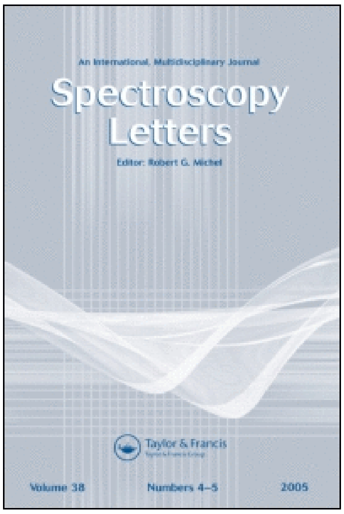

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^{15}N NMR SPECTROSCOPY OF PYRAZOLINES-2 AND THEIR SALTS

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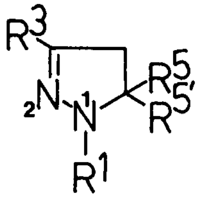
KEY WORDS: Protonation, Quaternisation

^{15}N NMR Spectroscopy is one of the most powerful tools to study the structure of organic molecules.[1-3] Δ^2-pyrazolines 1 are heterocyclic hydrazones, which as a result of their cyclic structure, are stable in acidic media. Thus, their protonation has been studied by ^{1}H and ^{13}C NMR spectroscopies.[4,5] Pyrazolines are protonated and quaternarized at N_1, 2 and 3. It is possible to obtain the isomeric quaternary salts 4 by C-protonation of Δ^3-pyrazolines.[6]



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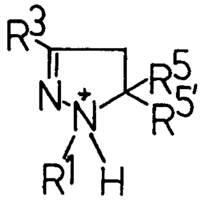

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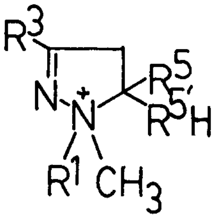

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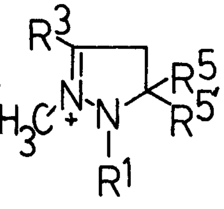
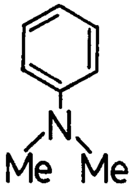
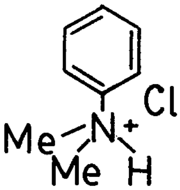


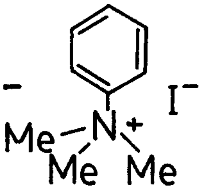
4

It is known[7] that protonation of an sp^2 pyridine-type N-atom is accompanied by a relatively large upfield shift in the ^{15}N resonance of *ca*. 100 ppm, whereas protonation of an aliphatic amine N-atom gives a much smaller downfield shift of *ca*. 10 ppm. In order to compare the chemical shifts of pyrazolines 1 neat or in DMSO-d_6 with those in trifluoroacetic acid (salts 2), it is important to determine if a solvent effect modifies the protonation effect, as happens in ^{13}C NMR experiments.[5]

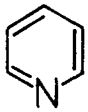
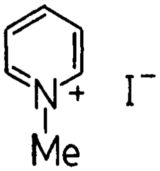
As a model of N_1-atom behaviour we have selected *N*,*N*-dimethylaniline, to take into account the conjugation with the double bond, an as a model of N_2-atom, pyridine. The observed chemical shifts with regard to nitromethane as an external reference are given below:







DMSO-d_6	-338.2	-328.9	-322.5
TFAA	-332.5	-331.2	-325.0

		
DMSO-d_6	-56.8^{8}	-173.7^{8}
TFAA	-170.8^{8}	-175.8^{8}

Trifluoroacetic acid produces slight upfield shifts in quaternary salts (averaged value, -2.3 ppm); thus it is possible to decompose the effects observed for *N*,*N*-dimethylaniline and pyridine into two terms:

$$-338.2 \Longrightarrow -332.5 = +5.7 = \Delta_{prot} + \Delta_{solv} = \underline{+8.0} - 2.3$$

$$-56.8 \Longrightarrow -170.1 = -113.3 = \Delta_{prot} + \Delta_{solv} = \underline{-111.0} - 2.3$$

in quite good agreement with literature data.[7]

Results concerning the pyrazolines and their salts are gathered in Tables 1 to 4. The chemical shifts reported in Tables 1 and 2 are additive. The following contributions can be calculated by multiple regression (Table 5). All are as expected, except the fact that *N*-methylation in position 1 affects N_2 more than N_1. As these values are different for pyrazolines 1 and for pyrazolinium salts 2, the protonation effects depend on the substituents. Taking into account the aferementioned additivity they can be summarized as follows:

Scheme 1

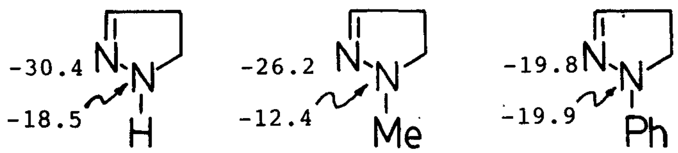


TABLE 1. ^{15}N chemical shifts of Δ^{2}-pyrazolines

Comp.	R^1	R^3	R^5	$R^{5'}$	N_1	N_2
1a[a]	H	H	H	H	-251.5	-34.6
1b[a]	H	CH_3	H	H	-255.0	-49.6
1c[a]	H	CH_3	CH_3	CH_3	-228.2	-48.9
1d[a]	H	CH_3	H	C_6H_5	-242.2	-49.6
1e[a]	CH_3	H	H	H	-250.9	-24.8
1f[a]	CH_3	CH_3	H	H	-254.8	-32.2
1g[a]	CH_3	CH_3	CH_3	CH_3	-228.5	-34.8
1h[a]	CH_3	CH_3	H	C_6H_5	-244.3	-33.8
1i[b]	C_6H_5	CH_3	H	H	-231.6	-57.2

[a] Neat; [b] DMSO-d_6

TABLE 2

^{15}N chemical shifts of Δ^{2}-pyrazolines in TFAA

Comp.	R^1	R^3	R^5	$R^{5'}$	N_1	N_2
2a	H	H	H	H	-269.6	-67.8
2b	H	CH_3	H	H	-270.6	-80.3
2c	H	CH_3	CH_3	CH_3	-253.1	--80.7
2d	H	CH_3	H	C_6H_5	-257.8	-81.4
2e	CH_3	H	H	H	-263.3	-48.2
2f	CH_3	CH_3	H	H	-264.1	-63.2
2g	CH_3	CH_3	CH_3	CH_3	-247.1	-62.2
2h	CH_3	CH_3	H	C_6H_5	-254.2	-62.7
2i	C_6H_5	CH_3	H	H	-248.6	-79.6

TABLE 3

^{15}N chemical shifts of 1,1-disubstituted-Δ^{2}-pyrazolinium salts

Comp.	R^1	R^3	R^5	$R^{5'}$	N_1	N_2
3f[a]	CH_3	CH_3	H	H	-252.1	-46.6
3f[b]	CH_3	CH_3	H	H	-254.3	-49.0
3i[a]	C_6H_5	CH_3	H	H	-239.0	-48.9

[a]DMSO-d_6; [b]TFAA

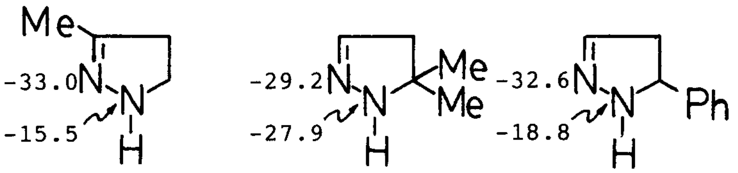


Table 3 values show that solvent effects in salt 3f, bearing the positive charge on N_1, is about -2.3 ppm. This value can be substracted, if necessary, from the effects shown in Scheme 1 to calculate the protonation effects, Δ_{prot}. Comparison of salts 2 and 3, bearing the same substituents, are reported in Scheme 2.

Scheme 2

3f-2f 3i-2i

TABLE 4

^{15}N chemical shifts of 1,2-disubstituted-Δ^2-pyrazolinium salts

Comp.	R^1	R^3	R^5	$R^{5'}$	N_1	N_2
4f[a]	CH_3	CH_3	H	H	-243.4	-151.5
4g[a]	CH_3	CH_3	CH_3	CH_3	-232.2	-153.2
4g[b]	CH_3	CH_3	CH_3	CH_3	-232.7	-153.6
4h[a]	CH_3	CH_3	H	C_6H_5	-233.1	-153.7

[a] DMSO-d_6; [b] TFAA

The fact that methylation effects on N_2 are so different (14.2 and 30.7 ppm) can be due to an interaction between the N_2 lone pair and the steric congestion in 3i.

There are no solvent effects in salts 4 (Table 4) and both chemical shifts are rather insensitive to substituent effects.

Although the result here reported clearly agree with the fact that protonation of Δ^2-pyrazolines 1 takes place at N_1, with formation of salts 2, the situation is complex due to the following facts:

i) owing to the conjugated aza-enamine structure, protonation on N_1 affects both nitrogen chemical shifts.

ii) the effects of protonation and quaternisation

TABLE 5

Substituent contributions to the ^{15}N chemical shifts

	N_1 of 1	N_2 of 1	N_1 of 2	N_2 of 2
Constant[a]	-250.8	-36.8	-269.3	-67.2
1-Methyl	-0.5	14.3	5.6	18.5
1-Phenyl	23.0	-9.2	21.6	1.4
3-Methyl	-3.9	-11.2	-0.9	-13.8
5,5-Dimethyl	26.6	-0.9	17.2	0.3
5-Phenyl	11.6	-0.8	11.3	-3.0

at position 1 are rather complicated and depend on the substituents.

iii) the presence in trifluoroacetic solution of a small amount of diprotonated cation cannot be excluded, even though the second pK_a has never been attained.[9]

EXPERIMENTAL PART

Natural abundance ^{15}N NMR spectra were recorded at 20.28 MHz on a Bruker AM-200 spectrometer (Centre Interuniversitaire de RMN de Marseille). Nitromethane was used as external standard and no corrections for bulky differences were applied. The ^{15}N spectra were obtained using the INEPT pulse sequence.[10] The width of a nitrogen 90° pulse was 26 μs and the width of a proton 90° pulse was 28 μs. The delay time τ between the pulses was set equal to 0.125 s which corresponds to $J_{NH}/4$ mean value for long range NH couplings.[1] The ^{15}N spectra of **1b** were obtained using the conventional acquisition mode. In this last case, traces of $Cr(acac)_3$ were added to shorten the T_1 relaxation times; the delay between pulses and the pulse angle were 5 s and 70°, *ca*. 20 μs, respectively.

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