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Basicity of 1-nitroaryl-4,5-dihydropyrazoles: pK_a measurements and theoretical calculations

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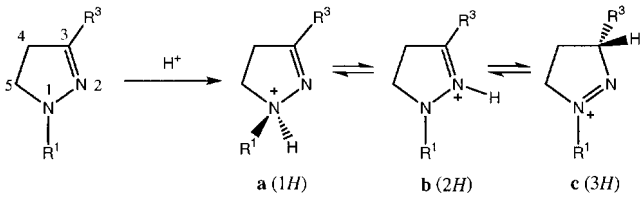
ABSTRACT: The basicity of simple 4,5-dihydropyrazoles (Δ^2-pyrazolines) was previously discussed on the basis of protonation at position 1 in the case of 1-unsubstituted, 1-methyl and 1-phenyl derivatives. The pK_a of 15 4,5-dihydropyrazoles substituted at position 1 by *p*-nitrophenyl, 2,4-dinitrophenyl and 2,4,6-trinitrophenyl groups have now been determined. After examining some linear free energy relationships, to discuss these pK_a values further, DFT theoretical calculations, including temperature effects, were carried out on the parent compounds (no *C*-substituents) for the 1-unsubstituted, 1-methyl, 1-phenyl, 1-*p*-nitrophenyl and 1-(2′,4′,6′)trinitrophenyl series. These calculations predict an inversion of N-1 and N-2 basicity between 1-phenyl and 1-*p*-nitrophenyl-4,5-dihydropyrazoles. Since there were no experimental data for the protonation of 4,5-dihydropyrazoles in the gas phase, chemical ionization mass spectrometry was used to try to determine the structure of protonated 1-methyl- and 1,3-dimethyl-5-phenyl-4,5-dihydropyrazoles (**3** and **7**, respectively). In both cases, it appears that these pyrazoles are protonated on N1, but the production of another isomeric species cannot be completely ruled out for **7H**$^+$. Copyright © 2000 John Wiley & Sons, Ltd.

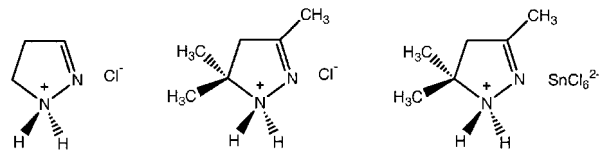
KEYWORDS: pyrazolines; pyrazoles; basicity measurements; mass spectrometry; linear free energy relationships; *ab initio* calculations

INTRODUCTION

Although 4,5-dihydropyrazoles (Δ^2-pyrazolines) have important applications and continue to be the subject of many studies,[1–5] there is only one old report on their basicity.[6] This work concerned *N*-H- and *N*-methyl-4,5-dihydropyrazoles whose pK_as were discussed on the basis of independent determination of the protonation site.[6] For *N*-H, *N*-Me and *N*-Ph-4,5-dihydropyrazoles, it has long been established, by NMR and UV spectroscopy, that the conjugated acids have the structure **a** (1*H*-4,5-dihydropyrazol-2-ium).[7–9]



Protonation on C-3 with the formation of cation **c** is the easiest process to determine because the formation and breaking of a C—H bond is slow, therefore, cation **c**, if present, will show individual signals in the NMR spectra. This cation has never been observed. As in other cases of prototropic tautomerism involving nitrogen atoms, the problem of the equilibrium between cations **a** and **b** is that only averaged signals are expected in NMR because the proton migration is very fast. The experiments we carried out in the past[7–9] can be interpreted as showing cation **a** being largely predominant for R^1 = H, CH_3 and C_6H_5. In the solid state, the crystal structure of three salts of type **a**, R^1 = H, has been determined by x-ray for compounds **1**,[10] **2a**[11] and **2′a**.[11]



In the present work we have carried out three types of experiments: (i) linear correlations between pK_a values, both determined in the present work and from the literature (we have collected in Table A1 in the Appendix all the data from the literature necessary for these correlations); (ii) theoretical calculations on 4,5-dihy-

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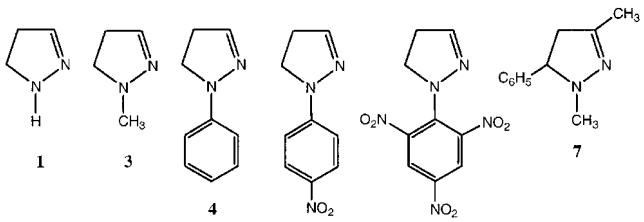
Table 1. pK_a values of 1-nitroaryl-4,5-dihydropyrazoles and absorption maxima of the neutral form (B) and the conjugated acid (BH^+)

Compound	pK_a (a)	pK_a (b)	λ_{max} (B) (nm)	$\lambda_{max}(BH^+)$ (nm)
5	-3.33 ± 0.03	—	416	362
8	-2.04 ± 0.03	-2.10 ± 0.04	428	366
9	-3.30 ± 0.04	-3.30 ± 0.04	416	365
10	-2.39 ± 0.03	—	431	357
11	-2.91 ± 0.03	-2.87 ± 0.04	418	360
12	-4.30 ± 0.04	—	396	318
13	-2.87 ± 0.04	-2.89 ± 0.05	408	322
14	-2.91 ± 0.03	-2.90 ± 0.05	408	320
15	-4.27 ± 0.03	—	396	325
16	-3.98 ± 0.04	-3.93 ± 0.04	399	310
17	-2.05 ± 0.05	—	410	318
6	-5.09 ± 0.04	—	390	314
18	-3.91 ± 0.09	-3.90 ± 0.05	399	328
19	-4.25 ± 0.04	-4.25 ± 0.06	400	324
20	-5.13 ± 0.03	—	390	315
21	-4.88 ± 0.05	—	396	320

dropyrazoles **1, 3–5** and **6** and their N-1, N-2 and C-3 protonated, cations **1a–c** to **6a–c**: and (iii) collisional activation (CA) studies of the cations formed from 4,5-dihydropyrazoles **3** and **7** in the chemical ionization ion source of a tandem mass spectrometer.



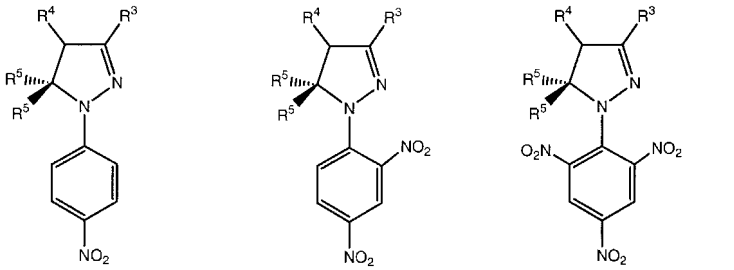
1 **3** **4** **5** **6** **7**

EXPERIMENTAL

Materials. The synthesis of and spectroscopic data for all the 4,5-dihydropyrazoles used in this study (**3–21**) can be found in the literature.[12–17]

Basicity measurements. The pK_a values of the 16 dihydropyrazoles **5, 8–17, 6** and **18–21** in water at 20 °C are reported in Table 1. The absorption maxima of the neutral and conjugated acids, used for the spectrophotometric determination of the pK_as, are also reported. Those labelled (a) were determined by the Halevi–Nussim method[18] and those labelled (b) by the general method (for more details, see Ref. 6). The last method confirms that *N*-nitroaryl-4,5-dihydropyrazoles are Hammett bases (the slopes of the experimental lines are close to unity).[19]

Mass spectrometry. The spectra were recorded on a large-scale tandem mass spectrometer of $E_1B_1©E_2©E_3B_2E_4$ geometry (E represents electric sector, B magnetic sector and © the collision cells installed in various field-free regions) (Micromass, AutoSpec 6F).[20] 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



5, $R^3 = R^4 = R^5 = H$
8, $R^3 = CH_3$, $R^4 = R^5 = H$
9, $R^3 = C_4H_9$-*t*, $R^4 = R^5 = H$
10, $R^3 = H$, $R^4 = CH_3$, $R^5 = H$
11, $R^3 = R^4 = H$, $R^5 = CH_3$

12, $R^3 = R^4 = R^5 = H$
13, $R^3 = CH_3$, $R^4 = R^5 = H$
14, $R^3 = C_2H_5$, $R^4 = R^5 = H$
15, $R^3 = H$, $R^4 = CH_3$, $R^5 = H$
16, $R^3 = R^4 = H$, $R^5 = CH_3$
17, $R^4 = H$, $R^3 = R^5 = R^5 = CH_3$

6, $R^3 = R^4 = R^5 = H$
18, $R^3 = CH_3$, $R^4 = R^5 = H$
19, $R^3 = C_4H_9$-*t*, $R^4 = R^5 = H$
20, $R^3 = H$, $R^4 = CH_3$, $R^5 = H$
21, $R^3 = R^4 = H$, $R^5 = CH_3$

Table 2. Theoretical calculations (B3LYP/6–31G*): absolute values in hartree (1 hartree = 2625.50 kJ mol^{-1}) and relative values in kJ mol^{-1}

Compound	E_{total}	E_{rel}	E^{298}	ΔE^{298}	$E_{prot}{}^{298}$	G^{298}	ΔG^{298}	$G_{prot}{}^{298}$
1	−227.38474		−227.28524			−227.31741		
1a	−227.74316	0.00	−227.62896	0.00	903.06	−227.66236	0.00	879.42
1b	−227.74084	6.11	−227.62741	4.08	898.97	−227.66004	6.10	873.31
1c	−227.73514	21.07	−227.62228	17.55	885.51	−227.65651	15.36	864.06
3	−266.69849		−266.56989			−266.60536		
3a	−267.06460	0.87	−266.92098	4.43	922.40	−266.95709	6.38	897.20
3b	−267.05883	15.99	−266.91620	16.96	909.87	−266.95213	19.38	884.20
3c	−267.06493	0.00	−266.92266	0.00	926.82	−266.95952	0.00	903.59
4	−458.44230		−458.25776			−458.30234		
4a	−458.80228	28.70	−458.60357	29.70	908.53	−458.64846	29.09	882.49
4b	−458.80088	32.36	−458.60270	31.99	906.25	−458.64745	31.74	879.84
4c	−458.81321	0.00	−458.61488	0.00	938.24	−458.65954	0.00	911.58
5	−662.94970		−662.75975			−662.81128		
5a	−663.28732	22.77	−663.08387	24.08	851.61	−663.13568	23.83	825.46
5b	−663.28789	21.27	−663.08486	21.49	854.20	−663.13662	21.37	827.92
5c	−663.29599	0.00	−663.09304	0.00	875.68	−663.14476	0.00	849.29
6	−1071.91431		−1071.71495			−1071.77834		
6a	−1072.25134	0.00	−1072.03878	0.00	850.84	−1072.10167	0.00	822.64
6b	−1072.24734	10.50	−1072.03485	10.31	840.53	−1072.09863	7.98	814.67
6c	−1072.24930	5.35	−1072.03750	3.35	847.48	−1072.10161	0.15	822.49

reagent gas at an estimated 0.5–1 Torr ion source pressure (1 Torr = 133.3 Pa). The samples were introduced with a direct insertion probe or via a heated (180 °C) septum inlet device.

The high-energy (8 keV) collisional activation (CA) spectra were obtained by pressurizing the collision cell localized in front of E_3 with oxygen (ca 50–70% transmittance) and scanning the field of E_3; the fragments were collected with an off-axis photomultiplier detector in the field-free region. Resolved CA spectra were obtained by using linked scanning of the fields $E_3B_2E_4$. In the neutralization–reionization (NR) experiment, the collision with oxygen was preceded by collision with xenon, the residual non-neutralized ions being removed from the fast neutral beam by floating at 9 kV an intermediate calibration source inserted between the neutralization and reionization cells.

The low-energy CA spectra were obtained by using the mass spectrometer in its 'hybrid' mode, E_1B_1©E-q©$E_3B_2E_4$.[21] In this configuration, a radiofrequency-only quadrupole collision cell fitted with deceleration and reacceleration lenses replaces the neutralization collision cell. Briefly, the experiments consists of the retardation (ca 20–30 eV) of a beam of mass-selected ions and collision of the ions with argon in the quadrupole. After reacceleration at 8 keV, the fragments were mass analysed by scanning the field of B_2. CA (O_2) mass spectra of selected fragments were obtained by using linked scanning of the fields $E_3B_2E_4$.

Calculations. The *ab initio* calculations on model compounds **a, b** and **c** (R^3 = H) were carried out with the Gaussian 98 package[22] at the B3LYP/6–31G* level.[23] The minimum nature of the structure was confirmed by frequency calculations, all frequencies being real. The thermochemical properties of each tautomer were calculated at 298.15 K and 1 atm pressure. The results are reported in Table 2.

RESULTS AND DISCUSSION

A difficulty is encountered when discussing the pK_a measurements of 1-(4′-nitrophenyl)-(**5, 8–11**), 1-(2′,4′-dinitrophenyl)-(**12–17**) and 1-(2′,4′,6′-trinitrophenyl)-4,5-dihydropyrazoles (**6, 18–21**) in Table 1. For these weakly basic compounds, protonation NMR experiments failed because strongly acidic media would be necessary and they are incompatible with the presence of nitro groups. Moreover, 'model compounds,' that is, quaternary ammonium salts similar to **a** and **b**, are unknown for nitrophenyl-4,5-dihydropyrazoles. Considering that the site of protonation is not known, there are two questions that need to be answered: do all the compounds in Table 1 protonate on the same nitrogen, N-1 or N-2?; and, is it possible by correlation analysis to determine the site of protonation?

Empirical modelling

The data in Table 1 can be analysed using an additive model with compound **5** as reference. The procedure consists in building up an absence (0)/presence (1) matrix with the different substituents of 4,5-dihydropyrazoles corresponding to an equation of the form $pK_a = pK_{a(0)} + \Sigma R_i X_i$, where R_i is the effect of the substituent i and X_i is 0 or 1. For instance, 3,5,5-trimethyl derivatives

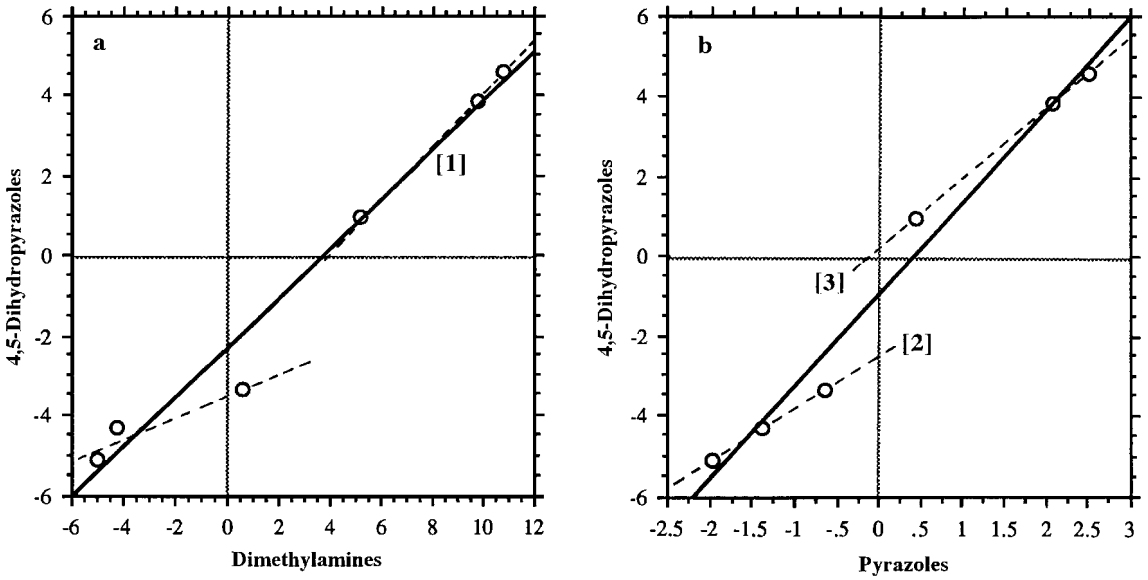


Figure 1. Plots of pK_a' values of 4,5-dihydropyrazoles vs those of dimethylamines and pyrazoles

have a 1 in the column '3-methyl' and another 1 in the column '5,5-dimethyl,' whereas 3-methyl derivatives have, respectively, a 1 and a 0, allowing us to calculate the 5,5-dimethyl effect. The results of the multiple regression are as follows: intercept, $pK_{a(0)} = -3.30 \pm 0.05$ [close to the pK_a of (**5**)], 3-methyl 1.30 ± 0.06, 3-ethyl 1.35 ± 0.08, 3-*tert*-butyl 0.91 ± 0.08, 4-methyl 0.07 ± 0.06, 5-methyl 0.32 ± 0.06, 5,5-dimethyl 0.91 ± 0.06, 1-dinitrophenyl -0.96 ± 0.05 and 1-trinitrophenyl -1.86 ± 0.05 ($n = 15$, $r^2 = 0.998$). These results suggest that all these compounds behave similarly in the face of protonation, pointing to a common structure for the cation. Note finally that the absorption maxima of the B and BH^+ species also follow a similar additive model.

The effects of the 1-substituent are indicative that the protonation takes place on N-2 (cation **b**) because protonation on N-1 (cation **a**) should produce effects similar to those of anilines [for *N*,*N*-disubstituted anilines (Table A1), the replacement of *p*-nitrophenyl by dinitro and trinitrophenyl groups lowers the pK_a by 4.8 and 5.6, respectively pK_a unit, respectively] whereas protonation on N-2 should produce effects similar to those of pyrazoles (Table A1); the replacement of *p*-nitrophenyl by dinitro and trinitrophenyl substituents lowers the pK_a by 0.7 and 1.3 pK_a unit respectively. Clearly, the behaviour is similar to that of pyrazoles, that is, compounds **5, 6** and **8–21** seem to protonate on N-2. Another indication, albeit a circumstantial one, is that the hypsochromic effect produced by protonation is 70 ± 20 nm in 1-nitrophenyl-4,5-dihydropyrazoles (Table 1) whereas in nitroanilines it varies from 120 to 150 nm.[18,24]

It is possible to go further, but that requires the knowledge of the pK_a of 1-phenyl-4,5-dihydropyrazole **4**. This compound dimerizes in an acidic medium,[25] thus preventing the precise determination of its basicity. It is nevertheless possible to obtain a rough estimate of its $pK_a = 1.0 \pm 0.5$ by potentiometry. Using the compounds in Table A1, it can be shown that the pK_a of six parent 4,5-dihydropyrazoles, 1*H*-(**1**) (Table A1), 1-methyl-(**3**) (Table A1), 1-phenyl-(**4**), 1-*p*-nitrophenyl-(**5**), 1-(2′,4′-dinitro)phenyl-(**12**) and 1-(2′,4′,6′-trinitro)phenyl-(**6**) are best correlated, the first three with those of dimethylamine (Table A1, **46**), trimethylamine (Table A1, **51**) and *N*,*N*-dimethylaniline (Table A1, **52**) and the last three with the corresponding pyrazoles (Table A1, **63–65**):

$$pK_a(\mathbf{1},\mathbf{3},\mathbf{4}) = -(2.3 \pm 0.2) + (0.64 \pm 0.02)pK_a \quad (\mathbf{46},\mathbf{51},\mathbf{52})\ (n = 3, r^2 = 0.9993) \qquad (1)$$

$$pK_a(\mathbf{5},\mathbf{12},\mathbf{6}) = -(2.48 \pm 0.01) + (1.323 \pm 0.008)pK_a \quad (\mathbf{63}\text{–}\mathbf{65})\ (n = 3, r^2 = 1.0000) \qquad (2)$$

Other correlations involving the six 4,5-dihydropyrazoles (**1, 3–6, 12**) and either dimethylamines or pyrazoles show the presence of two families, the best overall squared correlation coefficient (r^2) being about 0.97. Correlations with other nitrogen bases were attempted but all of them failed.

Our conclusion is that the presence of one nitro group on the phenyl ring is sufficient to change the protonation site from N-1 to N-2. Nevertheless, the correlation of the six 4,5-dihydropyrazoles with dimethylamines (models of N-1 protonation) and pyrazoles (models of N-2 protonation) is reasonable. This means that the transmission of substituent effects in 4,5-dihydropyrazoles from N-1 to N-2 appears to be fairly efficient.

An examination of the plots (Fig. 1) shows that the

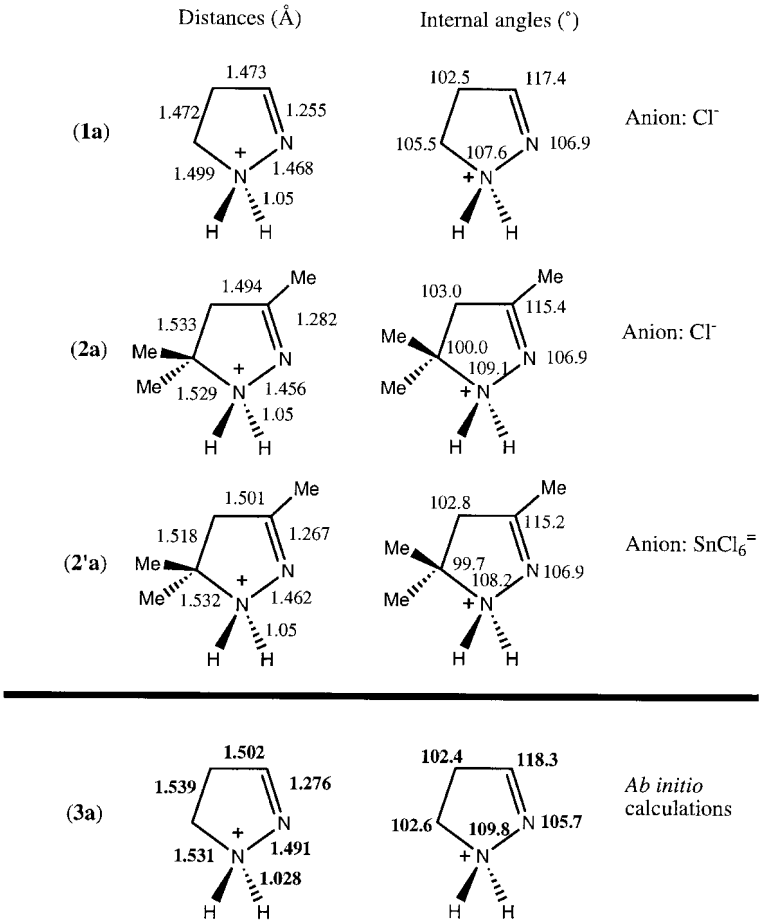


Figure 2. Comparison between calculated and experimental (x-ray) geometries of *N*-unsubstituted 4,5-dihydropyrazoles

points belong to two families. In the case of dimethylamines, model of protonation on N-1 [Fig. 1(a)], the three more basic 4,5-dihydropyrazoles correspond to Eqn. (1) and the other three points are not well correlated, which is not surprising if the remaining 4,5-dihydropyrazoles protonate on N-2. In the case of pyrazoles, the curious thing is that in addition to the line corresponding to Eqn. (2), the three more basic 4,5-dihydropyrazoles which protonate on N-1 (R^1 = H, CH_3, C_6H_5) also correlate perfectly with pyrazoles [Fig. 1(b), Eqn. (3)]:

$$\mathrm{p}K_a(\mathbf{1},\mathbf{3},\mathbf{4}) = (0.253 \pm 0.001) + (1.761 \pm 0.001)\mathrm{p}K_a(\mathbf{60–62}) \quad (n = 3, r^2 = 1.000) \qquad (3)$$

Note that the slopes of Eqns ((1)–(3)) cannot be compared, because Eqn. (1) uses amines as reference compounds whereas Eqns (2) and (3) use pyrazoles, which are much less basic than amines. Equation (2) has a slope, 1.323, closer to 1 than Eqn. (3), 1.761, because in the former case both compounds protonate on N-2 whereas in the latter we are comparing compounds which protonate on different nitrogen atoms.

The *C*-substituent effects are similar to those reported for *N*-H- and *N*-methyl-4,5-dihydropyrazoles (Table A1: **1, 2, 3, 22–24, 26, 27, 36, 37** and **38**).[6] The only exception concerns the 5,5-dimethyl effect. Compare, for instance, the pair 4,5-dihydropyrazole (**1**) (pK_a = 4.62) and 3,5,5-trimethyl-4,5-dihydropyrazole (**2**) (pK_a = 5.19) or the corresponding *N*-methyl derivatives **3** (pK_a = 3.88) and **38** (pK_a = 4.68) (Table A1) with the pair **12** (pK_a = −4.30) and **17** (pK_a = −2.05) (Table 1). In the *N*-H- and *N*-methyl series, there is an increase of only 0.57 and 0.80 pK_a units, respectively, whereas in the 2′,4′-dinitrophenyl series, the increase is 2.25 pK_a units. These differences are probably related to a modification of the conformation of the *N*-substituent or of an *ortho*-nitro group produced by the *gem*-dimethyl group at position 5.

Theoretical calculations

We shall only discuss energy values except for the geometry of **1a**. In Fig. 2 are compared the calculated geometry of **1a** with the x-ray geometries of **1a** (chloride: PYZOLC), **2a** (chloride: VIDKUO) and **2′a** (hexachlor-

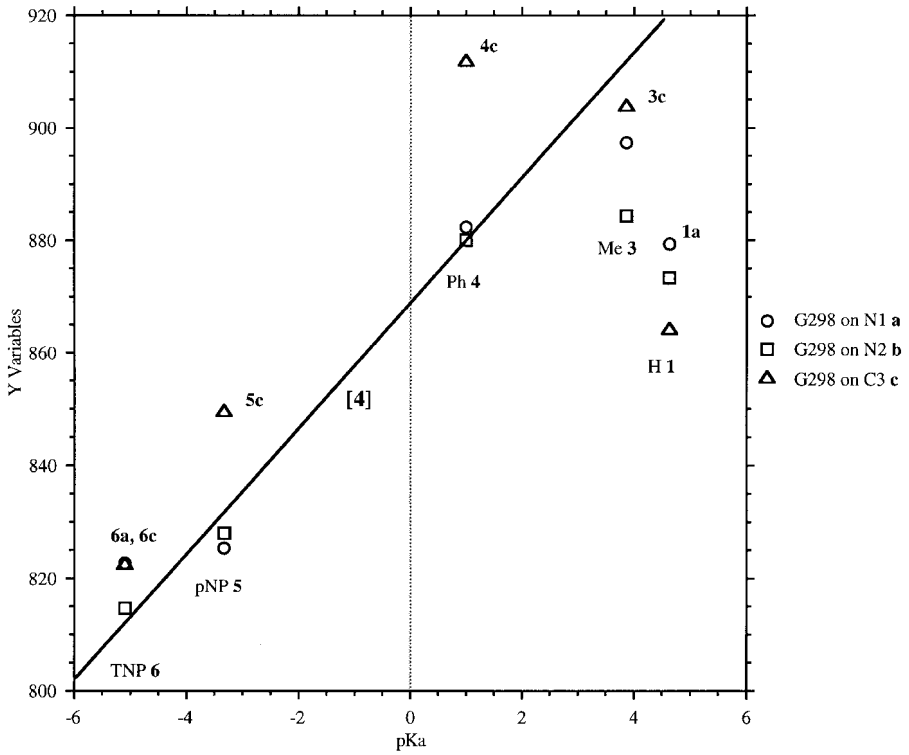


Figure 3. Plot of G_{prot}^{298} vs pK_a of 4,5-dihydropyrazoles

otin monohydrate: VIDLAV) (CSD refcodes: Version 5.08 with program[26]).

Apparently, the calculated geometry is closer to those determined recently for 1,1-di-*H*-3,5,5-trimethyl-4,5-tetrahydropyrazolium salts **2a**[11] than to the structure of **1a** determined by Nardelli and Fava in 1962.[10] However, the quality of this old structure (Weissenberg photographs) is relatively poor ($r = 0.09$) and the differences are not significant in terms of the precision achieved.

Concerning the energies reported in Table 2, e.g. G_{prot}^{298}, it appears that the most stable cations are **1a, 3c, 4c, 5c** and **6a** (although **6c** is very close in energy) whereas, in fact, the most stable cations in solution are **1a, 3a, 4a** and, probably, **5b** and **6b**. Therefore, the theoretical results are highly unsatisfactory. Attempts to include solvent effects [polarized continuum model, (PCM)][27] produced small modifications in a direction opposite to the experiment. Probably, it is necessary to consider specific solvation of the cations. For instance, cation **6a** presents an intramolecular hydrogen bond between the N^+—H and one of the *ortho*-nitro groups (1.664 Å) which is probably absent in water. Nevertheless, there is some useful information in Table 2. For instance, a plot of G_{prot}^{298} energies vs the aqueous pK_as (Fig. 3) shows some regularities.

The decrease in the basicity of the 1-aryl series, **4, 5, 6**, is well reproduced by the calculations assuming that these cations have the structure **c**. As structure **c** can be excluded for **4**, it is more reasonable to assume that these cations have the structures **4a, 5b** and **6b** [Eqn. (4)]:

$$G_{prot}^{298} = (870 \pm 4) + (11.4 \pm 1.1)\text{p}K_a (n = 3, r^2 = 0.99) \quad (4)$$

The *N*-unsubstituted **1** and *N*-methyl derivatives **3** clearly behave differently and no correlation is found for **1a, 3a** and **4a**. Even the statistical correction (0.3 pK_a units)[6] that has to be applied to **1a** (because it has two NH to lose whereas the *N*-substituted compounds have only one) increasing its relative basicity to 4.92 (see Table A1) is insignificant when compared with the non-linearity of the plot.

Mass spectrometry of protonated pyrazolines

Protonation of gaseous organic molecules can be readily performed in the CI source of a mass spectrometer[28] and preferred sites of protonation have been suggested in several instances on the basis of CA spectra of the mass-selected protonated molecules.[29] This methodology is based on the recognition of structurally significant fragmentation induced by interaction with a target in the high translational energy (8 keV) regime. Neutralization–reionization (NR)[30] spectra have also been used to localize protonation sites.[31]

In the context of the present work, most of the

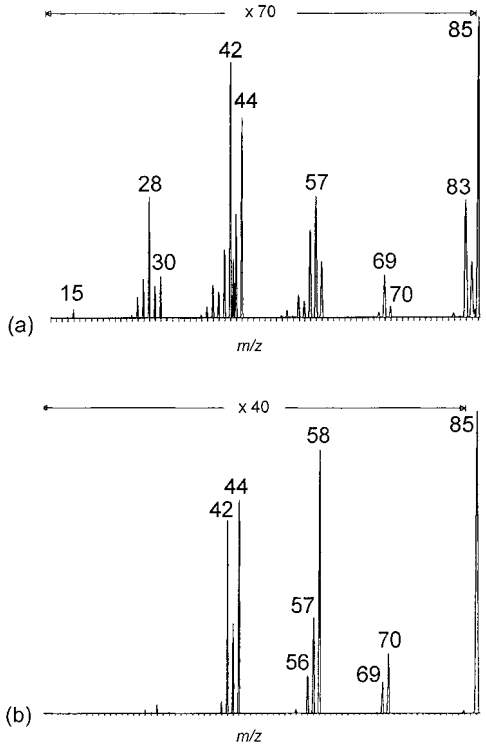
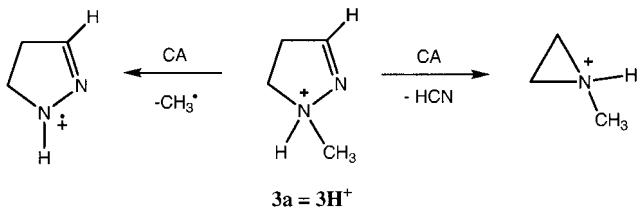


Figure 4. (a) High-energy (8 keV) CA spectrum of protonated 1-methyl-4,5-dihydropyrazole **3H**$^+$ (*m/z* 85) (oxygen collision gas, linked-scan mode); (b) low-energy (20–30 eV) CA spectrum of the same ions (argon collision gas, B scan)

experiments were performed on 1-methyl-4,5-dihydropyrazole (**3**). The CA spectrum of **3H**$^+$ ions (this corresponds to the protonated form of **3** without any hypothesis about the structure being **a, b** or **c**), recorded in the linked-scan mode (see Experimental), is depicted in Fig. 4. This spectrum appears to be satisfactorily reproduced whatever the nature of the reagent gas used (methane, methanol or self-CI conditions) and this can be interpreted as the result of the production of only one protonated species in the gas phase. Nevertheless, the spectrum appears to be fairly complex without significant peaks allowing the connectivity to be determined. The peak at *m/z* 44 could indicate the protonation at N-1 [$CH_3N^+(H)=CH_2$ ions], but this peak is already present without the presence of the collision gas (the same for *m/z* 58, 56 and 42) and may therefore result from a rearrangement process. The presence of a methyl group



3a = 3H$^+$

Scheme 1

in the cation is indicated by peaks at *m/z* 70 and 15, but these peaks are of low intensity.

The lack of structural information derived from the high-energy CA spectrum may be the result of the superimposition of the unimolecular (metastable) processes with the purely collision-induced dissociations, but consecutive fast dissociations may also be responsible for the complexity of the spectrum. We therefore decided to look at the collision-induced dissociations in the low-energy region (typically 20–30 eV) making use of our tandem mass spectrometer in its hybrid configuration.

The low-energy CA spectrum is indeed drastically simplified and, if we except the unimolecular processes (*m/z* 42, 44, 56 and in part 58), the observed collision-induced dissociations consist of the losses of a methyl radical (*m/z* 70) and HCN (*m/z* 58). These fragmentations can be interpreted as resulting from an N-1 protonation of 1-methyl-4,5-dihydropyrazole (**3**) (Scheme 1) to yield cation **3a**.

The structures assigned to these fragment ions correspond to the parent dihydropyrazole radical cations and protonated aziridine. These attributions are supported by the high-energy (8 keV) collisional activation of these ions, experiments allowed owing to the use of our hybrid (sector–quadrupole–sector) mass spectrometer (Fig. 5).

The loss of a hydrogen atom is by far the most significant fragmentation of the *m/z* 70 ions [Fig. 5(a)]:

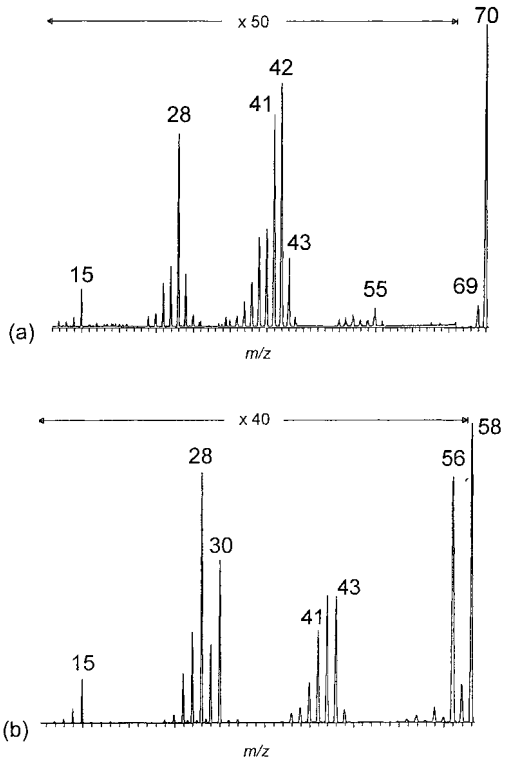


Figure 5. High-energy (8 keV) CA spectra of the *m/z* 70 (a) and 58 (b) ions produced in the quadrupole collision cell (oxygen collision gas, linked-scan mode)

this fragmentation is expected on the basis of an earlier systematic investigation of dihydropyrazole upon electron ionization and involves probably a hydrogen atom at position 5.[32]

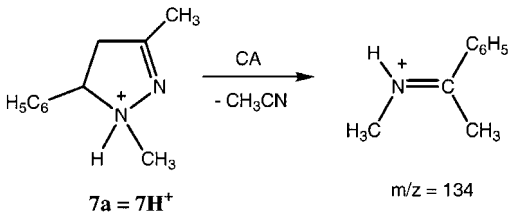
Five stable isomeric $C_3H_8N^+$ cations have been identified in previous work by means of MI and CA spectra, labelling experiments and theoretical calculations.[33] In a more recent study, we had the opportunity to reinvestigate the CA spectra of these various isomers together with cyclic species obtained by protonation of azetidine and 2-methylaziridine CR. Flammary and L. Gallez, unpublished results. The CA spectrum shown in Fig. 5(b) is found to be very similar to the spectrum of the iminium ions, $CH_3N^+(H)=CHCH_3$, generated by demethylation (α-cleavage) of ionized methylisopropylamine. The similarity of the CA spectrum of the proposed protonated methylaziridine is nevertheless not unexpected as these ions can be readily isomerized into the iminium structure by ring opening and a 1,2-hydrogen shift. Remember also that the *m/z* 58 peak is also in part due to a unimolecular process.

The neutralization–reionization spectrum of the $\mathbf{3H}^+$ ions was also recorded using xenon and oxygen in sequence. The major feature of the spectrum is the complete absence of a recovery signal corresponding to survivor ions; this behaviour is expected for an N-1 protonated species, **3a**, which, upon vertical neutralization, should produce an unstable hypervalent radical.

The behaviour of 1,3-dimethyl-5-phenyl-4,5-dihydropyrazoline (**7**) was found to be completely different. The CA spectrum of the protonated molecules $\mathbf{7H}^+$ (*m/z* 175, not shown) appears to be dependent on the nature of the CI reagent gas and this may be interpreted on the basis of the production of a mixture of isomeric protonated species. This is also supported by the unexpected complexity of the MIKE spectrum of these *m/z* 175 ions where more than eight competitive reactions were detected.

The major difference in the CA spectra was the increased intensity of the peak at *m/z* 134 when methanol was used as the reagent gas, and this could be indicative of the occurrence of the N-1 protonated species as shown in Scheme 2.

In the low kinetic energy regime, the major reaction leads to *m/z* 71 ions (loss of 104 u, probably neutral styrene) [Fig. 6(a)]. The CA spectrum of these *m/z* 71 ions depicted in Fig. 6(b) does not allow the connectivity



Scheme 2

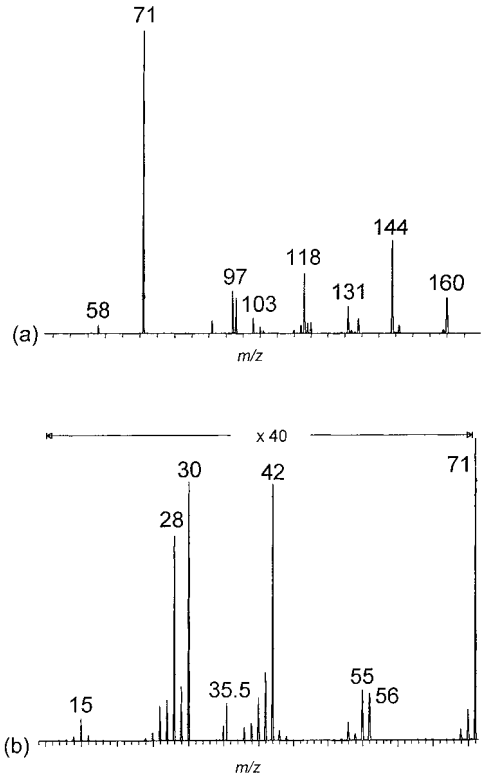


Figure 6. Methanol chemical ionization of 1,3-dimethyl-5-phenyl-4,5-dihydropyrazole (**7**): (a) low-kinetic energy CA spectrum (argon) of decelerated $\mathbf{7H}^+$ ions (*m/z* 175) and (b) CA (O_2) spectrum of the reaccelerated *m/z* 71 fragment ions

of the atoms to be determined unambiguously. Nevertheless, the production of a protonated nitrilimine structure, $CH_3CH{\equiv}N^+{-}N(H)CH_3$, could also indicate preferential protonation at N-1, **7a**.

CONCLUSIONS

The long-neglected study of 4,5-dihydropyrazoles has been resumed. Although the different approaches failed to give a coherent picture, it is safe to assume that these compounds protonate on N-1, both in the gas phase and in solution, when $R^1 = H$ or CH_3 and on N-2 when R^1 is a nitroaryl group. The case when $R^1 = C_6H_5$ is borderline and the protonation position may depend on the phase.

Acknowledgements

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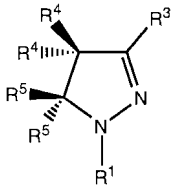
APPENDIX

Table A1. Literature pK_a values of 4,5-dihydropyrazoles and some useful nitrogen bases equation



No	Compound	R^1	R^3	R^4	R^4	R^5	R^5	pK_a	Ref.
1	4,5-Dihydropyrazole	H	H	H	H	H	H	4.62	6
22	3-Methyl-4,5-dihydropyrazole	H	CH_3	H	H	H	H	5.56	6
23	3-Ethyl-4,5-dihydropyrazole	H	C_2H_5	H	H	H	H	5.47	6
24	3-*tert*-Butyl-4,5-dihydropyrazole	H	*t*-C_4H_9	H	H	H	H	5.35	6
25	3-Phenyl-4,5-dihydropyrazole	H	C_6H_5	H	H	H	H	4.46	6
26	4-Methyl-4,5-dihydropyrazole	H	H	CH_3	H	H	H	4.58	6
27	5-Methyl-4,5-dihydropyrazole	H	H	H	H	CH_3	H	4.30	6
2	3,5,5-Trimethyl-4,5-dihydropyrazole	H	CH_3	H	H	CH_3	CH_3	5.19	6
28	5,5-Tetramethylene-4,5-diHpz	H	H	H	H	$(CH_2)_4$		4.20	6
29	5,5-Pentamethylene-4,5-diHpz	H	H	H	H	$(CH_2)_5$		4.16	6
30	3-Methyl-5,5-pentamethylene-4,5-diHpz	H	CH_3	H	H	$(CH_2)_5$		5.17	6
31	3-Bromo-5,5-tetramethylene-4,5-diHpz	H	Br	H	H	$(CH_2)_4$		2.70	6
32	3-Bromo-5,5-pentametylene-4,5-diHpz	H	Br	H	H	$(CH_2)_5$		2.68	6
33	3-Methyl-5-phenyl-4,5-dihydropyrazole	H	CH_3	H	H	C_6H_5	H	4.26	6
34	3-Phenyl-5-methyl-4,5-dihydropyrazole	H	C_6H_5	H	H	CH_3	H	4.17	6
35	3-Methyl-4-phenyl-4,5-dihydropyrazole	H	CH_3	C_6H_5	H	H	H	4.62	6
3	1-Methyl-4,5-dihydropyrazole	CH_3	H	H	H	H	H	3.88	6
36	1,3-Dimethyl-4,5-dihydropyrazole	CH_3	CH_3	H	H	H	H	4.85	6
37	1,5-Dimethyl-4,5-dihydropyrazole	CH_3	H	H	H	CH_3	H	3.56	6
38	1,3,5,5-Tetramethyl-4,5-dihydropyrazole	CH_3	CH_3	H	H	CH_3	CH_3	4.68	6
39	1,3-Dimethyl-5-phenyl-4,5-dihydropyrazole	CH_3	CH_3	H	H	C_6H_5	H	3.50	6
40	Ammonia	—	—	—	—	—	—	9.22	34
41	Methylamine	—	—	—	—	—	—	10.26	34
42	Aniline	—	—	—	—	—	—	4.58	34
43	*p*-Nitroaniline	—	—	—	—	—	—	1.11	34
44	2,4-Dinitroaniline	—	—	—	—	—	—	−4.54	34
45	2,4,6-Trinitroaniline	—	—	—	—	—	—	−9.41	34
46	Dimethylamine	—	—	—	—	—	—	10.74	34
47	*N*-Methylaniline	—	—	—	—	—	—	4.86	34
48	*N*-Methyl-*P*-nitroaniline	—	—	—	—	—	—	0.55	34
49	*N*-Methyl-2,4-dinitroaniline	—	—	—	—	—	—	−4.80	34
50	*N*-Methyl-2,4,6-trinitroaniline	—	—	—	—	—	—	−5.83	34
51	Trimethylamine	—	—	—	—	—	—	9.74	34
52	*N*,*N*-Dimethylaniline	—	—	—	—	—	—	5.15	34
53	*N*,*N*-Dimethyl-*p*-nitroaniline	—	—	—	—	—	—	0.60	34
54	*N*,*N*-Dimethyl-2,4-dinitroaniline	—	—	—	—	—	—	−4.23	34
55	*N*,*N*-Dimethyl-2,4,6-trinitroaniline	—	—	—	—	—	—	−4.98	34
56	Hydrazine	—	—	—	—	—	—	7.93	34
57	Methylhydrazine	—	—	—	—	—	—	8.20	34
58	Phenylhydrazine	—	—	—	—	—	—	5.28	34
59	*p*-Nitrophenylhydrazine	—	—	—	—	—	—	3.70	34
60	Pyrazole	—	—	—	—	—	—	2.48	35
61	1-Methylpyrazole	—	—	—	—	—	—	2.06	35
62	1-Phenylpyrazole	—	—	—	—	—	—	0.43	35
63	1-*p*-Nitrophenylpyrazole	—	—	—	—	—	—	−0.64	35
64	1-(2′,4′-Dinitrophenyl)pyrazole	—	—	—	—	—	—	−1.38	35
65	1-(2′,4′,6′-Trinitrophenyl)pyrazole	—	—	—	—	—	—	−1.97	35

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