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McLafferty-type rearrangement of protonated *N*-[nicotinoyl] phenylethyl amines and consequent elimination of styrene

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RATIONALE: McLafferty rearrangements occur in radical cations of molecules containing a carbonyl group and a γ hydrogen atom but are not common in the $[M+H]^+$ ions of carbonyl compounds. We propose to investigate the collision-induced dissociation (CID) of the $[M+H]^+$ ions of nicotinoyl and picolinoyl amides of 1- and 2-phenylethylamines to explore the possibility of McLafferty-type rearrangement.
METHODS: The compounds for study were synthesized by the reaction of methyl nicotinate or methyl picolinate with 1- and 2-phenylethylamines. The CID mass spectra of electrospray ionization (ESI)-generated protonated molecules were obtained using a QSTAR XL quadrupole time-of-flight (QTOF) mass spectrometer, and density functional theory (DFT) calculations using the B3LYP method were employed to elucidate the fragmentation mechanisms. The total electronic and thermal energies of intermediate transition states (TSs) and product ions are reported relative to those of the $[M+H]^+$ ions.
RESULTS: CID of the $[M+H]^+$ ions of *N*-[nicotinoyl]-2-phenylethylamine (1) yielded product ions of *m/z* 105 (1-phenylethyl cation) and 123 ($[M+H–styrene]^+$ cation). The competitive formation of the ions of *m/z* 123 and 105 is proposed to involve a McLafferty-type rearrangement. Similarly, the $[M+H]^+$ ions of the isomeric compound 2 and the *N*-[picolinoyl] phenylethyl amines (3 and 4) dissociate to yield ions of *m/z* 123 and 105.
CONCLUSIONS: A molecule of styrene was eliminated from the ESI-generated $[M+H]^+$ ions of *N*-[nicotinoyl] phenylethylamines and the isomeric *N*-[picolinoyl]phenylethylamines, through a mechanism involving a McLafferty-type 1,5-H shift. The transition state energy for the 1,5-H shift is less for the amides of 1-phenylethylamine than for the amides of 2-phenylethylamine. The process occurs as a charge remote process and the presence of the pyridine ring is essential for the process.

A 1,5-H shift occurring prior to fragmentation, via loss of an alkene, in molecular radical cations produced by electron ionization (EI) of carbonyl compounds is known as a McLafferty rearrangement.[1–4] Ion fragmentations with special reference to the McLafferty-type rearrangement is explained in a recent review.[5] Such rearrangements of protonated molecules have been reported but the fragmentation occurs at a site remote from the positive charge[6–10] or the negative charge.[11] McLafferty-type rearrangements have been observed in the electrospray ionization (ESI) collision-induced dissociation (CID) fragmentation of lithiated molecules.[12] Remote charge fragmentations of even-electron ions have been reported for lithiated long-chain fatty acid molecules under high-energy collision conditions.[13]

We report the rearrangements of protonated nicotinoyl and picolinoyl amides of 1- and 2-phenylethylamine when the internal energy of these species has been increased or enhanced by collision. The molecules under investigation have a carbonyl group and γ-hydrogen atoms, the requirements in EI for observing McLafferty rearrangements leading to the elimination of an alkene.[6] To understand the possible mechanisms of rearrangements and fragmentations, *N*-(nicotinoyl)-2-phenylethylamine and a set of related isomeric compounds (**1–6**, Scheme 1) have been synthesized and their ESI-CID mass spectra investigated. The feasibility of rearrangement of the protonated molecules involving a 1,5-H shift was investigated using density functional theory (DFT) calculations. The results of the investigation are likely to provide information regarding isomer distinction and fragmentation processes, useful for the identification of *N*-(nicotinoyl)amines by ESI mass spectrometry.

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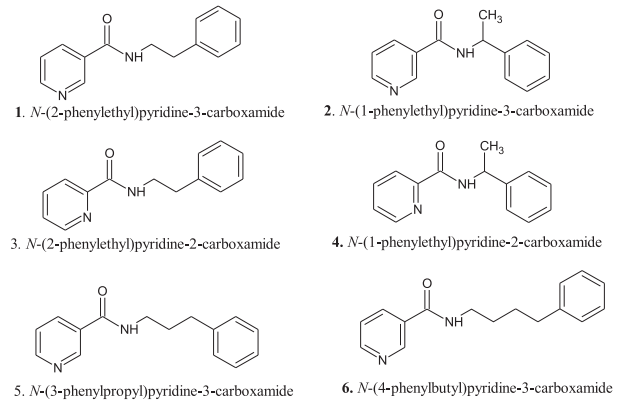
EXPERIMENTAL

Synthesis

The compounds **1**, **2**, **5**, **6** were synthesized (Scheme 1) by reaction between methyl nicotinate and the 2-phenylethylamine.[14,15] Compounds **3** and **4** were synthesized from methyl picolinate and 1-phenylethylamine. The procedure used for the formation of the esters was



Scheme 1. Compounds under investigation.

similar to that given in Dermer and King.[15] The compounds were purified by column chromatography, characterized by NMR spectroscopy and used for mass spectral study.

Mass spectra

The mass spectra of the compounds were obtained in positive ion mode using the electrospray ionization (ESI) source of a Thermo LCQ Advantage ion trap mass spectrometer (ThermoFinnigan, San Jose, CA, USA). The ESI-generated $[M+H]^+$ ions were then used as precursor ions to acquire CID product ion spectra. The typical source conditions were: spray voltage, 5 kV; capillary voltage, 15–20 V; heated capillary temperature, 200°C; tube lens offset voltage, 20 V; sheath gas (N_2) pressure, 20 psi; with helium used as the damping gas. For the ion trap analyzer, the automatic gain control setting was 2×10^7 counts for a full-scan mass spectrum and 2×10^7 counts for a full-scan product ion mass spectrum with a maximum ion injection time of 200 ms. The collision energies used were about 30 eV.

Accurate mass measurements were performed using a quadrupole time-of-flight (QTOF) mass spectrometer (QSTAR XL, Applied Biosystems/MDS Sciex, Foster City, CA, USA), equipped with an ESI source. The data acquisition was under the control of AnalystQS software (Applied Biosystems/MDS Sciex). The typical source conditions were: capillary voltage, 5.00 kV; declustering potential, 60 V; focusing potential, 260 V; resolution 8000 (full-width at half-maximum). Ultra-high-purity nitrogen was used as the curtain gas and collision gas, whereas zero air was used as the nebulizer gas. The ESI-generated $[M+H]^+$ ions were selected by the quadrupole and the product ions formed in the collision cell were then detected by the TOF analyzer. The samples were infused into the ESI source at a flow rate of 10 μL/min using an in-built syringe pump.

DFT calculations

These were carried out by using the Gaussian 09 software package for windows.[16] The structures of the $[M+H]^+$ ion, intermediates, transition states and product ions were optimized using a B3LYP/6-31G(d,p) basis set and the relative energies of the product ions are reported in kJ/mol, relative to those of the $[M+H]^+$ ions. The total electronic and thermal energies were used to calculate the relative energies after applying vibrational corrections. The transition state structures were confirmed by performing intrinsic reaction coordinate (IRC) path calculations. The optimized structures are given in the Supporting Information.

RESULTS AND DISCUSSION

N-[Nicotinoyl]-2-phenylethylamine (1)

The ESI-CID mass spectrum of the $[M+H]^+$ ion of *N*-[nicotinoyl]-2-phenylethylamine showed abundant product ions of *m/z* 105, 106, 108, 120 and 123 (Fig. 1). The ion of *m/z* 105 is probably the 1-phenylethyl cation, formed by a cleavage of the C–N bond with a simultaneous H shift (Scheme 2). The ion of *m/z* 106 corresponds to the nicotinoyl cation. Proposed structures for ions of *m/z* 108 and 120 are protonated pyridine-3-aldehyde and the $[M-H]^+$ ion of 2-phenylethylamine, respectively. The high-resolution ESI-CID mass spectrum of the $[M+H]^+$ ion revealed that the elemental compositions of the product ions correspond to those of the proposed structures (Table 1). The formation of the ion of

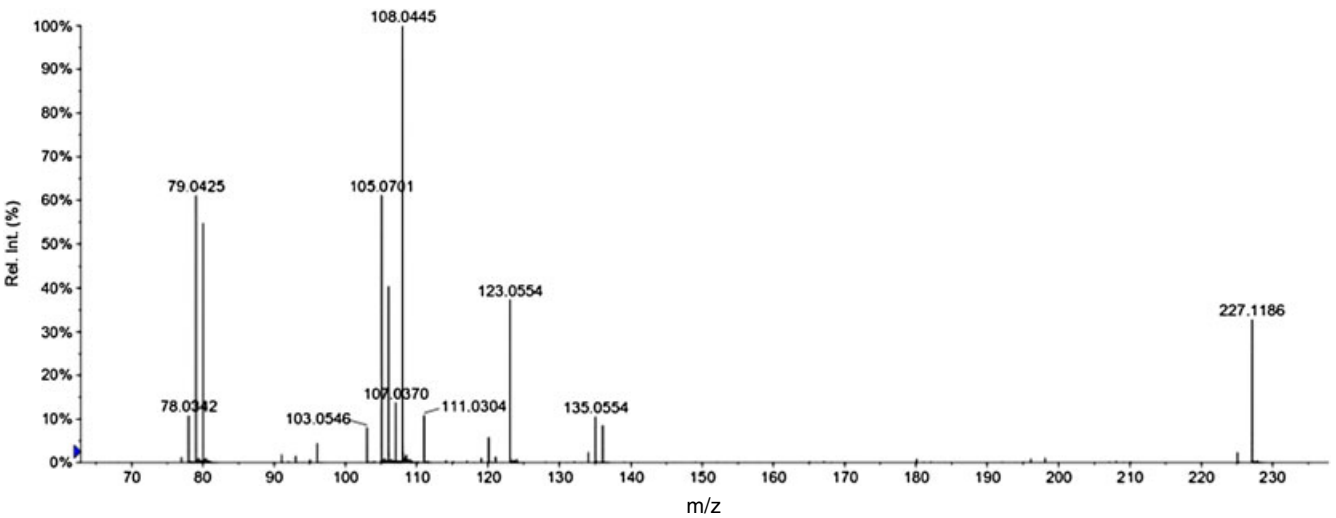
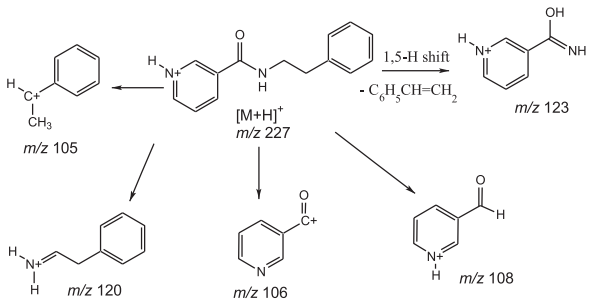


Figure 1. High-resolution ESI-CID mass spectrum of the $[M+H]^+$ ion of *N*-[nicotinoyl]-2-phenylethylamine.



Scheme 2. Fragmentation pathways of the $[M+H]^+$ ions of compound 1.

m/z 123 involves a 1,5-H shift from the CH_2 group to the carbonyl oxygen with simultaneous bond cleavage. This reaction is similar to the McLafferty rearrangement observed for the radical cations of carbonyl compounds generated by EI.[1] The presence of the pyridine nitrogen is essential for the observation of the McLafferty-type rearrangement since the ESI-CID mass spectrum of the $[M+H]^+$ ion of the *N*-benzoyl-2-phenylethylamine shows *m/z* 105 as the only product ion (benzoyl cation). The proposed structures of the product ions of compound **1** indicate that the protonated molecule undergoes extensive rearrangement prior to dissociation. The mechanisms of the fragmentations were investigated by DFT calculations.

Theoretical calculations

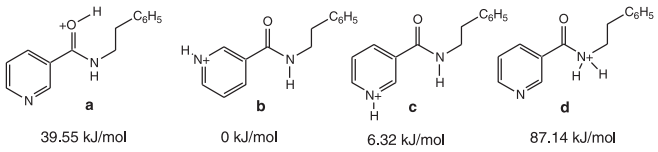
There are three possible protonation sites for *N*-[nicotinoyl]-2-phenylethylamine; i.e. the carbonyl oxygen, the nitrogen of the pyridine ring and the amide nitrogen. There are four possible structures of the $[M+H]^+$ ions, **a**, **b**, **c** and **d**, optimized using the B3LYP/6-31G(d,p) method and their relative energies are given in Scheme 3. The lowest energy structure of the $[M+H]^+$ ion (**b**) has the extra proton on the ring nitrogen and the next structure (**c**), the rotational isomer, is slightly higher in energy. Structure **b** is considered as the most likely structure for the $[M+H]^+$ ion.

The formation of structure **d** involves either direct protonation of the amide nitrogen or the transfer of the proton from the carbonyl oxygen to the amide nitrogen in **a**. The C–N bond length in the optimized structure of **d** is longer than usual (1.584 Å).[17–19] The relative energy of the transition state for the rearrangement of **a** to **d** is 156.32 kJ/mol. The formation of the nicotinoyl cation (*m/z* 106) can be explained from structure **d**. The ion-neutral complex, INC-1, between the nicotinoyl cation and 2-phenylethylamine (Scheme 4) is formed by elongation of the C–N bond in **c**. Dissociation of INC-1 produces the ion of *m/z* 106, the nicotinoyl cation, a process that requires high energy (sum of the energy of cation + neutral = 307.14 kJ/mol). In a less energy demanding process, the transfer of a hydride ion from the CH_2 group of the neutral part of the complex to the carbonyl carbon of the cation produces an ion-neutral complex, INC-2, between pyridine-3-aldehyde and the $[2\text{-phenylethylamine–H}]^+$ cation. This ion-neutral complex, INC-2, is the probable precursor for the ions of *m/z* 120 and 108. The formation of the product ion of *m/z* 120, $[2\text{-phenylethylamine–H}]^+$ cation involves the separation of the ion from the neutral in INC-2 (reaction energy = 176.35

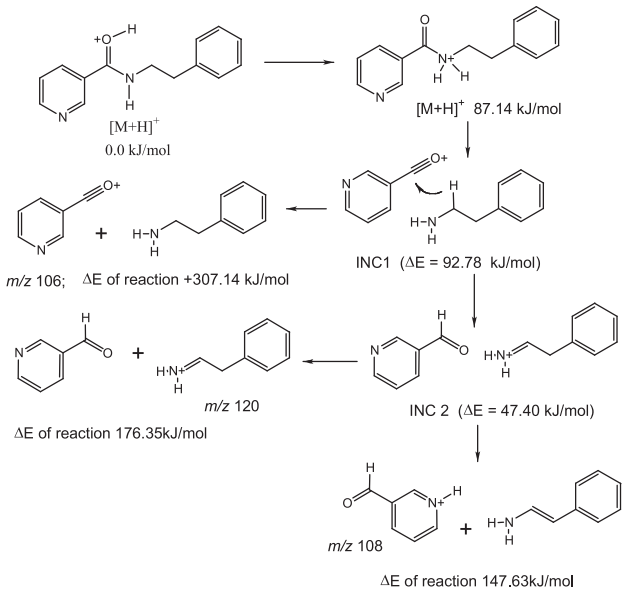
Table 1. Measured masses and elemental compositions of the $[M+H]^+$ and major product ions of compounds 1–6

Compound No.	$[M+H]^+$	$[M+H–styrene]^+$	$[M+H–122]^+$	*m/z* 106	*m/z* 108
1	227.1186 $C_{14}H_{15}N_2O$ Calc.	123.0554(39) $C_6H_7N_2O$ Calc.	105.0701(63) C_8H_9 Calc.	106.0294(41) C_6H_4NO Calc.	108.0449(100) C_6H_6NO Calc.108.0444
	227.1179	123.0552	105.0698	106.0287	
2	227.1179 $C_{14}H_{15}N_2O$ Calc.	123(100)	105(16)	ND	ND
	227.1179				
3	227.1181 $C_{14}H_{15}N_2O$ Calc.	123(10)	105.0701(100)	ND	ND
	227.1179				
4	227.1179 $C_{14}H_{15}N_2O$ Calc.	123.0550(85) $C_6H_7N_2O$ Calc.	105.0698(100) C_8H_9 Calc.	ND	ND
	227.1179	123.0552	105.0698		
5	241.1329 $C_{15}H_{17}N_2O$ Calc.	123.0550(14) $C_6H_7N_2O$* Calc.	ND	106.0289(100) C_6H_4NO Calc.	108.0451(60) C_6H_6NO Calc.108.0444
	241.1335	123.0552		106.0287	
6	255.1489 $C_{16}H_{19}N_2O$ Calc.	123.0557(27) $C_6H_7N_2O$* Calc.	ND	106.0289(100) C_6H_4NO Calc.	108.0441(60) C_6H_6NO Calc.108.0444
	255.1492	123.0552		106.0287	

ND = not detected
*The neutral eliminated is a homologue of styrene.
The figures in parentheses denote percentage relative abundances/



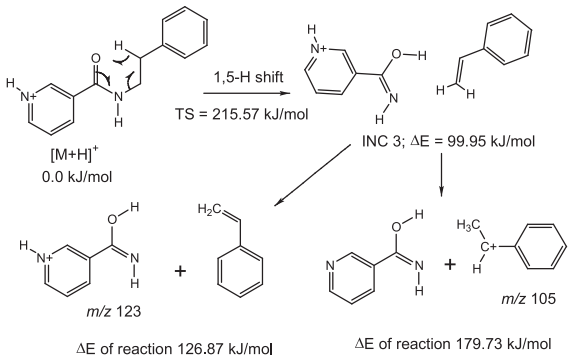
Scheme 3. The possible structures of $[M+H]^+$ ions of compound 1 and their DFT-calculated energies relative to the lowest energy structure (b), at the B3LYP/6-31G(d, p) level.



Scheme 4. Proposed mechanism of formation of *m/z* 106, 108 and 120 from the $[M+H]^+$ ion of compound 1, based on DFT calculations. Reaction energy represents the sum of the energies of cation + neutral relative to that of the $[M+H]^+$ ion.

kJ/mol). In another fragmentation pathway, the transfer of a proton from the cation part to the aldehyde part generates the ion of *m/z* 108, protonated pyridine-3-aldehyde (reaction energy = 147.62 kJ/mol).

Another important fragmentation pathway for the $[M+H]^+$ ion of compound **1** is the formation of the ion of *m/z* 123. A McLafferty-type fragmentation mechanism involving a 1,5-H shift is proposed for the formation of this ion. The 1,5-H-migration, in structure **b** from the benzylic CH_2 group to the carbonyl oxygen, leads to the cleavage of the C–N bond and the formation of an ion-neutral complex, INC-3 (Scheme 5). The relative energy for the optimized transition state is 215.57 kJ/mol for the H-migration and the total energy of INC-3 is 99.95 kJ/mol. The ion and neutral are not co-planar and the O-H hydrogen is close to the double bond of the styrene. There are two dissociation pathways for INC-3. The first dissociation channel, that of direct separation of the ion from the neutral, affords the ion of *m/z* 123 with styrene being the neutral eliminated. The second channel is that of the transfer of a proton from the ion part to the styrene, resulting in the formation of the ion of *m/z* 105. The *enol* form (**e**) of ring N-protonated nicotinamide is considered to be the likely structure for the ion of *m/z* 123 but the lower energy structure is the *keto* form (**f**). The O-protonated nicotinamide structure (**g**) for the ion of *m/z* 123

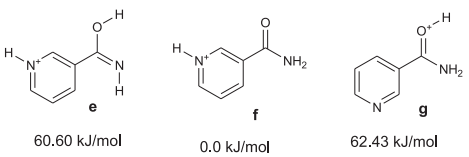


Scheme 5. Proposed mechanism of styrene elimination from the $[M+H]^+$ ion of compound 1, based on DFT calculations. Reaction energy is the sum of the energies of the cation + neutral, relative to that of the $[M+H]^+$ ion.

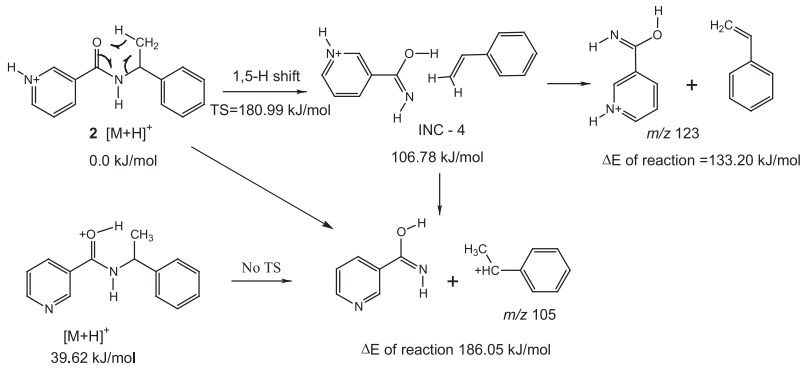
cannot be ruled out since H-migration between the ion part and the neutral part of INC-3 is possible. Their relative energies are given in Scheme 6.

N-[Nicotinoyl]-1-phenylethylamine (2)

To further understand the mechanism of the fragmentation leading to the formation of *m/z* 123, the ESI-CID mass spectrum of the $[M+H]^+$ ion of the isomeric compound, N-[nicotinoyl]-1-phenylethylamine (**2**) was investigated. The CID mass spectrum shows only two product ions (Table 1), i.e. *m/z* 123 ($C_6H_7N_2O$, 100%) and 105 (C_8H_9, 15%). The proposed structures of *m/z* 123 and 105 are ring N-protonated nicotinamide (enol) and the 1-phenylethyl cation. DFT calculations show that the lowest energy structure of the $[M+H]^+$ ion is formed by protonation of the ring N-atom. The proposed mechanism for the formation of the ions of *m/z* 123 and 105 involves a 1,5-H shift from the CH_3 group to the carbonyl oxygen, a McLafferty-type rearrangement, leading to the formation of an ion-neutral complex, INC-4 (Scheme 7). The energy of the transition state for the 1,5-H shift is 180.69 kJ/mol relative to the $[M+H]^+$ ion which is lower than that for compound **1**. There are two dissociation channels for the INC-4 complex. The first, direct separation of the ion from the neutral, affords the ion of *m/z* 123, with styrene being the neutral eliminated. The second is the transfer of a proton from the ion part to the styrene resulting in the formation of the ion of *m/z* 105. Alternatively, the ion of *m/z* 105 may be formed from the $[M+H]^+$ ion by a simple cleavage if protonation occurs at the carbonyl oxygen atom. The $[M+H]^+$ ion obtained by the carbonyl O-protonation is 39.62 kJ/mol higher in energy than the ring N-protonated ion. Furthermore, the formation of the ion of *m/z* 105 is a higher energy process than the formation of the product ion of *m/z* 123.



Scheme 6. The possible structures of *m/z* 123 fragment ions of compound 1, and their relative energies.



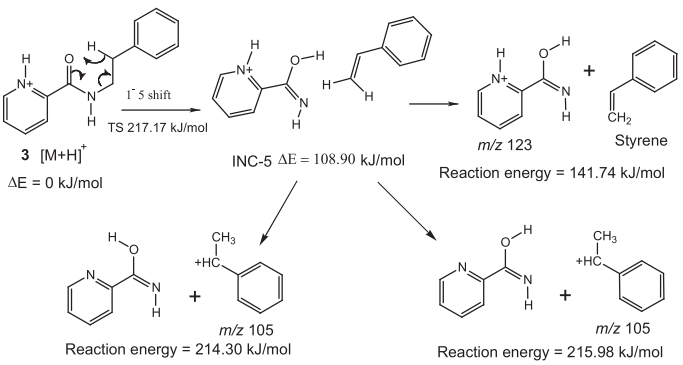
Scheme 7. Proposed mechanism of fragmentations of the $[M+H]^+$ ions of *N*-[nicotinoyl]-1-phenylethylamine (2).

N-[Picolinoyl]-2-phenylethylamine (3)

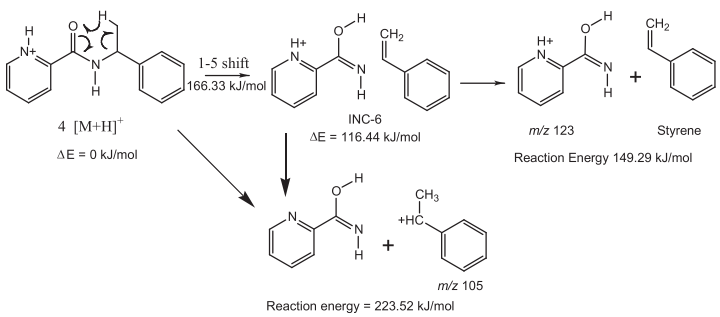
To establish further details of the fragmentation mechanism another isomer of compound **1** in which the position of the ring nitrogen is changed, *N*-[picolinoyl]-2-phenylethylamine (**3**), was synthesized and the product ion mass spectrum of the $[M+H]^+$ ion (*m/z* 227) was investigated. The CID mass spectrum shows only two product ions, *m/z* 105 and 123 (Table 1), indicating that a McLafferty-type rearrangement is occurring. The best protonation site for compound **2** is the pyridine nitrogen. A 1,5-H shift from the CH_2 group to the carbonyl oxygen results in the cleavage of the NH–CH_2 bond to form an ion-neutral complex, INC-5, in which the ion part is the protonated *enol* form of picolinamide and the neutral part is styrene (Scheme 8). The energy of the transition state for the 1,5-H shift is comparable with that of compound **1**. Direct dissociation of INC-5 yields the ion of *m/z* 123 and styrene as the neutral. In a second pathway, the shift of a proton from the cation part to the neutral affords the *m/z* 105 product ion.

N-[Picolinoyl]-1-phenylethylamine (4)

The ESI-CID mass spectrum of the $[M+H]^+$ ion of the isomeric compound, *N*-(picolinoyl)-1-phenylethylamine (**4**), shows only two product ions, *m/z* 105 and 123 (Table 1). The ion of *m/z* 105, probably the 1-phenylethyl cation, is the base peak (100%) and the relative abundance of the *m/z* 123 ion is 85%. The formation of these ions indicates that a McLafferty-type rearrangement is possible in the $[M+H]^+$ ion of compound **4** (Scheme 9). A 1,5-H shift from the methyl group to the carbonyl oxygen yields an ion-neutral complex, INC-6, consisting of the cation of *m/z* 123 and styrene. Separation of



Scheme 8. Proposed mechanism of fragmentation of $[M+H]^+$ ions of compound 3.



Scheme 9. Proposed mechanism of fragmentation of $[M+H]^+$ ions of compound 4.

the ion and neutral gives the product ion of *m/z* 123. The TS energy for the 1,5-H shift is lowest for compound **4** at 166.33 kJ/mol. The ion of *m/z* 105 may be formed by the simple cleavage of the C–N bond in the $[M+H]^+$ ion or from the INC-6 complex by the transfer of a proton from the ionic part to the styrene neutral.

N-[Nicotinoyl]-3-phenyl-1-propylamine (5) and *N*-[nicotinoyl]-4-phenyl-1-butylamine (6)

The ESI-CID mass spectra of the $[M+H]^+$ ions of compounds **5** and **6** show product ions of *m/z* 123 (Table 1), indicating that a McLafferty-type rearrangement occurs when the number of CH_2 groups is increased to three or four.

CONCLUSIONS

The investigation of six carbonyl compounds that are amides of nicotinic acid and picolinic acid demonstrates that McLafferty-type rearrangements are possible in low-energy $[M+H]^+$ ions of carbonyl compounds. The reaction is essentially a charge remote process and the pyridine ring is important for keeping the positive charge in a suitable position remote from the carbonyl group. DFT calculations show that the TS energy for the 1,5-H shift is lower for the amides of the 1-phenylethylamine than for the amides of 2-phenylethylamine.

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