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^{15}N NMR spectroscopy of partially saturated pyrazoles

Lara De Benassuti, Teresa Recca and Giorgio Molteni*

Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, Via Golgi 19, 20133 Milano, Italy

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Abstract—Partially saturated pyrazoles, namely 1-(4-substituted)phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazoles, were submitted to extensive ^{15}N NMR spectroscopic analyses, performed in natural abundance. Nitrogen chemical shifts were measured by means of INEPT and HMBC experiments, while long range proton–nitrogen scalar coupling values were taken through *J*-HMBC experiments. A linear plot between nitrogen chemical shifts and Hammett σ_p was observed, enabling us to relate quantitatively the observed chemical shifts to the electronic features of the substituent in the 1-position of the 4,5-dihydropyrazole ring.

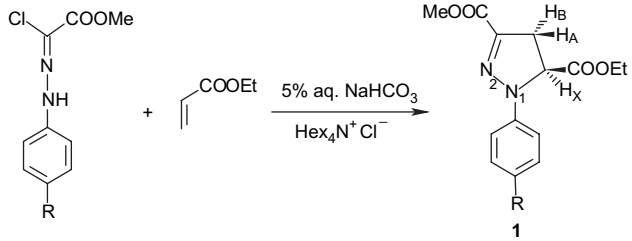
1. Introduction

Due to its relevance in both chemical and biological research, increasing attention has been devoted to the field of ^{15}N NMR spectroscopy.[1] In particular, the chemical shifts of some aromatic azoles have been investigated through ^{15}N NMR spectroscopy of ^{15}N-enriched substrates,[2,3] but there is a lack of data concerning partially saturated rings.

As a representative of such systems, 4,5-dihydropyrazoles are particularly attractive compounds since they display a number of interesting features. Several 4,5-dihydropyrazole derivatives find application as anti-inflammatory, antipyretic or analgesic agents,[4] dyestuffs[5] and couplers in colour photography.[6] In order to gain more insight about the spectroscopic features of these compounds, we decided to submit a series of 1-(4-substituted)phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazoles **1** to extensive ^{15}N NMR spectroscopic analyses.

2. Results and discussion

First, analytically pure samples of compounds **1** were obtained following a nitrilimine-based cycloadditive protocol, which has been developed in our group,[7] concerning the regioselective synthesis of 5-substituted 4,5-dihydropyrazoles (Scheme 1). The choice of water as an unusual reaction medium relies upon two major points: (*i*) cycloaddition rates are significantly increased with respect to the classic method and (*ii*) the separation of products is performed by simple filtration of the reaction crude products. As expected, cycloadducts **1** were formed as the only regioisomers, whose ^{1}H NMR spectra are in full agreement with those reported in the literature for similar 1-aryl-3-alkoxycarbonyl-5-substituted-4,5-dihydropyrazoles.[8–10] The diastereotopic hydrogens bonded to the C-4 position of the 4,5-dihydropyrazole ring appear as two distinct doublet of doublets in the range δ_H 3.20–3.80. This represents the AB portion of the ABX set of signals, which is typical of compounds such as **1**. The X portion of the latter signals appears as a doublet of doublets and is found between δ_H 4.80 and 5.10 being clearly related to the resonance of the proton in the C-5 position.



a: R = H, **b:** R = Me, **c:** R = OMe, **d:** R = Cl, **e:** R = NO_2

Scheme 1.

The ^{15}N nuclear shielding data of 4,5-dihydropyrazoles **1** were obtained through both ^{15}N INEPT and HMBC ^{1}H–^{15}N sequences of pulses (see Section 4) and are summarised in Table 1. It may be pointed out that since $\Delta\delta$ values of Table 1 are referred to compound **1a** (R=H), negative values of $\Delta\delta$ indicate that the nitrogen resonance is shifted upfield. A variety of solvents were used, namely $CDCl_3$, acetone-d_6, DMSO-d_6 and deuterated benzene, while the sample concentration was always 0.50 M. We were confident to assign

* Corresponding author. Tel.: +39 02 50314141; fax: +39 02 50314139; e-mail: giorgio.molteni@unimi.it

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Table 1. ^{15}N chemical shifts of 1-(4-substituted)phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazoles **1**

R	Solvent	δN_1	δN_2	$\Delta\delta N_1$	$\Delta\delta N_2$
MeO	$CDCl_3$	−218.77	−21.54	−1.75	1.55
Me	$CDCl_3$	−217.36	−22.39	−0.34	0.70
H	$CDCl_3$	−217.02	−23.09	0.00	0.00
Cl	$CDCl_3$	−218.36	−24.69	−1.34	−1.60
NO_2	$CDCl_3$	−214.09	−27.66	2.93	−4.57
MeO	$(CD_3)_2CO$	−219.21	−21.62	−1.56	1.75
Me	$(CD_3)_2CO$	−218.15	−22.54	−0.50	0.83
H	$(CD_3)_2CO$	−217.65	−23.37	0.00	0.00
Cl	$(CD_3)_2CO$	−219.09	−25.18	−1.44	−1.81
NO_2	$(CD_3)_2CO$	−213.88	−28.65	3.77	−5.28
MeO	DMSO-d_6	−219.94	−23.26	−1.64	1.92
Me	DMSO-d_6	−218.72	−24.41	−0.42	0.77
H	DMSO-d_6	−218.30	−25.18	0.00	0.00
Cl	DMSO-d_6	−219.25	−26.53	−0.95	−1.35
NO_2	DMSO-d_6	−215.49	−29.06	2.81	−3.88
MeO	C_6D_6	−218.80	−20.66	−1.67	1.41
Me	C_6D_6	−217.58	−21.14	−0.45	0.93
H	C_6D_6	−217.13	−22.07	0.00	0.00
Cl	C_6D_6	−218.81	−23.43	−1.68	−1.36
NO_2	C_6D_6	−214.20	−26.46	2.93	−4.39

chemical shift values for N_1 and N_2 on the basis of their very different chemical nature, which means that the sp^2-hybridised N_2 must be strongly deshielded with respect to N_1, as confirmed by 2D-HMBC experiments. This agrees with the known chemical shift of both sp^2 and sp^3 nitrogens of simple heterocycles.[11] It is worth noting that all the above experiments were performed in natural abundance thus avoiding the synthesis of ^{15}N-enriched compounds. To the best of our knowledge, the present paper represents the first study of partially saturated azoles performed in natural abundance. The lack of ^{15}N labelled substrates did not produce excessive time-consuming experiments. As can be inferred from Table 1, change of solvent had little effect on nitrogen nuclear shielding. This latter comment can be visualised in a more intuitive way by Figure 1, in which ^{15}N INEPT spectra of compound **1c** is provided in all the mentioned solvents. Although it is known that nitrogen chemical shifts of aromatic azoles are somewhat affected by the change of the solvent,[12–14] it may be recalled that these variations occur mainly because of explicit hydrogen bonding, a kind of interaction which is clearly lacking in our case. On the other hand, more significant changes of nitrogen nuclear shielding were produced by the change of R as illustrated by Figure 2 in which are shown the ^{15}N INEPT spectra of 4,5-dihydropyrazoles **1c** and **1e** in acetone-d_6. As can be seen from both Table 1 and Figure 2, the N_1 nucleus is shifted downfield according to the electron withdrawing character of R, while the N_2 chemical shift followed the reverse trend. This latter observation is consistent with the upfield shift of some nitrogens,[15] which is due to the dominance of the increase in the molecular-plane shielding over the decrease in the out-of-plane shielding. To this point, we were pleased to find that a plot of $\Delta\delta N_2$ versus Hammett σ_p (Fig. 3) resulted in a linear correlation, which was obtained by a standard least-squares method.[16] In benzene, the very good correlation coefficient ρ=0.9988 was found for the straight line having equation $\Delta\delta N_2 = -5.756\sigma_p - 0.0947$, while other solvents also show linear correlations with similar slope.[17] This indicates that the solvent has little effect on the electron redistribution mechanism, which is operating in the 4,5-dihydropyrazole ring of cycloadducts **1**. Disappointingly, plots of $\Delta\delta N_1$ against Hammett σ_p resulted in a scattering of points. The origin of this complex behaviour is yet unclear.

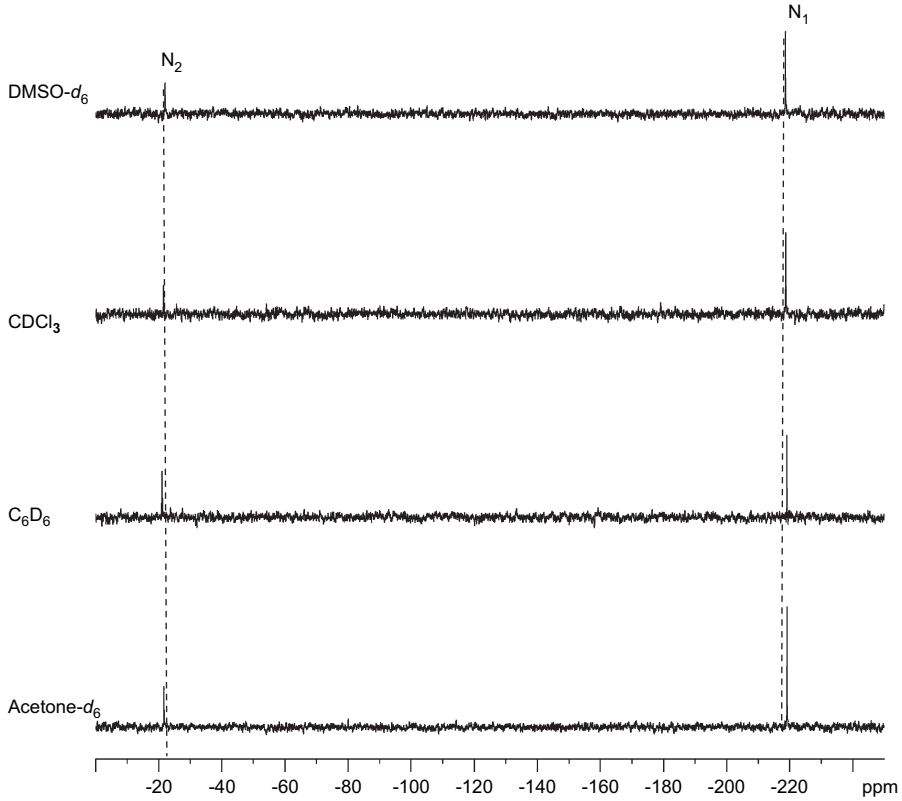

Figure 1. ^{15}N INEPT spectra of 4,5-dihydropyrazole **1c**.

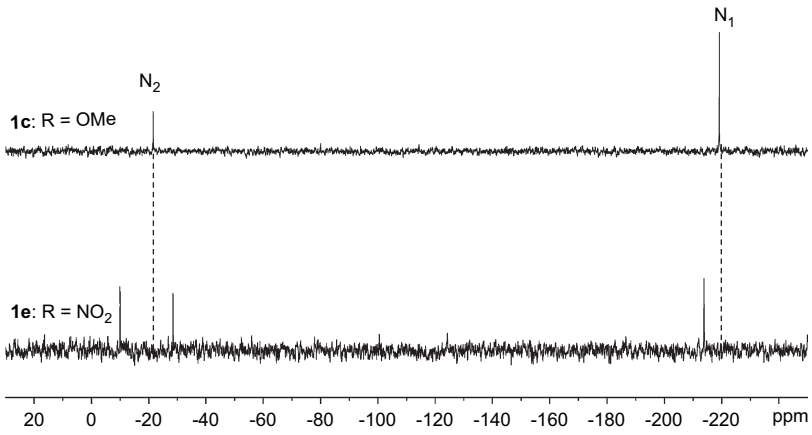

Figure 2. ^{15}N INEPT spectra of 4,5-dihydropyrazoles **1c** and **1e** in acetone-d_6. Resonance at $\delta=-10.07$ ppm is related to the ^{15}N of the nitro group of **1e**.

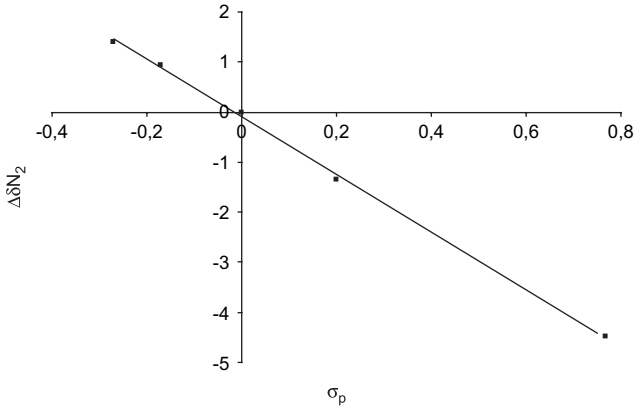

Figure 3. Linear plot of $\Delta\delta N_2$ versus Hammett σ_p in C_6D_6.

Finally, due to the usefulness of $^3J_{N-H}$ scalar couplings in the characterisation of isomeric pyrazoles,[3] we measured the ^{15}N–C–C–H couplings of the 4,5-dihydropyrazole ring of **1** by means of *J*-HMBC experiments. The ^3J values listed in Table 2 encompass the range 5.7–6.4 Hz and are larger than that of aromatic pyrazoles[3] and are scarcely dependent on the nature of R.

Table 2. ^3J Values of 4,5-dihydropyrazole cycloadducts **1** measured in DMSO-d_6[a]

Type of ^3J	R				
	OMe	Me	H	Cl	NO_2
$^3J_{N_1-H_A}$	6.2	6.2	6.1	6.2	6.2
$^3J_{N_1-H_B}$	6.2	6.2	6.1	6.3	6.2
$^3J_{N_2-H_A}$	6.4	6.2	5.7	6.1	6.2
$^3J_{N_2-H_B}$	6.1	6.2	6.2	6.2	6.2
$^3J_{N_1-H_X}$	6.2	6.1	6.2	6.2	6.2

[a] ^3J Values are given in hertz.

3. Conclusions

Three major conclusions may be drawn from the present paper: (*i*) ^{15}N NMR spectroscopic data (chemical shifts and scalar coupling constants) concerning partially saturated pyrazoles were reported for the first time by means of experiments performed in natural abundance; (*ii*) solvent changes had little or no influence on the chemical shifts; (*iii*) a linear plot of $\Delta\delta N_2$ versus Hammett σ_p was observed, enabling us to relate quantitatively the observed chemical shift to the electronic features of R.

4. Experimental

Compounds **1a–1c** and **1e** are known in the literature.[7]

4.1. 1-(4-Substituted)phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazoles 1

A mixture of the appropriate hydrazonoyl chloride (1.0 mmol), ethyl acrylate (0.40 g, 4.0 mmol), tetrahexyl ammonium chloride (38 mg, 0.1 mmol) and 5% aqueous sodium hydrogen carbonate (12 mL) was mechanically shaken at room temperature for 2 h. In the case of R=H, Me, MeO, the mixture was filtered; the solid material was washed with water (2×25 mL) and dried giving pure **1a–1c**. Isolated yields of products **1a–1c** were as follows: **1a**: 0.25 g, 90%; **1b**: 0.28 g, 95%; **1c**: 0.29 g, 95%.

In the case of R=Cl the mixture was filtered; the solid material was washed with water (10 mL) and dried. Crystallisation from *i*-Pr_2O/*i*-PrOH gave pure **1d** (0.24 g, 76%) as a pale yellow powder having mp 83 °C. IR (Nujol) 1735, 1730 (cm^{-1}); ^{1}H NMR ($CDCl_3$) δ: 1.18 (3H, t, *J*=7.0), 3.23 (1H, dd, *J*=17.0, 6.7), 3.53 (1H, dd, *J*=17.0, 12.5), 3.81 (3H, s), 4.22 (2H, q, *J*=7.0), 4.88 (1H, dd, *J*=12.5, 6.7), 7.0–7.4 (4H, m); ^{13}C NMR ($CDCl_3$) δ: 22.3 (CH_3), 50.4 (CH_2), 52.7 (CH_3), 53.1 (CH_2), 65.5 (CH), 118.3 (CH), 127.0–130.0, 133.4 (C), 140.7 (C), 144.6 (C), 168.3 (C), 170.9 (C); MS *m/z* 310 (M^+). Anal. Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.11; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 54.07; H, 4.90; Cl, 11.48; N, 8.97.

In the case of R=NO_2 the mixture was taken up with CH_2Cl_2 (40 mL). The organic layer was washed with water (2×25 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with Et_2O. The fraction with R_f=0.57 was crystallised from hexane/toluene affording pure **1e** (35 mg, 11%).

4.2. ^{15}N NMR spectroscopic experiments

NMR spectra were acquired on a Bruker Avance 400 MHz (40.560 MHz for ^{15}N) or on AMX 300 MHz (30.424 MHz

for ^{15}N) spectrometer, both equipped with a 5 mm inverse *z*-gradient probe.

^{15}N chemical shifts were measured both directly, via INEPT experiments, and indirectly, via ^{1}H–^{15}N long range correlation.

The INEPT spectra were recorded over a range of 300 ppm with a *J* value of 5 Hz and a relaxation delay of 2 s.

The HMBC spectra are recorded with a *J* value of 5 Hz, spectral width of 300 ppm in F1 dimension, a relaxation delay of 1.5 s; data matrices of 1024×256 points (eight scans) were zero filled in F1 dimension to 1024 points.

$J_{H–N}$ long range were recorded by means of *J*-HMBC experiment of samples in DMSO-d_6 solution, with the following parameters: relaxation delay 4.0 s, scaling factor=23, J=4 Hz, 16 scans.

In all experiments nitromethane was used as reference of ^{15}N chemical shifts (δ=0 ppm).

Acknowledgements

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17. (a) In $CDCl_3$: $\Delta\delta N_2=-5.956\sigma_p-0.177$; ρ=0.9947; (b) In $(CD_3)_2CO$: $\Delta\delta N_2=-6.861\sigma_p-0.202$; ρ=0.9958; (c) In DMSO-d_6: $\Delta\delta N_2=-5.473\sigma_p+0.0503$; ρ=0.9837.