Computational and Theoretical Chemistry 1005 (2013) 35–44

Contents lists available at SciVerse ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

On constitutional isomers and tautomers of oxadiazolones and their mono- and disulfur analogues ($C_2H_2N_2XY$; X, Y = S, O)

Grażyna Karpińska [a], Jan Cz. Dobrowolski [a,b,*]

[a] National Medicines Institute, 30/34 Chełmska Street, 00-725 Warsaw, Poland
[b] Industrial Chemistry Research Institute, 8 Rydygiera-Street, 01-793 Warsaw, Poland

ARTICLE INFO

Article history:
Received 19 October 2012
Received in revised form 5 November 2012
Accepted 6 November 2012
Available online 29 November 2012

Keywords:
Oxadiazolone
Thiadiazolone
Constitutional isomers
Tautomers
Sulfur derivatives
DFT

ABSTRACT

The constitutional isomers and tautomers of oxadiazolones, as well as their mono- and disulfur analogues, were calculated at the B3LYP/aug-cc-pVDZ level. Four groups of 30 molecules each were considered: oxadiazolone, oxadiazolthione, thiadiazolone, and thiadiazolthione isomers. The compounds were categorized into six groups according to permutations of three heteroatoms in the five-membered ring. Additionally, each of the constitutional isomer was considered to have five tautomers conserving stable five-membered ring: two NH tautomers, two rotameric OH (or SH) forms and one CH_2 tautomer. It appeared that the largest difference between oxadiazolone O and S analogues is produced by the kind of chalcogen atom in the ring, which is strained when the O atom is in the ring while much less strained when the S-atom, of much larger van der Waals radius, is built into the ring. The external chalcogen is only modifying the general energetic factors. The comparison of energetics of analogous groups of molecules with thiadiazole and oxadiazole rings is done in details as well as differences resulting from different external chalcogen atoms are discussed as well. The presence of water surrounding was mimicked with the IEF-PCM implicit water model which did not change general isomer relative stability picture, but for some special cases indicated an extra stability of the forms with external OH or SH groups. The aromaticity monitored by the structural HOMA aromaticity index shows that the systems are not additionally stabilized by pi-electron delocalization. The fair linear correlation between the aromaticity indices of oxadiazolones and oxadiazolthiones shows that the pi-electron system in the studied systems is not sensitive to change of the external chalcogen group.

1. Introduction

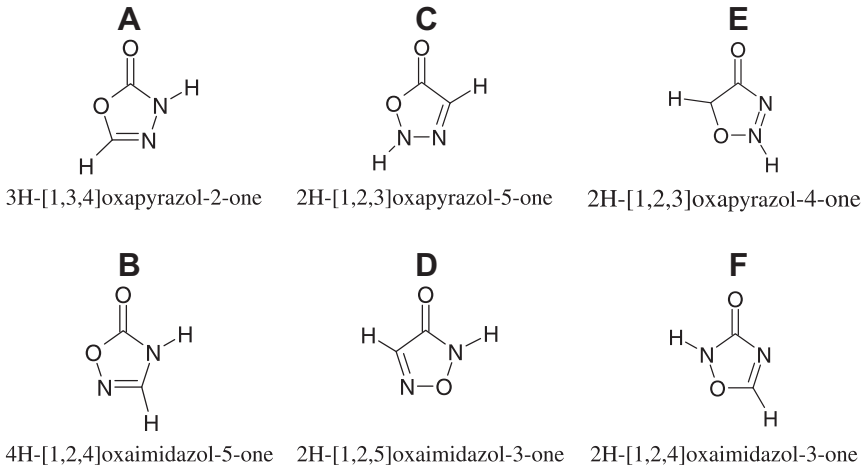
The oxadiazoles are diazoles with an additional oxygen atom built into the five-membered diazole ring, whereas in oxadiazolone isomers an additional carbonyl group is attached to one of the ring carbon atom (Scheme 1). This class of heterocycles is important for medicinal chemistry and organic synthesis. Indeed, the oxadiazole derivatives exhibit a wide range of biological activity: they are partial agonists of 5-HT_4 [1], 5-HT_{1B} serotonin receptors [2], inhibitors of severe acute respiratory syndrome [3], and exhibit antibacterial activity [4]. Moreover, they are building blocks for anti-inflammatory [5], antifungal [6–8], antiparasitic [9], and antimicrobial [10–13] drugs. In addition, they show anticonvulsant [14], anti-HIV [15], and antituberculostatic activity [16]. They have also been used in pesticide chemistry [17], polymer [18], and material science [19–21]. Owing to their manifold activity, still new oxadiazole derivatives are synthesized and examined for their biological activity to search for and develop desired properties such as, for example, analgesic, antiviral, or anticancer activity [5,22].

Despite of importance of oxadiazoles to pharmacy and medicine, so far, very little computational work has been devoted to oxadiazoles and there was no systematic computational study on their isomerism and stability. For instance, the calculated spectral properties of alkoxy 1,3,4-oxadiazoles were shown to depend mainly on the HOMO orbital [23]. Also, the vibrational spectra were calculated and analyzed for 2-aryl-1,3,4-oxadiazole derivatives [24]. Thermal stability and the pyrolysis mechanism of 2,5-dipicryl-1,3,4-oxadiazole were studied at the UB3LYP/6-31G* level [25,26]. The intramolecular proton-transfer process, rotational process, and optical properties were studied for 1,3,4-oxadiazoles with TD-DFT methods [27]. The hyperpolarizability and molecular frontier orbital energy of some donor–acceptor oxadiazoles were investigated in the context of possible non-linear optical properties by *ab initio* and DFT methods [28]. The luminescence properties of selected oxadiazoles were successfully supported by DFT calculations [29].

The aim of this study was to determine tautomeric preferences of constitutional isomers of oxadiazolone and their tautomers as

* Corresponding author at: National Medicines Institute, 30/34 Chełmska Street, 00-725 Warsaw, Poland. Tel.: +48 22 568 2421.
E-mail address: janek@il.waw.pl (J.Cz. Dobrowolski).

2210-271X/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.comptc.2012.11.003



Scheme 1.

well as their sulfur isomers of general formula ($C_2H_2N_2XY$; X, Y = S, O). So far, there was no systematic computational study on stability of these compounds. The results presented here are expected to be helpful in projecting syntheses and in more reliable consideration of tautomers in drug design.

2. Calculations

All the calculations were performed using the hybrid B3LYP DFT functional [30,31] whose reliability in calculations of the ground state geometries has been widely assessed [32]. The aug-cc-pVDZ basis set was employed [33–36]. This basis set is known to be fair in describing both organic molecules and their hydrogen-bonded systems [32,36]. For each optimized structure all harmonic vibrational frequencies were positive, so all structures correspond to molecules in their minima of potential energy hypersurfaces. The relative abundance of the most stable conformations was then estimated by using the Gibbs free energy referred to the most stable isomer. All the calculations were performed using the Gaussian 03 program [37].

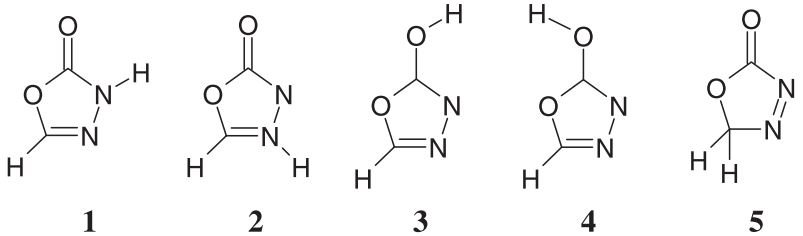
Estimation of relative stability of series of isomers is one of the main objective of this study. The error of energy differences is therefore an important and delicate issue. Indeed, it is known that for set of molecules belonging to different structural classes the absolute error in energy (heats of formation) may exceed 10 kcal/mol [38]. However, for selected type of reactions and small variation of functional groups, the error can be reduced to ca. 1 kcal/mol [39,40]. Nevertheless, a careful verification of the error of energy differences was beyond this study. Here, we deal with relative Gibbs free energies of series of constitutional isomers and tautomers. In such a case, several terms, that would introduce additional errors, are canceled. Therefore, we roughly estimate the error to ca. 2 kcal/mol. It is clear, that the differences placed within 2 kcal/mol interval must be treated with caution, yet, we believe that large differences estimated in this study cannot be reversed by an increased level of theoretical approximation.

3. Results and discussion

When studying all possible constitutional isomers of oxadiazolone preserving five-membered ring with the second O-atom attached to the ring, one has to consider all permutations of the three heteroatoms in the ring except the C-atom to which the external heteroatom is attached to. There are three different constitutional isomers with two adjacent N-atoms, derivatives of oxapyrazolone, and analogously there are three derivatives of oxaimidazolone, where the two N-atoms are separated either by C or O-atom (Scheme 1). All these types are labeled by the letters from A to F (Scheme 1). Each of the above compounds may undergo tautomeric changes related to the attachment of the "acidic" H-atom either to one of the N-atoms in the ring, the external heteroatom, or possibly to the C-atom in the ring to form CH_2 group (Scheme 2). These tautomers are labeled by numbers from 1 to 5. Attachment of the H-atom to the ring O or S atom results in ring opening and such non-heterocyclic structures are not considered further. Thus, in this study we considered 30 of $C_2H_2N_2O_2$ and 30 of $C_2H_2N_2S_2$ structures as well as 30 of $C_2H_2N_2OS$ and 30 of $C_2H_2N_2SO$ structures differing by external or internal position of the S-atom. However, not all considered structures appeared to be stable at the chosen computational level.

3.1. Oxadiazolone isomers

The schemes of the B3LYP/aug-cc-pVDZ optimized constitutional isomers of 3H-[1,3,4]oxapyrazol-2-one (A1) and their tautomers are gathered in Table 1. The Gibbs free energies referred



Scheme 2.