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Direct Quantification of Chemical Warfare Agents and Related Compounds at Low ppt Levels: Comparing Active Capillary Dielectric Barrier Discharge Plasma Ionization and Secondary Electrospray Ionization Mass Spectrometry

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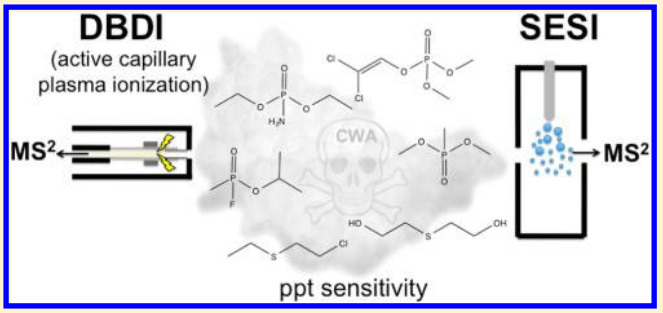
Supporting Information

ABSTRACT: A novel active capillary dielectric barrier discharge plasma ionization (DBDI) technique for mass spectrometry is applied to the direct detection of 13 chemical warfare related compounds, including sarin, and compared to secondary electrospray ionization (SESI) in terms of selectivity and sensitivity. The investigated compounds include an intact chemical warfare agent and structurally related molecules, hydrolysis products and/or precursors of highly toxic nerve agents (G-series, V-series, and "new" nerve agents), and blistering and incapacitating warfare agents. Well-defined analyte gas phase concentrations were generated by a pressure-assisted nanospray with consecutive thermal evaporation and dilution. Identification was achieved by selected reaction monitoring (SRM). The most abundant fragment ion intensity of each compound was used for quantification. For DBDI and SESI, absolute gas phase detection limits in the low ppt range (in MS/MS mode) were achieved for all compounds investigated. Although the sensitivity of both methods was comparable, the active capillary DBDI sensitivity was found to be dependent on the applied AC voltage, thus enabling direct tuning of the sensitivity and the in-source fragmentation, which may become a key feature in terms of field applicability. Our findings underline the applicability of DBDI and SESI for the direct, sensitive detection and quantification of several CWA types and their degradation products. Furthermore, they suggest the use of DBDI in combination with hand-held instruments for CWAs on-site monitoring.



Throughout the last century, chemical warfare agents (CWAs) have been developed and used in various conflicts.[1] The latest use of these internationally outlawed weapons in Syria in 2013 caused more than 1000 casualties. In response, the mission sent by the United Nations (UN) collected samples which proved the use of the organophosphorus G-type nerve agent isopropylmethylphosphonofluoridate (sarin) on a large scale.[2] In light of this, the need for rapid, selective, and accurate analysis techniques for CWAs and their degradation products, as well as their further improvement becomes increasingly apparent. Although there are already several techniques available, most techniques utilize extensive sample preparation steps and chromatographic separation before detection, e.g., gas chromatography (GC), high performance liquid chromatography (HPLC), or capillary electrophoresis (CE).[3−7] Although the resulting preconcentration enhances the sensitivity of the follow up detection, it also obviates real-time application of these techniques as required for field measurements.

Direct identification of CWAs and their degradation products is therefore mainly restricted to spectrometric methods like ion mobility spectrometry (IMS) or mass spectrometry (MS). D'Agostino and Chenier[8] reported promising results using desorption electrospray ionization (DESI) and MS/MS to directly identify various nerve agents on solid phase microextraction (SPME) fibers. Nilles et al.[9] presented a direct quantification and sufficiently good correlations for the detection of most nerve agents and one blistering agent (sulfur mustard) using direct analysis in real time (DART) ionization mass spectrometry. Seto et al.[10] investigated the applicability of counterflow introduction APCI-ionization for direct detection of sarin, tabun, sulfur mustard, and lewisite. On a commercial ion trap instrument, mounted on a movable tray, they achieved limits of detection (LOD) in the lower $\mu g/m^3$ range. By applying proton-transfer-reaction mass spectrometry, Kassebacher et al.[11] detected the CWA phosgene and some riot control agents with an estimated detection limit of some tens of ppbv. Additionally Cooks' group reported the application of a field deployable (hand-held) ion trap mass spectrometer for chemical warfare agent simulants.[12] The instrument was

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running on a passive membrane inlet with internal electron impact ionization and was combined with some preconcentration adsorption tubes, in front of the inlet, to enhance sensitivity. As a result, they present limits of detection in the ppb range (which includes the enrichment step).

Previous findings in our group, by Dumlao et al.,[13] showed the applicability of the recently developed active capillary ionization technique that is based on a dielectric barrier discharge ionization (DBDI), for the detection of CWA related compounds in the gas phase above different forensic matrices. Additionally, preliminary results for the combination with a portable mass spectrometer (Mini 10.5, Aston Laboratories, USA) were presented. However, these results were restricted solely to qualitative analyses.

This study presents major improvements made to the existing active capillary DBDI source and compares it to secondary electrospray ionization (SESI), with focus on the direct and sensitive quantification of chemical warfare related compounds. We evaluated the performance of each ionization method for 13 CWA related compounds, covering structurally related substances, hydrolysis products and/or precursors of nerve agents (G-series, V-series agents), blistering agents, and psychic warfare agents as well as the nerve agent sarin. Both methods are compared in terms of their selectivity, sensitivity, and applicability on the basis of MS/MS spectra and calibrations of the investigated compounds.

EXPERIMENTAL SECTION

Chemicals and Solvents. Dimethyl methylphosphonate (DMMP) (97%), pinacolyl methylphosphonate (PMP) (97%), diethyl ethylphosphonate (DEEP) (>98%), malathion (analytical standard), phoxim (PHX) (analytical standard), dichlorvos (DCV) (analytical standard), scopolamine (98%), 2-chloroethyl ethylsulfide (CEES) (98%), and diethyl phosphoramidate (DEPA) (98%) were obtained from Sigma-Aldrich Chemical Co. (St. Louis, USA). Methylphosphonic acid (MPA) (98%) was purchased from ABCR GmbH & Co. KG (Karlsruhe, Germany), and thiodiglycol (TDG) (99%) was from ACROS ORGANICS (Geel, Belgium). Diisopropyl methylphosphonate (DIMP) (95%) was purchased from Alfa Aesar GmbH & Co KG (Karlsruhe, Germany). Samples of isopropyl-methylphosphonofluoridate (GB or sarin, respectively) (>98%, stock solution: 0.1% in hexane) were measured under the supervision of SPIEZ LABORATORY (Spiez, Switzerland). All chemicals were used without further purification.

To simulate G-series nerve agents, DMMP, DEEP, DIMP, and DEPA are commonly used, because of their structural similarities. PMP is a primary hydrolysis product of the G-series nerve agent soman. Methylphosphonic acid is a secondary hydrolysis product of different nerve agents. The organophosphorus pesticide malathion was used as a proxy for V-series nerve agents, due to the fact that it is comparable in terms of structure, molecular weight, and volatility. Dichlorvos and phoxim pesticides were chosen since they are structurally related to some suspected "new" nerve agent structures. Despite the fact that these agents are covered only indirectly in the chemical weapons convention, they are believed to have comparable or even higher toxicity than the V-series agents. For simulation of blistering agents, e.g., sulfur mustard, the structurally related CEES and TDG (as a direct hydrolysis product) have been investigated. Another group of nonlethal warfare agents are the incapacitating warfare agents, e.g., 3-chinuclidinyl-benzilate (BZ). Therefore, the structurally related compound, the *Solanaceae* (nightshade) poison, scopolamine, was also included in this study.

Individual stock solutions (1000 μg/mL each) were prepared in pure HPLC-grade methanol or, in the case of GB, in dry HPLC-grade *n*-hexane, respectively. Depending on the experiment, diluted samples were generated out of these stock solutions with varying concentrations. Supporting Information Table ST1 shows the structures of all investigated compounds and their related warfare agents.

Safety Considerations. Most of the chemicals used in this study are included in, or closely related to, schedule 1, 2, or 3 of the CWC.[14] Almost all of the substances used here, especially, the intact CWAs, are extraordinary toxic and should only be handled with extreme caution, adequate safety equipment, and only by trained personnel!

MS Instrumentation. MS and MS/MS data were recorded on a LCQ DECA XP ion trap mass spectrometer (Thermo Scientific, St Jose, USA) operated in positive ion mode. Both sources (SESI and DBDI) were directly connected to the inlet capillary of the mass spectrometer by means of a leak tight fitting.

Active Capillary Plasma Source. The principle of the active capillary plasma source has already been described in detail in previous reports.[15,16] Briefly, a quartz glass capillary (ID 0.7 mm, OD 1.0 mm) is connected to the inlet of the mass spectrometer. The constant underpressure in the instrument ensures a fixed flow rate of 1.7 L/min through the capillary. A stainless steal capillary (ID 0.5 mm, OD 0.6 mm) inserted into the glass capillary serves as first electrode. The counter-electrode is a 5 mm wide copper ring (ID 1.0 mm) surrounding the capillary. By applying a sine modulated (5750 Hz) high voltage (1.5−4 kV, peak to peak) to the electrodes, the plasma is ignited inside the capillary by a dielectric discharge, which then ionizes the passing air and sample molecules. Modifications were made to the plasma source used in the previous studies, including the construction of a PVC/PTFE casing to enable a leak and pressure tight connection to the tubes, ensuring minimal dead volumes and a protection of the user and the quartz capillary. A scheme of the actual source is included as SFigure 1 in the Supporting Information.

Secondary Electrospray Source. The SESI source was of similar design as the one used by Martinez-Lozano Sinues et al.[17] It consists of a stainless steel cylinder (ID 2.5 cm, length 4 cm), which is closed by a glass window on both sides to enable optical spray observation by a microscope. The (nano-)spray capillary is inserted in the center of the cylinder by a PEEK fitting. On the opposite side, the cylinder is connected to the inlet of the mass spectrometer by a short stainless steel fitting. Perpendicular to the ionization spray and MS inlet axis, the sample is introduced through a 2.0 mm stainless steel inlet. The instrument's constant underpressure ensures a fixed sample flow rate of about 1.7 L/min into the SESI ionization chamber. A fused silica nanospray capillary (Ø20 μm) was used for the ionization spray. Spray electrification was achieved by inserting an electrified platinum wire, held at 2.7 kV, in the spray solution reservoir. HPLC grade water containing 0.1% v/v formic acid was used as a spray solution. The spray solution was introduced by applying a constant overpressure on the reservoir (800 mbar), thus enabling a constant solvent delivery to the spray source. The whole SESI chamber was heated to 120 °C to avoid sample vapor adsorption on the chamber surface.

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Sample Preparation and Experimental Setup. A pressure-assisted nanospray was used for gas phase sample generation. Assuming a laminar flow profile in the capillary, the amount of analyte introduced into the gas stream was calculated following Poisseuille's formula. Accordingly, the flow rate Q is given as $Q = \pi R^4 \Delta P/(8\ \mu L)$, where ΔP is the pressure drop along the capillary, R is its inner radius, L is its length, and μ is the viscosity of the liquid passing through. The following parameters were kept constant for all experiments, L = 24 cm, R = 15 μm, μ (methanol) 5.84 × 10^{-4} Pa·s and μ (hexane) 3.10 × 10^{-4} Pa·s, and ΔP = 880 mbar, resulting in a flow of 1.25 × 10^{-11} m^3/s for, e.g., methanol. A typical sample concentration of 1 μg/mL DMMP (M = 124.09 g/mol) in MeOH infused at flow rate Q calculated above and dispersed in an air carrier flow of 5 L/min (0.00341 mol/s) results in a gas phase concentration of 29.8 ppt. A constant carrier gas flow was maintained by means of a mass-flow controller (Bronkhorst High Tech B.V., Ruurlo, Netherlands). By varying the sample solutions concentrations, defined gas phase concentrations, in the range of <1 ppt up to 100 ppb, could be generated.

The defined sample gas stream was then directed to the ionization source (DBDI or SESI) through a small stainless steel tube (ID 4 mm, OD 6 mm, length 5 cm), heated to 120 °C (controlled by a PID thermal regulator with thermocouple) and connected by a t-piece, releasing the rest of the unused sample gas flow (3.3 L/min) to the fume hood through flexible PVC tubing. The entire system setup, with the DBDI in place, is depicted in Figure 1.

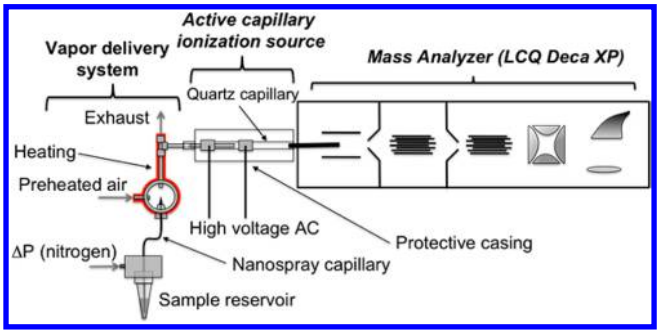

Figure 1. Schematic drawing of the system setup, including the vapor delivery system for the generation of ppt gas phase concentrations, the active capillary ionization source, and a scheme of the LCQ Deca XP mass analyzer. (Note: Not to scale for better representation.)

Identification and Calibration. All compounds were identified according to their MS/MS spectra using single reaction monitoring (SRM) after collision induced dissociation (CID). For each measurement point, an average of ~40 s of analyte infusion was recorded. For calibration, three replicate measurements for each concentration were averaged and the intensity of the most abundant fragment was plotted against the corresponding gas phase concentration. The standard deviation represents the deviation of these three replicate measurements. The LOD was then calculated for each compound according to IUPAC[18] using the 3s blank method. For both ionization methods, detailed information on the SRM transitions, relative abundance of in-source fragmentation, and assigned fragments for each substance are included in STable 2 in the Supporting Information.

RESULTS AND DISCUSSION

In a previous report,[13] the active capillary plasma ionization source applicability was demonstrated for DMMP, DEEP, and DEPA. However, this study focused on the feasibility of infield measurements in combination with hand-held instruments and was restricted solely to qualitative analysis of these three analytes. Our study now expands and evaluates the sensitivity, selectivity, and in source fragmentation of the active capillary DBDI-method for 13 different substances, which are or are closely related to nerve, blister, and incapacitating warfare agents. For evaluation of the sensitivity capabilities, a quantitative comparison with a secondary electrospray ionization (SESI) source is presented.

Sample Generation. For the accurate gas phase concentration generation for calibration, a pressure- and heat-assisted nanospray evaporator was constructed. The system can continuously produce very stable and reproducible gas phase concentrations ranging from <1 ppt to 100 ppb depending on the injected liquid sample concentrations. Figure 2 depicts a typical SRM system response of three consecutive DCV injections of 8.4 and 16.8 ppt. The square shape of the injections proves the reproducible and fast sample delivery to the MS.

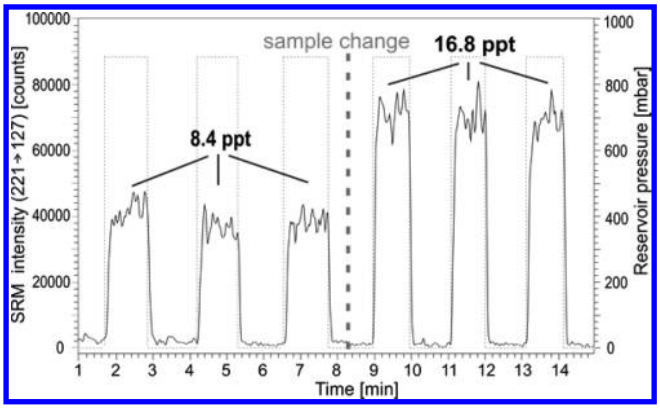

Figure 2. DBDI SRM signal (221 m/z → 127 m/z) for three consecutive generations of two different dichlorvos gas phase concentrations (8.4 and 16.8 ppt) (solid line). The dotted line shows the pressure applied to the nanospray sample reservoir (right y-axis).

For the comparison with SESI, the evaporation and transfer system temperature was limited to 120 °C. In the case of a much less volatile species, e.g., scopolamine or MPA, some adsorption and fronting effects, due to incomplete evaporation/adsorption, were observed. Due to the temperature limit mentioned above, these adsorption effects could not be overcome by heating, and hence, three out of the 13 substances tested were omitted from quantification, although they were easily ionized and detected with both sources (see the Supporting Information).

CWA Related Compounds. Figure 3 depicts, exemplary for all CWA-related compounds, the MS and the MS^2 spectra for both ionization methods for malathion, TDG, and DIMP. As mentioned, the MS spectra of DBDI and SESI are very similar hinting at a related ionization mechanism. The MS^2 spectra of the SRM transition used for quantification are identical for both ionization methods, as they only depend on the internally applied CID, which was the same in both cases.

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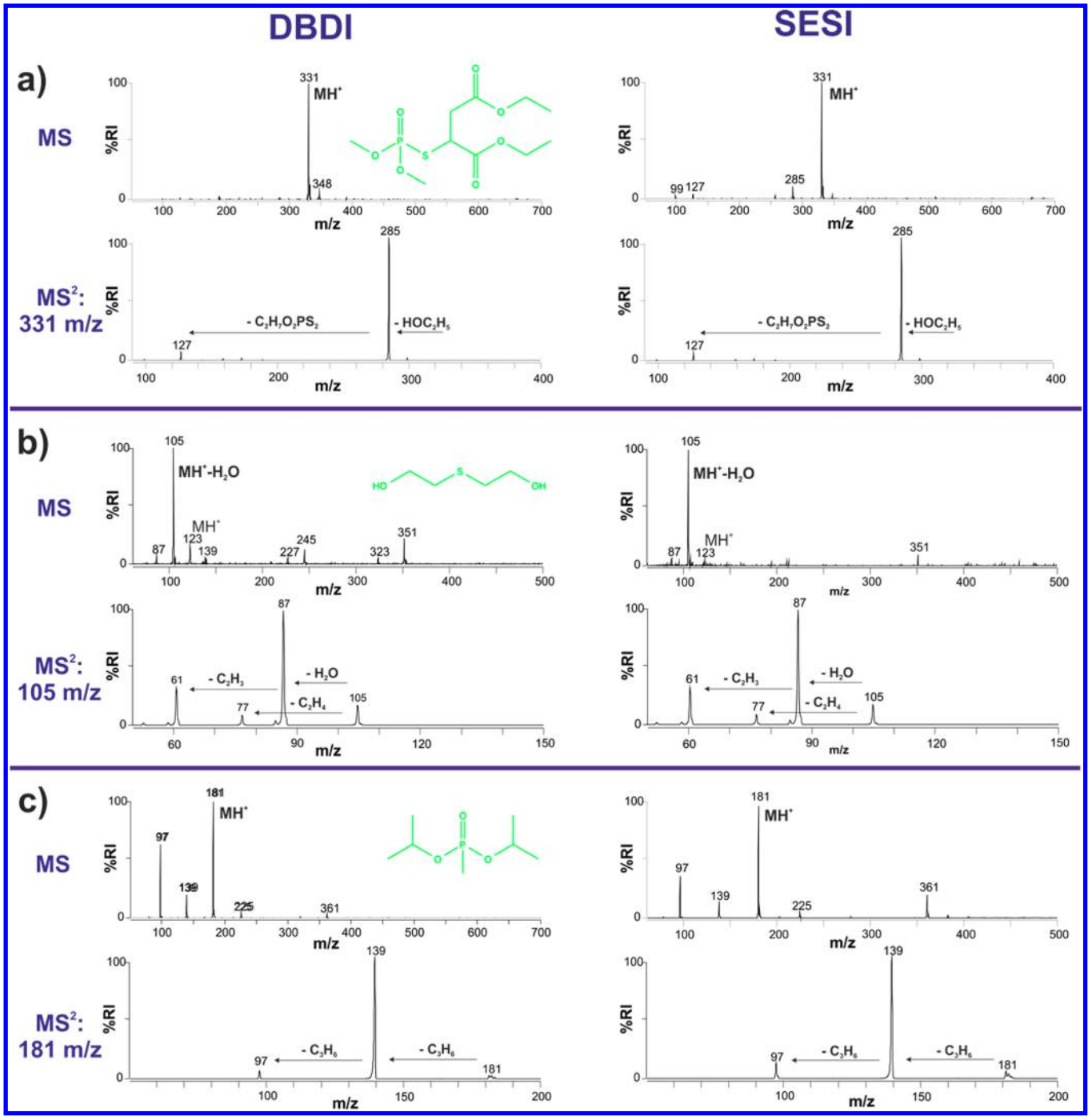

Figure 3. MS, MS/MS spectra, and molecular structures (green) for (a) malathion, (b) thiododiglycol (TDG), and (c) diisopropylmethylphosphonate (DIMP) acquired with active capillary plasma ionization (DBDI) (left column) and secondary electrospray ionization (SESI) (right column). Identical instrument settings were used for each component for both ionization methods. SESI spray voltage was 2.7 kV. DBDI voltage was 1.6 kV (p-p). Isolation window width for MS^2 experiments was 2.0 m/z. MS spectra were background subtracted.

The most abundant signal for malathion was the singly protonated molecule at 331 m/z. In this case, also, minor in-source fragmentation was observed for SESI in contrast to the active capillary source. Because the ion formation in SESI already takes place outside the inlet capillary in the SESI chamber, this can be explained by collision-induced fragmentation of the ions on their way through the chamber into the capillary. This theory is also supported by the fact that the observed in-source fragmentation correlates with the fragments observed in MS^2-experiments. In accordance with García-Reyes et al.,[19] the MH^+ CID fragmentation shows a cyclization under loss of one ethanol molecule to 285 m/z as the most abundant signal. Second, dissociation of the P−S bond is observed leaving a characteristic fragment at 127 m/z. This bond dissociation would also be expected in the corresponding V-series nerve agents since they all contain a characteristic P−S bond. For the blistering agent HD (sulfur mustard) degradation product, TDG, both ionization methods provided protonated molecule peaks at 123 m/z. The most abundant signal, however, was at 105 m/z, corresponding to the loss of a

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Table 1. Calibration Results for CWA Related Components Measured by DBDI and SESI

method	compound	number of calibration points	calibration range [ppt]	slope	intercept	R^2	LOD [ppt]
DBDI	DMMP	7	4.3−4328	345 ± 3	1200 ± 5505	0.9996	3.6
	DEEP	6	3.4−1128	8368 ± 118	−39777 ± 56884	0.9992	5.0
	DEPA	7	3.7−3653	8248 ± 64	−6761 ± 93607	0.9997	1.4
	DIMP	7	3.1−3122	2131 ± 40	−23300 ± 49513	0.9983	11.1
	malathion	7	3.0−3014	20629 ± 86	−83102 ± 103586	0.9999	4.1
	DCV	6	2.6−848	2774 ± 33	25830 ± 18530	0.9994	8.4
	PHX	7	1.9−1886	5679 ± 33	11877 ± 24812	0.9998	2.2
	CEES	4	45−1504	4.4 ± 0.04	47 ± 35	0.9998	58.4
	TDG	8	4.6−15348	159 ± 0.4	4639 ± 2314	0.9999	35.1
SESI	DMMP	7	4.5−4500	291 ± 2	−51 ± 4013	0.9997	1.1
	DEEP	7	3.4−3386	7585 ± 174	−137974 ± 236178	0.9985	14.1
	DEPA	7	3.7−3653	4192 ± 76	−46157 ± 111219	0.9984	12.0
	DIMP	5	3.1−312	3403 ± 83	−12926 ± 12295	0.9982	3.9
	malathion	7	1.7−1703	18134 ± 387	62932 ± 307735	0.9969	3.5
	DCV	7	2.5−2546	4001 ± 36	−83699 ± 36791	0.9996	20.9
	PHX	7	1.9−1886	4420 ± 34	−35048 ± 25501	0.9997	8.1
	CEES	4	45.1−1505	6.5 ± 0.3	355 ± 209	0.9967	124.7
	TDG	7	4.6−4604	230 ± 2	−686 ± 3967	0.9996	7.6

water molecule. The loss of a second water molecule at 87 m/z was also detected in MS mode and used for quantification in MS^2 mode. For DBDI, a protonated dimer at 245 m/z was found, but not for SESI, although the same declustering and tuning settings of the instrument were used. This may be attributed to a higher local ion density inside the active capillary or to a different ionization mechanism for both methods. On the other hand, a signal at 351 m/z was observed in both methods, which later was found to be a neutral TDG (122.19 g/mol) adduct with a protonated plasticizer ion (229 m/z). The plasticizer was identified by investigating the tubing used with MS/MS and high-resolution mass spectrometry on a TripleTOF 5600 instrument (AB SCIEX, Framingham, USA) equipped with a SESI source. From the molecular formula $C_{12}H_2O_4$ and the corresponding MS/MS spectra, dibutylmaleate (DBM, 228.28 g/mol) was identified, which is a common tubing plasticizer. In several studies, DIMP is used as a less toxic structural analogue to sarin. The MS spectra of DIMP are similar for SESI and DBDI. Both exhibit the MH^+ as the most abundant signal and the protonated dimer $2MH^+$. In addition, a significant in-source fragmentation is observed for both methods, showing the loss of one and two isopropyl groups at 139 m/z and 97 m/z. The same fragmentation patterns were observed for MS^2 experiments. This loss of the alkyl group is well-known and occurs for DEEP, DEPA, and PMP, which are all used as mimics for the G-series nerve agents. However, out of these, DIMP showed the strongest tendency for the in-source decay (see Table 1). Note: the DBDI and SESI MS spectra of all the substances investigated, as well as the corresponding MS^2 calibration plots, are available in the Supporting Information.

Sensitivity Comparison. The calibration results, parameters, and LODs for all CWA related substances investigated with DBDI and SESI are summarized in Table 1. For all calibrations, 7 to 8 points, covering a concentration range of 3 to 4 orders of magnitude and three replicates, were recorded. However, for some substances, the linear dynamic range was smaller, as indicated in Table 1. For SESI, an average correlation of 0.9980 ± 0.0019 was found. For DBDI, this was 0.9995 ± 0.0005, averaged over all nine calibrations. Although no internal standard was used, these results prove the quality and reproducibility of both the sample delivery system and the ionization methods. Depending on the substance, DBDI generally provided slightly more constant ionization conditions, as seen in the correlation average and Table 1. For both methods and all substances, the calculated LODs are in the low ppt range (gas phase concentration), showing the unique sensitivity of both ionization methods. This corresponds to absolute detection limits in the lower femtogram range.

To the best of our knowledge, there are only very few reports on CWA related substances using direct MS detection. For the most part, the results do not even approach these low ppt detection levels. For example, for the pesticides dichlorvos, malathion, and phoxim, we found LODs of 8.4, 4.1, and 2.2 ppt for DBDI and 20.9, 3.5, and 8.1 ppt for SESI, respectively. This is far better than current reports on, e.g., dichlorvos detection with LC-MS/MS analysis in aqueous samples showing LODs of around 100 ppt[20] or 700 ppt for GC/MS,[21] especially when taking into account that our results are based on direct MS/MS quantification without any chromatographic enrichment. Since dichlorvos and phoxim are structurally closely related to (((2-chloroethoxy)-fluoro-hydroxy-phosphinyl)oxy)carbonimic-chloridefluoride, alias agent A230 (a suspected "new" nerve agent),[22] one can reasonably assume the suitability of the active capillary DBDI-MS/MS or SESI-MS/MS for the direct detection and quantification of these agents. There is a recent report by Seto et al.[23] on intact chemical warfare agents, which presented LODs in the sub $\mu g/m^3$ range, i.e., close to ours. For this study, they used direct MS/MS or MS/MS/MS detection with a counterflow APCI on a comparable ion trap instrument. However, their reported calibration concentrations (mg/m^3) are more than 3 orders of magnitude above the reported LODs ($\mu g/m^3$), and their linear regressions either included the origin (e.g., single point MS^3 calibration for sarin with R^2 = 1.0) or may even have been forced through it (e.g., two-point MS^2 calibration for chloropicrin with R^2 = 0.9994). Moreover, the calibration ranges presented were very narrow, hardly spanning 1−2 orders of magnitude. Therefore, their findings remain somewhat inconclusive. For our results, the multiple orders of magnitude in concentration range produce errors in the linear regression intercept as shown in Table 1. As the absolute sensitivity for each substance is represented more directly by

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the linear regressions slope, further discussion on sensitivity will be based on the slope rather than the calculated LOD, which is strongly influenced by the intercept. The highest sensitivity in our experiments was found for the pesticide malathion (around 20 000 counts/ppt). Assuming one ion per count, this would correspond to a total detection efficiency of 3×10^{-5} for all introduced molecules, which includes not only the ionization efficiency but also the quadrupole and octapole transmission, the trapping time, and the fragmentation and detection by MS/MS. DBDI generally was slightly more sensitive than SESI; however, significant sensitivity differences for both methods were observed. For example, for the sulfur mustard related substances TDG and CEES, SESI was slightly more sensitive, and for the pesticides DCV and PHX, the response was quite different for both systems. In general, the sensitivity seems related to the size/cross section and hydrophobicity of the molecule. DMMP, TDG, and CEES are the smallest molecules, which express the lowest slopes, whereas malathion is ionized with the highest efficiency as it has the largest cross section. Although there are some initial insights,[24] further investigations into the DBDI and SESI ionization mechanism may be necessary to clarify these observed differences and commonalities and the extraordinary sensitivity.

Analysis of the Intact CWA Sarin. Besides the structurally related compounds, a sample of an intact warfare agent was also included in this study. The G-series nerve agent sarin was chosen as an example to demonstrate the applicability of this system for intact nerve agents. Figure 4 depicts the MS and

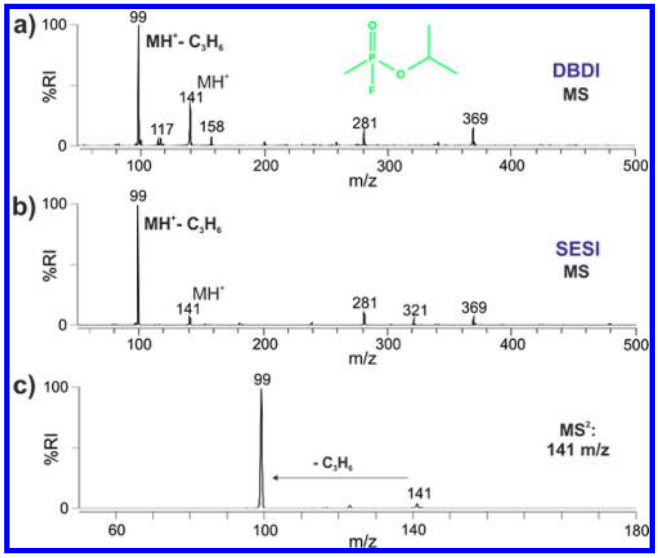

Figure 4. MS and MS/MS (c) spectra and molecular structures (green) for a concentration of 500 ppt Sarin (GB) acquired with DBDI (a) and SESI (b). Spray voltage was 2.7 kV for SESI, and DBDI voltage amplitude was 1.6 kV p-p. Isolation window width for MS^2 experiments was 1.0 m/z.

MS^2 spectra acquired by means of DBDI and SESI for a 500 ppt sample concentration. For both methods, the most abundant peak is at 99 m/z, which corresponds to $CH_3P(OH)_2F^+$, the main fragment of sarin. This fragmentation is due to elimination of an isopropyl group, which was also observed for DIMP, as mentioned above. This therefore proves DIMP to be the CWA simulant most closely reassembling sarin for this study. The molecular ion MH^+ was also present in both spectra with a relative intensity of 43% for DBDI and 12% for SESI, respectively. For DBDI, a sarin–water cluster $M^{+\bullet} + H_2O$ was observed at 158 m/z as well. Therefore, we conclude that in this case active capillary DBDI is a softer ionization method than SESI. For both sources, other related signals were present at 281 m/z and 369 m/z, but these were more intense for DBDI. The 281 m/z corresponds to the dimer $2MH^+$ whereas the 369 m/z was identified to be a sarin adduct with the previously mentioned plasticizer dibutylmaleate (228.28 g/mol). The ion observed at 369 m/z was identified as a DBM-H^+ adduct to a neutral sarin molecule (140.09 g/mol). Relative to the 229 m/z signal (100% RI), only a minor amount of 141 m/z (6% RI) was found as CID fragments of 369 m/z. Further MS^2 spectra of the MS signals discussed here are available in the Supporting Information as SFigures 2–4.

To determine the sensitivity, a SRM-based calibration was performed for sarin on the transition of 141 m/z to 99 m/z, for both ionization methods. For DBDI, a slope of 300 ± 4 with an intercept of 6571 ± 4225 (calibration range 7.4–2452 ppt, m = 3, n = 6, R^2 = 0.9998) was found, resulting in an LOD of 22.6 ppt. With SESI, a slope of 136 ± 5 with an intercept of 24 174 ± 50 836 (calibration range 24–24 523 ppt, m = 3, n = 7, R^2 = 0.9926) and an LOD of 188 ppt was achieved. In comparison with DBDI, the higher detection limit for SESI is due to the reduced generation of MH^+ in the source and therefore a reduced MS^2 signal intensity. Nevertheless, both methods proved to be suited for the direct detection and quantification of intact nerve agents. For MS^2-based detection of sarin, DBDI proved to be more sensitive as it provided softer ionization conditions.

CONCLUSIONS

In the current report, we demonstrated the direct MS-based quantification of intact CWAs, precursors, and degradation products, as well as structurally related components at low ppt levels. For sample generation, a heat-assisted nanospray evaporation setup was constructed, which could continuously and reproducibly provide defined ppt to ppb concentrations for all CWA related compounds. The two ionization methods compared in this study were the active capillary plasma ionization (DBDI) and secondary electrospray ionization (SESI). Overall, both ionization sources exhibited a comparable performance and LODs ranging from 1.4 to 58.4 ppt for DBDI and 1.1 to 188 ppt for SESI, respectively. In most cases, the active capillary source provided a larger linear dynamic range (>3 orders of magnitude), as well as a more robust and softer ionization, which led to an overall more sensitive detection. Our results show that, out of the commonly used simulants, DIMP mimicked the fragmentation behavior of sarin most closely. For the detection of the intact warfare agent sarin, we found MS^2 detection limits of 22.6 ppt for DBDI and 188 ppt for SESI. This emphasizes the applicability of both ionization techniques for the direct and sensitive detection of chemical warfare agents in the gas phase. Since the combination of the active capillary plasma ionization source with a portable MS (Mini 10.5, Aston Laboratories) was already shown in a previous report,[13] our findings may help to overcome the sensitivity limitations of actual portable mass spectrometers and contribute to a possible on-site and real-time identification and quantification of CWAs and their related compounds. Finally, the versatility, robustness, soft ionization, and extraordinary sensitivity (few femtograms) shown here also emphasize the use of the active capillary plasma ionization for many other possible applications.

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■ ASSOCIATED CONTENT

Supporting Information

Additional information on the molecular structures, MS and MS^2 spectra, and calibration curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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