

THE ^1H AND ^{13}C N.M.R. RULES FOR THE ASSIGNMENT OF 1,3- AND 1,5-
DISUBSTITUTED PYRAZOLES: A REVISION

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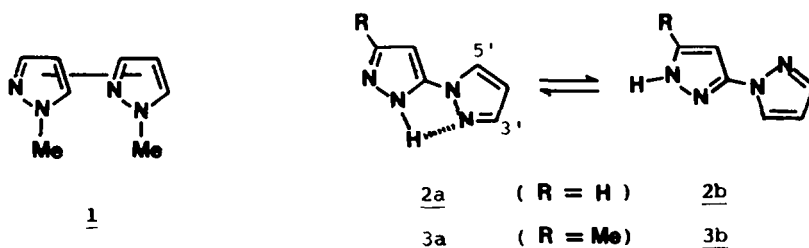
Abstract: The H-5 signal of N-substituted pyrazoles is not shifted to low field values on increasing solvent polarity when a nitrogen lone pair lies very close to the measured proton (H-bond). Typical examples of this "abnormal" behaviour are provided by C,N'-linked, pyrazole-containing heterocyclic dimers. On the contrary, models selected in the 1,1'-bipyrazole and 2,2'-biindazole series (N,N'-linkage) showed normal shifts, due to their non-coplanar conformation around the N-N bond. For the assignment of disubstituted pyrazoles, a proton-coupled ^{13}C n.m.r. spectrum is recommended as an alternative method.

The unambiguous assignment of 1,3- and 1,5-disubstituted pyrazoles constitutes a classical problem which has usually been resolved by ^1H n.m.r. spectroscopy. Among the different empirical methods employed, one should first mention those based on the different chemical shift values, and on the vicinal coupling constants to H-4, when this position is free of substituents. In both of these methods, the differences between the isomeric pyrazoles are in general quite small, and both isomers are usually necessary to confirm the assignment. On the other hand, many exceptions are known, especially when considering chemical shift values for pyrazoles substituted by functional groups different from the simple alkyl or aryl ones.¹

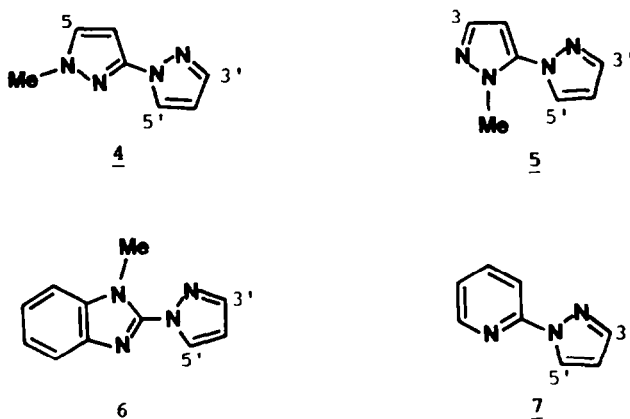
A third method, developed in 1966 by Elguero and Jacquier, is based on the great downfield shifts observed for the H-5 signal when the solvent is gradually changed from benzene to the more polar CDCl_3 , DMSO, or HMPA. On the contrary, the chemical shift of H-3 is almost independent of the solvent, moving slightly upfield when increasing solvent polarity.^{2,3}

These solvent-dependency rules have been widely employed, due to their broad scope, ease of determination, and the possibility of assignment with only one isomer, especially for 1,3-disubstituted pyrazoles (big H-5 shift). A very elegant example of the application of the Elguero and Jacquier method was provided by Habraken *et al.* to determine the correct structure of the six isomeric C,C'-bonded N,N'-

dimethylbipyrzoles of general formula 1.⁴ However, when the same authors tried to apply the method to the N,C'-bonded dimers 3(5)-(1-pyrazolyl)pyrazole 2 and 3(5)-methyl-5(3)-(1-pyrazolyl)pyrazole 3, they found that none of the signals shifted appreciably when changing the solvent (CDCl₃, DMSO-d₆, HMPA), a fact being attributed to intramolecular hydrogen bonding in the presumably more stable tautomer 2a or 3a.⁵



To verify this hypothesis, and due to our interest in bipyrzolyll derivatives,^{6,7,8} we decided to study the ¹H n.m.r. spectra of 2 and some related N,C'-bonded heterocyclic dimers as 4-6 or the 2-(1-pyrazolyl)pyridine 7.⁹



The spectra, recorded in three different solvents (200 MHz), revealed (Table 1) that H-5' signals remain almost unchanged when going from C₆D₆ to CDCl₃, except in the case of 5 ($\Delta\delta = \text{CDCl}_3 - \text{C}_6\text{D}_6 = +0.65$ ppm). This behaviour ruled out the Habraken hypothesis on intramolecular hydrogen bonding to explain the absence of solvent effect in 2, since hydrogen bonding is not possible in 4, 6, and 7. On the other hand, H-3(5) of 2 is strongly deshielded ($\Delta\delta = +0.97$ ppm), a typical characteristic of a H-5 proton. This seemed to indicate that the major tautomer in the equilibrium 2a \rightleftharpoons 2b is indeed 2b, and not 2a, as proposed by Habraken.

Clearly, the absence of solvent-shifts can be attributed to structural factors, namely the presence in all of these models, but in 5, of a "pyridine" lone-pair in an "ortho" position of the heterocycle which is C-linked to the 1-pyrazolyl substituent. Although conformational studies on C,N'-linked dimers of heteroaromatic systems have been performed only at a theoretical level,^{13,14} dihedral angles are not too high. For example, N-phenylpyrrole has a minimum of energy at an angle of twist of about 40°. ¹⁴ Moreover, in the compounds of Table 1, the presence of nitrogen lone-pairs in both

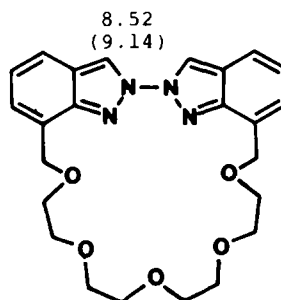
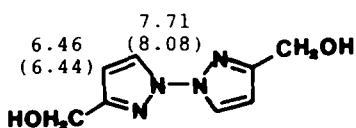
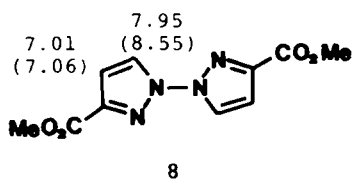
rings, which strongly tend to point "anti" to each other, further increases the interaction with H-5. Consequently, a close proximity of H-5 to the lone-pair of the neighbouring ring is to be expected, and the anisotropic environment created is mainly responsible of the observed chemical shift, independently of any solvent effect.

Compound	H-3 or H-5			H-3'			H-5'		
	C ₆ D ₆	CDCl ₃	DMSO-d ₆	C ₆ D ₆	CDCl ₃	DMSO-d ₆	C ₆ D ₆	CDCl ₃	DMSO-d ₆
<u>2</u>	6.63	7.60	7.80	7.60	7.72	7.66	8.07	8.09	8.20
<u>4</u>	6.65	7.33	7.74	7.63	7.67	7.66	8.21	8.05	8.16
<u>5</u>	7.39	7.43	7.52	7.54	7.71	7.84	6.93	7.58	8.16
<u>6</u>	--	--	--	7.48	7.82	7.96	8.40	8.40	8.48
<u>7</u>	--	--	--	7.62	7.74	7.81	8.64	8.57	8.64

Table 1. ¹H N.m.r. chemical shifts (δ , ppm) of N,C'-Linked bipyrazoles and related structures.

A different situation results when a coplanar conformation is disfavoured, or when conformational freedom is hampered by covalent bonding, in such a way that the lone-pair is kept away from the neighbourhood of H-5. N,N'-Linked biazoles provide good examples of both situations. For example, both the 1,1'-bipyrazole derivatives 8 and 9 agree with the Elguero-Jacquier rules (see values of δ on the figures; values in parentheses correspond to DMSO-d₆, the others to CDCl₃): H-5 is shifted by +0.60 ppm in 8 and by +0.37 ppm in 9 when moving from CDCl₃ to DMSO-d₆. As we have already demonstrated,^{15,16} N,N'-linked biazoles have the unique property, not found in C,N'- or C,C'-dimers, of being in a perpendicular or quasi perpendicular conformation, both in solution or in the solid state.

A more dramatic situation is observed in macrocycles. Besides the N,N'-bond, model 10 is an example of a macrocyclic 2,2'-biindazole¹⁷ in which the less favored interactions (H...H and N...N) have been forced against the most favored (H...N) by covalent bonding. As expected, a large solvent effect of +0.62 ppm was found.



From the examples shown we can conclude that the assignment of substituted pyrazoles based on ^1H n.m.r. chemical shifts in different solvents is dependent on structural effects that ought to be evaluated in each case. In particular, these criteria should not apply when H-5 is H-bonded intramolecularly to a close lone-pair (attractive H...N interaction).¹⁶

^{13}C n.m.r. offers an alternative method for the assignment of substituted pyrazoles. The signal corresponding to C_4 is always shifted upfield from C_3 and C_5 (at ca. 100 ppm), and C_5 appears usually at lower frequencies (125-135 ppm) than C_3 (135-150 ppm). Although this has been applied and reported in the literature for the unambiguous assignment of pyrazolyl structures,^{5,18-20} both isomers are in general necessary when the relevant signal appears in the neighbourhood of 135 ppm.

The use of $^1\text{J}(\text{C-H})$ coupling constants for the assignment is also of limited value. For N-substituted pyrazoles, a close relationship between the nature of the substituent and both chemical shifts and ^1J coupling constants has been observed. Thus, when the N-substituent is an electron-withdrawing group, signals are shifted low field with a simultaneous increase of ^1J values. In extreme cases, the rule $^1\text{J}(\text{C}_5\text{-H}_5) > ^1\text{J}(\text{C}_3\text{-H}_3) > ^1\text{J}(\text{C}_4\text{-H}_4)$ could be formulated. However, in a broad group of N-substituted pyrazoles the proximity of the values makes the assignment based on ^1J values somewhat difficult.²¹

We have recently reported an alternative method, based on the determination of the long-range coupling constants $^{13}\text{C}\text{-}^1\text{H}$. Although only four N-substituted pyrazoles were initially studied,²² a more recent survey of 19 pyrazoles²³ is fully consistent with the following observations:

- i) For C-3 two long-range coupling constants can be observed. The larger (ca. 8 Hz) correspond to $^3\text{J}(\text{C}_3\text{-H}_5)$ and the smaller (ca. 4-6 Hz) to $^2\text{J}(\text{C}_3\text{-H}_4)$.
- ii) For C-4 two long-range coupling constants can also be observed, the larger (ca. 10 Hz) corresponding now to $^2\text{J}(\text{C}_4\text{-H}_3)$ and the smaller (ca. 9 Hz) to $^2\text{J}(\text{C}_4\text{-H}_5)$.
- iii) The higher value obtained in C-5 (ca. 8-10 Hz) correspond to $^2\text{J}(\text{C}_5\text{-H}_4)$ and the smaller (ca. 4 Hz) to $^3\text{J}(\text{C}_5\text{-H}_3)$.

In the case of pyrazoles bearing solely a N-substituent, the differentiation of ^2J from ^3J would usually require proton-decoupling experiments, but for the 1,3- vs. 1,5-disubstituted cases, only ^2J coupling constants are observed. For these pyrazoles, the following simplified rule can be stated: if the ^2J coupling constant of the lower field carbon (C_3 or C_5) ranges from 4 to 6 Hz, it corresponds to a C_3 atom. If it ranges from 8 to 10 Hz, it belongs to a C_5 ring atom. The main interest of this method is that it can be applied to any 1,3- or 1,5-disubstituted pyrazole, and requires only one solvent and one isomer to unambiguously assign the correct structure.

Application of these rules to compounds 2b, 4, 5, 6, and 7 (Table 2) constitutes an example of their reliability. We have reported elsewhere other examples of application of the rule to disubstituted pyrazoles.^{10,22} The underlined coupling constants (see Table) demonstrate, without any doubt, the pattern of substitution of each compound.

Compound	C ₃	C ₄	C ₅	C _{3'}	C _{4'}	C _{5'}
<u>2b</u>	149.5 (³ J=8.4)	95.1 (¹ J=181.3) (² J=8.9)	130.5 (¹ J=188.2) (² J= <u>7.9</u>)	140.8 (¹ J=186.1) (² J= <u>5.8</u>) (³ J=8.5)	107.0 (¹ J=177.9) (² J=10.3)	127.5 (¹ J=189.5) (² J= <u>9.2</u>) (³ J=4.7)
<u>4</u>	149.5 (a)	95.9 (¹ J=181.9) (² J=8.8)	131.6 (¹ J=186.6) (² J= <u>8.1</u>) (³ J _{NMe} =2.7)	140.7 (¹ J=185.8) (² J= <u>5.8</u>) ^b (³ J=8.5) ^b	106.7 (¹ J=177.1) (² J=10.6)	126.9 (¹ J=189.9) (² J= <u>9.2</u>) ^b (³ J=4.5) ^b
<u>5</u>	138.1 (¹ J=187.3) (² J= <u>4.2</u>)	100.1 (¹ J=178.9) (² J=10.9)	139.0 (a)	141.9 (¹ J=186.8) (² J= <u>6.1</u>) ^b (³ J=8.6) ^b	107.2 (¹ J=178.4) (² J=10.5)	131.3 (¹ J=189.1) (² J= <u>9.2</u>) ^b (³ J=4.5) ^b
<u>6</u>				142.2 (¹ J=187.2) (² J= <u>5.7</u>) (³ J=8.8)	107.3 (¹ J=178.9) (² J=10.4)	130.8 (¹ J=193.1) (² J= <u>9.6</u>) (³ J=4.4)
<u>7</u>				141.4 (¹ J=185.8) (² J= <u>5.9</u>) (³ J=8.8)	107.2 (¹ J=177.3) (2x ² J=9.6)	126.4 (¹ J=192.0) (² J= <u>9.4</u>) (³ J=4.3)

(a) Broad signal; complex multiplet.

(b) Assigned by selective proton-decoupling experiments.

Table 2. ¹³C N.m.r. chemical shifts (δ , ppm) and coupling constants (Hz) of N,C'-Linked bipyrazoles and related structures in CDCl₃.

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