

## Structure of 3(5)-Methyl-4-nitropyrazole in the Solid State: Tautomerism, Crystallography and the Problem of Desmotropy

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The first example of desmotropy in azoles has been found concerning 3-methyl-4-nitropyrazole and its tautomer, 5-methyl-4-nitropyrazole: the crystal and molecular structure of both tautomers has been determined by X-ray analysis, <sup>13</sup>C CPMAS NMR spectroscopy has been used for studying the isomerization processes in the solid state.

The relationship between crystallography and tautomerism is quite complex; the three following situations have been found (i) first, more than 99% of the cases correspond to 'only one tautomer is present in the solid state' (in some cases, probably with the same frequency as in other crystals, polymorphism is observed).<sup>1</sup> The two remaining and rare cases are (ii) two tautomers in an exact 1:1 ratio are found in the crystal<sup>2,3</sup> and (iii) two tautomers crystallize in two different crystals. This last case, called desmotropy, is very rare, some examples are doubtful,<sup>4</sup> others correspond to a tautomer and the hydrate of the other (e.g. benzotriazole *N*-oxide and 1-hydroxybenzotriazole, this case being not a clean example of desmotropy).<sup>5</sup> Concerning the very significant case of annular tautomerism of pyrazoles (prototropy involving only ring N-H atoms),<sup>6</sup> all the published crystal structures<sup>7</sup> belong to the general case (i), the only exception being that both tautomers of 3(5)-methylpyrazole **1a** and **1b** exist as guests in an inclusion compound [case (ii)].<sup>8</sup> There is no known example of desmotropy in azoles. Herein we describe the first example of such behavior in the case of 3(5)-methyl-4-nitropyrazole **2**.

When the solid-state <sup>13</sup>C CPMAS NMR spectrum of 3(5)-methyl-4-nitropyrazole **2** was recorded,<sup>9,10</sup> the signals were assigned to the 5-methyl tautomer **2b**. In particular, the compound presents a signal at  $\delta$  11.2 which can only be a 5-methyl group (the *C*-methyl groups of 1,3-dimethyl-4-nitropyrazole **3** and 1,5-dimethyl-4-nitropyrazole **4** resonate at  $\delta$  12.9 and 11.2 respectively). Nevertheless, in order to have an absolute proof of its tautomerism in the solid state, we decided to determine its crystal structure.

Compound **2** was prepared according to Knorr<sup>11</sup> by nitration of **1**, it melts at 125 °C after crystallization in 95% ethanol.<sup>12</sup> Our 1966 sample was used to determine its tautomeric structure by <sup>13</sup>C CPMAS NMR in 1988.<sup>9</sup>

Suitable colourless single crystals of **2a** and **2b** were obtained from chloroform-cyclohexane and ethanol-water, respectively and showed slightly different crystal habits (square and rectangular plates respectively) and quite different unit-cell dimensions and symmetries.<sup>†</sup> There are no significant differences in the molecular structures of the four (**2a**) and three (**2b**) crystallographically independent molecules in the asymmetric unit as tested by half-normal probability plots.<sup>19</sup> The only remarkable differences between both tautomers are the angles at C(3) and C(5) [108.4(2),

107.5(2)° for **2a**; 103.9(3), 107.5(4)° for **2b**, on average]. The presence of the Me and NO<sub>2</sub> substituents closes and opens, respectively, the ring angles compared with the pyrazole geometry [angles at N(1), N(2),... 112.4(4), 103.8(4), 112.3(5), 105.0(5) and 106.6(5)°],<sup>17</sup> in agreement with the deformations produced by these groups in the benzene ring.<sup>20</sup>

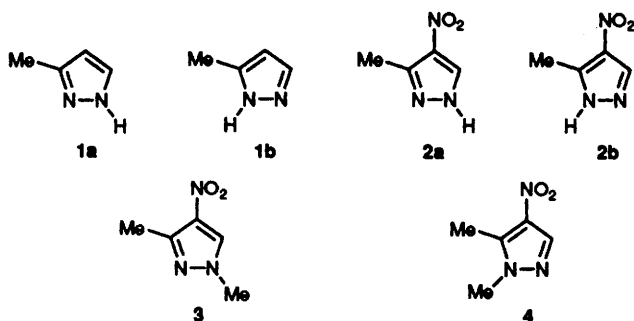
To discuss the geometry of pyrazole rings it is useful to calculate the difference of the angles at the nitrogen atoms,  $\Delta^\circ(\text{N}) = [\text{N}(2)-\text{N}(1)-\text{C}(5)] - [\text{N}(1)-\text{N}(2)-\text{C}(3)]$ , and the difference of CN bonds lengths,  $10^2 \Delta r(\text{NC}) = ([\text{N}(1)-\text{C}(5)] - [\text{N}(2)-\text{C}(3)])$ . Using these coordinates, the structures of pyrazoles were analysed.<sup>7</sup> For NH-pyrazoles, the following averaged values were found:  $\Delta^\circ(\text{N}) = 8.9^\circ$  (from 7.0 to 11.3°) and  $10^2 \Delta r(\text{NC}) = 1.9 \text{ \AA}$  (from -0.1 to 4.6);  $\Delta^\circ(\text{N})/10^2 \Delta r(\text{NC}) = 7.4^\circ/0.0 \text{ \AA}$  and  $8.8^\circ/2.1 \text{ \AA}$  for **2a** and **2b** respectively. Thus, **2b** has a typical NH-pyrazole geometry while **2a**, although clearly more distorted, still has values inside the observed ranges.

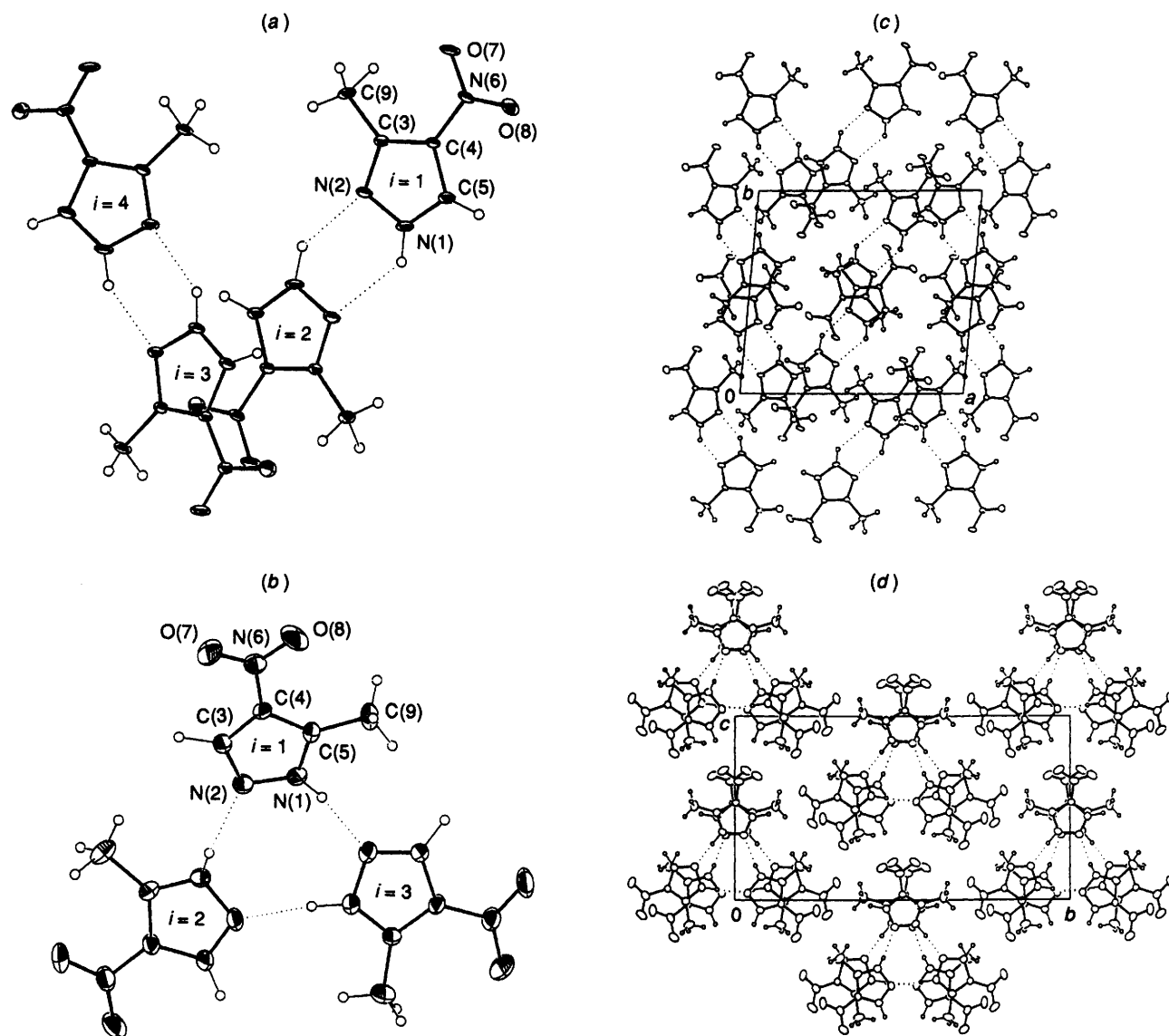
None of the pyrazole rings deviate significantly from planarity, the nitro group being almost coplanar with the ring.<sup>‡</sup>

The four independent molecules in **2a** form two pairs of hydrogen-bonded dimers almost related by a pseudo-twofold axis, Fig. 1(a).<sup>21</sup> The dimers are mainly packed through weak hydrogen interactions of two types: (a) N-H/C-H...O<sub>2</sub>N-, (b) C-H...electronic  $\pi$  cloud of pyrazole and some stacking of the heterocyclic rings, Fig. 1(c). In **2b**, the three independent molecules are connected in trimers through hydrogen bonds, Fig. 1(b). The three-dimensional structure is formed by piles of stacked trimers related by the a glide plane (the corresponding spacing is approximately half the *a* axis) packed by weak C-H...O<sub>2</sub>H- hydrogen interactions, Fig. 1(d). The trimer conformation, considering the six nitrogen atoms, is a slightly distorted boat as measured by the ring puckering parameters [ $\phi_2 = 5.7(16)$ ,  $\theta_2 = 92.7(16)^\circ$  vs. 0, 90° and  $q_2 = 0.298(8)$ ,  $q_3 = -0.014(8) \text{ \AA}$ ].<sup>22</sup>

In view of these results, the <sup>13</sup>C CPMAS NMR spectra of both samples were recorded (see Table 1, in solution both samples yield identical spectra).<sup>§</sup>

Some signals appear at identical or nearly identical positions in the solid-state spectrum of the NH-tautomer and in the solution spectrum of the corresponding *N*-methyl derivative (**2a** vs. **3**, **2b** vs. **4**). Others show differences of 2–3 ppm. Nevertheless, it is clear that solid-state <sup>13</sup>C NMR spectroscopy can be used to identify the tautomeric structure of compound **2** (not so the melting points, since those of both tautomers coincide).<sup>¶</sup> Using this technique, the following observations were made: (i) when the Knorr nitration procedure is followed,<sup>11</sup> the compound which precipitates by addition of water is tautomer **2a**. (ii) This 'crude' compound yields each tautomer depending on the solvent used for the crystallization. (iii) Each tautomer is transformed into the other by crystallization in the appropriate solvent. Thus **2a** crystallized in ethanol-water yields **2b** and this tautomer, in turn, is converted into **2a** by crystallization in chloroform-cyclohexane. (iv) Tautomer **2a** is indefinitely stable but tautomer **2b**, in the solid state, is transformed into tautomer **2a** on standing.





**Fig. 1** (a) Crystallographically independent molecules of **2a** showing 30% probability ellipsoids for the non-hydrogen atoms. Interactions for hydrogen-bonding systems lengths (Å) angles (°). N(11)–H(11)⋯N(22) 0.85(5), 2.919(4), 2.28(5), 132(3); N(21)–H(21)⋯N(12) 0.89(5), 2.921(4), 2.20(4), 138(5); N(31)–H(31)⋯N(42) 0.90(5), 2.931(4), 2.24(4), 134(3); N(41)–H(41)⋯N(32) 0.85(5), 2.903(4), 2.24(5), 135(4). (b) As for (a) for **2b**. N(11)–H(11)⋯N(32) 1.00(8), 2.875(7), 1.90(8), 163(8); N(21)–H(21)⋯N(12) 0.88(7), 2.872(9), 2.04(8), 157(7); N(31)–H(31)⋯N(22) 1.00(9), 2.900(7), 1.93(9), 162(10). (c) Crystal packing of **2a**, view down the *c* axis. (d) Crystal packing of **2b** view down the *a* axis.

**Table 1**  $^{13}\text{C}$  NMR chemical shifts of compound **2**

NMR conditions	Sample	C <sub>3</sub>	C <sub>4</sub>	C <sub>5</sub>	Me
[ $^2\text{H}_6$ ]dmsO	<b>2</b>	141.7(CMe)	132.4	134.6(CH)	11.6
Solid <b>2a</b>	$\text{CHCl}_3\text{-C}_6\text{H}_{12}$	147.2(CMe)	132.1	132.1(CH)	12.9
Solid <b>2b</b>	$\text{EtOH-H}_2\text{O}$	137.2(CH)	132.4	142.6(CMe)	11.2
[ $^2\text{H}_6$ ]dmsO	<b>3</b>	144.9(CMe)	132.1	132.1(CH)	12.9
[ $^2\text{H}_6$ ]dmsO	<b>4</b>	135.4(CH)	132.4	139.9(CMe)	11.2

The transformation took 6 d, and the  $^{13}\text{C}$  CPMAS spectra at intermediate times show both tautomers to be present. (v) The fact that **2a** is more stable than **2b** is not an intrinsic property, since theoretical calculations at the HF/6-31G\*\* level of accuracy,<sup>24</sup> with complete optimization of the geometry (*C<sub>s</sub>* point-group symmetry was assumed, the nitro group being coplanar with the pyrazole ring)|| lead to the following values (in Hartrees): **2a** –467.3183, **2b** –467.3196, the 5-methyl tautomer being more stable than the 3-methyl one by 0.8 kcal mol<sup>-1</sup>. A possible explanation involves crystal packing energies, as the higher density of the dimeric structure **2a** compared with **2b** seems to suggest.

This work was supported by the Dirección General de Investigación Científica y Técnica, Project Nos. PB90-0070 and PB90-0226-C02.

Received, 12th October 1993; Com. 3/06098E

#### Footnotes

† Crystal data for **2a**:  $\text{C}_4\text{H}_5\text{N}_3\text{O}_2$ , triclinic,  $P\bar{1}$ ,  $a = 12.7068(6)$ ,  $b = 11.5857(14)$ ,  $c = 7.6762(15)$  Å,  $\alpha = 99.863(10)$ ,  $\beta = 93.992(9)$ ,  $\gamma =$

84.123(8)°,  $V = 1105.9(3) \text{ \AA}^3$ ,  $D_c = 1.527 \text{ g cm}^{-3}$ ,  $Z = 8$ ,  $\mu = 10.30 \text{ cm}^{-1}$ , crystal dimensions  $0.33 \times 0.33 \times 0.07 \text{ mm}$ , 3627 independent reflections.  $R(R_w) = 0.049(0.058)$  for 2326 [ $I > 3\sigma(I)$ ] observed reflections. Max. final  $\Delta F$  peak  $0.27 \text{ e \AA}^{-3}$ . One reflection affected by secondary extinction was omitted in the last cycles of refinement.

**Crystal data for 2b:**  $\text{C}_4\text{H}_5\text{N}_3\text{O}_2$ , monoclinic,  $Ia$ ,  $a = 7.1127(4)$ ,  $b = 21.2843(15)$ ,  $c = 11.8897(7) \text{ \AA}$ ,  $\beta = 104.997(7)^\circ$ ,  $V = 1738.7(2) \text{ \AA}^3$ ,  $D_c = 1.457 \text{ g cm}^{-3}$ ,  $Z = 12$ ,  $\mu = 9.83 \text{ cm}^{-1}$ , crystal dimensions  $0.33 \times 0.17 \times 0.07 \text{ mm}$ , 1437 independent reflections.  $R(R_w) = 0.053(0.056)$  for 1080 [ $I > 3\sigma(I)$ ] observed reflections. Max. final  $\Delta F$  peak  $0.24 \text{ e \AA}^{-3}$ .

In spite of the number of independent molecules in the asymmetric unit (4 and 3 for **2a** and **2b** respectively) no cell reductions were possible.<sup>13</sup> Nevertheless, quite often the pyrazole derivatives<sup>14–16</sup> and the pyrazole itself<sup>17</sup> crystallizes with several molecules in the asymmetric unit. Seifert XRD3000-S diffractometer, Cu-K $\alpha$  radiation, graphite monochromator,  $\omega/2\theta$  scan,  $\theta_{\text{max}} = 65^\circ$ , XRAY80 computer program. Direct methods applied to difference structure factors (DIRDIF).<sup>18</sup> Refinement on  $F_o$  with full matrix. Anisotropic thermal model for the non-hydrogen atoms while H atoms, obtained unambiguously from difference Fourier synthesis were refined isotropically. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ A table of experimental and theoretically selected geometric parameters ( $\text{\AA}$ ,  $^\circ$ ) for **2a** and **2b** has been deposited at CCDC.

§ The  $^{13}\text{C}$  CPDAS NMR spectra were recorded on a Bruker AC-200 (UNED) using the same conditions that those already described.<sup>23</sup>

¶ Before crystallization the compound melts at  $134\text{--}135^\circ\text{C}$ ; crystallized in ethanol–water it melts at  $131\text{--}135^\circ\text{C}$  and crystallized in chloroform–cyclohexane it has a m.p.  $130\text{--}133^\circ\text{C}$ .

|| Theoretical geometries are in fairly good agreement with the experimental ones. The largest discrepancies concern the angle at C(4) (which bears the nitro group) and the double-bond/single-bond length alternance, which appears exaggerated in the calculated geometries.

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