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Mass Spectrometry of Imidazole-4(5)-carboxaldehyde and Some 1-Methyl and Nitro Derivatives

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The mass spectra of imidazole-4(5)-carboxaldehyde, its two 1-methyl derivatives, 4(5)-nitroimidazole, 5(4)-nitroimidazole-4(5)-carboxaldehyde and 1-methyl-5-nitroimidazole-4-carboxaldehyde are presented and discussed in comparison with those of other imidazole-carboxaldehydes and nitroimidazoles earlier reported. The imidazole-carboxaldehydes and their 1-methyl derivatives exhibit the characteristic fragmentation of aromatic aldehydes, and differences between the isomers can be observed. The nitroimidazoles show the fragmentation typical of aromatic nitrocompounds. In the *o*-nitroimidazole-carboxaldehydes, the typical losses of aldehydes do not occur, but primary *ortho* effects between the formyl and nitro groups give rise to important fragmentation routes. In their 1-methyl derivatives, the presence of the methyl group adjacent to the nitro group originates additional double and secondary *ortho* effects. For some of these transformations, fragmentation mechanisms are proposed.

INTRODUCTION

Nitroimidazoles are important because of the antimicrobial properties associated with some compounds of this type, and ample mass spectral data on these compounds are available. Nevertheless, there are no mass spectrometric data on nitroimidazole-carboxaldehydes and even studies on imidazole-carboxaldehydes are rather scarce, as only the mass spectra of some imidazole-2-carboxaldehydes[1,2] have been reported. In the mass spectra of nitroimidazole-carboxaldehydes, the appearance of *ortho* effects between adjacent nitro and formyl groups, similar to those described for *o*-nitrobenzaldehyde,[3] is to be expected. The comparison of the new findings with the *ortho* effects occurring between the nitro and alkyl groups in alkylnitroimidazoles[4–9] permits a better understanding of the fragmentation of substituted nitroimidazoles.

In order to investigate the mass spectrometric behaviour of imidazole-carboxaldehydes with the formyl group in the 4- and 5-positions, and the *ortho* effect due to the presence of a nitro group, compounds **1** and **2** were examined.

In compounds **2** there is a rapid equilibrium between two tautomers, resulting in equivalence of positions 4 and 5. The spectra were obtained using electron impact ionization and the composition of all ions discussed was confirmed by accurate mass measurement at high resolving power.

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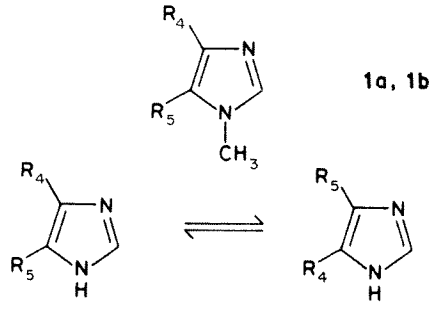

	R_4	R_5		R_4	R_5
1a	CHO	H	**2a**	CHO	H
1b	H	CHO	**2b**	NO_2	H
1c	CHO	NO_2	**2c**	CHO	NO_2

RESULTS AND DISCUSSION

Imidazole-carboxaldehydes (1a, 1b and 2a)

The mass spectra of the compounds (Fig. 1) show consecutive losses of H˙ and CO along with direct loss of the CHO˙ moiety, all of which are common fragmentation routes in aromatic aldehydes.[10] In

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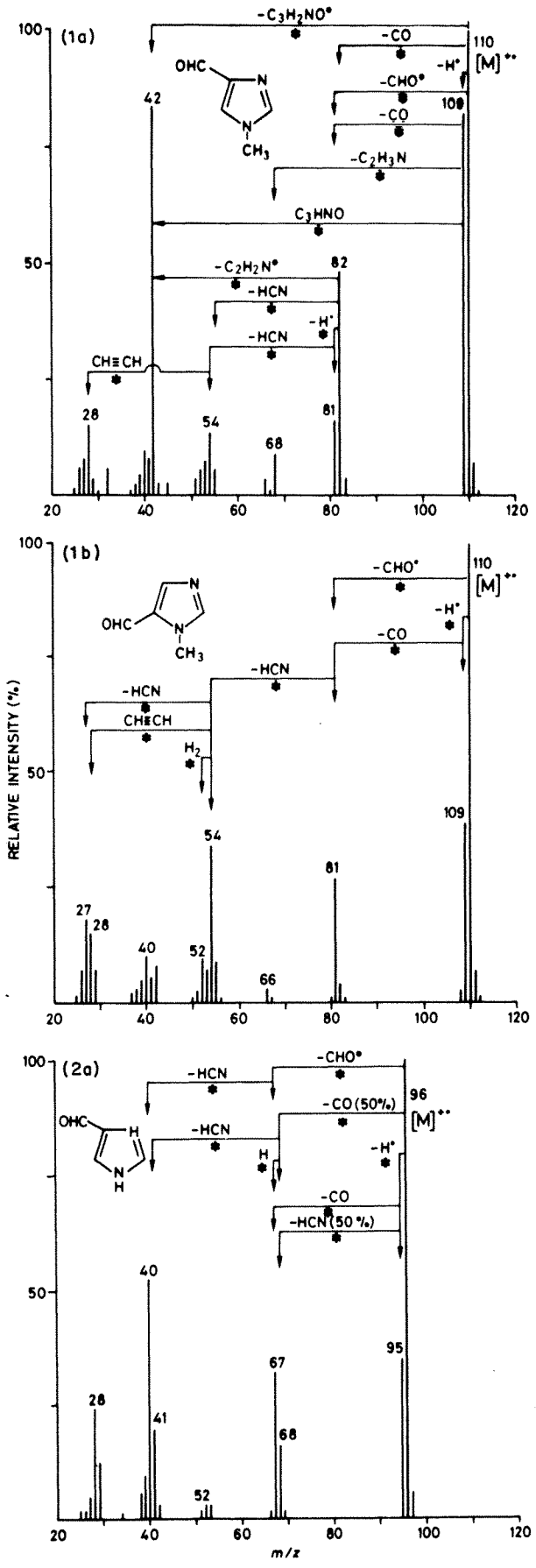
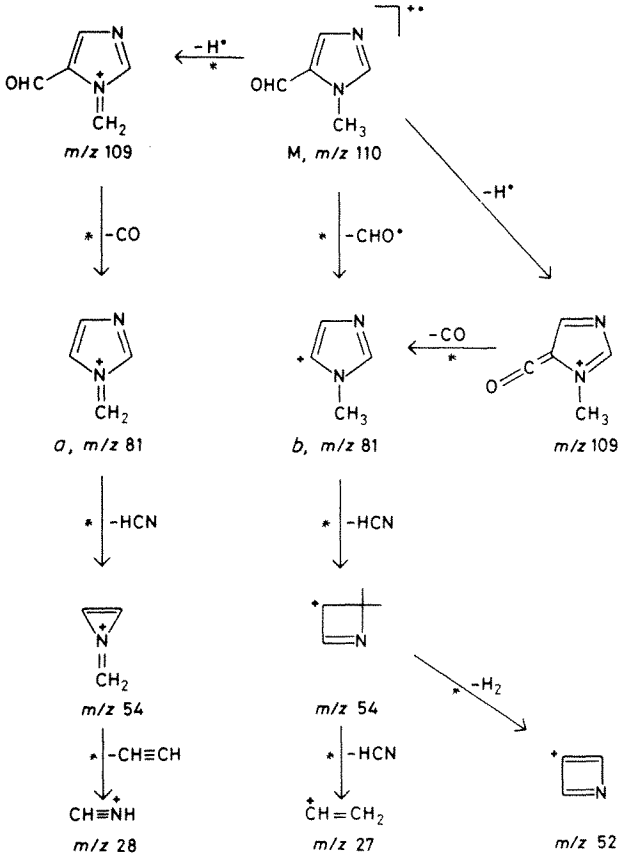


Figure 1. Mass spectra (70 eV) of 1-methylimidazole-4-carboxaldehyde (**1a**), 1-methylimidazole-5-carboxaldehyde (**1b**) and imidazol-4(5)-carboxaldehyde (**2a**).

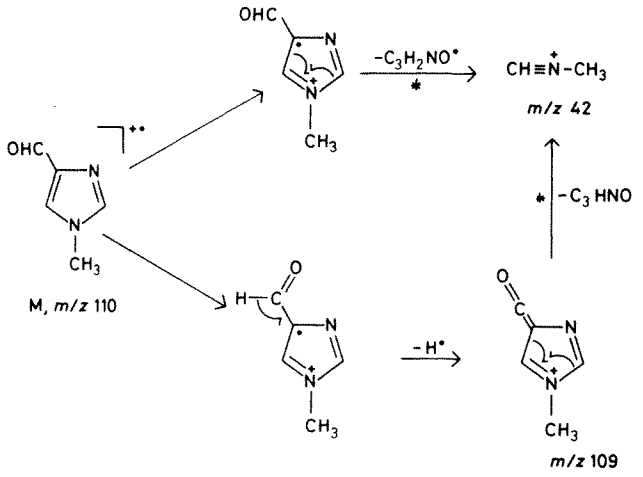
addition, the 1-methylimidazole-4-carboxaldehyde (**1a**) and the imidazole-4(5)-carboxaldehyde (**2a**) lose CO from the molecular ion. In **1a**, the $[M-CO]^{+\cdot}$ and $[M-CHO]^{+}$ ions decompose like the $[M]^{+\cdot}$ and $[M-H]^{+}$ ions of the 1-methylimidazole[1]; in **2a**, similar behaviour is observed with respect to the imidazole;[1] but in **1b**, the $[M-CHO]^{+}$ peak gives rise to a peak at *m/z* 54, exhibiting additional fragmentation routes. This last fact is attributed to the existence of *m/z* 81 ions with two different structures, *a* and *b* (Scheme 1), originated by losses involving hydrogen atoms from the methyl and formyl groups, respectively.

In 1-methylimidazole-4-carboxaldehyde (**1a**), the strong peak at *m/z* 42 is due to ions derived directly from the $[M]^{+\cdot}$ and $[M-H]^{+}$ ions, added to that resulting from the *m/z* 82 ion. A mechanism (Scheme 2), similar to that postulated for the 1-methyl-4-nitroimidazole,[7] explains the formation of the *m/z* 42 ion and the high abundance of the $[M-H]^{+}$ peak.

The formation of $[M-H]^{+}$ ions by loss of a hydrogen atom from the methyl group or from the imidazole ring, both common losses in the 1-methylimidazole[11] and imidazole,[12] seems to be negligible in **1a** but must be taken into account in **1b** and **2a**, since the typical metastable peak originated by these transitions is only observed in compounds **1b** and **2a**. The loss of H$^{\cdot}$ from the methyl group is in agreement with the fragmentation pattern suggested above for **1b** (Scheme 1). The elimination of HCN from the



Scheme 1. Fragmentation of 1-methylimidazole-5-carboxaldehyde (**1b**).



Scheme 2. Formation mechanisms for $[M-H]^{+}$ and *m/z* 42 ions in 1-methylimidazole-4-carboxaldehyde (**1a**).

$[M-H]^{+}$ ion, a typical loss in imidazoles,[1] is only significant in the imidazole-4(5)-carboxaldehyde (**2a**).

In comparing the mass spectra of the 1-methyl derivatives **1a** and **1b**, and that reported[1] for the 2-formyl isomer, it can be seen that either 2- or 4-formyl substitution favours the primary expulsion of CO over the loss of CHO$^{\cdot}$; however, the 4-formyl derivative shows very strong $[M-H]^{+}$ and *m/z* 42 peaks in contrast to the low abundance exhibited by these peaks in the 2-formyl isomer; finally, the formyl group attached at the 5-position facilitates the loss of the CHO$^{\cdot}$, suppressing the primary loss of CO. In the spectrum of the imidazole-2-carboxaldehyde,[1] the $[M-CO]^{+\cdot}$ peak is greater than the $[M-CHO]^{+}$ peak, and the reverse occurs in the 4(5)-formyl isomer (**2a**). This compound exhibits a fragmentation intermediate between those that would be expected from the two tautomeric forms.

Nitroimidazole derivatives (2b, 1c and 2c)

As in the methyl-nitroimidazoles,[7] the presence of the nitro group in the compounds eliminates the $[M-H]^{+}$ ion and originates primary losses of O, NO$^{\cdot}$ and $NO_2^{\cdot}$, as well as the loss of CO from the $[M-NO]^{+}$ ion (Fig. 2). The appearance of a pressure-dependent peak, $[M+1]^{+}$, indicates the formation of an $[M+H]^{+}$ ion by an ion/molecule reaction. The fact that the $[M+H]^{+}$ ion is also observed in 1-methyl-5-nitroimidazole but not in the imidazole or in the imidazole-carboxaldehydes, suggests for this ion the structure indicated in Scheme 3.

The nitroimidazole-carboxaldehydes **1c** and **2c**, which possess adjacent formyl and nitro groups, show a complete suppression of the primary fragmentation of aldehydes. As demonstrated for *o*-nitrobenzaldehyde,[3] the very low abundance of the molecular ions suggests negligible isomerization to the nitroso acid derivative. On the other hand, several *ortho* effects, some of which are the origin of the main fragmentation routes, are detected.

The fragmentation pattern of 5(4)-nitroimidazole-4(5)-carboxaldehyde (**2c**) (Scheme 4) corroborates the

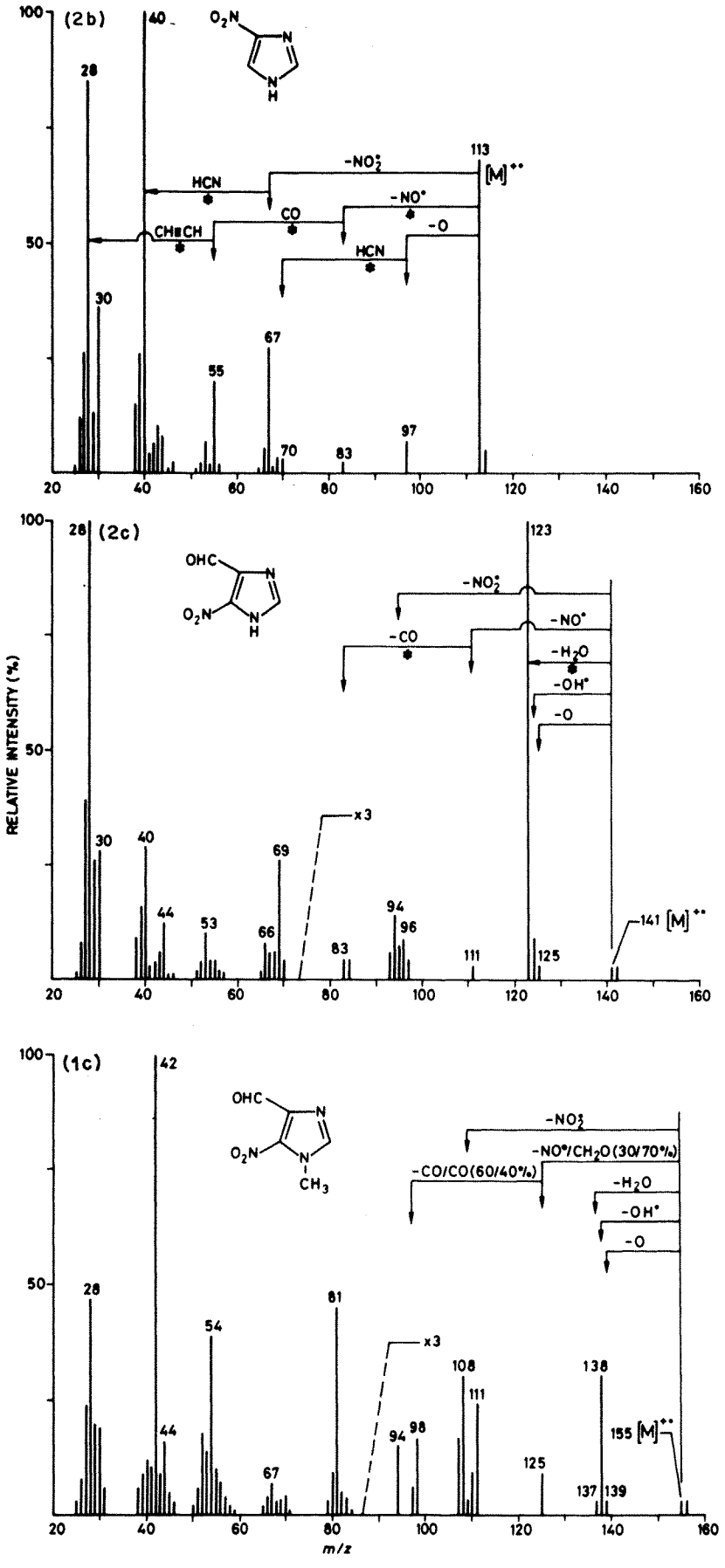
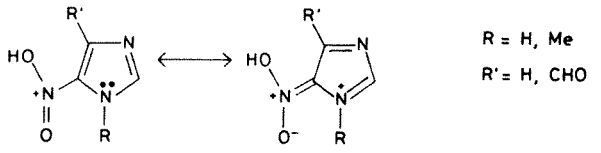


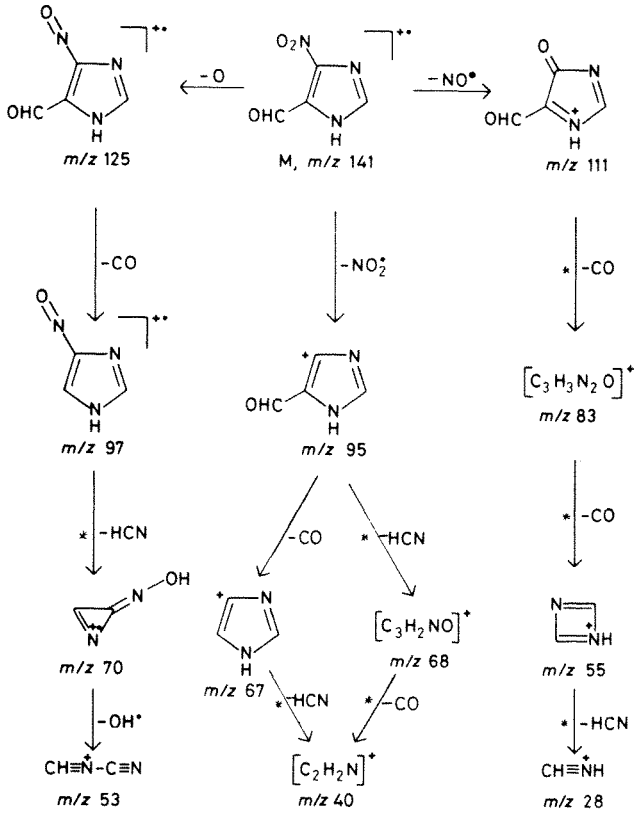
Figure 2. Mass spectra (70 eV) of 4(5)-nitroimidazole (**2b**), 5(4)-nitroimidazole-4(5)-carboxaldehyde (**2c**) and 1-methyl-5-nitroimidazole-4-carboxaldehyde (**1c**).



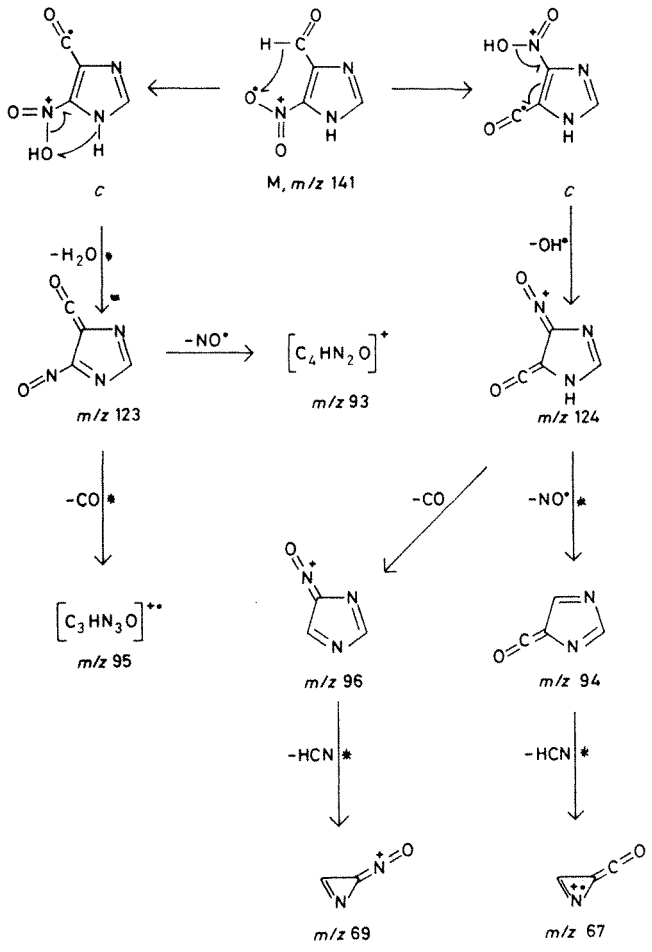
Scheme 3. Structure of $[M + H]^+$ ions in nitroimidazoles.

presence of the formyl group. The *ortho* effects result in primary losses of OH$^\cdot$ and H_2O (Scheme 5). Upon exchange with D_2O, label retention in the m/z 124 ion, no shift of the m/z 123 ion and a metastable peak for the elimination of DHO from the deuterated molecular ion, were found. These observations are consistent with the H-shift from the formyl group to the nitro group, form *c*, followed either by loss of OH$^\cdot$ or by the elimination of H_2O via a mechanism similar to that reported for *o*-methyl-nitroimidazoles.[8]

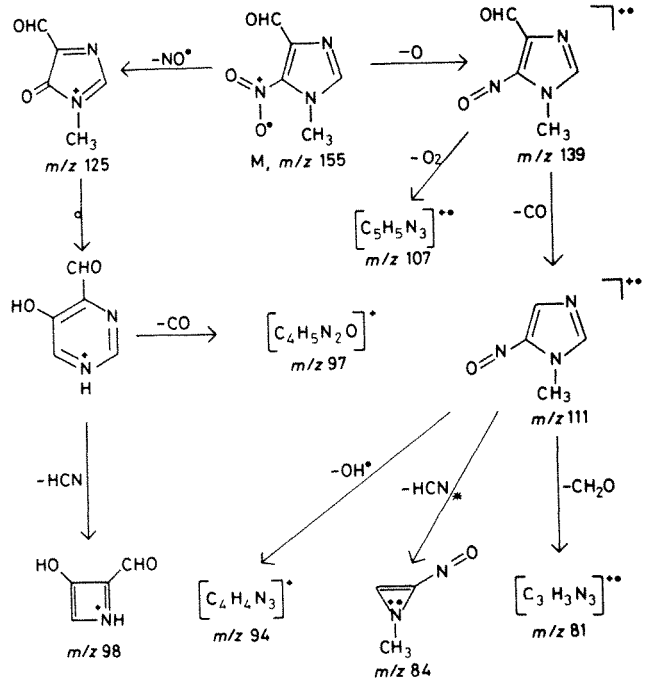
In the methyl derivative **1c**, secondary *ortho* effects are observed (Scheme 6). The losses of OH$^\cdot$ and CH_2O from the m/z 111 ion are those reported from the $[M - O]^{+\cdot}$ ion in 1-methyl-5-nitroimidazole.[7] The loss of O_2 from the $[M - O]^{+\cdot}$ ion, not observed in **2c**, suggests that the methyl group is involved in permitting a ring expansion. The loss of HCN from the $[M - NO]^+$ ion, not occurring in **2c**, is postulated by a H-shift from the methyl group to the oxygen, followed by a ring expansion. Regarding primary *ortho* effects, the loss of OH$^\cdot$ is the origin of an important fragmentation route. Surprisingly, $[M - H_2O]^{+\cdot}$ and $[M - CH_2O]^{+\cdot}$ ions are observed, but



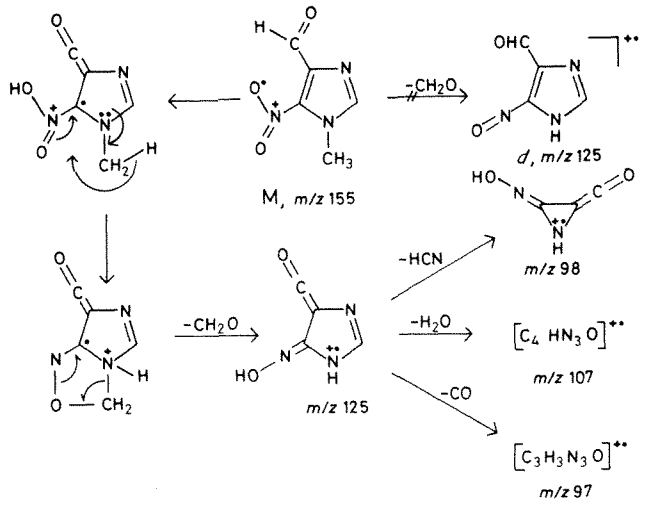
Scheme 4. Partial fragmentation of 5(4)-nitroimidazole-4(5)-carboxaldehyde (**2c**).



Scheme 5. Losses of OH$^\cdot$ and H_2O in 5(4)-nitroimidazole-4(5)-carboxaldehyde (**2c**).



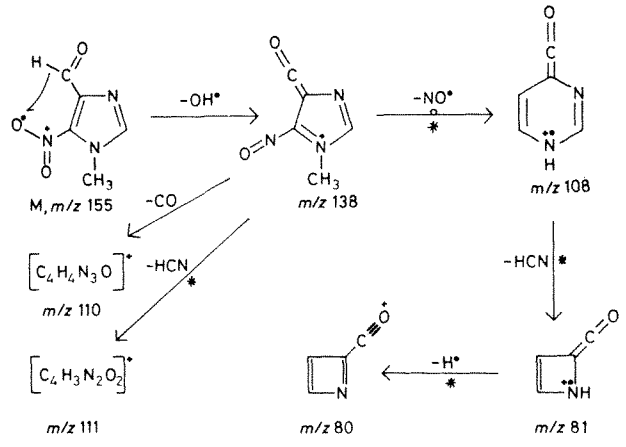
Scheme 6. Secondary *ortho* effects in 1-methyl-5-nitroimidazole-4-carboxaldehyde (**1c**).



Scheme 7. Loss of CH_2O in 1-methyl-5-nitroimidazole-4-carboxaldehyde (**1c**).

there is no CHO· loss. The loss of H_2O is due to a double H-transfer from formyl and methyl groups, since there is no mobile hydrogen in the imidazole ring. It seems that these two groups are also involved in the loss of CH_2O, since an elimination involving the methyl and nitro groups would bring about an $[M-CH_2O]^{+\cdot}$ ion different from the one observed; i.e. any one of the mechanisms postulated[5,9] for the loss of CH_2O in the *o*-alkylnitroimidazoles would lead to a *d* ion (Scheme 7) with the same structure as the *m/z* 125 ion in **2c** (Scheme 4), which only loses CO, while the *m/z* 125 ion in **1c** loses H_2O, CO and HCN. In agreement with these findings, the expulsion of CH_2O can be explained by assuming an initial H-transfer from the formyl group to the nitro group, followed by a migration of hydrogen from the methyl group to the methyl-carrying nitrogen atom.

In the methyl-nitroimidazoles, it has been postulated by Luijten and van Thuijl[9] that the losses of OH· and CHO· and/or CH_2O originate from a common precursor ion, which is due to the H-shift from the methyl group to nitro group. In **1c**, the lack of



Scheme 8. Loss of OH· in 1-methyl-5-nitroimidazole-4-carboxaldehyde (**1c**).

$[M-CHO]^+$ ions and the above-mentioned mechanism for the formation of $[M-CH_2O]^{+\cdot}$ ions suggest that the initial H-shift from the methyl group does not occur. Therefore, it seems that the loss of OH· begins with a migration of the hydrogen atom from the formyl group (Scheme 8), as in compound **2c**. The main fragmentation route from the $[M-OH]^+$ ion is due to the loss of NO·, rendering the *m/z* 108 ion whose structure is formulated assuming a H-transfer from the methyl group to the vacant 5-position, followed by a ring expansion.

In summary, the *ortho* effects involving the nitro and formyl groups are the most significant, and in the trisubstituted derivative **1c**, the interactions between the nitro group and each adjacent substituent are affected by the presence of the other group.

EXPERIMENTAL

Mass spectral data were obtained with an MS 30 mass spectrometer operated under the following conditions: electron energy, 70 eV; electron beam current, 100 μA; accelerating voltage, 4 kV; source temperature, 200 °C. Samples were introduced by means of a solid probe heated at temperatures of 50–275 °C, except **1b**, which was analysed via a gas chromatograph. Accurate mass measurements were carried out at a resolving power of 10000 (10% valley), with an error within 10 ppm. Metastable peaks were registered at a resolution of 1000 and at an electron beam current of 500 μA. Metastable mass measurements were correct to within 500 ppm. The exchange of the N-bonded hydrogen atom by deuterium was performed by introducing D_2O into the source via a separate inlet system.

Preparation of compounds

1-Methylimidazole-4-carboxaldehyde (1a). Compound **1a** was obtained from 1-methyl-4-(D-*arabino*tetritol-1-yl)-imidazole[13] by sodium metaperiodate oxidation as follows: a solution of starting compound (5 mmol) in 20 ml of water was ice-cooled and an aqueous solution of $NaIO_4$ (15 mmol in 30 ml of H_2O) was added with stirring. After 15 min, the solution was extracted with chloroform (3 × 20 ml). The chloroform extracts were water-washed and dried on anhydrous sodium sulphate. After evaporation under reduced pressure, the residue was crystallized from methanol. Yield 68%; m.p. 65–67 °C.

Imidazole-4(5)-carboxaldehyde (2a). Compound **2a** was obtained from 4(5)-(D-*arabino*tetritol-1-yl)-imidazole by metaperiodate oxidation as described earlier;[14] m.p. 173–174 °C (lit. m.p. 173–174 °C).

1-Methylimidazole-5-carboxaldehyde (1b). Compound **1b** was synthesized by methylation of **2a** as described in the literature.[15] Because of the hygroscopic character of **1b**, its complete purification by crystallization was not possible. Therefore, it was introduced in the mass spectrometer via a gas chromatograph. A column

(2 m × 1/8 inch) packed with 10% FFAP on Chromosorb AW-DMS, maintained at 115 °C, was used. The helium flow rate was 60 $cm^3 min.^{-1}$ The compound showed a retention time of 2.5 min.

4(5)-Nitroimidazole (2b). Compound **2b** was prepared by nitration of imidazole, m.p. 308–310 °C (lit.[16] m.p. 308–310 °C).

1-Methyl-5-nitroimidazole-4-carboxaldehyde (1c) and 4(5)-nitroimidazole-5(4)-carboxaldehyde (2c). Compounds **1c** and **2c** were obtained,[17] respectively, from 1-methyl-4-(D-*arabino*tetritol-1-yl)-imidazole[13] and 4-(D-*arabino*tetritol-1-yl)-imidazole,[18] by the sequential reactions that follow: acetylation with acetic anhydride in pyridine, nitration with concentrated nitric acid in trifluoroacetic anhydride, deacetylation with ammonia in methanol and, finally, oxidation with sodium metaperiodate as described for **1a**. Compound **1c** was crystallized from ethanol; m.p. 103–104 °C. Compound **2c** was crystallized from water; m.p. 232–233 °C (lit.[19] m.p. 231–232 °C).

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