Research Note

^1H and ^{13}C NMR study of perdeuterated pyrazoles

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Abstract. The ^1H and ^{13}C chemical shifts as well as the ^1H – ^2H and ^2H – ^{13}C coupling constants of perdeuterated 3,5-dimethylpyrazole and 3,5-diphenylpyrazole have been measured and the values compared with those of the unlabelled compounds.

1. Introduction

The difficulty of proton exchange with deuterium in pyrazoles increases in the order: N–H (simple agitation with D_2O and/or CH_3OD) > H-4 (heating in a sealed tube with D_2O) > H-3,5 (heating in a sealed tube with D_2O and NaOD 1N) $\gg$ C– CH_3 $\gg$ C– C_6H_5 (supercritical deuterium exchange) [1–5].

For the kind of NMR experiments we are carrying out (proton/deuteron transfer in the solid state monitored by ^{15}N CPMAS NMR spectroscopy [6–10]), the proton at position 1 should be alternatively H/D/H/D. The determination of the isotopic enrichment by MS is inconclusive because the relative isotopic enrichment of each position is almost impossible to determine. Moreover, the very easy NH/ND exchange further complicates the problem.

For this reason we decided to determine the isotopic purities of two pyrazoles, see Fig. 1, 3,5-dimethylpyrazole **1** and 3,5-diphenylpyrazole **2** by NMR (notice that owing to annular prototropy, positions 3 and 5 of pyrazoles are usually magnetically equivalent). These two pyrazoles are of interest because of their solid state properties: the first one crystallizes in cyclic trimers and the second one in cyclic tetramers, both showing proton transfer along the N–H $\cdots$ N hydrogen bond [6–8].

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Fig. 1. The pyrazoles studied in this research: 3,5-dimethylpyrazole **1** and 3,5-diphenylpyrazole **2**.

2. Experimental

All the compounds discussed here have been described [11]. ^1H and ^{13}C NMR spectra were obtained using Varian Inova 400 and Unity 500 MHz instruments. The ^{13}C NMR spectra were recorded proton-decoupled without NOE enhancement in order to obtain quantitative results. The chemical shifts are accurate to 0.005 and 0.05 ppm for ^1H and ^{13}C NMR, respectively. Coupling constants are accurate to 0.1 Hz for ^1H NMR and 0.5 Hz for ^{13}C NMR.

3. NMR results and discussion

The spectra of **1b** were recorded in acetone- d_6 at 400 MHz (^1H) and 100 MHz (^{13}C) (20 mg in 0.6 ml). The ^1H NMR spectrum consists of a quintuplet at 2.135 ppm and a slightly broad singlet at 5.612 ppm. The first signal corresponds to a CHD_2 group with $^2J_{\text{HD}} = 2.30$ Hz and the second one to the H-4 proton of a hexadeuterated species. The first signal integrates 98 and the second 2, thus the exchange at position 4 seems to be more complete than that at the methyl groups, but one has to consider that there are six methyl protons and only one H-4, thus the relative ratio of deuteration is 89/11. A very small triplet ($^2J_{\text{HD}} = 2.40$ Hz) appears at 2.151 ppm, which could be evidence for the presence of a diprotonated species [3(5)- CH_2D -5(3)- CD_3 -pyrazole]. The ^1H NMR spectrum of **1a** in CDCl_3 shows signals at 2.21 (methyl groups) and 5.76 ppm (H-4) [12].

The ^1H -decoupled ^{13}C NMR spectrum of **1b** (17 200 scans) shows three signals: a complex multiplet centered at 11.61 ppm, a triplet at 104.08 ppm ($^1J_{\text{CD}} = 26.35$ Hz) and a broad signal at 144 ppm (C-3 and C-5, the broadening is due to a slow NH (or ND) proton exchange). Near the C-4 triplet, there is a small singlet at 104.31 ppm resulting from a compound with an H-4 proton, the isotopic shift, $\Delta\delta$, being 0.23 ppm. The probability that a dimethyl pyrazole contains one proton at the 4-position and is also monoprotonated at the methyl group is very low, so this signal probably corresponds to the 3,5-di CD_3 -4-H pyrazole species. Unlabelled 3,5-dimethylpyrazole in CH_2Cl_2 produces signals at 104.8 ppm (C-4), 145.3 (C-3, C-5) and 12.9 ppm (methyl groups) [13]. As no data in acetone were available and no ^1H - ^{13}C coupling constants of **1a** have been determined, we recorded its ^{13}C NMR spectrum in this solvent (same concentration). As a result of a slow prototropic exchange, the signal corresponding to the C-3 and C-5 carbons is very broad (144.2 ppm) and even the signal corresponding to the methyl groups is slightly broadened (12.15 ppm, $^1J_{\text{CH}} = 125.5$ Hz); only the signal of C-4 is well resolved (104.10 ppm, $^1J_{\text{CH}} = 171.6$ Hz, $^3J_{\text{CH}} = 3.2$ Hz).

A deconvolution of the signal of C-4 (the singlet of the C–H of **1a** plus the triplet of the C–D of **1b**) shows that there are 94% of C–D and 6% of C–H. Thus, the exchange of the methyl groups corresponds to 8% of CHD_2 .

The spectra of **2b** were recorded in acetone- d_6 at 500 MHz (^1H) and 125 MHz (^{13}C) (30 mg in 0.6 ml). The ^1H NMR spectrum shows only singlets (ignoring the NH there are no isotopomers with two protons, only species H_1D_{11}): 5.62 (H-4), 7.33 (H_{para}), 7.46 (H_{meta}) and 7.90 (H_{ortho}). The respective integrals are 4.23 (1 H-4), 13.77 (2 H_{para}), 27.48 (4 H_{meta}) and 27.84% (4 H_{ortho}), which correspond to a ratio 4.23/6.88/6.87 and 6.96. This indicates that the three positions of the phenyl ring have been deuterated to the same extent and that H-4 has been deuterated 1.6 times more completely.

The ^1H -decoupled ^{13}C NMR spectrum of **2b** (10 000 scans) shows four signals (the signal corresponding to C-3 and C-5 is very broad as a result of a slow prototropic exchange and cannot be observed):

(1) pyrazole C-4: C–D species 110.09 ppm (triplet, $^1J_{\text{CD}} = 26.75$ Hz), C–H species 100.27 ppm ($\Delta\delta = 0.18$ ppm);

(2) phenyl C_{ortho} : C–D species 125.67 ppm (triplet, $^1J_{\text{CD}} = 24.4$ Hz), C–H species 125.95 ppm ($\Delta\delta = 0.28$ ppm);

(3) phenyl C_{para} : C–D species 128.07 ppm (triplet, $^1J_{\text{CD}} = 24.4$ Hz), C–H species 128.35 ppm ($\Delta\delta = 0.28$ ppm);

(4) phenyl C_{meta} : C–D species 129.05 ppm (triplet, $^1J_{\text{CD}} = 24.05$ Hz), C–H species 129.33 ppm ($\Delta\delta = 0.28$ ppm).

The chemical shifts are close to those described for compound **2a** in CDCl_3 [13].

Deconvolution of these signals yields the following percentages of C–H: C-4 (1.7%), C_{para} (2.1%), C_{meta} (2.4%) and C_{ortho} (3.0%). A comparison of these results with those obtained by ^1H NMR shows the consistency of the data although deconvolution introduces some error (probably all the phenyl carbons are deuterated at 97.5%).

3.1. Deuteration

This study has established not only that CH/CD replacement is very high (nearly 95%) but also that there are some differences between carbons. Pyrazole deuteration at position 4 is higher than that of the methyl or phenyl groups at positions 3 and 5, assuming the deuteration of the phenyl rings is equal in all positions. This assumption is consistent with previous findings [14].

3.2. Isotope shifts ($\Delta\delta$)

Some results from the literature [15,16] are worth revisiting: CD_3COCD_3 , $\delta^{13}\text{C}$ (Me) = 29.9; CH_3COCH_3 , $\delta^{13}\text{C}$ (Me) = 30.7, $\Delta\delta = 0.5$ ppm; C_6D_6 , $\delta^{13}\text{C} = 128.0$, C_6H_6 , $\delta^{13}\text{C} = 128.5$ ppm, $\Delta\delta = 0.5$ ppm. The observed $\Delta\delta$ values for *ipso* effects are 0.18–0.28 ppm in compounds **1** and **2**. A comparison of **1a** and **2a** shows a $\Delta\delta = 0.54$ ppm (*ipso* effect) for the methyl groups and of 0.30 ppm for C-4 (six deuterium atoms at three bonds distance), values in agreement with those reported above and in the literature [17,18].

3.3. Coupling constants

The theoretical ratio $J_{\text{HX}}/J_{\text{DX}} = \gamma_{\text{H}}/\gamma_{\text{D}}$ is equal to 6.51 [19]. For instance, C_6D_6 , $^1J_{\text{CD}} = 24$ Hz, C_6H_6 , $^1J_{\text{CH}} = 161$ Hz [14] ($J_{\text{HX}}/J_{\text{DX}} = 6.71$). In the case of compound **1**, for **1a** $^1J = 171.6$ Hz and for **1b** $^1J = 26.35$ Hz, then $J_{\text{HX}}/J_{\text{DX}} = 6.51$.

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