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Structure and Tautomerism of 3(5)-Amino-5(3)-arylpyrazoles in the Solid State and in Solution: an X-Ray and NMR Study

Jairo Quiroga Puello* and Braulio Insuasty Obando

Departamento de Química, Universidad del Valle, A.A. 25360, Cali (Colombia)

Concepción Foces-Foces* and Lourdes Infantes

Departamento de Cristalografía, Instituto de Química Física 'Rocasolano', CSIC, Serrano 119, E-28006 Madrid (Spain)

Rosa María Claramunt,* Pilar Cabildo and José Antonio Jiménez

Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey s/n, 28040 Madrid (Spain)

José Elguero

Instituto de Química Médica, CSIC, Juan de la Cierva 3, E-28006 Madrid (Spain)

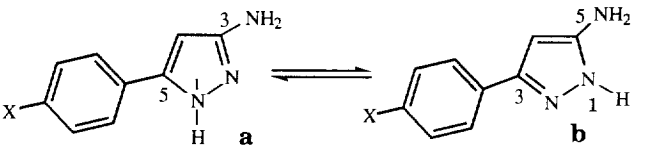
Dedicated to the memory of Professor Gerrit L'abbé

Abstract.— The crystal and molecular structures of five 3(5)-amino-5(3)-arylpyrazoles differing in the nature of the substituent at the *para* position of the phenyl ring (**1**: X = H; **3**.H_2O: X = OCH_3; **4**: X = Cl; **5**: X = Br and **6**: X = NO_2) have been determined by X-ray analysis. Three situations were detected in the crystal structures: the 3-tautomer is present in **1**, **3** and **4**; the 5-tautomer is only found in **6** and both tautomers (1:1) are observed in **5**. The crystal packings are governed by N-H···N/O hydrogen bonds and also by O-H···N interactions in the monohydrate of **3**. It is worth noting that in **1**, **3**, **4** and **5** there are N-H···π(arene) contacts that might play a role in stabilizing the packing. Solid state ^{13}C NMR results are consistent with the above crystallographic conclusions, thus allowing to determine that the only compound for which no good crystals have been obtained, the *p*-methyl derivative **2** should be a 3-amino tautomer. NMR solution studies (^1H and ^{13}C) allow to determine the 3-amino/5-amino tautomeric equilibrium constant, K_T, which obeys a Hammett relationship with σ_p. Geometry optimizations of the 3 and 5-tautomers at semi-empirical level (AM1) were performed. In all compounds, the 3-tautomer has been found to possess a relatively lower energy by approximately 2 kcal mol^{-1}. The potential energy surface as a function of the hybridization of the amino group and its conformation have also been analyzed. © 1997 Elsevier Science Ltd.

INTRODUCTION

The tautomerism of 3(5)-aminopyrazoles has two aspects. The first one concerns the amino group and it is well known that these compounds exist in the amino form and never in the imino one.[1-3] Thus, this aspect will no longer be considered. The second one concerns the annular tautomerism, that is, the position of the NH ring proton. This aspect is nearly unknown and since we were able to obtain a series of six 3(5)-amino-5(3)-arylpyrazoles, **1**-**6**, we decided to study their annular tautomerism in the solid state and in solution. Compounds

1-6 differ only in the nature of the substituent at the *para* position of the phenyl ring: **1** (X = H, phenyl), **2** (X = CH_3, *p*-tolyl), **3** (X = OCH_3, *p*-anisyl), **4** (X = Cl), **5** (X = Br) and **6** (X = NO_2). The solution of the problem was possible because we were able to obtain good crystals of five out of six compounds.



RESULTS AND DISCUSSION

Chemistry. 3(5)-Aminopyrazoles are common compounds because their synthesis is straightforward from β-ketonitriles, β-iminonitriles or β-chlorocinnamonitriles and hydrazines.[4-12] Recently, Schrader and Kirsten have found that dipeptides are stabilized in the β-sheet conformation by three-point binding through hydrogen bonds to 3-amino-NH-pyrazoles binding sites, increasing the interest of these bases.[13] Compounds **1-6** were prepared according to the procedures described in the literature (see Experimental Section).[14,15] The parent compound, **1** (X = H), has been described many times[4-9] and it is now commercially available.

X-ray Crystallographic Study. All compounds (Fig. 1 and Table 1) exhibit the same pattern of bond lengths and angles regardless of the tautomer present in the structure (**a** and **b** in Table 1 stand for the 3- and 5-tautomer respectively). The amino group has a distorted sp^3 hybridization and in all compounds the N6 atom is out of the pyrazole plane. The greatest deviations are observed in **1a**, molecule 2 in **4a** and in **5b** showing N-N-C-N6 torsion angles up to 173.3(3)°. The hybridization of the N6 atom as measured by the sum of angles around it, Σα[N], cover a range between 335(6)° for **1a** and 350(4)° for **6b**. This parameter is correlated with the C3/C5-N6 bond, the greater the Σα[N6], the lower the C-N distance, that means a greater delocalization with the pyrazole ring in molecule 1 of **4a** and in **6b**. This result is supported by the semi-empirical calculations (see below, Fig. 3b). Apart from that, the main differences between both tautomers are located in the exocyclic angles at C3 or C5 where the amino group is attached and to the angle between the pyrazole and the phenyl ring (Table 1). The conformation of the amino groups are intermediate between the corresponding perpendicular (τ = N-C-N-H: ±30°/±150°) and the parallel one (τ = 0/±120° or ±60/180°), Table 1. The methoxy and the nitro group in **3a** and **6b** are rotated by -4.7(2)° and -6.5(3)° with respect to their phenyl rings. These features are similar to those recently reported for 5-amino-1-t-butyl-4-cyano-3-phenylpyrazole and for the corresponding *p*-methoxy and *p*-chloro derivatives[16] (respectively TEQYET, TEQYIX and TEQYUJ, CSD refcodes).[17] The amino groups [with an almost perpendicular conformation: N-C-N-H torsion angles in the 25(2)-45(3)° range] also deviate from the pyrazole ring [N-N-C-N= 176.6(3)° on average] and the C-N(amino) distances of 1.361(2), 1.375(3) and 1.382(7) Å correspond to Σα[N6] values of 359(3), 349(3) and 337(5)° respectively. Other 3- and 5-amino pyrazole derivatives retrieved from the CSD[17] (ACYMPZ,[18] JACZES,[19] MAPARY,[20] PACAPZ,[21] VORNIZ,[22] WIKVIV,[23] and YELKEF;[24] no atomic coordinates for YELKEF were available neither from the CSD nor from the journal) show Σα[N] values in the 334-360° range (JACZES, VORNIZ). Except for 5-amino-3-(methoxycarbonyl)-1-methylpyrazole (JACZES, τ = 55/177°), the remaining sp^3 amino groups exhibit the distorted perpendicular conformation.

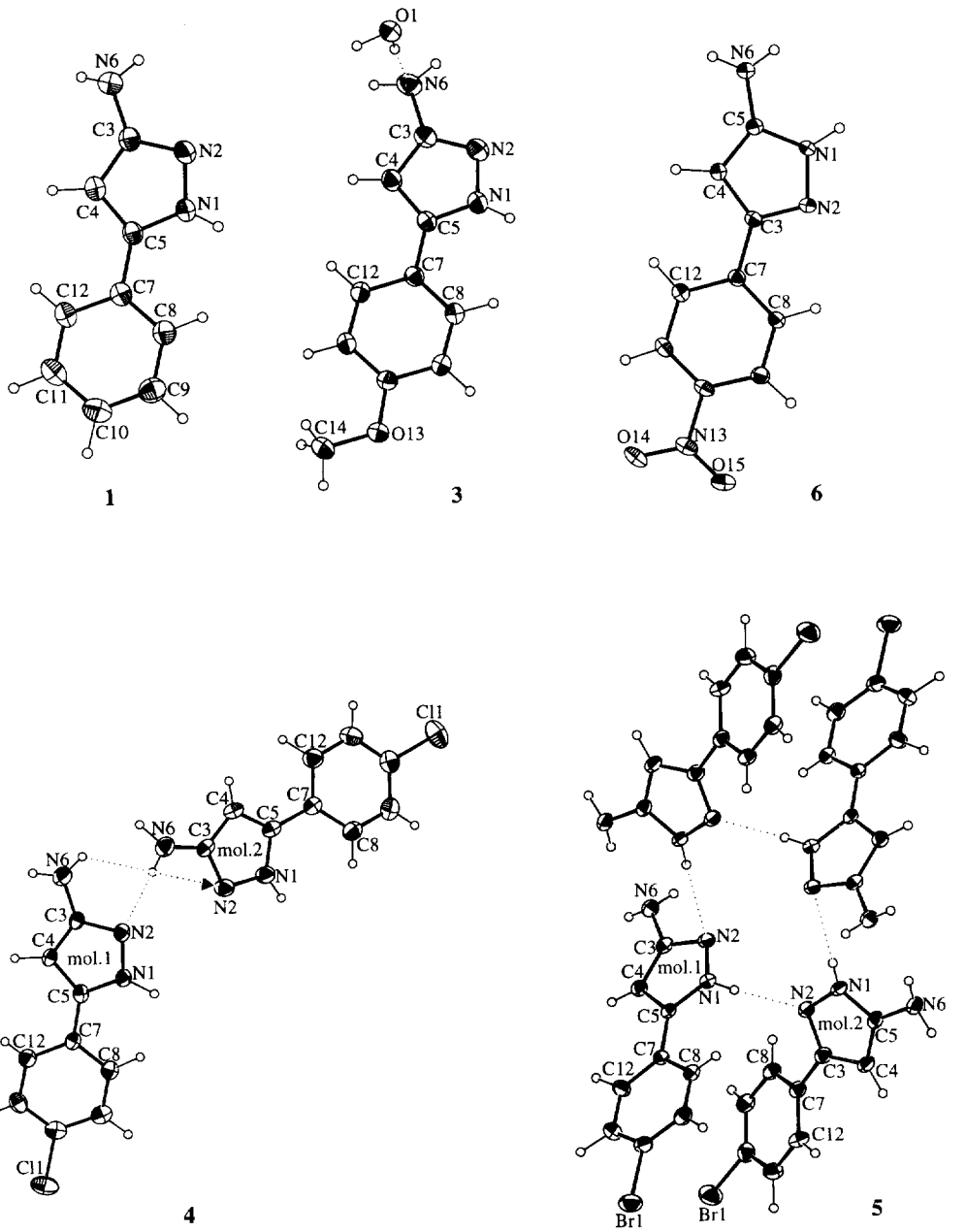


Fig. 1.- Perspective views of the asymmetric units. In **5** the centrosymmetric tetrameric unit formed by both tautomers is shown. Displacement ellipsoids are scaled to 30% probability level. Dotted lines mean hydrogen bonds.

Table 1. Selected intra and inter molecular parameters (Å,°). See Fig. **1** for the atom labelling scheme. CA and CB represent the centroid of the pyrazole and phenyl rings respectively.

	1a	**3a**	**4a**.mol.1	**4a**.mol.2	**5a**	**5b**	**6b**
N1-N2	1.369(3)	1.372(2)	1.376(5)	1.371(5)	1.372(8)	1.369(8)	1.360(2)
N2-C3	1.323(4)	1.326(3)	1.338(5)	1.329(6)	1.333(9)	1.328(7)	1.331(3)
C3-C4	1.402(4)	1.394(2)	1.396(6)	1.386(6)	1.399(10)	1.405(10)	1.411(3)
C4-C5	1.372(4)	1.382(2)	1.385(6)	1.368(6)	1.389(9)	1.377(9)	1.379(3)
C5-N1	1.346(3)	1.345(2)	1.345(5)	1.338(6)	1.353(9)	1.350(8)	1.349(3)
C3/5-N6	1.393(4)	1.399(2)	1.372(6)	1.402(6)	1.387(9)	1.383(10)	1.368(3)
C5/3-C7	1.466(3)	1.469(2)	1.458(6)	1.464(6)	1.456(9)	1.472(9)	1.467(3)
C5-N1-N2	113.0(2)	111.5(1)	112.3(3)	113.0(4)	112.0(5)	112.3(5)	113.0(2)
N1-N2-C3	103.8(2)	104.9(1)	104.3(3)	103.6(3)	104.3(5)	104.3(5)	104.2(2)
N2-C3-C4	111.7(2)	111.5(2)	111.4(3)	111.4(4)	112.1(6)	111.7(6)	111.6(2)
C3-C4-C5	105.7(2)	105.2(2)	105.7(4)	106.4(4)	104.8(6)	105.2(6)	104.9(2)
C4-C5-N1	105.8(2)	106.9(2)	106.4(3)	105.6(4)	106.7(6)	106.6(6)	106.3(2)
N2/1-C3/5-N6	121.8(3)	121.2(2)	120.4(4)	121.1(4)	119.7(6)	122.4(6)	121.2(2)
C4-C3/5-N6	126.4(3)	127.2(2)	128.2(4)	127.4(4)	128.1(6)	130.9(7)	132.4(2)
Σα[N6]	335(6)	342(3)	349(8)	343(9)	341(12)	346(15)	350(4)
N1/2-N2/1-C3/5-N6	173.3(3)	177.1(2)	-177.4(4)	-173.7(4)	-176.1(6)	-174.3(6)	-176.7(2)
N2/1-C3/5-N6-H61	13(3)	20(2)	-9(4)	0(5)	-33(6)	-19(10)	-25(2)
N2/1-C3/5-N6-H62	138(3)	154(2)	-151(5)	-132(5)	-167(7)	-159(6)	-168(2)
N1/2-C5/3-C7-C8	10.5(4)	-0.2(3)	-13.7(6)	-10.1(7)	-5.0(10)	-27.9(10)	14.3(3)
C8-C7-C12	118.3(3)	117.6(2)	118.2(4)	117.8(4)	117.6(6)	118.3(7)	118.4(2)
C9-C10-C11	119.4(3)	119.6(2)	121.6(4)	120.0(5)	121.9(7)	120.3(7)	122.0(2)

Compound	D-H...A	D-H	D...A	H...A	D-H...A
1a	N1-H1...N6(x,y+1,z)	0.86(5)	3.169(4)	2.51(4)	134(3)
	N6-H61...N2(-x,y-1/2,3/2-z)	0.87(5)	3.138(4)	2.37(5)	148(4)
	C9-H9...CA(1/2-x,1-y,1/2+z)	0.98(5)	3.706(4)	2.97(5)	133(3)
	N6-H62...CB(1/2-x,-y,z-1/2)	0.88(5)	3.818(3)	2.96(5)	164(4)
3a	O1-H11O1...N6(x,y,z)	1.00(3)	2.827(2)	1.84(3)	174(3)
	N1-H1...O1(1-x,1-y,1-z)	0.92(3)	2.836(2)	1.93(3)	172(2)
	O1-H12O1...N2(x,y-1,z)	0.96(4)	2.865(2)	1.93(4)	165(3)
	N6-H61...O1(1-x,1/2+y,3/2-z)	0.94(3)	2.982(2)	2.16(3)	145(2)
	N6-H62...CB(x,1/2-y,1/2+z)	0.97(3)	3.453(2)	2.49(3)	172(3)
	C14-H143...CB(-x,y-1/2,1/2-z)	1.01(3)	3.634(2)	2.72(3)	151(2)
4a	N6-H61(mol.2)...N2(mol.1)(x,y,z)	0.84(7)	3.213(6)	2.41(6)	159(6)
	N6-H61(mol.1)...N2(mol.2)(x,y,z+1)	0.89(5)	3.182(6)	2.32(5)	163(4)
	N1-H1(mol.1)...N2(mol.1)(1/2-x,-y,z-1/2)	0.99(6)	2.973(5)	1.99(5)	175(5)
	N1-H1(mol.2)...N6(mol.2)(x,y,1-z)	1.05(7)	3.124(6)	2.20(7)	146(5)
	N6-H62(mol.2)...N2(mol.2)(x,1/2-y,1/2+z)	1.01(9)	3.522(6)	2.58(8)	156(7)
	C12-H12(mol.2)...CB(mol.2)(x,1/2-y,1/2+z)	1.07(5)	3.711(6)	2.88(5)	135(4)
	N6-H62(mol.1)...CA(mol.1)(x,1/2-y,1/2+z)	0.89(7)	3.698(5)	3.09(7)	127(6)
	C9-H9(mol.1)...CA(mol.2)(1/2-x,-y,z-1/2)	0.99(6)	3.654(5)	2.85(6)	138(4)
	Cl1(mol.1)...Cl1(mol.2)(x-1/2,y,-1/2-z)		3.288(2)		
5a+b	N1-H1(mol.1)...N2(mol.2)(x,y,z)	0.86(11)	2.884(8)	2.05(11)	162(10)
	N1-H1(mol.2)...N2(mol.1)(-x,1-y,1-z)	0.76(10)	3.070(7)	2.32(10)	175(11)
	N6-H61(mol.1)...N2(mol.1)(-x,-y,1-z)	0.83(13)	3.105(10)	2.29(13)	166(10)
	N6-H61(mol.2)...N6(mol.1)(-x,1-y,1-z)	0.81(10)	3.062(8)	2.28(10)	163(13)
	N6-H62(mol.2)...CA(mol.1)(x,3/2-y,1/2+z)	0.98(8)	3.480(7)	2.70(9)	137(8)
	CB(mol.1)...CB(mol.2)(x,y,z)		3.998(4)		
	Br1(mol.1)...Br1(mol.1)(1-x,2-y,1-z)		3.381(1)		
6b	N6-H61...O15(3/2+x,1/2-y,z-1/2)	0.91(3)	3.056(3)	2.17(3)	165(2)
	N6-H62...N2(5/2-x,y-1/2,1/2-z)	0.99(3)	3.068(3)	2.10(3)	165(2)
	N1-H1...O14(3/2+x,1/2-y,z-1/2)	0.82(2)	3.091(2)	2.28(2)	172(2)
	CA...CB(1+x,y,z)		3.701(1)		

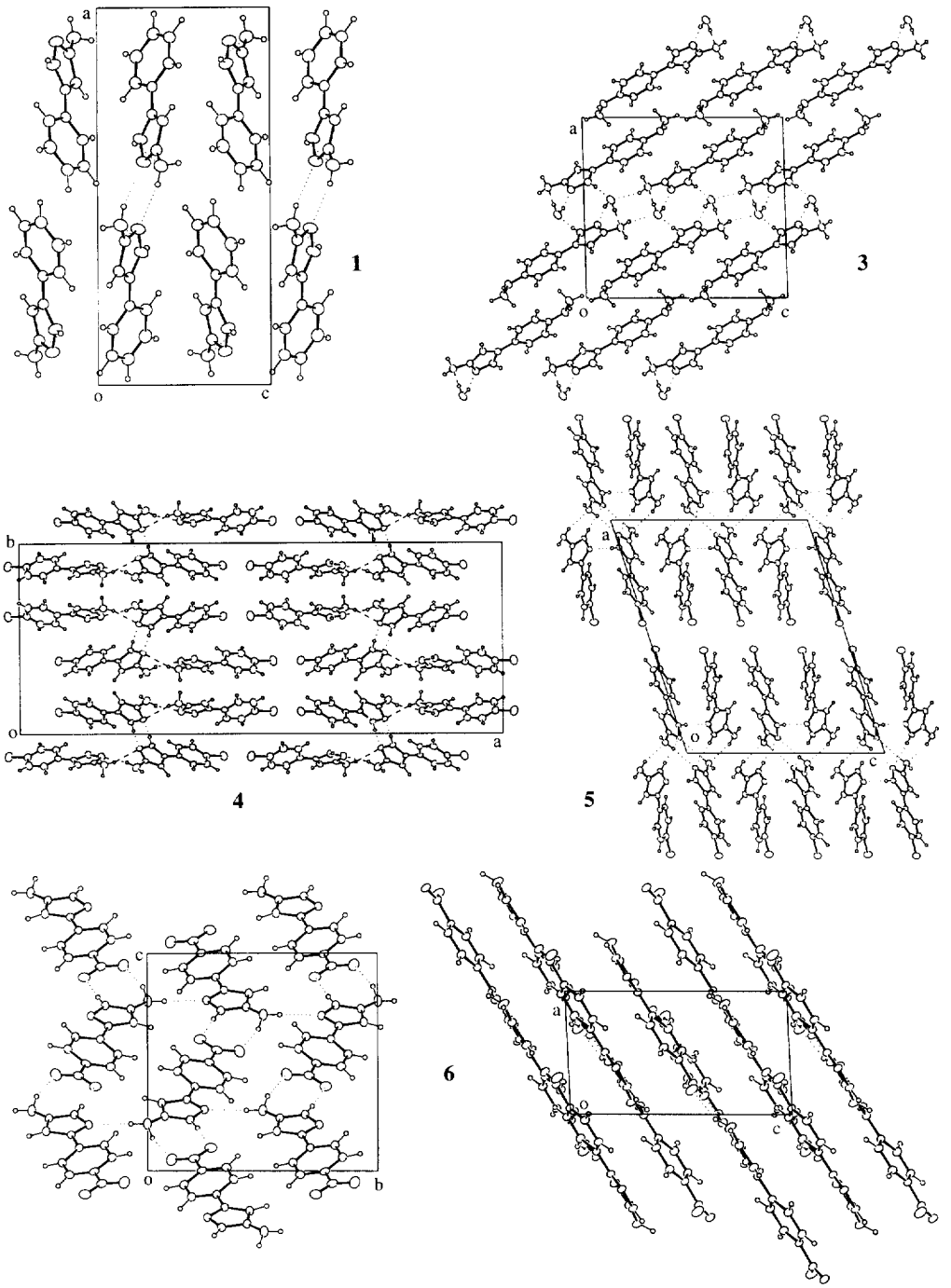


Fig. 2.- Packing diagrams for all compounds. Compound **6** is viewed down the **a** and **b** axes showing the packing in layers.

The packing arrangement of all compounds is shown in Fig. 2 being mainly due to N-H···N/O hydrogen bonds and also to O-H···N interactions in which the cocrystal water molecule is involved (**3a**). In **1a**, **3a**, **4a** and **5** where the number of potential hydrogen bond donors is greater than the hydrogen bond acceptor sites, one of the amino hydrogen atoms is engaged in N-H···π cloud contacts with the pyrazole and phenyl rings. It shows H···centroid distances in the 2.49(3)-3.09(7) Å range (Table 1) similar to that reported for two-center interactions in tetraphenylborates with organic ammonium cations [2.55(8)-3.08(44) Å].[25]

In **1a**, one N-H of the amino forms chains around a twofold screw axis parallel to the **b** axis reinforced by a second interaction with the N-H of the pyrazole that relates molecules by translation along the same axis. These chains are then linked by C-H···π cloud (pyrazole ring) and N-H···π cloud (phenyl rings) interactions. In **3a**, the water molecule acts as donor and acceptor of two hydrogen bonds each and dimers are formed through this water and the N-H of the pyrazole around inversion centers. A further hydrogen bond of the water molecule to the amino group [O1-H12(O1)···N2] leads to a chain-like arrangement of molecules around **b** and these chains are then cross-linked into sheets by other N-H···O bond. The three-dimensional structure is obtained joining these sheets though N/C-H···π interactions. The two independent molecules in **4a** exhibit a different pattern of hydrogen bonds. Both are linked via two analogous N-H(amino)···N bonds giving rise to chains running along **c** and leaving the other N-H of one amino group free of interaction while the remaining N-H amino bond is involved in N-H···π cloud contacts. The N-H of one pyrazole connects pairs of chains around symmetry centers. The formation of layers is due to week C/N-H···π cloud contacts and short Cl···Cl contacts[26] are found between layers (Fig. 2). In **5**, tetrameric units are formed around inversion centers through the N-H···N interactions of the pyrazole rings. The amino···amino interactions are responsible for the stabilization of the the tetramers and for the formation of chains along the **b** axis. The chains are linked through N-H···π contacts (Table 1). Short Br···Br contacts[26] are also observed. In **6b**, chains of molecules linked though N-H···O=N hydrogen bond, which extend along the **c** axis, are joined by means of N-H···N bonds into layers parallel to the (103) plane. No hydrogen bonds link one layer to the next although the stacking between phenyl and pyrazole rings is observed (Fig. 2 and Table 1).

NMR Spectroscopy. We have used ^{13}C (Table 2), ^{15}N (Table 3) and ^{1}H NMR spectroscopies (Table 4) to determine the structure of arylaminopyrazoles.

^{13}C NMR. The ^{13}C chemical shifts of the corresponding twelve *N*-methyl derivatives, 1-methyl-3-amino-5-aryl-pyrazoles **c** and 1-methyl-3-aryl-5-aminopyrazoles **d**, were already described by Wrzeciono,[11] and his results (Table 2) proved invaluable for solving the problem. We and others have described the ^{13}C NMR spectra in solution of a number of aminopyrazoles,[27-30] and Ege has published the ^{13}C NMR spectrum of compound **1** in DMSO-d_6 solution but his values also given in Table 2 obviously contain some assignment errors.[31] Compounds **5** and **6** present very large signals in DMSO-d_6 (slow prototropic exchange) and their spectra were also recorded in a mixture of DMSO-d_6+CF_3CO_2H. This modifies the chemical shifts (note C4 at 93.2 and 95.9 instead of 85-90 ppm for DMSO-d_6 solutions).

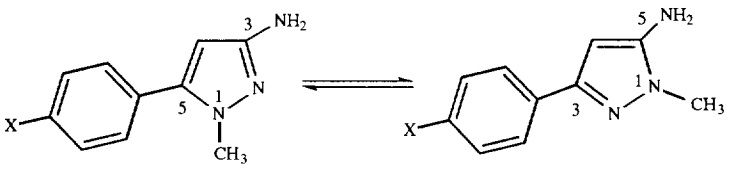
Table 2. ^{13}C chemical shifts of 3(5)-aryl-5(3)-aminopyrazoles and their *N*-methyl derivatives

Comp	X	NR	C-NH_2	C-4	C-Ar	C_i	C_o	C_m	C_p	Me (MeO)
1[a]	H	NH (3+5-NH_2)	155.5(br)	90.5	147.9(br)	132.4	126.6	130.0	129.3	------
1[b]	H	NH (3-NH_2) NH (5-NH_2)	156.2(br) 149.5(br)	89.3(br) 85.2(br)	142.4(br) 149.5(br)	130.4(br) 134.7(br)	124.8 ^1J=159.7 ^3J=^3J=7.0	128.7 ^1J=160.7 ^3J=7.2	127.4 ^1J=161.4	------
1[b,e]	H	NH (3+5-NH_2)	153.1	87.8	153.2	132.1	124.8	128.6	127.3	------
1[d]	H	NH (3-NH2)	155.5	93.4	142.8	131.3 129.8	128.8 124.1	128.8	126.2	------
1c[b,f]	H	NMe (3-NH_2)	154.3	92.6	143.5	130.8	128.1	128.6	127.9	------
1d[b,f]	H	NMe (5-NH_2)	148.0	85.4	147.9	134.4	124.4	128.2	126.7	------
2[b]	Me	NH (3+5-NH_2)	153.3(br)	87.3 ^1J=172.7	145.2(br)	136.5	124.6 ^1J=160.5 ^3J=6.5	129.1 ^1J=159.7	136.5	20.8 ^1J=126.3 ^3J=4.3
2[c]	Me	NH (3+5-NH_2)	149.8	89.4	147.3	123.7	125.8	129.5	140.5	20.3
2[d]	Me	NH (3-NH_2) NH (3-NH_2)	155.3 156.8	93.7 89.2	143.8 141.9	131.1	126.6 125.4	128.0	136.2 135.0	23.1 21.7

2c[b,f]	Me	NMe (3-NH_2)	154.3	92.5	143.6	n.o.	128.0	129.2	137.4	20.8
2d[b,f]	Me	NMe (5-NH_2)	147.9	85.2	147.8	131.7	124.6	128.8	135.8	20.7
3[b]	OMe	NH (3+5-NH_2)	153.3	86.9 ^1J=172.9	144.9	124.5	126.0 ^1J=158.6 ^3J=7.5	113.9 ^1J=159.3 ^3J=4.6	158.5	55.0 ^1J=144.1
3[d]	OMe	NH (3-NH_2)	155.7	89.3	141.2	123.0 126.1	127.1	111.0 117.5	157.6	53.7
3c[b,f]	OMe	NMe (3-NH_2)	154.1	92.2	143.2	123.2	129.4	114.1	159.1	55.2
3d[b,f]	OMe	NMe (5-NH_2)	147.8	85.1	147.9	127.2	125.9	113.8	158.4	54.9
4[b]	Cl	NH (3+5-NH_2)	152.4	86.8 ^1J=173.4	145.2	131.2	126.4 ^1J=162.8 ^3J=7.2	128.6 ^1J=166.8 ^3J=5.0	131.5	------
4[c]	Cl	NH (3+5-NH_2)	149.1	92.9 ^1J=181.7	146.6	130.2	127.4 ^1J=164.0 ^3J=7.0	128.8 ^1J=168.3 ^3J=5.0	130.2	------
4[d]	Cl	NH (3-NH_2) NH (3-NH_2)	154.9 156.7	93.8 89.5	143.1 143.1	130.3	126.3	128.1	136.5	------ ------
4c[b,f]	Cl	NMe (3-NH_2)	154.4	92.8	142.1	129.6	129.8	128.6	132.8	------
4d[b,f]	Cl	NMe (5-NH_2)	148.2	85.8	146.9	131.4	126.3	128.8	133.2	------

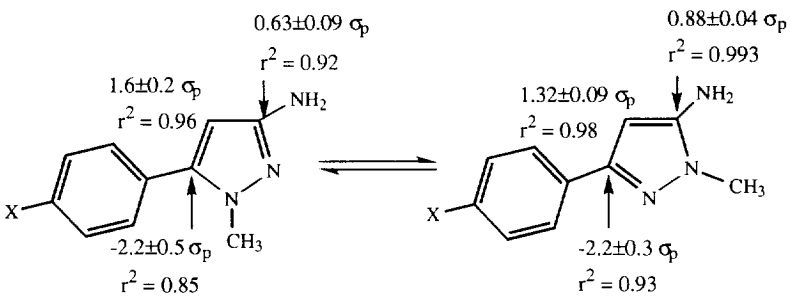
5[b]	Br	NH (3+5-NH_2)	151.4(br)	86.8(br)	145.9(br)	126.7	126.7	131.4	120.0	------
5[c]	Br	NH (3+5-NH_2)	146.6	93.2 ^1J=179.0	144.9	127.1	128.0 ^1J=162.6 ^3J=6.5	132.3 ^1J=167.1 ^3J=5.0	123.2	------
5[d]	Br	NH (3-NH_2) NH (5-NH_2)	157.1 151.7	90.4 87.3	143.6 147.2	126.4	126.4	131.0	116.9 118.8	------ ------
5a[b,f]	Br	NMe (3-NH_2)	154.5	92.9	142.3	129.9	130.0	131.6	121.4	------
5b[b,f]	Br	NMe (5-NH_2)	148.2	85.8	146.7	133.6	126.6	131.2	119.6	------
6[b]	NO_2	NH (3+5-NH_2)	150.1(br)	86.0(br)	147.8(br)	140.7(br)	125.4	124.0	146.0	------
6[c]	NO_2	NH (3+5-NH_2)	147.9	95.9 ^1J=181.5	143.8	134.4	127.2 ^1J=166.8 ^3J=6.9	124.7 ^1J=170.8 ^3J=4.4	145.6	------
6[d]	NO_2	NH (5-NH_2)	149.2	83.3	145.2	140.0	124.1	124.1	145.2	------
6c[b,f]	NO_2	NMe (3-NH_2)	154.8	93.9	141.5	137.0	129.0	123.9	146.7	------
6d[b,f]	NO_2	NMe (5-NH_2)	148.7	86.4	145.9	140.8	125.2	123.8	145.8	------

[a] Solvent: CD_3OD; [b] Solvent: DMSO-d_6; [c] Solvent DMSO-d_6+CF_3CO_2H; [d] CPMAS; [e] From ref. 31; [f] From ref. 11. (br) Broad signal.

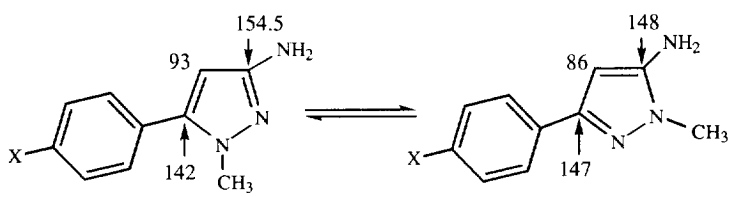


c **d**

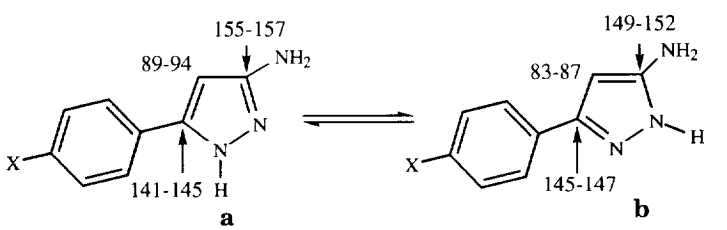
Wrzeciono's values for *N*-methyl derivatives show small differences of ^{13}C chemical shifts depending on the nature of X. We have found that these chemical shifts follow Hammett's type relationships, using σ_p values,[32] the following equations are found:



The sensitivity (ρ) decreases, in absolute value, with the distance to X. This dependence explains why the three pyrazole ring carbons slightly differ and only averaged values can be given for both isomers:

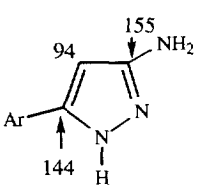


We will use these criteria to assign the structure of the NH tautomers in the solid state:

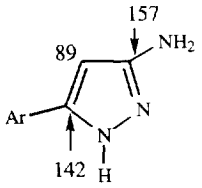


a **b**

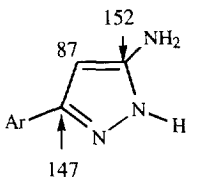
Although the consistency of *N*-methyl values in solution[11] and NH values in the solid state is very satisfactory, nevertheless, the spread on the last values is too large. We have to assume that another factor is present in the solid state and we propose that this factor is somewhat related to the amino group. According to the CPMAS values there are four situations, two for each tautomer:



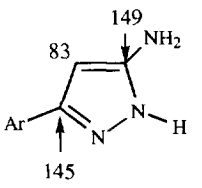
A



B



A



B

According to these rules, in the solid state compound **1** is a type **A** 3-amino-5-phenylpyrazole **a**; compound **2** is 3-amino-5-*p*-tolylpyrazole **a** with both **A** and **B** type structures; compound **3** is a type **B** 3-amino-5-anisyl-pyrazole **a**; compound **4** is 3-amino-5-*p*-chlorophenylpyrazole **a** with both **A** and **B** type situations; compound **5** is a mixture of two tautomers 3-amino-5-*p*-bromophenylpyrazole **a** (**B** type) and 3-*p*-bromophenyl-5-aminopyrazole **b** (**A** type); finally, compound **6** is 3-*p*-nitrophenyl-5-aminopyrazole **b** (**B** type).

An examination of the crystallographic results (Table 1) shows that the amino group is out of the pyrazole plane as measured by the N-N-C-N torsion angle. If the absolute value is considered, two families are found: one around the mean value of 173.8(3)° (**1a**, molecule 2 of **4a**, **5b**) and another around 176.8(4)° (**3a**, molecule 1 of **4a**, **5a**, **6b**). In summary, the compounds could be described as **1aA**, **2aA** and **2aB**, **3aB**, **4aA** and **4aB**, **5aB** and **5bA**, **6bB**.

^{15}N NMR. In solution, compound **1** (Table 3) shows a narrow signal for the amino group but very broad signals for the ring nitrogens due to annular tautomerism and this study was not pursued. The solid state results are reported in Table 3.

Table 3. ^{15}N NMR chemical shifts in solid state of 3(5)-amino-5(3)-arylpyrazoles at 298K.

Compound	N-1	N-2	NH_2	others
1[a] (H)	-203.3	-118.1	-327.3 (br)	---
2 (CH_3)	-199.7	-109.8 -130.3	-333.5 (br)	---
3 (OCH_3)	-196.7	-118.3	-333.1 (br)	---

4 (Cl)	-198.7	-110.9 -129.9	-334.7 (br)	---
5 (Br)	-196.1	-121.9	-333.3 (br)	---
6 (NO_2)	-200.7	-110.6	-331.8 (br)	-7.3 (NO_2)

[a] In DMSO-d_6 the chemical shift values of compound **1** are: δ(N-1): -200 (vbr), δ(N-2): -115 (vbr) and δ(NH_2): -338.9 (s) ppm.

To use ^{15}N chemical shifts for studying the annular tautomerism of pyrazoles it is necessary that the effects of the substituents at positions 3 and 5 on δN-1 and δN-2 should be quite different, even more when using CPMAS results with its broad signals. We have already warned about the difficulties involved in this approach,[33-35] but we must confess that we were disappointed because no signal (N-1, N-2 or NH_2) is related in any way to annular tautomerism or to situations **A-D**. For instance, compound **5** which is a mixture of 3-amino and 5-amino tautomers presents only one signal for each nitrogen atom. The only congruent observation is that the two compounds, **2** and **4**, which exists as mixtures of type **A** and type **B** stuations show two signals for N-2.

NMR Spectroscopy (solution results). ^{13}C NMR. In DMSO-d_6 solution, compound **1** presents a very unusual behaviour: the signals of both tautomers are observed. Although broad, they allow to determine by deconvolution that there is 54% of 3-amino-5-phenyl and 46% of 3-phenyl-5-aminopyrazole, that is, K_T = 1.174. For the other compounds, we have interpolated the experimental values using the values of *N*-methyl derivatives after correcting for the *N*-methyl effect (from compound **1**: +1.9 on C-3, -3.3 on C-4 and -1.1 ppm on C-5 for 3-aminopyrazoles and +1.6 on C-3, -0.2 on C-4 and +1.5 ppm on C-5 for 5-aminopyrazoles).[1,11] The results (average over the three pyrazole carbons) are the following ones (percentages of 3-amino tautomers): compound **2**, 58±3%; compound **3**, 55±5%; compound **4**, 42±2%; compound **5**, 34±4%, and compound **6**, 0%. A Hammett type relationship between log K_T and σ_p yields eq. (1) (for compound **6** we have used 1% of 3-amino tautomer).

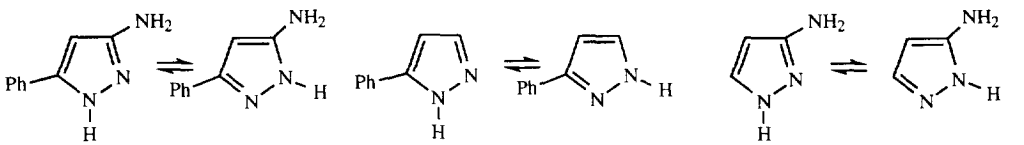
$$\log K_T = -2.1\pm0.3\ \sigma_p,\ n = 6,\ r^2 = 0.91 \qquad (1)$$

The relationship is only moderately good but it provides some rationale to the tautomeric behaviour of arylaminopyrazoles in solution. Moreover, there is also a relationship between the tautomerism in the solid state and in solution:

Compound	% of 3-amino tautomer in DMSO-d_6	Tautomer present in the solid state
1 (X = H)	54	3-amino
2 (X = Me)	58	3-amino
3 (X = MeO)	55	3-amino

4 (X = Cl)	42	3-amino
5 (X = Br)	34	3-amino + 5-amino
6 (X = NO_2)	0-1%	5-amino

Although this relation may seem obvious to the non-informed it is, to the best of our knowledge, the first time that it has been experimentally proved, at least for annular tautomerism. In the case of compound **1**, the result (54/46), compared with that of 3(5)-phenylpyrazole (72/28),[33] allows to determine the equilibrium constant for 3(5)-aminopyrazole (75/25) in good agreement with AM1 calculations (ΔG = -0.7 kcal mol^{-1}).[36]



NMR Spectroscopy (solution results). ^{1}H NMR. The results reported in Table 4 are those expected for the average signals of rapid prototropic tautomerism with one notable exception. Compound **1** shows two signals for both the NH and NH_2 groups. This is very unusual and allows a direct determination of the equilibrium mixture by simple deconvolution of the signals (being broad they overlap). The result, 56/44, is consistent with that obtained by ^{13}C NMR (54/46). A NOESY experiment to prove that the less abundant tautomer has the amino and NH protons close (5-amino tautomer) failed because annular tautomerism related the four signals.

Semiempirical calculations.

In order to rationalize some experimental observations, the stability of the 3 and 5-tautomers have been tested by semiempirical calculations at AM1 level.[37] Moreover the potential energy surface and the variation of the C-N(amino) distances [d(C-N)] as a function of the hybridization of the amino group (sum of bond angles = $\Sigma\alpha$[N]) and its disposition (N-C-N-H torsion angle = τ) with respect to the pyrazole ring (Fig. 3) has been calculated. In all the studied compounds, the 3-tautomer is more stable than the 5-one, the smaller difference between both tautomers was found in **6**. At molecular level, the agreement with the experimental results is quite good (Table 1 and 5). The potential energy surface was computed as a function of the hybridization of the amino group and the complete rotation of one of their hydrogen atoms with respect to the pyrazole ring (Fig. 3). It presents two global minima at ($\Sigma\alpha$[N]= 335° and τ = 15°/-15°, d = 1.401 Å) corresponding to equivalent dispositions of the amino group on each side of the pyrazole ring, that means before and after the inversion of the amino group. The crystallographically observed conformations can be regarded as one of the two possible energy minimized structures although slightly distorted. Similar results were obtained for tetramethyl-*p*-phenylendiamine ($\Sigma\alpha$[N], τ, d: 348°, 25°, 1.44 Å).[38] The maximum, at 7.3 kcal mol^{-1}, displays sp^2 hybridization and the amino group perpendicular to the pyrazole ring, Fig. 3b ($\Sigma\alpha$[N] = 360° and τ = 90° and d = 1.385 Å). The shortest C-N distance of 1.372 Å is obtained when the amino group is coplanar with the pyrazole ring.

Table 4. ^{1}H NMR data in solution of 3(5)-amino-5(3)-arylpyrazoles at 298K.

Compound	Solvent	H-4	NH	NH_2	R_3 or R_5	CH_3
1 (X =H)	DMSO-d_6	5.83 (br)	11.98 (br) (3-NH_2, 56%) 11.58 (br) (5-NH_2, 44%)	4.66 (br) (3-NH_2) 5.03 (br) (5-NH_2)	7.24 (t, 1H, H-*p*, ^3J=7.1); 7.36 (t, 2H, H-*m*, ^3J=7.5); 7.67 (d, 2H, H-*o*, ^3J=6.9)	—
	CD_3OD	5.90 (s)	n.o.	n.o.	7.20-7.45 (m, 3H, H-*p* and H-*m*) 7.60 (d, 2H, H-*o*, ^3J=8.0)	—
	THF-d_8	5.74 (s)	10.9 (vbr)	4.23 (br)	7.13-7.33 (m, 3H, H-*p* and H-*m*) 7.60 (d, 2H, H-*o*, ^3J=7.2)	—
2 (X = CH_3)	DMSO-d_6	5.73 (s)	11.72 (br)	4.75 (br)	7.17 (d, 2H, H-*m*, ^3J=7.9) 7.53 (d, 2H, H-*o*)	2.29 (s)
	$CDCl_3$	5.88 (s)	n.o.	4.10 (vbr)	7.20 (d, 2H, H-*m*, ^3J=7.1) 7.42 (d, 2H, H-*o*)	2.37 (s)
3 (X = OCH_3)	DMSO-d_6	5.66 (s)	n.o.	4.70 (vbr)	6.92 (d, 2H, H-*m*, ^3J=8.6) 7.55 (d, 2H, H-*o*)	3.75 (s)
4 (X = Cl)	DMSO-d_6	5.74 (s)	n.o.	4.87 (br)	7.40 (d, 2H, H-*m*, ^3J=8.6) 7.53 (d, 2H, H-*o*)	—
5 (X = Br)	DMSO-d_6	5.74 (s)	11.75 (br)	4.89 (br)	7.53 (d, 2H, H-*m*, ^3J=8.6) 7.60 (d, 2H, H-*o*)	
	$CDCl_3$	5.90 (s)	n.o.	3.44 (vbr)	7.40 (d, 2H, H-*m*, ^3J=8.3) 7.52 (d, 2H, H-*o*)	—
6 (X = NO_2)	DMSO-d_6	5.88 (br)	11.90 (br) 12.2 (sh)	5.14 (br)	7.91 (d, 2H, H-*o*, ^3J=8.7) 8.20 (d, 2H, H-*m*)	—

(br) Broad; (s) singlet; n.o. not observed; (vbr) very broad; (sh) shoulder.

Table 5. Selected geometrical parameters (Å,°) from the AM1 calculations.

	1a	1b	3a	3b	4a	4b	5a	5b	6a	6b
C3/5-N6	1.399	1.393	1.400	1.393	1.399	1.392	1.399	1.392	1.397	1.390
C5/3-C7	1.450	1.456	1.449	1.455	1.449	1.456	1.449	1.456	1.448	1.456
Σα[N6]	336	339	336	339	337	340	337	340	337	340
N1/2-N2/1-C3/5-N6	-175.9	-173.1	-175.9	-173.1	-176.0	-173.1	-176.0	-173.1	-176.0	-172.9
N2/1-C3/5-N6-H61	-16	-19	-16	-19	-16	-18	-16	-18	-16	-18
N2/1-C3/5-N6-H62	-143	-148	-143	-148	-143	-148	-143	-149	-144	-149
N1/2-C5/3-C7-C8	27.1	27.0	28.5	25.6	27.0	26.8	26.3	26.7	24.4	27.0
ΔH (kcal/mol)	0.00	2.21	0.00	2.10	0.00	1.88	0.00	1.86	0.00	1.22

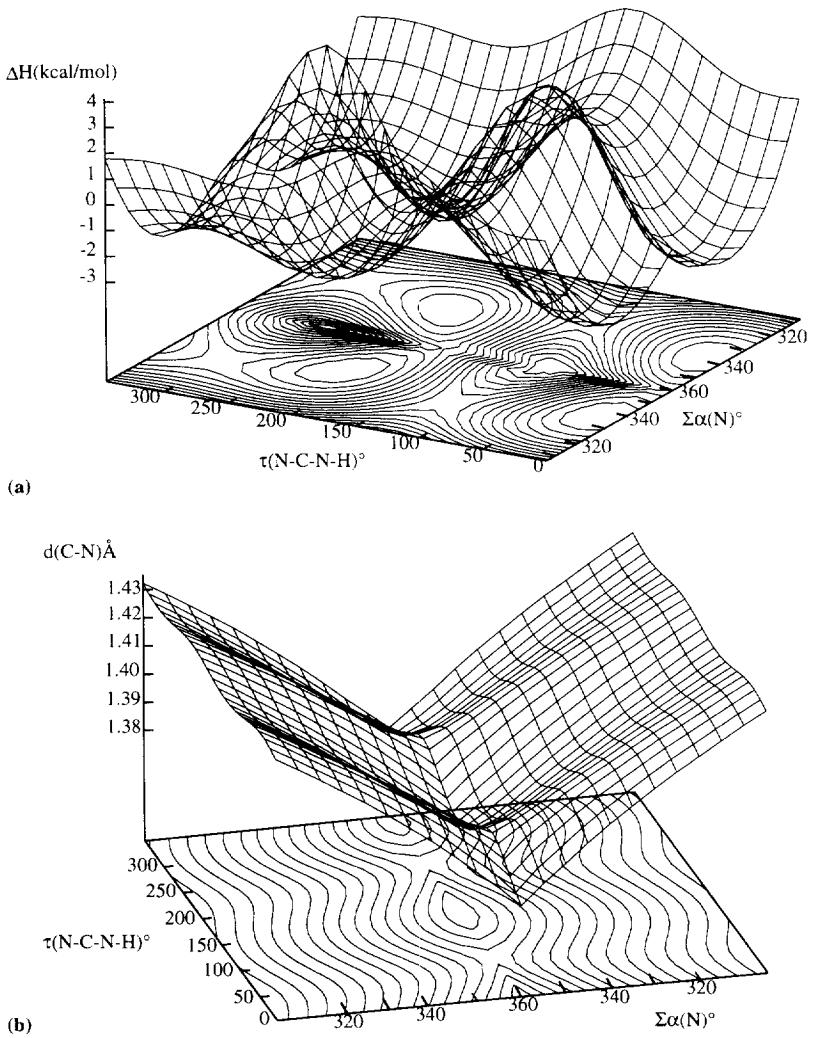


Fig. 3.-Potential energy surface **(a)** and the variation of the C-N(amino) distances **(b)** as a function of the hybridization of the amino group and its disposition with respect to the pyrazole ring.

EXPERIMENTAL SECTION

Synthesis.- Melting points were determined on a Büchi 510 and Reichert-Thermovar instruments and are uncorrected. ^{1}H and ^{13}C FT-NMR spectra were recorded at 200 (400) and 50 (100) MHz on Bruker AC200 and AMX400 spectrometers. The chemical shifts were measured relative to TMS. ^{13}C CPMAS NMR spectra were recorded at 100 MHz on a Bruker MSL400 spectrometer with the following conditions: 5 s of recycle delay, 90° pulse of 5.45 μs and sw = 35211.3 Hz (350 ppm), AQ = 0.116 s. ^{15}N CPMAS NMR spectra were recorded on a Bruker MSL 300 spectrometer working at 300.13 MHz for protons and 30.41 MHz for ^{15}N. The spectrometer was equipped with a 7 mm high speed CPMAS probehead from Bruker. The spinning speeds were of the order of 5 kHz. All spectra were referenced to external solid $^{15}NH_4Cl$ and changed to external CH_3NO_2 through the following equation: $\delta(\text{ext. } CH_3NO_2) = \delta[^{15}NH_4Cl(\text{solid})] - 338.1$ ppm.[35]

Compounds **1-6** have been prepared from the corresponding β-chlorocinnamonitriles and hydrazine hydrate according to the procedures described in refs. 14 and 15; since they have m.p. identical to those reported there, no analysis was carried out on the samples. Crystals were obtained in a variety of conditions, mostly in ethyl acetate-hexane. Compound **6** was crystallized in a mixture of MeOH-H_2O-THF.

X-ray Analysis.- The crystal data and refinement parameters are reported in Table 6. Crystals of compounds **5** and **6** were cooled at 200 K with an Oxford Cryostream device since the first set of data collected at room temperature did not afford reliable results. Semi-empirical (ψ scan) absorption corrections were applied for **4a** and **5**, however as the refinement in **4a** did not progress below final R value of 0.13, empirical absorption correction was performed.[39] The two independent molecules in the asymmetric unit of **4a**, as it is shown in Fig. 1, are almost related by a symmetry center at [0.549(3), 0.245(8), 0.176(4)].[40]

All structures were solved by direct methods (SIR92)[41] and refined by least-squares procedures on Fobs. All hydrogens were obtained from difference Fourier synthesis and included and refined isotropically in the last cycles. The displacement parameters of some hydrogen atoms in **5** had to be fixed in the last cycles of refinement. The final difference synthesis in **5** shows peaks located between the bromide atoms along the **c** axis (Fig. 2). They were found at short distances of both independent Br atoms to be assigned to disorder water or solvent molecules. Several attempts to perform different types of absorption correction failed. The scattering factors were taken from the *International Tables for X-Ray Crytallography*.[42] The calculations were carried out with the XTAL,[43] PESOS[44] and PARST[40] set of programs running on a MicroVAX3100-85 computer.[45]

Acknowledgements

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Table 6a. Crystal analysis parameters.

	1a	**3a**	**4a**
Crystal data			
Formula	$C_9H_9N_3$	$C_{10}H_{11}N_3O.H_2O$	$C_9H_8N_3Cl$
Crystal habit	Colourless, plate	Colourless, plate	Colourless, plate
Crystal size (mm)	0.50 x 0.43 x 0.03	0.47 x 0.23 x 0.07	0.50 x 0.27 x 0.03
Symmetry	Orthorhombic, $P2_12_12_1$	Monoclinic, $P2_1/c$	Orthorhombic, Pbca
Unit cell determination:	Least-squares fit from 50 reflexions (θ<42°)	Least-squares fit from 71 reflexions (θ<45°)	Least-squares fit from 52 reflexions (θ<36°)
Unit cell dimensions (Å,°)	a=17.2032(12)	a=13.0244(8)	a=39.1719(31)
	b=5.8710(3)	b=5.5752(2)	b=15.4835(6)
	c=7.8114(4)	c=14.4165(7)	c=5.8663(1)
	90, 90, 90	90, 91.231(5), 90	90, 90, 90
Packing: V(Å³), Z	788.94(6), 4	1046.59(7), 4	3557.98(28), 8
Dc(g/cm³), M, F(000)	1.340, 159.19, 336	1.315, 207.23, 440	1.446, 387.27, 1600
$\mu(cm^{-1})$	6.76	7.78	34.06
Experimental data			
Technique	Four circle diffractometer: Philips PW1100, Bisecting geometry Graphite oriented monochromator. $\omega/2\theta$ scans.Detector apertures 1 x 1°. 1 min./reflex. CuKα. θ_{max}= 65. Scan width= 1.5°		
Number of reflexions:			
Independent	811	1791	3041
Observed (2σ(I) criterion)	736	1439	2059
Max-min transmission factor:	-	-	0.998-0.600
Standard reflexions:	2 reflexions every 90 minutes. No variation		
Temperature (K):	295	295	295
Solution and refinement			
Solution	Direct methods: Sir92		
Refinement:			
Least-Squares on Fo	Full matrix		
Secondary extinction (10^4)	0.225(13)	0.131(3)	0.014(1)
Parameters:			
Number of variables	145	188	299
Degrees of freedom	591	1251	1760
Ratio of freedom	5.1	7.7	6.9
Final shift/error			
H atoms	From difference synthesis		
Weighting-scheme	Empirical as to give no trends in $<\omega\Delta^2F>$ vs. <|Fobs|> and $<\sin\theta/\lambda>$		
Max. thermal value (Å²)	U22(C11)=0.087(2)	U22(N6)=0.077(1)	U22(Cl1 mol.2)=0.109(1)
Final ΔF peaks ($eÅ^{-3}$)	±0.14	±0.20	±0.33
Final R and Rw	0.038, 0.045	0.037, 0.045	0.060, 0.073

Table 6b. Crystal analysis parameters.

	5a+b	**6b**
Crystal data		
Formula	$C_9H_8N_3Br$	$C_9H_8N_4O_2$
Crystal habit	Colourless, plate	Deep red, prism
Crystal size (mm)	0.70 x 0.20 x 0.07	0.60 x 0.17 x 0.10
Symmetry	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/n$
Unit cell determination:	Least-squares fit from 70 reflexions (θ<42°)	Least-squares fit from 47 reflexions (θ<45°)
Unit cell dimensions (Å,°)	a=19.4409(15) b=6.3695(3) c=15.5874(11) 90, 107.844(6), 90	a=6.3575(4) b=12.0596(8) c=11.4679(9) 90, 92.448(9), 90
Packing: V(Å^3), Z	1837.32(16), 4	878.42(9), 4
Dc(g/cm^3), M, F(000)	1.721, 476.17, 944	1.544, 204.19, 424
μ(cm^{-1})	57.19	9.63
Experimental data		
Technique	Four circle diffractometer: Philips PW1100, Bisecting geometry Graphite oriented monochromator. $\omega/2\theta$ scans.Detector apertures 1 x 1°. 1 min./reflex. CuKα. θ_{max}= 65. Scan width= 1.5°	
Number of reflexions:		
Independent	3150	1496
Observed (2σ(I) criterion)	2286	1282
Max-min transmission factor:	0.996-0.513	-
Standard reflexions:	2 reflexions every 90 minutes.	
	1% decay	No variation
Temperature (K):	200	200
Solution and refinement		
Solution	Direct methods: Sir92	
Refinement:		
Least-Squares on Fo	Full matrix	
Secondary extinction (10^4)	0.035(14)	0.040(1)
Parameters:		
Number of variables	292	168
Degrees of freedom	1994	1114
Ratio of freedom	7.8	7.6
Final shift/error		
H atoms	From difference synthesis*	
Weighting-scheme	Empirical as to give no trends in <$\omega\Delta^2$F> vs. <|Fobs|> and <sinθ/λ>	
Max. thermal value (Å^2)	U33(Br1 mol.2)=0.0803(6)	U33(O15)=0.069(1)
Final ΔF peaks (eÅ^{-3})	±1.99*	±0.21
Final R and Rw	0.055, 0.062	0.041, 0.052

*see experimental section

the laboratory of Professor H.-H. Limbach (FUB, Berlin) whose help and that of O. Klein we greatly acknowledge. The ^{13}C CPMAS NMR spectra have been recorded at 100 MHz in Bruker Analytische Messtechnik GmbH by Dr. H. Forster through the help of Dr. C. Marfisi (Bruker Española, S. A.). We also acknowledge the assistence of Dr. M. D. Santa María and M. J. Retuerce from the UNED.

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