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On the double benzylic hydrogen migration in the molecular ion of *N*-(5-phenylvaleryl)-1-azacyclopentane-2-thione

H. Yamaoka [a,*], I. Kusagi [a], K. Isa [b], Y. Maekawa [b], N.M.M. Nibbering [c]

[a] *Department of Environmental Sciences, Faculty of Science, Osaka Women's University, 2-1 Daisen-cho, Sakai, Osaka 590-0035, Japan*
[b] *Faculty of Education and Regional Studies, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8057, Japan*
[c] *Laser Centre and Chemistry Department, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands*

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Dedicated to Alan Marshall on the occasion of his 60th birthday and in recognition of his many contributions to the development of Fourier transform ion cyclotron resonance mass spectrometry with many thanks (from N.M.M. Nibbering) for his long-standing friendship.

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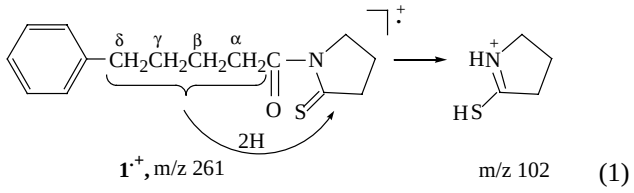
Abstract

It is shown on the basis of deuterium labeling that in the metastable molecular ions of *N*-(5-phenylvaleryl)-1-azacyclopentane-2-thione, decomposing by unimolecular fragmentation, both benzylic hydrogens migrate to the thiolactam ring to generate the protonated γ-thiobutyric lactam species with *m*/*z* 102. A mechanism is given for the formation of these ions that is proposed to be mediated by intramolecular acid–base reactions and an ion/molecule complex.

Keywords: Double hydrogen rearrangement; Deuterium labeling; Metastable ions; Multisector mass spectrometry; Mechanism; Acid–base reaction; Ion/molecule complex; *N*-(5-Phenylvaleryl)-1-azacyclopentane-2-thione

In this brief communication an interesting observation will be reported concerning the formation of the *m*/*z* 102 ions from the metastable *m*/*z* 261 molecular ions of the five-membered ring thiolactam *N*-(5-phenylvaleryl)-1-azacyclopentane-2-thione (**1**). This formation requires the migration of two hydrogen atoms from the 5-phenylvaleryl group to the thiolactam ring as pictured overall in Eq. (1):



1$^{\cdot+}$, m/z 261 m/z 102 (1)

This should be considered as a novel prototype of a double hydrogen rearrangement in which the thiocarbonyl group plays a significant role as one of the proton acceptor sites. Double hydrogen rearrangements are well known in mass spectrometry and occur in molecular ions of various classes of compounds, like esters, ethers, and γ-arylalkanols [1–4]. For example, the 70 eV electron ionization mass spectrum of *n*-butyl-propionate contains a peak at *m*/*z* 75 due to a double hydrogen rearrangement yielding protonated propionic acid. This peak is much larger than the peak at *m*/*z* 74 due to the single McLafferty hydrogen rearrangement, yielding the molecular radical cation of propionic acid [5]. At 12 eV electron ionization the peak at *m*/*z* 75 becomes even the base peak in the spectrum [5]. In the metastable molecular ions of γ-arylalkanols not only a double hydrogen rearrangement, but even a triple hydrogen rearrangement occurs prior to unimolecular fragmentation [4]. For the γ-arylalkanol *trans*-2-(4′-dimethylaminobenzyl)-1-indanol deuterium labeling has shown that the origin of the three hydrogen atoms, participating in the triple hydrogen rearrangement, originate with extraordinarily high specificity from the C(1), C(2), and O positions of the alcohol moiety [4].

Originally the double hydrogen rearrangements were rationalized to occur in covalently bonded ion structures via differently sized transition states [1–3,5]. Later on arguments were put forward that such double hydrogen rearrangements

* Corresponding author. Tel.: +81-72-222-4811x4338; fax: +81-72-238-5539.
E-mail address: yamaoka@center.osaka-wu.ac.jp (H. Yamaoka).

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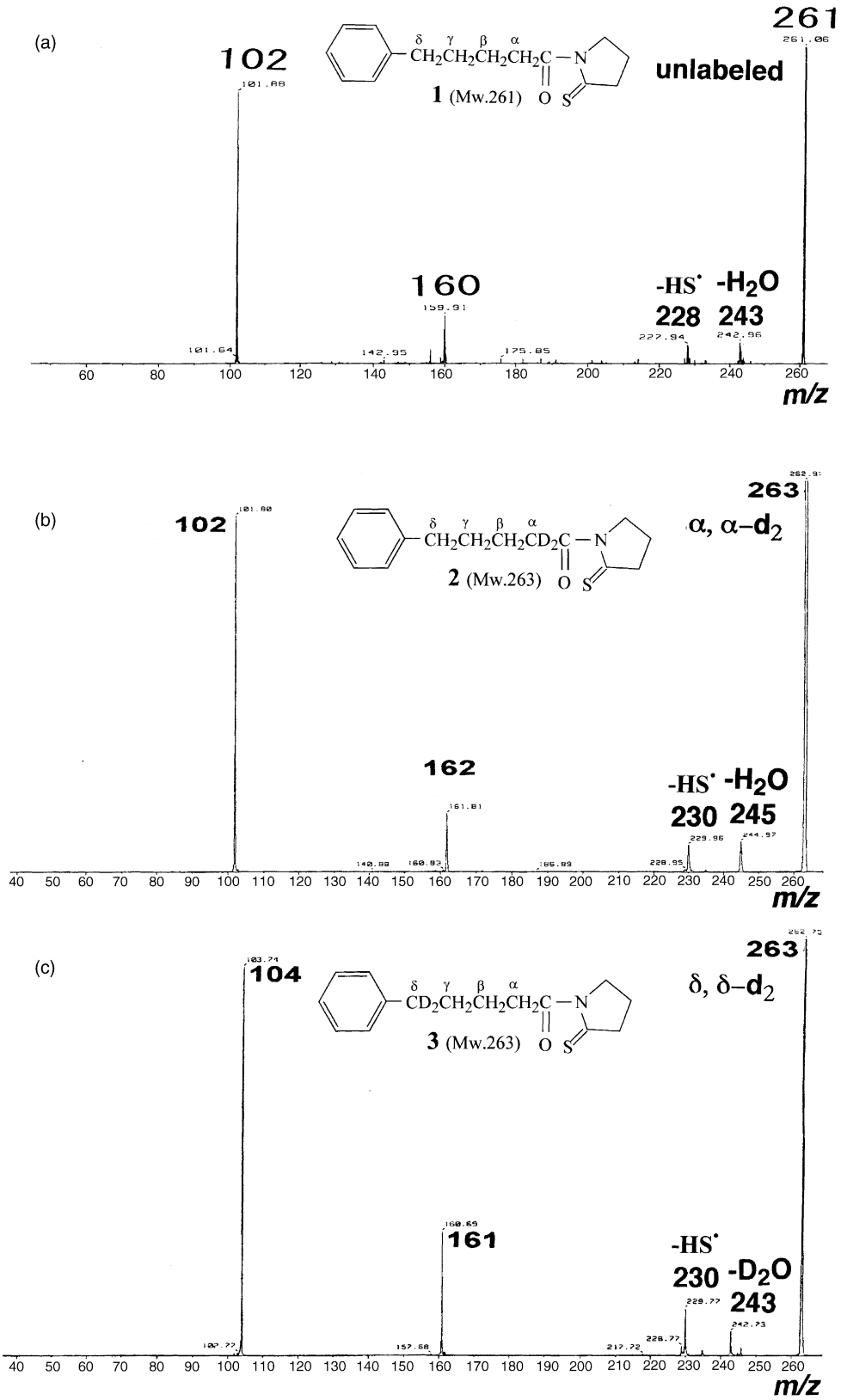


Fig. 1. Metastable ion spectra of the molecular ions $\mathbf{1}^{\bullet+}$ (panel a), $\mathbf{2}^{\bullet+}$ (panel b), and $\mathbf{3}^{\bullet+}$ (panel c) decomposing in the third field free region of a double reversed (BE/BE) four-sector tandem mass spectrometer (see text).

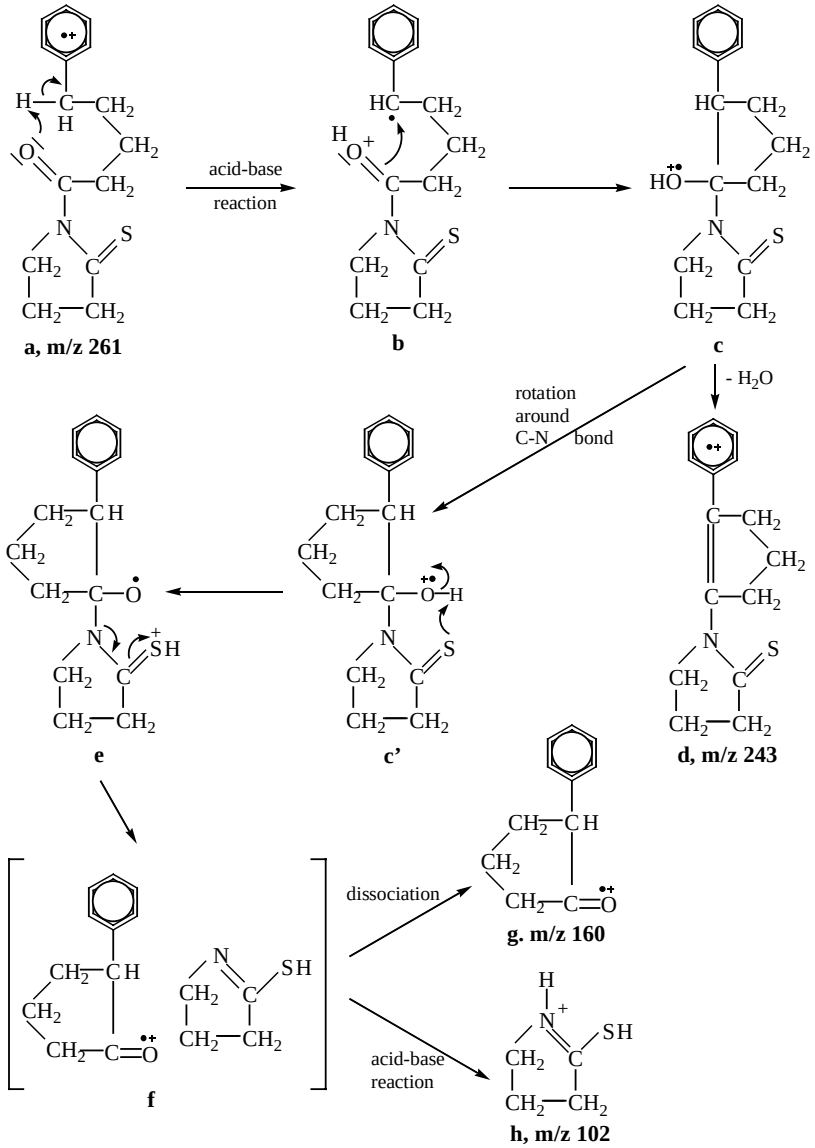
are mediated by ion/neutral complexes at some stage of the unimolecular dissociation [6] as suggested for the double and triple hydrogen rearrangements in the molecular ions of the γ-arylalkanols [4].

Fig. 1(a) shows the metastable ion spectrum for the *m*/*z* 261 molecular ion **1**$^{\bullet+}$ of unlabelled *N*-(5-phenylvaleryl)-1-azacyclopentane-2-thione decomposing in the third field free region of a double reversed (BE/BE) four-sector tandem mass spectrometer (JMS 700T, JEOL, Tokyo, Japan), that is following its selection by the first double focusing mass spectrometer at a mass resolving power of 1000 (10% valley definition) in the region between the first electric sector and the second magnet and recorded with use of the second double focusing mass spectrometer at a mass resolving power of 1000 (10% valley definition) by use of a B/E linked scan [7].

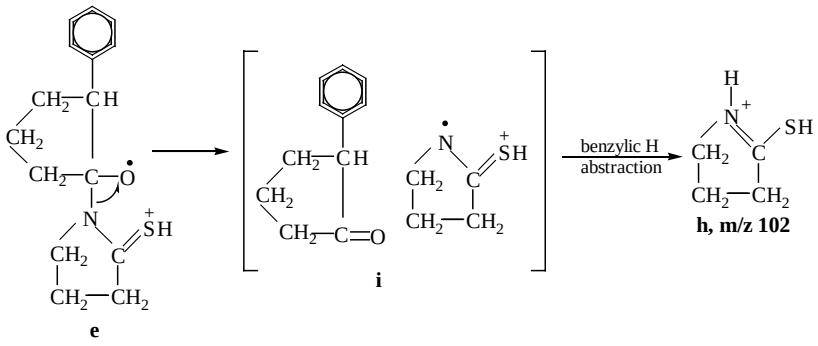
It shows the peak at *m*/*z* 102 due to the ions generated via a double hydrogen rearrangement in addition to the peaks at *m*/*z* 160 and 243, the last being due to loss of a water molecule from ionized **1**.

To establish the origin of the hydrogens involved in the double hydrogen rearrangement, the analogues of **1**, specifically deuterated in the α-position, **2**, and the δ-position, **3**, of the 5-phenylvaleryl group have been synthesized. The metastable ion spectra of their molecular ions **2**$^{\bullet+}$ and **3**$^{\bullet+}$ decomposing in the third field free region, as described above, are given in Fig. 1(b) and (c), respectively.

It is clear that the peak at *m*/*z* 102 in Fig. 1(a) does not shift in Fig. 1(b), but shifts completely to *m*/*z* 104 in Fig. 1(c). This leads to the interesting observation and conclusion that both benzylic hydrogens are transferred in the double hydrogen rearrangement to the thiolactam ring. A mechanistic proposal for this rearrangement is presented in Scheme 1. Assuming that in the molecular ion **1**$^{\bullet+}$ the charge is located in the phenyl ring, which seems not unreasonable consid-



Scheme 1.



Scheme 2.

ering available thermochemical data [8], the first reaction step is proposed to be an intramolecular acid–base reaction in which the carbonyl oxygen atom (base) abstracts a proton from the benzylic position (acid) sequence **a** → **b** in Scheme 1.

Subsequently, a ring closure occurs in ion **b** by attack of the radical in the benzylic position upon the protonated carbonyl group to give the 1-thiolactam, 2-phenyl substituted cyclopentanol radical cation **c**. Support for the formation of ion **c** is provided by the metastable ion spectra in Fig. 1(a–c), showing that *m*/*z* 243 in Fig. 1(a) shifts to *m*/*z* 245 in Fig. 1(b), but stays at *m*/*z* 243 in Fig. 1(c) (a small peak is present at *m*/*z* 245 in Fig. 1(c) indicating a minor contribution of H_2O loss for which no explanation can be presented in the absence of more extensive deuterium labeling experiments). This means that the water molecule lost from part of the molecular ions $\mathbf{1}^{\bullet+}$ to give the ions *m*/*z* 243 contains both original benzylic hydrogens, which is consistent with the structure of ion **c**, see sequence **c** → **d** in Scheme 1 (it should be noted that the 1,2-elimination of water in sequence **c** → **d** might also proceed in two steps after intramolecular charge transfer in ion **c** from the OH group to the phenyl ring: abstraction of the benzylic hydrogen as proton by the thiocarbonyl sulfur atom, followed by transfer of this proton from the sulfur atom to the OH group and then loss of water, also resulting in the formation of ion **d**). Following a rotation around the C–N bond in ion **c** to give ion **c**′, the sulfur atom of the thiocarbonyl group can then abstract as base the hydroxylic proton to give ion **e**. This ion may then break up by a heterolytic cleavage of the C–N bond into the ion/molecule complex **f**, consisting of the radical cation of 2-phenyl-cyclopentanone and the neutral enol form of γ-thiobutyric lactam. Support for this ion/molecule complex **f** is provided by the metastable ion spectra in Fig. 1(a–c) showing the peaks at *m*/*z* 160, 162, and 161, respectively. They correspond to the radical cations of 2-phenylcyclopentanone and its 5,5-dideutero and 2-deutero analogues, respectively, generated by dissociation of ion/molecule complex **f** into its constituents, that is ion **g** and the neutral enol of γ-thiobutyric lactam.

In addition to this dissociation, the ion/molecule complex **f** may react further via an acid–base reaction, in which the radical cation of 2-phenylcyclopentanone transfers its benzylic proton to the neutral enol of γ-thiobutyric lactam to give ion **h**, that is protonated γ-thiobutyric lactam. This ion should then contain both benzylic hydrogens as observed indeed.

In principle ion **e** could also break up by a homolytic cleavage of the C–N bond into an ion/molecule complex **i**, consisting of neutral 2-phenylcyclopentanone and the radical cation of the enol of γ-thiobutyric lactam (see Scheme 2).

A benzylic hydrogen atom abstraction from the 2-phenylcyclopentanone by the radical cation of the enol of γ-thiobutyric lactam in ion/molecule complex **i** would then also lead to the formation of ion **h**. Although this possibility cannot be fully excluded, it seems unlikely as ion/molecule complex **i** would then be expected to dissociate also into neutral 2-phenyl-cyclopentanone and the radical cation of the enol of γ-thiobutyric lactam with *m*/*z* 101, which is not observed (see Fig. 1(a)).

Double hydrogen rearrangements, in which the migrating hydrogen atoms originate from one position, as described in this communication, are extremely rare, if known at all. For example, deuterium labeling almost four decades ago has shown that the two hydrogens to form protonated ethanol from the radical cation of ethyl *n*-hexyl ether originate to the major part, but not exclusively from the C5 position [9]. In that case the double hydrogen rearrangement is initiated by an intramolecular radical abstraction reaction, while in the present case by an intramolecular acid–base reaction.

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