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Intramolecular Charge Transfer in the Gas Phase: Fragmentation of Protonated Sulfonamides in Mass Spectrometry

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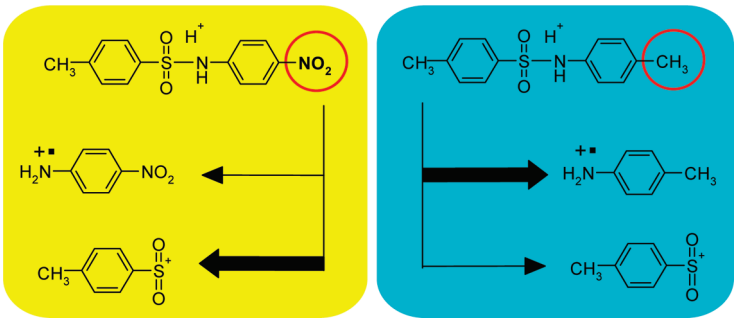

The fragmentation of protonated molecules (MH^+) in mass spectrometry usually results in even-electron product ions, but the MH^+ ions of sulfonamides are different as they often produce dominant radical cations of the constituent amines. For a series of benzenesulfonamides of anilines that bear various substituents, we found that the sulfonamides are preferentially protonated at the nitrogen, which is different from the carboxylic amides. Upon N-protonation, the S−N bond dissociates spontaneously to produce an intermediate [sulfonyl cation/aniline] complex. Within the ion−neutral complex, charge transfer between the two partners occurs in the gas phase to give rise to the ionized anilines. A substantial energy barrier was found to govern the reaction, which is consistent with the outer-sphere electron transfer mechanism. This energy barrier prevents the charge transfer when a strong electron-withdrawing substituent is attached to the aniline moiety. In contrast, when the aniline bears an electron-donating group, charge transfer is still more favorable than the dissociation of the intermediate ion−neutral complex, in spite of the existence of the energy barrier, and therefore dominates. A correlation was observed between the intensities of the ionized anilines and the ionization energies of these anilines.

Introduction

Electrospray ionization (ESI) mass spectrometry, which is convenient for structural determination for organic chemists, produces protonated molecules (MH^+) that are even-electron ions. This differs from the legacy electron ionization (EI) where the odd-electron molecular ions ($M^{+\bullet}$) are generated. Fragmentation of the $M^{+\bullet}$ ions in EI can be triggered by either the formal positive charge or the unpaired electron and is usually governed by the Stevenson's rule,[1] which states that the fragment that has lower ionization energy (IE) retains the positive charge. The reactions of the MH^+ ions formed in ESI, on the other hand, are directed by the formal charge[2] and do *not* often produce odd-electron fragment ions. However, when a reaction of the MH^+ ions does give rise to an odd-electron product ion especially when this reaction is overwhelming, it is not only interesting but also necessary to investigate the underlying mechanism.

In the pharmaceutical industry, the number of new chemical structures discovered is increasing exponentially. Compounds containing an oxidized sulfur such as sulfones or

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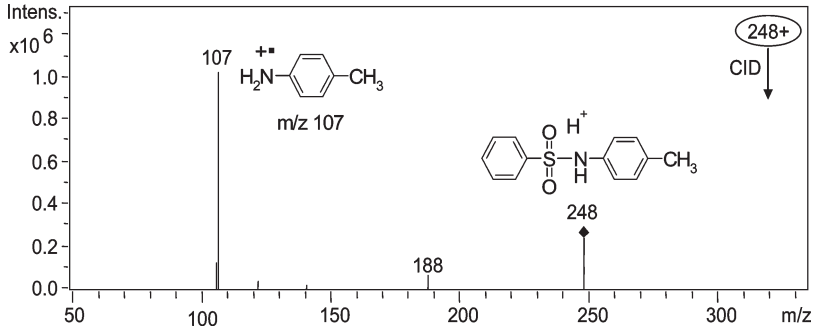

FIGURE 1. CID mass spectrum of the MH^+ ion (m/z 248) of benzenesulfonyl *p*-methylaniline. The m/z 107 ion is identified as the $M^{+\bullet}$ ion of the aniline.

sulfonamides play a significant role in developing therapeutics for diabetes and Alzheimer's disease as well as bacterial infections.[3] In the ESI mass spectrometry of these compounds, significant odd-electron ions of the constituent amines are often observed.[4] For example, benzenesulfonyl methylaniline is a simple sulfonamide, and the collision-induced dissociation (CID) mass spectrum of its MH^+ presented in Figure 1 shows a dominant ion at m/z 107. This ion is identified[5] as the $M^{+\bullet}$ ion of methylaniline; however, the reaction mechanism for its formation is unknown.

Fragmentation of organic ions in the gas phase may involve rearrangements to a variety of intermediates. An interesting and important intermediate is the nonconventional ion−neutral complex,[6] which is formed in the *unimolecular* fragmentation of ions but similar in terms of chemical properties to the intermediates found in *bimolecular* reactions such as the S_N2 nucleophilic displacement.[7] In the past decades, considerable experimental and theoretical calculation studies have demonstrated that ion−neutral complexes are ubiquitous intermediates in gas-phase unimolecular reactions.

In an ion−neutral complex, the nascent *discrete* ionic and neutral fragments formed upon cleavage of one or multiple bonds are held together to a certain distance by electrostatic interactions. During its appreciable lifetime, various chemical reactions may take place either in the ionic fragment alone or between the two partners *prior* to the final separation. The most common reaction is the transfer of a proton[8] or a small alkyl carbocation[9] from the charged to the neutral species, and in these reactions the proton affinity (PA)[10] or carbocation affinity[11] of the relevant neutral species dictates inter alia formation of the final product ions. The ion−neutral complex also mediates isomerization, which is another major reaction that takes place en route to the products. In the fragmentation of ionized ethylene glycol,[12] it was found that the reaction proceeds to an ion−neutral complex where the neutral species catalyzed the isomerization of the ionic partner. This has stimulated an intensive interest[13] in understanding the role of the neutral species in this type of reactions. Isomerization may also involve electrophilic aromatic substitution within an ion−neutral complex. For some benzyl-containing molecules, it was found[14] that the benzyl cation formed upon initial bond cleavage can attack another aromatic moiety of the molecule to enable the subsequent elimination.

The reaction of the MH^+ ions of sulfonamides exemplified in Figure 1 that leads to the formation of the $M^{+\bullet}$ ions of the constituent amines is *unlike* any of those known reactions. We hypothesized that the reaction should undergo cleavage of the SO_2−N bond followed by charge transfer[4a] between the two newly formed fragments. To prove this mechanism we decided to synthesize and characterize a series of simple

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TABLE 1. Major Product Ions in the CID Mass Spectra of the MH^+ Ions of Sulfonamides $R'C_6H_4SO_2-NHC_6H_4R$

compd	R′	R	MH^+ (*m*/*z*)	$RC_6H_4NH_2^{+\bullet}$	$R'C_6H_4SO_2^+$	other ions				
1	H	H	234	93 (100) [a]	141 (0.1)	109 (12.2)	108 (8.4)			
2	H	*p*-CH_3	248	107 (100)	141 (0.3)	188 (9.8)	122 (5.6)	106 (14.6)		
3	H	*m*-CH_3	248	107 (100)	141 (0.01)	188 (4.8)	123 (6.4)	122 (22.5)	106 (3.0)	
4	H	*p*-NH_2	249	108 (43.3)	141 (0.06)	123 (2.2)	107 (100)	80 (3.5)		
5	H	*m*-NH_2	249	108 (100)	141 (0.05)	185 (4.6)	124 (3.4)	123 (12.3)	107 (9.0)	80 (6.2)
6	H	*o*-NH_2	249	108 (100)	141 (0.002)	107 (4.0)				
7	H	*p*-F	252	111 (100)	141 (0.1)	192 (10.3)	127 (1.3)	126 (4.3)	110 (4.9)	
8	H	*p*-Cl	268	127 (100)	141 (0.2)	208 (11.5)	143 (1.0)	142 (3.3)	126 (4.2)	
9	H	*m*-Cl	268	127 (100)	141 (13.2)	208 (3.9)	143 (44.3)	142 (35.6)		
10	H	*o*-Cl	268	127 (100)	141 (1.7)	143 (8.7)	142 (3.6)			
11	H	*p*-NO_2	279	138 (0.3)	141 (3.0)	262 (100)	122 (2.4)			
12	CH_3	H	248	93 (100)	155 (16.9)	109 (29.9)	108 (8.8)	107 (8.9)		
13	CH_3	*p*-CH_3	262	107 (100)	155 (0.3)	188 (40.9)	123 (1.4)	122 (7.3)	106(30.0)	
14	CH_3	*p*-NH_2	263	108 (32.0)	155 (0.2)	123 (14.3)	107 (100)	80 (4.3)		
15	CH_3	*p*-Cl	282	127 (100)	155 (17.8)	208 (43.6)	144 (2.6)	143 (1.7)	142 (8.4)	126 (8.2)
16	CH_3	*p*-NO_2	293	138 (0.1)	155 (13.0)	276 (100)				

[a] *m*/*z* (rel intensity, %).

sulfonamides from the anilines whose IE values can be varied in the range of 7.0−8.5 eV by introducing different substituents. If their fragmentation reactions follow the charge transfer mechanism, then the intensities of the $M^{+\bullet}$ ions of the anilines should correlate with their IE values. In this paper we report the results from the characterization of these sulfonamides by mass spectrometry in conjunction with auxiliary theoretical calculations.

Results and Discussion

The structures of the sulfonamides studied are given in Table 1 along with the CID mass spectra of their MH^+ ions. In general, the mass spectra of these compounds are very similar to that shown in Figure 1 for the *p*-methylaniline sulfonamide. The $M^{+\bullet}$ ions of the constituent anilines are found as the base peak in the spectra in most cases. Another interesting reaction[15] involving transfer of an oxygen atom is also observed (not pursued here). The $C_6H_5SO_2^+$ ion of *m*/*z* 141 from compounds **1**−**11** and the $CH_3C_6H_4SO_2^+$ ion of *m*/*z* 155 from compounds **12**−**16** are important (although less than 1% of the base peak in many cases) because they represent a complementary reaction channel and are used as a reference in our data analysis. The accurate masses of these ions for a representative compound given in Table S1 in the Supporting Information are consistent with the assigned structures.

Sites of Protonation. In contrast to the extensive studies on protonation of the carboxylic amides, studies on the sulfonamides are very limited. It was only shown by NMR that the sulfonamides were preferably protonated at the nitrogen in solutions.[16] In the case of $CH_3SO_2NH_2$, theoretical calculations[16d] indicated that N-protonation was marginally more favorable by only 3 kcal/mol.

To quantitatively describe the energy requirements for the fragmentation reactions of the MH^+ ions of sulfonamides that we prepared (Table 1), theoretical calculations were performed with the Density Functional Theory (DFT) at the B3LYP/6-31G(d) level. We first focused on protonation of the sulfonamides at the oxygen and nitrogen sites leading to two different MH^+ ions, MH1 and MH2, respectively. As the data in Table 2 show, from the unsubstituted sulfonamide (**1**) to those bearing either a strong electron-releasing group (**4**, R = *p*-NH_2) or a strong electron-withdrawing group (**11**, R = *p*-NO_2), the energy of MH1 is consistently higher than that of MH2 by 10−12 kcal/mol, and there is a high energy barrier (TS1) to the interconversion between MH1 and MH2. This indicates that protonation at the nitrogen is more favorable, in agreement with the previous findings[16] but on the side opposite to the carboxylic amides where the carbonyl oxygen is the preferred site for protonation.[17]

TABLE 2. Calculated Relative Energies of Various Species of $C_6H_5SO_2-NHC_6H_4R$ (kcal/mol)

compd	R	MH1	TS1	MH2	MH3
1	H	11.5	31.7	0	4.6
4	*p*-NH_2	20.7	27.5	7.8	0
11	*p*-NO_2	10.7	31.8	0	6.5

Protonation at other sites especially the NH_2 and NO_2 groups in such substituted molecules may be competitive. The nitro group is known to be favorable in protonation[18] and should be responsible for the dominant loss of OH from the MH^+ ions of compounds **11** and **16** (Table 1). However, cleavage of the sulfonamide bond from MH1 that is also present in the total ion population requires that a proton be transferred from oxygen to nitrogen to give rise to MH2 in spite of the existence of a high energy barrier.

Ion−Neutral Complexes. When protonation occurs at the nitrogen of the sulfonamides to form the MH2 ion, what we found interesting during theoretical calculations is that once the external proton is attached to the nitrogen, the SO_2-N bond appears to dissociate spontaneously, and the two resulting fragments are still held together electrostatically as a stable [sulfonyl cation/aniline] complex. We believe that it is within this ion−neutral complex intermediate that an electron is transferred from the neutral aniline to the sulfonyl cation although the electron transfer mechanism (see more details below) could be complicated. We also found that upon electron transfer, the resulting $M^{+\bullet}$ ion of aniline and

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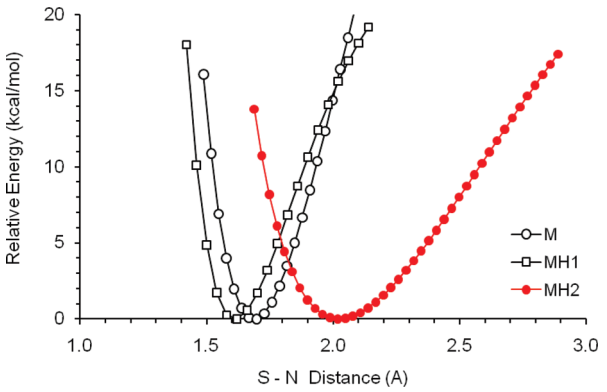

FIGURE 2. Relative systemic energies of M, MH1, and MH2 of compound **1** as a function of the S−N distance.

the intact neutral sulfonyl radical also form a stable ion−neutral complex, MH3, which is only 4.6 and 6.5 kcal/mol higher in energy than MH2 for compounds **1** and **11**, respectively, but 7.8 kcal/mol lower in energy than MH2 for compound **4** (Table 2).

The structural determination of MH2 is critical in understanding the mechanism of electron transfer. We have compared the calculated properties of the neutral molecule (M), the O-protonated species (MH1), and the two ion−neutral complexes, MH2 and MH3, using compound **1** as a tool molecule. First, a noticeable difference is observed in the S−N bond length. It is 1.70 Å in M, which is in good agreement with a typical value (1.65 Å) reported elsewhere for aliphatic sulfonamides.[19] Protonation at the oxygen does not stretch the S−N bond but slightly shortens it to 1.63 Å in MH1, indicating shifting of the lone pair of electrons on the nitrogen to sulfur. However, the length of this bond is increased to 2.05 Å in MH2 and 3.94 Å in MH3, appreciably longer than a covalent S−N bond.[19] In addition, the systemic energies were also calculated as a function of the S−N distance over a width of approximately 1.2 Å for these species. As partially shown in Figure 2, the most stable structure of M resides in a very narrow and steep energy well, and the energy is very sensitive to both compressing *and* stretching of the S−N bond. MH1 is similar. However, for MH2, the energy is only sensitive to compressing but quite tolerable for stretching. Therefore, when the S−N bond is elongated by an additional 0.5 Å from the minimum structures, the systemic energy rises sharply by 28 kcal/mol for M and 20 kcal/mol for MH1, but only slightly by 8 kcal/mol for MH2 and marginally by 3 kcal/mol for MH3 (curve not shown). This is also consistent with the calculated bond orders. The S−N bond order is 0.76 and 0.80 in M and MH1, respectively, close to that (0.85) for a simple aliphatic sulfonamide,[19b] but dropped to only 0.32 in MH2 and to nearly zero in MH3. When a small amount of energy is provided to MH2, which can be achieved in collisional activation, the S−N bond order rapidly decreases to almost zero.

In the ground states of all these protonated species, many vibrational movements of one ring relative to another are found at low frequencies (Table S3 in the Supporting Information).

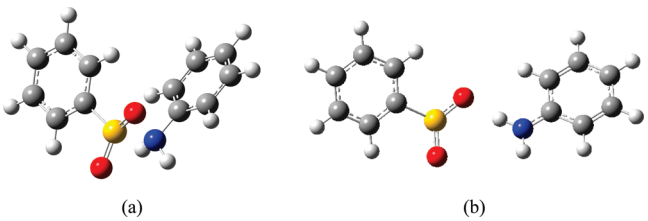

FIGURE 3. Optimized structures of (a) the MH2 ion formed upon protonation at the nitrogen of *N*-phenyl benzenesulfonamide and (b) the MH3 ion after charge transfer between the two partners.

For both M and MH1, the S−N distance remains unchanged in *all* these low-frequency vibrations. However, there are several movements of MH2 (11.9, 185.1, 219.9, 343.0, and 368.8 cm^{-1}) and MH3 (19.8, 36.6, 58.7, and 119.0 cm^{-1}) in which the two aromatic rings are shifting or clapping with randomly changing S−N distances. This is in agreement with the fact that the S−N bond is intact in M and MH1 but ruptured in MH2 and MH3.

It is also worth comparing the fine geometric structures of MH2 and MH3 with an isolated phenylsulfonyl or aniline species in an appropriate charge state. As shown in Figure 3 or Table 3, in the MH2 complex, the phenyl ring and the SO_2 group of the phenylsulfonyl moiety is nearly coplanar as in a detached phenylsulfonyl *cation*, and the lengths of the two S−O bonds (1.45 Å) are similar to those in an isolated phenylsulfonyl cation (1.44 Å) but shorter than in the neutral phenylsulfonyl radical (1.49 Å). A positively charged sulfur draws electrons from the oxygens and thereby shortens the S−O bonds. The aniline moiety of MH2 shows a pyramidal nitrogen, and its N−C bond length of 1.45 Å is close to that of a standalone *neutral* aniline (1.40 Å)[19c] but significantly longer than 1.34 Å in the radical cation of aniline (Table 3). In the neutral aniline, the lone pair of electrons on the pyramidal nitrogen[19a] is not effectively delocalized to the phenyl ring, whereas in the aniline radical cation the nitrogen is coplanar with the aromatic ring. Therefore, it is the geometry of the amino group that makes the N−C bond of aniline longer in the neutral molecule but shorter in the cation.

After the electron transfer, in MH3, the phenylsulfonyl moiety becomes neutral in which the two S−O bonds are 1.49 or 1.51 Å long, consistent with 1.50 Å in a solitary phenylsulfonyl *radical*, while the aniline moiety shows a completely planar nitrogen with the N−C bond shortened to 1.334 Å, close to 1.336 Å in a desolate aniline radical *cation* (Table 3). These parameters of the fine geometries of MH2 and MH3 are auxiliary but supportive attributes describing the two species as ion−neutral complexes.

The N-protonation of sulfonamides and the ensuing cleavage of the S−N bond is similar to that of the carboxylic amides. Earlier theoretical calculation studies have demonstrated that N-protonation of the amides decreases the C(O)−N bond order[20] and increases the bond length[21] although to a much lesser extent than the sulfonamides we just described, yet it is widely accepted that an intermediate ion−neutral complex is formed upon cleavage of the amide bond.[17] Therefore, it is reasonable to establish the similarity that

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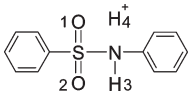
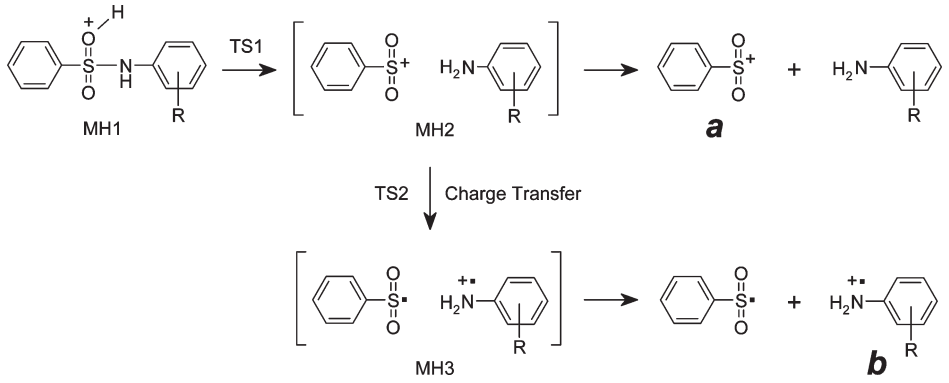
TABLE 3. Bond Distances (Å) and Angles (deg) of Relevant Species Involved in the Reactions of Compound 1



	M	MH1	MH2	MH3	TS1	$C_6H_5SO_2^+$	$C_6H_5SO_2^{\bullet}$	$C_6H_5NH_2^{+\bullet}$	$C_6H_5NH_2$
R(S−N)	1.703	1.626	2.052	3.935	1.931				
R(S−O1)	1.462	1.624	1.454	1.505	1.544	1.443	1.490		
R(S−O2)	1.463	1.450	1.451	1.492	1.456	1.443	1.490		
R(O1−H4)		0.982	2.678	1.802	1.227				
R(N−H3)	1.017	1.022	1.025	1.016	1.027			1.016	1.013
R(N−H4)		3.424	1.027	1.035	1.382			1.016	1.013
R(N−C)	1.424	1.455	1.448	1.334	1.426			1.336	1.400
∠(O1−S−O2)	122.66	112.57	125.27	118.46	121.07	127.42	122.10		
∠(O1−H4−N)		47.06	78.95	174.14	123.83				
∠(H3−N−H4)		103.87	107.31	116.74	115.96			116.57	111.05

SCHEME 1



both the amides and sulfonamides dissociate heterolytically upon protonation at the nitrogen leading to an intermediate [acyl cation/amine] or [sulfonyl cation/amine] complex. The nitrogen in both amides and sulfonamides is the site for dissociative protonation[22] that causes fragmentation.

Charge Transfer Reaction. As described in Scheme 1, upon fragmentation of the sulfonamide bond, dissociation of the MH2 complex gives rise to the sulfonyl cation, but formation of the complementary aniline radical cation is hypothesized to involve a charge transfer process. To tackle this new mechanism, we first calculated the energy requirements for the two reactions, and then explored experimentally the relationship between the product ion intensities and the IE values of anilines.

The charge transfer involves transfer of an electron from the aniline to the sulfonyl group, which could follow either the inner-sphere or the outer-sphere mechanism,[23] depending on how the two reactants (as in a *bimolecular* reaction) approach each other. An inner-sphere electron transfer is characterized by its barrierless feature and the reaction is driven by the difference of the total energies between the products and the reactants. In contrast, the outer-sphere reaction is marked with a transition state of high energy barrier.[23]

With merely the energies of the products for a reaction shown in Scheme 1, it is difficult to create a potential energy profile because it is unclear about the transition state, TS2, if it does exist. For example, our calculations indicate that charge transfer to form ion **b** is more favorable than dissociation of MH2 to form ion **a** by 17.6 kcal/mol for sulfonamide **1** (R = H) and by 42 kcal/mol for compound **4** (R = *p*-NH_2). This is consistent in a general sense with the IE of the anilines and with the observed intensities of the two product ions (Table 1). However, for compound **4**, even though the energy threshold for the formation of the sulfonyl cation is 42 kcal/mol higher than that for charge transfer, the sulfonyl cation is still detectable in the time window in the mass spectrometric experiment. Does this imply that there is actually an energy barrier[24] to the charge transfer, which would narrow the gap in energy requirements for the two channels to much less than 42 kcal/mol? We went on to examine a third compound, sulfonamide **11** (R = *p*-NO_2) in a search for the energy barrier.

It is interesting that for compound **11** the two reaction channels shown in Scheme 1 are almost isoenergetic, with the formation of the aniline cation (ion **b**, *m*/*z* 138) demanding only 0.7 kcal/mol more than that for the competing reaction (ion **a**, *m*/*z* 141). However, what we observed in mass spectrometry was that the intensity of the ion *m*/*z* 138 was only 10% of that of the ion *m*/*z* 141 (Table 1). This observation reveals a compelling evidence that there *must* exist a substantial energy barrier to the charge transfer process. As illustratively shown in Figure 4, in the potential energy profile for the charge transfer step, the transition state (TS2), which is estimated to

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(24) (a) Tu, Y.-P.; Holmes, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 3695–3700. (b) Tu, Y.-P.; Holmes, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 5597–5602.

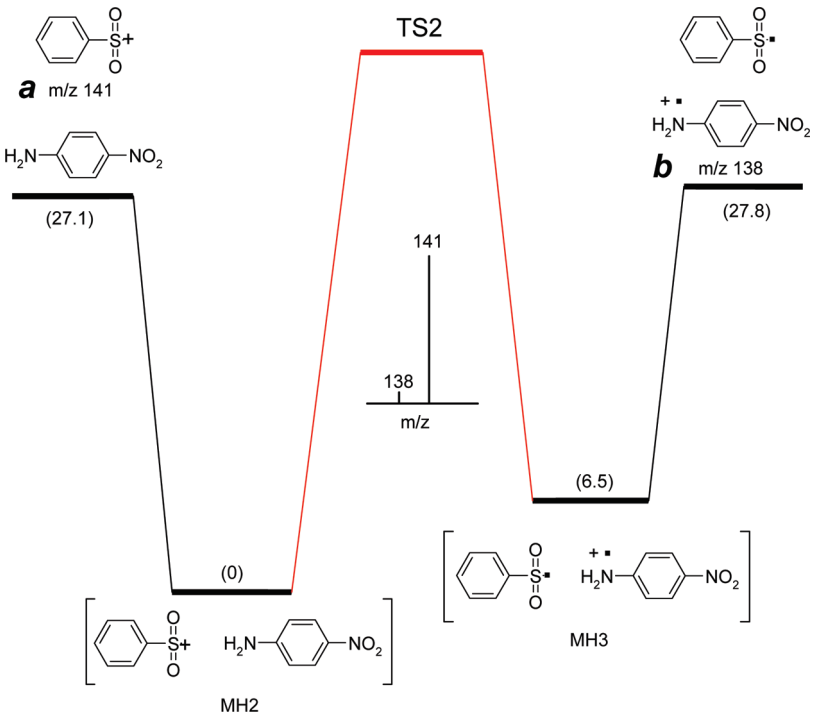

FIGURE 4. Potential energy diagram for the charge transfer involved in the fragmentation of compound **11**. Relative energies (kcal/mol) are calculated by using DFT at the B3LYP/6-31G(d) level of theory. The transition state (TS2) is approximately placed based on the competitiveness of the two product ions (*m*/*z* 138 and 141) observed in the mass spectrum, which is depicted at the center of the diagram.

be 10 kcal/mol above the threshold for ion **a**, governs the reaction and is accountable for the low intensity of ion **b**. Therefore, given the fact that MH2 is determined to be an ion−neutral complex and now the existence of a significant activation energy, we believe that the charge transfer follows the outer-sphere mechanism initiated from MH2 upon protonation of the sulfonamide nitrogen.

Compared with the dissociation of MH2, charge transfer through TS2 is unfavorable energetically for compound **11**. The existence of TS2 should also make this reaction unfavorable entropically, and this could be probed by examining the CID mass spectra at various collision energies. Unfortunately loss of OH from the nitro-protonated[18] species of **11** is dominant, making observation of the interested reactions difficult at higher collision energies. So compound **14** was used instead for this purpose. The breakdown graph showing only the two interesting product ions in Figure 5 reveals that as the collision energy (and therefore the internal energy) increases, the intensity of the sulfonyl cation increases whereas that of the aniline cation decreases. Simple bond cleavage (to ion **a**, *m*/*z* 155) is favorable entropically at higher energies over a reaction that requires reorientation to the transition state to allow the subsequent electron transfer (to ion **b**, *m*/*z* 108).

Apparently a significant amount of work is still required to gain more insight into the energetics and the structures of the transition states in this case as well as in other electron transfer reactions. Nonetheless, we were interested to see whether a correlation could be established between the intensities of the $M^{+\bullet}$ ions of the constituent anilines and the ionization energies[25] of these anilines. Qualitatively, a lower IE results

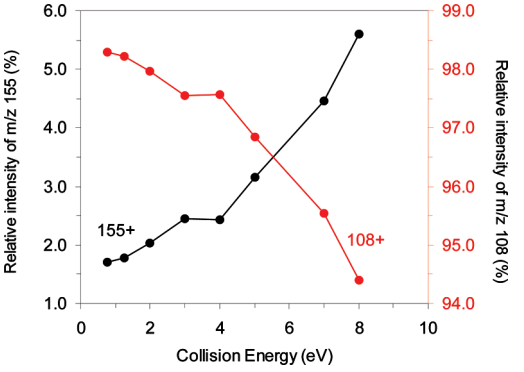

FIGURE 5. Dependency of the formation of the sulfonyl cation (*m*/*z* 155) and the aniline cation (*m*/*z* 108) of compound **14** on the collision energy. Intensities corrected for the secondary fragmentation of the aniline ion.

in a higher intensity of the $M^{+\bullet}$ ion; as the IE of the substituted aniline increases, the aniline becomes harder to ionize, and the dissociation of the complex leading to the $R'C_6H_4SO_2^+$ ions becomes more noticeable. For example, in the cases of sulfonamides **4** and **11**, the IE values of the constituent anilines *p*-$RC_6H_4NH_2$ are 7.6 and 8.6 eV for R = NH_2 and NO_2, respectively, and the observed intensity ratios[26] of the $M^{+\bullet}$ ions of the anilines over the common sulfonyl cation (*m*/*z* 141) decreased significantly from R = NH_2 to R = NO_2.

To further evaluate the influence of IE on the fragmentation reactions of protonated sulfonamides, the relative intensities of the aniline cations in the CID mass spectra of

(25) http://webbook.nist.gov/chemistry/. Whenever possible, the evaluated values or values from the same laboratory were used.

(26) Intensities of the $M^{+\bullet}$ ions of anilines are corrected for the secondary loss of hydrogen.

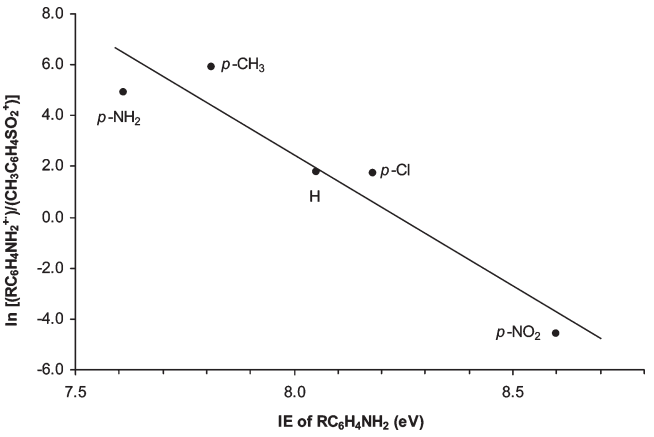

FIGURE 6. Correlation of ln[(aniline$^{+\bullet}$)/(sulfonyl^{+})] with the ionization energies of the constituent anilines for toluenesulfonamides **12**−**16**.

sulfonamides **1**−**11** (Table 1) are plotted against the IE values of the constituent anilines. The relationship between IE and the $M^{+\bullet}$ ion intensity qualitatively described above holds true as expected (curve not shown). However, the data points are rather scattered, with only an $R^2 = 0.58$ for the regression. There are a couple of major causes for this low performance. First, the IE values of the anilines are not as precisely determined as other properties. Just for the unsubstituted aniline alone, there are more than 30 values ranging from 7.48 to 8.35 eV in the literature.[25] Additionally, as seen in Table 1, the common sulfonyl cation that is used as the comparator is detected at very low levels; for most of these compounds, it is below 1% of the aniline cation, which is almost always the base peak (except **11**). For example, the intensity ratio of $107^{+}/141^{+}$ for compound **3** is 1×10^4, and that of $108^{+}/141^{+}$ for compound **6** is even higher, reaching 5×10^4. This requires a considerably wide dynamic range for the mass spectrometer to accurately measure these two complementary ions. To improve the experimental accuracy, compounds **12**−**16** were prepared and characterized in the same fashion. The toluenesulfonyl cation, which is more stable than the benzenesulfonyl cation, is observed at increased intensities (Table 1). As a result, the correlation of the aniline ion intensity with the IE for those compounds is much improved as shown in Figure 6 with an $R^2 = 0.90$. Nonetheless, these efforts have demonstrated that formation of the ionized anilines observed in the fragmentation of sulfonamides depends on how easy the constituent anilines are to ionize, as the charge transfer is a major step in the fragmentation reaction.

Conclusions

In the fragmentation of protonated sulfonamides, $R'C_6H_4SO_2NHC_6H_4R$, the dominant product ions observed are the ionized anilines, $RC_6H_4NH_2^{+\bullet}$. Theoretical calculations showed that the sulfonamides are preferentially protonated at the nitrogen, but this protonation causes the S−N bond to dissociate spontaneously, resulting in an intermediate [sulfonyl cation/aniline] complex. The subsequent reaction is the charge transfer between the two partners within the complex, which is found to involve a substantial activation energy associated with the outer-sphere mechanism. This energy barrier does prevent charge transfer in sulfonamides that bear an electron-attracting substituent on the aniline. However, when an electron-donating group is attached to the aniline, charge transfer is still more favorable than the dissociation of the intermediate ion−neutral complex.

Experimental Section

All compounds used in this study were synthesized in our laboratory following procedures described elsewhere.[27] The structures were confirmed using ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry after purification of the crude products. The compounds were redissolved in methanol containing 1% acetic acid at a concentration of approximately 1 μg/mL. The solutions were infused into the ion source for analysis with a syringe pump at a flow rate of 3 μL/min.

Mass spectral data were obtained from an ion trap mass spectrometer operated in the positive ion mode with an electrospray ionization (ESI) ion source and the software package provided by the vendor. The capillary voltage was set at −4000 V, and ion source temperature at 250 °C. Nitrogen was used as the nebulizing gas at a pressure of 15 psi and as the drying gas at a flow rate of 5 L/min. The CID mass spectra were obtained using helium as the collision gas at a collision energy achieved by a voltage of 0.7 V. Accurate mass was measured on an FT-ICR mass spectrometer with an ESI ion source. The capillary voltage was set at −4300 V, and the source temperature at 350 °C. Nitrogen was used as the nebulizing and drying gases, and argon as the collision gas.

Theoretical calculations were carried out by the DFT method with a 6-31G(d) basis set in the Gaussian 03 program.[28] The candidate structures of the reactants, products, and transition states were optimized by calculating the force constants. No symmetry constrains were imposed in the optimizations. The reaction pathways were traced forward and backward by the intrinsic reaction coordinates (IRC) method. All optimized structures were subjected to vibrational frequency analysis for zero-point energy (ZPE) correction. The energies discussed are the sum of electronic and thermal energies of the optimized structures.

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Supporting Information Available: Accurate masses of the major product ions for compound **3**, geometries and Cartesian coordinates, and major vibrational frequencies in the low region of the optimized structures for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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