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Study on reactions of long-lived phenoxathiin radical cation with aliphatic alcohols, phenol and phenyl halides in ambient condition by fused-droplet electrospray ionization mass spectrometry

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The reactions of phenoxathiin radical cations with diverse organic compounds in ambient conditions were realized by using fuseddroplet electrospray ionization mass spectrometry. In the investigation, the phenoxathiin radical cation was prepared by electrospray ionization. The reactants included aliphatic alcohols, phenol and phenyl halides and the reaction studies showed the unique reactivity the of phenoxathiin radical cation towards neutral organic compounds in ambient conditions, which has not been revealed in previous studies.

Keywords: FD-ESI, phenoxathiin radical cation, reactivity investigation, radical chemistry

Introduction

There has been longstanding interest in understanding the reactivity of radical cations.^{1,2} The motivation for these studies ranges from fundamental interest in organic synthesis^{3,4} to biological chemistry.^{5,6} Among the studies, sulfur-containing radical cations such as the phenoxathiin radical cation (1^{•+}, Scheme 1)^{7,8} gained much attention from chemists. It was found that the radical cation of 1^{•+} had an impressive reactivity toward various small molecular compounds, such as amines,^{9,10} ketones,¹¹ alkenes,^{12,13} alkines,¹⁴ anisole^{15,16} and so on.¹⁷ Moreover, Everitt and co-workers¹⁸ found that 1^{•+} can interact with DNA and showed marked bacteriostatic action on *Streptococcus*. All these findings motivated chemists to study the reaction characteristics of the radical cation 1^{•+} towards diverse organic compounds. Early investigations of 1^{•+} were carried out in solution. 1^{•+} could be prepared and stored as phenoxathiin radical cation perchlorate (1^{•+} ClO_4^{-}),⁹ which was synthesized by perchloric acid oxidation of phenoxathiin solution in anhydrous benzene.⁷



However, the reactant of $1^{\bullet+} \operatorname{ClO}_4^-$ was extremely hazardous and explosive when initiated by the friction of transfer, which restricted the proper studies of $1^{\bullet+}$.¹⁵ As a consequence, it is necessary to develop a feasible method to prepare fresh phenoxathiin radical cations, as well as for the following studies of its reaction.

Our primary studies showed that phenoxathiin could easily give its radical cation 1^{•+} in electrospray ionization conditions, which made it possible to perform a study on the reactivity of 1^{•+}. Fused-droplet electrospray ionization mass spectrometry (FD-ESI/MS),^{19,20} which was also defined as extractive electrospray ionization mass spectrometry (EESI-MS),²¹ based on liquid-liquid extraction between the colliding microdroplets,^{20,22} is an important technology for performing studies on organic reactions in ambient conditions.²³⁻²⁵ The FD-ESI set-up consists of two independent spray tips: one is an electrospray to generate the ionic substance, and the other is a neutral spray to provide neutral reactant. The present paper describes the application of FD-ESI-tandem mass spectrometry (MS/MS) for studying the reactivity of 1*+ in ambient conditions with various compounds, including aliphatic alcohols, phenol and phenyl halides. Our studies showed the unique reactivity of radical cation 1*+ towards diverse neutral organic compounds in ambient conditions, which has not been studied previously.

Experimental Chemicals and reagents

Phenoxathiin (1) and D5-phenol were purchased from Sigma (St Louis, MO, USA). Phenol (C₆H₅OH), *n*-butyl alcohol $(n-C_4H_9OH)$, isoamylol $((CH_3)_2CHCH_2CH_2OH)$ cyclohexanol ($C_{4}H_{11}OH$), chlorobenzene ($C_{4}H_{5}Cl$), bromobenzene $(C_{4}H_{5}Br)$ and iodobenzene $(C_{4}H_{5}I)$ were of analytical grade and purchased from Sinopharm Chemical Reagent Co. Ltd (Shanghai, China). Methanol (CH₃OH, HPLC grade), acetonitrile (CH₃CN, HPLC grade), ethanol (CH₃CH₂OH, HPLC grade) and isopropanol [(CH₃)₂CHOH, HPLC grade] were from Dima Technology Inc. (Richmond Hill, VA, USA). The solution of 1 for ESI and FD-ESI analysis was prepared by dissolving 0.5 mg 1 in 1.0 mL solvent. The solution was fed into the ESI ion source through an infusion syringe pump with a flow rate at 10 µL min⁻¹. Aliphatic alcohols, phenol D5-phenol, and phenyl halides (C_6H_5X , X = Cl, Br, I) were dissolved in acetonitrile.

Mass spectrometry experiments

The ESI mass spectrometric experiments were carried out on a Finnigan TSQ (Thermo Finnigan, Quantum Access) triple quadrupole mass spectrometer fitted with an ESI source (ESI-TSQ-MS). The mass spectrometric conditions were used as follows: ionization voltage at +4.0 kV, capillary offset at 37V, capillary voltage at 10.24 V, spray current at 2.44 μ A and capillary temperature at 275°C. The stainless steel spray needle is 143.5 mm (length)×0.10 mm (ID) H0.23 mm (OD). Nitrogen gas was used as the nebulizing gas which was set at 20 psi.The nebulizing gas for the neutral spray tip was also nitrogen with a pressure of about 15 psi.

The fused-droplet electrospray ionization (FD-ESI) source was constructed on the basis of the ESI-TSQ-MS. As shown in Figure 1, 1 mmol L⁻¹ acetonitrile solution of phenoxathiin was introduced from the electrospray tip, while the neutral reactants (such as methanol, ethanol and so on) or their acetonitrile solutions were fed through the neutral spray tip. Collision-induced dissociation (CID) experiments were performed with argon at various collision energies ($E_{lab} = 0-30 \text{ eV}$) and collision gas pressure of 1.0 mTorr.

Computational details

Density functional calculations were performed by using Becke's three-parameter hybrid exchange-correlation functional²⁶ containing the non-local gradient correction of Lee, Yang and Parr (B3LYP) within the Gaussian03 program.²⁷ The basis set used for the remaining atomic species was 6-31G with the important addition of the polarization functions (d) for all atoms, including the hydrogen atoms.²⁸

Results and discussions Formation of 1^{•+} by electrospray ionization

The experiment for generating 1^{•+} was achieved by analysis of acetonitrile solution of 1 (phenoxathiin) with electrospray ionization mass spectrometry. Generally, the neutral analytes in ESI are charged by acid/base chemistry or by adduct formation (such as $[M+H]^+$, $[M+Na]^+$ and so on).^{29,30} However, those aromatic compounds³¹ with low ionization energy can generate $M^{\bullet+}$ in the positive ion mode due to single-electron transfer (SET) process within the charge-transfer complexation³² or at the metal-solution interface of the ESI needle.^{33,34} This





provides an alternative approach 35,36 to generate $1^{\bullet \star}$ other than the organic synthesis method. 37

The ESI mass spectrum of acetonitrile solution of **1** showed the clean signal of **1**^{•+} at m/z 200 [Figure 2(a)], which allowed the further investigation on the reactivity of **1**^{•+} by FD-ESI-MS. Moreover, as phenoxathiin can be easily oxidized to form phenoxathiin S-oxide, ³⁸ the S-hydroxyl phenoxathiinium cation **2**⁺ at m/z 217³³ [Figure 2(b)] could be detected when we analyzed the phenoxathiin sample which was stored for about 1 week after the first experiment. The CID experiment of **1**^{•+} indicates the losses of S, CO and HCO[•] to form the ions of m/z 168, m/z172 and m/z 171, respectively [Figure 2(c)]. In the MS/MS for CID of the ion **2**⁺ at m/z 217 [Figure 2(d)], **2**⁺ gives the product ion **1**^{•+} of m/z 200 by the loss of an AOH radical.

Ambient reactions of 1** with aliphatic alcohols

The ambient reactions between 1^{•+} and aliphatic alcohols were monitored by FD-ESI-MS. In the FD-ESI-MS experiments, the solution of 1 in acetonitrile was fed into the ion source through the electrospray tip **A** to give 1^{•+}. Meanwhile, the reactant of methanol was imported into the ion source through the neutral spray tip **B**. Such an experimental set-up allowed the reaction of 1^{•+} with methanol under conditions of colliding microdroplets (shown in Figure 1). The product ions subsequently experienced the desolvation³⁹ and then were further detected using a mass spectrometer.

Figure 3 shows the reaction results of $1^{\bullet+}$ with methanol [Figure 3(a)] and ethanol [Figure 3(b)]. Besides the ion of m/z 217, the spectra show the *S*-methoxyl phenoxathiinium cation (3^{+} at m/z 231) and the *S*-ethoxyl phenoxathiinium cation (4^{+} at m/z 245) as the major products, respectively. Scheme 2 shows the possible reaction pathway of $1^{\bullet+}$ with neutral aliphatic alcohols^{40,41} in ambient conditions.

The MS/MS spectrum of $\mathbf{3}^{*}$ (*m*/*z* 231) gave the major product ion of $\mathbf{1}^{*+}$ (*m*/*z* 200) and the minor product ion of *m*/*z* 216 [Figure 4(a)]. The generation of $\mathbf{1}^{*+}$ at *m*/*z* 200 from $\mathbf{3}^{*}$ at *m*/*z* 231 indicated the homolytic cleavage of the sulfur-oxygen bond¹⁵ in $\mathbf{3}^{+}$ to form $\mathbf{1}^{*+}$ by loss of an * OCH₃ radical. This phenomenon can be attributed to those weak S-X (X = N, O, C,





S) bonds.⁴² The fragment ion at m/z 216 corresponding to the S-oxide phenoxathiin radical cation was formed through the carbon-oxygen bond homolysis of **3**⁺ (Scheme 3) with the loss of a ${}^{\circ}$ CH₃ radical. However, the CID mass spectrum [Figure 4(b)] of **4**⁺ gave the fragment ion ${\bf 1}^{\bullet+}$ of m/z 200 and the fragment ion ${\bf 2}^{\bullet+}$ of m/z 217. It is interesting that the generation of m/z 217 from **4**⁺ at m/z 245 suggested a β -H abstraction process via loss of neutral ethylene, which proved to be one of the main products in the solution of condensed phase reactions between ${\bf 1}^{\bullet+}$ and aliphatic alcohols^{43,44} (Scheme





at m/z 273, (e) 7⁺ at m/z 287, (f) 8⁺ at m/z 299.



3). DFT calculations for the two possible gas-phase dissociations of 4^+ at m/z 245 were shown in Figure 5: [1] β -H abstraction to form 2^+ of m/z 217 via the transition state with an energy barrier of 311.9 kJ mol⁻¹ and the relative energy of products with 117.6 kJ mol⁻¹; [2] C–O band homolysis to form ion of m/z 216 via the transition state with an energy barrier of 343.3 kJ mol⁻¹ and relative energy of products with 333.2 kJ mol⁻¹. The calculations indicated that the fragment pathway of β -H abstraction to form 2^+ at m/z 217 is thermodynamically favored by 215.6 kJ mol⁻¹ to the pathway of the carbon-oxygen bond homolysis to the ion at m/z 216. Meanwhile the energy barrier of β -H abstraction to form $\mathbf{2}^+$ at m/z 217 is lower by 31.4 kJ mol⁻¹ than the pathway of the carbon-oxygen bond homolysis to form the ion at m/z 216. These results supported the proposed dissociation pathway of $\mathbf{4}^+$ at m/z 245 to form $\mathbf{2}^+$ at m/z 217 by β -H abstraction process.







Meanwhile, similar results were obtained from the reaction of 1^{•+} with isopropanol, *n*-butanol, isopropanol and cyclohexanol. They gave the S-alkoxyl phenoxathiinium cations of 5⁺ at *m/z* 259, 6⁺ at *m/z* 273, 7⁺ at *m/z* 287 and 8⁺ at *m/z* 299 as the major product ions in the ambient reactions with 1^{•+}, respectively. The CID mass spectra of 5⁺-8⁺ (Figure 4) showed that the ion of 1^{•+} at *m/z* 200 by homolytic cleavage of sulfuroxygen bond and the ion of 2⁺ at *m/z* 217 by loss of olefin Y (Scheme 3) via β -H abstraction are the major products. These experimental results clearly demonstrated the reactivity of 1^{•+} towards alcohols in ambient conditions.⁴⁵ These results suggested that the S-alkoxyl phenoxathiinium cations (shown in Scheme 3) might be the reactive intermediates of solution reactions of 1^{•+} with aliphatic alcohols.⁴⁶⁻⁴⁸

Ambient reaction of 1^{•+} with phenol

The ambient reaction of $1^{\bullet+}$ with phenol⁴⁹ was performed and the FD-ESI mass spectrum gave a strong signal at m/z 293 (Figure 6). Two possible structures, 9^+ and 10^+ , were proposed for the ion at m/z 293 and they were shown in Scheme 4. To further confirm the structure of the ion at m/z 293, D₅-phenol (C₆D₅OH) was employed as the reactant. Figure 7(a) shows the reaction result of 1^{+} and C_4D_5OH , which gives two product signals at m/z 297 and m/z 298. Based on such results, we deduced that the ion at m/z 297 is isotope peak A of D4-9⁺ (Scheme 5), generated through the electrophilic substitution of 1^{•+} toward the aromatic ring of the D5-phenol.⁵⁰⁻⁵² According to Scheme 5, the ion at m/z 298 might come from the contribution of $D5-10^+$ (A isotope peak, ${}^{12}C_{18}^{-1}H_8^{-2}D_5^{-16}O_2^{-32}S^+$, formed through the phenolic hydroxylation of 1^{•+} by phenol), or the contribution of (A+1) isotopic peak of $D4-9^+$ (${}^{13}C^{12}C_{17}{}^{1}H_9{}^{2}D_4{}^{16}O_2{}^{32}S^+$, formed through the electrophilic substitution of 1^{•+} toward the aromatic ring of D5-phenol. The experimental ratio (shown in Table 1) of m/z 200 to m/z 201 obtained from the MS/MS spectrum of m/z 298 [Figure 7(b) and Scheme 6] indicates that the ion at m/z 298 is a mixture of isotopic peak A of D5-10⁺ $({}^{12}C_{18}{}^{14}H_{8}{}^{2}D_{5}{}^{16}O_{2}{}^{32}S^{+}, m/z$ 298) and isotopic peak (A + 1) of **D4-9**⁺ $[{}^{13}C^{12}C_{17}{}^{1}H_{9}{}^{2}D_{4}{}^{16}O_{2}{}^{32}S^{+}, m/z$ 298). The experimental results showed the unique reactivity of 1^{•+} towards phenol in ambient conditions.

Ambient reactions of 1^{•+} with phenyl halides

In solution condition at room temperature, $\mathbf{1}^{\bullet \star}$ had been found not to react with phenyl halides or at least too slowly





Table 1. Calculations for the product ratio of I_{200} to I_{201} obtained from m/z 298.

Ratio	Precursor ions	Ratio of product ions
Theoretical ratio	A+1 peak of D4-9 ⁺ at <i>m/z</i> 298	<i>I</i> ₂₀₀ : <i>I</i> ₂₀₁ ≈ 1:2
Theoretical ratio	A of D5-10 ⁺ at <i>m/z</i> 298	<i>I</i> ₂₀₀ : <i>I</i> ₂₀₁ = 1:0
Experimental ratio	Signal at m/z 298	<i>I</i> ₂₀₀ : <i>I</i> ₂₀₁ ≈ 9:10
l is the relative abundance of the ion.		

to observe.^{7,53} However, the FD-ESI mass spectra [Figures 8(a)–(c)] of the ambient reactions of $1^{\bullet+}$ with phenyl halides clearly showed a product ion at m/z 277.^{54–56} The corresponding possible structure of 11^{\bullet} is shown in Scheme 7. This experiment indicates that $1^{\bullet+}$ has significant reactivity towards



phenyl halides directly (Scheme 5) in FD-ESI condition. The CID experiment of the ion 11^+ at m/z 277 [Figure 8(d)] indicated 1^{++} at m/z 200 as the major fragment ion, which confirmed the possible structure of 11^+ .

Conclusions

This study showed the reactivity of phenoxathiin radical cation with alcohols, phenol and phenyl halides in ambient reactions and these reactions were monitored by an simply FD-ESI-MS(/MS) experimental set-up. The experimental results showed that the S-alkoxyl phenoxathiinium cations are the key intermediates of the reactions between phenoxathiin radical cation and alcohols. The phenol can react with phenoxathiin radical cation to produce isomer product ions in ambient condition. In addition, it has been proved that phenyl halides react with phenoxathiin radical cations in ambient conditions. The reaction of phenoxathiin radical cations with phenyl halides generated electrophilic aromatic substitution product ions which had not been observed in the solution before. All these findings not only provided an alternative approach to studying organic reactions of highly



reactive phenoxathiin radical cations with diverse organic compounds, but also showed the remarkable convenience of FD-ESI-MS/MS for probing organic reactions in ambient reactions.

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