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Supramolecular structure of 1*H*-pyrazoles in the solid state: a crystallographic and *ab initio* study

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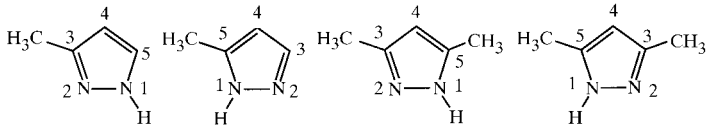
The secondary structure of 1*H*-unsubstituted pyrazole derivatives bearing only one hydrogen donor group and one or more acceptor groups has been analyzed in terms of some descriptors representing the substituents at C3 and C5. The substituent at C4 appears to affect mainly the tertiary or quaternary structure of these compounds. The proposed semi-quantitative model, which explains most hydrogen-bonded motifs as a combination of the effects of substituents at C3 and C5, has also been examined as a function of the steric and polarizability effects of these substituents represented by molar refractivity. The model also applies to other five-membered rings (1,2,4-triazoles, 1,2,4-diazaphospholes and 1,2,4-diazaarsoles). Furthermore, *ab initio* calculations at RHF/6-31G* have been performed to discover the relative stability of three of the four hydrogen-bond patterns displayed by several symmetrical pyrazoles (dimers, trimers, tetramers). The fourth motif, catemers, has only been discussed geometrically.

1. Introduction

To discuss the structure of the *N*-unsubstituted pyrazoles in the solid state, it is necessary first to clarify the nomenclature and numbering of pyrazoles in relation to tautomerism. In pyrazoles and, in general, azoles, the number 1 atom is that bearing the substituent, either H or *R*. Annular tautomerism (Elguero *et al.*, 1976; Minkin *et al.*, 2000) involves the exchange of the N—H hydrogen atom between the different N atoms of the azole ring. For instance, pyrazoles are named as if it was the *C*-substituent which changes position in the ring and this can cause confusion. As an example, 3(5)-methylpyrazole (I) corresponds to a mixture in any proportion of tautomers (I*a*) and (I*b*). If, in some special circumstances, only one tautomer is present then it should be named 3-methylpyrazole (I*a*) or 5-methylpyrazole (I*b*).



(I*a*) (I*b*) (II*a*) (II*b*)

It is very common in azoles that the substituents at the 'tautomeric' positions, *i.e.* 3 and 5 in pyrazoles, are identical. In that case, there is no problem of nomenclature; for instance, both tautomers of 3,5-dimethylpyrazole (II) have the same name because they are identical. Nevertheless, it is very important to remember that the proton exchange that transforms (I*a*) into (I*b*) is also operating in (II*a*)/(II*b*).

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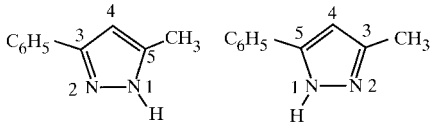
Table 1
N-Unsubstituted pyrazoles bearing identical substituents at positions 3 and 5.

	R^3	R^4	R^5	Structure	CSD code	Reference
1	H	H	H	Catemer	PYRZOL	Larsen *et al.* (1970)
2	H	CH_3	H	Trimer	–	Goddard *et al.* (1999)
3	H	Ad†	H	Catemer	NOPRUF	Cabildo *et al.* (1994)
4	H	NO_2	H	Trimer‡	WIKZUL	Llamas-Saiz *et al.* (1994)
5	H	Br	H	Trimer‡	–	Foces-Foces *et al.* (1999)
6	CH_3	H	CH_3	Trimer‡	DASXEA	Baldy *et al.* (1985)
6				Trimer‡	DASXEA10	Smith *et al.* (1989)
7	CH_3	CH_3	CH_3	Catemer	–	Infantes, Foces-Foces & Elguero (1999)
8	CH_3	NO_2	CH_3	Catemer‡	LETNAZ	Foces-Foces *et al.* (1993)
9	CH_3	Br	CH_3	Catemer‡	–	Foces-Foces *et al.* (1999)
10	^{t}Bu	H	^{t}Bu	Dimer‡	YULNUO	Aguilar-Parrilla *et al.* (1995)
11	^{t}Bu	NO	^{t}Bu	Dimer‡	RIVBAZ	Fletcher *et al.* (1997)
12	^{t}Bu	NO_2	^{t}Bu	Dimer	WILBAU	Llamas-Saiz *et al.* (1994)
13	C_6H_5	H	C_6H_5	Tetramer‡	LADBIB	Aguilar-Parrilla *et al.* (1992)
13				Tetramer‡	LADBIB01	Raptis *et al.* (1993)
14	C_6H_5	NO_2	C_6H_5	Dimer	WILBEY	Llamas-Saiz *et al.* (1994)
15	C_6H_5	Br	C_6H_5	Dimer‡	LADBEX	Aguilar-Parrilla *et al.* (1992)
16	CF_3	H	CF_3	Tetramer‡	–	Alkorta *et al.* (1999)

† 1-Adamantyl. ‡ Proton disorder (see text).

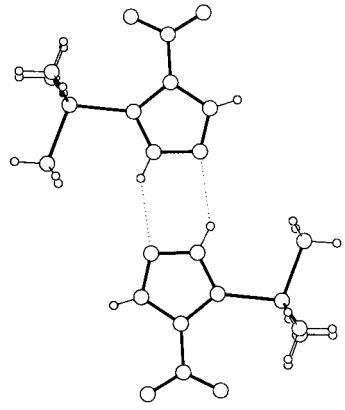
One of the cases where only one tautomer is present occurs in crystals. In most examples, only one tautomer is observed and must be named accordingly. The rare cases of desmotropy (each tautomer crystallizing in a different solvent) are not a problem, for instance, one being (I*a*) and the other (I*b*). However, there are two important exceptions. The first occurs when both tautomers are found in the same crystal, as in 3(5)-phenyl-5(3)-methylpyrazole (III). This compound crystallizes as a tetramer formed by two molecules of (III*a*) and two molecules of (III*b*) (Maslen *et al.*, 1974; Moore *et al.*, 1975). The accurate name should be (3-phenyl-5-methylpyrazole)$_2$(3-methyl-5-phenyl-pyrazole)$_2$, but it is too cumbersome.



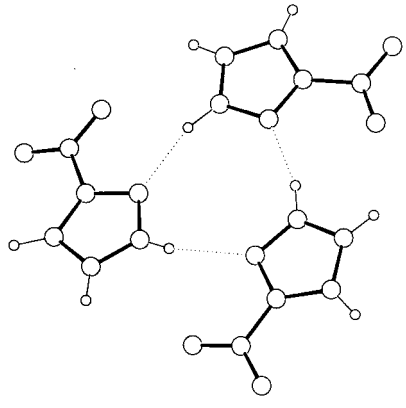
(III*a*) (III*b*)

The second exception (which can co-exist with the first) is more important because, rather frequently, in 1*H*-pyrazoles the N—H hydrogen atom appears disordered. Leaving aside, for the moment, whether the disorder is static or dynamic, the consequence is that both tautomers are present in the crystal in proportions which are not necessarily equal. Then, an unsolved problem of nomenclature arises. In the case of (I), we will use 3-methylpyrazole (I*a*) if this is the tautomer present in the crystal and 3(5)-methylpyrazole when the N—H hydrogen atoms are disordered, but in the case of (II) we have to use 3,5-dimethylpyrazole in both cases, not knowing if it is (II*a*) (ordered) or a mixture of (II*a*) and (II*b*) (disordered).

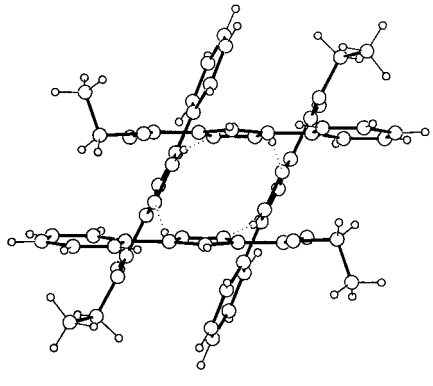
We have already discussed the geometrical information concerning the hydrogen-bond (HB) patterns in pyrazoles (Elguero *et al.*, 1994; Llamas-Saiz *et al.*, 1994, and references therein). More recently, we reported the structure of a series of *C*-ethoxy-carbonylpyrazoles, which led us to suggest a simple model relating the hydrogen-bonding motifs to the substituents R^3 and R^5 (Infantes, Foces-Foces, Claramunt *et al.*,



(*a*)



(*b*)



(*c*)

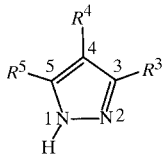
Figure 1
Examples of the three hydrogen-bonding motifs: (*a*) dimers in VEHCOA (**21**), (*b*) trimers in RIKNOO (**38**) and (*c*) tetramers in FAQSIZ (**29**).

Table 2
N-unsubstituted pyrazoles bearing different substituents at positions 3 and 5 with localized NH protons (only the tautomer present in the crystal is reported).

	R^3	R^4	R^5	Structure	CSD code	Reference
17	H	H	†	Dimer	TEHQAY	Halcrow *et al.* (1996)
18	H	CH_3	CH_3	Trimer	–	Infantes, Foces-Foces & Elguero (1999)
19	H	C_6H_5	N_3	Catemer	PAZDPY	Domiano & Musatti (1974)
20	H	NO_2	CH_3	Trimer	HEHVAR	Foces-Foces *et al.* (1994)
21	H	NO_2	$Si(CH_3)_3$	Dimer	VEHCOA	Bottaro *et al.* (1990)
22	CH_3	H	^{t}Bu	Tetramer	–	Foces-Foces & Trofimenko (1999)
23	CH_3	NO_2	H	Dimer	HEHTUJ	Foces-Foces *et al.* (1994)
24	C_6H_5	H	^{t}Bu	Tetramer	–	Foces-Foces & Trofimenko (1999)
25	C_6H_5	Br	H	Trimer	PAMTAY	Aguilar-Parrilla *et al.* (1992)
26	CO_2	$MeCF_3$	H	Trimer	LETCES	Beagley *et al.* (1994)
27	CO_2Et	H	H	Catemer	FAQROE	Infantes, Foces-Foces, Claramunt *et al.* (1999)
28	CO_2Et	H	CH_3	Catemer	FAQSAR	Infantes, Foces-Foces, Claramunt *et al.* (1999)
29	CO_2Et	H	C_6H_5	Tetramer	FAQSIZ	Infantes, Foces-Foces, Claramunt *et al.* (1999)
30	CO_2Et	Me	H	Catemer	FAQSEV	Infantes, Foces-Foces, Claramunt *et al.* (1999)
31	CO_2Et	C_6H_5	H	Catemer	FAQSOF	Infantes, Foces-Foces, Claramunt *et al.* (1999)
32	CO_2Et	Br	H	Catemer	FAQSUL	Infantes, Foces-Foces, Claramunt *et al.* (1999)
33	CO_2Et	Br	CH_3	Catemer	FAQTAS	Infantes, Foces-Foces, Claramunt *et al.* (1999)
34	CO_2Et	Br	C_6H_5	Tetramer	FAQTIA (& 01)	Infantes, Foces-Foces, Claramunt *et al.* (1999)
35	CO_2Et	‡	$Si(CH_3)_3$	Tetramer	GIRNEA	Bettison *et al.* (1988)
36	CF_3	H	2-Thienyl	Dimer	–	Foces-Foces *et al.* (2000)
37	CF_3	H	^{t}Bu	Tetramer	–	Foces-Foces & Trofimenko (1999)
38	NO_2	H	H	Trimer	RIKNOO	Foces-Foces *et al.* (1997)

† 2′,5′-Dimethoxyphenyl. ‡ —C≡C—TMS.

1999). The hydrogen-bonding network present in all these 1*H*-pyrazoles is very complicated when several donor and acceptor groups, in addition to those of the pyrazole, are present in the structures. The aim of the present paper is to



(IV)

advance our understanding of these systems and the relationships between different types of substituents at the C atoms of the ring [R^3, R^4 and R^5 in (IV)] and the crystal structure of NH-unsubstituted pyrazoles.

2. A simple model to classify 1*H*-pyrazole networks

To gain insight into the factors that appear to govern the formation of hydrogen-bonding motifs in pyrazoles, two cases have been excluded from this study:

(i) hydrates, salts and inclusion complexes since, for instance, water and hosts perturb the HBs, and

(ii) compounds where at least one of the *C*-substituents is a good hydrogen-bond donor (CO_2H, CH_2OH, NHR,...), since it directs the hydrogen-bond network, the last case being rather common.

Tables 1–3 contain all the information presently available for structures of neutral pyrazoles fulfilling the restriction that there must be only one hydrogen-bond donor in the molecule, pyrazole N1—H, and one or more acceptor groups, including the pyrazole —N2═ atom. Most examples were retrieved from the Cambridge Structural Database (Allen *et al.*, 1991, Version of October 1999; CSD hereinafter), but some unpublished results are also included (Foces-Foces & Trofimenko, 1999; Foces-Foces *et al.*, 2000). The 47 retrieved pyrazoles belong to two categories: (*a*) without either O or N atoms in the substituents and (*b*) with O or N atoms in the substituents. The compound NIBFIN was not considered because the R^3 substituent (4-phenoxyphenyl) has conformational mobility about the O atom linking the aryl rings and its steric and electronic properties are difficult to assess. All 20 pyrazoles belonging to (*a*) and 21 out of 26 compounds in subset (*b*) crystallized with one of the following four hydrogen-bonding patterns: dimers, trimers, tetramers and catemers through N—H···N hydrogen interactions using both N atoms of the pyrazole. In the five remaining compounds, the NH of the pyrazole is involved in hydrogen-bonding interactions with Osp^2 or Nsp^2 atoms of the substituents (VAXLAH, BEWLEU and LEVVAJ, RIZYEE, YAXZOM, respectively).

The 41 compounds are regularly distributed into the four hydrogen-bonding motifs: dimers and trimers are equally populated with 9 compounds each, there are 10 tetramers and the catemer motif has 13 representatives. The topology of the cyclic motifs does not correspond to any of the top 24 synthons involving *D*—H···*A* (*D*, *A* = O or N), which frequently appear in the structures of organic compounds (Allen *et al.*, 1998). Figs. 1(*a*)–(*c*) show examples of dimers, trimers and tetramers, while Figs. 2(*a*)–(*d*) show four examples of catemers corresponding to four helical arrangements of pyrazoles in which 2, 3, 4 and 6 molecules are required for one turn (pitch 2, 3, 4 and 6).

Table 3
N-Unsubstituted pyrazoles bearing different substituents at positions 3 and 5 with disordered NH protons (both tautomers present in the crystal are reported using different numbers for each tautomer: **39**/**42**, **40**/**43** and **41**/**44**).

	R^3	R^4	R^5	Structure	CSD code	Reference
39	H	H	Ad†	Catemer‡	–	Claramunt *et al.* (1997)
40	CH_3	H	C_6H_5	Tetramer‡	MEPHPY	Maslen *et al.* (1974)
40				Tetramer‡	MEPHPY 01	Moore *et al.* (1975)
41	CH_3	Br	C_6H_5	Tetramer‡	–	Llamas-Saiz *et al.* (1999)
42	Ad†	H	H	Catemer‡	–	Claramunt *et al.* (1997)
43	C_6H_5	H	CH_3	Tetramer‡	MEPHPY	Maslen *et al.* (1974)
43				Tetramer‡	MEPHPY 01	Moore *et al.* (1975)
44	C_6H_5	Br	CH_3	Tetramer‡	–	Llamas-Saiz *et al.* (1999)

† 1-Adamantyl. ‡ Proton disorder (see text).

The structures with cyclic hydrogen-bonding motifs (dimers, trimers and tetramers) can be represented using the centroid of the pyrazole ring (neglecting the *C* substituents) with lines connecting these points to simulate the hydrogen bonds. To describe these polygons, we use the distance between centroids d (Å) and the angle ψ (°). The angle ψ suffices to describe the small pseudo-rings, $\psi = 0$ and 60° for dimers and trimers (Fig. 3). Planar tetramers (unknown) will have $\psi = 90°$, but they can fold to attain a tetrahedral disposition of the four points ($\psi = 60°$) or even less. This conformation will be the **supramolecular** counterpart of the **molecular** structure of *ortho*-tetraphenylene (BASCIH, tub-shaped, ψ = 66.3°; Irngartinger & Reibel, 1981). Rather than the angle ψ, it is possible to use the distance r between the planes containing the opposite corners, $r = 0$ Å for a square tetramer, $r = 1.155$ Å for a regular tetrahedron inscribed in a sphere of radius = 1 Å and in general, $r^2 = 4\,(1 - 2A)/(1 + 2A)$ [$A = (\sin \psi/2)^2$].

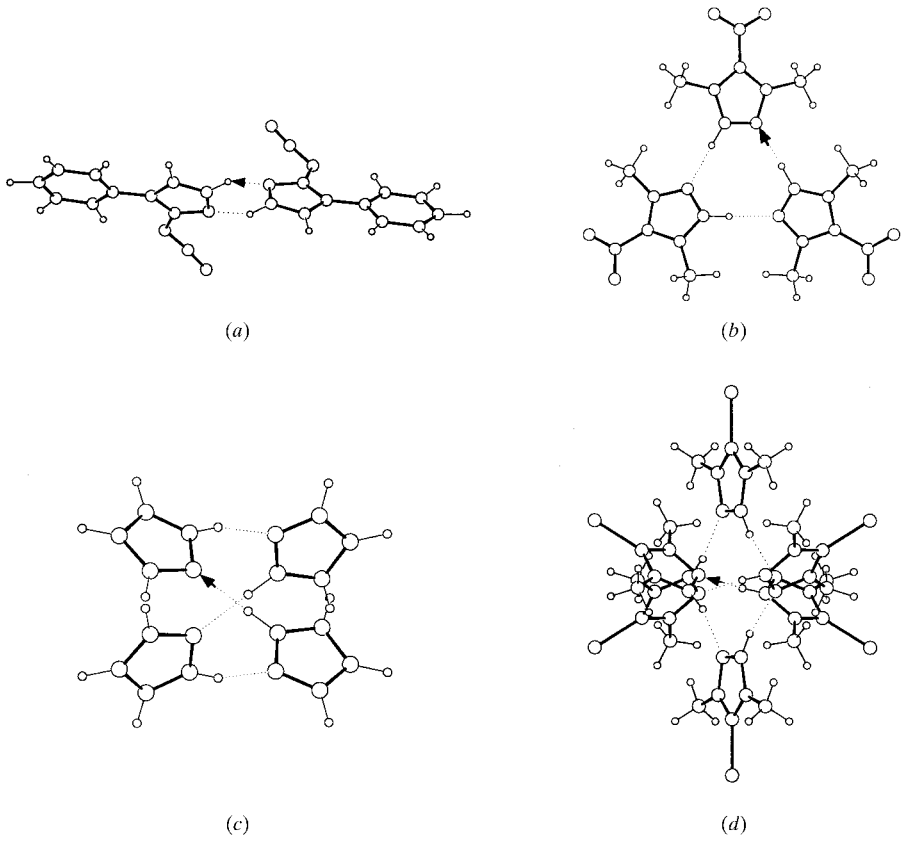


Figure 2
The four helical arrangement of molecules in the catemer motif: (*a*) PAZDPY (**19**), (*b*) LETNAZ (**8**), (*c*) PYRZOL (**1**) and (*d*) in 3,5-dimethyl-4-bromopyrazole (**9**), where 2, 3, 4 and 6 molecules are required for one turn, respectively (pitchs 2, 3, 4 and 6).

2.1. Theoretical calculations

For comparison purposes we have carried out *ab initio* calculations on dimers, trimers and tetramers of the parent pyrazole **1** (bold arabic numbers refer to the structures given in Tables 1–7), 3,5-dimethylpyrazole **6**, 3,5-di-*tert*-butylpyrazole **10**, and three unreported pyrazoles: 3,5-difluoro **53**, 3,5-dichloro **54** and 3,5-dibromo **55**. All the monomers and complexes mentioned before have been fully optimized at the RHF/6-31G* (Hehre *et al.*, 1972; Clark *et al.*, 1983; Frisch *et al.*, 1984) computational level within the *Gaussian*98 set of programs (Frisch *et al.*, 1998), maintaining the following symmetry: C_s for the monomers, C_{2h} for the dimers, C_{3h} for the trimers and S_4 for the tetramers. The complexation energy has been obtained as the difference between the energy of the corresponding complex and the sum of the energies of the isolated monomers. The geometrical results of these calculations are also reported in Table 4. The only experimental data are those of the 3,5-dimethylpyrazole trimer (**6**, DASXEA10, Table 1) and the 3,5-di-*tert*-butylpyrazole dimer (**10**, YULNUO, Table 1). In both cases, the agreement between monomers is good, but the N—H···N hydrogen bonds are shorter in the crystal than in the calculated structures (see below).

For the dimers, the average experimental value for d_1 is 4.75 Å, while the calculated value is 4.85 Å; therefore, d_1 is slightly longer in the 'gas phase' than in the crystal. For trimers ($\psi_i \simeq 60°$), d_i (i = 1, 2, 3) = 5.13 and 5.36 Å, respectively, excluding **10**. Tetramers are the most interesting case and all the examples, both experimental and calculated, correspond to distorted tetrahedra, and, in this small zone, r (Å) = 2.5 − 0.23ψ (°). Geometries range about the regular tetrahedron [$\psi = 60°$, $r = 1.155$ Å], from the most flat, 3,5-dibromopyrazole **55** [$\psi = 73.1°$, $r = 0.825$ Å] to the most folded, FAQSIZ **29** [$\psi = 42.1°$, $r = 1.536$ Å]. The distances d_i (i = 1, 2, 3, 4) are between 5.06 and 5.30 Å, respectively, again excluding **10**. The calculated

Table 4
Experimental and calculated bond distances and angles between the pyrazole centroids characterizing the three cyclic hydrogen-bond motifs (Å, °).

d_1 and d_2 represent the distance between the centroid of pyrazole 1 with the previous and the following one, and ψ_1 and ψ_2 are the angles at centroids 1 and 2, and so on. Distances and angles up to d_4 and α_4 are given when several independent molecules are present in the hydrogen-bond motif.

		d_1	d_2	d_3	d_4	ψ_1	ψ_2	ψ_3	ψ_4
Experimental geometries									
Dimers									
10	YULNUO	4.745 (2)							
11	RIVBAZ	4.811 (1)							
12	WILBAU	4.813 (1)							
14	WILBEY	4.712 (3)							
15	LADBEX	4.684 (3)							
17	TEHQAY	4.790 (2)							
21	VEHCOA	4.747 (2)							
23	HEHTUJ	4.743 (2)							
23	HEHTUJ	4.739 (2)							
36	CF_3/Thpz	4.704 (9)							
Trimers									
2	4-Mepz	5.154 (1)	5.184 (1)	5.128 (2)	–	59.5 (1)	60.0 (1)	60.6 (1)	–
4	WIKZUL	5.123 (2)	5.109 (2)	5.118 (2)	–	60.0 (1)	60.1 (1)	59.9 (1)	–
5	4-Brpz	5.139 (4)	5.139 (4)	5.149 (4)	–	60.1 (1)	59.9 (1)	59.9 (1)	–
6	DASXEA	5.206 (6)	5.206 (6)	5.206 (6)	–	60.0 (1)	60.0 (1)	60.0 (1)	–
18	3,4-DiMepz	5.148 (2)	5.160 (2)	5.163 (2)	–	60.1 (1)	59.8 (1)	60.1 (1)	–
18	3,4-DiMepz	5.161 (2)	5.153 (2)	5.165 (2)	–	60.1 (1)	60.0 (1)	59.9 (1)	–
20	HEHVAR	5.128 (4)	5.125 (3)	5.150 (4)	–	60.3 (1)	59.9 (1)	59.8 (1)	–
25	PAMTAY	5.012 (4)	5.181 (4)	5.181 (4)	–	61.7 (1)	58.6 (1)	59.7 (1)	–
26	LETCES	5.111 (3)	5.183 (3)	5.168 (3)	–	60.3 (1)	59.2 (1)	60.6 (1)	–
38	RIKNOO	5.148 (2)	5.169 (2)	5.212 (2)	–	60.7 (1)	59.5 (1)	59.9 (1)	–
38	RIKNOO	5.176 (2)	5.145 (2)	5.156 (2)	–	59.9 (1)	60.3 (1)	59.7 (1)	–
Tetramers									
13	LADBIB	5.145 (2)	5.030 (2)	5.184 (2)	5.030 (2)	64.1 (1)	63.7 (1)	63.7 (1)	64.1 (1)
16	3,5-DiCF_3	5.202 (3)	4.998 (4)	5.225 (4)	4.995 (3)	47.6 (1)	50.0 (1)	47.5 (1)	50.1 (1)
22	Me/^{t}Bu	5.110 (2)	5.110 (2)	5.110 (2)	5.110 (2)	54.3 (1)	54.3 (1)	54.3 (1)	54.3 (1)
24	Ph/^{t}Bu	5.026 (16)	5.026 (16)	5.026 (16)	5.026 (16)	47.6 (2)	47.6 (2)	47.6 (2)	47.6 (2)
29	FAQSIZ	5.136 (1)	4.850 (1)	5.136 (1)	4.850 (1)	41.3 (1)	42.9 (1)	41.3 (1)	42.9 (1)
34	FAQTIA	4.970 (2)	4.970 (2)	4.970 (2)	4.970 (2)	41.5 (1)	41.5 (1)	41.5 (1)	41.5 (1)
35	GIRNEA	4.910 (10)	4.910 (10)	4.910 (10)	4.910 (10)	48.5 (1)	48.5 (1)	48.5 (1)	48.5 (1)
37	CF_3/^{t}Bu	5.112 (14)	5.112 (14)	5.112 (14)	5.112 (14)	54.0 (2)	54.0 (2)	54.0 (2)	54.0 (2)
37	CF_3/^{t}Bu	5.165 (17)	5.165 (17)	5.165 (17)	5.165 (17)	52.5 (2)	52.5 (2)	52.5 (2)	52.5 (2)
40/43	MEPHPY	5.214 (2)	5.129 (2)	5.078 (2)	5.214 (2)	63.5 (1)	64.4 (2)	64.4 (2)	63.5 (1)
41/44	Me/Br/Ph	4.929 (3)	5.026 (3)	4.929 (3)	5.154 (3)	42.5 (1)	42.5 (1)	41.9 (1)	41.9 (1)
Calculated geometries									
Dimers									
1	Pyrazole	4.858							
6	3,5-DiMe	4.859							
10	3,5-Di-^{t}Bu	4.902							
53	3,5-diF	4.823							
54	3,5-diCl	4.841							
55	3,5-diBr	4.832							
Trimers									
1	Pyrazole	5.317	5.317	5.317	–	60	60	60	–
6	3,5-DiMe	5.428	5.428	5.428	–	60	60	60	–
10	3,5-Di-^{t}Bu	7.681	7.681	7.681	–	60	60	60	–
53	3,5-diF	5.297	5.297	5.297	–	60	60	60	–
54	3,5-diCl	5.383	5.383	5.383	–	60	60	60	–
55	3,5-diBr	5.375	5.375	5.375	–	60	60	60	–
Tetramers									
1	Pyrazole	5.304	5.304	5.304	5.304	65.80	65.80	65.80	65.80
6	3,5-DiMe	5.311	5.311	5.311	5.311	63.51	63.51	63.51	63.51
10	3,5-Di-^{t}Bu	6.018	6.018	6.018	6.018	53.16	53.16	53.16	53.16
53	3,5-diF	5.293	5.293	5.293	5.293	68.80	68.80	68.80	68.80
54	3,5-diCl	5.295	5.295	5.295	5.295	63.56	63.56	63.56	63.56
55	3,5-diBr	5.311	5.311	5.311	5.311	73.09	73.09	73.09	73.09

Table 5
1*H*-1,2,4-Triazoles.

There is only one hydrogen-bond donor in the molecule, the NH of the five-membered ring, and several acceptor groups (see text).

	R^3	R^4	R^5	Structure	CSD code	Reference
45	NO_2	N	H	Catemer	CIFROY	Evrard *et al.* (1984)
46	Cl	N	Cl	Trimer	VITRUL	Starova *et al.* (1990)
47	Br	N	Br	Trimer	NABVIV	Valkonen *et al.* (1985)

distances for trimers and tetramers are also longer than the experimental values.

Compound **10**, with its two *tert*-butyl substituents has a normal distance between centroids only in the case of the dimer (0.04 Å longer than the remaining calculated dimers). The tetramer has a d_i value 0.72 Å longer, but the trimer, the most congested of all the cyclic structures, is 2.32 Å longer! In this case, the monomers are so far apart that the structure is no longer stable.

The catemers found so far in pyrazoles belong to four families (Figs. 4 and 5: order 2, 3, 4 (crossed) and 6 (crossed). Some situations such as uncrossed catemers of the orders 4 and 6 are still unknown, probably because the central channel

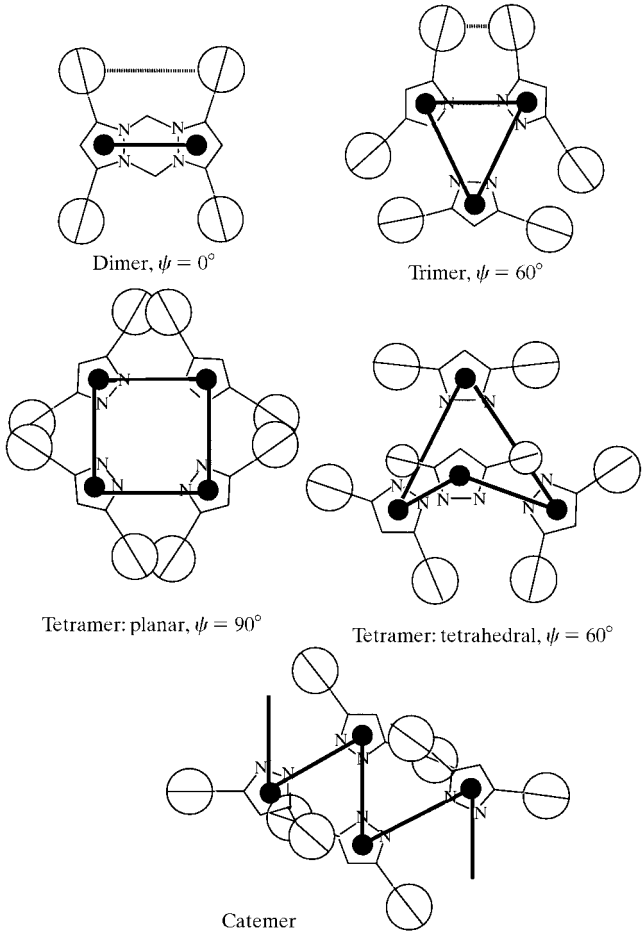


Figure 3
The four main motifs of hydrogen-bonded pyrazoles represented using the ring centroids. Note in the tetrahedral tetramer that the bold lines connect exclusively centroids of hydrogen-bonded pyrazoles.

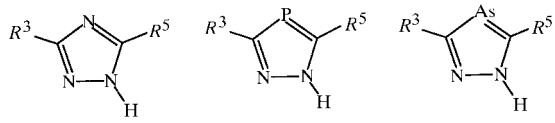
Table 6
All the reported compounds satisfying the condition to have only one hydrogen bond donor in the molecule, the NH of the five-membered ring, and several acceptor groups.

	R^3	R^4	R^5	Structure	CSD code	Reference
(*a*) 1*H*-1,2,4-diazaphospholes						
48	H	P	H	Catemer	HELMOA	Polborn *et al.* (1999)
49	^{t}Bu	P	^{t}Bu	Dimer	MEPHPY	Polborn *et al.* (1999)
50	CF_3	P	N(^{i}Pr)$_2$	Dimer	KORHII	Grobe *et al.* (1992)
51	CO_2Me	P	N(^{i}Pr)$_2$	Dimer†	KORHOO	Grobe *et al.* (1992)
(*b*) 1*H*-1,2,4-diazaarsoles						
52	H	As	H	Catemer	HELPOD	Polborn *et al.* (1999)

† −H···N/O═C contacts; proton disorder (see text).

will lead to worse packing unless they crystallize with some guest molecules. The catemers have distances between centroids of 5.1–5.2 Å, which is similar to those found in trimers and tetramers. Those of Fig. 4 correspond to compounds **1**, **8** and **9** (Table 1) and **19** (Table 2). To calculate the pitch of the helix, we have to divide the separation by the number of pyrazoles, that is, order 2, 2.9 Å; order 3, 1.35 Å; order 4, 1.75 Å and order 6, 2.8 Å. It appears that the helix pairs 2 and 6, and 3 and 4 are related.

3. Extension of the model to other compounds: 1,2,4-triazoles, 1,2,4-diazaphospholes and 1,2,4-diazaarsole



There are three other heterocycles which can be considered as 4-N (V), 4-P (VI) and 4-As (VII) pyrazoles (Tables 5 and 6). Two out of the four standard hydrogen-bonding motifs of pyrazoles are also observed in the closely related 1*H*-unsubstituted 1,2,4-diazaphospholes (VI) or diazaarsoles (VII) (retrieved from the CSD), with the N2 as the only acceptor in the molecule (Table 6). However, only three of the eight 1*H*-1,2,4-triazoles (V) present similar N—H···N contacts, giving rise to trimers and catemers, see Table 5. The remaining triazoles form chains through N—H···N contacts, where the acceptor is the N4 of the triazole, as in the parent compound (TRAZOL), or through other N atoms of the substituents (BNITRB10, CIJFOQ, GOJKIZ, KOBYOP). Despite the few examples of 1*H*-unsubstituted 1,2,4-diazaphospholes and diazaarsoles, these compounds present hydrogen-bonding networks which are consistent with our semi-qualitative model (see below).

4. An empirical model that corresponds to the data of the 51 compounds of Tables 1–3, 5 and 6

An examination of the results reported in these tables allows the detection of some regularities. Three assumptions are

Table 7
Classification of hydrogen-bond patterns in NH-azoles.

Entries in italics represent the compounds above the diagonal passing through the ^{t}Bu groups the model predicts to form trimers of catemers

R^5	R^3 = H	R^3 = CH_3 Cl Br	R^3 = CO_2R NO_2 N_3 CF_3	R^3 = C_6H_5 2-thienyl 1-adamantyl	R^3 = ^{t}Bu $Si(CH_3)_3$ $N(^iPr)_2$ Di(OMe)Ph
H	*Trimers or catemers* ***1–5***, ***48***, ***52***	*Trimers or catemers* ***18***, ***20***†	*Trimers or catemers* ***19***, ***26***, ***27***, ***30***, ***31***, ***32***, ***39***, ***45***	*Trimers or catemers* ***25***, ***39/42***	Dimers or tetramers **17**, **21**
CH_3 Cl Br		*Trimers or catemers* ***6–9*** ***46***, ***47***	*Trimers or catemers* ***33***	Dimers or tetramers **34**, **40/43**, **41/44**	Dimers or tetramers **22**
CO_2R NO_2 N_3 CF_3			Dimers or tetramers **16**	Dimers or tetramers **29**, **36**	Dimers or tetramers **35**, **37**, **50/51**
C_6H_5 2-thienyl 1-adamantyl				Dimers or tetramers **13–15**	Dimers or tetramers **24**
^{t}Bu $Si(CH_3)_3$ $N(^iPr)_2$ Di(OMe)Ph					Dimers or tetramers **10–12**, **49**

† Exception: **23** (CH_3/H: dimer).

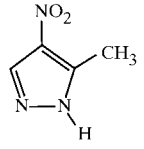
necessary to classify the 51 compounds (pyrazoles, 1,2,4-triazoles, diazaphospholes and diazaarsoles):

(i) The substituent at position 4 seems to have no effect on the HB pattern, as far as the secondary structure is concerned.

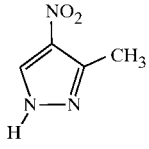
(ii) The effect of substituents at positions 3 and 5 are independent of their position and must be considered together as the sum of their effects.

(iii) Only two motifs are distinguishable from the four classes: trimers and catemers on the one hand, and dimers and tetramers on the other.

These assumptions should be considered as first approximations that can be neglected until a more refined model is available. Table 7 summarizes all the information about the motifs when the substituents are classified into five categories, this being the minimum number necessary to correctly classify most compounds (51 out of a total of 52).



(20)



(23)

The only exception is 3(5)-methyl-4-nitropyrazole **20/23**. This compound is the only pyrazole that presents desmotropy, *i.e.* that each tautomer crystallizes separately depending on the solvent used (Foces-Foces *et al.*, 1994). The model we propose does not differentiate between tautomers, therefore, both are predicted to belong to the family of trimers or catemers, which is the case for **20** (a trimer), but not for **23** (a dimer, Table 2). Polymorphism should also be a good test for the model because it predicts that all polymorphs would crystallize in the same motif. Unfortunately, no example of polymorphism has been fully reported, although 3(5)-phenyl-5(3)-methylpyrazole **40/43** is polymorphic (Elguero *et al.*, 1995), but the structure of only one polymorph has been determined (Maslen *et al.*, 1974; Moore *et al.*, 1975).

If the boxes are numbered from 1 (H) to 5 (^{t}Bu and other substituents), then the model predicts that if the sum of both substituents is 2, 3, 4 or 5, the compound will crystallize as catemers or trimers, and if the sum is 6, 7, 8, 9 or 10, then dimers or tetramers will be formed. This means that compounds in all 'boxes', off-diagonal in Table 7, crystallize in these two motifs. Since the classification has been an *ad hoc* process, one may wonder if it is related to some conventional property of the substituent. An examination of the five boxes of Table 6 makes it clear that the substituents are of increasing size. Attempts to correlate the qualitative sequence 1–5 with some steric parameter such as Taft's E_s (Taft, 1956), Gallo's S_0

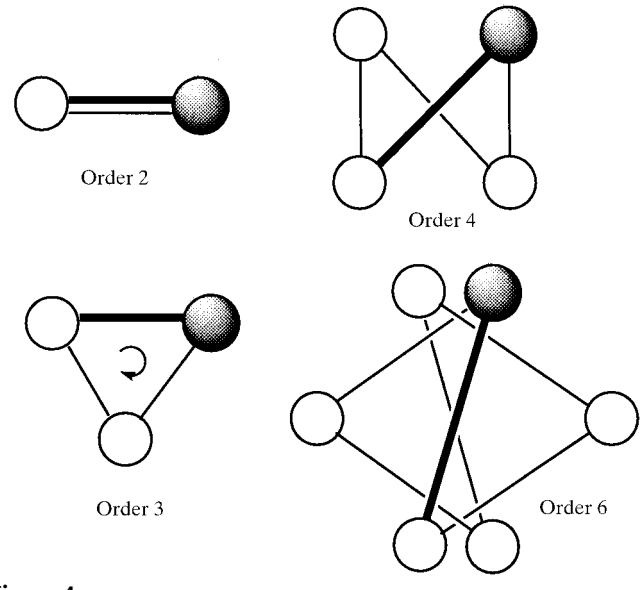


Figure 4
The four subclasses of catemers viewed from the top of the helixes (only the centroids are represented).

Table 8
MR values of substituents from Hansch *et al.* (1995).

Substituent	*MR*
H	0.10
Me	0.56
CO_2Me	1.29
CO_2Et	1.75
N_3	1.02
NO_2	0.74
NO	0.52
CF_3	0.50
C_6H_5	2.54
^{t}Bu	1.96
$SiMe_3$	2.50
F	0.09
Cl	0.60
Br	0.89
Neopentyl	2.42
p-Tolyl	3.00
^{i}Pr	1.50
3-PhOPh	5.25
Estimated	
2,5-diMeOPh	3.00
1-Ad	2.82
2-Thienyl	2.50
$(i\text{-}C_3H_7)_2N$	1.95

(Berg *et al.*, 1980), Charton's ν (Charton, 1975), Beckhaus's S_F (Beckhaus, 1978), Hirota's Ω_s (Komatsuzaki *et al.*, 1990) and Jenkins ***S*** (Baxter *et al.*, 1996) were only moderately successful. Part of the problem arises from the incompleteness of these scales, where only a limited number of substituents have been characterized.

Better results were obtained with the molar refractivity *MR*, a mixed steric polarizability parameter (Kubinyi, 1995). This parameter is known for a large variety of substituents (Hansch *et al.*, 1995) and the missing values can be estimated from other properties. Table 8 contains the MR values for the substituents of Table 7.

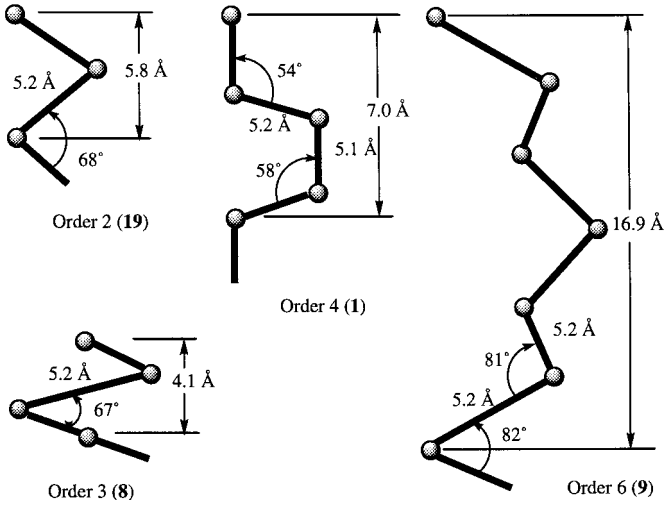


Figure 5
A lateral view of the four subclasses of catemers helixes (only the centroids are represented) corresponding to Figs. 2(*a*)–(*d*).

Rather than comparing the category indices 1–5 to *MR*, we have found it more illuminating to sum the *MR* contributions of R^3 and R^5 and to verify if they classify correctly the two hydrogen-bonding motifs. The result is represented in Fig. 6. There is a narrow barrier ($\Sigma MR_{3,5} = 2.4$) which separates the two motifs, with some exceptions. One of these is **23**, already discussed. The other compound wrongly predicted is **16** (3,5-bis-trifluoromethylpyrazole), a tetramer (Alkorta *et al.*, 1999) with $\Sigma MR_{3,5} = 1.00$, which corresponds to trimers or catemers. On the other side are compounds **25**, 3-phenyl-4-bromopyrazole (trimer), $\Sigma MR_{3,5} = 2.64$, and **39**/**42**, 3(5)-adamant-1-ylpyrazole (catemer), $\Sigma MR_{3,5} = 2.92$, which are predicted to crystallize as dimers or tetramers.

Therefore, the box ordering appears to be related to a known property *MR* (linear combinations of steric and polarizability parameters are possible alternatives). It remains to rationalize the last problem: why do trimers and catemers form on the one hand and dimers and tetramers on the other?

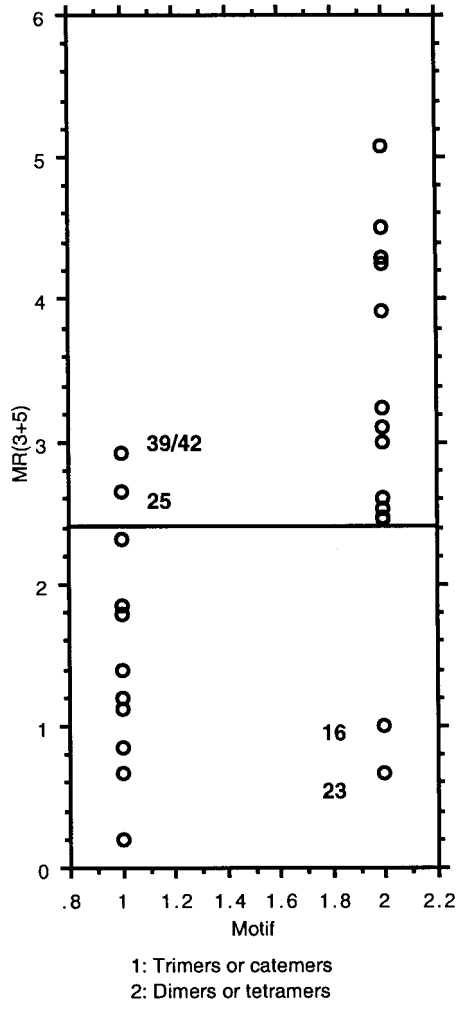


Figure 6
Classification of the four main motifs according to the sum of molar refractivities of the substituents at positions 3 and 5.

Table 9
RHF/6-31G* calculations (values in hartrees) of monomers, dimers, trimers and tetramers.

Pyrazoles	Pyrazole **1**	3,5-Dimethyl **6**	3,5-Di-*tert*-butyl **10**	3,5-Difluoro **53**	3,5-Dichloro **54**	3.5-Dibromo **55**
Monomer	−224.79349	−302.87629	−537.07999†	−422.49013	−1142.58605	−5363.39895
Dimer	−449.60428	−605.76971	−1074.17683	−844.99841	−2285.18904	−10726.81502
Trimer	−674.41611	−908.66006	−1611.24412	−1267.50847	−3427.79046	−16090.23530
Tetramer	−899.22379	−1211.55414	−2148.34109	−1690.01230	−4570.39153	−21453.64891

† This value corresponds to conformation *B*, the value for monomer *A* is −537.07928 hartrees (1.86 kJ mol^{-1} less stable).

Table 10
Relative energies (values in kJ mol^{-1}) for RHF/6-31G* calculations (1 hartree = 2625.50 kJ mol^{-1}).

Pyrazoles	Pyrazole **1**	3,5-Dimethyl **6**	3,5-Di-*tert*-butyl **10**	3,5-Difluoro **53**	3,5-Dichloro **54**	3,5-Dibromo **55**
12 monomers	93.8	92.2	63.4	97.5	89.1	100.0
Six dimers	28.7	27.7	**0.0**	29.1	25.3	35.5
Four trimers	4.41	3.95	3.0	1.9	8.0	3.5
Three tetramers	**0.0**	**0.0**	23.7	**0.0**	**0.0**	**0.0**
12 monomers	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Six dimers	−65.1	−64.5	−63.4	−68.4	−63.8	−64.5
Four trimers	−89.4	−78.3	−10.4	−95.6	−81.1	−96.5
Three tetramers	−93.8	−92.2	−39.7	−97.5	−89.1	−100.0

5. *Ab initio* calculations on dimers, trimers and tetramers: an attempt to provide a theoretical base to the model

It is reasonable to assume that the formation of crystals proceeds sequentially. In the case of NH-pyrazoles, triazoles, diazaphospholes and arsoles, the first two molecules link by an N—H···N hydrogen bond, then they either form a dimer or a third molecule is linked, and so on (Fig. 7). At this moment, if a fifth azole is linked to the four preceding ones, a chain is always formed since no pentamers or hexamers have been found.

We decided to approach the problem of the **relative** stability of the cyclic structures (dimers, trimers and tetramers) by carrying out calculations on pyrazoles **1**, **6**, **10**, **53**, **54** and **55**. The absolute energies are gathered in Table 9.

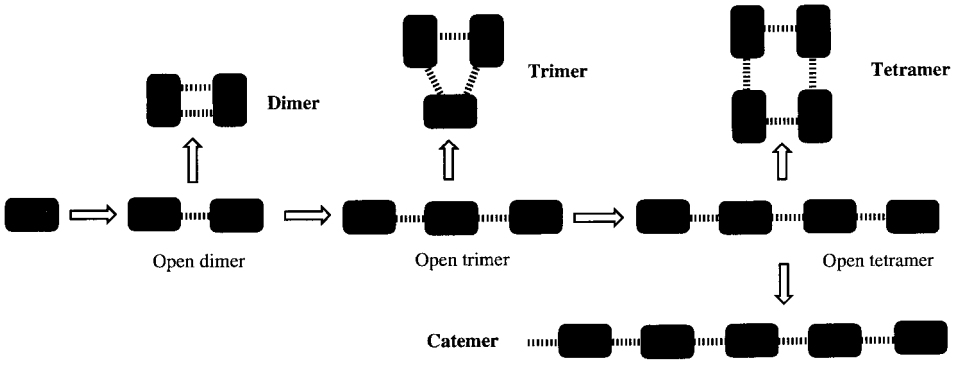
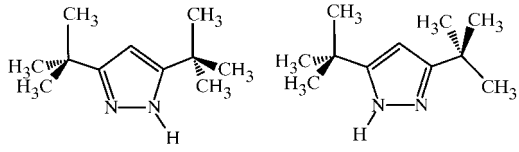


Figure 7
Schematic representation of the growth of pyrazole motifs.

In the case of 3,5-di-*tert*-butylpyrazole **10**, two conformations found in the crystal were calculated, *A* and *B*, with *B* being the most stable (Table 9). The calculated dimer, trimer and tetramer of this pyrazole correspond to conformation *B*.



For comparison purposes, the structures should have the same number of pyrazoles and the same number of hydrogen bonds. This last requirement prevents the discussion of catemers; moreover, there are several classes of catemers (see previous discussion) which will make it extremely difficult to build up a chain model that can be extrapolated to an infinite length. Therefore, we have decided to compare (Table 10) six dimers, four trimers and three tetramers to have in all cases 12 pyrazoles and 12 hydrogen bonds.

Excluding the extremely hindered derivative **10**, in all other cases the tetramers are the most stable. This is probably a consequence of cooperative (non-pairwise) effects (Mó *et al.*, 1992; González *et al.*, 1996), which overstabilizes the structure with the most hydrogen bonds. With regard

to 12 isolated monomers, Table 10 shows that all the dimers are of similar energies, but not so the trimers and tetramers, which are very sensitive to steric effects, especially the trimers. The relative energies of trimers and tetramers are linearly related: four trimers = (47 ± 7) + (1.43 ± 0.08); three tetramers, $n = 6$, $r^2 = 0.989$.

For the trimers the order is: Br < F < H < Cl < CH_3 < *tert*-C_4H_9. This order does not follow any steric parameter or atomic radii; probably in the case of halogen atoms, there are attractive halogen···halogen interactions, which are more important for bromine than for chlorine (Desiraju, 1989; Molins *et al.*, 1990; Desiraju, 1995; Navon *et al.*, 1997; Boese *et al.*, 1997; Kowalik *et al.*, 1999), which interfere with the pure steric effects.

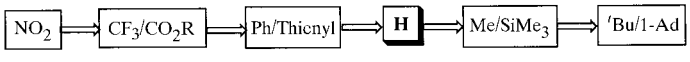
Returning to Fig. 7, we can imagine the nucleation process as involving several aggregates in equilibrium. The first step is the formation of one hydrogen bond. At this moment, entropic factors favor the formation of a cyclic **dimer**. However, dimers are the least stable of all associating mechanisms (Table 10) owing to the non-linearity of the N—H···N bonds (135–140°), unless the pyrazole has bulky substituents (or more precisely, 3,5-substituents with large *MR* values); therefore, a third pyrazole will link to the open dimer to form an open trimer. Again, entropic factors will drive the structure towards a cyclic **trimer**. This is a stable situation, but is the most sensitive to steric effects. In some cases, a fourth pyrazole is linked to one of the extremities of the open trimer and the process repeats again. Cyclic **tetramers** have a similar intrinsic stability to cyclic **trimers**, but they are less sensitive to steric effects and less planar. This model does not explain why pyrazole itself does not crystallize as a **trimer**, but forms a **catemer**. Probably these chains are enthalpically favored, but typical solid-state effects cannot be ruled out.

6. Conclusions

This work has provided information about several topics related to the structure of NH-pyrazoles in the solid state:

(i) Hydrogen-bonding network: The picture which emerges is of a bimodal distribution of structures: either trimers/catemers or dimers/tetramers. The selection seems to be based on steric and polarizability effects, but we have been unable to find a criterion that decides systematically between trimers and catemers as well as between dimers and tetramers.

(ii) Tautomerism: Our packing model does not distinguish between tautomers, since it uses the algebraic sum of the MR values of R^3 and R^5. Nevertheless, Tables 2 and 3 contain information about the preferred tautomer. The order of preference for a substituent to be at position 3 decreases (or to be at position 5 increases) as shown below.



This is the same order as the Hammett σ_m (Hansch *et al.*, 1995) varies with substituents. The only exception in Table 2 is the anomalous compound **23**, which is a 3-methyl-5H derivative. The results of Table 3 show that H and 1-Ad on the one hand and Me and Ph on the other can accept both positions when there is proton disorder. Note that for this set of substituents, *MR* and σ_m are unrelated ($r^2 = 0.18$) as can be expected for parameters describing essentially steric and electronic effects, respectively.

Proton transfer in the solid state: To have comparable experimental and calculated geometries, as described by the centroids, the calculated d_i values have to be multiplied by 1.038 (from 5.428/5.206 in trimer **6** and from 4.902/4.745 in dimer **10**). The fact that the crystal produces a kind of contraction of the dimers, trimers and tetramers is related to the low activation barriers to proton transfer found in crystals (Aguilar-Parrilla, Cativiela *et al.*, 1992; Aguilar-Parrilla, Scherer *et al.*, 1992; Aguilar-Parrilla *et al.*, 1995; Claramunt *et al.*, 1997; Elguero *et al.*, 1995).

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