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Studies on the Intramolecular C–H···X (X = O, S) Interactions in (*S*)-*N*-Acyl-4-isopropyl-1,3-thiazolidine-2-thiones and Related 1,3-Oxazolidin-2-ones

**Anabel Cosp,[†] Igor Larrosa,[†] Josep M. Anglada,*[‡] Josep M. Bofill,*[†,§]
Pedro Romea,*[†] and Fèlix Urpí*[†]**

*Departament de Química Orgànica, Universitat de Barcelona, Martí i Franqués 1-11,
08028 Barcelona, Catalonia, Spain, Centre Especial de Recerca en Química Teòrica
(CeRQT), PCB Josep Samitier 1, 08028 Barcelona, Catalonia, Spain,
Institut d'Investigacions Químiques i Ambientals de Barcelona, Departament de
Química Orgànica Biològica, IIQAB-CSIC, Jordi Girona 18,
08034 Barcelona, Catalonia, Spain*

promea@qo.ub.es

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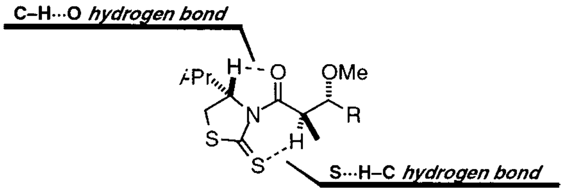
ABSTRACT



Two intramolecular C–H···X (X = O, S) interactions in (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones are documented through crystallographic and spectroscopic evidence and high-level theoretical calculations. The key role played by the sulfur atoms has been made clear by comparison with structurally related (*S*)-*N*-acyl-4-isopropyl-1,3-oxazolidin-2-ones.

The better understanding of noncovalent interactions has driven recent advances in many areas of modern science. In particular, the key role played by hydrogen bonds (Y−H···X) in chemistry and biology has been recognized for a long time.[1] Traditionally, they had been restricted to systems where X and Y were highly electronegative atoms, but those cases involving a C−H bond donor have recently attracted considerable interest due to their influence on conformational analysis and supramolecular chemistry.[1d,2] Nowadays, the existence of C−H···O hydrogen bonds is well established,[2,3] but little is known about the significance of related C−H···S interactions despite the widespread presence of sulfur on many synthetic and natural molecular architectures.[4,5] In this context, we describe in this Letter our studies on the intramolecular C−H···X (X = O, S) interactions observed in the (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones **1** and **2**[6] and the structurally related (*S*)-*N*-acyl-4-isopropyl-1,3-

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[†] Universitat de Barcelona.

[‡] IIQAB-CSIC.

[§] CeRQT.

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(5) For theoretical studies on C−H···S interactions, see: (a) Rovira, C.; Novoa, J. J. *Chem. Phys. Lett.* **1997**, *279*, 140. (b) Hartmann, M.; Wetmore, S. D.; Radom, L. *J. Phys. Chem. A* **2001**, *105*, 4470.

10.1021/ol0347848 CCC: $25.00

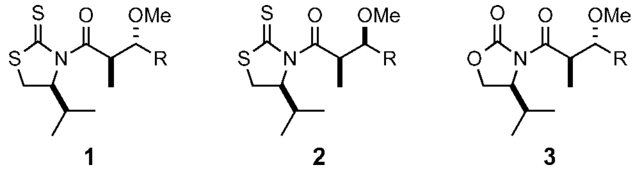

Figure 1.

oxazolidin-2-ones **3**, shown in Figure 1 through crystallographic and spectroscopic evidence and high-level theoretical calculations.

Three criteria[1,2] are usually engaged to judge whether a hydrogen bond is present through the analysis of the crystal structure determined by X-ray diffraction: (1) an H···X distance (X acting as the H-bond acceptor) close to the sum of the van der Waals radii of H and X; (2) a near-linear Y−H···X bond angle (θ) or, somewhat more conservatively, greater than 110°; and (3) an appropriate directionality at the atom acceptor, that is the H···X−C angle (ϕ).[7] In our case, the distances between the COCH hydrogen and the C=S sulfur observed in **1c** (R = 4-ClPh) and **2c** (R = 4-ClPh) fall in the range 2.46−2.49 Å (see Figure 2), values remarkably shorter than the sum of the van der Waals radii[8] for H and S (H = 1.20 Å, S = 1.80 Å); the C−H···S angles (θ) are greater than 130°, and the H···S=C angles (ϕ) are roughly 80°.[9,10] These structural data stressed the likelihood of a C−H···S=C hydrogen bond.[11] Moreover, similar trends were observed for the NCH···O=C distances (2.20−2.25 Å), which are less than the sum of the van der Waals radii[8] (H = 1.20 Å, O = 1.52 Å), and the NC−H···O (100−107°)[12] and the NCH···O=C (85−89°) angles.

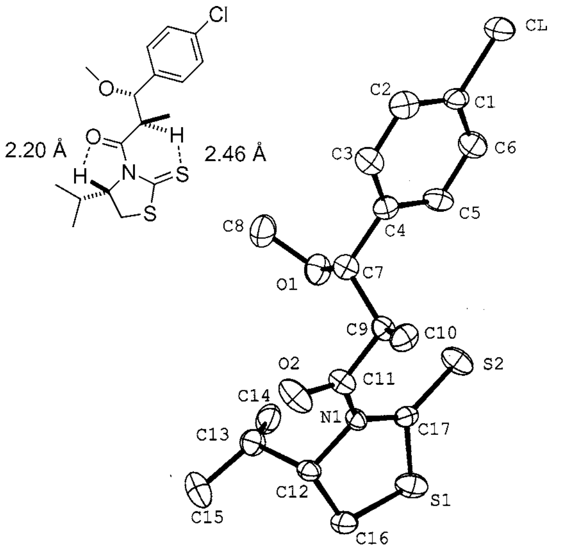

Figure 2. ORTEP diagram of **1c**.

Additionally, the NCH and COCH hydrogens of **1** and **2** displayed unusual chemical shifts higher than 5 ppm in the ^1H NMR spectra. It was also determined that the chemical shift of the proton resonances of **1c** (R = 4-ClPh) are not significantly affected by the polarity of the solvent or the temperature (see Supporting Information). Moreover, NOE studies on **1c** showed the spatial proximity between the isopropyl methine hydrogen, $C\mathit{H}(CH_3)_2$, and the OCH_3 group, which suggests that its conformation in solution resembles that adopted in the crystal (see Figure 2).

Therefore, the crystallographic and spectroscopic data pointed to the existence of two C−H···X intramolecular interactions both in crystal and in solution, irrespective of the radical R and the stereochemistry of the adducts **1** or **2**. However, they can simply be taken as experimental facts and it would be worthwhile supporting these data with arguments rooted in theoretical grounds. These considerations have prompted us to carry out high-level theoretical calculations to probe deeply into the knowledge of the corresponding evolved interactions in the aforementioned compounds.

Starting from conformations such as that depicted in Figure 2, we performed a full geometry optimization using Density Functional Theory (DFT)[13] with the B3LYP[14,15] functional on several **1**−**3** compounds, verifying that the optimized structures correspond to minima by means of vibrational analysis calculation. Both NMR chemical shift calculations[16] and topological analyses of the calculated electron density, based on the theory of atoms in molecules (AIM) by Bader,[17]

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(8) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(9) Crystallographic data for **1c** and **2c** can be found as supplementary publication numbers CCDC-150271 and CCDC-150270, respectively, at the Cambridge Crystallographic Data Centre.

(10) Selected crystallographic data for **1c**: d(CH···S) = 2.46 Å, d(CH···O) = 2.20 Å, θ(C−H···S) = 142°, θ(C−H···O) = 107°, ϕ(H···S=C) = 79°, ϕ(H···O=C) = 85°. For **2c**: d(CH···S) = 2.49 Å, d(CH···O) = 2.25 Å, θ(C−H···S) = 130°, θ(C−H···O) = 100°, ϕ(H···S=C) = 82.5°, ϕ(H···O=C) = 89°.

(11) Silks et al. uncovered a C−H···Se=C hydrogen bond in the products arising from a stereoselective aldol reaction based on a chiral *N*-acyl selone, which are similar to the adducts considered in the present work: Michalczyk, R.; Schmidt, J. G.; Moody, E.; Li, Z.; Wu, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3067.

(12) These angle values are far from the model geometry. However, deviations from the linear arrangement have been previously reported in the case of other intramolecular interactions. For a recent exemple, see: Donati, A.; Ristori, S.; Bonechi, C.; Panza, L.; Martini, G.; Rossi, C. *J. Am. Chem. Soc.* **2002**, *124*, 8778.

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(16) Theoretical ^1H NMR chemical shifts have been obtained by B3LYP single-point calculations at the optimized geometries and using the GIAO method. See: (a) Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251. (b) Cheeseman, J. R.; Trucks, G. W.; Keith, T. A.; Frisch, M. J. *J. Chem. Phys.* **1996**, *104*, 5497. In that case, the 6-311+G(2d,p) basis set was used: Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

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Table 1. Experimental and Theoretical ^{1}H NMR Chemical Shifts of NCH and COCH Hydrogens of Adducts **1** and **2**

			δ (NCH)		δ (COCH)	
entry	adduct	R	exp	calcd	exp	calcd
1	**1a**	H	5.23	5.74	4.95	5.67
2	**1b**	Ph	5.36	5.71	5.26	5.80
3	**1c**	4-ClPh	5.35	5.64	5.25	5.94
4	**2b**	Ph	5.24	5.70	5.27	5.86
5	**2c**	4-ClPh	5.23	5.61	5.28	5.91
6	**3a**	H	4.52	4.33	4.20	4.58
7	**3b**	Ph	4.30	4.41	4.40	4.59
8	**3c**	4-ClPh	4.52	4.39	4.34	4.51

were next performed[18] in those minima.[19] According to Bader's theory, the bonding interaction is described in terms of the electron density (ρ), its gradient vector field ($\nabla\rho$), and its laplacian ($\nabla^2\rho$). If there is a chemical bond between two atoms (such as a hydrogen bond), they are directly connected by a trajectory called the "bond path". Then, the bond path is an intrinsic property of each compound and the type of pairwise atomic interaction is characterized by the sign of the laplacian at the point where $\nabla\rho = \mathbf{0}$ (bond critical point or bcp). On the basis of the AIM theory, Popelier et al.[20,21] proposed a set of criteria for characterizing weak bond interactions, which has been already applied across the literature.[2c] Taking into account that our system involves intramolecular interactions, we have considered the following Popelier criteria: (1) the topology of the bond path to be sure that the path links the hydrogen and the acceptor atoms; (2) the ρ and the $\nabla^2\rho$ values at the bcp, which should range between 0.002 and 0.035 au and 0.024−0.139 au, respectively; and (3) the mutual penetration of the hydrogen and the acceptor atom, $\Sigma\Delta r$.[22]

In the case of 1,3-thiazolidine-2-thiones **1** and **2**, the computed geometrical parameters[23,24] match the crystallographic data[10] and the calculated NMR shifts also agree quite well with the experimental values (see entries 1−5 in Table 1), with differences of 0.5−0.7 ppm for the COCH hydrogen and of 0.3−0.5 ppm for the NCH hydrogen. Moreover, the topological analyses of the electron density point out the existence of a bcp for the COC−H···S=C and NC−H···O=C interactions, which can be unambiguously assigned to true hydrogen bond interactions according to the values of ρ, $\nabla^2\rho$, and mutual penetration $\Sigma\Delta r$ (see entries 1−5 in Table 2).

Therefore, the unexpected chemical shifts observed in the case of NCH and COCH hydrogens can be clearly attributed to the deshielding produced by the two intramolecular hydrogen bonds. Although these C−H···X hydrogen bonds are usually classified as weak interactions, both the experimental and theoretical results suggest that for **1** and **2**, the conformation presenting both C−H···X interactions is the most stable and confers to these species an additional rigidity.

This approach has been extended to 1,3-oxazolidin-2-ones **3** due to their structural similarity with **1** and **2**. The topological analyses of the electron density proved that a bcp exists in the COCH···O=C area, which was confirmed as a true hydrogen bond by the corresponding ρ, $\nabla^2\rho$, and $\Sigma\Delta r$ values. However, no bcp was found in the NCH···O=C region (see entries 6−8 in Table 2). As a consequence, theoretical calculations anticipated that just a single C−H···X interaction acts in the oxazolidine-derived adducts **3**. This prediction is supported by the excellent agreement between the calculated geometrical parameters[25] and the crystallographic data of **3c**.[26] In general, the calculated COCH···O=C distances range between 2.186 and 2.197 Å and the COC−H···O (θ) and COCH···O=C (ϕ) angles are greater than 120 and 97°, respectively. Otherwise, although the NCH···O=C distances are shorter than the sum of the van der Waals radii, the too small NC−H···O ($\theta \leq 97°$) and NCH···O=C ($\phi \leq 86°$) angles do not produce any bonding interaction, which emphasize the importance of the directionality of the hydrogen bonds. Finally, the good resemblance between the theoretical and the experimental ^{1}H chemical shifts (see entries 6−8 in Table 1) constitutes another proof of the accuracy of our approach.

The larger size of sulfur than oxygen might be the origin of the observed differences between **1**, **2** and **3**. In the case of the COCH···X (X = S, O) interaction, the hydrogen bond is established through a six-membered ring, which facilitates the H···X (X = S, O) contact. The six-membered cyclic structure and the chemical groups involved suggest that this kind of interaction might be associated to a resonance assisted hydrogen bond (RAHB).[1d,27] Differently, the intramolecular NCH···O interaction, when it occurs, is formed through a five-membered ring, which is known to be less favored than a six-membered ring in this kind of process.[28] Then, the substitution of sulfur by oxygen changes the geometry of the molecule, alters the directionality of the hydrogen bonds, and makes the NC−H···O contact less efficient in the case of adducts **3**.

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[18] Topological analyses of the wave function have been carried out over the B3LYP/6-311+G(2d,p) density.

[19] Geometry optimizations and NMR calculations have been done using the Gaussian 98 program package. Frisch, M. J. et al. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

[20] Kock, U.; Popelier, P. L. A. *J. Phys. Chem.* **1995**, *99*, 9747.

[21] Popelier, P. L. A. *J. Phys. Chem. A* **1998**, *102*, 1873.

[22] For a similar analysis recently reported, see: Mallinson, P. R.; Smith, G. T.; Wilson, C. C.; Grech, E.; Wozniak, K. *J. Am. Chem. Soc.* **2003**, *125*, 4259.

[23] Topological parameters of the wave function have been carried out using the AIMPAC program. Bader, R. F. W. http://www.chemistry.mcmaster.ca/aimpac (downloaded May 2002).

[24] Selected calculated parameters for **1c**: d(CH···S) = 2.40 Å, d(CH···O) = 2.18 Å, θ(C−H···S) = 136.4°, θ(C−H···O) = 104.6°, ϕ(H···S=C) = 83.1°, ϕ(H···O=C) = 89.2°. For **2c**: d(CH···S) = 2.40 Å, d(CH···O) = 2.18 Å, θ(C−H···S) = 137.6°, θ(C−H···O) = 104.5°, ϕ(H···S=C) = 82.7°, ϕ(H···O=C) = 89.0°.

[25] Selected calculated parameters for **3c**: d(COC−H···O^1) = 2.19 Å, d(NC−H···O^2) = 2.42 Å, θ(COC−H···O^1) = 122.4°, θ(NC−H···O^2) = 96.5°, ϕ(COC−H···O^1) = 97.6°, ϕ(NC−H···O^2) = 85.5°.

[26] Unity cell of **3c** contains two molecules with slightly different geometries. Selected crystallographic data for **3c**: d(COC−H···O^1) = 2.29 and 2.14 Å, d(NC−H···O^2) = 2.54 and 2.63 Å, θ(COC−H···O^1) = 120 and 132°, θ(NC−H···O^2) = 90 and 85°, ϕ(COC−H···O^1) = 97 and 96°, ϕ(NC−H···O^2) = 81 and 79°.

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[28] (a) Crehuet, R.; Anglada, J. M.; Bofill, J. M. *Chem. Eur. J.* **2001**, *7*, 2227. (b) Anglada, J. M.; Aplincourt, P.; Bofill, J. M.; Cremer, D. *ChemPhysChem* **2002**, *3*, 215.

Table 2. Topological Properties of the C−H···X Interactions of Adducts **1**−**3**

			NCH			COCH		
entry	adduct	R	ρ (X···H)	$\nabla^2\rho$ (X···H)	$\Sigma\Delta r$[a]	ρ (X···H)	$\nabla^2\rho$ (X···H)	$\Sigma\Delta r$[a]
1	**1a**	H	0.027	0.097	0.499	0.020	0.055	0.557
2	**1b**	Ph	0.023	0.098	0.505	0.021	0.055	0.576
3	**1c**	4-ClPh	0.023	0.097	0.495	0.022	0.056	0.599
4	**2b**	Ph	0.023	0.097	0.504	0.021	0.055	0.586
5	**2c**	4-ClPh	0.023	0.098	0.490	0.021	0.055	0.600
6	**3a**	H				0.019	0.068	0.501
7	**3b**	Ph				0.019	0.069	0.529
8	**3c**	4-ClPh				0.019	0.069	0.516

[a] Mutual penetration, $\Sigma\Delta r$, for the hydrogen and the acceptor atom has been computed considering the van der Waals radii (Å) of the corresponding atoms.

In summary, two intramolecular C−H···X (X = O, S) interactions have been identified in **1** and **2** by means of crystallographic and spectroscopic evidence and high-level theoretical calculations. According to these calculations, the NC−H···O interaction, established through a five-membered ring, vanishes in **3**, probably due to changes in the geometry of the molecule. These results, potentially useful in crystal engineering, stress the importance of directionality in hydrogen bonding.

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Supporting Information Available: Selected calculated parameters of **1**−**3** and ^{1}H NMR spectra of **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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