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2,4,6-TRIS(AZOL-1-YL)-1,3,5-TRIAZINES: A NEW CLASS OF MULTIDENTATE LIGANDS

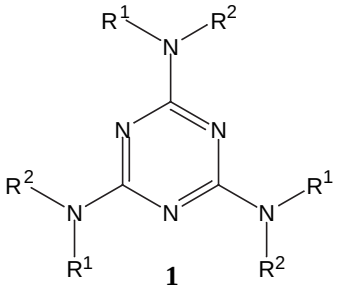
Viktor Milata,[1] Rosa María Claramunt,[1]* Pilar Cabildo,[1] María Dolores Santa María,[1] Pilar Cornago,[1] Lourdes Infantes,[2] Felix H. Cano,[2] and Jose Elguero[3]

[1]*Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey 9, E-28040 Madrid, Spain*
[2] *Departamento de Cristalografía, Instituto de Química-Física Rocasolano, CSIC, Serrano 119, E-28006 Madrid, Spain*
[3]*Instituto de Química Médica, CSIC, Juan de la Cierva 3, E-28006, Madrid, Spain*

Abstract- The synthesis of thirteen tris(azol-1-yl)-*s*-triazines (azole = pyrazoles, imidazoles, 1,2,4-triazole and benzimidazoles) is described. Particularly interesting are the compounds derived from *C*-adamantylazoles (4-adamantylpyrazole, 2-adamantylimidazole and 2-adamantylbenzimidazole) because of their high lipophilicity. The crystal and molecular structures of 2,4,6-tris(2-phenylimidazol-1-yl)-1,3,5-triazine (**6c**) and 2,4,6-tris(2-phenylbenzimidazol-1-yl)-1,3,5-triazine (**8c**) have been determined by X-Ray analysis. The molecular structure can be described as a propeller taking into account the twists existing between the central ring and the substituents. The crystal structure of both compounds show a distorted hexagonal packing of chains. All trisazolyltriazines have been fully characterized by ^{1}H-, ^{13}C- and ^{15}N-NMR spectroscopy. The ^{13}C and ^{15}N chemical shifts in $CDCl_3$ and trifluoroacetic acid have been used to discuss the conformation and the site of protonation.

INTRODUCTION

The 1,3,5-triazine systems tri-substituted by amines at positions 2, 4 and 6 are of considerable interest. These compounds (**1**) the simplest representative being melamine (**2**), are easily obtained from 2,4,6-trichloro-1,3,5-triazine (**3**) (trivial name: cyanuric chloride) by nucleophilic substitution.[1]



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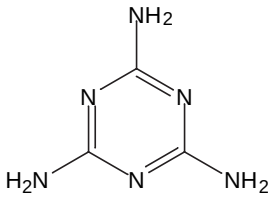

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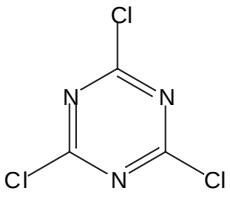

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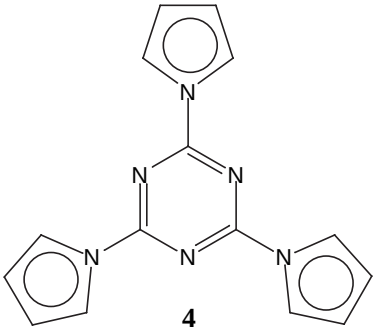
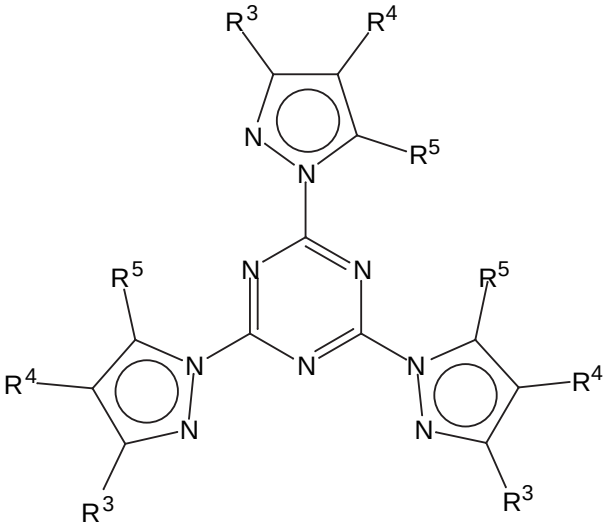


4

Melamine has been used extensively by Whitesides to built up supramolecular crystal structures.[2,3] Other related derivatives have shown interesting properties in crystal structure engineering,[4] and in dendrimers.[5] There are some studies dealing with their affinity for flavin (electronic communication),[6] as well as with their important biological properties.[7] Fujita has published a series of remarkable papers describing the supramolecular organometallic structures derived from tris(4-pyridyl)-1,3,5-triazines.[8]

A particular sub-field is constituted by trisazolyl-*s*-triazines (**4**) where the substituents are 1-azolyl groups. The bibliography on these compounds is scarce. We have described some 2,4,6-tris(pyrazol-1-yl)-1,3,5-triazines (**5a**)[9-11] and (**5b**)[12] including their chemical properties and structural characterisation. Other authors have described the use of **5c** to prepare Re fluxional complexes[13] as well as 1:1, 1:2 and 1:3 Eu(III) complexes and to demonstrate that their luminescence is sensitive to the π-π stacking and H-bonding interactions.[14]



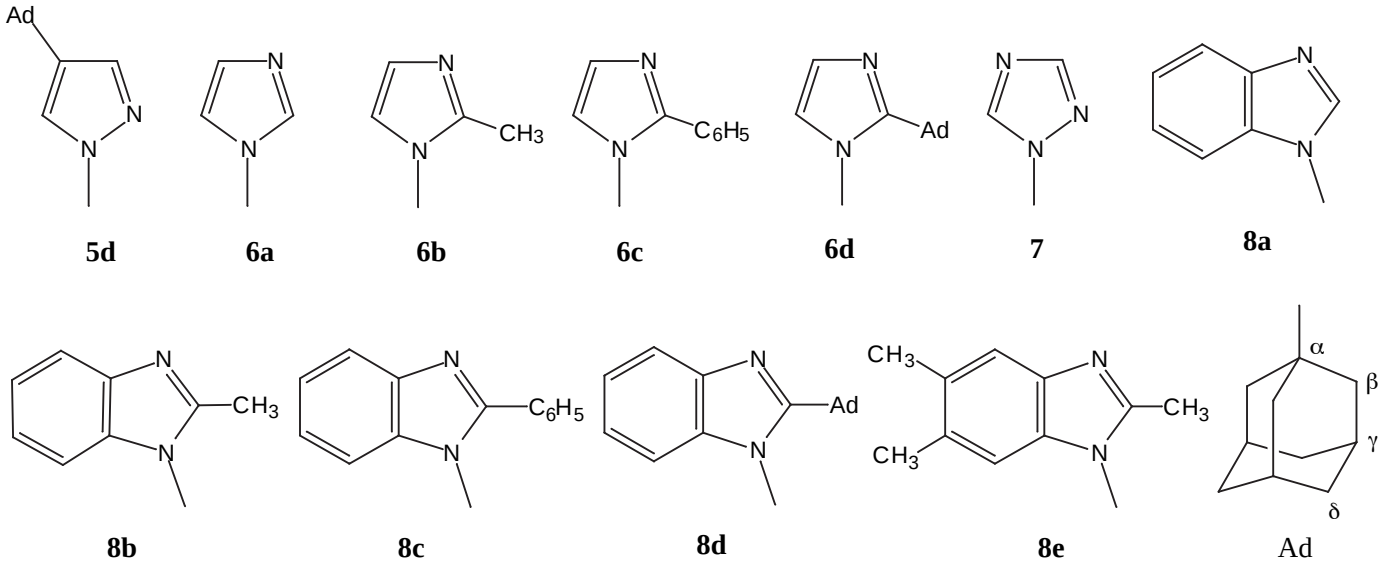
5a $R^3 = R^4 = R^5 = H$
5b $R^3 = R^5 = H$, $R^4 = CH_3$
5c $R^3 = R^5 = CH_3$, $R^4 = H$

Other azoles have been even less studied. Triazines bearing 1-benzimidazolyl substituents are described in patents (fungicides and antitumor compounds).[15,16] Those substituted with two 1-imidazolyl residues have aromatase inhibitory activity (the same paper has reported mono-substituted 1-pyrazolyl and 1-*v*-triazolyl derivatives).[17]

Chemistry

Starting from cyanuric chloride and NH-azoles, named **5aH**-**8eH**, we have prepared the thirteen trisazolyl-*s*-triazines corresponding to the radicals of Scheme 1 plus two known derivatives (**5a**) and (**5c**) (literature

yields about 70% for **5a** and about 30% for **5c**).[9-13] The starting azoles are commercial compounds save the three adamantyl derivatives (**5dH**, **6dH** and **8dH**). The yields are between moderate and good: **5a**: 75, **5c**: 29, **5d**: 48, **6a**: 55, **6b**: 34, **6c**: 62, **6d**: 25, **7**: 64, **8a**: 82, **8b**: 58, **8c**: 57, **8d**: 46, and **8e**: 53 %.



5d **6a** **6b** **6c** **6d** **7** **8a**

8b **8c** **8d** **8e**

Scheme 1. The azol-1-yl substituents on 1,3,5-triazine ring. For the corresponding azoles, an **H** is added

For the preparation of the starting *C*-adamantylazoles (**5dH**, **6dH** and **8dH**) we have modified the methods described in the literature. 4-Adamantylpyrazole (**5dH**) has been synthesized according to a known procedure consisting in the adamantylation of pyrazole,[18] but the isolation procedure has been modified because the use of the method described for its isolation leads to considerable decomposition. Of the three products present in reaction mixture, only the desired compound has an acidic proton. Therefore the transformation into the corresponding sodium salt can be exploited for its separation after extraction of the *N*-adamantylated species (1-adamantyl and 1,4-diadamantylpyrazole) with hexane. Chromatography of 2-adamantylimidazole (**6dH**)[19] appears to be the best method for its purification. 2-Adamantylbenzimidazole (**8dH**) has been synthesized by ring closure of the appropriate benzenediamine in benzene with *p*-toluenesulfonic acid as catalyst[20] with better results than those obtained previously with polyphosphoric acid ethyl ester (PPE).[21] When anhydrous *p*-toluenesulfonic acid or an equimolar mixture of *p*-toluenesulfonic acid and tosyl chloride is used, the *N*-tosyl derivative was formed. This compound can be hydrolysed in alkaline media to desired product, which has been prepared as described in the experimental part.

The preparation of triazines requires activation of the appropriate *N*-H azole, because the leaving group ability of the chlorine atoms in cyanuric chloride (**3**) is not sufficient, compared with similar compounds like hexachloro-cyclotriphosphazene.[22] The corresponding azoles were therefore converted into their sodium salts using sodium hydride in tetrahydrofuran as solvent. In the case of 2-(1-adamantyl)imidazole (**6dH**), the salt must be prepared at 0 ℃ because it decomposes, in other cases a reflux about 1 h is recommended. By addition of **3** to an excess of azole, in a 1:3 molar ratio, only the tris-substituted products are formed (the addition of **3** must be slow and afterwards the temperature could be elevated to reflux). In

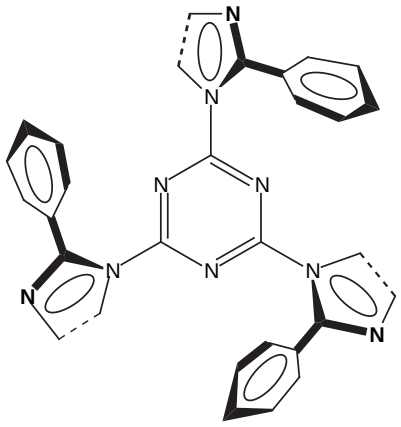
all cases, only tri-substituted derivatives have been isolated, in agreement with other authors.[23] It seems that the successive azole groups activate the remaining chlorine atoms.

Most compounds here reported being "symmetric", only one isomer is possible. Only in the case of 1,2,4-triazole (**7H**), there is the possibility of mixture of isomers 1*H*- and 4*H*-substituted. It is well know that arylation of 1,2,4-triazole (**7H**) yields, in general, 1-aryl derivatives.[24] Then, as expected, in the case of **7**, NMR spectra demonstrated that only substitution through the nitrogen atom in position 1 has occurred. In the case of benzotriazole, a complex mixture of 1- and 2-benzotriazolyltriazines was obtained and the study was not proceeded further.

Note that when the colour of the reaction mixture started to darken, the reaction must be stopped as soon as possible. All the products bound very strongly to solvents and removing them requires heating to about 95 ℃ for 2 days (the samples after drying became colourless). Many of them, when heated, partially sublime about 30 ℃ before the melting point. Recrystallisation from DMSO causes decomposition of the products.

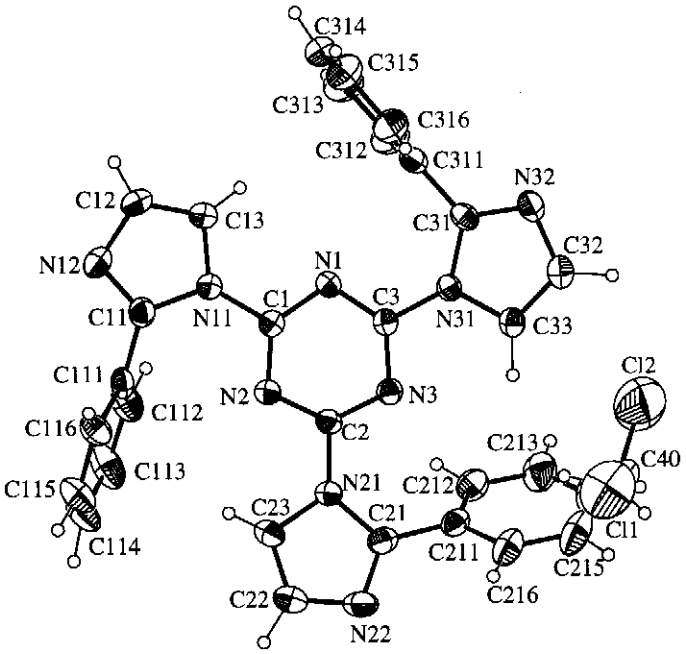
X-RAY STRUCTURE DETERMINATION

The molecular structure and the atom labelling scheme of **6c** and **8c** are depicted in Figure 1. The bond distances and angles of the triazine rings, Table 1, are not significantly different from those of the 1,3,5-triazine itself (CSD refcode: TRIAZIN).[25] When the bond distances in the imidazole rings are compared with the mean values retrieved from the Cambridge Structural Database, CSD,[26] the single and double bonds appear to be elongated and shortened respectively, which suggests a of the π-electronic system in the ring. This is a consequence of the powerful electron-withdrawing effect of the 1,3,5-triazine ring, comparable to a 2,4,6-trinitrophenyl group. The fusion bond (Ci2-Ci3) in the benzimidazoles of **8c** is obviously longer than the corresponding double bond in the imidazoles of **6c**. The C-N distances between the triazine and the azolyl substituents are elongated with respect to the tabulated value of 1.371(16) Å for Car-N(sp^2 planar) bond.[26]



The conformation of the molecules shows the imidazole and benzimidazole rings rotated out of the triazine plane, -5.7(7)° in **6c** and -15.0(7)° in the more crowded **8c** (Table 1), which corresponds to a propeller-like

(a)



(b)

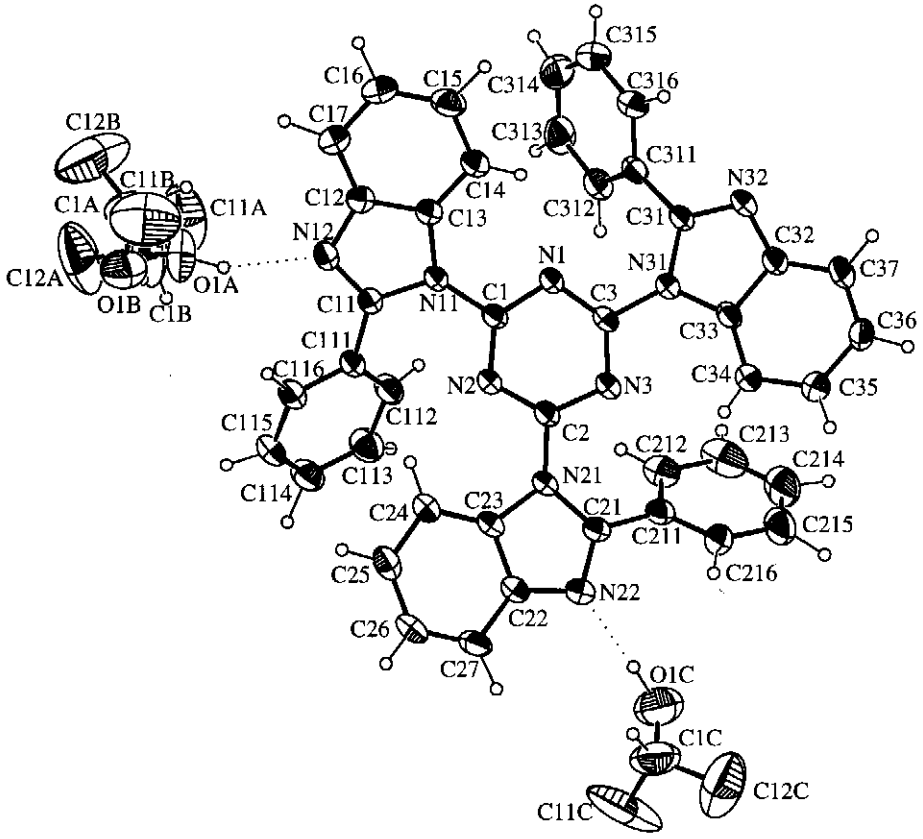


Figure 1. Molecular structure and atomic numbering of the triazine derivates: **(a) 6c** and **(b) 8c**. Displacement ellipsoids are scaled to enclouse 30% probability, and the hydrogen atoms are denoted as spheres of 0.1Å radii.

Table 1. Selected geometrical parameters (Å,°)

Compd	**6c**				**8c**			
N1-C1	1.329(6)	C2-N3	1.318(6)		N1-C1	1.335(6)	C2-N3	1.343(6)
C1-N2	1.323(6)	N3-C3	1.339(6)		C1-N2	1.317(7)	N3-C3	1.337(7)
N2-C2	1.325(6)	N1-C3	1.320(6)		N2-C2	1.316(5)	N1-C3	1.324(5)
C1-N1-C3	112.8(4)	N2-C2-N3	127.3(4)		C1-N1-C3	112.9(4)	N2-C2-N3	126.6(5)
N1-C1-N2	127.5(4)	C2-N3-C3	113.0(4)		N1-C1-N2	126.7(5)	C2-N3-C3	112.4(4)
C1-N2-C2	112.6(4)	N1-C3-N3	126.8(4)		C1-N2-C2	114.1(4)	N1-C3-N3	127.3(4)
	i=1	i=2	i=3			i=1	i=2	i=3
Ci-Ni1	1.401(6)	1.394(6)	1.397(6)			1.400(5)	1.397(7)	1.403(6)
Ni1-Ci1	1.393(6)	1.396(7)	1.392(6)			1.418(6)	1.407(6)	1.417(7)
Ci1-Ni2	1.299(8)	1.300(7)	1.306(6)			1.286(6)	1.300(7)	1.295(6)
Ni2-Ci2	1.388(9)	1.387(9)	1.389(7)			1.401(8)	1.407(6)	1.380(7)
Ci2-Ci3	1.317(10)	1.330(9)	1.342(7)			1.392(6)	1.375(8)	1.414(7)
Ci3-Ni1	1.389(7)	1.398(7)	1.396(6)			1.417(7)	1.432(6)	1.415(6)
Ci1-Ci11	1.472(7)	1.486(7)	1.470(7)			1.479(8)	1.481(6)	1.470(7)
Ci3-Ci4	-	-	-			1.400(9)	1.390(6)	1.367(8)
Ci4-Ci5	-	-	-			1.368(9)	1.395(9)	1.390(8)
Ci5-Ci6	-	-	-			1.398(8)	1.385(10)	1.393(9)
Ci6-Ci7	-	-	-			1.395(11)	1.366(7)	1.344(9)
Ci7-Ci2	-	-	-			1.367(8)	1.395(9)	1.398(7)
Ni-Ci-Ni1	115.7(4)	115.8(4)	114.4(4)			115.5(4)	117.3(4)	115.4(4)
N2/3/1-Ci-Ni1	116.8(4)	116.9(4)	118.8(4)			117.8(4)	116.1(4)	117.3(4)
Ci-Ni1-Ci3	124.7(4)	123.2(4)	123.5(4)			125.2(4)	124.8(4)	125.0(4)
Ci-Ni1-Ci1	129.1(4)	130.6(4)	130.2(4)			128.1(4)	128.9(4)	128.3(4)
Ci3-Ni1-Ci1	105.9(4)	105.9(4)	106.4(4)			105.8(4)	105.7(4)	106.4(4)
Ni1-Ci1-Ni2	110.6(4)	110.8(4)	110.9(4)			111.7(4)	112.1(4)	111.6(4)
Ci1-Ni2-Ci2	105.9(5)	106.0(5)	105.8(4)			107.5(4)	106.3(4)	107.4(4)
Ni2-Ci2-Ci3	111.1(6)	111.4(6)	111.2(5)			109.8(5)	111.0(5)	110.7(5)
Ci2-Ci3-Ni1	106.5(5)	105.9(5)	105.7(4)			105.2(4)	104.8(4)	103.9(4)
Ci7-Ci2-Ci3	-	-	-			122.1(5)	121.1(5)	119.0(5)
Ci2-Ci3-Ci4	-	-	-			121.7(5)	122.8(5)	121.9(5)
Ci3-Ci4-Ci5	-	-	-			115.8(6)	115.4(5)	117.1(5)
Ci4-Ci5-Ci6	-	-	-			122.9(6)	121.8(6)	121.7(6)
Ci5-Ci6-Ci7	-	-	-			120.8(7)	122.1(6)	120.9(6)
Ci6-Ci7-Ci2	-	-	-			116.8(6)	116.9(6)	119.5(6)
Ni1-Ci1-Ci11	125.3(4)	125.7(4)	125.3(4)			125.8(4)	125.8(4)	126.4(4)
Ni2-Ci1-Ci11	123.9(5)	123.4(5)	123.8(4)			122.2(4)	121.9(5)	121.8(5)
Ci1-Ci11-Ci12	120.3(5)	122.1(5)	122.3(5)			123.2(5)	121.3(5)	122.5(5)
Ci1-Ci11-Ci16	121.1(4)	118.8(5)	119.3(5)			116.8(5)	117.8(5)	118.7(5)
Ci12-Ci11-Ci16	118.6(5)	119.1(5)	118.4(6)			119.8(5)	120.9(6)	118.4(5)
C3/1/2-Ni-Ci-Ni1	178.5(4)	-177.6(4)	178.7(4)			-178.6(4)	-176.2(4)	-178.3(4)
N2/3/1-Ci-Ni1-Ci1	-5.8(7)	-5.7(7)	-5.7(7)			-15.9(7)	-14.6(7)	-14.4(7)
Ci-Ni1-Ci1-Ci11	-13.3(8)	-9.3(8)	-0.5(7)			-17.5(8)	-15.4(8)	-12.6(8)
Ci3-Ni1-Ci1-Ci11	173.2(5)	176.5(5)	-179.0(4)			172.7(5)	172.8(5)	173.5(5)
Ni1-Ci1-Ci11-Ci12	-72.7(7)	-56.3(7)	-87.1(7)			-38.0(8)	-46.2(8)	-49.7(8)

Table 2. Selected intra- and inter-molecular contacts to **6c** and **8c** (Å,°).

D-H...A	D-H	H...A	D...A	D-H...A
Compound **6c**				
C13-H13...C3136	0.89(5)	3.02(5)	3.860(7)	158(4)
C13-H13...N1	0.89(5)	2.56(5)	2.782(8)	95(4)
C23-H23...C1116	0.89(6)	2.94(6)	3.752(7)	153(4)
C23-H23...N2	0.89(6)	2.48(6)	2.746(7)	98(4)
C33-H33...C2126	1.02(5)	2.88(6)	3.782(6)	149(3)
C33-H33...N3	1.02(5)	2.42(5)	2.724(6)	96(3)
C312-H312...C2123 (3/2-x,1/2+y,1/2-z)	0.92(8)	3.33(7)	3.581(7)	98(5)
C212-H212...C3136 (3/2-x,y-1/2,1/2-z)	0.94(6)	3.11(6)	3.731(7)	125(5)
C112-H112...C3133 (3/2-x,y-1/2,1/2-z)	0.95(7)	2.79(7)	3.545(6)	137(7)
C32-H32...C0103 (3/2-x,1/2+y,1/2-z)	1.01(5)	3.53(5)	3.737(5)	94(3)
N32...C0103 (3/2-x,1/2+y,1/2-z)			3.169(4)	
C113-H113...N32 (x,y-1,z)	0.91(7)	2.71(7)	3.519(8)	150(6)
C1113...C2123 (1-x,1-y,-z)			3.777(3)	
C23-H23...C0103 (1-x,1-y,-z)	0.89(6)	3.55(5)	3.892(6)	106(4)
Cl1...C2126			3.884(5)	
Cl1...C1116 (x-1/2,1/2-y,1/2+z)			3.870(5)	
C315-H315...Cl1 (1/2+x,3/2-y,z-1/2)	1.03(12)	2.76(11)	3.549(10)	134(9)
C316-H316...Cl1 (1/2+x,3/2-y,z-1/2)	0.98(9)	2.96(10)	3.489(8)	115(7)
Compound **8c**				
C14-H14...C3136	0.94(5)	3.15(5)	3.558(6)	108(4)
C14-H14...N1	0.94(5)	2.41(6)	2.933(7)	115(5)
C24-H24...C1116	0.98(7)	3.06(7)	3.642(7)	119(5)
C24-H24...N2	0.98(7)	2.37(7)	2.931(7)	116(4)
C34-H34...C2126	0.83(7)	3.03(7)	3.452(7)	114(5)
C34-H34...N3	0.83(7)	2.52(6)	2.908(7)	110(5)
C35-H35...C1113 (1-x,1-y,-z)	0.90(6)	3.21(5)	3.521(7)	103(3)
C216-H216...C1217 (1-x,1-y,-z)	1.06(8)	3.02(8)	3.800(8)	131(6)
C14-H14...C2123 (1-x,1-y,-z)	0.94(5)	3.39(6)	3.873(7)	115(4)
C316-H316...C2227 (1-x,1-y,-z)	0.96(8)	3.14(7)	3.912(8)	139(5)
C24-H24...C3133 (1-x,1-y,-z)	0.98(7)	3.39(7)	3.559(7)	92(4)
C35-H35...N12 (1-x,1-y,-z)	0.90(6)	2.90(6)	3.321(8)	111(4)
C314-H314...C1113 (1-x,-y,-z)	1.07(10)	2.79(9)	3.617(8)	134(5)
C313-H313...C1217 (1-x,-y,-z)	0.94(8)	2.99(7)	3.661(8)	129(6)
C115-H115...N32 (x-1,y,z)	0.98(7)	2.77(8)	3.506(9)	133(5)
O1A-H1A...N12	0.90(8)	2.07(10)	2.893(6)	153(11)
O1B-H1B...O1A	1.22(10)	1.68(9)	2.821(10)	152(9)
O1C-H1C...N22	1.15(-)	1.87(-)	2.968(9)	156(-)
C116-H116...O1A	1.07(6)	2.91(5)	3.623(8)	124(4)
C216-H216...O1C	1.06(8)	3.21(8)	3.573(12)	101(5)
C36-H36...O1B (1-x,1-y,-z)	1.01(6)	2.58(6)	3.486(9)	149(6)
C113-H113...O1C (1-x,1-y,1-z)	1.07(9)	2.75(8)	3.501(9)	127(7)
C212-H212...O1C (1-x,1-y,1-z)	0.97(6)	2.70(7)	3.584(12)	151(5)
C112-H112...O1C (1-x,1-y,1-z)	0.84(7)	3.11(5)	3.591(9)	119(5)
C27-H27...O1B (-x,1-y,-z)	1.00(6)	3.04(7)	3.586(12)	115(4)
C213-H213...O1B (1+x,y,1+z)	1.02(9)	2.85(8)	3.779(15)	152(6)

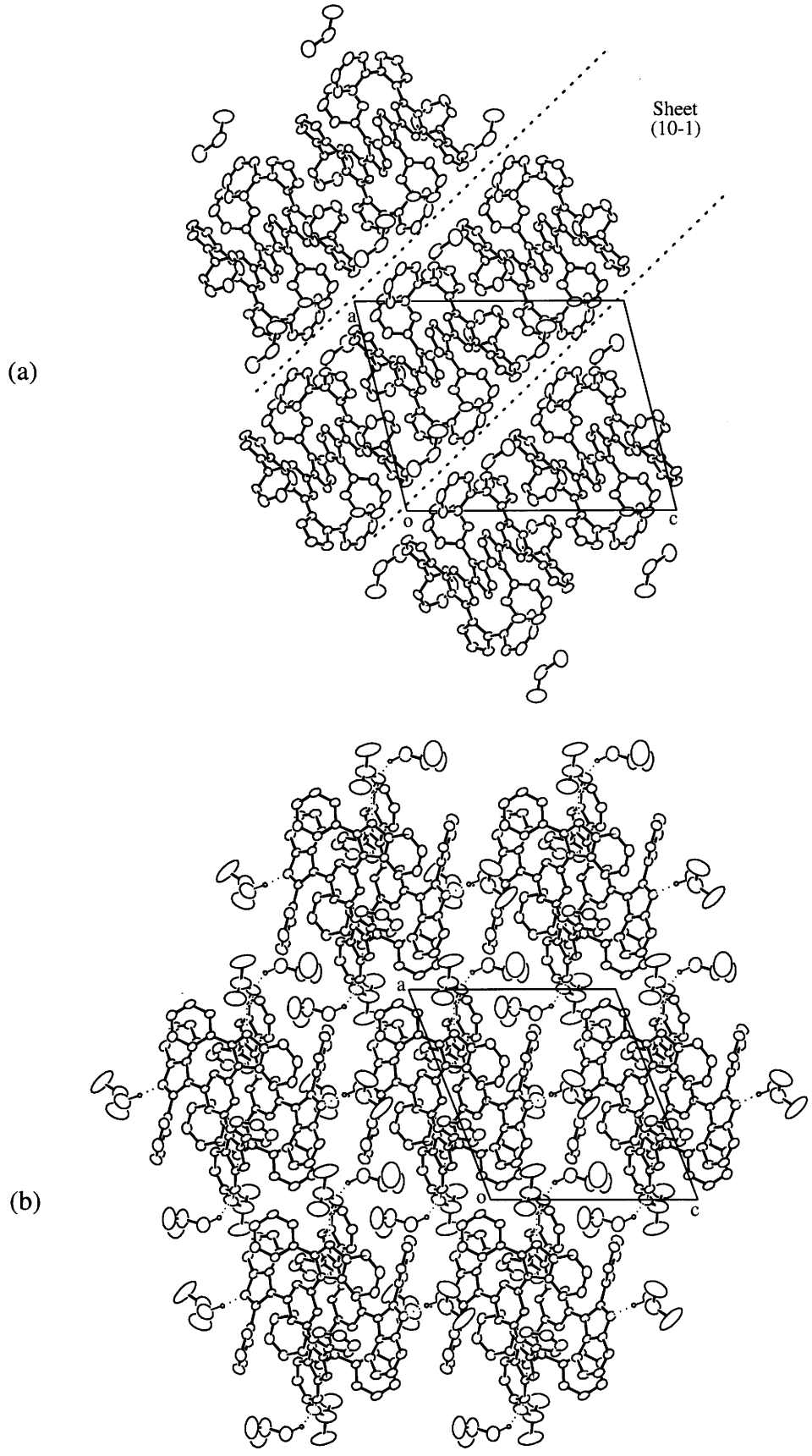


Figure 2. View of the packing of compounds **(a) 6c** and **(b) 8c**, both along the **b** axis and both showing the pseudohexagonal packing of rods parallel to that axis and centered at (3/4,0,1/4) and (1/2,0,0). Hydrogen atoms have been omitted for more clarity.

structure. Until now, none of the 2,4,6-tris(aromatic ring)-1,3,5-triazines retrieved from the CSD[25] displayed the three substituents twisted in the same sense; the angles between triazine and aromatic ring are less than 15°, except in NUNGUY where θ = 16-33°. The dihedral angles about the imidazole(benzimidazole)/2-phenyl inter-ring bonds are different for each substituent showing that the propeller lacks a C_{3v} structure and, on average, 72° and 45° for **6c** and **8c** respectively (Table 1). The hydrogen atoms Hi3 in **6c** and Hi4 in **8c** (i = 1, 2, 3), seem to promote the "tightening" of the molecules, forming bifurcated hydrogen bond interactions Ci3/4-Hi3/4···Ni/π cloud(phenyl ring), Table 2.

In **6c** the molecules related by a twofold screw axis at (3/4, 0, 1/4) and equivalent ones, are assembled into chains, mainly by C-H···π cloud interactions, Table 2. These chains are then linked through π···π stackings, forming the (1, 0, -1) sheets of the tertiary structure. Finally, the crystal is built up by the union of these sheets through contacts involving the chlorine atoms of the solvent. In **8c** there are dimers of centrosymmetric molecules joined through several CH···π/N contacts. The tertiary structure is formed by layers (001), within which it can be distinguished chains along the **b** axis, by CH···π interactions, or along the **a** axis, by CH···N contacts; the 3D structure is formed through interactions involving the isopropanol molecules. All together, the packing of both compounds can be described topologically as a distorted hexagonal packing of chains,[27] Figure 2. The chains in **6c** and **8c** present internal $p112_1$ and p-1 crystallographic rod groups, respectively.[28] Compound (**6c**) has two enantiomeric types of chains, C_0 and C_{-1}, packing one around each other with necklace topology, $C_0(2_1)$:2[C_0, C_{-1}, C_{-1}], C_0 and one C_{-1} slid so as to produce the glide plane **n**. Compound (**8c**) has all the chains equal and without sliding each other, giving a packing $C_0(-1)$:6[C_0]. There are no voids in the structures and the total packing coefficients are 0.66 and 0.65 for **6c** and **8c**.[29]

NMR SPECTROSCOPIC RESULTS

The assignment of the ^{1}H and ^{13}C chemical shifts of the tris(azolyl)triazines has been made by analogy with other azole derivatives reported in the literature.[30,31] For the tris(1-benzimidazolyl)triazines, the ^{13}C NMR values have been assigned by analogy with other benzimidazoles.[30-32]

From these data and through (^{1}H-^{13}C) HMQC and (^{1}H-^{13}C) HMBC correlations, the ^{1}H chemical shifts of compounds (**8a**, **8b**, **8c** and **8e**) have been assigned simultaneously confirming the ^{13}C chemical shifts. In the case of compound (**8d**) the assignment of H4 and H7 is based on the value of ^{3}J(^{1}H-^{1}H). For this compound as well as for (**8c**) H7 present a coupling of 8.2 Hz while for H4 this coupling is only 7.9 Hz.

The ^{13}C chemical shifts of the azole residues are affected only to a small extent by the nature of the substituent, only in compound (**8b**) the general rule δC6 ≥ δC5 is reversed.

Table 3. ^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) of tris(1-azolyl)triazines in $CDCl_3$

Compd	2(3)[a]	4	5	Coupling constants and other signals
5a	7.95	6.59	8.79	$^3J_{(H4,H5)}$= 2.8, $^3J_{(H4,H3)}$= 1.5, $^4J_{(H3,H5)}$= 0.7

5c	2.32	6.09	2.80	$^4J_{(H4,Me5)}$= 0.8	
5d	7.87	----	8.44		Ad: 1.78(Hδ), 1.93(Hβ), 2.08(Hγ)
6a	8.69	7.27	7.92	$^4J_{(H2,H4)}$= 0.8, $^4J_{(H2,H5)}$= 1.3, $^3J_{(H4,H5)}$ ≅ 1.7	
6b	2.94	7.05	7.86	$^3J_{(H4,H5)}$= 1.8	
6c	----	6.50	6.95	$^3J_{(H4,H5)}$ ≅ 1.8	Ph: 7.51(5H)
6d	----	7.05	7.65	$^3J_{(H4,H5)}$ ≅ 1.7	Ad: 1.71(Hδ), 2.02(Hβ), 2.23(Hγ)
7[b]	8.81	----	10.36		

[a] Position 3 in pyrazoles (**5**) and in 1,2,4-triazole (**7**) and position 2 in imidazoles (**6**); [b] In TFA.

Table 4. ^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) of tris(1-benzimidazolyl)-triazines in $CDCl_3$

Compd	2	4	5	6	7
8a	9.22	7.96 $^3J_{(H4,H5)}$ = 7.6	7.52 $^4J_{(H5,H7)}$ = 1.2	7.59 $^4J_{(H4,H6)}$ = 1.2	8.56 $^3J_{(H6,H7)}$ = 8.1
8b	3.07	7.78 $^3J_{(H4,H5)}$ = 8.0	7.39 $^4J_{(H5,H7)}$ = 1.2	7.33 $^4J_{(H4,H6)}$ = 1.2	8.29 $^3J_{(H6,H7)}$ = 8.1
8c	7.61 (H2,H6) 7.40 (H3-H5 and H4)	7.79 $^3J_{(H4,H5)}$ = 7.9	7.34 $^4J_{(H5,H7)}$ = 1.0	7.10 $^4J_{(H4,H6)}$ = 1.0	7.19 $^3J_{(H6,H7)}$ = 8.2
8d	1.84(Hδ), 2.7 (Hβ and Hγ)	7.83 $^3J_{(H4,H5)}$ = 7.9	7.36 $^4J_{(H5,H7)}$ = 1.0	7.26 $^4J_{(H4,H6)}$ = 1.0	7.73 $^3J_{(H6,H7)}$ = 8.2
8e	3.03	7.52	2.40	2.33	8.17

Table 5. ^{13}C NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) of tris(1-azolyl)triazines in $CDCl_3$

Compd	C-Triazine	C-2 (Me-2)	C-3 (Me-3)	C-4	C-5 (Me-5)	Others
5a	163.7	----	146.1 ^{1}J=188.7	110.4 ^{1}J=179.7	130.7 ^{1}J=195.9	----

			^{3}J=9.0 ^{2}J=6.1	$^{2}J_{H3}$=9.2 $^{2}J_{H5}$=9.2	^{2}J=9.3 ^{3}J=3.9	
5c	164.3	----	153.3 ^{2}J=^{2}J=5.9 14.0 ^{1}J=127.9	111.9 ^{1}J=174.2	144.4 ^{2}J=^{2}J=7.4 15.5 ^{1}J=130.3	
5d	163.4	----	144.2 ^{1}J=185.0 ^{3}J=8.6	137.8	125.6 ^{1}J=192.9 ^{3}J=2.7	31.6 (Cα) 43.4 (Cβ) ^{1}J=126.0 28.4 (Cγ) ^{1}J=133.2 36.6 (Cδ) ^{1}J=126.6
6a	162.7	136.7 ^{1}J=218.6 ^{3}J=9.9 ^{3}J=5.8	----	132.4 ^{1}J=193.1 ^{2}J=^{3}J=11.0	116.5 ^{1}J=198.2 ^{2}J=17.2	----
6b	163.4	147.5 19.0 ^{1}J=130.8	----	129.2 ^{1}J=191.7 ^{2}J=19.2	118.2 ^{1}J=196.5 ^{2}J=16.5	----
6c	162.7	148.9	----	129.6 ^{1}J=192.0 ^{2}J=9.3	119.0 ^{1}J=199.1 ^{2}J=16.7	132.9 (1') 129.4 (2') ^{1}J=162.5 128.3 (3') ^{1}J=162.0 129.1 (4') ^{1}J=161.0
6d	165.8	157.1	----	128.1 ^{1}J=191.6 ^{2}J=9.2	121.1 ^{1}J=194.0 ^{2}J=16.6	37.9 (Cα) 40.4 (Cβ) ^{1}J=128.9 28.4 (Cγ) ^{1}J=131.8 36.4 (Cδ) ^{1}J=125.5
7[a]	162.5	----	150.6 ^{1}J=222.4 ^{3}J=10.6	----	145.9 ^{1}J=228.9 ^{3}J=5.5	----

[a] In TFA.

Table 6. ^{13}C NMR chemical shifts (δ in ppm) and coupling constants (*J* in Hz)of tris(1-benzimidazolyl)-triazines in $CDCl_3$

Compd	C-Triazine	C-2	Me, Ph, Ad	C-3a	C-4	C-5
8a	163.2	141.6 ^{1}J=218.4	----	143.1[a] ^{1}J=164.3 ^{3}J=8.8	120.9 ^{1}J=162.3 ^{3}J=8.0	126.4

8 b Ω	164.2	152.2	19.0	143.0	119.8	125.1
		^{2}J=7.6	^{1}J=130.8	^{3}J=5.7	^{1}J=162.8	
^{1}J=160.8						
				^{3}J=9.0	^{3}J=7.8	^{3}J=7.8
8 c	164.4	153.5	131.6, ^{3}J=6.9 (C1')	143.0	120.2	125.0
			128.5, ^{1}J=159.8 ^{3}J=6.9 (C3')	^{3}J=6.0	^{1}J=163.3	
^{1}J=159.5						
			129.2, ^{1}J=162.0 (C2')	^{3}J=9.4	^{3}J=8.3	^{3}J=7.8
			130.2, ^{1}J=161.5 ^{3}J=7.5 (C4')			
8 d	167.0	161.9	38.7 (Cα)	142.1	120.0	124.5
			40.9 (Cβ) ^{1}J=131.4	^{3}J=5.8	^{1}J=162.4	
^{1}J=161.1						
			28.4 (Cγ) ^{1}J=132.3	^{3}J=9.7	^{3}J=8.5	^{3}J=7.8
			36.4 (Cδ) ^{1}J=130.5			
8 e	164.0	151.5	19.1	141.4	119.9	133.5
		^{2}J=7.6	^{1}J=130.7	^{3}J=6.1	^{1}J=159.7	^{3}J=6.1
					^{3}J=4.7	

Compd	Me-5	C-6	Me-6	C-7	C-7a
8a	----	127.0	----	115.7	130.7[a]
		^{1}J=162.2		^{1}J=169.4	
		^{3}J=7.9		^{3}J=8.4	
8b	----	124.7	----	115.1	133.2
		^{1}J=161.2		^{1}J=167.4	^{3}J=6.9
		^{3}J=7.9		^{3}J=7.9	^{3}J=11.2
8c	----	125.2	----	114.3	133.8
		^{1}J=161.1		^{1}J=169.3	^{3}J=9.2
		^{3}J=7.6		^{3}J=8.3	^{3}J=9.2
8d	----	124.5	----	112.6	134.7
		^{1}J=161.0		^{1}J=165.7	^{3}J=8.8
		^{3}J=7.8		^{3}J=8.5	^{3}J=8.8
8e	20.1	133.8	20.4	115.8	131.5
	^{1}J=126.4	^{3}J=6.1	^{1}J=126.6	^{1}J=164.5	^{3}J=6.9
	^{3}J=4.8		^{3}J=5.5	^{3}J=5.9	

[a] This compound is very insoluble and the signals of C-3a and C-7a in the ^{13}C NMR ^{1}H-coupled spectrum are too small to measure the coupling constants.

The ^{15}N NMR triazine signals for all compounds are highly shielded compared with those of triazine itself (-98.5 ppm)[33] or even with regard with 2,4,6-trichloro-1,3,5-triazine (-109.0 ppm, this work).

Table 7. ^{15}N NMR chemical shifts (δ in ppm) referenced to external nitromethane

Compd	Solvent	N-Triazine	N-1	N-2	N-3(4)
5a	$CDCl_3$	-173.5	-160.2	-78.5	----
	CF_3CO_2H	-173.9	-169.9	-173.9	----
5b	$CDCl_3$	-176.4	-162.4	-80.3	----
5c	$CDCl_3$	-167.1[a]	-166.5[a]	-81.6	----
5d	$CDCl_3$	-176.1	-163.0	-80.6	----
6a	$CDCl_3$	-172.1	-192.6	----	-109.6
	CF_3CO_2H	-158.2	-191.7[a]	----	-199.3[a]
6b	$CDCl_3$	-167.8	-195.9	----	-111.1
6c	$CDCl_3$	-163.3	-197.2	----	-104.7
6d	$CDCl_3$	-141.2	-197.6	----	-113.2
7	CF_3CO_2H	-160.3	-154.1[a]	-100.8	-157.0[a]
8a	CF_3CO_2H	-157.0	-207.8[a]	----	-211.7[a]
8b	$CDCl_3$	-158.3	-209.2	----	-123.7
8c	$CDCl_3$	-150.5	-214.4	----	-116.9
8e	$CDCl_3$	-160.1	-209.8	----	-124.8

[a] The assignment of these pairs of signals is only tentative.

From these ^{15}N chemical shifts it is possible to estimate the torsion angles θ between the azolyl residues and the triazine central ring. Using the torsion angles of the crystallographic study (**6c** 5.7° and **8c** 15.0°) and assuming that pyrazoles unsubstituted at position 5 **5a**, **5b** and **5d** should be planar and that there is a linear relationship between $\delta^{15}N$ in $CDCl_3$ and θ it is possible to do it. The torsion angles should be: **5a** 0° (H-5), **5b** 0° (H-5), **5c** 4.5° (Me-5), **5d** 0° (H-5), **6a** 1.4° (H-2 and H-5), **6b** 3.9° (Me-2), **6c** 5.7° (Ph-2), **6d** 19.4° (Ad-2), **8a** 8.7° (H-2, assuming a $\delta^{15}N$ in $CDCl_3$ of -159 ppm), **8b** 9.5° (Me-2), **8c** 15.0° (Ph-2) and **8d** 23° (Ad-2, see below). These angles correspond to an equation:

$$\delta^{15}N = -(174.6\pm0.6) + (1.74\pm0.06)\ \theta,\ n = 12,\ R^2 = 0.987$$

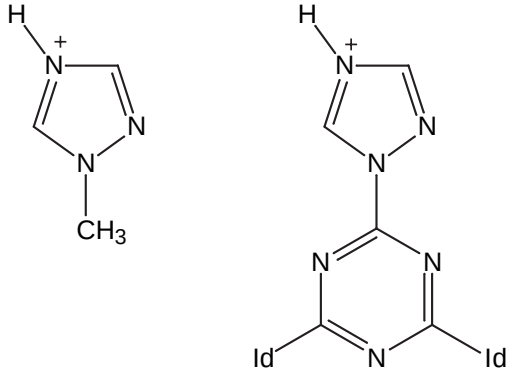
The angles reflect the increase of steric effects in position 2 of imidazoles and benzimidazoles and position 5 of pyrazoles. In ^{13}C NMR spectrum, we have to use the signals of the azolyl substituents. For instance, the difference between the chemical shifts of carbons C-4 and C-5 in imidazoles decrease monotonously with the increase of θ: **6a** 15.9 ppm, 1.4°; **6b** 11.0 ppm, 3.9°; **6c** 10.6 ppm, 5.7° and **6d** 7.0 ppm, 19.4°. The contrary happens with the difference between the chemical shifts of carbons C-4 and C-7 in benzimidazoles: **8a** 5.2 ppm, 8.7° (but the spectrum was recorded in TFA); **8b** 4.7 ppm, 9.5°, **8c** 5.9 ppm, 15.0° and **8d** 7.4 ppm, 23°.

$\delta^{13}C(\text{imidazoles}) = (14.1\pm1.6) - (0.40\pm0.16)\ \theta$, n = 4, $R^2 = 0.76$ (compound **6a** clearly deviates)
$\delta^{13}C(\text{benzimidazoles}) = (3.1\pm0.3) + (0.19\pm0.02)\ \theta$, n =4, $R^2 = 0.97$

The ^{15}N chemical shifts in TFA of compounds (**5a**, **6a**, **7** and **8a**) (the last two rather insoluble in $CDCl_3$) prove that all these compounds are protonated in these conditions. Most of them are protonated exclusively on the azole. The pyrazole derivative (**5a**) shows an almost negligible effect on the triazine signal and the characteristic effects on N-1 and N-2.[34] Although not identical to those measured in *N*-methylpyrazole, they are quite close indicating that the three pyrazoles are protonated to some extent (a monoprotonation would have produced a third of the effects). A salt of pyrazole (**5a**) has been studied by X-Ray crystallography and the proton is on the pyrazole ring.[35]

The imidazole derivative (**6a**) shows both the characteristics effects on imidazole nitrogen atoms,[34] but also a significant effect (+13.9 ppm) on the triazine nitrogen. Protonation of pyridine produces a shift of + 89 ppm[34] (other authors describe larger effects, up to 115 ppm)[36] but the protonation of 1,3,5-triazine in TFA should lead to a monocation which an average shift of about 30 ppm, thus, +14 ppm indicate a partial protonation.[37]

In the case of the 1,2,4-triazolyl derivative (**7**) there is no information about the triazine because the compound cannot be recorded in $CDCl_3$. On the other hand, something curious happens to the azole nitrogen chemical shifts. 1-Methyl-1,2,4-triazole protonates exclusively at N-4 with chemical shifts of -164.3 ppm (N-1), - 81.2 ppm (N-2) and -208.5 ppm (N-4).[34] In the case of **7**, the observed chemical shifts (Table 7) are only consistent with a mixture of cations (**7aH**$^+$) and (**7bH**$^+$). The stability of **7bH**$^+$ is probably due to an intramolecular hydrogen bond with the triazine nitrogen:



7aH$^+$ **7bH**$^+$

This work provides, for the first time, a comprehensive description of trisazolyl-*s*-triazines a promising class of multidentate ligands with possible use for extracting heavy metals. The structure in the solid state and in solution, the protonation site and the conformation of these compounds have been explored. The sensitivity of some derivatives to hydrolysis is a possible limiting factor in the use of trisazolyl-*s*-triazines as ligands and as drugs.

EXPERIMENTAL

The melting points were determined with a hot-stage microscope and are uncorrected. Column chromatography was performed on silica gel Merck 60 (70-230 mesh), TLC on glass sheets of silica gel SDS 60 F_{254} (layer thickness 2 mm), both using a mixture chloroform - methanol (10 : 1) as eluent. The R_f values were measured and reaction were monitored on TLC aluminum sheets of silica gel Merck 60 F_{254} (layer thickness 0.2 mm) with the same eluent. MS spectra (electron impact 60-70 eV) were obtained with Shimadzu QP-5000 and VG Autospec spectrometers. ^{1}H NMR (at 400 MHz), ^{13}C NMR (at 100 MHz) and ^{15}N NMR (at 40.56 MHz) spectra were obtained using a Bruker DRX 400 instrument. Coupling constants (J in Hz) are given with an accuracy of $^2J_{CH}$ ± 0.5 Hz, $^3J_{CH}$, $^4J_{CH}$ ± 0.2 Hz). Chemical shifts (δ) in ppm were measured using the signal of the solvent as an internal standard, in the case of TFA-d_1, external DMSO-d_6 has been used. ^{15}N NMR chemical shifts were obtained by the Inverse Gated ^{1}H-Decoupling Technique and are referenced to an external sample of nitromethane.

Starting materials.

Imidazole, 2-methylimidazole, pyrazole, 2-methylbenzimidazole (Fluka), 2-phenylimidazole (Acros), 3,5-dimethylpyrazole (Janssen Chimica), 1,2,4-triazole, benzimidazole (EGA Chemie), 2,5,6-trimethyl-benzimidazole (Aldrich), and 2-phenylbenzimidazole (Lancaster) are commercial products. 4-Adamantyl-pyrazole (**5dH**) and 2-adamantylimidazole (**6dH**) have been prepared respectively according to Cabildo *et al.*[18] and to Pellicciari *et al.* [19] The method of isolation has been modified in the following way. The combined dichloromethane extracts were dried over magnesium sulfate and evaporated to dryness and combined with the dry precipitate from the reaction to obtain 1.9-2.4 g of a mixture. Of this raw reaction mixture, 2.4 g were dissolved in 40 mL of dry THF and 0.315 g (12.5 mmol) of 95 % NaH was added. When the effervescence ended, the mixture was stirred at room temperature for 30 min. After evaporation of the solvent, the solid residue is extracted with 3 x 50 mL of hot hexane (after evaporation, 0.72 g of a mixture of 1-adamantylpyrazole and 1,4-diadamantylpyrazole was obtained). To the dry solid residue is added carefully 50 mL of water (to destroy the excess of NaH) and neutralised with 32% HCl, extracted with CH_2Cl_2, washed with water, dried over magnesium sulfate and evaporated to dryness to give about 1.1 g of pure product (the method for isolation can be scaled up).

2-Adamantylbenzimidazole (**8dH**):[20,21] To 1 g (0.0036 mmol) of *N*-(1-adamantylcarbonyl)benzene-1,2-diamine in benzene (20 mL) was added 0.66 g (0.0035 mmol) of *p*-toluenesulfonic acid [monohydrate or a mixture 0.33 g (0.0017 mmol) of monohydrate and 0.33 g (0.0017 mmol) of tosyl chloride] and the mixture is heated to 120 °C for 48 h. When the monohydrate is used, the product crystallised after cooling, in the case of using its mixture with tosyl chloride, the *N*-tosyl-2-(1-adamantyl)benzimidazole is formed. The last compound can be hydrolysed in 10 % sodium hydroxide to afford the desired product.

General procedure for preparation of **5a-8e**:

The appropriate N-H azole (30 mmol) is added, under stirring and in small portions, to 0.834 g (33 mmol, 95 %) of sodium hydride in dry THF (60 mL). When the effervescence is damped, the mixture is refluxed for 1 h. Then is added drop-wise a solution of 1.844 g (10 mmol) of 2,4,6-trichloro-1,3,5-triazine (**1**)

dissolved in dry THF (20 mL) and reaction is monitored using TLC. After finishing the reaction, the solvent is evaporated under vacuum to dryness and water is carefully added (50 mL). The product is separated or appropriately purified. To remove the rests of solvents a vacuum drying (2 days at 95 ℃) is required.

Tris(pyrazolyl-1-yl)-1,3,5-triazine (**5a**), tris(imidazol-1-yl)-1,3,5-triazine (**6a**), tris(1,2,4-triazolyl-1-yl)-1,3,5-triazine (**7**), tris(benzimidazolyl-1-yl)-1,3,5-triazine (**8a**) and tris(2-(1-adamantyl)benzimidazolyl-1-yl)-1,3,5-triazine (**8d**) were purified according to the following procedure: The separated product is washed with water to remove the unreacted azole and dried.

Tris(2-methylimidazol-1-yl)-1,3,5-triazine (**6b**), tris(2-phenylimidazol-1-yl)-1,3,5-triazine (**6c**), tris(2-methyl-benzimidazolyl-1-yl)-1,3,5-triazine (**8b**), tris(2-phenylbenzimidazolyl-1-yl)-1,3,5-triazine (**8c**) and tris(2,5,6-trimethylbenzimidazolyl-1-yl)-1,3,5-triazine (**8e**) were extracted with dichloromethane, evaporated and chromatographed on column and finally dried under reduced pressure.

Table 8. Physico-chemical properties of compounds (**5a** – **8e**)

No.	Formula	Mp (℃) Yield (%)	Elemental analysis (calculated/found) % C	% H	% N	R_f $CHCl_3/CH_3OH$, 10:1 $M^{+\cdot}$ (rel. intensity)
5a	$C_{12}H_9N_9$	240-243 75.0				0.30 279 (95)
5c	$C_{18}H_{21}N_9$	241-244 29.4				0.71 363 (65), 95 (100)
5d	$C_{42}H_{51}N_9.CH_2Cl_2$	187-191 48.2	67.35 67.19	6.97 7.07	16.44 16.25	0.63 681(44), 145(100)
6a	$C_{12}H_9N_9$	259-261 54.8	51.61 51.77	3.25 3.21	45.14 45.07	0.16; 0.51 (1:1) 279 (100)
6b	$C_{15}H_{15}N_9$	267-270 34.3	56.07 55.88	4.71 4.89	39.23 38.93	0.72 321 (100)
6c	$C_{30}H_{21}N_9$	194-196 62.1	70.99 71.07	4.17 4.22	24.84 25.01	0.47 507 (100)
6d	$C_{42}H_{51}N_9.2H_2O$	256-258 25.3	70.26 70.03	7.72 7.59	17.56 17.33	0.60 682 (18)
7	$C_9H_6N_{12}$	> 375 63.8	38.30 38.01	2.14 2.30	59.56 59.43	0.12; 0.53 (1:1) 282 (100)
8a	$C_{24}H_{15}N_9$	364-366 81.9	67.12 65.74	3.52 3.73	29.35 29.50	0.73 429 (100)
8b	$C_{27}H_{21}N_9.2\ H_2O$	194-195 58.3	65.89 66.15	4.96 4.74	24.84 24.60	0.48 471 (100)
8c	$C_{42}H_{27}N_9$	149-151 56.7	76.70 76.72	4.14 4.19	19.17 19.31	0.66 657 (100)
8d	$C_{54}H_{57}N_9$	301-305 46.2	77.95 78.02	6.90 6.83	15.15 15.27	0.74 831 (100), 832 (64)
8e	$C_{33}H_{33}N_9.H_2O$	274-276 53.4	69.09 69.10	6.15 6.09	21.97 21.79	0.53 555 (100)

Table 9. Crystal analysis parameters at room temperature.

	(6c)	(8c)
Crystal data		
Formula	$C_{30}H_{21}N_9 \cdot CH_2Cl_2$	$C_{42}H_{27}N_9, 3C_3H_8O$
Crystal habit	Colourless, prism	Colourless, prism
Crystal size (mm)	0.67 x 0.27 x 0.23	0.43 x 0.30 x 0.13
Symmetry	Monoclinic, $P2_1/n$	Triclinic, P-1
Unit cell determination:		
Least-squares fit from reflexions ($\theta<35°$)	72	58
Unit cell dimensions (Å,°)	a=13.9256(14)	a=14.088(2)
	b=12.3379(8)	b=13.635(3)
	c=17.4265(19)	c=12.996(1)
	α=90	α=93.075(11)
	β=104.008(7)	β=111.251(1)
	γ=90	γ=92.207(12)
Packing: V(Å^3), Z	2905.1(3), 4	2318.9(4),2
Dc(g/cm^3)	1.355	1.200
M	592.5	838.0
F(000)	1224	888
μ(cm^{-1})	23.18	6.11
Experimental data		
Technique	Four circle diffractometer: Seifert XRD3000-S, Bisecting geometry. Graphite oriented monochromator. $\omega/2\theta$ scans. (θ_{max} = 65°) Detector apertures 2 x 2°. CuKα.	
Scan width:	1.6°	1.6°
Time/reflex	32 sec./reflex.	32 sec./reflex.
Number of reflexions:		
Independent	4893	7580
Observed	2642 (2σ(I) criterion)	3557 (2σ(I) criterion)
Standard reflexions:	2 reflexions every 60 minutes. 3.4% decay corrected	2 reflexions every 60 minutes. 4.4% decay corrected
Max-min transmision factor	1.000-0.650	-
Solution	Direct methods	Direct methods
Refinement:		
Least-Squares on Fo	Full matrix	Full matrix
Secondary extinction (x10^4)	0.02(1)	0.46(2)
Number of variables	468	680
Degrees of freedom	2174	2877
Ratio of freedom	5.6	5.2
Max/average final shift/error	0.0024/0.0001	0.098/0.004
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 (Å^2)	U33[Cl2]=0.288(5)	U33[C11c]=0.49(7)
Final ΔF peaks (eÅ^{-3})	-0.85/0.71	-0.55/0.77
Final R	0.064	0.074
Final Rw	0.073	0.062

Tris(3,5-dimethylpyrazolyl-1-yl)-1,3,5-triazine (**5c**) was purified by column chromatography.
Tris(4-(1-adamantyl)pyrazolyl-1-yl)-1,3,5-triazine (**5d**) was isolated according to procedure described for **6b**, but to obtain analytical samples requires preparative thin layer chromatography on silica gel.
Tris(2-(1-adamantyl)imidazol-1-yl)-1,3,5-triazine (**6d**). Addition of the 2-(1-adamantyl)imidazole requires cooling to 0 °C and stirring 2 hours at 0 °C, isolation of the product was carried out similarly to **5d**.

X-Ray Crystallography

A summary of data collection and refinement process is given in Table 9. The crystal of **8c** was sealed into a glass capillary to prevent air decomposition. The structures were solved by direct methods, SIR92,[38] and they were refined with a full matrix least squares procedure on Fobs. In the case of **6c** empirical absorption corrections were applied.[39] Except the hydrogen atoms of the isopropyl groups in **8c**, all remaining hydrogen atoms were located on the corresponding difference Fourier syntheses and most of them were refined isotropically in the last cycles; some hydrogen atoms of the solvent molecules including the hydrogen of the hydroxyl group in the C molecule of isopropanol were kept fixed. In both structures, no disorder model for the solvents could be modelled in spite of the values of the thermal displacement parameters for the chlorine atoms in **6c** and for the isopropyl groups in **8c**. The atomic scattering factors were taken from the International Tables for X-Ray Crystallography[40] and most of the calculations were carried out with the XTAL,[41] PESOS,[42] and PARST[43] programs running on an AXP 600 computer.

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