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Scrubbing Ions with Molecules: Kinetic Studies of Chemical Noise Reduction in Mass Spectrometry Using Ion−Molecule Reactions with Dimethyl Disulfide

Michael J. Y. Jarvis,[†] **Gregory K. Koyanagi,**[†] **Xiang Zhao,**[†] **Thomas R. Covey,**[‡] **and Diethard K. Bohme***[,†]

Department of Chemistry, Centre for Research in Mass Spectrometry, York University, Toronto, ON, Canada M3J 1P3, and MDS Sciex, 74 Four Valley Drive, Concord, ON, Canada L4K 4V8

The kinetics and product distributions of the reactions of dimethyl disulfide (DMDS) have been investigated with a group of chemical background ions commonly observed in atmospheric pressure ionization (API) mass spectrometry (MS) in order to assess the value of this molecule in filtering (or "scrubbing") these ions by changing their mass/charge (m/z) ratio. The measurements were taken with a novel electrospray ionization/selected ion flow tube/QqQ tandem mass spectrometer. The background ions studied include those with m/z 42 (protonated acetonitrile, ACN), 83 (protonated ACN dimer), 99 (protonated phosphoric acid), 117 (water cluster of m/z 99), 131 (methanol cluster of m/z 99), 149 (protonated phthalic anhydride, formed from the phthalates), and 327 (protonated triphenyl phosphate). In addition, reactions of DMDS have been studied with two model analytes−protonated caffeine and doubly protonated bradykinin−in order to assess the selectivity of DMDS reactivity. All the measurements were taken at 295 ± 2 K in helium buffer gas at a pressure of 0.35 ± 0.01 Torr. DMDS was observed to react efficiently with m/z 42 ($ACNH^+$), 149 (from phthalates), and 99 (protonated phosphoric acid), with k/k_c = 0.91, 0.47, and 0.38, respectively. Only proton transfer was observed with $ACNH^+$, followed by the secondary reaction of $[DMDSH]^+$ with DMDS to yield $[CH_3S-S(CH_3)-SCH_3]^+$. Ligation of DMDS was the dominant primary channel observed for the reaction of the m/z 149 background ion; however, some proton transfer also was observed. Both of these primary product ions react further with DMDS to yield $[CH_3S-S(CH_3)-SCH_3]^+$, the structure of which we have determined computationally using DFT calculations. Only the sequential ligation with two DMDS molecules was observed for the reaction of the m/z 99 ion. Reactions of DMDS with m/z 117 $[H_3PO_4 + H + H_2O]^+$ and m/z 131 $[H_3PO_4 + H + MeOH]^+$ were observed to proceed with k/k_c = 0.71 and 0.058, respectively. Ligand substitution of DMDS for H_2O predominated (~94%) over DMDS ligation (~6%) in the reaction with m/z 117, while only DMDS ligation was observed for the reaction of m/z 131 with DMDS. In contrast, the reactions of DMDS with ions of m/z 83 (protonated dimer of ACN) and 327 (protonated triphenyl phosphate) were extremely inefficient, with k/k_c = 0.0042 and 0.0079, respectively. The higher reactivity of DMDS toward $ACNH^+$ (m/z 42) compared to $(ACN)_2H^+$ (m/z 83) is attributed to the lower proton affinity of the unsolvated ACN. The reactivity of DMDS toward the two model analyte ions studied−protonated caffeine and doubly protonated bradykinin−was negligible, with k/k_c = 0.0073 and 0.010, for the respective reactions. These results suggest that, under appropriate reagent pressure conditions, DMDS can be an appropriate reagent for chemically filtering out many common API-MS background ions, without significantly affecting the observed intensity of analyte peaks.

Selective ion−molecule reactions have long been used as tools to aid in the elucidation of ion structures in solution[1,2] and in the gas phase.[3,4] The most well-known of these is the hydrogen−deuterium exchange reaction;[5] however, many other selective derivatization reactions[6,7] also have been used to identify specific functional groups contained in analyte ions. Selective reactions involving dimethyl disulfide (DMDS) have proven to be useful for identifying a number of structural features in analyte ions. For example, selective derivatization reactions of DMDS have previously been used to screen for the presence of the primary *N*-oxide functionality.[8] In addition, reactions of either dimethyl disulfide

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* Corresponding author: (e-mail) dkbohme@yorku.ca.
[†] York University.
[‡] MDS Sciex.

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or dimethyl diselenide have been used to differentiate between distonic radical cations and conventional radical cations in the gas phase.[9,10] Recently, Guo et al. have suggested[11] that the selective reactivity of dimethyl disulfide can be harnessed in order to react out undesirable chemical background ions that are commonly observed in both electrospray ionization[12,13] (ESI) and atmospheric pressure chemical ionization[14] (APCI) mass spectrometry. To demonstrate the potential of this approach, Guo et al. have studied the reactions of DMDS with various common chemical background ions, as well as many model analyte ions, using a modified triple quadrupole mass spectrometer. Using a "zero-neutral loss" scan, they filtered out any ions that experienced a shift in m/z upon reaction with DMDS.

In this work, motivated by the results reported by Guo et al.,[11] we have studied the reaction chemistry and kinetics for reactions of various chemical background ions with DMDS, using our novel electrospray ionization/selected ion flow tube/QqQ (ESI/SIFT/QqQ) tandem mass spectrometer. We have also measured the reactivity of DMDS with model analyte ions, to verify that DMDS does not react significantly with protonated analytes that are commonly studied by API-MS (both ESI-MS and APCI-MS). These are the first quantitative kinetic and product distribution measurements for such reactions. In addition, we have used computational quantum chemistry to provide insight into the structures and energies of some of the reaction products.

EXPERIMENTAL SECTION

All of the measurements reported in this work were obtained with the ESI/SIFT/QqQ tandem mass spectrometer, which has been described in detail recently.[15] The common chemical background ions studied were generated by electrospraying 30−70 μM solutions of the compounds of interest, which were diluted in water, methanol, or acetonitrile. Ions are mass analyzed with a quadrupole mass filter and injected through an aspirator-like interface into the flow tube, continuously flushed with helium buffer gas at 0.35 ± 0.01 Torr and 295 ± 2 K. The ions undergo $\sim 10^5$ collisions with He atoms prior to entering the reaction region of the flow tube, which ensures that they have reached a translational temperature equal to the tube temperature of 295 ± 2 K prior to reacting with DMDS.

DMDS vapor was diluted in He gas in a reservoir system and introduced via a needle valve into the reaction region of the flow tube. Downstream of the reaction region, a second quadrupole mass filter was used to monitor the intensities of reactant and product ions as a function of the flow of DMDS.

Table 1. Rate Coefficients (k)[a] and Reaction Efficiencies (k/k_c) Measured for Reactions of Various Chemical Background Ions with DMDS in Helium at 0.35 ± 0.01 Torr and 295 ± 2 K

reactant	m/z	k^b	$k_c{}^c$	k/k_c
[phthalic anyhdride + H]$^+$	149	7.5×10^{-10}	1.6×10^{-9}	0.47
[triphenylphosphate + H]$^+$	327	1.1×10^{-11}	1.4×10^{-9}	0.0079
$[H_3PO_4]H^+$	99	6.8×10^{-10}	1.8×10^{-9}	0.38
$[H_3PO_4]H^+(H_2O)$	117	1.2×10^{-9}	1.7×10^{-9}	0.71
$[H_3PO_4]H^+(CH_3OH)$	131	9.9×10^{-11}	1.7×10^{-9}	0.058
$[CH_3CN + H]^+$	42	2.1×10^{-9}	2.3×10^{-9}	0.91
$[(CH_3CN)_2 + H]^+$	83	7.6×10^{-12}	1.8×10^{-9}	0.0042
[caffeine + H]$^+$	195	1.1×10^{-11}	1.5×10^{-9}	0.0073
[bradykinin + 2H]$^{+2}$	531	2.6×10^{-11}	2.6×10^{-9}	0.010

[a] In units of cm^3 molecule^{-1} s^{-1}. [b] The estimated uncertainty is ±30%. [c] k_c is the collision rate coefficient calculated using the algorithm of the modified variational transition-state/classical trajectory theory developed by Su and Chesnavich.[19]

Rate coefficients for the primary reactions of the reactant (chemical background) ions with DMDS are determined with an uncertainty of ±30% from the rate of decay of the reactant ion intensity using pseudo-first-order kinetics.[16,17] Higher-order rate coefficients may be obtained by fitting the experimental data to the solutions of the system of differential equations for sequential reactions.

Dimethyl disulfide (99.0+%) was obtained from Sigma-Aldrich Co. and used without further purification.

RESULTS AND DISCUSSION

In this work, we have investigated the reaction chemistry and kinetics for reactions of DMDS with several of the most common API-MS chemical background ions, as well as some model analyte ions. In addition, we have used computational quantum chemistry to provide insight into the structures and energies of some of the reaction products.

There are many sources of chemical background ions in API-MS experiments, including both ionized contaminants (or their fragments) and stable solvent "cluster" ions.[18] For this exploratory investigation, we have focused specifically on a small group of common background ions, which include the following: an ion with m/z 149, formed from phthalates; the protonated triphenyl phosphate ion (m/z 327); the $[H_3PO_4 + H]^+$ ion (m/z 99); stable "cluster" ions involving water, methanol, and acetonitrile. All of these ions were generated by ESI from 30 to 70 μM solutions in water, methanol, or acetonitrile and injected directly into the flow tube at 0.35 Torr and 295 ± 2 K, where they were allowed to react with a controlled amount of the DMDS reagent, introduced via a needle valve.

The results of the rate coefficient (k) measurements are shown in Table 1, along with calculated reaction efficiencies given as k/k_c (where k_c is the capture or collision rate coefficient). The collision

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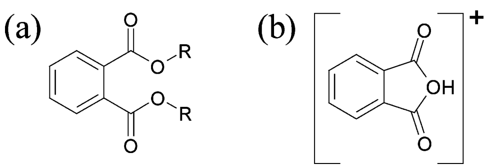

Figure 1. (a) Chemical structures of the phthalates. For phthalic acid, R = H. (b) Common API-LC/MS chemical background ion (protonated phthalic anhydride) with *m*/*z* 149, formed from the phthalates.

Table 2. Proton Affinities[a] (PA) of Some Molecules Commonly Observed as Protonated Background Ions in API-LC/MS Experiments[b]

chemical name	PA[c]
phthalic anyhdride	unknown
acetonitrile	186
phosphoric acid	197 (expt), 199 (comp)[d]
acetonitrile dimer	unknown
(3(5)-methylpyrazole)	216
(4-methylpyrazole)	217
(1-methylpyrazole)	218
(1-methylimidazole)	229
(4-methylimidazole)	228
(2-methylimidazole)	230
triphenylphosphate	230[e]
dimethyl disulfide	195

[a] In kcal mol^{-1}. [b] Several isomers of methylpyrazole and methylimidazole are included because these have the same chemical composition as the acetonitrile dimer ($C_4H_6N_2$), which is commonly observed as a protonated background ion. The proton affinity of DMDS is given, for comparison. [c] PA values are from ref 21, unless otherwise indicated. [d] From ref 28. [e] From ref 27.

rate coefficient (k_c) has been calculated using the algorithm of the modified variational transition-state/classical trajectory theory developed by Su and Chesnavich.[19] Values of α(DMDS) = 10.51 Å^3 and μ_D(DMDS) = 1.95 D were used for the polarizability and dipole moment, respectively. The empirical method proposed by Miller and Savchik[20] was used to calculate the average molecular polarizability of DMDS. For the reactions studied here, the values of k_c range from 1.4×10^{-9} to 2.6×10^{-9} cm^3 molecule^{-1} s^{-1}.

Reaction of DMDS with the *m*/*z* 149 Background Ion, Formed from Phthalates. The background ion at *m*/*z* 149 (see Figure 1b) is formed from the family of compounds known as the phthalates (Figure 1a) and is formally known as phthalic anhydride. To generate the ion for these experiments, a solution containing ~50 μM phthalic acid (R = H in Figure 1a) was used. The efficiency of the reaction of the *m*/*z* 149 background ion with DMDS was determined to be $k/k_c = 0.47$. Two primary channels were observed. The dominant channel (81%) was addition of DMDS to yield the cluster ion, with *m*/*z* 243. A lesser channel (19%) was proton transfer from protonated phthalic anhydride (PHANH$^+$), to yield the protonated DMDS ion, with *m*/*z* 95. The proton affinity (PA) of phthalic anhydride is unknown, but PA(DMDS)[21] = 195 kcal mol^{-1}, so we can assume that PA(phthalic anhydride) < 195 kcal mol^{-1}. For a complete summary of proton affinities of the chemical species studied in this work, see Table 2. Both of the observed product ions reacted further with DMDS to generate an ion with *m*/*z* 141, which corresponds to a singly charged ion with the chemical composition of trimethyl trisulfide, $(CH_3)_3S_3$ (TMTS$^+$). (Note that reaction 3 has been reported previously.[8]) The measured experimental reaction profiles for the reaction of DMDS with protonated phthalic anhydride (*m*/*z* 149) is given in Figure 2A. The solid lines represent kinetic fits to the experimental data. The reaction sequence is given by reactions 1–3:

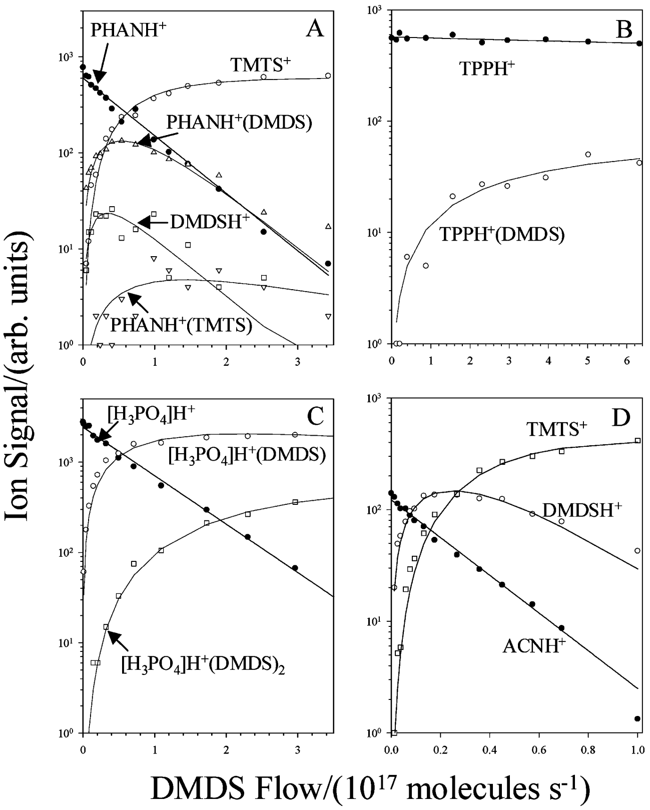

Figure 2. Measured ion profiles for the reactions of common MS chemical background ions with DMDS, at 295 ± 2 K in helium buffer gas at a pressure of 0.35 ± 0.01 Torr. The ion signal (*y*-axis) is given as a function of flow of DMDS (*x*-axis) in units of molecules per second. The solid lines represent kinetic fits to the experimental data. (A) *m*/*z* 149 ion, protonated phthalic anhydride, PHANH$^+$, formed from phthalates; (B) *m*/*z* 327 ion, protonated triphenyl phosphate, TPPH$^+$, (C) *m*/*z* 99 ion, protonated phosphoric acid, $[H_3PO_4]H^+$, (D) *m*/*z* 42 ion, protonated acetonitrile, ACNH$^+$.

$$\mathrm{PHANH^+ + DMDS \rightarrow PHANH^+(DMDS)} \quad (1a)$$

$$\mathrm{\rightarrow DMDSH^+ + PHAN} \quad (1b)$$

$$\mathrm{PHANH^+(DMDS) + DMDS \rightarrow TMTS^+ + (PHAN + CH_3SH)} \quad (2)$$

$$\mathrm{DMDSH^+ + DMDS \rightarrow TMTS^+ + CH_3SH} \quad (3)$$

We have performed quantum chemical calculations to provide some insight into the energetics of reaction 3 and the structure of the product ion with *m*/*z* 141. All calculations were performed

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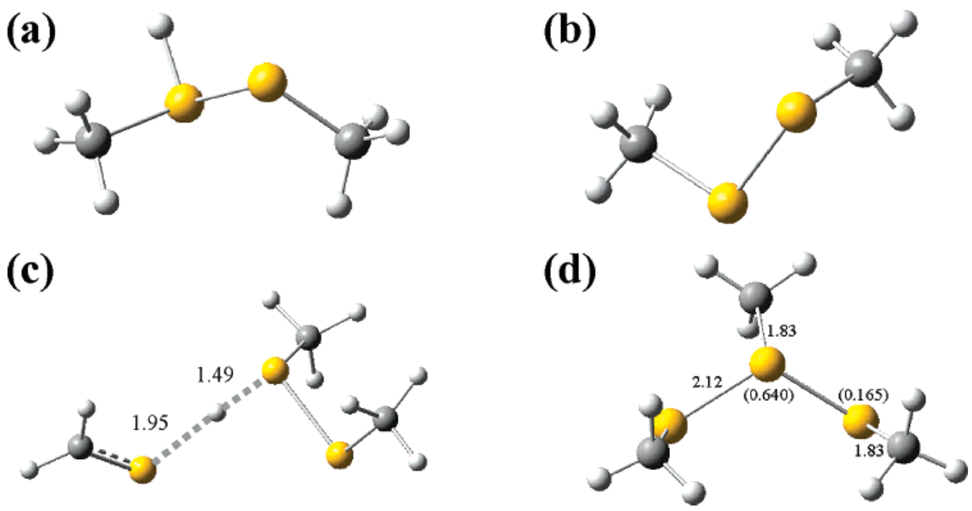

Figure 3. Computed minimum energy structures using the B3LYP (Becke-3 Lee−Yang−Parr) hybrid functional at the 6-311++G(d,p) level of theory. (a) Protonated DMDS. (b) Neutral DMDS. (c) Possible (higher-energy) structure for the product ion at *m*/*z* 141 with the chemical formula $(CH_3S)_3$. This structure is 15.1 kcal mol^{-1} higher in energy than that shown in (d), and the overall reaction to generate this product is endothermic by 7.4 kcal mol^{-1}. (d) Lowest energy structure for the $(CH_3S)_3$ product ion at *m*/*z* 141. The overall reaction to generate this ion (from (a) and (b)) has an enthalpy of $\Delta H_0 = -7.7$ kcal mol^{-1}. The neutral product that is also formed in this reaction (not shown here) is CH_3SH.

Table 3. Computed Energetics[a] for Reactants Products Involved in the Reaction $[(CH_3S)_2 + H]^+ + (CH_3S)_2 \rightarrow CH_3SH + (CH_3S)_3^+$

structure	energy (hartrees)
$H_3C{-}S{-}S{-}CH_3$	−876.210 154
$[H_3C{-}SH{-}S{-}CH_3]^+$	−876.512 353
$[H_3C{-}S{-}S(CH_3){-}S{-}CH_3]^+$	−1314.037 169
$(H_2C{-}S)\cdots H^+\cdots(CH_3{-}S{-}S{-}CH_3)$	−1314.013 047
$H_3C{-}SH$	−438.697 605

[a] All calculations were are performed with the B3LYP hybrid density functional method, using the 6-311++G(d, p) basis set. All stationary points were characterized by harmonic vibrational frequency calculations and these established that all the reported structures (see Figure 3) are at minimums.

with the B3LYP hybrid density functional method[22,23] and achieved with the Gaussian 03 suite of programs.[24] In all cases, the thermochemistry calculated here has been corrected for zero-point energy effects. The 6-311++G(d, p) basis set[25,26] was used for all of the elements. All stationary points were characterized by harmonic vibrational frequency calculations, and these established that all the reported structures are at minima. The computed structures are shown in Figure 3, and all calculated energies are tabulated in Table 3. Our calculations indicate that the lowest energy isomer of the $TMTS^+$ product ion has the chemical structure $[CH_3S{-}S(CH_3){-}SCH_3]^+$ (see Figure 3d). An alternate structure corresponding to the proton-bound cluster of CH_2S and DMDS ($CH_3S{-}SCH_3$) has been calculated to be 15.1 kcal mol^{-1} higher in energy (see Figure 3c). The overall reaction leading to the formation of the lower-energy structure has been calculated to have a reaction enthalpy of $\Delta H_0 = -7.7$ kcal mol^{-1} (reaction 4) while the overall reaction 5 leading to the formation of the proton-bound species is calculated to be endothermic, with $\Delta H_0 = 7.4$ kcal mol^{-1}.

$$[CH_3SSCH_3 + H]^+ + CH_3SSCH_3 \rightarrow [CH_3SS(CH_3)SCH_3]^+ + CH_3SH \quad (4)$$

$$[CH_3SSCH_3 + H]^+ + CH_3SSCH_3 \rightarrow [CH_2S{-}H{-}CH_3SSCH_3]^+ + CH_3SH \quad (5)$$

Reaction of DMDS with the *m*/*z* 327 (Triphenyl Phosphate + H)$^+$ Background Ion. The familiar chemical background ion at *m*/*z* 327 is the singly protonated form of the triphenyl phosphate molecule, $TPPH^+$ (see Figure 4a). This molecule is very commonly used as a plasticizer and a flame retardant in many polymers and films and thus finds it way into many MS samples via leaching from plastic containers, tubing, etc., and so the *m*/*z* 327 ion is often observed as a significant peak in LC−MS experiments.[18] To generate $TPPH^+$ for our

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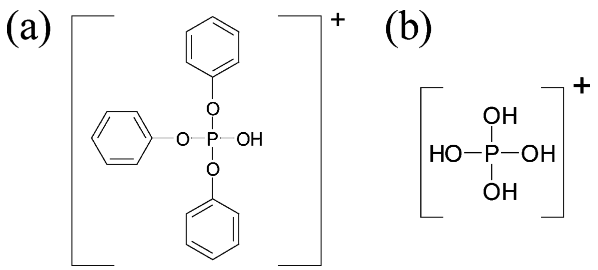

Figure 4. API-LC/MS chemical background ions originating from triphenyl phosphate, commonly used as a plasticizer additive and a flame retardant (a) Protonated triphenylphosphate (*m*/*z* 327). (b) $[H_3PO_4 + H]^+$ background ion (*m*/*z* 99), resulting from the sequential loss of phenyl groups from protonated triphenyl phosphate.

experiments, we prepared a solution of ~50 μM triphenylphosphate dissolved in acetonitrile, water, and methanol containing 1% formic acid. The reaction of DMDS with $TPPH^+$ was observed to be slow compared to some of the other reactions studied in this work, with a measured reaction efficiency of $k/k_c = 0.0079$. Only clustering of DMDS, reaction 6, was observed.

$$TPPH^+ + DMDS \rightarrow TPPH^+(DMDS) \qquad (6)$$

At the pressure of the buffer gas in these experiments, reaction 6 is likely to proceed in a termolecular fashion with He atoms acting as the third body. The large difference in the PA of DMDS (PA = 195 kcal mol^{-1})[21] and triphenyl phosphate (PA = 230 kcal mol^{-1})[27] precludes the possibility of an exothermic proton-transfer reaction. Figure 2B shows the measured experimental profile of reactant and product ion intensities for the reaction of protonated triphenyl phosphate with DMDS. Solid lines represent kinetic fits to the experimental data.

Reaction of DMDS with the *m/z* 99 (H_3PO_4 + H)$^+$ Background Ion, Derived from Triphenyl Phosphate. The sequential loss of phenyl groups from the triphenyl phosphate molecule, discussed above, leads to the formation of stable fragment molecules, which may also appear as protonated impurity ions in typical mass spectra.[18] The $[H_3PO_4]H^+$ ion with *m*/*z* 99 is a protonated fragment of triphenyl phosphate (see Figure 4b), which is derived from the loss of three phenyl groups. Under the correct declustering conditions, this impurity ion can be more intense than its progenitor at *m*/*z* 327 in API-LC/MS experiments. In this work, we have generated the $[H_3PO_4]H^+$ ion from a dilute (~1.5%) solution of phosphoric acid in water and methanol. Upon reaction with DMDS, the $[H_3PO_4]H^+$ ion rapidly clusters with the reagent molecule to form the $[H_3PO_4]H^+$(DMDS) product ion at *m*/*z* 193. The effective bimolecular reaction efficiency of this reaction, reaction 7, was determined to be $k/k_c = 0.38$.

$$[H_3PO_4]H^+ + DMDS \rightarrow [H_3PO_4]H^+(DMDS) \qquad (7)$$

This primary product ion was observed to cluster more slowly with a second DMDS molecule, resulting in the formation of a $[H_3PO_4]H^+(DMDS)_2$ product ion at *m*/*z* 287. Morizur et al.[28] reported an experimental value for $PA(H_3PO_4)$ = 197 kcal mol^{-1} and a theoretical (computed) value for $PA(H_3PO_4)$ = 199 kcal mol^{-1}. The known proton affinity of DMDS is lower (PA = 195 kcal mol^{-1}),[21] and so the bimolecular proton transfer from phosphoric acid to DMDS is thermodynamically forbidden. The measured reaction profile for the reaction of $[H_3PO_4]H^+$ with DMDS is shown in Figure 2C, where the solid lines represent kinetic fits to the experimental data.

Under low declustering conditions, it is quite common to also observe clusters of background ions with one or more solvent molecules. For this reason, we have also investigated the reactivity of DMDS toward clusters of the $[H_3PO_4]H^+$ ion with the common HPLC solvents methanol and water. Both the $[H_3PO_4]H^+(H_2O)$ and $[H_3PO_4]H^+(CH_3OH)$ ions were generated, and mass selected, from the same solution that was used to produce the $[H_3PO_4]H^+$ ion.

Upon being introduced to DMDS, the $[H_3PO_4]H^+(H_2O)$ impurity ion at *m*/*z* 117 was observed to react almost exclusively by fast, bimolecular ligand switching of DMDS with H_2O, reaction 8, with a measured reaction efficiency of $k/k_c = 0.71$.

$$[H_3PO_4]H^+(H_2O) + DMDS \rightarrow [H_3PO_4]H^+(DMDS) + H_2O \qquad (8)$$

A very small amount of clustering of DMDS also was observed, producing the $[H_3PO_4]H^+(H_2O)(DMDS)$ ion at *m*/*z* 211. As observed in our previous experiment, the principal primary product ion, the $[H_3PO_4]H^+$(DMDS) ion at *m*/*z* 193, clusters with a second DMDS molecule to produce $[H_3PO_4]H^+(DMDS)_2$ with *m*/*z* 287.

The reaction of the cluster ion $[H_3PO_4]H^+(CH_3OH)$ with DMDS was significantly slower than that of the H_2O-containing cluster ion, with a measured reaction efficiency of $k/k_c = 0.058$, and proceeds only by termolecular clustering of DMDS to produce the $[H_3PO_4]H^+(CH_3OH)(DMDS)$ ion at *m*/*z* 225. No bimolecular ligand switching of DMDS with MeOH was observed.

Reaction of DMDS with [ACN + H]$^+$ (*m/z* 42) and [2ACN + H]$^+$ (*m/z* 83). The protonation of acetonitrile (ACN), a common electrospray ionization solvent, leads to the observation of impurity ions with *m*/*z* 42, $ACNH^+$, and *m*/*z* 83 $(ACN)_2H^+$ in many mass spectra. To generate these ions for this study, a water/acetonitrile/formic acid (50:50:0.1%, v) solution was electrosprayed. The protonated acetonitrile monomer was observed to react readily with DMDS under our experimental conditions according to reaction 9 (see Figure 2D), with $k/k_c = 0.91$.

$$ACNH^+ + DMDS \rightarrow DMDSH^+ + ACN \qquad (9)$$

Proton transfer was the only primary reaction channel that was observed, in agreement with previous observations which did not include a rate coefficient.[8] This proton-transfer reaction is expected based on the known PA of the two neutral species, PA(ACN)[21] = 186 kcal mol^{-1}, and PA(DMDS)[21] = 195 kcal mol^{-1}. Protonated DMDS was then observed to react quickly with a second DMDS molecule to generate a secondary product ion with *m*/*z* 141, as has been observed previously.[8] As discussed above, our calcula-

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$$\begin{tikzcd}
MH^{+}\cdot S \arrow[r, dashed, "PA_{sol}"] & M\cdot S + H^{+} \arrow[d, dashed, "D(M\text{-}S)"] \\
MH^{+} \arrow[u, dashed, "-D(MH^{+}\text{-}S)"] \arrow[r, "PA"'] & M + H^{+}
\end{tikzcd}$$

Figure 5. Schematic representation of the relationship between the proton affinity of a bare (unsolvated) molecule, M, and that of the solvated molecule, M•S, where S represents a solvent molecule. In general, the presence of a solvent molecule will cause an increase in the proton affinity, i.e., $PA_{sol} > PA$, since $D(MH^{+}-S) > D(M-S)$.

tions indicate that this secondary product ion has the chemical structure $[CH_3S-S(CH_3)-SCH_3]^+$.

In sharp contrast with the reactivity of the protonated acetonitrile monomer, the protonated dimer ion $(ACN)_2H^+$ with m/z 83 exhibited very little reactivity toward DMDS. A small amount of clustering with DMDS was observed, resulting in the formation of the m/z 177 ion, which in turn reacted to give the secondary product $[CH_3S-S(CH_3)\text{-}SCH_3]^+$ with m/z 141, however the reaction efficiency was measured to be only $k/k_c = 0.0042$. The significant difference in reactivity of the m/z 42 $ACNH^+$ ion and the m/z 83 $(ACN)_2H^+$ ion is most likely caused by a known "solvent effect" - an increase in the PA of any species, upon solvation. In general, the solvation energy of a protonated species, $D(MH^+\text{-}S)$, is larger than that of the corresponding neutral species, $D(M-S)$, owing to the additional charge/dipole and charge/induced-dipole interactions. Consequently, the PA of the solvated species must be higher than that of the neutral species. The appropriate thermodynamic cycle is illustrated in Figure 5 from which it is apparent that

$$PA_{sol} = PA + D(MH^+-S) - D(M-S) \tag{10}$$

If the PA of the acetonitrile dimer (a "self-solvated" acetonitrile molecule) is more than 9 kcal mol^{-1} higher than that of the acetonitrile monomer (PA = 186 kcal mol^{-1}),[21] then the transfer of a proton to DMDS is an endothermic reaction. If such is the case, we would not expect DMDS to exhibit a high degree of reactivity toward the protonated acetonitrile dimer, which is in agreement with the experimental observation.

Alternatively, the striking difference in reactivity of $ACNH^+$ and $(ACN)_2H^+$ may be indicative of an appreciable difference in structure between these two ions. In actual fact, there are more than a half-dozen possible, stable structures having the chemical formula $C_4H_6N_2$, many of which are cyclic, and include several isomers of both methylimidazole (PA range = 227−230 kcal mol^{-1})[21] and methylpyrazole (PA range = 216−218 kcal mol^{-1}).[21] If the m/z 83 chemical background ion is in fact the protonated form of one of these molecules, then there is no reason to assume that its chemical reactivity with DMDS should parallel that of protonated acetonitrile, especially since the proton-transfer reaction to DMDS would be endothermic by more than 20 kcal mol^{-1}.

Reactions of DMDS with sample analyte ions. If a neutral reagent molecule is to be used to eliminate chemical background ions in mass spectrometry, its reactivity must be selective, and limited only to background ions, not analyte ions. Therefore, in order to properly assess the potential of reactions with dimethyl disulfide (DMDS) as a means of "scrubbing" chemical background ions, it is necessary to convince ourselves that DMDS does not react significantly with protonated analytes that are commonly studied using Atmospheric Pressure Ionization (API). In this work, we have investigated the reactivity of DMDS toward two compounds that serve as models of common protonated analytes: protonated caffeine, and doubly protonated bradykinin.

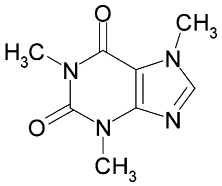

Figure 6. Chemical structure of caffeine, used in this study as a model analyte. The protonated caffeine molecule has a mass/charge ratio of 195.

The structure of the caffeine molecule is shown in Figure 6. The protonated caffeine ion was electrosprayed from a 50 μM solution in water/methanol/formic acid (50:50:0.1% vol). Although a very small decay in the intensity of the protonated caffeine ion was observed upon reaction with DMDS, no product ions were detected. The reaction efficiency was measured to be only $k/k_c = 0.0073$.

Bradykinin is a model peptide, consisting of nine amino acids with the sequence arg − pro − pro − gly − phe − ser − pro − phe − arg. A 30 μM solution of bradykinin dissolved in methanol was electrosprayed, and the doubly protonated parent ion with m/z 531 was mass selected and reacted with DMDS. As with protonated caffeine, a very small decay of the signal intensity of the (bradykinin + $2H)^{2+}$ parent ion was observed as the flow of DMDS was increased; however, no product ions were detected. The reaction efficiency was measured to be $k/k_c = 0.010$.

Although we have by no means conducted an exhaustive survey of all common LC−MS analytes, it is encouraging that the two examples that we have examined thus far have both proven to be quite unreactive toward dimethyl disulfide. Future work in our laboratory will be directed toward assessing the reactivity of a host of other common analyte ions toward DMDS. We aim to provide more conclusive, quantitative evidence to assess the possible use of selective ion−molecule reactions to "scrub" common MS chemical background ions.

CONCLUSIONS

In the work reported here, several ions that are commonly observed as chemical background in API-MS experiments have been generated by ESI. We have studied the reaction kinetics and product distributions for reactions of DMDS with these common MS chemical background ions using a selected ion flow tube operated at 295 ± 2 K and a helium buffer gas pressure of 0.35 ± 0.01 Torr. Our goal has been to assess the effectiveness of using ion−molecule reactions with DMDS to filter out chemical background ions, prior to sampling, by altering the m/z ratio of these ions. If a neutral reagent molecule is to be effective at scrubbing chemical background ions in mass spectrometry, it must be selective in its reactivity. Specifically, it must exhibit a high degree of reactivity toward chemical background ions and a low degree of reactivity toward analyte ions. This requirement poses quite a challenge since typical analyte and background ions possess a wide range of structural features.

The common MS chemical background ions investigated include those with *m/z* of 42 (protonated ACN), 83 (protonated ACN dimer), 99 (protonated phosphoric acid), 117 (water cluster of *m/z* 99), 131 (methanol cluster of *m/z* 99), 149 (protonated phthalic anhydride, formed from the phthalates), and 327 (protonated triphenyl phosphate). These chemical background ions originate from phthalates, plasticizer additives, and solvents present in the API-LC/MS mobile phase. Our measurements indicate reaction efficiencies ranging from 0.42% (for *m/z* 83) to 91% (for *m/z* 42). The various reaction channels observed include adduct formation, proton transfer, and ligand switching.

Of the background ions studied, we conclude that DMDS would be useful for the reactive removal of the ions having *m/z* 42, 99, 117 (*m/z* 99 + H_2O), 149, and to a much lesser extent *m/z* 131 (*m/z* 99 + CH_3OH). Reactions of DMDS are inefficient with the background ions having *m/z* 83 (the protonated dimer of ACN) and 327 (protonated triphenyl phosphate, commonly used as both a plasticizer additive and a flame retardant) and, thus, would be ineffective at removing these ions, except perhaps at high pressures of DMDS. At increased pressures of DMDS, slow termolecular reactions become more favorable, and thus, it may be possible to reactively alter the *m/z* of even those background ions that react inefficiently with DMDS, by judicious selection of the pressure conditions.

In several of the reactions studied, we have observed the formation of a secondary product ion with *m/z* 141, corresponding to a singly charged ion with the chemical composition $(CH_3)_3S_3$. From our kinetic profiles, it is clear that this product ion is produced from a secondary reaction of either protonated DMDS or the protonated DMDS–adduct of a reactant ion (e.g., [phthalic anhydride]H^+(DMDS), see Figure 2A). To gain insight into the structure of the product ion with *m/z* 141, we have performed quantum chemical calculations using the B3LYP hybrid density functional method and the Gaussian 03 suite of programs. Our calculations indicate that the lowest-energy isomer for the *m/z* 141 product ion has the chemical structure $[CH_3S{-}S(CH_3){-}SCH_3]^+$ (see Figure 3d), which is 15.1 kcal mol^{-1} lower in energy than an alternative structure consisting of a proton-bound cluster of CH_2S and DMDS. The formation of the lower-energy structure from the reaction of a DMDS molecule with a protonated DMDS molecule has been calculated to have a reaction enthalpy of $\Delta H_0 = -7.7$ kcal mol^{-1}.

We also have measured the reactivity of DMDS toward two model analytes—protonated caffeine and doubly protonated bradykinin—to investigate the selectivity of reactions of DMDS. For both of these model analytes, the measured reaction efficiencies with DMDS were quite low: $k/k_c = 0.0073$ and 0.010 for the reactions with (caffeine + H)$^+$ and (bradykinin + 2H)$^{+2}$, respectively. Although this does not by any means constitute a comprehensive survey of MS analytes, these early results support the idea that DMDS may be sufficiently selective in its reactivity to be useful for filtering out chemical background ions, prior to sampling, by reactively altering their *m/z*. This method of scrubbing impurity ions should prove effective for analysis of analyte ions with proton affinities larger than PA(DMDS) = 195 kcal mol^{-1}, such as the amino acids (PA range from 211 to >243 kcal mol^{-1})[29] and indeed most amines.

This work was inspired by a recent, complementary study published by Guo et al.,[11] who have reported qualitative measurements of the reactions of DMDS with a large number of chemical background ions. In their experimental setup, Guo et al. estimated the pressure of DMDS to be a few milliTorr—more than 1000 times higher than the typical reagent pressures used in our selected ion flow tube studies. In addition, the internal energy content of the reactants differs between the experiments of Guo et al. and those described in this study. In the former case, experiments were performed in a modified triple quadrupole mass spectrometer, with collision energies ranging from 3 to 5 eV, whereas in this study, all experiments were performed under thermal conditions. These differences in both DMDS pressure and internal energy may explain some of the discrepancies between the findings of these two studies.

For example, in this work we have measured the efficiencies of the reactions of DMDS with protonated triphenyl phosphate (*m/z* 327) and the protonated acetonitrile dimer (*m/z* 83) to be $k/k_c = 0.0079$ and $k/k_c = 0.0042$, respectively, and thus conclude that these ion–molecule reactions would not be useful for chemically reacting out the background ions. In contrast, Guo et al.[11] found that the protonated acetonitrile dimer ion (*m/z* 83) reacts to produce the $[CH_3S{-}S(CH_3){-}SCH_3]^+$ product ion (*m/z* 141) and that the protonated triphenyl phosphate ion (*m/z* 327) clusters with DMDS under the high reagent-pressure conditions of their experiments. Apparently even inefficient reactions of DMDS with background ions can be useful for reacting out chemical background ions under high-pressure conditions. Of course, it is important to recognize that reactions of DMDS with analyte ions will also become more significant at high DMDS pressures, and so we must expect some degree of analyte ion signal attenuation. Clearly, a balance must be struck between the desire to maximize the suppression of chemical background ions by *increasing* the reagent pressure and the need to minimize the extent of analyte ion signal attenuation by *decreasing* the reagent pressure.

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