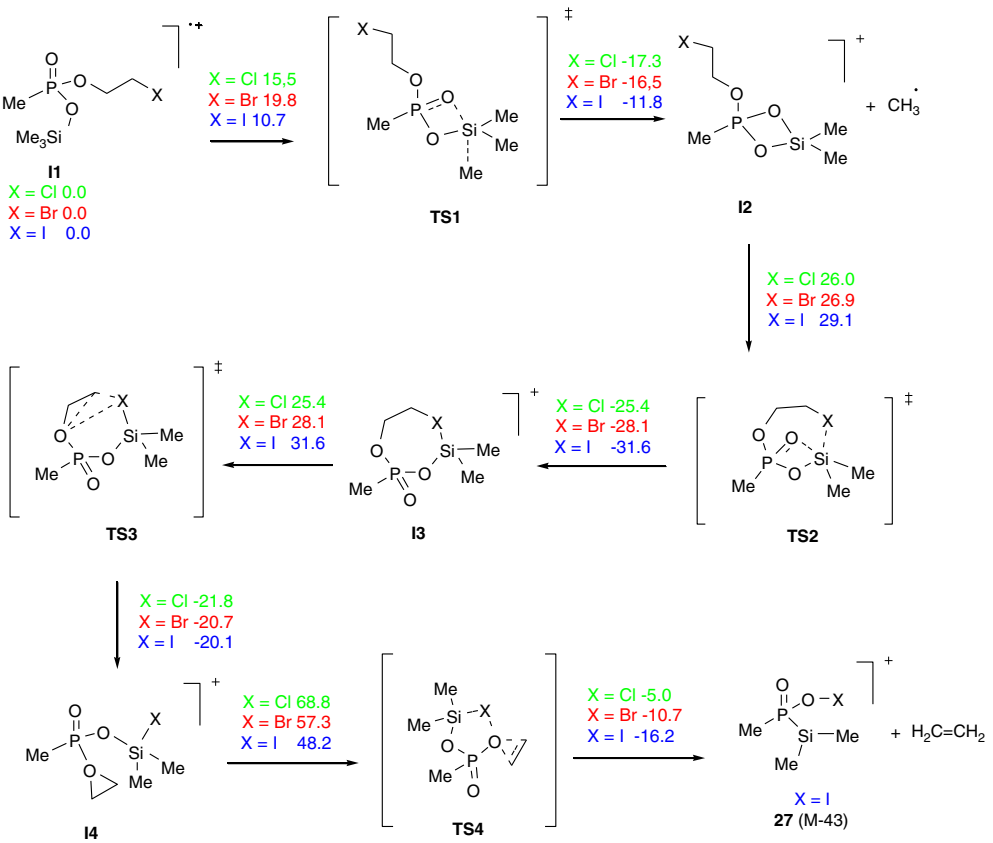
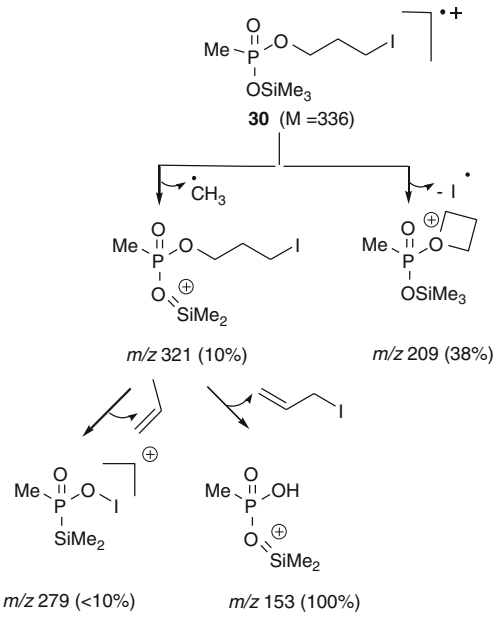


Figure 2. EI Mass spectrum of 2-chloroethyl trimethylsilyl methylphosphonate **1**

confirmed that transition states connect with the corresponding intermediates by means of application of the eigenvector corresponding to the imaginary frequency and subsequent optimization of the resulting structures. All energies collected in the text are Gibbs energies at 298 K.



Scheme 3. Calculated reaction pathway for the fragmentation of **I1**. $\Delta G^{\ddagger}$ values are given in kcal mol^{-1}



Scheme 4. Proposed fragmentation pattern for 3-iodopropyl trimethylsilyl methylphosphonate **30**

Results and Discussion

Unmodified mono-haloethylphosphonates (HAPs) cannot be analyzed by GC since their high polarity and nonvolatile nature preclude their submission without degradation. To overcome this problem, these compounds were treated with BSTFA to form the corresponding monosilylated derivatives **1–12**. Table 1 compiles the most significant ions observed in the EI mass spectra of the prepared TMS derivatives while the corresponding mass spectra can be found in the Supplementary Material (SF1–16). Peaks for the molecular ions were not observed. The molecular mass of **1**–**12** was confirmed, however, by GC/MS(CI) (Supplementary Material SF17–19).

Data in Table 1 show that the first fragmentation corresponds to a methyl radical elimination, probably from the trimethylsilyl group, to form the corresponding fragments **25**. The loss of a methyl radical bonded to the silicon atom is a well known fragmentation in the mass spectrometry of these derivatives [33]. This elimination is independent of the nature of the halogen atom (chlorine or bromine) in the molecule. Variation of the alkyl group attached to phosphorus atom produces no significant effect in the general fragmentation of these TMS derivatives. The loss of a methyl radical is followed by the elimination of a vinyl halide molecule (CH_2=CHX) to form the base peak of the spectra (**28**), except when the halogen is iodine (compounds **3**, **6**, **9**, and **12**). The formation of fragments such as **26** for chlorine and bromine derivatives can be explained as a result of a direct elimination of a halogen radical from the undetected molecular ion (Scheme 2). On the other hand, iodine derivatives behave differently; the loss of a methyl group produces fragments of very low abundance, which subsequently undergo an ethylene molecule elimination leading to fragments such as **27**. Accurate mass measurements confirm these two consecutive eliminations. Figure 1 (compound **3**) is representative of the behavior of these iodinated TMS derivatives, whereas Figure 2 shows the spectra of a chlorine homologue (**1**) for comparison.

To explore the remarkable differences between iodides (**3**, **6**, **9**, and **12**) and their chloro- and bromo-substituted congeners, DFT calculations were carried out for compounds **1**, **2**, and **3** (R = Me, X = Cl, Br, I) (see computational procedures and Scheme 3). Regardless of the halogen, the loss of one Me-group attached to the silicon easily occurs from the initially formed radical cation **I1**. This process is assisted by the P=O bond forming the cyclic intermediates **I2** through **TS1**. This step is more difficult for bromide **2** ($\Delta G^{\ddagger}$ = 19.8 kcal mol^{-1}) and for chloride **1** ($\Delta G^{\ddagger}$ = 15.5 kcal mo–^{1}) being easiest for iodide **3** ($\Delta G^{\ddagger}$ = 10.7 kcal mol^{-1}). Nevertheless, the differences encountered between the three halogens have to be found lately in the reaction mechanism leading to **27**, since the evolution of **I2** to **28** or **29** takes place irrespective of the halogen. Subsequently, **I2** evolves to **I3** through **TS2**, which involves the attack of the halogen (Cl, q = –0.03; Br, q = 0.01; I, q = 0.12) to the electron deficient silicon center (when X = Cl, q=1.58; X = Br, q = 1.58; X = I, q = 1.58). In this step, the oxygen tethered to the silicon in **I2** is displaced, forming the cyclic intermediate **I3**. Now, the

Table 2. Significant Peaks **31**–**36** (*m/z*, Relative Peak Intensities) in the Mass Spectra of Chloride and Bromide bisHAPs

Compound	R	X	**31**	**32**	**33**	**34**	**35**	**36**
13 $C_5H_{11}Cl_2PO_3$	Me	Cl	185 (100)	159 (32)	97 (34)	63 (42)	141 (74)	79 (62)
16 $C_6H_{13}Cl_2PO_3$	Et	Cl	199 (100)	173 (11)	111 (29)	63 (26)	155 (83)	93 (30)
19 $C_7H_{15}Cl_2PO_3$	Pr	Cl	213 (100)	-	125 (23)	63 (40)	169 (76)	107 (<2)
22 $C_7H_{15}Cl_2PO_3$	*i*Pr	Cl	213 (100)	187 (19)	125 (15)	63 (32)	169 (73)	107 (<2)
14 $C_5H_{11}Br_2PO_3$	Me	Br	229 (81)	203 (21)	97 (41)	107 (100)	185 (48)	79 (74)
17 $C_6H_{13}Br_2PO_3$	Et	Br	243 (92)	217 (24)	111 (34)	107 (100)	199 (64)	93 (44)
20 $C_6H_{13}Br_2PO_3$	Pr	Br	257 (59)	229 (25)	125 (18)	107 (100)	213 (32)	107 (25)
23 $C_6H_{13}Br_2PO_3$	*i*Pr	Br	257 (100)	231 (18)	125 (20)	107 (100)	213 (62)	107 (<2)

Table 3. Significant Peaks **37**–**41** (*m/z*, Relative Peak Intensities) in the Mass Spectra of Iodine bisHAPs

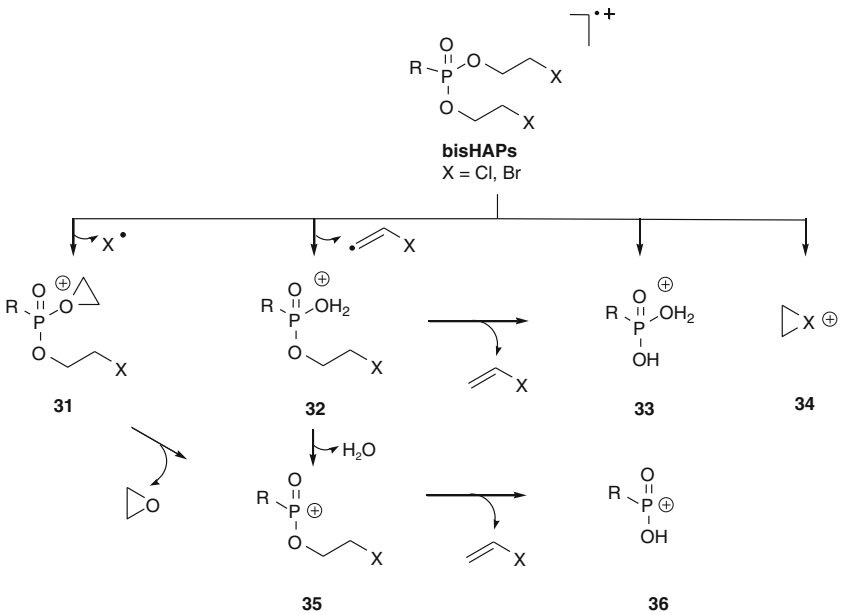
Compound	R	**37**	**38**	**39**	**40**	**41**
15	Me	250 (38)	97 (18)	123 (100)	79 (22)	155 (84)
$C_5H_{11}I_2PO_3$		249.9190		123.0165		154.9340
18	Et	264 (28)	111 (24)	137 (100)	93 (16)	155 (75)
$C_6H_{13}I_2PO_3$		263.9308		137.0324		154.9340
21	Pr	278 (22)	125 (25)	151 (100)	107 (13)	155 (70)
$C_7H_{15}I_2PO_3$		277.9475				
24	*i*Pr	278 (26)	125 (25)	151 (100)	107 (9)	155 (65)
$C_7H_{15}I_2PO_3$		277.9755		151.0617		154.9444

energies for this displacement are very similar for the three halogens with the iodine being slightly disfavored. Cyclic cation **I3** evolves to **I4** by an intramolecular attack of the oxygen tethered to the halogenoethenyl chain. The energies involved are again similar for the three halogens with iodine being slightly disfavored compared with chlorine or bromine. The final step of the mechanism consists of the extrusion of an ethylene molecule from **I3** to give the observed **27** (M-43). This process is analogous to one reported for the fragmentation of halogen-substituted amines via intramolecular halogen transfer [34]. This rate-determining step is clearly favored for the more nucleophilic iodine ($\Delta G^{\ddagger}$ = 48.2 kcal mol^{-1}) compared with chlorine ($\Delta G^{\ddagger}$ = 68.8 kcal mol^{-1}) or bromine ($\Delta G^{\ddagger}$ = 57.3 kcal mol^{-1}). These energies are congruent with the experimentally observed behavior of compounds **1**–**3**.

To discard other possible fragmentation pathways, we have computed the direct halogen transfer to the P=O bond in **I1** as an alternative hetero McLafferty type six-membered rearrangement to explain both the Me and ethylene eliminations, together with the reactivity differences between halogens. So far, we have been unable to find a reaction pathway connecting **I1** with the product resulting from the transfer of the iodine atom to the P=O bond. However, a high energy pathway connecting **I1** with **27** (M-43) was found by attacking the silicon atom of **I1** with the oxygen tethering the halogenoethenyl chain. This pathway is similar to the one depicted in Scheme 3. Although this pathway is also suitable to explain the different behavior of iodine compared with chlorine or bromine, the energies involved in the key step are >100 kcal mol^{-1}. Therefore, it seems less probable than the proposed mechanism pathway in Scheme 3. It is remarkable that although some heteroatom transfers have been reported as examples of the hetero McLafferty rearrangement [35–39], no data for similar iodine consecutive transfers have been described in the literature.

The proposed mechanism for the formation of fragment **27** (Scheme 2) is supported by the mass spectra of 3-iodopropyl trimethylsilyl methylphosphonate **30** (M = 336, SF20) which was prepared (see Experimental) using 3-iodopropanol as the corresponding alcohol. The spectrum reveals a base peak at *m/z* 153, the proposed formation of which begins with Me-cleavage. Formation of an oxetane ring, however, is disfavored since its transition state homologous to **TS2** in Scheme 3 would have an eight-membered ring. Instead, the elimination of methyl radical is followed by the loss of a propenyliodide molecule (168 Da) to form the main fragment at *m/z* 153 (Scheme 4). Nevertheless, the fragment at *m/z* 279, generated as a consequence of consecutive eliminations of methyl radical and propylene molecule (42 Da), involving a iodine atom transfer similar to the calculated in Scheme 2, is formed albeit in low abundance (<10%). All the attempts to compute a reaction pathway connecting **I2** (Scheme 3) to the corresponding **I3** for the homologous **30** were fruitless.

Finally, a comparative study was made with the corresponding ethyl trimethylsilyl alkylphosphonate acids [4, 40] (SF21–24). Similar to the results for compounds **1**–**12**, the elimination of the methyl radical (M-15) that forms product-ions as **25** (Scheme 2, X = H) followed by the loss of an ethylene molecule leads to the base peaks with structure identical to **28**.



Scheme 5. Proposed fragmentation pattern for bis(2-chloroethyl) and bis(2-bromoethyl) alkylphosphonates

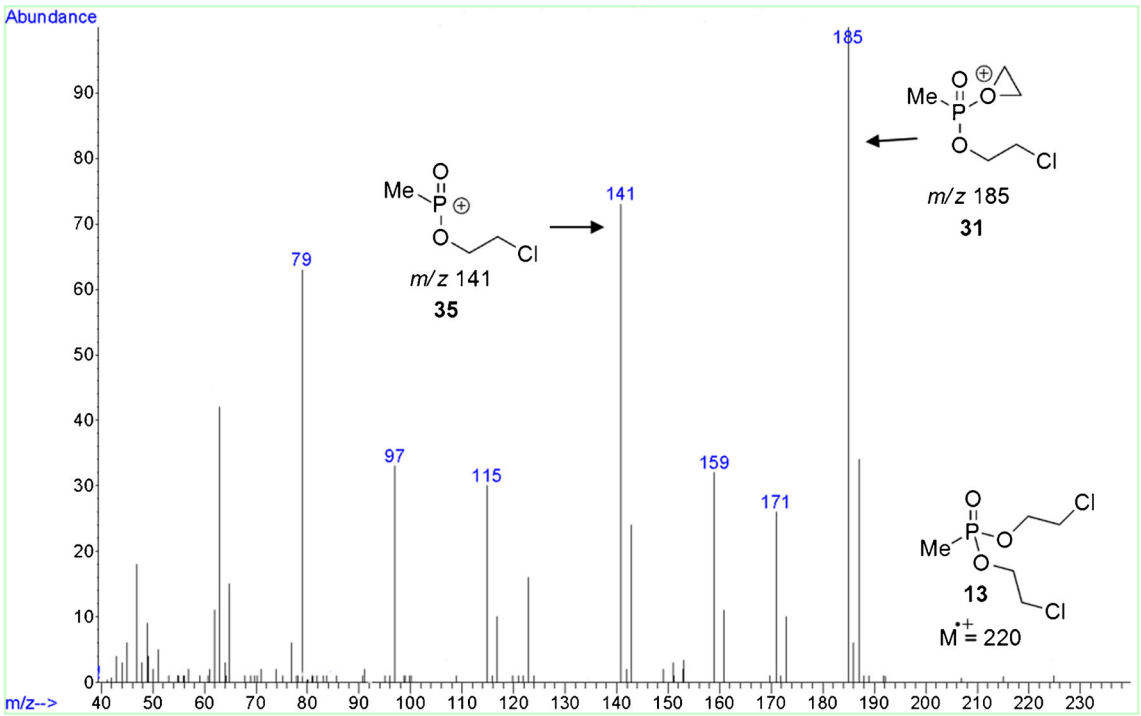


Figure 3. EI Mass spectrum of bis(2-chloroethyl)methylphosphonate **13**

The EI mass spectra of all bisHAPs studied (**13**–**24**) lacked the odd-electron molecular ions (Tables 2 and 3, SF 25–40). The molecular masses of these compounds were confirmed by GC/MS(CI) (SF 41–43). Furthermore, fragments from the cleavage of the P–C bond were also absent from the spectra, whereas this dissociation was detected in the mass spectra of α-amino phosphonates [41] and spiro alkylphosphonates [42]. Again, the nature of the halogen atom (X) plays a crucial role in the fragmentation pathway of compounds **13**–**24**.

Thus, the homolytic cleavage of the C-halogen bond with the subsequent loss of the corresponding halogen radical is the main fragmentation for chlorinated bisHAPs to form the ion fragments **31** (Table 2 and Scheme 5). Figure 3 shows the EI mass spectrum of bis(2-chloroethyl)methylphosphonate **13** (M

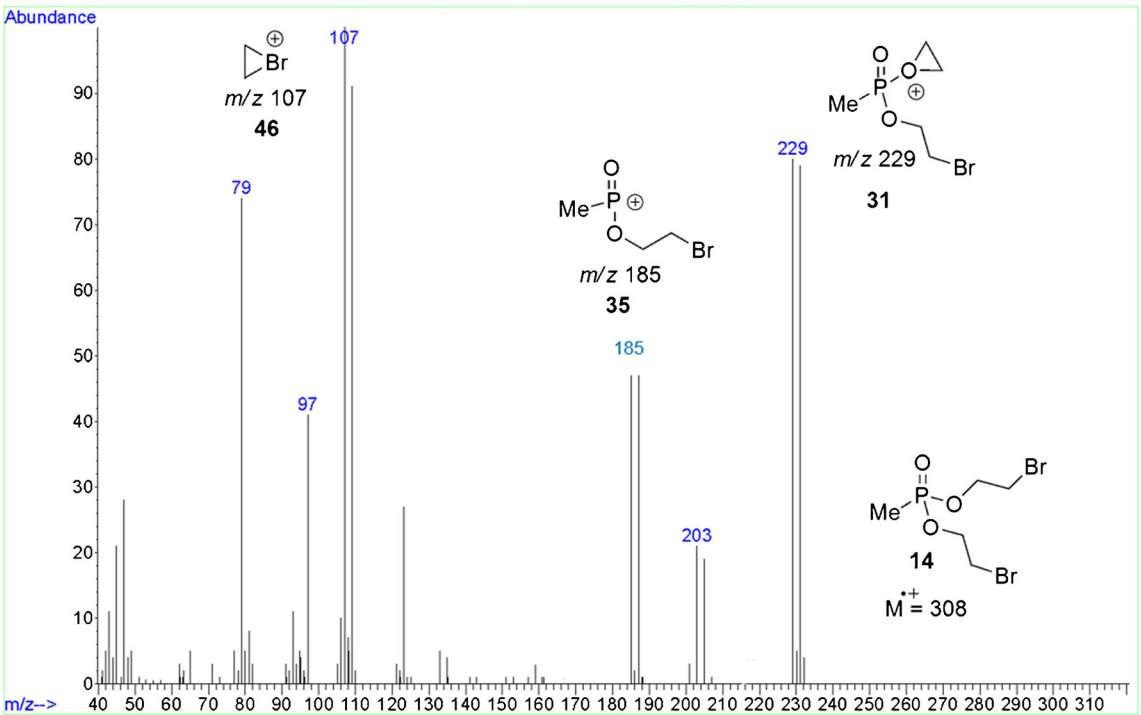
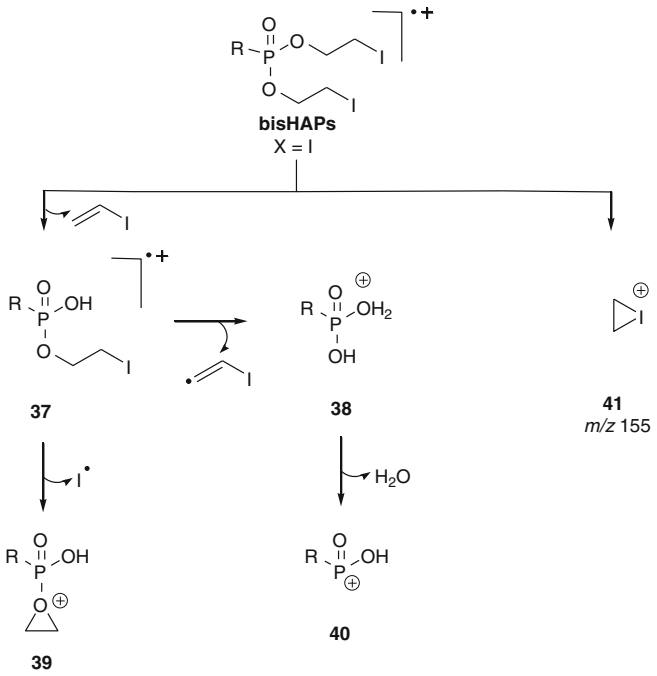


Figure 4. EI Mass spectrum of bis(2-bromoethyl)methylphosphonate **14**



Scheme 6. Proposed fragmentation pattern for bis(2-iodoethyl) alkylphosphonates

= 220) with the base peak at *m/z* 185 (fragment type **31**, R = Me, X = Cl). Although brominated bisHAPs also eliminate bromine radical to form an ion at *m/z* 229, this ion is not the base peak. The main peak for the brominated compounds corresponds to the three membered cyclic ion $[C_2H_4Br]^+$ (**34**, X = Br, *m/z* 107). Figure 4 shows the EI mass spectrum of bis(2-bromoethyl)methylphosphonate **14** (M = 308). Fragmentations involving a double hydrogen atom transfer to the P=O bond (McLafferty + 1 rearrangement) can also be observed for chlorine and bromine bisHAPs. Thus, the elimination of a halogen vinylidene radical (XCH=CH$^\bullet$) leads to the formation of fragments type **32**, which evolve either by loss of a water molecule, forming **35**, or by elimination of a vinylhalogenide molecule leading to **33**. The subsequent elimination of a vinyl halide molecule (CH_2=CHX) from **35** generates the fragment ion **36** (Scheme 5).

To better understand the mass spectrometry of these halogenated compounds, a comparative study with the corresponding diethyl alkylphosphonates (dEAPs) was carried out [4, 40, 43]. Similar to the observed fragmentations of bisHAPs, diethyl methylphosphonate and diethyl ethylphosphonate (SF 44–45) undergo a McLafferty type-rearrangement with a double hydrogen atom transfer to the P=O bond with loss of a halogen vinylidene radical (XCH=CH$^\bullet$) forming ions at *m/z* 125 and 139, respectively [4, 40, 43]. Two subsequent eliminations of ethylene and water molecules, respectively, lead to the formation of the most significant peaks of the spectra.

Differences were found, however, between the fragmentations of bisHAP chlorides, bromides, and iodides (Table 3 and Scheme 6). The reason could be attributed to the C-I bond's lower dissociation energy compared with those for the C–Cl and C–Br bonds [44, 45]; this would lead to a different fragmentation mechanism. The mass spectra of the iodides lack M^+ and $[M - I]^+$ ions. Instead, a molecule of vinyl iodide is promptly eliminated, affording fragments such as **37**, which evolve either by undergoing a McLafferty rearrangement with double hydrogen transfer to form **38**, or by loss of an iodine radical to form **39**. Additionally, a direct elimination of

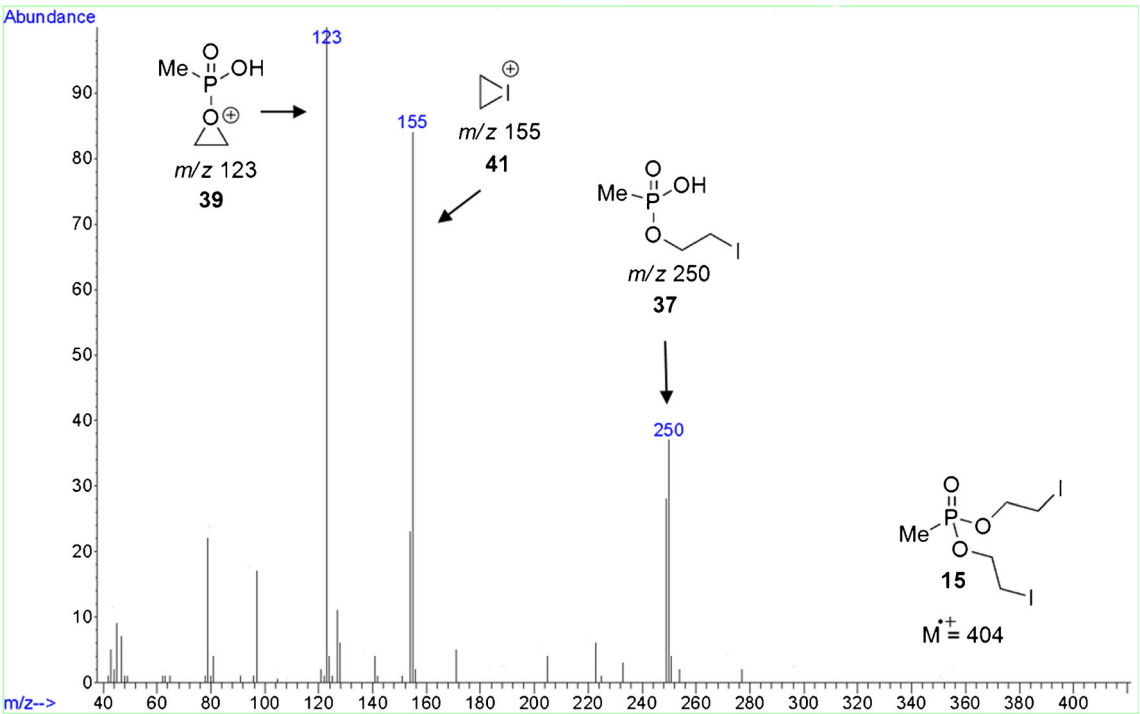


Figure 5. EI Mass spectrum of bis(2-iodoethyl)methylphosphonate **15**

iodoethylene radical (155 Da) produces fragments in low abundance. The EI mass spectrum of bis(2-iodoethyl)methylphosphonate **15** (Figure 5) reveals peaks at *m/z* 155 $[C_2H_4I]^+$ and the product of elimination of 155 Da (M-155, *m/z* 249). The presence of both fragments indicates that a competition process to retain the charge between these fragments is taking place. The fragment at *m/z* 155 (**41**) shows a higher abundance because it can retain the charge more easily than the other fragment (M-$ICH_2CH_2^{\bullet}$).

Although it was mentioned above that the nature of the alkyl group attached at the phosphorus atom (methyl and ethyl) plays no significant role in the fragmentation patterns, the small differences in the pathways between compounds bearing propyl and *iso*propyl groups are worth of discussion. These differences are more easily observed in the chlorine derivatives **19** and **22** (SF 27, 30). Thus, **22** with an *iso*propyl group attached at the P atom undergoes a fragmentation pathway where both the elimination of the chlorine radical and the McLafferty fragmentation with double hydrogen transfer (ML + 1) produces peaks at *m/z* 213 (**31**, R= C_3H_7, X = Cl) and *m/z* 187 (**32**, R= C_3H_7, X = Cl), respectively. Elimination of a water molecule from **32** produces the fragment **35** at *m/z* 169 (R = C_3H_7, X = Cl). By contrast, the linear propyl group (**19**) induces a different pathway where **43** (M-Cl, *m/z* 213) undergoes the elimination of an ethylene molecule (28 Da) from the linear propyl moiety forming a fragment at *m/z* 185, which cannot be observed in the mass spectrum of **22**. The absence of fragment **32** (*m/z* 187) indicates that in this case, the double H rearrangement does not take place for **22**.

Conclusions

Two new classes of mono- and bis-haloethylphosphonates listed in Schedule 2.B.04 of the CWC were synthesized and studied by GC-MS. For trimethylsilylated HPAs a clear halogen-dependent differential behavior in their fragmentation patterns was observed. Thus, chlorine and bromine derivatives fragment by losing a Me group bonded to the silicon, followed by extrusion of a vinylhalide molecule. In contrast, iodine substituted HPAs follow a much more complex fragmentation pattern, including three iodine migrations. This fragmentation behavior has been further examined by DFT calculations, which are fully consistent with the experimental data. The newly described behavior of iodine derivatives of Schedule 2.B.04 may be important in the analysis of these compounds.

Fragmentation of bis-HPAs is also halogen-dependent. Thus, the main fragmentation of dichloro and dibromo bis-HPAs is the cleavage of the carbon–halogen bond with loss of the corresponding halogen radical. In contrast, diiodo HPAs present as the base peak fragment originated through two consecutive eliminations of vinyliodide and a iodine radical, respectively.

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