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Conformational study of *S*-alkylated isothiosemicarbazones

Alessandra Forni[a]* and Julieta Gradinaru[b]

[a]Istituto CNR di Scienze e Tecnologie Molecolari, via Golgi 19, I-20133 Milan, Italy, and [b]Institute of Chemistry of the Academy of Science of Moldova, Str. Academiei 3, MD-2028 Chisinau, Republic of Moldova

Correspondence e-mail: aforni@istm.cnr.it

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A theoretical investigation of the conformational preferences of *S*-alkylated isothiosemicarbazones was performed. The structures of such compounds cluster in two groups, according to the different orientation of the $-SR$ group with respect to the hydrazine N atom of the thiosemicarbazide. While the *trans* arrangement may be more stable for the isolated molecules, owing to N—H···N intramolecular interactions, the *cis* form is preferred by most compounds in the solid state, as the result of interplay between intra- and intermolecular effects.

1. Introduction

Derivatives of thiosemicarbazide, $N^1H_2-N^2H-C(=S)-N^3H_2$ (thsc), and *S*-alkylisothiosemicarbazide, $N^1H_2-N^2=C(-SR)-N^3H_2$ (S*R*-thsc), have received much attention because of their biological activity, which was shown to be related to their metal-complexing ability (Campbell, 1975; Padhyé & Kauffman, 1985; West *et al.*, 1993; Casas *et al.*, 2000).

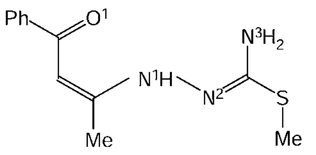
In the solid state, the thiosemicarbazide backbone is usually almost planar, but structures of thiosemicarbazones and *S*-alkylisothiosemicarbazones differ in the preferred relative disposition of the atoms N^1 and S with respect to the N^2-C bond. In the first derivatives, the S atom is generally *trans* to N^1, thus placing the N^1 and N^3 atoms in positions suitable for intramolecular hydrogen bonding (Chattopadhyay *et al.*, 1989; Casas *et al.*, 2000). On the other hand, derivatives of S*R*-thsc prefer the *cis* form (Shova *et al.*, 1985; Gerbeleu *et al.*, 1999; Casas *et al.*, 2000). A Cambridge Structural Database (CSD; Allen *et al.*, 1983) survey (Forni & Gradinaru, 2002) indicated that all but one of the 18 retrieved S*R*-thsc compounds have at least one NH group that could potentially act as a donor group in the opposite *trans* orientation, but only five of them adopt it.

These considerations prompted us to undertake a theoretical study aimed at understanding the relative importance of intra- and intermolecular forces in determining the relative stability of the two conformations in *S*-alkylisothiosemicarbazones. In this communication, we report the results of *ab initio* calculations on isolated molecules of selected S*R*-thsc derivatives, in both *cis* and *trans* orientation, in order to extract information about intramolecular effects.

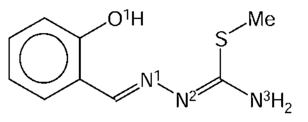
2. Conformational study

The four S*R*-thsc derivatives shown were chosen for the theoretical investigation. The first compound (I) (Forni & Gradinaru, 2002) is one of the few derivatives of S*R*-thsc where the $-SR$ group is *trans* to the N^1 atom, while (II) (CSD refcode CIWWAG; Argay *et al.*, 1983), (III) (GAZVOS; Bourosh *et al.*, 1987) and (IV) (DISKIZ; Simonov *et al.*, 1985) assume the *cis* orientation in the solid state. Compounds (I)–(III) present at least one NH group that could form an intramolecular hydrogen bond in the *trans* orientation, while (IV) is the only S*R*-thsc derivative where no potential NH donor is present. On the other hand, in (II)–(IV), as in all the *cis* S*R*-thsc derivatives, the S and N^1 atoms are favourably oriented to give intramolecular through-space 1,4 S···N interactions [$r_{S\cdots N}$ = 2.737, 2.705 and 2.801 Å, in (II), (III) and (IV), respectively], similar to the frequently observed 1,4 S···O interaction (Kucsman & Kapovits, 1985; Burling & Goldstein, 1992, 1993; Markham & Bock, 1997).

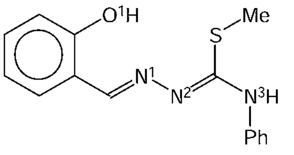
Geometry optimization of both conformations of (I)–(IV) was performed at several levels of theory using the *GAUSSIAN*98 program (Frisch *et al.*, 1998). In particular, restricted Hartree–Fock (RHF) calculations with several basis sets (3-21G*, 6-31G**, 6-31++G** and 6-311++G**) and B3LYP density functional calculations with only the



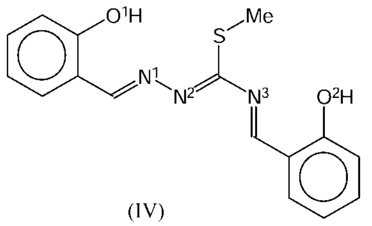
(I)



(II)



(III)



(IV)

larger basis sets were performed. It should be stressed that a full conformational analysis, which is beyond the aim of the present work, was not attempted. Optimization was limited to the two isomers having *cis* and *trans* configurations at the $N^2{=}C$ double bond, starting from the experimental geometry for one isomer and from the corresponding one with the opposite configuration at the $N^2{=}C$ double bond for the other isomer.

The experimental geometries were acceptably reproduced by the *ab initio* calculations on the molecules in the appropriate conformation, *i.e.* with the $N^1-N^2{=}C-S$ sequence *trans* for (I) and *cis* for (II)–(IV). The experimental and theoretical (RHF/6-31++G** and B3LYP/6-31++G**) geometries are compared in Table 1, where the values of the r.m.s. differences in bond distances (Δd), angles (Δa) and torsions (Δt) are reported. The r.m.s. differences were calculated on all geometrical parameters except those involving H atoms, which were completely missing in the structure of (III) and partially missing in (IV). The relatively high r.m.s. differences in the torsion angles of (I) and (IV) are ascribed to the rotation of side groups in the isolated (theoretical) molecules, *i.e.* the phenyl in (I) and one hydroxyphenyl in (IV), which in the crystal (experimental) are nearly coplanar with the thsc backbone. The values of the $N^1-N^2{=}C-S$ torsion angle χ, also reported in Table 1, indicate that the two *cis* and *trans* conformations were well described by theory in all cases.

The experimental geometry of the strongest intramolecular and intermolecular hydrogen bonds in (I)–(IV) is reported in Table 2. In the case of the intramolecular interactions, the corresponding theoretical values for the molecules in the appropriate conformation are also shown in Table 2. The pattern of hydrogen bonds was fully reproduced by the theoretical calculations, the lower agreement with respect to the other geometrical parameters being due to the well known errors in the X-ray location of H atoms. The shorter contact corresponds to a 1,6 $D-H\cdots A$ interaction in both (I) ($N^1-H\cdots O^1$) and (II)–(IV) ($O^1-H\cdots N^1$), suggesting that its presence should not affect the conformation adopted by the thsc group.

In Table 3, the computed $\Delta E = E_{\rm cis} - E_{\rm trans}$ energy differences are reported, a positive value indicating a greater stability of the *trans* form with respect to the *cis* form. RHF results obtained with different basis sets indicate that a fairly good convergence was generally attained at the larger basis set. B3LYP calculations confirmed RHF results as far as the different stability of the two conformations was concerned.

Table 1
Root-mean-square differences for bond distances Δd (Å), angles Δa (°) and torsions Δt (°) between experimental and theoretical geometries and $N^1-N^2{=}C-S$ torsion angles χ (°) in (I)–(IV).

Theoretical geometries obtained with the 6-31++G** basis set. All the geometrical parameters involving H atoms were excluded from the calculation of Δd, Δa and Δt. The optimized *trans*/*cis* geometry was used for (I)/(II)–(IV).

	(I)	(II)	(III)	(IV)
$\Delta d_{\rm RHF}$	0.023	0.021	0.014	0.015
$\Delta d_{\rm B3LYP}$	0.027	0.022	0.017	0.022
$\Delta a_{\rm RHF}$	1.5	1.3	1.4	1.0
$\Delta a_{\rm B3LYP}$	0.9	1.0	1.0	1.3
$\Delta t_{\rm RHF}$	13	6	6	18
$\Delta t_{\rm B3LYP}$	11	5	6	17
$\chi_{\rm exp}$	−179.5(2)	4.5	6.2	0.8
$\chi_{\rm RHF}$ (*cis*)	−6.2	−3.2	0.0	1.5
$\chi_{\rm B3LYP}$ (*cis*)	−8.5	−3.6	0.0	1.6
$\chi_{\rm RHF}$ (*trans*)	177.8	−178.7	173.4	179.9
$\chi_{\rm B3LYP}$ (*trans*)	177.1	−177.9	171.6	178.2

Table 2
Strongest hydrogen-bonding and short-contact geometry in compounds (I)–(IV) (Å, °).

The first line contains the experimental values, the second and the third lines contain the theoretical values (RHF/6-31++G** and B3LYP/6-31++G**, respectively).†

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
(I)				
$N^1-H\cdots O^1$	0.86	1.91	2.581 (3)	134
	1.001	*1.914*	*2.670*	*130*
	1.035	*1.727*	*2.592*	*138*
$N^1-H\cdots N^3$	0.86	2.32	2.667 (3)	104
	1.001	*2.463*	*2.659*	*90*
	1.035	*2.429*	*2.693*	*93*
$\mathbf{N^3}-H^{3B}\cdots O^{1(i)}$	0.86	2.08	2.898 (3)	157
$N^3-H^{3A}\cdots N^{3(i)}$	0.86	2.52	3.228 (4)	140
(II)				
$O^1-H\cdots N^1$	0.69	2.06	2.673	148
	0.953	*1.934*	*2.740*	*141*
	0.990	*1.792*	*2.668*	*146*
$N^3-H\cdots N2^{2(ii)}$	0.73	2.30	3.010	165
(III)‡				
$O^1-H\cdots N^1$	–	–	2.582	–
	0.952	*1.941*	*2.742*	*141*
	0.989	*1.799*	*2.674*	*146*
$O^1\cdots N^{3(iii)}$	–	–	3.085	–
(IV)				
$O^1-H\cdots N^1$	0.728	2.046	2.648	140
	0.953	*1.937*	*2.741*	*141*
	0.990	*1.790*	*2.663*	*145*
$O^2-H\cdots N^3$	0.855	1.889	2.616	142
	0.953	*1.905*	*2.722*	*142*
	0.995	*1.742*	*2.635*	*147*

Symmetry codes: (i) $1-x, -1-y, -z$; (ii) $1-x, -y, 1-z$; (iii) $-x, \frac{1}{2}+y, \frac{1}{2}-z$. † *trans* geometry for (I), *cis* geometry for (II)–(IV). ‡ H atoms are missing in the structure of compound (III).

Table 3
Computed ΔE energy differences (kcal mol^{-1}) between *cis* and *trans* conformations.

	$\Delta E = E_{\rm cis} - E_{\rm trans}$					
Compound	RHF/3-21G*	RHF/6-31G**	RHF/6-31++G**	RHF/6-311++G**	B3LYP/6-31++G**	B3LYP/6-311++G**
(I)	3.967	3.379	3.630	3.503	2.469	2.541
(II)	4.451	3.317	3.507	3.486	1.958	2.131
(III)	−2.695	−0.364	0.026	−0.177	−1.737	−1.750
(IV)	−2.690	−1.364	−1.245	−1.318	−1.858	−1.570

All calculations on (I) and (II) resulted in a positive ΔE value. The greater stability of the *trans* form can be clearly explained by the formation of an intramolecular hydrogen bond [$\rm N^1{-}H\cdots N^3$ in (I), $\rm N^3{-}H\cdots N^1$ in (II)]. This interaction is then preferred to the 1,4 $\rm N^1\cdots S$ contact that would take place in the opposite conformation. Moreover, a somewhat weak interaction, as indicated by the relatively small ΔE values, had to be anticipated, owing to geometrical constraints placing the interacting atoms far from the ideal linear arrangement [see the $\rm N^1{-}H\cdots N^3$ angle of (I) in Table 2].

When considering the conformation assumed by the two compounds in the solid state, one can deduce that in (II), which crystallizes in the less stable *cis* orientation, intermolecular forces, such as the nearly linear $\rm N^3{-}H\cdots N^2{}_{1-x,-y,1-z}$ hydrogen bond, predominate over the weak intramolecular $\rm N{-}H\cdots N$ interaction.

In (IV), intramolecular hydrogen bonds within the thsc unit cannot occur and the *cis* form, which is stabilized by the 1,4 $\rm N^1\cdots S$ through-space interaction and takes the phenyl rings far away from each other, becomes the more stable one. In the case of (III), the *trans* conformation, while allowing the formation of an intramolecular $\rm N^3{-}H\cdots N^1$ bond, brings the phenyl rings too close to each other. Interplay between the two effects results in nearly comparable RHF energy values for the two conformations when the larger basis sets are considered but in a greater stability of the *cis* form as far as DFT results are concerned. The preferred orientation of (III) and (IV) in both gas and crystal phase can then be explained by taking into account only intramolecular effects.

We can then conclude the following:

(i) The preference of S*R*-thsc derivatives in the solid state towards the *cis* orientation of the —S*R* group with respect to the hydrazine N atom cannot be ascribed, as a rule, to intramolecular effects alone. They are sufficient to explain the adopted conformation in compounds such as (III) and (IV), where steric effects may assume an important role.

(ii) In the absence of steric hindrance, as in most of the S*R*-thsc derivatives retrieved from the CSD, the molecular conformation in the solid state results from an interplay between intra- and intermolecular forces. While the possibility of an intramolecular $\rm N{-}H\cdots N$ interaction clearly favours the *trans* orientation, as demonstrated by the calculations on (I) and (II), generally this interaction seems to be of minor importance with respect to packing forces, which drive the compounds towards the opposite arrangement. As a consequence, most S*R*-thsc derivatives unexpectedly assume in the solid state the less stable *cis* conformation, as shown by (II).

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