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4-Nitropyrazole: a nitrogen or an oxygen base in the gas phase?

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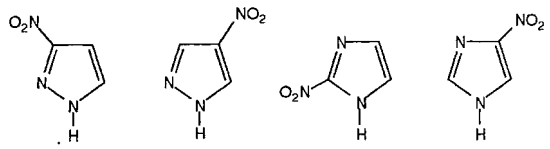
ABSTRACT: Protonated 3- and 4-nitropyrazoles were subject to collisional activation and neutralization–reionization mass spectrometric studies using a large scale tandem mass spectrometer. The gas phase basicities of 2- and 4-nitroimidazoles were determined by means of Fourier transform ion cyclotron resonance spectroscopy. These and other neutral and protonated molecules were studied by *ab initio* methods up to and including the CCSD(T)/6–31 + G* level. This information was used to assess the site of protonation of 3-nitro- and 4-nitropyrazole in the gas phase: at the equilibrium these compounds protonate on the heterocyclic nitrogen rather than on the oxygen of the nitro group. Copyright © 1999 John Wiley & Sons, Ltd.

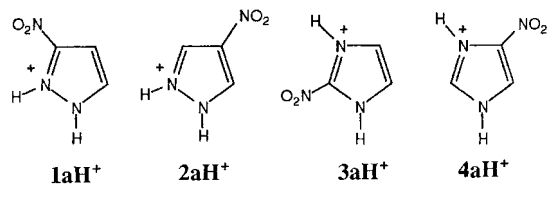
KEYWORDS: nitroimidazoles; nitropyrazoles; protonation; ion cyclotron resonance mass spectrometry; collision activation; neutralization and reionization mass spectrometry; *ab initio*

INTRODUCTION

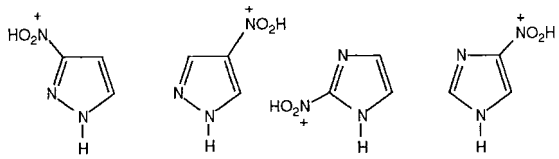
It was suggested in a previous work[1] that the acid–base properties of 3-nitropyrazole (**1**) could be 'abnormal' when compared with those of 4-nitropyrazole (**2**). Furthermore, it has been shown that amphiprotic compounds like pyrrole and indole carboxylic acids behave as NH acids in the gas phase and not as OH acids, as would be expected.[2] Therefore, we have decided to examine whether 4-nitropyrazole protonates on the azole N2 nitrogen atom (**2aH**$^+$ cation), like pyrazole itself, or on the nitro group, i.e. on the oxygen (**2bH**$^+$ cation), as other nitro derivatives.[3]



1 **2** **3** **4**



1aH$^+$ **2aH**$^+$ **3aH**$^+$ **4aH**$^+$

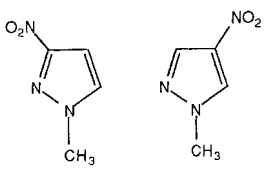


1bH$^+$ **2bH**$^+$ **3bH**$^+$ **4bH**$^+$

EXPERIMENTAL

Materials

The synthesis of compounds **1–6** has been described in previous publications.[1,4,5]



5 **6**

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Mass spectrometry

The spectra were recorded on a large-scale tandem mass spectrometer of $E_1B_1©E_2©©E_3B_2©E_4$ geometry (E stands for electric sector, B for magnetic sector and © for the collision cells installed in various field-free regions, Micromass, Autospec 6F).[6] Typical conditions were 8 kV accelerating voltage, 1 mA emission current, 70 eV ionization electron energy and 200 °C ion source temperature. Chemical ionization was performed using either methane or methanol as the reagent gas at an estimated 0.5–1 Torr ion source pressure. The samples were introduced with a direct insertion probe or via a heated (180 °C) septum inlet device.

The collisional activation (CA) spectra were obtained by presurizing the collision cell located in front of E_3 with oxygen (ca 70% transmittance) and scanning the field of E_3; the fragments were recorded with an off-axis photomultiplier detector in the fifth-free region. In neutralization–reionization (NR) experiments,[7] the collision with oxygen was preceded by collision with xenon (also 70% transmittance), the residual non-neutralized ions being removed from the fast neutral beam by floating at 9 kV an intermediate calibration source situated between the neutralization and reionization cells.

Resolved CA spectra were recorded using a linked scanning of the fields $E_3B_2E_4$, the fragments being detected by the final off-axis photomultiplier.

FT-ICR mass spectrometry

Gas-phase basicities were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS-47 Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer.[8–11] The gas-phase basicities of compounds **3** and **4** were determined through the study of the position of equilibrium (1), where B is the compound of unknown basicity (**3** or **4**) and B_{ref} is a reference base:

$$BH^+(g) + B_{ref}(g) \rightleftharpoons B(g) + B_{ref}H^+(g) \quad K_p, \delta GB \quad (1)$$

K_p is the equilibrium constant, and δ *GB* is given by $\delta GB = -RT \ln K_p$, being the difference between the gas-phase basicities of B and B_{ref}. The gas-phase basicity of a base B is the standard Gibbs energy change for reaction (2):

$$BH^+(g) \rightleftharpoons B(g) + H^+(g) \quad (2)$$

The experimental details of these measurements have been given elsewhere.[12] We present in Table 1 the results leading to the determination of the *GB* values of **3** and **4**.

Computational details

Standard *ab initio* and density functional theory calculations were carried out by means of the Gaussian-94 series of programs[13] at several levels of the theory, B3LYP/6–31*G** B3LYP/6–311 + *G** and CCSD(T)/6–31 + *G**.[14–21] The geometries of the systems included in this study were optimized using the B3LYP density functional method[18–21] together with 6–31+*G** basis set expansion. This level of theory has been found to yield reliable geometries for a wide variety of chemical compounds.[22–28] The corresponding vibrational frequencies as well as the zero point energy (ZPE, not scaled) corrections were evaluated at the same level. The minimum energy structure for the cations protonated on the nitro group has the O–H proton directed towards the second oxygen.

We assess the importance of high-order correlation contributions to energy, as they may play a non-negligible role both for azoles and the nitro group. For this purpose we carried out CCSD(T)/6–31 + *G** single point calculations[29] for some suitable cases that might be controversial. In all these high-correlated calculations the B3LYP/6–31 + *G** optimized geometries were used.

RESULTS AND DISCUSSION

Collisional activation mass spectrometry

Although the electron ionization mass spectrometry (EIMS) of nitrodiazoles was studied in a series of remarkable papers by Luitjen and van Thuijl,[30–33] the behaviour of the protonated molecules generated by chemical ionization (CIMS) has not, to the best of our

Table 1. Experimental results pertaining to the determination of the gas-phase basicities of 2-nitroimidazole (**3**) and 4-nitroimidazole (**4**)[a]

Compound	Reference	*GB* (B_{ref})[b]	δ *GB*	*GB* (compound)	*GB* (compound, average)
3	$(C_2H_5)_2S$	827.0	6.1	833.1	833.7 ± 0.8
	$(n-C_3H_7)_2S$	834.9	−0.7	834.2	
4	$(CH_3CO)_2CH_2$	836.8	4.1	840.9	841.6 ± 0.9
	$(n-C_4H_9)_2S$	842.1	0.1	842.2	

[a] All values in kJ mol^{-1}.
[b] All the *GB* values for the reference bases are taken from Hunter and Lias.[37]

knowledge, received much attention.[34] In fact, only the CA spectra of protonated nitrobenzenes have already been studied and interpreted on the basis of preferential protonation at the nitro groups.[35] Before looking at the nitropyrazoles, we therefore investigated the CA/NR data of nitrobenzene itself **7** as a model for oxygen protonation.

The CA spectrum of protonated nitrobenzene, $\mathbf{7H}^+$ (*m/z* 124), is shown in Fig. 1 (a). This spectrum features three intense peaks at *m/z* 107, 94 and 77 corresponding to the losses of HO$^\cdot$, NO$^\cdot$ and HNO_2, respectively. In fact, without the presence of the collision gas, two unimolecular reaction channels are operating: the loss of NO$^\cdot$ and the loss of $NO_2^\cdot$ [metastable ion (MI) spectrum: *m/z* 94/*m/z* 78 = 2.1]. These slow reactions are thus most probably rearrangement reactions and do not therefore require ring protonation. Thermodynamically, the losses of NO$^\cdot$ and of $NO_2^\cdot$ are also predicted to be the easiest reactions: $\sum \Delta H_f = 813$ kJ mol^{-1} (ionized phenol plus NO$^\cdot$) and 1009 kJ mol^{-1} (ionized benzene plus $NO_2^\cdot$) compared with 1021 kJ mol^{-1} (ionized nitrosobenzene plus HO$^\cdot$) and 1047 kJ mol^{-1} (phenyl cation plus nitrous acid).[36] From proton affinity measurement, the heat of formation of protonated nitrobenzene has been estimated as 789 kJ mol^{-1}.[36]

Upon neutralization–reionization [Fig. 1 (b)], a weak, but significant, recovery signal is detected at *m/z* 124 for 'survivor ions'. The peaks for the losses of NO$^\cdot$ and HNO_2 are still intense, while the peaks corresponding to the unimolecular dissociations are now of very low intensity. Such a behaviour is not unexpected, as it is usually admitted that more average energy is deposited in the ions in NR than in CA, thus favouring simple cleavage over rearrangement reactions. The disappearance of the charge stripping signal in NRMS (*m/z* 62) is also expected and attributed to a lower probability of $M \rightarrow M^{2+}$ double ionization compared with the $M^+ \rightarrow M^{2+}$ single ionization seen in the CA spectrum. Another significant difference between the CA and NR spectra is also observed at *m/z* 30 corresponding to the reionization of NO$^\cdot$ lost in the metastable fragmentation. NO_2^+ is also observed, but its intensity is surprisingly lower.

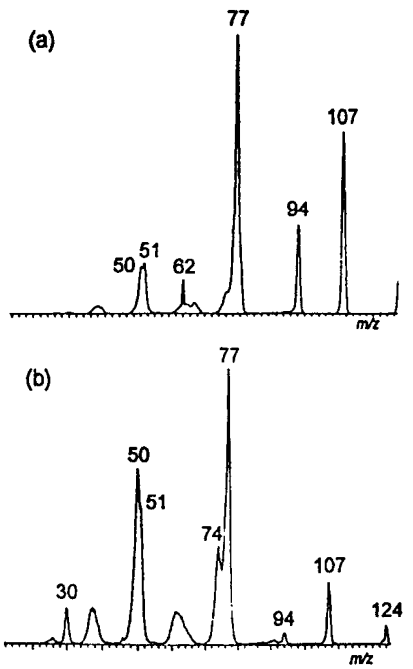
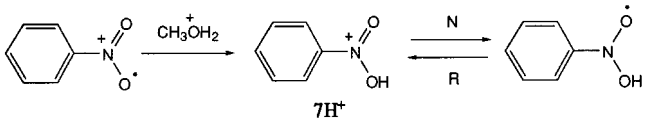


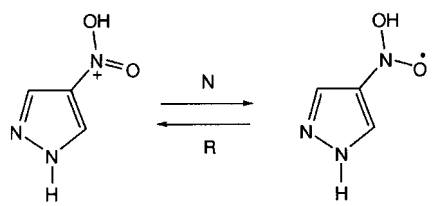
Figure 1. CA (O_2) (a) and NR (Xe/O_2) (b) spectra of protonated nitrobenzene (*m/z* 124)

Taken together, these data clearly indicate preferential protonation of the nitro group over ring protonation. Diagnostic peaks appears to be the collision-induced losses of a hydroxyl radical and nitrous acid. The recovery signal in the NR spectrum is tentatively ascribed to the production of a nitroxide in the gas phase.



The MI and CA data of the isomeric protonated nitropyrazoles are collected in Table 2. Just as in the case of protonated nitrobenzene, $\mathbf{7H}^+$, the CA spectrum of $\mathbf{2H}^+$ features a very strong loss of HO$^\cdot$ in agreement with preferential oxygen protonation. All other peaks are of low intensity (less than 10%). Among these peaks, the loss of 46 Da (*m/z* 68, loss of $NO_2^\cdot$) is worthy of note and could be interpreted as the result of ring nitrogen protonation. However, in contrast to the case of nitrobenzene, the loss of OH$^\cdot$ is the less energy-demanding reaction (base peak of the MI spectrum, Table 2).

Upon neutralization–reionization (Fig. 2), the loss of HO$^\cdot$ remains a prominent process and new peaks are observed at *m/z* 46 and 30 corresponding to the reionization of the neutrals lost in the unimolecular fragmentations (MI spectra). The recovery signal is of low intensity and could be associated again with the production of a nitroxide.



The behaviour of protonated 3-nitropyrazole $\mathbf{1H}^+$ appears to be intermediate between those of protonated nitrobenzene and 4-nitropyrazole. The main unimolecular reactions are again the losses of $NO_2^\cdot$ and NO$^\cdot$, but a peak for an HO$^\cdot$ is also detected. Upon collisional activation, this last reaction is strongly enhanced, pointing to the occurrence of a simple cleavage reaction and thus protonation on the oxygen. Another significant

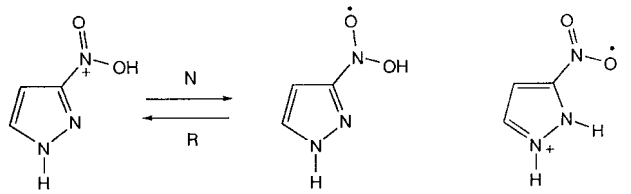
Table 2. MI and CA (O_2) spectra of the protonated 3-nitro- and 4-nitropyrazoles (*m/z* 114) (*m/z* 98–57 regions; abundances relative to the most intense peak)

	m/z	98	97	84	70	68	67	66	57[a]
1H$^+$	MI		15	36		100			
	CA	24[b]	95	12	1	100	16[b]	6[b]	1
2H$^+$	MI		100	3		14			
	CA	<1[b]	100	<1	4	10	4[b]	2[b]	2

[a] Charge stripping peaks.
[b] Shoulders.

reaction induced by collision is the loss of 16 Da (O), which is more probably ascribed to a ring nitrogen protonated species.

Upon neutralization–reionization, the loss of HO$^\cdot$ remains very intense, but the peaks at *m/z* 98, 84 and 68 disappear. The intense peaks detected at *m/z* 30 and 46 are due to reionization of NO$^\cdot$ and $NO_2^\cdot$ lost in the metastable reactions. It emerges from these results that protonation of 3-nitropyrazole could yield a mixture of O- and ring N-protonated species. The species protonated on oxygen could be responsible of the observation of the weak recovery signal and the loss of 17 Da, while the N-protonated species could generate an unstable neutral dissociating spontaneously between the neutralization and reionization cells with, *in fine*, formation of new intense fragments seen at *m/z* 66, 51 and 40.



1bH$^+$

If these conclusions really apply, one can predict the behaviour of the protonated 1-methyl 3- and 4-nitropyrazoles upon collisional activation: a very intense loss of HO$^\cdot$ for **5H**$^+$ and an increased intensity of the losses of $NO_2^\cdot$ and O for **6H**$^+$. That is effectively the case shown in Fig. 3 by the peaks at *m/z* 82 and 112 for **5H**$^+$, and peaks of very low abundance in the case of **6H**$^+$.

In summary, nitrobenzene, **7**, protonates on the nitro group (that is, on the oxygen) with formation of the **7bH**$^+$ cation. The nitropyrazoles, **1** and **2**, protonate preferentially also on the nitro groups, resulting in the **1bH**$^+$ and **2bH**$^+$ cations, but there is possibly a small proportion of protonation on the azole (N-protonation) which leads to **1aH**$^+$ and **2aH**$^+$ cations. This second kind of protonation is clearly more important for 3-nitro- than for 4-nitropyrazoles.

FT-ICR mass spectrometry

To have more experimental data for the following section, the gas-phase basicities of two nitro-imidazoles which are known to protonate on the imidazole, were measured: 2-nitroimidazole (**3**), $GB = 833.9 \pm 0.4$ kJ mol^{-1}, and 4-nitroimidazole (**4**), $GB = 841.8 \pm 0.8$ kJ mol^{-1}. In this work, we do not take into account the annular tautomerism of 3(5)-nitropyrazole and 4(5)-nitroimidazole because both tautomers have very similar energies:[1,5] in any case, the tautomers depicted are the most stable. The other experimental *GB* values of Table 3 are from Hunter and Lias .[37]

Theoretical calculations

FT-ICR techniques provide accurate values for the gas-phase basicities of the systems investigated, but unfortunately do not provide any information on the protonation site. Hence, in order to assess which is the preferred protonation site of the nitropyrazoles under investigation we have carried out some preliminary calculations at the B3LYP/6–31 + *G** level. The calculations indicate that the cations formed upon protonation at the ring nitrogen

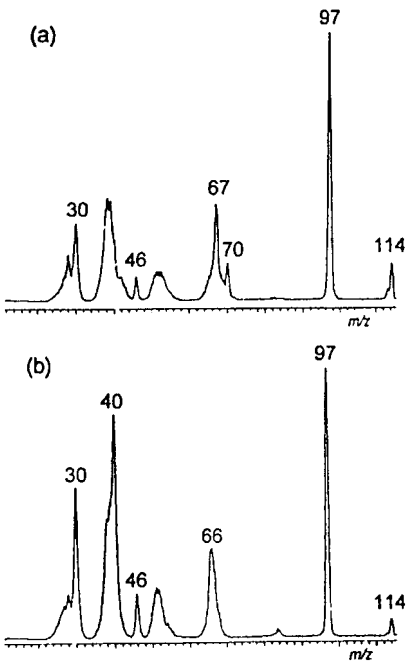


Figure 2. NR spectra (xenon/oxygen) of protonated 4- (a) and 3- (b) nitropyrazoles (*m/z* 114)

Figure 3. CA (O_2) spectra (partial) of protonated 1-methyl-3-nitro (a) and 1-methyl-4-nitro (b) pyrazoles (*m/z* 128) (linked E/B/E scans)

of the azoles are more stable than those formed upon protonation at the oxygen atom of the nitro group (see Table A1 in the appendix). Although the energy gap between both forms is quite large for nitroimidazoles, these results cannot be taken as conclusive for nitropyrazoles, since the gap is of the same order of magnitude as the errors associated with this level of theory. An alternative way to look into the problem would be to establish a correlation between experimental values and theoretical estimates, including systems whose protonation site is unambiguously known. For this purpose we have considered nitrobenzene and nitromethane. Unfortunately, the linear correlation found for those compounds, which protonate at the nitro group, has a different slope and a different intercept than that found for the azoles (see Fig. 4). Furthermore, using the experimental gas-phase basicity of 3- and 4-nitropyrazoles, and assuming that both correlations were correct, one should conclude that these compounds should protonate at the nitro group rather than at the ring nitrogen.

At this point it seems necessary to find a level of theory which brings both correlations to a single one. For this purpose we have decided either to significantly enlarge the basis set used in the B3LYP calculations, or to include high-order correlation effects in standard *ab initio* calculations through the use of CCSD(T) formalism together with a 6–31 + G^* basis set expansion. The raw computational results at levels B3LYP/6–311 + G^* and CCSD(T)/6–31 + G^* are given in the Appendix. These data were used to compute the *GB* values of the various species studied in this work as well as those of nitromethane, nitrobenzene, pyrazole and imidazole, taken as appropriate references. These results are presented in Table 3 together with the experimental results.

$$GB[\text{B3LYP}/6\text{–}311 + G^*]/\text{kJ mol}^{-1} = -(72 \pm 34) + (1.08 \pm 0.04)GB(\text{exp})/\text{kJ mol}^{-1}$$
$$n = 8, R^2 = 0.991,\ \text{SD} = 6.4 \quad (3)$$

$$GB[\text{CCSD(T)}/6\text{–}31 + G^*]/\text{kJ mol}^{-1} = -(102 \pm 18) + (1.11 \pm 0.02)GB(\text{exp})/\text{kJ mol}^{-1}$$
$$n = 8, R^2 = 0.998,\ \text{SD} = 3.4 \quad (4)$$

Inspection of these results indicates that both compu-

Table 3. Experimental and computed gas-phase basicities of the various molecules studied in this work[a]

	Compound	*GB*[B3LYP/6–311 +*G**]	*GB*[CCSD(T)/6–31 +*G**]	*GB* (experimental)
	leading to **1aH**$^+$	783.5	776.4	
1				789.0[b]
	leading to **1bH**$^+$	758.3	743.8	
	leading to **2aH**$^+$	782.6	776.1	
2				788.7[b]
	leading to **2bH**$^+$	759.6	746.2	
	leading to **3aH**$^+$	824.3	824.3	
3				833.7[c]
	leading to **3bH**$^+$	755.2	737.0	
	leading to **4aH**$^+$	829.9	828.7	
4				841.6[c]
	leading to **4bH**$^+$	777.1	761.7	
	Nitromethane	697.5	693.8	721.6[d]
	Nitrobenzene	766.9	748.4	769.5[d]
	Pyrazole	859.4	849.6	860.5[d]
	Imidazole	907.1	903.7	909.2[d]

[a] All values in kJ mol^{-1}.
[b] From Abboud *et al.*[12] and Notario *et al.*,[38] re-scaled according to Hunter and Lias[37]
[c] This work.
[d] From [37]

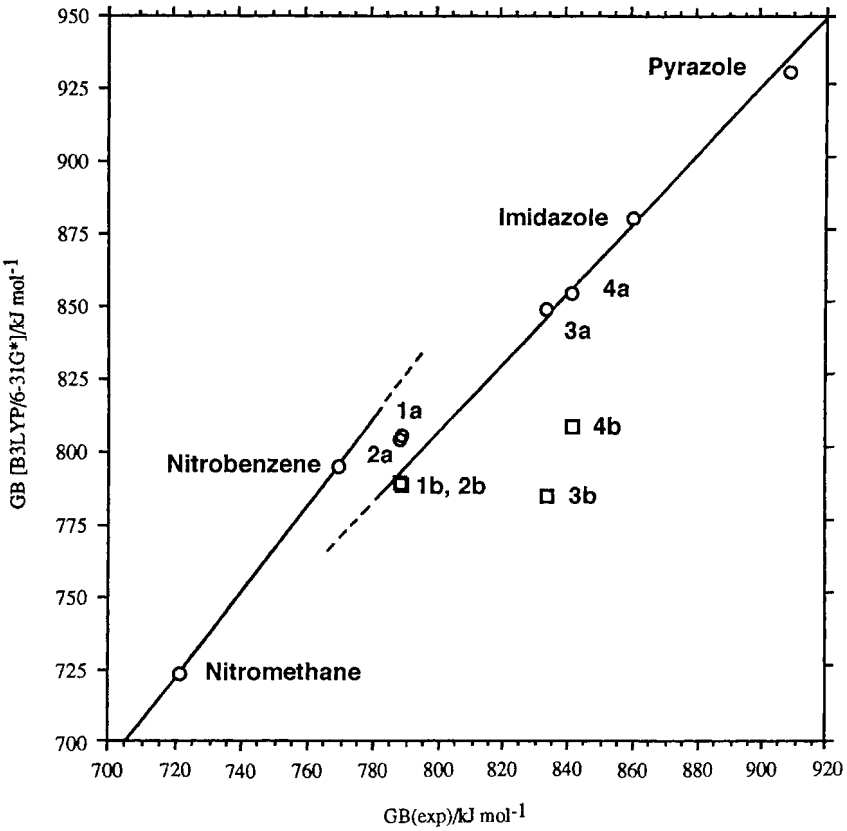


Figure 4. Plot of B3LYP/6–31 + *G** calculations against experimental *GB* values. Open circles correspond to the protonation on the ring nitrogen (**a** cations). Open squares correspond to the protonation on the nitro group of nitroazoles (**b** cations)

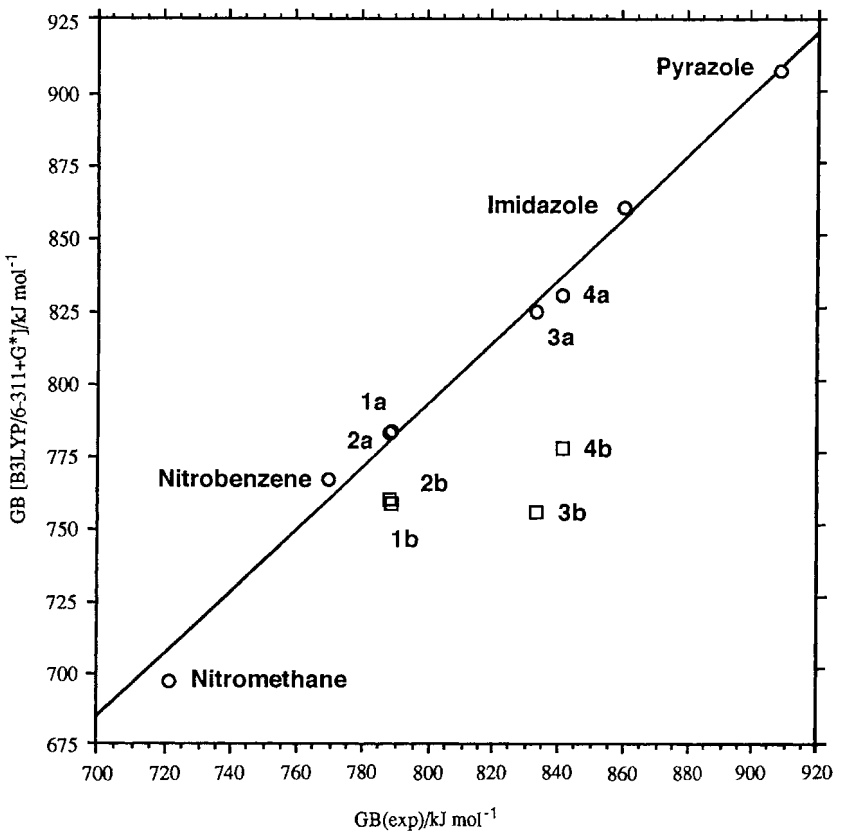


Figure 5. Plot of B3LYP/6–311 + *G** calculations against experimental *GB* values. Same conventions as in Fig. 4

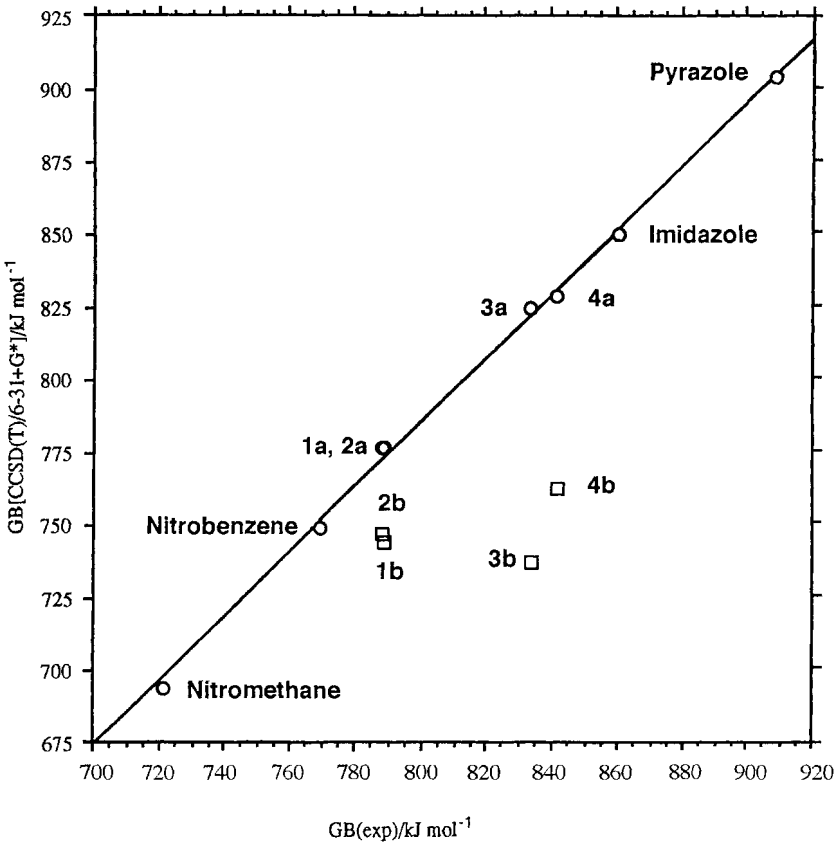


Figure 6. Plot of CCSD(T)/6–31 + *G** calculations against experimental *GB* values. Same conventions as in Fig. 4

tational methods perform well in the sense that a unique linear correlation including oxygen- and nitrogen protonated species has been found [eqns (3) and (4) and Fig 5 and Fig 6]. Both levels of theory confirm that 3- and 4-nitropyrazoles should protonate at the ring nitrogen, even though the energy gap with respect to the nitro-protonated species is much smaller than that typically found for the imidazole analogues.

The most significant discrepancy between both linear correlations corresponds to nitromethane. Actually, if the point corresponding to nitromethane is removed and Eqn. (3) is used, the estimated gas-phase basicity of nitromethane is 704 kJ mol^{-1}, while if Eqn. (4) is used, the estimated value is 718 kJ mol^{-1}, much closer to the experimental value (721.6 kJ mol^{-1}).

This discrepancy might indicate the existence of some additional problem, as a tautomerism of the protonated form of nitromethane not taken into account in our analysis. Nevertheless, when this point is removed from both linear correlations, our previous conclusions remain unchanged, although the correlation based on B3LYP calculations improves [eqs (5) and (6)].

$$GB[\mathrm{B3LYP/6\text{–}311} + G^*]/\mathrm{kJ\ mol^{-1}} = (20 \pm 29) + (0.98 \pm 0.04)GB(\mathrm{exp})/\mathrm{kJ\ mol^{-1}}$$
$$n = 7, R^2 = 0.994,\ \mathrm{SD} = 4.2 \quad (5)$$

$$\mathrm{GB[CCSD(T)/6\text{–}31} + G^*]/\mathrm{kJ\ mol^{-1}} = (75 \pm 17) + (0.92 \pm 0.02)\mathrm{GB(exp)/kJ\ mol^{-1}}$$
$$n = 7, R^2 = 0.997,\ \mathrm{SD} = 2.7 \quad (6)$$

CONCLUSIONS

These results strongly suggest that compounds **1** and **2** protonate on the heterocyclic nitrogen, rather than on the oxygen of the nitro group. Notice, however, that the differences in stabilities of the couples **1aH**$^+$/**1bH**$^+$ and **2aH**$^+$/**2bH**$^+$ are modest, in the range 25–30 kJ mol^{-1}. *These values are sufficiently small to easily allow the formation of 1bH*$^+$ *and 2bH*$^+$ *under conditions of mild excitation and thus rationalize the behaviour of the CA/NR experiments*. An intriguing possibility opened by these experiments is the possibility of finding other heterocyclic systems wherein protonation of the nitro group could be favoured thermodynamically, under equilibrium conditions, over the protonation of the aza nitrogen(s).

Acknowledgements

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Table A1. Calculated differences in stability (in kJ mol^{-1})

Compound	B3LYP/6–31 + G^* + ZPE	B3LYP/6–311 + G^* + ZPE	CCSD(T)/6–31 + G^* + ZPE
1aH$^+$/ 1bH$^+$	16.1	24.6	31.9
2aH$^+$/ 2bH$^+$	13.5	22.3	29.2
3aH$^+$/ 3bH$^+$	63.1	68.6	89.3
4aH$^+$/ 4bH$^+$	45.2	52.5	66.7

Table A2. Summary of the computational results of this work (all values in hartees)[a]

	B3LYP/6–311 + G^*			CCSD(T)/6–31 + G^*		
Compound	E_0	H_{298}	G_{298}	E_0	H_{298}	G_{298}
1	−430.74351	−430.73651	−430.77431	−429.52370	−429.51670	−429.55450
1aH$^+$	−431.05183	−431.04451	−431.08272	−429.82932	−429.82200	−429.86021
1bH$^+$	−431.04247	−431.03533	−431.07314	−429.81715	−429.81001	−429.84782
2	−430.74633	−430.73935	−430.77699	−429.52637	−429.51939	−429.55703
2aH$^+$	−431.05408	−431.04671	−431.08507	−429.83165	−429.82429	−429.86264
2bH$^+$	−431.04558	−431.03837	−431.07630	−429.82052	−429.81331	−429.85125
3	−430.76170	−430.75475	−430.79225	−429.54049	−429.53354	−429.57105
3aH$^+$	−431.08548	−431.07837	−431.11620	−429.86430	−429.85719	−429.89502
3bH$^+$	−431.05931	−431.05210	−431.08990	−429.83118	−429.82397	−429.86177
4	−430.76354	−430.75655	−430.79425	−429.54383	−429.53684	−429.57453
4aH$^+$	−431.08965	−431.08257	−431.12036	−429.86949	−429.86240	−429.90019
4bH$^+$	−430.06964	−431.06250	−431.10025	−429.84406	−429.83692	−429.87467
Nitromethane	−245.03842	−245.03400	−245.06423	−244.33601	−244.33159	−244.36182
NitromethaneH$^+$	−245.31203	−245.30656	−245.33927	−244.60990	−244.60442	−244.63713
Nitrobenzene	−436.76439	−436.75667	−436.79555	−435.47674	−435.46903	−435.50791
NitrobenzeneH$^+$	−437.06583	−437.05778	−437.09767	−435.77110	−435.76306	−435.80295
Pyrazole	−226.18967	−226.18251	−226.21349	−225.50280	−225.49564	−225.52662
PyrazoleH$^+$	−226.52431	−226.51930	−226.55082	−225.83371	−225.82871	−225.86022
Imidazole	−226.20404	−226.19931	−226.23032	−225.51762	−225.51290	−225.54390
ImidazoleH$^+$	−226.55946	−226.55474	−226.58580	−225.87178	−225.86705	−225.89812

[a] 1 hartree = 2625.50 kJ mol^{-1}.

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