Intermolecular Proton Transfer in Host–Guest Crystals: the Case of Pyrazole Included in 1,1-Di(2,4-dimethylphenyl)but-2-yn-1-ol, an X-Ray and Solid-State $^{13}C/^{15}N$ NMR Study

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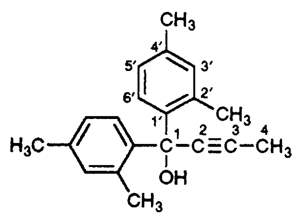
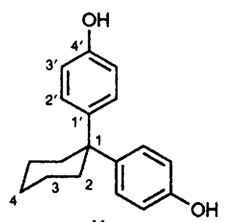
The first example of a cyclic intermolecular solid-state proton transfer involving nitrogen and oxygen atoms is described, which takes place in a cyclic 2:2 complex formed by inclusion of pyrazole in the host, 1,1-di(2,4-dimethylphenyl)but-2-yn-1-ol; the system has been studied by a combination of X-ray crystallography and dynamic high resolution solid-state $^{13}C/^{15}N$ NMR spectroscopy.

Pyrazoles unsubstituted on the nitrogen atoms[1] have two interesting properties: (*i*) they belong to the rare molecules which show intermolecular proton exchange (annular tautomerism)[2] in the solid state;[3,4] (*ii*) they are able to form inclusion compounds with suitable hosts.[5] So far, no evidence for annular tautomerism has been observed for this class of compounds.[5] We present in this paper the first example of the occurrence of both phenomena and, to the best of our knowledge, the only known example of dynamic proton exchange in an inclusion compound. A combination of X-ray crystallography and dynamic ^{13}C and ^{15}N NMR spectroscopy under the conditions of cross polarization (CP) and magic angle spinning (MAS) has been used. Two hosts were considered, 1,1-di(2,4-dimethylphenyl)but-2-yn-1-ol **H$_1$**[6] and 1,1-di(*p*-hydroxyphenyl)cyclohexane **H$_2$**,[7] and four guests, pyrazole **G$_1$**, 3-methylpyrazole **G$_2$**, 5-methylpyrazole **G$_3$** (**G$_2$** and **G$_3$** exist in solution and in the gas phase as an almost 50:50 equilibrium mixture)[8] and 3,5-dimethylpyrazole **G$_4$**.

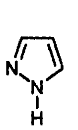
In previous studies it was shown that, depending on the C-substituents, bulk crystalline pyrazoles form catamers,



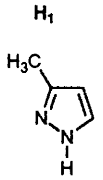
H$_1$



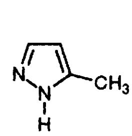
H$_2$



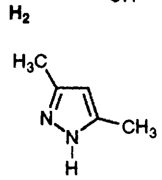
G$_1$



G$_2$

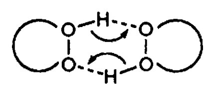


G$_3$



G$_4$

cyclic dimers, trimers (**G$_4$**) or cyclic tetramers in which degenerate double, triple or quadruple proton transfer takes place (**1**, **2** and **3**).[3,4] In the first pyrazole inclusion complex **H$_1$G$_2$G$_3$** whose structure was determined previously (Fig. 1)[5] a mixed cyclic complex **4** is formed; however, the protons were found to be localized in this compound.[5] Therefore, it was decided to prepare other clathrates and suitable crystals were obtained for **H$_1$G$_1$** and for **H$_2$G$_4$**. The ^{13}C CPMAS spectra of



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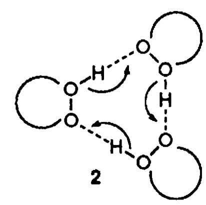

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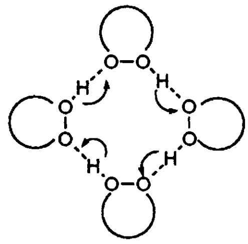

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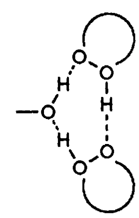

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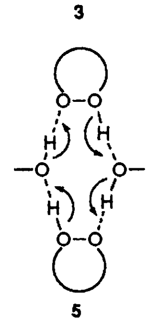

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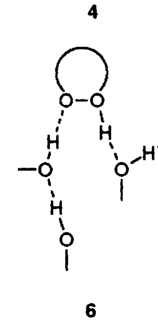

6

$\mathbf{H_2G_4}$ did not show any sign of a solid state tautomerism;†‡ by contrast, evidence for such a process was obtained from the spectra of $\mathbf{H_1G_1}$.§

In order to understand these results, the structures of both compounds were determined (Figs. 2 and 3).¶ The host $\mathbf{H_2}$ has two OH-groups and forms with $\mathbf{G_4}$ a two-dimensional hydrogen bonded $(\mathbf{H_2G_4})_n$ network according to model **6**, where the protons are localized. The guest molecules join together these chains *via* OH···N and NH···O bonds [Fig. 3(*b*)] in a similar way as has been observed when phenols are the guests of $\mathbf{H_2}$.[7] The structure of pyrazole $\mathbf{G_1}$ included into the tertiary alcohol $\mathbf{H_1}$ corresponds to a cyclic dimer $(\mathbf{H_1G_1})_2$ as illustrated in **5**. The X-ray structure (Fig. 3) corresponds to a disorder between two situations, that depicted in **5** and the corresponding one with four protons transferred. These protons were located from a difference synthesis performed at the last stages of the refinement using a complete model excepting these atoms. The estimated populations of the two tautomers were 0.6 : 0.4 (Fig. 3). The geometry of the pyrazole ring in $(\mathbf{H_1G_1})_2$ is intermediate between that of pyrazoles in the situations described in **1–3**,[3,4] and that of a pyrazole without proton transfer.[11]

To further characterize the solid-state tautomerism of $(\mathbf{H_1G_1})_2$ by ^{15}N CPMAS NMR experiments, the doubly ^{15}N labelled analogue $(\mathbf{H_1G'_1})_2$ was prepared. The results of

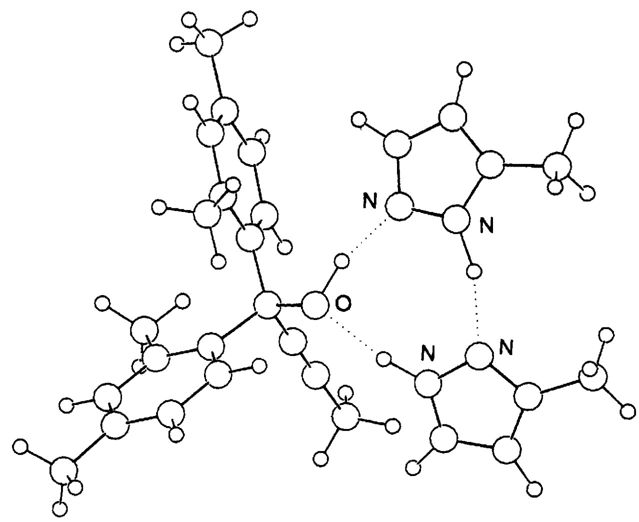

Fig. 1 Molecular structure of the asymmetric unit cell $(\mathbf{H_1G_2G_3})^5$

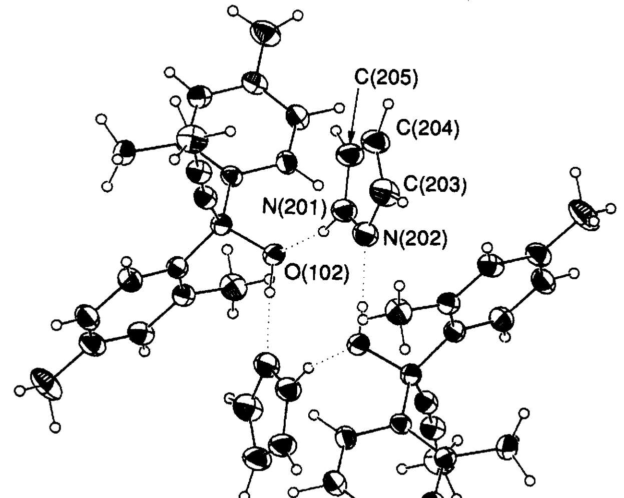

Fig. 2 Molecular structure of $(\mathbf{H_1G_1})_2$ dimers centrosymmetrically related showing 30% probability ellipsoids for the non-hydrogen atoms. The hydrogen atoms involved in the interactions are those corresponding to the highest population (60%). Selected bond distances, bond angles for the pyrazole ring and hydrogen bonds geometry are (Å, °): 1.336(4), 1.324(5), 1.363(6), 1.363(6), 1.329(5) for N(201)–N(202), N(202)–C(203), *etc.*, distances; 109.5(3), 106.4(3), 110.9(4), 104.4(3), 108.8(3) for angles at N(201), N(202), *etc.*; N(201)–H(201A)···O(102) 0.80(7), 2.859(4), 2.10(7), 157(6); O(102)–H(102A)···N(202) 0.85(8), 2.802(4), 1.95(8), 172(6), N(202)–H(201B)···O(102) 0.90(13), 2.802(4), 1.97(12), 151(9), O(102)–H(102B)···N(201) 1.09(9), 2.859(4), 1.78(9), 170(8).

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† ^{13}C CP/MAS NMR spectra in the solid state were recorded at 50 MHz with a Bruker AC-200 using experimental conditions previously described.[9] The signals corresponding: to **G2** appear at δ 13.6 (CH$_3$), 145.7 (C-3), 101.9 (C-4) and 130.6 (C-5); to **G3** appear at 10.2 (CH$_3$), 137.7 (C-3), 103.9 (C-4) and 137.7 (C-5). At low temperature in hexamethylphosphorous triamide (HMPT), the prototropy of 3(5)-methylpyrazole is frozen and the signals of both tautomers can be observed:[10] 3-methyl tautomer, δ 13.68 (CH$_3$), 146.05 (C-3), 103.17 (C-4) and 128.34 (C-5) and 5-methyl tautomer, δ 10.55 (CH$_3$), 137.18 (C-3), 103.17 (C-4) and 138.59 (C-5).

‡ When a solution of $\mathbf{H_2}$ (0.5 g, 1.9 mmol) and $\mathbf{G_4}$ (0.2 g, 2.1 mmol) in methanol (5 ml) was kept at room temp. for 12 h, a 1 : 1 complex of $\mathbf{H_2}$ and $\mathbf{G_4}$ was obtained as colourless prisms (0.37 g, 50% yield, m.p. 188–191 °C). The host : guest ratio was determined by ^{1}H NMR spectroscopy and elemental analysis. The ^{13}C NMR spectrum in [^{2}H$_6$]DMSO shows signals of the host at δ 44.1 (C-1), 36.5 (C-2), 25.9 (C-3), 22.5 (C-4), 139.0 (C-1′), 127.5 (C-2′ and C-6′), 114.8 (C-3′ and C-5′), 154.6 (C-4′), and those of the guest at δ 11.5 (CH$_3$-3 and CH$_3$-5, br), 147 (C-3, br), 103.2 (C-4) and 139 (C-5, br); the signals corresponding to $\mathbf{G_4}$ in the ^{13}C CP/MAS NMR spectrum appear at δ 8.5 (CH$_3$-5), 12.7 (CH$_3$-3), 147.6 (C-3), 104.5 (C-4) and 138.9 (C-5). In solution (low temperature in HMPT) the values are: δ 10.61 (CH$_3$-5), 13.84 (CH$_3$-3), 146.53 (C-3), 102.67 (C-4) and 138.03 (C-5).[10] In the solid state at 233 K (complex **2**, tautomerism frozen) the observed values are: δ 10.5 (CH$_3$-5), 12.8 (CH$_3$-3), 147.5 (C-3), 104.8 (C-4) and 139.3 (C-5).[10]

§ When a solution of $\mathbf{G_1}$ (0.5 g, 1.8 mmol) and $\mathbf{H_1}$ (0.15 g, 2.2 mmol) in cyclohexane (5 ml) was kept at room temp. for 12 h, a 1 : 1 complex of $\mathbf{G_1}$ and $\mathbf{H_1}$ was obtained as colourless prisms (0.4 g, 70% yield, m.p. 103–105 °C). The host : guest ratio was determined by ^{1}H NMR spectroscopy and elemental anslysis. The ^{13}C NMR spectrum in CDCl$_3$ shows the following signals: δ 81.7 (C-1), 74.3 (C-2), 83.2 (C-3), 3.8 (C-4), 139.1 (C-1′), 137.1 (C-2′), 127.2 (C-3′), 136.0 (C-4′), 125.8 (C-5′), 132.8 (C-6′), 21.0 (CH$_3$-2′), 20.7 (CH$_3$-4′) (guest signals) and 133.4 (C-3 and C-5, br) and 104.7 (C-4) (host signals). The signals corresponding to $\mathbf{G_1}$ in the ^{13}C CP/MAS spectrum at room temp. are only clearly observed for C-4 (δ 104.7); those expected at δ 128 and 138 for C-3 and C-5 cannot clearly be distinguished from the lines of the host.

¶ *Crystal data* for $\mathbf{H_1G_1}$: $C_{20}H_{22}O{\cdot}C_3H_4N_2$, M = 346.47, monoclinic, $P2_1/c$, a = 7.9175(3), b = 10.0919(5), c = 24.7882(15) Å, β = 91.423(5)°, V = 1980.0(2) Å^3, Z = 4, D_c = 1.162 g cm^{-3}, μ = 5.21 cm^{-1}.

For $\mathbf{H_2G_4}$: $C_{18}H_{20}O_2{\cdot}C_5H_8N_2$, M = 364.49, monoclinic, $P2_1/c$, a = 10.8156(5), b = 11.9788(7), c = 31.1299(36) Å, β = 93.836(8)°, V = 4024.1(6) Å^3, Z = 8, D_c = 1.203 g cm^{-3}, μ = 5.71 cm^{-1}. A total of 3372 and 5030 independent reflections up to θ_{max} = 65 and 55° were measured on a Philips PW1100 diffractometer with graphite monochromated Cu-Kα radiation using $\omega/2\theta$ scans. The structures were solved by direct methods (SIR88) and refined by least-squares procedures to give $R(R_w)$ = 0.056 (0.065) and 0.107 (0.130) for 2287 and 3301 observed reflections [$I > 3\sigma(I)$]. The poor quality of $\mathbf{H_2G_4}$ crystals prevented any improvement in the refinement. All hydrogen atoms were obtained from the corresponding difference Fourier synthesis, the highest peak in the final difference map being 0.22 and 0.51 eÅ^{-3}, respectively. Atomic coordinates, bond distances and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

experiments performed on $(\mathbf{H_1G'_1})_2$ at 2.1 T are shown in Fig. 4. At low temperatures two sharp lines‖ characteristic for protonated and non-protonated nitrogen atoms are observed. As the temperature is increased, the lines broaden and eventually coalesce as expected for a moderately fast proton exchange process.[3,4] The highest temperature where a spectrum could be obtained was 370 K, just below the melting point at 376 K. The spectrum at 253 K was measured after the spectrum at 370 K to check the reversibility of the process. Note that the low frequency line arising from the protonated nitrogen atom exhibits a larger broadening as compared with the high frequency line. We ascribe this effect to a process which averages both dipolar ^{1}H–^{15}N interactions as well as the chemical shift anisotropies. A further indication for this interpretation is that there seems to be no major spectral change when the ^{1}H decoupling is suppressed at 370 K. At present, it is not clear whether this process is the proton transfer itself, molecular motions associated with the proton transfer, or independent molecular motions. This complication prevents a detailed lineshape analysis at present. A magnetization transfer experiment performed at 305 K** revealed an equilibrium constant of proton tautomerism K close to unity and a rate constant of about 75 s^{-1}. Within the margin or error, these findings are consistent with the value of 60 : 40 for the two tautomers estimated by X-ray analysis. The rate constant is much smaller as compared with those corresponding to processes **1** to **3**.[3,4]

Further various one- and two-dimensional NMR experiments will be carried out in the future to completely characterize the details of the proton transfer and of the molecular motions in $(\mathbf{H_1G_1})_2$.

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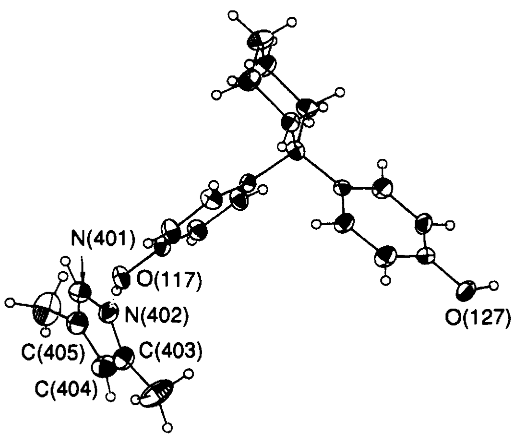
(*a*)



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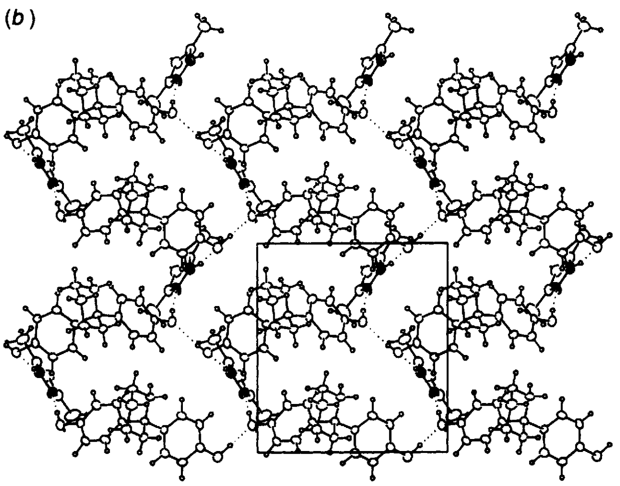

Fig. 3 (*a*) Molecular structure of one of the two independent $(\mathbf{H_2G_4})$ molecules; (*b*) crystal packing as viewed along the *c* axis showing the hydrogen bond network. Selected bond distances, bond angles and hydrogen bonds geometry are (Å, °): 1.353(12), 1.305(12), 1.399(15), 1.334(14), 1.357(13) and 1.346(11), 1.300(13), 1.417(15), 1.350(15), 1.321(13) for N–N, N–C, *etc.*, distances of the pyrazole; 110.8(8), 105.5(8), 110.7(9), 106.1(9), 106.8(9), 113.0(8) and 113.0(8), 105.3(8), 109.9(9), 105.6(9), 106.3(9) for intracyclic pyrazole angles at atoms N(301), N(302), *etc.*, and N(401), N(402), *etc.*, for both molecules; O(117)–H(117)···N(402) 0.86(13), 2.662(10), 1.88(14), 150(12); N(401)–H(401)···O(227) 0.99(12), 2.961(10), 2.00(12), 163(10); O(227)–H(227)···O(217)i 0.82(12), 2.717(9), 1.91(12), 167(12); O(217)–H(217)···N(302) 0.87(13), 2.688(11), 1.84(13), 167(12); N(301)–H(301)···O(127)ii 0.97(11), 2.940(10), 1.99(12), 164(10); O(127)–H(127)···O(117)iii 0.67(14), 2.741(9), 2.08(14), 167(16); symmetry code: i = −1 + *x*,*y*,*z*, ii = *x*, 1 + *y*,*z*, iii = 1 + *x*,*y*,*z*.

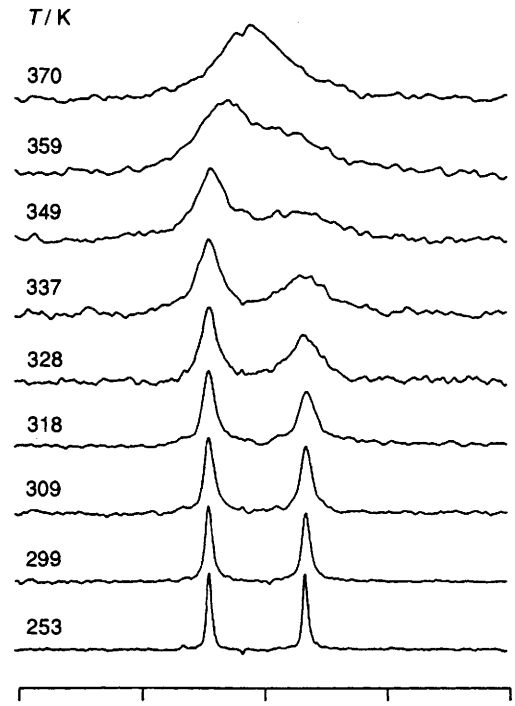

Fig. 4 9.12 MHz ^{15}N CPMAS NMR spectra of $(\mathbf{H_1G'_1})_2$ as a function of *T*. Spinning speeds between 2 and 3 kHz, 5.3 μs 90° pulses, 42 kHz ^{1}H decoupling field, 4 s recycle delay, CP times between 2 and 8 ms. Number of scans from 253 to 370 K: 150, 400, 400, 800, 550, 120, 3900, 15 400 and 5000.

‖ At 253 K the signal of both nitrogen atoms appear at δ 165 (N–H) and 245 (–N=) (Ref. ext. $^{15}NH_4Cl$). Bulk crystalline pyrazole exhibits signals at δ 170 (N–H) and 248 (–N=).[12]

** The ^{15}N magnetization transfer experiment was performed at 7 T (30.41 MHz). The analysis was done as previously.[13] The data were best interpreted assuming an equilibrium constant $K = k_{12}/k_{21} = 1$ (50 : 50 tautomer ratio) and a rate constant of $k_{12} = k_{21} = 75$ s^{-1}. This value is uncorrected for ^{15}N spin diffusion. A data set of $K = 0.67$ (60 : 40 tautomer ratio), $k_{12} = 63$ s^{-1} and a spin diffusion rate constant of $\sigma = 2.5$ s^{-1} cannot yet be excluded. In order to decide this problem additional experiments are necessary.

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