

Collisionally induced loss of NO₂ radical from protonated nitroimidazoles and nitropyrazoles

Robert Flammang^{a,*}, José Elguero^b, Hung Thanh Le^c, Pascal Gerbaux^a,
Minh Tho Nguyen^c

^a *Laboratory of Organic Chemistry, Department of Organic Chemistry, University of Mons-Hainaut, Avenue Maistriau 19, B-7000 Mons, Belgium*

^b *Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain*

^c *Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium*

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Abstract

The collisionally induced loss of NO₂ of protonated nitroimidazoles and nitropyrazoles was investigated for the possible generation of hydrogen shift isomers of imidazole and pyrazole radical cations. Ab initio calculations at B3LYP/6-31+G(d,p) level have been used to rationalize the experimental findings. © 2002 Published by Elsevier Science B.V.

1. Introduction

In recent years, the potential existence of several distonic (hydrogen shift) isomers of substituted benzenic compounds has been reported. For instance, by using consecutive collisional activation and/or ion–molecule reactions, distonic isomers of ionized aniline [1–3], benzonitrile [4] and benzaldehyde [5] have been identified in the gas phase. Some typical examples are given in Scheme 1. Theoretically, it has been calculated that these distonic ions are less stable than their ‘conven-

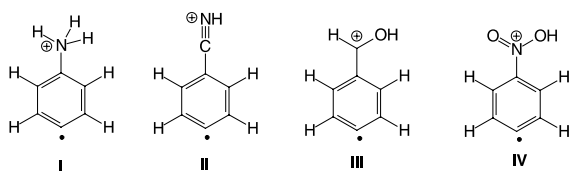
tional’ isomers, but protected against isomerization by sizeable energy barriers.

Most of these distonic ions have been prepared by chemical ionization (protonation) of iodinated compounds followed by a collisional induced loss of an iodine atom. This protonation–dehalogenation sequence was nevertheless found inefficient in the case of 4-iodonitrobenzene, and the production of ions **IV** has been successfully realized by protonation of 1,4-dinitrobenzene followed by a collision induced loss of a nitrogen dioxide radical [6].

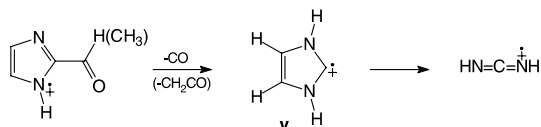
In fact, the characterization of these ions has followed the discovery of hydrogen shift isomers of some heterocycles initially reported by the groups of Schwarz and Terlouw [7–13]. For instance, decarbonylation of ionized 2-formylimidazole generated imidazole-2-ylidene radical

* Corresponding author. Fax: +32-65-373515.

E-mail address: robert.flammang@umh.ac.be (R. Flammang).



Scheme 1.



Scheme 2.

cation V readily differentiated from ionized imidazole by the intense loss of ethyne in its CA spectrum, see Scheme 2 [14]. The same for the ions produced by the loss of ketene from 2-acetylimidazole [15].

We report here on the behaviour of some protonated nitroimidazoles and nitropyrazoles upon collisional activation (high or low kinetic energy regimes) with various target gases making use of a large scale tandem mass spectrometer of sector–quadrupole–sector configuration. The aim of the study was the possible generation of ‘non-classical’ heterocyclic radical cations.

2. Methods

The spectra were recorded on a large-scale tandem mass spectrometer (Micromass AutoSpec 6F, Manchester) combining six sectors of $cE_1B_1cE_2qcE_3B_2cE_4$ geometry (E_i stands for electric sector, B_i for magnetic sector, q for a quadrupole collision cell and c for conventional collision cells). Typical conditions have been reported elsewhere [16].

The installation of the radiofrequency-only quadrupole collision cell (Qcell) inside the instrument between E_2 and E_3 has also been reported [17]. This modification allows the study of associative ion–molecule reactions and the study of collisional activation of decelerated ions (ca. 20–30 eV kinetic energy). Briefly, the experiments utilizing the quadrupole consist of the selection of a

beam of fast ions (8 keV) with the three first sectors ($E_1B_1E_2$), the deceleration of these ions to approximately 20–30 eV. The interaction between the ions and the reagent gas is thereafter realized in the Qcell and, after reacceleration at 8 keV, all the ions generated in the quadrupole are separated and mass measured by scanning the field of the second magnet. The high-energy CA spectra of mass-selected ions generated in the Qcell can be recorded by a scanning of the field E_4 after selection of the ions with E_3 and B_2 .

The imidazoles were commercially available (Aldrich) and used without further purification.

The synthesis of the nitropyrazoles was described in previous publications [18–20].

Ab initio calculations with the GAUSSIAN 98 series of programs [21] have been employed to derive some useful quantitative parameters for interpreting the experimental results. Geometries of the considered structures were optimized using density functional theory [22] with its popular hybrid functional B3LYP [23,24] in conjunction with the 6-31G+(d,p) basis set. The zero-point vibrational energies (ZPE) were estimated at this level. Geometries of considered structures were then reoptimized making use of the larger 6-311++G(d,p) basis set including diffuse functions for investigating the influence of basis set on the theoretical values of proton affinities. However, the basis set effect was found to be really small in this case. Throughout this section, the relative energies mentioned were derived from, unless otherwise noted, (U)B3LYP/6-31+G(d,p) + ZPE calculations.

3. Results and discussion

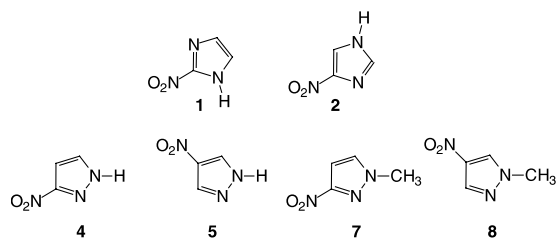
3.1. Collisional activation experiments performed on nitroimidazoles

Methane chemical ionization of 2-nitroimidazole **1** yields abundant protonated molecules $\mathbf{1H}^+$ (m/z 114) which decompose mainly upon collisional activation with argon (low energy regime) by loss of NO_2 . If protonation takes place at the dicoordinated ring nitrogen, such a reaction should produce imidazole-2-ylidene radical cation

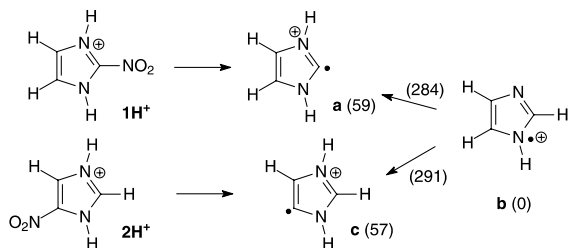
(m/z 68), a distonic isomer of ionized imidazole **b** (Schemes 3 and 4). This is supported by calculated proton affinities, see Fig. 1, indicating that nitrogen protonation is favored by 60–70 kJ mol⁻¹ over oxygen protonation.

In its hybrid sector–quadrupole–sector configuration, the AutoSpec 6F mass spectrometer allows also the recording of *high energy CA spectra* of ions generated within the quadrupole collision cell (see experimental) [17]. As for a consequence, the drawbacks of the MS/MS/MS methodology (severe loss of sensitivity and resolution increasing with the mass difference between the parent and the fragment ions) can be overcome.

The high energy CA spectrum of the [$1\text{H}^+-\text{NO}_2$]⁺ ions, depicted in Fig. 2a, features a very intense signal for a loss of ethene (m/z 42, carbodiimide $\text{HN}=\text{C}=\text{NH}$ ions) not observed in the CA spectrum of the ‘conventional’ imidazole ions (Fig. 2d). In fact, this loss of ethene was previously reported for [$\text{M}-\text{CO}$]⁺ ions of 2-formylimidazole [14] and for [$\text{M}-\text{CH}_2\text{CO}$]⁺ ions of 2-acetylimidazole [15] (Fig. 2b) and ascribed to the generation of imidazole-2-ylidene **a** ions as described in Scheme 2. The loss of ethene was nevertheless less intense than in the case of the [$1\text{H}^+-\text{NO}_2$]⁺ ions suggesting that the protona-



Scheme 3.



Scheme 4.

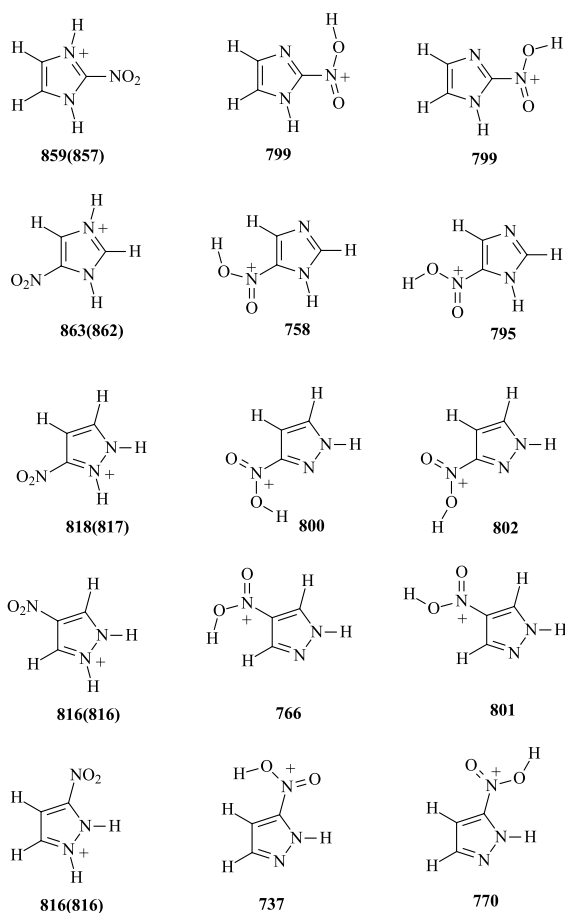


Fig. 1. Calculated proton affinities of nitropyrazole and nitroimidazole (kJ mol⁻¹). Values in parentheses obtained from B3LYP/6-311++G(d,p) optimisation calculations + ZPE.

tion–fragmentation sequence of 2-nitroimidazole produces a beam of distonic ions of higher purity.

Protonation of 4-nitroimidazole **2** followed by loss of NO_2 provides a CA spectrum (see Fig. 2c) not too different from the spectrum of ionized imidazole, but relative abundances of the fragments indicate the formation of an isomeric species, probably imidazole-4-ylidene ion **c**.

Relative energies (kJ mol⁻¹) of imidazole radical cation **b** and its isomers **a**, **c** together with those of the 1,2-H shift transition structures connecting them are also given in Scheme 4. The results are consistent with previous estimations [14] and indicate that the conventional ion **b** is the most

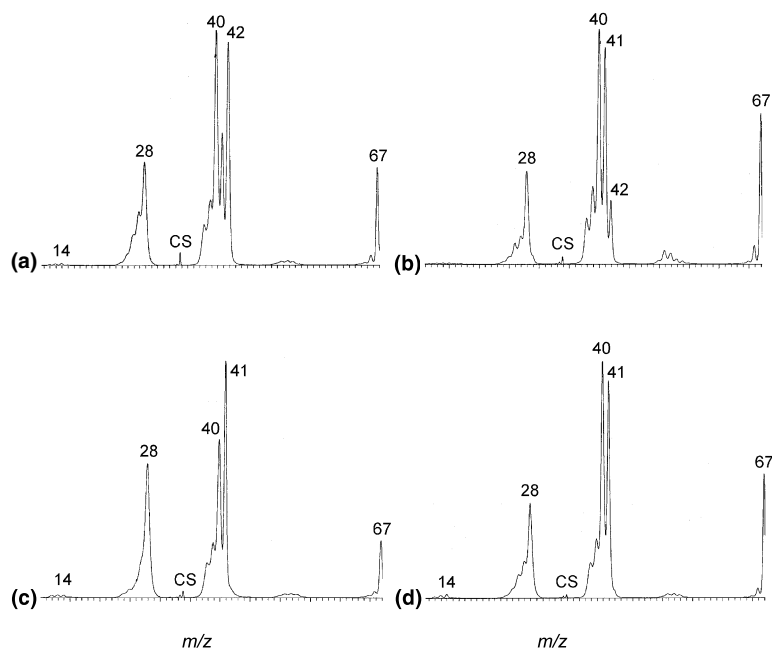


Fig. 2. High energy CA spectra (nitrogen collision gas, 8 keV) of $C_3H_4N_2^+$ ions: $[1H^+-NO_2]^+$ (a), $[M-CH_2CO]^+$ of 2-acetylimidazole (b), $[2H^+-NO_2]^+$ (c) and ionized imidazole 3^+ (d).

stable, but the distonic **a** and **c** species are also found to be remarkably stable, lying 59 and 57 kJ mol^{-1} , respectively, above ion **b**. The energy barrier for their interconversion are rather large amounting to 284 and 291 kJ mol^{-1} for the transition structures connecting **b/a** and **b/c**.

3.2. Collisional activation experiments performed on nitropyrazoles

3-Nitropyrzazole **4** is also readily protonated in the chemical ionization ion source using methane as the reagent gas [25]. The metastable protonated molecules decompose mainly by loss of NO (23%) and NO_2 (77%) radicals. Upon collisional excitation (argon collision gas, low kinetic energy regime), the loss of NO_2 (m/z 68) is strongly enhanced by a factor of ca. 200, the same for a loss of OH (m/z 97), while the loss of NO (m/z 84) remains unchanged (Fig. 3a). This is indicative of simple cleavage processes. These fragmentations could be in agreement with the formation of a mixture of isomeric (oxygen and nitrogen) protonated species and this is again in agreement

with the calculated proton affinities of Fig. 1 indicating that the 60–70 kJ mol^{-1} PA's differences in the imidazole series is now reduced to ca. 15 kJ mol^{-1} .

The CA spectrum of the m/z 68 ions generated by the collision induced loss of NO_2 is compared to the CA spectrum of the molecular ions of pyrazole in Fig. 4. The two spectra are clearly different indicating the occurrence of isomeric $C_3H_4N_2$ ions. In particular, an intense peak at m/z 30 ascribed to $HN=NH$ ions (a C, H₄, N composition for these ions appears unlikely), is not seen in the case of the conventional radical cations **e**. The higher intensity of the peak at m/z 38 is also worthy of note. These observations could indicate the formation of the ylide ions **d**. However, by using perdeuterated methanol chemical ionization, the expected displacement of the peak at m/z 30 to m/z 32 is *not* observed indicating that this ion does not incorporate hydrogen atoms and is thus ascribed to isobaric m/z 68 ions in the low-energy CA spectrum of the $4H^+$ ions. These ions could have the C_3H_2NO composition (loss of H_2 , N_2 , O), that is nitrosocyclopropenylydene ions (or a

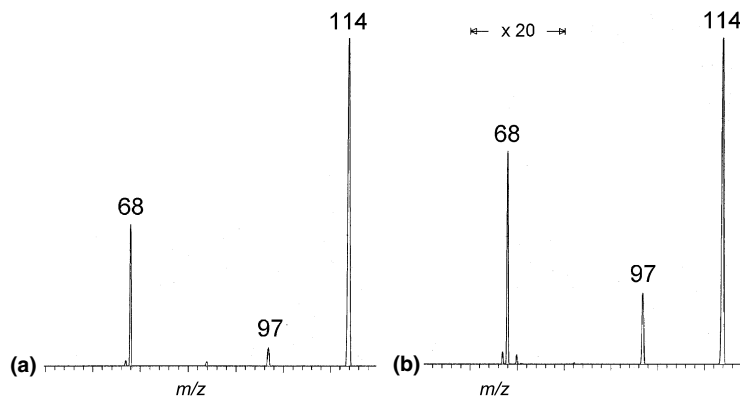


Fig. 3. Low energy CA spectra (argon) of protonated 3-nitropyrzazole $4H^+$ (a) and protonated 4-nitropyrzazole $5H^+$ (b). Kinetic energy of the ions: 20–30 eV.

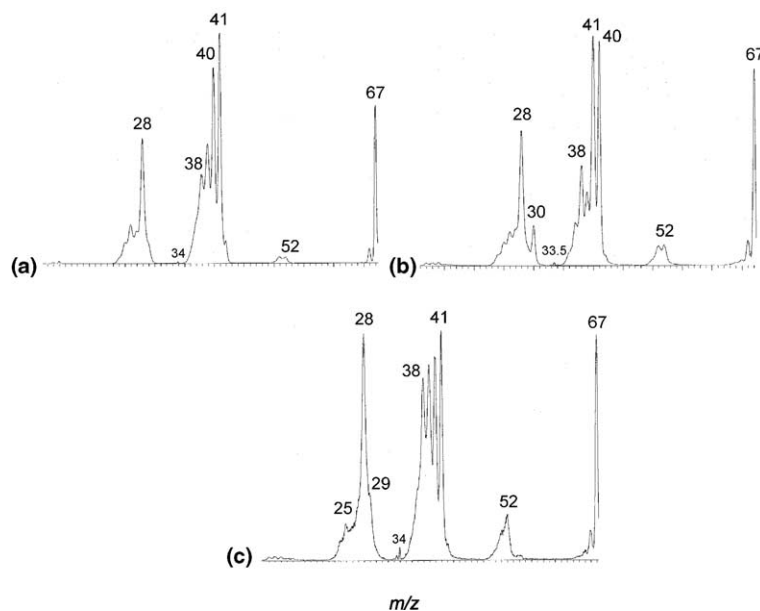


Fig. 4. CA (N_2) mass spectra of (a) pyrazole radical cations e , of (b) $[4H^+-NO_2]^+$ radical cations and of (c) $[5H^+-NO_2]^+$ radical cations. Kinetic energy of the ions: 8 keV.

complex between NO^+ and cyclopropenyliidene ion [26]).

A careful examination of the very low intensity peaks in the m/z 10–20 region and in the doubly charged ions region indicates nevertheless that the ions produced in the fragmentation process differ from the conventional ions e . For instance, the base peak of the charge stripping spectrum of ions

e observed at m/z 34 is displaced at m/z 33.5 for ions d .

This conclusion has been supported by the study of protonated 3-chloropyrazole [27] which, after collisional dechlorination, gives a CA spectrum identical to the spectrum shown in Fig. 4b except for the peaks at m/z 30 (absent) and 38 (reduced intensity).

Table 1
High energy CA spectra (nitrogen collision gas) of $C_4H_6N_2^{+}$ radical cations generated by loss of NO_2 (argon collision gas) from protonated 1-methylnitropyrazoles **7–8** and electron ionization of 1-methylpyrazole **6**, 3(5)-methylpyrazole **9** and 4-methylpyrazole **10** (loss of hydrogen(s) not included, the same for peaks less than 5%)

<i>m/z</i>	67	66	55	54	53	52	42	41	40	39	38	28	27	26	15
7H⁺	–	15	100	45	21	50	92	29	38	23	20	47	28	28	8
8H⁺	–	37	23	58	40	99	51 ^a	29	37	51	64	100	51	36	14
6	–	9	51	100	44	67	60	24	40	47	51	93	60	64	13
9	5	17	72	100	62	78 ^b	46	40	72	58	45	87	92	50	–
10	–	–	43	100	28	47	–	55	25	28	23	81	43	24	–

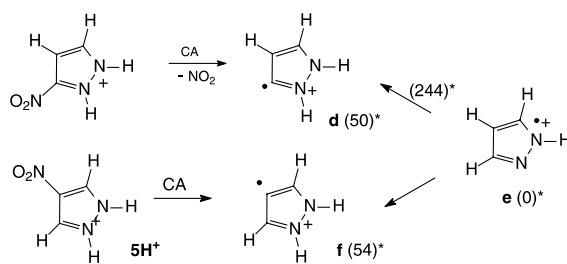
^a *m/z* 43 (32%).
^b *m/z* 51 (90%).

This situation is drastically modified for the isomeric 4-nitropyrazole **5** and after protonation, the most intense dissociation induced by collision is the loss of a hydroxyl radical (*m/z* 97), the sole reaction observed in the absence of a collision gas) (Fig. 3b).

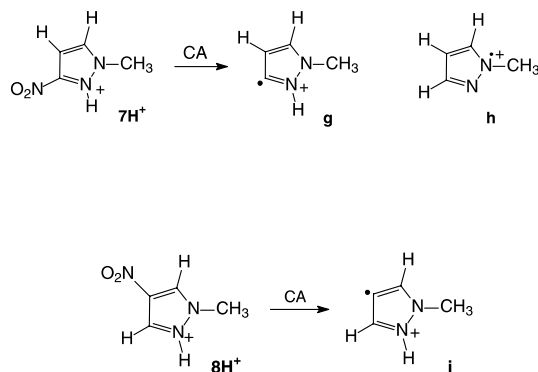
The CA spectrum of the $[5H^+-NO_2]^+$ radical cations (*m/z* 68) is again markedly different from the spectra of ions **e** and **d** indicating the formation of an isomeric structure **f**, see Fig. 4c.

Similar experiments have been performed on 1-methyl-3-nitropyrazole **7**. Again, the ions produced in the protonation–fragmentation (loss of NO_2) sequence are unambiguously found different from the conventional 1-methylpyrazole radical cations **h** (Table 1).

The difference of behaviour between **4H⁺** and **5H⁺** is also found between **7H⁺** and **8H⁺**. For protonated 1-methyl-4-nitropyrazole **8H⁺**, the loss of $OH\cdot$ generates the most intense peak in the low energy CA spectrum; the loss of NO_2 is nevertheless observed at *m/z* 82 and the high energy CA



Scheme 5. (* refers to calculations of [27])



Scheme 6.

spectrum of these ions (Table 1) differs from the spectra of ions **g** and **h**. A 1,3-distonic connectivity **i** is therefore proposed for these ions as indicated in Schemes 5 and 6.

For the sake of comparison, the CA spectra of isomeric 3-methyl- and 4-methyl-pyrazole radical cations are also given in Table 1.

4. Conclusion

A variety of $C_3H_4N_2$ and $C_4H_6N_2$ ions has been produced by electron ionization of pyrazoles (imidazole) or protonation–fragmentation (loss of NO_2) of nitropyrazoles (nitroimidazoles). The identification of these ions was based on MS/MS/MS experiments making use of a hybrid mass spectrometer of sector–quadrupole–sector configuration. Contrasting with the case of the imidazoles, structural significant fragmentations are in most cases not detected in the CA spectra of the pyrazole series. It is nevertheless tentatively proposed that distonic species are formed starting with the nitropyrazoles. The sites of protonation of nitroimidazoles and nitropyrazoles were determined to be dicoordinated ring nitrogen and their proton affinities were also estimated.

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