The structure of halogeno-1,2,4-triazoles in the solid state and in solution

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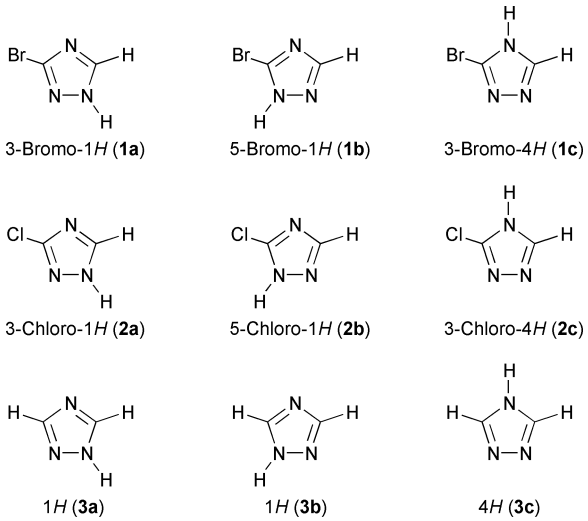
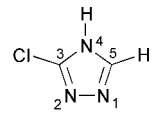
The X-ray molecular structures of two halogenotriazoles, 3-chloro- and 3-bromo-1*H*-1,2,4-triazole, have been determined, thus ending a controversy that made these compounds an exception to a general rule concerning their annular tautomerism. ^{13}C and ^{15}N NMR experiments in the solid state are complex because of the dipolar couplings with the halogens. The complex signal of the carbon atom bearing the halogen has been analysed and the residual ^{13}C–X dipolar couplings determined. However, since the tautomeric structures are known, the spectra can be analysed. Solution NMR, at low temperatures (178 K) at which the tautomerism of triazoles is blocked, and using as models 1,2,4-triazole itself and its 1-methyl derivative, allowed us to determine that the same tautomers, 3-halo-1*H*-1,2,4-triazole, are present in methanol.

Without the determination, by X-ray crystallography, of the molecular structure of azoles unsubstituted on the nitrogen it is almost impossible to know their tautomeric form in the solid state and the type of hydrogen bonds they form. We have devoted some effort to these questions, attempting to predict these properties from the accumulated experience of our work and those of other authors. We feel that in the case of pyrazoles, we have attained an acceptable level of prediction,[1,2] but this is not so for other azoles.

On the other hand, there is abundant information about the tautomerism of azoles in solution.[3,4] Besides, we have postulated that the most abundant tautomer in solution is the same as the tautomer present in the solid state (the presence of two tautomers in the solid state is very infrequent).[5,6] Therefore, it was a surprise when we found, while exploring the Cambridge Structural Database (CSD),[7] that the structure of 3(5)-bromo-1,2,4-triazole (**1**, BIJLEL) was reported as 4*H*, **1c**.[8] This was in contradiction to all previous knowledge on 1,2,4-triazoles, which indicates that only 1*H* tautomers are stable, at least in solution. To predict whether **1a** or **1b** would be the more stable is a subtler question, which needs a careful discussion. In any case, at that moment we decided to determine the structure of compound **1** and its chloro analogue **2**.

A search in the literature shows that the structure of 3(5)-chloro-1,2,4-triazole (**2**) was reported by the same group as being also the 4*H* tautomer **2c**[9] (this structure is not reported in the CSD).[7] Since no coordinates were available for BIJLEL (**1c**), we will limit the discussion of the structure to the chloro derivative **2c** (Fig. 1). It has been established by Bonati[10] and afterwards by ourselves,[11] that the nitrogen atom bearing the proton has the largest internal angle (in pyrazoles, the angle at the NH is on average 111.6° while the other nitrogen shows values centred on 105.0°).[10] It is clear that structure **2c** cannot be correct. Since there is a hydrogen bond between N(1) and N(4),[9] probably the assignment of these two atoms was wrong.





Bond angles:

N(1)-N(2)-C(3) = 101.4(8)
C(3)-N(4)-C(5) = 101.9(8)
C(5)-N(1)-N(2) = 110.8(8)

Hydrogen bond: N(1)···N(4)

Fig. 1 Experimental bond angles of 3(5)-chloro-1,2,4-triazole, **2**.[9]

Table 1 Crystal and refinement data for $C_2H_2BrN_3$ (**1a**) and $C_2H_2ClN_3$ (**2a**)

	1a	**2a**
Empirical formula	$C_2H_2BrN_3$	$C_2H_2ClN_3$
Formula weight	147.98	103.52
T/K	296(2)	296(2)
Crystal system	Orthorhombic	Orthorhombic
Space group	*Pbca*	*Pca*2(1)
a/Å	8.2101(8)	10.849(2)
b/Å	9.940(1)	3.7618(9)
c/Å	10.638(1)	9.863(2)
u/Å^3	868.1(2)	402.5(2)
Z	8	4
Abs. coeff./mm^{-1}	9.292	0.756
Reflect. collected	3352	1804
Indep. reflect.	600 [R(int) = 0.0347]	667 [R(int) = 0.0295]
R [$I^2 > 2\sigma(I_o^2)$]	0.0240 (493 refl. obsv.)	0.0213 (617 refl. obsv.)
wR indices[a] (all data)	0.0607	0.0667

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

Experimental

Materials

Compounds **1** and **2** have been described several times.[12–15] We have followed the procedure of Manchot *et al.*,[12] which uses the action of HBr (**1**) or HCl (**2**) on the diazonium salt of 3(5)-amino-1,2,4-triazole. The compounds melt at (°C): **1**, 186–8 (ethyl acetate); **2**, 168–9 (ethyl acetate). Compound **3** is commercially available and 1-methyl-1,2,4-triazole (**4**), an oil, was prepared according to ref. 16.

Some ^{1}H NMR data, not used in the later discussion, but useful to characterise the compounds are: **1** (CD_3OD, 178 K): δ 8.74 (CH), 15.02 (NH); (DMSO-d_6, RT): δ 8.56 (CH), 14.46 (NH); **2** (CD_3OD, 178 K): δ 8.75 (CH), 14.93 (NH); (DMSO-d_6, RT): δ 8.57 (CH), 14.17 (NH); **3** (CD_3OD,178 K) 8.31 (H-3), 8.90 (H-5); (DMSO-d_6, RT): δ 8.28 (H-3 and H-5), 14.07 (NH); **4** (CD_3OD, RT): δ 3.93 (Me), 7.94 (H-3), 8.39 (H-5); (DMSO-d_6, RT): δ 3.85 (Me), 7.92 (H-3), 8.43 (H-5); (cyclohexane-d_{12}, RT) 3.76 (Me), 7.69 (H-3) 7.73 (H-5); (liquid) 3.40 (Me), 7.52 (H-3), 7.92 (H-5). These assignments are consistent with those reported in the literature.[16]

Table 2 Bond lengths (Å) and angles (°) for $C_2H_2XN_3$ (X = Br, **1a**; X = Cl, **2a**)

	1a		**2a**	
	Expt.	Calc.	Expt.	Calc.
C3–X1	1.868(3)	1.876	1.707(2)	1.724
N1–C5	1.319(6)	1.350	1.316(3)	1.349
N1–N2	1.356(4)	1.359	1.367(3)	1.359
N1–H1	0.81	1.011	0.90	1.010
N2–C3	1.308(4)	1.324	1.313(3)	1.324
C3–N4	1.346(4)	1.358	1.350(3)	1.358
N4–C5	1.323(5)	1.322	1.329(4)	1.322
C5–H5	0.9167	1.081	0.9109	1.081
N1···N4′[a]	2.847(4)	—	2.865(3)	—
N4′···H1[a]	2.06	—	1.97	—
C5–N1–N2	110.7(3)	110.6	110.7(2)	110.6
C5–N1–H1	129.7	130.0	124.4	130.0
N2–N1–H1	119.0	119.5	124.7	119.4
C3–N2–N1	101.1(3)	100.9	100.8(2)	100.8
N2–C3–N4	116.1(3)	116.4	116.4(2)	116.5
N2–C3–X1	122.3(2)	121.2	121.8(2)	121.2
N4–C3–X1	121.6(2)	122.4	121.8(2)	122.3
C5–N4–C3	102.0(3)	102.1	101.7(2)	102.0
N4–C5–N1	110.0(4)	110.0	110.5(2)	110.0
N4–C5–H5	125.2	126.2	121.4	126.2
N1–C5–H5	124.7	123.8	128.1	123.8
N1–H1–N4′[a]	164.1	—	172.2	—

[a] Primed atoms: $-x + 1/2, y + 1/2, z$ for **1a** and $-x + 3/2, y, z - 1/2$ for **2a**.

X-Ray data collection and structure refinement

Suitable crystals for X-ray diffraction experiments were obtained by crystallisation from ethyl acetate (**1**) and benzene (**2**, same melting point as in ethyl acetate). Data collection was carried out at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.710 73 Å) operating at 50 kV and 10 mA for **1** and 50 kV and 20 mA for **2**. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s covered 0.3 in ω. The cell parameters were determined by least-square fits from 82 reflections in the range $18° < 2\theta < 30°$ for **1** and 72 reflections in the range $25° < 2\theta < 38°$ for **2**. Reflection ranges for the data collection were $3.75° < \theta < 23°$ for **1** and $3.76° < \theta < 26°$ for **2**. The first 50 frames were collected at the end of the data collection to monitor crystal decay. Structures were solved by direct methods (SHELXS-97)[17] and refined by full-matrix least-squares procedures on F^2 for all reflections (SHELXL-97).[17] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located on a difference Fourier map and refined riding on their respective carbon or nitrogen atom with the thermal parameters related to the bonded atoms. Crystal data and other structure determination details are presented in Table 1.

CCDC reference numbers 161111 and 161112. See http://www.rsc.org/suppdata/nj/b1/b103405g/ for crystallographic data in CIF or other electronic format.

^{1}H, ^{13}C and ^{15}N NMR spectroscopy

^{1}H (400.13 MHz), ^{13}C (100.62 MHz) and ^{15}N (40.56 MHz) NMR spectra were obtained using a Bruker DRX 400 instrument (corresponding to 9.4 T). Variable temperature ^{1}H, ^{13}C and ^{15}N NMR experiments were recorded on the same spectrometer using CD_3OD as solvent. 2D inverse proton detected heteronuclear shift correlation spectra, HMBC, were obtained using the standard pulse sequence.[18] Solid state ^{13}C (50.32 MHz) and ^{15}N (20.28 MHz) CPMAS NMR spectra were obtained on a Bruker AC-200 spectrometer at 298 K using a 7 mm Bruker DAB 7 probehead that achieves rotational frequencies of about 3.5–4.5 kHz and on a Bruker MSL 400 (^{13}C 100.63 MHz). Samples (approximately 200 mg of material) were carefully packed in ZrO_2 rotors and the standard CPMAS pulse sequence was applied.[2]

Computational details

Geometries of the studied stationary structures were fully optimised with the internal 6-31G* basis set[19] at the Becke3LYP[20] theoretical level using procedures implemented

in the Gaussian 98 system programs.[21] B3LYP/6-31G* calculations have demonstrated their utility for the determination of tautomeric equilibria.[4,22] Harmonic frequency calculations[23] verified the nature of the stationary points as minima (all real frequencies) at each level of theory considered, and were used to provide an estimation of the zero-point vibrational energies (ZPVE), which are not scaled. The theoretical absolute NMR shieldings have been computed using the GIAO method[24] at the same computational level. GIAO/B3LYP/6-31G* calculations provide reasonable absolute shieldings for ^{13}C and ^{15}N nuclei.[25]

In Table 2 are reported the experimental and calculated geometries of **1a** and **2a**. Excluding the Y–H distances (Y = N or C), which are usually shorter by X-ray than calculated, the agreement is fairly good. The largest deviations in bond angles concern C(5)–N(1)–H(1) and N(2)–N(1)–H(1) for compound **2a**: probably H(1) is not well located in this case (compare with the same angles in **1a**).

Results and discussion

The tautomerism of 1,2,4-triazole and its C-halogen derivatives

Many theoretical studies have been devoted to the parent 1,2,4-triazole **3** where only two tautomers, **3a** and **3c**, are possible. **3a** and **3b** represent two energetically equal, but statistically distinct species, the reason why tautomer **3a** is twice as probable as **3c**.[3,4] Some results have been summarised in a review by Minkin *et al.* where differences in stability of about 5 kcal mol^{-1} (ΔH values) in favour of **3a** are reported.[4] Two important papers are those of Palmer *et al.*[26] and of Hillier *et al.*[27] They found a difference of 2.4 (double zeta basis) and 6.3 kcal mol^{-1} [SCF(6-31G**//3-21G) + ZPE + MP2], respectively, in favour of **3a**; the latter authors, who have also calculated solvent effects, conclude that they cannot alter the fact that the concentration of the rare tautomer (**3c**) would be still extremely low. More recently, the problem was examined by Schaad *et al.* who found a difference of 7.0 kcal mol^{-1} (MP2/6-31G*), pointing out that the proportion of the minor tautomer would be significant at high temperatures in the gas phase.[28] We have calculated a ΔG of 6.9 kcal mol^{-1} at 298.15 K.[29] Both tautomers have nearly identical entropies (**3a**, 63.94 and **3c**, 62.77 cal mol^{-1} K^{-1}), therefore, the temperature should not affect the equilibrium in a marked way. In the case of the highly explosive 3(5)-amino-5(3)-nitro-1,2,4-triazole while HF/6-311 + G** calculations predict the 3-amino-5-nitro tautomer to be the most stable, MP2, MP4 and DFT calculations, with the same base, predict correctly that the most stable tautomer is the 3-nitro-5-amino one.[30] Therefore, we have used DFT calculations for this study.

For the chlorotriazole **2**, Sauvaitre *et al.*, in 1980, reported CNDO/2 calculations that favour **2c**, followed by **2a** (0.95 kcal mol^{-1} higher) and then by **2b** (7.77 kcal mol^{-1} higher than **2a**).[9] Note that in the case of **1**, Flammang *et al.* concluded that a mixture of **1a** and **1b** is necessary to explain the mass spectrum of **1** but that **1c** is not present.[15]

At the B3LYP/6-31G* level, the most stable tautomer is **2a** (−701.840 58 hartrees), followed by **2b** (0.27 kcal mol^{-1} higher) and by **2c** (7.63 kcal mol^{-1} above **2a**). It is reasonable to assume that the CNDO/2 calculations were correct but, by mistake, the authors exchanged the values of the three tautomers (in our hands, CNDO calculations afford **2a** 0.00, **2b** 2.16 and **2c** 6.90 kcal mol^{-1}). Taking into account the ZPE, thermal and entropy corrections (T = 298.15 K), the respective values, at the B3LYP/6-31G* level, are **2a** (−701.818 74 hartrees) 0.00, **2b** 0.31, **2c** 7.11 kcal mol^{-1}.

In the case of **1**, the values are **1a** (ΔH = −2813.347 54 and ΔG = −2813.327 46 hartrees) 0.00 and 0.00, **1b** −0.39 and −0.32, **1c** 6.90 and 6.32 kcal mol^{-1}. Therefore, tautomers **a** and **b** are of similar energy, although in the case of the chloro derivative, **2a** is the more stable while in the case of the bromo compound **1b** is the most stable. These calculations agree with the results of Flammang *et al.*[15]

X-Ray crystal and molecular structure

An X-ray study of compounds **1a** and **2a** has been carried out. In both cases the crystals consist of molecules bonded through hydrogen bonds. Selected bond lengths, angles and features of hydrogen bonds are collected in Table 2. Molecular drawings of **1a** and **2a** are presented in Fig. 2. The molecules in **1a** are arranged in chains parallel to their *b* axis *via* N1–H1···N4 ($-x + 1/2$, $y + 1/2$, z) hydrogen bonds (HBs). The molecules in **2a** are disposed in chains parallel to their *c* axis *via* N1–H1···N4 ($-x + 3/2$, y, $z - 1/2$) HBs. In both cases, an analysis of the intermolecular distances shows that the chains are independent. Fig. 3 illustrates the crystal packing of **1a** and **2a**. In both compounds, C5–N1–N2 > N1–N2–C3, confirming the position of the N–H found on the difference Fourier map.

The N–H···N hydrogen bond of 1*H*-1,2,4-triazoles present in the solid state could be between N1–H and either N2, as in pyrazoles, or N4, as in imidazoles. A recent survey[1] of the CSD[7] shows that there are eight structures, three of them of the type N1–H···N2 and five of the type N1–H···N4.

The two structures reported here belong to the second class. Following the criteria used in ref. 1 to describe chains (catemers) using the centroids of the rings linked through the hydrogen bonds, compounds **1a** and **2a** form catemers of order 2 in both cases (centroid 1–centroid 2, the third molecule being identical to the first one). For bromotriazole **1a**, the distances 1–2 and 2–3 are 5.037 Å, the angle 1–2–3 is 161.3° and the distance 1–3 is 9.940 Å. For chlorotriazole **2a**, the distances 1–2 and 2–3 are 5.091 Å, the angle 1–2–3 is 151.2° and the distance 1–3 is 9.863 Å (see ref. 1 for more details).

Compared with the helixes of order 2 found in pyrazoles (1–2 5.2 Å, 1–2–3 68°, 1–3 5.8 Å),[1] the main difference is that in pyrazoles the HB donor and HB acceptor sites are on proximal sites of a pentagon and in a triazole with 1,4 connectivities, as in an imidazole, the sites are in distal positions.

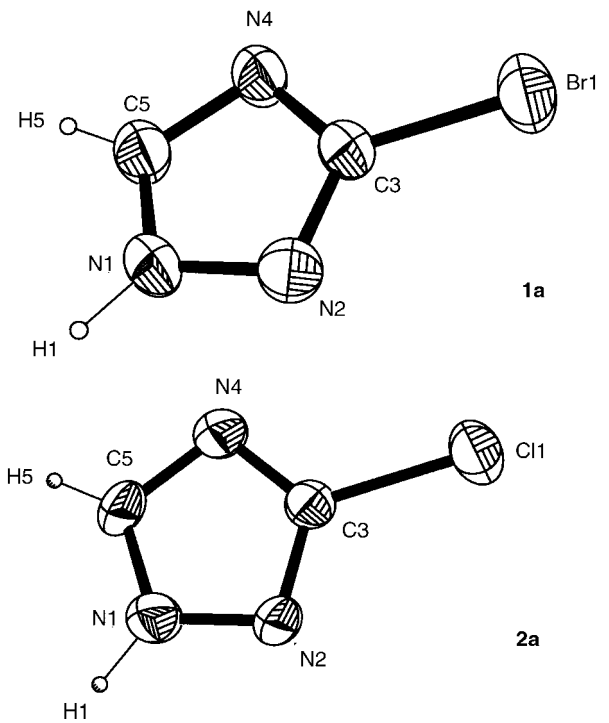


Fig. 2 ORTEP view of the molecular structures for **1a** and **2a** in the solid state, showing the atom numbering (50% probability ellipsoids).

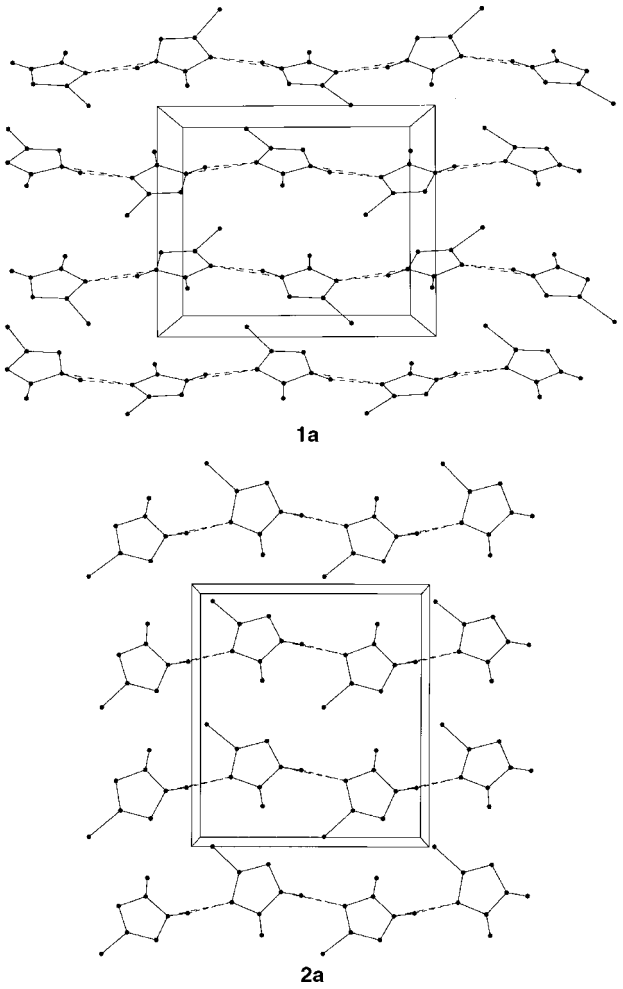


Fig. 3 Molecular packing along the *b* axis for **1a** and *c* axis for **2a**.

Therefore, for pyrazoles and triazoles with 1,2 connectivities,[1] angles close to 72° are expected whereas for imidazoles and triazoles with 1,4 connectivities, angles close to 144° are expected.

Vibrational spectroscopy

Since Garrigou-Lagrange *et al.*[9] reported high quality IR data for **2**, we decided to compare the calculated frequencies (scaled by a factor of 0.963)[31] with the experimental results. In Table 3 are reported, for compound **2**, the calculated frequencies and the experimental results obtained, in the solid phase, by Garrigou-Lagrange *et al.*[9] as well as by Grinshtein *et al.*[32] and Mel'nikov *et al.*[33] The last authors carried out a normal coordinates calculation of tautomer **2a** while the first used tautomer **2c**, based on their erroneous analysis of the X-ray structure.

We have carried out a statistical analysis of the Table 3 data. The three scaled values (calculated × 0.963) and the experimental ones were fitted to linear regressions given in eqn. (1)–(3).

$$\text{Experimental} = (34 \pm 11) + (0.995 \pm 0.009)\cdot\text{Calc.}(\mathbf{2a}), \quad n = 17,\ R^2 = 0.9988 \quad (1)$$

$$\text{Experimental} = (37 \pm 10) + (0.950 \pm 0.008)\cdot\text{Calc.}(\mathbf{2b}), \quad n = 17,\ R^2 = 0.9989 \quad (2)$$

$$\text{Experimental} = (65 \pm 18) + (0.943 \pm 0.009)\cdot\text{Calc.}(\mathbf{2c}), \quad n = 17,\ R^2 = 0.9967 \quad (3)$$

Although we are comparing solid state (intermolecular hydrogen bonded) and gas phase data, the results are surprisingly good.

Table 3 Calculated harmonic frequencies of chlorotriazoles (**2**) and experimental results, all in cm^{-1}

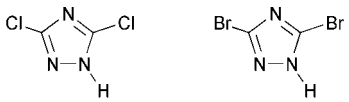
Tautomer **2a**	Tautomer **2b**	Tautomer **2c**	Expt[9,32,33]
260.46	249.26	243.65	290
336.32	318.88	316.90	345
504.20	500.70	498.23	505
528.86	518.58	510.58	505
676.65	692.41	673.33	640
729.72	701.78	678.83	718
842.00	895.14	815.04	878
984.81	972.60	945.73	975
996.45	1020.59	1009.84	1000
1106.42	1117.37	1035.33	1085
1175.15	1212.25	1108.07	1185
1274.50	1264.47	1208.66	1260
1328.45	1312.50	1333.85	1290
1408.79	1406.01	1423.57	1380
1487.76	1475.00	1511.15	1480
1540.70	1561.51	1537.10	1535
3282.24	3286.77	3287.98	3139
3651.34	3656.33	3649.15	—

Eqn. (3) is the worst, not only because of the lower correlation coefficient but also because it has the largest intercept and the slope most different from 1. The correlation coefficients and the intercepts of eqn. (1) and (2) are nearly identical, but eqn. (1) should be preferred because the slope is the closest to 1 (0.995 ± 0.009). Therefore, structure **2a** appears to provide the best agreement between the calculated and experimental vibrational spectra, thus providing additional support for this structural assignment in the solid phase.

Solid state ^{13}C and ^{15}N CPMAS NMR spectroscopy and the problem of residual couplings

Since we know, from the X-ray section, that both compounds under study exist in the solid state as tautomers **a** (**1a** and **2a**), the CPMAS spectra have to be assigned to these structures (see Table 4). These chemical shifts are directly measured from the spectra for the CH groups, but for CX, dipolar indirect coupling interactions with the halogen nuclei complicate the spectra considerably. High resolution solid state ^{13}C NMR spectra for ^{13}C nuclei directly bonded to quadrupolar nuclei ($^{35,37}Cl$ or $^{79,81}Br$) show characteristic bandshapes arising from second-order quadrupolar effects *via* dipolar and/or indirect coupling. To fully assign the spectra, the quadrupolar effects were analysed, as described below (note that 4.7 and 9.4 T correspond to 200 and 400 MHz instruments, respectively).

Theoretical calculations of the $^{13}C,^{35,37}Cl$ and $^{13}C,^{79,81}Br$ residual dipolar coupling have been analysed as in previous publications.[34] We have included in these calculations not only **1** and **2** but two other compounds, 3,5-dichloro-1,2,4-triazole (**5**) and 3,5-dibromo-1,2,4-triazole (**6**), from another publication where only ^{15}N NMR was discussed.[35] These calculations require the knowledge of the X–C bond lengths, which in the case of **1a** (C–Br = 1.868 Å), **2a** (C–Cl = 1.707 Å), **5** (C3–Cl = 1.695, C5–Cl = 1.703 Å) and **6** (C3–Br = 1.848, C5–Br = 1.896 Å) are all known from the X-ray structures (this work and ref. 35).



3,5-Dichloro-1*H* (**5**) 3,5-Dibromo-1*H* (**6**)

For the $^{13}C,^{35,37}Cl$ residual dipolar coupling, a 1 : 1 symmetric splitting is expected (valid for $1 < |\chi/\nu_s| < 3$). In this case, a polynomial fit to the exact solution gives:

$$s\ (\text{splitting}) = D(0.581\ R + 0.033\ R^2 - 0.021\ R^3) \quad (4)$$

where D is the dipolar coupling constant and $R = |\chi/\nu_2|$. For large values of the ratio $|\chi/\nu_s|$ ($3 < |\chi/\nu_s| < 5$) one has to

Table 4 CPMAS NMR spectra of **1a** and **2a**. Determination of the appearance of the carbon signals linked to halogen atoms

B/T	^{13}C MHz	ν_s/MHz	χ^{32}/MHz	$R = \lvert\chi/\nu_s\rvert$	Appearance
2a: ^{13}C,$^{35/37}$Cl residual dipolar coupling[a]					
4.7	50.3	19.6 (^{35}Cl) 16.3 (^{37}Cl)	−70	3.57	2 : 1 : 1 Triplet
9.4	100.6	39.2 (^{35}Cl) 32.6 (^{37}Cl)	−70	1.78	1 : 1 Symmetric doublet
1a: ^{13}C,$^{79/81}$Br residual dipolar coupling					
4.7	50.3	50.1 (^{79}Br) 54.0 (^{81}Br)	535.8 (^{79}Br)) 447.6 (^{81}Br)	10.64 (^{79}Br) 8.26 (^{81}Br)	Quadruplet[b]
9.4	100.6	100.2 (^{79}Br) 108.0 (^{81}Br)	535.8 (^{79}Br) 447.6 (^{81}Br)	5.39 (^{79}Br) 4.14 (^{81}Br)	Quadruplet[c]

[a] Only the effect of the major ^{35}Cl isotope was considered, the effect of the minor ^{37}Cl isotope is expected to produce a reduction of the splitting by *ca.* 5%. [b] Quadruplet at 4.7 T: $\nu_1 = -0.559\ J_{79} + 1.779\ D'_{79}$, $\nu_1 = 1.92$ kHz $= 38.2$ ppm; $\nu_2 = 0.663\ J_{79} + 0.295\ D'_{79}$, $\nu_2 = 0.18$ kHz $= 3.6$ ppm; $\nu_3 = -1.111\ J_{79} - 0.744\ D'_{79}$, $\nu_3 = -0.56$ kHz $= -11.1$ ppm; $\nu_4 = 0.998\ J_{79} - 1.340\ D'_{79}$, $\nu_4 = -1.55$ kHz $= -30.8$ ppm. [c] Quadruplet at 9.4 T: $\nu_1 = -0.332\ J_{79} + 2.006\ D'_{79}$, $\nu_1 = 2.10$ kHz $= 20.9$ ppm; $\nu_2 = 0.440\ J_{79} + 0.073\ D'_{79}$, $\nu_2 = -4 \times 10^{-3}$ kHz ≈ 0.0 ppm; $\nu_3 = -1.334\ J_{79} - 0.996\ D'_{79}$, $\nu_3 = -0.74$ kHz $= -7.4$ ppm; $\nu_4 = 1.220\ J_{79} - 1.110\ D'_{79}$, $\nu_4 = -1.35$ kHz $= -13.4$ ppm.

resort to exact calculations, which predict a broad triplet with intensities in the ratio 2 : 1 : 1 (the intrinsic asymmetry of these triplets depends on the sign of χ) or use eqn. (5)–(7):[34]

$$\nu_1 = D(0.821\ R - 0.307\ R^2 + 0.051\ R^3) \quad (5)$$

$$\nu_2 = D(0.173\ R^2 - 0.043\ R^3) \quad (6)$$

$$\nu_3 = D(-0.405\ R + 0.066\ R^2 - 0.004\ R^3) \quad (7)$$

Therefore, for **2** at 9.4 T, the line shape is an almost symmetric doublet, although the splitting obtained from eqn. (4) is 1.02 units of D. Assuming a C–Cl distance of 1.707 Å, $D = 596$ Hz for the ^{13}C,^{35}Cl pair, the calculated splitting at 9.4 T is 607 Hz or (at 100.6 MHz) 6.1 ppm. The experimental spectrum, Fig. 4, shows three lines, 154.4 and 148.0 (centred at 151.2 ppm, separation 6.4 ppm), arising from C3 and 145.4 ppm arising from C5.

The same compound at 4.7 T should present a 2 : 1 : 1 asymmetric triplet (assuming χ to be negative). Approximate second-order effects given by the exact approach for $\lvert\chi/\nu_s\rvert = 3.6$ are +0.75, −0.23 and −1.24 units of D or +8.9, −2.7 and −14.7 ppm, respectively. Assuming the signal is centred at 150.5 ppm (solution chemical shift, see Table 5), the multiplet should appear at 159.4 (double intensity), 147.8 and 135.8 ppm. Using the NQS sequence, the 2 : 1 : 1 triplet (see Fig. 5) appears at 159.3, 148.3 and 135.6 ppm. The CH (C5) signal was observed using the normal sequence at 145.2 ppm. The same approach was used for the ^{13}C NMR spectrum of 3,5-dichloro-1,2,4-triazole (**5**) recorded at 100.6 and 50.3 MH [100.6 MHz: doublet, theoretical separation 6.1 ppm, experimental separation 5.8 ppm (151.3 and 145.5 ppm). 50.3 MHz: triplet at 155.0, 143.4 and 131.4 ppm (calculated from solution chemical shift, 146.1 ppm) and 154, 142 and 130 ppm (experimental)].

The case of the bromine derivative is more complex. When the quadrupole coupling constant (χ) becomes much larger than the resonance frequency of quadrupolar nuclei (ν_s), inverse first-order theory may be applicable. In this case, for the coupling between spin-1/2 (^{13}C) and spin-3/2 (^{79,81}Br) nuclei, and considering the existence of indirect J coupling, the ^{13}C lines are predicted to be:[34]

$$\begin{aligned}\nu(\pm 3/2) = \pm[&3/4(p_{79}\cdot J_{79} + p_{81}\cdot J_{81}) \\ &- (3/2)(p_{79}\cdot D'_{79} + p_{81}\cdot D'_{81}) \\ &+ 2\{[1p_{79}\cdot J_{79} + p_{79}\cdot D'_{79})/R_{79}] \\ &+ [(p_{81}\cdot J_{81} + p_{81}\cdot D'_{81})/R_{81}]\}\end{aligned} \quad (8)$$

$$\begin{aligned}\nu(\pm 1/2) = \pm[&1/4 + \pi/3\sqrt{3}(p_{79}\cdot J_{79} + p_{81}\cdot J_{81}) \\ &+ (1/2)(p_{79}\cdot D'_{79} + p_{81}\cdot D'_{81}) \\ &- 2\{[1p_{79}\cdot J_{79} + p_{79}\cdot D'_{79})/R_{79}] \\ &+ [(p_{81}\cdot J_{81} + p_{81}\cdot D'_{81})/R_{81}]\}\end{aligned} \quad (9)$$

where $R = \chi/\nu_s$, $J_{81}/J_{79} = D'_{81}/D'_{79} = \gamma_{81}/\gamma_{79} = 1.078$; $p_{79} = 0.505$, $p_{81} = 0.495$, $J_{79} = -0.18$ kHz and $D'_{79} = 1.02$ kHz ($r = 1.868$ Å).

From Table 4, compound **1** should give for C3 a quartet at $\nu_1 = 159.1$, $\nu_2 = 138.2$ (solution chemical shift, see Table 5), $\nu_3 = 130.8$ and $\nu_4 = 124.8$ ppm (100.6 MHz) and $\nu_1 = 176.4$, $\nu_2 = 141.8$, $\nu_3 = 127.1$ and $\nu_4 = 107.4$ ppm (50.3 MHz) (besides the CH signal at 144.7 ppm). Experimentally, we have observed 159.6, 136.9 (coincides with the chemical shift of C3

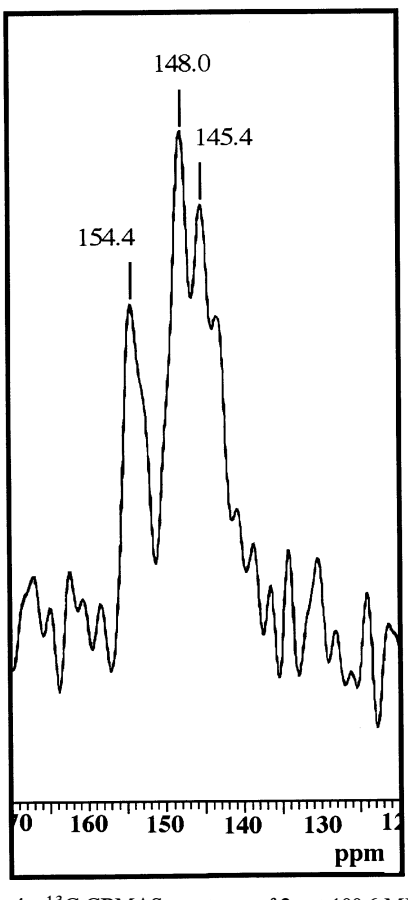


Fig. 4 ^{13}C CPMAS spectrum of **2a** at 100.6 MHz.

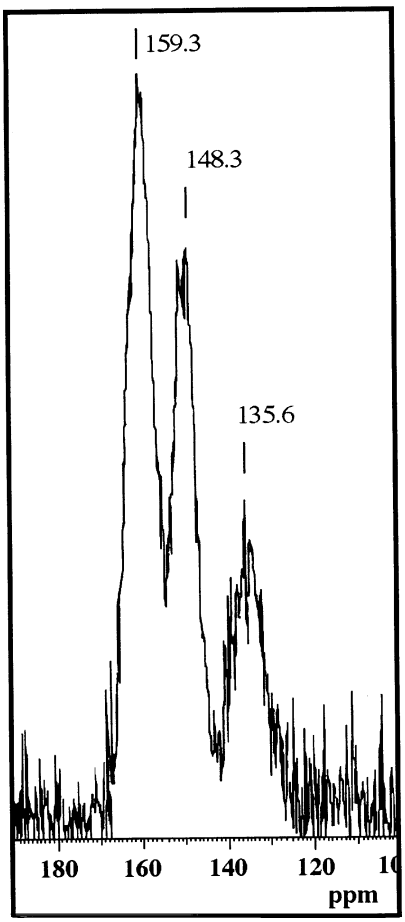


Fig. 5 ^{13}C CPMAS spectrum of **2a** at 50.3 MHz (NQS sequence).

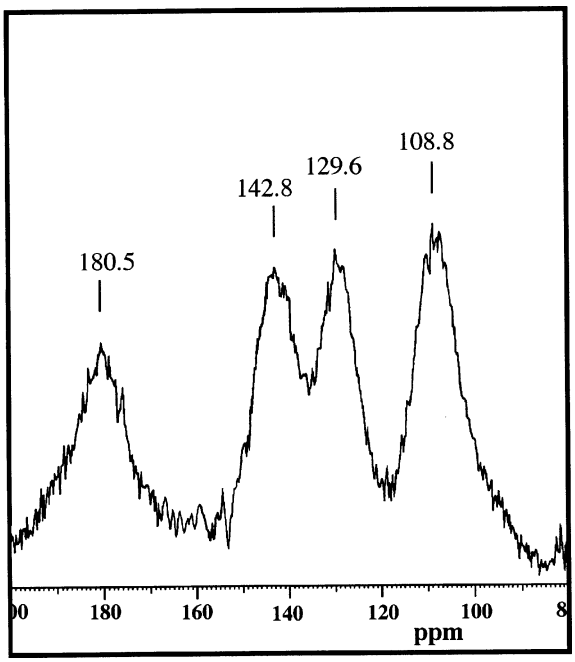


Fig. 6 ^{13}C CPMAS spectrum of **1a** at 50.3 MHz (NQS sequence).

since the effect is nil, Table 4), 134.0 and 126.5 ppm (100.6 MHz) and 178.8, a signal under the CH (145.5 ppm), 130.5 and 108.6 ppm (50.3 MHz). Using the NQS sequence, the quartet corresponding to C3 appears at 180.5, 142.8, 129.6 and 108.8 ppm (Fig. 6). The agreement is highly satisfactory. For compound **6** the spectrum calculated at 4.7 T is $\nu_1 = 172.5$, $\nu_2 = 137.9$, $\nu_3 = 123.2$ and $\nu_4 = 103.6$ ppm and the experimental one is $\nu_1 = 174.0$, $\nu_2 = 135.6$, $\nu_3 = 124.3$ and $\nu_4 = 103.9$ ppm.

In the case of compounds **5** and **6**, due to proton exchange, C3 and C5 are magnetically equivalent.[35] The $^{15}N,^{35,37}Cl$ and $^{15}N,^{79,81}Br$ residual dipolar couplings have not been analysed since we have only observed a broadening of all signals. These effects arise from non-bonded intramolecular and intermolecular $^{15}N,^{35,37}Cl$ (or $^{15}N,^{79,81}Br$) interactions. It is clear that these remote interactions will influence the ^{15}N NMR bandshape, to an extent that depends on the magnitude of ^{15}N–X distance and the angle between the ^{15}N–X vector and the main axis of the EFG tensor at the halogen nucleus.

Solution NMR studies (^{13}C and ^{15}N)

In Table 5 we have collected all the available information for compounds **1** to **3** (irrespective of their tautomerism) as well as for compound **4** (1-methyl-1,2,4-triazole). We have selected this compound, devoid of tautomerism, because there are very accurate values for $\delta^{15}N$ measured by Witanowski and Webb.[36]

To estimate the ^{13}C chemical shifts of tautomers **1a**, **1b**, **2a** and **2b** we need the C-substituent effects of chlorine and bromine. Those of benzenes cannot be used since they are rather different from those of azoles.[37] On the other hand, it is reasonable that the SCSs (substituent chemical shifts) we have

Table 5 ^{13}C and ^{15}N chemical shifts in ppm (and some couplings with ^1H in Hz) of compounds **1-4**

	Solvent	C3	C5	N1	N2	N4
1	CPMAS	136.9[a]	144.7	−156.7	−89.8	−130.4
	DMSO-d_6 (RT)	138.2 $^3J = 14.5$	146.2 $^1J = 213.6$	−154.7	−97.6	−125.8
	CD_3OD (178 K)	140.4	147.2	−164.6	Not obs.	−136.5
2	CPMAS	150.6–151.2[a]	145.3	−159.9	−98.9	−137.6
	DMSO-d_6 (RT)	150.5 $^3J = 14.8$	145.7 $^1J = 213.8$	−161.2	−100.8	−130.8
	CD_3OD (178 K)	152.2	146.8	−167.6	Not obs.	−143.0
3	CPMAS	148.5	145.3	−159.9	−89.6	−141.6
	DMSO-d_6 (RT)	147.0 $^1J = 202.2$	147.0 $^1J = 202.2$	−126.6	−126.6	−135.7
	CD_3OD (178 K)	151.9	145.0	−170.5	−100.2	−145.3
4	Cyclohexane[b,c]	154.1	144.5	−176.07	−78.95	−122.91
	DMSO-d_6[b,d]	151.3	144.4	−170.85	−81.28	−126.99
	CH_3OH[b]/CD_3OD[e]	152.4	145.7	−171.28	−85.56	−137.28
	Liquid[f]	153.2	146.3	−171.3	−83.0	−130.2

[a] The ^{13}C chemical shifts of the C–X signals in the solid state have been obtained from the analysis of the complex multiplets (see preceding discussion, Table 4). [b] ^{15}N chemical shifts from ref. 31 (two decimals). [c] N–CH_3 36.8 ppm. [d] N–CH_3 35.6 ppm. [e] N–CH_3 36.7 ppm. [f] N–CH_3 37.6 ppm.

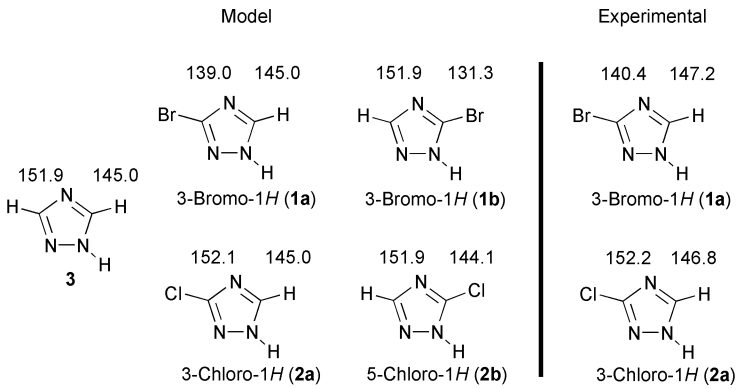


Fig. 7 Calculated (additive model, see text) and experimental (CD_3OD at 178 K, Table 5) ^{13}C chemical shifts of halogeno-1,2,4-triazoles.

determined for pyrazoles[38] could be used for 1*H*-1,2,4-triazoles: Cl3 on C3 +0.2, Cl3 on C5 0, Cl5 on C5 −0.9, Cl5 on C3 0, Br3 on C3 −12.9, Br3 on C5 0, Br5 on C5 −13.7, Br5 on C3 0 ppm. With these effects and the values for 1*H*-1,2,4-triazole itself **3** in CD_3OD at 178 K (Table 5), we have built up Fig. 7. Model values have been calculated by adding to the chemical shifts of **1** the SCSs of pyrazoles.

At 178 K the prototropic exchange is blocked and, since only two carbon signals were observed for **1** and **2**, only one isomer is present. From the Fig. 7 data it is clear that **1** exists as tautomer 1*H*-3-Br (**1a**).

In the case of the chlorine derivative **2**, the SCSs of the chlorine in pyrazoles are too weak to be useful, although the model predictions are closer to tautomer 1*H*-3-Cl (**2a**). Although the data in DMSO-d_6 at RT correspond to average signals (see **3** in Table 5), the similitude of the chemical shifts with those in CD_3OD at 178 K points to the clear predominance of the same tautomers in this solvent. Finally, note that the CPMAS data, where the tautomeric structure is known, are very similar to those in DMSO-d_6.

The ^{15}N chemical shifts in CD_3OD are difficult to interpret because of the lack of information of ^{15}N halogen SCSs in azoles.[39] However, there is an indirect way to prove that the tautomers are **1a** and **2a**. The technique used (HMBC)[18] allows one to observe the nitrogen signals that are close to CH protons (in the case of compounds **1** and **2** in DMSO-d_6 using the "inversed gated ^1H-decoupling technique", N2 was observed, see Table 5). Since only N1 and N4 are observed, this means that the halogen is on C3. It is now possible to calculate the SCSs: Br3 on N1 (+5.9 ppm) and on N4 (+8.8 ppm) and Cl3 on N1 (+2.9 ppm) and on N4 (+2.3 ppm).

Experimental chemical shifts (δ) *vs.* calculated absolute shieldings (σ)

We have calculated the absolute shielding of compounds **1a**, **1b**, **1c**, **2a**, **2b**, **2c**, **3a**(**3b**), **3c** and **4** at the GIAO/B3LYP/6-31G* level. It is known that the calculation of one-bond halogen effects need relativistic corrections,[40] that are outside our possibilities. Without these corrections, the calculations for *ipso* halogenated carbons yield meaningless results; for instance, in diphenyl ethers, C(Ar)–Br SCS is measured to be −3.8 ppm and calculated as +8.3 ppm; for C(Ar)–Cl SCS is measured to be +5.3 ppm and calculated as 0.5 ppm, for one given position.[41] For this reason we have excluded these carbons from our calculations.

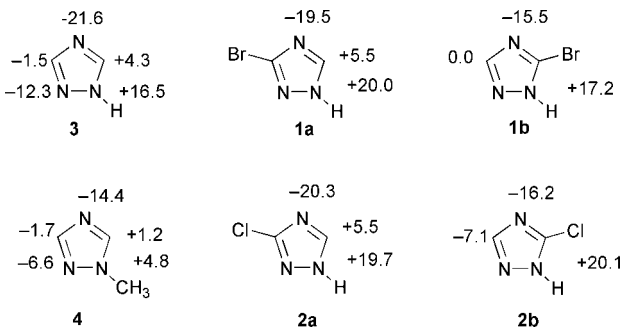


Fig. 8 ^{13}C and ^{15}N chemical shift differences between values in CD_3OD at 178 K (Table 5) and those calculated with eqn. (10) in cyclohexane-d_{12}.

As Witanowski and Webb reported, their ^{15}N chemical shifts are well reproduced by the calculations.[36] The data for compound **4** in cyclohexane-d_{12} lead to the following equation:

$$\delta = (201.6 \pm 0.8) - (322.6 \pm 0.9)C/N - (1.067 \pm 0.008)\sigma,$$
$$n = 6,\ R^2 = 1.000 \quad (10)$$

where C/N has the value 0 for ^{13}C and the value 1 for ^{15}N. This equation allows one to predict the chemical shifts in cyclohexane from the calculated σ values. Excluding from the discussion the highly improbable **c** tautomers, the remaining estimated values in cyclohexane could be compared with those in methanol at 178 K (Fig. 8).

The values for the *N*-methyl derivative **4** are purely experimental (Table 5), all the others correspond to the difference $\delta(CD_3OD, \text{exp.}) - \delta(CyH, \text{calc.})$ The first comment is that the solvent effects are so large that it is worthless to compare σ calculated values with δ values in methanol or DMSO. The second is that since N2 values are missing from Table 5 and since *ipso* carbon calculations cannot be used, only three values remain for comparison. Finally, as concerns the tautomerism of halogenotriazoles, the approach involving mixing experimental and calculated values is rather disappointing.

Conclusion

The tautomeric structures of halo-1,2,4-triazoles have been unambiguously determined for X = Cl and X = Br. The results can probably be extrapolated to X = F and X = I, which would also exist as **a** tautomers (1*H*-3-halo). In all cases, the halogen substituent prefers to occupy the 3-position, a conclusion that is valid for all phases (gas, solution and solid). The tautomeric proton at N1 links, through hydrogen bonds, to the N4 of another molecule, forming spread chains. The existence of catemers prevents proton transfer between molecules in the solid state, a possible mechanism of self-decoupling, observed for the cyclic trimers of 3,5-dihalo-1,2,4-triazoles.[35]

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