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Structural, topological and vibrational properties of an isothiazole derivatives series with antiviral activities

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ABSTRACT

In this work, the structural, topological and vibrational properties of an isothiazole derivatives series with antiviral activities in gas and aqueous solution phases were studied by using DFT calculations. The self consistent reaction field (SCRF) method was combined with the polarized continuum (PCM) model in order to study the solvent effects and to predict their reactivities and behaviours in both media. Thus, the 3-mercapto-5-phenyl-4-isothiazolecarbonitrile (I), 3-methylthio-5-phenyl-4-isothiazolecarbonitrile (II), 3-Ethylthio-5-phenyl-4-isothiazolecarbonitrile (III), *S*-[3-(4-cyano-5-phenyl)isothiazolyl] ethyl thiocarbonate (IV), 5-Phenyl-3-(4-cyano-5-phenylisothiazol-3-yl) disulphanyl-4-isothiazolecarbonitrile (V) and 1,2-Bis(4-cyano-5-phenylisothiazol-3-yl) sulphanyl Ethane (VI) derivatives were studied by using the hybrid B3LYP/6-31G* method. All the properties were compared and analyzed in function of the different R groups linked to the thiazole ring. This study clearly shows that the high polarity of (I) probably explains its elevated antiviral activity due to their facility to traverse biological membranes more rapidly than the other ones while in the (IV) and (V) derivatives the previous hydrolysis of both bonds increasing their antiviral properties inside the cell probably are related to their low S-R bond order values. In addition, the complete vibrational assignments and force constants are presented.

1. Introduction

Our investigations are focalized on the study of derivatives of five/six members heterocycles linked or fused to one benzene ring such as, benzothiazol, benzofuran, benzimidazole, benzoxazine, benzopyran and quinazoline derivatives [1–6] because they present a broad range of biological activities, including antiviral, antitumour, antibacterial, and anti-inflammatory activities and, for these reasons, they are of great chemical, pharmacological and medicinal interest [7–14]. In this sense, the knowledge of all their properties, in particular the structural property is significant in the organic chemistry of synthesis for the design of new drugs with better properties [7–14]. In this work, in order to provide new insights to the structural, electronic, topological and vibrational properties of six members of an isothiazole derivatives series, which were synthesized by Cutri et al. [15–18] as HIV replication inhibitors agents, are evaluated in gas and aqueous solution phases because, so far, these properties for those six species were not reported. All these derivatives have a common structure constituted by the isothiazole ring (Th) where three H atoms are replaced respectively by a phenyl ring (Ph) and the C≡N and R groups whose structures have a simplified molecular formula: PhThCNS-R, where R is constituted by the different −H, $-CH_3$, $-CH_2-CH_3$, $-COO-CH_2-CH_3$, −SCNThPh, and $-(CH_2)_2-$SCNThPh moieties and, whose chemical names are: 3-mercapto-5-phenyl-4-isothiazolecarbonitrile, 3-methylthio-5-phenyl-4-isothiazolecarbonitrile, 3-Ethylthio-5-phenyl-4-isothiazolecarbonitrile, *S*-[3-(4-cyano-5-phenyl)isothiazolyl] ethyl thiocarbonate, 5-Phenyl-3-(4-cyano-5-phenylisothiazol-3-yl) disulphanyl-4-isothiazolecarbonitrile and 1,2-Bis(4-cyano-5-phenylisothiazol-3-yl) sulphanyl Ethane. Here, all these molecules were theoretically modelled and optimized by using the hybrid B3LYP method with the 6-31G* basis set in gas phase and in aqueous solution [19,20]. The solvent effects and the solvation energies of those six species were studied by using the SCRF calculations with the PCM and SMD models [21–23]. The volume variations that experiment these species when the medium changes from the gas phase to the aqueous solution were

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computed by using the Moldraw program [24] while the natural population atomic charges (NPA), bond orders, stabilization energies and topological properties were calculated by using the NBO [25,26] and AIM [27,28] calculations. Besides, the molecular electrostatic potentials derived from the Merz-Kollman (MK) charges [29] were employed in order to localize those possible electrophilic and nucleophilic sites of each species while the highest occupied molecular orbital (HOMO) and the lowest occupied molecular orbital (LUMO) orbitals were computed to calculate the corresponding gap energies and some useful descriptors [30–35] in order to predict their reactivities and behaviours in both media. In this work, the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and global nucleophilicity index (ε) [30–34] descriptors were calculated. Here, this latter index was recently proposed by Kiyooka et al. [35]. On the other hand, to identify these six species in both media by using the vibrational spectroscopy it is necessary to perform the complete assignments of all the vibration modes, thus, the SQM methodology [36] and the Molvib program [37] were used to calculate the force fields of all the species by using the internal normal coordinates. Therefore, in the present work the force constants together with the corresponding force fields were also calculated by using the hybrid B3LYP/6-31G* method. In addition, the infrared and Raman spectra predicted by using the same level of theory were compared in both media. Here, the structural and vibrational properties studied were evaluated in function of the number of C atoms belonging to the different R groups linked to the isothiazole ring. In addition, the different donor and acceptor sites of H bonds formation in each isothiazole derivative were clearly identified. Finally, our results highly justify those results reported by Cutrí et al. [15] in which the presence of a thioalkyl chain in the 3-position, these are in the (II), (III) and (VI) derivatives caused a loss of anti-HIV activity and, also, why the (I), (IV) and (V) derivatives are effective against both HIV-1 and HIV-2.

2. Computational details

The structure of the common isothiazole (Th) skeleton showing the different phenyl (Ph), C≡N and R (H, CH_3, CH_2–CH_3, SCNThPh, COO–CH_2–CH_3 and $(CH_2)_2$–SCNThPh) groups together with their corresponding molecular formulae can be seen in Fig. S1 while their corresponding names and identifications are summarized in Table 1. Initially, the structures of these six derivatives were modelled by means the *GaussView* program [38] and, later their structures were optimized in gas phase by using the hybrid B3LYP/6-31G* method [19,20] with the Gaussian 09 package program [39]. It is necessary to clarify that the potential energy curves (PECs) were studied for all the derivatives and that, of all those conformations with minima energies, only the properties observed for those most stable structures were here presented. In fact, for the compounds I and II, the PECs described by the N2–C3–S19–H20 and N2–C3–S19–C20 dihedral angles, respectively show only two conformations with minima energies for each compound while in the compound III the PECs described by the N2–C3–S19–C20 and C3–S19–C20–C23 dihedral angles show a total of five conformations. For the compound IV, the PECs described by the N2–C3–S19–C20, C3–S19–C20–O21, C3–S19–C20–O22, S19–C20–O22–C23 and C20–O22–C23–C24 dihedral angles predicted eleven conformations while, in the compound V, the PECs described by the N2–C3–S19–S20 and C3–S19–S20–C21 dihedral angles show only three conformations with minima energies. Finally, for VI the PECs described by the N2–C3–S19–C42, C3–S19–C42–C39, N22–C21–S20–C39, C21–S20–C39–C42 and S19–C42–C39–S20 dihedral angles show eleven conformations with minima energies. The six most stable structures together with the corresponding labelled atoms are presented in Fig. 1. The optimization of each structure in aqueous solution was performed

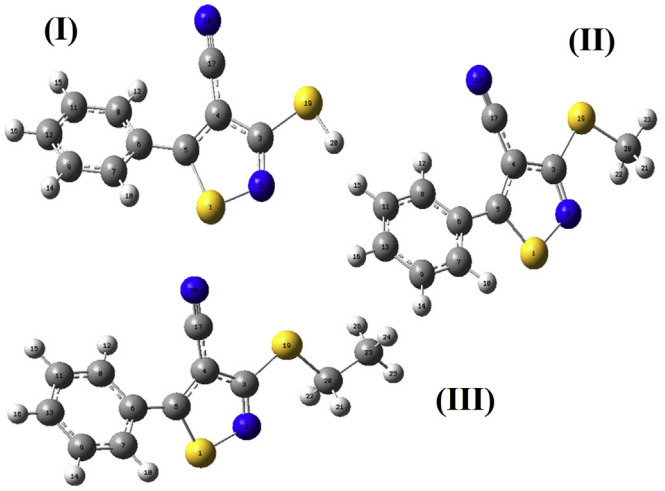

Fig. 1. Theoretical molecular structures of 3-mercapto-5-phenyl-4-isothiazolecarbonitrile, 3-methylthio-5-phenyl-4-isothiazolecarbonitrile and 3-ethylthio-5-phenyl-4-isothiazolecarbonitrile and the atoms numbering.

Table 1
Calculated total energy (E), dipolar moment (μ) and volume values for the series of isothiazolecarbonitrile studied.

GAS PHASE/B3LYP/6-31G* method						
Series	PhThCNS-R	Names	Nº C atoms	E (Hartrees)	μ (Debye)	V_G(Å^3)
I	–H	3-Mercapto-5-phenyl-4-isothiazolecarbonitrile	0	−1290.5291	4.08	205.2
II	–CH_3	3-Methylthio-5-phenyl-4-isothiazolecarbonitrile	1	−1329.8470	3.75	228.3
III	–CH_2–CH_3	3-Ethylthio-5-phenyl-4-isothiazolecarbonitrile	2	−1369.1616	3.61	246.2
IV	–COO–CH_2–CH_3	*S*-[3-(4-cyano-5-phenyl)isothiazolyl] ethyl thiocarbonate	3	−1557.7192	2.28	282.0
V	–SCNThPh	5-Phenyl-3-(4-cyano-5-phenylisothiazol-3-yl) disulphanyl-4-isothiazolecarbonitrile	10	−2579.8538	0.0	398.8
VI	–$(CH_2)_2$–SCNThPh	1,2-Bis(4-cyano-5-phenylisothiazol-3-yl) sulphanyl Ethane	12	−2658.4934	0.21	440.0
Aqueous solution PCM/B3LYP/6-31G* method						
Series	**PhThCNS–R**	**Names**	**Nº C atoms**	***E* (Hartrees)**	**μ (Debye)**	**V_{AS} (Å^3)**
I	–H	3-Mercapto-5-phenyl-4-isothiazolecarbonitrile	0	−1290.5372	5.56	209.5
II	–CH_3	3-Methylthio-5-phenyl-4-isothiazolecarbonitrile	1	−1329.8544	5.07	226.5
III	–CH_2–CH_3	3-Ethylthio-5-phenyl-4-isothiazolecarbonitrile	2	−1369.1689	4.94	244.6
IV	–COO–CH_2–CH_3	*S*-[3-(4-cyano-5-phenyl)isothiazolyl] ethyl thiocarbonate	3	−1557.7297	3.42	279.4
V	–SCNThPh	5-Phenyl-3-(4-cyano-5-phenylisothiazol-3-yl) disulphanyl-4-isothiazolecarbonitrile	10	−2579.8676	0.0	398.2
VI	–$(CH_2)_2$–SCNThPh	1,2-Bis(4-cyano-5-phenylisothiazol-3-yl) sulphanyl Ethane	12	−2658.5076	0.26	439.4

Abbreviations: Ph: phenyl ring, C_6H_5; Th: isothiazole ring, C_3NS.