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Flat *versus* twisted rotamers of 2,4-disubstituted thiazoles: the effect of intermolecular hydrogen bonds

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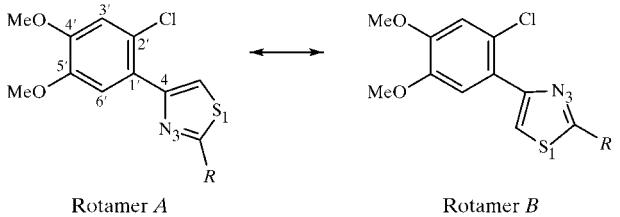
In the title compounds, 2-amino-4-(2-chloro-4,5-dimethoxyphenyl)-1,3-thiazole, $C_{11}H_{11}ClN_2O_2S$, (I), and 4-(2-chloro-4,5-dimethoxyphenyl)-2-methyl-1,3-thiazole, $C_{12}H_{12}ClNO_2S$, (II), the dihedral angles between the thiazole moiety and the chloroaryl group are 51.61 (10) and 8.44 (14)°, respectively. This difference is a consequence of intermolecular hydrogen bonds forcing the stabilization of a twisted rotamer in (I). Substitution of the amino function by a methyl group precludes these contacts, giving a flat rotamer in (II).

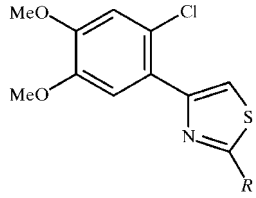
Comment

During the synthesis of a large series of new polysubstituted 2,4-diarylthiazoles (Sánchez-Viesca & Gómez, 1998, and references therein; Sánchez-Viesca & Berros, 1999), we established, on the basis of ^{1}H NMR data and IR spectroscopy, that these compounds present different rotamers in solution, *A* and *B*, depending on the substitution of the thiazole ring (see *Scheme* below).



Rotamer *A* Rotamer *B*

In the case of 2-amino-4-(2-chloro-4,5-dimethoxyphenyl)-1,3-thiazole, (I), the IR spectrum in the solid state (KBr wafer) indicates the presence of intermolecular associations. In $CHCl_3$ solution, these interactions disappear, as confirmed by IR spectroscopy and by paramagnetic shifts in the ^{1}H NMR spectrum. In contrast, 4-(2-chloro-4,5-dimethoxyphenyl)-2-methyl-1,3-thiazole, (II), seems to be stabilized as a unique rotamer, both in solution and in the solid state, in agreement with the observed paramagnetic shifts in its ^{1}H NMR spectrum (Sánchez-Viesca & Berros, 1999; Jeffrey, 1997). In order to assess the influence of the group substituting the 2-position of the thiazole ring, the single-crystal X-ray structures of (I) and (II) have been determined, and the results are presented here.



(I) $R = NH_2$
(II) R = Me

Compounds (I) and (II) display the same core formula, but the 2-position of the thiazole moiety is substituted by an amino group in (I) and by a methyl group in (II). Thus, they have the same $F(000)/Z$ ratio, where $F(000)$ corresponds to a pure electron count. No unusual geometric parameters were observed.

In both molecules, the 4-position of the thiazole is substituted by a chloroaryl group. For (I), the dihedral angle between the mean planes formed by the thiazole ring (S1/C2/N3/C4/C5) and the chloroaryl group (C1′–C6′) is 51.61 (10)° (Fig. 1). For compound (II), the equivalent dihedral angle is 8.44 (14)°, yielding a molecule which is virtually planar overall (Fig. 2). For the five similar 2,4-disubstitued thiazoles previously reported, this angle is in the range 6.2–58.8°. However, bite dihedral angles have been observed for 2-aminothiazoles, *e.g.* 6.2° for 2-amino-4-phenylthiazole (Au-Alvarez *et al.*, 1999) and 19.2° for the corresponding hydrobromide monohydrate complex (Form *et al.*, 1974). Substantially larger dihedral angles are observed if the 2-position is substituted by a bulky secondary or tertiary amine (Jain *et al.*, 2000; Maurin *et al.*, 1999; Kutschabsky *et al.*, 1990). For the five

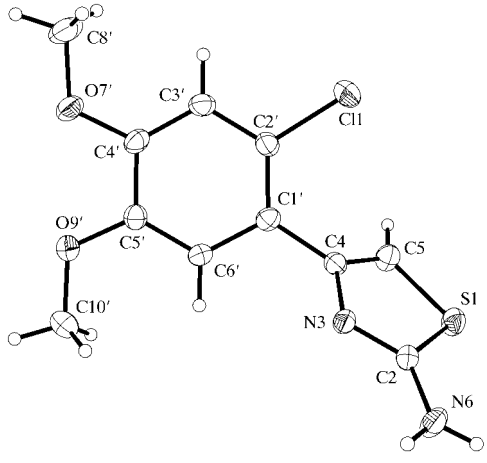


Figure 1
A view of the molecular structure of (I) in a projection normal to the mean plane of the chloroaryl group. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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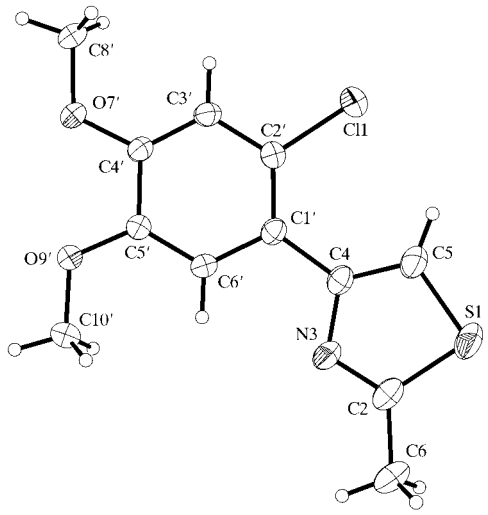

Figure 2
A view of the molecular structure of (II) in a projection normal to the mean plane of the chloroaryl group. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

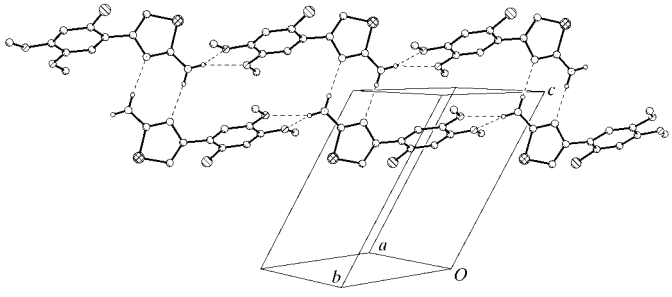

Figure 3
The hydrogen-bond network observed in (I), viewed along the [110] axis of the triclinic cell. For the sake of clarity, H atoms not involved in this network have been omitted.

examples mentioned above, a phenyl, dimethylphenyl or chlorophenyl group occupies the 4-position of the thiazole, and these probably do not participate significantly in the definition of the dihedral angle.

The present X-ray study unambiguously determines that compounds (I) and (II) are stabilized in the solid state as rotamers *A* (*Scheme* above). However, it is not possible to invoke steric hindrance to explain the very different dihedral angles observed. Rather, this difference is a consequence of the intermolecular hydrogen-bonding schemes in (I) and (II).

In the case of (I), the NH_2 group is able to form hydrogen bonds with the methoxy moieties of a symmetry-related molecule, as well as with the N atom of the thiazole ring of another molecule, this contact being virtually linear (Table 1). These contacts generate infinite chains along the [110] axis (Fig. 3) and seem to force the molecule to adopt a twisted conformation, with the thiazole–chloroaryl dihedral angle far from 0°. This arrangement also explains the absence of intramolecular hydrogen bonds in (I); considering atoms Cl1 and N3 as potential acceptors, the observed contacts are C5—H5*A*···Cl1 and C6′—H6′*A*···N3, with angles of 99.4 and 93.9°, respectively, *i.e.* with electrostatic interaction energies approaching zero.

For (II), where the NH_2 group is replaced by a methyl group, which is not an efficient donor, the intermolecular hydrogen-bonding scheme is withdrawn, allowing the relaxation of the molecule towards an almost flat rotamer. The only intermolecular contact detected in (II) arises between the two methoxy groups of the chloroaryl moiety (Table 2). Nevertheless, the decrease in the thiazole–chloroaryl dihedral angle is still insufficient for the formation of strong or moderate intramolecular hydrogen bonds; the C5—H5*A*···Cl1 and C6′—H6′*A*···N3 contacts display angles of 124.3 and 104.9°, respectively.

In conclusion, we have established that, for the 2,4-disubstituted thiazoles under consideration here, the intermolecular hydrogen bonds determine which rotamer is stabilized in the solid state, and a flat rotamer can be obtained by suppressing these intermolecular contacts. In other words, it is possible to tune the level of electronic delocalization between the thiazole and the chloroaryl moieties in the solid state by changing the substituent at the 2-position of the thiazole ring.

Experimental

The title thiazole derivatives (I) and (II) were prepared according to the general methods published by Sánchez-Viesca & Berros (1999) and Katritzky & Rees (1984).

Compound (I)

Crystal data

$C_{11}H_{11}ClN_2O_2S$
M_r = 270.73
Triclinic, $P\overline{1}$
a = 7.2398 (11) Å
b = 8.6611 (12) Å
c = 11.0585 (18) Å
α = 107.840 (12)°
β = 106.719 (13)°
γ = 97.729 (11)°
V = 613.04 (18) Å^3
Z = 2
D_x = 1.467 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 50 reflections
θ = 3.5–11.9°
μ = 0.47 mm^{-1}
T = 293 (2) K
Plate, pale pink
0.5 × 0.3 × 0.1 mm

Data collection

Siemens *P*4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (*XSCANS*; Siemens, 1991)
T_{min} = 0.929, T_{max} = 0.954
3417 measured reflections
2756 independent reflections
1831 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 27.5°
$h = -1 \rightarrow 9$
$k = -10 \rightarrow 10$
$l = -14 \rightarrow 14$
3 standard reflections
every 97 reflections
intensity decay: 4.5%

Table 1
Hydrogen-bonding and short intermolecular contact geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N6—H6*B*···O7′^{i}	0.86	2.58	3.051 (3)	116
N6—H6*B*···O9′^{i}	0.86	2.37	3.204 (3)	162
N6—H6*A*···N3^{ii}	0.86	2.21	3.035 (3)	161

Symmetry codes: (i) $x-1, y-1, z$; (ii) $-x, -y, -z$.

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0329P)^2 + 0.2732P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.051$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.113$	$\Delta\rho_{max} = 0.24$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.29$ e Å^{-3}
2756 reflections	
165 parameters	
H-atom parameters constrained	

Compound (II)

Crystal data

$C_{12}H_{12}ClNO_2S$	$D_x = 1.448$ Mg m^{-3}
$M_r = 269.74$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 50 reflections
$a = 7.3379$ (9) Å	$\theta = 4.7$–$11.5°$
$b = 19.242$ (2) Å	$\mu = 0.47$ mm^{-1}
$c = 8.7798$ (8) Å	$T = 298$ (2) K
$\beta = 93.738$ (9)°	Irregular, colourless
$V = 1237.1$ (2) Å^3	0.8 × 0.4 × 0.1 mm
$Z = 4$	

Data collection

Siemens *P*4 diffractometer	$R_{int} = 0.022$
ω scans	$\theta_{max} = 25°$
Absorption correction: ψ scan (*XSCANS*; Siemens, 1991)	$h = -1 \rightarrow 8$
$T_{min} = 0.808$, $T_{max} = 0.954$	$k = -22 \rightarrow 1$
2900 measured reflections	$l = -10 \rightarrow 10$
2183 independent reflections	3 standard reflections every 97 reflections
1701 reflections with $I > 2\sigma(I)$	intensity decay: 1%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0570P)^2 + 0.4857P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.041$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.119$	$\Delta\rho_{max} = 0.34$ e Å^{-3}
$S = 1.08$	$\Delta\rho_{min} = -0.31$ e Å^{-3}
2183 reflections	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
167 parameters	Extinction coefficient: 0.012 (2)
H-atom parameters constrained	

For both structures, H atoms were placed in idealized positions and refined using a riding model, with free isotropic displacement parameters and fixed distances of N—H = 0.86 Å, aromatic C—H = 0.93 Å and methyl C—H = 0.96 Å.

Table 2
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C8′—H8′A···O9′^{i}	0.96	2.51	3.461 (3)	174

Symmetry code: (i) $1-x, 2-y, 1-z$.

For both compounds, data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1995); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1182). Services for accessing these data are described at the back of the journal.

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