Tetrahedron Vol. 47, No. 8, pp. 1393-1398, 1991
Printed in Great Britain

0040-4020/91 $3.00+.(
Pergamon Press plc

NOE DIFFERENCE SPECTROSCOPY AS A VERSATILE TOOL FOR SPECTRAL AND STRUCTURAL ASSIGNMENT IN VARIOUS N-1 SUBSTITUTED PYRAZOLES

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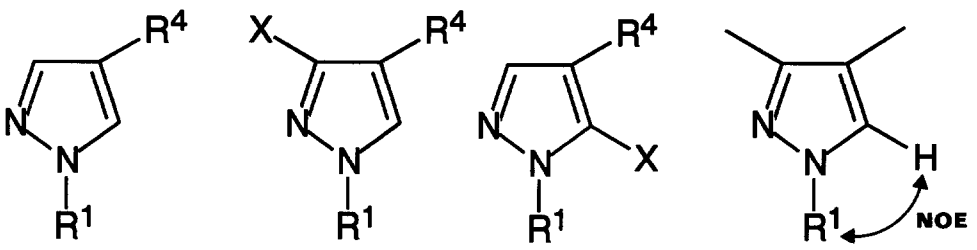
(*Received in Germany* 6 *August* 1990)

Abstract - *NOE difference spectroscopy is proposed as a simple method for the discrimination between pyrazole H-3 and H-5 resonances in various 1-substituted and 1,4-disubstituted pyrazoles as well as for the differentiation between isomeric pairs of 1,3,4- and 1,4,5-trisubstituted, or 1,3- and 1,5-disubstituted pyrazoles, respectively, utilizing a through-space connection between a pyrazole H-5 proton and protons of the N-1 substituent.*

INTRODUCTION

The NMR spectroscopic determination of structure and the correct assignment of NMR lines with N-1 substituted pyrazoles of type **A** - **C** in some cases is a non-trivial task.[1,2] One problem consists in the assignment of the proton NMR signals due to H-3 and H-5 in "symmetrical" pyrazoles of type **A**, on the other hand the unambiguous differentiation between isomeric pairs of "asymmetric" systems of type **B** and **C** can be difficult. These two problems are closely related, as for the latter case it is obvious that from the correct assignment of the pyrazole-H signal(s) the relevant isomeric structure follows definitely. The main methods based on ^{1}H NMR spectroscopy to assign pyrazole-H resonances and thus to discriminate between isomeric pyrazole derivatives of type **B** and **C** (employing coupling constants, solvent effects, line-broadening of the H-3 resonance due to the quadrupole-relaxation effect of ^{14}N-2, paramagnetic shift reagents,..) are excellently summarized in ref..[1] However, no general approach so far exists and some of these empirical rules suffer from certain limitations and cannot be used without hesitation. There are also some reports on the utility of ^{13}C NMR spectroscopy for the identification of isomeric pyrazole derivatives, [3,4,5] which in many cases seems to be superior to proton NMR spectroscopy.[3]

In the present study homonuclear NOE (Nuclear Overhauser Enhancement) difference spectroscopy utilizing a through-space connection between the pyrazole H-5 and protons of the N-1 substituent (as indicated in formula **D**) is proposed as a simple method for the assignment of pyrazole-H resonances and for the differentiation between "asymmetric" isomers in various pyrazole derivatives of type **A** - **C**. To the best of our knowledge,[6] this approach so far has not been used for assignments and structural determination of pyrazole derivatives.[11]



In the following, the application of this new method shall be presented using some representative examples (see Table 1) with previously assigned structure.

RESULTS AND DISCUSSION

Upon irradiation of the methyl-H resonance of 1-methylpyrazole (**1a**) in $CDCl_3$-solution an enhancement of the central pyrazole-H resonance (7.34 ppm) was observed, whereas the low-field pyrazole-H signal at δ 7.48 ppm remained unaffected. Thus, the resonance at δ 7.34 ppm has to be be attributed to the pyrazole H-5 due to the spatial closeness of H-5 and the methyl protons. In d_6-DMSO solution, a perturbation of the methyl-H resonance of **1a** led to a significant enhancement of the signal at lowest field (7.64 ppm), which must be due to H-5, whereas the central resonance showed no effect. These findings are in full agreement with literature data[11] as the ^{1}H-NMR spectrum of **1a** ($CDCl_3$ solution) is reported to exhibit the pyrazole H-5 signal at lower frequencies (higher field) than the pyrazole H-3 signal, whereas in d_6-DMSO the pyrazole H-5 resonance appears at higher frequencies (H-5: 7.66 ppm, H-3: 7.41 ppm).[12] Similarly, with 4-bromo-1-methylpyrazole (**1b**) and the nitropyrazoles **1c** and **1d** strong enhancements of one pyrazole-H resonance obtained after irradiation of the methyl protons permit the unequivocal assignment of the pyrazole H-5 signal (like with **1a** also in the spectra of **1b** the signals of H-3 and H-5 were found to change place when switching from $CDCl_3$ to d_6-DMSO solution).

The potential of the NOE method to discriminate between isomeric pairs of "asymmetric" pyrazole derivatives is demonstrated in Figure 1. Irradiation of the N-methyl resonance in compound **1e** leads to a significant enhancement of the signal attributable to the aromatic proton indicating an 1,3,4-substitution pattern, wheras with **1f** the pyrazole-H signal is nearly unaffected. Instead, a NOE is observed on the C-methyl signal, which is consistent with two adjacent methyl groups in 1- and 5-position of the pyrazole moiety.

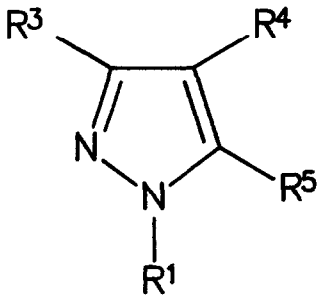


Table 1: Compounds Investigated

Comp. No.	R^1	R^3	R^4	R^5	Ref. Prep.
1a	CH_3	H	H	H	14
1b	CH_3	H	Br	H	15
1c	CH_3	NO_2	H	H	16
1d	CH_3	H	NO_2	H	17
1e	CH_3	CH_3	NO_2	H	18
1f	CH_3	H	NO_2	CH_3	18
2a	CH_2Ph	H	Br	H	19
2b	CH_2Ph	H	CH=NOH	H	20
3a	SEM[a]	H	H	H	21
3b	SEM[a]	H	Br	H	21
3c	SEM[a]	H	H	SPh	21
4	t-BDMSi[b]	H	Br	H	22
5	$COCH_3$	H	Br	H	23
6	Ph	H	NO_2	H	24
7	p-NO_2-C_6H_4	H	NO_2	H	24
8	SO_2Ph	Br	Br	H	22
9a	COPh	H	Br	H	25
9b	COPh	Br	Br	H	26

[a] SEM = $-CH_2-O-CH_2-CH_2-Si-(CH_3)_3$
[b] t-BDMSi = $-Si(CH_3)_2C(CH_3)_3$

Table 2: ^{1}H-NMR Data (δ, ppm) and NOE Data of Compounds Investigated

Comp. No.	Solvent[a]	R^1	R^3	R^4	R^5	Ref. NMR[b]	Irrad. Reson.	NOE on
1a	a	3.82	7.38	6.20	7.64	12	CH_3	H-5 (H-4)
	b	3.90	7.48	6.23	7.34	12	CH_3	H-5 (H-4)
1b	a	3.82	7.48	--	7.90	27	CH_3	H-5
	b	3.88	7.43	--	7.37	12	CH_3	H-5
1c	a	3.96	--	7.00	7.97	--	CH_3	H-5
1d	a	3.90	8.21	--	8.82	27	CH_3	H-5
1e	a	3.81	2.39	--	8.73	--	N-CH_3	H-5
1f	a	3.81	8.16	--	2.58	--	N-CH_3	C-CH_3
2a	a	5.30 (CH_2), 7.30 (Ph)	7.55	--	8.06	--	CH_2	H-5 (Ph)
2b	a	5.36 (CH_2), 7.29 (Ph)	7.82	7.34 (CH), 11.20 (OH)	8.34	20	CH_2 H-5	H-5 (Ph) CH_2 (CH=N)
3a	a	-0.07($SiCH_3$), 0.80($SiCH_2$), 3.50(CCH_2O), 5.39(NCH_2)	7.50	6.29	7.84	21	N-CH_2	H-5 (C-CH_2-O)
3b	b	-0.02($SiCH_3$), 0.90($SiCH_2$), 3.54(CCH_2O), 5.38(NCH_2)	7.49	--	7.58	21	N-CH_2	H-5 (C-CH_2-O)
3c	a	-0.11($SiCH_3$), 0.69($SiCH_2$), 3.46(CCH_2O), 5.45(NCH_2)	7.69	6.69	7.20	21	N-CH_2	-- (C-CH_2-O)
4	a	0.44 ($SiCH_3$), 0.84 (CCH_3)	7.77	--	8.08	(22)	Si-CH_3	H-5
	b	0.46 ($SiCH_3$), 0.90 (CCH_3)	7.69	--	7.57	22	SI-CH_3	H-5
5	c	2.64	7.81	--	8.41	--	CH_3	H-5
6	a	7.40-7.70 (H-3,4,5 of Ph), 7.88-8.02 (H-2,6 of Ph)	8.53	--	9.62	(28)	H-5 H-3	H-2,6 of Ph --
7	a	8.15-8.30 (H-2,6 of R^1), 8.33-8.47 (H-3,5 of R^1)	8.63	--	9.83		H-5 H-3 R^1-2,6	-- H-2,6 of R^1 H-5
8	a	7.69-7.87 (H-3,4,5 of Ph), 7.97-8.10 (H-2,6 of Ph)	--	--	8.90	22	H-5	H-2,6 of Ph
9a	a	7.43-7.78 (H-3,4,5 of Ph), 7.92-8.04 (H-2,6 of Ph)	8.07	--	8.81	(25)	H-5	--
9b	a	7.45-7.73 (H-3,4,5 of Ph), 7.90-8.02 (H-2,6 of Ph)	--	--	8.89	26	H-5	--

[a] a: d_6-DMSO b: $CDCl_3$ c: d_6-acetone

[b] Ref. in parentheses: reported NMR recorded not in the same solvent than in this study

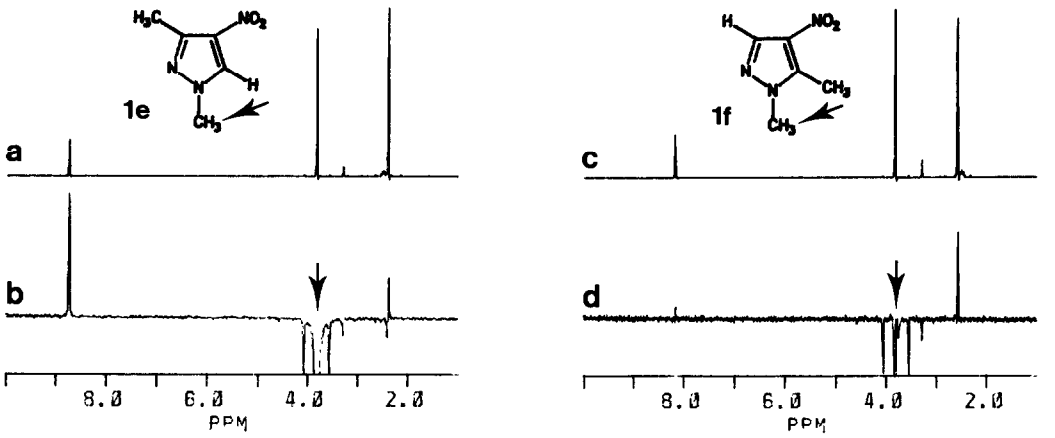


Figure 1: a) ^{1}H-NMR spectrum of **1e** b) NOE difference of **1e** resulting from irradiation of N-CH_3 c) ^{1}H-NMR spectrum of **1f** d) NOE difference spectrum of **1f** resulting from irradiation of N-CH_3

The NOE method shown above to be suitable for 1-methylpyrazoles was extended to a variety of other N-substituted pyrazoles as given in Table 1 (^{1}H-NMR and NOE data are summarized in Table 2). Excellent results were obtained with 1-benzylpyrazoles (**2a, 2b**; irradiation of the benzylic methylene protons, Figure 2a,b), 1-[2-(trimethylsilyl)ethoxymethyl]pyrazoles (**3a,b**; irradiation of N-CH_2-O), and the 1-tert.butyltrimethylsilylpyrazole **4** (irradiation of Si-CH_3). With compound **3c**, no NOE on the low-field pyrazole-H signal could be detected indicating the substituent attached to position 5 of the pyrazole ring.[13] Expectedly, perturbation of the methyl frequency in 1-acetyl-4-bromopyrazole (**5**) leads to a markedly smaller NOE on the pyrazole H-5 (compared to the NOE detected with **1b**) due to a larger distance of the spins involved, but the observed effect is strong enough to allow an unambiguous assignment.

In all cases discussed above the perturbed resonances are singlets being well separated from the pyrazole-H signals. With compounds **6** - **9** the situation is more complicated as the phenyl H-2 and H-6 protons (being close to the pyrazole H-5) show complex multiplet signals which are difficult to irradiate properly. In these cases it turned out to be more advantageous to perturb the pyrazole-H transitions and to observe NOE's on the protons of the benzene moiety. As an example compound **6** may serve (Figure 2c,d): only irradiation of the pyrazole-H transition at lower field leads to a significant enhancement of phenyl-H signals indicating the former resonance to be due to H-5. Similar results were obtained with compound **7**. Analogously, even with compound **8a**, where the distance between the involved protons is increased, the method turned out to be suitable, as the signal of the phenyl H-2,6 protons was enhanced sufficiently. Only with compounds **9a** and **9b** we failed in detecting NOE's on phenyl-H resonances upon irradiation of the pyrazole H-5 transition.

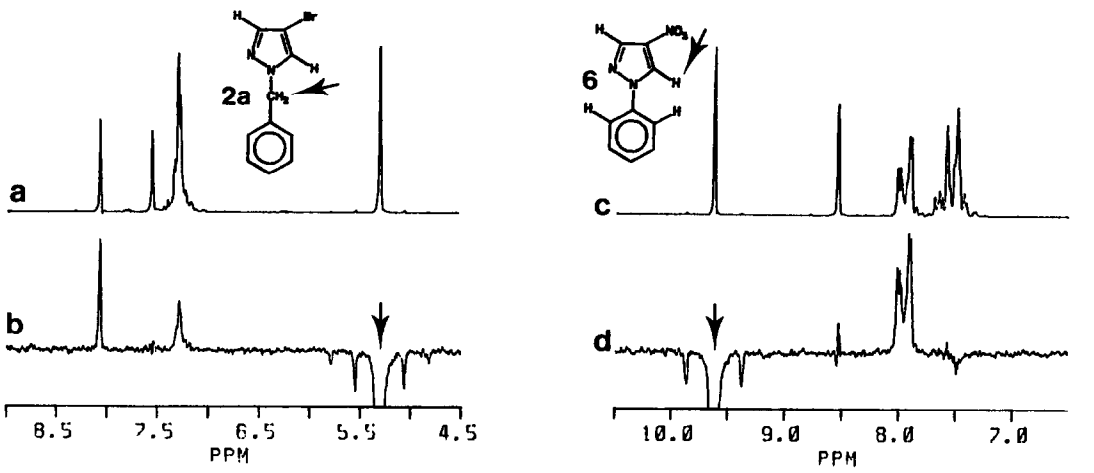


Figure 2: a) ^{1}H-NMR spectrum of **2a** b) NOE difference spectrum of **2a** resulting from irradiation of N-CH_2- c) ^{1}H-NMR spectrum of **6** d) NOE difference spectrum of **6** resulting from irradiation of pyrazole H-5

In summary, such homonuclear NOE-difference experiments have proven to be a versatile tool for the unambiguous identfication of pyrazole H-5 resonances and thus for the differentiation between regioisomers for a variety of 1-substituted pyrazoles (compounds **1** - **8**). The presented method is expected to work also with additional pyrazole derivatives bearing other usual N-1 (protecting) groups not included in this investigation (CMe_3, $SiMe_3$, CH_2OR, CH_2NRR', ..), provided that the N-1 substituent bears suitable protons which can be used as probes for the detection of a through-space connection to the pyrazole H-5, and that on the other hand selective irradiation is possible.

EXPERIMENTAL

NOE-Difference spectra were recorded at 30°C from non-degassed solutions (approx. 0.2 M) on a Bruker AC-80 spectrometer (operating frequency 80.13 MHz) equipped with an Aspect 3000 computer. Acquisition parameters: 8 K data points; spectral width 1365 Hz; acquisition time: 3 s; digital resolution: 0.33 Hz/point; pulse width: 3 μs (90°); relaxation delay: 1 - 3 s; irradiation time: 3 s; irradiation power: 45 - 50 L; number of scans: 160. The use of d_6-DMSO or d_6-acetone as solvent (sharp and intense lock signal[9]) turned out to be advantageous throughout this study.

Acknowledgement. The author is grateful to Prof. U. Wrzeciono and Dr. M. K. Bernard, Karol Marcinkowski Medicinal Academy Poznań, Poland, for providing samples of compounds **1c-f**, **6**, and **7**.

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