The Tautomerism of 3(5)-Phenylpyrazoles: An Experimental (^{1}H, ^{13}C, ^{15}N NMR and X-Ray Crystallography) Study

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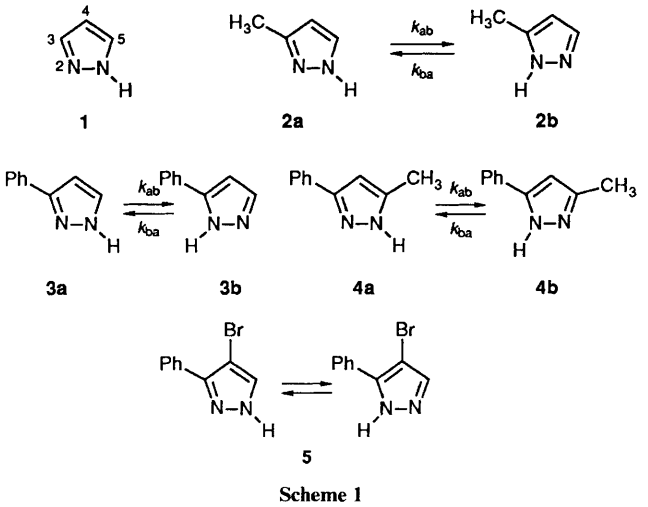
3(5)-Phenyl- and 5(3)-methyl-3(5)-phenylpyrazole have been studied using multinuclear NMR spectroscopy at low temperature to determine the tautomeric equilibrium constants in the slow proton exchange regime by simple signal integration. In order to compare the results in solution with those in the solid state, the X-ray structure of a derivative of the first, namely 4-bromo-3-phenylpyrazole was determined [triclinic, $P\bar{1}$, a = 13.0867(8), b = 13.2546(7), c = 7.8079(3)Å, α = 100.015(4), β = 93.648(3), γ = 84.923(5)°, Z = 6]. The conclusions are that 3(5)-phenylpyrazoles exist in solution as mixtures rich in the 3-phenyl tautomer which is also the tautomer present in the solid state, whereas they form monomers which are hydrogen bonded to the solvent in liquids like THF and self associate in inert solvents.

It has long been known that pyrazole tautomeric equilibrium constants (K_T) can be determined by NMR spectroscopy;[1–13] however, to our knowledge the method has scarcely been used. Table 1 summarises all previous information on this topic. Depending on the nature and position of the pyrazole C-substituents, the solvent, the concentration and the temperature, the N–H proton exchange rate can be slowed down to the point where separate signals are observed for positions 3 and 5 (carbons 3 and 5, protons 3 and 5, and substituents at positions 3 and 5) and for nitrogens at positions 1 and 2. Most of these studies deal with pyrazole itself (**1**) or with pyrazoles carrying identical substituents at positions 3 and 5, *i.e.* with pyrazoles for which K_T = 1. For 3(5)-azidopyrazole only the major tautomer (the 3-substituted) has been observed by NMR spectroscopy from which it has been concluded that K_T = 0.[11] Finally, the only case of a tautomeric mixture whose equilibrium constant has been determined by NMR spectroscopy is that of 3(5)-methylpyrazole (**2**). This compound was found to exist in hexamethylphosphorotriamide (HMPT) at −20 °C as a mixture of 46% of 3-methyl-**2a** and 54% of 5-methylpyrazole **2b**.[10]



Scheme 1

In view of this situation we decided to study the case of compounds **3** [3(5)-phenylpyrazole] and **4** [5(3)-methyl-3(5)-phenylpyrazole]. Compound **4** is the only non-symmetric pyrazole which seems to exist in the solid state as a 50:50 mixture of tautomers **4a** and **4b**[14,15] (compound **2** is a liquid at room temperature). The structure of 3(5)-phenylpyrazole has not been reported, but since we experienced difficulties in obtaining suitable crystals of pyrazole **3** [whereas, in contrast, those of 4-bromo-3(5)-phenylpyrazole **5** were of good quality], we decided to determine the X-ray structure of the latter; compound **5** may be a reasonable model for **3** because the insertion of the bromine atom at position 4 is not expected to have a large effect on the **3a** ⇌ **3b** tautomerism.

Experimental

The $^{15}N_2$ labelled pyrazole **4'** was prepared following the described synthesis of 5(3)-methyl-3(5)-phenylpyrazole[16] but using $^{15}NH_2$–$^{15}NH_2$ instead of hydrazine.

Single crystals for diffraction measurements were grown by slow evaporation of an ethanolic solution of compound **5**. Tables 2 and 3 contain, respectively, the main characteristics of the crystallographic analysis and the final fractional coordinates with the numbering referred to in Fig. 1. The main features are shown in Table 4.

There are three crystallographically independent molecules forming a trimer through N–H···N hydrogen bonds which have the protons localized. Neutral scattering factors were taken from ref. 17. Data processing and computation were carried out on a Vax 6410 computer using the following programs: XRAY80 SYSTEM,[18] PESOS,[19] PARST,[20] and PLUTO.[21,*]

* Lists of thermal components, hydrogen parameters and bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1992, issue 1.

Table 1 Literature results on pyrazole NMR spectroscopy with 'blocked' tautomerism

Pyrazole	^{1}H	^{13}C	^{15}N
Pyrazole **1**		Ether–THF [1–4] Acetone [5] DMSO [6] HMPT [7]	DMSO [8,9]
3(5)-Methyl **2**		HMPT [7]	
3,5-Dimethyl		HMPT [7]	
3(5)-Phenyl **3**		HMPT–Acetone [10]	
3-Azido	Acetone [11] DMSO [11]	DMSO [11]	
4-Nitro	Acetone [11,12] DMSO [11]	DMSO [11]	
3,5-Dimethyl-4-nitro	Acetone [12] Methanol [13]	Methanol [13]	
4-Chloro-3,5-dimethyl	Methanol [13]	Methanol [13]	

Table 2 Crystal analysis parameters for compound **5** at room temperature

Crystal data	
Formula	$C_9H_7N_2Br$
Crystal habit	Prism, transparent, colourless
Crystal size/mm	0.27 × 0.33 × 0.13
Symmetry	Triclinic, $P\bar{1}$
Unit cell determination:	Least-squares fit from 66 reflections ($\theta < 45°$)
Unit cell dimensions/Å, °	a = 13.0867(8) b = 13.2546(7) c = 7.8079(3) 100.015(4), 93.648(3), 84.923(5)
V/Å^3, Z	1326.9(1), 6
D_c/g cm^{-3}, M, F(000)	1.675, 223.07, 660
μ/cm^{-1}	59.12
Experimental data	
Technique	Four-circle diffractometer: Philips PW1100 Bisecting geometry Graphite oriented monochromator: Cu-Kα $\omega/2\theta$ scans, scan width: 1.5° θ_{max} 65° 1 min/reflections
Number of reflections:	
Independent	4515
Observed	4103 [3$\sigma(I)$criterion]
Standard reflections:	2 reflections every 90 min No variation
Min–max abs. correction:	0.726–1.623
Solution and refinement	
Solution	Patterson
Refinement	Least-squares on F_0
Parameters:	
Number of variables	409
Degrees of freedom	3694
Ratio of freedom	10.0
H atoms	Difference synthesis
Final shift/error	0.18
Weighting scheme	Empirical as to give no trends in $\langle w\Delta^2F\rangle$ *vs.* $\langle\|F_{obs}\|\rangle$ and $\langle\sin\theta/\lambda\rangle$
Max thermal value	U_{33}(BrC) = 0.0887(6) Å^2
Final ΔF peaks	1.50 e Å^{-3} near Br of molecule B
Final R and R_w	0.071, 0.087

Table 3 Final atomic coordinates for **5**

Atom	x/a	y/b	z/c
BrA	0.380 30(6)	0.424 44(5)	1.104 92(9)
N(1)A	0.564 0(5)	0.191 5(5)	0.877 1(8)
N(2)A	0.479 0(4)	0.140 1(4)	0.862 7(6)
C(3)A	0.404 4(4)	0.207 5(4)	0.931 1(7)
C(4)A	0.446 2(5)	0.302 0(4)	0.989 5(7)
C(5)A	0.546 3(5)	0.288 2(6)	0.952 7(8)
C(6)A	0.300 4(4)	0.177 4(4)	0.939 1(6)
C(7)A	0.282 2(5)	0.084 2(5)	0.983 3(7)
C(8)A	0.183 5(5)	0.058 0(5)	0.994 4(7)
C(9)A	0.100 2(5)	0.123 5(6)	0.957 2(9)
C(10)A	0.117 0(5)	0.215 2(6)	0.910 4(9)
C(11)A	0.214 4(5)	0.242 5(5)	0.899 8(8)
BrB	0.958 75(6)	0.129 36(7)	0.370 44(10)
N(1)B	0.740 6(4)	0.008 2(4)	0.584 9(6)
N(2)B	0.742 3(3)	0.096 1(4)	0.700 3(6)
C(3)B	0.812 5(4)	0.150 6(4)	0.650 9(7)
C(4)B	0.854 7(4)	0.094 8(5)	0.498 6(7)
C(5)B	0.808 4(5)	0.004 3(5)	0.462 7(7)
C(6)B	0.836 6(4)	0.249 5(4)	0.759 5(7)
C(7)B	0.837 4(5)	0.259 1(5)	0.938 3(8)
C(8)B	0.858 9(5)	0.351 1(5)	1.042 2(10)
C(9)B	0.878 7(5)	0.433 2(6)	0.971 3(10)
C(10)B	0.878 6(6)	0.425 1(5)	0.793 4(11)
C(11)B	0.858 2(5)	0.332 8(5)	0.686 5(9)
BrC	0.402 20(6)	−0.356 83(6)	0.544 99(12)
N(1)C	0.489 9(4)	−0.073 3(5)	0.680 9(8)
N(2)C	0.581 9(4)	−0.117 2(4)	0.631 5(6)
C(3)C	0.569 9(4)	−0.218 0(4)	0.577 5(7)
C(4)C	0.467 3(4)	−0.233 8(4)	0.593 7(7)
C(5)C	0.420 4(5)	−0.141 3(5)	0.661 1(8)
C(6)C	0.658 9(4)	−0.288 9(4)	0.522 5(6)
C(7)C	0.765 5(5)	−0.267 5(5)	0.595 8(8)
C(8)C	0.842 1(5)	−0.333 9(6)	0.546 6(10)
C(9)C	0.829 6(6)	−0.423 5(5)	0.427 0(9)
C(10)C	0.734 2(6)	−0.445 2(5)	0.356 7(9)
C(11)C	0.648 5(5)	−0.379 3(5)	0.402 8(7)

The ^{13}C NMR spectra of unlabelled compounds **3** and **4** were recorded on Varian XL200 and Varian Unity spectrometers (University of Zaragoza) working at 50.31 and 75.43 MHz, respectively ($SiMe_4$ internal reference; chemical shifts expressed as δ values). The ^{1}H and ^{15}N NMR spectra of labelled pyrazole **4′** were recorded on a Bruker MSL300 NMR-spectrometer (Freie Universität, Berlin) working at 300.13 MHz (^{1}H) and 30.41 MHz (^{15}N). ^{15}N chemical shifts were expressed in ppm from an external sample of saturated $^{15}NH_4Cl$ in D_2O. To avoid catalytic effects on the prototropic exchange, silica coated NMR tubes were employed and the

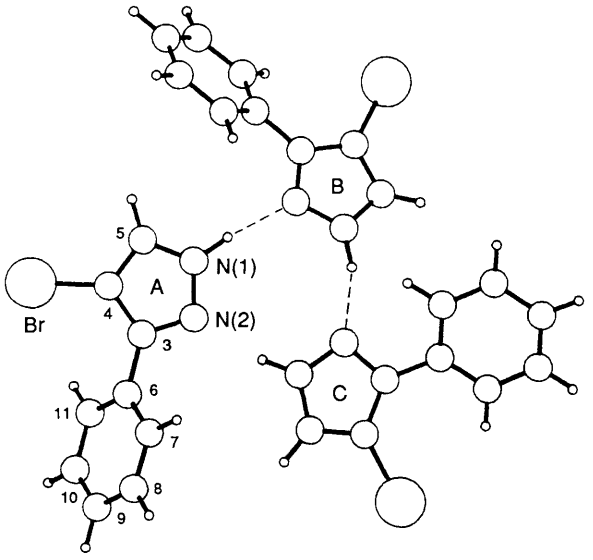


Fig. 1 A view of the trimer with the atomic numbering

Table 4 Selected geometrical characteristics of the trimer/Å, °

	Molecule		
Bond	A	B	C
N(1)–N(2)	1.344(8)	1.343(6)	1.340(7)
N(1)–C(5)	1.322(9)	1.335(8)	1.320(10)
N(2)–C(3)	1.336(7)	1.332(8)	1.349(7)
C(3)–C(4)	1.402(8)	1.405(7)	1.394(8)
C(4)–C(5)	1.349(9)	1.368(9)	1.357(8)
C(5)–N(1)–N(2)	111.8(6)	111.5(5)	111.5(6)
N(1)–N(2)–C(3)	106.2(5)	107.0(4)	106.5(5)
N(2)–C(3)–C(4)	108.2(5)	108.3(5)	107.9(5)
C(3)–C(4)–C(5)	106.7(5)	106.6(5)	106.7(5)
C(4)–C(5)–N(1)	107.1(6)	106.6(5)	107.5(6)
N(2)–C(3)–C(6)–C(7)	41.1(8)	36.8(8)	29.3(8)
N(1)···N(2)	2.869(7)	2.851(7)	2.931(8)
N(1)–H(1)	0.92(12)	0.88(11)	0.92(7)
H(1)···N(2)	1.97(12)	1.98(11)	2.05(7)
N(1)–H(1)···N(2)	166(11)	170(9)	162(7)

sealed NMR samples were prepared using a vacuum line as described previously.[22]

Results and Discussion

Molecular Structure of Compound **5**.—As in compound **4**,[14] the pyrazole ring appears delocalized with the characteristic shortening of the formal single bonds and a lengthening of the formal double bonds. As in other pyrazoles with the H(1) proton localized,[23,24] the C(5)–N(1)–N(2) bond angle is greater than the N(1)–N(2)–C(3) one,[25] the sum of both angles being 218° and a difference of 5°. The distribution of the other angles within the pyrazole rings is quite even, although somehow larger than usual at C(3) and C(5).[26] This is certainly due to the electronic and steric requirements of Br(4).

The three crystallographically independent molecules form a trimer through hydrogen bonds, as in 3,5-dimethylpyrazole,[26] the difference being that in the present case the supermolecule is less symmetric. The trimers stack along the *c* axis, through symmetry centres, involving two pyrazole rings; the third one, askew with regard to that axis, is not involved in the stacking (see Fig. 2).

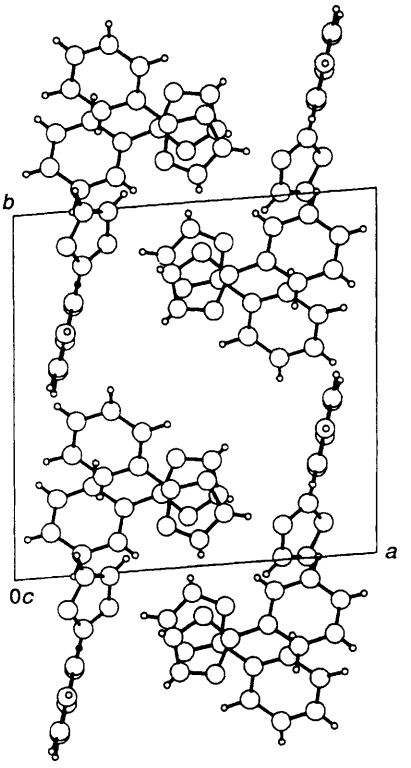
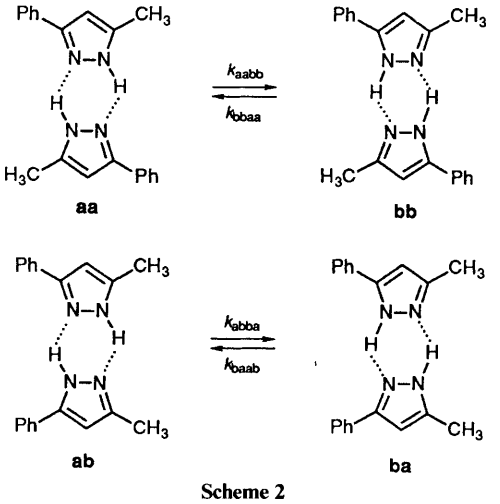


Fig. 2 The packing as seen along the *c*-axis

NMR Spectroscopy.—All the chemical shifts necessary for the discussion are collected in Table 5. Assignment of the signals was straightforward due to the wealth of data on pyrazole NMR spectroscopy.[1–13,27,28]



Scheme 2

The NMR spectra of compounds **3** and **4**, at low temperatures, correspond to mixtures of both tautomers, the signals belonging to the less abundant ones, **3b** and **4b**, being broader than those of the dominant ones, **3a** and **4a**. This is a simple consequence of the fact that the backward **b**–**a** rate is greater than the forward **a**–**b** rate. In principle, one can imagine two different tautomeric processes each involving a double proton transfer in cyclic dimers as shown in Scheme 2. In the first non-degenerate process two **a** tautomers form a homodimer which reacts to form a homodimer consisting of two **b** tautomers (**aabb**-process). The second process is degenerate and involves heterodimers consisting of one **a** and one **b** tautomer (**abba**-process). These exchange processes lead to averaged signals at room temperature. It is interesting to compare the

Table 5 ^{1}H, ^{13}C and ^{15}N chemical shifts and ^{1}H–^{15}N and ^{15}N–^{15}N coupling constants (magnitudes only) of pyrazoles **3**, **4** and **4′**

Pyrazole	Nucleus	Solvent	T/K	Signals
3(5)-Phenyl **3**	^{13}C	DMSO	300	148.1 (C3–Ph), 102.2 (C4), 132.8 (C5–H), 133.0 (C-1′), 125.4 (C-2′,6′), 128.8 (C-3′,5′), 127.6 (C-4′)[28]
1-Methyl-3-phenyl	^{13}C	DMSO	300	150.2 (C3), 102.5 (C4), 132.1 (C5), 133.7 (C-1′), 125.1 (C-2′,6′), 128.5 (C-3′,5′), 127.2 (C-4′)[28]
1-Methyl-5-phenyl	^{13}C	DMSO	300	138.2 (C3), 106.8 (C4), 143.1 (C5), 131.5 (C-1′), 128.4 (C-2′,6′), 128.8 (C3′,5′), 128.4 (C-4′)[28]
3(5)-Phenyl **3**	^{13}C	HMPT–acetone	253	**3a**. 149.7 (C3), 101.1 (C4), 134.5 (C5), 134.5 (C-1′), 124.8 (C-2′,6′), 128.1 (C-3′,5′), 126.5 (C-4′) **3b**. 139.3 (C3), 101.1 (C4), 141.1 (C5), 129.9 (C-1′), 124.8 (C-2′,5′), 128.1 (C-3′,5′), 128.8 (C-4′)
5(3)-Methyl-3(5)-phenyl **4**	^{13}C	HMPT	300	148.2 (C3–Ph), 100.5 (C4), 141.0 (C5–Me), 11.2 (Me), 133.9 (C-1′), 125.0 (C-2′,6′), 128.2 (C-3′,5′), 126.6 (C-4′)
1,5-Dimethyl-3-phenyl	^{13}C	DMSO	300	148.4 (C3), 102.0 (C4), 139.6 (C5), 10.7 (Me), 133.8 (C-1′), 124.8 (C-2′,6′), 128.4 (C-3′,5′), 126.9 (C-4′)
1,3-Dimethyl-5-phenyl	^{13}C	DMSO	300	146.1 (C3), 105.1 (C4), 143.4 (C5), 13.2 (Me), 130.5 (C-1′), 128.2 (C-2′,6′), 128.6 (C-3′,5′), 128.1 (C-4′)
5(3)-Methyl-3(5)-phenyl **4**	^{13}C	HMPT	253	**4a**. 150.1 (C3), 100.3 (C4), 138.7 (C5), 10.3 (Me), 135.0 (C-1′), 125.0 (C-2′,6′), 128.2 (C-3′,5′), 126.6 (C-4′) **4b**. 147.2 (C3), 101.1 (C4), 142.4 (C5), 13.5 (Me), 130.4 (C-1′), 125.0 (C-2′,6′), 128.2 (C-3′,5′), 126.6 (C-4′)
[$^{15}N_2$]-5(3)-Methyl-3(5)-phenyl **4′**[a]	^{1}H	[$^{2}H_8$]THF	175	**4a′**. 12.40 (N1-H), ^{1}J = 104, ^{2}J = 7.3 **4b′**. 12.75(br) (N1-H), ^{1}J = 104
	^{15}N	[$^{2}H_8$]THF	175	**4a′**. 182.4 (N1), 270.0 (N2), ^{1}J(NH) = 104, ^{2}J(NNH) = 7.3, ^{1}J(NN) = 11.6 **4b′**. 172.0(br) (N1), 275.6 (N2), ^{1}J(NH) = 104
	^{1}H	[$^{2}H_8$]Toluene	190	**4a′**. 14.60 (N1-H), ^{1}J = 104 **4b′**. 15.07(br) (N1-H), ^{1}J = 104
	^{15}N	[$^{2}H_8$]Toluene	190	**4a′**. 187.8 (N1), 256.4 (N2), ^{1}J(NN) = 11.6 **4b′**. 182.0(br) (N1), 266.1 (N2)

[a] ^{1}J(NH) was verified by decoupling the $^{15}N_1$ atom and ^{2}J(NNH) by decoupling the $^{15}N_2$ atom while measuring the ^{1}H resonance.

Table 6 Contribution of the substituents on pyrazole ^{13}C chemical shifts in ppm

	Position		
Substituents	3	5	4
R^2	0.996	0.92	0.97
3-Methyl	7.9	0.2	−0.8
5-Methyl	−0.5	8.2	−1.0
3-Phenyl	11.6	2.5	−4.0
5-Phenyl	0.8	11.7	−3.8

^{13}C chemical shifts of a given tautomer with those of the corresponding *N*-methyl derivatives,[27] since they are often used as model compounds for the calculation of tautomeric equilibrium constants by interpolation.[29] The most noticeable effect ($\Delta\delta = \delta_{NMe} - \delta_{NH}$) concerns carbons C(4) and C(1′) of 5-phenyl derivatives **3b** and **4b**: 4.8 and 3.2 ppm, respectively. The deshielding of the *N*-methyl derivatives relative to the NH-tautomer corresponds to a twist of the 5-phenyl ring produced by the *N*-methyl group.[30] As a consequence, *N*-methylpyrazoles should not be used as model compounds when there is a substituent at position 5 whose effect depends on its conformation.

Since we now have the chemical shifts of C(3), C(4) and C(5) in the absence of prototropy for compounds **1**,[6] **2a**,[6] **2b**,[6] **3a**, **3b**, **4a** and **4b** (Table 3), it is possible to calculate by multiregression the contributions (in ppm) of each substituent on the pyrazole chemical shifts (Table 6).

These increments clearly show that the contribution depends on the substituent but not on the tautomeric position (3 or 5): 3(R) on C(3) ~ 5(R) on C(5), 3(R) on C(4) ~ 5-R on C(4).

Some typical low temperature ^{1}H, ^{15}N and $^{15}N\{^{1}H\}$ NMR spectra of 0.32 mol dm^{-3} solutions of the ^{15}N labelled compound **4′** in [$^{2}H_8$]THF and [$^{2}H_8$]toluene are shown in Fig. 3. A signal pattern as expected for the slow exchange regime *i.e.* for an AMX spin system, where A = ^{1}H and M,X = ^{15}N, is observed for both tautomers. The NMR lineshapes depend on the pseudo-first-order rate constants k_{aabb}, k_{abba}, k_{bbaa} and k_{baab} of the forward **aabb** and **abba** and the backward **bbaa** and **baab** proton exchange process, where $k_{aabb}/k_{bbaa} = k_{abba}/k_{baab} = K_T$, the equilibrium constant of the tautomerism. The ^{15}N spectra, however, depend on the sums $k_{ab} = k_{aabb} + k_{abba}$, and $k_{ba} = k_{bbaa} + k_{baab}$, all pseudo-first-order rate constants which can be distinguished by ^{1}H NMR spectroscopy. This is because the **abba** process only modulates the scalar ^{1}H–^{15}N coupling but not the proton chemical shifts. In contrast, the **aabb** process modulates both nuclear interactions. A detailed lineshape analysis of the signals in order to distinguish both processes was, however, beyond the scope of this study. The values of the coupling constants (Table 5) are independent of the solvent. They are similar for **4a′** and **4b′** and similar to those reported in the literature for other pyrazole derivatives: $|^{1}J(^{1}H–^{15}N)|$ = 105.6 Hz for indazole,[31] and $|^{1}J(^{15}N–^{15}N)|$ = 13.4 Hz in 1-(CD$_3$)OH pyrazole.[32] Values of $^{2}J(^{15}N–N–^{1}H)$ have not yet been reported. The line positions of the labile protons of both tautomers are shifted to lower field when changing the solvent from THF to toluene. This phenomenon can easily be explained as follows. In THF, the pyrazole molecules are hydrogen bonded to the solvent whereas in toluene they are subject to self association *via* hydrogen bonds. The low field shift indicates that the hydrogen bonds between pyrazole molecules are stronger than between pyrazole and THF which can be taken as evidence for the formation of cyclic dimers or trimers in inert solvents as well as in the solid state. Similar low field shifts on cyclic H-bond formation were previously observed for the cyclic complex formation of amidines.[33] The effect of pyrazole association is also manifest in the ^{15}N NMR spectrum where strong low field shifts are observed for the N(1) signals and high field shifts for the N(2) signals. Note that the shifts are now different for both tautomers

Table 7 Tautomeric equilibrium constants and energy differences (the percentages are given with a ±2% error)

Pyrazole	Solvent	T/K	Percentages	K_T[a]	ΔG/kJ mol^{-1}
3(5)-Me **2**	HMPT	256	46% **2a**; 54% **2b**	0.85	+0.34
3(5)-Ph **3**	HMPT–acetone	253	72% **3a**; 28% **3b**	2.57	−1.98
3(5)-Ph, 5(3)-Me **4**	HMPT	253	75% **4a**; 25% **4b**	3.0	−2.31
($^{15}N_2$) **4′**	[$^2H_8$]THF	175	83% **4a′**; 17% **4b′**	4.9	−2.31

[a] Defined as K_T = [**a**]/[**b**].

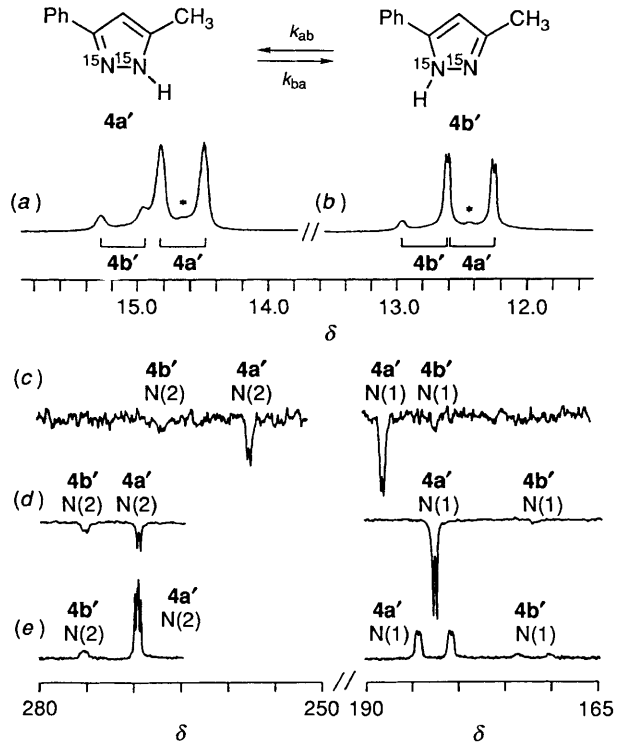


Fig. 3 ^{1}H NMR spectra of 0.32 mol dm^{-3} solutions of **4′**: (*a*) in [$^2H_8$]toluene, T = 190 K; (*b*) in [$^2H_8$]THF, T = 175 K. The signal denoted with an asterisk stems from residual ^{1}H–^{14}N groups. (*c*)–(*e*) ^{15}N NMR spectra of 0.32 mol dm^{-3} solutions of **4′**: (*c*) in [$^2H_8$]toluene, T = 190 K; (*d*, *e*) in [$^2H_8$]THF, T = 175 K; (*c*) [$^2H_8$]Toluene with {^{1}H}-decoupling; (*d*) [$^2H_8$]THF with {^{1}H}-decoupling; (*e*) [$^2H_8$]THF without {^{1}H}-decoupling.

which may reflect the circumstance that **4a′** will dominantly form homoassociates whereas **4b′** mainly forms heterodimers with **4a′**. Note also interesting NOE effects on the ^{15}N signals of both tautomers. It has been previously shown[34] that, in the presence of proton exchange, the steady state NOE of protonated NH atoms is decreased and that of non-protonated N atoms is increased by the proton exchange with respect to the intrinsic NOE values in the absence of exchange. Thus, the signal intensity ratios in the {^{1}H} decoupled ^{15}N spectra give interesting information about the proton exchange pathways. The signal intensity I(**4a′**N$_1$)/I(**4b′**N$_2$) and I(**4a′**N$_2$)/I(**4b′**N$_1$) are equal to the equilibrium constant K_T of the **ab** tautomerism which indicates magnetization transfer within the two pairs by proton exchange. The total NOE values of the two pairs **4a′**N$_1$/**4b′**N$_2$ and **4a′**N$_2$/**4b′**N$_1$ is, however, different because (i) the intrinsic NOE values of unprotonated and protonated nitrogen atoms are different and (ii) neither the **aabb** nor the **abba** proton exchange process can lead to magnetization transfer between the two pairs.

Tautomeric Equilibrium Constants.—From literature results on compound **2**,[7] and the above experiments, the data for Table 7 were collected.

The two main conclusions of these data are: (i) The ΔG_T = $-RT\ln K_T$ values are independent of the solvent; (ii) ΔG_T values are additive (K_T for the same temperature being proportional), −1.98 − 0.34 = −2.32 (the corresponding K_T values are: 2.57/0.85 = 3.02).

In conclusion, the methyl group has a slight preference for occupying the 5-position whereas the phenyl group has clearly more preference for the 3-position, both effects being weak.

Conclusions

The tautomeric equilibrium of non-symmetric pyrazoles was studied in the liquid state by NMR spectroscopy and in the solid state by diffraction techniques. Whereas these compounds form quasi-monomers hydrogen bonded to the solvent in liquids such as THF, acetone, DMSO or HMPT, they form self associates, probably cyclic dimers, in inert solvents. The equilibrium constants of tautomerism are not much affected by the hydrogen-bonded state. Therefore, it is understandable that there is a relationship between the predominance of a pyrazole tautomer in solution and the tautomer present in the solid state where most often cyclic structures are formed. In the case of 3(5)-methylpyrazole **2** where both tautomers have almost the same energy (ΔE = −1.67 kcal mol^{-1}), both exist in near 50:50 proportion in solution; since this compound is one of the few NH-pyrazoles liquid at room temperature, its X-ray structure is not known; however, it has been possible to determine the X-ray structure of an inclusion compound of 3(5)-methylpyrazole in a host with the interesting observation that both tautomers are present.[35] In the case of 3(5)-phenylpyrazole **3**, the major tautomer in solution is the 3-phenyl one, **3a**,* which is also the structure found in the solid for compound **5**, confirming that the effect of the bromine atom at position 4 on the tautomeric equilibrium is small. Finally, for 5(3)-methyl-3(5)-phenylpyrazole **4** there seems to be an inconsistency since the major tautomer in solution is clearly the 5-methyl-3-phenyl tautomer **4a** whereas in the solid state both are present.[14,15] The structure of this pyrazole in the crystal is worth examining again by X-ray crystallography and solid state NMR spectroscopy.

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* 3-21G//3-21G calculations on fully optimized geometries[36] also favours **3a** over **3b** by 4.2 kJ mol^{-1}.

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