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# Structural investigations of 5-hydroxy-4,5-dihydroisoxazoles

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#### ABSTRACT

The X-ray diffraction data determined for eight 3-(R<sup>3</sup>), 4-(R<sup>4</sup>), 4,4-(R<sup>4</sup>/R<sup>4'</sup>) and/or 5-(R<sup>5</sup>) 5-hydroxy-4,5dihydroisoxazoles [where  $R^3 = Ph$ ,  $R^4/R^{4'} = H/H$ ,  $R^5 = CCl_3$  (1);  $R^3 = 4-Br-C_6H_4$ ,  $R^4/R^{4'} = H/H$ ,  $R^5 = CCl_3$  (2);  $R^{3} = \text{thien-2-yl}, R^{4}/R^{4'} = H/H, R^{5} = \text{CCl}_{3} (3); R^{3} = \text{Ph}, R^{4} = \text{Ph}, R^{4'} = \text{OH}, R^{5} = \text{Me} (4); R^{3} = \text{Me}, R^{4}/R^{4'} = \text{N-OH}, R^{5} = \text{Me} (5); R^{3} = \text{CF}_{3}, R^{4}/R^{4'} = H/H, R^{5} = \text{CMe}_{2}\text{CH}_{2}\text{OH} (6); R^{3} = H, R^{4} = 4\text{-I-C}_{6}H_{4}, R^{4'} = H, R^{5} = 4\text{-I-C}_{6}H_{4} (7);$  $R^{3}/R^{4} = -(CH_{2})_{3}$ ,  $R^{4'} = H$ ,  $R^{5} = CF_{2}CF_{2}H$  (8); are discussed. The crystalline structure of compounds 1-3 is described for the first time and crystalline structure of compounds 4-8 has already been described in literature. It was found that the supramolecular auto-organization of **1-8** is characterized by hydrogen bonds invariably involving the hemiacetal hydroxyl group. Compound 5 is the only exception, where the hydroxyl oxime group is the participant in the hydrogen bond. Compounds 4 and 8 present intermolecular contact between the hydroxyl group of the hemiacetal and the nitrogen atom of the 4,5-dihydroisoxazole ring. Compound 7 presents similar interaction, where the hydroxyl contact is with the oxygen atom of the 4,5-dihydroisoxazole ring. Moreover, the crystal structure of compound 6 was stabilized by O–H···O interaction between the hydroxyl group of hemiacetal and the hydroxyl group of the alcohol function attached at the 5-position of 4,5-dihydroisoxazole. The crystal structure of compounds 1-3, as described here for the first time, was similar to that of compounds **4** and **7**, showing a hydrogen bond O(51)-H(51) $\cdots$ N(2) between the hydroxyl group and the nitrogen atom of the isoxazoline ring. This means that the crystal structure of these compounds was governed by hydrogen bonds O-H···N, involving the hydroxyl of the hemiacetal group and the nitrogen atom of the 4,5-dihydroisoxazole ring. This interaction is relatively robust, showing a pattern in the crystal packing. Compounds 1-3 also have their crystal stabilized by more weak interactions of type Cl...Cl, involving the chlorine atom of the trichloromethyl group.

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# 1. Introduction

Isoxazoles and their derivatives have been of continuous interest because of the numerous applications for such heterocycles in the pharmaceutical [1–4] and agrochemical industries [1]. Generally, the pharmacological activity is closely related to the molecular recognition of the active substance by the active site. Therefore, a detailed understanding of these molecular interactions is essential for the development of quantitative approaches to molecular recognition. Recently, a specific molecular interaction where halogen atoms act by their positive potential surface is under active investigation [5]. Such interaction is now referred to as halogen bonding to emphasize the characteristics in parallel with those of hydrogen bonding in terms of strength and directionality [6].

\* Corresponding author. Tel./fax: +55 55 3220 8756. E-mail address: mmartins@base.ufsm.br (M.A.P. Martins). Over the last 20 years, our research group has developed syntheses of new trihalomethyl substituted heterocycles by conventional method [7], using ionic liquid [8], microwave [9] or ultrasonic irradiation [10]. Recently, we have also directed our attention to the understanding of molecular and supramolecular structural properties of these compounds and their role in biological systems.

Recently, we have revised the synthesis and spectroscopic properties of 5-halomethyl-5-hydroxy-4,5-dihydroisoxazoles [11]. Moreover, a structural characterization of these compounds from X-ray data, including intermolecular interactions, has not yet been performed. Intermolecular contacts which have been described for similar compounds, such as 4,5-dihydroxy-5-methyl-3,4-diphenyl-4, 5-dihydroisoxazole **(4)** [12], 5-hydroxy-3,5-dimethylisoxazol-4 (5*H*)-one oxime **(5)** [13], 3-trifluoromethyl-5-hydroxy-5-(1,1-dimethyl-2-ethoxyethyl)-4,5-dihydroisoxazoles **(6)** [14], 4,5-di (4-iodophenyl)-5-hydroxy-4,5-dihydroisoxazoles **(7)** [15] and 3-hydroxy-3-(1,1,2,2-tetrafluoroethyl)-3a,4,5,6-tetrahydro-3*H*-cycloi soxazole **(8)** [16], are presented in Fig. 1.



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Fig. 1. General structure for the studied 4,5-dihydroisoxazoles.

In this context, this work aims to describe the structure of three new 4,5-dihydroisoxazoles (1–3) and establish a comparison with the structures of already described 4,5-dihydroisoxazoles (4–8), in order to identify and characterize the supramolecular syntons present in these compounds (Fig. 1). Furthermore, the experimental geometrical data were compared with the results obtained from semi-empirical molecular orbital methods RM1, AM1, PM3 and DFT calculations.

## 2. Experimental

## 2.1. Synthesis

5-Trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles (1–3) were synthesized by cyclocondensation reaction of 1,1,1-trichloro-4methoxy-4-aryl(heteroaryl)-3-buten-2-ones with hydroxylamine hydrochloride in the presence of pyridine. This reaction was carried out in accordance with previously reported procedures [17]. The crystals used for the data collection were obtained by re-crystallization of compounds from methanol followed by slow evaporation at room temperature.

#### 2.2. Crystallographic data collection and refinement

X-ray data were collected on a Bruker SMART CCD diffractometer [18]. Data were collected using graphite-monochromatized Mo K $\alpha$  radiation with  $\lambda = 0.71073$  Å. The structures were solved with direct methods and refined on F2 by full-matrix least-squares by SHELXL97 [19]. Hydrogen atoms were included in the refinement in calculated positions with C–H distances of 0.93 Å (aromatic CH), 0.97 Å (methylene CH<sub>2</sub>), 0.98 Å (methine CH) and 0.82 Å (OH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to *U*iso (H) c 1.5 *U*eq for Csp<sup>3</sup>, and 1.2 for Csp<sup>2</sup>. Molecular graphics were prepared using ORTEP3 for Windows [20]. The crystal data and details concerning data collection and structure refinement are given in Supplementary material.

#### 3. Computational details

The geometry of compounds was optimized using semi-empirical RM1, AM1 and PM3 methods implemented in the HyperChem 8.0.6 package [21]. The structures were full optimized without fixing any parameter and, thus, bringing all geometric variables to their equilibrium values. The energy minimization protocol employed the Polak-Ribiere conjugated gradient algorithm. Convergence to a local minimum was achieved when the energy gradient was  $\leq 0.01$  kcal mol<sup>-1</sup>.

DFT calculations were carried out using Gaussian 03 package of programs [22]. Dihedral angle H51-O51-C5-C51 of compounds **1–3** were changed from 0° to 360° in steps of 10° optimizing the geometry at the HF/cc-pVTZ level. The geometry of the most stable conformers was fully re-optimized without any constrain at the B3LYP/cc-pVTZ level of theory. All geometries were verified as minima on the potential energy by calculating the Hessian matrices by harmonic frequency calculations.



**Fig. 2.** A stereoview of part of the crystal structure for **1**, **2** and **3**, showing the formation of a hydrogen-bonded chain and  $CI \cdots CI$  interactions (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

# 4. Results and discussion

Intermolecular contacts of 4,5-dihydroisoxazoles **4–7** found in literature are characterized by hydrogen bonds invariably involving the hydroxyl group of hemiacetal. There is only one exception, which is compound **5**, where the hydroxyl oxime group is the participant in the hydrogen bond. Compounds **4** and **8** present an

Table 1
Hydrogen bond geometry for structures 1-3 [Å], °.

Comp.	D–H···A	D-H	H···A	$D{\cdots}A$	$D{-}H{\cdots}A$	Symmetry codes
1 2	$O(51)-H(51)\cdots N(2)$ $O(51)-H(51)\cdots N(2)$	0.78 1.00	2.05 1.83	2.827(2) 2.818(5)	174.5 172.8	-x + 1/2, y - 1/2, -z + 1/2 -x + 1/2, y - 1/2, -z + 3/2
3	$O(51)-H(51)\cdots N(2)$	0.820	2.04	2.8569(17)	175.5	-x + 1/2, y + 1/2, -z + 1/2

 Table 2

 Halogen Bond Geometry for Structures 1–3 [Å], °.

Comp.	C−Cl···Cl	$Cl{\cdot}\cdot{\cdot}Cl$	C−Cl···Cl	Symmetry codes
1	$Cl(2) \cdot \cdot \cdot Cl(2)$	3.285(1)	133.5	-x + 1/2, -y + 5/2, -z + 1
2	$Cl(1) \cdot \cdot \cdot Cl(1)$	3.250(2)	130.4	-x + 3/2, -z + 2
2	C−Cl(3)···Br	3.584(0)	120.9	-x, -y, 1-z
3	$Cl(2) \cdot \cdot \cdot Cl(2)$	3.397(9)	150.9	-x, -y + 2, z
3	$Cl(1) \cdot \cdot \cdot Cl(1)$	3.407(11)	149.6	-x, y, -z + 1/2



Fig. 3. The two geometries for halogen bonds (R = organic group, X = Cl, Br and I).

intermolecular contact between the hydroxyl group of hemiacetal and the nitrogen atom of the 4,5-dihydroisoxazole ring, with O(51)-H(51)···N(2) angles of 168° and 173.5°, respectively. Compound **7** presents similar interaction; however, the hydroxyl contact is with the oxygen atom of the 4,5-dihydroisoxazole ring. Structure **7** was deposited in the CCDC, but without hydrogen atoms and geometric parameters of this interaction, which were not found in the publication [15]. As previously mentioned, compound **5** had its crystal stabilized by a hydrogen bond between the hydroxyl group of the oxime function and the nitrogen atom of the 4,5-dihydroisoxazole ring with an O···N distance of 2.762 Å and O-H···N angle of 176.2°. Conversely, crystal structure of compound **6** was stabilized by an O-H···O interaction, between hydroxyl groups of alcohol function attached at 5-position of 4,5dihydroisoxazole.

Crystal structures of compounds 1-3, as described here for the first time, were similar to those of compounds 4 and 7. In other words, the crystal formation of these compounds was governed by hydrogen bonds  $O-H \cdots N$  to **1–4** and  $O-H \cdots O$  to **7**, involving the hemiacetal hydroxyl group and the nitrogen or oxygen atom of the 4,5-dihydroisoxazole ring. This interaction was relatively robust, showing a pattern in the crystal packing. Compounds 1-3 showed a hydrogen bond  $O(51)-H(51)\cdots N(2)$  between the hydroxyl group and the nitrogen atom of the heterocyclic ring, forming infinite chains along one plane (Fig. 2). The contact distances  $O(51) \cdots N(2)$  and contact angles  $O(51)-H(51) \cdots N(2)$  are depicted in Table 1. The interatomic distances observed for these contacts were shorter than the sum of van der Waals radii of the acceptor and donor  $(D \cdot \cdot A)$  atoms of the proton involved in the interaction [23]. Compounds 1-3 also had their crystal structures stabilized by more weak interactions of type Cl...Cl, involving chlorine atoms of the trichloromethyl group. Although the interatomic distances are shorter than the sum of van der Waals radii of the chlorine atom, this interaction in compounds 1-3 has a weak angular directionality. Interatomic distances of Cl...Cl and interaction angles are shown in Table 2. In addition, compound 2 has a Cl...Br



Fig. 4. Representation of the supramolecular synthon found in compounds 1-8.



Fig. 5. View of the asymmetric unit of compounds 1–3, showing the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary radii.

Table 3Torsional angle and  $\Delta E$  of conformers determined by HF/cc-pVTZ level.

Comp.	Conformer	H(51)–O(51)–C(5)–C(51) Angle(°)	$\Delta E$ (kcal mol <sup>-1</sup> )	μ (D)
1	Ι	64.6	0.00	2.66
	II	305.3	4.00	4.20
2	Ι	63.3	0.00	1.64
	II	305.7	4.02	3.33
3	Ia	64.8	0.00	3.08
	Ib	64.6	1.11	2.66
	IIa	305.6	4.07	4.68
	IIb	304.9	5.07	4.10

intermolecular contact, whose interatomic distance is shorter than the sum of van der Waals radii of chlorine and bromine atoms. However, like the Cl···Cl interaction, this interaction has a weak angular directionality, with a C(1)–Cl(3)···Br angle of 120.9° and C–Br···Cl angle of 152.1°.

The presence of these interactions involving halogen atoms in compounds **1–3** leads us to discuss here their angular requirements. Covalently-bonded halogen interacted through positive electrostatic regions with a negative site, such as a lone pair of a Lewis base. In particular, in the bonded halogen atom, the anisotropically distributed electron density resulted in a negative charge concentrated in the equatorial area and a positive charge along the C-X bond, which is called a  $\sigma$ -hole [6a]. This leads to two preferred



Fig. 6. Energy scan for the dihedral angle H(51)–O(51)–C(5)–C(51) from 0° to 360° for compound 1.



**Fig. 7.** The six optimized structures.

geometries for halogen...Lewis base or halogen...halogen contacts (Fig. 3). The first arrangement (Type I, Fig. 3) occurs when  $\theta_1 = \theta_2$ , (where  $\theta_1$  and  $\theta_2$  are the R-X<sub>1</sub>···X<sub>2</sub> and X<sub>1</sub>···X<sub>2</sub>-C angles, respectively). The second geometry (Type II, Fig. 3) arises when  $\theta_1 = 180^\circ$  and  $\theta_2 = 90^\circ$ ; the perpendicular arrangement. Therefore, from the angular information selected in Table 2, it is possible to state that the halogen bonds (Cl···Cl and Cl···Br) observed in compounds 1-3 were similar to those geometries shown in Type I drawing in Fig. 3. In other words, halogen ··· halogen contacts found in compounds **1–3** have a weak angular directionality, and  $\theta_1$  was not exactly equal to  $\theta_2$ . Crystal stabilization of compound **3**, as in compounds 1 and 2, has an extra interaction, where the sulfur atoms were responsible for the extra stabilization, rather than the halogen atoms. The interaction of the type S...S had an interatomic distance of 3.437(9) Å for  $S(32) \cdots S(32) (-x + 1/2, -y + 3/2)$ 2, -z + 1) and C(31)–S(32)···S(32) of 163.9°. This S···S interaction, in compound 3, different from the halogen ... halogen contacts found in compounds 1-3, presents an angle closer to 180°. This interaction, similar to the halogen ... halogen interaction, can be explained by the non-spherical distribution of charge in the potential surface ( $\sigma$ -hole) of the covalently bonded sulfur atom. In accordance, the sulfur atom has positive points in the potential surface  $(\sigma$ -hole), one for each covalent bond formed. Therefore, from structural X-ray analysis of compounds 1-8, it is clear that the  $O(51)-H(51)\cdots N(2)$  intermolecular hydrogen bond is an important supramolecular synthon in 4,5-dihydroisoxazoles, due to its robustness, demonstrated by its presence in five of the eight compounds described here (Fig. 4). In addition, it was found that the supramolecular synthon  $O(51)-H(51)\cdots N(2)$  was sensitive to the addition of a substituent with a hydroxyl group in some position of the ring (4 and 5), as an oxime (compound **5**) and an alcohol (compound **6**). On the other hand, this supramolecular synthon was not altered by the presence of interactions involving halogenated groups or atoms and sulfur atoms. This can be explained by the higher ability of oxygen atoms to participate in intermolecular interactions, which is a consequence of the higher dipole in oxygen atoms, in relation to halogen or sulfur atoms. In this case, halogen…halogen (**1–3**) and sulfur–sulfur (**3**) interactions perform an auxiliary role in the extra stabilization of the crystal in compounds **1–3**.

We consider it to be worth mentioning some geometric data for compounds 1-3, which is characterized by the molecular structure represented by ORTEP in Fig. 5. The five-membered 4,5-dihydroisoxazole ring was found as an essentially planar structure for compounds 1-3. These data are in full agreement with compounds 4-8 [12–16]. The C(4)–C(3)–C(31)–C(36) torsion angles made by phenyl and 4-bromophenyl show that these groups are nearly planar to the 4,5-dihydroisoxazole system. The C(4)-C(3)-C(31)-C(36)torsion angles were of  $-0.4(3)^{\circ}$  and  $0.8(6)^{\circ}$  for compounds 1 and 2, respectively. Similarly, the 4,5-dihydroisoxazole 3 makes C(4)-C(3)-C(31)-C(35) torsion angle of  $-3.0(3)^\circ$ , demonstrating that the thien-2-yl group shares the same plane of the 4,5-dihydroisoxazole ring. This planarity between the 4,5-dihydroisoxazole and its substituent in the 3-position is associated with the electronic resonance between the N(2)=C(3) bond of the heterocycle and its substituents attached at the 3-position.

#### Table 4

Experimental data and data calculated by RM1, AM1, PM3 and B3LYP/cc-pvtz level for bond lengths and bond angles.

Bond length	X-ray	RM1	AM1	PM3	B3LYP <sup>a</sup>
Compound 1					
O(1)-N(2)	1.416(2)	1.351	1.314	1.408	1.405
C(3)-N(2)	1.289(3)	1.325	1.325	1.309	1.280
C(4) - C(3)	1.493(3)	1.496	1.524	1.508	1.505
C(4) - C(5)	1.524(3)	1.539	1.549	1.551	1.528
C(5) - O(1)	1.457(3)	1.423	1.477	1.445	1.432
C(5)-O(51)	1.368(3)	1.373	1.393	1.395	1.389
C(51)-C(5)	1.556(3)	1.514	1.547	1.544	1.566
C(31)-C(3)	1.460(3)	1.440	1.454	1.460	1.466
Compound <b>2</b>					
O(1) - N(2)	1.412(4)	1.350	1.313	1.406	1.401
C(3) - N(2)	1.277(5)	1.325	1.325	1.309	1.280
C(4) - C(3)	1.485(5)	1.496	1.523	1.508	1.505
C(4) - C(5)	1.531(5)	1.539	1.550	1.552	1.529
C(5) - O(1)	1.460(5)	1.424	1.479	1.446	1.434
C(5)-O(51)	1.370(5)	1.372	1.393	1.395	1.388
C(51)-C(5)	1.549(6)	1.513	1.547	1.543	1.566
C(31)-C(3)	1.470(5)	1.440	1.454	1.461	1.465
Compound 3					
O(1) = N(2)	1 416(19)	1 350	1 3 1 3	1 406	1 401
C(3) = N(2)	1 283(2)	1 3 2 5	1 3 2 5	1 300	1 280
C(3) = R(2)	1.203(2) 1.404(2)	1.525	1.525	1.505	1.200
C(4) - C(5)	1.434(2) 1.537(2)	1 5 3 0	1.525	1.500	1.505
C(4) - C(3)	1.557(2) 1.455(2)	1.333	1.330	1.332	1.323
C(5) = O(1) C(5) = O(51)	1.433(2) 1.265(2)	1,424	1,475	1 205	1 2 0 0
C(5)=O(51)	1.505(2) 1.546(2)	1.572	1.555	1.595	1.566
C(31) - C(3)	1.340(2) 1.440(2)	1.515	1.547	1.545	1.300
c(31) $c(3)$	1.440(2)	1.110	1.454	1.401	1.405
Bond angle					
Compound <b>1</b>					
C(3) = N(2) = O(1)	109 90(18)	110 5	111 9	1124	109.8
N(2) = C(3) = C(4)	112 9(2)	112.2	111.5	111.5	113.2
C(3) = C(4) = C(5)	102.3(2) 102.85(17)	100.1	100.4	101.3	100.6
O(1) = C(5) = C(4)	102.03(17) 104.28(17)	106.1	104.1	106.5	105.0
N(2) = O(1) = C(5)	109.9(3)	110.1	1118	108.2	109.1
N(2) = C(3) = C(31)	103.3(3) 121 7(2)	173.7	126.5	174.2	121.7
O(1) = C(5) = C(51)	105 14(17)	108.4	109.6	109.8	106.7
O(51) - C(5) - O(1)	109.11(17) 109.32(18)	111 9	113.6	112.2	110.6
O(51) - C(5) - C(51)	105.52(10) 105.96(18)	107.5	103.7	104 7	110.0
	105.50(10)	107.5	105.7	10 1.7	110.7
Compound $2$	110 2(2)	110.0	111.0	112 5	100.0
C(3) = N(2) = O(1) N(2) = C(2) = C(4)	112.2(3)	110.0	111.9	112.5	109.9
N(2) = C(3) = C(4) C(2) = C(4) = C(5)	102 8(2)	112.2	100.4	1012	115.5
O(1) - C(5) - C(4)	102.3(3)	106.0	104.1	101.5	100.0
N(2) = O(1) = C(4)	109.7(3)	110.1	111 8	100.4	100.0
N(2) = O(1) = O(3) N(2) = O(3) = O(31)	103.3(3) 121.0(4)	173.6	176.4	100.2	105.5
$\Omega(2) = C(3) = C(31)$ $\Omega(1) = C(5) = C(51)$	121.0(4) 105 $4(3)$	108.3	100.4	100.8	106.6
O(51) - C(5) - O(1)	109.4(3)	112.1	113.7	112.3	110.0
O(51) - C(5) - C(51)	105.8(3)	107.5	103.6	104 7	110.7
Commound 2	105.0(5)	107.5	105.0	101.7	110.0
C(2) N(2) O(1)	100.07(12)	110.2	1117	112.2	100 5
N(2) = N(2) = O(1)	109.97(13) 112.54(15)	110.2	111.7	112.2	112.6
$\Gamma(2) = C(3) = C(4)$ $\Gamma(3) = C(4) = C(5)$	102 11(12)	00.0	100.2	101.1	100 2
O(1) = O(5) = O(4)	102.11(13)	33.9 106 0	100.2	101.1	100.5
N(2) = O(1) = O(4)	104.35(12) 110.01(12)	1110.2	1110	100.5	100.2
N(2) = O(1) = C(3) N(2) = C(3) = C(21)	122 62(12)	1246	111.0	100.0	109.9
$\Omega(2) = C(3) = C(31)$ $\Omega(1) = C(5) = C(51)$	105 83(13)	124.0	100.0	125.0	122.2
O(51) = O(51) = O(51)	105.83(13)	112.0	112.6	112.0	110.7
O(51) - C(5) - O(1)	103.03(13) 110.12(14)	107.5	102.6	104.6	110.0
O(31) - C(3) - C(31)	110.12(14)	107.5	105.0	104.0	110.7

Basis set cc-PVTZ was used.

We have complemented the structural analysis of compounds **1–3** with theoretical calculations. DFT calculated relative energies of the major possible conformers of **1–3** compounds are given in Table 3. The DFT calculated relative energies can be achieved by an energy scan of  $0^{\circ}$  to  $360^{\circ}$  for dihedral angle H(51)-O(51)-C(5)-C(51) (Fig. 6). The so resulting most stable conformers in the gas phase are not present in the solid phase. In the gas phase, the energy scan shows that for compounds **1** and **2**, conformer **I** was the most stable structure by a difference in energy of about 4 kcal·mol<sup>-1</sup> in relation



**Fig. 8.** Plot of experimental and theoretical bond lengths for compounds **1–3**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to the second more stable structure represented by conformer II. Compound 3, due to the additional presence of the thien-2-yl substituent, shows four possible structures. Calculated relative energies show that conformer **Ia** with the sulfur and oxygen atoms on the same side was the most stable structure by about 1 kcal mol<sup>-1</sup> in relation to the other possible structures (Fig. 7). An explanation of this behavior was given by Lombardo et al. to similar found [24] in terms of the lack of ability, in the gas phase, to form intramolecular interactions, as the molecule is isolated and not interacting with other molecules at all. They rationalized that when the molecule is in the bulk, several other molecules surround it and the intermolecular interactions control the mutual spatial distribution. In the solid state, where several other interactions contribute to final balance of the structure, the intramolecular interaction found in gas phase is not so relevant. Thus, we believed that this can be occurring in our study. Although the discrepancies between conformers found in gas or solid phase, the geometry of conformers was so similar. The selected bond lengths and bond angles for the more stable conformers of compounds 1-3, obtained from semiempirical and DFT calculations and from X-ray diffractometry are presented in Table 4. The simple linear regressions between experimental bond lengths and bond angles from X-ray (average to compounds 1-3) with semi-empirical calculated data (RM1, AM1 and PM3) and DFT calculations showed good and similar correlation coefficients. The correlation of semi-empirical and DFT methods with experimental data showed values of r = 0.925, 0.879, 0.985 and 0.988, for bond lengths, and *r* = 0.936, 0.942, 0.925, 0.950 for bond angles, obtained by the methods RM1, AM1 PM3 and DFT, respectively. In addition, calculated and experimental data were also analyzed statistically. The sum of bond length errors resulted in positive values for the RM1 method and negative values for the others. This indicates that the RM1 method provided longer bond lengths than did the experimental data, while the other methods described shorter lengths than did the experimental data. The average unsigned bond length errors also resulted in positive values for the RM1 method and negative values for the others, with AM1 and DFT vielding the lowest errors. In addition, inspection of Fig. 8 reveals that DFT was the method that best described the bond length of compounds 1-3 and the AM1 method was the method that most failed to describe the O(1)-N(2) bond (Fig. 8).

The sum of bond angle errors resulted in negative values for all methods, showing that the bond angle was described as smaller than that from experimental data, and DFT was the method that best described the bond angle for compounds 1-3.

# 5. Conclusions

In summary, the crystal structure of 5-trichloromethyl-5-hydroxv-4.5-dihvdroisoxazoles 1-3 has been characterized and discussed together with similar structures (4-8) described in the literature and it was shown that the supramolecular auto-organization of 5-hydroxy-4,5-dihydroisoxazoles is characterized by hydrogen bonds invariably involving the hydroxyl of the hemiacetal group. There was only a small substituent effect at the 4-position of 5-hydroxy-4,5-dihydroisoxazoles when the substituent was an oxime group. In other words, the crystal of these compounds was governed by hydrogen bonds O–H···N (O), involving the hydroxyl group of hemiacetal and the nitrogen/oxygen atom of the 4,5dihydroisoxazole ring. Therefore, this interaction could be considered a relatively robust supramolecular synthon showing a pattern in the crystal packing for the eight 5-hydroxy-4,5-dihydroisoxazoles with different substitutions. In addition, the crystal structure of compounds 1-3 also had its crystal stabilized by more weak interactions of type Cl...Cl, involving the chlorine atom of the trichloromethyl group. We believe that the Cl...Cl interaction, in these three compounds, could also be considered a supramolecular synthon, due to its presence in all three compounds substituted by the chlorinated group. The semi-empirical and DFT calculations gave similar data in comparison with the experimental data for bond lengths and angles, where DFT calculations resulted in better correlations in all cases.

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## **Appendix A. Supplementary material**

CCDC numbers of compounds 1-3 is 681049, 681048 and 681050, respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax:+44(0) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.09.051.

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