Structure of chiral pyrazoles in the solid state and in solution

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The X-ray molecular structures of three chiral pyrazoles bearing (4*S*)-4-benzyloxazolidin-2-ones or (2*R*)-bornane-10,2-sultams at position 3(5) have been studied by single crystal X-ray diffraction and by NMR. In the solid state, the same pyrazole tautomer **a** has been found for the three compounds, that with the chiral group in the 3-position. Their crystal structures consist of infinite chains (catemers) formed by N–H···O=X (X: C, S) hydrogen bonds. The use of solid-state ^{13}C NMR spectroscopy demonstrated that the pyrazole is also an **a** tautomer. ^{13}C NMR spectra in methanol solution yield average signals even at −80 °C; nevertheless, interpolation allows one to estimate that in solution tautomer **a** also predominates.

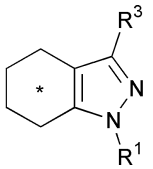
The development of enantioselective catalytic reactions requires new chiral ligands.[1] In this very active field of research, some of the most popular ligands are pyrazoles, either in themselves[2] or as tris(pyrazol-1-yl)borates [scorpionates].[3] Therefore, the importance of inducing enantiomeric excesses by using stereogenic ligands has resulted in much interest in preparing chiral pyrazoles, principally N-unsubstituted ones, because they can be used to synthesise the corresponding scorpionates.

We hope that the full characterisation of new chiral pyrazoles will prompt other chemists to use them as auxiliary ligands. A subsidiary reason is to complete the knowledge of NH-pyrazoles in the solid state, as far as both hydrogen bonds (HBs) and tautomerism are concerned. The HBs in crystals of pyrazoles are today one of the cases for which new theoretical models are being developed, for instance, in proton transfer (SSPT: solid-state proton transfer).[4,5] Moreover, a systematic classification of HB motifs and tautomerism in these compounds has been recently successfully completed.[6] For both SSPT and HB patterns, chiral pyrazoles are interesting substrates.

These compounds are still uncommon and most of them are synthesised from the chiral pool of natural ketones, which are carbocyclic derivatives. We have summarised in Table 1 the most studied cases. Leaving aside steroidal pyrazoles, prepared as drugs and unsuitable as ligands, most known examples result from ketones having an α-methylene group. Therefore, before the compounds described in this paper, the only chiral pyrazoles used were fused pyrazoles.

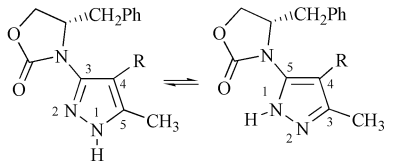
Recently, we reported the synthesis of a completely different family of chiral pyrazoles bearing (4*S*)-4-benzyloxazolidin-2-ones or (2*R*)-bornane-10,2-sultams at position 3(5).[3,7] In view

Table 1 Synthesis of chiral fused pyrazoles from natural ketones



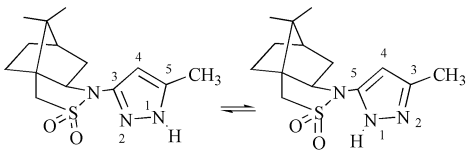
Carbonyl compound	Type of pyrazole	Synthesis ref.
Camphor	3(5),4-Disubstituted	7–9[a]
Camphor	3,4-Disubstituted (phosphine)	12
Camphor	1,3,5-Trisubstituted	13, 14
(+)-3-Methylcyclohexanone	3(5),4-Disubstituted	15
(−)-Menthone	3(5),4-Disubstituted	16
(−)-Menthone	3,4-Disubstituted (borate)	17
(−)-Menthone	3,4,5-Trisubstituted	18–21
(−)-Menthone	3,4-Disubstituted (phosphine)	12
Isopinocamphone	3(5),4-Disubstituted	22
(+)-Pulegone	3(5),4-Disubstituted	23
(+)-Pulegone	3,4-Disubstituted (borate)	24
(−)-Menthone	3,4-Disubstituted (phosphine)	12
(+)-3-Carene	3,4,5-Trisubstituted	25, 26
Steroids	3,4- and 3,4,5-Substituted[b]	27–36

[a] X-Ray structure reported in ref. 10, 11. [b] Stanozolol.[27]



1a, 2a, 3a **1b, 2b, 3b**

1a and **1b**: R = H; **2a** and **2b**: R = CH_3; **3a** and **3b**: R = CH_2Ph



4a **4b**

of the scarcity of structural studies concerning chiral pyrazoles, we decided to undertake the examination of four of these compounds, **1** to **4**, by X-ray crystallography and solid and solution NMR.

Experimental

X-Ray crystallography

Suitable crystals for X-ray diffraction experiments were obtained by crystallisation from diethyl ether (**2a** and **3a**) or diethyl ether–chloroform (**4a**). Data collection was carried out at room temperature on an Enraf–Nonius CAD4 diffractometer using graphite-monochromated Mo-Kα radiation ($\lambda = 0.710\,69$ Å). Structures were solved by direct methods (SHELXS-86)[38] and refined by full-matrix least-squares procedures on F^2 for all reflections (SHELXL-97).[39] The known configuration of the chiral pyrazoles was used in the refinement. Only in the case of **4a**, containing a sulfur atom, was the analysis of the Flack parameter possible [$-0.04(7)$] and confirmed the configuration used. Hydrogen atoms bonded to nitrogen were located on a difference Fourier map. Crystal data and other structure determination details are presented in Table 2.

CCDC reference number 440/237. See http://www.rsc.org/suppdata/nj/b0/b005920j/ for crystallographic files in .cif format.

NMR experiments

Variable temperature ^{1}H and ^{13}C NMR experiments were recorded on a Varian Unity-500 spectrometer operating at 499.88 and 125.71 MHz, respectively, using CD_3OD as solvent. Monodimensional experiments were performed using standard conditions. 2D Inverse proton detected heteronuclear shift correlation spectra, HMQC and HMBC, were obtained with the following conditions: data were collected in a 4096*128 matrix with a spectral width of 8000 Hz in the proton domain and 25 000 Hz in the carbon domain, and processed in a 4096*512 matrix. The HMQC experiment was optimised for a one-bond heteronuclear coupling constant of 145 Hz and the HMBC experiment for long range coupling constants of 8 Hz. CPMAS NMR spectra have been obtained on a Bruker AC-200 spectrometer at 298 K using a 7-mm Bruker DAB 7 probehead that achieves rotational frequencies of about 3.5–4.5 kHz. Samples (approximately 200 mg of material) were carefully packed in ZrO_2 rotors and the standard CPMAS pulse sequence was applied.[40]

Results and discussion

X-Ray crystal and molecular structure

In the solid state, compounds **2**, **3** and **4** have been obtained as tautomers **a** (Fig. 1). The geometry of pyrazoles is similar for the three compounds and only minor differences can be appreciated in **4a**. In this C4-unsubstituted pyrazole the N1–C5 and C4–C5 bond lengths are slightly shorter than the corresponding distances in **2a** and **3a**, and the C3–C4–C5 and N2–C3–C4 bond angles are, respectively, bigger and smaller than the corresponding angles in **2a** and **3a** (Table 3). Pyrazoles **2a** and **3a** show similar conformations (Fig. 1, Table 3). Pyrazole **4a** adopts two conformations in the solid state; that is the asymmetric unit of its crystal structure is formed by two molecules whose torsion angles around the C3–N7 bond are different (Fig. 1, Table 3).

Crystals of **2a**, **3a** and **4a** consist of only one enantiomer and therefore their space groups do not contain second-order symmetry operations. In all three cases, molecules are linked by N–H···O=X (X: C, S) hydrogen bonds forming infinite chains (catemers). An infinite chain is the most usual arrangement in the crystal structures of N-unsubstituted pyrazoles although other associations (dimers, trimers, tetramers) involving hydrogen bonds have been found.[42] Although the existence of N–H···O=X hydrogen bonds is a feature common to the three crystals, differences in the crystal packing, which can be attributed mainly to the different molecular geometry, can be observed (Fig. 2, Table 4).

The structure of **2a** is the simplest, with the crystal packing consisting of infinite chains parallel to the crystallographic vector *b* with only one N–H···O=C hydrogen bond present between two neighboring molecules of the chain. Two antiparallel chains pass through the unit cell.

The structure of **3a** is very similar to the structure described for **2a**. Here the crystal packing also consists of infinite chains parallel to the crystallographic vector *b*, and two antiparallel

Table 2 Crystal data and structure determination details

	2a	**3a**	**4a**
Chemical formula	$C_{15}H_{17}N_3O_2$	$C_{21}H_{21}N_3O_2$	$C_{14}H_{21}N_3O_2S$
Formula weight	271.32	347.41	295.40
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)	$P2_1$ (no. 4)
T/K	293	293	293
a/Å	6.486 (4)	6.601 (9)	9.309 (2)
b/Å	12.445 (1)	14.743 (4)	12.306 (4)
c/Å	18.327 (2)	18.895 (9)	13.322 (3)
β/°	90	90	104.80 (2)
μ/Å^3	1479.3 (9)	1839 (3)	1475.5 (7)
Z	4	4	4
mm^{-1}	0.083	0.082	0.225
Unique reflect, measured reflect. (R_{int})	1297, 1297(0)	1613, 1613(0)	2726, 2726(0)
$R(F)$, $R_w(F^2)^a$ [$I > 2\sigma(I)$]	0.041, 0.111	0.046, 0.098	0.030, 0.082
$R(F)$, $R_w(F^2)^a$ (all data)	0.048, 0.113	0.080, 0.102	0.033, 0.082

^{a} $R(F) = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$; $R_w(F^2) = [\Sigma\, w(F_o^2 - F_c^2)^2/\Sigma\, w(F_o^2)^2]^{1/2}$; ^{b} $[\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$

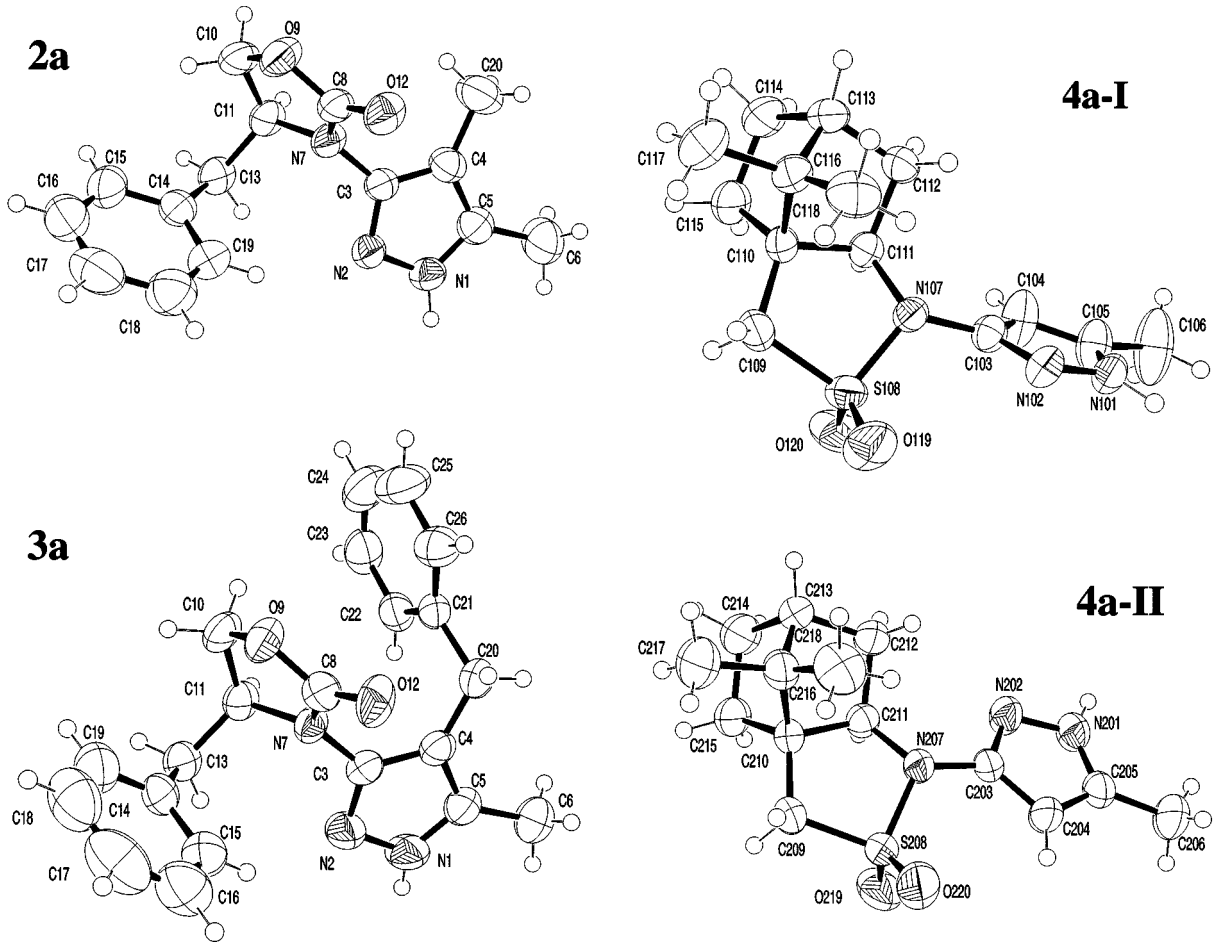


Fig. 1 Molecular structures of **2a**, **3a**, and **4a** in the solid state, showing the atom numbering (ORTEP plots at 50% probability, ORTEP-3).[41]

chains pass through the unit cell. The group space is the same, $P2_12_12_1$, but the relative orientation of neighbouring molecules in the chain is different and the interaction between them is also a little different, a three-centre hydrogen bond being present instead of the two-centre one described for **2a**. In this case, N1–H1, O9 and O12 are in a plane, the H1···O12 and N1···O12 distances have increased in relation to those in **2a**, whereas the H1···O9 and N1···O9 ones have decreased. The four atoms O9···N1H1···O12 define a geometry characteristic for a three-centre hydrogen bond.[44]

In the crystal structure of **4a** molecules **I** form infinite chains parallel to the crystallographic vector *b* with one N–H···O=S hydrogen bond between neighbouring units. Molecules **II** are bonded to molecules **I** by weak N–H···N(pz) hydrogen bonds and as a whole, a ···**I(II)**···**I(II)**··· arrangement is found.

Solid state ^{13}C CPMAS NMR

We have recorded the spectra of compounds **1** and **2** with the CPMAS technique. From the previous study, we know that **2** exists in the solid state as tautomer **2a**. The results of Table 5 [particularly the chemical shift of Me(6)] show that both pyrazoles have the same structure, that is, both are 3-(4*S*)-4-

Table 3 Selected geometrical parameters for molecules **2a, 3a** and **4a**

	2a	**3a**	**4a**[a]
Bond lengths/Å			
N1–N2	1.348 (4)	1.352 (5)	1.355 (3), 1.365 (3)
N2–C3	1.321 (3)	1.321 (4)	1.315 (3), 1.307 (4)
C3–C4	1.396 (4)	1.397 (5)	1.387 (4), 1.400 (4)
C4–C5	1.384 (4)	1.381 (5)	1.360 (4), 1.368 (4)
N1–C5	1.343 (4)	1.348 (5)	1.315 (4), 1.322 (4)
C3–N7	1.422 (3)	1.412 (5)	1.413 (3), 1.404 (3)
Bond angles/°			
N1–N2–C3	103.2 (2)	102.3 (3)	103.1 (2), 103.4 (2)
N2–C3–C4	113.5 (3)	114.3 (3)	111.9 (2), 112.1 (2)
C3–C4–C5	103.5 (3)	103.2 (3)	105.1 (3), 104.9 (3)
C4–C5–N1	106.4 (3)	106.4 (4)	106.2 (3), 106.2 (3)
C5–N1–N2	113.4 (2)	113.8 (3)	113.6 (2), 113.4 (3)
Torsion angles/°			
N2–C3–N7–C11	−73.8 (4)	−55.5 (5)	152.2 (2), 15.5 (4)
N7–C11–C13–C14	64.9 (3)	56.3 (5)	—
C11–C13–C14–C15/C19[b]	−80.3 (3)	−84.2 (5)	—

[a] Two molecules in the asymmetric unit. [b] C15 for **2a**, C19 for **3a**.

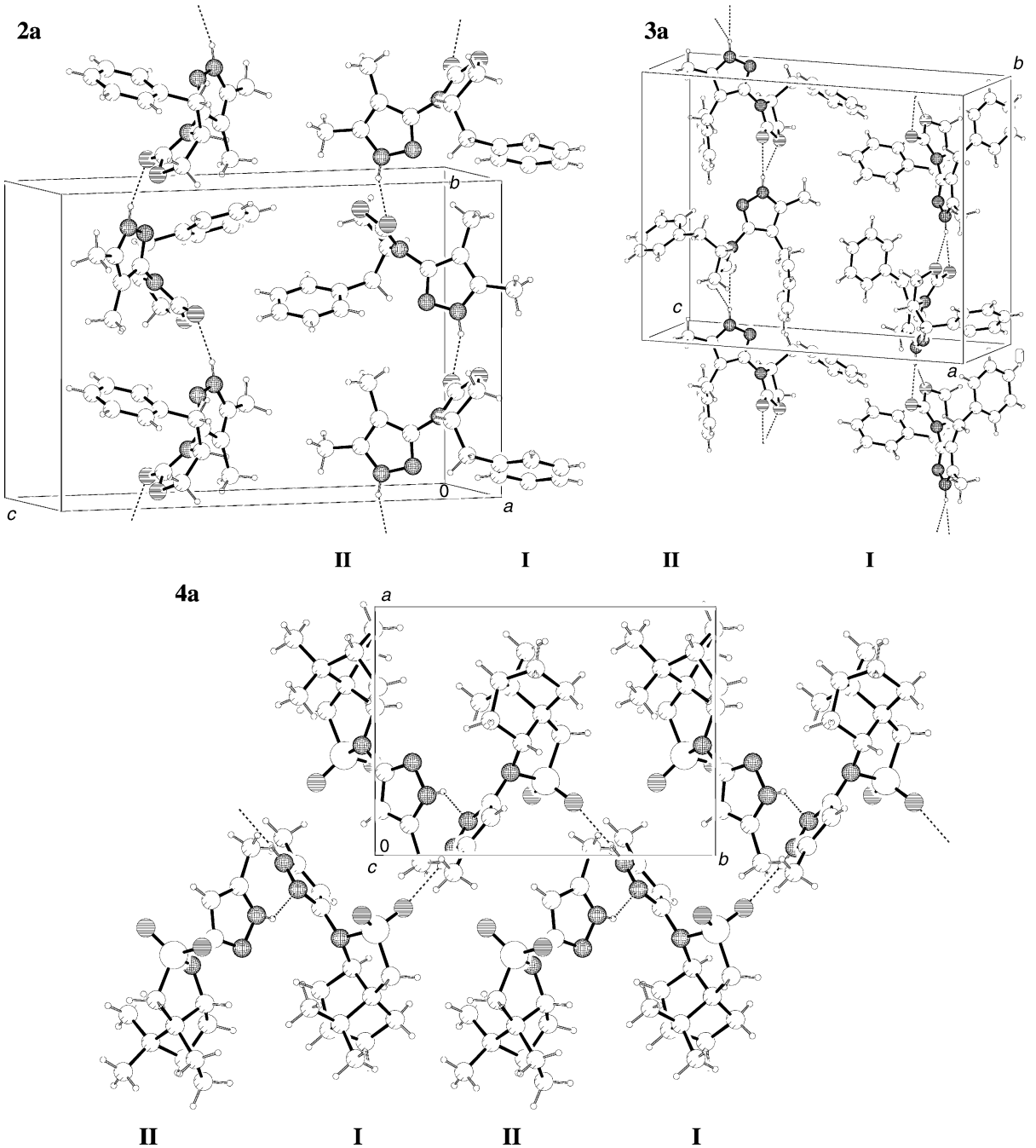


Fig. 2 Crystal structures of **2a**, **3a**, and **4a**, showing the hydrogen bonds (PLUTON).[43]

Table 4 Geometry of hydrogen bonds (distances/Å and angles/°)

2a			
N1—H1	N1···O12^a	H1···O12^b	N1—H1···O12^a
0.90 (4)	2.865 (3)	1.99 (4)	162 (4)
3a			
N1—H1	N1···O12^a	H1···O12^a	N1–H1···O12^a
0.86 (5)	3.136 (5)	2.28 (5)	177 (4)
	N1···O9^b	H1···O9^b	N1–H1···O9^a
	3.171 (5)	2.57 (5)	128 (4)
			O12^a···H1···O9^a
			55 (1)
4a			
N101–H101	N101···O120^a	H101···O120^a	N101–H101···O120^a
0.90 (5)	2.924 (4)	2.06 (5)	163 (5)
N201–H201	N201···N102	H201···N102	N201–H102···N102
0.82 (4)	3.075 (4)	2.41 (4)	139 (4)

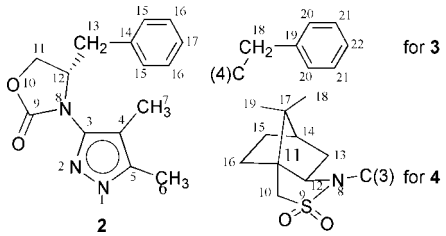
^{a} Symmetrically equivalent atom (2_1 parallel to *b*). ^{b} For comparison (see text): in **2a**, N1···O9^a 3.695 (4) Å and H1···O9^a 2.97 (4) Å.

Table 5 ^{13}C chemical shifts (ppm from TMS) for **1** and **2** in the solid state (CPMAS technique)

Carbon atom	**1**	**2**[a]
C(3)[b]	148.5	144.3
C(4)	96.7	109.1
C(5)[c]	143.5	144.3
Me(6)	9.3	7.7
Me(7)	—	5.5
C(9)=O	154.2	158.8
C(11)	66.7	67.1
C(12)	55.4	57.9
C(13)	36.5	34.4
C(14)	135.5	135.4
C(15)	132.0	132.0
C(16)	129.0	128.2
C(17)	127.0	128.2

[a] ^{15}N CPMAS chemical shifts: N(1) = −179.5, N(2) = −86.2, N(8) = −284.5 ppm. [b] Carbon atom bearing the oxazolidinone. [c] Carbon atom bearing the methyl group.

benzyloxazolidin-2-one tautomers **a**. For the NMR discussion we have used a different and more conventional numbering than for the crystallographic part:



The ^{15}N CPMAS NMR shifts of compound **2** are consistent with the structure. The signal at −284.5 ppm [N(8)] is typical of amides and carbamates,[45] while those at −179.5 [N(1)] and −86.2 [N(2)] ppm are similar to those reported, in the solid state, for 3,4,5-trimethylpyrazole.[46]

Solution NMR studies (^1H and ^{13}C)

We will first discuss the ^{13}C NMR results (Table 6). The reason is that thanks to the previous solid-state NMR study, we know the ^{13}C chemical shifts for tautomer **a** in the case of compounds **1** and **2**.

The presence of broad and very broad signals in the ^{13}C NMR spectra in methanol at 20 °C proves that both tautomers **a** and **b** are present. Observe that the broadening affects the "tautomeric" positions 3 and 5, including the *C*-methyl group (C6), while position 4 is not affected.

To interpret the solution results we need the chemical shifts of both tautomers. Owing to a large study of pyrazoles, which contains numerous data of NH pyrazoles in the solid state, some rules can be devised.[47] The effects (SCS: substituent chemical shifts) on the α position, that is, R^3 on C(3) and R^5 on C(5), are very similar for each substituent R (oxazolidinone, sultam or methyl groups). The same happens, but they are much smaller, for the γ effects, *i.e.* R^3 on C(5) and R^5 on C(3). We have summarised in Scheme 1, the results of the calculations for compound **1**.

The data for **5a**, **5b** and **6b** are from the literature.[37,47] The SCS, 12.0, 2.0 and 0.0 ppm obey the α, γ and far-away order,[47] but the actual values have been calculated to fit the experimental data: the CPMAS spectrum, the average spectrum in solution and the chemical shifts of **6b**. The tautomeric ratio, 4 : 1, for **1a** : **1b** is only a rough estimation.

The differences in chemical shifts between **1** and **2** (Tables 5 and 6) are due to the SCS of the methyl at position 4.[47] Concerning compound **4**, the slight differences with **1** (both unsubstituted at position 4) indicate that it is probably a mixture richer in tautomer **a** (perhaps 9 : 1).

The ^1H NMR spectra of the four pyrazoles were recorded at 500 MHz in CD_3OD at 21.4 °C. No broadening was observed and the study was not pursued further. Some significant signals are: 2.506 Me(6), 6.540 H(4) (**1**); 2.395 Me(6), 2.101 Me(7) (**2**); 2.453 Me(6), 3.995 and 3.938, $J = 15.9$ Hz $CH_2(18)$; 2.454 Me(6), 6.161 H(4) (**4**). In compounds **1** and **4** there is a ^4J coupling of 0.7 Hz between H(4) and Me(6). In general,[48] these couplings are indicative of the predominance of tautomer **b**, but in the present case they probably correspond to the presence of this tautomer (even in minor proportion) together with the perturbation of the π-system of the pyrazole ring due to the unusual 3-substituent.

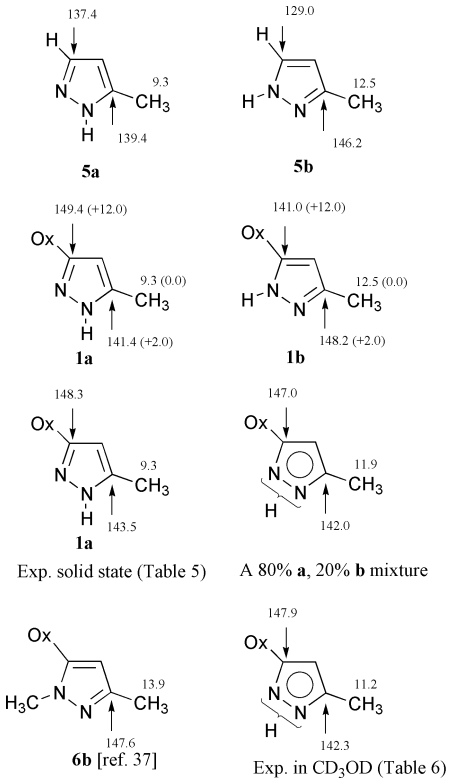
Variable temperature ^{13}C NMR experiments

These experiments have been carried out with compounds **1** and **3** between +40 °C and −80 °C. On cooling the signals broaden but remain at the same place [correcting for temperature effects on some signals unaffected by tautomerism, like C(14)]: no new signals appear. There are two possible

Table 6 ^{13}C chemical shifts (ppm from TMS) for in **1**–**4** CD_3OD at 20.0 °C

Carbon atom	**1**	**2**	**3**	**4**
C(3)[a]	147.9 (vbr)	144.7 (vbr)	144.8 (vbr)	145.9 (vbr)
C(4)	96.81	109.91	114.25	98.65
C(5)[b]	142.3 (vbr)	139.6 (vbr)	139.8 (vbr)	142.0 (vbr)
Me(6)	11.2 (br)	9.6 (br)	9.8 (br)	10.8 (br)
Me(7)	—	7.53	—	—
C(9)=O	157.34	158.60	158.60	—
C(10)	—	—	—	51.13
C(11)	68.13	69.10	69.26	50.98
C(12)	58.10	60.10	59.89	66.83
C(13)	38.20	39.43	39.41	45.83
C(14)	137.08	136.93	136.97	36.96
C(15)	131.26	130.33	130.07	27.88
C(16)	130.02	129.62	129.63	32.99
C(17)	128.44	127.91	127.87	48.95
C(18)	—	—	29.61	20.29[c]
C(19)	—	—	141.95	20.83[c]
C(20)	—	—	129.75	—
C(21)	—	—	129.54	—
C(22)	—	—	127.28	—

[a] Carbon atom bearing the oxazolidinone (br, broad; vbr, very broad). [b] Carbon atom bearing the methyl group. [c] The assignment of these signals can be interchanged.



Scheme 1

reasons for this failure. The first is that we have not succeeded in blocking the tautomerism, but with other pyrazoles, also in CD_3OD, the coalescence temperature is between -25 and $-40\,^{\circ}C$ (these pyrazoles have identical tautomers, $K_T = 1$).[49] The second is that the populations of both tautomers are very different from 1, such as 4 : 1 or 9 : 1; in this case only a small shift of the signals is expected.

Conclusion

The main difference concerning the HBs between the crystal and the solution is that the crystals tend to form intermolecular HBs while in solution intramolecular HBs (IMHBs) can be favoured. The reason is that a crystal is a collection of bonds (covalent and HBs, not taking into account other weaker forces) and the crystal packing needs intermolecular interactions. In solution, with the solvent playing a crucial role, IMHBs prevail in the monomers. This explains why the compounds of the present study exist in the solid state as tautomers **a** while in solution there is an important contribution of intramolecular hydrogen bonded tautomers **b**.

The results reported in this paper show that pyrazoles **1**–**4** are not good substrates for SSPT because they do not form cyclic motifs but catemers. On the other hand, the tautomerism in the solid state and in solution has been established unambiguously. We hope that the full characterisation of these new chiral pyrazoles will encourage other organic and inorganic chemists to use them, as they are readily accessible.

Acknowledgements

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