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Dissociative Benzyl Cation Transfer versus Proton Transfer: Loss of Benzene from Protonated *N*-Benzylaniline

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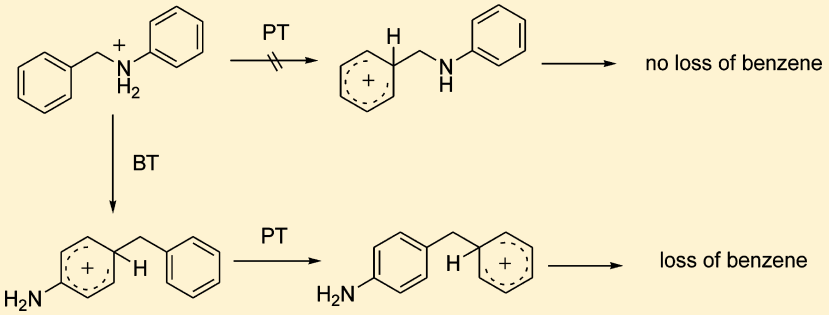
Supporting Information



ABSTRACT: In collisional activation of protonated *N*-benzylaniline, the benzene loss from the benzyl moiety is actually not the result of dissociative proton transfer (PT). In fact, benzyl cation transfer (BCT) from the nitrogen to the anilinic ring (*ortho* or *para* position) is the key step for benzene loss. Such dissociation occurs only after the benzyl group migrating from the site with the highest benzylation nucleophilicity (nitrogen) to a different one (aromatic ring carbon), which is described as dissociative benzyl cation transfer.

Electrospray ionization mass spectrometry (ESI-MS) not only is a versatile technique for the analysis of numerous molecules but also plays an important role in structural elucidation. However, the structural and mechanistic information based on interpretation of the fragmentation of gaseous ions is limited due to the widespread unexpected rearrangement reactions, which have attracted great interest since the early days of organic mass spectrometry.

To go deep into the fragmentation pathways of the protonated molecules (MH^+) formed in ESI-MS, one might first need to determine the initial protonation site, which usually possesses the highest proton affinity or gas basicity. The positive charge formed upon protonation usually triggers bond cleavages. However, it is often observed that the thermodynamically stable protonated ion is not fragile but can be fragmented after isomerization to the dissociative structure. Such observations led to a proposal of dissociative proton transfer in mass spectrometry of organic compounds and peptides.[1] As a typical example, loss of benzene is a common fragmentation reaction in the gas phase.[2−6] The phenyl ring possesses relatively low proton affinity (PA), which could hardly be the ionization group in ESI. Therefore, benzene loss is a result of dissociative proton transfer from the thermodynamically favorable protonation site to the *ipso* position of the phenyl ring in the fragmentation of various protonated compounds, e.g., dibenzyl ether,[3,4] benzophenone,[4] chalcones,[5] enaminones,[6] and *N*-benzylbutyrolactams.[7]

Although dissociative proton transfer has been successfully applied in many cases, it is not universal. An unwarranted application of this model may even result in serious errors. Recently, we observed the benzene loss in the fragmentation of protonated *N*-benzylaniline. At first glance, it can be well explained by invoking the dissociative proton transfer model, that is, proton transfer (PT) from the nitrogen to the *ipso* position of the phenyl ring leading to loss of benzene. However, in a more detailed study, the previous proposal was found to be completely wrong. Actually, the fragmentation reaction is initiated by benzyl cation transfer (BCT) rather than PT. The protonated *N*-benzylaniline first rearranges to the protonated 4-benzylaniline or 2-benzylaniline via BCT, and then loss of benzene can take place. Although the phenomenon of benzyl group rearrangement has been observed in several cases,[8] the intrinsic features of the BCT instead of the PT resulting in gaseous fragmentations indeed attract us. In this paper the dissociative benzyl cation transfer is identified as the main driving force of benzene loss.

Benzene loss (corresponding to m/z 106) along with the dominant benzyl cation at m/z 91 is observed in the fragmentation of protonated *N*-benzylaniline (Figure 1a), which was confirmed by the accurate mass determined on ESI-Q-TOF mass spectrometer (Supplementary Table S1). The loss of chlorobenzene in the CID mass spectrum of protonated *N*-(3-chlorobenzyl)aniline (Figure 1b) indicates that the lost benzene arises from the benzyl moiety but not the aniline moiety.

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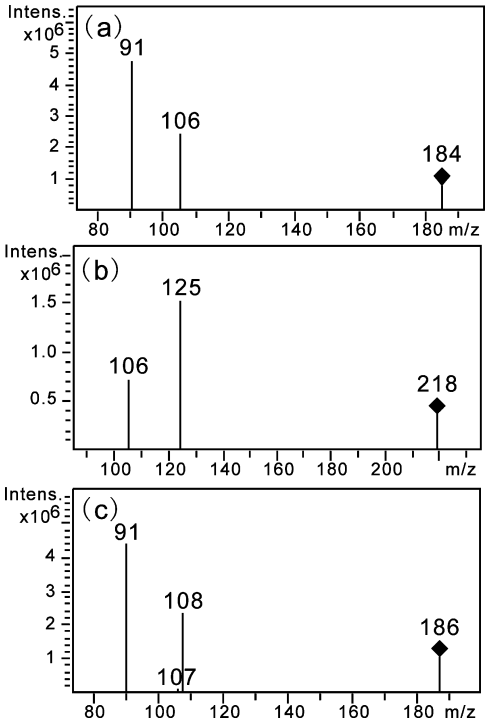


Figure 1. CID mass spectra of (a) protonated *N*-benzylaniline, (b) protonated *N*-(3-chlorobenzyl)aniline, and (c) *N*-(1′,1′-D_2)-benzylaniline cation.

To begin interpretation of the fragmentation of the protonated *N*-benzylaniline, we should first tackle where the protonation site is. In view of the protonation site, the unsubstituted *N*-benzylaniline would be similar to *N*-alkylamine, for which it has been concluded that the nitrogen atom is the preferred site for protonation in ESI mass spectrometry.[9] Then, considering also the fact that the dissociative proton transfer mechanism can be well applicable for elucidating the benzene losses from protonated gaseous organic molecules, we initially propose that the PT from nitrogen to the *ipso* carbon of the phenyl ring is required prior to the benzene loss in the fragmentation of protonated *N*-benzylaniline (Scheme 1).

However, it is surprisingly discovered in the CID spectrum of *N*-(1′,1′-D_2)benzylaniline cation (Figure 1c) that no deuterium atom is eliminated in the process of losing a benzene molecule, which is an experimental observation against the dissociative proton transfer mechanism. Moreover, the product ion at *m*/*z* 106 from benzene loss of protonated *N*-benzylaniline showed a CID mass spectrum *different* from that of the protonated *N*-methylene benzamine but *identical* to that of the 4-aminobenzyl cation (Supplementary Figure S5).

In view of the existence of the benzyl cation at *m*/*z* 91 and the known BCT in the gas-phase fragmentations of numerous benzylated cations, another plausible mechanism is postulated in Scheme 2. The benzyl group first transfers from the initial site with the highest benzylation nucleophilicity (nitrogen) to the anilinic ring. Electrophilic attack by the benzyl cation at the phenyl ring activates the ring hydrogen to be mobile. Once the proton is attached on the *ipso* site of the benzylic ring, the elimination of benzene occurs.

Why is dissociative benzyl cation transfer instead of dissociative proton transfer responsible for the benzene loss in the present case? Density functional theory (DFT) calculations at the B3LYP/6-311++G(2d,p) level of theory were performed to compare the energetics of the dissociative proton transfer mechanism and dissociative benzyl cation transfer mechanism, as shown in Figure 2.

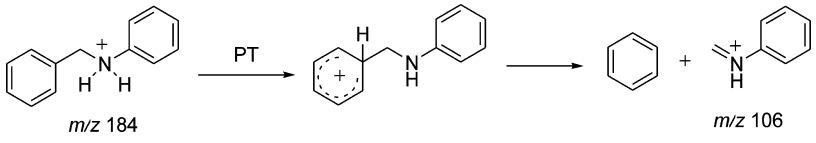
Dissociative PT of *N*-protonated *N*-benzylaniline (**M1**) forms an ion-neutral complex **INC2** in a shallow energy well 12.5 kcal mol^{-1} higher in energy than **M1**. The total energy of products from dissociative PT (ion **A1**) is 8.1 kcal mol^{-1} higher than that of the products from dissociative BCT to the *para* site (ion **A2-p**), close to the *ortho* site (ion **A2-o**), and 12 kcal mol^{-1} lower than the *meta* site (ion **A2-m**). Moreover, the transition state energy of dissociative PT is above the energy thresholds of BCT, even though there are several alternative pathways of sequential PT from **M2** to **INC3** in the BCT mechanism (Supplementary Figures S2−S4) and two pathways of PT from **M1** to **INC2** in the dissociative PT mechanism (Supplementary Figure S1). When the energies of the products and transition states are considered comprehensively, the dissociative BCT pathway is more favorable than the dissociative PT pathway in terms of energy.

By comparing the energy requirements of BCT to the different positions of aniline (*ortho*, *meta*, and *para*), the *para* position is the most favorable site for benzyl cation attack, while the *meta* position is the least favorable site for benzyl cation attack. The relative energies of **M2**, **INC3**, and ion **A2** all follow the order of *meta* > *ortho* > *para*. The energy barriers for PTs after BCT are close,[10] which is likely not a decisive factor for benzene loss through BCT.

Although the DFT calculations predict that ion **B** is the thermodynamically disfavored product in the CID fragmentation of protonated *N*-benzylaniline, ion **B** is still dominant (showed in Figure 1a) for that dissociation to afford ion **B** is the kinetically preferred pathway. The benzylic C−N bond cleavage has no inverse activation energy and is probably faster than other rearrangement processes. All of these theoretical results are consistent with those experimental results and also well support the proposed mechanism.

As known, the electrophilic substitution of aniline mainly occurs at the *para* or *ortho* position rather than the *meta* position. To further experimentally understand the sites of the BCT, the CID fragmentations of protonated *N*-benzyl-4-methylaniline, *N*-benzyl-2,2-dimethylaniline, and *N*-benzyl-2,2,4-trimethylaniline were studied (Figure 3). Though the signal peak corresponding to the benzene loss is observed in all of their fragmentations, the relative abundances (RAs) are distinct: when both of the *ortho* and *para* sites are occupied, the signal peak of benzene loss (*m*/*z* 148, Figure 3c) is extremely low (RA, 2%); when the *para* site is blocked, the peak of

Scheme 1. Proposed Mechanism of Benzene Loss Resulting from Dissociative Proton Transfer



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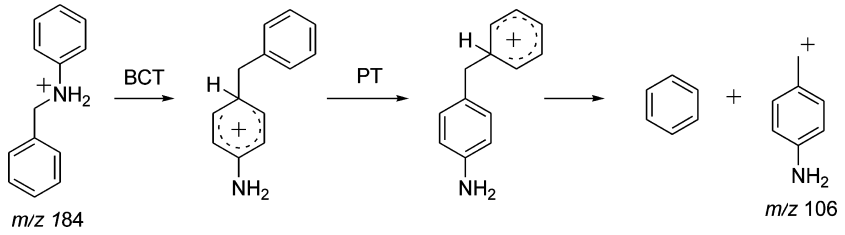
Scheme 2. Proposed Mechanism of Benzene Loss Resulting from Dissociative Benzyl Cation Transfer; *para*-Position Selected as an Example for Clear Illustration



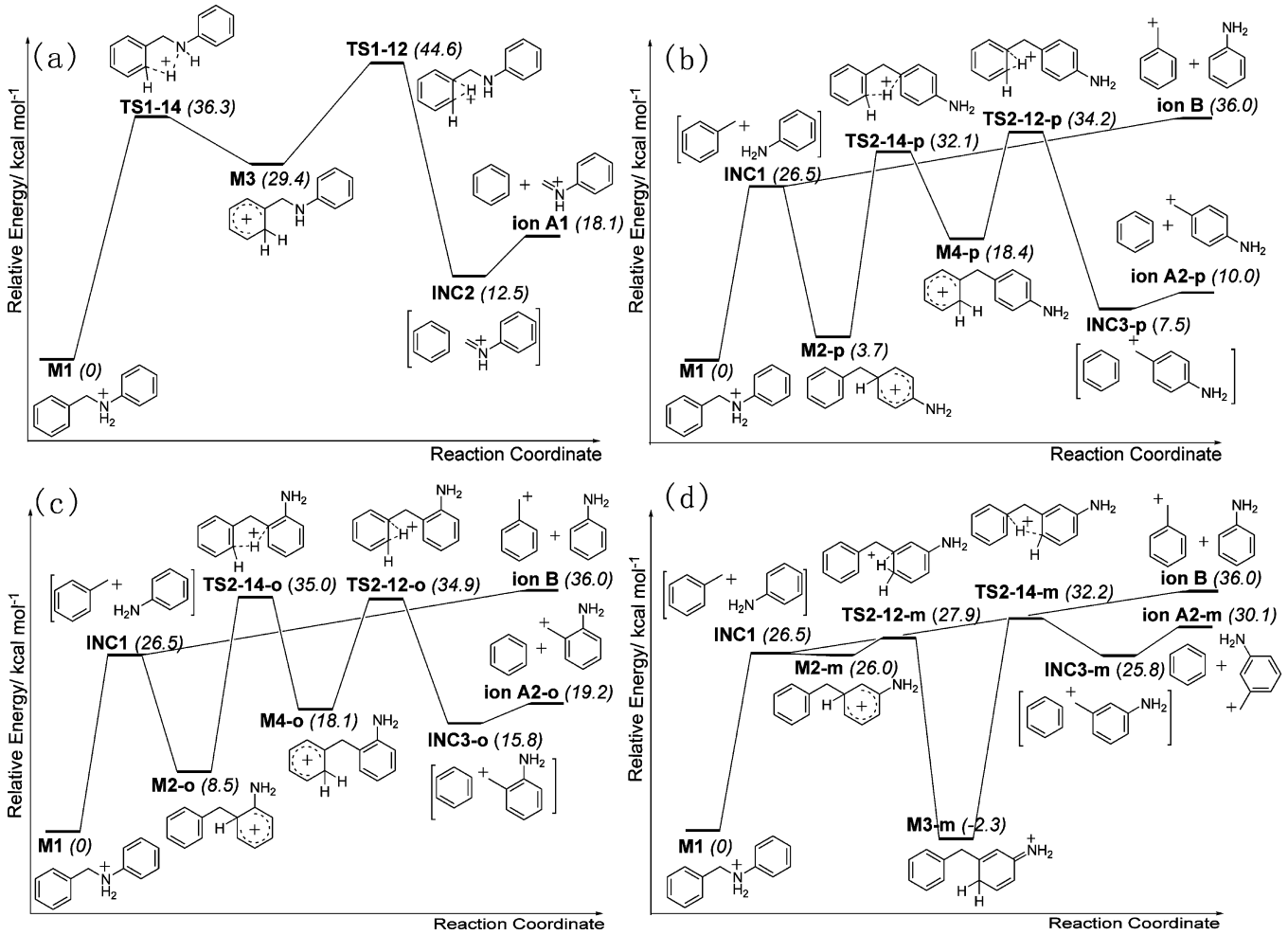


Figure 2. DFT potential energy surfaces of different pathways, (a) dissociative PT, (b) *para*-BCT, (c) *ortho*-BCT, and (d) *meta*-BCT, for fragmentation of protonated *N*-benzylaniline. All structures were optimized at the B3LYP/6-311++G(2d,p) level of theory in kcal mol^{-1} (in parentheses). The most favorable potential energy surface of each pathway is shown representatively, while other possible energy surfaces are presented in detail in Supplementary Figures S1−S4.

benzene loss (*m*/*z* 120, Figure 3a) is obviously observed (RA, 26%); and when the two *ortho* sites are substituted by methyl group, the RA of product ion at *m*/*z* 134 resulting from benzene loss (Figure 3b) increases to 85%. These observations live up to the orientation effect and reactivity in monosubstituted benzene rings toward electrophilic aromatic substitution. The fragment ions at *m*/*z* 106 (Figure 3a), *m*/*z* 120 (Figure 3b), and *m*/*z* 134 (Figure 3c) in the CID mass spectra, corresponding to the toluene loss, are the consequence of hydride transfer from the methyl group to the benzyl cation, as described previously.[2c,11] The existence of toluene loss also well confirms the mobility of benzyl cation. The peak at *m*/*z* 135 (Figure 3c) is the outcome of electron transfer from the 2,4,6-trimethylaniline to the benzyl cation as studied before.[8a] These experimental results are well consistent with the DFT calculations.

On the basis of the experimental and theoretical studies, the protonated *N*-benzylaniline cannot lose benzene without BCT. The benzene loss occurs only when the protonated *N*-benzylaniline is isomerized to the ring-protonated 2-benzylaniline or 4-benzylaniline through BCT. For comparison, the ring-protonated 4-benzylaniline can be generated from the *N*-protonated 4-benzylaniline through PT upon collisional activation. Actually, loss of benzene was observed in the fragmentation of the $[M + H]^+$ ion of 4-benzylaniline (Supplementary Figure S6).

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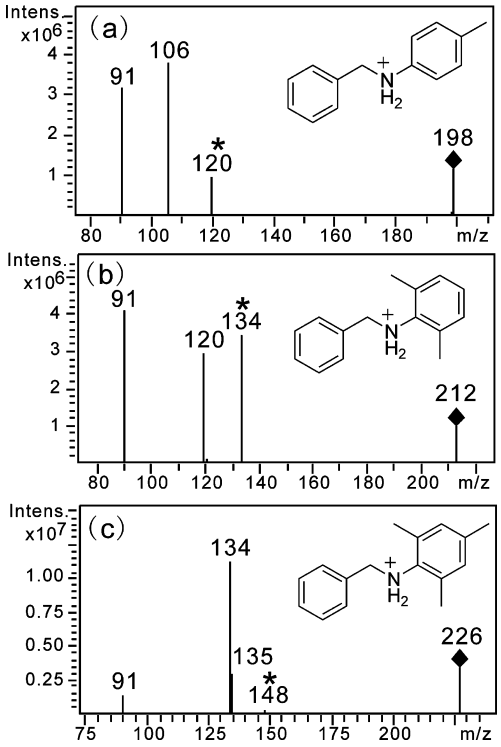

Figure 3. CID mass spectra of protonated (a) *N*-benzyl-4-methylaniline, (b) *N*-benzyl-2,2-dimethylaniline, and (c) *N*-benzyl-2,2,4-trimethylaniline. The signal peaks corresponding to benzene loss are marked with asterisks for clarity.

In summary, protonated *N*-benzylaniline investigated by ESI-MS/MS equipped with an ion trap cell eliminates the benzylic benzene under collisional activation. On the basis of the mass spectra data, along with deuterium-labeling experiments and theoretical calculations, a novel mechanism for this frangmentation reaction is proposed and confirmed as dissociative benzyl cation transfer. The *N*-protonated *N*-benzylaniline does not proceed to lose benzene via dissociative proton transfer. After the benzyl group transfers from the nitrogen atom to the ring carbon of aniline, the formed protonated 4-benzylaniline (or 2-benzylaniline) can carry out benzene loss. The order of priority for benzyl cation transfer to the phenyl ring of aniline is *para* > *ortho* ≫ *meta*, which is well verified by the blocking experiments with methyl group on different positions of aniline.

EXPERIMENTAL SECTION

All of the *N*-benzylaniline derivatives were synthesized and purified with the corresponding benzaldehyde and aniline following the reported procedures.[12] The structures were confirmed by mass spectrometry and NMR spectroscopy. *N*-Benzylaniline: ^{1}HNMR (500 MHz, $CDCl_3$) δ (ppm) 7.71 (m, 4H), 7.65 (t, 1H), 7.57 (t, 2H), 7.13 (t, 1H), 6.96 (d, 2H), 4.60 (s, 2H), 4.23 (s, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ (ppm) 148.2, 139.5, 129.3, 128.6, 127.5, 127.2, 117.5, 112.9, 48.1. HRMS (ESI-Q-TOF) calcd for $C_{13}H_{13}N$ [M + H^+] 184.1121, found 184.1128.

The CID experiments were performed in the positive-ion mode using a Bruker Esquire 3000^{plus} mass spectrometer equipped with an ESI source and an ion trap analyzer. All theoretical calculations were carried out using the Gaussian 03 package of programs. The experimental methods for mass spectrometric analysis and theoretical calculations are described in Supporting Information.

ASSOCIATED CONTENT

Supporting Information

CID mass spectra, figures, Cartesian coordinates, total energies, zero point energy corrections and the number of imaginary frequencies of all optimized structures discussed in the text, and the experimental methods used for mass spectrometric analysis and theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) The energy barrier of the alternative 1,4-PT to the *ortho* position of benzylic ring followed by a low-energy 1,2-PT to the *ipso* site is higher than that of direct 1,3-PT after BCT to *ortho* or *para* position and close to the energy of 1,2-PT to the *ortho* site of anilinic ring and then 1,5-PT to the *ortho* position of benzylic ring followed by 1,2-PT to the *ipso* site. Meanwhile, the 1,2-PT followed by 1,4-PT after *meta*-BCT has the lowest energy barrier.
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