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The Structure of Pyrazoles in the Solid State: A Combined CPMAS, NMR, and Crystallographic Study

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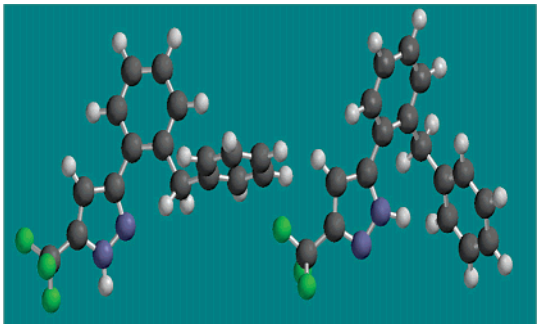

The structures of six *N*-unsubstituted pyrazoles, three already known and three newly synthesized, have been studied by a combination of X-ray crystallography, multinuclear NMR (solution and solid state), and density functional theory (DFT) calculations. In those cases where crystal structure and CPMAS NMR were available, the agreement was almost perfect, allowing a prediction of the tautomer (with certitude) and the tetrameric structure (with high probability) in the case of 5-isopropyl-3-phenyl-1*H*-pyrazole without knowing the X-ray structure. In the case of the 5-(2-benzylphenyl)-3-trifluoromethyl-1*H*-pyrazole above represented, the DFT calculations at the B3LYP/6-31G** level justify the great stability of this tautomer by the presence of an intramolecular N−H···π interaction, present in solution.

Introduction

Although less relevant biologically than *N*-unsubstituted imidazoles, *N*-unsubstituted pyrazoles are much more interesting in what concerns the N−H···N hydrogen bonds (HBs) network in their crystals (the HBs of the remaining N*H*-azoles, 1,2,3- and 1,2,4-triazoles, tetrazoles, and their benzo derivatives are all either of the "pyrazole-type" or the "imidazole-type"). The 1,3-disposition of the nitrogen atoms in imidazoles leads exclusively to the formation of chains, called catemers,[1] while the 1,2-disposition in pyrazoles leads to at least five motifs (Scheme 1, the Etter/Bernstein graph set descriptors are given for each motif).[2,3]

The question arises, is there any relationship between the nature of the *C*-substituents in the monomer and the hydrogen bond pattern present in the crystal? In the year 2000, we published a paper on this problem where two important conclusions were reached.[4] The first and most important one was that to find a pattern, the structures must be grouped in

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SCHEME 1. The Motifs Found in N*H*-Pyrazole Crystals

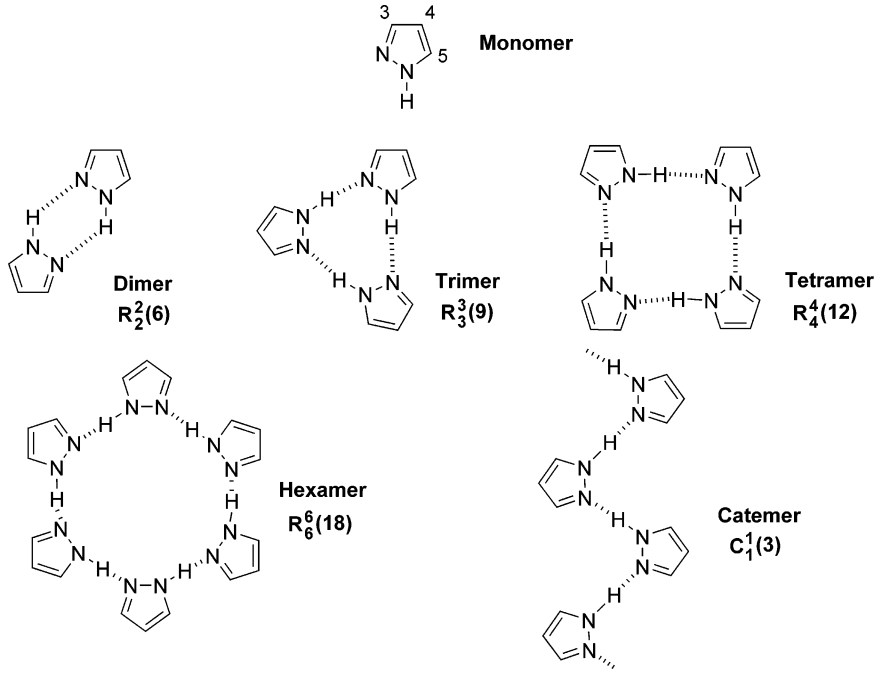

TABLE 1. Literature Data on Pyrazoles 1, 2, 3, and 5 of Scheme 1

pyrazole	mp (°C)	X-ray	solution NMR	CPMAS NMR	PT[a]
1 (polymorph B)[b]	114−125[9]		9−11	9−11	no (NMR)[9]
1 (polymorph A)[b]	122.5[9]	tetramer[13,14]	15	9	yes (NMR)[9]
2	83[12b]	tetramer[16]	16	16	yes (NMR)[16]
3	122[17]	tetramer[18]	18	no	no (X-ray)[18]
5	91[12c]				

[a] PT: proton transfer. [b] In the literature (no polymorph specified) the reported mp is 128.[12a]

two classes: (i) trimers and catemers and (ii) dimers and tetramers (hexamers were not known at that time but they belong to the even class). The second conclusion was that the first family consists of N*H*-pyrazoles with small substituents at positions 3 and 5 (substituents at position 4 were found irrelevant), whereas the second set corresponds to bulky ones. The best descriptor for the substituent size was the molar refractivity, MR (according to the IUPAC, the molar refractivity is the molar volume corrected by the refractive index; it represents size and polarizability of a fragment or molecule).[5] Four years later, Infantes and Motherwell reexamined this problem from another crystallographic point of view.[6] The two sets of N*H*-pyrazoles[4,6] differ not only because new structures have been published but because Infantes and Motherwell eliminate HB acceptor groups as CO_2R. Fayos, Infantes, and Cano used a neural network for predicting the secondary structure in N*H*-pyrazoles.[7] More recently, we proposed a mixed ab initio calculated/experimental crystallography approach.[8]

To progress in the understanding of the N−H···N HBs formed by the crystallization of N*H*-pyrazoles, more experimental data are needed. In this paper we will compare the solid-state properties of the pyrazoles reported in Scheme 2 and described in Table 1. The new *N*-methyl derivatives **7** and **8** have been prepared as models to study tautomerism. A priori we will name **a** the tautomer with the phenyl (or benzylphenyl) group at position 3 and **b** the other one, without any assumption about their relative stabilities.

The results will be presented in the following order: (1) Density functional theory (DFT) calculations of the isolated molecules (energies and dipole moments); (2) crystallographic results plus differential scanning calorimetry (DSC); (3) solution multinuclear magnetic resonance (NMR) studies; (4) solid-state NMR (CPMAS) results; and (5) general conclusions.

We had already identified two polymorphs of 3(5)-methyl-5(3)-phenyl-1*H*-pyrazole **1**:[9] a polymorph B devoided of dynamic properties (no proton transfer, PT) for which no X-ray structure could be determined but probably being a tetramer

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SCHEME 2. C-Phenyl-1*H*-pyrazoles 1−6 and *N*-Methyl Derivatives 7−8

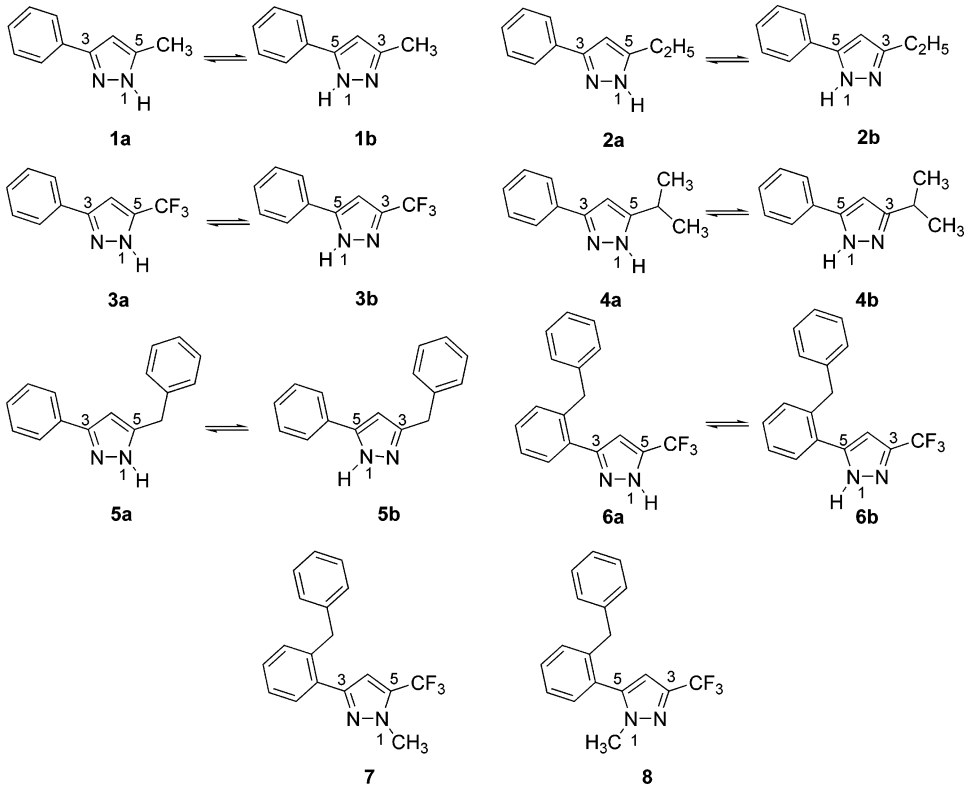

TABLE 2. DFT Calculations (B3LYP/6-31G) of Pyrazoles 1−6[a]**

pyrazole	tautomer **a**	tautomer **b**	μ **a**	μ **b**	ΔE (**a** − **b**)	% at 298.15 K
1	**−496.7779**	−496.7773	3.01	2.14	−1.63	66% **1a**/34% **1b**
2	**−535.7052**	−535.7047	3.02	2.16	−1.31	63% **2a**/37% **2b**
3	−794.1501	**−794.1510**	0.38	5.23	2.42	27% **3a**/73% **3b**
4	**−574.9935**	−574.9932	3.03	2.15	−0.79	58% **4a**/42% **4b**
5	**−727.3917**	−727.3908	3.14	2.57	−2.36	72% **5a**/28% **5b**
6	−1064.4112	**−1064.4160**	0.24	5.48	12.63	0.6% **6a**/99.4% **6b**

[a] Energies are given in hartree including ZPE correction, dipole moments are in D, and relative energies are in kJ mol^{-1}.

formed by only one tautomer (the 3-phenyl-5-methyl one **1a**) and presenting three peaks in DSC (after cooling, three peaks were observed again); and a polymorph A of known X-ray structure,[13,14] presenting PT[9] and formed by two 3-phenyl-5-methyl **1a** and two 3-methyl-5-phenyl **1b** tautomers. Since these tetramers have different tautomeric composition they are desmotropes.

Results and Discussion

1. Theoretical Calculations. We report in Table 2 the results of the calculations (underlined the most stable tautomer). The B3LYP/6-31G** level of the calculations is adequate to our purpose. There are no problems of optimization for most compounds; only in the case of **6** has it been necessary to carry out an exploration of the conformational space to find the tautomers of minimum energy (Figure 1).

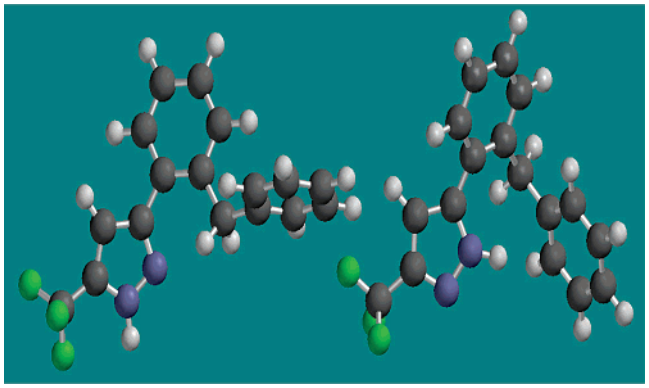

FIGURE 1. The minimum energy conformation of tautomers **6a** (left) and **6b** (right, showing the N−H···π hydrogen bond).

If we make the simplification to consider that the six pyrazoles have only three different substituents, phenyl (Ph),

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TABLE 3. Summary of the Crystallographic Work

compound		X-ray	tautomer	proton transfer (method)	motif composition
1(B)[a]	Ph/Me	tetramer[13,14]	2 **1a**+2 **1b**	yes (by NMR)[9]	**1a1a1b1b/1b1b1a1a**
2	Ph/Et	tetramer[16]	3 **2a**+1 **2b**	yes (by NMR)[16]	**2a2a2a2b/2b2b2b2a**
3	Ph/CF_3	tetramer[18]	4 **3b**	no (by X-ray)[18]	**3b3b3b3b**
4	Ph/*i*-Pr	not determined			
5	Ph/Bn	dimer	2 **5a**	no (by X-ray)	**5a5a**
6	BnPh/CF_3	dimer	2 **6b**	no (by X-ray)	**6b6b**

[a] B polymorph.

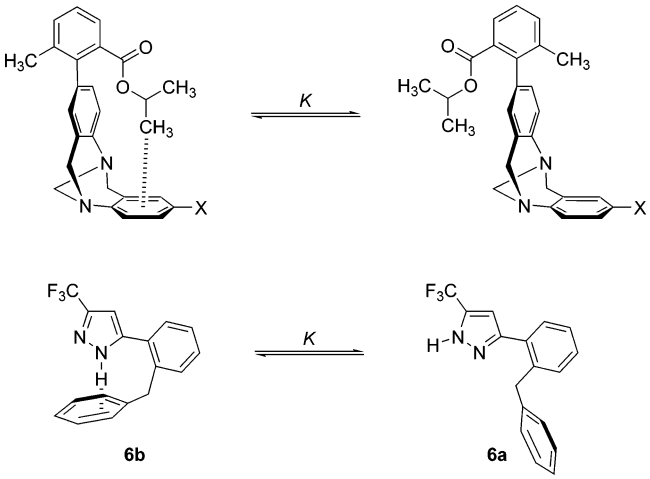
benzylphenyl (BnPh), and trifluoromethyl (CF_3), that is, assuming that the four alkyl groups (Me, Et, ^{i}Pr, and Bn) are equivalent as far as tautomerism and dipole moments ($\Delta\mu = \mu\mathbf{a} - \mu\mathbf{b}$) are concerned, then we can establish the following equations:

$$\Delta E(\mathbf{a} - \mathbf{b})\ (\text{kJ mol}^{-1}) = -(1.5 \pm 0.3)\text{Ph} + (3.9 \pm 0.7)\text{CF}_3 + (8.7 \pm 1.0)\text{BnPh},\quad n = 6,\quad r^2 = 0.993 \quad (1)$$

$$\Delta\mu(\text{D}) = (0.80 \pm 0.08)\text{Ph} - (5.65 \pm 0.17)\text{CF}_3 + (0.41 \pm 0.23)\text{BnPh},\quad n = 6,\quad r^2 = 0.999 \quad (2)$$

Equation 1 shows that the difference in stability between both tautomers (**a** − **b**, in kJ mol^{-1}) is related to the tendency of both the phenyl (1.5 kJ mol^{-1}) and trifluoromethyl (3.9 kJ mol^{-1}) groups to prefer the 3 position (tautomer **a** in the first case and **b** in the second), while the benzylphenyl group has a strong (8.7 kJ mol^{-1}) and unexpected tendency to occupy the 5 position (**6b** tautomer). This is accounted for by the existence of an intramolecular N−H···π (phenyl) HB in tautomer **6b** (H···C_{ipso} = 2.404 Å and H···C_{ortho} = 2.631 Å). Although this HB disappears in the solid state as stronger intermolecular N−H···N HBs are formed, in solution, **6b** shows a behavior similar to the Wilcox's torsion balance but using tautomerism coupled with rotation (Scheme 3).[19]

SCHEME 3. A Comparison of Wilcox's Torsion Balance (top) and Tautomeric Balance of 6



Concerning the difference in dipole moments between both tautomers, from tautomer **a** to tautomer **b**, in the six pyrazoles the only important change is that produced by the trifluoromethyl group.

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TABLE 4. The HBs Present in the Crystal Structures (Å, deg)

compd		*d*(N−H)	*d*(H···N)	*d*(N−N)	∠NHN
1[a]	N1···H16···N1[b]	*1.458(4)*	*1.458(4)*	2.913(1)	176.4(4)
	N2···H18···N3	*1.41(4)*	*1.44(4)*	2.852(2)	178(3)
	N4···H17···N4[b]	*1.413(4)*	*1.413(4)*	2.824(5)	175(4)
	N2[b]···H18[b]···N3[b]	*1.41(4)*	*1.44(4)*	2.852(5)	178(3)
2[c]	N1−H1···N7	0.86	2.05	2.881(8)	160.9
	N4−H4···N5	0.86	2.08	2.926(9)	167.9
	N6−H6···N2	0.86	2.07	2.921(7)	170.1
	N8−H8···N3	0.86	2.02	2.840(7)	159.6
3[d]	N1−H27···N6	0.933	1.962	2.856	159.7
	N3−H28···N8	0.929	1.953	2.854	163.0
	N5−H26···N4	0.993	1.873	2.844	165.0
	N7−H25···N2	0.906	2.005	2.866	158.3
5	N1−H1···N4	0.86	2.20	2.875(7)	135.6
	N3−H3···N2	0.86	2.25	2.917(7)	134.2
	N5−H5···N6′[e]	0.86	2.26	2.942(7)	136.7
6	N1−H1···N2′[f]	0.89(2)	2.21(2)	2.931(3)	138(2)

[a] In this case the data are in italics to show they correspond to *neutron diffraction* results, where the HB is almost lineal and the hydrogen atoms were located in the middle of the N−H···N HB. H16, H17, and H18 are HA, HB, and HC, described in ref 14. [b] Binary axis 1 − *x*, *y*, −*z* − 1/2. [c] Data taken from ref 16. [d] Data taken from ref 18. [e] 1 − *x*, −*y* + 2, −*z*. [f] −*x* + 1, −*y* + 1, −*z* + 1.

2. X-ray Structures and DSC Experiments. In Table 3 are gathered the crystallographic results related to pyrazoles **1**−**6**. 3(5)-Methyl-5(3)-phenyl-1*H*-pyrazole (**1**), 3(5)-phenyl-5(3)-1*H*-pyrazole (**2**), and 3(5)-phenyl-5(3)-trifluoromethyl-1*H*-pyrazole (**3**) had previously been solved, and 3(5)-isopropyl-5(3)-phenyl-1*H*-pyrazole (**4**) could not be determined as no quality crystals were obtained.

In the 3(5)-benzyl-5(3)-phenyl-1*H*-pyrazole (**5**), three independent molecules of tautomer **5a** were identified in the structural determination (Figure 2). The three molecules show some differences between them in the dihedral angles: 15.1° (pyrazole and phenyl rings), 83.2° (phenyl of the benzyl), 69.1° (between the two phenyl rings) for the first molecule, 9.2°, 71.3°, and 63.9° for the second and 13.4°, 88.9°, and 80.1° for the third one. Two of these independent molecules are linked by hydrogen bonds, and the third one is bonded through hydrogen bonds with a centrosymmetric one (Table 4).

These hydrogen bonds led to dimers of two types, which are sandwiched along the *b* axis bonded with weak hydrogen bonds, C44−H44···N4 and C12−H12···N2, and form one-dimensional chains between dimers of distinct types (Table 5).

Moreover, a very weak interaction C20−H20···C10 between dimers of different chains led to a thick layer (approximately 12.52 Å) parallel to the (−101) plane (Figure 3).

The crystal structure of 3(5)-(2-benzylphenyl)-5(3)-trifluoromethyl-1*H*-pyrazole (**6**) shows the presence of molecules **6b** bonded through hydrogen bonds as dimeric species (Figure 4). The hydrogen lengths and angles of N−H···N hydrogen bonds

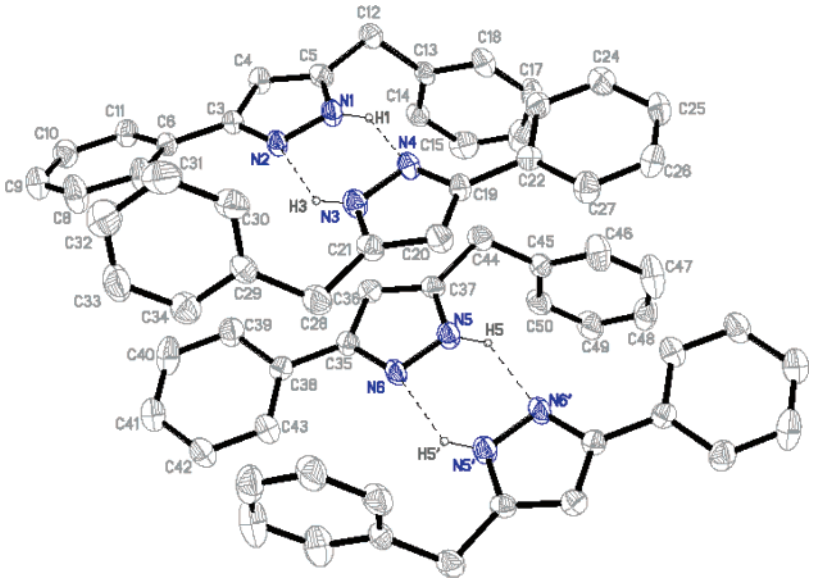

FIGURE 2. ORTEP view of the three independent molecules in the asymmetric unit plus the fourth one generated by symmetry of 5-benzyl-3-phenyl-1*H*-pyrazole (**5a**) showing two dimers.

TABLE 5. Secondary Hydrogen Bonds in Compound 5

X−H···Y	*d*(X−H)	*d*(H···Y)	*d*(X−Y)	∠XHY
C44−H44···N4	0.97	2.80	3.48	128.2
C12−H12···N2	0.97	2.68	3.59	157.0 ($-x$, $-y+1$, $-z$)
C20−H20···C10	0.93	2.78	3.70	168.5 ($x+{}^1/_2$, $-y+{}^3/_2$, $+{}^1/_2$)

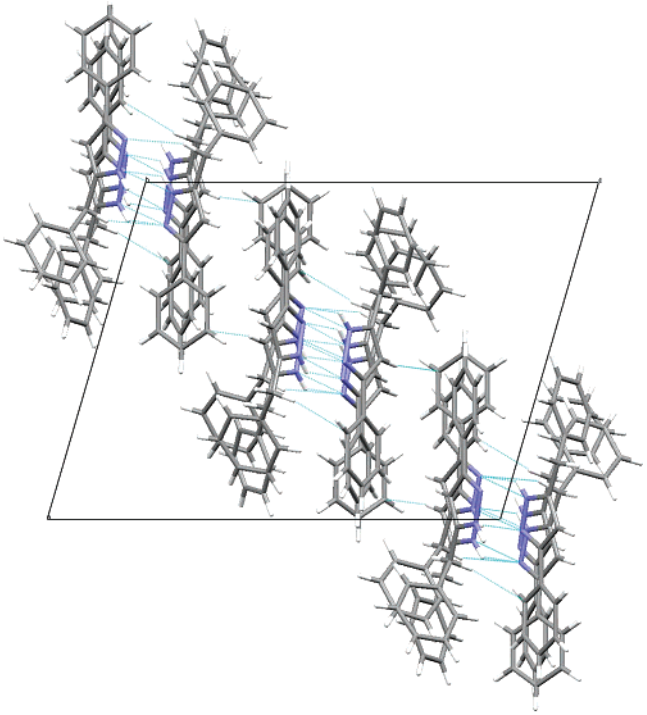

FIGURE 3. 2D network along *b* axis of 5-benzyl-3-phenyl-1*H*-pyrazole (**5a**).

are collected in Table 4. These dimeric species are within van der Waals distances and the packing is presented in Figure 5.

The analysis of the data of Table 4 affords the following information: the reliable *d*(N−N) distance has an average value of 2.90 Å, and it is only slightly sensitive to the presence of phenyl groups at position 5 that diminishes the distance in 0.02 Å. With respect to the NHN angle, its value depends on the compound being a tetramer (about 170°) or a dimer (about 135°).

Concerning annular tautomerism, all the 3(5)-trifluoromethyl substituted NH-pyrazoles so far described are 3-CF_3 derivatives, for instance, **6**, **3**, 5-(2-thienyl)-3-trifluoromethyl-1*H*-pyrazole (dimer), and 5-*tert*-butyl-3-trifluoromethyl-1*H*-pyrazole (tetramer).[4] This is consistent with the energy calculations of the monomers in the gas phase.

Differently to pyrazoles **4** and **5** that correspond to unique crystalline forms, compound **6** presents polymorphism. The three polymorphs found for pyrazole **6** melt at 85.1, 108.1, and 70.7 °C; only for the form melting at 85.1 °C were suitable crystals for X-ray obtained and the structure determined. The problem was studied by DSC: When compound **6** was crystallized in acetonitrile/petroleum ether and the solvent slowly evaporated, crystals melting at 85.1 °C were obtained presenting a unique endothermic peak. The crystals formed from the same solvent but by a brusque cooling of the hot solution, show two endothermic peaks (108.1 and 70.7 °C) with different intensities depending on the crystalline crops and the DSC heating/freezing conditions. These polymorphs are metastable forms that evolve at room temperature to the stable 85.1 °C form but with very different rates, that of 108.1 °C in 24 h and that of 70.7 °C in one month. Desmotropy, different tautomers, cannot be excluded since it has been observed in other pyrazoles,[4,20] but it is improbable owing to the large difference in stability between **6a** and **6b**.

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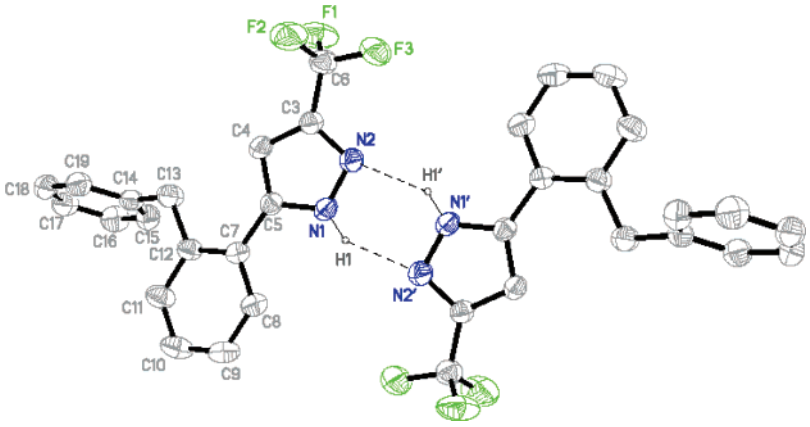


FIGURE 4. ORTEP view of the dimer formed by H-bonding of one independent molecule of 5-(2-benzylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**6b**) with its centrosymmetric counterpart.

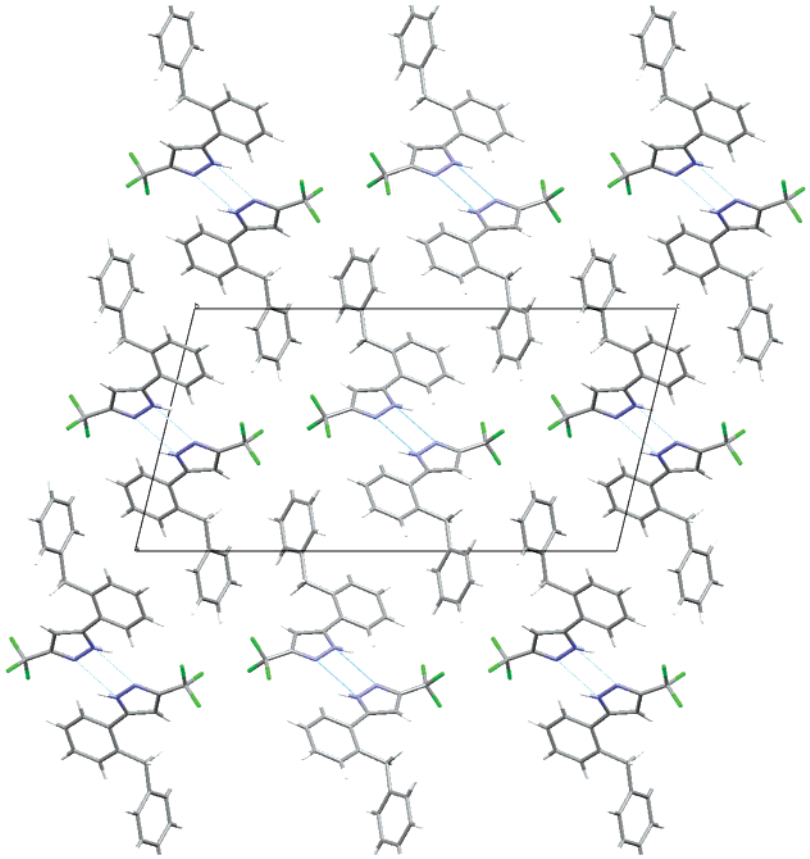
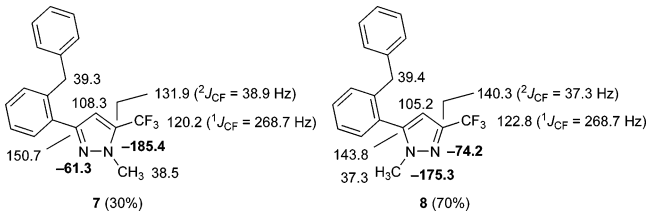


FIGURE 5. Packing along *b* axis of 5-(2-benzylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**6b**).

3. Solution NMR Studies. As a large number of studies dealing with ^{1}H NMR,[21] ^{13}C NMR,[22] and ^{15}N NMR[11] spectroscopy of pyrazoles have been done, there are seldom assignment problems. Only in the case of **6** did we find it useful to prepare the *N*-methyl derivatives **7** and **8** (for the assignment of other 3(5)-trifluoromethylpyrazoles, see ref 23). Scheme 4 shows the most relevant data for these two compounds determined in HMPA-d_{18}.

SCHEME 4. ^{13}C NMR and ^{15}N NMR (bold) Chemical Shifts of Pyrazoles 7 and 8



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SCHEME 5. ^{1}H−^{15}N Couplings Involving the Protons Marked in Blue

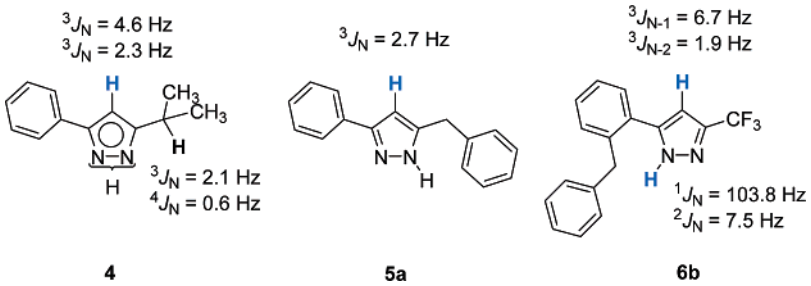

TABLE 6. Selected NMR Data for the Pyrazole Nuclei of Compound 4 at 300 K

solvent	tautomers percentage	^{1}H NMR H-4	^{1}H NMR H-1	^{13}C NMR C-3	^{13}C NMR C-4	^{13}C NMR C-5	^{15}N NMR N-1	^{15}N NMR N-2
$CDCl_3$, 0.05 M	average	6.38		149.6[a]	99.2	154.0[b]		
DMSO-d_6, 0.05 M	**4a** 77	6.45	12.55	149.9	98.3	150.8		
	4b 23	6.45	12.81	[c]	99.1	[c]		
HMPA-d_{18}, 0.3 M	**4a** 82	6.41	13.46	150.1	97.7	150.5	−175.4	−87.7
	4b 18	6.49[d]	13.70	158.3	98.6	142.5	−182.5	−83.3
CPMAS	**4a**			150.7	99.7	152.3	−169.7(3)[e]	−101.5(3)[e]
				151.5		151.5	−171.6(1)[e]	−103.7(1)[e]
				152.3		150.7		

[a] C−Ph. [b] C−^{i}Pr. [c] Not observed. [d] Broad. [e] At 200 K.

The complete ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR results for pyrazoles **4**, **5**, and **6** are reported in Tables S1, S2 and S3 in the Supporting Information. In $CDCl_3$ or CD_2Cl_2 only average signals were observed, but in the more polar solvents DMSO-d_6 and HMPA-d_{18} the existence of two tautomers in the cases of 3(5)-isopropyl-5(3)-phenyl-1*H*-pyrazole (**4**) and 3(5)-benzyl-5(3)-phenyl-1*H*-pyrazole (**5**) was clearly observed. All the signals that appear at different chemical shift values for both tautomers in **4** and **5** lead, after integration, to the same proportions. Particularly useful have been the NH signals in ^{1}H NMR and carbon C-4 in ^{13}C NMR, as well as both nitrogen chemical shifts in ^{15}N NMR (Tables 6−8). A useful criterium to confirm the assignment of signals to the minor tautomer, **4b**, is that they are broader than those of the major one, **4a**. This is a simple consequence of the fact that the minor tautomer has an activation barrier lower than that of the major tautomer.

Noteworthy are the ^{1}H−^{15}N coupling constants measured in the labeled derivatives (Scheme 5). In the literature, there are some values regarding the $^1J(^1H-^{15}N)$ coupling constant in pyrazoles,[11,24] but the $^2J(^1H-^{15}N)$coupling constant between H-1 and N-2 (7.5 Hz in **6b**) has been measured for the first time. The couplings with H-4 are in the range of those reported for *N*-substituted pyrazoles (between 5 and 6 Hz with N-1 and about 1 Hz with N-2 (average 3.5 Hz)). The fact that two different couplings are observed for **4** in $CDCl_3$ should correspond to an average of tautomers in a 75% **4a**/25% **4b** proportion assuming the couplings of H-4 with N-1 and N-2 in the absence of prototropy are 5.75 and 1.15 Hz. For 1-benzylpyrazole (compound **156** of ref 21, p 47) it was reported ^3J(N1H4) = 5.8 and ^3J(N2H4) = 1.1 Hz.

4. Solid-State NMR. In the solid state, NH-pyrazoles bearing different substituents at positions 3 and 5 have three possibilities: (i) to exist in only one tautomer without any dynamic process; this is the most common case and for a new pyrazole this situation would be predicted to be found experimentally; (ii) both tautomers are present in the crystal but nothing dynamic is occurring (no known example); (iii) both tautomers are present in the crystal and the N*H* proton is exchanging between the nitrogen atoms of two adjacent molecules (solid state proton transfer, SSPT), and that is the case, for instance, of compounds **1** and **2**.

3(5)-Isopropyl-5(3)-phenyl-1*H*-pyrazole (4). This compound, whose crystal structure has not been determined, shows very well resolved ^{13}C and ^{15}N CPMAS NMR spectra and the data are gathered in Table 6. In the ^{13}C CPMAS NMR shown in Figure 6, the fact that eight signals are observed for the two methyl groups and four signals for the CH (two superimposed) of the isopropyl substituent points toward **4** being a tetramer, and the chemical shifts of C-3 and C-5 (about 151.5 ppm) point to a **4a4a4a4a** structure. This guess is completely confirmed, as explained later on, by the ^{15}N CPMAS NMR.

3(5)-Benzyl-5(3)-phenyl-1*H*-pyrazole (5). Having determined by crystallography that pyrazole **5** is a **5a5a** dimer, the only comment about the ^{13}C CPMAS NMR data of Table 7 concerns the multiplicity of signals. Carbon atoms C-3 and C-5 appear as three signals while C-4 and the benzylic CH_2 are split into two signals with the intensities being in a 2:1 ratio. This is consistent with the existence of three independent molecules in the crystal.

3(5)-(2-Benzylphenyl)-5(3)-trifluoromethyl-1*H*-pyrazole (6). The results shown in Table 8 concerning pyrazole **6** leave no doubt that there is only one independent molecule and that this molecule is tautomer **6b** (tautomer **6a** should resemble **7**, see Scheme 4). Thus, again X-ray and CPMAS NMR are in perfect agreement.

Solid-state ^{15}N CPMAS NMR chemical shifts are the most appropriate to study the static and dynamic structure of N*H*-pyrazoles. This is mainly because the signals of both nitrogen atoms are separated by 70−80 ppm. In general, labeling with ^{15}N greatly facilitates these studies, especially if something dynamic intervenes.

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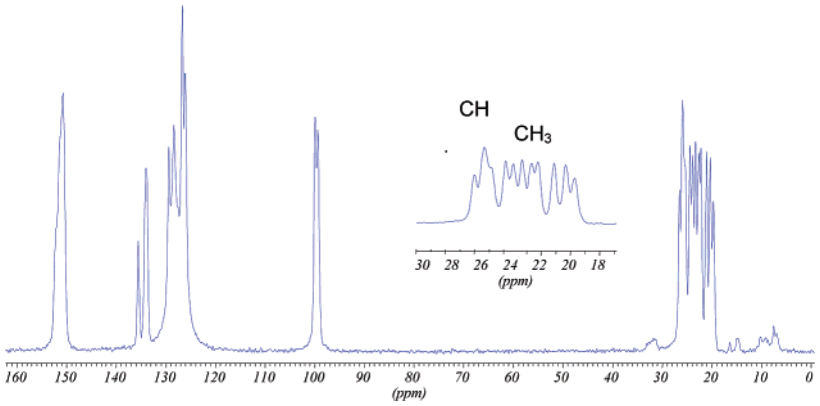

FIGURE 6. ^{13}C CPMAS NMR spectrum of 3(5)-isopropyl-5(3)-phenyl-1*H*-pyrazole (**4**).

TABLE 7. Selected NMR Data for the Pyrazole Nuclei of Compound 5 at 300 K

solvent	tautomers percentage	^{1}H NMR H-4	^{1}H NMR H-1	^{13}C NMR C-3	^{13}C NMR C-4	^{13}C NMR C-5	^{15}N NMR N-1	^{15}N NMR N-2
CD_2Cl_2, 0.14 M	average	6.39	10.08	149.7[a]	102.1	147.4[b]		
DMSO-d_6, 0.04 M	**5a** 55	6.44	10.08	150.5	101.1	143.1		
	5b 45	6.44	12.96	152.2	101.1	143.1		
HMPA-d_{18}, 0.2 M	**5a** 65	6.39[c]	13.72[c]	150.7	100.5	143.1	−172.5	−87.4
	5b 35	6.39[c]	13.90[c]	151.5	101.0	143.3	−180.7	−80.3
CPMAS[d]	**5a**			148.5	102.3(1)	141.4	−174.5	−89.7
				149.0	103.5(2)	142.3		−90.2
				149.8		143.3		−92.2
								−93.3

[a] C−Ph. [b] C−Bn. [c] At 280 K. [d] At 183 K

TABLE 8. Selected NMR Data for the Pyrazole Nuclei of Compound 6b at 300 K

solvent	^{1}H NMR H-4	^{1}H NMR H-1	^{13}C NMR C-3	^{13}C NMR C-4	^{13}C NMR C-5	^{15}N NMR N-1	^{15}N NMR N-2
$CDCl_3$, 0.05 M	6.53	10.60	143.4	103.9	143.8		
DMSO-d_6, 0.05 M	6.69	13.79	141.3	103.5	142.9		
HMPA-d_{18}, 0.05 M	6.58	14.65	141.7	103.5	143.5	−163.9	−80.3
CPMAS			142.4	104.0	142.4	−177.1	−87.2

We have summarized the situation as far as pyrazoles **1**−**6** are concerned in Scheme 6 (the data for pyrazole **3** are from ref 25) which shows the consistency of the chemical shifts for both kinds of nitrogen atoms. The only compounds showing proton transfer are **1** (polymorph A) and **2**.

In the case of **1**, we have reported the spectra at 298 K of polymorph B (formed exclusively by tautomer **1a** and most probably a tetramer) and that of polymorph A at 263 K.[9] The small splitting in **1B** is due to two conformations in a 1:2 ratio of molecule **1a** in the **1a1a1a1a** crystal. The large splitting of **1A** is due to the suppression of the **1a1a1b1b** ⇌ **1b1b1a1a** proton transfer at 183 K thus explaining why they are of the same intensity (50% of **1a** and 50% of **1b**). On cooling, the signals of **1a** (N-1, 170.4; N-2, 102.0 ppm) and **1b** (N-1, 176.3; N-2, 96.5 ppm) are observed.[9] Note that the signals of **1a** are inside those of **1b**. The more complex case of **2** (only the low-temperature spectrum is shown)[16] is similar, but the mixture of **2a2a2a2b** and **2b2b2b2a** is no longer 50:50 but 75:25.[16]

The case of pyrazole **3** will be discussed in details in a future publication together with other trifluoromethylpyrazoles (in DMSO-d_6 the N nuclei resonate at −171.2, N-1, and −82.1, N-2).[25] What is noteworthy here is to point out the presence of exclusively tautomer **3b** with a 5-phenyl substituent in the tetramer.[18] Analogously simple is the case of the other trifluoromethyl derivative **6**. The *o*-benzyl substituent on the phenyl ring at position 5 modifies the chemical shifts of the N-2 nitrogen atom from −97.4 (**3**) to −87.2 (**6**). Although we have been unable to grow crystals of the other polymorphs of **6**, we have succeeded in recording a beautiful ^{15}N CPMAS NMR spectrum of one of them, polymorph B (mp 70.7 °C) shown in Scheme 6.

The case of the phenyl-benzyl-pyrazole **5** is a little more complex. The X-ray results show that this compound crystallizes forming two dimers, one with two independent molecules and the other with only one. This could explain why four signals are observed for N-2. What is more surprising is the position of the signal of the N-2 is observed about −91 ppm. This is consistent with other 3-phenyl pyrazoles where the N-2 appears about −102 ppm, because in dimers, compared to tetramers, the N-2 signal is shifted about 10 ppm.[10]

We leave to the end the case of the 3(5)-isopropyl-5(3)-phenyl-1*H*-pyrazole (**4**), because lacking the crystallographic information we have to rely on the solid NMR study to determine its structure. We have concluded from the ^{13}C CPMAS NMR study that it is probably a **4a4a4a4a** tetramer. The position of the ^{15}N signals, about −102 and −170 ppm is consistent with a 5-alkyl-3-phenyl tautomer **4a** and, since the spectrum is independent of the temperature, that no PT occurs. Two signals are observed for each N atom in a 3:1 ratio but this is not an indication of a **4a4a4a4b** tetramer because the small signals are not between the larger ones such as in 2. We conclude that it is a **4a4a4a4a** tetramer with two or four

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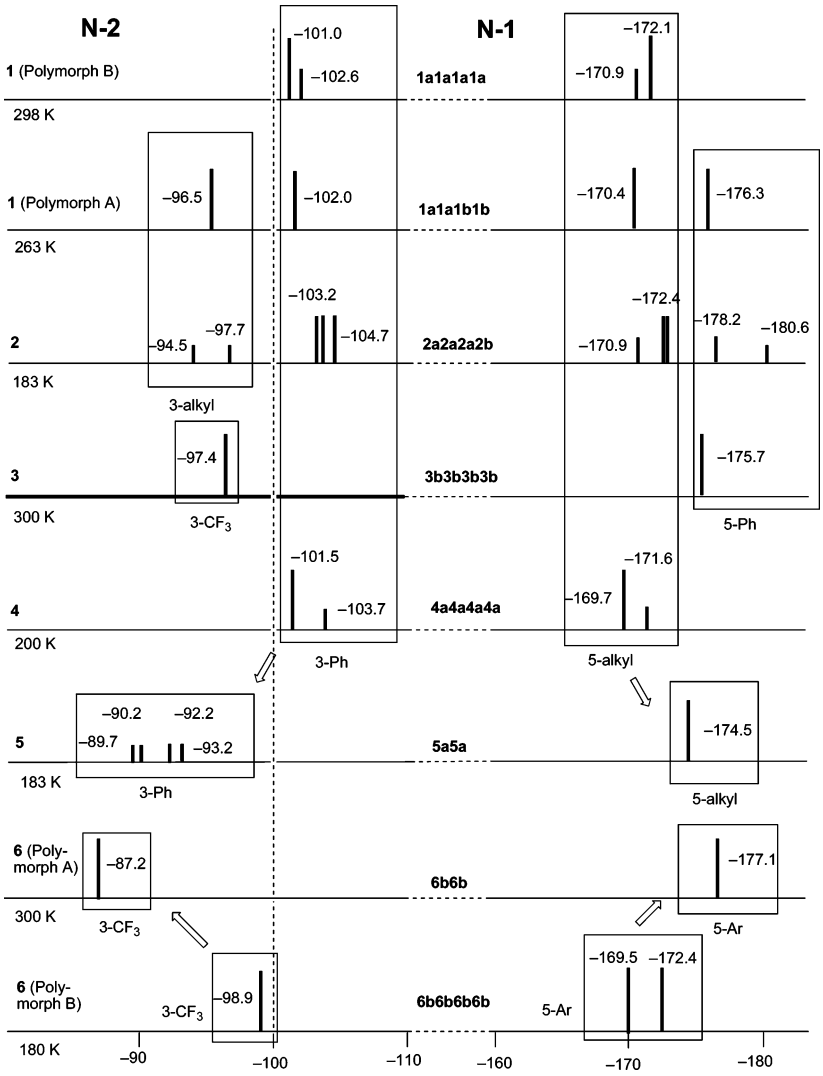
SCHEME 6. ^{15}N CPMAS NMR Chemical Shifts of Pyrazoles 1−6



independent molecules, one of them being more different than the other three.

We have published a paper where the differences in ^{15}N chemical shifts between solid state and solution are related empirically to the X-ray structure.[10] The four main HB motifs have the following values of $\Delta\delta$ of, respectively, N-1 and N-2: catemer 0/−9 ppm; dimer 0/−8 ppm; trimer 1/−2 ppm; tetramer 6/−19 ppm (note the already commented about 10 ppm difference between dimers and tetramers in what concerns N-2). For compound **3**, a tetramer, the effects are −4/−15 ppm, and for compound **4** (Table 6) we have found 6/−15 ppm, both consistent with a tetramer although N-2 seems superior as a probe. For compound **5** (Table 7) the $\Delta\delta$ values are 1/-6 ppm, typical of a dimer, but for dimer **6** (Table 8) the values are −13/−7 ppm; the effect on N-2 is normal but that on N-1 is abnormal (−13 ppm). The polymorph represented in Figure 6 has $\Delta\delta$ values of −7/−19, so the value of N-2 points out toward a **6b6b6b6b** tetramer, but the value for N-1 shows again a deviation of −13 ppm (from +6 to −7 ppm), probably due to the N−H$\cdots\pi$ interaction in the Wilcox's torsion depicted in Scheme 3.

5. General Conclusions. In the present paper on the properties of pyrazoles in the solid state and about how the C-substituents determine the hydrogen-bonded supramolecular structure, we have reached the following conclusions:

(1) Density functional calculations at the B3LYP/6-31G** level allowed us to determine the minimum energies of the optimized geometries as well as dipole moments, of the two N*H* tautomers in six related pyrazoles **1**−**6** and to predict the tautomeric composition in the equilibrium at 298.15 K.

(2) The substituents determine the major tautomer in solution and in the solid state: 5-alkyl-3-phenyl tautomers **a** are more stable than 3-alkyl-5-phenyl ones **b** (**1a1a1a1a**, **4a4a4a4a**, **5a5a**), but the differences in energy are small and in some cases mixtures of **a** and **b** are observed in the crystals (**1a1a1b1b**, **2a2a2a2b**). 5-Aryl-3-trifluoromethyl **b** (**3b3b3b3b**, **6b6b**, **6b6b6b6b**) are much more stable than 3-aryl-5-trifluoromethyl **a** ones.

(3) The presence of one CF_3 substituent prevents proton transfer (PT) in the solid state as the energies of both states, **6b6b** before and **6a6a** after the PT, are much different, thus confirming our previuos results obtained for **1a1a1b1b**/**1b1b1a1a** and **2a2a2a2b**/**2b2b2b2a**.

(4) With substituents such as those of Scheme 2, empirical NMR models predict that they should crystallize as dimers or tetramers.[4,6−8]

(5) ^{13}C and ^{15}N CPMAS NMR are in agreement with the crystallographic results allowing a determination of dimer or tetramer motif (**1a1a1a1a**, **4a4a4a4a**, **6b6b6b6b**) when no crystal structure is available, where the chemical shift of N-2 is particularly useful for this purpose.

(6) To the already known case of **1** (**1a1a1a1a** vs **1a1a1b1b**, desmotropy) we have added a new case of polymorphism, that of **6b6b** dimer versus **6b6b6b6b** tetramer.

Experimental Section

General Methods. Mass spectra were recorded in a mass spectrometer coupled with a gas chromatographer (EI 60 eV). For each sample only the molecular ion and the base peak are reported. DSC were recorded in a calorimeter using samples of 3−5 mg in sealed aluminum pans with heating/freezing rates of 5−15 °C min^{-1}.

Synthesis of β-Diketones. General Procedure. Compounds **9**, **10**, and **11** were obtained by Claisen condensation between acetophenone (or 2-benzylacetophenone) and the corresponding ester.

4-Methyl-1-phenylpentane-1,3-dione (9).[26] Yellow-reddish liquid, yield 30%. ^1H NMR ($CDCl_3$): δ 1.22 [6H, H-5], 2.62 [1H, H-4], 6.19 [1H, H-2], 7.47 [3H, $2H_m$,$1H_p$], 7.88 [2H, $2H_o$], 15.39 [1H, OH], 100% enol.

1,4-Diphenylbutane-1,3-dione (10). Pale yellow solid, yield 98%, mp 52 °C (lit. 52 °C).[27] ^1H NMR ($CDCl_3$): δ 3.70 [2H, H-4], 6.10 [1H, H-2], 7.10−7.79 [8H, H_{arom}], 7.80 [2H, $2H_o$], 15.50 [1H, OH], 100% enol.

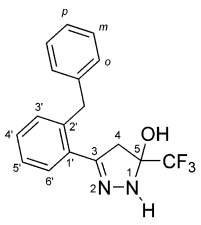
1-(2-Benzylphenyl)-4,4,4-trifluorobutane-1,3-dione (11).[28] Pale orange liquid, yield 93%. ^1H NMR ($CDCl_3$): δ 4.17 [2H, CH_2], 6.10 [1H, H-2], 7.00−7.27 [7H, H_{arom}], 7.35 [1H, H-4′], 7.45 [1H, H-6′], 14.58 [1H, OH], 100% enol.

Synthesis of Pyrazoles. General Procedure. Compounds **4**, **5**, and **6** and their [$^{15}N_2$] labeled analogues, **4***, **5***, and **6*** were prepared by reacting the corresponding β-diketones **9**, **10**, and **11** with 98% hydrazine hydrate (^{14}N) or hydrazine sulfate (^{15}N).

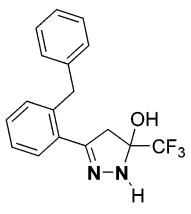
3(5)-Isopropyl-5(3)-phenyl-1*H*-pyrazole (4). From 380 mg (2 mmol) of **9**, a white solid, mp 109.5 °C, was obtained (316 mg, 1.7 mmol, 85%). *m*/*z* (EI) 186 [(M+) (64)], 171 (100). Anal. Calcd for $C_{12}H_{14}N_2$ (186.12): C, 77.4; H, 7.6; N, 15.0. Found: C, 77.1; H, 7.4; N, 14.7.

3(5)-Benzyl-5(3)-phenyl-1*H*-pyrazole (5). From 476 mg (2 mmol) of **10**, a yellow-orange solid, mp 88.9 °C [lit. 91 °C],[9c] was obtained (346 mg, 1.48 mmol, 74%).

3(5)-(2-Benzylphenyl)-5(3)-trifluoromethyl-1*H*-pyrazole (6). Compound **6** was prepared from **11** in two steps. To 612.6 mg (2 mmol) of **11** in 10 mL of ethanol were added dropwise with a gentle stirring, 3 mmol of 98% hydrazine hydrate (153 mg, 0.15 mL). The mixture is stirred for 4 h. Half of the ethanol is evaporated under reduced pressure. The solution, on standing 24 h at room temperature, affords a white paste of 3-(2-benzylphenyl)-5-trifluoromethyl-1*H*-pyrazolin-5-ol (**12**), which was purified by column chromatography over silica gel (70−230 mesh), using as eluent dichloromethane/ethanol 98:2. Yield 85% (544 mg, 1.7 mmol).



12



12*

N = ^{15}N

The ^{15}N labeled compound **12*** was prepared from [$^{15}N_2$] hydrazine sulfate, that needs previous treatment with 10% sodium hydroxide to liberate the [$^{15}N_2$] hydrazine. Compounds **12** and **12*** were fully characterized by ^1H, ^{13}C, and ^{15}N NMR spectroscopy (δ and *J*s) and the data are supplied in Table S4 of the Supporting Information.

Transformation of 12 into 6. An amount of 544 mg (1.7 mmol) of pyrazoline **12** are dissolved in 20 mL of ethanol, and 1 mL of 37% hydrochloric acid is added. The mixture is refluxed 1 h with stirring. The solvent is evaporated under reduced pressure, 20 mL of water is added, and the aqueous solution is neutralized with 2.5 M sodium hydroxide. The solution was extracted thrice with ether, and the ethereal solution was dried over magnesium sulfate, filtered, and evaporated to dryness. 3(5)-(2-Benzylphenyl)-5(3)-(trifluoromethyl)-1*H*-pyrazole (**6**) was obtained as a white solid (464 mg, 1.53 mmol, 90%) polymorph with mp 85.1 °C from acetonitrile/petroleum ether by slow evaporation. *m*/*z* (EI) 302 (M^+, 100). Anal. Calcd for $C_{17}H_{13}F_3N_2$ (302.29): C, 67.5; H, 4.3; N, 9.3. Found: C, 67.4; H, 4.5; N, 9.1.

***N*-Methyl Derivatives 7 and 8.** A mixture of 500 mg (1.65 mmol) of pyrazole **6**, 235 mg (1.65 mmol) of methyl iodide, and 88.8 mg (1.65 mmol) of sodium methoxide in 50 mL of methanol were heated at reflux for 4 h. The solvent was evaporated to dryness, and the residue was dissolved in the minimum amount of water and neutralized with 50% HCl aq. The solution was extracted three times with hot chloroform (50 mL), and the chloroform layer was evaporated. The residue contains starting pyrazole **6** and a 30:70 mixture of pyrazoles **7** and **8** that was not separated and used as such for NMR studies. Yield 300 mg, 0.95 mmol, 58%.

NMR Spectroscopy. (a) In Solution. The measurements were carried out on a 9.4 T spectrometer (400.13 MHz for ^1H, 100.62 MHz for ^{13}C, and 40.56 MHz for ^{15}N) using a 5 mm X−H inverse detection probe provided with a *z*-gradient coil. The chemical shifts (δ in ppm) of ^1H and ^{13}C are referred to the corresponding solvents: $CDCl_3$ (7.26), CD_2Cl_2 (5.32), DMSO-d_6 (2.49), HMPA-d_{18} (2.52), and $CDCl_3$ (77.0), CD_2Cl_2 (53.8), DMSO-d_6 (39.5), HMPA-d_{18} (35.8), respectively. For the ^{15}N NMR spectra, nitromethane (0.00) was used as an external reference. Coupling constants *J* are given in Hz.

Digital resolution was 0.34 Hz/point for ^1H NMR, 0.63 Hz/point for ^{13}C NMR, and 0.44 Hz/point for ^{15}N NMR. Monodimensional ^{15}N NMR spectra were obtained using the *inverse gated* sequence. The 2D ($^1H-^1H$) gs-COSY, ($^1H-^{13}C$) gs-HMQC, and ($^1H-^{13}C$) gs-HMBC spectra were recorded and processed using Bruker software in a mode nonsensitive to the phase. Gradient selection was selected by means of a pulse sequence truncated at 5% in the sinusoid with a 1 ms duration.

(b) In the Solid-State. ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CP/MAS NMR spectra were recorded in a wide-bore 9.4 T spectrometer provided with a 4 mm DVT probe. The samples were previously compacted in zirconia rotors with Kel-F caps. The used rotation frequencies were 12 kHz for the ^{13}C experiments and 6 kHz for the ^{15}N ones. For ^1H decoupling, the TPPM sequence was used. ^{13}C chemical shifts are referred to glycine (176.1 ppm); those of ^{15}N are referred to $^{15}NH_4Cl$ and converted to nitromethane by the relationship: $\delta\ ^{15}N\ (CH_3NO_2\ ext.) = \delta\ ^{15}N\ [NH_4Cl\ (s)] - 338.1$ ppm.

(c) Variable Temperature. In solution and solid-state NMR at 9.4 T, variable temperature (VT) experiments were carried out to study proton-transfer dynamics in the temperature range of 300−180 K. A temperature unit was used to control the cooling gas together with an exchanger to reach low temperatures. To avoid the problems due to air humidity at low temperatures, we used pure nitrogen obtained by evaporation of liquid nitrogen as the bearing, driving, and cooling gas. In solid NMR measurements zirconia caps were necessary.

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TABLE 9. Crystal Data and Structure Refinement for Compounds 5 and 6

crystal data	**5**	**6**
empirical formula	$C_{48}H_{42}N_6$ (3 molecules)	$C_{17}H_{13}F_3N_2$
fw	702.88	302.29
wavelength (Å)	0.71073	0.71073
cryst syst	monoclinic	monoclinic
space group	*P*2(1)/*n*	*P*2(1)/*c*
a (Å)	14.078(2)	12.191(1)
b (Å)	15.693(2)	5.1933(5)
c (Å)	18.185(2)	23.579(2)
β (deg)	106.286(3)	103.880(2)
V (Å^3)	3856.2(8)	1449.2(2)
Z	4	4
density (calcd) (Mg/m^3)	1.211	1.386
abs coeff (mm^{-1})	0.072	0.110
F(000)	1488	624
theta range (deg)	1.63 to 25.0	1.72 to 28.85
index ranges	−16, −18, −19 to 16, 18, 21	−14, −6, −29 to 15, 7, 30
reflns collected	19937	8664
independent reflns	6769 [*R*(int) = 0.2098]	3456 [*R*(int) = 0.0440]
data/restraints/params	6769/0/488	3456/0/238
R^a [$I > 2\sigma(I)$]	0.0642 (1527 obsd reflns)	0.0463 (1901 obsd reflns)
$R\ w_F{}^b$ (all data)	0.198	0.1240

^{a} $\sum||F_o| - |F_c||/\sum|F_o|$. ^{b} $\{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

Crystal Structure Determination. Suitable crystals for X-ray diffraction experiments were obtained by crystallization of **5** in chloroform/hexane and **6** from acetonitrile/petroleum ether. Data collection for both compounds was carried out at room temperature on a CCD diffractometer using graphite-monochromated Mo Kα radiation (= 0.71073) operating at 50 kV and 30 mA. In both cases, data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 30 s covered 0.3 in. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 50 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. A summary of the fundamental crystal and refinement data is given in Table 9.

The structures were solved by direct methods and refined by full-matrix least-squares procedures on F^2 (SHELXL-97).[29] All non-hydrogen atoms were refined anisotropically. For **5**, all hydrogen atoms were included in their calculated positions and refined riding on the respective carbon or nitrogen bonded atoms; for **6** the hydrogens were located in a difference Fourier synthesis and their coordinates were refined. Final *R* (*R*w) values were 6.42 (19.8) for **5** and 4.36 (12.4) for **6**. Largest peaks and holes in the final difference map were 0.184 and −0.195 and 0.249 and −0.235 e $^{-3}$ for **5** and **6**, respectively.

Theoretical Calculations. Energy calculations were carried out at the hybrid Becke B3LYP/6-31G** level with basis sets of Gaussian-type functions[30] within the Windows Titan 1.0.5 package[31] and include zero point energy (ZPE) corrections. Starting geometries for the calculations were the optimized ones obtained at the HF/6-31G** level, and no symmetry restrictions were imposed. In all pyrazoles, the final geometries really correspond to the minima as no imaginary frequencies appear.

In the case of both tautomers of compound **6**, the exploration of the conformational space was achieved at the same level using a systematic search. The three angles that define the conformation of the benzyl-phenyl group were explored using a 2(pyrazole−C_6H_4/phenyl) × 3(C_6H_4/phenyl−CH_2) × 3(CH_2−C_6H_5/phenyl).

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Supporting Information Available: Tables of atom coordinates and absolute energies to document the computational B3LYP/6-31G** calculations for tautomers **a** and **b** of compounds **1**−**6** (pages S1−S26) and the complete ^{1}H NMR, ^{13}C NMR, and ^{15}NMR data (chemical shifts in ppm and coupling constants *J* in Hz) of pyrazoles **4**, **5**, and **6** as well as those of pyrazoline **12** (Tables S1−S4, pages S27−S40). This material is available free of charge via the Internet at http://pubs.acs.org.

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