Mass Spectrometry of Nitroazoles

1–The Mass Spectra of Methyl Substituted Nitropyrazoles

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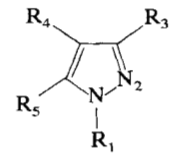
The mass spectra of all isomers of methylnitropyrazoles are reported. Generally, the spectra are characteristic of nitropyrazoles. In some cases however, *ortho* effects occur, recognizable by primary losses of, for example, OH˙, H_2O, CHO˙, CH_2O.

INTRODUCTION

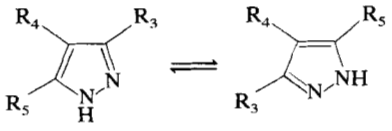
The presence of two totally different fragmentation directing substituents in relatively simple compounds may have a profound influence on their behaviour upon electron impact. In pyrazoles, introduction of a nitro group results in primary fragments in which the ring appears to remain intact,[1] whereas methylpyrazoles almost exclusively lose a hydrogen radical, followed by ring expansion.[2] Moreover, interaction of adjacent substituents can, in principle, give rise to *ortho* effects.

Mass spectral data on methylnitropyrazoles are scarce: only the mass spectrum of 1-methyl-5-nitropyrazole (**2c**) has been reported;[3] Ferguson and Schofield have observed that it is subject to primary loss of CHO˙.[3b]

The following compounds have been studied:



1a, 1b, 1c
2a, 2b, 2c



3a, 3b, 3c

	R_1	R_3	R_4	R_5
1a	NO_2	CH_3	H	H
1b	NO_2	H	CH_3	H
1c	NO_2	H	H	CH_3
2a	CH_3	NO_2	H	H
2b	CH_3	H	NO_2	H
2c	CH_3	H	H	NO_2
3a	—	CH_3	H	NO_2
3b	—	NO_2	CH_3	H
3c	—	CH_3	NO_2	H

In compounds **3a**, **3b**, **3c** there is a rapid equilibrium between two tautomers resulting in equivalence of positions 3 and 5. For compounds **2a**, **2b**, **2c** CD_3 and $^{13}CH_3$ labelled analogues have also been studied.

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RESULTS AND DISCUSSION

1-Nitro compounds (1)

The mass spectra of these compounds are given in Fig. 1.

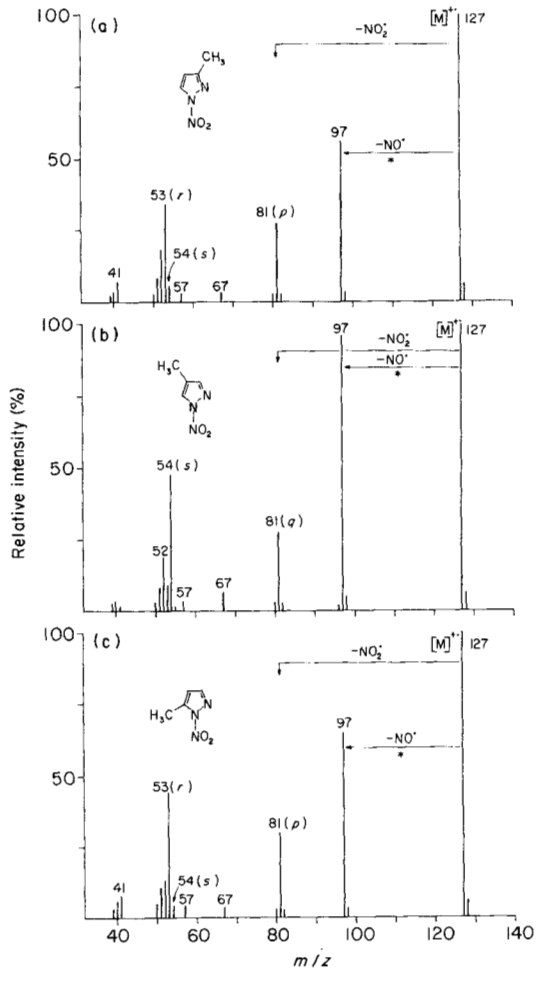

Figure 1. Mass spectra (70 eV) of 1-nitropyrazoles: (a) 3-methyl- (**1a**); (b) 4-methyl- (**1b**); (c) 5-methyl- (**1c**).

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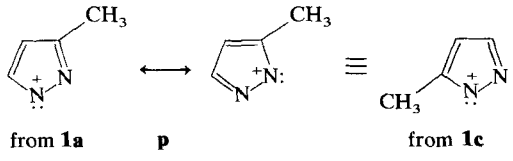
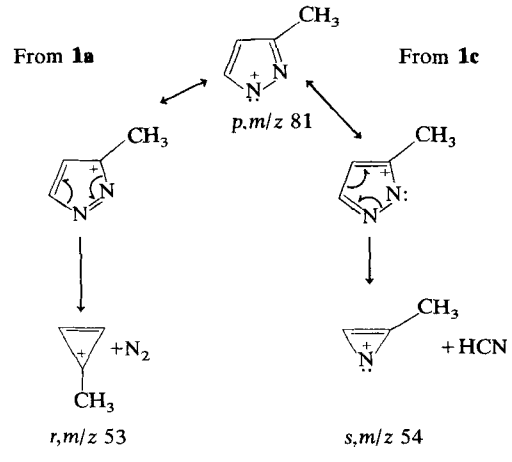
The main common features are a major loss of NO$^{\cdot}$, the absence of a $[M-O]^{+\cdot}$ fragment and a $[M-NO_2]^+$ ion, *m/z* 81, of moderate intensity which is the main source of secondary fragmentations.

Part of the cluster at *m/z* 80–82 (uncorrected spectra), is probably also due to thermochemically formed methylpyrazole (*m/z* 82), generated by wall reactions during introduction of the compounds **1** into the ion source. Inlet and source temperatures were kept below 110 °C, but this reaction apparently takes place to some extent. (The mass spectra in Fig. 1 have been corrected for thermal decomposition.) An analogous mass spectral reaction has been reported for several aromatic nitramines.[5] (In solution, certain 1-nitropyrazoles rearrange to C-nitro isomers above 140 °C.[4])

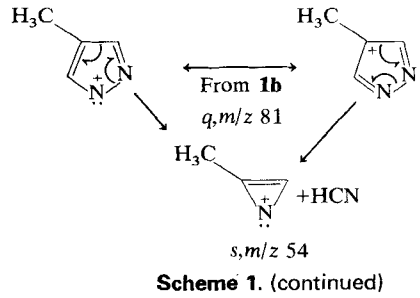
A noticeable difference between the spectra is given by the cluster at *m/z* 50–55. The spectra of **1a** and **1c** have the most abundant ion at *m/z* 53, $[C_4H_5]^+$, whereas in **1b** no abundant *m/z* 53 ion is observed. However, the peak at *m/z* 54, $[C_3H_4N]^+$, which is absent in **1a** and **1c** is the most prominent ion in the spectrum of **1b**. Accelerating voltage scans show *m/z* 53 to be generated from *m/z* 81 (loss of N_2), and in **1b** *m/z* 54 is also produced from *m/z* 81 (loss of HCN). The common behaviour pattern for the $[M-NO_2]^+$ ions *p* of **1a** and **1c** is not surprising as their structures are equivalent:



Because the mass spectra of 3-methyl- and 4-methylpyrazole, recorded under similar conditions, are almost identical,[6] possible thermal formation (*vide supra*) of these impurities cannot account for the observed difference. Therefore it must be due to the position of the methyl group, as rationalized in Scheme 1:

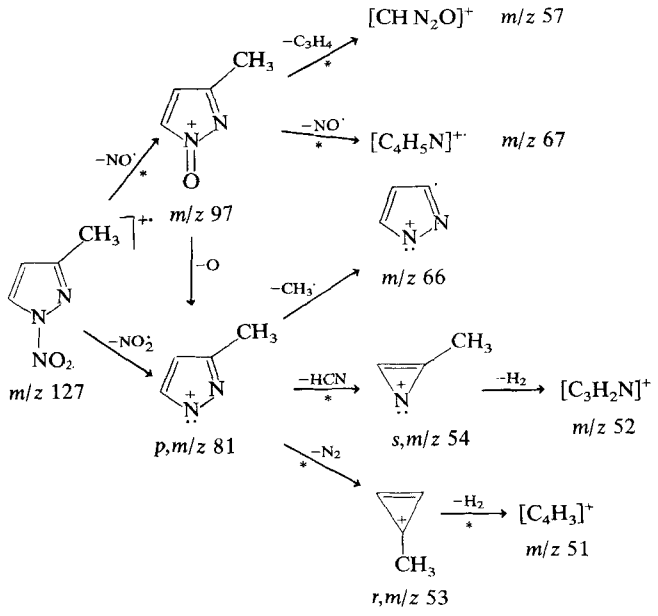


Scheme 1. Fragmentation of the $[M-NO_2]^+$ ions of methyl-1-nitropyrazoles **1a**, **1b**, **1c**.



Scheme 1. (continued)

The scheme explains production of ion *s* by loss of HCN from *q* when the methyl group is in the 4-position (**1b**), and the identical behaviour of the $[M-NO_2]^+$ ions *p* from **1a** and **1c** yielding ions *r* and *s* by respective secondary losses of N_2 and HCN. For this group of compounds the $[M-H]^+$ ions are negligible, in contrast to the methylpyrazoles. In addition, no *ortho* effects have been observed. The fragmentation pathways of 1-nitro-3-methylpyrazole (**1a**) are given in Scheme 2:



Scheme 2. Fragmentation of 1-nitro-3-methylpyrazole (**1a**).

1-Methyl compounds (2)

The mass spectra of the compounds are presented in Fig. 2.

1-Methyl-3-nitropyrazole (2a). The mass spectrum is characterized by a very stable molecular ion. Although fragments at *m/z* 111 and 97 are indicative of the presence of a nitro group the $[M-NO_2]^+$ fragment, *m/z* 81, is of low abundance. Instead an *m/z* 80 ion is formed, either by primary loss of HNO_2, or by subsequent loss of H$^{\cdot}$ from *m/z* 81. Accelerating voltage scans show that loss of HCN from *m/z* 81–79 is responsible for a cluster around *m/z* 53.

The ion $[C_4H_5N_2O]^+$, *m/z* 97, is also capable of ejecting CO, leading to $[C_3H_5N_2]^+$, *m/z* 69, which may further decompose in two ways; one generating *m/z* 43, $[CH_3N_2]^+$ by loss of C_2H_2, the other *m/z* 42,

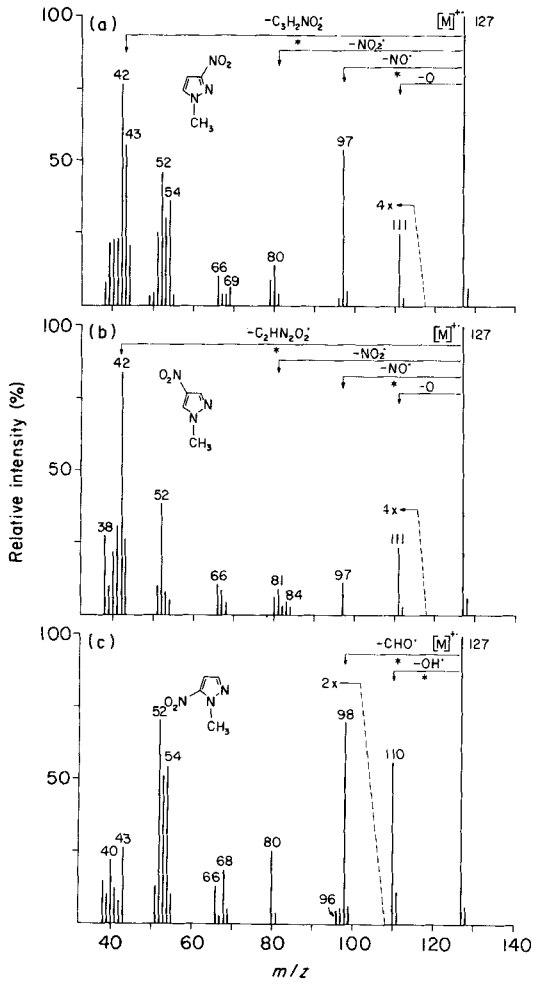
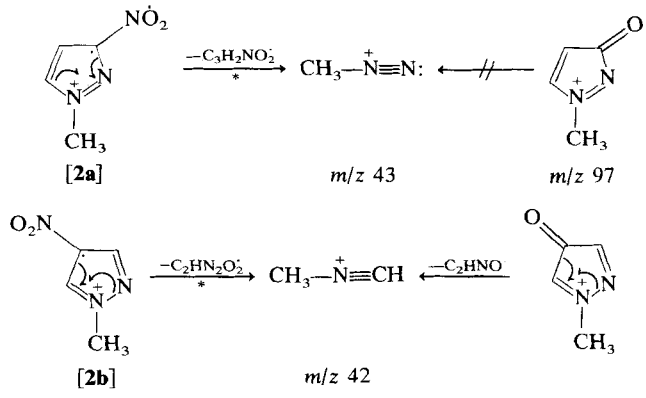
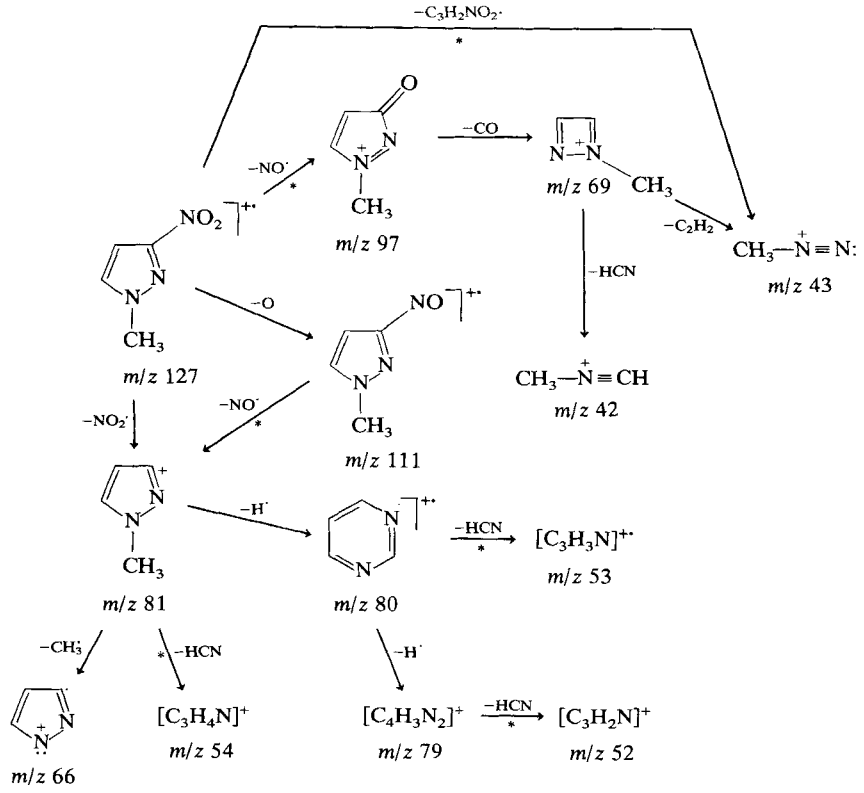


Figure 2. Mass spectra (70 eV) of 1-methylpyrazoles: (a) 3-nitro- (**2a**); (b) 4-nitro- (**2b**); (c) 5-nitro (**2c**).

$[C_2H_4N]^+$ by loss of HCN. Analogous fragmentations in the $^{13}CH_3/CD_3$ labelled compounds show only fragments generated by loss of unlabelled HCN/C_2H_2. This could be an indication for the structure of *m/z* 69 given in Scheme 3. Another interesting process is the direct formation of $[CH_3N_2]^+$, *m/z* 43, from the molecular ion by loss of $C_3H_2NO_2^{\cdot}$ as evidenced by a second field free region metastable transition. Fragmentations are summarized in Scheme 3.

1-Methyl-4-nitropyrazole (2b). As compared with its 3-isomer (**2a**), some differences are noteworthy. The direct formation from the molecular ion of *m/z* 43, $[CH_3N_2]^+$, found with **2a**, is not observed in **2b**. Instead *m/z* 42, $[C_2H_4N]^+$, is generated in a one-step reaction from the molecular ion. Furthermore, *m/z* 42 is also formed from the $[M-NO]^+$ ion, *m/z* 97, while the analogous ion, *m/z* 97, in **2a**, does not fragment to generate *m/z* 43 and/or *m/z* 42. The formation of the stable $[C_2H_4N]^+$ ion might be responsible for the low abundance of the $[M-NO]^+$ ion in **2b** relative to **2a**. The two processes can be represented as follows:

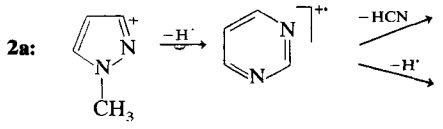




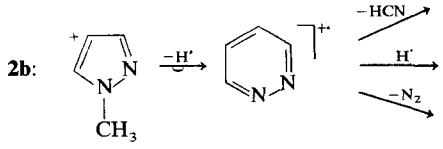
Scheme 3. Fragmentation of 1-methyl-3-nitropyrazole (**2a**).

In accordance with the above, complete label retention is found for the two product ions of the CD_3 and $^{13}CH_3$ analogues. A second difference between **2a** and **2b** is the behaviour of the $[M-O]^{+\cdot}$ ion, *m/z* 111. In **2a** it loses NO$^{\cdot}$ exclusively, whereas in **2b** it also expels HCN (*m/z* 84), followed by loss of CNO$^{\cdot}$, another route to the most abundant fragment ion *m/z* 42. Again the methyl group appears not to be involved in the breakdown sequence 127 → 111 → 84 → 42, since D and ^{13}C labels are retained completely.

The degradation of the $[M-NO_2]^+$ ion, *m/z* 81, is a further point of interest. According to Scheme 3, the ions *m/z* 81–79 in **2a** all lose HCN, thereby generating fragments *m/z* 54–52 of approximately equal abundance, whereas *m/z* 81 in **2b** yields one abundant ion at *m/z* 52, $[C_3H_2N]^+$. The fact that the $[M-NO_2-H]^{+\cdot}$ ion of **2b**, *m/z* 80, expels N_2, whereas the corresponding ion from **2a** does not, appears to be in agreement with the following possible ring expanded structures for *m/z* 80:[10]



Pyrimidine

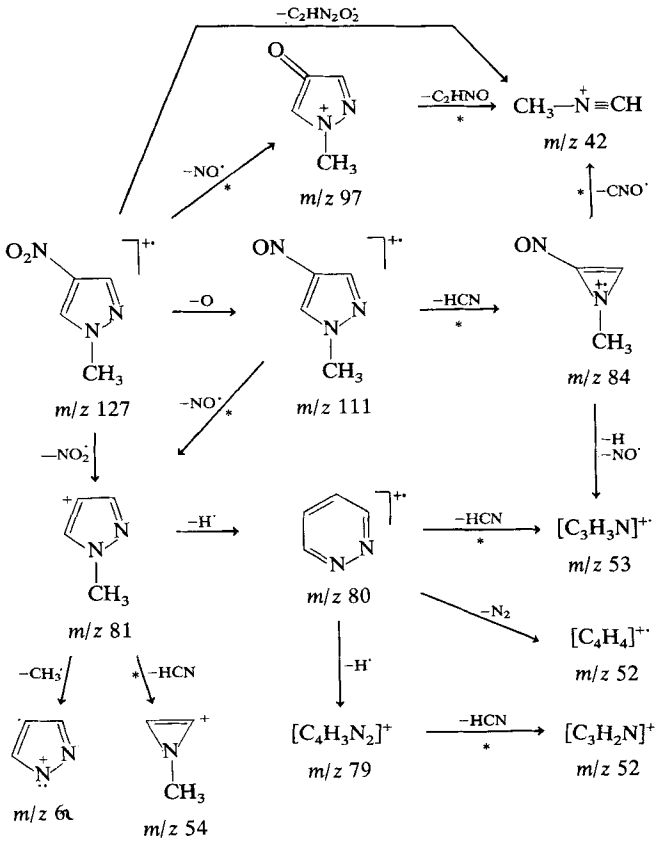


Pyridazine

The above observations are presented in Scheme 4.

1-Methyl-5-nitropyrazole (2c). A molecular ion of lower relative abundance, as compared with the two previous compounds, is a noticeable feature in the mass spectrum. The fragmentation pattern does not suggest the presence of a nitro group. The adjacent substituents give rise to two *ortho* effects. The first, loss of OH$^{\cdot}$ from the molecular ion, has been observed in analogous cases, e.g. in *o*-nitrotoluene.[7] Subsequent losses of NO$^{\cdot}$ and HCN, and the fact that in the $^{13}CH_3$ compound the label is retained for the last process, indicate that no ring expansion occurs and that the remaining oxygen atom in the $[M-OH]^+$ ion, *m/z* 110, occupies its original position. For *o*-nitrotoluene it has been suggested that this is not the case.

The second *ortho* effect is less common; it involves loss of CHO$^{\cdot}$ from the molecular ion.[3b] The mass spectra of the labelled analogues show unambiguously that the carbon and hydrogen atoms lost originate from the methyl group. Detailed treatment of *ortho* effects of the present compounds will be given in a forthcoming paper.[8] Ejection of NO$^{\cdot}$ from this $[M-CHO]^+$ ion, *m/z* 98, gives rise to $[C_3H_4N_2]^{+\cdot}$, *m/z* 68. This ion is probably identical with the pyrazole molecular ion since its further degradation is wholly similar.[1]



Scheme 4. Fragmentation of 1-methyl-4-nitropyrazole (**2b**).

A second major breakdown process of the $[M-CHO]^+$ ion is successive expulsion of two hydrogen radicals to give *m/z* 96, which product ion can lose either N_2 or NO$^{\cdot}$, giving rise to ions $[C_3H_2NO]^+$, *m/z* 68 and $[C_3H_2N_2]^{+\cdot}$, *m/z* 66, respectively. In the CD_3 compound this sequence is entirely shifted to 100 → 98 → 96 → 68 and 66, showing that the two hydrogen radicals lost originate from the methyl group.

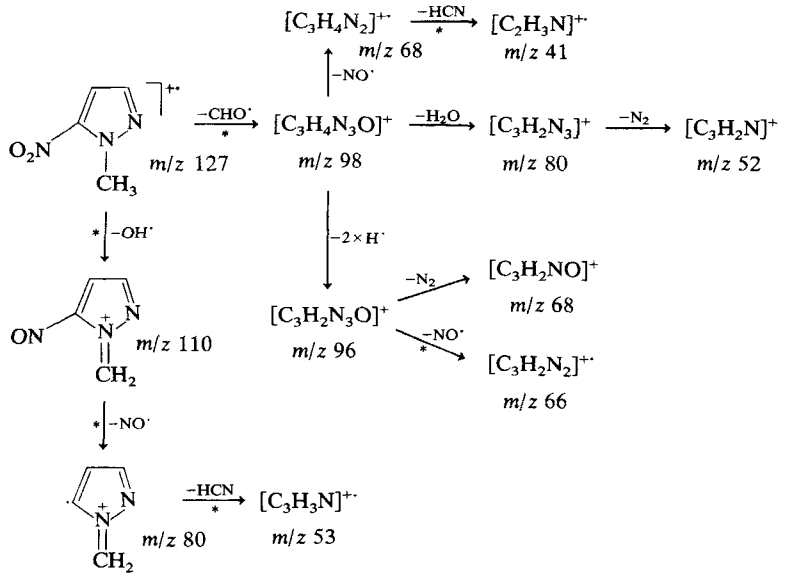
Further inspection reveals that *m/z* 80 constitutes a doublet of roughly equal abundance, $[C_4H_4N_2]^{+\cdot}$, or $[M-OH-NO]^{+\cdot}$ and $[C_3H_2N_3]^+$. As expected, the first ion is found at *m/z* 82 and 81 respectively in the CD_3 and $^{13}CH_3$ compounds, whereas the second ion is still observed at *m/z* 80, thus representing a net loss of CD_3O_2 or $^{13}CH_3O_2$. Accelerating voltage scans show that $[C_3H_2N_3]^+$ is formed from $[M-CHO]^+$ by loss of H_2O (D_2O). These fragmentations are given in Scheme 5.

A primary process 127 → 43 or 42, observed for **2a** and **2b**, appears to be absent.

C-Methyl-C-nitro compounds (3)

The mass spectra of these compounds are found in Fig. 3.

3(5)-Methyl-5(3)-nitropyrazole (3a). A stable molecular ion and fragments at *m/z* 111, 97 and 81 reveal the nitro group. A $[M-OH]^+$ ion is also present and is



Scheme 5. Fragmentation of 1-methyl-5-nitropyrazole (**2c**).

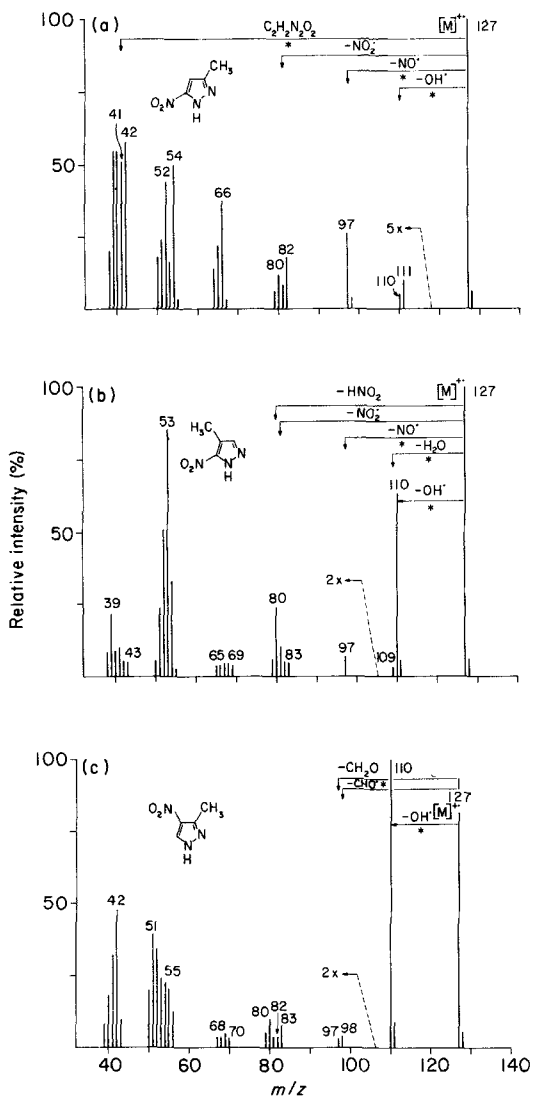
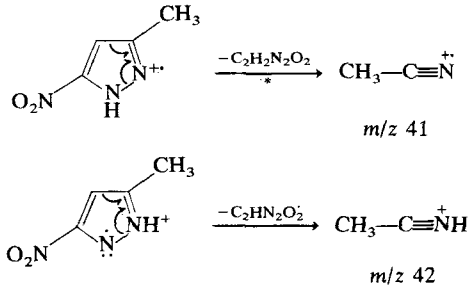


Figure 3. Mass spectra (70 eV) of (a) 3(5)-methyl-5(3)-nitro- (**3a**), (b) 3(5)-nitro-4-methyl- (**3b**) and (c) 3(5)-methyl-4-nitropyrazole (**3c**).

formed directly from the molecular ion by a process involving the labile N-bonded hydrogen. This ion is capable of expelling N_2, giving rise to $[C_4H_4NO]^+$, *m/z* 82. Ions at *m/z* 65, $[C_4H_3N]^{+\cdot}$ and *m/z* 52, $[C_4H_4]^{+\cdot}$, might be generated from this secondary ion by loss of OH· and NO· respectively. Only the last fragmentation could be detected as a second field free region metastable transition.

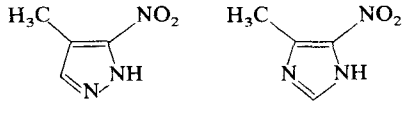
By analogy with **2a** and **2b**, a one-step reaction is found from the molecular ion to *m/z* 41, $[C_2H_3N]^{+\cdot}$. Although the corresponding second field free region metastable transition was not found, *m/z* 42, $[C_2H_4N]^+$, could equally well be formed in a direct process. It should be noted that, assuming this direct generation of *m/z* 42 and 41, the two possible tautomeric molecular ions can constitute the precursors.



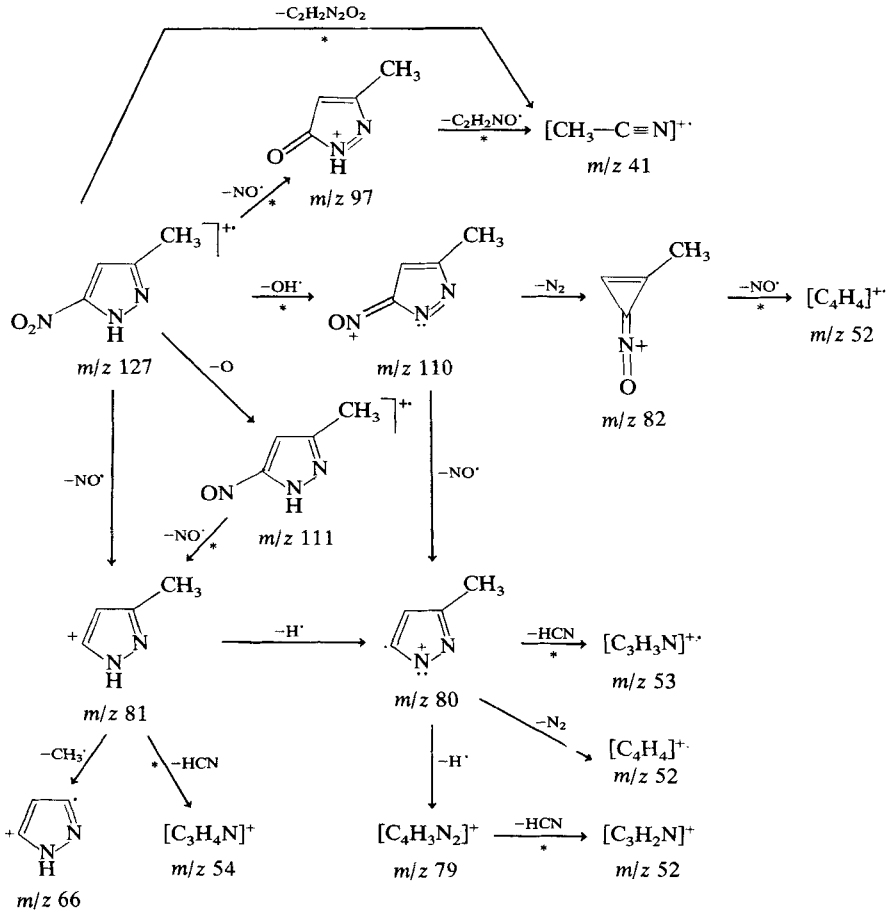
Fragmentations of **3a** are summarized in Scheme 6.

3(5)-Nitro-4-methylpyrazole (3b). In this compound, the adjacent substituents cause two *ortho* effects: primary loss of OH· in an abundance comparable with **2c**, and primary loss of a water molecule, as reported for its isomer 4(5)-methyl-5(4)-nitroimidazole **(4)**.[9] Details of these effects will be discussed in a forthcoming paper.

Other primary fragmentations include losses of



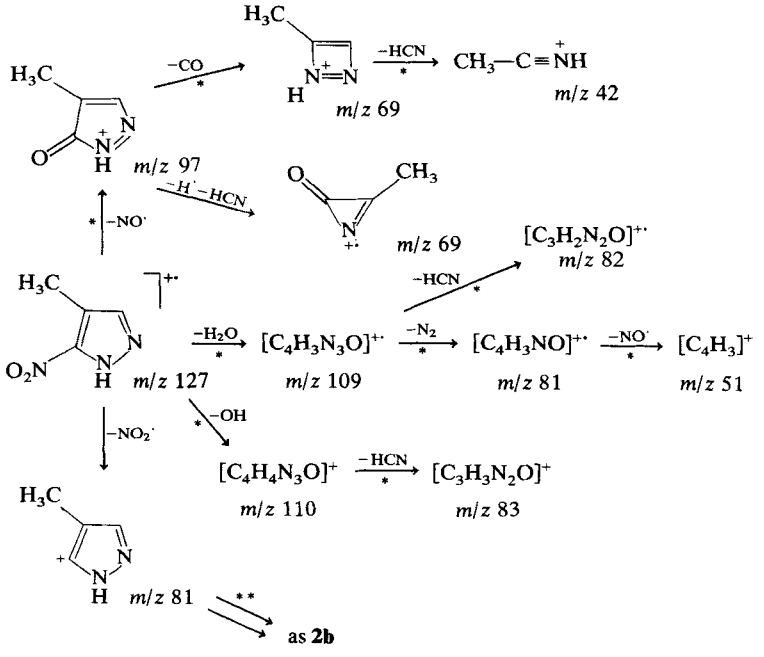
3b **4**



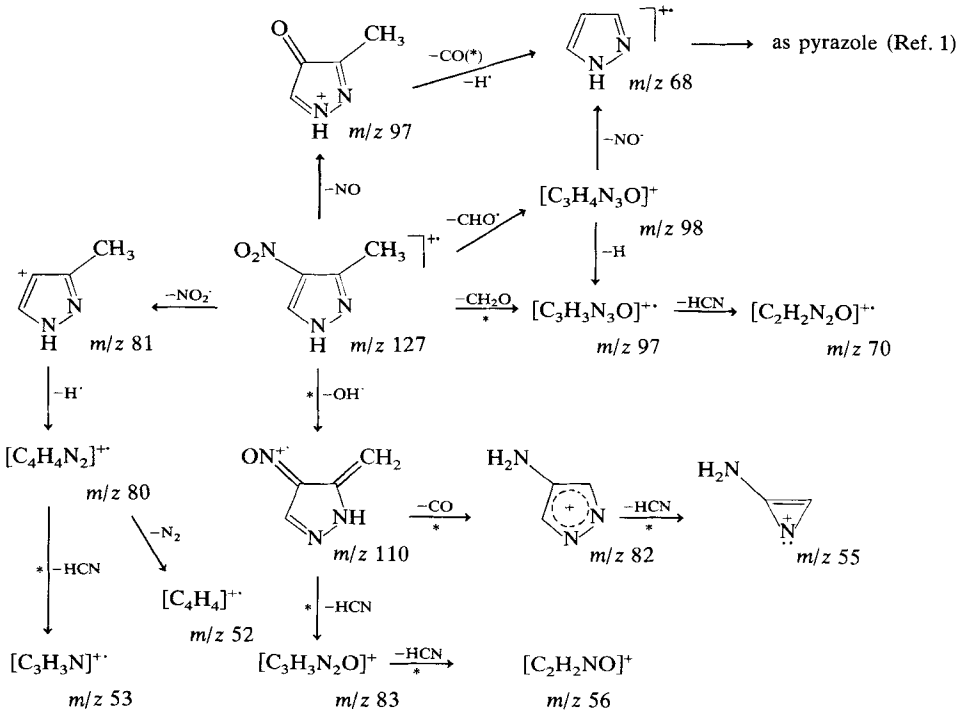
Scheme 6. Fragmentation of 3(5)-methyl-5(3)-nitropyrazole (**3a**).

$NO_2^{\cdot}$ and HNO_2, leading to *m/z* 81 and 80. Subsequent losses of H$^{\cdot}$ and HCN are responsible for the cluster at *m/z* 52–54, also observed with **2a** and **2b** though to a different extent.

As in **2a** loss of CO from the $[M-NO]^+$ ion, *m/z* 97, is observed. In **2a** subsequent reactions of the product ion *m/z* 69 lead to *m/z* 43 and 42, by respective losses of C_2H_2 or HCN. In **3b** only loss of HCN is found, indicating that the structure of *m/z* 69 in this case (Scheme 7) is different from the ion in **2a** (Scheme 3). The second fragment found in the doublet at *m/z* 69 is $[C_3H_3NO]^{+\cdot}$. A possible route leading to this ion is loss of H$^{\cdot}$ and HCN from the $[M-NO]^+$ ion, *m/z* 97.



Scheme 7. Fragmentation of 3(5)-nitro-4-methylpyrazole (**3b**).



Scheme 8. Fragmentation of 3(5)-methyl-4-nitropyrazole (**3c**).

3(5)-Methyl-4-nitropyrazole (3c). Principal primary losses are those of NO·, NO_2·, OH·, CHO· and CH_2O, the last three of which are due apparently to *ortho* effects. The $[M-OH]^+$ ion is capable of ejecting HCN, the product ion of which can degrade further by a second HCN loss to $[C_2H_2NO]^+$, *m/z* 56. A second, quite interesting fragmentation of $[M-OH]^+$ is loss of CO, yielding $[C_3H_4N_3]^+$, *m/z* 82. This process appears to be analogous with the scheme proposed by Meyerson *et al.*[7] for the loss of CO from the $[M-OH]^+$ ion of *o*-nitrotoluene. The mechanism, and the fact that two other isomers with adjacent substituents, **2c** and **3b**, do not show the sequence $[M]^{+\cdot} \rightarrow [M-OH]^+ \rightarrow [M-OH-CO]^+$, will be discussed in a forthcoming paper. Primary loss of NO· leads to $[C_4H_5N_2O]^+$, *m/z* 97, followed by loss of CO and H· to produce the pyrazole molecular ion, *m/z* 68.

The predominant breakdown process of the $[M-NO_2]^+$ ion is abstraction of H·, yielding *m/z* 80. In the event of ring expansion of $[M-NO_2]^+$, *m/z* 81, in **3a**, **3b**, **3c**, and subsequent loss of a hydrogen radical one would anticipate the formation of the pyridazine molecular ion as in **2b**. In all three cases the product ions *m/z* 80 indeed show the fragmentation behaviour of this species; loss of H·, HCN and N_2.[10]

Finally, two primary losses are those of CHO· and CH_2O. The $[M-CHO]^+$ ion, *m/z* 98, loses a hydrogen radical, followed by expulsion of HCN to yield $[C_2H_2N_2O]^{+\cdot}$, *m/z* 70, in contrast to the $[M-CHO]^+$ ion of **2c**, which shows an entirely different breakdown pattern (Scheme 5). The fragmentation of **3c** is given in Scheme 8.

CONCLUSIONS

In the compounds investigated the nitro group generally directs the fragmentation in such a manner that $[M-H]^+$, characteristic of methyl substituted azoles,[1,2] is barely observed. In some cases loss of OH·, and/or H_2O, CHO·, CH_2O are found, these losses being due to *ortho* effects. Only one compound having adjacent substituents, **1c**, did not show such a fragmentation. Probably this is due to the relative weakness of the N–NO_2 bond, and consequently fragmentation processes involving rupture of this bond compete effectively with processes likely to have rather low frequency factors.

Common features for each group of compounds have also been observed. Thus, the 1-nitro compounds **(1)** readily lose NO· to such an extent that relative abundances of the $[M]^{+\cdot}$ and $[M-NO]^+$ ions are comparable.

The 1-methyl derivatives **(2)** show, with one exception **(2c)**, a very abundant molecular ion and the fragmentation characteristics of aromatic nitro compounds. The exception is due to an *ortho* effect resulting in loss of OH· and CHO·, and consequently the presence of a nitro group is totally obscured at first sight.

Compounds **3**, with the two substituents at ring carbon atoms, have slightly less abundant molecular ions and in two cases a strong $[M-OH]^+$ ion. 3(5)-Methyl-5(3)-nitropyrazole **(3a)** is rather difficult to recognize from a comparison with its 1-methyl-3-nitro **(2a)** and 1-methyl-4-nitro **(2b)** isomers. In all the last three cases substituents are non-adjacent, illustrating that observation of *ortho* effects plays an important role in structure determination from mass spectra.

EXPERIMENTAL

Mass spectral data were obtained with an AEI MS 902 mass spectrometer. Samples were introduced through an all-glass heated inlet system at temperatures

of 120 °C above ambient, except for compounds **1** (90 °C above ambient) to minimize thermal rearrangements.[4] Elemental compositions of ions were determined at a resolving power above 10 000; fragmentation schemes were derived from accelerating voltage scans using an energy resolving variable monitor slit set at 80% transmission to obtain symmetrical peak shapes and consequently improved mass determinations.

Compounds **1**, **3a**, **3b** were prepared according to literature procedures.[4] Compounds **2a** and **2c** were prepared as follows.[2] Equimolar amounts of CH_3ONa in methanol, 3(5)-nitropyrazole[4] and methyl iodide (CH_3I, CD_3I, $^{13}CH_3I$) were left to stand for 48 h in a closed reaction vessel. Upon evaporation of the solvent, dichloromethane was added, and NaI precipitated. After filtration and reduction to a small volume, the solution was separated on a short silicagel column[11] and eluted with hexane/dichloromethane 1:1. A total yield of 80% (60% of **2a**, 20% of **2c**) was obtained. Purity, >99%, was checked on a GCMS system, using a 5% SE-30 packed column. **2a** is a white crystalline solid, m.p. 80–82 °C (lit. 81 °C[4]), **2c** a yellowish liquid, b.p. 78–80 °C/18 mm (lit. 186 °C[4]).

Compounds **2b** and **3c** were prepared as follows: 4 g (49 mmol) of the appropriate (1-, 3-) methylpyrazole were dissolved in 10 cm^3 of concentrated sulfuric acid (188 mmol). To the cooled (0 °C) stirred mixture was added 5 cm^3 of fuming nitric acid (d 1.5, 119 mmol), followed by another 20 cm^3 of concentrated sulfuric acid. The temperature was allowed to rise to ambient whilst stirring, and after 1 h brought to 80–90 °C. The mixture was stirred and kept at this temperature for 6 h, left to cool and poured on ice. After addition of base to pH 8, extraction with ethyl acetate, drying and removal of the solvent, the residues were crystallized from benzene/methanol 10:1, giving yields of 75%. M.p. **2b** 91–93 °C (lit. 92 °C[12]), m.p. **3c** 133–134 °C (lit. 134 °C[4]). The NMR spectra were in accordance with the proposed structures.

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