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Competing benzyl cation transfers in the gas-phase fragmentation of the protonated benzyl phenylalaninates

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ABSTRACT

In this study, the competing benzyl cation transfer reactions have been explored by investigating the gas phase chemistry of the protonated benzyl phenylalaninates. Protonation at the carboxylic O atom results in the breakage of the ester C—O bond to afford the benzyl cation, which undergoes the competing migration to the amino N atom or the phenyl ring C atom. Both the amino and the phenyl ring hydrogen atoms can be activated to be mobile due to the electrophilic attack of the transferring benzyl cation, and migration of the activated hydrogen atom to the carboxylic hydroxyl leads to ($H_2O + CO$) elimination of the precursor ion. Interestingly, it is much more preferred for the benzyl cation to transfer to the phenyl ring via the amino N, leading to the stepwise benzyl cation transfer, albeit the amino N atom contains more nucleophilic affinity. The mechanistic processes have been confirmed by the MS^3 spectra data, along with D-labeling experiments and theoretical calculations.

1. Introduction

Since the introduction by Yamashita and Fenn in 1984 [1], electrospray ionization mass spectrometry (ESI-MS) has been widely applied in analyzing a large variety of compounds [2–6]. In particular, collision-induced dissociation (CID) enjoys its unique advantages in structure elucidation by providing abundant fragmentation data [4,5]. However, the MS-based structural elucidation has also been challenged by the widespread unexpected rearrangement reactions, such as the benzyl cation transfer [7–15], occurring in the fragmentation process, and these reactions have attracted great interest among analysts since the early days of organic mass spectrometry.

Benzyl cation is a highly reactive intermediate in various chemical and biochemical reactions [16]. Fragmentation of the protonated benzylated derivatives is facile to afford the benzylium-contained ion/neutral complex (INC). Besides the direct separation to form benzyl cation, many interesting product ions have been generated in mass spectrometry via the INC-mediated reactions, such as electrophilic aromatic substitution [7–13], hydride transfer [17], electron transfer [18] and nucleophilic aromatic substitution [14,15]. Benzyl cation has been previously reported to migrate to the phenyl ring mediated by the benzylium-contained INC [7–15]. In our previous work, benzyl cation has been found to be directly transferred to the amino nitrogen before dissociation of the protonated benzyl prolinates occurs [19]. Phenylalanine possesses both amino nitrogen and phenyl ring, both of which can accept the electrophilic attack of the transferring benzyl cation. With this in mind, benzyl phenylalaninate was selected as a model molecule in this work to extend the mechanistic investigation on the competing benzyl cation transfers.

2. Experimental

2.1. Materials

O-Benzylated phenylalanine derivatives (compounds **1**–**7** in Scheme 1) were synthesized according to the classical method, involving reaction of *Boc*-protected phenylalanine with the corresponding benzyl chloride in the presence of Cs_2CO_3 [20]. The subsequent deprotection of *Boc* is carried out in the presence of TFA–DCM (V_{TFA}:V_{DCM} = 1:1) to obtain the target compounds [21]. The *N*-benzylated phenylalanine derivative (compound **8**) was obtained from the reaction of phenylalanine with benzyl chloride in the presence of K_2CO_3 in water, according to a procedure described in the literature [22]. *N*-benzylated 2-phenylethanimine

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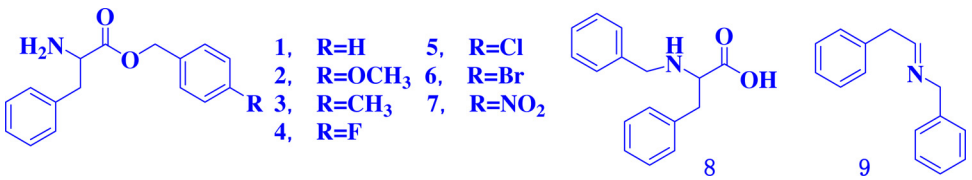


Scheme 1. Structures of substituted benzyl phenylalaninates (**1**–**7**), *N*-benzylated phenylalaninate (**8**) and *N*-benzylated 2-phenylethanimine (**9**).

(compound **9**) was synthesized by phenylacetaldehyde and benzylamine in the presence of $MgSO_4$ in ethanol solution. All compounds were purified after synthesis, and their structures were further confirmed by ^1H NMR, ^{13}C NMR and MS.

2.2. Mass spectrometry

The ESI-MS/MS experiments were performed on an LCQ advantage mass spectrometer (Thermo Fisher Company, USA), equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (Version 1.4). Typical parameters for the operation of the ESI-MS were used as previously described [19].

Accurate MS of the product ions were measured by a micrOTOF-QII (Q-TOF) mass spectrometer (Bruker Company, USA), equipped with an ESI ion source. The collision energy of the CID for the selected ions was set at 8 eV with Argon being used as the collision gas. The instrument was operated at a resolution higher than 15,000 full width at half maximum at *m*/*z* 922 using the micrOTOF-Q control program (Version 2.3). The data were analyzed using the Data Analysis Version 4 software package delivered by Bruker Daltonics.

2.3. Theoretical calculations

The theoretical calculations were performed using the Gaussian 03 program [23]. The structures of the reactants, transition states, intermediates and products were optimized using the density functional theory (DFT) method at the B3LYP/6-31 + G(2d,p) level. All reactants, intermediates and products were identified as the true minima by the absence of imaginary frequencies. Transition states, on the other hand, were identified by the presence of one single imaginary vibration frequency and the normal vibrational mode. The transition states were further confirmed using the intrinsic reaction coordinates calculations. The energies discussed here are the sum of the associated electronic and thermal free energies. The DFT-optimized structures were shown by GaussView (Version 3.09) software to give higher quality images of these structures. Hard data on geometries of all the structures considered are available in the Supplementary material.

3. Results and discussion

3.1. Dissociation of the protonated benzyl phenylalaninates

Investigation of the competing benzyl cation transfer reactions have been carried out by exploring the fragmentation behaviors of the protonated substituted benzyl phenylalaninates (Table 1). Benzyl phenylalaninate (**1**) was selected as a model to perform a detail investigation. Fig. 1(a) describes the CID-MS spectrum of $[\mathbf{1}+H]^+$, in which the fragment ion at *m*/*z* 91 is the benzyl cation, originating from the direct decomposition of $[\mathbf{1}+H]^+$. Ammonia elimination of $[\mathbf{1}+H]^+$ leads to the fragment ion at *m*/*z* 239, which subsequently undergoes the H_2O elimination to give the product ion at *m*/*z* 221. The simultaneous (H_2O + CO) expulsion of $[\mathbf{1}+H]^+$ occurs to afford the most abundant ion at *m*/*z* 210 in the CID-MS spectrum via the benzyl cation transfer [19,24]. The subsequent ammonia elimination of the ion at *m*/*z* 210 results in the product ion at *m*/*z* 193. Also, the product ion at *m*/*z* 120 is assigned to the 2-phenylethaniminium, resulting from the simultaneous loss of ($PhCH_2OH$ + CO). The elemental compositions of these fragment ions have been determined by analyzing their accurate masses using high resolution Q-TOF mass spectrometer (Supplementary Table 1S and Fig. 1S).

All of the protonated substituted benzyl phenylalaninates show similar fragmentation behaviors, indicating a much favorable dissociation channel of losing (H_2O + CO) via benzyl cation transfer (Table 1 and Supplementary Fig. 2S). The favorable reaction of (H_2O + CO) elimination was also consolidated by investigating the breakdown curves at various collisional energies (Supplementary Fig. 3S).

Two sites (the amino nitrogen atom and the A ring carbon atom) in the structure of phenylalanine was found to potentially accept the electrophilic attack of the transferring benzyl cation, and the potential reaction channels of the competing benzyl cation transfer are proposed in Scheme 2. In path-a, the benzyl (B ring) cation is transferred from the ester oxygen atom O4 to the amino

Table 1
The CID MS data of the protonated phenylalanine substituted-benzyl esters in Scheme 1 at the normalized collision energy (NCE) of 24%.

Compound	R	$[M+H]^+$ *m*/*z* (%)	Product ions, *m*/*z* (%)					
			Losing (CO + H_2O) ion **a** or **b**	[**a**–NH_3]$^+$ or [**b**–NH_3]$^+$	Losing NH_3 ion **c**	[**c**–H_2O]$^+$	Losing (CO + $PhCH_2OH$) ion **d**	R-$C_7H_6^+$
1	—H	256 (43.3)	210 (100%)	193 (21.3%)	239 (15.4%)	221 (9.8%)	120 (4.5%)	91 (23.0%)
2	—OCH_3	286 (7.6)	–	–	–	–	120 (0.8%)	121 (100%)
3	—CH_3	270 (21.7)	224 (13.4%)	207 (1.7%)	253 (0.8%)	235 (0.9%)	120 (0.1%)	105 (100%)
4	—F	274 (33.0)	228 (94.2%)	211 (8.3%)	257 (14.4%)	239 (3.0%)	120 (1.6%)	109 (100%)
5	—^{35}Cl	290 (73.3)	244 (91.1%)	227 (7.1%)	273 (13.4%)	255 (2.2%)	120 (1.7%)	125 (100%)
	—^{37}Cl	292 (67.6)	246 (94.5%)	229 (9.4%)	275 (14.6%)	257 (3.2%)	120 (2.0%)	127 (100%)
6	—^{79}Br	334 (35.6)	288 (100%)	271 (8.1%)	317 (11.6%)	299 (2.7%)	120 (1.2%)	169 (88.7%)
	—^{81}Br	336 (33.9)	290 (100%)	273 (9.4%)	319 (10.9%)	301 (2.4%)	120 (1.1%)	171 (94.5%)
7	—NO_2	301 (100)	255 (51.4%)	238 (22.1%)	284 (10.6%)	266 (7.6%)	120 (40.6%)	136 (<0.1%)

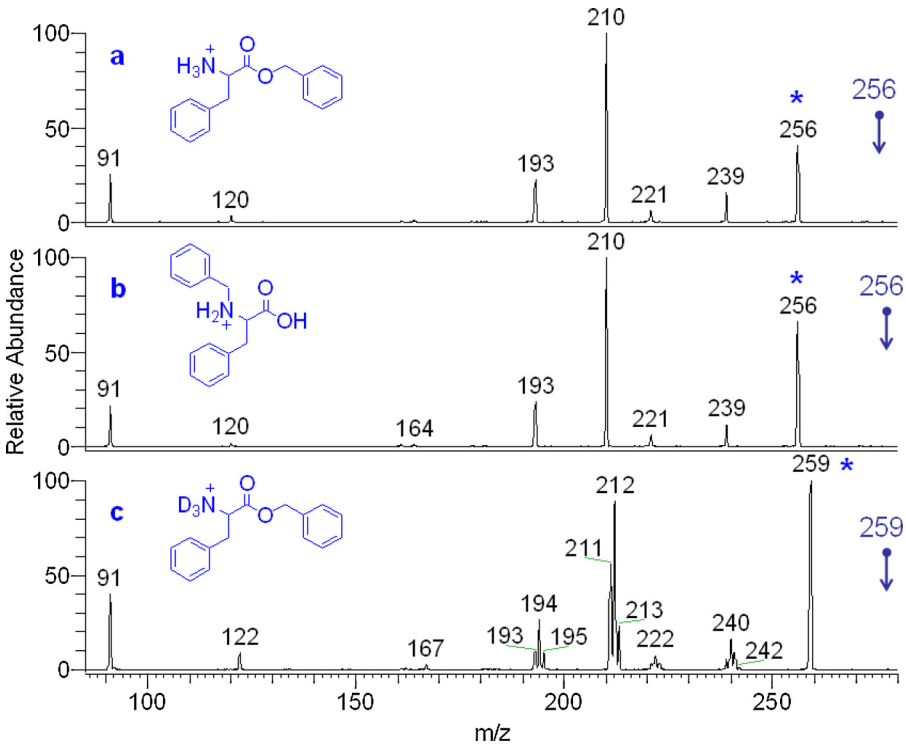
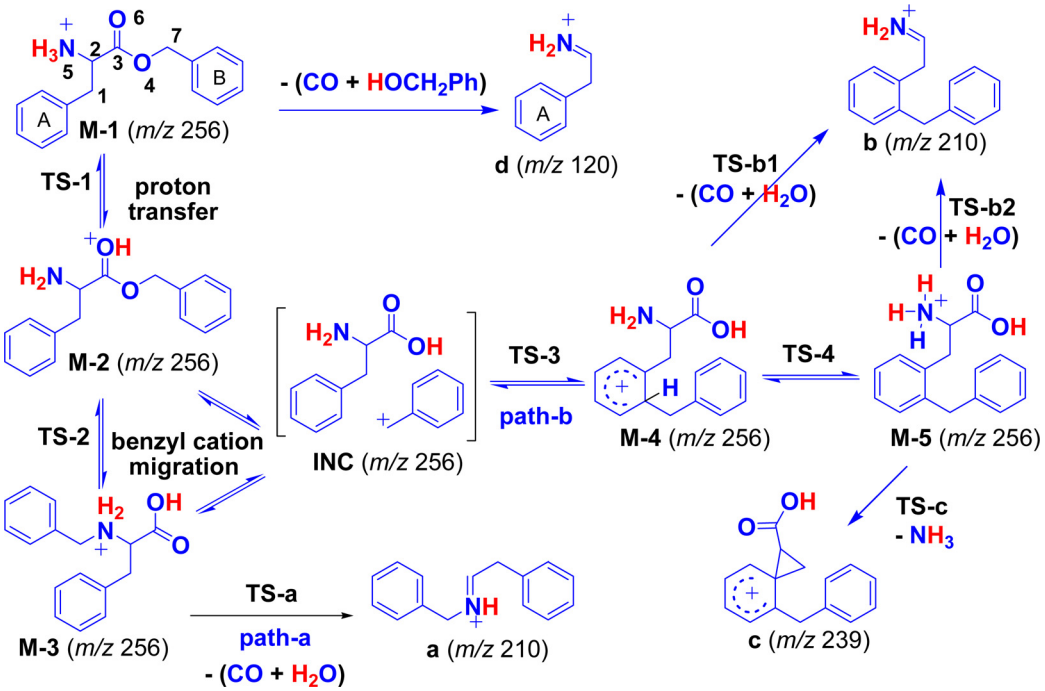


Fig. 1. Collision-induced dissociation mass spectra of (a) the $[\mathbf{1}+H]^+$ ion at *m/z* 256, (b) the $[\mathbf{1}-2H+3D]^+$ ion at *m/z* 259.

nitrogen N5, followed by the loss of $(CO+H_2O)$ to produce the ion **a**, protonated *N*-benzyl-2-phenylethanimine (*m/z* 210) [19,24]. Isomerization of $[\mathbf{1}+H]^+$ via path-a leads to the protonated *N*-benzylated phenylalanine ($[\mathbf{8}+H]^+$), which also shows a much favorable pathway of losing $(CO+H_2O)$ (Fig. 1(b). In path-b, the benzyl cation is transferred to the phenyl ring (the A ring) carbon (possibly at the *ortho* position) in a multi-step process, which triggers the $(CO+H_2O)$ elimination to afford the fragment ion **b**, protonated 2-(2-benzylphenyl) ethamine (*m/z* 210). Thus, the product ion at *m/z* 210 may be a mixture of ion **a** and ion **b** in the CID experiments.

At first glance, ion **a** is much more easily formed than ion **b**, since the amino N rather than the phenyl ring C potentially favors to capture the transferring benzyl cation due to its much higher nucleophilic affinity (this will be discussed in the following section of theoretical calculation). Nevertheless, further investigation on



Scheme 2. Proposed reaction channels for fragmentation of $[\mathbf{1}+H]^+$.

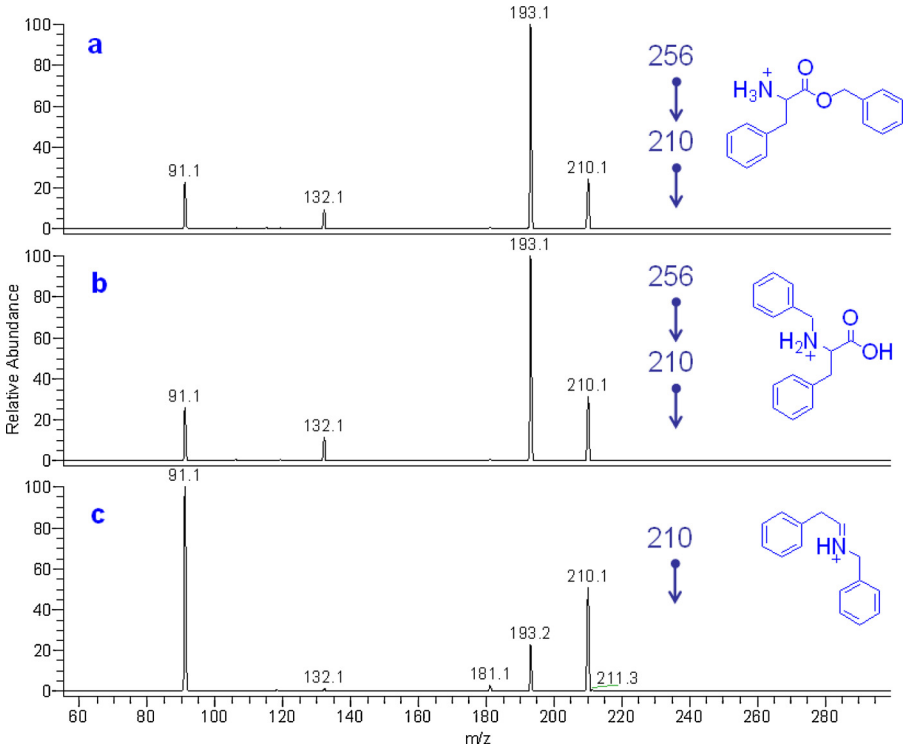
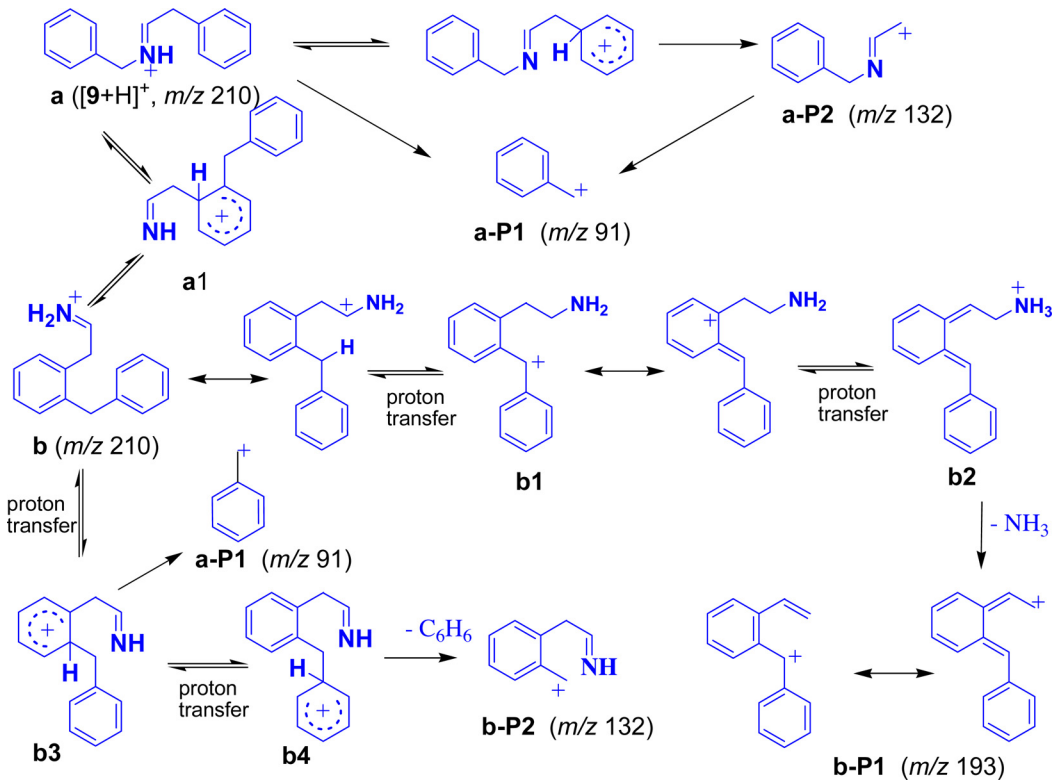


Fig. 2. Collision-induced dissociation mass spectra of (a) the ion at *m/z* 210 from dissociation of [**1** + H]$^+$, (b) the ion at *m/z* 210 from dissociation of [**8** + H]$^+$, and (c) the ion of [**9** + H]$^+$ at the collision energy of 12 eV.

the fragmentation behavior of the fragment ion at *m/z* 210 leads to a much different conclusion, that benzyl cation is more facile to transfer to the phenyl ring when the decomposition occurs via losing (CO + H_2O).

As displayed in Fig. 2(c), dissociation of [**9** + H]$^+$ favors to afford the benzyl cation (*m/z* 91) via the direct cleavage of the C—N bond, rather than to generate the fragment ion at *m/z* 193 via NH_3 elimination, due to its non-terminal amine structure (Scheme 3).



Scheme 3. The proposed fragmentation pathways of the ion **a** and the ion **b**.

In comparison, the protonated 2-(*o*-benzyl) phenylethanimine favors to undergo NH_3 elimination instead of direct decomposition, due to the terminal amine group. Fragmentation of the ion at *m/z* 210, originated from dissociation of $[\mathbf{1}+H]^+$, results in a dominant product ion at *m/z* 193 via NH_3 elimination and the minor benzyl cation (Fig. 2(a)). The above results undoubtedly demonstrate that the ion **b**, formed via the reaction channel of path-b, is the dominant component of the mixture ions at *m/z* 210.

Interpreting the formation of the fragment ion at *m/z* 132 in Fig. 2(a) will further witness the above result (Scheme 3). The fragment ion **a**-**P2** (*m/z* 132), resulting from benzene elimination of the ion **a** ($[\mathbf{9}+H]^+$), readily undergoes further decomposition to generate benzyl cation, indicating a low abundance in the CID spectrum. Whereas, the benzene elimination product (**b**-**P2**, *m/z* 132) from the ion **b** is a stable substituted benzyl cation, which is in agreement with a relative abundant signal in the CID-MS spectrum.

On the basis of the above analysis, we can conclude that benzyl cation is more facile to transfer to the phenyl ring (path-b) rather than to the amino N5 (path-a) in the process of decomposition of $[\mathbf{1}+H]^+$. Interestingly, the ion at *m/z* 210, derived from dissociation of $[\mathbf{8}+H]^+$, the protonated *N*-benzylated 2-phenylethanimine, shows the much similar CID-MS spectrum with that of the *m/z* 210 ion from $[\mathbf{1}+H]^+$ (Fig. 2(a,b)), indicating that benzyl cation is also facile to transfer to the phenyl ring from the amino N5 prior to the $(CO+H_2O)$ elimination of $[\mathbf{8}+H]^+$.

3.2. D-labeling experiments

To provide more evidences of the competing benzyl cation migration reactions, a deuterium labeling experiment has been carried out for compound **1** (Fig. 1(c)). An abundant deuterated molecule $[\mathbf{1}-2H+3D]^+$ at *m/z* 259 was obtained by the positive ESI of the methanol-d4 solution of **1**.

The product ion **d** is produced by the simultaneous loss of $(PhCH_2OH+CO)$, triggered by migration of the ionizing proton on the amino N5. As expected, the mass of the ion **d** shifts to 122 Da in the tandem MS spectrum of $[\mathbf{1}-2H+3D]^+$. No H/D exchange reaction has been observed for the product ions of d and the benzyl cation, indicating that the H-scrambling does not occur in **M-1** between the amino hydrogen and the phenyl one.

If the $(CO+H_2O)$ elimination of $[\mathbf{1}+H]^+$ occurs only via the channel of path-a, two amino protons in **M-1** migrate to the neutral fragment of H_2O, and only one amino proton remains in the fragment ion **a**. As a result, there will be only a signal with 1 Da mass shift for ion **a**, resulting from dissociation of $[\mathbf{1}-2H+3D]^+$ via losing (D_2O+CO). Actually, the presence of another deuterated ions (*m/z* 212 and *m/z* 213) in the CID-MS spectrum indicates an alternative accessible reaction channel of losing (H_2O+CO) from $[\mathbf{1}+H]^+$.

As for the reaction channel of path-b, migration of the activated phenyl proton, originating from the electrophilic attack by the benzyl cation, to the carboxylic hydroxyl leads to dissociation of **M-4** via losing (H_2O+CO). Herein, two of amino protons remain in the fragment ion **b**, indicating a mass shift of 2 Da for ion **b** resulting from dissociation of $[\mathbf{1}-2H+3D]^+$ via losing (DHO + CO). Alternatively, isomerization of **M-4** leads to **M-5** through transfer of the activated phenyl proton to the amino N5, and the subsequent migration of one of the amino protons to the carboxylic hydroxyl initiates the decomposition of **M-5** to give the product ions at *m/z* 211 via losing (D_2O+CO) and at *m/z* 212 via losing (DHO + CO), respectively. The significantly more abundance of the ion at *m/z* 212 is a consequence of the considerable kinetic isotope effect, k_H/k_D [25,26]. Additionally, the presence of the minor product ion at *m/z* 213 indicates the occurrence of H-scrambling between amino proton and the phenyl ring hydrogen in **M-5**, which has been consolidated by the occurrence of H-scrambling in the NH_3 elimination of $[\mathbf{1}-2H+3D]^+$.

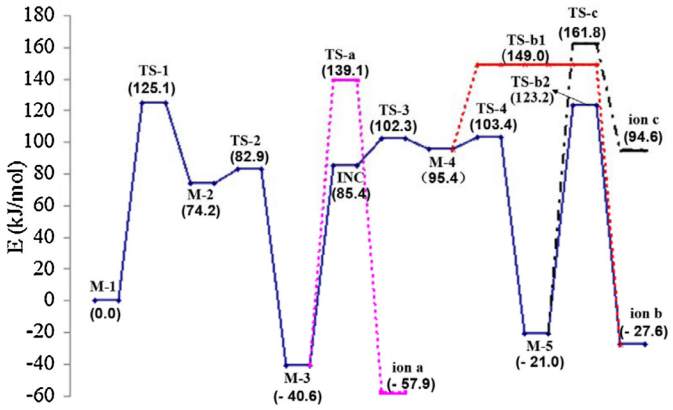


Fig. 3. Potential energy diagram for fragmentation of $[\mathbf{1}+H]^+$.

3.3. Theoretical calculation

To gain more detailed insights into the competing benzyl cation migration reactions, DFT calculations have been preformed at the B3LYP/6 − 311 + G(2d,p) level of theory for the fragmentation of the typical ion $[\mathbf{1}+H]^+$. Fig. 3 displays a potential energy diagram for the dissociation reactions as presented in Scheme 2, and the details structures of the corresponding species are available as Fig. 4S in the Supplementary data. The virtual reaction channels might be more complicated than those in Scheme 2, since the H-scrambling process occurs effectively according to the D-labeling experimental results.

To begin interpretation of the mechanistic fragmentation of $[\mathbf{1}+H]^+$, we should first tackle the original protonation site of the molecule. There are two potential protonation sites for **1**, including (i) the amino N5 (**M-1**) and (ii) the carbonyl O6 (**M-2**). The calculated free energy of **M-1** is 74.2 kJ/mol lower than that of **M-2**, indicating that the N5 atom is the much more preferred site for protonation in ESI-MS analysis. The stability of **M-1** is attributed to an intramolecular N5—H . . . O6 hydrogen bond (1.922 Å), as available in Fig. 4S in the Supplementary data. Many attempts have been made to optimize the structure of the *O*-protonated **1**, with the orientation of the ionizing proton towards the amino group, but all of the final structures result in **M-1**. Thus, rotation of the ester group around the C2—C3 bond of **M-2**, with the energy barrier of 125.1 kJ/mol relative to **M-1**, can be viewed as the mechanistic process of the interconversion between these two isomers.

Protonation at the carboxylic O6 in **M-2** weakens the O4—C7 bond, as indicated by the lengthened bond length (1.500 Å in **M-1** vs >1.566 Å in **M-2**, as shown in Fig. 4S in the supporting information). The disruption of the O4—C7 bond, upon collisional activation, leads to the transferring benzyl cation. In the reaction channel of path-a, migration of the benzyl cation in **M-2** to the amino N5 leads to **M-3** with a small energy barrier (**TS-2**) of 82.9 kJ/mol. Stabilized by an intramolecular N—H . . . O hydrogen bond (2.000 Å), **M-3** is located at the minimum in the potential energy surface of path-a, which lies 40.6 kJ/mol in free energy below **M-1**. The calculated results demonstrate that $[\mathbf{8}+H]^+$ (**M-3**) is less unfavorable to undergo fragmentation than $[\mathbf{1}+H]^+$ (**M-1**), which is in agreement with the CID-MS experimental results (Fig. 1(a,b)). Due to the electrophilic attack of the benzyl cation, one of the amino protons (H5) is activated to be transferable in **M-3** [19]. The subsequent fragmentation of **M-3** occurs via migration of

the activated amino proton to the carboxylic hydroxyl O6, which results in the ion **a** via the simultaneous loss of ($H_2O + CO$). Elimination of ($H_2O + CO$) is the key step in path-a, with an accumulated energy barrier (**TS-a)** of 139.1 kJ/mol.

Alternatively, decomposition of **M-3** (or **M-2**) can lead to a temporary system of ion-neutral complex (**INC**), consisting of benzyl cation and phenylalanine. **INC** is energetically accessible to undergo further reaction to form **M-4** via electrophilic attack of the benzyl cation at the phenyl ring carbon (possibly at the *ortho* position) in path-b, which surmounts a small energy barrier (**TS-3**) of 102.3 kJ/mol. It is noteworthy that **M-4** is located at 136.0 kJ/mol in free energy above **M-3**, indicating that the phenyl ring C contains much lower electrophilic affinity than the amino N5. Thereby, formation of **M-4** is energetically accessible to come from **M-3** rather than **M-2**, which has been supported by the MS^3 experimental results (Fig. 2).

As shown in Scheme 2, **M-4** undergoes dissociation in two reaction channels. In path-b1, the activated phenyl ring proton, due to the electrophilic attack of the benzyl cation, is subsequently transferred to the carboxylic hydroxyl O6, leading to the simultaneous elimination of ($H_2O + CO$). The accumulated energy barrier (**TS-b1**) is 149.0 kJ/mol in free energy, relative to **M-1**. The resulted fragment ion **b** (*m*/*z* 210) shares the same mass with ion **a**. In path-b2, the activated phenyl ring proton in **M-4** is transferred to the amino N5, leading to formation of an intermediate **M-5**, with a slight energy barrier (**TS-4**) of 103.4 kJ/mol. The formed **M-5** then undergoes ($H_2O + CO$) elimination to produce the fragment ion **b**. The accumulated energy barrier (**TS-b2**) is 123.2 kJ/mol in free energy, relative to **M-1,** demonstrating a much more feasible reaction channel losing ($H_2O + CO$) than path-b1 (**TS-b1**). **M-5** can also undergo NH_3 elimination to generate the fragment ion **c**. The accumulated energy barrier (**TS-c**) is assessed to be 161.8 kJ/mol in free energy.

Analysis of the potential energy surface in Fig. 3 demonstrates that there are three fragmentation channels leading to the product ion at *m*/*z* 210 (ion **a** and **b**), of which path-b2 (stepwise benzyl cation migration via **TS-b2)** is the kinetically most favorable one. On the other hand, the reaction channel of NH_3 elimination via **TS-c** is kinetically and thermodynamically less favorable than the above three pathways. However, the fragment ion **c**, resulting from NH_3 elimination, is also observed in the CID-MS spectrum (Fig. 1(a)), and thereby the relatively more facile channels does occur accessibly under the same conditions, which is in good agreement with the experimental results. That is, the protonated benzyl phenylalaninates undergo two competing channels of benzyl cation migration (to amino or to the phenyl ring) in the dissociation process, of which the more favorable one is the stepwise benzyl cation migration.

4. Conclusion

Two interesting competing reactions of the benzyl cation transfer, to the amino nitrogen and the phenyl ring carbon (possibly at the *ortho* position), have been proposed in dissociation of the protonated benzyl phenylalaninates. Both the amino and the phenyl ring hydrogen atoms can be activated to be mobile due to the electrophilic attack of the transferring benzyl cation. The amino N rather than the phenyl ring favors to accept the electrophilic attack of the benzyl cation, whereas it is much more preferred for benzyl cation to transfer to the phenyl ring from the amino N, leading to the stepwise benzyl cation migration. The activated proton then migrates to the carboxyl hydroxyl or to the amino, which leads to the elimination of ($CO + H_2O$) or NH_3. The mechanistic processes have been confirmed by the MS^3 spectra data, along with D-labeling experiments and theoretical calculations. The above results presented in this work will not only provide a more detailed understanding of the role of the transferring benzyl cation, but can be very helpful to explain some puzzling gas-phase reactions of the analogous species used for structural elucidation.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijms.2014.05.011.

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