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Protonated *N*-benzyl- and *N*-(1-phenylethyl)tyrosine amides dissociate via ion/neutral complexes

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RATIONALE: The collisional-induced dissociations (CID) of the $[M+H]^+$ ions of molecules having benzyl groups attached to N-atoms have been proposed to involve migration of the benzyl group through the intermediacy of ion/neutral complexes (INCs). We report the investigation of the mechanism of dissociation of protonated *N*-benzyl- and *N*-(1-phenylethyl)tyrosine amides by electrospray ionization (ESI) tandem mass spectrometry (MS/MS) and density functional theory (DFT) calculations.
METHODS: The amides were synthesized from the corresponding amino acids and amines. The ESI-MS/MS spectra were recorded using an Agilent QTOF 6540 mass spectrometer. The DFT calculations were performed by using Gaussian 09 software. The structures of the $[M+H]^+$ ions, intermediates, products and transition states (TS) were optimized at the B3LYP/6-31G(d,p) level of theory.
RESULTS: CID of the $[M+H]^+$ ions of *N*-benzyltyrosine amide yields two product ions due to rearrangements: (i) the $[M+H–74]^+$ ion (*m/z* 197) due to benzyl migration to the hydroxyphenyl ring and (ii) the $[M+H–45]^+$ ion (*m/z* 226) due to benzyl migration to the NH_2 group. DFT calculations suggest that the rearrangements occur through an INC in which the benzyl cation is the cation partner. The $[M+H]^+$ion of *N*-(1-phenylethyl)tyrosine amide rearranges to an INC of the 1-phenylethyl cation. Subsequent elimination of styrene occurs by transfer of a proton from the 1-phenylethyl cation to the neutral partner.
CONCLUSIONS: The $[M+H]^+$ ions of both *N*-benzyl (**1**) and *N*-(1-phenylethyl) (**2**) tyrosine amide rearrange into INCs. The dissociation of $[M+H]^+$ ion of **1** yields the benzyl cation and $[M+H–74]^+$ and $[M+H–45]^+$ due to benzyl migration to the hydroxyphenyl ring and NH_2 group, respectively. However, the formation of the $[M+H–74]^+$ ion is not observed when the aromatic ring is deactivated. The $[M+H]^+$ ion of **2** either dissociates to form the 1-phenylethyl cation or $[M+H–styrene]^+$. Copyright © 2015 John Wiley & Sons, Ltd.

Electrospray ionization coupled with collision-induced dissociation (CID) of protonated molecules is one of the methods for obtaining structural information about organic compounds. It has been proposed that the dissociation pathways of protonated molecules containing benzyl groups attached to amino groups involve ion/neutral complexes (INCs) as intermediates in which the benzyl cation is the cation part. The intermediate INCs have been considered responsible for the formation of product ions resulting from benzyl migrations. Examples include benzyl cation migration followed by HCN elimination in protonated *N*-benzylbenzaldimines,[1] hydride ion transfer via an INC in protonated *N*-benzylpiperidines,[2] the dissociation of protonated 2,4,6-tribenzyltriazine yielding the 2-benzyl benzyl cation due to the migration of a benzyl group,[3] and protonated benzylamines yielding the product ions $[M+H–NH_3]^+$ and $[M+H–toluene]^+$ due to benzyl migration.[4] The protonated benzyl ester of proline dissociates to an INC in which the cation part is the benzyl cation followed by simultaneous elimination of H_2O and CO.[5] The loss of benzene from protonated *N*-benzylaniline,[6] *N*-benzyltetrahydroquinolines,[7] and *N*-benzylindoline[8] has been proposed to involve the migration of the benzyl group to other parts of the molecule via INCs. The migration of the fluorobenzyl cation between remote amidic nitrogen atoms has been proposed.[9] Group migrations have been observed during the fast atom bombardment (FAB) mass spectral fragmentations of protonated trimethylsilyl ethers and INCs have been proposed as intermediates.[10]

To investigate the possible rearrangements of the $[M+H]^+$ ions upon CID by performing ESI mass spectrometric experiments, we have selected the *N*-benzyl amides of the amino acids tyrosine, nitrotyrosine and phenylalanine, compounds **1–6** (Scheme 1). Due to the presence of the *N*-benzyl group, the $[M+H]^+$ ions of **1–6** are likely to show the migration of the benzyl group onto the aromatic ring or

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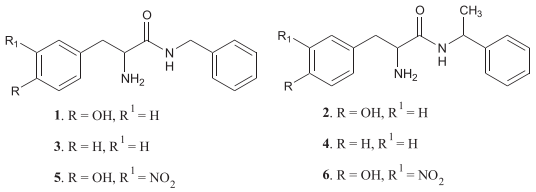

Scheme 1. Compounds under investigation.

NH_2 group prior to dissociations via intermediate INCs. Further, tyrosine amides and substituted derivatives are pharmaceutically important compounds.[11] The feasibility of the rearrangement of the protonated molecules into INCs and their dissociation mechanisms will be investigated by density functional theory (DFT) calculations.

EXPERIMENTAL

Synthesis

Compounds **1–6** were synthesized from the N-protected (butoxycarbonyl, BOC) amino acid.[12] The BOC-protected amino acid is treated with benzylamine or 1-phenyl-ethylamine in the presence of T3P (1-propane phosphonic anhydride) and DIPEA (diisopropylethylamine) at 60°C.[13] The resulting amide is deprotected using trifluoroacetic acid in dichloromethane at room temperature.

Mass spectra

An 1200 series liquid chromatography (LC) instrument (1290 Infinity; Agilent Technologies, USA) attached to a quadrupole time-of-flight mass spectrometer (QTOF LC/MS 6540 series; Agilent Technologies, USA) was used for the analysis. The effluent from LC was directly attached to an electrospray ionization (ESI) source operated in positive mode. The data acquisition was under the control of Mass Hunter Workstation software. The typical operating source conditions for MS scan were optimized as follows: fragmentor voltage was set at 150 V, the capillary at 3500 V, the skimmer at 65 V, nitrogen as the drying gas (325°C,8 L/min), and nebulizing (35 psi) gas. For collision-induced dissociation (CID) (or CAD) experiments, keeping MS1 static, the precursor ion of interest was selected using the quadrupole analyzer and the product ions were analyzed using a TOF analyzer. Ultra high purity nitrogen was used as collision gas. The MS/MS spectrum of compound **1** was collected at 15 eV and the others at 10 eV.

DFT calculations

The structures of the $[M+H]^+$ ions, intermediates, product ions and transition states (TS) were optimized at the B3LYP/6-31G(d,p) level using the Gaussian 09 software package for Windows.[14] Frequency calculations were performed to make sure that there are no imaginary frequencies for the ground-state structures and there is one imaginary frequency for the TS structures. The relative energies of the $[M+H]^+$ ions, intermediates, product ions and TS were determined using the total electronic and thermal energies.

RESULTS AND DISCUSSION

The ESI mass spectra of the compounds showed abundant ions corresponding to the protonated molecules. CID of the $[M+H]^+$ ions (*m/z* 271) of *N*-benzyltyrosine amide (**1**) yields product ions at *m/z* 226, 197, 136 and 91(Fig. 1). The ions of *m/z* 136 and 91 (benzyl cation) are formed by simple cleavage reactions. The accurate masses of the these product ions (*m/z* 226 and 197; Table 1) indicate that the formation of these ions involves eliminations of CH_3NO and $C_2H_6N_2O$ from the $[M+H]^+$ ion. The molecular formulae of the product ions indicate that both aromatic rings are being retained in the product ions. Further, CID of the $[M+H]^+$ ion of compound **3** does not yield the product ion $[M+H-74]^+$, indicating that the presence of a phenolic OH group is essential for the elimination of $C_2H_6N_2O$ from the $[M+H]^+$ ion. In addition, the dissociation of the $[M+H]^+$ ion of compound **5**, a

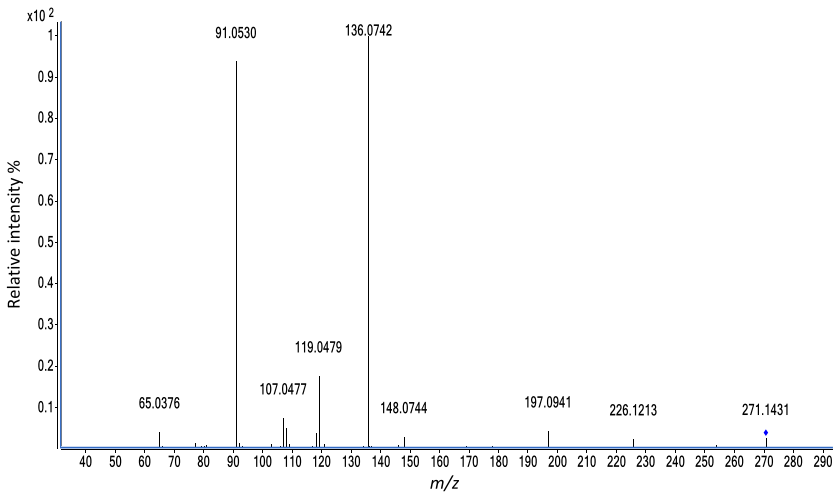

Figure 1. High-resolution ESI-CID mass spectrum of the $[M+H]^+$ ion of *N*-benzyltyrosine amide.

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Table 1. Measured accurate masses and elemental compositions of $[M+H]^+$ ions and product ions of compounds **1–6**

Compound	$[M+H]^+$	$[M+H-45]^+$	$[M+H-74]^+$	$[M+H-104]^+$	Other ions
1. *N*-benzyltyrosine amide	271.1431 Calc. 271.1441 $C_{16}H_{19}N_2O_2$	226.1213 Calc. 226.1226 $C_{15}H_{16}NO$	197.0941 Calc. 197.096091 $C_{14}H_{13}O$	Not applicable	136 (100) 91 (95)
2. *N*-(1-phenylethyl)tyrosine amide	285.1586 Calc. 285.1597 $C_{17}H_{21}N_2O_2$	ND	ND	181.0957 Calc. 181.0971 $C_9H_{13}N_2O_2$	136 (55) 105 (100)
3. *N*-benzylphenylalanine amide	255.1489 Calc. 255.1491 $C_{16}H_{18}N_2O$	210.1276 Calc. 210.1277 $C_{15}H_{16}N$	ND	ND	120 (100) 91 (30)
4. *N*-(1-phenylethyl)-phenylalanine amide	269.1652 Calc. 268.1648 $C_{17}H_{20}N_2O$	ND	ND	165.1024 Calc. 165.1022 $C_9H_{13}N_2O$	120 (75) 105 (100)
5. *N*-benzyl-3-nitrotyrosine amide	316.1295 Calc. 316.1291 $C_{16}H_{18}N_3O_4$	271.1077 Calc. 271.1077 $C_{15}H_{15}N_2O_3$	ND	ND	181 (30) 91 (100)
6. *N*-(1-phenylethyl)-3-nitrotyrosine amide	330.1443 Calc. 330.1448 $C_{17}H_{20}N_3O_4$	ND	ND	226.0814 Calc. 226.0822 $C_9H_{12}N_3O_4$	181 (20) 105 (100)

N.B. Figures in parentheses represent relative abundances
ND – not detected

compound in which a nitro group is present at the *ortho*-position of the OH group, does not yield the $[M+H-74]^+$ ion indicating that the deactivation of the hydroxyphenyl ring inhibits this fragmentation. Hence it is proposed that the mechanism of formation of $[M+H-74]^+$ involves the migration of the benzyl group to the hydroxyphenyl group and intramolecular electrophilic substitution. Moreover, compounds **3** and **5** show the product ion $[M+H-45]^+$ ion in the CID mass spectra of the respective $[M+H]^+$ ions indicating that this process is due to the migration of the benzyl group to the NH_2 group of the amino acid.

The CID mass spectrum of the $[M+H]^+$ ion (*m/z* 285) of compound **2** in which the amide nitrogen is attached to the 1-phenylethyl group (Fig. 2) shows product ions of *m/z* 105 (1-phenylethyl cation), 136 (formed by simple cleavage) and 181, $[M+H-104]^+$. The measured accurate mass of the ion of *m/z* 181 (181.0957, $C_9H_{13}N_2O_2$) corresponds to the loss of the elements of styrene from the protonated molecule (Table 1). In addition, the $[M+H]^+$ ions of compounds **4** and **6** dissociate via elimination of a molecule of styrene indicating that the 1-phenylethyl cation cannot migrate to the phenyl groups of the respective amino acids. The difference in the dissociations of the $[M+H]^+$ ions of compounds **1**, **3** and **5** from those of **2**, **4** and **6** may be due to the difference in the reactivity of the benzyl cation and 1-phenylethyl cation as electrophiles.

The mechanisms of dissociations of the $[M+H]^+$ ions of compounds **1** and **2** were investigated by DFT calculations. Calculations show that the protonation occurs either on the NH_2 group or the carbonyl oxygen for both compounds **1** and **2**. The total energies of the NH_2-protonated and *O*-protonated structures are close to each other (Table 2). In the

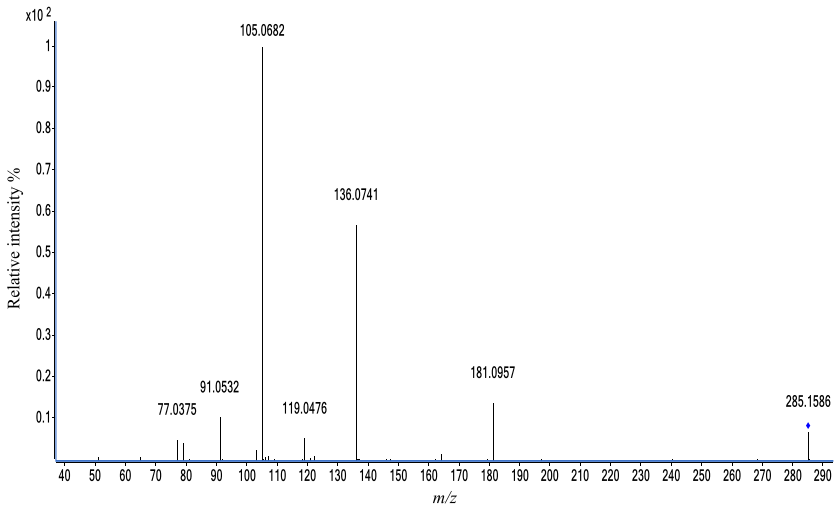
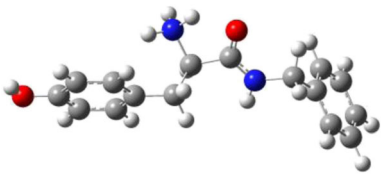
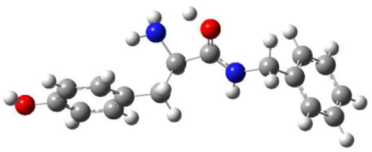
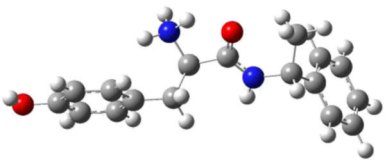
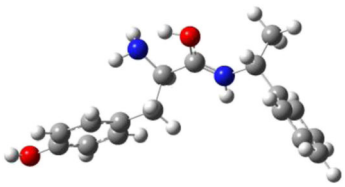
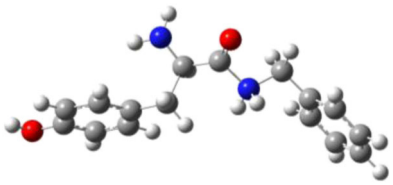
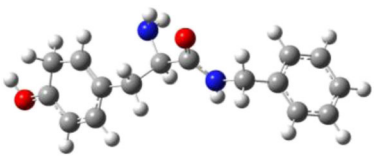


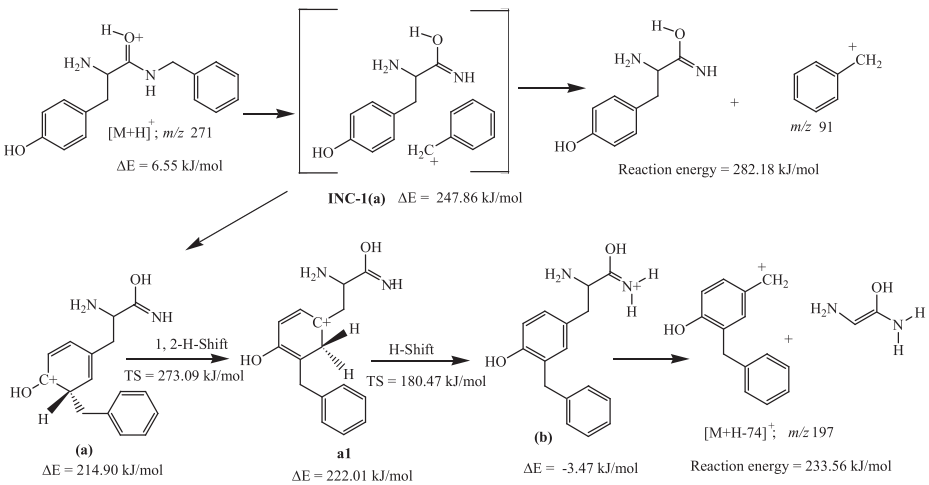
Figure 2. High-resolution ESI-CID mass spectrum of the $[M+H]^+$ ion of *N*-(1-phenylethyl)tyrosine amide.

NH_2-protonated structure the carbonyl oxygen atom is H-bonded to the ammonium ion and in the *O*-protonated ion the proton is H-bonded to the NH_2 group. Another possible site for protonation is the amide-*N*; the energy of the resulting $[M+H]^+$ ion is 121.58 kJ/mol higher compared to the NH_2-protonated molecule. A fourth protonation site visualized for the molecule is the hydroxyphenyl ring. Calculations show that the total energy of the ring-protonated structure is 132.72 kJ/mol higher compared to that of the NH_2-protonated molecule. Moreover, protonation at the hydroxyphenyl ring cannot activate the benzyl group to cause migration.

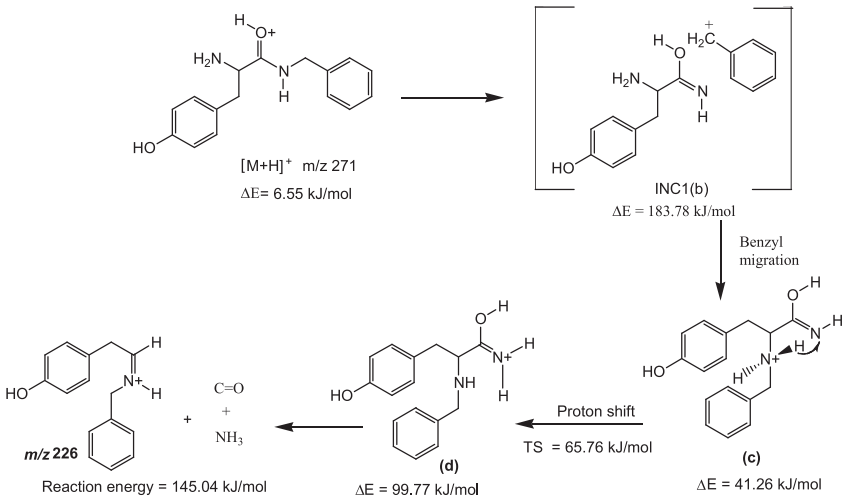
The elongation of the *N*-benzyl bond in the *O*-protonated molecule leads to the formation of an ion/neutral complex (INC-1; Schemes 2 and 3). Two possible structures were

Table 2. Optimized (B3LYP/6-31G(d,p) structures of $[M+H]^+$ ions of **1** and **2**

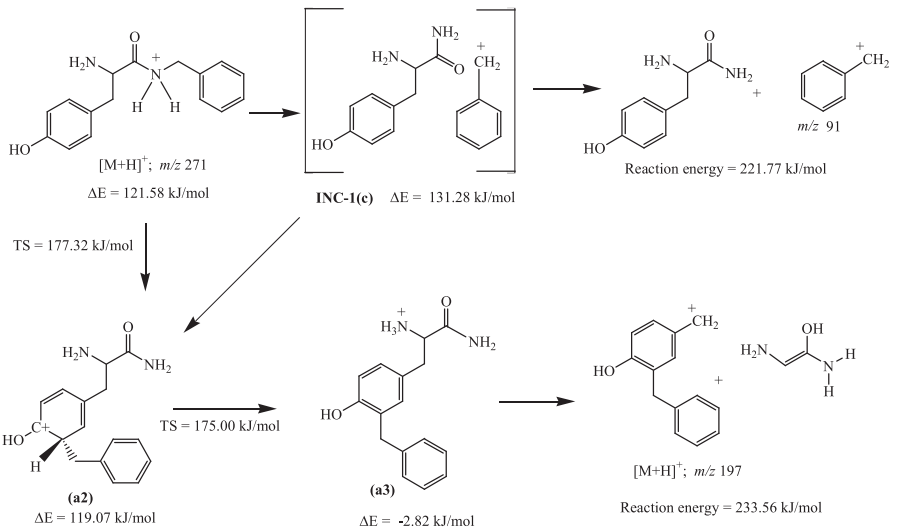
Compound	*N*-Protonated	*O*-Protonated
N-benzyltyrosine amide (**1**)	 ΔE = 0.00 kJ/mol	 ΔE = 6.55 kJ/mol
N-[1-phenylethyl]tyrosine amide (**2**)	 ΔE = 0.00 kJ/mol	 ΔE = 5.55 kJ/mol
Compound **1**	 Amide-*N* protonated ΔE = 121.58 kJ/mol	 Ring protonated ΔE = 132.72 kJ/mol



Scheme 2. Proposed mechanism of formation of the ion of *m/z* 197 from the $[M+H]^+$ ion (*O*-protonated) of compound **1** based on the DFT calculations. Reaction energy represents the sum of the energies of cation + neutral relative to that of the $[M+H]^+$ ion.

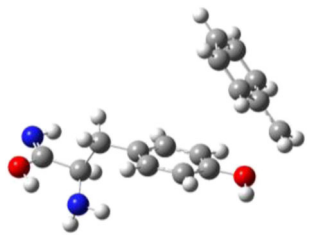


Scheme 3. Proposed mechanism of formation of the ion of *m/z* 226 from the $[M+H]^+$ ion (*O*-protonated) of compound **1** based on the DFT calculations. Reaction energy represents the sum of the energies of cation + neutral relative to that of the $[M+H]^+$ ion.



Scheme 4. Alternate mechanism of formation of the ion of *m/z* 197 via the amide-*N*-protonated $[M+H]^+$ ion of compound **1** based on the DFT calculations. Reaction energy represents the sum of the energies of cation + neutral relative to that of the NH_2-protonated $[M+H]^+$ ion.

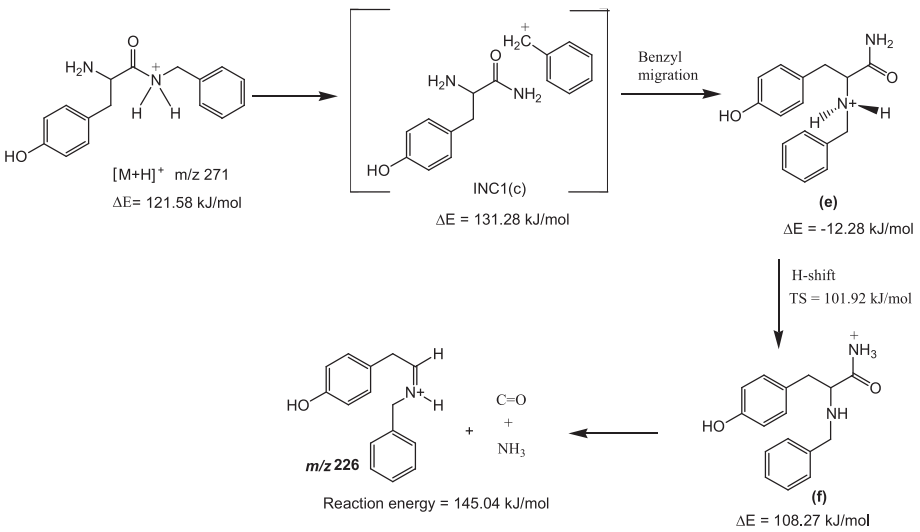
Table 3. DFT-optimized structures of **INC-1a** and **INC-1b** at the B3LYP/6-31G(d,p) level



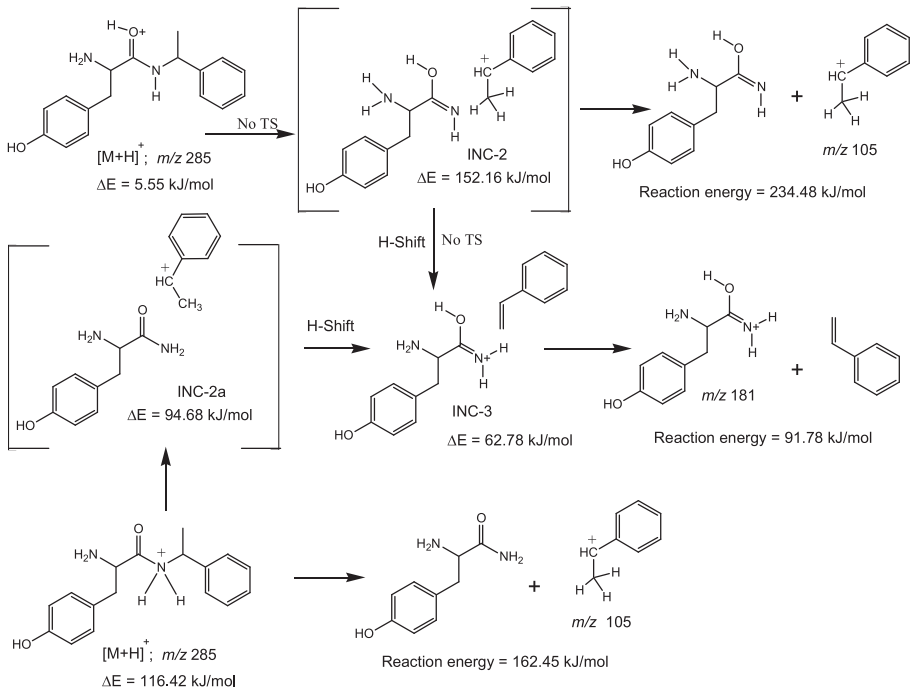
INC-1a

INC-1b

obtained for INC-1: (**a**) the benzyl cation is close to the hydroxyphenyl group (relative energy 247.86 kJ/mol) and (**b**) the benzyl cation is close to the carbonyl group of the neutral (relative energy 183.78 kJ/mol) (Table 3). The separation of the ion and neutral in INC-1 to yield the benzyl cation (*m/z* 91) requires high energy, i.e. the sum of the energy of [product ion + neutral] is 282.18 kJ/mol relative to that of the $[M+H]^+$ ion. There are two ways in which the benzyl cation can be attached to the neutral partner of INC-1. In route 1, the benzyl cation attacks the hydroxyl phenyl ring and electrophilic substitution occurs at the *ortho*-position of the OH group to yield an intermediate '**a**' (Scheme 2). A 1,2-H shift followed by the transfer of the aromatic proton to the NH occurs in intermediate '**a**' to afford the intermediate '**b**'. The dissociation of '**b**' yields the product ion of *m/z* 197, $[M+H–74]^+$. In route 2, the benzyl cation reacts with the NH_2 group of the neutral partner of INC-1 to generate an intermediate '**c**' (Scheme 3). A 1,4-H shift occurs in



Scheme 5. Alternate mechanism of formation of the ion of *m/z* 226 from the $[M+H]^+$ ion [amide-*N*-protonated] of compound **1** based on the DFT calculations. Reaction energy represents the sum of the energies of cation + neutral relative to that of the $[M+H]^+$ ion.



Scheme 6. Proposed mechanism of elimination of styrene from the $[M+H]^+$ ion of compound **2** based on the DFT calculations. Reaction energy represents the sum of the energies of cation + neutral relative to that of the $[M+H]^+$ ion.

intermediate '**c**', from the quaternary nitrogen atom to the NH group, to yield an intermediate '**d**'. The product ion of *m/z* 226, $[M+H-45]^+$, is formed by the dissociation of '**d**', probably due to the elimination of NH_3 and CO.

An alternate pathway for the production of the ion of *m/z* 197 involves the elongation of the *N*-benzyl bond in the amide-*N*-protonated molecule leading to INC-1c (Scheme 4). The benzyl cation in INC-1c migrates and attacks the hydroxyphenyl ring leading to an intermediate, **a2**, followed by 1,2-shift of the aromatic hydrogen. The resulting intermediate is unstable and rearranges to intermediate **a3** which dissociates to form the product ion of *m/z* 197. The reaction energy for the dissociation is higher than the energy required for the dissociation of INC-1c to produce the benzyl cation. In addition, the intermediate INC-1c leads to an alternative route for the formation of the ion of *m/z* 226 (Scheme 5). The benzyl cation migrates to the NH_2 group to generate intermediate '**e**'. The transfer of a proton from the charge site to the NH_2 group leads to the elimination of [NH_3+ CO] to yield the product ion of *m/z* 226. Although the relative energy of the amide-*N*-protonated molecule is much higher than the *O*-protonated and NH_2-protonated molecules, it provides lower energy pathways for the formation of ions of *m/z* 197 and 226.

Two possible pathways for the formation of the ion of *m/z* 181 from the $[M+H]^+$ ion of compound **2** were explored by DFT calculations. The transition state (TS) for the McLafferty type 1,5-H shift from the methyl group to the carbonyl oxygen could not be determined and hence this pathway was ruled out. The calculation of the energy profile for the elongation of the C–N bond in the $[M+H]^+$ ion to yield an ion/neutral complex (INC-2) shows that the process does not involve a TS (there is no reverse barrier) but the energy increases gradually until the $[M+H]^+$ ion is transformed into the ion/neutral complex INC-2. The neutral partner of INC-2 is the enol form of tyrosine amide and the cation partner is the 1-phenylethyl cation. Further, calculation of the energy profile, obtained by incrementing the C–H bond length in steps of 0.1 Angstrom, for the transfer of a proton from the 1-phenylethyl cation of INC-2 to the NH group of the neutral partner, indicates that the transformation of INC-2 to INC-3 occurs without a transition state (Scheme 6). The energy profile diagrams are given in the Supporting Information. The elimination of styrene occurs from INC-3. Moreover, if protonation occurs at the amide-*N* an alternate low-energy pathway can be visualized for the formation of the ions of *m/z* 105 and 181 involving INC-2a in which the neutral partner is tyrosine amide (Scheme 3).

CONCLUSIONS

ESI-CID pathways of the $[M+H]^+$ ions of compounds **1–6** were investigated. DFT calculations indicate that the $[M+H]^+$ ions of *N*-benzyl- and *N*-(1-phenylethyl)tyrosine amides dissociate via INCs. The INC formed from the $[M+H]^+$ ion of **1** has two dissociation pathways involving benzyl cation migration (i) to the hydroxyl phenyl ring leading to the product ion of *m/z* 197, $[M+H-74]^+$, and (ii) to the NH_2 group leading to the product ion of *m/z* 226, $[M+H-45]^+$. However, when the aromatic ring is deactivated as in phenylalanine or nitrotyrosine (**3** and **5**) the formation of $[M+H-74]^+$ is not observed. When the substituent on the amide-*N* is a 1-phenylethyl group (**2**), the INC formed from the protonated molecule losses styrene by transferring a proton from the 1-phenylethyl cation to the neutral partner.

Acknowledgements

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