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Intramolecular methyl migration in the protonated *N*,*N*′-dimethylpropane-1,3-diamine and *N*,*N*′-dimethylethane-1,2-diamine

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Abstract

Intramolecular methyl migration in the protonated *N*,*N*′-dimethylpropane-1,3-diamine and *N*,*N*′-dimethylethane-1,2-diamine were studied by tandem mass spectrometry. Using density function theory at B3lyp/6-31g (d) level, intramolecular S_N2 methyl migration in the protonated *N*,*N*′-dimethylpropane-1,3-diamine and *N*,*N*′-dimethylethane-1,2-diamine were found to proceed by a high-energy inversion mechanism or by a high-energy retention mechanism. With the number of bond between two nitrogen atoms in diamine increasing, the inversion mechanism becomes more favorable.

Keywords: Intramolecular methyl migration; Diamine; Tandem mass spectrometry; Density function theory

1. Introduction

Intramolecular methyl migration is well known in the organometallic reactions and in the rearrangements of carbenium ions, but they have few precedents in the chemistry of coordinatively saturated, even-electron ions composed of first-row elements. Exhilaratingly, Wolfe's group has ever used ab initio molecular orbital theory to simulate the transition state of the intramolecular S_N2 methyl migration between two oxygens [1]. Besides, to the best of our knowledge, it is difficult to find another representative example about intramolecular methyl migration.

Recently, Wolfenden has reported that the migration of methyl groups between aliphatic amines could take place in water, shown in Scheme 1. Besides the bimolecular methyl transfer between an ammonium ion and an amine (1a, 1c) (for 1d, $(CH_3)_3S^+$ can be selected as methyl donor), intramolecular methyl migration can also take place in the protonated *N*,*N*′-dimethylpropane-1,3-diamine in water (1b) [2]. In addition to the apparent novelty of this reaction, it will be of interest to examine whether the similar reactions occur in the gas-phase. This ideal prompts our exploration of this migration via an approach of tandem mass spectrometry (MS/MS).

It is well known that tandem mass spectrometry not only provides extensive structural information for organic molecules, but also can act as an important tool for mechanistic studies in gas-phase organic chemistry [3]. More recently, our group has reported the gas-phase sulfonyl-sulfinate rearrangement of protonated 4,6-dimethoxy-2-(methylsulfonyl) pyrimidine and gas-phase retro-Michael type fragmentation reactions of 2-hydroxybenzyl-*N*-pyrimidinylamine derivatives studied by MS/MS technique [4,5]. In the present work, gas-phase reactions of *N*,*N*′-dimethylpropane-1,3-diamine (**1**) and *N*,*N*′-dimethylethane-1,2-diamine (**2**) were studied and reported.

2. Experimental

2.1. Material

N,*N*′-dimethylpropane-1,3-diamine (**1**), *N*,*N*′-dimethylethane-1,2-diamine (**2**), *N*,*N*-dimethylpropane-1,3-diamine, *N*,*N*-dimethylethane-1,2-diamine, *N*,*N*,*N*′,*N*′-dimethylpropane-1,3-diamine, *N*,*N*,*N*′,*N*′-dimethylethane-1,2-diamine were

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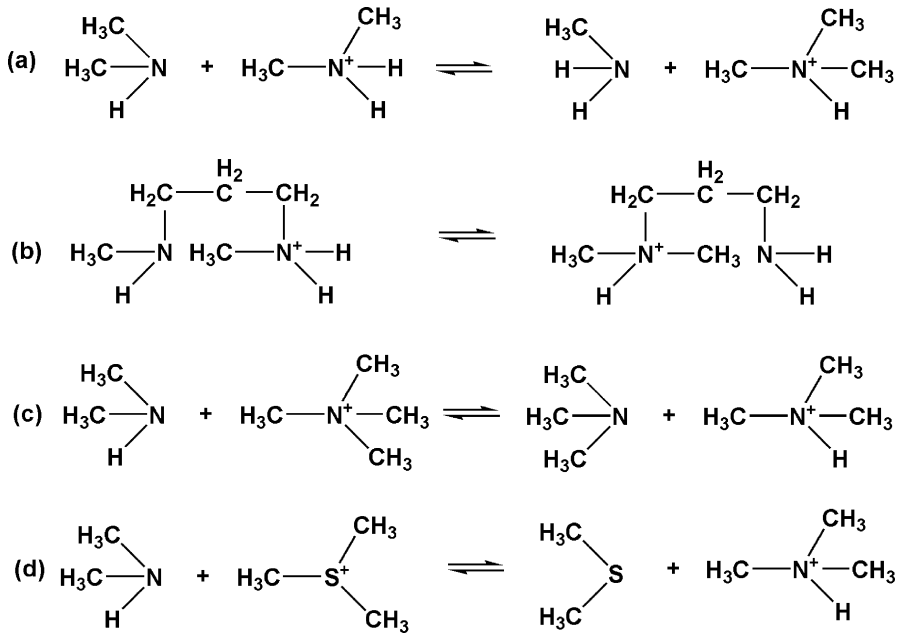


Scheme 1. The migration of the methyl groups between aliphatic amines in water.

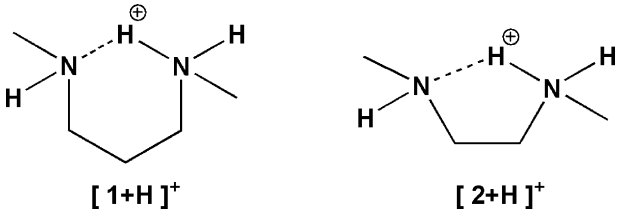
obtained from Aldrich Chemical Co. (Milwaukee, MN, USA). All sample solutions were prepared at approximately 1 mg/ml with methanol in the ESI-MS/MS experiments. In addition, Sample was dissolved in the D_4-methanol in the H–D exchange experiment.

2.2. SCI and MS/MS experiments

All mass spectra were obtained using an internal source ion trap mass spectrometer (Saturn 2000; Varian, Walnut Creek, CA, USA). No CI reagent gas was used. The SCI was operated in the mass selective instability mode and was connected by a heated transfer line (280 °C) to a Varian 3800 model gas chromatograph equipped with splitless injection and a programmable on-column injector. Samples were introduced into the ion trap by GC via a 1079 injection port. A VF-5 fused silica capillary column (30 m × 0.25 mm × 0.25 μm) (Varian) was used to study the cleavage behavior of diamine under the following conditions: injector temperature 250 °C; temperature program, 1 min at 50 °C then 45 °C/min to 250 °C. The carrier gas was helium with a constant flow of 1 ml/min. The temperatures of the trap, transfer line and manifold were 200, 280 and 60 °C, respectively. Full scan data acquisition was achieved for the mass range *m/z* 40–250 at 0.77 s/scan. For collisionally activated dissociation (CAD) experiments, the collisional activation time was 20 ms and the collision energy was about 25 V (Using non-resonant excitation mode).

2.3. ESI-MS/MS analysis

The ESI-MS/MS experiments were performed on the TSQ mass spectrometer (Thermo, USA) using the product ion scan mode via Q1 mass-selection of the desirable product ion, q2 collision-induced dissociation (CID) with He, and Q3 mass analysis of the CID ionic fragments. The collision energy ranged from 15 to 20 eV, depending on the dissociation lability of the precursor ion. CID of the $\mathbf{d}_3$-$[\mathbf{1}+\mathbf{D}]^+$ ion was achieved by dissolving **1** in CD_3OD to support the gas-phase intramolecular methyl migration in the protonated diamine. The sample solution was infused into the ESI interface using a syringe pump at a flow rate of 5 μl/min.



Scheme 2. Structures of protonated *N,N′*-dimethylpropane-1,3-diamine and *N,N′*-dimethylethane-1,2-diamine.

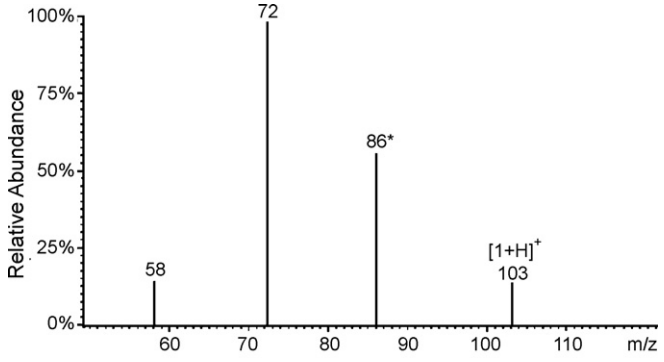
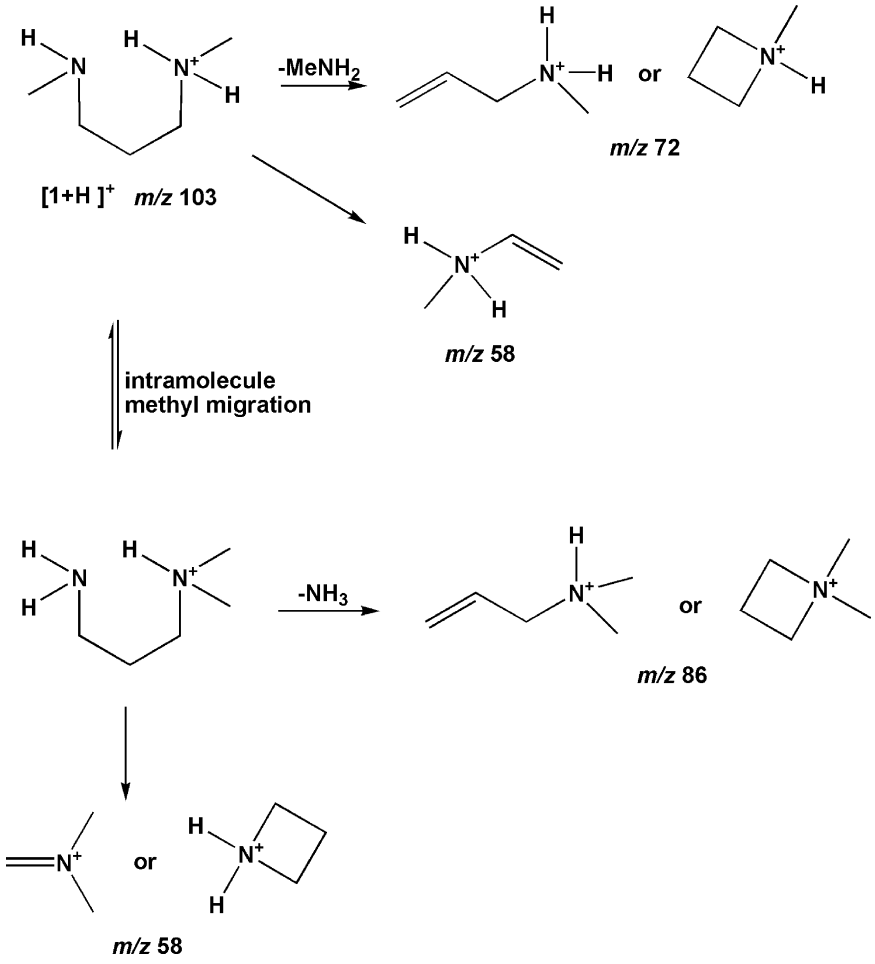


Fig. 1. Tandem mass spectrum of the protonated *N,N′*-dimethylpropane-1,3-diamine.



Scheme 3. The proposed fragmentation process of ion $[\mathbf{1}+\mathbf{H}]^+$.

2.4. Theoretical calculations

DFT calculations (B3lyp/6-31g (d)) for methyl migration were performed by the Gaussian 98w programs (Gaussian Inc., Pittsburgh, PA, USA) [6]. The search for possible minima on the hypersurface and the geometry optimization of the species of interest were performed first by the semiempirical method PM3. The structures found were re-optimized using B3lyp/6-31g (d).

3. Results and discussion

The protonated diamine, which can be easily obtained by chemical ionization or self-chemical ionization technique, has been studied extensively for long time [7,8]. It is widely accepted that these compounds undergo protonation reactions that are stabilized through intramolecular hydrogen bonding resulting in cyclic cationic structures [9,10], shown in Scheme 2. Here, ions $[\mathbf{1}+\mathbf{H}]^+$ and $[\mathbf{2}+\mathbf{H}]^+$ were prepared by SCI technique in gas chromatography–ion trap mass spectrometer (GC–ITMS).

In the ion trap, ion $[\mathbf{1}+\mathbf{H}]^+$ can be isolated using a broadband waveform to eject all other unwanted ions, then under the suitable exciting voltage, it can dissociate and the corresponding spectrum is shown in Fig. 1. For product ions at *m/z* 58 and 72, it is easy to deduce the fragment process from ion $[\mathbf{1}+\mathbf{H}]^+$. However, for the product ion at *m/z* 86, it is difficult to explain the loss of NH_3 (−17 Da, NH_3 is proposed) directly from ion $[\mathbf{1}+\mathbf{H}]^+$. An intramolecular methyl migration is then proposed and shown in Scheme 3 to explain the formation of *m/z* 86. Structures of the product ions are also proposed as depicted in Scheme 3. Intramolecular methyl migration in ion $[\mathbf{1}+\mathbf{H}]^+$ leads to the formation of the protonated *N*,*N*-dimethylpropane-1,3-diamine, which loses NH_3 easily. In other words, on the basis

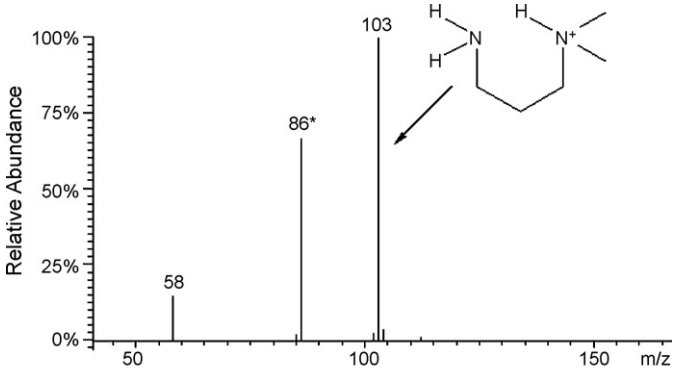


Fig. 2. Tandem mass spectrum of the protonated *N*,*N*-dimethylpropane-1,3-diamine.

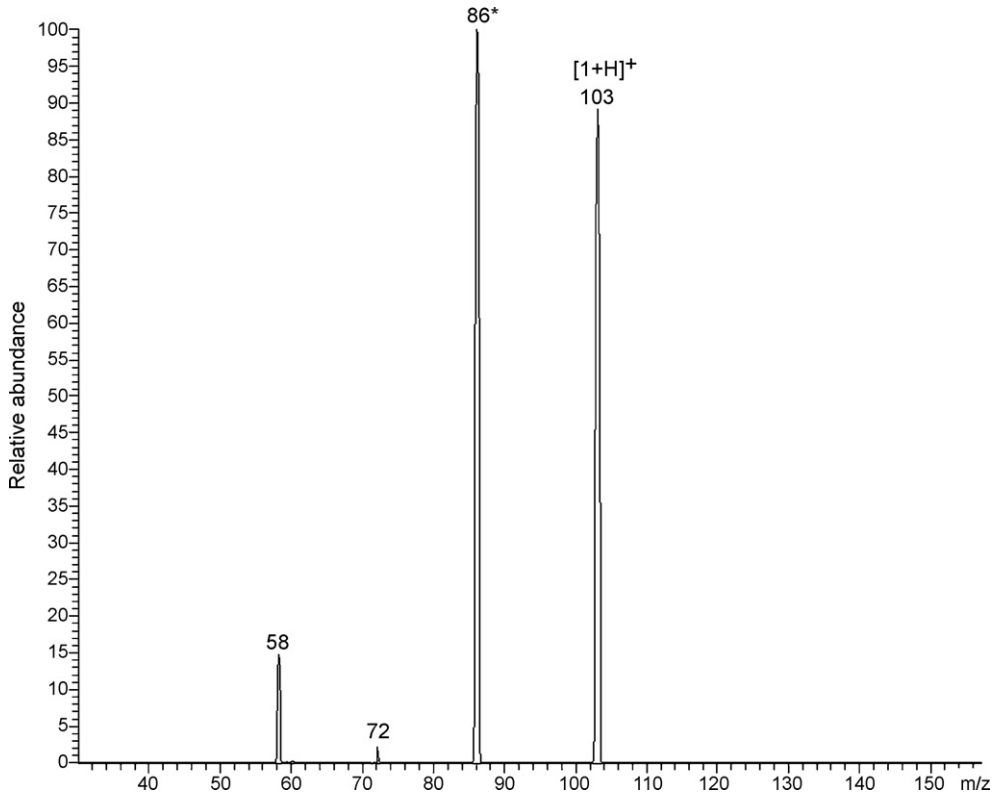


Fig. 3. Positive ESI tandem mass spectrum of the protonated *N*,*N*′-dimethylpropane-1,3-diamine.

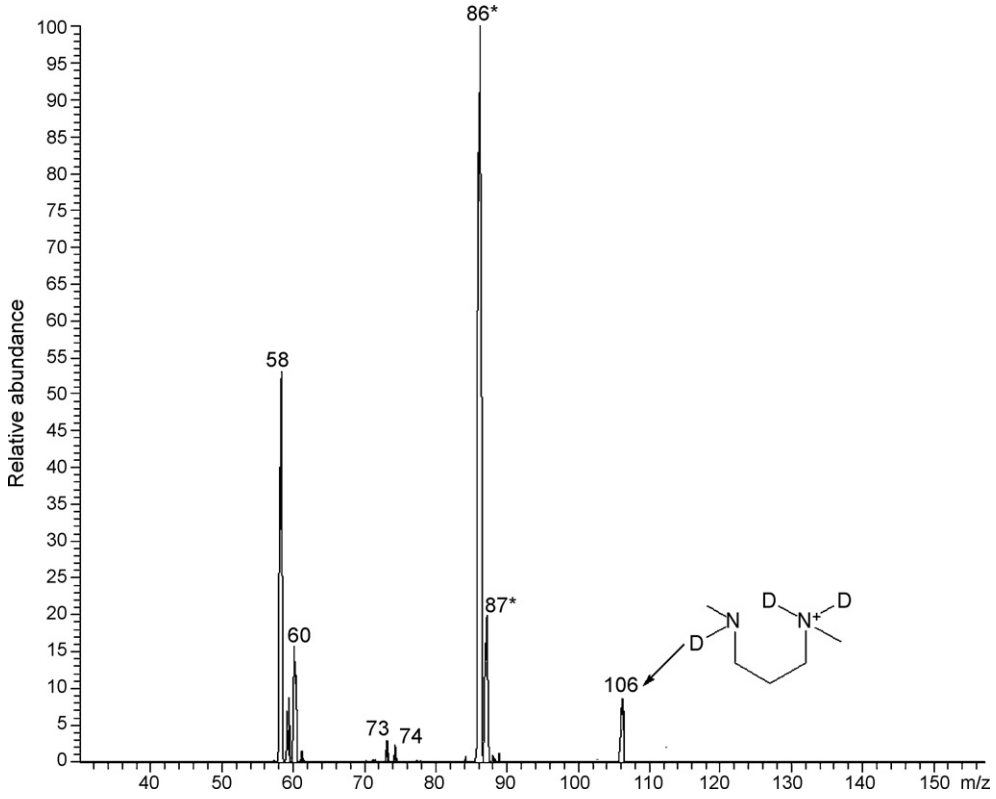
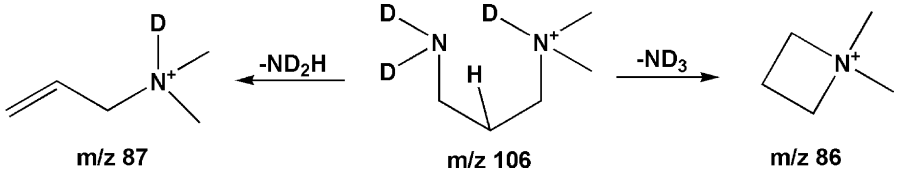


Fig. 4. Positive ESI tandem mass spectrum of the ion $\mathbf{d}_3$-[**1** + **D**]$^+$.



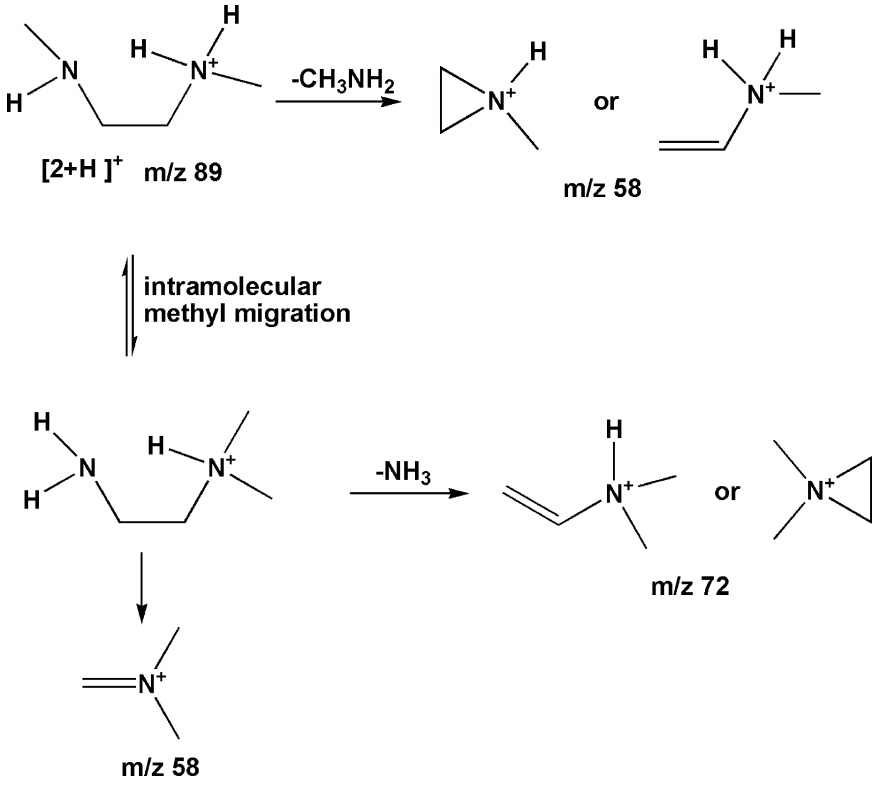
Scheme 4. Two proposed pathways of losing amine from the protonated *N*,*N*-dimethylpropane-1,3-diamine.

of the product ion at *m*/*z* 86, intramolecular methyl migration in ion $[\mathbf{1}+\mathbf{H}]^+$ can be inferred.

In order to prove our supposition, MS/MS experiment of protonated *N*,*N*-dimethylpropane-1,3-diamine was performed in ITMS and the spectrum is shown in Fig. 2. The protonated *N*,*N*-dimethylpropane-1,3-diamine was also obtained by SCI technique and the protonation site is tertiary amino group, for the proton affinities of tertiary amino groups are larger then those of primary amines. It is found that only two kinds of product ions at *m*/*z* 58 and 86 are obtained, corresponding to the cleavage process in Scheme 3. This experiment supports our inference regarding the intramolecular methyl migration in the protonated *N*,*N*′-dimethylpropane-1,3-diamine.

Similar intramolecular methyl migration was also found in the electrospray ionization tandem mass spectrometry experiments performed on the triple sequence quadruple (TSQ) mass spectrometer. The ESI tandem mass spectrum of ion $[\mathbf{1}+\mathbf{H}]^+$ is depicted in Fig. 3, which is consistent with that in Fig. 2, except the difference in the abundance of the product ions. Moreover, hydrogen/deuterium (H/D) exchange experiments were also performed. All of the hydrogen atoms at two N atoms were replaced by deuterium and ion $\mathbf{d}_3$-$[\mathbf{1}+\mathbf{D}]^+$ could be obtained. The ESI tandem mass spectrum of ion $\mathbf{d}_3$-$[\mathbf{1}+\mathbf{D}]^+$, which has an *m*/*z* of 106, is shown in Fig. 4. Observation of the product ions at *m*/*z* 86 and 87 indicates that two kinds of neutral fragment ND_3 and ND_2H could be lost. Then two pathways of losing amine were proposed and shown in Scheme 4. One is that $-ND_2$ is eliminated with neighboring hydrogen; the other is that $-ND_2$ is eliminated with deuterium at the second nitrogen atom.

On the other hand, intramolecular methyl migration in protonated *N*,*N*′-dimethylethane-1,2-diamine $[\mathbf{2}+\mathbf{H}]^+$, which was produced by SCI technique in GC–ITMS, can also take place. The tandem mass spectrum of ion $[\mathbf{2}+\mathbf{H}]^+$ is depicted in Fig. 5 and the corresponding structures of the product ions are shown in Scheme 5. Similar to $[\mathbf{1}+\mathbf{H}]^+$, product ion at *m*/*z* 72 is obtained by loss of NH_3 from protonated *N*,*N*-dimethylethane-1,2-diamine, which is formed by the intramolecular methyl migration in ion $[\mathbf{2}+\mathbf{H}]^+$. At the same time, MS/MS experiment of protonated *N*,*N*-dimethylpropane-1,2-diamine was performed in GC–ITMS and the spectrum is shown in Fig. 6. The protonated *N*,*N*-dimethylpropane-1,2-diamine was also obtained by SCI technique and the protonation site is tertiary amino group. It is found that only two kinds of product ions at *m*/*z* 58 and 72 are obtained, corresponding to the cleavage



Scheme 5. The proposed fragmentation process of ion $[\mathbf{2}+\mathbf{H}]^+$.

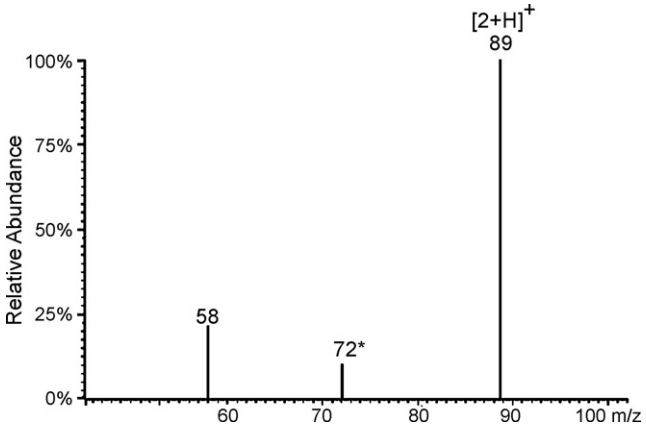


Fig. 5. Tandem mass spectrum of the protonated *N*,*N*′-dimethylethane-1,2-diamine.

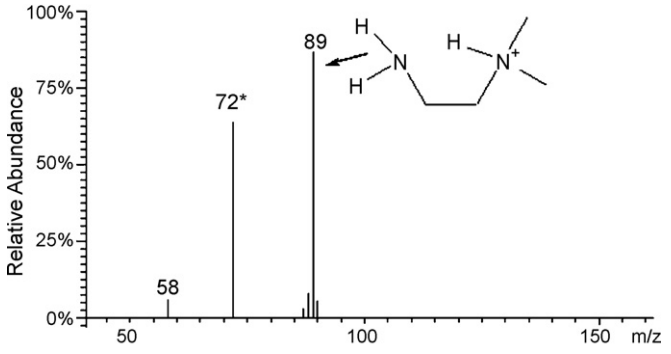


Fig. 6. Tandem mass spectrum of the protonated *N*,*N*-dimethylethane-1,2-diamine.

process in Scheme 5. Finally, an ESI-MS/MS experiment with ion $[\mathbf{2}+\mathbf{H}]^+$ on the TSQ mass spectrometer was also tried, however, we could not get the product ion at *m*/*z* 72, which may be explained that intramolecular methyl migration did not take place under this condition. The possible reason would be that the time ion $[\mathbf{2}+\mathbf{H}]^+$ trapped in quadrupole is so short that ion $[\mathbf{2}+\mathbf{H}]^+$ could not absorb enough energy to support the intramolecular methyl migration.

Here, the symmetrical diamines used in the present work only have one methyl group at each nitrogen atom. For those symmetrical diamines, which have two methyl groups at each nitrogen atom, such as *N*,*N*,*N*′,*N*′-dimethylpropane-1,3-diamine and *N*,*N*,*N*′,*N*′-dimethylethane-1,2-diamine, we could not determine whether the intramolecular methyl migration take place.

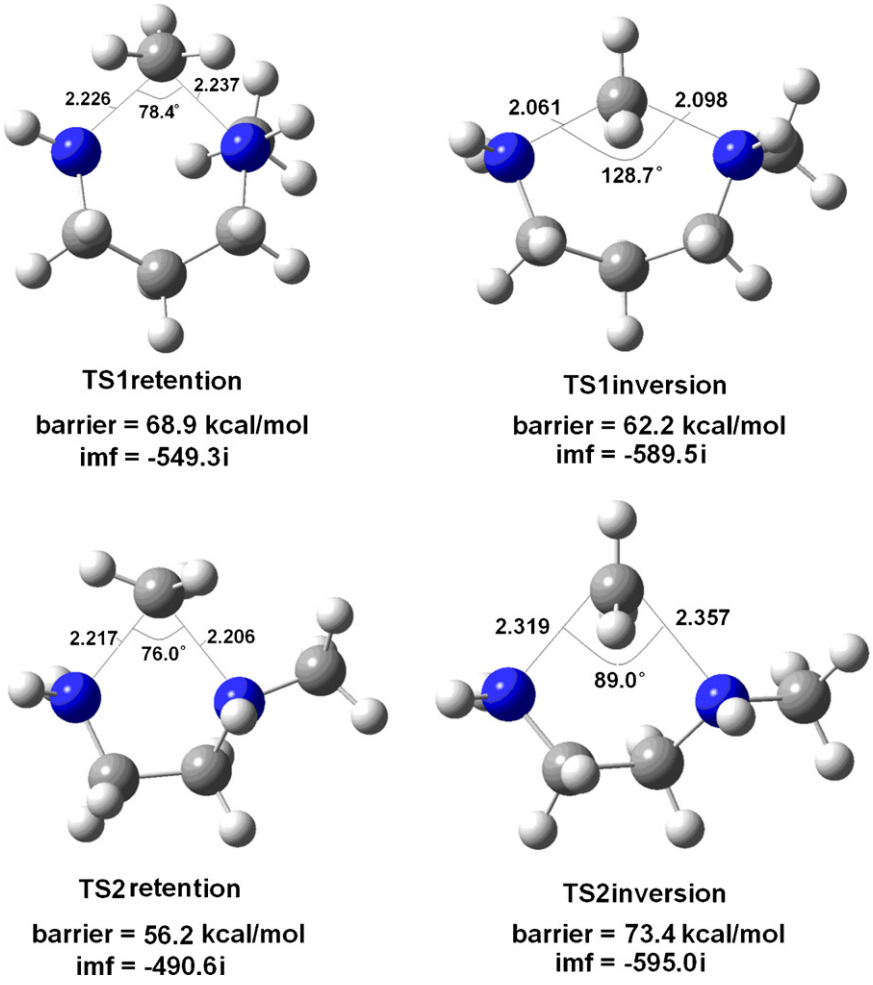


Fig. 7. Optimized structures and barriers of the transition states for methyl migration in protonated *N*,*N*′-dimethylpropane-1,3-diamine and *N*,*N*′-dimethylethane-1,2-diamine.

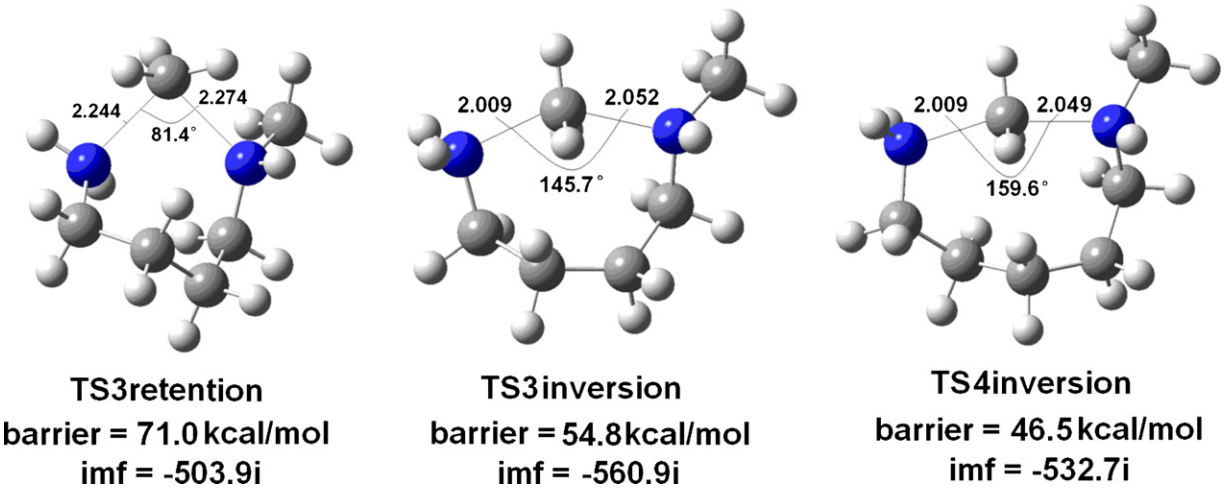


Fig. 8. Optimized structures and barriers of the transition states for methyl migration in protonated *N*,*N*′-dimethylbutane-1,4-diamine and *N*,*N*′-dimethylpentane-1,5-diamine.

However, according to the Shaffer's work [11], the intramolecular methyl migration does not occur in the protonated diamines, which have two methyl groups at each nitrogen atom.

A large number of studies show that methyl migration proceeds via a simple S_N2 transition state [12–14]. Using DFT method at B3lyp/6-31g (d) level, intramolecular S_N2 methyl migration in ions $[\mathbf{1}+\mathbf{H}]^+$ and $[\mathbf{2}+\mathbf{H}]^+$ are found to proceed either by a high-energy inversion mechanism or by a high-energy retention mechanism. A schematic transition state is shown in Fig. 7. For the intramolecular methyl migration in ion $[\mathbf{1}+\mathbf{H}]^+$, the barrier is 68.9 kcal/mol in the retention mechanism and 62.2 kcal/mol in the inversion mechanism, respectively. Obviously, the inversion mechanism has a lower DFT activation energy. On the contrary, for the intramolecular methyl migration in ion $[\mathbf{2}+\mathbf{H}]^+$, the retention mechanism is prior, and the barrier is 56.2 kcal/mol, which is less than that in the inversion mechanism by 17.2 kcal/mol.

In addition, we also simulated the intramolecular S_N2 transition state in protonated *N*,*N*′-dimethylbutane-1,4-diamine and *N*,*N*′-dimethylpentane-1,5-diamine. For the protonated *N*,*N*′-dimethylbutane-1,4-diamine, both mechanisms exist. However, intramolecular methyl migration in protonated *N*,*N*′-dimethylpentane-1,5-diamine is found to proceed exclusively by a high-energy inversion mechanism. The detailed transition states are depicted in Fig. 8. With the number of bond between two nitrogen atoms in diamine increasing, the inversion mechanism becomes more favorable and the barrier becomes smaller. The N–C–N bending vibration in the inversion transition state also becomes easier.

In order to provide the evidence to the theoretical calculation, energy-resolved reaction mass spectra were employed. In Fig. 9, the *x*-axes represents the collision energy, the *y*-axes represents the ratio of the abundance of ion ($m/z=86$) to ion ($m/z=103$), on the other hand, in Fig. 10, the *y*-axes represents the ratio of the abundance of ion ($m/z=72$) to ion ($m/z=89$). Compared with these two charts, the fragment from ion $[\mathbf{2}+\mathbf{H}]^+$ by loss of NH_3 cannot be observed until the collision energy was enhanced to about 25 V, whereas the fragment from ion $[\mathbf{1}+\mathbf{H}]^+$ by loss of NH_3 can easily be observed when the collision energy was very small. Supposing the ability of the protonated *N*,*N*-dimethylpropane-1,3-diamine and *N*,*N*-dimethylethane-1,2-diamine losing ammonia is similar, it can be

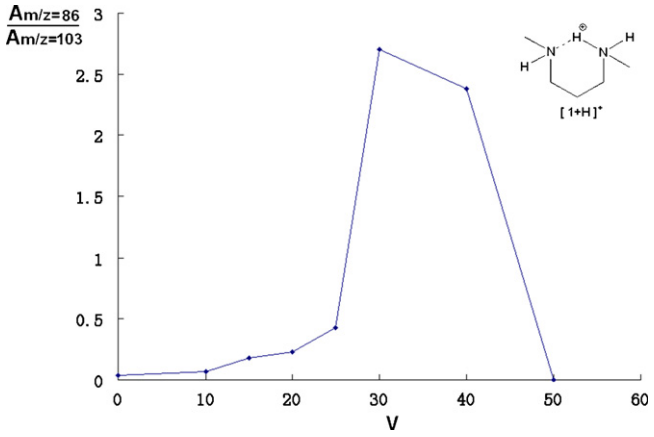


Fig. 9. Energy-resolved reaction mass spectrum of the protonated *N*,*N*′-dimethylpropane-1,3-diamine.

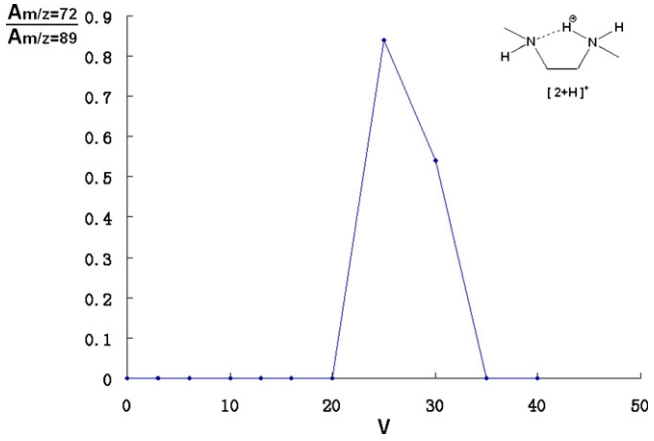


Fig. 10. Energy-resolved reaction mass spectrum of the protonated *N*,*N*′-dimethylethane-1,2-diamine.

deduced that the intramolecular methyl migration in the protonated *N*,*N*′-dimethylpropane-1,3-diamine is easier. Contrasted with DFT calculations, obviously, the high-energy inversion mechanism is more suitable for the intramolecular methyl migration in the protonated diamine.

In general, we provide another example about intramolecular methyl migration in the metal-free small molecule. Intramolecular methyl migration in the protonated *N*,*N*′-dimethylpropane-1,3-diamine and *N*,*N*′-dimethylethane-1,2-diamine were studied by tandem mass spectrometry. DFT calculations exhibit two kinds of mechanism of this methyl migration: retention mechanism and inversion mechanism, however, energy-resolved reaction mass spectrum indicates that the high-energy inversion mechanism is more suitable for the intramolecular methyl migration in the protonated diamine.

Acknowledgement

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