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# Mass spectrometric study on *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) for Chemical Weapons Convention verification purposes

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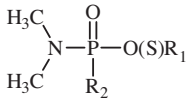
ABSTRACT

Modified microsynthesis of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) which are included in schedule 2 of Chemical Weapons Convention (CWC) annex of chemicals, is reported. Retention indices and electron ionization mass spectral data with fragmentation routes for these chemicals are also given. Mass spectrometric studies revealed that their fragmentations were dominated by alkene elimination, McLafferty rearrangement, α-cleavage, amine elimination, etc. Conclusions were confirmed using MS/MS experiments, fragment ions of deuterated analogs and density functional theory calculations.



## 1. Introduction

The CWC prohibits the production, storage and use of chemical weapons (CWs), and stated that all member states must destroy all the CWs over a fixed period of time [1]. Millions of chemicals are listed in CWC annex of chemicals in three distinct schedules. On the other hand, the CWC verification also includes identification of degradation products of CWC chemicals. Such large number of CWC-related chemicals puts more complexity to the analytical activities under CWC verification requirements which need unambiguous identification of chemicals in complex environmental samples. Mass spectrometry with gas chromatography inlet provides key technique for analysis of the CWC-related chemicals [2]. For successful identification of the CWC-related chemicals in real samples or samples of OPCW official proficiency tests (PTs) [3], the availability of mass spectra and interpretation skills are essential requirements. Actually, it is impossible to have a collection of mass spectral data of all CWC-related chemicals. However, spectra of a class of chemicals tend to be similar. In recent years, some studies have been reported which include mass spectra of the CW agents, their precursors and degradation products such as *N*,*N*-dialkylaminoethanols, alkylphosphonates, *N*,*N*-dialkylphosphoramidates, sulfur and nitrogen mustard, methylphosphonites, *N*,*N*-dialkylaminoethane-2-sulfonic acids, *N*-oxides of aminoethanols, *N*,*N*-dialkylaminoethane-2-thiols, alkyl methylphosphoric acids [4–14]. One of the CWC-related chemicals is *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates). To the best of our knowledge, there is no data in mass spectral libraries for such compounds. The general structure of these chemicals is shown below.




All these chemicals are placed in the CWC as schedule 2.B.4, which includes all compounds with phosphorus bonded to methyl, ethyl, isopropyl, or propyl moieties. The microsynthesis and understanding of mass spectral data for these compounds are of immense help to those involved in the verification analysis of the CWC-related chemicals. Herein, we wish to report a general microsynthesis protocol for a pool of the *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolate) **5** (Fig. 1). Electron ionization mass spectra of *N*,*N*-dimethyl alkylphosphoramidic chlorides **3** and *O*(*S*)-alkyl

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*N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolate) **5** with possible fragmentation routes are also investigated by MS/MS experiments, fragment ions of deuterated analogs and energy calculations.

## 2. Experimental

### 2.1. Reagents and chemicals

Dimethylamine, triethylamine and all the alcohols/thiols required for the microsynthesis of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) were purchased from Sigma–Aldrich, Fluka and Merck companies and were used as received. Alkyl (methyl, ethyl and *n*-propyl) phosphonic dichlorides were synthesized in-house by the existing method [15].

### 2.2. GC/MS and GC/MS/MS analysis

The GC/MS analyses were performed by an Agilent 6890N gas chromatography equipped with a 5973 mass selective detector. HP-5MS capillary column of length 30 m, 320 μm i.d. and 0.25 μm film thickness and helium as carrier gas at constant flow of 1.8 mL $min^{-1}$ were used. The oven temperature was set at 40 °C for 3 min and then was increased to 280 °C (6 min) with ramp 10 °C/min. The samples were injected in splitless mode at an injection temperature of 250 °C. The temperatures of the EI source and analyzer were kept at 230 and 150 °C, respectively. The scan range was 35–500 amu. GC/MS/MS analyses were performed with an Agilent 7890N gas chromatography interfaced to a 7000A Triple Quadruple mass spectrometer. The GC conditions were the same as mentioned above. The MS/MS analyses were carried out using nitrogen as collision gas, at collision energy of 10 eV and a source temperature of 180 °C.

### 2.3. Computational details

All geometry optimizations and frequency calculations of all species were carried out using the Gaussian 03 program [16]. Density functional theory with the Becke three parameters hybrid functional (DFT-B3LYP) calculations were performed with a 6-311++G (2d, 2p) basis set for all atoms. Vibrational frequencies are calculated at the same level to ensure that each stationary point is a real minimum. Harmonic-oscillator approximation is also used for the thermodynamic partition functions. After geometry optimization and frequency calculations, zero-point energies (ZPEs) and thermal corrections are obtained at 298 K. Bond dissociation enthalpy (BDE) of P—O and P—S bond was extracted from enthalpies as calculated by Gaussian 03 (BDE = $-\Delta H = -((H_2 + H_3) - H_1)$ which *H* is the enthalpy of species [17].

### 2.4. General procedure for the microsynthesis of O-alkyl N,N-dimethylamino alkylphosphonates

To a solution of dimethylamine hydrochloride **1** (0.2 mmol) and alkyl (methyl, ethyl and *n*-propyl) phosphonic dichlorides **2** (0.2 mmol) in $CH_2Cl_2$ (300 μL), triethylamine (0.6 mmol) in $CH_2Cl_2$ (300 μL) was added dropwise, while stirring. The reaction mixture was stirred at ambient temperature for 10 min then alcohol **4** (0.2 mmol) in $CH_2Cl_2$ (300 μL) was added dropwise to the solution. The mixture was stirred for an additional 10 min. Triethylamine hydrochloride salt was filtered off and the resulting solution was analyzed by GC/MS.

### 2.5. General procedure for the microsynthesis of S-alkyl N,N-dimethylamino alkylphosphonothiolates

To a solution of dimethylamine hydrochloride **1** (0.2 mmol) and alkyl (methyl, ethyl and *n*-propyl) phosphonic dichlorides **2** (0.2 mmol) in $CH_2Cl_2$ (300 μL), triethylamine (0.4 mmol) in $CH_2Cl_2$ (300 μL) was added dropwise, while stirring. The reaction mixture was stirred at ambient temperature for 10 min. Triethylamine hydrochloride salt was filtered off and the resulting solution was added dropwise to a solution of sodium thiolate **4** in 300 μL $CH_2Cl_2$. The mixture was stirred for 10 min at ambient temperature. The resulting precipitate was filtered off and the solution was analyzed by GC/MS.

## 3. Results and discussion

### 3.1. Synthesis

The microsynthesis of the *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) **5** generally involves two steps: the initial addition of dimethylamine hydrochloride **1** to alkylphosphonic dichlorides **2** in the presence of triethylamine as a base to form *N*,*N*-dimethyl alkylphosphoramidic chlorides **3** and subsequently reaction with alcohols/sodium thiolates **4** to yield desired products **5** (Fig. 1).

In synthesis of tabun family, straightforward route for preparation of *N*,*N*-dimethylphosphoramidic chloride is the reaction of anhydrous gaseous dimethylamine with phosphoryl chloride [18]. This procedure suffers from reaction conditions such as using of an excess of phosphoryl chloride. On the other hand, handling and use of a stoichiometric amount of gaseous dimethylamine is difficult. Another method consists of introduction a single dimethylamino group to phosphorus atom, under harsh condition by refluxing dimethylamine hydrochloride in an excess of phosphoryl chloride for 20 h [19]. It is evident that development of an efficient protocol is required to access *N*,*N*-dimethyl alkylphosphoramidic chlorides.

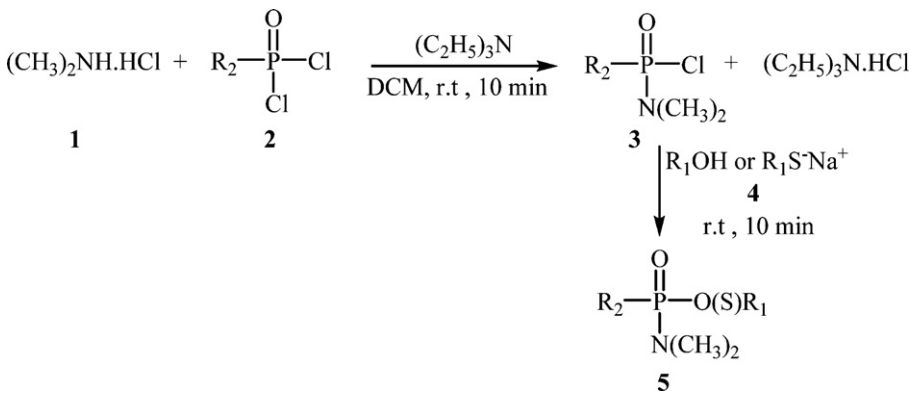



**Fig. 1.** Synthesis route of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) **5**.

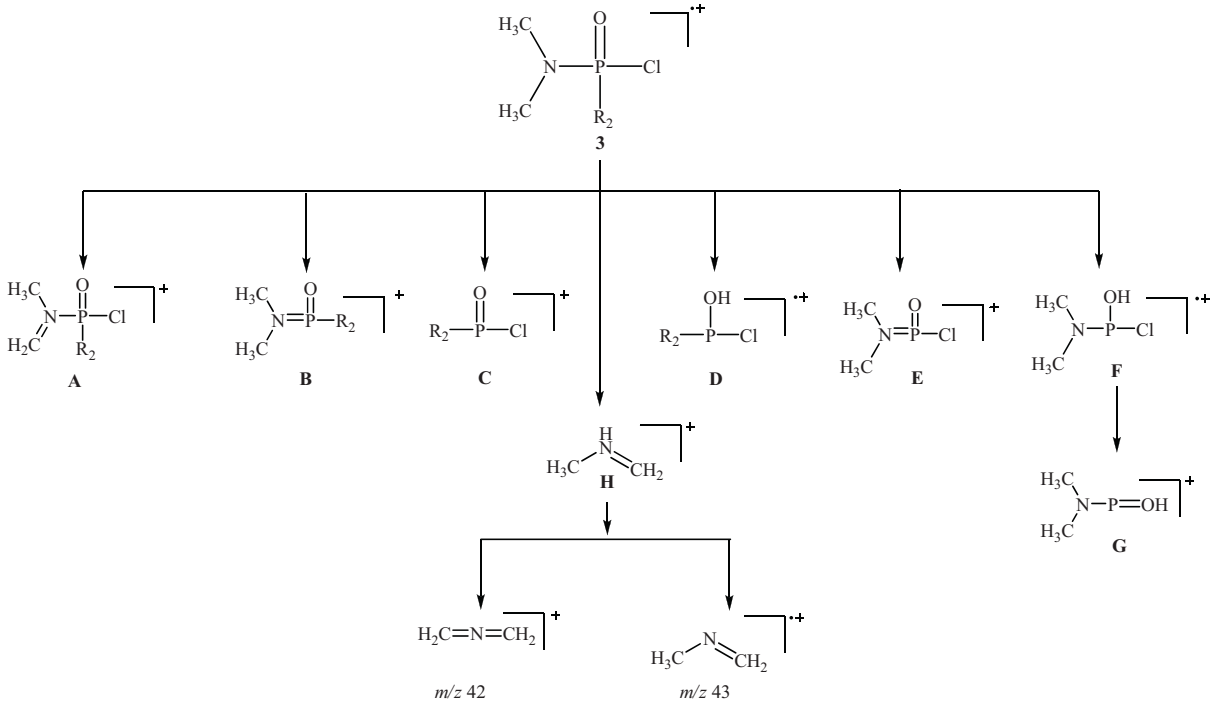



**Fig. 2.** Plausible fragmentation ions of *N*,*N*-dimethyl alkylphosphoramidic chlorides **3**.

Dropwise addition of triethylamine to dimethylamine hydrochloride gently produced dimethylamine in dichloromethane solution which then reacted with alkylphosphonic dichlorides to form *N*,*N*-dimethyl alkylphosphoramidic chlorides. The GC/MS analysis of the mixture in the initial step clearly indicated the formation of *N*,*N*-dimethyl alkylphosphoramidic chloride. It should be mentioned that *N*,*N*-dimethyl alkylphosphoramidic chlorides **3** are also included in CWC, schedule 2.B.4. Subsequently, conversion of **3** to the corresponding *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) **5** was observed within 10 min. The main feature of this microsynthetic protocol is the immediate synthesis of the CWC-related chemicals under mild conditions.

### 3.2. Mass spectra analyses

As shown in Fig. 2, the ion [A] is formed by the hydrogen radical loss from molecular ion of **3** through α-cleavage. The molecular ion also fragmented to [B] ($[M-Cl]^+$) by elimination of chlorine radical as expected. The ion [B] has the second highest relative abundance in the mass spectra of *N*,*N*-dimethyl alkylphosphoramidic chlorides **3**. Ions [C] and [D] were formed through cleavage of *N*,*N*-dimethylamino and $CH_3{-}N{=}CH_2$ respectively from the molecular ion. Ion [E] is formed via cleavage of P-alkyl bond from **3**. Ion [F] is formed by the loss of alkene involving hydrogen transfer from P-alkyl group to P=O group. It is interesting to note that, isobaric fragment ions [D] and [E] of the *N*,*N*-dimethyl propylphosphoramidic chloride are indistinguishable but the presence of ions [D] and [E] in the mass spectra of the other homologous, indicates operation of both mechanisms. On the other hand, the product ion scan of ion at *m*/*z* 126 in spectrum of *N*,*N*-dimethyl propylphosphoramidic chloride by MS/MS showed that it further fragmented to most relative intense ions *m*/*z* 42, 44 and 83 which indicates preference of α-cleavage of alkyl radical from molecular ion over α-cleavage of *N*,*N*-dimethylamino substituent. Ion [G] was formed by elimination of a chlorine radical from [F]. The base peak [H] was produced from *N*,*N*-dimethylamino group which fragmented to ions *m*/*z* 42 and 43 by hydrogen loss.

Expected isotopic ratios of chlorine containing fragments were observed, as is evident from the relative abundances listed in Table 1. With these encouraging results, attention was focused on the spectra of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) **5**. Major EI fragment ions of these compounds as well as their retention indices (RI) are given in Table 2 and the plausible fragmentation routes of **5** are illustrated in Fig. 3. Retention indices were calculated according to the Van Den Dool and Kratz formula [20].

EI-MS spectra of the title chemicals also exhibited some isobaric ions (hence indistinguishable), as listed in Table 2. Presence of these ions in the spectra of other homologous indicates both mechanisms. Mass spectral appearance of these compounds is influenced by the alkyl groups on phosphorous and oxygen/sulfur (Fig. 4). The most important fragmentation in mass spectra of **5** was McLafferty rearrangement of alkyl group on oxygen/sulfur (Fig. 5), which led to ion [A]. The alkyl is left as an alkene. For *O*-methyl and *O*-phenyl analogs (Table 2, entries 1, 11, 19, 36, 37 and 38), formation of allylic or vinyllic group is not possible. Consequently, spectra for these chemicals are distinct (Table 2). This supported the proposed mechanism for the formation of [A]. Formation of ion [B] from **5** is through loss of alkyl radical on oxygen/sulfur.

The fragment [C] can be formed from molecular ion. It is worth to note that relative intensity of [C] for alkylphosphonates depends on the size of alkyl group. The larger alkyl group ($\geq C_4$) leads to intense peak for ion [C]. In such cases, this ion peak is the highest or the second highest peak in the spectra. Formation of ion [C] can be explained by McLafferty + 1 rearrangement that involves an initial hydrogen migration (1,5 C—O H shift) to the oxygen-bearing radical site, leading to a distonic species. An ion and a neutral species are produced after single bond cleavage. Then a hydrogen atom is transferred from the neutral molecule to the radical cation, yielding a cation and a stable radical fragment. This may explain why this mechanism is favorable with larger alkyl groups ($\geq C_4$). Indeed, in such cases, stable allylic radicals are expelled [21] (Fig. 6).

No formation of [C] from *O*-methyl and *O*-phenyl analogs could confirm this proposed fragmentation. It is interesting to note that,

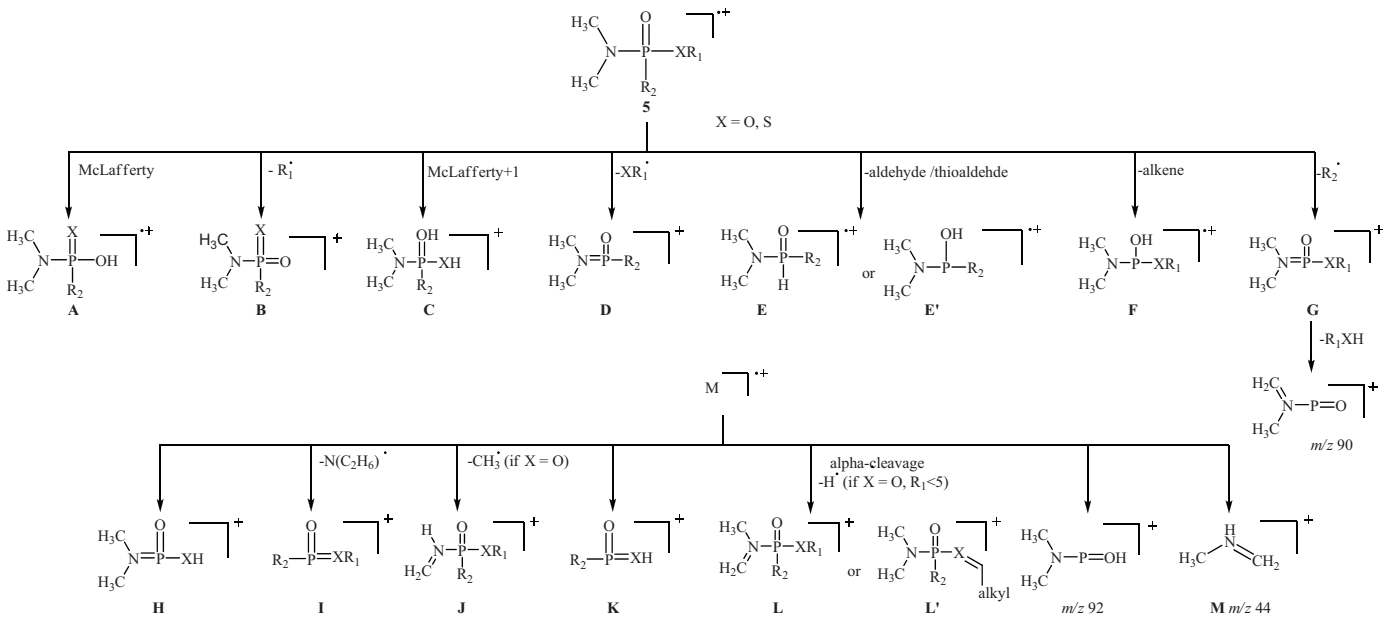



**Fig. 3.** Proposed fragmentation routes for *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) **5**.

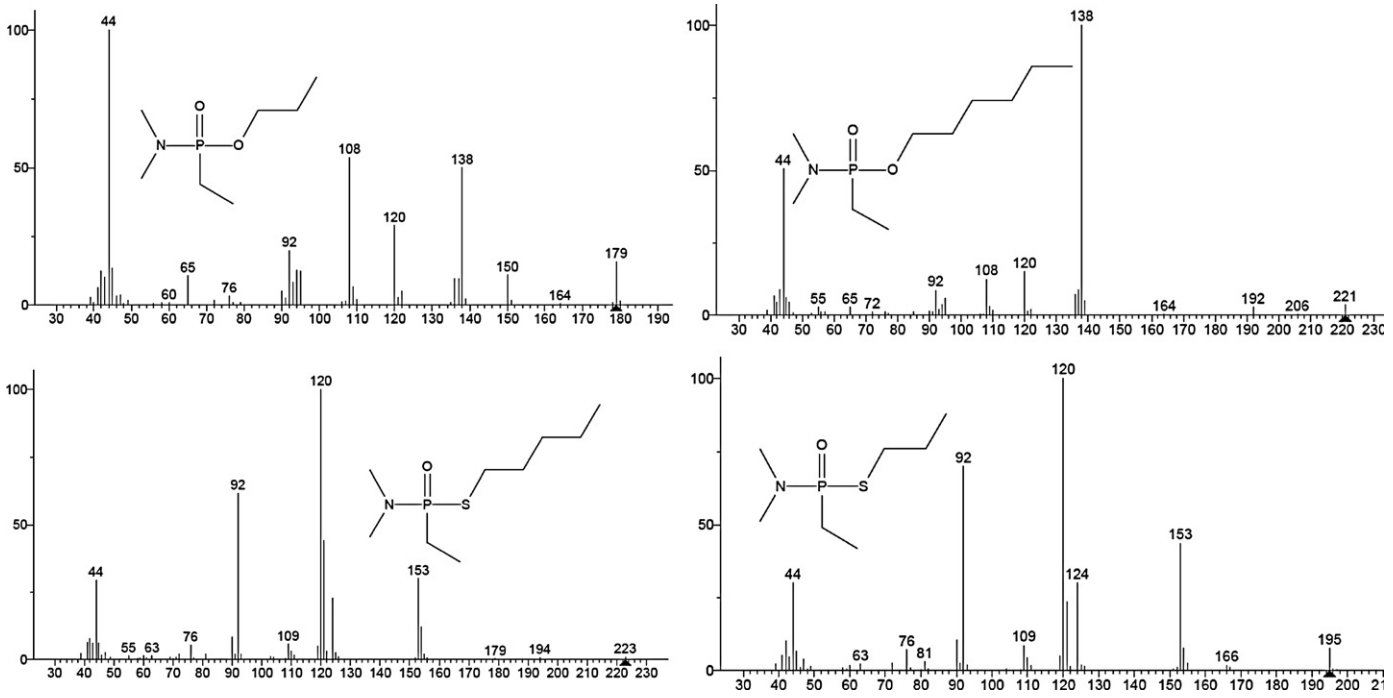


**Fig. 4.** Representative EI-MS mass spectra of **5**.

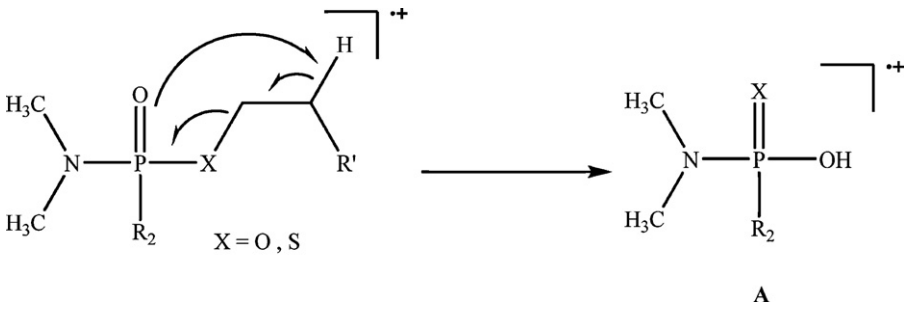
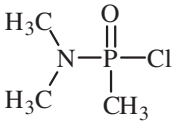
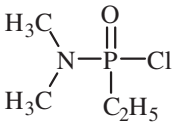
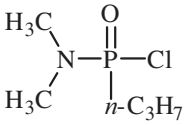



**Fig. 5.** McLafferty rearrangement on chemical **5**.

**Table 1**
GC/MS data of *N*,*N*-dimethyl alkylphosphonamidic chlorides **3**.

| Structure | Retention index (RI) | M•+ | Fragment ions (% relative abundances) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | [A] | [B] | [C] | [D] | [E] | [F] | [G] | [H] |
|  | 1095 | 141 (14) 143 (4) | 140 (4) 142 (2) | 106 (48) – | 97 (12) 99 (6) | 98 (9) 100 (3) | 126 (7) 128 (2) | – – | – – – | 44 (100) – – |
|  | 1164 | 155 (13) 157 (4) | 154 (3) 156 (2) | 120 (38) – | 111 (6) 113 (4.) | 112 (7) 114 (2) | 126 (18) 128 (6) | 127 (3) 129 (1) | 92 (27) – – | 44 (100) – – |
|  | 1243 | 169 (13) 171 (4) | 168 (1) 170 (1) | 134 (22) – – | 125 (2) 127 (24) | 126[a] (24) 128[a] (8) | 126[a] (24) 128[a] (8) | 127 (24) 129 (7) | 92 (41) – – | 44 (100) – – |

[a] Isobaric ions.

relative intensity of ion [C] in *O*-propyl is higher than *O*-isopropyl analogs (entries 3, 4, 13 and 14, Table 2). This difference may be used for identification of propyl and isopropyl moieties on these chemicals. Ion [D] in mass spectra of **5** is formed by the elimination of *O*(*S*)-alkyl radical from molecular ion. It is important to note that the base peak for the most alkylphosphonothiolates is ion [D] (entries 24–34, Table 2). On the other hand, bond dissociation enthalpy (BDE) of P—O bond in *O*-ethyl *N*,*N*-dimethylamino methylphosphonate (entry 2, Table 2), as calculated by Gaussian 03, was found to be higher by 107 kJ mol$^{-1}$ than of BDE of P—S bond in *S*-ethyl *N*,*N*-dimethylamino methylphosphonothiolate (entry 24, Table 2). The higher relative intensity of ion [D] for alkylphosphonothiolates than alkylphosphonates and BDE calculations showed that P—S bond cleavage in alkylphosphonothiolates requires less energy than P—O bond cleavage in alkylphosphonates. Low intensity ion [E]/[E′] for alkylphosphonates was formed through loss of aldehyde/ketone from molecular ion [5]. In contrast, the relative intensity of ion [E]/[E′] for alkylphosphonothiolates with loss of thioaldehyde/thioketone is moderate. For *O*-phenyl derivative loss of an aldehyde molecular is not possible (Table 2, entry 36). It is interesting to note that fragment ion [E]/[E′] was ascribed to two possible structures shown in Fig. 7. Formation of ion [E]/[E′] can be explained by hydrogen migration involving oxygen and phosphorus atoms. The free energy of the $[CH_3\text{-}P(N(CH_3)_2)OH]^{\bullet+}$, as calculated by Gaussian 03, was found to be lower by 58 kJ mol$^{-1}$ than that of the $[CH_3\text{-}PO(N(CH_3)_2)H]^{\bullet+}$, indicating the former as the preferred structure rather than the later.

The formation of ion [F] was attributed to loss of alkene from the molecular ion. Support for this route was provided by precursor ion scan of ion *m*/*z* 153 in *S*-ethyl *N*,*N*-dimethylamino propylphosphonothiolate spectrum (entry 32, Table 2) and analysis of mass spectra of deuterated analogs. Ion [F] was not observed in mass spectrum

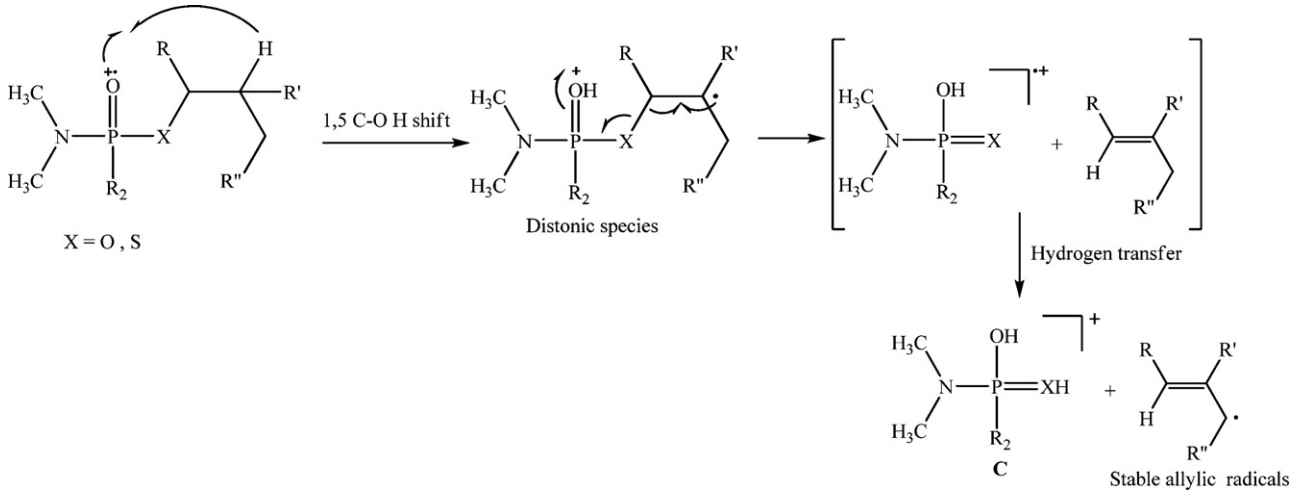



**Fig. 6.** Proposed mechanism for formation of ion [C].

**Table 2**
GC/MS data of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) **5**.

| Entry | Substituent | | Retention index (RI) | $M^{\bullet+}$ | Fragment ions (% relative abundances) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $XR_1$ | $R_2$ | | | [A] | [B] | [C] | [D] | [E'] | [F] | [G] | [H] | [I] | [J] | [K] | [L] | [M] |
| 1 | $OCH_3$ | $CH_3$ | 933 | 137 | – | 122[a] | – | 106 | 107 | – | 122[a] | 108 | 93 | 122[a] | 79 | 136 | 44 |
| | | | | (38) | – | (21) | – | (12) | (<1) | – | (21) | (<1) | (61) | (21) | (37) | (4) | (100) |
| 2 | $OC_2H_5$ | $CH_3$ | 1096 | 151 | 123 | 122 | 124 | 106 | 107[a] | – | 136[a] | 108 | 107[a] | 136[a] | 79 | 150 | 44 |
| | | | | (28) | (2) | (9) | (1) | (24) | (3) | – | (2) | (28) | (3) | (2) | (20) | (<1) | (100) |
| 3 | *n*-$OC_3H_7$ | $CH_3$ | 1177 | 165 | 123 | 122 | 124 | 106 | 107 | – | 150[a] | 108 | 121 | 150[a] | 79 | 164 | 44 |
| | | | | (10) | (7) | (14) | (47) | (42) | (3) | – | (1) | (18) | (<1) | (1) | (8) | (<1) | (100) |
| 4 | *i*-$OC_3H_7$ | $CH_3$ | 1119 | 165 | 123 | 122 | 124 | 106 | 107 | – | 150[a] | 108 | 121 | 150[a] | 79 | 164 | 44 |
| | | | | (23) | (17) | (21) | (10) | (49) | (5) | – | (5) | (14) | (<1) | (5) | (6) | (<1) | (100) |
| 5 | *n*-$OC_4H_9$ | $CH_3$ | 1270 | 179 | 123 | 122 | 124 | 106 | 107 | – | – | 108 | – | – | 79 | – | 44 |
| | | | | (7) | (9) | (15) | (95) | (42) | (3) | – | – | (14) | – | – | (6) | – | (100) |
| 6 | 2-$OC_4H_9$ | $CH_3$ | 1204 | 179 | 123 | 122 | 124 | 106 | 107 | – | 164[a] | 108 | – | 164[a] | 79 | 178 | 44 |
| | | | | (2) | (14) | (12) | (58) | (63) | (4) | – | (3) | (10) | – | (3) | (4) | (<1) | (100) |
| 7 | *n*-$OC_5H_{11}$ | $CH_3$ | 1366 | 193 | 123 | 122 | 124 | 106 | 107 | – | 178[a] | 108 | – | 178[a] | 79 | – | 44 |
| | | | | (6) | (10) | (11) | (100) | (31) | (2) | – | (<1) | (8) | – | (<1) | (4) | – | (72) |
| 8 | 2-$OC_5H_{11}$ | $CH_3$ | 1288 | 193 | 123 | 122 | 124 | 106 | 107 | – | 178[a] | 108 | – | 178[a] | 79 | – | 44 |
| | | | | (2) | (10) | (11) | (100) | (56) | (4) | – | (3) | (8) | – | (3) | (4) | – | (93) |
| 9 | *n*-$OC_6H_{13}$ | $CH_3$ | 1469 | 207 | 123 | 122 | 124 | 106 | 107 | – | 192[a] | 108 | – | 192[a] | 79 | – | 44 |
| | | | | (3) | (8) | (8) | (100) | (23) | (1) | – | (<1) | (5) | – | (<1) | (2) | – | (47) |
| 10 | *n*-$OC_7H_{15}$ | $CH_3$ | 1569 | 221 | 123 | 122 | 124 | 106 | 107 | – | – | 108 | – | – | 79 | – | 44 |
| | | | | (2) | (7) | (7) | (100) | (18) | (1) | – | – | (3) | – | – | (2) | – | (39) |
| 11 | $OCH_3$ | $C_2H_5$ | 1118 | 151 | – | 136[a] | – | 120 | 121 | 123 | 122 | 108 | 107 | 136[a] | 93 | 150 | 44 |
| | | | | (44) | – | (3) | – | (3) | (<1) | (8) | (71) | (11) | (30) | (3) | (1) | (4) | (100) |
| 12 | $OC_2H_5$ | $C_2H_5$ | 1158 | 165 | 137[a] | 136[a] | 138 | 120 | 121[a] | 137[a] | 136[a] | 108 | 121[a] | 150 | 93 | 164 | 44 |
| | | | | (45) | (9) | (30) | (1) | (16) | (3) | (9) | (30) | (81) | (3) | (1) | (39) | (1) | (100) |
| 13 | *n*-$OC_3H_7$ | $C_2H_5$ | 1245 | 179 | 137 | 136 | 138 | 120 | 121 | 151 | 150 | 108 | 135 | 164 | 93 | 178 | 44 |
| | | | | (15) | (9) | (9) | (50) | (29) | (2) | (1) | (11) | (53) | (<1) | (<1) | (8) | (<1) | (100) |
| 14 | *i*-$OC_3H_7$ | $C_2H_5$ | 1185 | 179 | 137 | 136 | 138 | 120 | 121 | 151 | 150 | 108 | 135 | 164 | 93 | 178 | 44 |
| | | | | (25) | (14) | (20) | (11) | (33) | (6) | (1) | (<1) | (39) | (<1) | (3) | (4) | (<1) | (100) |
| 15 | *n*-$OC_4H_9$ | $C_2H_5$ | 1338 | 193 | 137 | 136 | 138 | 120 | 121 | 165 | 164 | 108 | 149 | – | 93 | – | 44 |
| | | | | (7) | (11) | (10) | (100) | (27) | (2) | (1) | (6) | (37) | (<1) | – | (4) | – | (86) |
| 16 | *n*-$OC_5H_{11}$ | $C_2H_5$ | 1440 | 207 | 137 | 136 | 138 | 120 | 121 | – | 178 | 108 | – | 192 | 93 | – | 44 |
| | | | | (5) | (7) | (8) | (100) | (18) | (1) | – | (3) | (19) | – | (<1) | (2) | – | (61) |
| 17 | *n*-$OC_6H_{13}$ | $C_2H_5$ | 1540 | 221 | 137 | 136 | 138 | 120 | 121 | – | 192 | 108 | – | 206 | 93 | – | 44 |
| | | | | (3) | (8) | (7) | (100) | (15) | (1) | – | (3) | (12) | – | (<1) | (2) | – | (51) |
| 18 | *n*-$OC_7H_{15}$ | $C_2H_5$ | 1640 | 235 | 137 | 136 | 138 | 120 | 121 | – | 206 | 108 | – | – | 93 | – | 44 |
| | | | | (2) | (8) | (5) | (100) | (12) | (1) | – | (3) | (8) | – | – | (1) | – | (39) |
| 19 | $OCH_3$ | *n*-$C_3H_7$ | 1184 | 165 | – | 150[a] | – | 134 | – | 123 | 122 | 108 | 121 | 150[a] | 107 | 164 | 44 |
| | | | | (43) | – | (5) | – | (2) | – | (43) | (63) | (1) | (14) | (5) | (<1) | (1) | (100) |
| 20 | $OC_2H_5$ | *n*-$C_3H_7$ | 1236 | 179 | 151 | – | 152 | – | – | 137 | 136 | 108 | – | 164 | 107 | 178 | 44 |
| | | | | (38) | (2) | – | (<1) | – | – | (41) | (21) | (76) | – | (3) | (13) | (<1) | (100) |
| 21 | *n*-$OC_3H_7$ | *n*-$C_3H_7$ | 1327 | 193 | 151[a] | 150[a] | 152 | 134 | 135 | 151[a] | 150[a] | 108 | 149 | 178 | 107 | 192 | 44 |
| | | | | (17) | (27) | (12) | (45) | (22) | (1) | (27) | (12) | (60) | (<1) | (1) | (7) | (<1) | (100) |
| 22 | *n*-$OC_4H_9$ | *n*-$C_3H_7$ | 1414 | 207 | 151 | 150 | 152 | 134 | 135 | 165 | 164 | 108 | 163 | 192 | 107 | 206 | 44 |
| | | | | (7) | (9) | (7) | (100) | (21) | (2) | (8) | (5) | (89) | (<1) | (1) | (4) | (<1) | (98) |
| 23 | *n*-$OC_5H_{11}$ | *n*-$C_3H_7$ | 1514 | 221 | 151 | 150 | 152 | 134 | 135 | 179 | 178 | 108 | – | 206 | 107 | – | 44 |
| | | | | (5) | (8) | (5) | (100) | (15) | (1) | (3) | (3) | (25) | – | (1) | (1) | – | (66) |
| 24 | $SC_2H_5$ | $CH_3$ | 1290 | 167 | 139 | 138 | – | 106 | 107 | – | 152[a] | 124 | 123 | 152[a] | 95 | – | 44 |
| | | | | (26) | (5) | (1) | – | (100) | (25) | – | (<1) | (6) | (1) | (<1) | (11) | – | (30) |
| 25 | *n*-$SC_3H_7$ | $CH_3$ | 1376 | 181 | 139 | 138 | 140 | 106 | 107 | – | – | 124 | 137 | – | 95 | – | 44 |
| | | | | (6) | (31) | (<1) | (7) | (100) | (22) | – | – | (6) | (<1) | – | (8) | – | (29) |
| 26 | *n*-$SC_4H_9$ | $CH_3$ | 1479 | 195 | 139 | 138 | 140 | 106 | 107 | – | – | 124 | 151 | – | 95 | – | 44 |
| | | | | (3) | (29) | (<1) | (14) | (100) | (25) | – | – | (5) | (<1) | – | (6) | – | (28) |
| 27 | *n*-$SC_5H_{11}$ | $CH_3$ | 1582 | 209 | 139 | 138 | 140 | 106 | 107 | – | – | 124 | 165 | – | 95 | – | 44 |
| | | | | (1) | (27) | (<1) | (12) | (100) | (41) | – | – | (4) | (<1) | – | (4) | – | (27) |
| 28 | $SC_2H_5$ | $C_2H_5$ | 1360 | 181 | 153[a] | 152[a] | 154 | 120 | 121 | 153[a] | 152[a] | 124 | 137 | – | 109 | – | 44 |
| | | | | (36) | (10) | (7) | (1) | (100) | (30) | (10) | (7) | (30) | (1) | – | (12) | – | (31) |
| 29 | *n*-$SC_3H_7$ | $C_2H_5$ | 1443 | 195 | 153 | 152 | 154 | 120 | 121 | 167 | 166 | 124 | 151 | – | 109 | – | 44 |
| | | | | (7) | (43) | (1) | (7) | (100) | (23) | (1) | (1) | (30) | (<1) | – | (8) | – | (30) |
| 30 | *n*-$SC_4H_9$ | $C_2H_5$ | 1547 | 209 | 153 | 152 | 154 | 120 | 121 | 181 | 180 | 124 | 165 | – | 109 | – | 44 |
| | | | | (4) | (37) | (<1) | (15) | (100) | (26) | (<1) | (1) | (26) | (<1) | – | (7) | – | (28) |
| 31 | *n*-$SC_5H_{11}$ | $C_2H_5$ | 1641 | 223 | 153 | 152 | 154 | 120 | 121 | – | 194 | 124 | 179 | – | 109 | – | 44 |
| | | | | (1) | (30) | (<1) | (12) | (100) | (43) | – | (<1) | (22) | (<1) | – | (5) | – | (29) |
| 32 | $SC_2H_5$ | *n*-$C_3H_7$ | 1431 | 195 | 167 | 166 | 168 | 134 | 135 | 153 | 152 | 124 | 151 | – | 123 | – | 44 |
| | | | | (18) | (4) | (2) | (<1) | (83) | (21) | (25) | (4) | (23) | (1) | – | (6) | – | (28) |
| 33 | *n*-$SC_3H_7$ | *n*-$C_3H_7$ | 1519 | 209 | 167[a] | 166[a] | 168 | 134 | 135 | 167[a] | 166[a] | 124 | 165 | – | 123 | – | 44 |
| | | | | (5) | (44) | (3) | (6) | (94) | (18) | (44) | (3) | (27) | (<1) | – | (6) | – | (27) |
| 34 | *n*-$SC_4H_9$ | *n*-$C_3H_7$ | 1618 | 223 | 167 | 166 | 168 | 134 | 135 | 181 | 180 | 124 | – | – | 123 | – | 44 |
| | | | | (2) | (32) | (1) | (14) | (100) | (24) | (8) | (1) | (25) | – | – | (5) | – | (25) |
| 35 | $OC_3H_5$ | $CH_3$ | 1179 | 163 | 123 | 122 | 124 | 106 | 107 | – | 148[a] | 108 | 119 | 148[a] | – | 162 | 44 |
| | | | | (19) | (4) | (100) | (2) | (59) | (12) | – | (6) | (8) | (8) | (6) | – | (1) | (98) |
| 36 | OPh | $CH_3$ | 1529 | 199 | – | 122 | – | 106 | – | – | 184[a] | 108 | 155 | 184[a] | 79 | 198 | 44 |
| | | | | (35) | – | (<1) | – | (100) | – | – | (10) | (1) | (3) | (10) | (<1) | (3) | (59) |
| 37 | $OCD_3$ | $CH_3$ | 1080 | 140 | – | 122 | – | 106 | 108 | – | 125[a] | 109 | 96 | 125[a] | 79 | 139 | 44 |
| | | | | (20) | – | (<1) | – | (3) | (<1) | – | (11) | (<1) | (40) | (11) | (1) | (2) | (100) |
| 38 | $OCD_3$ | $C_2H_5$ | 1104 | 154 | – | – | – | – | – | 126 | 125 | 109 | 110 | 139 | 93 | 153 | 44 |
| | | | | (19) | – | – | – | – | – | (4) | (36) | (16) | (16) | (1) | (1) | (2) | (100) |

[a] Isobaric ions.

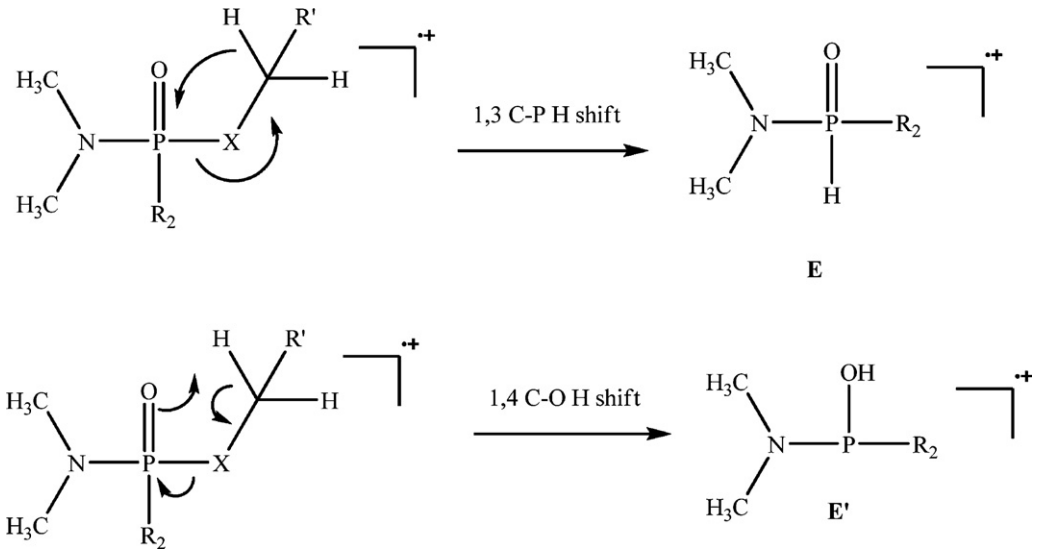



**Fig. 7.** Proposed mechanism for formation of ions [E]/[E′].

of *O*-methyl-$d_3$ *N*,*N*-dimethylamino methylphosphonates but it was presented in spectrum of *O*-methyl-$d_3$ *N*,*N*-dimethylamino ethylphosphonates *m*/*z* 126. Direct cleavage of the P-alkyl bond from the molecular ion led to ion [G]. Spectra of deuterated analogs showed *m*/*z* 125 corresponding to this fragment. Subsequently, ion [G] was fragmented to *m*/*z* 90 by elimination of alcohol/thiol from ion [G]. It is interesting to note that, ion [G] could be comprised of three possible resonance structures. Free energy difference between structure (2) and (3) is low (1 kJ $mol^{-1}$). However, the free energy of structure (1) was calculated to be 54 and 56 kJ $mol^{-1}$ higher than that structure (2) and (3) respectively. This revealed relative preference of formation of resonating forms (2) and (3) over (1) (Fig. 8).

Fragment ion [H] could be generated from the molecular ion with the loss of alkyl on oxygen/sulfur atom and cleavage of the P-alkyl bond. The product ion scan of ion [H] in mass spectrum of the *O*-ethyl *N*,*N*-dimethylamino propylphosphonate (*m*/*z* 108, entry 20, Table 2) revealed that it further fragmented to ions *m*/*z* 43, 44 and 65. Direct elimination of *N*,*N*-dimethylamino substituent from the molecular ion gave fragment [I]. This particular fragmentation was not common in alkylphosphonate analogs with larger *O*-alkyl group (>$C_4$); but it was observed for most of alkylphosphonothiolates. Despite of alkylphosphonothiolates (entries 24–34, Table 2) cleavage of a methyl radical from *N*,*N*-dimethylamino group is a common fragmentation mode which resulted ion [J] in the majority of alkylphosphonates. Fragmentation of deuterated analogs also showed this ion. Loss of *N*,*N*-dimethylamino group and alkyl on oxygen/sulfur from the molecular ion were attributed to formation of ion [K], which was observed in all the compounds. Formation of ion [L]/[L′] took place by α-cleavage a hydrogen radical from the molecular ion. Loss of hydrogen radical was possible by two routes, first from the *N*,*N*-dimethylamino group and second from the C—H bond cleavage of the *X*-alkyl group. Thus [L] and [L′] were isobaric. These ions were distinguished when the EI-MS of deuterated analogs were recorded. Spectra of deuterated *O*-methyl-$d_3$ *N*,*N*-dimethylamino methylphosphonates and *O*-methyl-$d_3$ *N*,*N*-dimethylamino ethylphosphonates showed only $[M-H]^+$ (*m*/*z* 139 and *m*/*z* 153, respectively). This supported the loss of hydrogen radical from the *N*,*N*-dimethylamino group. Furthermore the free energy of structure [L] was calculated to be 100 kJ $mol^{-1}$ lower than [L′]. This clearly indicates preference of formation of structure [L] over [L′].

Finally, it is worth to note that *O*-isopropyl *N*,*N*-dimethylamino methylphosphonate (entry 4, Table 2) is structurally similar to the nerve gas sarin, except that it contains a P—N instead of P—F bond. Comparison of mass spectrometry data of them should be useful for the identification and analysis of chemicals that are relevant to the CWC. EI-MS of *O*-isopropyl *N*,*N*-dimethylamino methylphosphonate shows some similarities and differences with sarin. The most difference is the presence of $M^{\bullet+}$ with relative moderate abundance in the mass spectrum of the *O*-isopropyl *N*,*N*-dimethylamino methylphosphonate, but $M^{\bullet+}$ of sarin was not observed in its mass spectrum. The elimination of an alkyl radical via α-cleavage and P—N cleavage were observed in all mass spectra of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates), while no corresponding P—$CH_3$ fragmentation and P—F bond cleavage were observed in sarin. On the other hand, loss of an allyl radical (M-$C_3H_5$) is demonstrated in the mass spectra of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) and sarin that gave rise to the ions at *m*/*z* 124 and 99 respectively. Similarly, the McLafferty rearrangement of isopropyl moiety on oxygen was observed in the mass spectra of both chemicals. It is interesting to note that, the second highest peak in the spectrum of *O*-isopropyl *N*,*N*-dimethylamino methylphosphonate is ion at *m*/*z* 106 that generated by elimination of *O*-isopropyl radical from molecular ion, while low relative intensity of corresponding fragment in mass spectrum of sarin (*m*/*z* 81) was observed.

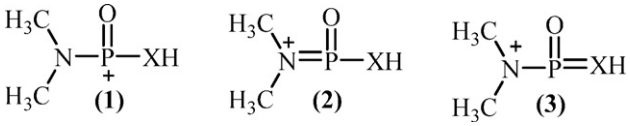



**Fig. 8.** Possible resonance structures of [G].

## 4. Conclusions

An improved process for microsynthesis of *O*(*S*)-alkyl *N*,*N*-dimethylamino alkylphosphonates (alkylphosphonothiolates) and their electron ionization mass spectrometric data were presented in this paper. The title chemicals synthesized under mild conditions. GC retention indices as well as mass spectral data with proposed fragmentation routes for 41 chemicals (3, 27 and 11 chemicals of *N*,*N*-dimethyl alkylphosphoramidic chlorides, *O*-alkyl *N*,*N*-dimethylamino alkylphosphonates and *S*-alkyl *N*,*N*-dimethylamino alkylphosphonothiolates, respectively) are also

given. These data could be useful for successful detection and identification of the CWC-related chemicals in real sample or during OPCW proficiency tests.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijms.2012.03.006.

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