RESEARCH ARTICLE

N-Centered Odd-Electron Ions Formation from Collision-Induced Dissociation of Electrospray Ionization Generated Even-Electron Ions: Single Electron Transfer via Ion/Neutral Complex in the Fragmentation of Protonated *N,N'*-Dibenzylpiperazines and Protonated *N*-Benzylpiperazines

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Abstract

Single electron transfer (SET) via ion/neutral complex (INC) was proposed and confirmed to be the key step in the formation of N-centered odd-electron ions from fragmentation of protonated even-electron ions in the present study. Upon collisional activation, the model compounds, protonated *N,N'*-dibenzylpiperazine and protonated *N*-benzylpiperazines initially dissociated to form intermediate INCs consisting of *N*-benzylpiperazine (or piperazine) and benzyl cation. In these ion/neutral complexes, SET reaction and direct separation as well as other reactions were observed and characterized experimentally and theoretically. Density functional theory calculations demonstrated that the energy requirement for homolysis of the precursor ion was so large that it could not be achieved, whereas the heterolytic dissociation followed by electron transfer via INC was energetically preferred. The SET process occurred only when the radical products were more stable than the separation products. The energy barrier for SET in the compounds studied was roughly estimated by comparison with other competing reactions. When the INC contained electron donor with lower ionization energy and electron acceptor with higher electron affinity, the SET reaction was more efficient.

Key words: Single Electron Transfer, Odd-Electron Ion, Even-Electron Ion, Electrospray Ionization Mass Spectrometry, Ion/Neutral Complex, *N*-Benzylpiperazine

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Introduction

Electrospray ionization (ESI) mass spectrometry, combined with low energy collision-induced dissociation (CID) technique, is one of the most widely used analytical methods. The ions generated in the positive ion electrospray ionization normally are closed-shell cations, such as $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$, and $[M+NH_4]^+$. When these closed-shell

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Figure 1. Compounds used for fragmentation studies. (1) *N,N'*-dibenzylpiperazine, (2) *N,N'*-bis(benzyl- d_7)piperazine

ions are subjected to CID, they commonly dissociate to daughter closed-shell ions and neutral fragments based on ‘even-electron rule’ [1]. It is rare that an electrospray ionization generated even-electron (EE) ion directly dissociates to form an odd-electron (OE) ion, though exceptions are more common in electron ionization (EI) [1–4] than in ESI mass spectrometry [5–12]. It is significant and desirable to investigate the underlying mechanism of formation of OE ions from EE ions because such considerations are important for a better understanding of ESI mass spectrometry. In our recent work, we revealed that the formation of ionized anilines in the fragmentation of protonated benzenesulfonamides resulted from intramolecular charge transfer via an intermediate [sulfonyl cation/aniline] complex rather than a simple S–N bond homolysis [13].

Unimolecular fragmentation of ions in mass spectrometry can be mediated by the non-conventional intermediate of ion/neutral complex [14–17]. Ion/neutral complexes have been found to be ubiquitous in gas-phase ionic reactions. Within an ion/neutral complex, the ion and neutral species are held together by electrostatic attractions, but still maintain their individual mobility. During its appreciable

lifetime, various chemical reactions may take place either in the ionic fragment alone or between the two components prior to the final separation. The well-documented reactions are isomerization, proton transfer and small alkyl carbocation transfer. In very recent years, several novel reactions were uncovered in ESI mass spectrometry, such as electrophilic aromatic substitution [18–20], hydride transfer [21, 22], transacylation [23], formaldehyde loss [24], and ester group transfer [25].

Within the ion/neutral complex, if the electrochemical potential between the two components is proper, single electron transfer (SET) may also occur. SET is a key step in numerous reactions and has been intensively investigated both experimentally and theoretically [26, 27]. Bimolecular electron transfer takes place when an electron-rich donor encounters an electron-poor acceptor. Han and Brauman [28] had reported SET between 3-nitrotoluene and benzyl anion via a collision complex measured with a pulsed ion cyclotron resonance spectrometer and they noticed that 40–80 kJ mol^{−1} was ample for electron transfer to occur.

In the study of fragmentations of protonated *N*-benzylpiperazines using ESI mass spectrometry, the formation of N-centered OE ions was discovered. The formation of OE ions from protonated tertiary amines also has been observed by others [5, 8]. In the present study, we focus on the mechanism for formation of OE ions from protonated *N*-benzyl compounds and provide a novel perspective. Since the ion/neutral complexes had been designated and confirmed as intermediates for other reaction pathways in the fragmentation of *N*-benzyl compounds [19–22], it is reasonable that the N-centered OE ions also derive from the ion/neutral complex intermediates. For the [benzyl cation/

Figure 2. CID mass spectra of the $[M+H]^+$ ion of Compound 1 (a) and Compound 2 (b). Fragmentation amplitude, 0.78 V

Figure 3. Potential energy diagram for the homolysis and heterolysis of the protonated 1,4-DBP using DFT at the B3LYP level of theory with the 6-31 G(d) basis set. A more detailed potential energy diagram for heterolysis is given in Figure 5

piperazine] complex, benzyl cation is electron deficient while piperazine is apt to donate electron, thus the electron transfer between them is feasible.

Experimental

Mass Spectrometry

All collision-induced dissociation (CID) experiments were performed using a Bruker Esquire 3000^{plus} mass spectrometer (Bruker-Franzen Analytik GmbH, Bremen, Germany) equipped with an electrospray ionization source and an ion trap analyzer in positive ion mode. Nitrogen was used as nebulizing gas at a pressure of 10 psi and drying gas at a flow rate of 5 L min⁻¹. The drying gas temperature was set at 250 °C and the capillary voltage was set at -4000 V. Solutions were infused to the mass spectrometer with a syringe pump at a flow rate of 6 μL min⁻¹. The CID mass spectra were obtained with helium as the collision gas at an appropriate collision energy after isolation of the desired precursor ion. The mass-window for precursor ion selection is between 0.8 and 1.0 *m/z* to ensure no ¹³C isotopic ions were included. Data reported here was acquired using the software Esquire 5.0.

The CID experiments were also carried out on a Varian 500-MS mass spectrometer equipped with an electrospray ionization source in positive ion mode, an ion trap analyzer and the Varian MS Workstation (Varian, Palo Alto, CA). Nitrogen gas was used as the nebulizing gas and the drying gas. Ionization was performed using the following settings: spray chamber temperature 50 °C, nebulizer pressure 35 psi, drying gas pressure 15 psi, drying gas temperature 350 °C, needle voltage 5000 V, spray shield voltage 600 V, infusion rate 10 μL min⁻¹. The CID mass spectra were obtained with helium as the collision gas after isolation of the desired precursor ion, and the collision energy (resonance mode) was adjusted properly to give suitable energy for the dissociation of all compounds studied.

Accurate mass was measured on an Apex III (7.0 Tesla) Fourier transform ion cyclotron resonance (FTICR) mass spectrometry (Bruker, Billerica, MA) equipped with an ESI source in the positive ion mode. Sodium trifluoroacetate was used as an external calibration compound. Nitrogen was used as nebulizing gas and drying gas. Argon was used as collision gas. The capillary voltage was set at -4269 V, and drying gas temperature was set at 150 °C.

Theoretical Calculations

All theoretical calculations were carried out using the Gaussian 03 package of programs [29]. Candidate structures of the reactants, products, intermediates, and transition states were optimized at the B3LYP (for open-shell ions, UB3LYP was used) level of theory with the 6-31 G(d) basis set. No symmetry constraints were imposed on the optimizations. The reaction pathways were traced forward and backward by the intrinsic reaction coordinate (IRC) method. All optimized structures were subjected to vibrational frequency analysis to ensure a transition state had only one imaginary vibrational frequency, while a local or global minimum had no imaginary vibrational frequency. The energies discussed here are the sum of electronic and thermal energies.

Scheme 1. Proposed mechanism for fragmentation of protonated 1,4-DBP

Figure 4. LUMO and HOMO of INC-1

Sample Synthesis and Preparation

The *N*-benzyl compounds were synthesized with the corresponding benzyl bromides and heterocycles (piperidine, piperazine, and morpholine). All compounds were purified after synthesis. The structures were confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Samples were dissolved in and diluted with methanol for mass spectrometric analysis.

Results and Discussion

Fragmentation of Protonated *N,N'*-Dibenzylpiperazine

It is well known that *N*-benzylpiperidine or *N*-benzylpiperazine derivatives are very important drug molecules (e.g., donepezil, roxatidine, imatinib). Electrospray ionization mass spectrometry (ESI-MS) has been routinely employed in the realm of drug discovery for quality control and metabolism study. Some interesting results were obtained during the analysis of a synthetic model compound, *N,N'*-dibenzylpiperazine (1,4-DBP), as shown in Figure 1, by positive ion ESI mass spectrometry. The typical CID mass spectrum of protonated 1,4-DBP is shown in Figure 2a, and the proposed fragmentation mechanism is given in Scheme 1. For Compounds 1 and 2, it is no doubt that the ionizing proton is added on the piperazine nitrogen. Upon collisional activation, the protonated 1,4-DBP firstly dissociates to form an intermediate, **INC-1**, by heterolytic cleavage of the $\text{C}^\alpha\text{--N}^1$ bond. It is noteworthy that the ion at m/z 91 here should be benzyl cation. Previous theoretical studies suggested that conversion of the benzyl cation to the tropylium ion must surmount a significant energy barrier ($65.0\text{ kcal mol}^{-1}$ [30], $67.8\text{ kcal mol}^{-1}$ [31]), so this process was usually not

Figure 5. Potential energy diagram for the formation of the product ions from the protonated 1,4-DBP using DFT at the B3LYP level of theory with the 6-31 G(d) basis set. The relative energy of $[1+\text{H}]^+$ is zero

Figure 6. Schematic potential energy diagram for the formation of the product ions from the protonated Compound **7** using DFT at the B3LYP level of theory with the 6-31 G(d) basis set. The relative energy of $[7+H]^+$ is zero

considered to occur in ESI mass spectrometry [32, 33] though rare exceptions had been reported in the fragmentations of some benzylpyridiniums [34–36]. For the occurrence of intra-complex reaction, **INC-1** should have suitable amount of internal energy, which is enough for further reaction between the ion and the neutral species but not enough for direct separation. These reactions are unusual or even impossible if the two components are connected by a covalent bond. The generation pathways for ion **c** and ion **d** were previously identified as ion/neutral complex-mediated hydride transfer reaction [21] and electrophilic aromatic substitution reaction [19], respectively. Ions **c** and **d** each have three possible isomers, as shown in Scheme 1. These two reactions indicate that the ion m/z 91 shows the benzyl cation reactivity. Herein ion **b** is more attractive because it

corresponds to an *N*-benzylpiperazine radical cation. In view of the occurrence of other two concomitant reactions, it seems reasonable that ion **b**, an odd-electron (OE) ion, is also formed from **INC-1**.

Because ion **b** is a minor product, the CID experiments of protonated 1,4-DBP were performed on three different instruments to examine the reliability of its fragmentation patterns. Their CID mass spectra are quite reproducible (Figures S1, S2, S3 in the online supplementary material). Furthermore the accurate masses of these product ions determined on FTICR mass spectrometer are consistent with their assigned structures (Table S1 in the online supplementary material). High resolution mass spectrometry data for other compounds are also presented in Table S1. Isotopic labeling experiment was also carried out to consolidate the mass spectrometric results. In the fragmentation of protonated Compound **2** (Figure 2b), the corresponding deuterated product ions resulting from ion/neutral complex-mediated fragmentations are formed.

The generation of ion **b** from $[1+H]^+$ may be ascribed to homolytic cleavage of the $C^\alpha-N^1$ bond or a combination of heterolytic cleavage of the $C^\alpha-N^1$ bond followed by single electron transfer (SET) between the two newly formed fragments. In order to gain insight into the reaction pathway for the formation of ion **b**, density functional theory (DFT) calculations were carried out at the B3LYP level of theory with the 6-31 G(d) basis set. A schematic potential energy diagram for the fragmentation of protonated 1,4-DBP is given in Figure 3 (full details of the structures and energies of species involved are presented in the online supplementary material). It requires $340.9 \text{ kJ mol}^{-1}$ for the transformation from the singlet protonated 1,4-DBP ($^1[1+H]^+$) to

Table 1. Product Ions in the Fragmentation of Protonated *N*-benzyl Compounds (Fragmentation Amplitude, 0.70 V)^a

Compound	X	R	$[M+H]^+$	ion e	ion f	ion g
3		<i>p</i> -CH ₃	191 (19.1) ^b	105 (100)	85 (16.9)	-
4		H	177 (7.4)	91 (100)	85 (59.0)	-
5	NH	<i>p</i> -CF ₃	245 (49.6)	159 (100)	85 (68.9)	86 (10.3)
6		<i>m</i> -NO ₂	222 (26.1)	136 (43.4)	85 (100)	86 (37.2)
7		<i>p</i> -NO ₂	222 (18.3)	136 (23.7)	85 (100)	86 (46.6)
8 ^c	CH ₂	<i>p</i> -NO ₂	221 (15.1)	136 (63.6)	84 (100)	85 (5.4)
9	O	<i>p</i> -NO ₂	223 (11.1)	136 (100)	86 (46.5)	87 (0.6)

^a Other ions for some compounds, see the CID spectra in the online supplementary material. The isolation width for all the precursor ions is between 0.8 and 1.0 m/z .

^b m/z (Relative abundance %).

^c Fragmentation amplitude of 0.92 V was used to produce abundant product ions.

Scheme 2. Proposed mechanism for fragmentations of protonated *N*-benzyl compounds

the triplet ($^3[1+H]^+$) so that this process is hardly to be achieved in ESI mass spectrometry. In contrast, the energy for the formation of **INC-1** from $^1[1+H]^+$ by the charge-directed heterolytic dissociation is only $178.4 \text{ kJ mol}^{-1}$, thus this process is much more favored. The subsequent single electron transfer from *N*-benzylpiperazine to benzyl cation is also favored in terms of energy because the total energy of ion **b** and benzyl radical is 18.9 kJ mol^{-1} lower than that of ion **a** and *N*-benzylpiperazine. Moreover, the intra-complex electron transfer within **INC-1** corresponds to the moving of an electron from its highest occupied molecular orbital (HOMO) to its lowest unoccupied molecular orbital (LUMO) [37–39]. The HOMO and LUMO of **INC-1** are shown in Figure 4. The HOMO is mainly located on the *N*-benzylpiperazine while the LUMO is mainly located on the benzyl cation. The DFT computed HOMO-LUMO energy gap for **INC-1** is only 49.9 kJ mol^{-1} . Therefore, the net result of SET is that an electron shifts from *N*-benzylpiperazine to benzyl cation. It is noteworthy that the fragmentation process from ion **b** to ion **c** by losing a hydrogen atom can be ignored in this case because of no observation of ion at m/z 175 in the MS^3 spectrum of ion **b** (m/z 176) under any collision energy (Figure S12 in the online supplementary material).

An energy barrier should exist for the SET reaction [40], which prevents the formation of ion **b**. For Compound **1**, there are four reactions via **INC-1** including SET. By comparing the energetics and intensities of the four product ions, it is possible to obtain valuable information about the activation energy of the SET reaction. The energy thresholds for the formation of the four product ions are compared in detail, as shown in Figure 5. The formation of benzylbenzyl

cation (ion **d**) from protonated dibenzylamine via ion/neutral complex had been studied by Attygalle et al. [19] and their deuterium labeling experiment indicated that ion **d** was a mixture of several isomers. In the present study, the calculated relative energies for isomers **d1**, **d2**, and **d3** are $200.7 \text{ kJ mol}^{-1}$, $198.4 \text{ kJ mol}^{-1}$, and $181.1 \text{ kJ mol}^{-1}$, respectively. Ion **c** is the most stable product ion (the relative energies for isomers **c1**, **c2**, and **c3** are 53.3 kJ mol^{-1} , 31.0 kJ mol^{-1} , and 15.8 kJ mol^{-1} , respectively), so it is the most abundant product. However, the deuterium labeling experiment (Figure 2b) indicates that the relative abundance of isomer **c3** (m/z 181) is much lower than that of the other two isomers (m/z 182). For the formation of ion **d** (**d1** as an example) and ion **c3**, the benzyl cation should move from one end of the piperazine ring to the other end, that is, **INC-1** must transform to **INC-3**. The electrophilic attack and the subsequent proton transfer for the formation of ion **d1** are almost barrierless, but the total energy of ion **d1** and piperazine is $200.6 \text{ kJ mol}^{-1}$ high. Although the total energy of ion **c3** and toluene is 15.8 kJ mol^{-1} low, it needs to surmount an energy barrier of 30.5 kJ mol^{-1} (**TS-4**) above **INC-3**. The intensities of ions **d** and **c3** are both much lower than that of ion **a**, which means rotation of the components within the ion/neutral complex should overcome a significant energy barrier. Ion **b** is also a minor product and its intensity is nearly equivalent to the intensity of ion **d**, though it is less stable than ion **d**. The energy for rotation should be lower than that for separation and higher than that of the final products. The energy barrier for SET reaction is almost equivalent to that for rotation, which is estimated to be $35\text{--}51 \text{ kJ mol}^{-1}$ above **INC-1**. It is worth noting that ion **a** is considerably higher than ions **b**, **c3**, and **d** in intensity while

Table 2. Relative Energies of Products in the Fragmentation of Protonated *N*-benzyl Compounds

Compound	X	R	$[M+H]^+$	Ion e+N-1	Ion f+N-2	Ion g+N-3
3	NH	<i>p</i> -CH ₃	0 ^a	202.0	64.0	236.5
4		H	0	226.1	57.7	231.6
5		<i>p</i> -CF ₃	0	244.6	36.1	210.7
6		<i>m</i> -NO ₂	0	258.6	25.8	202.7
7	CH ₂	<i>p</i> -NO ₂	0	261.7	19.8	191.5
8		<i>p</i> -NO ₂	0	263.6	11.5	250.0
9		<i>p</i> -NO ₂	0	240.1	25.1	229.0

^a Relative energy, kJ mol^{-1} .

its energy requirement is also higher. Under CID condition, the energy distribution for the precursor ions is from low to high. The ion/neutral complexes from high-energy precursor ions have short lifetime [15, 17, 21], which directly dissociate to form ion **a**. And part of high-energy precursor ions may directly dissociate to form ion **a** bypassing the formation of ion/neutral complex.

Fragmentation of Protonated *N*-Benzylpiperazines

A series of *N*-benzylpiperazines, *N*-(4-nitrobenzyl)piperidine, and *N*-(4-nitrobenzyl)morpholine, listed in Table 1, were used in an in-depth study on single electron transfer reactions via ion/neutral complex. The fragmentation mechanism for these compounds is proposed in Scheme 2. Several factors affect the efficiency of electron transfer processes in organic donor/acceptor dyads. The electron affinity (EA) of the electron acceptor and the ionization energy (IE) of the electron donor are two important factors. The piperazine radical cation is not formed in the fragmentation of protonated *N*-(4-methylbenzyl)piperazine (Compound 3) and *N*-benzylpiperazine (Compound 4), whereas this radical cation can be distinctly observed when a strong electron-withdrawing group, such as NO₂ and CF₃, connects to the phenyl ring. The reason is that electron-withdrawing groups increase the EA values of benzyl cations, which cause them more easily to accept electrons. In a comparison of the fragmentations of protonated Compounds 7, 8 and 9, the relative abundance of piperazine radical cation is much higher than that of piperidine radical cation and morpholine radical cation. The spin density distributions for several radical cations involved in the present study were calculated (Table S2 in the online supplementary material). Theoretical calculations show that the unpaired electron is equally delocalized to the two nitrogen atoms for piperazine radical cation (this result was also obtained by others [41, 42]), and is mainly centered on the nitrogen atom for piperidine radical cation and morpholine radical cation. It indicates that piperazine radical cation is more stable than the other two radical cations and the IE value of piperazine is lower than that of piperidine and morpholine. The theoretical calculations are well consistent with the experimental results.

To quantitatively understand the energy requirements for SET reactions via ion/neutral complex in the fragmentation of protonated *N*-benzyl compounds, the relative energies of the three competitive products (Scheme 2) are calculated using DFT at the B3LYP level of theory with the 6-31 G(d) basis set, and data are summarized in Table 2. It clearly shows that the radical cations can be generated from SET reactions only when the relative energies of the radical products are lower than that of the corresponding benzyl cations, and with the increase of their energy difference, the formation of radical cations are more and more favorable. Although ion **f** is the most stable ion in all cases, it is not always the major product. In some cases, especially for Compound 3, the ion/neutral complex with low stabilization

energy (defined as the energy difference between ion/neutral complex and separation products [15]) is easy to decompose [21], therefore the direct separation ion can be the dominant product. For Compound 7, the direct separation reaction is unfavorable, and the SET reaction is remarkably observable, so it is used as a model compound to further explore the energy barrier for SET. A schematic potential energy diagram for the fragmentation of protonated Compound 7 is given in Figure 6. The energy requirements for the formation of ions **e** and **f** are 261.7 kJ mol⁻¹ (product control) and 198.7 kJ mol⁻¹ (transition state control), respectively. The intensity of ion **g** is about a half as high as that of ion **f** and twice higher than that of ion **e**, so the activation energy for the formation of ion **g** should be lower than that of ion **e** and higher than that of ion **f**. An energy barrier of about 40–60 kJ mol⁻¹ for the SET reaction within the ion/neutral complex may be acceptable and reasonable.

Conclusions

The generation of N-centered radical cations in the fragmentation of protonated *N*-benzylpiperazines was studied experimentally and theoretically. The proposed mechanism for formation of odd-electron ions from collision-induced dissociation of even-electron ions is that a single electron transfer reaction takes place through an ion/neutral complex intermediate, which results from the protonation-triggered heterolytic cleavage of the benzylic C–N bond. The electron transfer between benzyl cation and piperazine within the complex is found to involve a substantial energy barrier by comparison with other competing fragmentations. The stability of the products is another crucial factor taking control of the electron transfer reaction. This study is a case for improved understanding of the production of odd-electron ions in ESI mass spectrometry and it also provides more knowledge about the role of ion/neutral complexes in mass spectrometry.

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