



Use of a hand-portable gas chromatograph–toroidal ion trap mass spectrometer for self-chemical ionization identification of degradation products related to O-ethyl S-(2-diisopropylaminoethyl) methyl phosphonothiolate (VX)

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ABSTRACT

The chemical warfare agent O-ethyl S-(2-diisopropylaminoethyl) methyl phosphonothiolate (VX) and many related degradation products produce poorly diagnostic electron ionization (EI) mass spectra by transmission quadrupole mass spectrometry. Thus, chemical ionization (CI) is often used for these analytes. In this work, pseudomolecular ($[M+H]^+$) ion formation from self-chemical ionization (self-CI) was examined for four VX degradation products containing the diisopropylamine functional group. A person-portable toroidal ion trap mass spectrometer with a gas chromatographic inlet was used with EI, and both fixed-duration and feedback-controlled ionization time. With feedback-controlled ionization, ion cooling (reaction) times and ion formation target values were varied. Evidence for protonation of analytes was observed under all conditions, except for the largest analyte, bis(diisopropylaminoethyl)disulfide which yielded $[M+H]^+$ ions only with increased fixed ionization or ion cooling times. Analysis of triethylamine-*d*₁₅ provided evidence that $[M+H]^+$ production was likely due to self-CI. Analysis of a degraded VX sample where lengthened ion storage and feedback-controlled ionization time were used resulted in detection of $[M+H]^+$ ions for VX and several relevant degradation products. Dimer ions were also observed for two phosphonate compounds detected in this sample.

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1. Introduction

Gas chromatography combined with mass spectrometry (GC–MS) routinely produces multi-dimensional and highly informative data in laboratory settings. Instrumentation for GC–MS analysis has advanced to provide increasingly smaller and more useful systems for on-scene detection and identification of chemicals. Typically, 70 eV electron ionization (EI) is used with a quadrupole mass filter detector [1]. When EI is used in this manner, unimolecular decomposition is the norm, producing neutral and ionic fragments without the potential for ion/molecule interactions. The resulting mass spectra are generally consistent, even with transiently elevated analyte flux in the mass spectrometer that occurs with GC–MS. Ion/molecule interactions are known to

occur at higher pressures, and also in ion storage mass spectrometers such as the quadrupole ion trap, although feedback control of ionization time can be used to lessen the potential for this.

In cases where 70 eV EI leads to little or no detectable molecular ion (M^+), chemical ionization (CI) or other soft ionization techniques may be helpful. Groenewold et al. created secondary pseudomolecular ions for the chemical warfare agent O-ethyl S-(2-diisopropylaminoethyl) methyl phosphonothiolate (VX) adsorbed to soil using a ReO_4^- ion beam. A laboratory-size ion trap mass spectrometer detected pseudomolecular ions diagnostic for the presence of VX without the use of a chromatographic separation step [2]. Petersson et al. demonstrated the ability to detect pseudomolecular ions for five chemical warfare agent simulants without chromatographic separation, using proton transfer ionization from H_3O^+ reagent ions. Analysis was completed using a laboratory-size high resolution time-of-flight mass spectrometer [3]. When chromatographic separation is to be used, laboratory instruments designed for GC–MS with CI are common. However, a combined capability for EI and CI analyses in a single fieldable GC–MS instrument is not routine.

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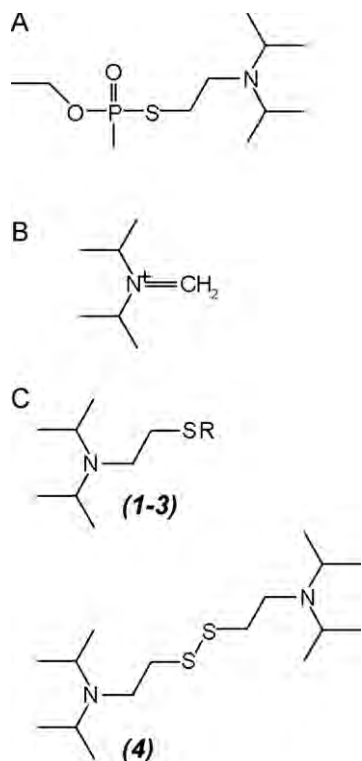


Fig. 1. (A) O-ethyl S-(2-diisopropylaminoethyl) methyl phosphonothiolate (VX); (B) relatively stable m/z 114 ion produced with 70 eV EI fragmentation of VX and VX degradation products containing the diisopropylaminoethyl structure; (C) degradation products of the chemical warfare agent VX, (1) R = Me, (2) R = Et, (3) R = iPr, (4) bis(diisopropylaminoethyl)disulfide.

An important example of a specialized application where both EI and soft ionization information would be helpful is provided by the need to detect and identify the chemical warfare agent VX (Fig. 1A) and many of its degradation products. With 70 eV EI and transmission quadrupole mass spectrometric detection, numerous VX-related analytes produce mass spectra with similar fragmentation patterns that provide little information regarding their respective molecular ions to assist with identification. In addition to a very small or absent signal for $M^{+\bullet}$, the resulting mass spectra for VX and most degradation products having the diisopropylaminoethyl group tend to show a base peak at m/z 114, in part due to the stability of the fragment ion represented by Fig. 1B. Thus, efforts to identify VX degradation products using mass spectral interpretation often have relied on CI mass spectrometry [4–7] as knowledge of pseudomolecular ions $[M+X]^+$ (where X is a proton or expected CI reagent adduct) is of great help in unambiguously identifying these analytes. To protect the health of military forces, first responders, or the general public in a scenario where VX exposure is possible, a small field-portable GC–MS system capable of separating and identifying these molecules would be useful. For example, in the event of VX release by terrorists it would be important to rapidly verify the presence or absence of intact VX material, and following decontamination, the presence of known VX degradation products.

The phenomenon of self-chemical ionization (self-CI) in mass spectrometers which employ ion storage was described by Ghaderi et al. [8]. These researchers used an ion cyclotron resonance mass spectrometer and showed production of $[M+H]^+$ ions, with small relatively acidic fragments obtained from the precursor molecules serving as proton donors. In EI, only a small fraction of the neutral species present is ionized. In a quadrupole ion trap mass spectrometer the non-ionized molecules present may be available to serve

as targets for the self-CI process, especially where internal ionization is used. Both protonation [9,10] and formation of protonated dimers $[2M+H]^+$ [10,11] have been shown to result from self-CI in ion trap instruments. Where protonation occurs by self-CI, evidence for $[M+H]^+$ ions may be observed in mass spectra at levels greater than expected for ^{13}C isotope effects, including instances where $M^{+\bullet}$ would not be observed under typical EI analysis conditions using a transmission quadrupole instrument.

In examining the phenomenon of self-CI using an ion trap mass spectrometer it is important to distinguish between protonation events and mass assignment shifts resulting from space charge effects that can also produce bar chart peaks at what appear to be m/z values for $[M+H]^+$ ions. In addition to loss of mass resolution, it is known that space charging can result in lower effective radiofrequency (RF) amplitude experienced by trapped ions as the range of m/z values is scanned during analysis. This causes ions to be ejected from the trap inappropriately late when scanning from low to high m/z , leading to incorrectly assigned (higher) m/z values [12].

In this work a person-portable toroidal ion trap mass spectrometer (TMS) with a GC inlet described previously [13,14] was used to study the potential for $[M+H]^+$ production by self-CI from four synthetically obtained VX degradation products. Fixed ionization times were varied, and analyses were also completed using feedback-controlled ionization time with differing ion formation target values to encourage interactions between neutral species and fragment ions present simultaneously in the TMS, while still controlling ion density. An additional approach was followed where the TMS was operated with feedback-controlled ionization time and a low ion target value to minimize the potential for space charge, but with extended ion cooling time (up to 492 ms) before beginning a scan to encourage self-CI protonation. This was studied with the VX degradation product bis(diisopropylaminoethyl)disulfide. Extended ion storage combined with feedback-controlled ionization time was also used to analyze a sample of VX spiked onto AgF, following heating overnight.

Separate TMS analyses of triethylamine and triethylamine- d_{15} were completed to provide evidence that self-CI protonation produced pseudomolecular ions for the analytes studied.

2. Experimental

2.1. Chemicals

Triethylamine (99%) and triethylamine- d_{15} (98%) were obtained commercially (Aldrich, Milwaukee WI). Analytical standards were synthesized for VX degradation product compounds by reacting 2-(diisopropylamino)ethyl chloride hydrochloride (97% purity, Aldrich) with two equivalents of the appropriate methyl, ethyl, or isopropyl thiolate sodium salt in acetonitrile. The respective purities and sources for the thiolate salts used to synthesize the VX degradation products displayed in Fig. 1C (compounds (1–3)) were >90% (Aldrich), 90% (Fluka, Steinheim Germany), and >90.0% (Fluka). Following reaction for several hours the desired end product was extracted into pentanes, along with the corresponding unwanted disulfide reaction product. The pentanes and relatively volatile disulfide were then removed under a steady stream of Ar at 45 °C until the disulfide compound was no longer observed as verified by GC–MS. Methods described by Hook et al. [7] were followed for synthesis of compound (4), bis(diisopropylaminoethyl)disulfide. Immediately following synthesis, the purity of each synthesized standard was shown to be >99% by gas chromatographic methods. Identities and purities were also verified by ^1H and ^{13}C NMR, and by GC–MS analysis using a transmission quadrupole detector operated under both EI and CI (NH_3) conditions.

A small amount of VX was obtained from and analyzed at Defence R&D Canada-Suffield (DRDC Suffield, Ralston, Alberta Canada) to provide an EI mass spectrum using a transmission quadrupole instrument. Additionally, to create a sample with VX and numerous VX degradation products for GC–TMS analysis at DRDC Suffield, a 20 mg aliquot of VX (90% purity by GC–MS) was applied to 50 mg of AgF placed in a glass vial. This vial was sealed with a septum cap and heated at 70 °C in a digitally controlled heater block overnight. Reaction of VX with AgF is known to produce *O*-ethyl methylphosphonofluoridate, a relatively volatile marker compound that may be readily sampled from air. Stringent standard operating safety precautions were followed for use of VX material, which included completion of work within a scrubber-equipped fume hood, and two-person chemical agent handling procedures. The VX material was handled by licensed DRDC Suffield personnel with appropriate personal protective equipment and military medical countermeasures readily available.

2.2. Samples and sampling

Sample introduction into the GC–TMS system was completed through the heated injector of the instrument from a solid phase microextraction (SPME) fiber (65 μ m PDMS/DVB coating thickness, Supelco, Bellefonte, PA). Except for compound (**4**), microliter volumes of neat liquid standard materials were added to a small cotton plug in the bottom of a 20 mm diameter 20 mL glass vial, while compound (**4**) was added directly to an identical glass vial without a cotton plug. The vials used included PTFE-lined septa and caps compatible with SPME headspace sampling.

For sampling triethylamine, the volume of analyte placed onto a cotton plug was 2.0 μ L, and sampling duration was 1 s, with the vial maintained at 40 °C in a digitally controlled heater block. Triethylamine-*d*₁₅ was dispensed in the same manner into a different vial, and sampled in the same way. For SPME sampling to simultaneously capture the synthetic sulfide compounds (**1–3**), approximately 10 μ L of each was added to a small cotton plug in a sampling vial as described above, with temperature maintained at 40 °C. For sampling of compound (**4**), 10 μ L of the synthetic standard was placed in a separate empty vial and maintained at 100 °C. These four analytes were loaded onto a single SPME fiber for analysis using a multi-step approach with compound (**4**) sampled first for 120 s, followed by sampling of compounds (**1–3**) for 5 s.

2.3. Instrumentation

A 5 m section of MXT-5 column (0.1 mm I.D., 0.4 μ m *d*_f, Restek, Bellefonte PA) was used in a person-portable GUARDION®-7 GC–TMS system (Torion Technologies, American Fork, UT). The column was resistively heated within a low thermal mass (LTM) assembly following the approach to heating and temperature sensing described earlier by Sloan et al. [15]. This type of LTM assembly is well suited for use in field-portable instrumentation based on its small size, weight, and low power consumption. The GC temperature program was 50–300 °C at a rate of 120 °C min^{−1}, with hold times at both the lower and upper temperature points of 10 and 40 s, respectively. The low thermal mass injector, and transfer lines from the injector to the analytical column and from the column to the mass spectrometer were maintained at 270 °C, and a splitless carrier gas flow was maintained for 1 s. The carrier gas used for all GC–MS analyses was ultra high-purity He.

Ion trapping occurred with constant RF conditions (1200 V_{p-p}, 4 MHz), and resonance ejection (low to high mass) was accomplished by scanning an RF field applied to the filament endcap (5 V_{p-p}) from 1.8 MHz to 110 kHz, providing a scan range of *m/z* 45–450. The EI source for the TMS detector was operated at 70 eV, and two general ionization timing approaches were followed. With

the simplest approach, formation of [M+H]⁺ can be promoted by simply extending a fixed ionization time to provide greater concentrations of self-CI reagents (acidic proton donor fragments) in the ion trap derived from greater quantities of M⁺ and product ions that result. The second approach used the standard operating mode for the TMS instrument where ionization time is dynamically managed. Total ion current (TIC) intensities and the rate of TIC increase in recently completed scans are used predictively to set the ionization time to a value between 0.2 and 60 ms to target creation of a constant number of ions. This ion target value is user-defined in the GC–TMS control software, with the default target value set at 10⁴ (arbitrary units). Higher target values lead to increased signal intensity, but with the potential for reduced mass resolution due to space charge, and more potential for ion/molecule interactions (i.e., self-CI or formation of neutral/fragment adducts).

To increase formation of [M+H]⁺ for compound (**4**) with less potential for space charge effects from increased fixed ionization times or high ion target values, several samples were analyzed using dynamic ionization time management with a relatively low ion target value of 5 × 10³. In these analyses self-CI was encouraged by increasing ion cooling time up to 492 ms in place of the standard 2.4 ms value used for other analyses. An extended ion cooling time of 120 ms and an ion target value of 10⁴ were also used for analysis of several samples of heat-degraded VX produced as described previously.

Comparative analyses to obtain both 70 eV EI and CI mass spectra were completed for compounds (**1–4**), and a 70 eV EI mass spectrum was obtained for VX using two separate Agilent 6890/5973 transmission quadrupole GC–MS systems (Agilent Technologies, Santa Clara, CA). In both systems, injection was carried out in the splitless mode. The injection solvent used was methylene chloride, and the 1.0 μ L volume injected contained 50 ng of each analyte. Injector and mass spectrometer transfer line temperatures were 250 and 280 °C respectively. The GC used to provide EI and CI mass spectra for compounds (**1–4**) was equipped with a DB-5MS column (J&W Scientific, Folsom CA) with 30 m length, 250 μ m I.D. and 0.25 μ m *d*_f, while the column used in the identical system for EI analysis of VX was a DB-1 type of the same manufacturer, and with the same dimensions and *d*_f. Initial column temperature was held at 40 °C for 30 s, followed by a temperature gradient at 30 °C min^{−1} to 300 °C with the final temperature held for 1 min. For EI analyses the mass spectrometer was operated with 70 eV ionization energy in scan mode (*m/z* 35–300). Solvent delay was 3.0 min and the source and quadrupole temperatures were set at 230 and 150 °C, respectively. For CI analyses, the same GC and solvent delay parameters were used as for the EI analyses, but the mass spectrometer was operated with 184 eV ionization energy, the source temperature was set to 250 °C, and a scan range of *m/z* 30–650 was used. Typical ion gauge pressure readings (uncorrected) during CI analyses were 2 × 10^{−4} Torr, with high purity NH₃ used as CI reagent gas. Reagent gas flow settings and tuning for CI analyses followed the instrument manufacturer's instructions.

3. Results and discussion

3.1. TMS analysis of triethylamine and triethylamine-*d*₁₅

Fig. 2 provides evidence that for triethylamine, the production of [M+H]⁺ occurs by self-CI, and not from protonation by an unrelated substance coincidentally present in the TMS, such as water. In the mass spectrum of triethylamine-*d*₁₅, peaks representing [M+D]⁺ and an ion possibly resulting from loss of CD₄ from that ion are observed. Analogous ions ([M+H]⁺ and [MH–CH₄]⁺) are noted in the mass spectrum for unlabeled triethylamine. Mass spectral peak resolution is better than unit mass and no evidence was noted for

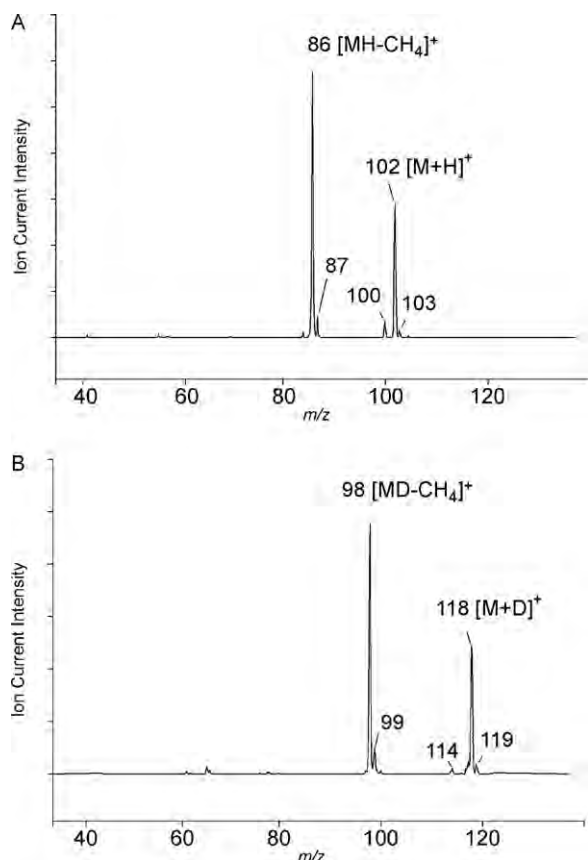


Fig. 2. TMS mass spectra obtained for: (A) triethylamine; (B) triethylamine-*d*₁₅.

space charge effects with these samples where dynamic ionization time management was used (5×10^3 ion target, 2.4 ms ion cooling time).

3.2. Comparative transmission quadrupole EI mass spectra

The mass spectra obtained for compound (1) and VX are represented by Fig. 3A and B, with EI analyses completed using transmission quadrupole instrumentation. A faint response for the respective molecular ion was seen for each of the synthetic sulfide compounds (1–3) (also see Table 1), but evidence for M^{•+} was not observed for compound (4) (mass spectrum not shown), nor for VX (Fig. 3B). The similarities between these spectra and the presence of only subtle differences complicate definitive identification through library matching, as some of the most diagnostic differentiating ions are present with only low intensity.

The NH₃ CI spectra obtained with a transmission quadrupole instrument were consistent with the observations of D'Agostino et al. [4]. Compounds (1–3) demonstrated very little fragmentation when NH₃ reagent gas was used. However, several fragment ions were noted for compound (4) with NH₃ CI (mass spectrum not shown).

3.3. Manipulation of [M+H]⁺ intensities

When fixed ionization times were prolonged for compounds (1–3), increasing intensities for [M+H]⁺ were observed relative to the m/z 114 ion found in the mass spectrum for each analyte (approaching 70–80%). An increase from 60 to 200 ms did not result in appreciably greater [M+H]⁺/m/z 114 ion ratios. Protonation of compound (4) was not observed except for analyses where ionization time was fixed at 200 ms.

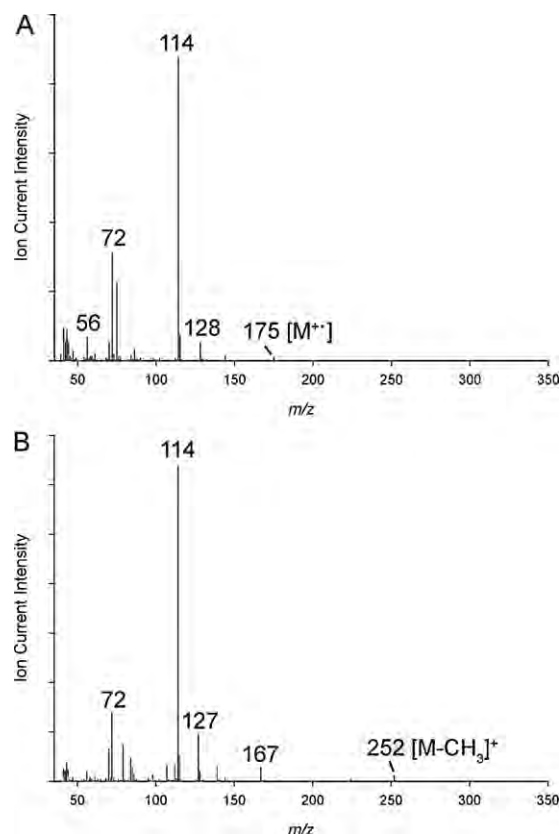


Fig. 3. Transmission quadrupole 70 eV EI mass spectra from GC–MS analysis of 50 ng liquid injections of: (A) compound (1); (B) VX.

Mass spectra collected for compound (4) with fixed ionization time of 200 ms produced a noticeable peak for [M+H]⁺, although mass assignment shifts were observed in spectra for all four analytes under these conditions. When this occurred, mass spectral peaks were well defined in profile view, but noticeably widened. Mass assignment shifts were noted for the lower m/z values, with ion current for m/z 193 and 321 appropriately assigned, likely due to lessened ion density by the time these ions were scanned from the TMS following initial removal of the lower m/z ions.

Table 1

Intensity of M^{•+} mass spectral peaks, replicate GC–MS analyses using transmission quadrupole instruments and 70 eV EI.

Analyte	Molecular weight (u)	M ^{•+} intensity as Percentage of base peak
(1) 2-(Diisopropylaminoethyl)methyl sulfide	175	1.2 1.2 1.2
(2) 2-(Diisopropylaminoethyl)ethyl sulfide	189	0.86 0.83 0.84
(3) 2-(Diisopropylaminoethyl)isopropyl sulfide	203	0.71 0.69 0.69
(4) bis(diisopropylaminoethyl)disulfide ((DES) ₂)	320	0 0 0
O-ethyl S-(2-diisopropylaminoethyl) methylphosphonothiolate (VX)	267	0 0 0

For compound (**4**), a clear signal was observed for $[M+H]^+$ with dynamic ionization time management, extended ion cooling time, and a relatively low ion target value. When 492 ms ion cooling time was employed the peak width at half height for the pseudomolecular ion observed at m/z 321 was calculated to be 1.2 u, while the widths for lower mass ions were better than unit mass, and no mass assignment shifts were observed. The longer ion storage time allowed for increased interaction of neutral compound (**4**), presumably with small acidic fragments derived from the EI process to produce the signal obtained for $[M+H]^+$.

Protonation of compound (**4**) was not observed in any analyses where dynamic ionization time management was used with typical ion cooling time of 2.4 ms. Mild loss of mass spectral resolution was observed when analyses were completed using feedback-controlled ionization time and an ion target value of 4×10^4 , although this was not accompanied by mass assignment shifts. For compounds (**1–3**), increasing the ion target value to 2×10^4 and 4×10^4 resulted in increasingly higher ratios of $[M+H]^+/m/z$ 114 ion intensities approaching 50–70%.

3.4. Degraded VX sample—chromatography and mass spectra

A chromatogram produced through GC–TMS analysis of degraded VX with SPME sampling is shown in Fig. 4. The sharp GC peak for compound (**4**) indicates that the GC–TMS system had no appreciable cold spots along the analysis flow path between the injector and the TMS detector. When analyzed using a stationary phase analogous to that used in this work along with a homologous series of *n*-hydrocarbon reference standards, D'Agostino et al. [4] calculated the retention index value for this compound following Van den Dool and Kratz [16] to be 2057.9, meaning that it typically elutes about midway between *n*-C₂₀ and *n*-C₂₁.

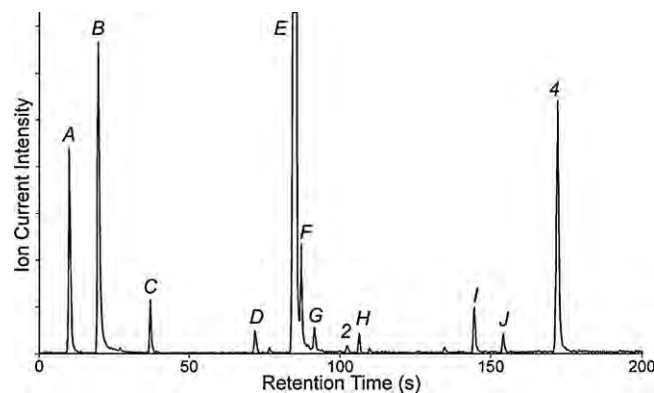


Fig. 4. GC–TMS chromatogram produced by analysis of sample collected after VX was added to AgF and maintained at 70 °C overnight. Dynamic ionization time management (ion target value set to 10^4), and 120 ms ion cooling time were used. Peak identities in order of elution: (A) thiirane, (B) diisopropylamine, (C) *O*-ethyl methylphosphonofluoridate, (D) diethyl methylphosphonate, (E) 2-(diisopropylamino)ethanethiol, (F) unknown analyte, probable $M^+ m/z$ 159, (G) *O,S*-diethyl methylphosphonothioate, compound (**2**), (H) unknown analyte, probable $M^+ m/z$ 157, (I) VX, (J) unknown analyte, likely bis(diisopropylaminoethyl)sulfide from presence of 114 m/z base peak and elution order ($[M+H]^+$ not visible in mass spectrum), compound (**4**). Pseudomolecular ions produced by protonation ($[M+H]^+$) were clearly discernible in the mass spectra of A, B, C, D, E, compound (**2**), (I) (VX), and compound (**4**).

An LTM GC heating module similar to that used here has been used as the inlet for several mass spectrometers which are less transportable than the TMS system [17]. In the cited work, rapid GC column heating allowed for analysis of compounds ranging in molecular weight from 140 (the chemical warfare agent sarin) to 466 u (T-2 toxin) by GC–MS in less than 4 min. However, the transportable GC–MS system used weighed more than three times that

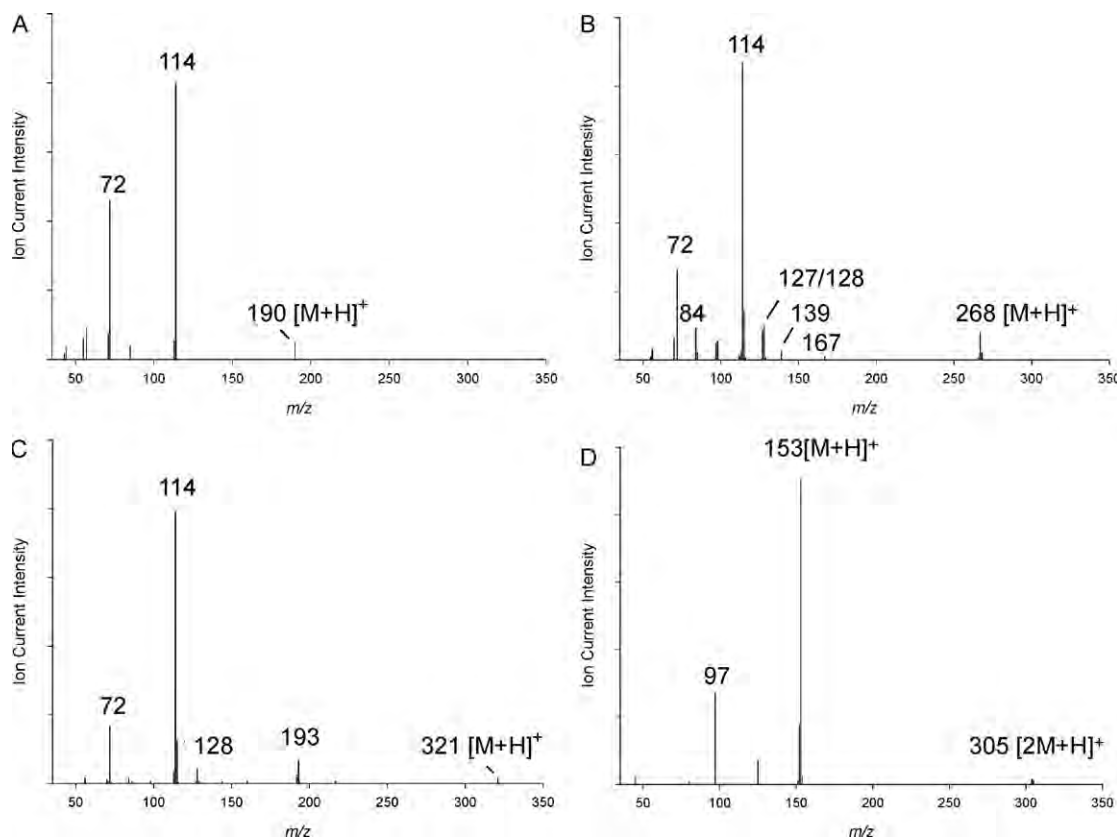


Fig. 5. TMS mass spectra obtained from analysis resulting in Fig. 4 chromatogram, dynamic ionization time management, 120 ms cool time and ion target value set at 10^4 : (A) compound (**2**), (B) VX, (C) compound (**4**), (D) diethyl methylphosphonate.

used here. The overall weight of the GC–TMS instrument used here is 14 kg, and it may be continuously operated for several hours using battery power and a self-contained carrier gas supply.

The GC–TMS analysis resulting in Fig. 4 chromatogram employed lengthened ion storage with feedback-controlled ionization. Small $[M+H]^+$ mass spectral peaks were noted for numerous analytes detected, including compound (2), VX, and compound (4) (Fig. 5A–C), while a much larger pseudomolecular ion peak was observed for the VX degradation product 2-(diisopropylamino)ethanethiol (GC peak E). While $[M+H]^+$ ions were observed for most of the analytes having the diisopropylaminoethyl functional group, diethyl methylphosphonate (GC peak D, mass spectrum shown in Fig. 5D) and *O*-ethyl methylphosphonofluoridate (GC peak C, mass spectrum not shown) produced signal for both $[M+H]^+$ and $[2M+H]^+$ ions. The formation of a protonated dimer, thought to proceed first from protonation of a neutral phosphonate molecule in the internal ionization trap, is consistent with earlier observations [18] for phosphonofluoridate nerve agent analytes.

The presence of both m/z 127 and 128 ions in the TMS mass spectrum obtained for VX (Fig. 5B) is consistent with simultaneously occurring EI and CI fragmentation pathways for this analyte. With EI only, a m/z 127 product ion is expected from the mass spectrometric analysis of VX (Fig. 3B). Using NH_3 CI and a magnetic sector instrument, D'Agostino et al. noted the presence of a m/z 128 ion from analysis of VX [4]. Rohrbaugh also showed that CH_4 CI of VX followed by collision induced dissociation of $[M+H]^+$ in a triple quadrupole instrument [19], and methanol CI using an ion trap instrument [6] led to observation of a m/z 128 product ion.

4. Conclusion

The potential usefulness of a person-portable GC–TMS system was explored for identification of pseudomolecular ions produced from VX degradation products that offer poorly-diagnostic mass spectra with 70 eV EI and transmission quadrupole mass spectrometry. Ions for $[M+H]^+$ were readily produced from three of the four VX degradation products studied under all analysis conditions, while either extended fixed-duration ionization time or extended ion storage time was required to produce and detect $[M+H]^+$ for compound (4). The highest quality TMS spectra for this analyte showing evidence for self-CI protonation were collected with feedback-controlled ionization time, low ion target values, and extended ion storage time provided by lengthening the ion cooling period. Samples collected from heat-degraded VX were

analyzed under these TMS conditions, and VX, compounds (2) and (4), and several additional VX degradation products were identifiable through detection of pseudomolecular ions. Analyses of triethylamine- d_{15} with the GC–TMS instrument provided evidence that self-CI is responsible for the observed production of pseudomolecular ions for the analytes studied. This proceeds from proton donation by small, acidic fragments that result from the initial 70 eV EI process.

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