Dimerization of ionized 4-(methyl mercapto)-phenol during ESI, APCI and APPI mass spectrometry

Lianming Wu,[a]* Marcos N. Eberlin,[b] Yuri E. Corilo,[b] David Q. Liu[a] and Hao Yin[c]

A novel ion/molecule reaction was observed to occur under electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and atmospheric pressure photo ionization (APPI) conditions, leading to dimerization of ionized 4-(methyl mercapto)-phenol followed by fast H. loss. The reaction is particularly favored during ESI, which suggests that this ion/molecule reaction can occur both in the solution inside the ESI-charged droplets and in the gas-phase environment of most other atmospheric pressure ionization techniques. The dimerization reaction is inherent to the electrolytic process during ESI, whereas it is more by ion/molecule chemistry in nature during APCI and APPI. From the tandem mass spectrometry (MS/MS) data, accurate mass measurements, hydrogen/deuterium (H/D) exchange experiments and density functional theory (DFT) calculations, two methyl sulfonium ions appear to be the most likely products of this electrophilic aromatic substitution reaction. The possible occurrence of this unexpected reaction complicates mass spectral data interpretation and can be misleading in terms of structural assignment as reported herein for 4-(methyl mercapto)-phenol. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: in-source dimerization; ion/molecule reaction; electrolytic oxidation; atmospheric pressure ionization; impurity analysis

Introduction

Chemical reactions are highly sensitive to structural changes in molecules and the presence, position and nature of functional groups. Ion/molecule reactions have therefore been studied extensively by mass spectrometry to characterize a myriad of reactant ions and neutral molecules.[1–5] These reactions performed in the diluted gas-phase environment of mass spectrometers have also provided access to intrinsic reactivities of naked molecules and ions and as such have contributed significantly to the elucidation of organic reaction mechanisms,[6] helping to bridge the gap between the gas-phase ion chemistry and the condensed-phase organic chemistry. The unexpected occurrence of such reactions is, however, undesirable when performing structural investigations of unknown molecules using mass spectrometry. The ion/molecule reaction products in the mass spectra may mislead the interpretation and lead to incorrect formula and structural assignments.

With the introduction of atmospheric pressure ionization techniques, including electrospray ionization (ESI),[7] atmospheric pressure chemical ionization (APCI),[8] atmospheric pressure photoionization (APPI),[9] sonic spray ionization (SSI)[10] and electrosonic spray ionization (ESSI),[11] it was found that these environments can favor the occurrence of ion/molecule reactions. For instance, several ion/molecule reactions such as the Meerwein reaction,[12] the Eberlin transacetalization reactions[13,14] and the reaction of the acetonyl anion with nitroaromatics,[15] could be performed at atmospheric pressure ionization environments. More recently, ion/molecule reactions were performed under the ambient environments using desorption electrospray ionization (DESI)[16] and desorption atmospheric pressure chemical ionization (DAPCI).[17] Furthermore, ion/molecule reactions via group transfer and dimer-

ization of the $C_{60}(CN)_2$ anion under the atmospheric pressure ionization conditions were also observed.[18] Herein we report the observation of an unexpected dimerization reaction (followed by fast H. loss) occurring during ESI, APCI and APPI of 4-(methyl mercapto)-phenol, an impurity identified in the synthesis of a pharmaceutical agent.

Experimental

Chemicals

An authentic sample of 4-(methyl mercapto)-phenol was purchased from Sigma-Aldrich (Milwaukee, WI, USA). The standard solution was prepared as 1 µg ml^{-1} in CH_3CN/H_2O (1 : 1).

Liquid chromatography-mass spectrometry

The liquid chromatography-mass spectrometry (LC-MS) experiments were performed on an Agilent 1100 LC system (Agilent Technologies, Wilmington, DE, USA) coupled to a Q-TOF Premier

* Correspondence to: Lianming Wu, Analytical Sciences, Chemical Development, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA. E-mail: lianming.2.wu@gsk.com

a Analytical Sciences, Chemical Development, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA

b ThoMSon Mass Spectrometry Laboratory, Institute of Chemistry, University of Campinas – UNICAMP, 13083-970, Campinas, São Paulo, Brazil

c Synthetic Chemistry, Chemical Development, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA

quadrupole orthogonal acceleration time-of-flight mass spectrometer with LockSpray™ controlled by MassLynx 4.1 (Waters Corporation, Manchester, UK). The LC autosampler injection volume was 10 μl. Chromatographic separation was achieved on a Luna C18 column (50 × 2.0 mm, 3 μm; Phenomenex, Torrance, CA, USA) with mobile phase A of 0.1% formic acid (FA) in water and mobile phase B of 0.1% FA in acetonitrile. When performing hydrogen/deuterium (H/D) exchange experiments, 0.1% FA in deuterated water (D_2O) was used replacing mobile phase A as described previously.[19] The column temperature was kept at 40 °C. The HPLC gradient was ramped linearly from 0% B to 95% B in 8 min with a flow rate of 1 ml min^{-1} directly into the APCI and APPI sources, while only 200 μl min^{-1} was split into the ESI source. All API sources were operated in the positive ion mode. The Q-TOF was calibrated with a sodium formate solution (0.01 mg ml^{-1}). Accurate mass measurements including the MS and M/MS experiments were obtained using the internal reference ion of *m/z* 556.2771 (protonated leucine-enkephalin) introduced via the Lockspray.

Gas chromatography-mass spectrometry

The gas chromatography-mass spectrometry (GC-MS) experiments were performed on an Agilent GC6890 coupled to an Agilent 5973 quadrupole mass selective detector with an electron ionization (EI) source or a chemical ionization (CI) source using methane as the reagent gas (Agilent, Palo Alto, CA, USA).

Nuclear magnetic resonance

The proton nuclear magnetic resonance (NMR) spectrum was obtained on a Bruker 300 NMR spectrometer (Bruker Instruments, Billerica, MA, USA).

Theoretical calculation

The energies as well as the charge and spin densities were calculated on the basis of density functional theory (DFT) using Becke's three-parameter hybrid functional with the Lee, Yang and Parr correlation (B3LYP) and 6-311G(d,p) basis set (i.e. DFT(B3LYP)/6-311G (d,p)).[20] Gaussian 03 (D.02) was used for all calculations.[21]

Results and Discussion

ESI, APCI and APPI MS of impurity I

During the analysis of a drug synthesis intermediate, an impurity (labeled as **I**) was detected by LC-MS. It was readily ionized using ESI and formed what appeared to be an abundant protonated molecule of *m/z* 279 (Fig. 1). Upon further analysis by APCI-MS and APPI-MS, it was found that, in addition to the ion of *m/z* 279, a minor ion of *m/z* 140 in the ESI-MS spectrum was now detected to be more abundant by APCI and APPI. The tandem mass spectrum for collision-induced dissociation (CID) of the ion of *m/z* 279 (Fig. 2(a)) shows no fragment ion of *m/z* 140, excluding the possibility of a precursor–product relationship between the ions of *m/z* 279 and *m/z* 140. The CID data also exclude an alternative interpretation where the ions of *m/z* 140 and *m/z* 279 can be a protonated molecule [M + H]$^+$ and its respective proton-bound dimer [2M + H]$^+$. Rather, these results suggest that the ions of *m/z* 140 and 279 arise from different molecules. However, the extracted ion
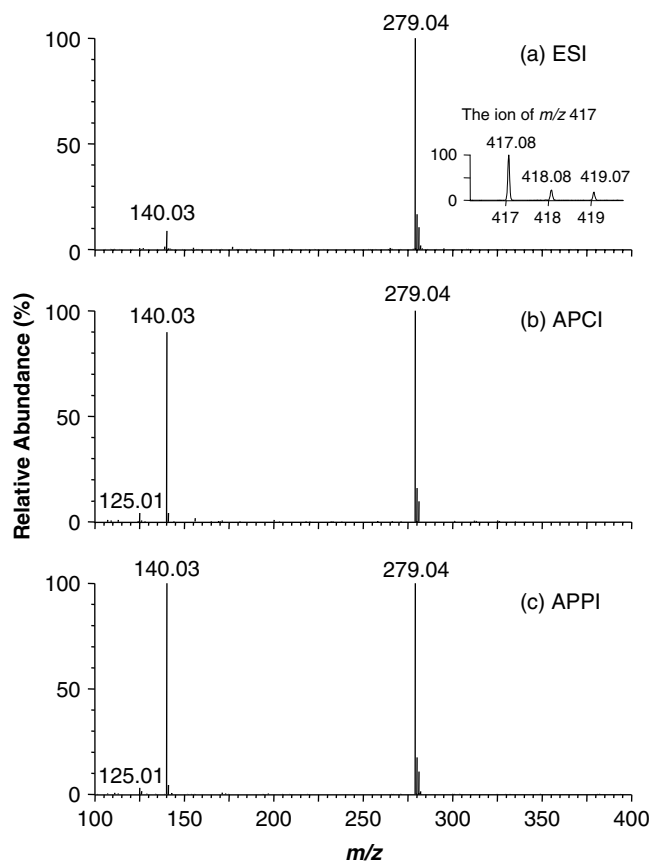
Figure 1. MS of impurity **I** by (a) ESI with spray voltage of 1 kV (insert: MS of the ion of *m/z* 417), (b) APCI with corona discharge voltage of 1 kV, and (c) APPI with repeller voltage of 1 kV.
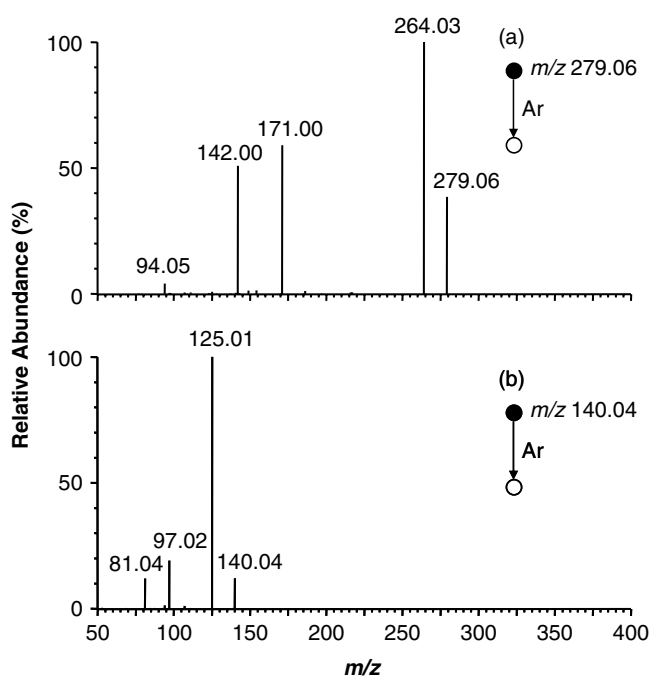

Figure 2. APCI-MS/MS of the ions of (a) *m/z* 279 and (b) *m/z* 140 for impurity **I**.

chromatograms (data not shown) of these two ions show exact co-elution, suggesting that both ions result from the ionization of the same molecule.

To investigate the apparent contradiction in the experimental data, the ion of m/z 140 was also subjected to CID and its MS/MS was recorded (Fig. 2(b)). Among other processes, the ion of m/z 140 was found to lose $CH_3^{\bullet}$ to yield the product ion of m/z 125. Because the dissociation by the loss of a radical is typical of, but not restricted to a radical cation, we assumed that impurity **I** with a molecular mass of 140 Da was present and was detected as its molecular ion. The structure and reactivity of the starting material led us to envisage 4-(methyl mercapto)-phenol (molecular mass of 140 Da) as impurity **I**. To confirm this assignment, the authentic sample of 4-(methyl mercapto)-phenol was prepared. It was observed that the authentic compound exhibits the same elution time as well as the same MS and MS/MS (data not shown) as impurity **I**, confirming impurity **I** as 4-(methyl mercapto)-phenol. However, this molecule fails to account for the presence of the abundant ion of m/z 279. A detailed investigation of the formation of the ions of m/z 140 and m/z 279 during the atmospheric pressure conditions of ESI, APCI and APPI was therefore performed and the results are discussed in the following sections.

Formation of the radical cation of 4-(methyl mercapto)-phenol

Although ESI and APCI tend to form protonated molecules,[7,8] 4-(methyl mercapto)-phenol was detected as its molecular ion of m/z 140. The favorable formation of the radical cation rather than the protonated molecule during ESI and APCI (as well as APPI) is probably due to the presence of the hydroxy and methylthio substituents (with the heteroatom lone electron pairs) attached to the phenyl ring.[22,23] This structural characteristic may aid in delocalization of the unpaired electron and the positive charge (as indicated by theoretical DFT calculations, see Fig. 3), thereby stabilizing the radical cation.[24] The ionization energy (IE) of a molecule is governed by its ability to give up an electron (i.e. to be oxidized) and heteroatoms connected to aromatic functional groups tend to lower the gas-phase IEs,[25,26] thus favoring the formation of radical cations.
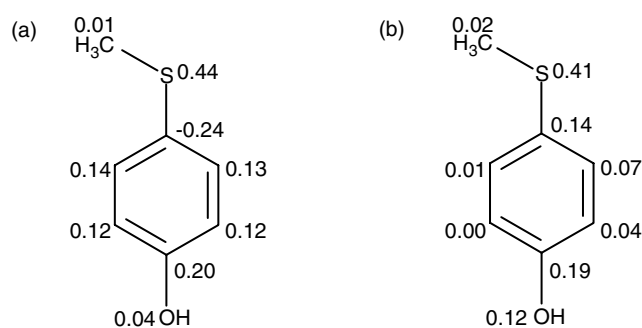
Figure 3. The calculated (a) atomic charge (with hydrogens summed into heavy atoms) and (b) Mulliken atomic spin density of ionized 4-(methyl mercapto)-phenol.

Dimerization of ionized 4-(methyl mercapto)-phenol via the ion/molecule reaction during ESI, APCI and APPI

Given the proposed structure for impurity **I**, it is postulated that the formation of the ion of m/z 279 arises from an ion/molecule reaction between ionized and neutral 4-(methyl mercapto)-phenol. This dimerization resulting from an electrophilic aromatic substitution reaction could lead (after fast H loss from the nascent adduct) to isomeric products via either pathway 1 or 2 (Scheme 1), depending on the attack at either the sulfur or the oxygen atom, respectively.[22,23] Dimerization via the formation of **1A-B** or **2A-B** is also consistent with gas-phase H/D exchange experiments via which the ion of m/z 279 is replaced by its deuterium isotopologue of m/z 281 (data not shown). This H/D exchange reactivity indicates the presence of two acidic OH groups.

From the calculated energies of the four possible products (see the inserts in Scheme 1), it is clear that **1A** and **1B** are the most thermodynamically favored products. In addition, the proposed dissociation pathway (as the rationale for **1A** in Scheme 2) along with the accurate mass measurements on the fragment ions of m/z 171 and m/z 142 (Fig. 2(b)) (corresponding to $[C_7H_7OS_2]^+$ and $[C_6H_6S_2]^+$ compositions within an error of 3.8 ppm, respectively) imply that there are two sulfur atoms attached to the same phenyl
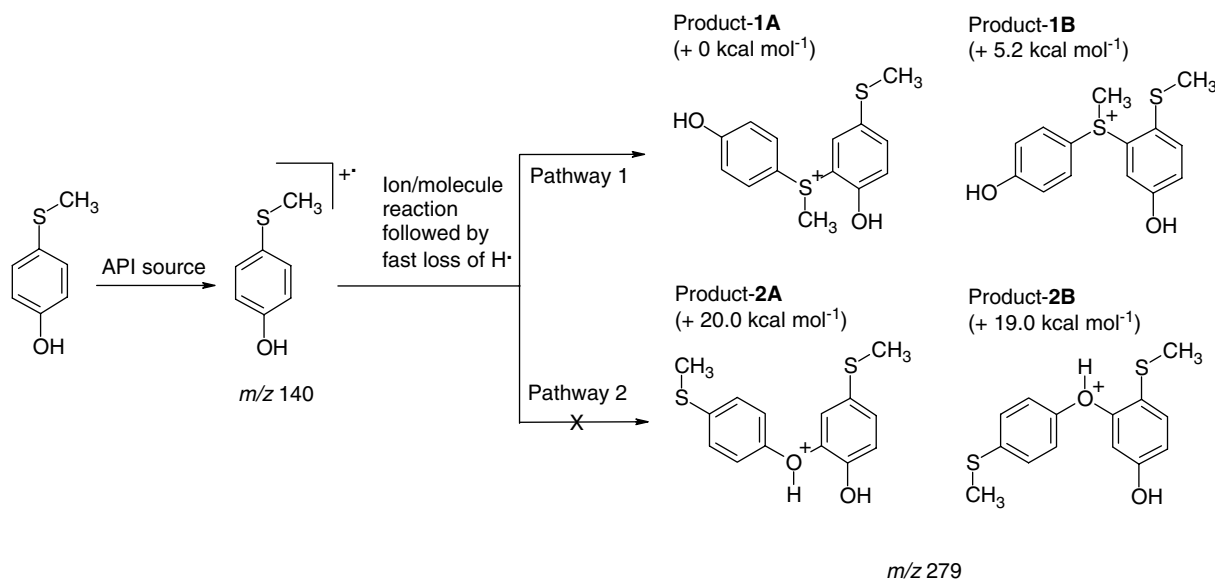
Scheme 1. Pathways for dimerization of ionized 4-(methyl mercapto)-phenol.
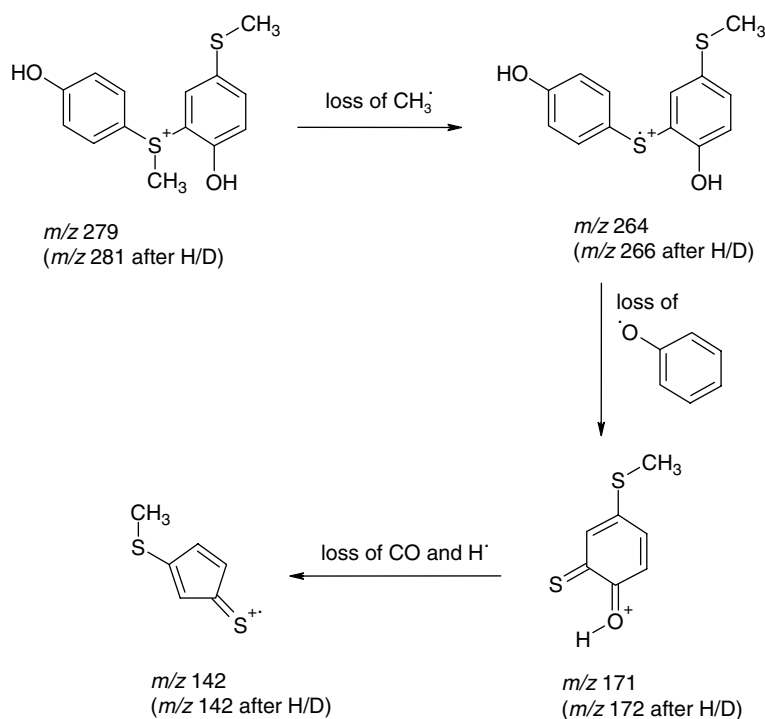
Scheme 2. Proposed dissociation pathways for product-**1A**.

ring. The structural assignments of the fragment ions (Scheme 2) are also consistent with the H/D exchange results. This connectivity further excludes the possibility of pathway 2 (Scheme 1). Furthermore, the neutral molecule of 4-(methyl mercapto)-phenol is believed to be favorable in its ketone form (Scheme 1), which would be attacked most efficiently by ionized 4-(methyl mercapto)-phenol. The proposed dimerization product of *m/z* 279, which results from the electrophilic aromatic substitution reaction, is therefore most likely **1A** and/or **1B**. Substituent effects are known to affect the electrophilic additions to the aromatic π bond.[27–30] Product-**1A** appears to be more stable than **1B** as oxygen might be able to donate electrons to the benzene ring more efficiently than sulfur via its π electrons. Consequently, the higher density of the negative charge can be placed via resonance to the adjacent site of the substitution of the cationic group of **1A**, hence stabilizing the gaseous ion. This stabilization is corroborated by DFT calculations showing that **1A** is 5.2 kcal mol^{-1} more stable than **1B** (Scheme 1).

Other experiments including proton NMR, GC-EI/MS and GC-CI/MS were performed to examine whether the dimerization occurs in solution. NMR detected only the monomer: 2.46 (singlet, 3 H); 5.08 (singlet but broad, 1 H); 6.81 (doublet, 2 H); 7.24 (doublet, 2 H). GC-EI/MS detected the ionized monomer of *m/z* 140, whereas GC-CI/MS also detected only the monomer as the protonated molecule of *m/z* 141. Because none of these techniques were able to detect the dimerization product of *m/z* 279, we conclude that this species is indeed a by-product of the atmospheric pressure ionization techniques.

Ionization environment favoring dimerization of ionized 4-(methyl mercapto)-phenol

Although EI-MS affords the formation of the molecular ion of *m/z* 140, the low pressure condition in the source fails to provide a proper environment for ion/molecule reactions to occur. The CI source can provide a sufficient environment for ion/molecule reactions, but 4-(methyl mercapto)-phenol is ionized by CI mainly by protonation, and the protonated molecule appears to be unable to dimerize. In contrast, the atmospheric pressure ionization conditions favor the dimerization reaction of ionized 4-(methyl mercapto)-phenol.

Comparing the ESI, APCI and APPI spectra (Fig. 1), it seems that the dimerization reaction occurs to a much greater extent during ESI. Under ESI, the source can actually work as an electrolytic cell.[31] Ions are formed or preexist in solution via an electrolytic process that occurs in the metal electrospray capillary.[32] Therefore, the formation of ionized 4-(methyl mercapto)-phenol and its dimerization reaction is inherent to the electrolytic process and may have occurred in solution inside the charged droplets.[33] As shown in Fig. 4(a), this electrolytic process was enhanced by increasing the ESI voltage, and the ion intensity of the dimerization product reached the maximum at $\geq$1 kV. Moreover, as illustrated in Fig. 5(a), the ion intensity of the dimerization product increased almost linearly when the flow rate was decreased, hence enhancing the electrolytic oxidation process. Further, when setting up the instrumental scan within the range from *m/z* 300 to 600, another ion of *m/z* 417.0648 was detected (Fig. 1(a) insert). The accurate mass measurement gave the formula as $C_{21}H_{21}O_3S_3$ within an error of 1.2 ppm, suggesting the occurrence of the trimerization reaction of ionized 4-(methyl mercapto)-phenol by the electrolytic oxidation.[33] However, the trimerization reaction product of *m/z* 417 was not observed during APCI and APPI under the same instrumental scan settings. All these pieces of evidence indicate that the dimerization reaction during ESI is electrochemical in nature.

The formation of the dimerization product during APCI and APPI (in which ionization occurs in the gas phase[34,35]) suggests that gas-phase ion/molecule reactions are also important for the dimerization reaction that produces the ion of *m/z* 279. Figure 4(b) and (c) shows the effects of the APCI corona discharge voltage and
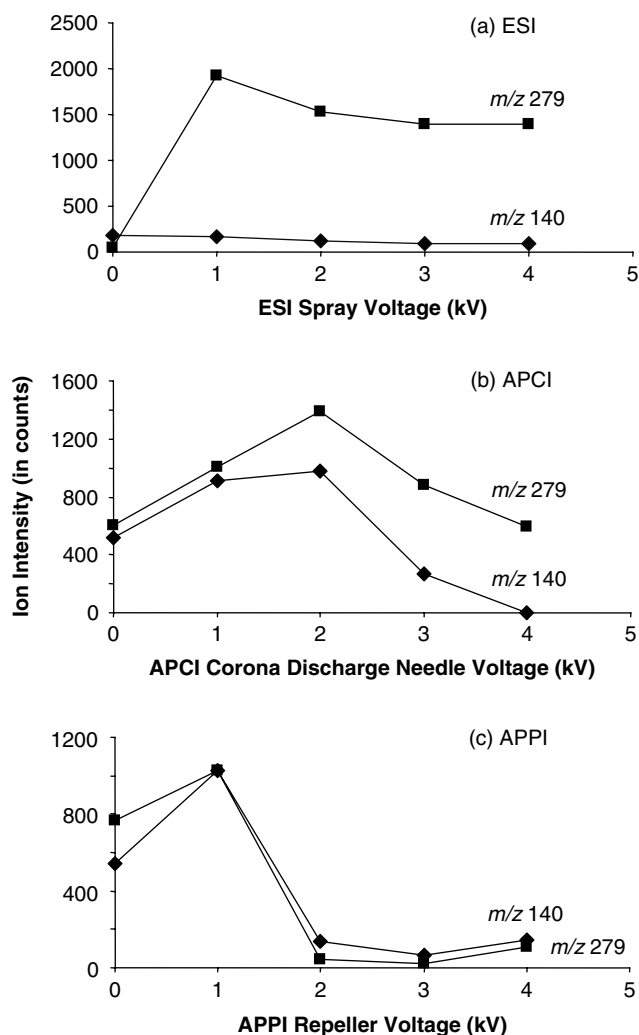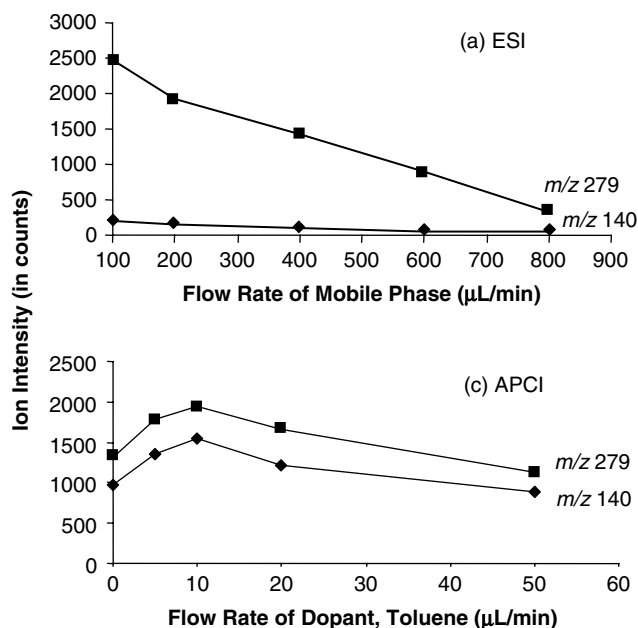
Figure 4. Ion intensities as a function of (a) ESI spray voltage, (b) APCI corona discharge needle voltage and (c) APPI repeller voltage. The mobile phase flow rates during ESI, APCI, and APPI were 200, 1000 and 1000 µl min^{-1} respectively.

Figure 5. Ion intensities as a function of the flow rate (a) of the mobile phase reaching the ESI source with a spray voltage at 1 kV and (b) of dopant (toluene) by post-column addition to the mobile phase before reaching the APCI source with a corona discharge needle voltage at 1 kV.

the APPI repeller voltage on the formation of ionized 4-(methyl mercapto)-phenol and the dimerization product. Note that the intense ions generated at zero voltage during APCI and APPI are probably via the thermal (spray) formation.[36] It appears that, during APCI and APPI, the dimerization product was formed by the ion/molecule chemistry, which is dependent on the formation of the radical cation of 4-(methyl mercapto)-phenol. To test this hypothesis, the post-column addition of toluene as the dopant during APCI was performed (Fig. 5(b)) to assist the generation of the radical cation.[37] As expected, both ionized 4-(methyl mercapto)-phenol and the dimerization reaction were enhanced by about 60% when 1% of toluene was present in the sample solution during APCI, although the dopant failed to improve the dimerization reaction when more than 5% toluene was present in the sample solution.

Conclusions

A novel ion/molecule reaction leading to the dimerization of ionized 4-(methyl mercapto)-phenol followed by fast H loss was

observed. The mechanism by which this unusual dimerization reaction occurs under ESI, APCI and APPI conditions has been suggested and tested. It was found that the reaction is particularly favored during ESI, which indicates that the reaction can occur both in solution inside the ESI-charged droplets and in the gas-phase environment of most other atmospheric pressure ionization techniques. During ESI, the dimerization (and trimerization, which was not observed during APCI and APPI) reaction is inherent to the electrolytic process. However, the dimerization reaction occurring during APCI and APPI is more dependent on the formation of ionized 4-(methyl mercapto)-phenol, suggesting that it is more by the ion/molecule chemistry in nature. On the basis of the combined data from MS/MS, accurate mass measurements, H/D exchange as well as DFT theoretical calculations, the methyl sulfonium ions **1A** and **1B** appear to be the most likely products of this electrophilic aromatic substitution reaction. In addition, the molecular calculations provided insights into understanding (1) the possible generation of radical cation of 4-(methyl mercapto)-phenol via delocalization of the unpaired electron and positive charge based on the calculated charge and spin densities and (2) the formation of more thermodynamically favorable dimerization products.

The possibility of forming ionized molecules and, more importantly, the occurrence of this unexpected dimerization reaction (as reported herein for 4-(methyl mercapto)-phenol) should therefore always be kept in mind when performing atmospheric pressure ionization experiments on this as well as analogous compounds.

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