# Structures of NH-pyrazoles bearing only *C*-methyl substituents: 4-methylpyrazole is a hydrogen-bonded trimer in the solid (100 K)

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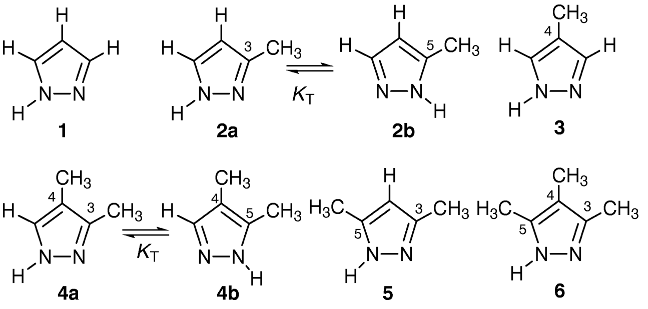
The X-ray molecular structure of 4-methylpyrazole (**3**) at 100 K has been determined. The compound crystallizes as a trimer with the N—H protons localized. 4-Methylpyrazole belongs to the series of eight NH-pyrazoles bearing only H and $CH_3$ substituents on the carbon atoms. There are two pairs of tautomers so the number of pyrazoles existing in solution is only six. The thermal behavior of the six pyrazoles was investigated by differential scanning calorimetry and their melting points analyzed on the basis of their solid state structures and number and position of *C*-methyl substituents.

There are six N*H*-pyrazoles that bear only C—H and C—$CH_3$ groups: pyrazole (**1**), 3(5)-methylpyrazole (**2**), 4-methylpyrazole (**3**), 3(5),4-dimethylpyrazole (**4**), 3,5-dimethylpyrazole (**5**) and 3,4,5-trimethylpyrazole (**6**); **2** and **4** exist as mixtures of tautomers in solution. Of these compounds, only **2** and **3** are reported as being liquids or low melting point solids at room temperature, in spite of both compounds having higher molecular weights than the parent pyrazole **1**. We were intrigued to know what the reason might be. *N*-Methyl-substituted pyrazoles are often liquids at room temperature, indicating that N—H···H hydrogen bonding in the solid makes an important contribution to raising the melting point, but there may be other factors. Present knowledge about the solid state crystal structures and melting points of the six compounds are summarized in Table 1.



As far as the solid state structures are concerned, the parent molecule, pyrazole (**1**), is found to be a catemer in the solid. Its molecules are hydrogen-bonded together to form infinite helical chains in the shape of a figure 8. Neutron diffraction studies reveal that no proton disorder is present. Of the remaining compounds, 3(5),4-dimethylpyrazole (**4**) and 3,5-dimethylpyrazole (**5**) are found to be trimers in the solid state, whereas 3,4,5-trimethylpyrazole (**6**) is a catemer like pyrazole itself. Moreover, **4** only exists as the **4b** tautomer and **5** is found to exhibit proton disorder. $^{13}C$ and $^{15}N$ CPMAS experiments show conclusively that the latter is of a dynamic nature.[12] Similar experiments have demonstrated that neither pyrazole itself (**1**)[13] nor 3,4,5-trimethylpyrazole (**6**) show any kind of dynamic behavior.[14]

As can be seen from Table 1, there is no information about

**Table 1** Structural data concerning the NH-pyrazoles **1**–**6**

| Pyrazole | Type of structure | Proton disorder | References (X-ray) | M.p./°C | References (m.p.) |
|---|---|---|---|---|---|
| **1** | Catemer | No | 1 | 69–70 | 7*a* |
| | | | 2 | 70 | 8 |
| | | | 3[a] | 69–70 | 9*a* |
| | | | 4[b] | 70 | 10*a* |
| **2** | Unknown[c] | — | — | 36–37 | 7*b* |
| | | | | Liquid | 8, 10*b*, 9*b* |
| **3** | Trimer | No | This work | 15.8–18.5 | 7*c* |
| | | | | Liquid | 8, 10*c*, 9*b* |
| **4** | Trimer[d] | No | 5 | 55–58 | 7*d* |
| | | | | 58 | 8 |
| | | | | 57–58 | 10*d* |
| **5** | Trimer | Yes | 6 | 107 | 7*e*, 8 |
| **6** | Catemer | No | 7 | 137–138 | 7*f*, 8 |
| | | | | 138–139 | 10*e* |

[a] Neutron diffraction. [b] At 295 and 108 K. [c] When **2** is included in 1,1-bis(2,4-dimethylphenyl)but-2-yn-1-ol as a guest, both tautomers **2a** and **2b** are present in the crystal of the 1 : 1 : 1 complex.[11] [d] Only the 4,5-dimethyl tautomer (**4b**) is present.[5]

the crystal structures of 3(5)-methylpyrazole (**2**) and 4-methylpyrazole (**3**). Reports on their melting points are also scarce. Although most authors described them as liquids (implied, at room temperature), in an authoritative book[7] they are described as low-melting solids. Studies on the liquid state show that compound **2** is most probably a near 50 : 50 mixture of tautomers **2a** and **2b**.[15,16] In compound **3** there can be only one tautomer. The melting points of the other compounds in the series also show some unusual trends: pyrazole (**1**), with its melting point of 69–70 °C, has a higher melting point than either 3(5)-methylpyrazole (**2**), 4-methylpyrazole (**3**) or 4,5-dimethylpyrazole (**4b**) (55–58 °C). 3,5-Dimethylpyrazole (**5**), although having the same molecular weight as **4**, has a much higher melting point (107 °C). The melting point of 3,4,5-trimethylpyrazole (**6**) lies, as expected on the basis of its molecular weight, still higher (138–139 °C).

In order to shed some light on the thermal behavior of the six compounds and determine whether their melting points are in some way related to their crystal structures, we have undertaken a detailed study of their thermal properties using differential scanning calorimetry (DSC) and investigated the solid state structure of 4-methylpyrazole (**3**). 4-Methylpyrazole is, from a practical point of view, by far the most interesting of all these pyrazoles. This compound is an inhibitor of liver alcohol dehydrogenase and is in clinical use for the treatment of alcohol, methylene glycol and methanol poisoning.[17–20]

## Results and discussion

The thermal behavior of compounds **1**–**6** in the ranges reported in Table 2 was investigated using DSC, in order accurately to determine their melting points and establish the existence of possible phase changes. *It is very important that the compounds were carefully dried before recording the DSC curves.* These NH-pyrazoles are hygroscopic and small amounts of humidity considerably depress their melting points. The results obtained are summarized in Table 2.

The melting points of compounds **1**, **4**, **5** and **6** derived here agree with those in the literature (Table 1). For **3**, however, the measured value of 27.4 °C [see Fig. 1(*a*)] is not consistent with literature values, since they are given variously as corresponding to a liquid, at least in northern countries, or as a compound that melts at 16–18 °C. Presumably, the low temperature melting points observed by other workers indicate the presence of dissolved water and explains why 4-methylpyrazole is often considered to be a liquid. The DSC scan of pure 3(5)-methylpyrazole (**2**), on the other hand, simply shows a glass transition temperature at −65.7 °C [at 5 °C min$^{-1}$, see also Fig. 1(*b*)]. Experiments carried out on the compound by solid state CPMAS NMR ($^{13}$C and $^{15}$N) show that it behaves like a glass at low temperatures (145 K).[21] The inability of **2** to crystallize on cooling may in fact be due to the presence of almost equal amounts of the 3-methylpyrazole (**2a**) and 5-methylpyrazole (**2b**) tautomers[15,16] in the liquid.[22] Attempts to crystallize one or both of the tautomers from the mixture have, however, hitherto been unsuccessful, but work is still in progress.

Table 2 Summary of DSC results for the NH-pyrazoles **1**–**6**

| Pyrazole | Melting point/°C | Crystallization point/°C | Phase transition | Scan range/°C |
|---|---|---|---|---|
| **1** | 70.1 | ≈45 | None | −20/+100 |
| **2** | — | — | — | −100/+100 |
| **3** | 27.4 | ≈20 | None | −85/+75 |
| **4** | 59.3 | ≈48 | None | +20/+100 |
| **5** | 108.4 | ≈97 | None | +25/+145 |
| **6** | 140.2<br>(80.5)[a] | ≈75 | Yes | +25/+180 |

[a] Metastable modification.

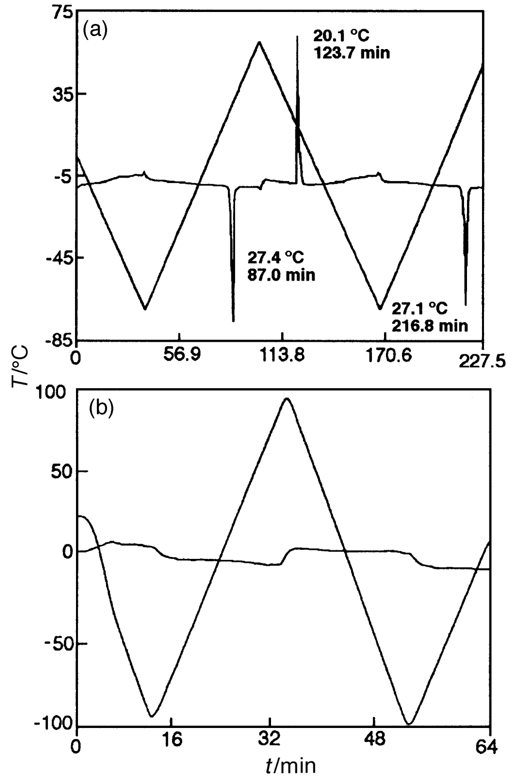


**Fig. 1** DSC records of (*a*) 4-methylpyrazole (**3**) and (*b*) 3(5)-methylpyrazole (**2**).

3,4,5-Trimethylpyrazole (**6**) is the only pyrazole that shows a phase transition in the range studied [see Fig. 2(*b*)]. Compared with 3,5-dimethylpyrazole (**5**) [Fig. 2(*a*)], which has a sharp melting point at 108.4 °C, **6** shows an endothermic phase transition at 140.2 °C (melting). On recooling, it solidifies at 74.5 °C and then melts again at 80.5 °C. The low-melting compound is probably a less stable polymorph[23] of **6**,

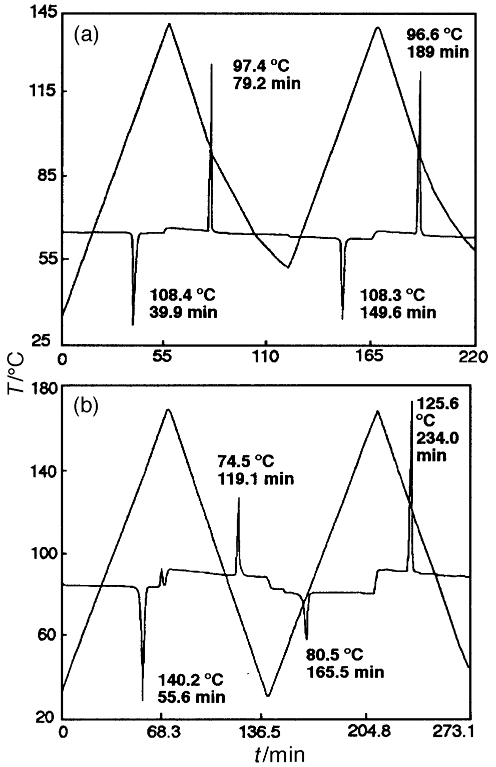


**Fig. 2** DSC records of (*a*) 3,5-dimethylpyrazole (**5**) and (*b*) 3,4,5-trimethylpyrazole (**6**).

in accordance with Ostwald's step rule.[24] We currently have no information about the structure of this polymorph. Other examples of polymorphism in NH-pyrazoles are known.[25]

Although it has not yet been possible to crystallize 3(5)-methylpyrazole (**2**), a single crystal of 4-methylpyrazole (**3**) has been successfully grown from the melt (see Experimental) and its crystal structure established.

The results of the X-ray structure determination of **3** are summarized in Fig. 3, which shows that the molecule exists as a N—H···N hydrogen-bonded trimer in the solid. There are three symmetry independent molecules in the trimer and comparable bond distances and angles within the molecules differ by less than experimental error. All hydrogen atoms could be located and their positions refined. There was no evidence of disorder of the hydrogen atoms in the structure. Indeed, in all three molecules the internal angle at the N atom carrying the H atom [average, 110.6(1) Å] is significantly larger than that at the N atom with the lone pair [average, 106.1(1) Å]. The trimer is not planar, as is observed for both 4,5-dimethylpyrazole (**4b**)[5] and 3,5-dimethylpyrazole (**5**),[6] and each molecule makes a different angle (6–12°) to the mean plane through N1, N3 and N5. This is presumably as a result of packing forces, since there is no evidence of pyramidalization of the N—H nitrogen atoms. The N—H···N distances [average, 2.88(2) Å] occur at the shorter end of the range of observed N—H···N distances and suggest a relatively strong hydrogen bond.[26]

This determination of the crystal structure of **3** brings the number of methyl-substituted pyrazoles that form trimers in the solid to three. Interestingly, this arrangement appears to be favored whatever the crystal environment. For example, in 3,5-dimethylpyrazole (**5**),[6] the trimers pack in a parallel fashion, in **3** they do not. Since the formation of a trimer rules out the possibility of the molecules forming other N—H···N hydrogen bonds in the solid, a major contribution to the difference in the melting points of the methyl-substituted pyrazoles must come from cohesive van der Waals forces. This explains the rough increase in melting point of these compounds with molecular weight, but not the almost 50 °C difference in melting points of 4,5-dimethyl-pyrazole (**4b**) and 3,5-dimethylpyrazole (**5**). Here we note that the two crystal structures are not directly comparable, since **5** exhibits proton disorder,[6] whereas **4** only exists as the **4b** tautomer.[5] Since hydrogen bonds are generally stronger and more directional than van der Waals forces, it is likely, however, that the unexpectedly high melting point of the parent compound, pyrazole (**1**), compared with the melting points of **3** and **4b**, is due to its having an extended N—H···N hydrogen-bonding pattern in the solid. Clearly, melting points cannot be derived from knowledge of the crystal and molecular structure alone. It is possible to write an empirical formula that reproduces the five known melting points based on contributions from the positions of the methyl substituents and the presence or not of trimers:

$$\text{m.p. } (^\circ\text{C}) = 70.1 + 43.6(3\text{Me}) - 5.5(4\text{Me}) + 32.0(5\text{Me}) - 37.3(\text{trimer}),$$
$$n = 5,\ r^2 = 1.000 \quad (1)$$

This equation predicts melting points of 76 °C for **2a**, 65 °C for **2b** and 71 °C for **4a**, assuming that they crystallize as trimers.

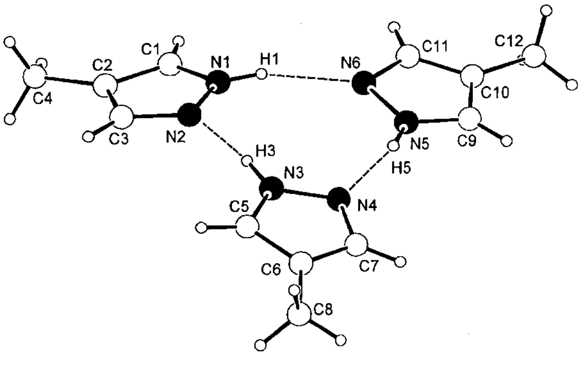


**Fig. 3** Crystal structure of 4-methylpyrazole (**3**). Selected distances (Å) and angles (°): N1—N2 1.343(2), N2···N3 2.893(2), N3—N4 1.344(2), N4···N5 2.902(2), N5—N6 1.349(2), N1···N6 2.855(2), C1—N1—N2 110.4(1), N1—N2—C3 106.0(1), C5—N3—N4 110.5(1), N3—N4—C7 105.7(1), C9—N5—N6 110.2(1), N5—N6—C11 106.4(1).

## Conclusion

Most of the *C*-methyl-substituted pyrazoles whose crystal structures have been determined to date, have been found to crystallize as trimers, indicating that the formation of trimers is a strong structure-determining factor in these compounds. The relatively low melting points of 4-methylpyrazole (**3**) and 4,5-dimethylpyrazole (**4b**) may result from the inability of these hydrogen-bonded trimers to form extended N—H···N hydrogen-bonded patterns in the solid, as is observed for pyrazole (**1**), which has a higher melting point. DSC studies reveal that **3** has a higher melting point than previously reported, 3(5)-methylpyrazole (**2**) forms a glass at low temperatures and 3,4,5-trimethylpyrazole (**6**) exhibits dimorphism. We are currently trying to obtain single crystals of one or both of the tautomers of **2** and the low temperature melting point phase of **6**.

## Experimental

DSC experiments were carried out on a SEIKO DSC 220C, connected to a Model SSC5200H Disk Station. The temperature scale was calibrated against the melting points of high purity indium and tin. Thermograms of samples, contained in hermetically sealed aluminium crucibles, were recorded over the entire temperature range (see Table 2) under nitrogen atmosphere at a scanning rate of 2 °C min$^{-1}$. The sample size was 3–10 mg.

### X-Ray analysis of 4-methylpyrazole (3)

4-Methylpyrazole (Aldrich 22,256-9) was purified by vacuum distillation. Two microliters of the compound were introduced into a 0.5 mm diameter glass capillary (glass No. 50, Hilgenberg) under argon and the capillary was sealed using a narrow $H_2$ flame. The sample was mounted on an Enraf-Nonius CAD4 diffractometer and cooled by a cold stream of $N_2$ gas. A single crystal was grown by zone crystallization directly on the diffractometer at −0.5 °C using a $CO_2$ laser to melt the sample; the melted region was drawn repeatedly from top to bottom of the capillary at a rate of 0.1 mm h$^{-1}$ until a single crystal was obtained.

**Crystal Data for 3.** $C_4H_6N_2$, $M_r$ = 82.11 g mol$^{-1}$, colorless, crystal size 0.48 × 0.48 × 0.60 mm, $a = 14.831(2)$, $b = 16.848(4)$, $c = 5.496(1)$ Å, $U = 1373.3(5)$ Å$^3$, $T = 100$ K, orthorhombic, $Pca2_1$ [No. 29], $Z = 12$, $d_{calc} = 1.19$ g cm$^{-3}$, $\mu = 0.08$ mm$^{-1}$, Enraf-Nonius CAD4 diffractometer, $\lambda = 0.710\,69$ Å, $\omega - 2\theta$ scan, 12 289 reflections, 3148 independent, 2943 observed [$I > 2\sigma(I)$], [$(\sin\theta)/\lambda]_{max} = 0.65$ Å$^{-1}$, no absorption correction, direct methods (SHELXS-97),[27] least-squares refinement[28] on $F_o^2$, C and N anisotropic, H isotropic, 235 refined parameters, $R = 0.036$ (obs. data), $R_w = 0.101$ (Chebyshev weights), final shift/error 0.001, residual electron density +0.235 e Å$^{-3}$.

A check for higher symmetry[29] revealed the presence of a possible C-centering of the unit cell (non-space-group translation 0.499, 0.510, 0.028), but many of the *hkl*: $h + k = 2n + 1$ ($n = 0, 1, 2, \ldots$) reflections have significant intensities, indicating that the chosen space group assignment is correct, which is confirmed by the subsequent successful refinement.

CCDC reference 440/086. See http://www.rsc.org/suppdata/nj/1999/237/ for crystallographic files in .cif format.

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