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The mass spectrometric behaviour of fluorinated ephedrines under different protonating conditions

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Abstract

The behaviour of di- and tri-fluorinated-ephedrines and -norephedrines has been studied by fast atom bombardment, atmospheric pressure chemical ionisation (APCI) and electrospray ionisation (ESI) experiments and compared with that of the unfluorinated analogues. Under all the employed ionisation conditions $[MH]^+$ and $[MH-H_2O]^+$ species are mainly produced. Both high- and low-energy collisional experiments were performed on the protonated molecules to put in evidence any possible significant differences due to different ionisation methods. Multiple MS/MS experiments, performed by ion trap, allowed establishment of the decomposition pathways at lower activation energy. The data thus obtained indicate that the presence of fluorinated substituents leads to a higher stability of the molecular species, with strengthening of the C(1)–C(2) bond of the molecule and with a lower proclivity to thermally-induced dehydration.

Keywords: Ephedrines; Fluorinated ephedrines; Mass spectrometry; Ionization methods

1. Introduction

It is well known that introduction of fluorine into natural or bioactive molecules does often bring about remarkable modification and improvement of the biomedicinal properties [1–4]. Many molecules containing the phenylethanolamine scaffold have a key biological role, acting as neurotransmitters and displaying a number of pharmacological actions at the central nervous system (CNS) level. However, relatively little is known concerning the biomedicinal features of fluorinated phenylethanolamines, in spite of the fact that 'in no other area of medicinal chemistry has the presence of fluorine made as profound an impact as in the treatment of disorders of the CNS' [5]. Most of the existing studies have been devoted to the medicinal chemistry of catecholamines, such as dopamine, norepinephrine and epinephrine, fluorinated on the aromatic ring [6]. Important studies and applications of ^{18}F ring-labelled catecholamines for positron emission tomography (PET) in the neurosciences (brain and heart) are also extant [7]. 3-Fluoromethyl-tetrahydroisoquinolines [8] and β-difluoromethamphetamines [9] are among the few examples of fluoroalkyl analogues of phenylethanolamines which can be found in the literature. We have recently disclosed the stereoselective synthesis of previously unknown di- and tri-fluorinated ephedrines [3,3-difluoro- and 3,3,3-trifluoro-2-methylamino-1-phenyl-propane-1-ol (compounds **3** and **4**, respectively)] [10] and -norephedrines [3,3-difluoro- and 3,3,3-trifluoro-2-amino-1-phenyl-propane-1-ol (compounds **5** and **6**, respectively)] [11], which are synthetic analogues of the natural pharmacologically relevant ephedra-alkaloids (compounds **1** and **2**). Within the frame of a research project aimed at the study of the biological and physical–chemical features of these novel compounds, we now report a mass spectrometric study.

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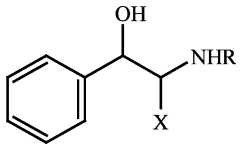


Number	Name	R	X
1	2-methylamino-1-phenyl-propane-1-ol (ephedrine)	CH_3	CH_3
2	2-amino-1-phenyl-propane-1-ol (norephedrine)	H	CH_3
3	3,3-difluoro-2-methylamino-1-phenyl-propane-1-ol	CH_3	CHF_2
4	3,3,3-trifluoro-2-methylamino-1-phenyl-propane-1-ol	CH_3	CF_3
5	3,3-difluoro-2-amino-1-phenyl-propane-1-ol	H	CHF_2
6	3,3,3-trifluoro-2-amino-1-phenyl-propane-1-ol	H	CF_3

Ephedrines, due to their pharmacological relevance, have been the object of many mass spectrometric investigations. Electron ionisation (EI) showed some limitations in the characterisation of this class of compounds, mainly due to their low volatility [12–14].

Diasteroisomeric and enantiomeric ephedrines have been characterised by gas chromatography combined with electron impact and chemical ionisation mass spectrometry. For this purpose *N*-acetyl *O*-trimethylsilyl derivatives were employed for the differentiation of diasteroisomeric hydroxyamines (ephedrine and ψ-ephedrine), while for enantiomers conversion into *N*(*R*)-α-phenylbutyryl *O*-trimethylsilyl derivatives was effective [15]. Under positive ion chemical ionisation (isobutane) conditions, abundant protonated molecules of the ephedrine derivatives were obtained.

The detection of the protonated molecules of underivatised ephedrines has been obtained by soft ionisation methods, field desorption and field ionisation, leading to the production of abundant protonated molecules MH^+, practically without any activation of decomposition channels [16].

Nowadays, new ionisation methods, electrospray ionisation (ESI) [17,18] and atmospheric pressure chemical ionisation (APCI) [19], have became available and more and more present in the pharmaceutical and biomedical laboratories. In order to make the possible uses of these ionisation techniques confident on their validity in solving structural problems, we thought it of interest to undertake an investigation of the behaviour of the new fluorinated derivatives **3**–**6**, compared with those of ephedrine (**1**) and norephedrine (**2**), based on the comparison of the results obtained by fast atom bombardment (FAB) [20], ESI and APCI, and we report and discuss here the results so achieved.

2. Experimental

FAB [20] mass spectra and Mass analysed ion kinetic energy (MIKE) [21] spectra of the FAB-generated protonated molecules of ephedrines were obtained using an AutoSpecQ mass spectrometer (Micromass, Manchester, UK), using Cs^+ ion bombardment (30 keV) ionisation and *m*-nitrobenzyl alcohol as matrix. The MIKE spectra were obtained by scanning the voltage of the second electric sector. Collisionally induced decomposition (CID) [22] MIKE spectra of MH^+ ions were obtained by introducing the collision gas (Ar) into the MIKE collision cell. In CID measurements the main beam of MH^+ ions was attenuated by 50% using the collision gas.

The APCI [19] mass spectra were obtained by using a TSQ 7000 triple-stage quadrupole mass spectrometer (Finnigan MAT, San Jose, CA, USA) in the positive ion mode. The APCI vaporiser was operated at 450 °C with a heated capillary temperature of 175 °C. The mass spectrometer was programmed to transmit the precursor ions through the first quadrupole to the central octapole, where the ions underwent collision-induced fragmentation, to the second quadrupole, where the product ions were analysed. A collision gas (Ar) pressure of 2 mTorr (1 Torr = 133.3 Pa) was employed and the collision offset was 20 V. The mass spectrometer was tuned to a peak width (measured at half height) of 1 *m*/*z* unit, and the API parameters were optimised for maximum sensitivity.

Electrospray ionisation (ESI) [17,18] experiments were performed using a LCQ instrument (Finnigan MAT) operating in positive ion mode. Samples were introduced by direct injection of their 10^{-6} M solutions. The ions were produced using a spray voltage, capillary voltage and capillary temperature of 4–5 kV, 3.7 V and 200 °C, respectively.

Samples **1** and **2** were purchased from Sigma (St. Louis, MO, USA); samples **3**–**6** were synthesised and purified according to the literature [10,11].

3. Results and discussion

Mass spectrometry is usually considered a powerful analytical technique for either qualitative investigations or quantitative measurements. The former aspect is based on the structural identification by the presence of molecular ion as well as of fragment ions, which are highly diagnostic for the structures present in the molecule.

To privilege the formation of molecular species, 'soft' ionisation methods have been developed, generally leading to protonated molecules. Thus the precursor of the possible fragments observed in the mass spectra originate from protonated species and their formation

can be rationalised much better in terms of molecule stability in acidic media than by the internal energy deposition related to the ionisation phenomenon. Furthermore, to achieve further structural information, MS/MS, privileging decomposition channels at low activation energy, can be successfully employed. These aspects were considered in the present investigation, with the particular aim to put in evidence possible differences between fluorinated and unfluorinated analogues.

The FAB spectra of compounds **1**–**6** are reported in Table 1. They mainly comprise two high-abundance peaks, corresponding to the protonated molecules and to $[MH-H_2O]^+$ species. Only in the case of compound **1** an abundant peak at *m/z* 58, corresponding to $CH_3–CH=N^+H–CH_3$ ions originating by cleavage in the β position to the nitrogen atom was detected. The analogous ions $X–CH=N^+H–R$ were undetectable for all the other compounds.

The primary water loss could indicate that the protonation has taken place on the hydroxyl oxygen atom. Proton affinity data would indicate that protonation would occur on the nitrogen atom (as an example the PA values of 2-propanol, 2-propanamine and diethylamine are 800.2, 900.3 and 925.0 kJ mol^{-1}, respectively) [23]. On the basis of molecular geometry, just by a survey with Cochranes (Oxford, UK) molecular building system, it appears that the distance between the proton attached to the nitrogen atom and the oxygen atom is of the order of 1.1 Å, indicating a possible easy interaction (intramolecular hydrogen bridging). In this case, for the water loss, the mechanism reported in Scheme 1 could be proposed. However, the direct protonation on the hydroxyl group cannot be excluded, considering that the protonation can be kinetically controlled.

Apart from the formation of the $CH_3–CH=N^+H–CH_3$ ions observed for **1** only, the FAB spectra do not show any differences between the behaviour of fluorinated versus unfluorinated compounds. In order to investigate possible differences the unimolecular MIKE spectra of FAB-generated MH^+ species were recorded. These show only the peak corresponding to $[MH-H_2O]^+$ species, and are not useful to identify specific fragmentation processes. Consequently high-energy collisional experiments were undertaken on the MH^+ ions of **1**–**6**. The CID MIKE spectra of MH^+ ions show the presence of many decomposition products whose likely structures are reported in Scheme 2. The most abundant fragment ion (***a***) is due to the primary water loss; the ion $[M-19]^+$, originating by sequential losses of $H^\bullet$ and H_2O (or vice versa) which was detected and discussed in the case of the EI mass spectrometry of ephedrine [12–14], is completely absent under the experimental conditions employed in the present investigation, as expected for an even-electron precursor ion. Other primary decomposition routes originate in the cleavages **1** and **2** reported in Scheme 2.

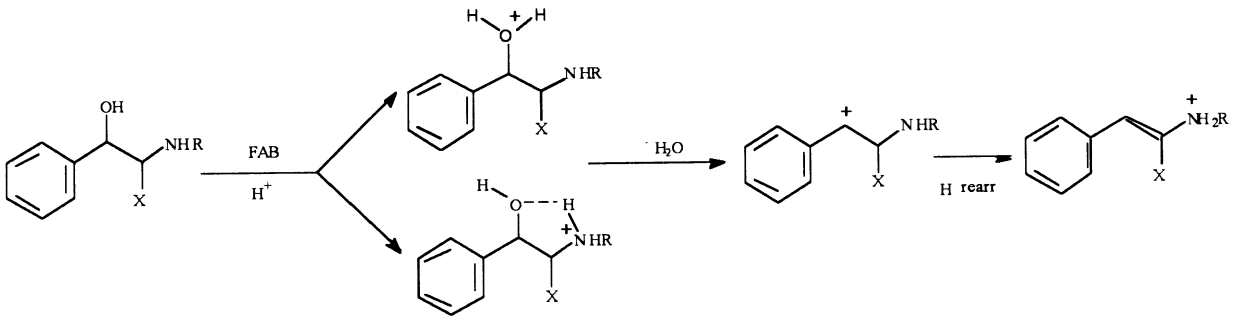
The ions ***b***, which were detected in the FAB spectra of **1** only, are present in the CID MIKE spectra of all the compounds. Their abundance is higher for unfluorinated compounds **1** and **2**, indicating that the presence of a fluorine-containing substituent X leads to a strengthening of the C–C bond implicated in this decomposition pathway. This is in agreement with reports in the literature that fluorination has a pronounced characteristic effect on adjacent bond strengths [24].

Ion ***a*** further decomposes through $X^\bullet$ loss giving rise to ions ***c*** (see Scheme 2). This fragmentation route is an exception to the even electron rule [25], but can be explained by the high stability of the decomposition products ($X^\bullet$ and the odd electron molecular ion of the conjugated structure reported in Scheme 2). In its turn ion ***c*** decomposes through $R^\bullet$ loss with and without H rearrangement, giving rise to the ions at *m/z* 118 and 117, already described among the EI-induced decomposition products of ephedrines [15]. Sequential losses of two hydrogen fluoride molecules from ion ***a*** are observed only for the fluorinated norephedrine derivatives **5** and **6**.

The spectra obtained under APCI conditions for **1**–**6** show mainly the same ions as those observed under FAB conditions, i.e. MH^+ and $[MH-H_2O]^+$. However, some minor peaks are also detectable at *m/z* 117 for **1** and **2**, 162 and 118 for **3**, 118 for **4** and 148 for **5** (see Table 2). It is worth noting that, while under FAB conditions the relative abundances of the $[MH-H_2O]^+$ ions were of the same order of magnitude for all the compounds, (in the range 26–57%), in the case of APCI measurements a clear difference is observed between unfluorinated (**1** and **2**) and fluorinated (**3**–**6**) derivatives. In fact for the former the relative abundance of

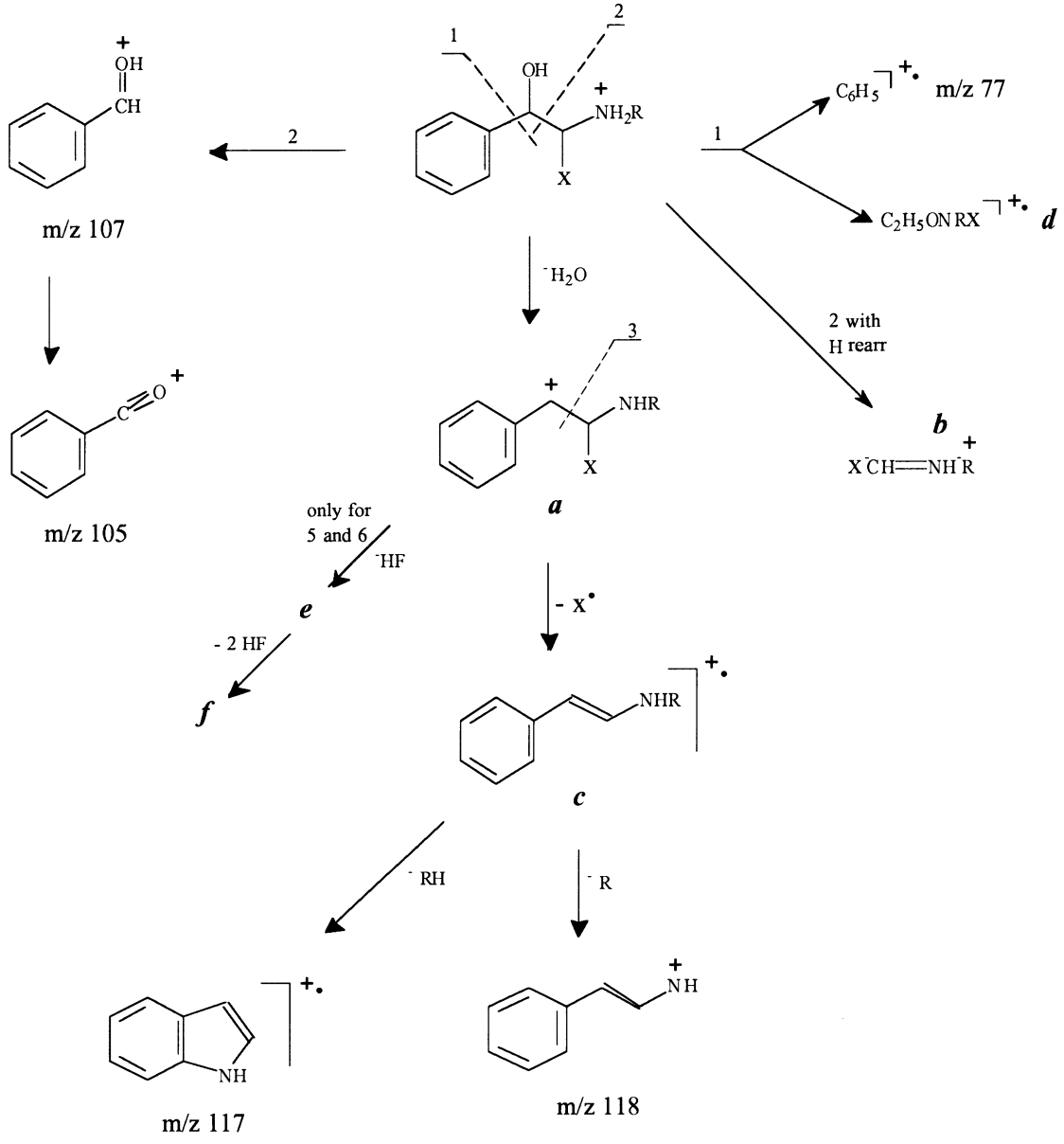
Table 1
FAB mass spectra ions of compounds **1**–**6**

Ionic species	1	2	3	4	5	6
MH^+	166 (100)	152 (100)	202 (100)	220 (100)	188 (100)	206 (100)
$[MH-H_2O]^+$	148 (26)	134 (41)	184 (35)	202 (57)	170 (40)	188 (35)
$X–CH=N^+H–R$	58 (80)					



Scheme 1.

$[MH-H_2O]^+$ ions is 44 and 57%, while for the latter it is in the range 6–8%. This result cannot be ascribed to a lower, intrinsic stability of the protonated molecule of **1** and **2** because, if this were the case, analogous behaviour would be observed also under FAB conditions. Considering the experimental set-up for APCI experiments,



Scheme 2.

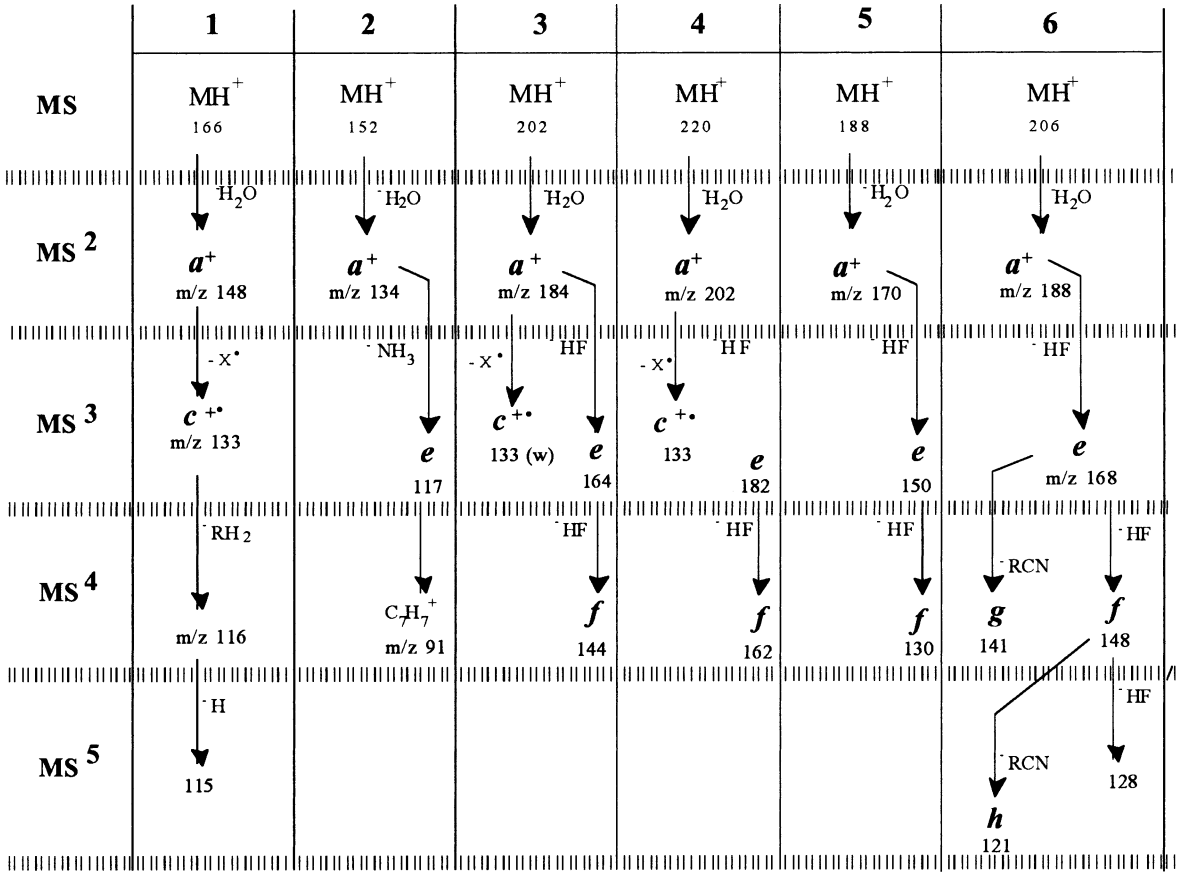
Table 2
APCI mass spectra ions of compounds **1**–**6**

Ionic species	**1**	**2**	**3**	**4**	**5**	**6**
MH^+	166 (100)	152 (100)	202 (100)	220 (100)	188 (100)	206 (100)
$[MH-H_2O]^+$	148 (44)	134 (57)	184 (6)	202 (8)	170 (8)	188 (8)
$[MH-2HF]^+$			162 (9)		148 (5)	
$[c\text{-R}]^{+\bullet}$			118 (3)	118 (1)		
$[c\text{-RH}]^{+\bullet}$	117 (1)	117 (5)				

Table 3
Low-energy MS/MS spectra of MH^+ species generated by APCI

Ionic species		**1**	**2**	**3**	**4**	**5**	**6**
a	$[MH-H_2O]^+$	148 (100)	134 (80)	184 (100)	202 (100)	170 (38)	188 (79)
c	***a***-X$^\bullet$	133 (38)	119 (4)	133 (98)	133 (32)	119 (35)	119 (40)
	c-R$^\bullet$					118 (8)	118 (8)
	c-RH	117 (40)	117 (100)	117 (3)		117 (8)	
b	X–CH=NH–R						
e	***a***-HF			164 (16)	182 (5)	150 (18)	168 (31)
f	***a***-2 HF			144 (96)	162 (8)	130 (100)	148 (73)
g	***e***-RCN				141 (22)		141 (100)

we propose that this different behaviour between **1**, **2** and **3**–**6** must be ascribed to different thermal stabilities of the analysed compounds. Thus compounds **1** and **2** might have undergone a partial, thermally-induced dehydration in the heated region of the APCI source (vaporiser operating at 450 °C).



Scheme 3. MS^n experiments on ESI-generated MH^+ species of **1**–**6** performed by ion trap.

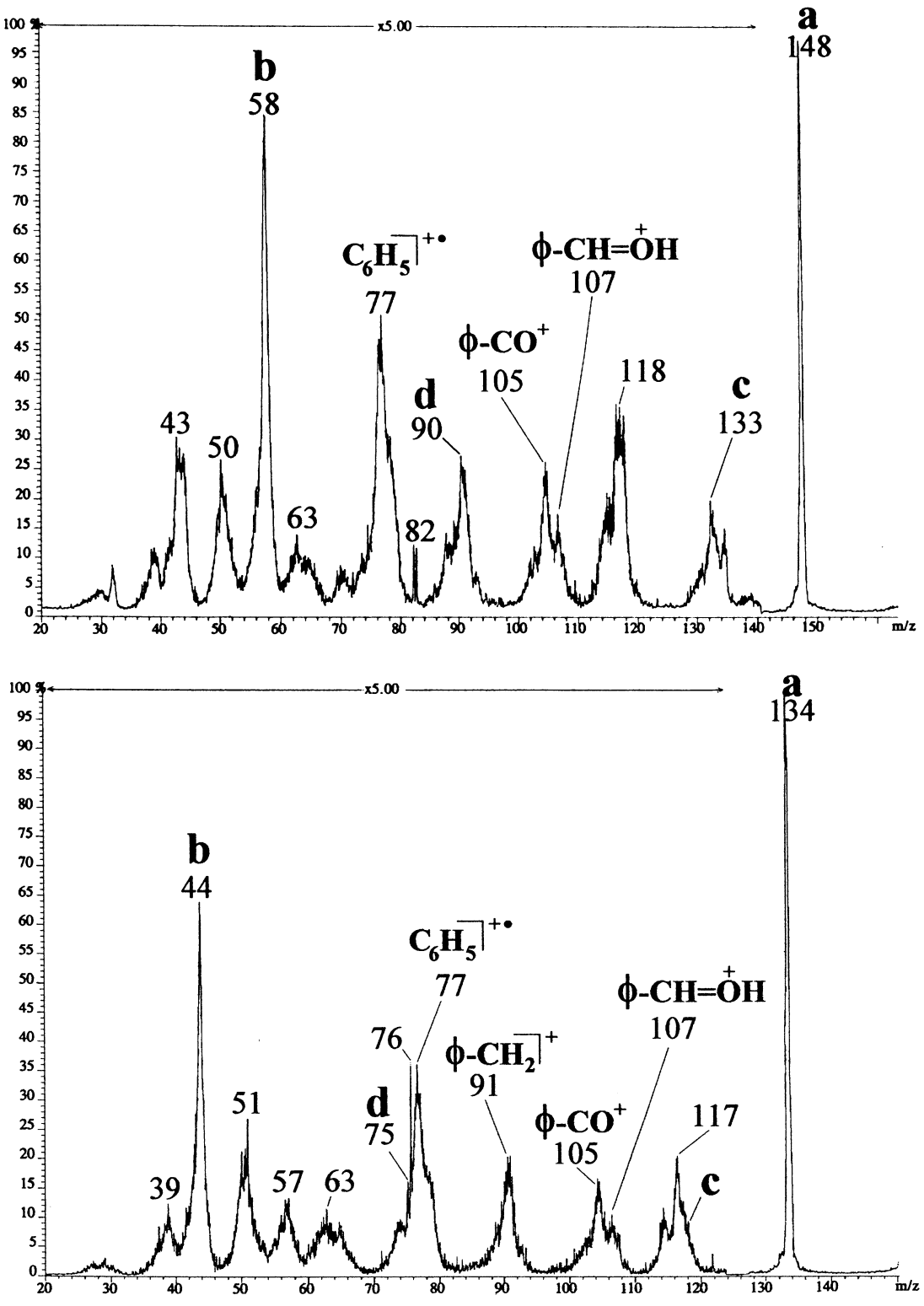


Fig. 1. CID MIKE spectra of MH^+ of compounds **1**(up) and **2** (down) ($\Phi = C_6H_5$).

The low-energy collision spectra of APCI-generated MH^+ species are reported in Table 3; these are similar to some extent to the high-energy spectra described above for the case of the FAB experiments.

Worth noting is the complete absence in the low-energy collision spectra of $X–CH=N^+H–R$ species (ions ***b***), detectable in the high-energy collision spectra and discussed above. The softer conditions of the low-

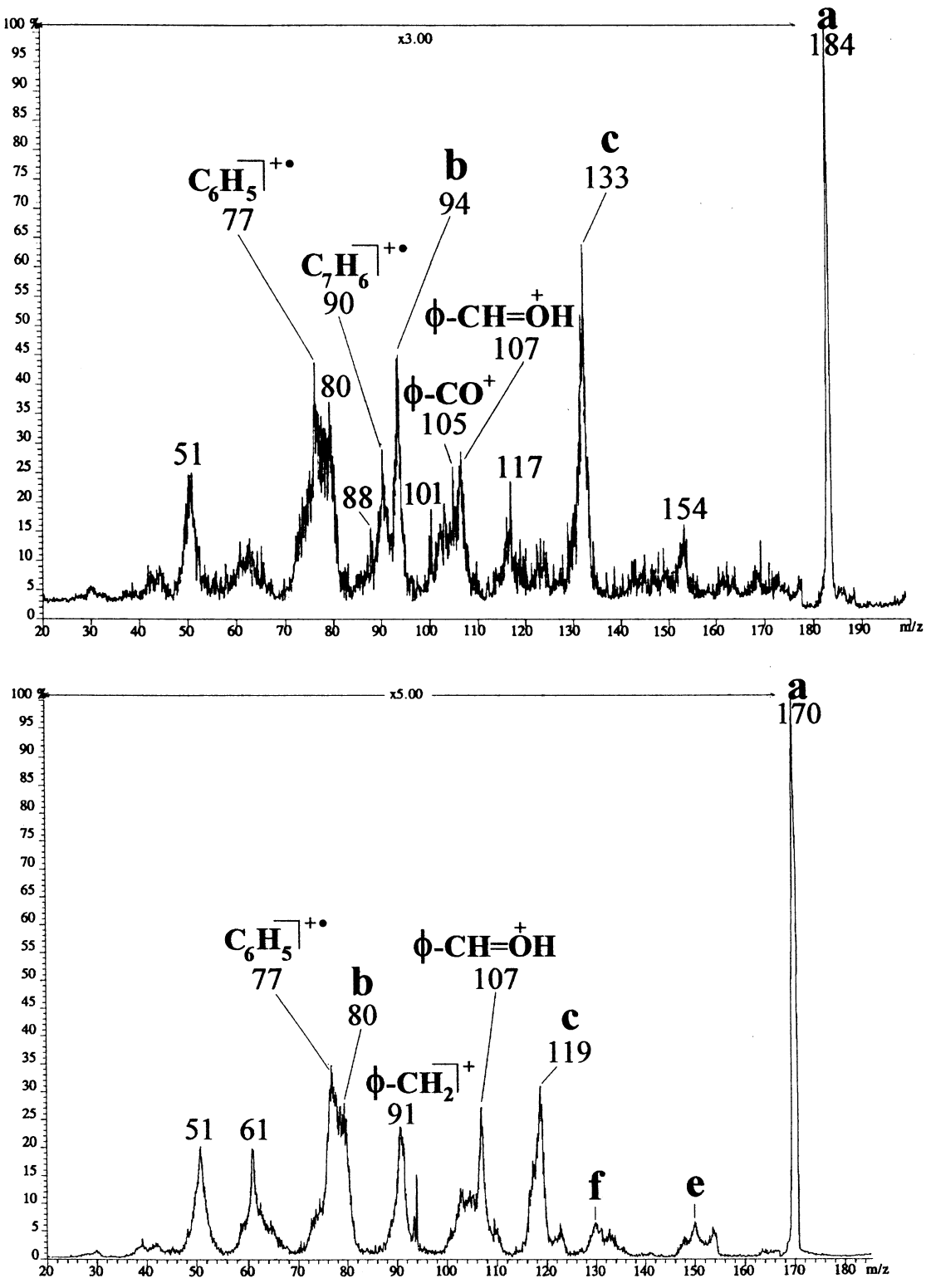


Fig. 2. CID MIKE spectra of MH^+ of compounds **3** (up) and **5** (down) ($\Phi = C_6H_5$).

energy collision experiments do not lead to an internal energy deposition high enough to activate this decomposition process and this result, together with the EI published data [15], is good evidence that the cleavage of the C(1)–C(2) bond is a high-activation energy decomposition process.

In the case of the electrospray measurements the spectra of **1**–**6** consist of MH^+ ions only: the ***a*** ions

which are readily detectable under both FAB and APCI conditions are completely absent in the ESI spectra. Hence collisional experiments in this case are essential to characterise **1**–**6**. By using an ion trap mass spectrometer, capable of MS^n experiments [26], it is possible to follow, step by step, the decomposition patterns of MH^+ ions. This aspect is well depicted by the data reported in Scheme 3. It must be stressed that the collisional experiments performed by ion trap are substantially different from those achieved by sector- or quadrupole-based instruments. In fact, while in the latter cases the internal energy distribution of the ions after collision is quite wide, reflecting the statistics of the collisional phenomena, in an ion trap the energy deposition can be considered as originating from a step-by-step phenomenon, necessarily favouring the decomposition channel(s) at lower critical energy [27].

The only decomposition pathway of the ESI-generated protonated molecules of **1**–**6** consists, under these conditions, of the primary H_2O loss. The alternative decomposition routes observed in the high energy collisions are in this case completely suppressed, proving that the water loss is the most energetically favoured process. The selection of the collisionally generated ***a*** ions and their further collision with He leads to the MS^3 spectra. The $X^\bullet$ radical loss, present for all the compounds in the high- and low-collision energy spectra above described, in this case is observed for compounds **1** and **4** only (in the case of **3** it leads to an extremely low-intensity signal). The MS^3 spectrum demonstrated another peculiar behaviour of **2**, proving that the abundant ion at *m*/*z* 117 originates from ion ***a*** through ammonia loss. All the fluorinated compounds show the sequential losses of two HF molecules from the ion ***a***, leading to ions ***e*** and ***f*** described above (see Table 3). Only in the case of compound **6** did MS^4 and MS^5 spectra indicate RCN losses, leading to ions ***g*** and ***h*** at *m*/*z* 141 and 121, respectively.

In conclusion, the present results can be summarised thus:

i) By FAB, MH^+ represent the most abundant ionic species while the $[MH–H_2O]^+$ ions are generated for all the compounds with similar yields. Only for **1** was there observed an abundant peak at *m*/*z* 58 corresponding to the $CH_3–CH=N^+H–CH_3$ ion, as already described among the EI-generated fragments of ephedrine. The analogous $X–CH=N^+H–R$ species are detectable only by high-energy collisional activation of MH^+ species, and their production is less favoured for the fluorinated derivatives, suggesting that the presence of fluorine leads to a strengthening of the C(1)–C(2) bond.

ii) By APCI, MH^+ still corresponds to the most intense peaks of the spectra, but $[MH–H_2O]^+$ ions are present at higher abundance for the unfluorinated derivatives **1** and **2**. This result may be explained by an easier thermally-induced pre-ionization dehydration of **1** and **2** occurring in the APCI ion source. The absence in low-energy collision spectra of the $X–CH=N^+H–R$ ions indicates that their formation requires high-internal energy precursors.

iii) Using ESI, MH^+ are the only ions produced. Multiple MS/MS experiments, easily obtained by ion trap, and the low-energy deposition typical of collisional experiments performed by ion trap, allow elucidation of the low-internal energy decomposition pathways which, for the fluorinated derivatives, consist of sequential losses of HF from the $[MH–H_2O]^+$ ionic species. Also under these conditions the $X–CH=N^+H–R$ ions are not produced.

The above discussed data show that the newest ionisation techniques, coupled with collision experiments, allow to achieve relevant information on the stability of the protonated molecules. In particular, the comparison of the behaviour of fluorinated and unfluorinated derivatives indicates that the presence of fluorinated substituents lead to a higher stability of the molecular species, due to a strengthening of the C(1)–C(2) bond of the molecules, and to a lower proclivity to thermally induced dehydration (Figs. 1 and 2).

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