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RESEARCH ARTICLE

Low-Energy Collision-Induced Dissociation Mass Spectra of Protonated *p*-Toluenesulfonamides Derived from Aliphatic Amines

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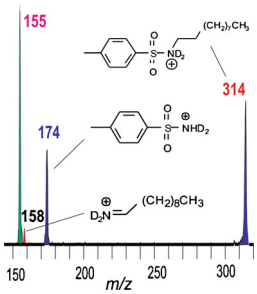

Abstract. Collision-induced fragmentation of protonated *N*-alkyl-*p*-toluenesulfonamides primarily undergo either an elimination of the amine to form CH_3-(C_6H_4)-SO_2^+ cation (*m/z* 155) or an alkene to form a cation for the protonated *p*-toluenesulfonamide (*m/z* 172). To comprehend the fragmentation pathways, several deuterated analogs of *N*-decyl-*p*-toluenesulfonamides were prepared and evaluated. Hypothetically, two mechanisms, both of which involve ion-neutral complexes, can be envisaged. In one mechanism, the S–N bond fragments to produce an intermediate [sulfonyl cation/amine] complex, which dissociates to afford the *m/z* 155 cation (Pathway A). In the other mechanism, the C–N bond dissociates to produce a different intermediate complex. The fragmentation of this [*p*-toluenesulfonamide/carbocation] complex eliminates *p*-toluenesulfonamide and releases the carbocation (Pathway B). Computations carried out by the Hartree-Fock method suggested that the Pathway B is more favorable. However, a peak for the carbocation is observed only when the carbocation formed is relatively stable. For example, the spectrum of *N*-phenylethyl-*p*-toluenesulfonamide is dominated by the peak at *m/z* 105 for the incipient phenylethyl cation, which rapidly isomerizes to the remarkably stable methylbenzyl cation. The peaks for the carbocations are weak or absent in the spectra of most of *N*-alkyl-*p*-toluenesulfonamides because alkyl carbocations, such as the decyl cation, rearrange to more stable secondary cations by 1,2-hydride and alkyl shifts. The energy freed is not dissipated, but gets internalized, causing the carbocation to dissociate either by transferring a proton to the sulfonamide or by releasing smaller alkenes to form smaller carbocations. The loss of the positional integrity in this way was proven by deuterium labeling experiments.

Key words: Collision-induced fragmentation, Sulfonamides, Fragmentation, Ion neutral complex

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Introduction

Aromatic sulfonamides are widely deployed as pharmacophores for drug industry. Several pharmaceuticals on the market, such as Sildenafil, Celecoxib, Aprenavir, and many others are sulfonamides [1]. LFI, one of the effective compounds known to reduce tissue damage associated with anthrax is also a sulfonamide [2]. In fact, sulfonamides are extensively used as antimicrobial agents in animal husbandry. Consequently, sulfonamide metabolic residues are commonly found in dairy products and meat [3]. Electrospray and atmospheric-pressure chemical ionization mass spectrometry in conjunction with liquid chromatography provides ideal analytical procedures for characterization and quantification of sulfonamides and their metabolites [4, 5]. However, to facilitate unknown metabolites identification by mass spectrometry, their fragmentation mechanisms must be well understood.

Mass spectrometric fragmentation of protonated and deprotonated sulfonamides have been extensively investigated [6–10]. However, most sulfonamides that have been investigated are those of aniline-based aromatics [6, 7, 11–13] or cyclic [14] and secondary amines [8]. Some protonated sulfonamides afford a unique loss of SO_2 by an intramolecular rearrangement [8]. Protonated benzenesulfonamides of anilines, on the other hand, frag-

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ment to produce radical cations [7]. The fragmentation mechanism described by Hu et al. for this fragmentation is of particular interest because it violates the so-called "even-electron" rule [6]. According to the proposed mechanism, the S–N bond of the sulfonamide dissociates spontaneously upon protonation of the molecule to produce an ion-neutral complex. A subsequent charge transfer between the two partners of the complex gives rise to ionized anilines [6]. In an investigation of fragmentation mechanisms of the benzenesulfonamides synthesized from aliphatic primary amines, we found that they undergo neither the SO_2 elimination nor the formation of radical cations. Our results from a number of derivatives enable several generalizations useful for interpreting CID spectra of protonated sulfonamides of open-chain aliphatic amines.

Experimental

Materials

All solvents and reagents were obtained from commercial suppliers (Aldrich Chemical Co., St. Louis, MO, USA) and used as purchased. The synthesis of [1,1-$^2H_2$]decanol, [2,2-$^2H_2$]decanol, [3,3-$^2H_2$]decanol, [4,4-$^2H_2$]decanol and [5,5-$^2H_2$]decanol was described previously [15, 16]. These alcohols were converted to corresponding aldehydes by oxidation with pyridiniumchlorochromate (see Supplementary Data for synthetic details). The aldehydes, decanal, [1-^{2}H]decanal, [2,2-$^2H_2$]decanal, [3,3-$^2H_2$]decanal, [4,4-$^2H_2$]decanal, and [5,5-$^2H_2$]decanal were converted to oximes by allowing them to react with NH_2OH, and then reducing the products with lithium aluminum hydride, or lithium aluminum deuteride, to generate amines. Amines were derivatized with *p*-toluenesulfonyl chloride to obtain sulfonamide. All sulfonamide products were detected as one spot upon thin-layer chromatographic analysis (precoated 0.25 mm silica gel plates from Fisher Scientific, Hampton, NH, USA). All products were detected as a single peak on gas-chromatographic analysis, except those for the oximes, which gave a double peak representing the *E* and *Z* isomers. EI mass spectra were recorded on a HP 5970 series Mass Selective Detector coupled to a Hewlett Packard 5890 Series II gas chromatograph.

Mass Spectrometry

The collision-induced dissociation (CID) mass spectra were recorded on a Micromass Quattro I tandem mass spectrometer equipped with an electrospray ion source. Samples were introduced to the source as acetonitrile-water-formic acid ($9{:}1{:}10^{-2}$) solutions, at a flow rate of 320 μL h^{-1}, for positive-ion MS analysis. The source temperature was held constant at 80°C. The capillary voltage was held at 4000 V. The argon gas pressure in the collision cell was set to attenuate precursor ion transmission by 30%–50%. For experiments performed in deuterated solvents D_2O (99.8 atom % D; Aldrich), and CD_3COOD (99 atom % D; Cambridge Isotope Lab., MA, USA) were used.

Computational Methods

All calculations were performed using the Gaussian 03 W program package [17]. Calculations were performed using the Hartree-Fock method. Calculated structures were opti-

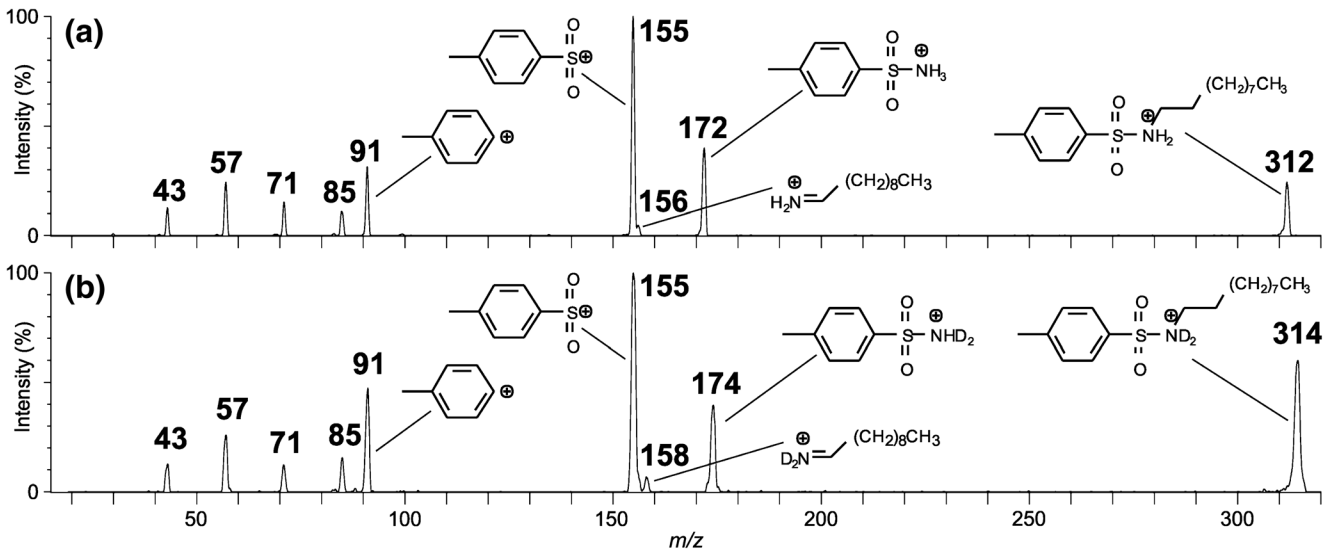


Figure 1. Product ion spectra of *m/z* 312 and 314 ions derived from *N*-decyl-*p*-toluenesulfonamide and *N*-decyl-*p*-[*N*-$^2H_2$]toluenesulfonamide by positive-ion electrospray ionization from respective CH_3CN/H_2O **(a)**, or CH_3CN/D_2O **(b)** solutions (collision energy setting, 15 eV)

mized to obtain stationary states using a 6-31G(d) split-valence basis set. Electronic energies of the structures were then recalculated using density functional theory with the B3LYP exchange-correlation functional [18, 19] and a 6-31+G(d) basis set. Frequency analysis of optimized structures was used to distinguish energy minima from saddle points. Zero-point energy corrections were made to the energies of stationary states, and the corrections were scaled by a factor of 0.9135 [20].

Results and Discussion

The CID mass spectrum recorded from the *m/z* 312 ion for protonated *N*-decyl-*p*-toluenesulfonamide (**1**) is depicted in Figure 1. To start with this spectrum is very different from those previously reported from other protonated sulfonamides because of the absence of a peak for a SO_2 loss [8, 13], or peaks that represent radical cations [7]. In contrast, the CID spectrum of protonated *N*-decyl-*p*-toluenesulfonamide showed an in-

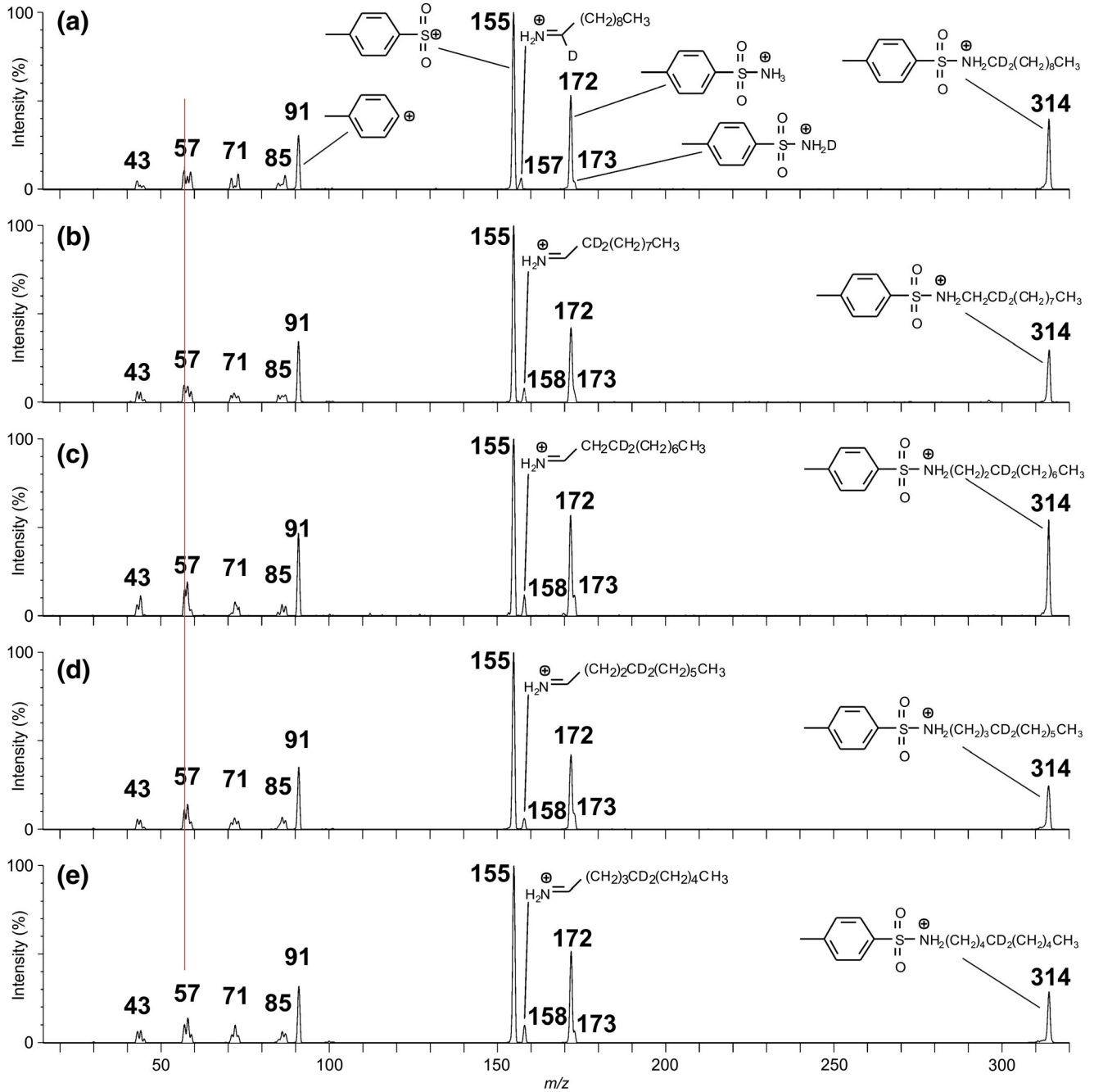
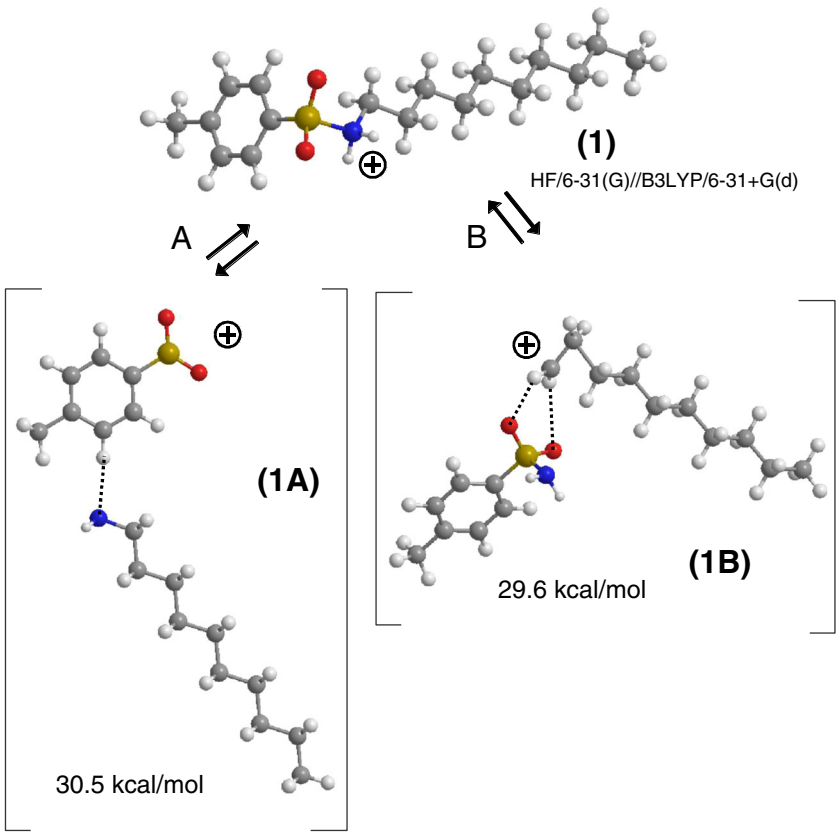


Figure 2. Product ion spectra of *m/z* 314 ions derived from *N*-[1-$^2H_2$]decyl-*p*-toluenesulfonamide **(a)**, *N*-[2-$^2H_2$]decyl-*p*-toluenesulfonamide **(b)**, *N*-[3-$^2H_2$]decyl-*p*-toluenesulfonamide **(c)**, *N*-[4-$^2H_2$]decyl-*p*-toluenesulfonamide **(d)**, and *N*-[5-$^2H_2$]decyl-*p*-toluenesulfonamide **(e)** by electrospray ionization from $CH_3CN/H_2O/H^+$ solutions (collision energy setting, 15 eV)

tense peak at *m/z* 172 for the formation of protonated *p*-toluenesulfonamide by an elimination of a decene molecule (Figure 1). For the formation of the *m/z*-172 ion, the C–N bond must be cleaved and a hydrogen atom from the decyl group must be transferred to the *p*-toluenesulfonamide moiety. Hydrogen transfers that occur to eliminate an alkene under CID conditions sometimes follow a specific pathway [21]. For example, upon collision-induced activation, the anion derived from 1-decyl sulfate anion undergoes fragmentation by transferring a proton specifically from the beta position of the decyl group to the sulfate group by a charge-driven mechanism to eliminate a decene molecule [21]. In contrast, the hydride transfer required for the loss of an alkene from "onium" cations, such as immonium, oxonium, and sulfonium, follows a less specific multistep pathway that involves ion-neutral-complex intermediates [22]. Before an ion-neutral-complex dissociates, the less stable cationic species within the complex undergoes rapid rearrangements by 1,2-hydride and alkyl shifts to more stable carbenium ions or proton-bridged complexes [22, 23]. Consequently, the positional integrity of hydrogen atoms in a carbenium ion is rapidly lost. Similar observations have been reported from protonated dibenzylamine, which eliminates ammonia upon activation [24]. Although the proton necessary for the loss of ammonia came from the aromatic ring, it did not originate from any specific position in the aromatic ring. The reasoning was that the ion-neutral complex formed from protonated dibenzylamine dissociated first to form an arenium ion, which allowed the deuterium atoms on the aromatic ring to scramble [25].

To determine if a specific hydrogen-atom transfer occurs during the loss of decene from protonated *N*-alkyl-*p*-toluenesulfonamides, several deuteriated *N*-decyl-*p*-toluenesulfonamides were synthesized and their CID spectra were recorded. The results obtained from *N*-decyl-*p*-[*N*-$^{2}H_{2}$]toluenesulfonamide cation (*m/z* 314) showed that the positional integrity of the protons is not lost when they are on the nitrogen atom (Figure 1b) because the spectrum showed a peak at *m/z* 174 without any adjacent peaks for any isotopologs. In contrast, the *m/z* 172 peak in all spectra recorded from several other isotopomers of *N*-[$^{2}H_{2}$]decyl-*p*-toluenesulfonamide (with the deuterium substitution on the alkyl chain) showed a small peak at *m/z* 173 indicating that the hydrogen atom that is transferred did not originate from any specific position of the decyl chain (Figure 2).

We envisaged that protonated *p*-toluenesulfonamides derived from aliphatic amines fragment upon activation by two different pathways (Scheme 1). A direct elongation and a heterolytic cleavage of the S–N bond could lead to the formation of the ion/neutral Complex A, which could then dissociate to form the *m/z* 155 ion (Pathway A, Scheme 1). Alternatively, a direct cleavage of the N–C bond could generate the ion/neutral Complex B (Pathway B, Scheme 1).



Scheme 1. Hypothetical pathways of formation and computed relative energies based on HF/6-31(G)//B3LYP/6-31+G(d) level of theory, of ion/neutral complexes formed upon collisional activation of protonated *N*-alkyl-*p*-toluenesulfonamides

Computations carried out by the Hartree-Fock method suggest that the Complex 1B (25.0 kcal/mol) is more favorable than Complex 1A (40.0 kcal/mol), although recalculated energies at the B3LYP/6-31+G(d) level predict Complex B (29.6 kcal/mol) and Complex A (30.5 kcal/mol) to be similar in energy. A peak for the incipient carbenium ion in the spectra of *N*-alkyl-*p*-toluenesulfonamides is generally weak or absent unless it is tertiary carbenium or any other relatively stable ion (Figure 3). For example, a prominent peak is observed at *m/z* 57 in the spectrum of protonated *N*-(*t*-butyl)-*p*-toluenesulfonamide (Figure 3a) but an analogous peak for a decyl cation is absent at *m/z* 141 in the spectrum of protonated *N*-decyl-*p*-toluenesulfonamides (Figure 1a). In other words, the intensity of the peak for the incipient carbenium ion depends on the relatively stability of carbenium ions. For example, the fragmentation spectrum of *N*-phenylethyl-*p*-toluenesulfonamide is entirely dominated by a peak at *m/z* 105 because the carbenium generated is particularly stable (Figure 4).

Within an ion/neutral complex, the two participants are held together only by Coulombic attractive forces (Scheme 1B). It is known that the carbenium ions isomerize within the complex to more stable forms by 1,2-hydride shifts [26]. Even the phenylethyl cation has been reported to isomerize to the more stable methylbenzyl cation [27, 28]. Our computations indicate the structure of the *m/z* 105 to be spiro[2.5]octa-5,7-dien-4-ylium cation (ethylenebenzenium cation) (Supplementary Figures 1 and 2). The stability of this ethylenebenzenium cation drives the fragmentation of protonated *N*-phenylethyl-*p*-toluenesulfonamide primarily by the Pathway B (Scheme 2).

In addition to the direct dissociation of Complex B, a proton transfer from the alkyl group to the amino group can also occur (Scheme 1). In this way, an alkene is eliminated and a protonated *p*-toluenesulfonamide (*m/z* 172) is produced. As mentioned previously, the single hydrogen atom that is necessary for the formation of the *m/z* 172 ion does not originate from any specific position of the decyl chain. This is evident because none of the spectra recorded from an array of *N*-[$^2H_2$]decyl-*p*-toluenesulfonamides showed a dominant peak specifically at *m/z* 173. Instead, the spectra showed a prominent peak at *m/z* 172 accompanied by a small peak at *m/z* 173 for the corresponding monodeuterio isotopolog (Figure 2).

In practice, a peak for the initial carbenium ion is rarely observed in the spectra of protonated sulfonamides derived from long-chain primary aliphatic amines (the same can be said for the ammonia loss from protonated aliphatic primary amines; unpublished observations). For example, a peak at *m/z* 141 is not observed for the decyl cation in the spectrum of *N*-decyl-*p*-toluenesulfonamides (Figure 1). The primary carbocations, such as the decyl cation, apparently rearrange

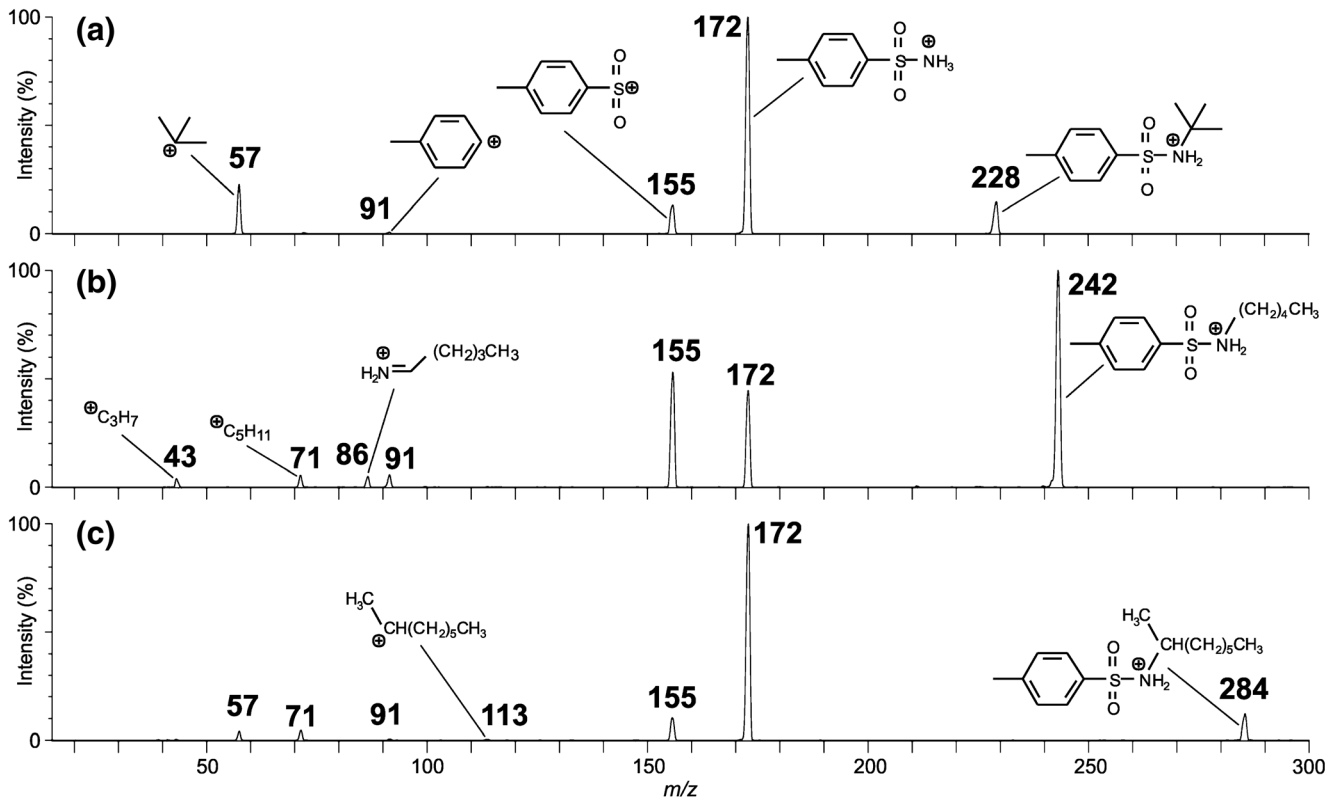


Figure 3. Product ion spectra of *m/z* 228, 242, and 284 ions generated by electrospray ionization from protonated *N*-(*t*-butyl)-*p*-toluenesulfonamide **(a)**, *N*-pentyl-*p*-toluenesulfonamide **(b)**, and *N*-(*2*-octyl)-*p*-toluenesulfonamide **(c)**, respectively (collision energy setting, 15 eV)

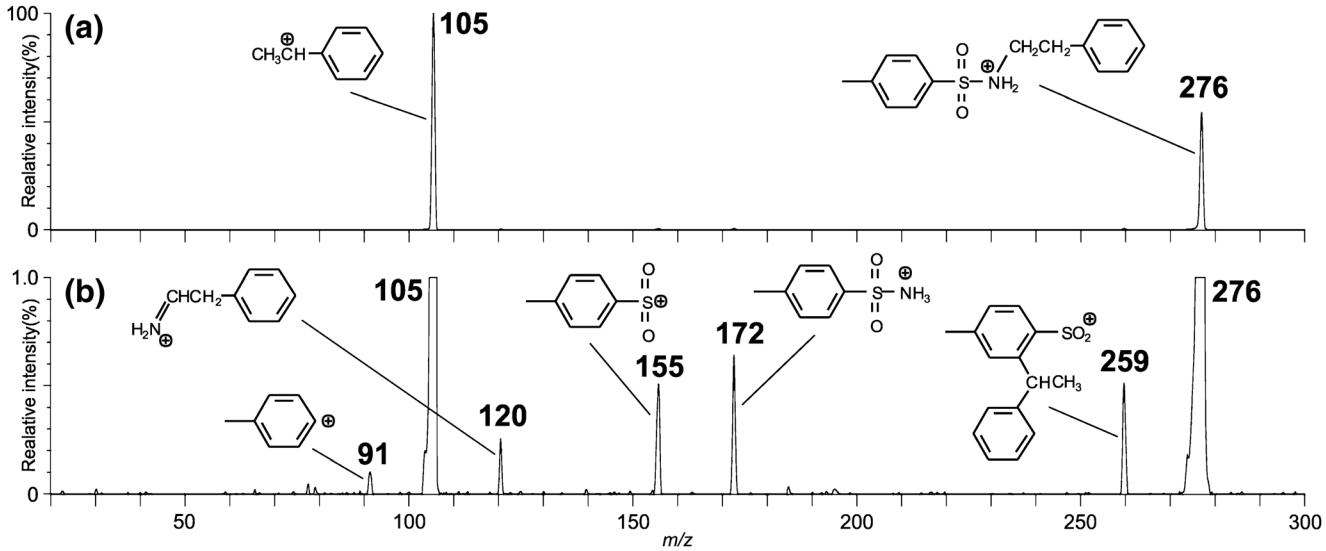
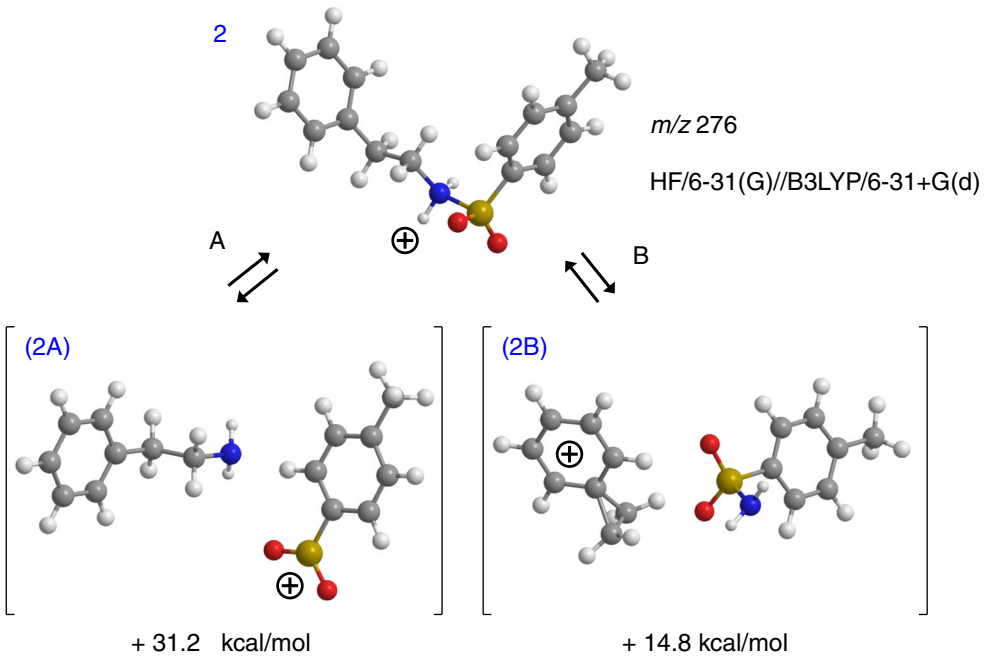


Figure 4. Product ion spectrum of *m/z* 276 ions of protonated *N*-phenylethyl-*p*-toluenesulfonamide **(a)** (collision energy setting, 15 eV); **(b)** represents a vertical expansion of 100 times to highlight the minor peaks

very rapidly to more stable secondary cations by 1,2-hydride shifts. By this process, which is generally referred to as "scrambling," the positional integrity of hydrogen atoms in the carbon chain is lost [25]. Consequently, the protonated *p*-toluenesulfonamide (*m/z* 172) formed by the alkene elimination acquired only a fraction of the deuterium labeling from any of the double-deuterium labeled alkyl groups in the sulfonamides used in this study. If the carbocation underwent total scrambling before the proton transfer occurs, the ratio of the intensities of the *m/z* 172 and 173 peaks should be the same for all the [$^1H_2$]-isotopologs. However, Figure 2 shows that the intensity of the *m/z* 173 peak is significantly higher in the spectra of sulfonamides of [3,3-$^2H_2$]decylamine and [4,4-$^2H_2$] decylamine (Figure 2c and d), which indicate that the proton transfer rate is higher than the scrambling rate.

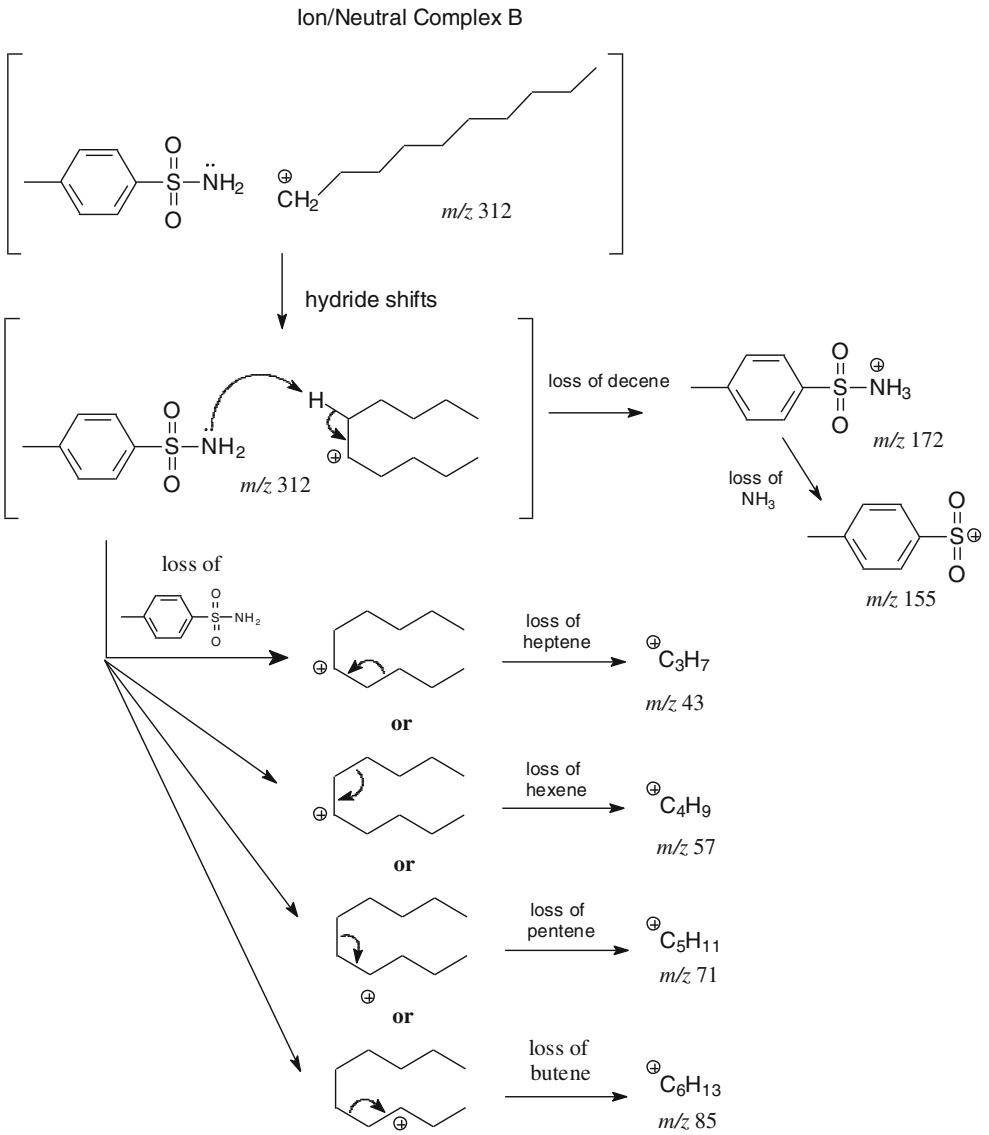
The energy freed by the rearrangement of the initial primary carbenium ion to a more stable secondary carbocation, however, is not dissipated to the surroundings. Instead, the energy gets internalized to vibrational modes



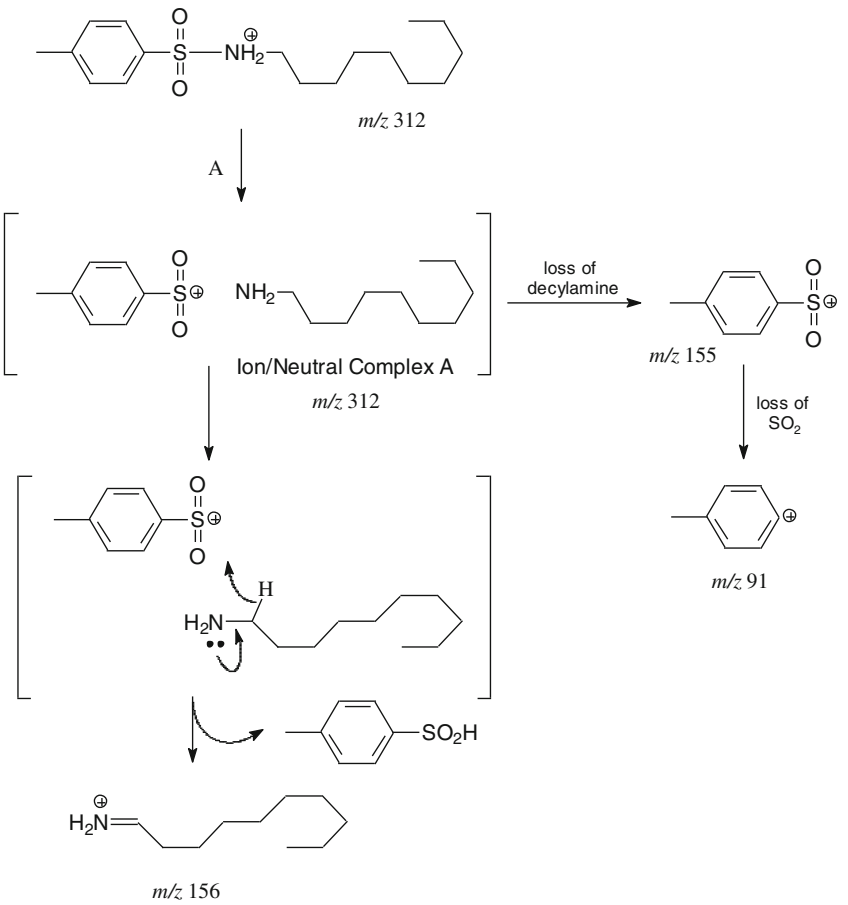
Scheme 2. Proposed formation of *m/z* 105 ion upon collisional activation of protonated *N* phenylethyl-*p*-toluenesulfonamide via ion-neutral Complex 2B. Relative energies presented are based on HF/6-31(G)//B3LYP/6-31+G(d) level of theory

and increases the internal energy of the ion providing impetus for the carbenium ion to undergo immediate fragmentation to smaller and more stable carbenium ions, usually by eliminating an alkene molecule. For example, the spectrum from *N*-decyl-*p*-toluenesulfonamide does not show a peak at *m/z* 141 for the decyl cation itself, but it shows a series of peaks at *m/z* 43, 57, 71, 85, and 99 for smaller carbocations (Figure 1). In the spectra of *N*-[$^2H_2$]decyl-*p*-toluenesulfonamides, all peaks for these smaller carbocations appeared as multiplets, indicating that "scrambling" has taken place in the initial precursor carbocation as envisaged by the proposed mechanism (Scheme 3; Figure 2).

The other significant peaks in the spectrum of protonated *N*-decyl-*p*-toluenesulfonamide are found at *m/z* 155, 156 (small), and 91. The formation of the *m/z* 155 ion can be rationalized by an ammonia loss from the *m/z* 172 ion (Scheme 3). The *m/z* 155 ion can then lose SO_2 to form the of *m/z* 91 ion. The low intensity peak at *m/z* 156 drew our attention because it represents an iminium ion. The formation of the *m/z* 156 ion should occur via a specific hydride transfer mechanism because deuterium-labeling studies showed a specific peak shift to *m/z* 157 for *N*-[1-$^2H_2$]decyl-*p*-toluenesulfonamide (Figure 2). The spectra of sulfonamides with $^2H_2$-labeling at 2-, 3-, or 4-position of the amino moiety showed the corresponding peak at *m/z* 158. This result established that the hydrogen transfer takes place explicitly from the position 1 of the carbon chain. Thus, the formation of the *m/z* 156 should not involve an unbound carbocation such that given in Pathway B because it would lead to deuterium scrambling. The fragmentation should occur via the ion/neutral Complex A, in which the amine participates as a neutral molecule (Scheme 4). The low



Scheme 3. Fragmentation of the *m/z* 312 ion for protonated *N*-decyl-*p*-toluenesulfonamide by Pathway B (note that only a few arbitrarily selected cations are illustrated here; many others are possible)



Scheme 4. Further fragmentation of protonated *N*-decyl-*p*-toluenesulfonamide (*m/z* 312) via Pathway A

intensity of the peaks is understandable because this is not an energetically favored pathway.

From the spectra of numerous sulfonamides that were investigated, it was evident that the relative ratios of the *m/z* 155 and 172 peaks were different for different compounds. According to the proposed pathways, both these ions could originate via ion-neutral Complexes A and B. To explore the feasibility whether these intensity differences could be correlated to the relative contributions of the two pathways to the fragmentation of the precursor ion, we recorded intensity profiles of the product ions generated upon collisional activation. Although it appeared challenging because to some extent *m/z* 155 ion could originate also from the *m/z* 172 ions by an ammonia loss, the breakdown profiles that were constructed for protonated *N*-pentyl-*p*-toluenesulfonamide and *N*-(2-octyl)-*p*-toluenesulfonamide revealed that the intensities of the *m/z* 155 and 172 peaks, obtained at low collision energies, are useful to determine the relative contribution of each pathway. Protonated *N*-pentyl-*p*-toluenesulfonamide is more defiant to fragmentation than that of the *N*-(2-octyl)-*p*-toluenesulfonamide, although the former is the smaller ion (Figure 5). At a laboratory-frame collisional energy of 4 eV, protonated *N*-pentyl-*p*-toluene sulfonamide (*m/z* 242) underwent only a little fragmentation to produce peaks at *m/z* 172 and *m/z* 155 with a relative intensity ratio of about 2:1. This ratio indicated that the fragmentation via Complex B is somewhat more favorable than the pathway involving Complex A. In contrast, protonated *N*-(2-octyl)-*p*-toluenesulfonamide (*m/z* 284) underwent more severe fragmentation, even at a laboratory-frame collisional energy as low as 4 eV. The *m/z* 284 ion dissociated to furnish an intense peak at *m/z* 172, and the intensity ratio of the *m/z* 172 to 155 peaks was about 30:1. This difference in ratios indicated that the replacement of the primary alkyl group with a secondary alkyl group significantly favors the formation of Complex B over Complex A. Apparently, the secondary alkyl group seems to lower the activation energy required for the formation of Complex B more than for the Complex A.

When the collision energy was increased above 8 eV, the peak intensity ratio between *m/z* 172 and *m/z* 155 began to drop for both compounds. This was expected because at higher collisions energies the *m/z* 172 ion starts to lose a molecule of ammonia by a secondary process to form the ion at *m/z* 155. In fact, at a collision energy setting of 11–14 eV, the peak intensity of *m/z* 155 becomes greater than that of the peak at *m/z* 172 for both compounds, indicating that at higher collision energies the *m/z* 155 ion originates more by the secondary fragmentation of the *m/z* 172 ion. This observation highlights the usefulness of the breakdown

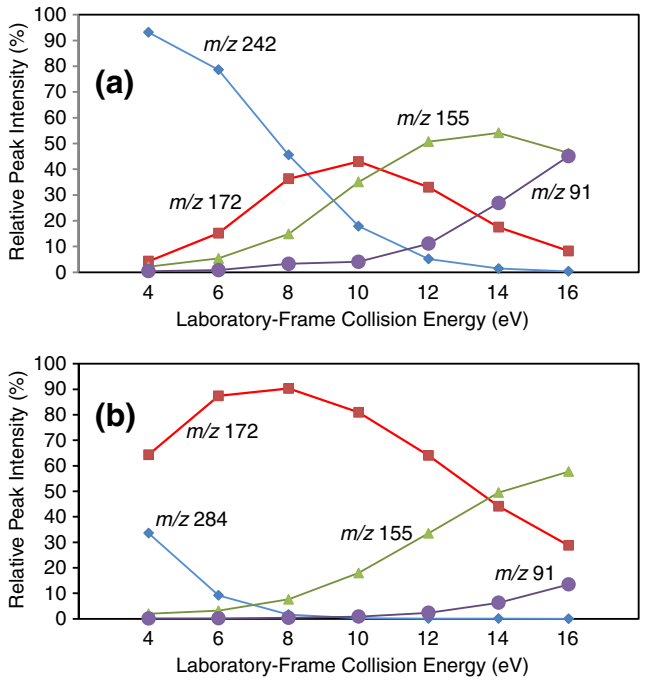
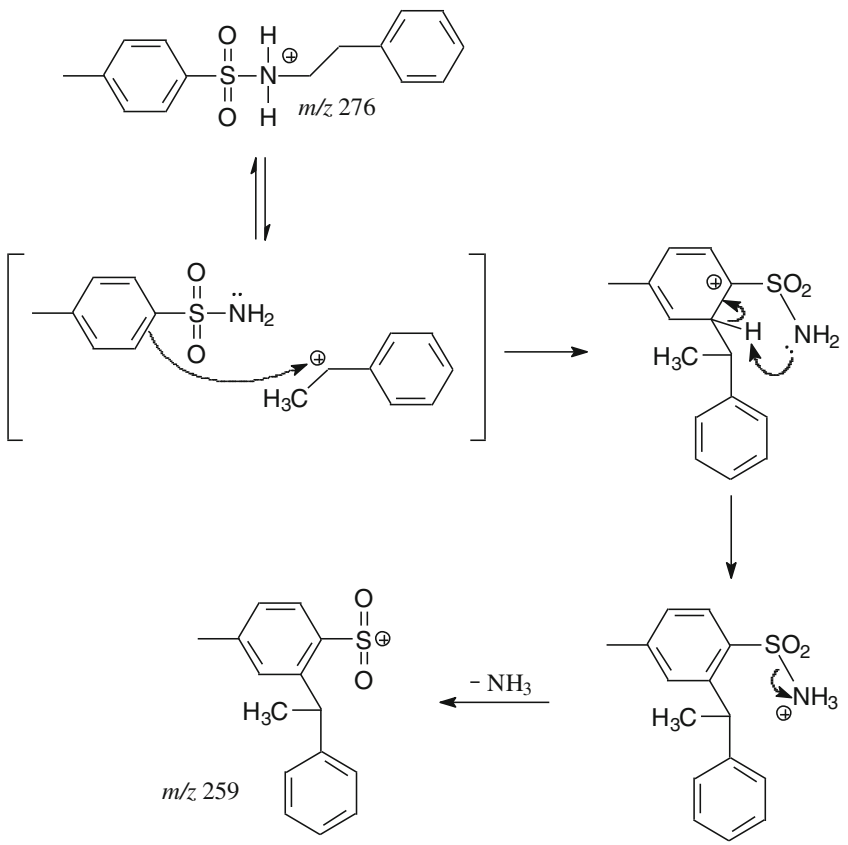


Figure 5. Plot of percentage relative intensities of peaks versus laboratory-frame collision energy for *m/z* 242 (-◆-), 172 (-■-), 155 (-▲-), and 91 (-●-) ions derived from *N*-pentyl-*p*-toluenesulfonamide **(a)**, and *m/z* 284 (-◆-), 172 (-■-), 155 (-▲-), and 91 (-●-) ions derived from *N*-(2-octyl)-*p*-toluenesulfonamide **(b)**, respectively

graphs to determine the fragmentation pathways. In other words, only results from low collision energies should be deployed to estimate which ion-neutral complex is energetically preferred.

The iminium ion that represents the peak at *m/z* 156 in the spectrum of protonated *N*-decyl-*p*-toluenesulfonamide is generated via Complex A (Scheme 4). Only a very small portion of the precursor ions follow this reaction channel via Complex A. Low intensity peaks for the iminium ions are observable for 2-octyl or *tert*-butyl derivatives, which indicate that only a minute percentage of the Complex A dissociates to form iminium ions.

The spectrum of protonated *N*-phenylethyl-*p*-toluenesulfonamide (*m/z* 276) shows a weak but significant peak at *m/z* 259 for an ammonia loss (Figure 4). Because the relative intensity of the *m/z* 259 peak is only about 0.5%, the vertical scale had to be multiplied by 100 to make it visible (Figure 4b). In a previous publication, we reported that protonated dibenzylamines, upon collision-induced activation, loses ammonia [24]. Tandem mass spectrometric experiments conducted with appropriate deuterium-labeled dibenzylamines confirmed that the additional proton required for this enigmatic ammonia loss originated from the ortho positions of the phenyl rings and not from the benzylic methylene groups. Thus, we envisaged that the ammonia loss observed from protonated *N*-phenylethyl-*p*-toluenesulfonamide would follow an analogous pathway



Scheme 5. Proposed fragmentation of the *m/z* 276 ion for protonated *N*-phenylethyl-*p*-toluenesulfonamide by Pathway A

(Scheme 5). The methylbenzyl cation could initiate an electrophilic attack on the phenyl group by removing a pair of electrons from the aromatic sextet yielding an arenium ion (Scheme 5). The highly reactive arenium ion then stabilizes itself by regenerating the aromatic ring by donating a ring proton to the amino group, thereby generating a protonated amine intermediate (Scheme 5), which then undergoes a charge-driven heterolytic cleavage to eliminate ammonia.

Conclusions

Protonated *N*-alkyl-*p*-toluenesulfonamides primarily undergo fragmentation by two pathways. One pathway (Pathway A) generates predominantly the *p*-toluenesulfonyl cation (*m/z* 155). The second pathway (Pathway B) generates protonated *p*-toluenesulfonamide (*m/z* 172) by eliminating an alkene, or a carbocation by eliminating *p*-toluenesulfonamide as a neutral molecule. The relative intensities of the peaks at *m/z* 155 and 172 indicate which fragmentation mechanism takes precedence. When the initial fragmentation produces a remarkably stable carbocation, such as the methybenzyl cation, the fragmentation follows overwhelmingly the Pathway B, and the spectra are virtually dominated by the peak for the carbocation, whereas the peaks at *m/z* 155 and 172 are negligibly small. On the other hand, when the fragmentation leads to a relatively unstable incipient carbocation, such as the decyl cation, Pathway A takes precedence. In general, the CID spectra of *p*-toluenesulfonamides derived from aliphatic amines are very different from those of aromatic amines. The positive ion CID spectra of aromatic amine derivatives are dominated by the peaks for SO_2 loss and radical cations derived from the amine moiety. Analogous peaks are not observed in the CID spectra of *p*-toluenesulfonamides derived from aliphatic amines.

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