

Detection of Aqueous Phase Chemical Warfare Agent Degradation Products by Negative Mode Ion Mobility Time-of-Flight Mass Spectrometry [IM(tof)MS]

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The use of negative ion monitoring mode with an atmospheric pressure ion mobility orthogonal reflector time-of-flight mass spectrometer [IM(tof)MS] to detect chemical warfare agent (CWA) degradation products from aqueous phase samples has been determined. Aqueous phase sampling used a traditional electrospray ionization (ESI) source for sample introduction and ionization. Certified reference materials (CRM) of CWA degradation products for the detection of Schedule 1, 2, or 3 toxic chemicals or their precursors as defined by the chemical warfare convention (CWC) treaty verification were used in this study. A mixture of six G-series nerve related CWA degradation products (EMPA, IMPA, EHEP, IHEP, CHMPA, and PMPA) and their related collision induced dissociation (CID) fragment ions (MPA and EPA) were found in each case to be clearly resolved and detected using the IM(tof)MS instrument in negative ion monitoring mode. Corresponding ions, masses, drift times, K_0 values, and signal intensities for each of the CWA degradation products are reported. (J Am Soc Mass Spectrom 2006, 17, 241–245) © 2006 American Society for Mass Spectrometry

Chemical warfare agents by convention are classified as lethal nerve, vesicant, blood, or pulmonary agents. Nerve agents, G-series (Sarin (GB), Cyclosarin (GF), Soman (GD), Tabun (GA), and V-series (VE, VG, VM, VX), all disrupt neurological regulation within biological systems through the inhibition of the enzyme acetylcholine esterase [1]. Vesicant agents (also known as bifunction alkylating agents) sulfur mustards (H, HD, HS), lewisite (L), nitrogen mustard gas (HN), and phosgene-oxime (CX) are the agents typically responsible for detrimental reactions with deoxyribonucleic acid (DNA) and intracellular glutathione (GSH) [2]. Blood born agents, such as prussic acid (AC) or cyanogen chloride (CK), prevent tissue utilization of oxygen by inhibition of the enzyme cytochrome oxidase [3]. Pulmonary agents, chlorine gas (C), chloropicrin (PS), diphosgene (DP), and phosgene (CG,) all react

with water to form hydrochloric acid and carbon monoxide to cause pulmonary edema [4]. Environment neutralization of these CWA typically involves the degradation of the parent compounds to yield various hydrolysis products [5–7]. The G-series nerve agents, which include GB, GF, GD, and GA, rapidly hydrolyze to form various alkyl phosphonic acids [8], whereas V-series nerve agents VE, VG, VM, and VX degrade to not only form alkyl phosphonic acids but phosphonothioic acids and various alkyl amino ethanol compounds [9]. The common sulfur and arsenic containing vesicants H, HD, HS, and L typically degrade to produce various sulfides, thiodiglycols, sulfones, and vinyl arsonous products, respectively [10]. Blood-born agents such as AC initially hydrolyze to formamide, and subsequently to ammonium formate, while CK readily hydrolyzes to hydrogen chloride and unstable cyanic acid. The cyanic acid further decomposes to carbon dioxide and ammonia [11]. Lastly, the pulmonary agents C, PS, DP, and CG as mentioned above hydrolyze into hydrochloric acid, hydrochlorous acid, carbon monoxide, and carbon dioxide [12].

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In general, CWA hydrolysis and degradation products have been found to exhibit a higher degree of stability and persistence in the environment than their corresponding parent agents [5]. Direct detection of these CWA degradation products has provided a convenient and indirect detection method for the presence or past presence of CWA. The degradation products of CWA are typically polar and nonvolatile in character, readily dissolving in aqueous environments. A host of stand alone analytical techniques in an assortment of forms [7, 13–19] have been employed for the analysis of these CWA degradation products with varying degrees of success. More recently; however, the development of an atmospheric pressure ion mobility spectrometer (AP-IMS) interfaced to a orthogonal reflector time-of-flight mass spectrometer (TOFMS) has demonstrated the capability through a variety of sample introduction and ionization modes to rapidly (<1 min) and sensitively (<100 ppb by weight for most compounds tested) detect, identify, and quantify aqueous vapor and aerosol phase CWA degradation products, respectively [20–22]. More importantly, with the prior development of the AP-IMS [23] with resolving powers similar to that of typical capillary gas chromatography and better than that of typical HPLC separations has facilitated the AP-IMS-TOFMS [simply referred to here as IM(tof)MS] the option to eliminate traditional chromatographic separations altogether and rely solely upon the rapid separation capabilities of the high-resolution AP-IMS before mass spectrometric analysis via the TOFMS. Although rapid detection of aqueous vapor and aerosol phase CWA degradation products have been demonstrated with IM(tof)MS technology in the positive ion monitoring mode, negative ion monitoring mode using IM(tof)MS has not been previously explored. It is, however, interesting to note that negative ion monitoring mode detection applications utilizing atmospheric pressure field asymmetric ion mobility mass spectrometry (FAIMS-MS) have been investigated, but not for compounds involving CWA degradation product research. Likewise, CWA degradation products have been studied using FAIMS but not in combination with MS [24]. Therefore, this paper seeks to explore the feasibility of using IM(tof)MS technology for the detection of CWA degradation products in negative ion monitoring mode. This improvement in IM(tof)MS development greatly expands the capacity of IM(tof)MS technology to significantly decrease the potential for false positive responses when screening for CWA.

Experimental

Chemicals and Solvents

The six G-series nerve related CWA degradation products (ethyl methyl phosphonic acid (EMPA), isopropyl methyl phosphonic acid (IMPA), ethyl hydrogen ethyl phosphonate (EHEP), isopropyl hydrogen ethyl phosphonate (IHEP), cyclohexyl methyl phosphonic acid (CHMPA), and pinacolyl

methyl phosphonic acid (PMPA) used in this study were obtained from Cerilliant (Round Rock, TX) as 1 $\mu\text{g/mL}$ (1000 ppm) certified reference materials (CRM) in methanol. These CRMs are used as analytical standard solutions for the detection of Schedule 1, 2, or 3 toxic chemicals or their precursors as stated in the CWC verification and related analysis annex [25]. Stock solutions for these CWA simulants/degradation products were prepared in ESI solvent (90.0% methanol, 10.0% water) at concentrations of 100 $\mu\text{g/mL}$ (100 ppm). Further dilutions of these stock solutions with ESI solvent ranged from 0.01 to 100 $\mu\text{g/mL}$ (10 ppb to 100 ppm), depending upon the experiment. The HPLC grade ESI solvents (methanol, water) were purchased from J. T. Baker (Phillipsburgh, NJ).

Instrumentation

The fundamental components (ESI source, AP-IMS drift tube, pressure interface, TOFMS analyzer, and data acquisition system) of IM(tof)MS technology as used in this study were constructed over a period of time in collaboration with Washington State University and Ionwerks Incorporated, where only the positive mode of operation have been previously described in detail [20–23, 26]. Thus, in light of previous work, only a brief outline of the experimental sequence in negative ion monitoring mode of operation is provided. A continuous flow (1.0 $\mu\text{L/min}$) of solvent was electrosprayed in the negative ion monitoring mode with a needle voltage drop of -4.1 KV with respect to the target screen of the APIMS. The APIMS was separated into two regions a desolvation (8.0 cm long) and a drift (18.0 cm long) that were maintained at a temperature of 225 $^{\circ}\text{C}$. Desolvated negatively charged ions from the electrospray process drifted through the APIMS tube under a weak uniform electric field (-430 V/cm), which facilitated separation based upon differing analyte mobility constants. A counter current flow of preheated nitrogen drift gas was introduced at the end of the drift region at a rate of 1.0 L/min. Ions, upon exiting of the APIMS drift tube (689 torr), traversed a pressure interface (1.2 torr) where ions were transported through a series of lenses into the TOFMS (4×10^{-6} torr) for analysis.

Data acquisition for this experimental sequence consisted of a timing mechanism that was comprised of a real-time two-dimensional (2-D) matrix of simultaneous mobility drift and mass flight times. Ions were typically gated for 200 μs into the drift region at a frequency of 25.0 Hz. This allowed for a maximum of 40 ms for AP-IMS mobility data to be acquired. The TOFMS extraction frequency was set to 50.0 kHz, which provided a mass spectrum that consisted of ions with flight times up to 20 μs . Therefore, within each 40 ms mobility time window there were effectively 2.00×10^3 TOF extractions. The AP-IMS Bradbury-Nielsen ion gate, TOFMS extractor, and TOFMS time-to-digital converter were all triggered by a personal computer (PC) based timing controller. Synchronization of this electronic hardware was facilitated by the use of a dual Pentium III workstation running Ionwerks

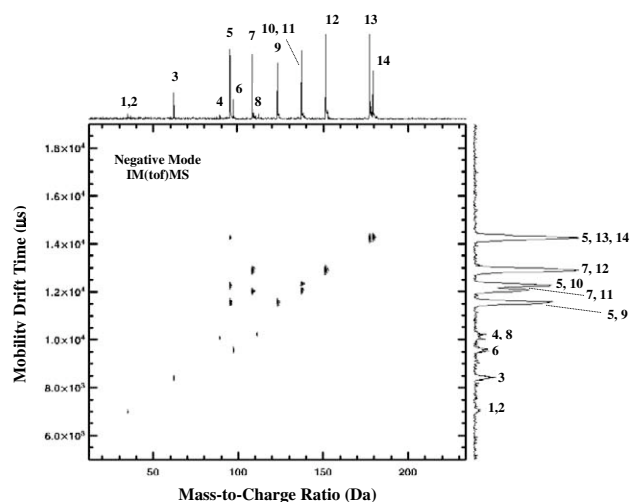


Figure 1. The IM(tof)MS of a 10 ppm liquid phase mixture containing all six G-series CWA degradation products are shown in negative ion monitoring mode by both the 2-D mobility-mass spectrum and extracted mobility-mass spectra. Here the ESI background solvent ions were identified as 1: Chloride ($^{35}\text{Cl}^-$), 2: Chloride ($^{37}\text{Cl}^-$), 3: Nitrate (NO_3^-), 4: Water cluster ($(\text{H}_2\text{O})_4\text{-OH}^-$), and the ions from the CWA degradation products were identified as 5: Fragmentation products methyl phosphonic acid (MPA-H^-), 6: Phosphate (H_2PO_4^-), 7: Fragmentation products ethyl phosphonic acid (EPA-H^-), 8: Phosphoric acid ester ($\text{CH}_3\text{HPO}_4^-$), 9: Ethyl methyl phosphonic acid (EMPA-H^-), 10: Isopropyl methyl phosphonic acid (IMPA-H^-), 11: Ethyl hydrogen ethyl phosphonate (EHEP-H^-), 12: Isopropyl hydrogen ethyl phosphonate (IHEP-H^-), 13: Cyclohexyl methyl phosphonic acid (CHMPA-H^-), 14: Pinacolyl methyl phosphonic acid (PMPA-H^-).

[27] three-dimensional (3-D) acquisition software. Experimental data acquisitions were run in triplicate for a typical run-time of 15.0 min per sample to provide clear ion statistics. This ensured that the effects of ionization efficiency and ion transmission were not a limiting factor when determining limits of detection. Once acquired, spectral compilations of data were then exported into Research Systems IDL virtual machine 6.0 software for processing [28].

Results and Discussion

A standard aqueous phase reference solution containing all six G-series CWA degradation products (EMPA, IMPA, EHEP, IHEP, CHMPA, and PMPA) were electrosprayed (9:1, methanol:water) at a rate of $1 \mu\text{l}/\text{min}$ into the IM(tof)MS instrument in negative ion monitoring mode. Figure 1 shows the 2-D IM(tof)MS separation of an acquisition (15.0 min) of a solution (10 ppm) conducted at an AP-IMS temperature of 225°C . The 2-D IM(tof)MS spectrum as seen in Figure 1 is also accompanied by a combination of both the extracted mobility (shown on the side of the 2-D spectrum) and mass (shown above the 2-D spectrum) spectra. Here, the ESI background solvent ions were identified as 1: chloride ($^{35}\text{Cl}^-$), 2: chloride ($^{37}\text{Cl}^-$), 3: nitrate (NO_3^-), 4: water cluster ($(\text{H}_2\text{O})_4\text{-OH}^-$), and the ions from the CWA degradation products were identified as 5: fragmenta-

tion products methyl phosphonic acid (MPA-H^-), 6: phosphate (H_2PO_4^-), 7: fragmentation products ethyl phosphonic acid (EPA-H^-), 8: phosphoric acid ester ($\text{CH}_3\text{HPO}_4^-$), 9: ethyl methyl phosphonic acid (EMPA-H^-), 10: isopropyl methyl phosphonic acid (IMPA-H^-), 11: ethyl hydrogen ethyl phosphonate (EHEP-H^-), 12: isopropyl hydrogen ethyl phosphonate (IHEP-H^-), 13: cyclohexyl methyl phosphonic acid (CHMPA-H^-), 14: pinacolyl methyl phosphonic acid (PMPA-H^-). Notice that the mobility spectrum alone yielded CWA degradation products that have similar mobilities, such as PMPA and CHMPA. This made it difficult to determine significant resolution of these two ions from the complete mixture by ion mobility alone. Further examination of Figure 1 also established that the mass spectrum alone could not resolve all of the CWA degradation products. This was due to ions (IMPA-H^-) and (EHEP-H^-) having the same mass flight times. However, the combination of ion mobility and mass spectrometry in tandem, i.e., IM(tof)MS, provided a powerful 2-D mode of acquisition for the identification and quantification of all aqueous CWA degradation products at once, making it possible to clearly determine each of the parent ions, respective fragments, signal intensity, mobility drift, and mass flight times produced from within a single experimental run.

Tabulated values for each of the CWA degradation products analyzed in this study are shown in Table 1. Here, the ions ($\text{M} - \text{N}^-$), masses, drift times, reduced mobility constants (K_0), and signal intensities are reported. All six G-series CWA degradation products produced both proton-loss parent ions, ($\text{M} - \text{H}^-$) and functional-group loss collision induced dissociation (CID) fragments upon transition of the IM(tof)MS pressure interface. More specifically, when fragmentation occurs between the pressure interface (1.2 torr) and the vacuum of the TOFMS (4×10^{-6} torr) the CID fragments observed possess the same mobility drift times as their respective parent ions. For example, PMPA produced both a parent (PMPA-H^-) and a methyl phosphonic acid CID fragment ($\text{PMPA-H-C}_6\text{H}_{12}^-$) ion with different mass flight times but identical mobility drift times. The fragment ion resulted from a collision induced rearrangement loss of the C_6 alkene. Likewise, IHEP produced both a parent (IHEP-H^-) and an ethyl phosphonic acid CID fragment ($\text{PMPA-H-C}_3\text{H}_6^-$) which only differed by their respective mass flight times. This trend was observed for all of the phosphonic acids; in each case CID of the ($\text{M} - \text{H}^-$) parent ion yielded fragment ions with losses of alkenes from the alkoxy groups due to CID rearrangements. As a side note, CWA-chloride adducts were not observed even for cases using elevated concentrations of CWA degradation products. The resulting K_0 values obtained for the examined CWA degradation products are, to our knowledge, the first ever published results for these compounds in the negative ion mode. Moreover, the comparison of these experimentally determined K_0 values to some of those found in literature for positive

Table 1. CWA degradation products identified by this study; ions, masses, drift times, K_o values, and signal intensities

	Ions (M + N) ^a	Mass (Da)	Drift Time (μ s)	K_o ^b (Lit K_o) ^c	Intensity ^d (RSD) ^e
EMPA	(M-H) ⁻	123.08	1.157×10^4	1.79 (1.75, 1.78)	252.6 (1.46)
	(M-H-C ₂ H ₄) ⁻	95.02	N/A ^a	N/A ^a	224.3 (1.58)
IMPA	(M-H) ⁻	137.10	1.226×10^4	1.70 (1.72)	295.2 (1.35)
	(M-H-C ₃ H ₆) ⁻	95.02	N/A ^a	N/A ^a	186.3 (1.58)
EHEP	(M-H) ⁻	137.10	1.206×10^4	1.73	267.2 (1.35)
	(M-H-C ₂ H ₄) ⁻	109.03	N/A ^a	N/A ^a	217.8 (1.38)
IHEP	(M-H) ⁻	151.13	1.292×10^4	1.63	483.3 (1.68)
	(M-H-C ₃ H ₆) ⁻	109.03	N/A ^a	N/A ^a	328.8 (1.38)
CHMPA	(M-H) ⁻	177.17	1.426×10^4	1.46	363.3 (1.63)
	(M-H-C ₆ H ₁₀) ⁻	95.02	N/A ^a	N/A ^a	41.3 (1.58) ^f
PMPA	(M-H) ⁻	179.18	1.426×10^4	1.46	323.5 (1.21)
	(M-H-C ₆ H ₁₂) ⁻	95.02	N/A ^a	N/A ^a	41.3 (1.58) ^f

^amobility information not applicable for CID fragment ions.^b K_o Values are in cm²V⁻¹s⁻¹.^cpositive mode literature K_o values²⁰.^dsignal intensity.^epercent relative standard deviation (RSD) for three experimental runs.^fcombined signal intensity from CHMPA and PMPA fragmentation.

mode [20], as shown in Table 1, helps to not only further validate the use of the IM(tof)MS instrument for the accurate identification of CWA degradation products but also to provide an insight as to how negatively charged ions behave as they move through the APIMS drift space. For example, both EMPA and IMPA exhibited a close similarity between their positive and negative mode K_o values, even though they were run on different occasions. Lastly, as might be expected, most CWA degradation products exhibited relatively similar signal intensities, mainly due to what appears to be common efficiency of proton extraction from hydroxyl (OH⁻) functional groups. It should be noted that IHEP showed the highest signal intensity followed by CHMPA and PMPA, respectively.

Conclusions

The main advantage of IM(tof)MS technology over IMS or MS technology alone is its ability to provide rapid 2-D data acquisition spectra with the capacity to electronically couple and decouple CID to generate ion fragmentation patterns. This in turn facilitates the identification of mobility selected parent ions, permitting rapid compound identification and significantly reducing the number of false positive responses [21]. Here, the employment of the IM(tof)MS in negative ion monitoring mode has shown the detection capacity (accuracy, precision, and robustness) to be used for a complex aqueous phase mixture of CWA degradation products. Using this approach, it was possible to clearly determine each of the parent ions, respective CID fragments, signal intensity, mobility drift, and mass flight times produced from within a single experimental run. The significance of this study now opens the door to IM(tof)MS technology as a means to conclusively detect Schedule 1, 2, and 3 toxic chemicals or their precursors as stated in the CWC verification and related analysis annex [25] in either positive ion monitoring

mode [20–22, 26] or negative ion monitoring mode, thereby increasing the reliability of identification and decreasing the potential for false positive responses. While this study was limited to the detection of a single class of G-series aqueous phase CWA degradation products in negative IM(tof)MS ion monitoring mode, the analytical principles demonstrated in this study are expected to be applicable to a wide range of compounds such as inorganic anions, explosives, sugars, and other analytes which can produce negative gas-phase ions.

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