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Gas-Phase Nucleophilic Aromatic Substitution between Piperazine and Halobenzyl Cations: Reactivity of the Methylene Arenium Form of Benzyl Cations

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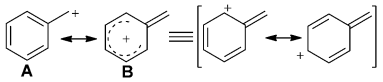
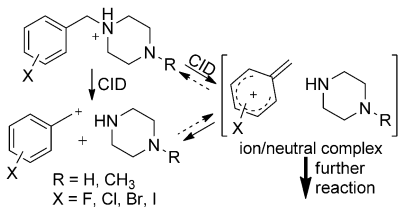
Nucleophilic aromatic substitution (S_NAr)[1] is one of the most fundamental reactions in organic chemistry. The most popular mechanism for S_NAr reactions is an addition–elimination process involving a σ complex (Meisenheimer complex) intermediate. Although S_NAr reactions in solution have been well documented, there are only a few reports on their gas-phase chemistry. Studying chemical reactions in the gas phase allows to determine the intrinsic features of reactions and to characterize the short-lived intermediates in isolation from solvent, counterion, catalyst interference and aggregation effects. The key stage in a S_NAr reaction is the formation of the σ complex, which has become a subject of special concern. The typical anionic σ complexes formed between anionic nucleophiles and aromatic substrates bearing strong electron-withdrawing groups are found to be relatively stable. In recent years there has been a breakthrough in studies on the gas-phase anionic S_NAr reactions[2] and anionic σ complexes alone.[3] Although several σ complex-type structures in the cationic state, such as $H^+C_6H_6$, $H^+C_6H_5F$ and $C_6H_6NH_3^+$, had been observed in the gas phase by spectroscopy,[4] they showed no aromatic substitution reactivity due to their poor leaving group. Cationic σ-complex-mediated S_NAr reactions in the gas phase are still rare. Among the few studies performed, the substrate is merely ionized halobenzenes and the nucleophile is ammonia or methyl isocyanide.[5] In this study, we report the gas-phase S_NAr reactions between piperazine (nucleophile) and halogen-substituted benzyl cations (substrate) using electrospray ionization mass spectrometry (ESI-MS).

Benzyl cations are highly reactive intermediates in various chemical and biochemical reactions.[6] It has been demonstrated that two major resonance forms (**A** and **B**), as shown in Scheme 1, contribute significantly to the total structure of the benzyl cation.[7] However the "methylene arenium" form (**B**) has little contribution in reactions, because the reaction of benzyl cation with electron-rich reagents nearly always occurs at the benzylic methylene group both in solution and in the gas phase due to its maintenance of the aromaticity of the product.[8] One exception in the gas phase was observed in the fragmentation reaction of Fréchet dendrons.[9] In that example, steric constraints force the intramolecular reaction to occur at the phenyl ring of the benzyl cation but not at the benzylic position. To our knowledge, the reaction of halobenzyl cations with piperazine reported here is the first non-restricted case in which the methylene arenium exhibits nucleophilic substitution reactivity at the phenyl ring.



Scheme 1. Resonance forms of a benzyl cation.

Because of the advantages of being solvent- and counterion-free, mass spectrometry can be exploited to synthesize ions[10] and study gas-phase organic reactions.[11] In the present study, the reactants of piperazine and halobenzyl cations were simultaneously in-situ-generated by collision-induced dissociation (CID) of protonated *N*-(halobenzyl)piperazines using an ESI ion trap mass spectrometer (Scheme 2).[12] The two nascent reactants with a suitable amount of internal energy are consequently trapped in an ion/neutral complex[13] through electrostatic interactions. The two components of the ion/neutral complex are able to rotate with respect to one another, and therefore they show reactivities similar to those expected for the isolated species. Under CID conditions, the inverse process, in which piperazine attacks the benzylic position of the halobenzyl cation, is prevented; hence, other reactions between the reactants are quite likely to take place. It should be added that the rear-



Scheme 2. Synthesis of the ion/neutral complex containing the reactants through the collision-induced dissociation method.

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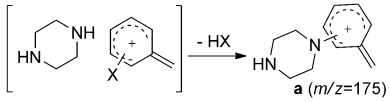
rangement barrier from benzylium to tropylium is quite substantial.[14] In ESI-MS, fragmentation of benzylated cations prefers to generate benzylium,[8d,e,9,15] although tropylium also can be formed in some cases.[16] In gas-phase reactions, tropylium is inert whereas benzylium is active towards hydride abstraction and electrophilic attack.[8c,14b,17] In view of their reactivity, the benzylium ions should be involved in the S_NAr reactions and evidences from both experiments and calculations are given in the following discussions.

The gas-phase S_NAr reactions between piperazine (or *N*-methylpiperazine) and a variety of halogen-monosubstituted benzyl cations were explored using the above method. The results are summarized in Tables 1–3, and their corresponding mass spectra are presented in the Supporting Information. A typical CID spectrum for the $[M+H]^+$ ion of *N*-(4-fluorobenzyl)piperazine is given in Figure 1. For all the compounds studied except the *meta*-chloro-substituted compound, the intra-complex substitution reaction leading to loss of hydrogen halide (HX) can be achieved.

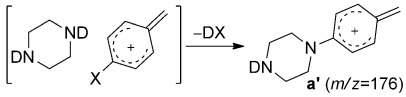
Table 1. S_NAr reactions between piperazine and halobenzyl cations.



Entry	X	Neutral loss	Relative abundance of ion **a** [%][a]
1	*p*-F	HF	56
2	*p*-^{35}Cl	H^{35}Cl	18
3	*m*-^{35}Cl	H^{35}Cl	0
4	*o*-^{35}Cl	H^{35}Cl	2
5	*p*-^{79}Br	H^{79}Br	15
6	*p*-I	HI	4

[a] The relative abundances of halobenzyl cations are 100% for all the compounds studied.

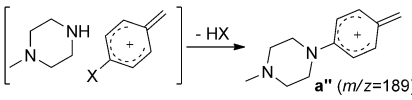
Table 2. S_NAr reactions between [D_2]piperazine and 4-halobenzyl cations.



Entry	X	Neutral loss[a]	Relative abundance of ion **a′** [%]
1	F	DF	55
2	^{35}Cl	D^{35}Cl	17
3	^{79}Br	D^{79}Br	15
4	I	DI	3

[a] No loss of HX is observed.

Table 3. S_NAr reactions between 1-methylpiperazine and 4-halobenzyl cations.



Entry	X	Neutral loss	Relative abundance of ion **a″** [%]
1	F	HF	39
2	^{35}Cl	H^{35}Cl	16
3	^{79}Br	H^{79}Br	11
4	I	HI	3

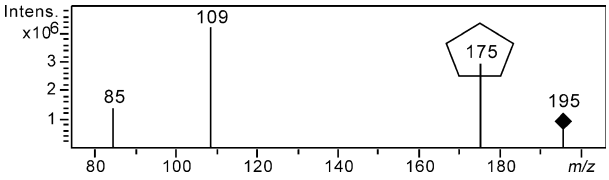
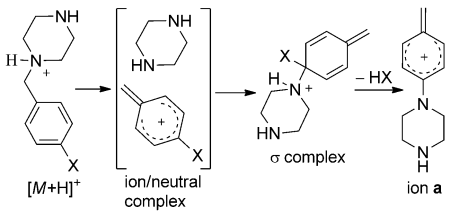


Figure 1. CID mass spectrum of the $[M+H]^+$ ion of *N*-(4-fluorobenzyl)-piperazine ($m/z=195$).

The most abundant ion in the fragmentation of all the compounds studied is the halobenzyl cation, which is attributed to the direct dissociation of the precursor ion or separation of the ion/neutral complex. It is noteworthy that the intra-complex reactions occur for only parts of complexes that have a suitable amount of internal energy, for example, enough to react but not enough to decompose.[18] The ion at $m/z=85$, confirmed to be protonated 1,2,3,6-tetrahydropyrazine in a previous study,[19] is the result of an intra-complex hydride-transfer reaction. This competing reaction channel provides positive evidence for the existence of the ion/neutral complex involving the two designated reactants. Furthermore, the occurrence of hydride abstraction reaction demonstrates that the $C_7H_6X^+$ ion in the complex must have the benzylium structure because the tropylium ion is known to be inert towards hydride abstraction.[8c,17] The signal at $m/z=175$, formed by loss of HX, is uniquely assigned to piperazinobenzlium, $HN(CH_2)_4N{-}C_6H_4CH_2^+$ (ion **a**). The mechanism for the generation of ion **a** is proposed in Scheme 3 (using the *para*-substituted ion as an example). In these cases, halobenzyl cations can be regarded as electron-deficient aromatic substrates, in which the methylene group on the phenyl ring is equivalent to a strong electron-withdrawing group (like NO_2). Within the [4-halobenzyl cation/piperazine] complex, the piperazine nucleophile attacks the *para* position of 4-halobenzyl cation (methylene arenium form) to form a cationic σ complex. The final product **a** is thus obtained after quick elimination of HX from the σ complex. For ion **a**, the benzyl cation is largely stabilized by the piperazine moiety, which may be the main driving force of this reaction.



Scheme 3. Proposed mechanism for the formation of ion **a**.

The structure of product ion from the loss of HX was confirmed by multistage mass spectrometry. Taking ion **a″** (see Table 3) as a representative example, a comparative ion with a definite structure of $CH_3N(CH_2)_4N{-}C_6H_4CH_2^+$ was designed and synthesized from protonated 4-(4-methylpiperazino)benzylamine by the elimination of ammonia.[20] The fragmentation pattern of this ion is exactly the same as that of ion **a″** (Figure 2). Therefore, the structure of ion **a″** is undoubtedly confirmed to be 4-(4-methylpiperazino)benzylium and the most likely reaction mechanism to form this ion is nucleophilic aromatic substitution.

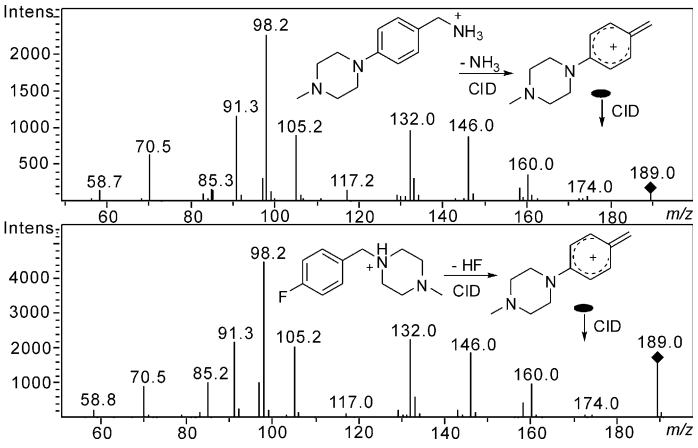


Figure 2. CID MS^3 spectra of the ion at $m/z = 189$ derived from a) protonated 4-(4-methylpiperazino)benzylamine ($m/z = 206$), b) protonated 1-(4-fluorobenzyl)-4-methylpiperazine ($m/z = 209$).

Moreover, the elimination of hydrogen halides from the protonated *N*-(4-halobenzyl)piperazines was further confirmed by isotopic labeling experiments. When deuterated substrates were employed, elimination of the corresponding deuterium halides was observed (Table 2). The proton affinity (PA)[21] of piperazine is 944 kJ mol^{-1}, whereas the PA of halobenzene is approximate 755 kJ mol^{-1}, which suggests that the ionizing proton is attached to the thermodynamically favored piperazine nitrogen under ESI conditions. Therefore, it is impossible that the loss of HX is initiated by protonation at the halogen substituent giving rise to phenyl cations. Proton transfer from nitrogen to halogen through the phenyl ring (ring-walk[22]) during collisional activation is also obviated because the loss of DX was observed only in the deuterium labeling experiments (Table 2). These results consolidate the reaction mechanism and the product structures presented above.

As shown in Scheme 1, the positive charge of the benzyl cation can be resided at the *para*- or *ortho* position, but not at the *meta* position, so the nucleophilic substitution can occur at the *para*- or *ortho* position rather than at the *meta* position. The experimental results are in good accordance with this criterion (see entries 2–4 in Table 1). The *m*-chlorobenzyl cation does not show S_NAr reactivity with piperazine, which supports that the methylene arenium is involved in loss of HX. If the *ortho*-, *meta*- and *para*-monosubstituted benzyl cations firstly rearrange to monosubstituted tropylium (then losing their positional identity), they should show no difference in the subsequent HX elimination reaction. Therefore, the involvement of tropylium ion in these S_NAr reactions can be ruled out. As one of the most typical features of an S_NAr reaction, fluoro is the best leaving group among the halogens in most S_NAr reactions.[23] In fact, the elimination of HF is much more efficient than that of HCl, HBr, and HI (see the relative abundances in Tables 1–3), which clearly indicates that these substitution reactions undertake an S_NAr mechanism. In the gas phase, the high stability of HF may be another reason for the efficient loss of HF.

To gain more insights into the mechanism of the present S_NAr reaction, DFT calculations were carried out at the B3LYP/6-311++G(2d,p) level of theory. The reaction of 4-chlorobenzyl cation with piperazine through the ion/neutral complex is used as a representative example. A schematic potential energy diagram for this reaction is given in Figure 3 and full details of the structures and energies of involved species are provided in the Supporting Information. The ion/neutral complex (Int-**1**), formed by dissociation of the precursor ion ($[M+H]^+$), is located 26.3 kJ mol^{-1} below the separated piperazine and 4-chlorobenzyl cation (ion **b**). Within Int-**1**, the piperazine nucleophile is able to attack the *para* position of ion **b** to give rise to a much more stable intermediate Int-**2**. Int-**2** lies in a local energy minimum that is 32.9 kJ mol^{-1} lower in energy than Int-**1**. Int-**2** is a covalently bonded complex, that is, a cationic σ complex, in which the calculated C(aryl)–N bond length is 1.57Å. The conversion of Int-**1** into Int-**2** is almost barrierless (see the Supporting Information; Figure S2 for more details). The subsequent HCl elimination leading to the formation of 4-piperazinobenzylium (ion **a**) is also favorable in terms of energy because the total energy of ion **a** and HCl is 94.5 kJ mol^{-1} lower than that of Int-**2**, although an energy barrier (TS-1) should be surmounted. The reaction for the nucleophilic attack of chlorotropylium by piperazine was also calculated (see dashed line in Figure 3), however the corresponding σ

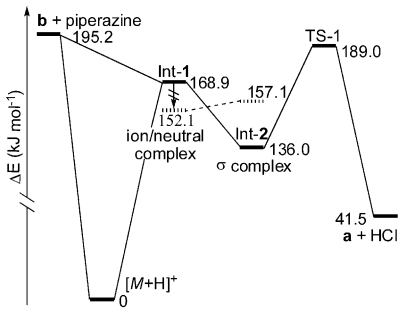


Figure 3. Calculated potential energy diagram for the nucleophilic aromatic substitution reaction between piperazine and 4-chlorobenzyl cation (**b**) at the B3LYP/6-311++G(2d,p) level. The solid line represents the involvement of benzylium ion and the dashed line represents the involvement of tropylium ion.

complex is 5.0 kJ mol^{-1} higher in energy than the ion/neutral complex, which means this reaction is not favored. Therefore, the tropylium isomer should be much less reactive towards the S_NAr reaction, which is in agreement with the experimental results. Although chlorotropylium is more stable than chlorobenzylium, the formation of chlorotropylium is still unfavorable because of the high rearrangement energy barrier (Figure S3 in the Supporting Information).[14] The theoretical calculations provide reasonable and reliable evaluation for the S_NAr reactions between halobenzyl cations and piperazine involving multistep addition–elimination pathways through a cationic σ-complex intermediate.

In conclusion, we have probed interesting gas-phase substitution reactions between piperazine and 4-halobenzyl cations using mass spectrometry. The reaction process was unambiguously confirmed to be nucleophilic aromatic substitution based on the combined experimental and theoretical results. A precursor ion/neutral complex and a successor cationic σ complex were identified to be the intermediates in this S_NAr reaction. This study revealed and verified the nucleophilic substitution reactivity of the methylene arenium form of halobenzyl cations at the phenyl ring. The results presented in this paper will improve our understanding of the resonance structures of benzyl cations and the classical nucleophilic aromatic substitution reactions.

Experimental Section

Mass spectrometry: All mass spectrometry experiments were performed on a Bruker Esquire 3000^{plus} ion trap mass spectrometer equipped with an ESI source in the 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. Samples were dissolved in and diluted with methanol. [D_4]Methanol was used as solvent for deuterium labeling experiments. Solution was 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 appropriate collision energies (fragmentation amplitude, 0.65–0.85 V) after isolation of the desired precursor ion.

General synthesis: The 4-(4-methylpiperazino)benzylamine was purchased from Chimica Laboratories (Jiaxing, Zhejiang). The *N*-halobenzylpiperazines were synthesized with corresponding halobenzyl bromides and piperazine or 4-methylpiperazine. All compounds were purified after synthesis. The structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

Theoretical calculations: All theoretical calculations were carried out at the B3LYP/6–311++G(2d,p) level of theory using the Gaussian 03 suit of programs.[24] Local minima (no imaginary frequency) or transition states (one imaginary frequency) were determined by frequency calculations at the same level. The minima connected by a given transition structure were confirmed by intrinsic reaction coordinate (IRC) calculations. The energies discussed here are the sum of electronic and thermal energies.

Acknowledgements

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Keywords: aromatic substitution · benzyl cation · gas-phase reactions · mass spectrometry · methylene arenium · nucleophilic substitution

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[18] The S_NAr reaction between piperazine and the halobenzyl cation also depends on the lifetime of the ion/neutral complex. At higher collision energies (and therefore higher internal energies), the direct dissociation is more favored. In fact, with the rise of collision energies, the relative intensity of the ion at $m/z = 175$ decreases (see the Supporting Information, Figure S1). In the experimental fragmentation amplitude range of 0.65–0.85 V, the changes are very small.

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