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Spectrometric studies and theoretical calculations of some β-ketonitriles

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ABSTRACT

The tautomerism of some β-ketonitriles is investigated by the analysis of their mass spectra and theoretical calculations performed at the MP2/6-31G(d,p) level. The mass spectra of some β-ketonitriles can provide valuable information regarding the keto-enol and nitrile-ketenimine equilibria taking place in the gas phase. The predictive value of this methodology is supported by the influence of the nature and size of substituents on tautomeric equilibria and the rather good correlation existing between the abundance ratios of selected fragments. Results show that the tautomeric equilibria of these bifunctional compounds can be evaluated by mass spectrometry.

1. Introduction

β-Ketonitriles constitute an important class of difunctional intermediates for the synthesis of many heterocycles, including dihydropyrans and dihydrothiopyrans [1], pyrazoles [2], pyrimidines [3], pyridones [4], quinolines [5], aminopyrazoles [6], aminoisoxazoles [7] and imidazoles [8] while decyanation provides ketones [8]. On the other hand, benzoylacetonitrile and its monofluoro analogues have been found to be effective inhibitors of adjuvant-induced arthritis in rats [9]. β-Oxopropionitriles having an α-carbonyl or thiocarbonyl substituent are reported as anti-inflammatory and antibacterial agents [10] and the α-aryl-β-ketonitriles constitute synthetic intermediates in the preparation of a series of biologically important molecules such as corticotrophin realizing factor (CRF) receptor antagonist [11]. In this respect, the diversity of the β-ketonitriles available significantly impacts the range of structures which can be accessed.

The reactivity of β-ketonitriles is related to their structure and their tautomeric equilibria; that is why it should be useful to determine the spectral behavior in order to study their tautomeric distribution. Some studies have been carried out by IR, UV and NMR spectrometries using solvents of different polarity. Aprotic solvents, like DMSO and pyridine, generally favor the enol forms [12].

Arndt et al. using the bromometric method established the enol content of 3-oxo-3-phenylpropanenitrile [13]. Bañkowska and coworker studied the influence of the substituents on the ability of enolization [14]. These results were confirmed by Russell and coworker [15] IR spectra in Nujol solution show that the enol form occurs exclusively, while in CCl_4 and $CHCl_3$ both tautomeric forms are present [16]. Measurements by UV indicate that in hydroxylic solvents the spectra show wavelength bands of high intensity corresponding to the conjugated system of the double bonds of the enol forms, those bands do not occur in the spectra taken in cyclohexane solutions. ^{1}H NMR spectra in chloroform-d_1 show the keto form and one of the possible enols; in DMSO-d_6 solutions two stereoisomeric enol forms are observed. Acidity constants were determined for the different tautomeric forms thus concluding that Z-enols are considerably more acidic than E-enols, which can be explained by a planar configuration of E-enols, which are, therefore, thermodynamically more stable than Z-enols [16].

Previous studies by mass spectrometry have examined the effect of the nature of substituents on the tautomerism of 5-triazinones in gas phase [17]. Other compounds like 2,4-hidroxyquinolines were also studied by this technique [18]. Studies on the heats of formation of keto-enol tautomers of carbonyl compounds were conducted on ions produced in the gas phase [19].

In this work, experimental evidence for the occurrence of the different tautomers of β-ketonitriles in gas phase by mass spectrometry is presented. The analysis of the corresponding spectra is done by assigning ion fragments to specific tautomers. The predictive value of this methodology is further supported by the influence of the substitution nature on the tautomeric equilibrium.

2. Results and discussion

In order to evaluate the occurrence of the different tautomeric equilibria mass spectra of 3-oxo-2-phenylbutanenitrile

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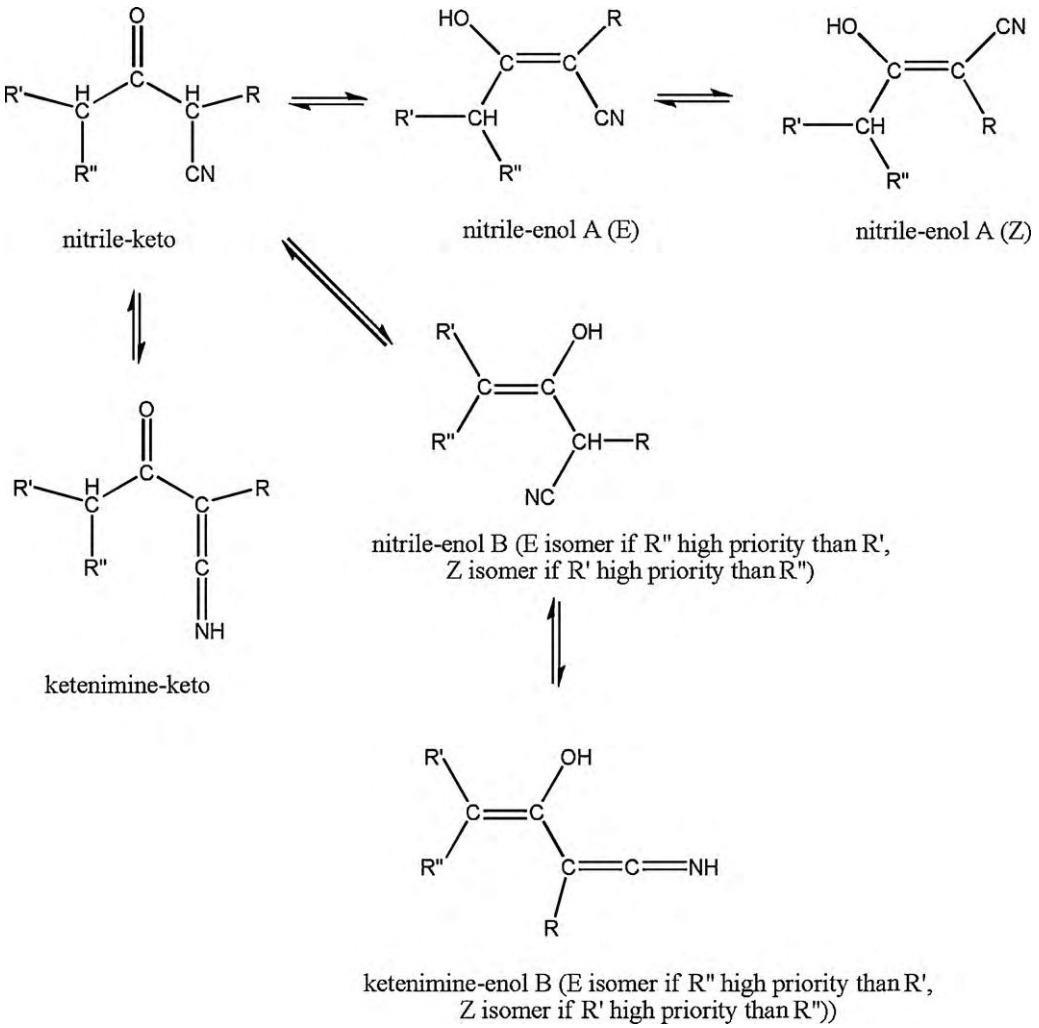


Scheme 1.

(**I**), 2,4-diphenyl-3-oxobutanenitrile (**II**), 2-methyl-3-oxo-4-phenylbutanenitrile (**III**), 2-(4-methoxyphenyl)-3-oxobutanenitrile (**IV**), 2-(4-methoxyphenyl)-3-oxo-4-phenylbutanenitrile (**V**) and 2-(4-chlorophenyl)-3-oxobutanenitrile (**VI**) (Table 1) were analyzed.Scheme 1 shows the possible tautomeric equilibria.

For the nitrile-enol form the Z isomer (Scheme 1) has not been considered since it has already been demonstrated that the isomer E is thermodynamically more stable [20] due to its lower dipolar and steric interaction and the absence of hydrogen bonds that might favor the Z isomer occurrence.

This is demonstrated by theoretical calculations performed at the MP2/6-31G(d,p) level realizing a frequency analysis in order to check if the optimized geometry is in the minimum as shown in Table 2 which includes all possible tautomers. These data are consistent with the highest stability assigned to the nitrile-keto form followed by the E isomer of the nitrile-enol A tautomer. During the discussion of fragmentation assignments, bold letters are used for the most likely tautomeric forms among those which can be considered as candidates for the formation of a particular fragment ion.

Fig. 1 shows the mass spectrum for 3-oxo-2-phenylbutanenitrile (**I**).

The ions at m/z 144 (methyl loss by α rupture) and m/z 116 (Scheme 2(a)) and those corresponding to the aromatic moiety (including the ions at m/z 89 and 90) can be justified from three tautomeric forms: **nitrile-keto**, **nitrile-enol A** and ketenimine-keto. The peak at m/z 117 can come from the **nitrile-keto**, ketenimine-keto, ketenimine-enol or nitrile-enol B forms, but not from nitrile-enol A (Scheme 2(b)) but also from the ketenimine to further fragment and form the ion at m/z 101 (Scheme 2(c)).

The ion at m/z 43 can be justified from the **nitrile-keto**, ketenimine-keto and ketenimine-enol tautomers (Scheme 2(d)). In each fragmentation pathway indicates the relative energy of the process.

The peak at m/z 142 $(M-OH)^+$ could be assigned to any **enol** form (nitrile or ketenimine). The m/z 133 $(M-CN)^+$ could be assigned

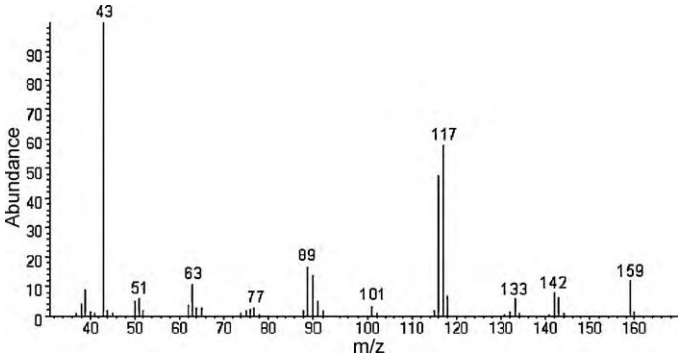
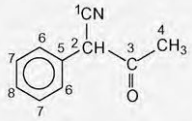
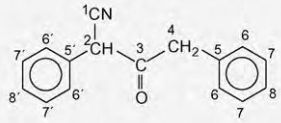
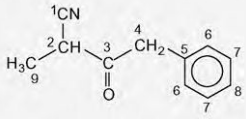
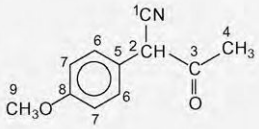
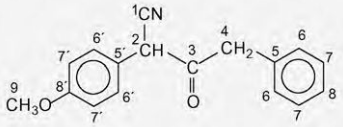
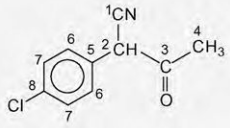


Fig. 1. Mass spectrum of 3-oxo-2-phenylbutanenitrile (**I**).

Table 1
Structure of selected β-ketonitriles.

Compound	Structure
3-Oxo-2-phenylbutanenitrile (**I**)	
2,4-Diphenyl-3-oxobutanenitrile (**II**)	
2-Methyl-3-oxo-4-phenylbutanenitrile (**III**)	
2-(4-Methoxyphenyl)-3-oxobutane nitrile (**IV**)	
2-(4-Methoxyphenyl)-3-oxo-4-phenyl butanenitrile (**V**)	
2-(4-Chlorophenyl)-3-oxobutanenitrile (**VI**)	

to **nitrile** form (keto or enol), although the fragmentation pathway shown in Scheme 3 involving the nitrile-enol B form (less likely according to Table 1) would give a reasonable mechanistic explanation.

The ion at *m*/*z* 132 $(M-CHN)^{+\bullet}$ could be assigned to any **nitrile** form after hydrogen rearrangement. The fragment at *m*/*z* 131 $(M-28)^{+}$ could be rationalized as the loss of the radical HCNH from a **ketenimine** form. Loss of CO through some sort of rearrangement could be a possible explanation as well (assignable to any **keto** form). A more clear indication of the ketenimine form would be the observation of a fragment formed by the loss of 16 amu (NH_2) from the molecular ion. It can be seen that the loss of methyl (alpha rupture) is more likely to occur from keto form (ΔE 52.94 kcal/mol vs. 104.4 kcal/mol for the enol form).As shown in Scheme 2(b) H rearrangement is favored in the case of the enol form (16.6 kcal/mol for the keto form, 12.5 kcal/mol for the enol form and 6.25 kcal/mol for the ketenime form).

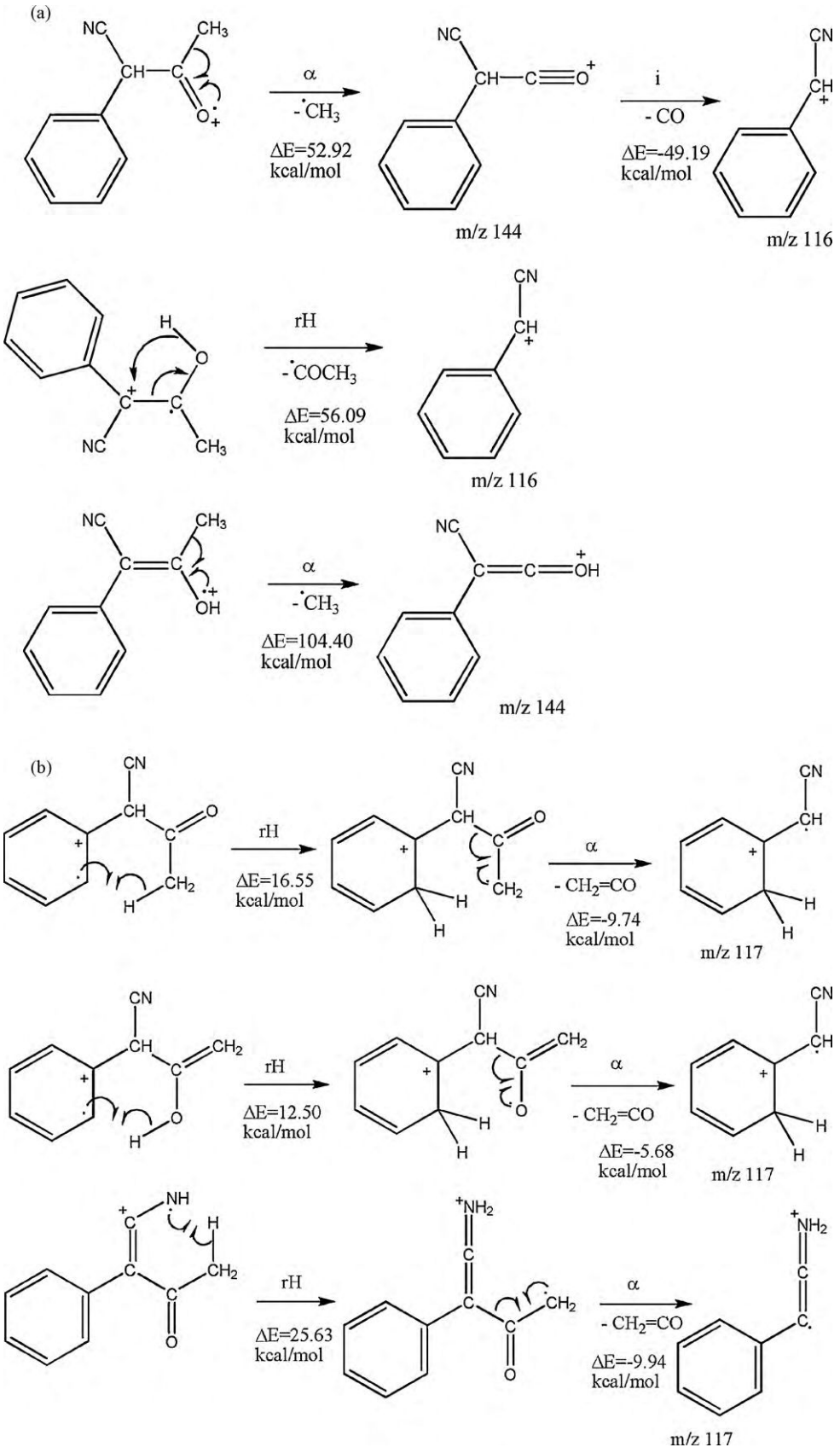
Fig. 2 shows the mass spectrum for 3-oxo-2-phenylbutanenitrile (**I**) after H/D exchange (CH_3OD). Experiments done with CH_3OD (Fig. 2) show that part of the ion at *m*/*z* 116 is shifted to *m*/*z* 117, and part of that one at *m*/*z* 117 shifts to *m*/*z* 118, which supports the fragmentation pathways in as shown in Scheme 2. The ion at *m*/*z* 133 $(M-CN)^{+}$ assignable to the nitrile-enol A form shows up as the ions at *m*/*z* 133 (159-CN), 134 (160-CN) and 135 (161-CN).

No shift is observed for the peak at *m*/*z* 101. Ions at *m*/*z* 144 $(159\text{-}H_2O)^{+\bullet}$; $(160\text{-}HDO)^{+\bullet}$; *m*/*z* 143 $(161\text{-}OD)^{+}$ and *m*/*z* 142 $(161\text{-}HDO)^{+\bullet}$, $(159\text{-}OH)^{+}$, $(160\text{-}OD)^{+}$ can be observed. The fact that the ion at *m*/*z* 144 shifts to *m*/*z* 145 indicates a methyl loss from the nitrile-enol A form or from the nitrile-keto form by considering that the C-2 hydrogen was exchanged.

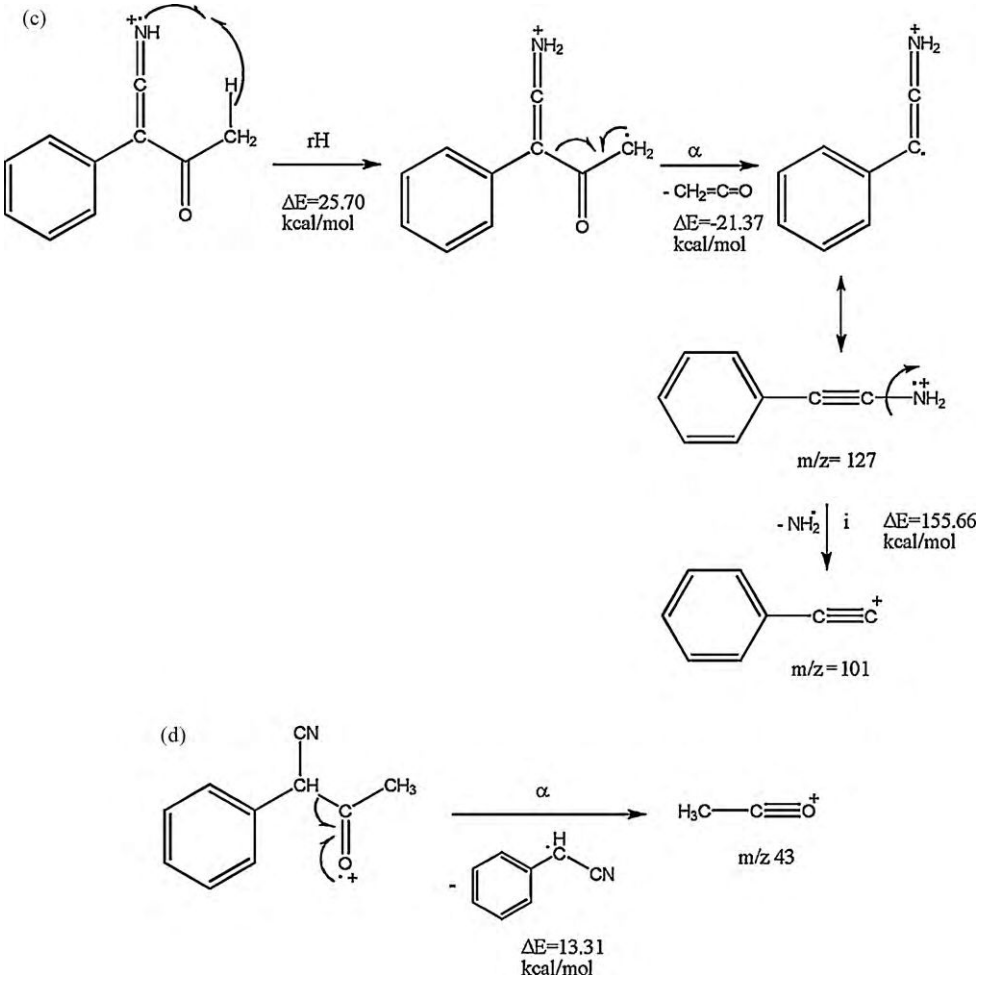
Table 2
Relative energies for the tautomers of selected β-ketonitriles by theoretical calculations (MP2/6-31G(d,p) level).[a].

Compound	Nitrile-enol A		Nitrile-enol B		Ketenimine-keto	Ketenimine-enol	
	E	Z	E	Z		E	Z
I	5.87	7.55	16.24		21.98	41.13	
II	4.34	12.37	10.89	9.43	22.30	38.66	53.71
III	3.10	20.26	10.36	13.13	20.26	36.42	34.21
IV	5.98	7.74	16.01		21.96	41.54	
V	4.81	6.63	13.51		22.05	38.09	35.87
VI	5.06	7.13	16.33		21.53	40.18	

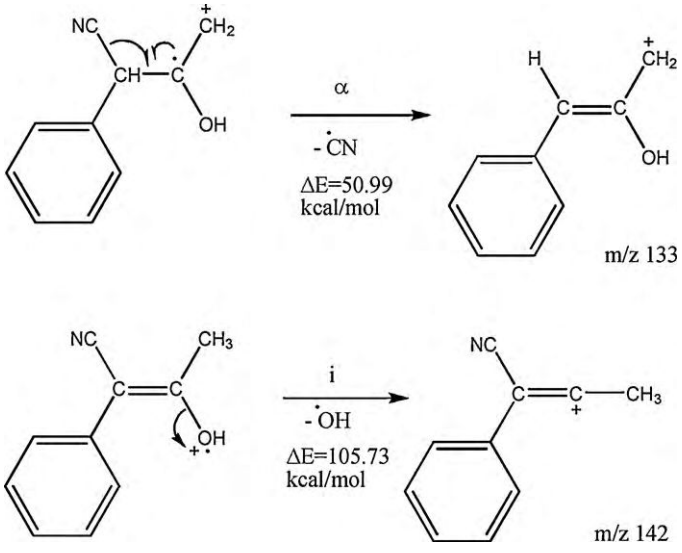
[a] Energies in kcal mol^{-1} are relative to the corresponding nitrile-keto tautomers. Calculations were performed by Gaussian 03.


(a)
α
- ·CH3
ΔE=52.92 kcal/mol
m/z 144
i
- CO
ΔE=-49.19 kcal/mol
m/z 116
rH
- ·COCH3
ΔE=56.09 kcal/mol
m/z 116
α
- ·CH3
ΔE=104.40 kcal/mol
m/z 144
(b)
rH
ΔE=16.55 kcal/mol
α
- CH2=CO
ΔE=-9.74 kcal/mol
m/z 117
rH
ΔE=12.50 kcal/mol
α
- CH2=CO
ΔE=-5.68 kcal/mol
m/z 117
rH
ΔE=25.63 kcal/mol
α
- CH2=CO
ΔE=-9.94 kcal/mol
m/z 117

Scheme 2.



Scheme 2. (*Continued*).



Scheme 3.

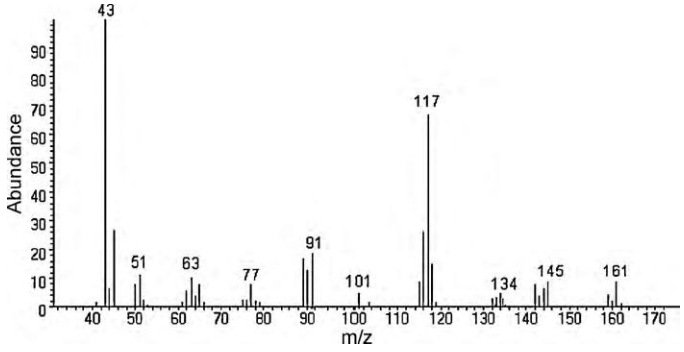
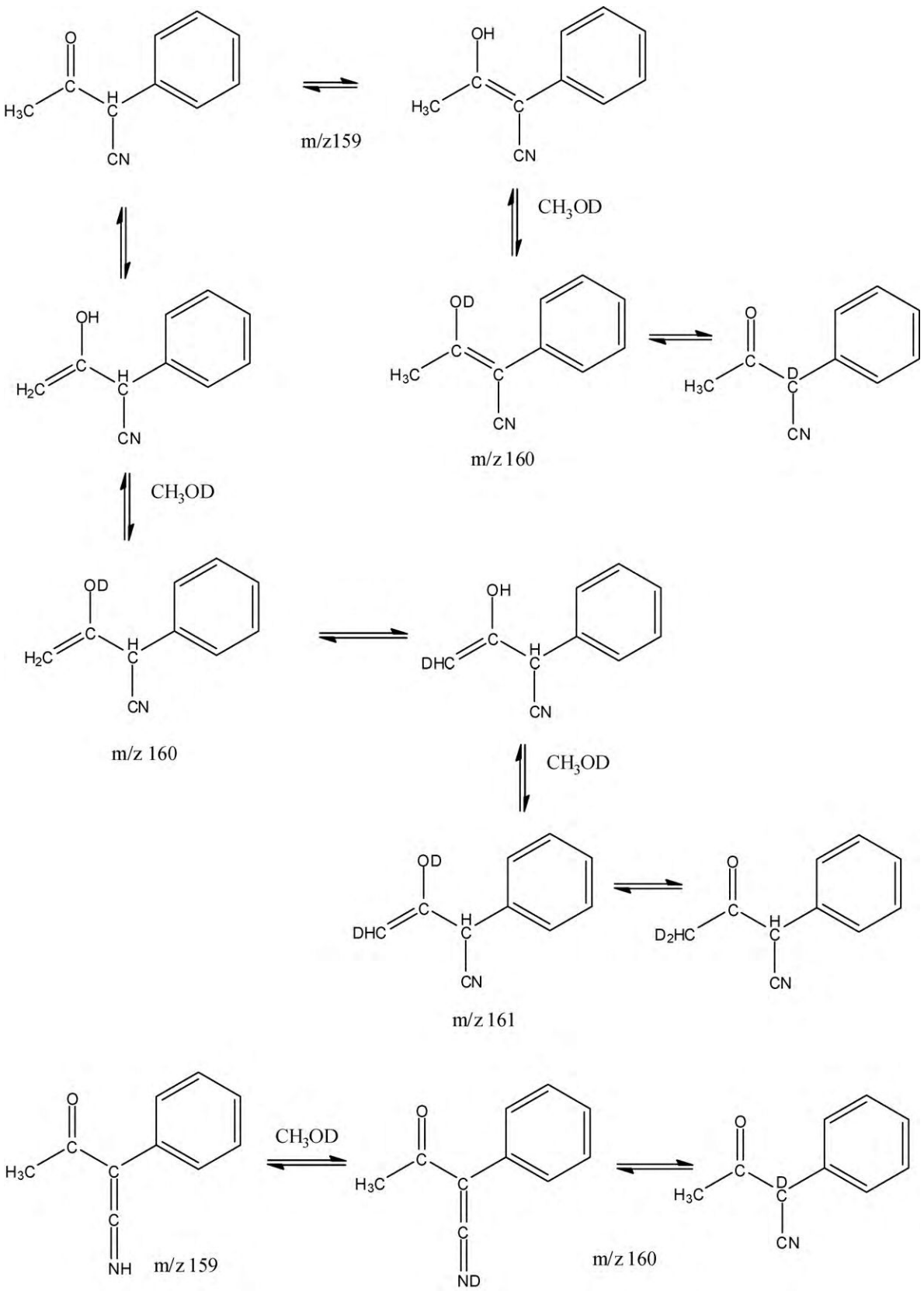


Fig. 2. Mass spectrum of 3-oxo-2-phenylbutanenitrile in CH_3OD (**I**).

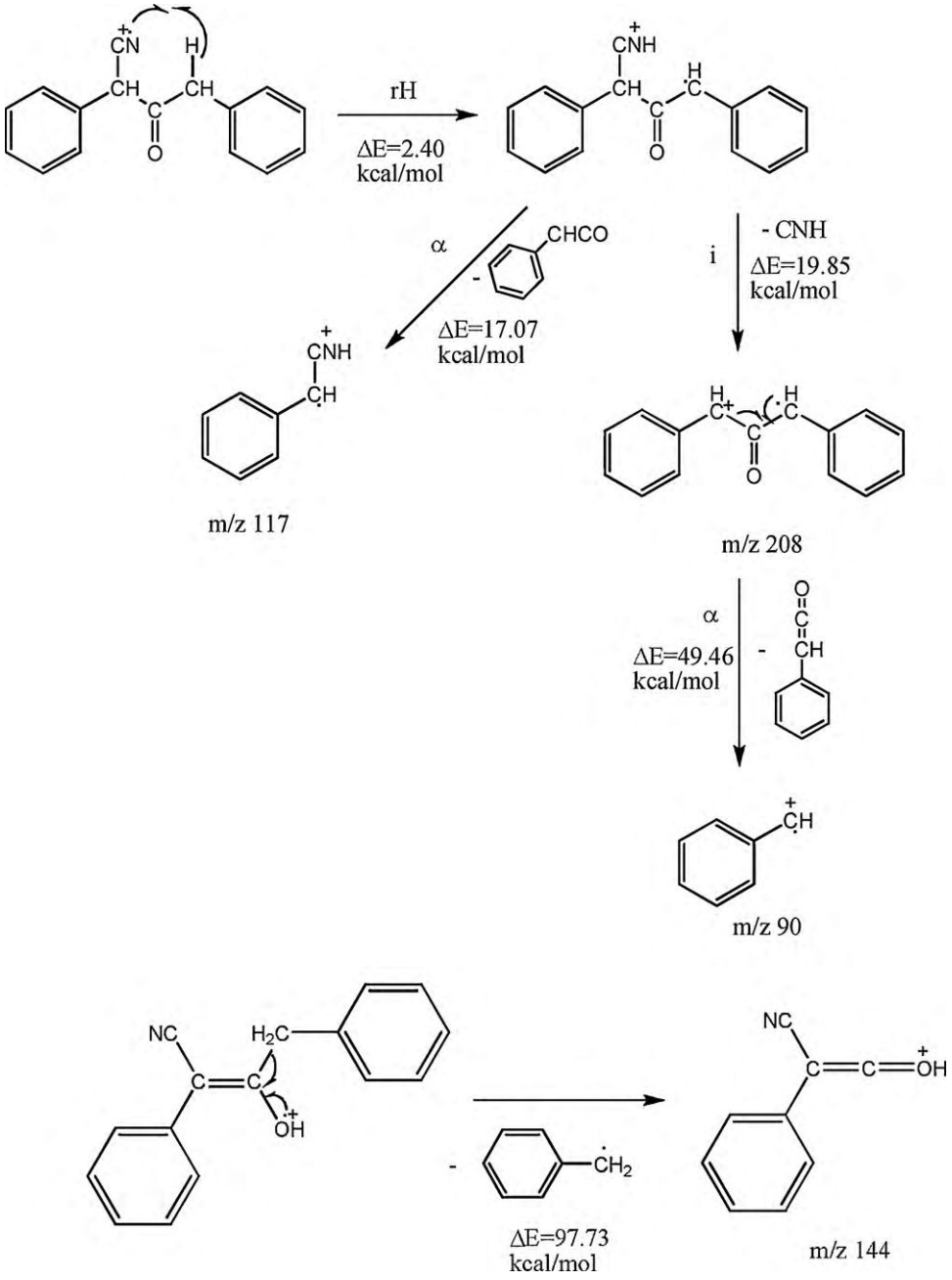
Ions at *m*/*z* 143 $(161\text{-OD})^+$ and *m*/*z* 142 $(160\text{-OD})^+$ can be observed. The fact that the ion at *m*/*z* 144 shifts to *m*/*z* 145 indicates a methyl loss from the **nitrile-enol A** form or from the **nitrile-keto** form by considering that the C-2 hydrogen was exchanged by deuterium. The ion at *m*/*z* 91 indicates that deuteration of the ions at *m*/*z* 89 and 90 has occurred, taking into account that they have exchangeable hydrogen atoms into their structures.

The exchange of two hydrogen atoms by deuterium suggests the occurrence of an additional equilibrium involving the nitrile-enol B as proposed in Scheme 4. This is also observable with the ion at *m*/*z* 45. The ion at *m*/*z* 133 $(M-CN)^+$ assignable to the nitrile forms shows up as the ions at *m*/*z* 133 (159-CN), 134 (160-CN) and 135 (161-CN). The ion at *m*/*z* 132 would be the loss of the radical HCND. Fig. 3 shows the mass spectrum for 2,4-diphenyl-3-oxobutanenitrile (**II**).

The peaks at *m*/*z* 208, 144 and those corresponding to the aromatic series can be justified from both nitrile-keto and nitrile-enol


m/z159
CH3OD
m/z 160
CH3OD
m/z 160
CH3OD
m/z 161
CH3OD
m/z 159
m/z 160

Scheme 4.



Scheme 5.

A tautomeric forms (Scheme 5). The ion analogue to the *m*/*z* 208 for **I** (*m*/*z* 132) is not significant.

The ions at *m*/*z* 144 and 116 can also be assigned to pathways analogous to those in Scheme 2(a). The fragment ion at *m*/*z* 90 can be only justified from the nitrile-keto form (Scheme 5).

The peaks at *m*/*z* 116, 144 and those corresponding to the aromatic series can be justified from both **nitrile-keto** and **nitrile-enol A** tautomeric forms (pathways analogous to those in Scheme 2(a)). The fragment at *m*/*z* 208 is assigned to the loss of HCN from the molecular ion.

The ion at *m*/*z* 119 can be justified from all the forms with the exception of the nitrile-enol A form (pathway analogous to the one in Scheme 2(c)). The fragment at *m*/*z* 207 (loss of the radical HCNH) seems to represent the occurrence of a **ketenimine** structure.

The base peak corresponds to the very stable tropilium ion (*m*/*z* 91), easily formed from the **keto** forms and the **nitrile-keto A**.

The peak corresponding to the ion at *m*/*z* 117 can be justified according to Scheme 2(b), from the **nitrile-keto**, ketenimine-keto, ketenimine-enol and nitrile-enol B tautomers. The fragment ion at *m*/*z* 101 can be only justified from the ketenimine tautomer (as in Scheme 2(c)).

As for compound **I** the fragment ion at *m*/*z* 209 $(M-CN)^+$ can be assigned to any **nitrile** form, the peak at *m*/*z* 218 $(M-OH)^+$ to any **enol** form (similar to Scheme 3). The ion at *m*/*z* 217 $(M-H_2O)^{+\bullet}$ can be justified by the **nitrile-enol A**, only enol form with rearrangeable hydrogen atoms.

By hydrogen/deuterium exchange experiments with CH_3OD, a behavior similar to the one already reported for (**I**): the ion at *m*/*z* 116 shifts to 117, the ion at *m*/*z* 117 to *m*/*z* 118 (partially); the ion at *m*/*z* 144 partially shifts to *m*/*z* 145. The ions at *m*/*z* 208 and 209 shift to *m*/*z* 210 and 211 and the molecular ion at *m*/*z* 235 to *m*/*z* 236 and *m*/*z* 237 was observed,

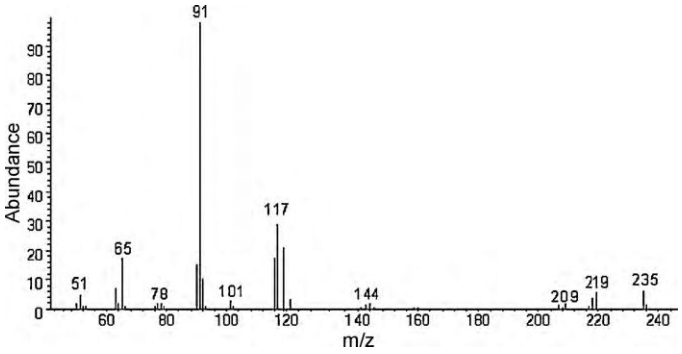


Fig. 3. Mass spectrum of 2,4-diphenyl-3-oxobutanenitrile (**II**).

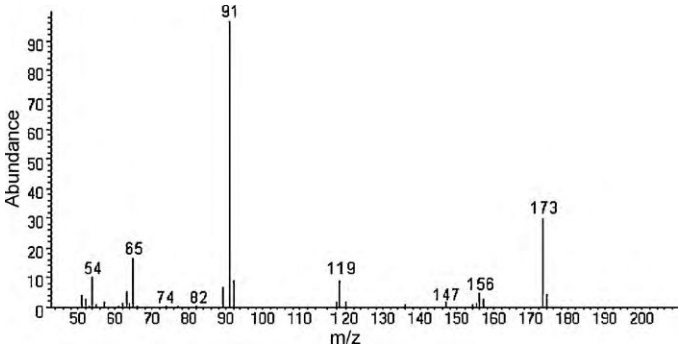


Fig. 4. Mass spectrum of 2-methyl-3-oxo-4-phenylbutanenitrile (**III**).

which indicates that the molecule has undergone double H/D exchange.

Fig. 4 shows the mass spectrum for 2-methyl-3-oxo-4-phenylbutanenitrile (**III**).

The peak at *m*/*z* 119 (similar to the one in Scheme 2(c)) can be justified from all the forms but the nitrile-enol A, while the ion at *m*/*z* 91 (same ion observed for compound **II**) is less likely to be formed from the nitrile-enol B or the ketenimine-enol forms. The low abundant *m*/*z* 82 would correspond to the *m*/*z* 144 of compound **II** (Scheme 2(a)). The ion at *m*/*z* 156 $(M-OH)^+$ and *m*/*z* 147 $(M-CN)^+$ (analogous to those in Scheme 3) can be assigned to different enol forms. It is not surprising to realize that the ion at *m*/*z* 156 is relatively more abundant due to conjugation effects. The peak at *m*/*z* 54 is analogous to the one t *m*/*z* 116 in Scheme 2(b).

Fig. 5 shows the mass spectrum for 2-(4-methoxyphenyl)-3-oxobutanenitrile (**IV**).

The peaks corresponding to the ions at *m*/*z* 174 (methyl loss by α rupture, Scheme 2(a)) and *m*/*z* 162 $(M-HCN)^{+\bullet}$ could be justified from the **nitrile-keto** and **nitrile-enol A** tautomers.

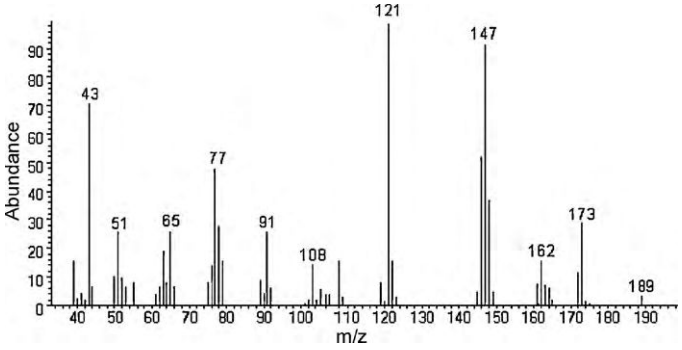


Fig. 5. Mass spectrum of 2-(4-methoxyphenyl)-3-oxobutanenitrile (**IV**).

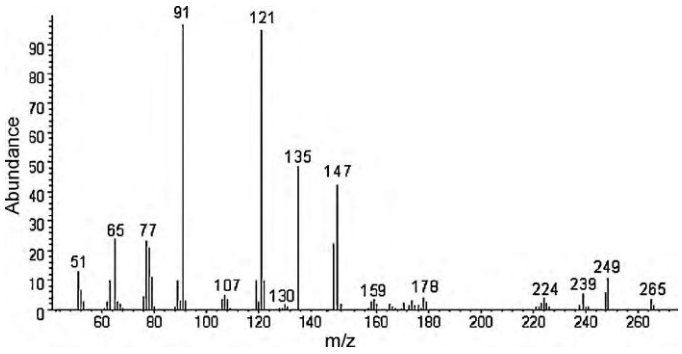


Fig. 6. Mass spectrum of 2-(4-methoxyphenyl)-3-oxo-4-phenylbutanenitrile (**V**).

The ketenimine-keto tautomer could also justify the methyl loss peak.

The ions at *m*/*z* 43 (Scheme 2(d)), and *m*/*z* 147 (McLafferty rearrangement on the aromatic ring) (analogous to those in Scheme 2(b)) can arise from all the tautomers but the nitrile-enol A. The peak at *m*/*z* 146 $(M-43)^+$ can be assigned to all tautomeric forms.

The fragment ion at *m*/*z* 172 $(M-OH)^+$ could be assigned exclusively to the **enol** forms. The ion at *m*/*z* 163 $(M-CN)^+$ (fragmentation pathways analogous to those in Scheme 4) could be assigned to any **nitrile-enol A** form.

Peaks at *m*/*z* 106–108 arise from the methoxyphenyl moiety and the ion at *m*/*z* 121 represents the corresponding tropilium ion whose formation likely involves the **keto** forms and the **nitrile-enol A** form. The ion at *m*/*z* 161 would indicate the occurrence of a **ketenimine** form (loss of the radical HCNH).

Fig. 6 shows the mass spectrum for 2-(4-methoxyphenyl)-3-oxo-4-phenylbutanenitrile (**V**).

The following assignments could be done: *m*/*z* 250 $(M-CH_3)^+$, to all tautomers; *m*/*z* 248 $(M-OH)^+$ to any **enol** form; *m*/*z* 247 $(M-NH_2)^+$, to the ketenimine form; *m*/*z* 239 $(M-CN)^+$ and *m*/*z* 238 $(M-CNH)^{+\bullet}$, to any **nitrile** *m*/*z* 174 that is analogous to *m*/*z* 144 for **I**, to the **nitrile-keto**, **nitrile-enol A** and ketenimine-keto forms; *m*/*z* 158 $(PhOCH3)^+$, to all tautomers; *m*/*z* 147 (McLafferty), to the **nitrile-keto** and ketenimino-keto forms (Scheme 2); *m*/*z* 146 (loss of CO from the ion at *m*/*z* 174), to the **nitrile-keto** and ketenimine-keto forms; *m*/*z* 121 (tropylium ion with the oxymethyl moiety) to the **keto** forms and the nitrile-enol A forms; *m*/*z* 119 to the **nitrile-keto** and the ketenimine forms.

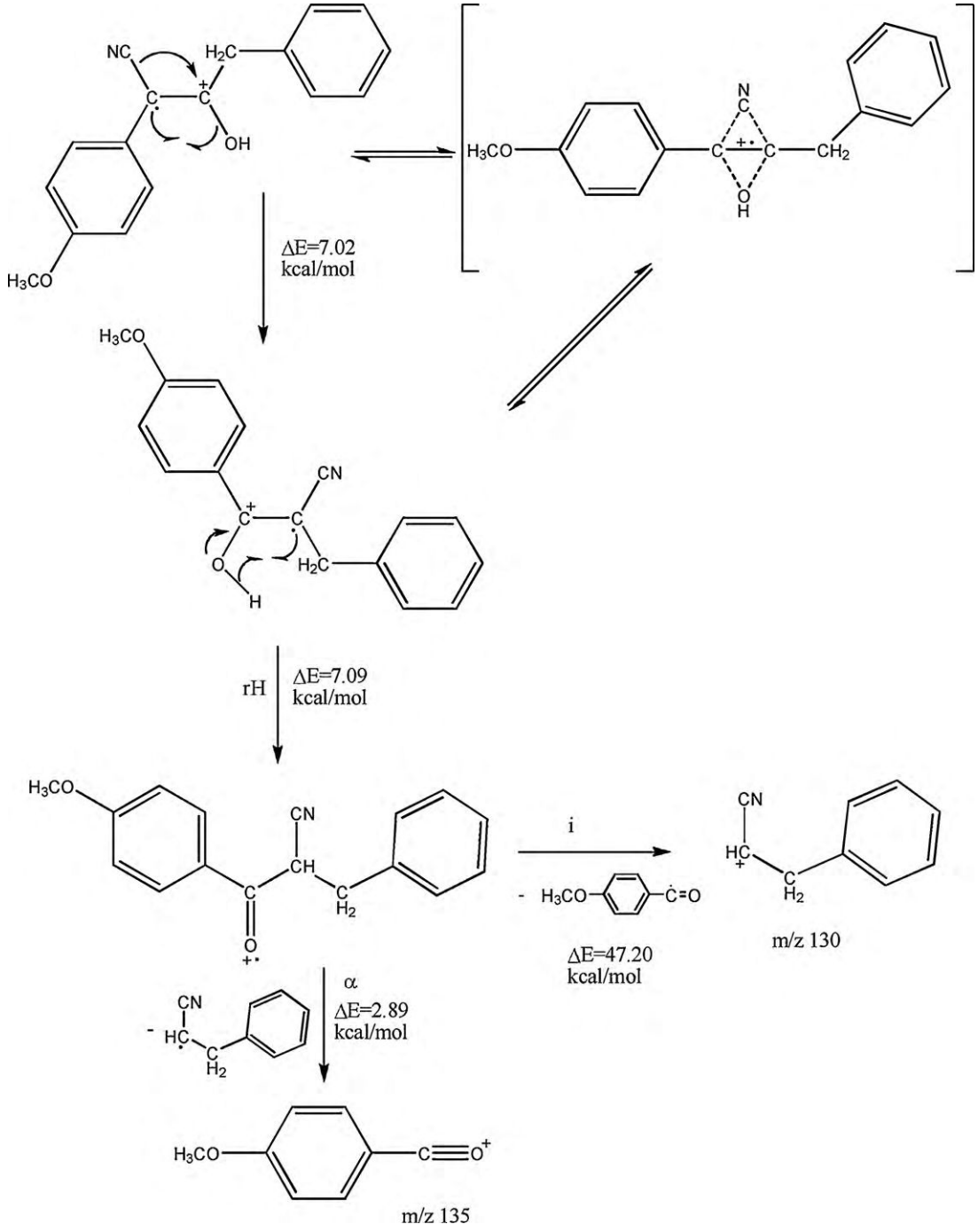
The main pathway for the ion at *m*/*z* 91 (tropilium ion) could involve the two **keto** forms and the **nitrile-enol A** tautomer. The peak at *m*/*z* 237 would be assigned to the **ketenimine** structures (loss of HCNH from the molecular ion) or any keto form (loss of CO).

The ion at *m*/*z* 135 appears to have no explanation. However it could be thought as a fragment with the structure $CH_3O–C_6H_4–CO^+$ which demands the exchange between the OH and CN groups in the nitrile-enol A ionic form (Scheme 6). It is possible that the electron-donating substituent favors occurrence of the nitrile enol A tautomer and the likelihood of the proposed pathway. In fact, the next compound (**VI**) shows the same spectral evidence (*m*/*z* 116) along with the additional support provided by the ion at *m*/*z* 117 (Scheme 2). The complementary ion (*m*/*z* 130) is also observed.

Fig. 7 shows the mass spectrum for 2-(4-chlorophenyl)-3-oxobutanenitrile (**VI**).

Fragment ions are: *m*/*z* 178 and 150; *m*/*z* 176 $(M-OH)^+$; *m*/*z* 175 $(M-H_2O)^{+\bullet}$; *m*/*z* 167 $(M-CN)^+$; *m*/*z* 166 $(M-HCN)^{+\bullet}$; *m*/*z* 151 (Scheme 2); *m*/*z* 43.

The ion at *m*/*z* 116 would correspond to the HCl loss from the ion at *m*/*z* 151. There is no evidence of the occurrence of a pathway analogous to the one depicted in Scheme 6.



Scheme 6.

Table 3
Some mass spectrometric data for selected β-ketonitriles.[a].

Compound	$[M]^+$	$[(M-OH)^+]$	$[(M-CN)^+]$	$[(M-NH_2)^+]$	$[(M-OH)^+]/[(M-NH_2)^+]$	$[(M-CHR'R''CO)^+]$	$[(M-CHR'R''CO)^+]/[(M-OH)^+]$	$[(M-CN)^+]/[(M-NH_2)^+]$
I	10.0	7.66	6.02	5.68	1.35	99.0	12.6	1.06
II	6.0	2.10	0.28	4.54	0.46	23.7	11.3	0.06
III	22.8	1.68	0.68	1.20	1.40	–	–	0.57
IV	3.1	7.86	5.4	13.92	0.56	82.8	10.5	0.39
V	2.8	4.94	1.74	6.80	0.73	58.1	11.7	0.26
VI	8.5	0.44	0.74	20.2	0.02	87.2	198.2	0.04

[a] For a better correlation the reported electron ionization data are displayed according to the following ratio: ion abundance × 1000/$\sum$ abundances.

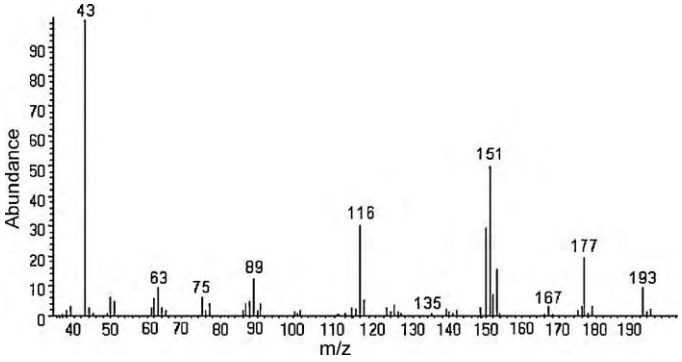


Fig. 7. Mass spectrum of 2-(4-chlorophenyl)-3-oxobutanenitrile (**VI**).

To evaluate the occurrence of the tautomers, specific fragmentations should be assigned. From the analysis of the mass spectrometric data, some of the ions can be assigned to the **enol** forms (loss of 17 amu and 18 amu) and others to the ketenimine forms (loss of 16 amu and 28 amu). Table 3 shows relevant data for the mass spectra of the selected β-ketonitriles. As already mentioned, no chromatographic separation was observed so that their mass spectra are the result of the individual tautomer mass spectra superposition.

Data analysis was done by considering the different factors that affect the tautomeric equilibrium including the relative stability of individual tautomers due to electronic effects on the carbonilo group, conformational issues on the keto structures, conjugation with the enol double bond and steric effects.

The abundance ratio $[(M-OH)^+]/[(M-NH_2)^+]$ could be associated with the enol/ketenimine ratio.

Factors that favor the enol form (nitrile-enol A, the most stable) are: steric effects (bulky groups in C-2) and electronic effects (donor substituents in the aromatic ring on C-2). Factors that favor the ketenimine form are: steric effects (bulky groups in C-2) and electronic effects (withdrawing substituents in the aromatic ring on C-2).

Compound **V** exhibits a structure similar to that of **IV** (as for compounds **II** and **I**), but steric hindrance against the formation of the enol form takes place due to the presence of the benzyl group, which determines the lower stability of the nitrile-enol A for **V** with respect to **IV** and for **II** with respect to **I**.

Compound **I** is similar to **IV**, but without the oxymethyl group in the *para* position of the ring. The lower enolic content of **I** can be explained in terms of electronic effects. The electron-donating oxymethyl group in the *para* position stabilizes the enol structure.

For compound **III**, its structure is similar to that of **II** but it does not exhibit conjugation extension in the respective enol form due to the absence of the aromatic ring and it does have a smaller group in C-2. Both factors favor the enol structure in **II**.

The relative lowest content of the enol form is observed for compound **VI**, despite the fact that it presents conjugation extension, the chlorine atom in the *para* position seems to decrease the electron density in the aromatic ring which would be the cause of a decrease of stability in the enol form.

Contrarily, compound **VI** has the highest ketenimine content likely due to the electron-withdrawing effect of chlorine which assists the delocalization of the nitrogen electron pair. For compound **III**, the absence of a bulky group could be translated in lower ketenimine content.

Low enol content due to the electronic effects (chlorine) could be the answer to the high $[(M-CR'R''CO)^+]/[(M-OH)^+]$ ratio (in correlation with the keto/enol ratio) for compound **VI** and to the relatively high content for compound **IV** (oxymethyl group). The nitrile/ketenimine ratio might be correlated with the $[(M-CN)^+]/[(M-NH_2)^+]$ ratio although no acceptable correlation has been found.

No good correlation has been observed between ion ratios and the theoretical calculations done for the tautomers (Table 2). The lack of specificity observed in the assignment of mass spectral peaks to single tautomers might be the reason for this behavior.

3. Conclusions

As shown in several papers [20–24] the usefulness of mass spectrometry (and GC/MS) to predict tautomeric behavior is demonstrated here along with additional support provided by theoretical calculations performed at the MP2/6-31G(d,p) level. The mass spectra of some β-ketonitriles can provide valuable information regarding the keto-enol and nitrile-ketenimine equilibria taking place in the gas phase (fast tautomerization equilibrium at the injection port of the gas chromatograph). The predictive value of this methodology is supported by the influence of the nature and size of substituents on tautomeric equilibria and the rather good correlation existing between the abundance ratios of selected fragments. Results show that the keto-enol equilibrium can be studied by mass spectrometry and not only ionization in the ion source has a negligible effect on the position of that equilibrium but also the chromatographic conditions (with exception of the injection port temperature) seem to exert no effect.

4. Experimental

4.1. Synthesis of β-ketonitriles

β-Ketonitriles not commercially available were synthesized and purified according to literature procedures or by their modified versions [12,25–27]. The compounds under study were identified by ^{1}H NMR and ^{13}C NMR in $CDCl_3$ with no observation of the enol forms (Table 4).

4.2. Gas chromatography–mass spectrometry

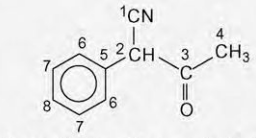
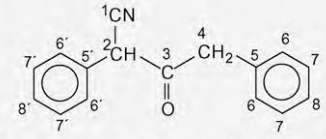
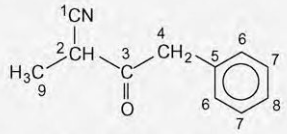
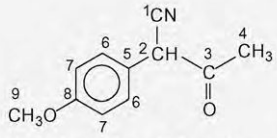
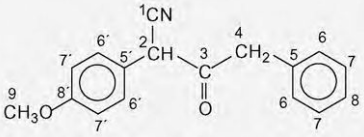
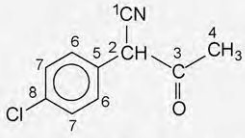
These determinations were performed by injection of methanol solutions (1 μl) in an HP 5890 Chromatograph coupled to an HP 5972 A mass selective detector. An HP5-MS capillary column (30 m × 0.25 mm × 5 μm) has been used with helium as the carrier gas (0.6 ml/min). The temperature set points were: 200 °C in the split injector, 300 °C in the interface, 185 °C in the ion source and the oven ramp started at 80 °C and ended at 200 °C with a heat rate of 10 °C/min. The electron energy was 70 eV, the pressure in the mass spectrometer was lower than 10^{-5} Torr thus precluding ion molecule reactions and the mass range was 50–350 amu.

Isotopic exchange was performed by dissolution of the corresponding compound in methanol-d_1. Mass spectra were analyzed one hour after dissolution.

The relevance of spectrometric data as a predictive tool in regard to tautomeric equilibria depends mainly on the fact that the contribution due to tautomerization of molecular ions in the gas phase does not take place or can be ignored. The importance of this point comes from the physicochemical properties of ionic and radical species, quite different from the neutral ones. This could be the reason for possible distortion of results and loss of the desirable predictive power of the methodology.

In the case of keto-enol tautomerism of a variety of carbonylic and thiocarbonylic compounds, it has been demonstrated that there is no significant interconversion of the tautomeric forms in the gas phase following electron impact ionization in the mass spectrometer (molecular ions, $M^{+\bullet}$, do not seem to undergo unimolecular tautomerization) [20–24] and, even more surprising, for

Table 4
NMR spectra (^{1}H and ^{13}C) for the selected β-ketonitriles (200 MHz, $CDCl_3$).

Compound	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
 3-oxo-2-phenylbutanenitrile (**I**)	2.1 (s, 3H (4)); 5.2 (s, 1H (2)); 7.3–7.6 (m, 5H)	14.3 (4); 45.0 (2); 120.0 (1); 127.8 (6, 8); 129.0 (7); 130.4 (5); 206.3 (3)
 2,4-diphenyl-3-oxobutanenitrile (**II**)	3.6 (s, 2H (4)); 5.3 (s, 1H (2)); 7.2–7.6 (m, 10H)	36.4 (4); 45.4 (2); 120.0 (1); 125.4 (8); 127.8 (6′, 8′); 128.5 (7); 129.1 (6, 7′); 130.1 (5′); 137.1 (5); 206.0 (3)
 2-methyl-3-oxo-4-phenylbutanenitrile (**III**)	1.3 (d, 3H (9)); 3.6–3.8 (q, 1H (2)); 3.9 (s, 2H (4)); 7.2–7.6 (m, 5H)	16.9 (9); 22.7 (2); 45.5 (4); 114.0 (1); 127.9 (6, 8); 129.1 (7); 130.3 (5); 205.8 (3)
 2-(4-methoxyphenyl)-3-oxobutane nitrile (**IV**)	2.1 (s, 3H (4)); 3.7 (s, 3H (9)); 5.2 (s, 1H (2)); 7.1–7.6 (m, 4H)	19.6 (4); 43.8 (2); 48.9 (9); 113.9 (7); 121.1 (1); 123.4 (5); 129.2 (6); 157.4 (8); 203.9 (3)
 2-(4-methoxyphenyl)-3-oxo-4-phenyl butanenitrile (**V**)	3,6 (s, 3H (9)); 3,9 (s, 2H (4)); 5,3 (s, 1H (2)); 6.9–8.0 (m, 9H)	36.4 (4); 44.7 (2); 48.1 (9); 113.9 (7′); 121.3 (1); 123.3 (5′); 125.1 (8); 129.2 (7); 130.1 (6′); 132.1 (6); 137.8 (5); 157.6 (8′); 204.7 (3)
 2-(4-chlorophenyl)-3-oxobutanenitrile (**VI**)	2.1 (s, 3H (4)); 4.6 (s, 1H (2)); 7.1–7.4 (m, 4H)	27.2 (4); 47.2 (2); 115.8 (1); 128.0 (5); 129.0 (7); 130.6 (6); 132.7 (8); 206.0 (3)

GC/MS experiments, once the solvent is separated after injection in the injection port of the gas chromatograph, tautomerism mechanisms (intermolecular, unimolecular) would not seem to take place even with no GC separation (under the selected experimental conditions). These conclusions are supported by temperature studies at the ion source (negligible effect) and at the injection port of the gas chromatograph with a shifting effect in agreement with the corresponding heats of tautomerization [21]. In fact, this process would take place very fast under the working conditions in the GC.

Separation of tautomers in the analytical column is frequently very difficult, consequently the different pathways of fragmentation of the tautomeric forms have to be used for the identification of individual tautomers [23]. For this reason and due to the high similarity between MS (commercial databases) and GC/MS spectra, analytical separation has not been considered critical for the present work. Analogously, it is thought that most of the conclusions could be useful to analyze spectra registered with mass spectrometers equipped with direct insertion probes.

4.3. Computational procedure

Theoretical calculations were carried out at the MP2 level using 6-31G(d,p) basis in the Gaussian 03 program [28].

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