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Solvent Effects in ^1H NMR Spectra of Pyrazoles

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The ^1H NMR spectra of nine 4-substituted 1,3,5-trimethylpyrazoles have been recorded in CCl_4/C_6H_6 solutions with varying mol fractions of benzene. The substituent influence on the chemical shifts and the aromatic solvent induced shifts are discussed, and the data for the 1-CH_3 hydrogens are successfully correlated with Hammett's σ-values.

A change in solvent from a non-aromatic one (such as cyclohexane, deuteriochloroform or carbon tetrachloride) to an aromatic one, generally causes solvent induced shifts. These aromatic solvent induced shifts, ASIS, defined by $\Delta = \delta_{\text{non-aromatic}} - \delta_{\text{aromatic}}$, measure the difference between the effect of the solvent on a given proton group and the protons of the internal references. These ASIS values have proven very helpful in determining the position of a given proton relative to polar sites (*cf.* reviews by Ronayne and Williams [1] and by Laszlo [2]). Elguero and coworkers [3–5] discovered that for 1-methyl substituted pyrazole derivatives, the chemical shifts are very sensitive to solvent effects, and that ring protons and methyl group protons in positions 1 and 5 are much more sensitive to solvent change (CCl_4 or $CDCl_3$ to C_6H_6) than ring protons and methyl group protons in positions 3 and 4. The following average solvent shifts were calculated $[\delta(CDCl_3) - \delta(C_6H_6)]$: 1-$CH_3$, 0.51 ppm; 3-$CH_3$, −0.02 ppm; 5-$CH_3$, 0.52 ppm. Some of the pyrazole solvent shifts of Elguero and coworkers [3–5] relevant to the present work are found in Table 1. In investigations of solvent shifts for pyrroles, indoles, and some of their methyl derivatives, Ronayne and Williams [6,7] discovered aromatic solvent induced shifts characteristic in magnitude and sign and thus useful in structure elucidation. In these π-excessive heteroaromatics, the benzene molecules are assumed to solvate the positive end of the pyrrole and indole dipoles, giving shifts diagnostic for 2- *versus* 3-substitution. The 3-H and 3-CH_3 resonances have ASIS between −0.54 and 0.05 ppm, whereas the 2-H and 2-CH_3 resonances have ASIS values between 0.03 and 0.45 ppm. The N−CH_3 resonances have values of ASIS between 0.65 and 0.80 ppm.

Table 1. ASIS $[\delta(CDCl_3) - \delta(C_6H_6)]$ or $[\delta(CCl_4) - \delta(C_6H_6)]$, in ppm) for some pyrazole derivatives (1-CH_3-3-R_3-4-R_4-5-R_5-pyrazole).[3–5]

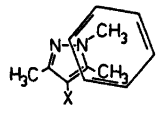
Compound R_3	R_4	R_5	ASIS 1-CH_3	R_3	R_4	R_5
H	H	H		−0.24	0.06	0.48[a]
H	H	H		−0.04	0.19	0.59[b]
CH_3	H	H	0.60	−0.01	0.11	0.50[b]
CH_3	Br	H	0.73	0.00		[b]
CH_3	Cl	H	0.78	−0.07		[b]
H	CH_3	H	0.50	−0.10	0.14	0.56[b]
H	H	CH_3	0.55		0.13	0.55[b]
H	Cl	CH_3	0.78			0.68[b]
CH_3	H	CH_3	0.49	−0.07	0.05	0.49[b]
H	Br	CH_3	0.78			0.68[b]

[a] Inert solvent: CCl_4. [b] Inert solvent: $CDCl_3$.

The discussion of the interaction between the polar solute and the aromatic solvent and the solvent shifts is based on the large magnetic anisotropy of the benzene ring. Ledaal [8] suggests that the dipole axis of the solute is located along the six-fold symmetry axis of the benzene ring. Ronayne and Williams [6] propose a model in which the benzene solvent molecules solvate each electron-deficient site of the solute, with the benzene molecule as far as possible away from the negative end of the local dipole with

its orientation determined by local dipole-induced dipole interactions. The interactions may occur in transient 1:1 collision complexes. Engler and Laszlo [9] have stressed the inadequacy of a fixed 1:1 complex as a model for these weak interactions. They introduce a general solvation model and express solvent shifts as products of a site factor for the proton groups of the solute and a solvent parameter.

With the simple 1:1 complex model, the interaction between the benzene solvent molecule and the pyrazole solute molecule is described by I, in analogy with the complex between pyrroles and indoles and aromatic solvents.[6,7] The dipole moment of the pyrazole ring is directed from N_1 towards N_2 and nearly parallel with the N–N bond.[10] It is then clear that ring protons and methyl group protons in positions 1 and 5 are in the strongly shielding region of the benzene ring. The benzene molecule

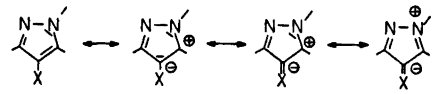


I

in I may be regarded as a symbol for the time-averaged solvent cloud around the pyrazole molecule.

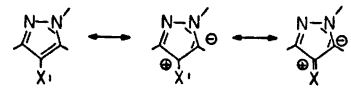
Even though several ^{1}H NMR studies of pyrazoles have appeared in the literature (see, *e.g.*, Refs. 3–5, 11–23), the spectrum of 1,3,4,5-tetramethylpyrazoles seems to be the only one determined for a 1,3,5-trimethyl-4-X-substituted pyrazole in CCl_4 solution. With 1,5- and 1,3-dimethylpyrazole as model compounds, Habraken *et al.*[21] assigned the signal at δ 2.04 to the 3-CH_3 protons and the signal at δ 1.98 to the 5-CH_3 protons, *i.e.* the 5-CH_3 protons absorb at higher field than the 3-CH_3 protons. For some 1-CH_3-4-X-substituted pyrazoles they discovered that in $CDCl_3$ solution, the 1-CH_3 protons are shifted downfield by electron-attracting substituents in position four, and similar displacements are found for the 3- and 5-proton peaks.

There is a strong resonance interaction between the 1-nitrogen atom in the pyrazole ring and –M substituents in position 4 (see II). This has been demonstrated in the slow hydrolysis of pyrazole-4-carboxylic esters,[24] in the



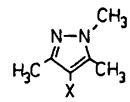
II

low frequency of the C=O stretching vibration of 4-acylpyrazoles,[25] and in the chemical shifts of the ring carbon atoms in ^{13}C investigations (Refs. 26–28).



III

To study the influence of –M (*cf.* II) and +M (*cf.* III) substituents on the aromatic solvent induced shifts, a number of 4-substituted 1,3,5-trimethylpyrazoles were synthesized and investigated (IVa-i).



IV

a. X=NH_2 f. X=I
b. X=CH_3 g. X=$CO_2C_2H_5$
c. X=H h. X=NO_2
d. X=Cl i. X=NO
e. X=Br

PREPARATIONS AND ^{1}H NMR SPECTRA

The compounds were synthesized by reported procedures: IVa,[29] IVb,[30] IVc,[30] IVd,[31] IVe,[32] IVf,[30] IVg,[33] IVh,[30] IVi.[34] The pyrazoles were distilled or recrystallized immediately before use.

The spectra were recorded on a Varian A-60 spectrometer in solutions (1 %, w/v) with increasing mol fraction of benzene: 0.000, 0.071, 0.287, 0.426, 0.673, 0.789, 0.928, 1.000. The spectra were recorded at normal probe temperature, *ca.* 310 K, using TMS as an internal standard. The chemical shifts were determined with the aid of sidebands generated by a Hewlett-Packard Model 200 oscillator and measured by a HP Model 3734 A frequency counter with scale expansion. The accuracy in the chemical shifts is presumed to be *ca.* 0.3 Hz. CCl_4 was chosen as the inert solvent for solubility reasons.

DISCUSSION

Signal assignments. The chemical shifts and solvent shift values for the 4-substituted 1,3,5-trimethylpyrazoles investigated are summarized

Table 2. Chemical shifts (δ-values) and ASIS (in ppm) for some 4-substituted 1,3,5-trimethylpyrazoles (IV).[a]

X	δ(1-CH_3)	ASIS	δ(3-CH_3)	ASIS	δ(5-CH_3)	ASIS	δ(5-CH_3) − δ(3-CH_3)
NH_2	3.567[a]		2.010[a]		2.073[a]		0.063
	3.217[b]	0.350	2.152[b]	−0.142	1.657[b]	0.416	
CH_3	3.573		2.017		2.067		0.050
	3.235	0.338	2.215	−0.198	1.638	0.429	
H	3.565		2.083		2.163		0.080
	3.158	0.407	2.283	−0.200	1.713	0.450	
Cl	3.645		2.103		2.177		0.074
	3.055	0.590	2.238	−0.135	1.638	0.539	
Br	3.675		2.100		2.193		0.093
	3.040	0.635	2.258	−0.158	1.625	0.568	
I	3.685		2.115		2.240		0.125
	3.042	0.643	2.267	−0.152	1.670	0.570	
$CO_2CH_2CH_3$	3.658		2.285		2.448		0.163
	3.005	0.653	2.627	−0.342	2.107	0.341	
NO_2	3.717		2.408		2.573		0.165
	2.775	0.942	2.450	−0.042	1.812	0.761	
NO	3.731		2.252		2.783		0.531
	2.775	0.956	2.373	−0.121	2.055	0.728	

[a] Refers to CCl_4 solution. [b] C_6H_6 solution.

in Table 2. The problem of assigning signals to protons 3 and 5 in the proton magnetic resonance spectrum of 1-methylpyrazole has been previously studied by means of coupling constants,[12] homo- and heteronuclear decoupling,[5] and deuterated pyrazole derivatives.[22] It has been found that in $CDCl_3$ and CCl_4 solution, H_5 in 1-methylpyrazole absorbs at higher field than H_3.

The signal assignments for the methyl hydrogens in positions 3 and 5 in the pyrazole series investigated in the present work were made by recording the spectra in CCl_4/C_6H_6 solutions with increasing benzene content. In accordance with the aromatic solvent shifts discussed above, the *C*-methyl resonance signal most affected by the solvent change is ascribed to the methyl hydrogens in position 5. The solvent dependence of the *C*-methyl hydrogens for three 1,3,5-trimethylpyrazoles is shown in Fig. 1. For all pyrazole derivatives the *C*-methyl resonance signal at lowest field (in CCl_4 solution) is most sensitive to solvent change, and is consequently ascribed to the methyl group in position 5. It is noticeable that in 1-methylpyrazole, H_3 absorbs at lower field than H_5. Habraken *et al.*[21] made the reverse assignments (*cf.* above) for the 3-CH_3 and 5-CH_3 protons in the tetramethylpyrazole. However, these assignments were based on the ^{1}H NMR spectra of 1,5- and 1,3-dimethylpyrazole, where the 3-CH_3 protons absorb at lower field than the 5-CH_3 protons (0.03 ppm).

A change in solvent from CCl_4 to $CDCl_3$ causes downfield shifts for the ^{1}H NMR signals of 1-methylpyrazole (for H_3 0.20 ppm, for H_5 0.11 ppm).[22] These solvents shifts can be understood as a consequence of hydrogen bonding between $CDCl_3$ and the pyridine nitrogen atom in the pyrazole ring ($Cl_3C-D\cdots N_2-N_1$) resulting in decreased electron density more pronounced in position 3 than in position 5. This is reflected in the shift changes given above. With the signal assignments made with the aid of ASIS for 1,3,5-trimethylpyrazole, the same order in downfield shifts is obtained for methyl groups 3 and 5 (0.09 and 0.01 ppm for a solvent change $CCl_4 \rightarrow CDCl_3$). This is further proof for the signal assignments made above.

The substituent dependence of the chemical shifts. The influence of substituents on chemical shifts of ring protons has been studied in benzenes and heterocycles. Linear correlations have sometimes been attempted between proton chemical shifts and substituent constants based on reactivity data.[35]

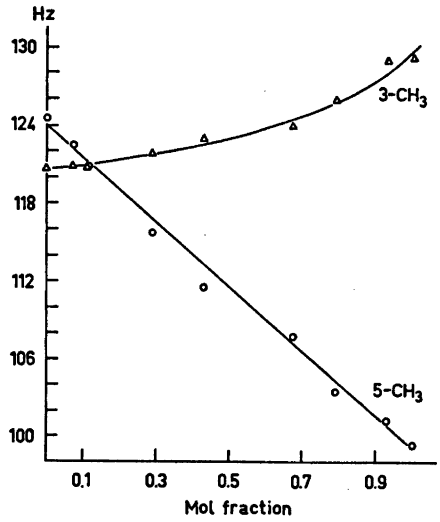


Fig. 1a. Chemical shifts (in Hz from TMS) for the 3-CH_3 and 5-CH_3 hydrogens in compound IVa *versus* mol fraction of benzene.

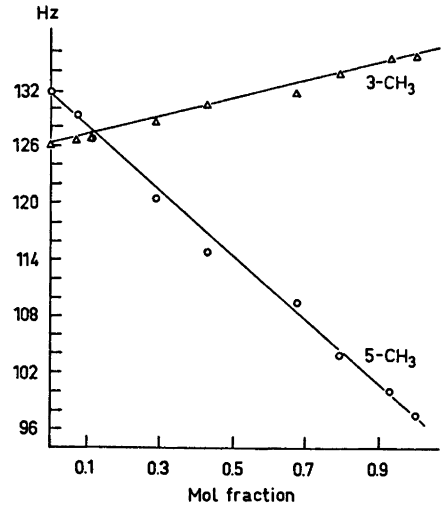


Fig. 1b. Chemical shifts (in Hz from TMS) for the 3-CH_3 and the 5-CH_3 hydrogens in compound IVe *versus* mol fraction of benzene.

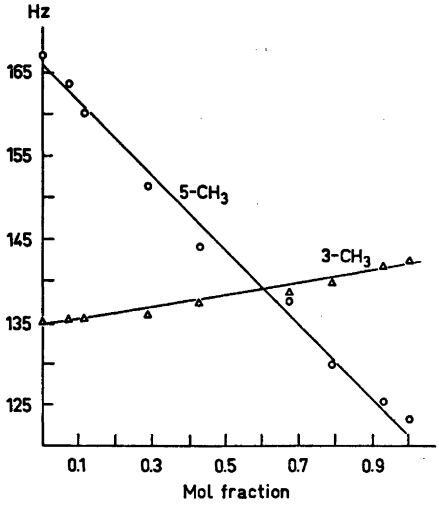


Fig. 1c. Chemical shifts (in Hz from TMS) for the 3-CH_3 and the 5-CH_3 hydrogens in compound IVh *versus* mol fraction of benzene.

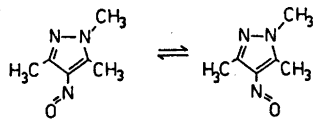
In the system investigated here, the methyl groups are connected to the substituent *via* the conjugated pyrazole system. The influence of substituents on chemical shifts of such methyl protons has been investigated for 2-CH_3-5-R-substituted thiophenes,[36] methoxy protons in substituted anisoles,[37] and substituted toluenes.[38]

Table 2 shows that a strong −M substituent in position 4 in the pyrazole ring causes a considerable downfield shift for the 1-CH_3 protons (IVc: δ(1-CH_3) = 3.565 ppm; IVh: δ(1-CH_3) = 3.717 ppm; CCl_4 solution). This can be understood as the result of the strong resonance interaction between positions 1 and 4 in the pyrazole ring (II). The inductive and magnetic anisotropy effects of the substituent on δ(1-CH_3) are assumed to be small. For stronger −M substituents in position 4 there is an increased contribution from the dipolar structures, resulting in reduced shielding (*via* inductive effects) and downfield shifts for the 1-CH_3 protons.

The chemical shifts of the 1-CH_3 protons are not susceptible to a +M substituent such as the amino group (IVc: δ(1-CH_3) = 3.565 ppm; IVa: δ(1-CH_3) = 3.567 ppm; CCl_4 solution). As is shown by III, a +M substituent, introduced in position 4, is conjugatively electron-donating to position 5 in the pyrazole ring, whereas only its inductive effect operates to positions 3 and 1. The change in electron density at the 1-CH_3 protons on introducing the amino group is consequently negligible and the chemical shift of the 1-CH_3 protons is not affected.

The difference in chemical shifts between methyl groups 5 and 3 (CCl_4 solution) is determined not only by resonance effects but also by field and anisotropy effects in a rather complex way. Table 2 shows that the shift difference increases with increasing −M capacity of the 4 substituents (0.08 ppm for IVc, 0.165 ppm for IVh). This is ascribed to a decrease in the π-electron density in position 5 (II) resulting in downfield shifts for 5-CH_3 protons. Position 3, on the other hand, is unaffected by this resonance effect. The inductive effect of the substituent is assumed to be the same in the two positions.

The large shift difference for the nitroso compound is ascribed to the anisotropy of the nitroso group. Positions along the N−O bond direction are deshielded and positions perpendicular to the bond are shielded.[39] For 1,3,5-trimethyl-4-nitrosopyrazole two planar conformations are possible (Va and Vb). It has been found that in CD_2Cl_2 solution at 240 K,



Va Vb

the conformer ratio Va/Vb is 4/1.[40] With an assumed dominance of conformer Va in CCl_4 solution at probe temperature, at which temperature the rotation of the nitroso group is fast on the NMR time scale, methyl group 5 is in the deshielded region and methyl group 3 in the shielded region. Thus the large shift difference is obtained.

The aromatic solvent induced shifts. The ASIS values are summarized in Table 2 and Fig. 4. Table 2 shows the ranges of the ASIS for the three methyl group protons: for 1-CH_3 0.338 − 0.956 ppm, for 3-CH_3 −0.342 to −0.042 ppm and for 5-CH_3 0.341 − 0.728 ppm. As discussed above, the signal assignments for the *C*-methyl protons were made by means of ASIS. For the 1-CH_3 and 5-CH_3 protons, the ASIS increases with increasing −M capacity of the substituent. This can be understood as the result of an increased order in the solvent cage around the partially positive 1-nitrogen atom and ring carbon atom 5 of the pyrazole ring (*cf.* II) as

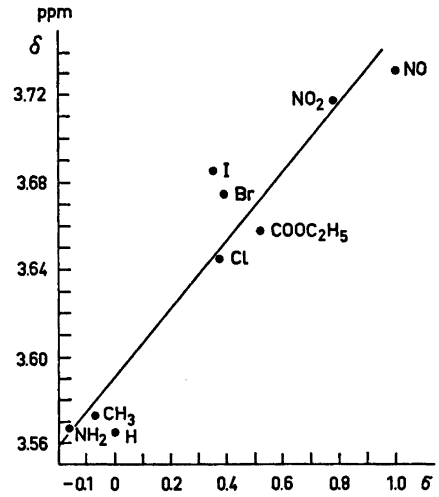


Fig. 2. Chemical shifts of the 1-CH_3 hydrogens (in ppm, from TMS, CCl_4 solution) *versus* Hammett's σ-values. The σ-values are taken from Jaffé.[49]

the benzene molecules interact with positive centers and avoid the negative parts. ASIS of the 3-CH_3 protons depend on the substituent in a complicated way. For the nitroso compound, it is possible that the isomer ratio Va/Vb may change from CCl_4 to C_6H_6 and that this change affects the ASIS.

The solvent shifts obtained for different positions in pyrroles, indoles,[6,7] and pyrazoles all emphasize the potential possibility of this technique for structure elucidation among azoles and diazoles.

Hammett correlations. In the pyrazole series, the Hammett equation has been used to relate reactivities in side-chains in positions 1 to σ_p values for the substituent in position 4. Good linear relations have been obtained between σ_p values and log *k* for the hydrolysis of 1-acylpyrazoles,[41] the ethanolysis of 1,1′-thiocarbonylbispyrazoles,[42] and the rotation of the dimethylamino group in 1-(*N*,*N*-dimethylthiocarbamoyl)-pyrazoles.[43] Discussions of the Hammett equation applied to heterocyclic compounds have been given by Jaffé [44] and by Gronowitz.[45]

A linear correlation is obtained for the trimethylpyrazoles between the chemical shifts (CCl_4 solution) of the 1-CH_3 protons and Hammet's σ-values, with a correlation coefficient of

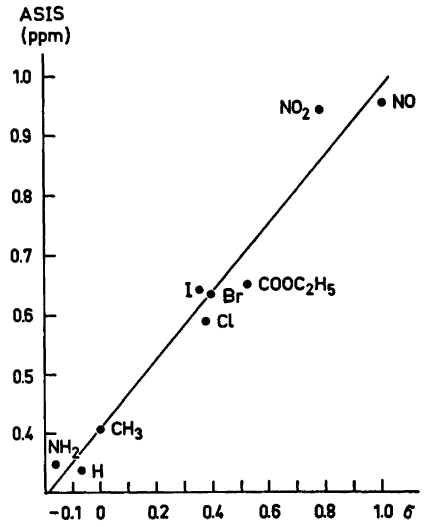


Fig. 3. Aromatic solvent induced shifts (ASIS) for the 1-CH_3 hydrogens *versus* Hammett's σ-values.

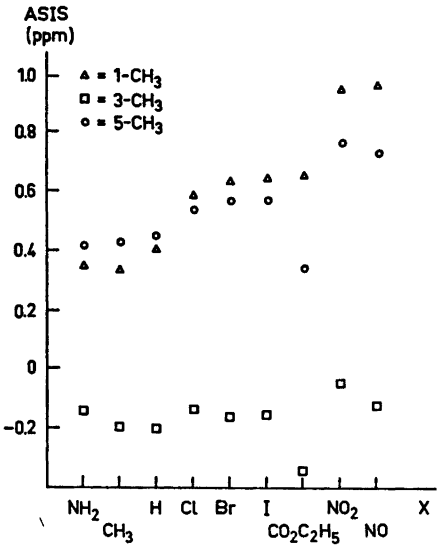


Fig. 4. Aromatic solvent induced shifts (ASIS) for the methyl groups in some 1,3,5-trimethyl-4-X-pyrazoles.

0.95 and a ϱ-value of 0.159 (Fig. 2). A −M substituent in position 4 is regarded to be *para*-related to position 1, a +M substituent, on the other hand *meta*-related (*cf.* II and III). Habraken *et al.*[46] showed that the nitroso group in 3,5-dimethyl-4-nitrosopyrazole is a more powerful electron attractor than the nitro group. Lüttke *et al.*[47] have reached the same conclusion in a study of nitroso- and nitrodimethylamine. For a *para* nitroso group, Habraken reports a σ_p^--value of 1.46, computed from pK_a data of pyrazoles. In this work, a σ_p-value of 1.0 is used for the nitroso group (calculated by subtracting the difference $\sigma_p^- - \sigma_p$ for the nitro group from σ_p^- for the nitroso group).

A survey of about 100 Hammett correlations of ^{1}H NMR data, made by Yokoyama *et al.*,[48] shows that most shift correlations give unsatisfactory correlation coefficients, *e.g.* $< 0.90 - 0.95$. Furthermore, the ϱ-values vary stronly between different series of compounds. From a study of 4-substituted 1-methylpyrazoles, a ϱ-value of 0.48 can be calculated ($r = 0.91$).[21] This refers to $CDCl_3$ solution, however, and ϱ-values are known to vary with the solvent.[48] For the methyl protons in $RC^6H^4CH_2-H$ a ϱ-value of 0.2 is given ($CDCl_3$ solution).[38] The methoxy methyl protons in *para*-substituted anisoles correlate with ϱ_p parameters with a ϱ-value of 0.19 (CCl_4 solution).[37] A positive ϱ-value means that the downfield shift increases when σ increases. The correlation coefficients for the systems above are unsatisfactory and this make a comparison of the different ϱ values uncertain.

An excellent linear correlation is obtained between the ASIS for the 1-CH_3 protons and Hammett's σ-values (Fig. 3) with a correlation coefficient of 0,98 and a ϱ-value of 0,57. On the basis of ASIS measurements on the methyl group in *para*-substituted toluenes, a ϱ-value of 0.41 can be calculated ($r = 0.97$).[38] ASIS of pyrazole derivatives seem to be somewhat more substituent dependent than in the benzene series.

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