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The Structure of a Non-Symmetric Disordered Tetramer: A Crystallographic and Solid State Multinuclear NMR Study of the Properties of 3(5)-Ethyl-5(3)-Phenyl-1*H*-Pyrazole

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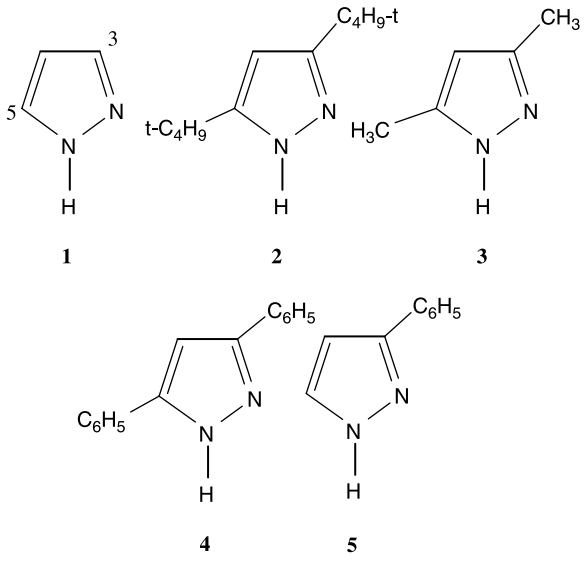
The X-ray structure and the solid-state NMR measurements, mainly ^{15}N CPMAS of the labelled compound, allow to determine the static and dynamic properties of 3(5)-ethyl-5(3)-phenyl-1*H*-pyrazole. The compound is a tetramer formed by three 5-ethyl-3-phenyl-1*H*-pyrazole and one 3-ethyl-5-phenyl-1*H*-pyrazole tautomers in dynamic equilibrium with the complementary situation.

Keywords: CPMAS NMR; Pyrazoles; Dynamic properties; X-ray structure determination

INTRODUCTION

Crystal engineering is the science of predicting the arrangement of molecules in crystals from the properties of the isolated molecule. This is known to be a very difficult problem because the potential hypersulface has many minima of similar energy. Besides methods attempting to solve this problem *ab initio* [1–4], the main avenue to crystal engineering is in the study of the weak interactions that glue together the molecules [5–8]. In this paper we will describe how hydrogen bonds, the stronger of these interactions, determine the secondary structure and the dynamic properties of a pyrazole. Thus a simple molecule will utilize several N–H···N hydrogen bonds to built up a supramolecular entity with properties that the monomer lacks.

N-Unsubstituted pyrazoles crystallise in different structural motives that determine their dynamic properties in the solid state (SSPT: solid state proton transfer) [9]. So far the following structures have been reported: long chains (catemers), for instance 1*H*-pyrazole itself **1** [10], dimers, for instance 3,5-ditert-butyl-1*H*-pyrazole **2** [10], trimers, for instance 3,5-dimethyl-1*H*-pyrazole **3** [10], tetramers, like 3,5-diphenyl-1*H*-pyrazole **4** [10], up to hexamers, the only example being that of 3-phenyl-1*H*-pyrazole **5** [11]. Other polymorphs of 3(5)-phenyl-1*H*-pyrazole are also known [12].



The necessary condition to observe SSPT is the cyclic structure of the motif, this excluding 1*H*-pyrazole **1**. However this condition is not sufficient, it is also a requisite that the structure

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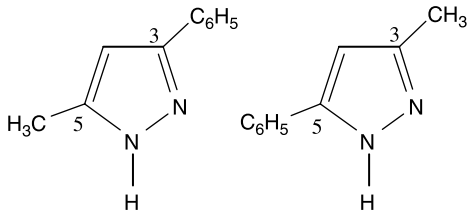
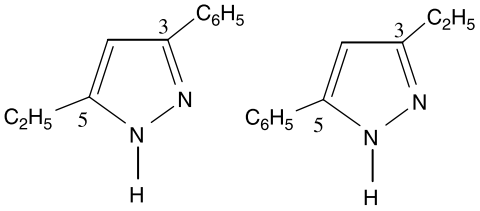
before and after the proton transfer remains the same: this is the case when both substituents at positions 3 and 5 of the pyrazole are identical (compounds **2**–**4**) [10]. If the substituents are different, but the number of pyrazoles in the cyclic structure is even (2, 4, 6), it is still possible to observe the SSPT process. Consider for instance the case of 3(5)-methyl-5(3)-phenyl-1*H*-pyrazole **6**.



6a **6b**



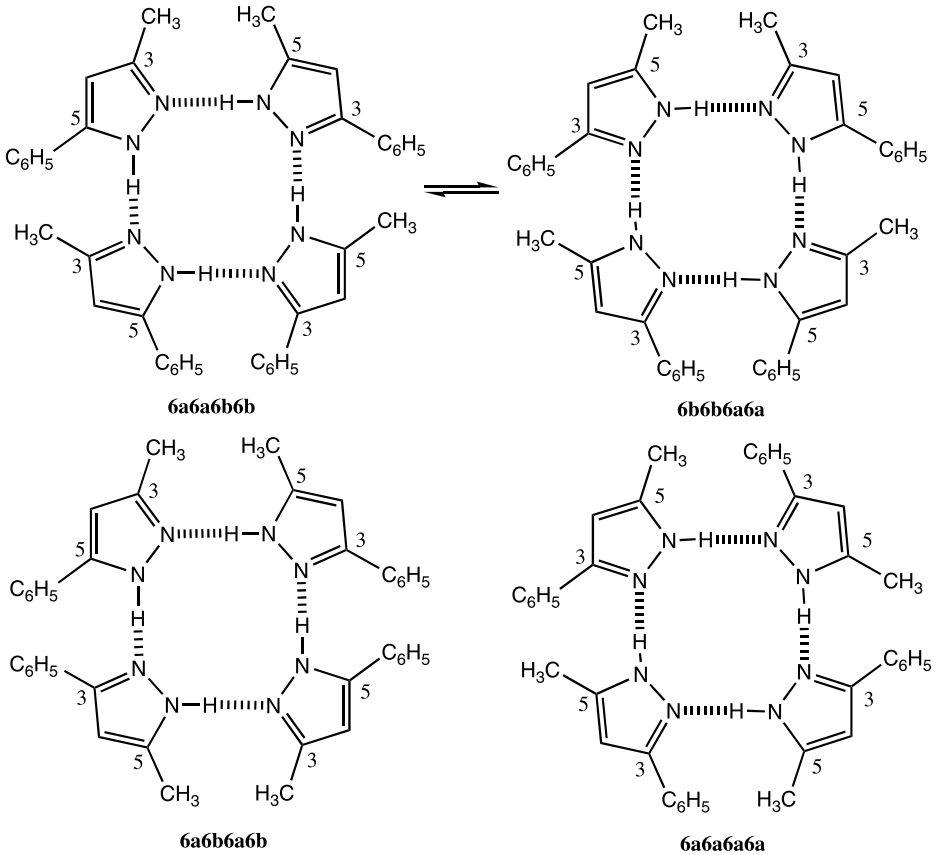
7a **7b**

The structure of **6** was solved by White *et al*. using both X-ray crystallography [13] and neutron diffraction methods [14]. The compound is a tetramer (**6a6a6b6b**, Scheme 1) formed by two tautomers 5-methyl-3-phenyl-1*H*-pyrazole **6a** and two tautomers 3-methyl-5-phenyl-1*H*-pyrazole **6b**. Since the quadruple proton transfer transforms **6a6a6b6b** into **6b6b6a6a** of the same energy in the absence of lattice effects, there is a dynamic SSPT that has been studied by solid-state CPMAS NMR [15]. Another tetramer with a 2:2 situation is possible (**6a6b6a6b**), but has not been observed. On the other hand, a polymorph **6a6a6a6a** is known [15], which does not present SSPT because it will lead to **6b6b6b6b** of higher energy. This summarises our present knowledge where **6** is concerned.

RESULTS AND DISCUSSION

Structural Study

Continuing with our systematic exploration of 3,5-disubstituted pyrazoles, we have prepared the hitherto unknown 3(5)-ethyl-5(3)-phenyl-1*H*-pyrazole **7** (yellow-reddish solid of mp: 82.5 °C, hexane) [16]. When determining its X-ray structure we have found that it is an unprecedented type of hydrogen-bonded tetramer formed by three tautomers of class **a** and one tautomer of class **b**. The average N···N



6a6a6b6b **6b6b6a6a**

6a6b6a6b **6a6a6a6a**

SCHEME 1 The 3(5)-methyl-5(3)-phenyl-1*H*-pyrazole tetramers.

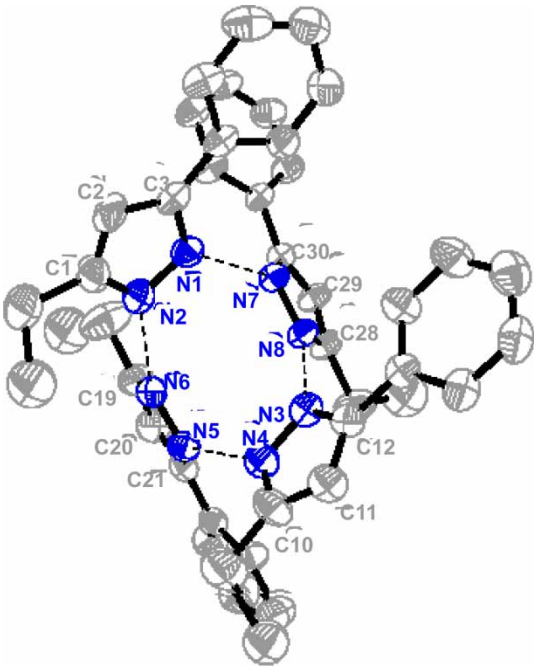


FIGURE 1 ORTEP plot of the 3(5)-ethyl-5(3)-phenyl-1*H*-pyrazole tetramer with 50% probability, N···N intermolecular bonds. Hydrogen atoms and the labelling of some atoms have been omitted for clarity.

distances are 2.87 Å (Fig. 1) very similar to that reported for **6a6a6b6b** (2.86 Å) [13,14]

The crystal packing in Fig. 2 shows the formation of a large sheet parallel to the (102) plane in which the tetramers are packed within normal van der Waals distances.

The NH protons are disordered even at low temperature, so there are two questions that could be asked. Is the disorder static or dynamic (SSPT)? What are the proportions of both tetramers **7a7a7a7b**/**7b7b7b7a** (either static mixture or dynamic equilibrium) (Scheme 2)? We have tried to answer these questions by a combination of DFT calculations, analysis of the X-ray geometries and ^{13}C and ^{15}N CPMAS NMR. For this last purpose, the [$^{15}N_2$]-labelled derivative of **7** was prepared.

Data on the Monomers

Energy calculations were carried out at the B3LYP/6-31G** and include ZPE corrections. **7a** is more stable than **7b** by 1.18 kJ mol^{-1}; this difference in energy corresponds to 62% of **7a** and 38% of **7b** at 298.15 K. Thus for the monomer m, the equilibrium constant K_m is 1.6316. If one assumes that the difference in energy between monomers is maintained in the tetramer it is easy to conclude that $K_t = K_m^2$. To $K_m = 1.6316$ corresponds to $K_t = 2.6620$, i.e. 73% of **7a7a7a7b** and 27% of **7b7b7b7a**. This is so because the **7a7a7a7b** tetramer (left) differs from the **7b7b7b7a** one (right) only in having a **7a7a** dimer instead of a **7b7b** dimer (the **7a7b** pair is common to both tetramers), thus the difference in energy should be twice the monomers **7a**–**7b** and the equilibrium constant the square ($\Delta G = -RT \ln K$).

In ^1H and ^{13}C NMR in DMSO-d_6 or in HMPA-d_{18} solution it is possible to observe the signals of the monomers, **7a** and **7b**, with proportions that slightly depends on the solvent and/or on the concentration. In the case of 0.07 M in DMSO the proportions are 67% of **7a**/33% of **7b** ($K_m = 2.0303$,). This K_m (solution) corresponds to $K_t = 4.1221$ (solid-state) (81% of **7a7a7a7b** and 19% of **7b7b7b7a**). The same situation arises in ^{15}N NMR in HMPA-d_{18}. This proves that, where tautomerism is concerned, that the situation in solution and in the solid state are similar.

Data on the Tetramers

In pyrazoles and in azoles in general, the differences between the internal NNC and NCC angles of the pentagon can be used to localise the NH proton, because the angles on N1 and C3 are larger than those on N2 and C5 [17–19]. From the theoretically optimised geometries of **7**, the differences in the angles are: 4.56° (NNC) and 5.76° (NCC) (concerning these angles **7a** and **7b** are very similar). The averaged values of the four molecules in the **7777** tetramer are: 3.2° (N) and 3.6° (C), values that can be interpolated between the calculated ones yielding 70% of NH using the NNC angles and 62% of NH using the NCC angles, that is, the NH proton is delocalised between 62% and 70% in one position (**7a7a7a7b**) and between 38% and 30% in the other (**7b7b7b7a**), in reasonable agreement with the above considerations based on the properties of the monomers.

In the ^{13}C and ^{15}N CPMAS spectra of **7**, the signals are broad at 300 K becoming narrow on cooling. For instance, the ^{13}C spectrum at 197 K corresponds to a mixture of **7a** and **7b** monomers, the first one being most abundant.

The ^{15}N CPMAS spectra at different temperatures are reported in Fig. 3, the first observation being the characteristic coalescence of a complicated dynamic NMR spectrum. As shown in Fig. 4 at 183 K, eight signals are observed, for N1 (−170.9, −172.4, −178.2, −180.6 ppm) and N2 (−94.5, −97.7, −103.2/−103.8, −104.7 ppm). Even without assigning the individual signals, the integration shows that there are 70% of **7a**-30% of **7b** (N2 region) or 68% of **7a**-32% of **7b** (N1 region). Assignment of the signals in Fig. 4 is based on the solution chemical shifts for **7a** and **7b** and is in turn founded on the fact that **7a** is more abundant than **7b** (calculations and ^1H and ^{13}C NMR data in solution). In terms of tetramers, these values correspond to 90% **7a7a7a7b**/10% **7b7b7b7a** or 86% **7a7a7a7b**/14% **7b7b7b7a**, respectively. The assignments of the 16 peaks by integration of individual signals in the N2 region of the spectrum are consistent with 88% **7a7a7a7b**/12% **7b7b7b7a**.

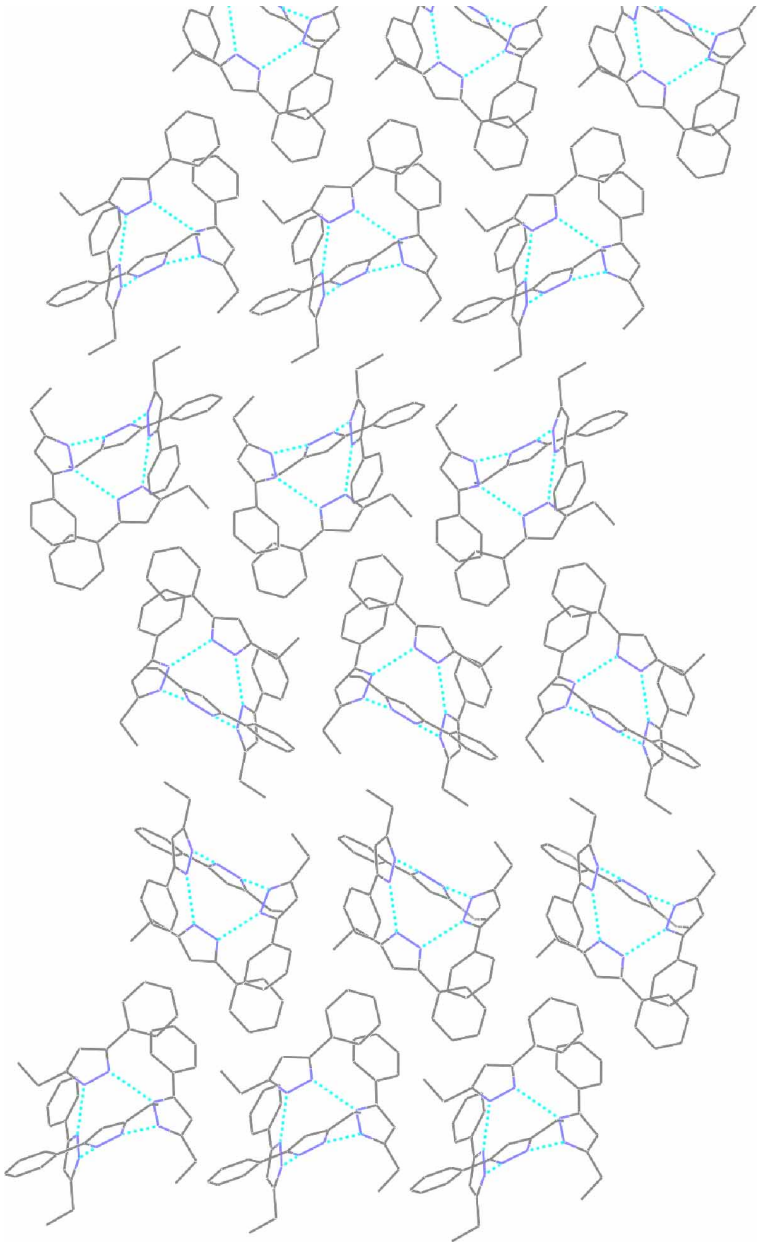
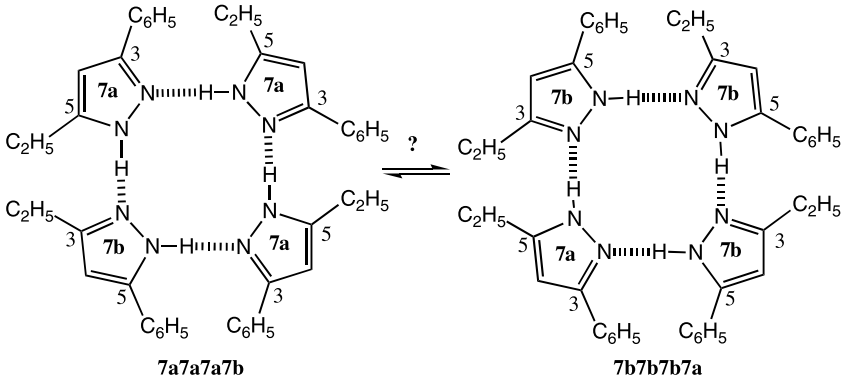


FIGURE 2 2D-network showing a sheet parrallel to 102 plane.



SCHEME 2 The 3(5)-ethyl-5(3)-phenyl-1*H*-pyrazole tetramer.

CONCLUSIONS

We have demonstrated without ambiguity that 3(5)-ethyl-5(3)-phenyl-1*H*-pyrazole **7** exists in the solid state as a dynamic equilibrium between two different tetramers **7a7a7a7b** and **7b7b7b7a**. The proportions have been determined on the ^{15}N CPMAS spectrum at 183 K, which are the most reliable, and correspond to about 88% of **7a7a7a7b**, and the existence of SSPT proved.

The different calculated percentages (in % of **7a7a7a7b**) are: 73% (from energy calculations of the monomers), 81% (from the ^{1}H NMR study of the monomers), 62-70% from the geometry of the tetramer (very sensitive to the models used), 86-90% (integration of signals in the ^{15}N CPMAS spectrum at 183 K), and 88% (integration of individual signals in the same spectrum).

The discovery that a minor change (replacing a methyl by an ethyl group) modifies the tautomeric structure of a pyrazole in the solid state (although both are tetramers) cannot be explained by energetic considerations but it is probably related to an increase in the size of the substituent (the ethyl being more similar to the phenyl ring than a methyl).

EXPERIMENTAL

NMR Experiments and Data

Solution

NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 40.56 MHz for ^{15}N) spectrometer with a 5 mm inverse-detection H-X probe equipped with a z-gradient coil, at 300 K. Chemical shifts (δ in ppm) are given from internal solvent, DMSO-d_6 2.49 for ^{1}H and 39.5 for ^{13}C, HMPA-d_{18} 2.51 for ^{1}H and 35.8 for ^{13}C and for ^{15}N NMR nitromethane (0.00) were used as external standard. Typical parameters for ^{1}H NMR spectra were spectral width 5631 Hz, pulse width 7.5 μs at an attenuation level of 0 dB and resolution 0.34 Hz per point. Typical parameters for ^{13}C NMR spectra were spectral width 20575 Hz, pulse width 10.6 μs at an attenuation level of -6 dB, relaxation delay 2 s,

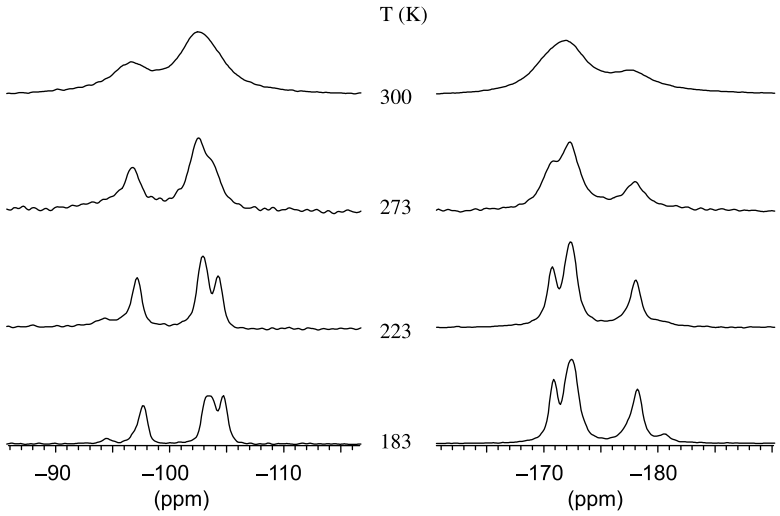


FIGURE 3 ^{15}N CPMAS NMR spectra as a function of temperature.

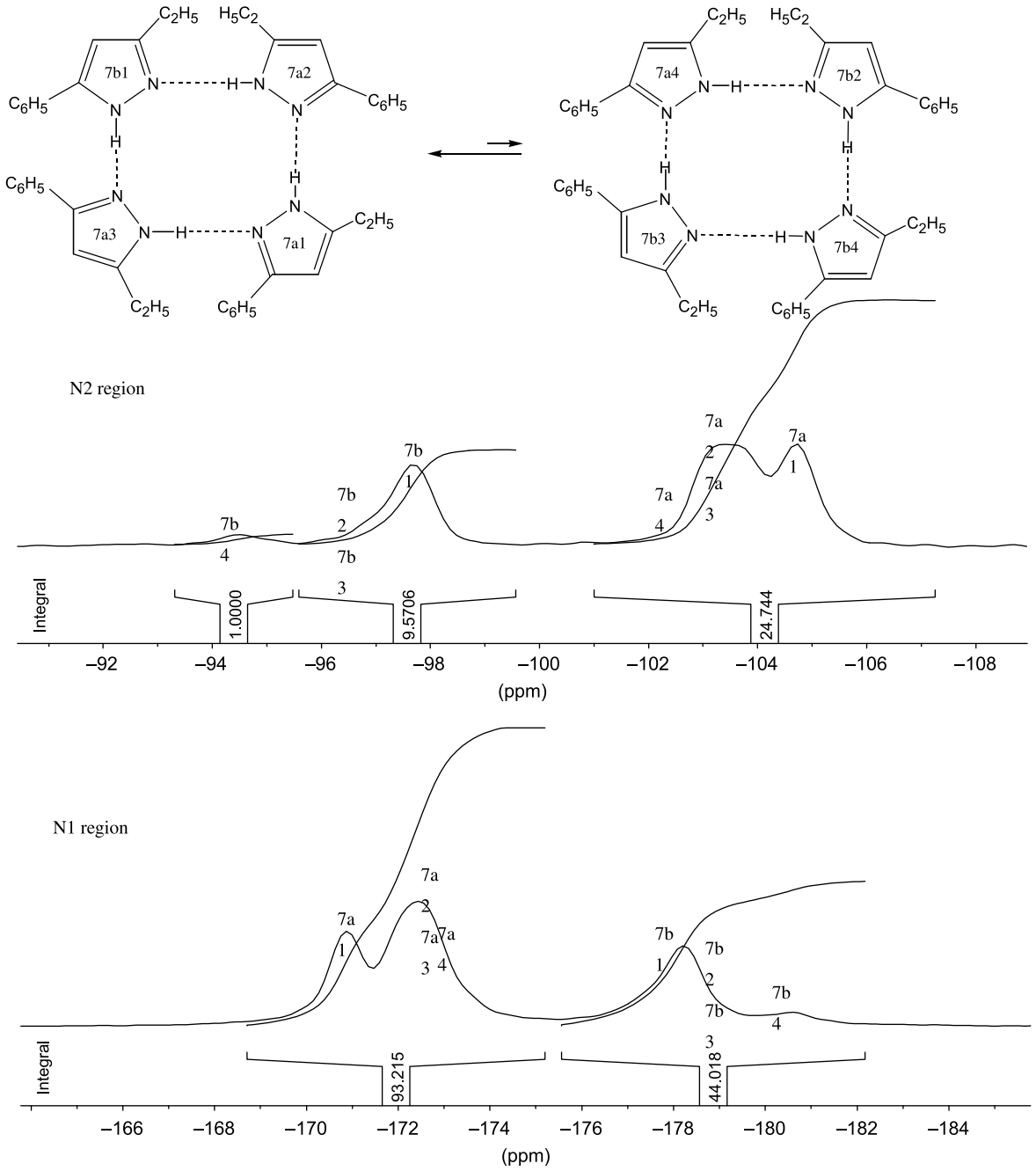


FIGURE 4 ^{15}N CPMAS NMR spectra at 183 K with assignment of the signals to tetramers **7a7a7a7b** and **7b7b7b7a**.

resolution 0.63 Hz per point; WALTZ-16 was used for broadband proton decoupling; the FIDS were multiplied by an exponential weighting (lb = 1 Hz for HMPA-d_{18} and 20 for DMSO-d_6) before Fourier transformation. 2D inverse proton detected heteronuclear shift correlation spectra, gs-HMQC (^{1}H-^{13}C) and gs-HMBC (^{1}H-^{13}C) were acquired and processed using standard Bruker NMR software. Selected parameters for (^{1}H-^{13}C) gs-HMQC and gs-HMBC spectra were spectral width 5631 Hz for ^{1}H and 20.6 kHz for ^{13}C, 1024 × 128 data set, number of scans 4 and relaxation delay 1s. The FIDs were processed using zero filling in the *F*1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation. In the gs-HMQC experiments GARP modulation of ^{13}C was used for decoupling. ^{15}N NMR was acquired using 1D sequence with inverse gated decoupling and typical parameters were spectral width 14368 Hz, pulse width 28.5 μs at an attenuation level of -3 dB, relaxation delay 30 s, resolution 0.44 Hz per point; WALTZ-16 was used for proton decoupling; the FIDS were multiplied by an exponential weighting (lb = 10) before Fourier transformation.

Solid State

^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra have been obtained on a Bruker WB 400 spectrometer using a 4 mm DVT probehead. Samples were carefully packed in a 4-mm diameter cylindrical zirconia rotors with Kel-F caps. Operating conditions involved 3.2 μs 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me_4Si (for the carbonyl atom δ (glycine) = 176.1 ppm) and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ ^{15}N(nitromethane) = δ ^{15}N(ammonium chloride) − 338.1 ppm. The typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 30 s; acquisition time, 30 ms; contact time, 2 ms; and spin rate, 12 kHz. In order to distinguish protonated and unprotonated carbon atoms, the NQS (Non-Quaternary Suppression) experiment by conventional cross-polarization was recorded; before the acquisition the decoupler is switched off for a very short time of 25 μs. And for ^{15}N CPMAS were: spectral width, 40 kHz; recycle delay, 30 s; acquisition time, 35 ms; contact time, 6 ms; and spin rate, 6 kHz. Variable temperature: a Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream an a exchanger to achive low temperatures. To avoid problems at low temperatures caused by air moisture, pure nitrogen was used as bearing, driving and cooling gas. To low temperature experiments we used zirconia caps.

Synthesis

3(5)-Ethyl-5(3)-phenyl-1H-pyrazole (7)

To a stirred suspension of 1-phenyl-1,3-pentanedione [20] (352 mg, 2 mmol) in EtOH (10 mL) an excess of 98% hydrazine monohydrate (153 mg, 3 mmol) was added dropwise. The mixture was heated at reflux for 4 h and then stirred for additional 12 h at room temperature. The solvent was removed under vacuum and the pale orange solid residue was purified by column chromatography (60 F_{254} silica gel, dichloromethane/ethanol 98:2). R*f* = 0.18, mp 82.5 °C. Yield: 290 mg, 84%. Anal. Calc. For $C_{11}H_{12}N_2$ (%): C, 76.71, H 7.02, N 16.27. Found: C, 76.45; H, 7.03; N, 16.23. ES-MS (m/z, %): 172, 100 $(M)^+$. ^{1}H NMR (0.07 M in DMSO-d_6): 1.20 (t, ^{3}J = 7.7 Hz, CH_3), 2.60 (q, ^{3}J = 7.7 Hz, CH_2), 7.24 (t, ^{3}J = ^{3}J = 7.1, H_p), 7.36 (m, H_m), 7.73 (m, H_o), 6.44 (s, H4), 12.53 (bs, NH **7a**), 12.82 (bs, NH **7b**). ^{1}H NMR (0.3 M in HMPA-d_{18}): 1.26 (bs, CH_3), 2.68 (bs, CH_2), 7.21 (bs, H_p), 7.33 (bs, H_m), 7.83 (bs, H_o, **7a**), 7.93 (bs, H_o, **7b**), 6.42 (bs, H4), 13.46 (bs, NH **7a**), 13.72 (bs, NH **7b**). ^{13}C NMR (0.07 M in DMSO-d_6): 13.6 (CH_3), 18.4 (CH_2, **7a**), 20.9 (CH_2, **7b**), 127.1 (C_p), 128.5 (C_m), 124.9 (C_o), 134.1 (C*i*), 150.2 (C3, **7a**), 153.9 (C3, **7b**), 99.6 (C4), 145.9 (C5, **7a**), 142.4 (C5, **7b**). ^{13}C NMR (0.3 M in HMPA-d_{18}): 14.2 (CH_3), 19.1 (CH_2, **7a**), 21.9 (CH_2, **7b**), 126.7 (C_p, **7a**), 127.3 (C_p, **7b**), 128.4 (C_m, **7a**), 128.7 (C_m, **7b**), 125.3 (C_o), 135.6 (C*i*, **7a**), 131.1 (C*i*, **7b**) 150.4 (C3, **7a**), 153.7 (C3, **7b**), 99.1 (C4, **7a**), 100.0 (C4, **7b**), 145.8 (C5, **7a**), 142.7 (C5, **7b**). ^{13}C CPMAS NMR at 197 K (relative intensity): CH_3 12.6 (25%), 14.3 (75%), CH_2 18.3 (50%), 19.3 (25%), 20.3 (25%), C_p 126.3 (50%), 126.8 (50%), C_m 128.6 (66%), 129.7 (33%), C_o 124.9 (33%), 124.4 (33%), 123.5 (33%), C_i 132.8 (100%), C3 150.1 (25%), 151.7 (50%), 153.6 (25%), C4 98.1 (25%), 99.7 (25%), 101.3 (25%), 101.8 (25%), C5 141.9 (25%), 145.3 (25%), 146.5 (25%), 147.8 (25%).

3(5)-Ethyl-5(3)-phenyl-1H-[$^{15}N_2$]-pyrazole ($^{15}N_2$-7)

To a stirred suspension of 1-phenyl-1,3-pentanedione (352 mg, 2 mmol) in EtOH (10 mL), was carefully added a solution of labeled $^{15}N_2$-hydrazine sulphate (264 mg, 2 mmol) dissolved in 2.4 mL of 10% aq NaOH and the mixture heated at reflux for 4 h. Stirring was continued for 12 h at room temperature. The aqueous layer was extracted four times with diethyl ether (20 mL) and the organic layer washed with a saturated solution of NaCl (100 mL) dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to give a solid product that was purified by column chromatography (60 F_{254} silica gel, dichlromethane/ethanol 98:2). Yield: 182 mg, 52%. ^{15}N NMR (0.3 M in HMPA-d_{18}): −73.8 (N1, **7a**), −182.1 (N1, **7b**), −87.7 (N2, **7a**), −81.8 (N2, **7b**).

X-ray Crystallography

Crystal data: $(C_{11}H_{12}N_2)_4$, colourless prisms of dimensions 0.26 × 0.24 × 0.20 mm^3, monoclinic, $P2_1/c$, a = 15.469(2), b = 9.7645(9), c = 26.930(3)Å, β = 93.352(2)°, V = 4060.8(7)$Å^3$, T = 296 K, ρ_{calcd} = 1.127 g cm^{-3}, Z = 4, μ = 0.068 mm^{-1}, F(000) = 1472, 20526 measured, 7150 independent reflections (Rint = 0.0627), were collected on a SMART CCD-BRUKER diffractometer. The structure was solved by direct methods and refined by full-matrix least squares on F^2 (SHELXTL Ver. 5.10). Significant no resolvable disorder was observed in the ethyl group. All non hydrogen atoms were refined anisotropically except for the ethyl carbon atoms which were isotropically refined using restrained C-C distances. Because it was not possible to locate in a difference Fourier synthesis the hydrogen atoms bonded to nitrogen atoms, all hydrogen atoms were included in calculated positions and refined riding on the respective carbon or nitrogen atoms. Final R indices [$I > 2\sigma(I)$] were R_1 = 0.107 for 2039 observed reflections for 450 parameters and 8 restrains and Rw_2 = 0.394. Due to the poor refinement a new set

of data was collected at low temperature (210 K), but subsequent refinement worsened giving rise to poorer agreement factors suggesting that a no resolvable disorder, of positional rather than thermal nature was observed. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-266670. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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