Solid State Structure of NH-Pyrazoles not Easily Amenable to Crystal Structure Determinations: The Case of 3(5)-Phenyl-5(3)-methylpyrazole and 3,5-Diphenyl-4-methylpyrazole

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The structures of 3(5)-methyl-5(3)-phenylpyrazole (polymorph **B**) and 3,5-diphenyl-4-methylpyrazole in the solid state cannot be determined by X-ray crystallography due to the lack of suitable monocrystals. The combined use of CPMAS nmr, DSC and powder diffraction provides information about the behaviour of these pyrazoles in the solid state, particularly, about N-H···N intermolecular proton transfer. 3(5)-Methyl-5(3)-phenylpyrazole is an example of the influence of polymorphism on the proton exchange since polymorph **A** (a tetramer formed by a mixture of both tautomers) presents the phenomenon but polymorph **B** (formed exclusively by 3-phenyl-5-methyl tautomer) is devoid of it.

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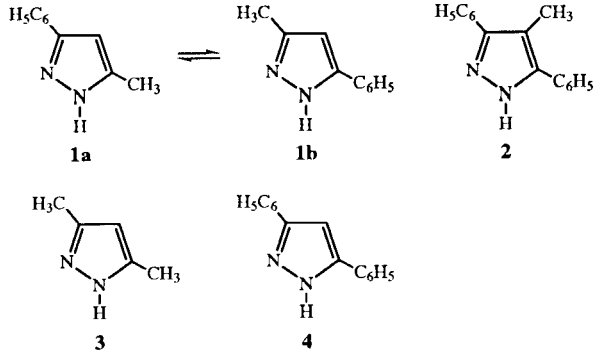
In the last years, we have carried out a systematic comparison of X-ray structures and ^{13}C and ^{15}N CPMAS nmr spectra of NH-pyrazoles [1-7]. The aim of the project was to determine the dynamic aspects of proton transfer in these heterocycles, which may occur in some pyrazoles through the network of intermolecular N-H···N hydrogen bonds. For several pyrazoles, an X-ray structure (NH proton disordered) and a dynamic process (usually determined by ^{15}N CPMAS nmr) were simultaneously observed; there were also cases of no disorder in crystallography and absence of the proton transfer (pyrazole itself is one of such examples [8,9]).

In this work we report two cases where proton transfer has been observed by nmr but in which the X-ray structure determination failed because of the difficulty to obtain suitable monocrystals. These two cases concern 3(5)-phenyl-5(3)-methylpyrazole **1** and 3,5-diphenyl-4-methylpyrazole **2**.

We have summarized in Table 1 all the information available on these two pyrazoles and on two related compounds: 3,5-dimethylpyrazole **3** and 3,5-diphenylpyrazole **4**.



1a **1b** **2**

3 **4**

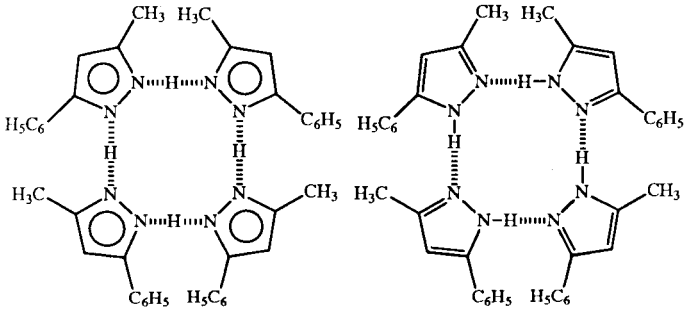
The structure of 3(5)-phenyl-5(3)-methylpyrazole was determined by White *et al.* by X-ray crystallography [10] and neutron diffraction [11]. In both cases, the authors came to the conclusion that this compound crystallizes in the form of a tetramer formed by two tautomers **1a** and two tautomers **1b** and that the N-H proton is shared between two pyrazoles, *i.e.* it is equidistant from both nitrogen atoms. Scheme 1 represents a view of this unusual structure.

Table 1

Structural Characteristics of Phenylmethylpyrazoles Unsubstituted on the N_1-Nitrogen Atom

Compound	R_3	R_4	R_5	X-ray structure	Proton transfer (kJ mol^{-1})	
1	$C_6H_5(CH_3)$	H	$CH_3(C_6H_5)$	Tetramer formed by **1a** and **1b**, proton shared [10,11]	Yes,	E_a = 47.0 (this work)
2	C_6H_5	CH_3	C_6H_5	Unknown	Yes,	E_a = 54.0 (this work)
3	CH_3	H	CH_3	Trimer, proton disordered [12]	Yes,	E_a = 50.5 [1]
4	C_6H_5	H	C_6H_5	Tetramer, proton disordered [2]	Yes,	E_a = 44.5 [2]

Scheme 1



On the left side the structure proposed by White is represented. Since the proton is located in the middle of the two nitrogen atoms, there is no sense to speak about tautomer **1a** and **1b**, but if the proton is classically represented, right side, both tautomers are clearly observed (the migration of the four protons yields an identical structure). A review of X-ray structures of pyrazoles, including NH-pyrazoles [13], reveals that this compound is the only representative of "proton shared".

Variable Temperature Solid-State ^{15}N CPMAS NMR Results.

This technique requires the preparation of [$^{15}N_2$] labelled compounds (see Experimental). To avoid losing any amount, the labelled sample of pyrazole **1** was recorded without crystallization. The spectrum at room temperature (Figure 1, bottom) shows four narrow signals at 166.0 and 167.2 ppm (NH) and 235.5 and 237.1 ppm (-N=). This spectrum is inconsistent with the shared proton structure of White [10,11] but also with a rapid equilibrium between two classical structures: in both cases, one or two signals in the 200 ppm zone are expected. Moreover, taking into account the effect of C-phenyl and C-methyl substituents on the ^{15}N chemical shifts of NH-pyrazoles [14], these signals correspond to the 3-phenyl-5-methyl tautomer **1a** (an identical conclusion is reached by using ^{13}C CPMAS nmr chemical shifts, see Experimental). The small chemical shift differences (1.2 ppm for the NH and 1.6 ppm for the -N=) could be due to different conformations of the phenyl ring (note that the signals at 166.6 and 237.1 ppm are twice as intense than those at 167.2 and 235.5 ppm). The "shared proton" of White structure could be doubted, but not the presence of tautomers **1a** and **1b** in identical amounts. Consequently, nmr and crystallography were inconsistent.

Crystallization of the crude product by slow evaporation of an ethanolic solution yielded a crystalline sample. We determined that these crystals were identical (same space group and same unit cell) to those of White [10,11]. The ^{15}N CPMAS nmr spectrum at room temperature (Figure 1, top) shows two broad signals. Therefore, a variable temperature experiment was carried out (Figure 2,

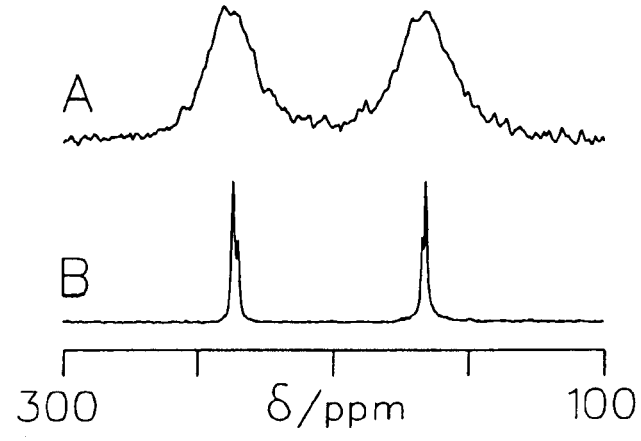


Figure 1. ^{15}N CPMAS nmr spectra of 3(5)-phenyl-5(3)-methylpyrazole **1** at room temperature (298 K). Top, polymorph **A**; bottom, polymorph **B**.

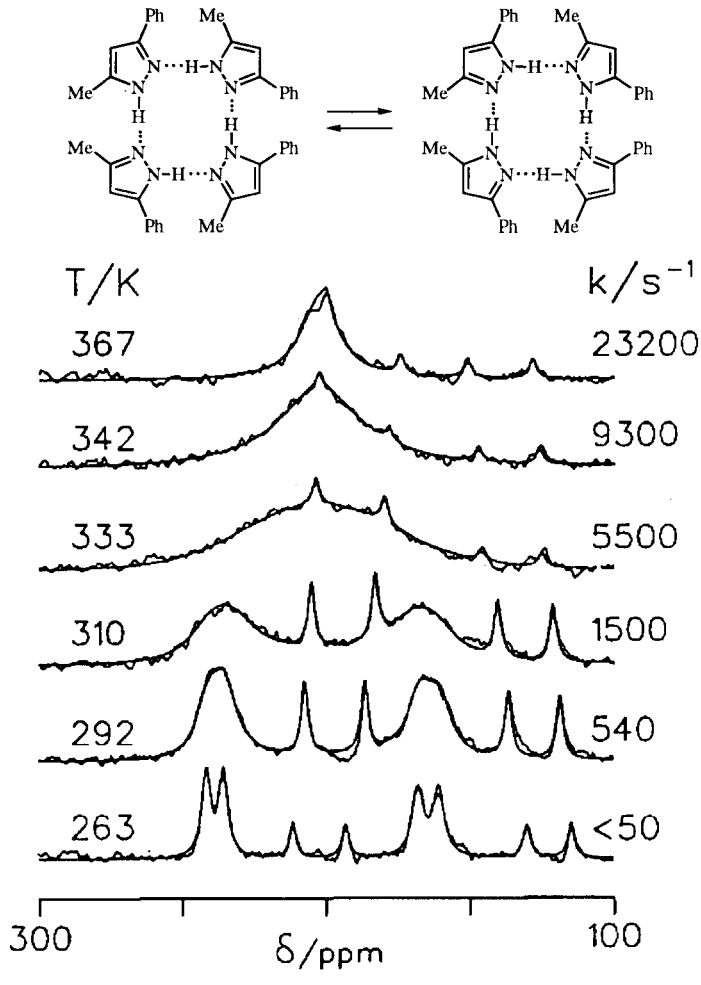
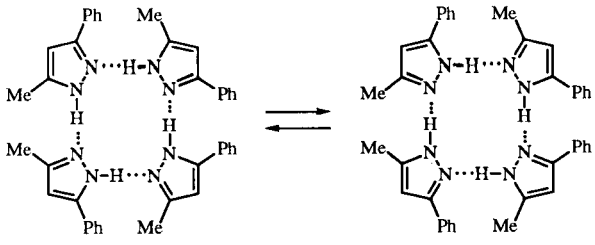


Figure 2. Superimposed experimental and calculated ^{15}N CPMAS nmr spectra of 3(5)-phenyl-5(3)-methylpyrazole **1** (polymorph **A**) at different temperatures.

experimental and calculated spectra superposed). At low temperature, four signals are observed at 161.8 ppm (NH



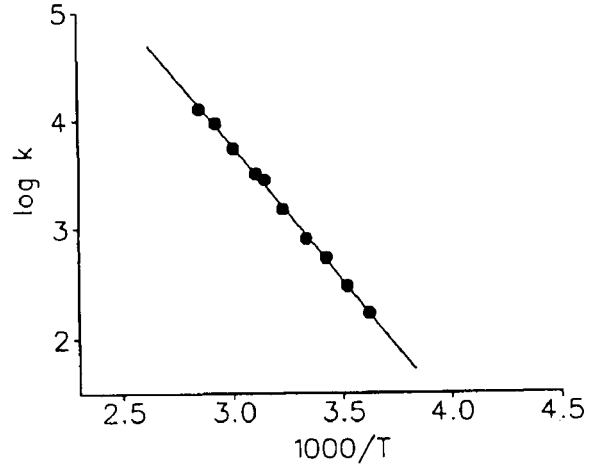


Figure 3. Arrhenius plot corresponding to 3(5)-phenyl-5(3)-methylpyrazole **1** (polymorph **A**).

of **1b**), 167.7 ppm (NH of **1a**), 236.1 ppm (-N= of **1a**) and 241.6 ppm (-N= of **1b**). The four sharp lines correspond to the ^{15}N chemical shifts thermometer TTAA [20]. The chemical shift assignment is based on the results obtained with this compound in solution [3]. The spectrum obtained at low temperature is partly consistent with the structure of White (both tautomers present) but it is inconsistent with the "shared proton" [where two signals at 199 ppm (N near the C-phenyl group) and 203 ppm (N near the C-methyl group) are expected]. The corresponding Arrhenius plot (Figure 3) provides the following values: an activation energy of E_a = 47.0 kJ mol^{-1} and a frequency factor of log A = 11.2. These values are very close to those of 3,5-diphenylpyrazole **4** (E_a = 44.5 kJ mol^{-1}, log A = 11.8). Thus, both tetramers are quite similar.

The conclusion is that 3(5)-phenyl-5(3)-methylpyrazole presents two polymorphs: one formed exclusively by the 3-phenyl-5-methylpyrazole **1a** tautomer (polymorph **B**) and the other formed by an equimolar mixture of **1a** and **1b** (polymorph **A**). Only the second one, a cyclic tetramer, shows proton transfer with an activation energy compatible with the nmr method (it is not possible to rule out a very slow proton transfer in the case of polymorph **B**).

3,5-Diphenyl-4-methylpyrazole **2**, labelled or not, never yielded convenient crystals although as many solvents as methanol, ethanol, propanol, benzyl alcohol, methylene chloride, chloroform, dimethyl sulfoxide, dimethylformamide, tetrahydrofuran, dioxane, acetone, methyl ethyl ketone, acetonitrile, benzonitrile, diethyleneglycol, acetic acid, and their mixtures were used (sublimation also failed to yield good crystals). Its ^{15}N CPMAS nmr spectrum shows broad signals at 163.5 ppm (NH) and at 247.5 ppm (-N=). Here, a variable temperature experiment was also carried out. The Arrhenius plot (Figure 4) leads to E_a = 54 kJ mol^{-1} and log A = 12.4. The similitude of values for compounds **1a/1b**, **2** and **4**, points out to similar structures, that is, **2** should also be a tetramer.

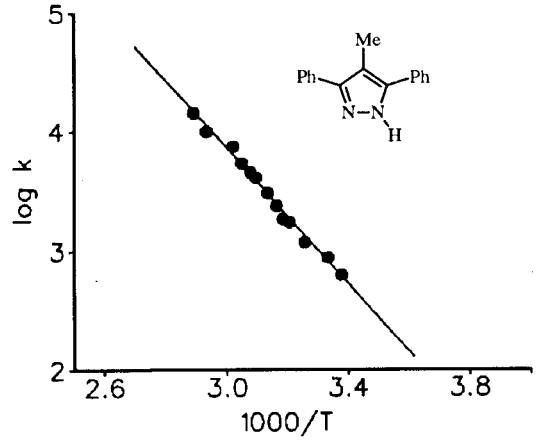


Figure 4. Arrhenius plot corresponding to 3,5-diphenyl-4-methylpyrazole **2**.

Differential Scanning Calorimetry.

The two polymorphs of **1** are formed by different tautomers: only **1a** in the crude and 2 **1a** + 2 **1b** in the crystalline variety. This special case of polymorphism, called desmotropy, was recently observed in the case of 3(5)-methyl-4-nitropyrazole where both tautomers crystallize separately depending on the solvent used for crystallization [15].

DSC experiments were carried out on three samples of 3(5)-phenyl-5(3)-methylpyrazole **1**: **A**, crystallized product (corresponding to the structure of White), **B**, crude product, and **C**, sublimed compound. Sample **1A** melts at 122.5° in the form of a unique narrow peak; sample **1B** shows three peaks (Figure 5) at 114.5°, 117.8° and 124.7°; sample **1C** behaves like **1B**. All samples, after cooling were heated again: in these conditions, three peaks were observed in all cases. Now, if the three-peak samples were cooled (three exothermic peaks near 70°) with liquid nitrogen and maintained at -196° during 5 minutes and then heated, the single peak behaviour (mp 120.2°) was always observed (an identical result was obtained if instead of cooling with liquid nitrogen, the resolidified sample was kept at room temperature for several days). In Scheme 2 the behaviour of **1A** during four cycles of heating and cooling is represented.

It is clear that the crystalline sample is a unique compound and that it is the most stable polymorph **A**. The crude compound is identical to that obtained by sublimation and represents a metastable polymorph **B**, possibly a mixture of two or three structures, all of them formed exclusively by tautomer **1a** (remember, Figure 1 bottom, that in the ^{15}N CPMAS nmr spectrum, compound **1B** presents resonance lines in a 2:1 ratio).

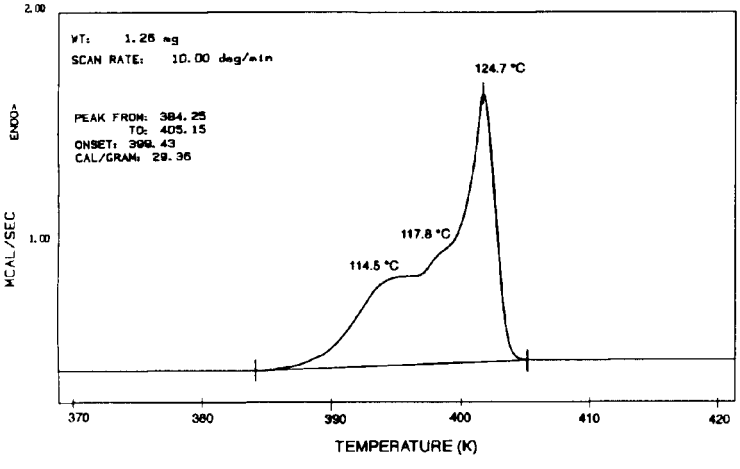
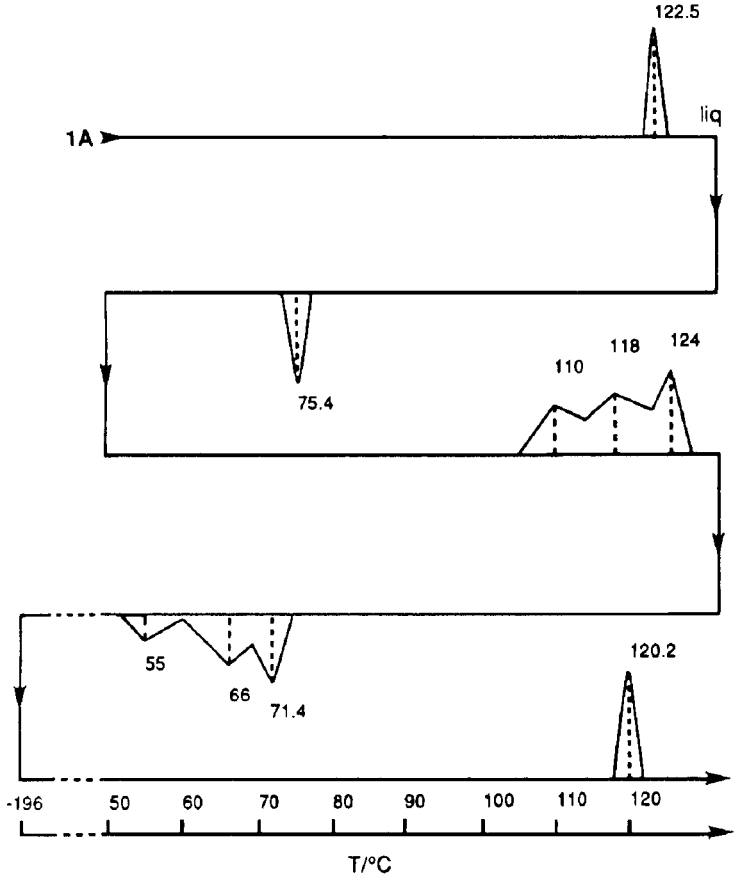


Figure 5. DSC of the polymorph **B** of 3-phenyl-5-methylpyrazole **1**.

Scheme 2



Powder Diffraction.

Since all efforts in producing single crystals of **2** failed, a microcrystalline powder diffractogram of the compound was registered. Fourteen well resolved, high relative intensity peaks were selected in order to index the diffractogram [16,17]. For this purpose, we have taken into account a density between 1.1 and 1.5 gr cm^{-3}, a unit cell volume of 18.18 $Å^3$ per molecule and Z = 2, 4, 8 or 16 molecules per unit cell. On the other hand, we have considered the analogous compound 3,5-diphenyl-4-bromopyrazole (a cyclic dimer [2]) as reference: it has a triclinic cell of dimensions about 9.91, 13.38, 9.89 Å, 102.2, 94.2 and 87.0°, 1277 $Å^3$ and Z = 4. The best solutions obtained, all of monoclinic or triclinic shapes, have similar cells to that of the reference compound and similar axes with values half or twice as compared to the dimer model. The cell giving the best refinement results is the monoclinic one, shown in Table 2.

Table 2

The Fourteen Peaks Used in the Adjustment of the Cell Parameters of Microcrystalline 3,5-Diphenyl-4-methylpyrazole **2**

2θ (obs.)°	I (rel.)	h	k	l	Δ2θ°
6.759	480	0	1	0	0.015
9.059	58	1	0	0	-0.056
9.656	113	0	0	1	0.074
11.324	39	1	1	0	-0.044
13.568	50	0	2	0	0.004
18.370	1000	2	0	-1	-0.011
19.279	250	2	1	0	0.032
20.413	203	0	3	0	0.011
20.748	209	0	1	2	-0.048
24.426	620	1	1	2	0.020
25.334	98	1	3	1	-0.025
28.075	117	3	1	0	0.021
28.675	58	1	0	-3	0.003
29.772	134	1	4	-1	0.009

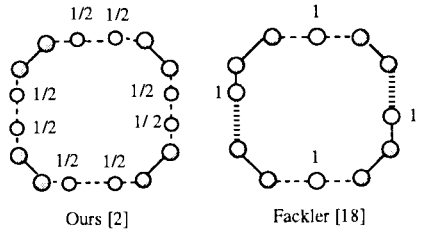
The possibility that the "proton shared" structure of compound **1** [10,11] might be due to the fact that data collection (X-ray and neutrons) was carried out at room temperature, was examined. In order to study this possibility, we carried out the following experiment. The sample was mounted on a steel pin to prevent frost and the unit cell and symmetry determined at 295 K. The crystal was then cooled to 150 K utilizing an Oxford cryostream cooler system. Several diffraction maxima of the reflections used to determine the room temperature cell, split up to four peaks. This fact gradually faded when the temperature was increased again from 150 K up to 295 K. By checking the same reflections at 200, 220, 240 and 295 K it appears that the monocrystal is transformed into a twin at low temperatures and that the process is reversible.

The geometry of White [10,11] can be discussed using Paul-Curtin diagrams [13], which are a representation of

differences in angles *vs* differences in bond lengths (multiplied by 100 to have comparable figures). A standard pyrazole geometry corresponds to $\Delta A(N) = 8.9°$, $100\Delta R(NC) = 1.9$ Å, $\Delta A(C) = 5.4°$, $100\ \Delta R(CC) = 2.8$ Å. The geometry of pyrazole **1A** has the following average values: $\Delta A(N) = 1.4°$, $100\Delta R(NC) = 0.8$ Å, $\Delta A(C) = 2.8°$, $100\ \Delta R(CC) = 2.4$ Å. These values correspond to a disordered structure for which the differences are blurred by dynamic proton disorder. Nevertheless, our results conclusively prove that White's structure, although formally correct, does not represent the reality. Pyrazole **1A** is a classical compound with dynamical disorder which should appear in crystallography as a mixture of two possible identical structures (see, Figure 2).

Under these conditions, eight "half-protons" should have been observed even if the refinement leads to a central blurred proton ("shared proton"). This is actually the case of pyrazole **4**, also a tetramer [2]. For this reason, the recent report [18] on the structure of **4** where, based on White's results [10,11], a "shared proton" is postulated (see Scheme 3) is certainly incorrect (a "shared proton" is also inconsistent with our nmr results on compound **4** [2]).

Scheme 3



Since compounds **1A** and **4** both crystallize in a tetrameric structure, any difference in their hydrogen bonds should appear in infrared spectroscopy. We have recorded the ir spectra (potassium bromide pellets) of both solid compounds. We have also prepared (by repeated dissolution in deuterium oxide and evaporation), the corresponding N-D derivatives: [^{2}H]1A and [^{2}H]4. 3(5)-Phenyl-5(3)-methylpyrazole presents the stretching NH at 3110 and 3070 cm^{-1} and the corresponding stretching N-D at 2300 and 2270 cm^{-1} (ν_{NH}/ν_{ND} ratio = 1.352); in the case of 3,5-diphenylpyrazole the corresponding four bands appear at 3065, 3000, 2240 and 2200 cm^{-1} (ν_{NH}/ν_{ND} ratio = 1.366). The theoretical ratio is 1.38 [19], thus both pyrazoles appear normal and rather similar. Finally, we can conclude that both pyrazoles have disordered but not "shared" protons.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet FT-5DX spectrophotometer. The ^{13}C CPMAS nmr spectra were recorded on a Bruker CXP 400 instrument (Madrid) working at 400 MHz (^{1}H) and 100 MHz (^{13}C). The ^{15}N CPMAS nmr spectra were recorded on a Bruker MSL 300 instrument (Berlin) working at 300.13 MHz (^{1}H) and 30.41 MHz (^{15}N). The Berlin spectrometer is equipped with a 5 mm high speed CPMAS probehead from Doty Scientific, USA. The spinning speeds were of the order of 7 to 9 kHz. Because of sample heating associated with these high speeds [20] the sample temperatures were determined by adding to the sample a small amount (0.5 - 2 mg) of the ^{15}N chemical shift thermometer TTAA enclosed in a small capsule. A Bruker B VT 1000 temperature unit was used to control the temperature of the bearing nitrogen gas stream and a home built heat exchanger to achieve low temperatures. The standard one-dimensional CPMAS pulse sequence [21] was used. General recording parameters: quadrature detection, 5 μs ^{1}H-90° pulse width, 8-15 ms CP times, 4 s recycle delay, spectral width of 15,000 Hz, line broadening of 20 Hz. Chemical shifts (ppm) were referred to solid $^{15}NH_4Cl$ as in our preceding papers [14].

Synthesis of [$^{15}N_2$]-3(5)-Phenyl-5(3)-methylpyrazole **1**.

This compound was prepared from commercially available benzoylacetone and [$^{15}N_2$]-hydrazine, following a classical procedure [22]. The ^{13}C CPMAS nmr spectra of the crude (polycrystalline) sample and of the crystalline sample (White's variety) were recorded: monocrystal (polymorph **A**, averaged signals of **1a** and **1b**): 11.7 (CH_3), 145.0 (C-CH_3) and 147.3 ppm (C-C_6H_5), polycrystal (polymorph **B**, tautomer **1a**) 8.8 (5-CH_3), 140.9 (C-CH_3) and 150.5 ppm (C-C_6H_5)

Synthesis of [$^{15}N_2$]-3,5-Diphenyl-4-methylpyrazole **2**.

This compound was prepared according to reference [23]. The main difficulty in preparing compound **2** is that the precursor, dibenzoylethane contains dibenzoylmethane as an impurity, and thus, the reaction with [$^{15}N_2$]-hydrazine yields a mixture of compounds **2** and **4**, which is very difficult to separate. To have pure dibenzoylethane [24] carefully dry solvents have to be used, because once the ammonium salt is formed it can react back to dibenzoylmethane.

DSC experiments were carried out on a Perkin-Elmer DSC-2C, connected to a Model 3600 Data Station. All the scans were made between 0-160°, interval of temperature of interest in this work. The temperature scale was calibrated by measuring the melting points of the recommended high purity standards: *n*-octadecane, gallium, benzoic acid, indium and tin. Thermograms of samples, in sealed aluminium pans, were recorded over the entire temperature range under nitrogen atmosphere at the scanning rate of 10° min^{-1} and a range of 10 mcal s^{-1}. The estimated error for temperature is ± 0.5°.

The powder diffractogram of pyrazole **2** was registered on a Philips PW1710 diffractometer between 4° and 55° in 2θ with CuK_α radiation at a speed of 0.017 2θ° per second. The low temperature experiments performed on a monocrystal of **1**, were carried out on a Philips PW 1100 four circle diffractometer.

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