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Tosyl oxygen transfer and ion–neutral complex mediated electron transfer in the gas-phase fragmentation of the protonated *N*-phenyl *p*-toluenesulfonamides

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ABSTRACT

In this work, an interesting oxygen transfer reaction in the gas phase dissociation of *N*-phenyl *p*-toluenesulfonamides has been explored by combination of the ESI–MS techniques and theoretical calculations. The protonated molecules underwent dissociation reactions, upon collisional activation, to give the [tosyl cation/aniline] ion–neutral complex (INC), in which the coupling reactions subsequently occurred to afford an ionic species of toluenesulfinate. The subsequent reactions of the toluenesulfinate species resulted in generation of the protonated 6-iminocyclohexa- 2,4-dienone or the 2-aminophenol radical cation, *via* cleavage of the S—O bond. The above processes involved the tosyl oxygen transfer, and calculation results indicated that both the *ortho*- and the *para*- positions at the aniline ring are favorite for the tosyl oxygen transfer, and formation of radical cation involved an INC mediated electron transfer. The isomeric *N*-methylphenyl *p*-toluenesulfonamides behaved significant difference in the CID–MS spectra, indicating that the three isomers can be distinguished by ESI–MS.

1. Introduction

Aromatic sulfonamides and their derivatives, which contain an oxidized sulfur group, play a significant role in developing therapeutics for diabetes and Alzheimer's disease as well as bacterial infections [1–6], and have been widely deployed as drug candidates in the pharmaceutical industry. To facilitate identification of sulfonamides and the relevant unknown compounds, sulfonamides have been extensively investigated experimentally and theoretically in explanation on their mechanistic fragmentation pathways occurring in electrospray ionization mass spectrometry [7–17]. Elimination of SO_2 has been reported to effectively occur in the tandem MS of the protonated and the deprotonated sulfonamides, which can be viewed as a structure specific mass spectrometric strategy for detection of sulfonamides [7–12]. The characteristic loss of SO has been observed in dissociation of *p*-amino-phenylsulfonyl cation *via* an intramolecular S_NAr reaction, accompanied with the transfer of the phenylsulfonyl oxygen [13–15]. Dissociation of protonated *N*-alkyl-*p*-toluenesulfonamides has been reported to occur effectively *via* cleavage of either the S—N bond or the N—C bond to form two different ion–neutral complexes, which leads to the *p*-tosyl cation and the protonated *p*-toluenesulfonamide (or carbocation), respectively [16]. Fragmentation of protonated benzenesulfonamides, on the other hand, mainly affords an ion–neutral complex (INC) [phenylsulfonyl cation/aniline], which undergoes the subsequent charge transfer between the two partners of the complex and gives rise to the radical cation of anilines [17]. Transfer of the tosyl oxygen has also been found in fragmentation of protonated sulfonamides [17], but no detailed mechanism has been documented to our knowledge. In this work, the *N*-phenyl *p*-toluenesulfonamides were selected as a model to perform a detailed mechanistic investigation on the transfer of tosyl oxygen, which leads to two fragment ions of the oxidized anilines.

2. Experimental

2.1. Materials

Toluenesulfonaniline derivatives (compounds **1**–**10** in Scheme 1) were synthesized according to the classical method,

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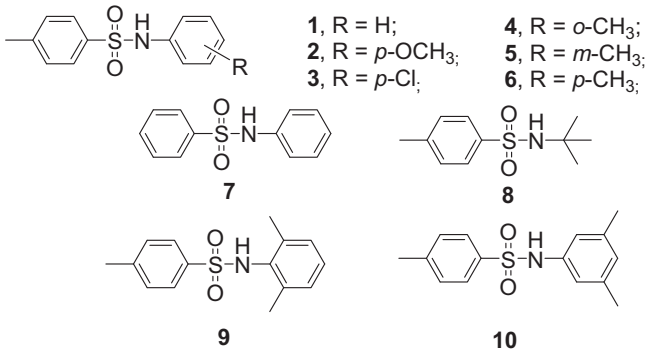


Scheme 1. The structures of sulfonamides.

involving reaction of *p*-toluenesulfonyl chloride (or benzenesulfonyl chloride) with the corresponding amine in the presence of pyridine [18]. All compounds were purified after synthesis, and their structures were further confirmed by MS.

2.2. Mass spectrometry

The ESI–MS/MS experiments were performed on an LCQ quadrupole ion trap mass spectrometer (Thermo-Finnigan LCQ Advantage MAX, ThermoFisher Scientific Inc., USA) [19], equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (Version1.4). Diluted solutions (about 10 ppm) were prepared by dissolving the sulfonamide sample in a mixed solvent of methanol and water (V:V = 1:1), and then were introduced into the source chamber at a flow rate of 5 μL min^{-1}. The sheath gas (N_2, 99.99%) was set at 25 arbitrary units (a.u.), the spray voltage at −4.5 kV, and the heated ion transfer tube (250 °C) at +55 V, respectively. The ion trap pressure of approximately 2×10^{-5} Torr was maintained with a Turbo pump and pure helium (99.999%) was used for the trapping and collision activation of the selected ions. The CID–MS experiments were performed by application of an excitation AC voltage to the end caps of the ion trap to induce collisions of the isolated ions (isolation width at 1.2 u.) for a period of 30 ms and variable excitation amplitudes. Note that the software of Finnigan ion trap applies a 'normalized collision energy' (see Finnigan Product Support Bulletin 104: http://www.thermo.com/eThermo/CMA/PDFs/Articles/articlesFile_21418.pdf) by which mass of the target ion is automatically considered in the calculation of the excitation amplitude in the CID experiments [20–23]. Each mass spectrum was the average of over 50 scans.

2.3. Theoretical calculations

The theoretical calculations were performed using the Gaussian 09 program [24]. The equilibrium geometries of the target species were optimized using the density functional theory (DFT) method at the B3LYP/6-311 + G(d,p) level. The optimized structures were identified as the true minima in energy by the absence of imaginary frequencies. Transition states, on the other hand, were identified by the presence of one single imaginary vibration frequency and the normal vibrational mode, and further confirmed by the intrinsic reaction coordinates (IRC) calculations. The electron excitation energy of a target species was obtained by the Configuration Interaction approach (CI-Singles). The energies discussed here are the sum of the associated electronic and thermal free Energies. The DFT optimized structures were shown by Gauss View (Version 3.09) software to give higher quality images of these structures. The energies discussed here are the sum of electronic and thermal free energy.

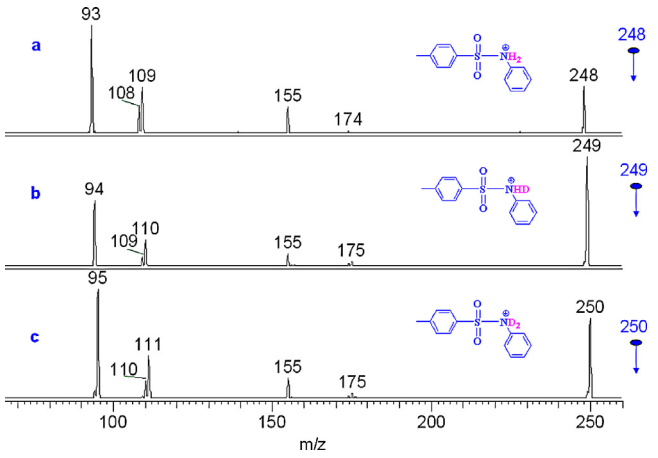


Fig. 1. The CID–MS spectrum of (a) $[\mathbf{1}+H]^+$, (b) $[\mathbf{1}+D]^+$ and (c) $[\mathbf{1}-H+2D]^+$.

3. Results and discussion

3.1. Dissociation of the protonated N-phenyl p-toluenesulfonamides

Investigation of the tosyl oxygen transfer reaction has been carried out by exploring the fragmentation behaviors of the protonated sulfonamides (Table 1). *N*-phenyl *p*-toluenesulfonamide (**1**) was selected as a model to perform a detail investigation. Fig. 1a describes the CID–MS spectrum of $[\mathbf{1}+H]^+$, in which the product ion at *m/z* 155 is ascribed to the tosyl cation (**a-1IP**), resulted from the direct separation of the [tosyl cation/aniline] INC, originating from dissociation of $[\mathbf{1}+H]^+$ (*m/z* 248). Also, charge transfer in the INC results in the aniline radical cation (**a-2IP**) at *m/z* 93 [17]. The fragment ions at *m/z* 108 and *m/z* 109 is attributed to the protonated quino-imines (*e.g.* **1c-1IP**) and the hydroxyaniline radical cation (*e.g.* **1c-2IP**), respectively. The product ion at *m/z* 174 is ascribed to be the protonated phenylsulfamic acid, resulting from toluene elimination and hydration of the precursor ion [25–29]. The elemental compositions of these fragment ions have been determined by analyzing their accurate masses measured with high resolution Q-TOF mass spectrometer (Supplementary Table S1 and Fig. S1). Thus, the potential fragmentation pathways were proposed in Scheme 2. Noteworthy, formation of the fragment ions at *m/z* 108 and *m/z* 109 can only be interpreted as a result of the transferring the tosyl oxygen to the aniline ring, which involves an interesting intramolecular oxidation-reduction reaction.

The proposed fragmentation pathways in Scheme 2 have been supported by the deuterium labeling experiments (Fig. 1). The deuterated molecule ($[\mathbf{1}+D]^+$, *m/z* 249) and the di-deuterated one ($[\mathbf{1}-H+2D]^+$, *m/z* 250) were generated by spraying a diluted methanol-d4 solution of **1** prepared freshly and that placed for several minutes, respectively. There is no external proton or sulfamidic hydrogen in the fragment ion of **a-1IP**, and thereby decomposition of the $[\mathbf{1}+H]^+$, $[\mathbf{1}+D]^+$ and $[\mathbf{1}-H+2D]^+$ species resulted in the tosyl cation with the same mass (155 Da) *via* the loss of $C_6H_5NH_2$, C_6H_5NHD and $C_6H_5ND_2$, respectively. The fragment ion **a-2IP** contains both external proton and sulfamidic hydrogen from the precursor ion. As expected, the corresponding mass (93 Da) of **a-2IP** shifts to 94 Da originating from $[\mathbf{1}+D]^+$, and to 95 Da from $[\mathbf{1}-H+2D]^+$, respectively. Similarly, the corresponding *m/z* of the ions at *m/z* 108 (*e.g.* **1c-1IP**) and *m/z* 109 (*e.g.* **1c-2IP**) shift to *m/z* 109 and *m/z* 110 in the CID–MS of $[\mathbf{1}+D]^+$ (Fig. 1-b), and to *m/z* 110 and *m/z* 111 in the CID–MS of $[\mathbf{1}-H+2D]^+$ (Fig. 1-c), respectively. Interestingly, no H/D exchange occurs for these fragment ions in the CID process.

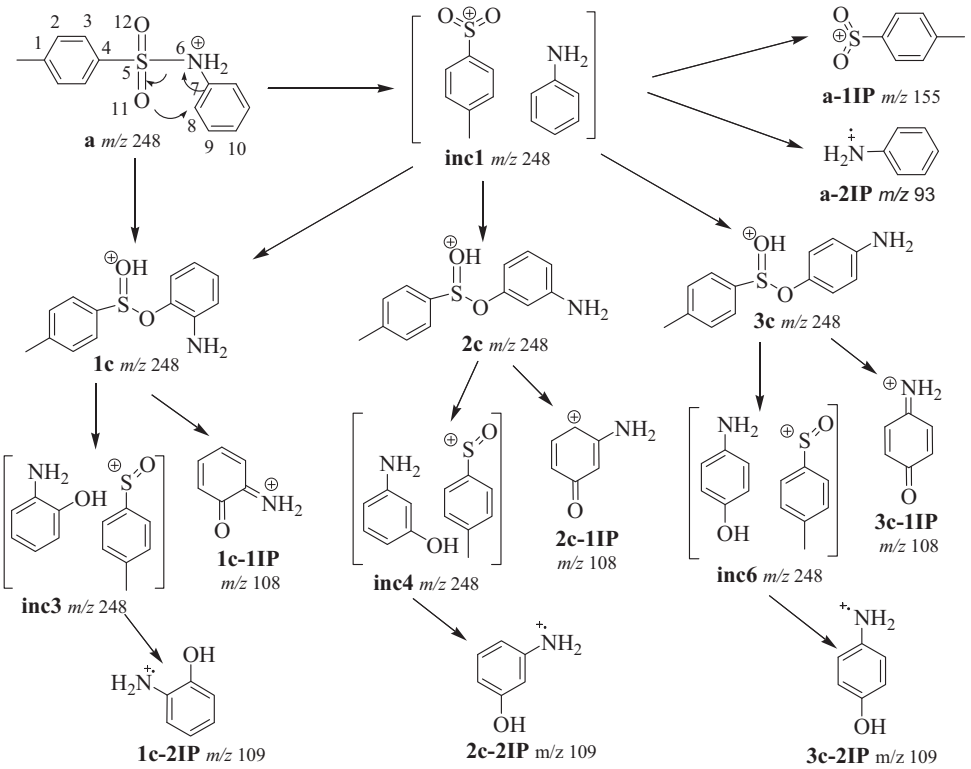
Table 1
The CID–MS data of the protonated *p*-toluenesulfonamides in Scheme 1 at the normalized collision energy (NCE) of 18%.

Compound	*R*	$[M+H]^+$ *m/z* (%)	Product ions, *m/z* (%)				
			Aniline radical cation $RC_6H_4NH_2^{+\cdot}$	Phenylsulfonyl cation $RC_6H_4SO_2^+$	Protoanted 6-imino cyclohexa2,4-dienone 1d-IP	Aminophenol radical cation 1e-IP	Others
1	H	248 (17.9)	93 (100.0)	155 (18.6)	108 (10.3)	109 (43.0)	92 (0.2)
2	*p*-CH_3O	278 (100.0)	123 (20.5)	155 (0.2)	138 (1.4)	–*	122 (0.5)
3	*p*-Cl	282 (16.6)	127 (100.0)	155 (19. 7)	–	143 (1.0)	126 (0.2)
4	*o*-CH_3	262 (17.5)	107 (100.0)	155 (0.1)	122 (4.8)	123 (11.5)	106 (4.0)
5	*m*-CH_3	262 (30.0)	107 (100.0)	155 (0.1)	122 (32.8)	123 (20.7)	106 (1.3)
6	*p*-CH_3	262 (7.4)	107 (100.0)	–	122 (0.4)	123 (1.1)	106 (15.0)
7	H	234 (6.7)	93 (100.0)	–	108 (8.7)	109 (11.8)	92 (0.04)
8**	–	228 (20.6)	–	–	–	–	172 (100.0)

* "–" Means "not detected".
** The backbone structure of 8 is significantly different to compounds **1**–**6**.

Migration of the tosyl oxygen has consolidated by comparing the fragmentation behavior of the derivatives of sulfonamide (Table 1). For compounds **2**–**6** with different substituents on the aniline ring, the fragment ions (*e.g.* **1c-1IP**, **1c-2IP**) formed *via* tosyl oxygen transfer showed a mass shift corresponding to the mass of the substituent. For example, compound **5** possesses a methyl group at the aniline ring, and thus there was an increasing mass shift of 14 Da for the relevant ionic fragments **1c-1IP (or 2c-1IP**, **3c-1IP)** (from *m/z* 108 to *m/z* 122) and **1c-2IP (or 2c-2IP**, **3c-2IP)** from *m/z* 109 to *m/z* 123**).** As for compound **7** with different substituent at the sulfonyl moiety, however, no mass shift was found for the relevant ionic fragments. Thereby, the ionic products **2d-IP** and **2e-2IP** come from the aniline moiety, which bonds with the transferring tosyl oxygen atom in the coupling way. However, no relevant product was obtained in dissociation of $[\mathbf{8}+H]^+$, indicating that migration of the tosyl oxygen in Scheme 2 is inhibited in fragmentation of protonated *N*-alkyl-*p*-toluenesulfonamides [16].

There are three potential sites (*ortho*, *meta* and *para*) at the aniline ring for the tosyl oxygen transfer. *N*-3,4,5-trimethylphenyl *p*-toluenesulfonamide (**9**, blocking the *meta* and the *para* positions), and *N*-2,6-dimethylphenyl *p*-toluenesulfonamide (**10**, blocking the *ortho* positions) were synthesized for the CID–MS experiments (Fig. 2). For compound **9**, both the radical ion of hydroxyaniline (*m/z* 151) and the protonated quino-imines (*m/z* 150) have been obtained in the ESI–MS/MS spectra, which consolidated that migration of the tosyl oxygen occurs to the *ortho* position in the CID process. For the occurrence of compound **10**, both the radical ion of hydroxyaniline (*m/z* 137) and the protonated quino-imines (*m/z* 136) have also been obtained in the CID–MS experiment, indicating that the tosyl oxygen can also be transferred to the *meta* or the *para* position of the aniline ring. Thereby, the tosyl oxygen atom can be transferred to the *ortho*, *meta*, and *para* positions of the aniline ring in the CID process. Further investigation was performed in the succeeding sections.



Scheme 2. The proposed oxygen transfer reactions in the fragmentation of $[\mathbf{1}+H]^+$.

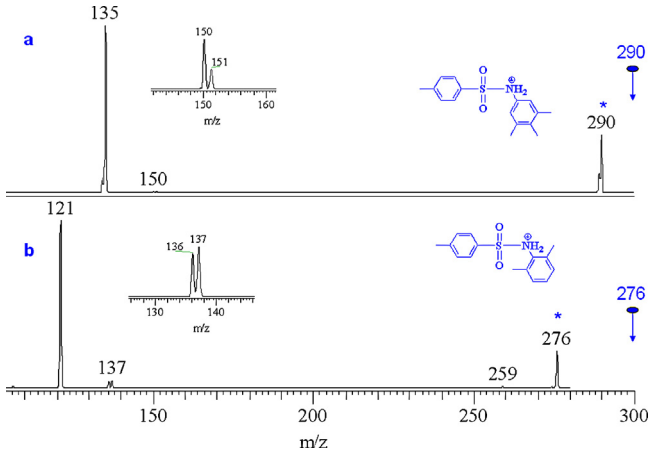


Fig. 2. The CID–MS spectra of (a) $[\mathbf{9}+H]^+$, and (b) $[\mathbf{10}+H]^+$.

3.2. The mechanistic pathway of the oxygen transfer

To gain more detailed insights into the competing oxygen migration reactions (Scheme 2), DFT calculations have been preformed at the B3LYP/6-311 + G(d,p) level of theory for fragmentation of the typical $[\mathbf{1}+H]^+$. Fig. 3 displays a potential energy diagram for the dissociation reactions as presented in Scheme 2, and the details structures of the corresponding species are available as Fig. 4 and Supplementary Fig. 2S.

To begin the mechanistic investigation on the oxygen transfer in fragmentation of $[\mathbf{1}+H]^+$, we should first identify the original protonation site of the molecule. There are two potential protonation sites for compound **1**: (i) protonation at the sulfonamic N6 to generate the ionic species **a** and (ii) at the tosyl O11 (or O12) to afford **b**. The calculated free energy of **a** is 36.5 kJ mol^{-1} lower than that of **b**, indicating a much more preferred protonation site of the sulfonamide N atom [17]. The sulfonamide N is also reported by the NMR investigation to be preferably protonated in solutions [30–33]. Noteworthy, inter-conversion between **a** and **b** is difficult to occur *via* 1,3-proton transfer, due to a considerable energy barrier (**a-TSb**) of 133.7 kJ mol^{-1}.

Protonation at the sulfonamide N6 in **a** weakens the N6—S5 bond, as indicated by the lengthened bond length (1.635 Å in **b** *versus* 2.073 Å in **a**). Cleavage of the N6—S5 bond in **a**, upon collisional activation, leads to formation of **inc1**, an ion–neutral complex (INC) consisting of a tosyl cation and a neutral aniline, which surmounts an energy barrier of 98.4 kJ mol^{-1} *via* the transition state of **a-TS1**. As for the optimized structure of **a-TS1** (Fig. 3), which has not been obtained previously [17], the vibrational mode

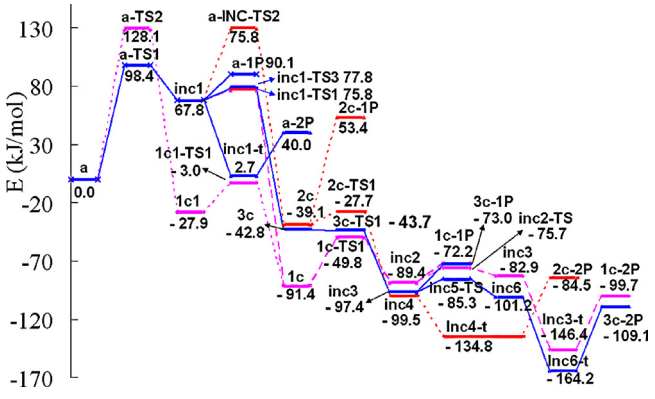


Fig. 3. The potential energy diagram for the oxygen transfer in dissociation of $[\mathbf{1}+H]^+$.

of the single imaginary frequency (i211.75 cm^{-1}) corresponds to extension of the N6—S5 bond (3.380 Å) accompanied with oscillation of the two amide protons to form two intramolecular hydrogen bonds (2.404 Å and 2.696 Å) with the two tosyl oxygen atoms.

INC is an interesting and important intermediate in the gas phase chemistry, and various chemical reactions may occur either in the ionic fragment alone or between the two partners prior to its final separation [16,17,34]. Interestingly, the calculated electronic excitation energy is negative (−0.6215 eV) for **inc1**, indicating that **inc1** can spontaneously undergo electron excitation along with electron transfer to generate the triple **inc1-t**, consisting of a *p*-tolylsulfinyl radical and an aniline radical cation. The triple **inc1-t** lies 65.2 kJ mol^{-1} below the singlet one in free energy. The more stability of **inc1-t** is attributed to the two stronger intramolecular hydrogen bonds (2.216 Å and 2.216 Å in **inc1** *versus* 2.134 Å and 2.053 Å in **inc1-t**) and the more p–π conjugation of the N6—C7 bond (1.348 Å in **inc1** *versus* 1.328 Å in **inc1-t**). Decomposition of **inc1** and **inc1-t** affords the tosyl cation (**a-1IP**, m/z 155) and the aniline radical cation (**a-2IP**, m/z 93), respectively.

Alternatively, the two partners in **inc1** can undergo the coupling reactions between the sulfonic group and the aniline ring, and afford protonated toluenesulfinates (*e.g.* **1c**), accompanied with migration of the activated hydrogen (the *ipso*-H on the analinic ring) to the sulfinyl O12. Due to the different coupling site (*ortho*, *meta*, and *para*) at the aniline ring, there are three potential isomeric species of protonated toluenesulfinates (**1c, 2c** and **3c**) *via* the transition state of **inc1-TS1**, **inc1-TS2** and **inc1-TS3**. As shown in Fig. 4, all these transition states show a shortening O11–C distance (2.248 Å in **inc1-TS1**, 1.706 Å in **inc1-TS2** and 2.699 Å in **inc1-TS3**) in structure. It should be noteworthy that this process involves migration of the tosyl O11 atom and reduction of the tosyl S5 atom. Also, **a** can directly undergo an intramolecular tosyl oxygen transfer reaction (**a-TS2**) to afford **1c**, *via* breakage of the N6—S5 bond (2.837 Å) and coupling of the tosyl oxygen with the phenyl ring (1.931 Å for the O11–C8 distance).

The subsequent dissociation of **1c** (**2c** or **3c**) *via* the breakage of the S5—O11 bond leads to completion of the tosyl oxygen transfer to the aniline ring, and affords the product ions of the protonated quino-imines (*e.g.* **1c-1IP**, m/z 108) and the hydroxyaniline radical cations (*e.g.* **1c-2IP**, m/z 109) in two competing reaction channels, respectively. Here, **1c** was selected as an example to illustrate the two competing dissociation channels. The subsequent charge-directed decomposition of **1c** leads to an INC of **inc2** *via* the transition state **1c-TS1**. Direct separation of **inc2** affords the protonated 6-iminocyclohexa-2,4-dienone (**1c-1IP**, m/z 108).

The mobile H8 in **inc2** can also be effectively transferred to phenolic oxygen O11 with a small energy barrier of 14.7 kJ mol^{-1}, which results in formation of another ion–neutral complex (**inc3**). Analogous to **inc1**, the triple state (**inc3-t**) of **inc3** is thermodynamically more stable than the corresponding singlet one by 63.5 kJ mol^{-1}. As shown in Fig. 4, there are two intramolecular hydrogen bonds in both **inc3** and **inc3-t**, with the types of N—H. . .O and O—H. . .O. The calculated electronic excitation energy is also negative one (−2.3467 eV), and thus **inc3** is spontaneously converted to the triple state one along with electron transfer between the two partners of the INC. Decomposition of **inc3-t** results in the 2-aminophenol radical cation (**1c-2IP**, m/z 109).

As shown in Fig. 3, the energy barrier of the four tosyl transfer processes follows the order of **2c-TS1** (128.9 kJ mol^{-1}) ~ **a-TS2** (128.1 kJ mol^{-1}) > **1c-TS3** (77.8 kJ mol^{-1}) ~ **3c-TS1** (75.8 kJ mol^{-1}). Thereby, **a** prefers to undergo the INC mediated tosyl oxygen migration in the CID process, rather than a direct transfer (*via* **a-TS2**). The order of prior site for most for the tosyl oxygen transfer is *ortho* ~ *para* > *meta* site in the anilinic ring. Analysis of the potential energy diagram in Fig. 3 indicated that the INC-mediated

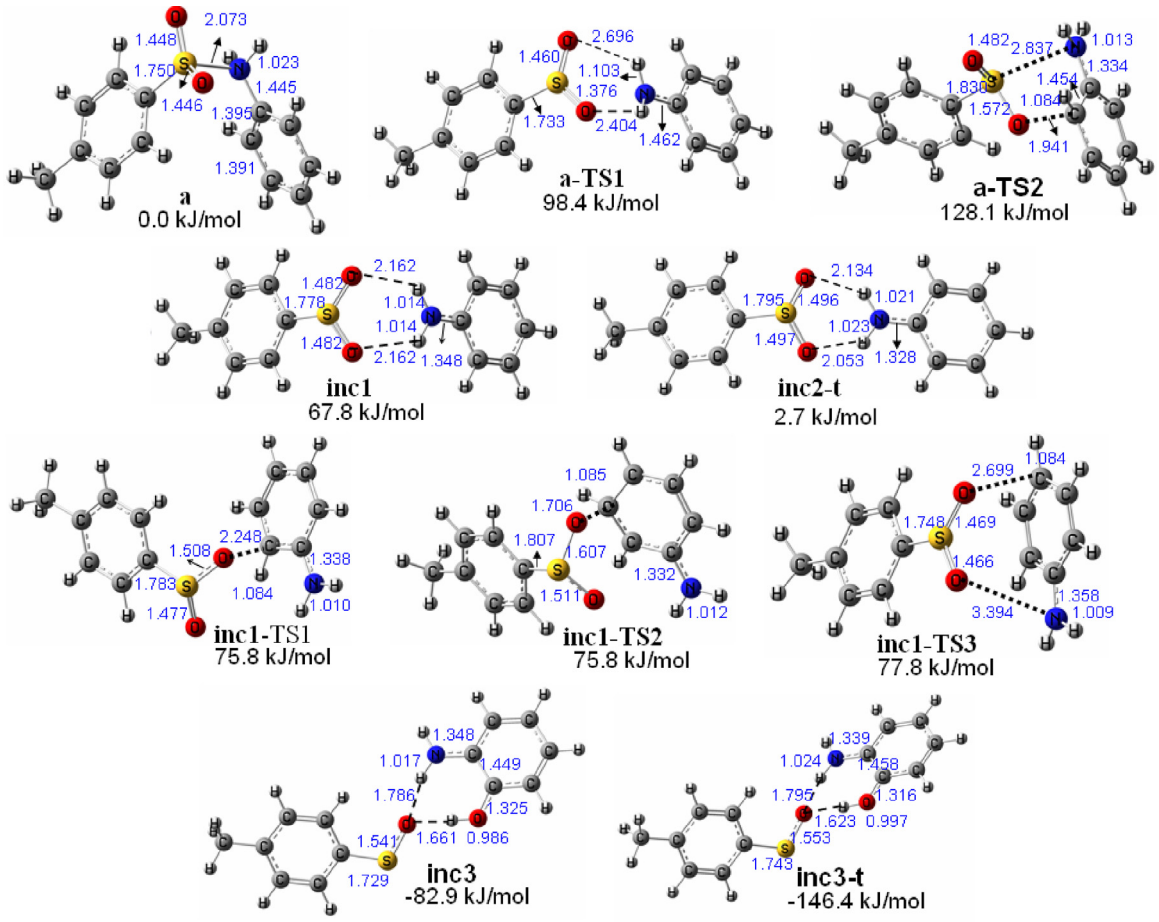


Fig. 4. The optimized structures of the key species involved tosyl oxygen transfer and ion–neutral complex mediated electron transfer in dissociation of [**1**+H]$^+$ at the b3lyp/6-311+g(d,p) level.

O—C coupling reaction is the common key step in the competing reaction channels of tosyl oxygen migration. Formation of the hydroxyaniline radical cation at *m/z* 109 (**1c-2IP**, **2c-2IP** or **3c-2IP**) is thermo-dynamically more favored than that of the protonated quino-imines at *m/z* 108 (**1c-1IP**, **2c-1IP** or **3c-1IP**), which is in good agreement with the experimental results (Table 1).

3.3. *Differentiation of the isomeric N-methylphenyl p-toluenesulfonamides*

Three methyl-substituted isomers (compounds **4**–**6**) were selected to investigate the positional factor on the fragmentation behaviors (Fig. 5). Different to compound **1**, the tosyl cation (*m/z* 155) was not observed in the CID–MS of the three isomers. Interestingly, an extra fragment ion at *m/z* 106 (**4-PH**, **5-PH** or **6-PH**), resulting from hydride transfer in the [tosyl cation/methylaniline] INC [34] (Scheme 1S), was observed in the CID–MS. Due to the difference in the substituent mode, the stability of the fragment ions at *m/z* 106 follows the order of **6-PH** (*para*, 15.0%) > **4-PH** (*ortho*, 4.0%) > **5-PH** (*meta*,1.0%), and thereby the relative abundance for the three ions obeys the same order in the CID–MS spectra, which was consolidated by analysis of the corresponding energy-resolved plots (the Supplementary Fig. 3S).

Moreover, significantly different abundance of the product ions at *m/z* 122 and *m/z* 123, formed *via* migration of the tosyl oxygen, was obtained in the MS/MS spectra in Fig. 5. As stated previously, the favorite site in the anilinic ring for the tosyl oxygen transfer follows the order of *meta-* < *ortho-* < *para-* in the CID process of [**1**+H]$^+$. As expected, the relative abundance of the fragment ion at *m/z* 122 from the three isomers follows the reverse order of *meta-* (32.8%) > *ortho-* (4.8%) > *para-* (0.4%), due to the block of a methyl group at different site of the aniline ring. Similar results have obtained for the fragment ions at *m/z* 123: *meta-* (20.7%) > *ortho-* (11.5%) > *para-* (1.1%). Additionally, the ion at *m/z* 123 is more abundant than the ion at *m/z* 122 for the *ortho-* and the *para*-isomers, while the *meta-* isomer shows the opposite result.

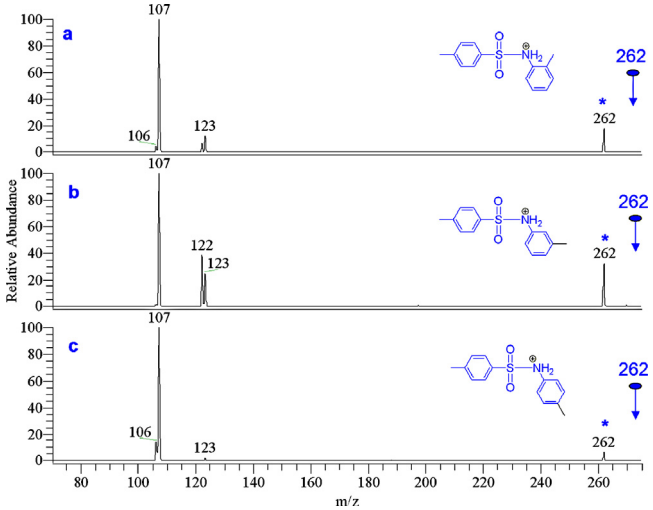


Fig. 5. The CID–MS spectra of three isomeric *p*-toluenesulfonyl methylanilines: (a) [**4**+H]$^+$, (b) [**5**+H]$^+$ and (c) [**6**+H]$^+$

In addition, it was observed that $[\mathbf{6}+H]^+$ (7.4%) is much more feasible to undergo fragmentation than the *ortho*- $[\mathbf{4}+H]^+$ (17.5%) and the *meta*-$[\mathbf{5}+H]^+$ (30.0%) isomers under the same CID conditions. These differences have been consolidated by analysis of the energy-resolved plots (Supplementary Fig. 3S), in which the three isomers show different main fragment ions with the relative abundance more than 10%: ions at *m*/*z* 107 and *m*/*z* 123 for $[\mathbf{4}+H]^+$, ions at *m*/*z* 107, *m*/*z* 122 and *m*/*z* 123 for $[\mathbf{5}+H]^+$, and ions at *m*/*z* 107 and *m*/*z* 106 for $[\mathbf{6}+H]^+$. As a result, the three isomers can be differentiated solely based on the tandem MS experiments.

4. Conclusion

The gas phase chemistry of the protonated *N*-phenyl *p*-toluenesulfonamides has been explored experimentally and theoretically, which leads to an interesting tosyl oxygen transfer reaction and INC-mediated electron transfer. Dissociation of the protonated molecules gave an INC of [tosyl cation/aniline], which underwent decomposition to generate the tosyl cation and the aniline radical ion. In addition, the coupling reactions between the two partners of the [tosyl cation/aniline] occurred to afford an ionic species of toluenesulfinate, which underwent the subsequent dissociation reactions to afford protonated quino-imines (*e.g.* **1c-1IP**) and the hydroxyaniline radical cation (*e.g.* **1c-2IP**). The above processes involve migration of the tosyl oxygen, and calculation results indicate that both the *ortho*- and the *para*-positions in the analinic ring are favorite for the tosyl oxygen transfer, and formation of radical cation involves the INC mediated electron excitation along with the electron transfer between the partners of the INC. In addition, significant difference in the product ion distribution has obtained in the CID–MS spectra of the three isomeric *N*-methylphenyl *p*-toluenesulfonylamides, indicating that these isomers can be distinguished by MS. The above results presented in this work will provide a better understanding of the radical ion formation in the ESI tandem MS spectra, and the mechanistic intramolecular migration of the tosyl oxygen. The relevant investigation will be preformed in our succeeding work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijms.2014.11.003.

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