Structure of 3-amino-4,5-dihydropyrazoles in acid media: X-ray structure of 3-amino-1-phenyl-4,5-dihydropyrazol-2-ium picrate and the origin of broad signals in ^{1}H NMR spectroscopy

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The origin of the broadening of NMR signals in 3-amino-4,5-dihydropyrazoles has been studied in the 1-phenyl series. It has been proved that the broadening is due to the presence of acid in some solvents, like deuteriochloroform, by reproducing it by addition of trifluoroacetic acid. To determine the protonation site of 3-amino-1-phenyl-4,5-dihydropyrazole **1**, the crystal structure of its picrate **5** was determined. Contrary to other dihydropyrazoles, **1** protonates on N^2, like an amidine.

We reported several years ago,[1-3] that 3-amino-4,5-dihydropyrazoles, for instance 3-amino-1-phenyl-4,5-dihydropyrazole **1**, presented an intriguing and unexplained behaviour in ^{1}H NMR spectroscopy: under some conditions, the spectra in deuteriochloroform were so broad that no signal other than that of the Me_4Si could be observed. This fact was also observed in the ^{1}H and ^{13}C NMR spectra of biologically active 3-amino-1-aryl-4,5-dihydropyrazoles [*e.g.*, in 3-amino-1-(*m*-trifluoromethylphenyl)-4,5-dihydropyrazole the anti-inflammatory agent BW-755C, **2**].[4]

This broadening of signals could be attributed either to slow prototropic exchange rates between tautomeric species and/or to slow equilibria between neutral and protonated forms.

Thus, we decided first to reproduce on modern spectrometers and under different experimental conditions, the broadening observed in the past using 60 MHz,[1,2] or 100 MHz instruments,[4] in order to provide a possible explanation.

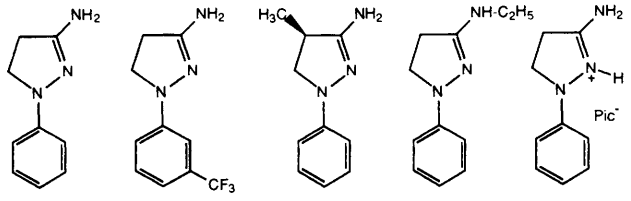
Experimental

The title compounds **1**, 3-amino-4-methyl-1-phenyl-4,5-dihydropyrazole **3**, 3-ethylamino-1-phenyl-4,5-dihydropyrazole **4** and 3-amino-1-methyl-1-phenyl-4,5-dihydropyrazol-1-ium iodide **8** were prepared according to previously described methods.[1,2] The ^{1}H and ^{13}C NMR spectra in solution were recorded on a Bruker AC200 instrument working at 200.13 (^{1}H) and 50.32 MHz (^{13}C) using standard conditions.[5] The ^{13}C CPMAS spectrum was recorded in the same instrument using the conditions described in ref. 6.

X-Ray structure determination

Crystals of 3-amino-1-phenyl-4,5-dihydropyrazol-2-ium picrate **5** suitable for X-ray analysis were obtained by slow evaporation of a saturated ethanol solution.

Crystal data. $C_9H_{11}N_3{\cdot}C_6H_3N_3O_7$, M = 390.3, a well formed yellow prism of 0.18 × 0.22 × 0.56 mm was used for data collection at room temperature. Monoclinic a = 7.717(3), b = 11.147(3), c = 20.076(2) Å, β = 98.60(2), V = 1707.5 Å^3, space group $P2_1/c$, Z = 4, D_x = 1.518 g cm^{-3}, Cu-Kα (Ni filtered).



1 2 3 4 5

Data collection and processing. Siemens AED diffractometer using $\theta/2\theta$ scan mode, scan speed 3/12 deg min^{-1}, scan width (1.20 + 0.14 tan θ) and θ in the range 3 < θ < 70 deg. Cell parameters were determined by least-squares fit to observed 2θ values for 29 centred reflections with 22.3 < θ < 40.6. Intensity checks for one standard reflection showed no significant variation. 3251 independent reflections were measured (h − 2 to 9, k − 13 to 10, l − 24 to 24) of which 1859 were observed with $I > 2\sigma(I)$. Lorentz and polarization (LP) and extinction corrections but no absorption was applied.

Structure analysis and refinement. The structure was solved by direct methods using SIR92[7] and refined using SHELX-92[8] by full-matrix least squares on F_o with anisotropic thermal parameters (rigid-body constraint for the two phenyl rings). Many H atoms (*e.g.* H1N2, H1N and H2N) were identified in the difference map, but all of them were constructed with the geometric options allowed in SHELX-92 and refined with isotropic U values. The weighting scheme $w = 1/[s(F_o^2) + (0.06P)^2 + 0.0122P]$ where $P = (F_o^2 + 2F_c^2)/3$, gave satisfactory agreement analyses. Max thermal value 10.02 Å^2, final ΔF peaks 0.70 e Å^{-3}. The final R indexes were respectively R = 0.0620 for 1859 reflections with $F_o > 4\sigma(F_o)$ and 0.0996 for all the 3251 data.¶

All the calculations were performed on the Gould computer system of the *Centro di Strutturistica Diffrattometrica del CNR*,

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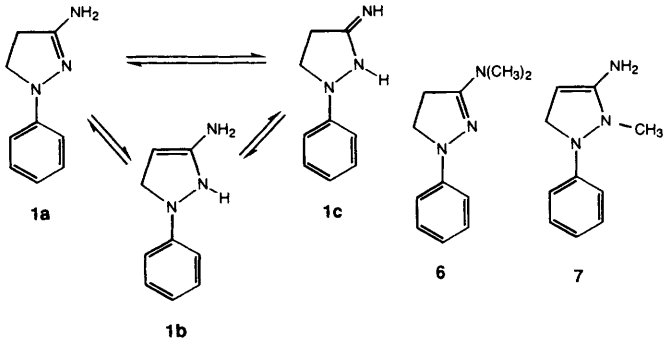
¶ Crystallographic data has been deposited. For details of the CCDC deposition scheme, see 'Instructions for Authors (1995)', *J. Chem. Soc., Perkin Trans. 2*, 1995, issue 1.

Parma, Italy. The SIR92 program was the PC version. Geometric and ancillary calculations were performed with PARST [9] and CRYSRULER [10] packages; drawings were made with ORTEX,[11] the McArdle version of the ORTEP.

Results and discussion

^{1}H NMR spectroscopy

If we consider, for instance, the case of 3-amino-1-phenyl-4,5-dihydropyrazole **1**, this compound could exist in three tautomeric forms: 3-amino-4,5-dihydropyrazole **1a**, 3-amino-2,5-dihydropyrazole **1b** and 3-imino-2,3,4,5-tetrahydropyrazole **1c**.



However, compound **6** was prepared [2] and it continues to show broad signals,[2] this observation excludes **1a**/**1c** and **1b**/**1c** tautomerism as being the origin of the observed broadening in spectra of **1**. A compound closely related to **7** was also prepared,[1] and showed a similar broadening, but in this case a tautomeric process involving an iminotetrahydropyrazole (an N^2-methyl derivative of **1c**) cannot be excluded. Thus, a slow tautomeric process involving **1a** and **1b** remains as a possible explanation for the broadening of ^{1}H NMR spectra of **1**.

Nevertheless, when spectra are recorded in the presence of various amounts of trifluoroacetic acid, drastic modifications are observed. In Figs. 1–3 are represented the ^{1}H NMR spectra of dihydropyrazoles **1**, **5** and **6** in $CDCl_3$ solution. Figures **a** correspond to the spectra recorded using $CDCl_3$ from a freshly open bottle and figures **b** to spectra of the same solutions after addition of small amounts of CF_3CO_2H. Using $CDCl_3$ exposed to light, spectra similar (more or less broadened) to figures **b** are obtained. In the case of the 4,5-dihydropyrazole **1**, the spectra correspond to the following chemical shifts: neutral form (Fig. **1a**) δ 2.88 (4a-H, 4b-H), 3.68 (5a-H, 5b-H) (AA'BB' system of the pyrazole ring), 6.95 (2'-H, 6'-H), 7.24 (3'-H, 5'-H), 6.76 (4'-H) (AA'BB'C system of the *N*-phenyl substituent); protonated form (2 mg of pyrazole in 0.5 cm^3 of $CDCl_3$ plus 2 mm^3 of CF_3CO_2H, Fig. **1c**) δ 3.13 (4a-H, 4b-H), 3.90 (5a-H, 5b-H) (AA'BB' system of the pyrazole ring), 6.99 (2'-H, 6'-H), 7.36 (3'-H, 5'-H), 7.13 (4'-H) (AA'BB'C system of the *N*-phenyl substituent).

These results pointed to the presence of DCl, formed by photolysis of $CDCl_3$, as the origin of the broadening described in earlier references.[1–4] To verify this hypothesis, two kinds of experiments were carried out: (*i*) addition of 'proton sponge' (1,8-bisdimethylaminonaphthalene) slowly transformed (24 h) spectra of figures **b** into those of figures **a**; (*ii*) by addition of a great excess of CF_3CO_2H, the signals of the spectra became narrow again (Fig. **1c**), but all of them are shifted downfield.

Other unpublished results,[12,13] are also consistent with traces of acid being at the origin of the broad signals. For instance, the broadening has never been observed in [$^2H_6$]DMSO nor in [$^2H_5$]pyridine.

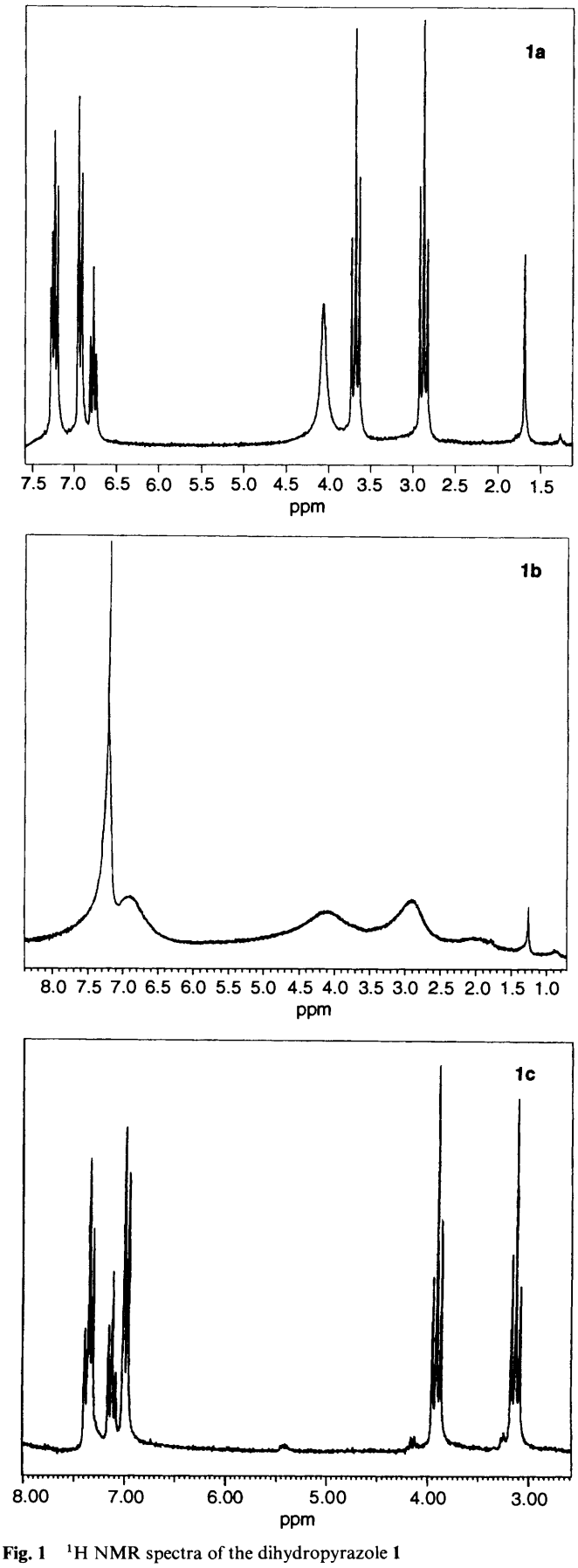
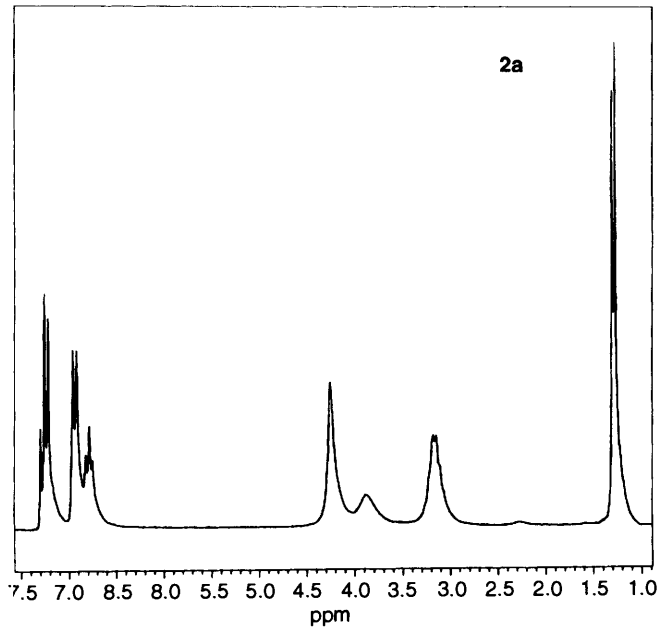


Fig. 1 ^{1}H NMR spectra of the dihydropyrazole **1**



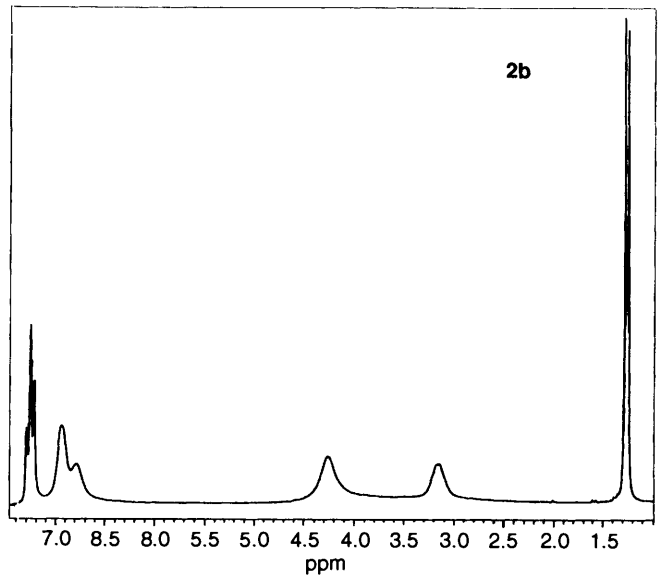


Fig. 2 ^{1}H NMR spectra of the dihydropyrazole **3**

Another interesting observation is that the broadening was rather insensitive to temperature changes.[1-3] This point could be puzzling as for ln k to be independent of temperature (in the range explored, -70 to $+70$ °C), $\Delta H^{\ddagger}$ has to be very small and $\Delta S^{\ddagger}$ very large and negative. Nevertheless, it must be considered that if the concentration of protons, C_{H^+}, is very low, then $\Delta S^{\ddagger}(\text{obs}) = R \ln C_{H^+} + \Delta S^{\ddagger}$, should appear as very large and negative.[14]

Unfortunately, important broadening can be reproduced by simulation using the Binsch DNMR4 program [15] only when the ratio [B]/[BH$^+$] is not too high (below 5). Obviously, this simulation uses an oversimplified model, assuming that two AA'BB' (or two AA'BB'C for the phenyl group) are exchanging with each other (one of the neutral molecule and one of the protonated form). For example, the equilibrium **1a**/**1b** cannot be simulated since an AA'BB' is exchanging with an A_2XY system in which one proton (the proton on N^2) belongs partially to the solvent. Chemical shifts were those corresponding to the spectrum of Fig. **1a** for the neutral species and of Fig.

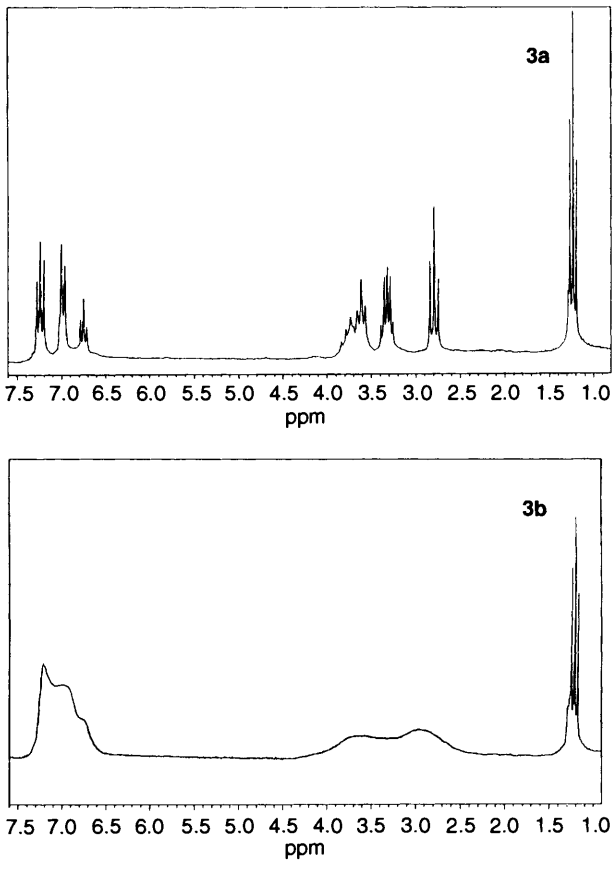


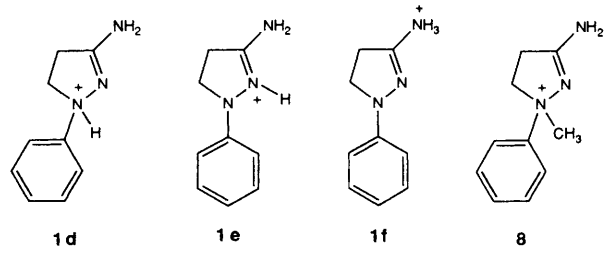
Fig. 3 ^{1}H NMR spectra of the dihydropyrazole **4**

1c for the protonated molecule. We used approximate coupling constants [16] and a T2 of 0.6 s for both entities. The result of the simulation is represented in Fig. 4.

Having established that the broadening of the signals is due to the presence of the conjugated acid, the structure of the protonated form is still to be determined.

All the spectroscopic evidence indicates that the major tautomer has the structure **1a**. In the solid state, the X-ray structures of compounds **1** and **2** have been determined: [17] they both exist as 3-amino-4,5-dihydropyrazoles **1a** and **2a**.

This observation is related to the protonation site of 3-amino-4,5-dihydropyrazoles. Taking for granted that these compounds, for instance **1**, exist as tautomer **1a** (the X-ray structure of 4,5-dihydropyrazole hydrochloride is known [18] and corresponds to a structure like **10** but with two protons on N^1, see **14**) there are three possible conjugated acids: **1d**, protonated on N^1, **1e**, protonated on N^2, and **1f**, protonated on the exocyclic amino group.



1d **1e** **1f** **8**

4,5-Dihydropyrazoles, for instance 3-methyl-1-phenyl-4,5-dihydropyrazole **9**, protonate and quaternarize at position 1 to afford cations **10** and **11**.[19,20] It is also known that dihydropyrazole **1** quaternarizes at position 1 affording salt

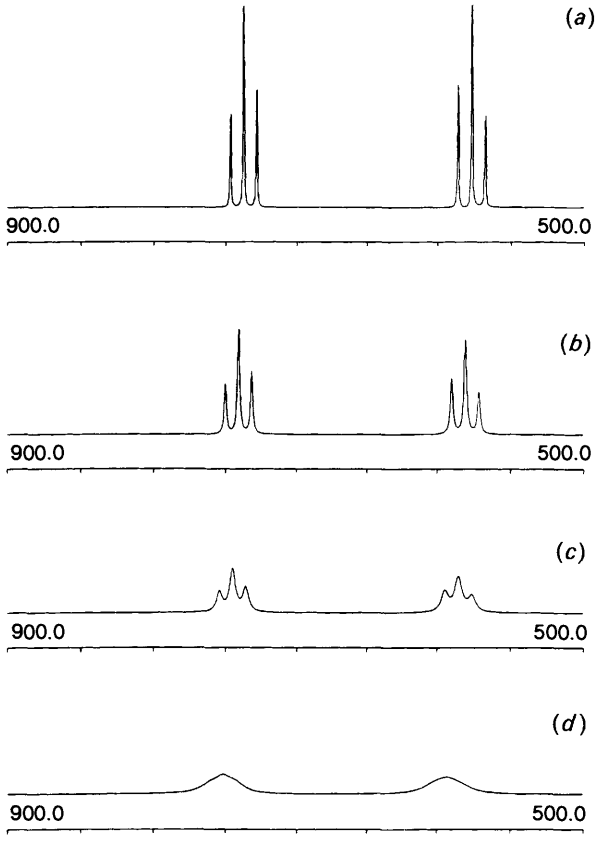
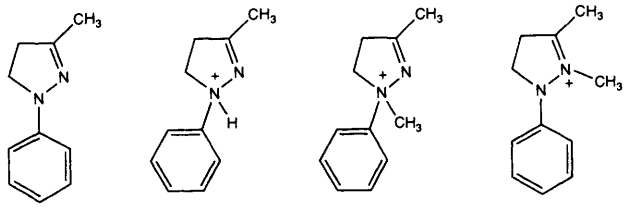


Fig. 4 ^{1}H NMR simulated spectra of the dihydropyrazole **1**: [B]/[BH] = 99:1 (*a*); 95:5 (*b*); 90:10 (*c*); 80:20 (*d*)

8.[21–23] It was tempting to assume that protonation of **1** also occurs at position 1 with formation of cation **1d**. Nevertheless, if protonation on the amino group seems highly improbable, protonation on N^2 leading to a cation **1e** stabilized by resonance, like the amidinium cation, is reasonable (amidrazones, which have the same functionality as 3-aminodihydropyrazoles, protonate on N^2).[24]



Although protonation of 'normal' dihydropyrazoles, that is, dihydropyrazoles without amino groups at position 3, takes place exclusively at position 1, it is possible to obtain both quaternary salts, **11** by direct quaternization and **12** by protonation of the corresponding 2,5-dihydropyrazole.[25] The study of model compounds **11** and **12** leads to some rules concerning the effect of a positive charge on NMR properties: (*i*) in ^{1}H NMR, if the charge is at position 1, there is a decrease in the sum of vicinal coupling constants of the CH_2CH_2 fragment ($\Sigma J = J_{cis} + J_{trans}$), this decrease amounts to 6.5 Hz, on the other hand, if the charge is at position 2, there is almost no effect on ΣJ;[26] (*ii*) in ^{13}C NMR, the most striking observation concerns the signal of the carbon atom at the *para* position of the *N*-phenyl ring: in **9** it appears at 118 ppm, in **10** at 132.5 ppm, in **11** at 132 ppm (the ^{13}C NMR spectrum of **12** has not been reported).[27–29]

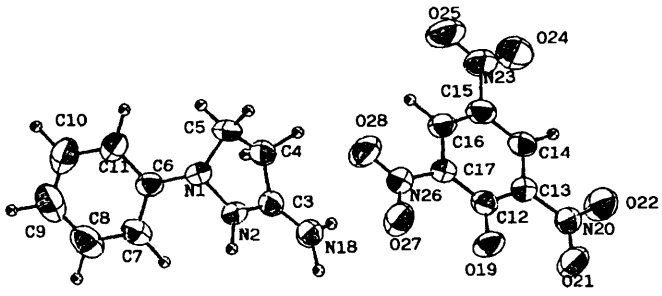


Fig. 5 Perspective view of compound **5** with the atomic numbering scheme used

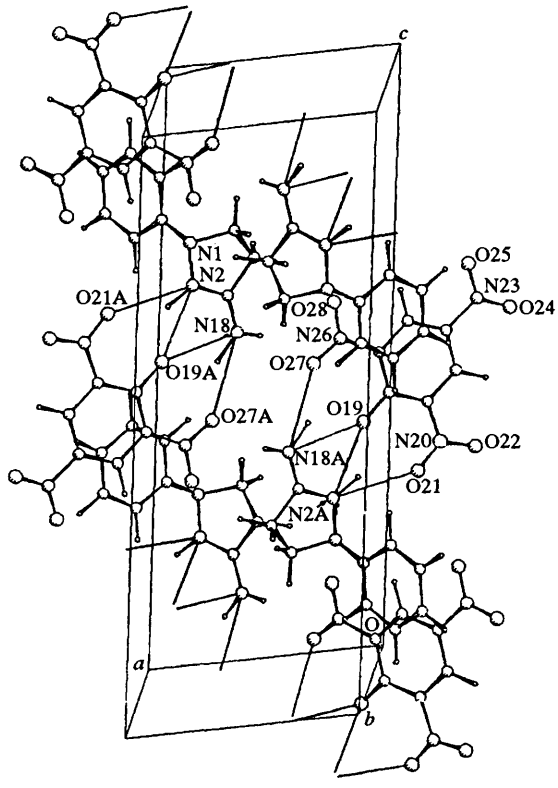


Fig. 6 Hydrogen bond network (simplified) of compound **5**

For 3-amino-1-phenyl-4,5-dihydropyrazole, the spectrum recorded in $CDCl_3$ corresponds to ΣJ = 18.6 Hz, δ(C4′) = 117.9 while the spectrum recorded in a $CDCl_3$–CF_3CO_2H mixture (narrow signals) corresponds to ΣJ = 16.3 Hz, δ(C4′) = 125.8 (pure CF_3CO_2H, Table 3). For compound **8** in [$^2H_6$]DMSO, the CH_2CH_2 system appears as an ABCD system (spectroscopic proof that quaternization took place at position 1) and δ(C4′) = 130.0 (Table 3).

The conclusion is that protonation of compound **1** does not occur at position 1, at least not at the extent that it occurs in the case of compound **9**. To clarify this matter it was decided to prepare the picrate of **1**, salt **5**, and to determine its structure by X-ray crystallography. Also, the ^{13}C CPMAS NMR spectra of **1** and **5**, were recorded. The results of Table 1 show that the chemical shifts of compound **1** in solution and in the solid state were almost identical, and since the solid state structure of **1** corresponds to tautomer **1a** so it will be for the solution. The ^{13}C chemical shifts of the picrate **5** in the solid state (this compound is very insoluble in [$^2H_6$]DMSO) and those of **1** and **5** in CF_3CO_2H are also similar, although differences of 3–4 ppm are observed.

Table 1 ^{13}C NMR parameters of 4,5-dihydropyrazoles

Compound	C3	C4	C5	C1′	C2′	C3′	C4′	Substituents
3-Methyl-4,5-dihydropyrazoles								
1-Phenyl **9**[a]	151.3	35.8	48.0	145.9	112.4	128.8	117.9	—
1-Phenyl **10**[b]	181.6	40.6	58.8	142.7	121.7	132.0	132.4	—
1-Methyl-1-phenyl **11**[c]	178.7	39.6	65.9	138.3	130.9	132.4	131.6	1-CH_3: 56.4
3-Amino-4,5-dihydropyrazoles								
1-Phenyl **1**[a]	153.3	32.5	49.6 (br)	148.7 (br)	112.7 (br)	128.7 (br)	117.8 (br)	—
1-Phenyl **1**[c]	155.3	32.4	48.6	149.1	112.2	128.6	116.2	—
1-Phenyl **1**[d]	156.1	32.6	46.0	146.8	117.8[e]	130.0	114.3	—
1-Phenyl **1e**[b]	166.1	29.1	54.5	145.3	116.6	128.7	125.8	—
1-Phenyl picrate **5**[b]	168.0	29.6	56.6	143.0	117.8	129.6	128.7	—
1-Phenyl picrate **5**[d]	163.2	30.5	57.3	149.8	116.3	128.8	128.8	—
1-Methyl-1-phenyl **8**[b]	169.0	30.6	68.5	146.5	118.1	129.8	130.5	1-CH_3: 57.9
1-Methyl-1-phenyl **8**[c]	168.6	32.1	66.8	149.6	120.5	129.9	130.0	1-CH_3: 59.1
4-Methyl-1-phenyl **3**[c]	158.5	39.2	56.2	149.1	112.2	128.6	116.3	4-CH_3: 16.2

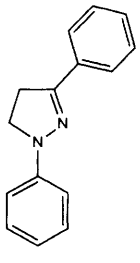
[a] $CDCl_3$. [b] CF_3CO_2H. [c] [$^2H_6$]DMSO. [d] Solid state. [e] Another signal at 110.6 ppm.

Table 2 Comparison of the 4,5-dihydropyrazole ring of four derivatives

	Picrate **5**	GERBOU **1**	DPPRZL **13**	PYZOLC **14**
N1–N2	1.424(3)	1.433(2)	1.338	1.468
N1–C5	1.500(4)	1.476(2)	1.493	1.498
N1–C6	1.428(3)	1.383(3)	1.423	—
N2–C3	1.313(4)	1.277(3)	1.333	1.255
C3–N18	1.305(4)	1.354(3)	—	—
C3–C4	1.484(5)	1.494(5)	1.488	1.473
C4–C5	1.505(5)	1.576(3)	1.520	1.472
C5–N1–C6	116.5(3)	120.5(1)	126.8	—
N2–N1–C6	113.8(2)	117.4(2)	121.0	—
N2–N1–C5	101.8(2)	109.0(1)	112.0	107.7
N1–N2–C3	114.0(3)	107.1(2)	109.4	106.9
N2–C3–C4	109.5(3)	155.2(2)	112.6	117.4
C3–C4–C5	101.3(3)	101.1(2)	102.4	102.5
N1–C4–C5	105.3(3)	102.6(1)	102.7	105.5
C5–N1–C6–C7	128.3(3)	158.1(1)	—	—
N2–N1–C6–C7	10.3(4)	−25.5(2)	—	—
C5–N1–C6–C11	−56.4(3)	−162.5(1)	—	—
N2–N1–C6–C11	−174.4(2)	21.1(2)	−174.0	—
C6–N1–C5–C4	−97.8(3)	−162.5(1)	176.0	—
N2–N1–C5–C4	26.6(3)	−22.4(2)	−7.7	—
C5–N1–N2–C3	−16.0(3)	15.7(2)	2.8	—
C6–N1–N2–C3	110.3(3)	157.3(1)	179.3	—
N1–N2–C3–N18	176.0(3)	178.5(2)	—	—
N1–N2–C3–C4	−1.7(4)	−1.8(2)	—	—
N2–C3–C4–C5	18.5(4)	−12.0(2)	−8.3	—
N18–C3–C4–C5	−159.2(3)	167.7(1)	—	—
C3–C4–C5–N1	−27.4(3)	19.6(1)	8.9	—
q_2	0.2771(35)	0.2125(1)	0.0918(2)	0.0001(4)
φ_2(°)	−39.82(67)	148.02(2)	123.54(14)	−80.13(39)

X-Ray structure of compound 5

An ORTEP view of compound **5** with the atomic numbering scheme used is shown in Fig. 5 and a PLUTO drawing with a simplified hydrogen bond network is represented in Fig. 6. The N1–C5 single bond distance is in agreement with those of the compounds reported in the Cambridge Structural Database (CSD)[30] and in Table 2 in which a comparison with the dihydropyrazole part of three compounds is performed (**1** GERBOU,[17] **13** DPPRZL[21] and **14** PYZOLC[18] are the reference codes of the compounds as classified by the CSD). The N2–C3 distance corresponds well with the mean value of those generally assumed for the N–C double bond[30] and is intermediate between those of **1** and **13**. On the other hand, the N1–N2 bond length is consistent with the N–N single bond and compares well with that of **1**; the same is verified also for the C3–C4 and C4–C5 distances of the 4,5-dihydropyrazole ring.



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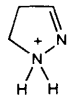

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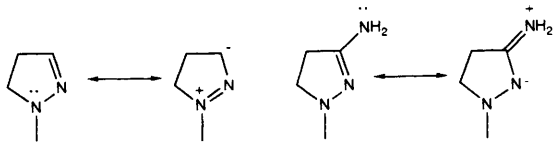
It must be observed that the C3–N18 distance of the title compound **5** is the shortest one, even shorter than that reported in ref. 30 for a C–N double bond; probably, the conjugation

Table 3 Comparison of picrate ion geometries (bond lengths in Å)

	C–O	C–N	N–O
Picrate **5**	1.320	1.448	1.222
Picric acid [35]			
Molecule I	1.312	1.462[a]	1.207[a]
Molecule II	1.358	1.460[a]	1.207[a]
Picric acid [36]			
Molecule I	1.310	1.452[a]	1.215[a]
Molecule II	1.369	1.466[a]	1.214[a]
Arithmetic mean	1.245	1.452	1.221
Walkinshaw [37]	1.241	1.456	1.220
Llamas-Saiz [39]	1.269	1.456	1.215
Frydenvang [40]	1.242	1.456	1.232

[a] Mean value in molecule.

with the phenyl ring is also responsible for the shortening of the C6–N1 distance.



Simple resonance considerations, represented above, account for these observations: (*i*) protonation on N1 suppress the 'enamine-like' resonance of 4,5-dihydropyrazoles,[31] this produces an increase (+0.13 Å) of the N1–N2 bond and a decrease of the N2–C3 bond (−0.08 Å); (*ii*) a 3-amino group introduces an amidine-like resonance which opposes the preceding one, this results in an increase (+0.10 Å) of the N1–N2 bond and a small decrease of the N2–C3 bond (−0.06 Å); (*iii*) protonation on N2 does not affect the N1–N2 bond length but, due to the amidinium cation resonance, increases the N2–C3 bond length (+0.04 Å) and decreases the exocyclic C3–N18 bond length (−0.05 Å).

Concerning bond angles, it can be said that the C3–C4–C5 and N1–C5–C4 angles are similar in all compounds, the N2–N1–C6 and N2–N1–C5 are shorter in **5** than in **1**, the remaining ones significantly greater, no trend being discernible on the examined compounds. The orientation of the phenyl ring with respect to the pyrazole one, defined by the torsion angle N2–N1–C6–C7, is quite different in **1** (15.0) and in **5** (60.8). This increase is probably related to the replacement of the lone pair of N2 by a hydrogen atom linked to a bulky picrate anion (in 1-phenylpyrazole, the dihedral angle increases from 26° in the neutral molecule [32] to 38° in the cation).[33]

The puckering parameters (puckering amplitude q_2 and phase angle φ_2) corresponding to molecules **1**, **5**, **13** and **14** are also reported in Table 2.[34] It can be noted that compound **14** (4,5-dihydropyrazol-1-ium cation) is planar and the 1,3-diphenyl derivative is nearly planar with a twist conformation. The dihydropyrazole **1** and its picrate **5** both have envelope conformations.

As far as the picrate part of the compound is concerned, it can be said that everything is in agreement with other picrates, as can be seen from Table 3 in which the mean distances of the oxidryl and nitro groups of **5** are compared with the results reported in the work of Walkinshaw [37] cited by Botoshansky *et al.*[38] and with the picrate of a pyrazole derivative.[39] The C10–O19 distance is longer in compound **5** probably because the O19 atom is involved in hydrogen bonds.

A number of hydrogen bonds makes the crystal significantly well packed (density = 1.518 g cm^{-3}, packing coefficient = 0.695).

Conclusions

It remains to be explained why broadening of signals due to the presence of acids is only observed for 3-amino-4,5-dihydropyrazoles and not at all for 'normal' dihydropyrazoles. We think that the reason might be the high thermodynamic and kinetic basicities of the former compounds. 'Normal' dihydropyrazoles have pK_a values in the range 4–6,[41] those of 3-aminodihydropyrazoles are not known (amidrazones have a pK_a = 10.0),[24] and since there are two conjugated acids in equilibrium, the thermodynamic values should be difficult to determine. The fact that the effect produced by adding protons can be reversed by 'proton Sponge' but that the reversibility is slow is a proof of the high kinetic basicity.

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