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RESEARCH ARTICLE

# Gas-Phase Chemistry of Benzyl Cations in Dissociation of *N*-Benzylammonium and *N*-Benzyliminium Ions Studied by Mass Spectrometry

Yunfeng Chai, Lin Wang, Hezhi Sun, Cheng Guo, Yuanjiang Pan

Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang, 310027, China

**Abstract**

In this study, the fragmentation reactions of various *N*-benzylammonium and *N*-benzyliminium ions were investigated by electrospray ionization mass spectrometry. In general, the dissociation of *N*-benzylated cations generates benzyl cations easily. Formation of ion/neutral complex intermediates consisting of the benzyl cations and the neutral fragments was observed. The intra-complex reactions included electrophilic aromatic substitution, hydride transfer, electron transfer, proton transfer, and nucleophilic aromatic substitution. These five types of reactions almost covered all the potential reactivities of benzyl cations in chemical reactions. Benzyl cations are well-known as Lewis acid and electrophile in reactions, but the present study showed that the gas-phase reactivities of some suitably ring-substituted benzyl cations were far richer. The 4-methylbenzyl cation was found to react as a Brønsted acid, benzyl cations bearing a strong electron-withdrawing group were found to react as electron acceptors, and *para*-halogen-substituted benzyl cations could react as substrates for nucleophilic attack at the phenyl ring. The reactions of benzyl cations were also related to the neutral counterparts. For example, in electron transfer reaction, the neutral counterpart should have low ionization energy and in nucleophilic aromatic substitution reaction, the neutral counterpart should be piperazine or analogues. This study provided a panoramic view of the reactions of benzyl cations with neutral N-containing species in the gas phase.

**Key words:** Benzyl cation, Methylene arenium, Ion/neutral complex, Electrophilic aromatic substitution, Electron transfer, Hydride transfer, Nucleophilic aromatic substitution, Proton Transfer

## Introduction

Benzyl cations are highly reactive intermediates in various chemical and biochemical reactions [1]. They are usually short-lived in solution and so it is difficult to characterize their properties in solution. They can be stabilized only under super-acidic conditions at low temperatures [2, 3] or by coordination to a metal center [4, 5]. Studying the structural properties and reactivities of benzyl cations is a subject of fundamental importance. Experimental observation supported by theoretical calculations indicates that two major resonance forms, as shown in Scheme 1, contribute significantly to the total electronic structure of the benzyl cation [1–6]. The well-known reactivity of benzyl

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*Correspondence to:* Yuanjiang Pan; *e-mail:* panyuanjiang@zju.edu.cn

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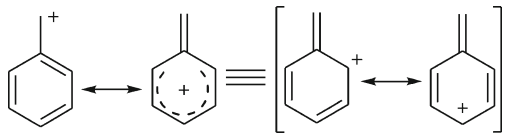


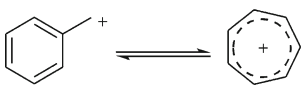
Scheme 1. Resonance forms of a benzyl cation

cation is electrophilicity due to the phenylmethyl cation character. In nearly all reactions of benzyl cations, the methylene carbon, but not the ring carbon, is the target of nucleophilic attack by nucleophiles because addition of a nucleophile at the phenyl ring (*ortho* or *para* position) breaks its aromaticity and, thus, such a reaction is not favored. The reaction of the ring-charged methylene arenium ion is unknown, except when it is coordinated to a metal center in solution [5] or constrained by steric effect in the gas phase [7]. We recently reported a gas-phase nucleophilic substitution reaction between piperazine and methylene arenium ions at the non-restricted state in mass spectrometry [8].

The rearrangement between benzyl cation and its isomer, tropylium ion, (Scheme 2) also receives considerable attraction and is still in debate [9–13]. Although tropylium is more stable than benzylium, theoretical calculations suggest that conversion of benzylium to tropylium must surmount a significant energy barrier which is about 280 kJ $mol^{-1}$ [14–16].

Benzyl cations are relatively stable in the gas phase. They are highly electron-deficient so that they can initiate electrophilic attack on electron-rich species. The best investigated reaction is the methylene transfer from the benzyl cations to the neutral toluene [11, 15, 17, 18]. The benzyl cation is also an ideal Lewis acid in that it is able to capture a hydride ion from a saturated hydrocarbon group but it does not donate a proton—it does not act as a Brønsted acid [19]. These two kinds of reactions are commonly used to distinguish benzyl cation from tropylium ion because tropylium ion is inert towards these reactions.

Benzyl cations can be easily obtained by fragmentation of the corresponding benzylated cations in mass spectrometry. In electrospray ionization mass spectrometry (ESI-MS), fragmentation of benzylated cations prefers to generate benzyl cations [7, 8, 20–30], though a few exceptions have been reported that tropylium ion can be co-produced in the fragmentation of benzylpyridinium ions [18, 31, 32]. Besides the formation of benzyl cations, other interesting ions resulting from hydride transfer [24, 25] or electrophilic aromatic substitution reactions [20–22] via the nonconventional ion/neutral complex (INC) can also be generated in the dissociation of benzylated cations.



Scheme 2. Benzylium-tropylium rearrangement

INCs have been found to be ubiquitous in gas-phase ionic reactions. Based on numerous experiments and theoretical calculations, the existence and importance of INCs in unimolecular fragmentation reactions in mass spectrometry have been well established and reviewed by several authors [33–38]. In an INC, the ionic and neutral species are bound together by electrostatic interactions, but still maintain their individual mobility. The excess energy derived from ionization or collisional activation and free rotation ability of an INC permit various interesting chemical reactions to occur before its final decomposition. Those reactions are geometrically impossible if the two components are connected by a covalent bond. Among the INC-mediated reactions, the well-documented reactions include cation rearrangement, hydrogen transfer, and small alkyl cation transfer.

By supposing the intermediacy of INCs, many unusual observations in the traditional electron ionization mass spectrometry (EI-MS) have been rationalized [33–38]. Consequently, a need for other examples of INC-mediated reactions is evident in order to better understand the fragmentation reactions in the contemporary ESI mass spectrometry, a method that has become one of the most popular analytical methods. Thus, renewed interest in studies on INC-mediated fragmentation reactions has emerged in recent years [8, 20–25, 39–47].

INCs are also significant for studying the reactivities of ions in gas phase. The ionic and neutral components of an INC show reactivities similar to those expected for the isolated species in the bimolecular reactions. In previous studies, we found dissociation of protonated *N*-benzyl amines gave rise to [benzyl cation/amine] complex and then nucleophilic aromatic substitution [8], electron transfer [23], or hydride transfer [24] could occur within the complex in different cases. In the present study, we systematically investigated the gas-phase reactions of benzyl cations with neutral *N*-containing species through INC intermediates in collision-induced dissociation of *N*-benzylated cations in ESI-MS. With these efforts, we try to figure out a more integrated landscape of the gas-phase reactivity of benzyl cations.

## Experimental

### *Mass Spectrometry*

All the collision-induced dissociation (CID) experiments were carried out using a Bruker Esquire $3000^{plus}$ mass spectrometer (Bruker-Franzen Analytik GmbH, Bremen, Germany) equipped with an electrospray ion source and ion trap analyzer in the positive ion mode. Nitrogen was used as the nebulizing gas at a pressure of 10 psi and the drying gas at a flow rate of 5 L/min. The dry 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. The CID mass

spectra were obtained with helium as the collision gas at an appropriate collision energy after isolation of the desired precursor ion. Samples were first dissolved in water (or methanol), then diluted with methanol. Methanol-$d_4$ was used as solvent for deuterium labeling experiment to form $[M+D]^+$ ion.

High-resolution CID mass spectra were measured on an Apex III (7.0 Tesla) FTICR mass spectrometer (Bruker, Billerica, MA, USA) equipped with an electrospray ion source in the positive ion mode. Sodium trifluoroacetate was used as an external calibration compound. Nitrogen was used as the nebulizing gas and drying gas. Argon was used as the collision gas. Solutions were infused to the mass spectrometer with a syringe pump at a flow rate of 3 μL/min. The following parameters were applied: capillary voltage, −4269 V; end plate, −3803 V; skimmer 1, 12.00 V; skimmer 2, 6.61 V; offset, 0.98 V; rf amplitude, 582.5 Hz; drying gas temperature, 150°C.

### *General Synthesis*

The *N*-benzyltriethylammonium bromide, *N,N'*-dibenzylimidazolium bromide, *N,N'*-dibenzylpiperazine, *N*-benzyl amines and their derivatives were synthesized with the corresponding benzyl bromides and amines. The compounds after synthesis were purified by extraction and silica gel flash chromatography. The structures were confirmed by NMR spectroscopy and mass spectrometry.

### *N-(4-methylbenzyl)triethylammonium bromide (9)*

4-Methylbenzyl bromide (1.5 mmol) and triethylamine (2 mL) were stirred at 70°C. After the completion of the reaction, the excess triethylamine was evaporated under reduced pressure to afford the product, which was further washed with ethyl acetate and dried under vacuum. $^1$HNMR: (500MHz, $D_2O$): δ (ppm)=7.30–7.35 (m, 4H), 4.29 (s, 2H), 3.13 (q, 6H), 2.31 (s, 3H) 1.31 (t, 9H); $^{13}$CNMR (125MHz, $D_2O$): δ (ppm)= 141.3, 132.3, 129.8, 124.0, 59.5, 52.0, 20.3, 6.9.

### *N,N'-dibenzylimidazolium bromide (11)*

Benzyl bromide (2 mmol), imidazole (2 mmol) and potassium carbonate (2.5 mmol) were stirred in acetonitrile (2 mL) at 70°C. After the completion of the reaction, the solvent was evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with water, dried over $Na_2SO_4$, and concentrated to afford the corresponding 1-benzylimidazole. Benzyl bromide (1.5 mmol) and 1-benzylimidazole (1 mmol) were stirred in acetonitrile (2 mL) at 70°C. After removal of the solvent, the crude product was washed with ethyl acetate to remove the excess benzyl bromide and dried under vacuum to afford the product. $^1$HNMR: (500MHz, $D_2O$): δ (ppm)=8.81 (s, 1H), 7.30-7.34 (m, 12H), 5.24 (s, 4H); $^{13}$CNMR (125MHz, $D_2O$): δ (ppm)= 135.4, 133.5, 129.4, 129.4, 128.6, 122.7, 53.0.

### *N,N'-bis(4-chlorobenzyl)piperazine (15)*

4-Chlorobenzyl bromide (2 mmol), anhydrous piperazine (1 mmol) and potassium carbonate (2.5 mmol) were stirred in tetrahydrofuran (2 mL) at room temperature. After the completion of the reaction, the solvent was evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by silica gel chromatography to give the product. $^1$HNMR: (500MHz, $CDCl_3$): δ (ppm)=7.23 (m, 8H), 3.43 (s, 4H), 2.42 (br, 8H); $^{13}$CNMR (125MHz, $CDCl_3$): δ (ppm)=136.8, 132.7, 130.5, 128.4, 62.2, 53.1.

### *N-(4-chlorobenzyl)piperazine (21)*

Anhydrous piperazine (6 mmol) and potassium carbonate (3 mmol) were dissolved in 5 mL tetrahydrofuran and stirred at room temperature. 4-Chlorobenzyl bromide (2 mmol) in tetrahydrofuran was added dropwise. After the completion of the reaction, the solvent was evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by silica gel chromatography to give the product. $^1$HNMR: (500MHz, $CDCl_3$): δ (ppm)=7.24-7.29 (m, 4H), 3.44 (s, 2H), 2.88 (t, 4H), 2.40 (br s, 4H), 2.08 (br s, 1H); $^{13}$CNMR (125MHz, $CDCl_3$): δ (ppm)=136.9, 132.9, 130.7, 128.6, 63.1, 54.5, 46.2.

## Results and Discussion

In the present study, the fragmentation reactions of several representative *N*-benzylated cations were investigated (data are shown in the following text). Ion/neutral complexes (INCs) were proposed as intermediates to rationalize their CID fragmentation reactions. Dissociation of these *N*-benzylated cations first generated INC intermediates consisting of the benzyl cation (or ring-substituted benzyl cation) and the neutral component. Five kinds of reactions within the INC intermediates were observed [i.e., hydride transfer (HT), proton transfer (PT), electron transfer (ET), nucleophilic aromatic substitution (NAS), and electrophilic aromatic substitution (EAS)]. Benzyl cations were also generated by direct fragmentation of the precursor ions or separation of the INCs, which would be not further illustrated in the following discussions.

### *Proton Transfer*

The fragmentation of quaternary ammonium ions ($R_4N^+$) has been reported in previous studies and the formation of INCs was considered to be involved in the fragmentations [48–51]. Their fragmentation mode was influenced by the nature of their

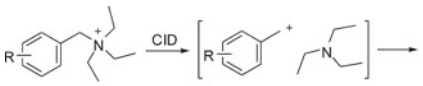
alkyl chains (R). In this study, the fragmentation reactions of *N*-benzyltriethylammonium ions containing different benzyl groups were studied. For these cations, the benzylic C–N bond is the most scissile one among the four C–N bonds. Thus, all the fragmentations were considered to be initiated by heterolytic cleavage of the benzylic C–N bond. Upon collisional activation, the *N*-benzyltriethylammonium ions first dissociate to form $[RC_6H_4CH_2^+/N(C_2H_5)_3]$ complexes. Intra-complex reactions between benzyl cation (or ring-substituted benzyl cation) and triethylamine produce some interesting product ions, as summarized in Table 1.

Ammonium ions were commonly observed in the fragmentation of alkylammonium ions through loss of alkene. However, no protonated triethylamine was produced in the fragmentation of a series of benzyltriethylammonium ions except for *N*-(4-methylbenzyl)triethylammonium ion (Cation **9**). The FTICR/CID spectrum of Cation **9** is shown in Figure 1. Three main product ions are observed in this spectrum, that is, iminium ion (*m/z* 100), protonated triethylamine (*m/z* 102), and 4-methylbenzyl cation (*m/z* 105). The accurate masses of these ions are consistent with the assigned structures (Table S1 in the online supplementary material). The mechanism for formation of ion at *m/z* 102 is proposed in Scheme 3. INC should be the intermediate in this reaction because the two reactive sites are spatially separated. The two species within an INC can rotate with respect to each other, which is one of the most important and well-know features for a true INC [36]. The precursor INC-**1** is first reoriented to the successor INC-**2** through rotation. Within INC-**2**, the 4-methylbenzyl cation can donate a proton from the methyl group to the triethylamine leading to the formation of protonated triethylamine. In contrast to many alkyl cations, the benzyl cations were generally considered not to be proton donors (i.e., Brønsted acids). A variety of benzyl cations (listed in Table 1) indeed do not show reactivity towards proton transfer. As an exception, the acidity of *para* methyl group of 4-methylbenzyl cation is dramatically enhanced by the methylene arenium character. This result is in agreement with similar phenomenon observed in solution when a methylene arenium molecule is coordinated to a metal center via the exocyclic double bond [4, 5]. In contrast, the 3-methylbenzyl cation cannot donate proton because the positive charge cannot reside at *meta* position and therefore the *meta* methyl group cannot react as a proton donor.

## *Hydride transfer and electron transfer*

Besides proton transfer, hydride transfer and electron transfer occur within the $[RC_6H_4CH_2^+/N(C_2H_5)_3]$ complex leading to the formation of iminium ion at *m/z* 100 and

**Table 1.** Product Ions Generated in ESI-IT/CID Experiments on *N*-Benzyltriethylammonium Cations[a]




| Cation | R | Precursor ion  | HT  | ET  |  | PT  |
|---|---|---|---|---|---|---|
| *1* | *p*-$NO_2$ | 237 (19.8)[b] | 136 (0.3) | 100 (31.1) | 101 (25.9) | 86 (100) | - |
| *2* | *m*-$NO_2$ | 237 (28.5) | 136 (0.7) | 100 (49.2) | 101 (24.7) | 86 (100) | - |
| *3* | *p*-$CF_3$ | 260 (22.6) | 159 (9.8) | 100 (83.8) | 101 (23.9) | 86 (100) | - |
| *4* | *p*-$^{35}Cl$ | 226 (22.6) | 125 (100) | 100 (62.9) | 101 (1.0) | 86 (1.8) | - |
| *5* | *p*-$^{79}Br$ | 270 (27.6) | 169 (100) | 100 (38.7) | 101 (0.5) | 86 (1.1) | - |
| *6* | H | 192 (21.7) | 91 (74.6) | 100 (100) | 101 (2.7) | 86 (2.5) | - |
| *7* | *m*-$OCH_3$ | 222 (26.9) | 121 (100) | 100 (47.1) | - | - | - |
| *8* | *m*-$CH_3$ | 206 (18.6) | 105 (100) | 100 (70.4) | - | - | - |
| *9* | *p*-$CH_3$ | 206 (21.0) | 105 (100) | 100 (36.3) | - | - | 102 (16.1) |
| *10* | *p*-$OCH_3$ | 222 (16.3) | 121 (100) | 100 (2.9) | - | - | - |

[a]Mass spectra are given in the online supplementary material.
[b]m/z (Relative abundance %)

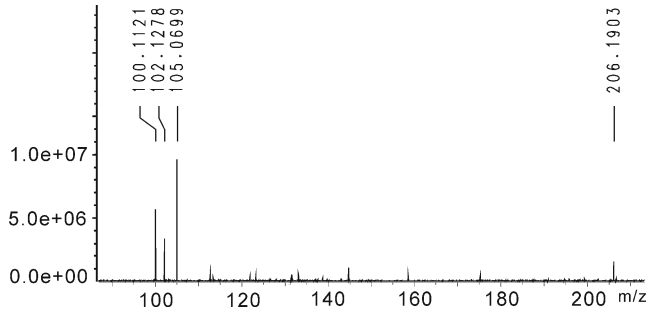
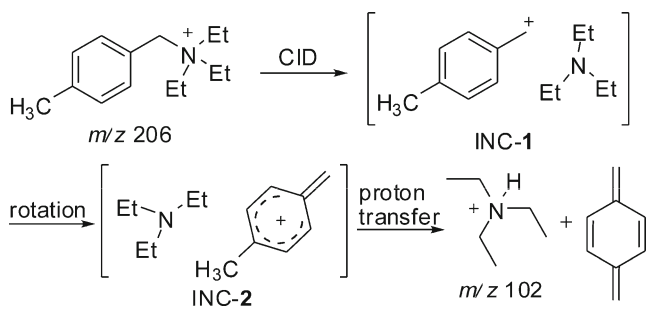



**Figure 1.** ESI-FTICR/CID spectrum for fragmentation of Cation **9** (*m/z* 206)

radical cation at *m/z* 101, respectively (Scheme 4). Benzyl cations are electron-deficient that they can accept either a pair of electrons (i.e., a hydride) or one electron. Electron-donating groups can stabilize the benzyl cation so that fragmentation of the *N*-benzyltriethylammonium cations bearing such substituents prefers to generate benzyl cations while the hydride transfer is not favored and the electron transfer does not take place (Table 1). As the enhancement of electron-withdrawing effect of the substituent, the benzyl cation becomes more electron-deficient so that the proportion of electron transfer reaction increases. For benzyl cations bearing strong electron-withdrawing groups, the electron transfer dominates over other reactions. The observable triethylamine radical cation at *m/z* 101 is not the major ion because it can further dissociate to form the dominant product ion at *m/z* 86 by loss of a methyl radical or it may also dissociate to form the ion at *m/z* 100 by loss of a hydrogen atom. The ionization energies (IEs) obtained from the NIST Chemistry WebBook for 3-nitrobenzyl radical, benzyl radical, and triethylamine are 8.6, 7.24, and 7.53 eV, respectively, which means the electron transfer between 3-nitrobenzyl cation and triethylamine is exothermic (1.1 eV), while the electron transfer between benzyl cation and triethylamine is endothermic (0.3 eV). Similar arguments hold true for the other cases. Therefore, the electron transfer reaction is favorable in the cases of Cations **1**, **2**, and **3**, and the sufficiently exothermic electron transfer within the INC also favors the subsequent α-cleavage of the triethylamine radical cation (*m/z* 101) to form the *N,N*-diethylmethyleneiminium ion (*m/z* 86).

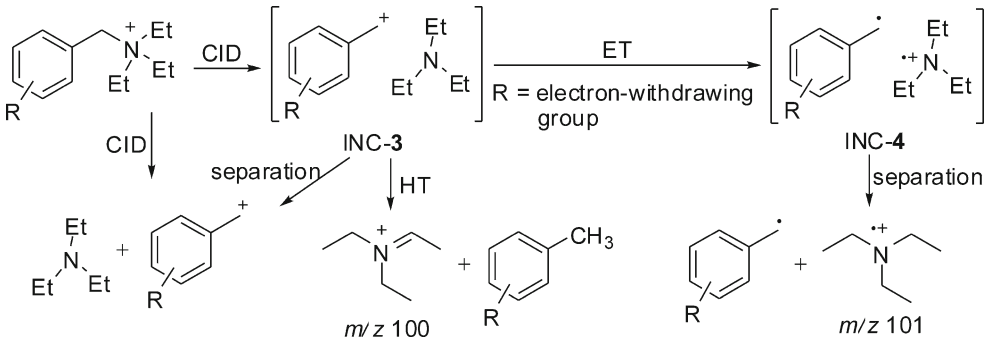



Scheme **3.** Proposed fragmentation mechanism for Cation **9** to form protonated triethylamine (*m/z* 102)

## *Electrophilic Aromatic Substitution*

Benzyl cation is an excellent electrophile that it can react with aromatic compounds by electrophilic attack. The attack at the phenyl ring has been reported in previous studies [20–22]. A new case that INC-mediated electrophilic aromatic substitution reaction between benzyl cation and imidazole derivatives was observed during the fragmentation of *N,N′*-dibenzylimidazolium cations (Table 2). The FTICR/CID spectrum of Cation **12** is shown in Figure 2. The elemental compositions of product ions are consistent with the assigned structures (Table S1 in the online supplementary material). Taking Cation **12** as an example, the EAS reaction mechanism is proposed in Scheme 5. The parent ion (*m/z* 263) initially dissociates to form the precursor complex INC-**5,** which can be further transformed to two successor complexes, INC-**6** and INC-**7**. Within INC-**6**, addition of the benzyl cation to the imidazole ring by electrophilic substitution enables the transfer of a proton to either of the two phenyl rings. The final product ion at *m/z* 185 is generated by loss of a benzene molecule. In other pathways, the benzyl cation can attack the phenyl ring via INC-**7** resulting in the formation of product ions including *m/z* 185, *m/z* 181, and *m/z* 95, which depends on the shift of the replaced proton. It is noteworthy that electrophilic substitution by the benzyl cation can occur at different positions of the aromatic ring, so product ions at *m/z* 185 and 181 are probably mixtures of several isomers, which has been investigated and demonstrated in the studies of other multi-benzyl-substituted compounds [20–22]. In this study, the isomerized product ions are no longer discussed in detail. However, the product ion at *m/z* 185 (loss of $C_6H_6$) can be formed from electrophilic attack by the benzyl cation either at the phenyl ring or at the imidazole ring, which can be distinguished by the deuterium labeling experiment. In the fragmentation of *N,N′*-bis(benzyl-$d_7$)-2-methylimidazolium cation (Cation **12**-$d_{14}$, *m/z* 277), both product ions at *m/z* 193 (loss of $C_6D_6$) and *m/z* 194 (loss of $C_6HD_5$ or $C_4H_5DN_2$) are formed (Figure S27 in the online supplementary material). The two ions with different elemental compositions both at *m/z* 194 can be further distinguished by determining their accurate masses. In the FTICR/CID mass spectrum (Figure S28 in the online supplementary material), the product ion from loss of $C_6HD_5$ appears at *m/z* 194.1641 (error, 1.5 ppm) and the product ion from loss of $C_4H_5DN_2$ (1-D-2-methylimidazole) appears at *m/z* 194.1828 (error, 1.5 ppm). Otherwise, the fragmentation of *N,N′*-bis(benzyl-$d_7$)imidazolium cation (Cation **11**-$d_{14}$ in Table 2) generates product ions at *m/z* 179 (loss of $C_6D_6$) and *m/z* 180 (loss of $C_6HD_5$). This experiment indicates that electrophilic attack by the benzyl cation at the phenyl ring and at the imidazole ring both contribute to the loss of benzene. The product ion at *m/z* 171 is obtained from hydride transfer through INC-**8** as shown in Scheme 6.

All the ions produced through benzyl cation rearrangement here can be considered as analogues of the



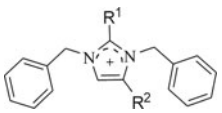

Scheme 4. Proposed fragmentation mechanism for *N*-benzyltriethylammonium cations to form ions at *m/z* 100 and *m/z* 101

benzyl cation. Formation of these ions is related to their energy threshold and the lifetime of the intermediates. For Cations **12** and **13**, when the imidazole ring is substituted by a methyl group, its electron density is increased, thus the electrophilic substitution at the imidazole ring becomes easier. As shown in Table 2, the relative abundance of ion **a** when generated from Cations **12** or **13** is higher than that from Cation **11**. Actually, the relative abundances of all the product ions except benzyl cation increase because a methyl substituent (electron-donating effect) makes the corresponding intermediates and product ions more stable.

## *Nucleophilic Aromatic Substitution*

The gas-phase nucleophilic aromatic substitution reactions of halobenzyl cations with piperazine (or *N*-methylpiperazine) via INC had been reported in a recent work [8]. In those unusual reactions, the benzyl cation reacts as a ring-charged methylene arenium ion, that is, the nucleophilic attack by nucleophile takes place at the phenyl ring but not at the methylene carbon. In the present study, the fragmentation reactions of various protonated *N*-halobenzyl amines were examined, as shown in Table 3. In the fragmentation of protonated *N,N′*-bis(4-halobenzyl)piperazines, loss of hydrogen halide (HX) was observed. The FTICR/CID spectrum of Cation **15** is shown in Figure 3. The accurate masses of product ions are consistent with the assigned structures (Table S1 in the online supplementary material). The product ion at *m/z* 125 is 4-chlorobenzyl cation and the ion at *m/z* 209 derives from hydride transfer. The proposed mechanism for loss of HX is given in Scheme 7. Fragmentation of the precursor cation initially forms INC-**9**, which then is reoriented to INC-**10** through rotation. Within INC-**10**, the NH group of piperazine adds as a nucleophile to the halogen-substituted

**Table 2.** Product Ions Generated in ESI-IT/CID Experiments on *N,N′*-Dibenzylimidazolium Cations[a]



| Cation | $R^1$ | $R^2$ | Precursor ion | Product ions | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | **a** | **b** | **c** | **d** | **e** |
| **11** | H | H | 249 (13.9)[b] | 171 (1.8) | 181 (0.4) | 81 (3.2) | 157 (1.0) | 91 (100) |
| **12** | $CH_3$ | H | 263 (26.4) | 185 (6.3) | 181 (3.3) | 95 (18.0) | 171 (8.8) | 91 (100) |
| **13** | H | $CH_3$ | 263 (20.6) | 185 (6.2) | 181 (1.2) | 95 (6.8) | 171 (12.0) | 91 (100) |
| **11**-$d_{14}$ | H | H | 263 (35.0) | 179 (0.5)<br>180 (1.1) | 194 (0.3) | 83 (1.3) | 163 (0.8) | 98 (100) |

[a]Mass spectra are given in the online supplementary material.
[b]m/z (Relative abundance %)

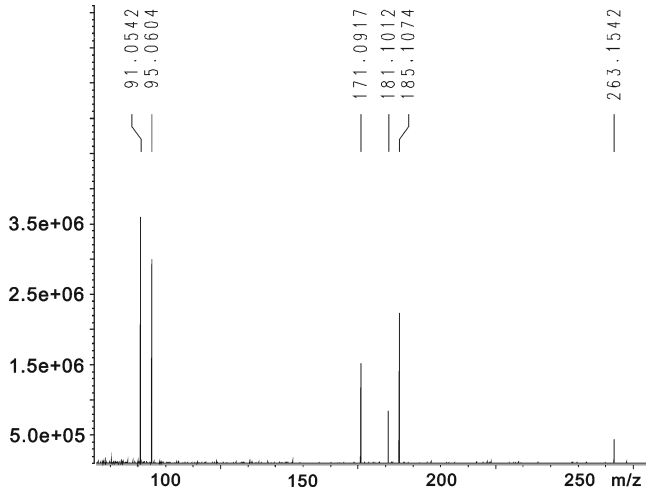
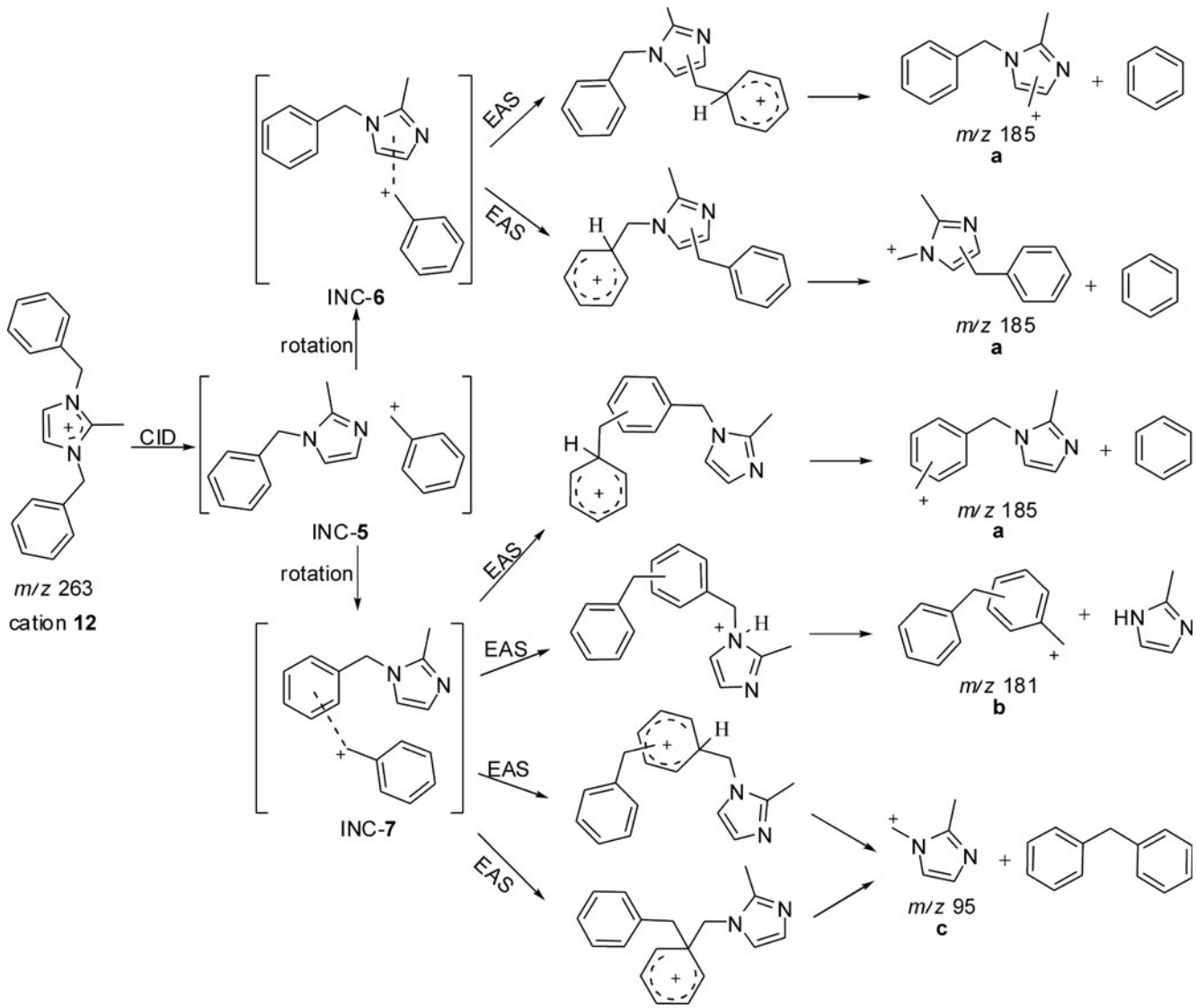
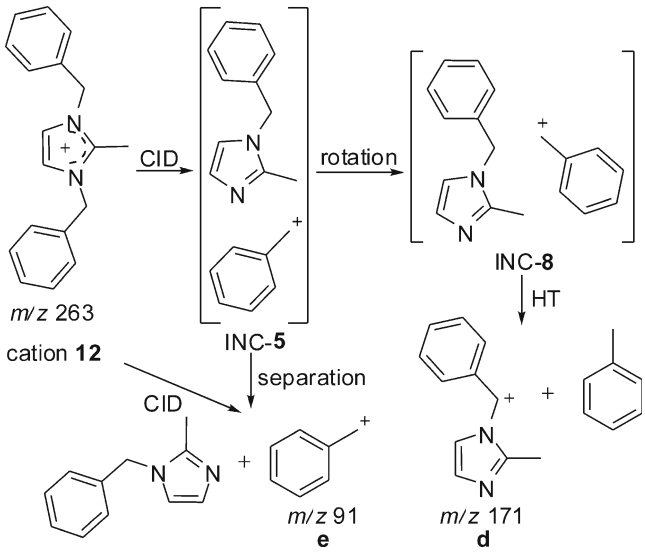



**Figure 2.** ESI-FTICR/CID spectrum for fragmentation of Cation **12** (*m/z* 263)

ring carbon to form a σ complex, which should be the key step in this reaction. The nature of X affects the rate of this step because an increase in the electron-withdrawing character of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, fluoride is the best leaving group among the halogens in most aromatic nucleophilic substitutions, which is different from the $S_N1$ and the $S_N2$ mechanisms, where fluoride is by far the poorest leaving group of the halogens [52]. In the reaction of 1-substituted-2,4-dinitrobenzenes with piperidine in methanol, when the substituent was F, the relative rate was 3300 compared with I=1 [53]. The very fact that the tendency for loss of HX in the fragmentation of protonated *N,N′*-bis(4-halobenzyl)piperazines HF >>HCl> HBr>HI is a good evidence for the nucleophilic aromatic substitution reaction mechanism. Besides the kinetic factor, the highly favorable thermochemistry of HF can



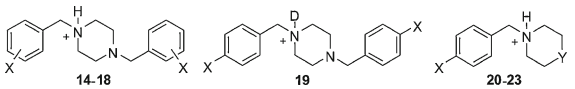

Scheme **5.** Proposed mechanism for EAS reactions in the fragmentation of Cation **12**




Scheme 6. Proposed mechanism for formation of ions **d** and **e** in the fragmentation of Cation **12**

be another reason for the efficient loss of HF. In the resonance of a benzyl cation, the positive charge cannot reside at the *meta* position of the phenyl ring where, hence, nucleophilic attack can not occur, so the *meta*-chloro-substituted cation (Cation **16**) cannot lose HCl.

**Table 3** Product Ions Generated in ESI-IT/CID Experiments on Protonated *N*-Halobenzyl Amines[a]




| Cation | X | Y | Precursor ion | Loss of HX | Other main ions |
|---|---|---|---|---|---|
| **14** | *p*-F | - | 303 (26.3)[b] | 283 (41.1) | 193 (100), 109 (95.5) |
| **15** | *p*-$^{35}$Cl | - | 335 (19.2) | 299 (13.1) | 209 (82.0), 125 (100) |
| **16** | *m*-$^{35}$Cl | - | 335 (20.8) | - | 209 (100), 168 (39.9), 125 (37.6) |
| **17** | *p*-$^{79}$Br | - | 423 (22.9) | 343 (10.5) | 253 (91.6), 169 (100) |
| **18** | *p*-I | - | 519 (27.9) | 391 (4.3) | 301 (52.6), 217 (100) |
| **19** | *p*-$^{35}$Cl | - | 336 (17.8) | 299 (13.5)[c] | 210 (100), 125 (90.9) |
| **20** | *p*-$^{35}$Cl | $CH_2$ | 210 (15.1) | - | 125 (100), 84 (14.4) |
| **21** | *p*-$^{35}$Cl | NH | 211 (24.5) | 175 (18.2) | 125 (100), 85 (23.5) |
| **22** | *p*-$^{35}$Cl | $NCH_3$ | 225 (11.5) | 189 (15.5) | 125 (100), 99 (58.0) |
| **23** | *p*-$^{35}$Cl | O | 212 (19.6) | - | 125 (100), 86 (6.8) |

[a]Mass spectra are given in the online supplementary material.
[b]m/z (Relative abundance %)
[c]Loss of DX

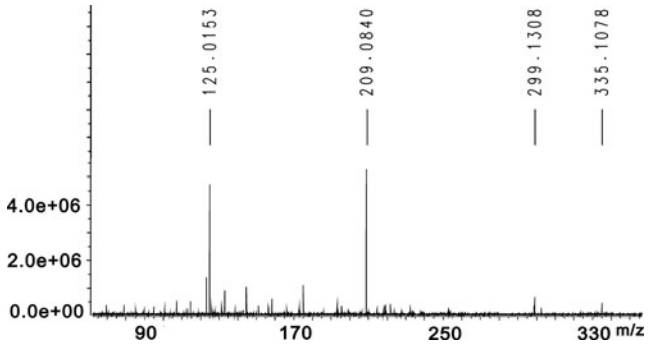
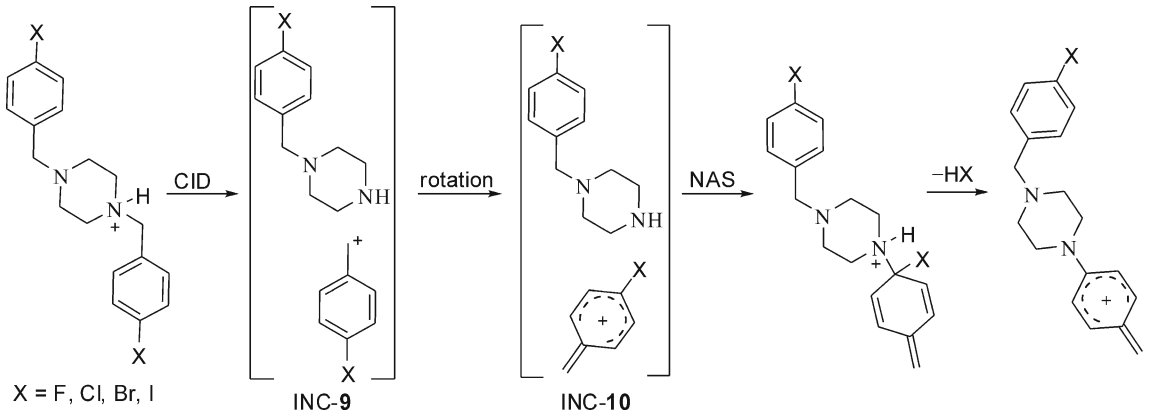



Figure 3. ESI-FTICR/CID spectrum for fragmentation of Cation **15** (*m/z* 335)

Only loss of DCl was observed in the fragmentation of deuterated *N,N′*-bis(4-chlorobenzyl)piperazine (Cation **19**). These results further proved the nucleophilic aromatic substitution mechanism for loss of HX in the fragmentation of protonated *N,N′*-bis(4-halobenzyl)piperazines.

Furthermore, the nucleophilic aromatic substitution reaction between different amines and 4-chlorobenzyl cation were investigated. In the comparison of piperidine, piperazine, *N*-methylpiperazine, and morpholine (Table 3), it is quite interesting and a wonder that only piperazine and *N*-methylpiperazine can be involved in such reactions, but the piperidine and morpholine cannot react with 4-chlorobenzyl cation to lose HCl. Experimental and theoretical studies indicate that the nucleophilicity of piperidine is stronger than that of piperazine [54, 55], so the nucleophilicity is probably not the reason. When the amine is diethylamine, diisopropylamine, or pyrrolidine, the loss of HCl is not observed as well (Figures S24–S26 in the online supplementary material). The hydride transfer reaction between these amines and 4-chlorobenzyl cation all can take place. At present, it seems that only amines containing piperazine structure can react with halobenzyl cations to lose hydrogen halide by nucleophilic attack at the phenyl ring. A proposed mechanism for such a special reaction is shown in Scheme 8 in which an intermediate Int-**N2** is supposed to be involved between the two INCs (INC-**11** and INC-**12**). Although the components within an INC are able to rotate almost freely, the transformation from INC-**11** to INC-**12** is unfavorable for *N*-(4-chlorobenzyl) amines without piperazine moiety, probably because other competing reactions are preferred and the lifetime of INC-**11** is not long enough for the transformation. The time constraint is an important factor influencing the INC-mediated reactions [24]. However, for *N*-(4-chlorobenzyl) piperazine and analogues, the formation of INC-**12** can be assisted by the second nitrogen atom ($N^2$) through forming an intermediate Int-**N2**. Int-**N2** may also be formed from the precursor ion through 4-chlorobenzyl cation transfer from $N^1$ to $N^2$ (not shown in the scheme). In Int-**N2**, the $N^1H$ group faces to and interacts with the phenyl ring, but the distance between it and the chlorine substituent is still long. After cleavage of the benzylic C–$N^2$ bond, $N^1H$ moves closely to the phenyl ring to form INC-**12**. This interesting issue is




Scheme 7. Proposed mechanism for loss of HX in the fragmentation of protonated *N,N'*-bis(4-halobenzyl)piperazines

worthy of being further studied in the future, and high-level theoretical calculations may provide useful help.

## Conclusions

In this study, *N*-benzylammonium and *N*-benzyliminium ions were studied by collisional activation in an ion-trap or Fourier transform ion cyclotron resonance mass spectrometer. The ion/neutral complexes consisting of the benzyl cations and the N-containing counterparts were proposed as intermediates to rationalize the fragmentation reactions of these ions. Five types of reactions within the complex, namely proton transfer, hydride transfer, electron transfer, electrophilic aromatic substitution, and nucleophilic aromatic substitution, were observed and comprehensively investigated.

The positive charge delocalization within the benzyl cation (or the ring-substituted benzyl cation) contributes to the diversified reactivities of the benzyl cations. When the charge is mostly localized at the methylene group, it can react as a Lewis acid to capture a hydride ion from the neutral amines, or react as an electrophile to attack the neutral aromatic rings. When the charge is localized predominantly in the ring, it can activate the *para*-methyl group to release a proton as a Brønsted acid, or act as a substrate for nucleophilic aromatic substitution at the phenyl ring in which the *para*-halogen groups can be replaced by a piperazine or analogues. The high electron-deficiency character of benzyl cations, especially those that bear a strong electron-withdrawing group, enables them to be electron acceptors to obtain an electron from tertiary amines with low ionization energy.

This study improves and enriches the gas-phase chemistry of benzyl cations. The general knowledge on ion/neutral complex-mediated reactions between benzyl cations and the neutral counterpart is also useful for understanding the fragmentation reactions of *N*-benzylated compounds.

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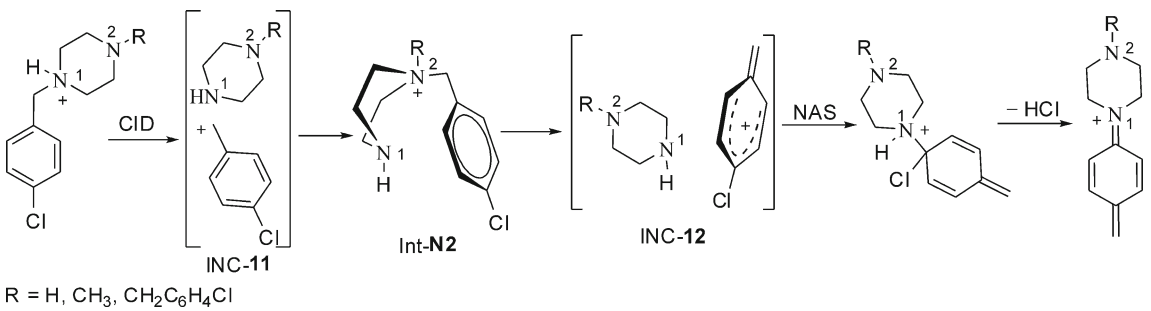


Scheme 8. Proposed mechanism for loss of HCl from protonated *N*-(4-chlorobenzyl)piperazine and analogues. The initial protonation site may be either of the two nitrogen atoms, but proton transfer between $N^1$ and $N^2$ in the boat conformation is feasible.

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