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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)

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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

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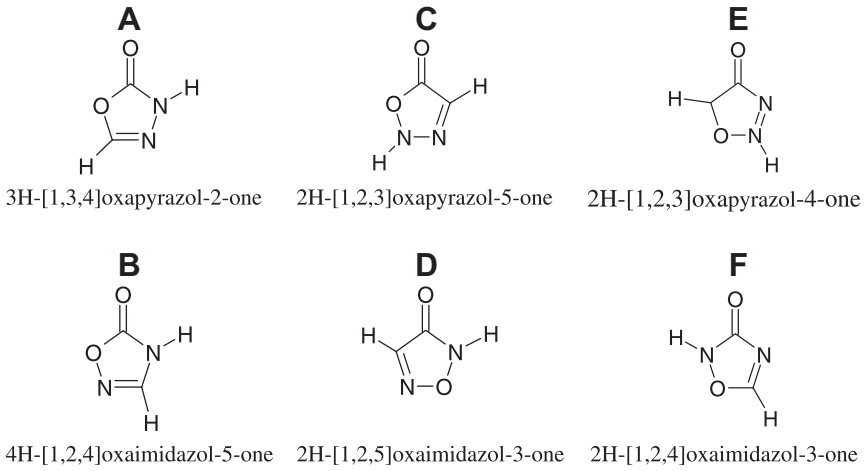
http://dx.doi.org/10.1016/j.comptc.2012.11.003



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].

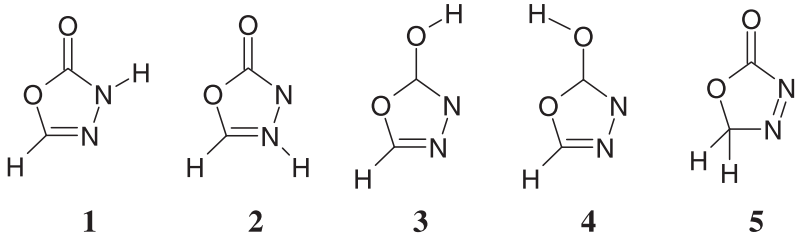
Estimation of relative stability of series of isomers is one of the main objective of this study. The error of energy differences is therefore an important and delicate issue. Indeed, it is known that for set of molecules belonging to different structural classes the absolute error in energy (heats of 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.

to the most stable constitutional isomer are given in square brackets, whereas the Gibbs free energies referred to the most stable tautomer of a particular constitutional isomer (comparison in rows) are given in parentheses. The following conclusions can be drawn from the inspection of Table 1:

Out of all oxadiazolone isomers, 3H-[1,3,4]oxapyrazol-2-one (A1) is the most stable. The next most stable is 4H-[1,2,4]oxaimidazol-5-one (B1), however, it is higher in Gibbs free energy than A1 by as much as 10 kcal/mol. 2H-[1-3]oxapyrazol-5-one (C1) and its tautomers (C2—C5) are less stable than A1 by at least 34 kcal/mol. Surprisingly, in the group of C1 tautomers, the CH_2 tautomer is the most stable. The tautomers of 2H-[1,2,4]oxaimidazol-3-one (D1) are even less stable: the stablest of them, D4, is less stable than A1 by ca 48 kcal/mol. Also the tautomers of 2H-[1-3]oxapyrazol-4-one (E1) are quite unstable: the most stable one (E3) is less stable than A1 by ca. 40 kcal/mol. Finally, the tautomers of 2H-[1,2,5]oxaimidazol-3-one (F1) form a group which is not very unstable since the stablest tautomer (F4) is less stable than A1 by ca. 20 kcal/mol.

In this moment one can formulate crude rules for stability of oxadiazolone isomers. The structures in which the three ring heteroatoms are separated by the CH group, e.g., structure types A, B and E, exhibit relative free Gibbs energy not higher than ca.12 kcal /mole. Moreover, oxadiazolone isomers with three neighboring heteroatoms, e.g., structure type C, D and F, are very unstable and their relative free Gibbs energy is higher than 35 kcal/mol. In A, B and E structures, the most stable, are those with the lactone group, and the least stable are cyclic urea analogues.

Let us now consider the columns in Table 1. The NH tautomers are placed in columns 1 and 2, the two rotamers of the OH tautomer in columns 3 and 4, and the CH_2 tautomers in column 5. The oxadiazolone isomers exhibit two double bonds which migrate as the acidic H-atom jumps between the electronegative centers (N, O, and C atoms). However, some of the tautomers cannot be easily represented by a classical structural formula, because, it is not possible to draw one of the double bonds in the manner satisfying classical valency rules. In other words, there is no unequivocal match of the double bonds in the ring. These structures are called non-Kekuléan, while those for which the unequivocal match exists, are called Kekuléan. Observe that the entire column 2 contains only non-Kekuléan structures. There are another four non-Kekuléan structures in positions B5, D5, F5, and E1 in Table 1. Observe also that in each group of tautomers (A–F), the non-Kekuléan structures are always the least stable ones, or even non-existing as a five-membered heterocycle (Table 1). Finally, let us stress that the most stable tautomers in the D, E, and F groups are the OH-tautomers stabilized by an intramolecular hydrogen bond (D4, E3, and F4, respectively), however, their rotamers (D3, E4, and F3) are almost equally stable.

Summing up this section, all the structures presented in Table 1, but 3H-[1,3,4]oxapyrazol-2-one and 4H-[1,2,4]oxaimidazol-5-one, seem to be unstable and hardly observable. However, some unstable structures can be synthesized by a clever method and therefore, cannot be a priori ruled out from considerations. This is why, we think that at least both 2H-[1,2,5]oxaimidazol-3-one and its OH tautomers are worth to be taken into account.

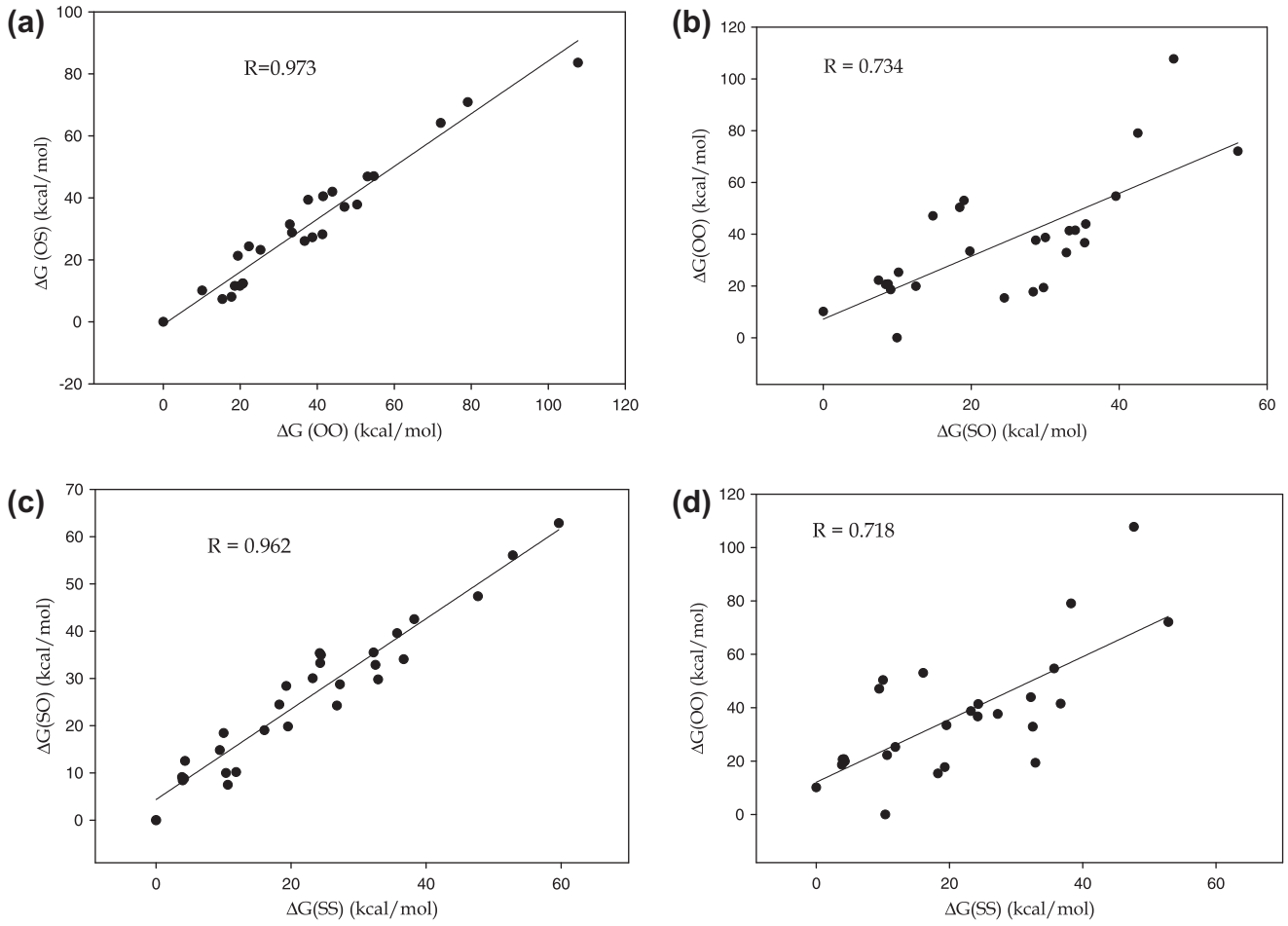


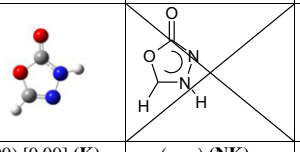
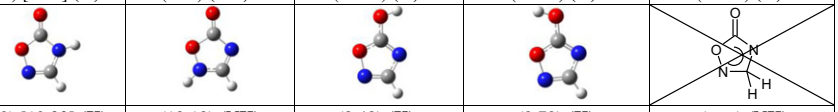
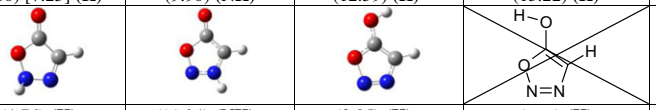
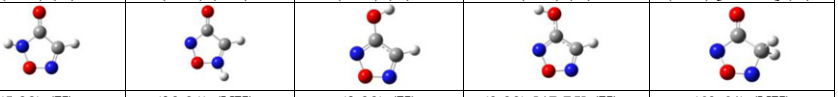
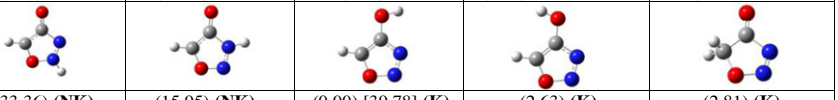
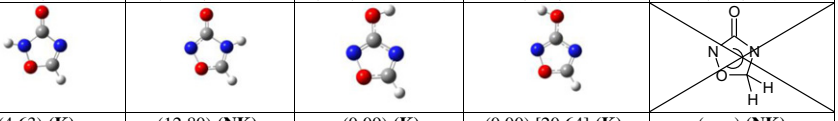
Fig. 1. Correlations between relative Gibbs free energies of (a) oxadiazolones and oxadiazoltiones, (b) thiadiazolones and oxadiazolones, (c) thiadiazolthiones and thiadiazolones, and (d) thiadiazolthiones and oxadiazoltiones. The $\Delta G(XY)$ notation means that the X atom is incorporated in the ring whereas the Y atom is the external one.

3.2. Oxadiazolthione isomers

In the oxadiazolthione isomers the heterocyclic ring remains identical to that of oxadiazolone isomers but the external heteroatom is S instead of O (Table 2). Since in oxadiazolthione isomers the heterocyclic ring strain remains very similar to that in oxadiazolone isomers we expected that energetic differences between isomers and tautomers remain similar. This is indeed the truth which is reflected by good linear correlation between relative Gibbs free energies of oxadiazolones and corresponding oxadiazolthiones (Fig. 1a). There are however some differences related to the fact that the substituent effect produced by the OH and SH groups, as well as by the C=O and C=S moieties, are different. Indeed, in monosubstituted benzenes, the OH group withdraws ca. 0.56 *e* from the sigma orbitals while donate ca. 0.12 *e* to the pi electron system of benzene, whereas the SH group withdraws ca. 0.15 *e* from sigma orbitals and donates ca. 0.09 *e* to the pi electron system [41]. The differences in action of the external O and S atoms in the C=O and C=S groups on heterocyclic system are connected to so called "natural" pi electronegativity of the two atoms which is equal to ca. 3.43 and 2.86, respectively [42], and which can be also reflected by recently constructed pEDA(=) descriptor [43].

The Gibbs free energy differences presented in Table 2 show that, in full analogy to the previously described oxadiazolone isomers, the 3H-[1,3,4] oxapyrazol-2-thione (A1) is the most stable oxadiazolthione structure. However, in contrast to data collected in Table 1, the oxapyrazol-2-thione tautomers, A3 and A4, are the next most stable forms. For oxadiazolthione isomers, the energy difference between A1 and B1 molecules is almost equal to that for oxadiazolone isomers. Yet now, the B1 molecule is less stable than A3 and A4 forms. The B1 form is the most stable in the B-type tautomers. However, the B3 and B4 rotamers are first, degenerated energetically and second, they are only 1.5 kcal/mol less stable than the B1 form. In oxadiazolone isomers the B3 and B4 rotamers themselves are separated by ca. 1.5 kcal/mol. This is a consequence of the difference between stabilizing and destabilizing factors coexisting when the intramolecular XH···Y hydrogen bonds is formed (where X= O for oxadiazolone isomers and X= S for oxadiazolthiones isomers and Y= O and N in the two cases) The XH···Y intramolecular hydrogen bond is always stabilizing but much stronger for the OH···Y than the SH···Y moiety, because the O atom is more electronegative than the S atom. In the B3 and B4 rotamers, two different electronegative elements, N and O, are adjacent to the XH group. So, formation of the intramolecular hydrogen bond with one of them, simultaneously results in a close

Table 1
The relative Gibbs free energies (kcal/mol) of oxadiazolone constitutional isomers and tautomers calculated based on B3LYP/aug-cc-pVDZ (gas, G) and B3LYP/IEF-PCM/aug-cc-pVDZ (water, W) levels. K and NK stand for Kekuléan and non-Kekuléan, respectively. The values in square brackets show difference to the most stable thiadiazolthione isomer while the values in parentheses show difference to the most stable tautomer of given type.

oxadiazolones					
	NH		**OH**		**CH_2**
	1	**2**	**3**	**4**	**5**
A					
G	(0.00) [0.00] **(K)**	(-----) **(NK)**	(15.36) **(K)**	(17.74) **(K)**	(19.37) **(K)**
W	(0.00) [0.00] **(K)**	(-----) **(NK)**	(15.42) **(K)**	(16.25) **(K)**	(19.56) **(K)**
B					
G	(0.00) [10.33] **(K)**	(12.12) **(NK)**	(8.48) **(K)**	(9.79) **(K)**	(-----) **(NK)**
W	(0.00) [7.25] **(K)**	(9.90) **(NK)**	(12.59) **(K)**	(13.22) **(K)**	(-----) **(NK)**
C					
G	(4.76) **(K)**	(11.04) **(NK)**	(3.85) **(K)**	(-----) **(K)**	(0.00) [34.66] **(K)**
W	(4.81) **(K)**	(6.79) **(NK)**	(3.65) **(K)**	(-----) **(K)**	(0.00) [33.217] **(K)**
D					
G	(5.99) **(K)**	(32.01) **(NK)**	(3.29) **(K)**	(0.00) [47.75] **(K)**	(60,64) **(NK)**
W	(4.21) **(K)**	(19.88) **(NK)**	(0.91) **(K)**	(0.00) [48.81] **(K)**	(40.34) **(NK)**
E					
G	(33.36) **(NK)**	(15.95) **(NK)**	(0.00) [39.78] **(K)**	(2.63) **(K)**	(2.81) **(K)**
W	(23.97) **(NK)**	(12.46) **(NK)**	(0.00) [40.88] **(K)**	(0.38) **(K)**	(2.18) **(K)**
F					
G	(4.63) **(K)**	(12.80) **(NK)**	(0.09) **(K)**	(0.00) [20.64] **(K)**	(-----) **(NK)**
W	(0.84) **(K)**	(3.53) **(NK)**	(0.03) **(K)**	(0.00) [21.68] **(K)**	(-----) **(NK)**

repulsive contact of the lone electron pairs of the second of them. However, the C—S distance is much longer than C—O one, and both the attractive and repulsive interactions are small and not differentiating the B3 and B4 rotamers.

Comparison of the energetics of the corresponding pairs of the OH and SH rotamers presented in Tables 1 and 2, shows that the significant differentiation between OH rotamers and slight differentiation of the SH rotamers is a kind of a rule in the oxadiazolone and oxadiazolthione structures. Indeed, each pair of the OH rotamers, but F3 and F4 for which the adjacent heteroatoms are the same, are separated energetically by at least 2.3 kcal/mol (Table 1). The largest difference occurs when instead of adjacent heteroatom the CH group is located (D3, D4; E3, E4). In the case of oxadiazolthione isomers, the maximum difference also occurs for situations when CH group is adjacent to the SH one, yet, it does not exceeds 1 kcal/mol (Table 2).

Observe that as for oxadiazolone isomers, the structures in the second column and B5, D5 and F5 entries correspond to the non-Kekuléan forms, which are the least stable forms in each row of the Table 2. Finally, let us stress that the most stable tautomers in the C, D, E, and F groups are the SH-tautomers stabilized by the intramolecular hydrogen bond (D4, E3, and F4, respectively), however, their rotamers (D3, E4, and F3) are almost equally stable.

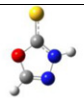
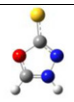
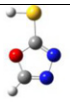
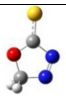
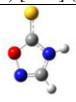
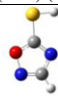
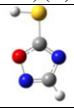
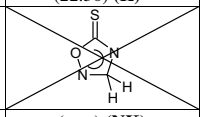
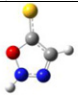
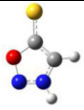
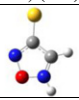
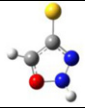
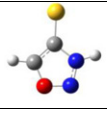
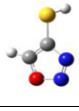
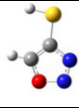
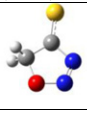
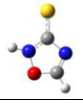
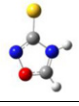
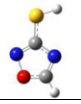
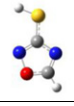
In general, the crude rules formulated for stability of oxadiazolone isomers are roughly conserved for oxadiazolthiones isomers. The most stable is always the Kekuléan structure and the least stable tautomer is the non-Kekuléan one.

3.3. Thiadiazolone isomers

The thiadiazolone isomers (Table 3) differ from oxadiazolone ones (Table 1) by the presence of the S-atom incorporated in the ring in the place of the O-atom. This is important difference because the S-atom has significantly larger van der Waals radius than that of the O-atom. In consequence, the ring in thiadiazolone isomers is much less strained than that in oxadiazolone isomers and thiadiazolone isomers are formed easier. Moreover, the energetical differences between the constitutional isomers A-F are smaller than for oxadiazolone isomers (Table 3). This is also the reason why the linear correlation between relative Gibbs free energies of thiadiazolones and corresponding oxadiazolones is significantly weaker (Fig. 1b) than in the case when the inserted heteroatom in the ring is the same (Fig. 1a).

Unexpectedly, for thiadiazolone isomers the most stable is the B1 isomer (4H-1-thiaimidazol-5-one, Table 3). Furthermore, the F3 isomer (1-thiaimidazol-3-ol), separated from the B1 form by

Table 2
The relative Gibbs free energies (kcal/mol) of oxadiazolthione constitutional isomers and tautomers calculated based on on B3LYP/aug-cc-pVDZ (gas, G) and B3LYP/IEF-PCM/aug-cc-pVDZ (water, W) levels. K and NK stand for Kekuléan and non-Kekuléan, respectively. The values in square brackets show difference to the most stable thiadiazolthione isomer while the values in parentheses show difference to the most stable tautomer of given type.

	oxadiazolthiones				
	NH		**SH**		**CH_2**
	1	**2**	**3**	**4**	**5**
A					
G	(0.00) [0.00] **(K)**	(17.50) **(NK)**	(7.35) **(K)**	(8.07) **(K)**	(21.30) **(K)**
W	(0.00) [0.00] **(K)**	(8.88) **(NK)**	(8.76) **(K)**	(8.96) **(K)**	(22.36) **(K)**
B					
G	(0.00) [10.12] **(K)**	(14.23) **(NK)**	(1.49) **(K)**	(1.48) **(K)**	(-----) **(NK)**
W	(0.00) [7.53] **(K)**	(10.96) **(NK)**	(6.92) **(K)**	(6.72) **(K)**	(-----) **(NK)**
C					
G	(14.22) **(K)**	(16.82) **(NK)**	(0.91) **(K)**	(0.00) [25.14] **(K)**	(6.30) **(K)**
W	(10.34) **(K)**	(8.72) **(NK)**	(0.141) **(K)**	(0.00) [28.27] **(K)**	(-----) **(K)**
D					
G	(9.78) **(K)**	(33.79) **(NK)**	(0.73) **(K)**	(0.00) [37.08] **(K)**	(46.50) **(NK)**
W	(7.38) **(K)**	(19.71) **(NK)**	(0.00) [39.79] **(K)**	(0.04) **(K)**	(44.52) **(NK)**
E					
G	(36.90) **(NK)**	(19.70) **(NK)**	(0.00) [27.27] **(K)**	(0.95) **(K)**	(13.24) **(K)**
W	(25.89) **(NK)**	(14.38) **(NK)**	(0.00) [30.09] **(K)**	(0.34) **(K)**	(13.03) **(K)**
F					
G	(11.11) **(K)**	(16.70) **(NK)**	(0.26) **(K)**	(0.00) [12.11] **(K)**	(58.44) **(NK)**
W	(4.37) **(K)**	(5.00) **(NK)**	(0.26) **(K)**	(0.00) [14.79] **(K)**	(54.39) **(NK)**

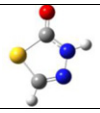
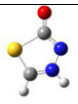
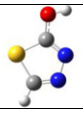
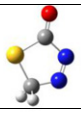
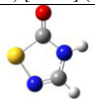
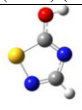
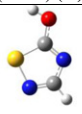
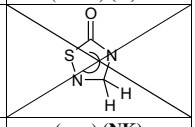
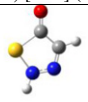
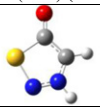
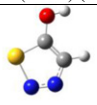
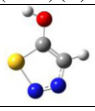
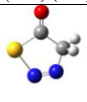
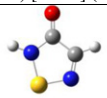
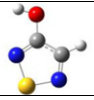
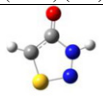
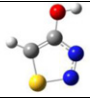
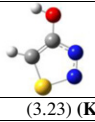
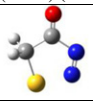
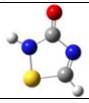
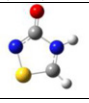
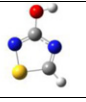
ca. 8.4 kcal/mol is the next most stable one. The A1 molecule (3H-1-thiapyrazol-2-one), which has been the most stable for oxadiazolone isomers, is now only the third most stable structure. Also, the crude rules can be formulated a bit differently. The (Kekuléan) B and F structures, in which the N-atoms are separated by the C-atoms, exhibit relative free Gibbs energy not higher than ca. 12 kcal/mole. The case in which the three heteroatoms are adjacent have to be divided into subcases: the case in which the N-atoms are separated by the S-atom and the case when the S-atom is adjacent to the NN-moiety. In the former case, D isomers, the energy of (Kekuléan) structures are ca. 15–20 kcal/mol energetically higher then the B1 structure, whereas in the later case, C and E forms, they are less stable by at least 28 kcal/mol. Unlike for oxadiazolone isomers, the cyclic urea derivatives, F, are quite stable (Table 3). For each type of constitutional isomers, the non-Kekuléan forms are the least stable. On the other hand, as for oxadiazolone isomers, the most stable tautomers in the D, E, and F groups are the OH-tautomers stabilized by an intramolecular hydrogen bond (D4, E3, and F3, respectively), however, their rotamers (D3, E4, and F4) are almost equally stable.

The stability of the OH tautomers of oxadiazolone isomers depends on kind of the adjacent heteroatom being the proton acceptor in the intramolecular H-bond. This is also the case for thiadiazolone isomers, however, now the S-atom is much less electronegative than N-atom, and the OH···S hydrogen bond is much weaker than the OH···N one formed in the second rotamer of the A and B type molecules. The difference is insignificant when S is at one side and the CH group on the other side of the C—OH moiety, as in the C isomers, whereas it is quite large when the CH group and the N-atom are adjacent to the C—OH group as in D and E isomers. Obviously, the difference is very small for the cyclic urea derivatives (F).

3.4. Thiadiazolthione isomers

The main difference between thiadiazolthione and thiadiazolone isomers comes from difference of external heteroatom. This is quite similar to difference between oxadiazolone and oxadiazolthione isomers described above. Thus, it can be expected that for thiadiazolthione isomers the relative stability of the groups of constitutional isomers, A–F, will be very similar to that for thiadiazolone isomers and, additionally, that the SH rotamers will be less differentiated by the intramolecular hydrogen bonds than the OH rotamers. This is indeed reflected by good linear correlation between relative Gibbs free energies of thiadiazolthione and corresponding thiadiazolone (Fig. 1c). Again, the linear correlation

Table 3
The relative Gibbs free energies (kcal/mol) of thiadiazolone constitutional isomers and tautomers calculated based on on B3LYP/aug-cc-pVDZ (gas, G) and B3LYP/IEF-PCM/aug-cc-pVDZ (water, W) levels. K and NK stand for Kekuléan and non-Kekuléan. respectively. The values in square brackets show difference to the most stable thiadiazolthione isomer while the values in parentheses show difference to the most stable tautomer of given type.

	thiadiazolones				
	NH		**OH**		**CH_2**
	1	**2**	**3**	**4**	**5**
A					
G	(0.00) [9.97] **(K)**	(14.26) **(NK)**	(14.50) **(K)**	(18.41) **(K)**	(19.81) **(K)**
W	(0.00) [11.65] **(K)**	(8.91) **(NK)**	(14.28) **(K)**	(15.55) **(K)**	(19.85) **(K)**
B					
G	(0.00) [0.00] **(K)**	(7.48) **(NK)**	(9.11) **(K)**	(12.52) **(K)**	(-----) **(NK)**
W	(0.00) [0.00] **(K)**	(5.02) **(NK)**	(12.10) **(K)**	(13.23) **(K)**	(-----) **(NK)**
C					
G	(0.00) [28.72] **(K)**	(6.76) **(NK)**	(6.62) **(K)**	(6.24) **(K)**	(4.15) **(K)**
W	(0.00) [29.59] **(K)**	(4.78) **(NK)**	(6.83) **(K)**	(6.69) **(K)**	(5.91) **(K)**
D					
G	(4.21) **(K)**	(27.71) **(NK)**	(3.62) **(K)**	(0.00) [14.82] **(K)**	(32.55) **(NK)**
W	(1.13) **(K)**	(15.18) **(NK)**	(1.33) **(K)**	(0.00) [18.39] **(K)**	(28.59) **(NK)**
E					
G	(26.03) **(NK)**	(9.54) **(NK)**	(0.00) [30.02] **(K)**	(3.23) **(K)**	(4.04) **(NK)**
W	(16.05) **(NK)**	(5.91) **(NK)**	(0.00) [32.83] **(K)**	(0.70) **(K)**	(3.37) **(NK)**
F					
G	(1.76) **(K)**	(11.41) **(NK)**	(0.00) [8.42] **(K)**	(0.35) **(K)**	(54.45) **(NK)**
W	(0.00) [8.37] **(K)**	(5.125) **(NK)**	(2.39) **(K)**	(2.14) **(K)**	(48.91) **(NK)**

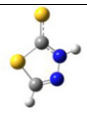
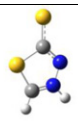
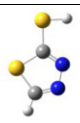
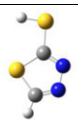
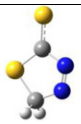
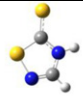
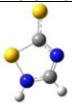
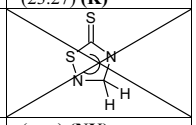
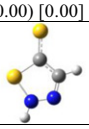
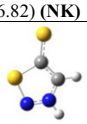
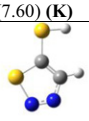
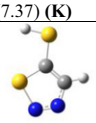
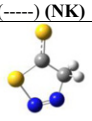
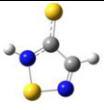
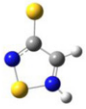
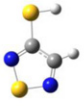
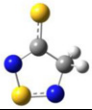
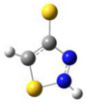
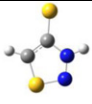
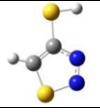
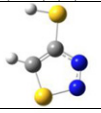
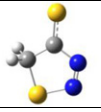
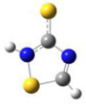
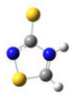
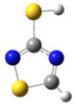
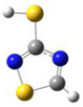
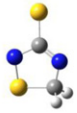
between relative Gibbs free energies of thiadiazolthiones and corresponding oxadiazolthiones with different heteroatom in the ring is much weaker (Fig. 1d).

Indeed, as for thiadiazolones, for thiadiazolthione isomers the most stable is the B1 form, the next most stable is the F4 molecule, and the A1 isomer is only the third most stable structure (Table 4). The fact that for thiadiazolone isomers the F3 molecule was more stable than F4 is not significant because the energetic gap between these rotamers is smaller than 0.4 kcal/mol. However, it is significant that for thiadiazolthione isomers the F4 isomer is higher in energy than B1 form by ca. 4. kcal/mol while for thiadiazolone isomers it is higher by over 8 kcal/mol. The (Kekuléan) B and F structures in which the N-atoms are separated by the C-atoms exhibit relative free Gibbs energy not higher than ca. 4.5 kcal/mol, while for thiadiazolone isomers it was ca. 12 kcal/mol. Thus the thiadiazolthione isomers seem to be even more stable than the thiadiazolone isomers. The D type isomers, in which the N-atoms are separated by the S-atom, are ca. 10–16 kcal/mol energetically higher than the most stable B1 structure. In the case when the S-atom is adjacent to the NN-moiety, C and E forms, they are less stable than the B1 molecule by at least 23 kcal/mol. Also, the cyclic urea derivatives, F, are quite stable (Table 4). For each type of constitutional isomers the non-Kekuléan forms are the least stable. Finally, the SH rotamers differ in energy by at most 1.1 kcal/mol and the largest difference occurs for situation when N-atom is on the one side of the C—SH group and the CH group is at the other side (E, Table 4).

3.5. A remark on influence of implicit water model

For the tautomeric equilibria of compounds with several proton-donor and proton-acceptor centers it is always a question to what extent the equilibria are influenced/changed by the water solution. Therefore, the presence of water surrounding the molecule was mimicked with the IEF-PCM implicit water model. The relative stabilization energies of all studied compounds in water are listed in Tables 1–4. In general, the relative stabilities in the gas phase and in water solutions are in fair agreement shown by linear correlation of data ($R = 0.972$, Fig. 2). The most spectacular situations may occur when a tautomer is the most stable in the gas phase becomes less stable in water or oppositely. However, this is not a case for oxadiazolone isomers (Table 1). Nevertheless, there

Table 4
The relative Gibbs free energies (kcal/mol) of thiadiazolthione constitutional isomers and tautomers calculated based on on B3LYP/aug-cc-pVDZ (gas, G) and B3LYP/IEF-PCM/aug-cc-pVDZ (water, W) levels. K and NK stand for Kekuléan and non-Kekuléan. respectively. The values in square brackets show difference to the most stable thiadiazolthione isomer while the values in parentheses show difference to the most stable tautomer of given type.

	thiadiazolthiones				
	NH		**SH**		**CH_2**
	1	**2**	**3**	**4**	**5**
A					
G	(0.00) [10.36] **(K)**	(16.44) **(NK)**	(7.91) **(K)**	(8.94) **(K)**	(22.54) **(K)**
W	(0.00) [11.56] **(K)**	(8.44) **(NK)**	(8.77) **(K)**	(8.89) **(K)**	(23.27) **(K)**
B					
G	(0.00) [0.00] **(K)**	(10.63) **(NK)**	(3.85) **(K)**	(4.30) **(K)**	(-----) **(NK)**
W	(0.00) [0.00] **(K)**	(6.82) **(NK)**	(7.60) **(K)**	(7.37) **(K)**	(-----) **(NK)**
C					
G	(3.01) **(K)**	(7.98) **(NK)**	(0.00) [24.23] **K)**	(0.19) **(K)**	(8.26) **(K)**
W	(0.88) **(K)**	(3.01) **(NK)**	(0.00) [26.66] **K)**	(0.13) **(K)**	(9.28) **(K)**
D					
G	(6.61) **(K)**	(28.08) **(NK)**	(0.57) **(K)**	(0.00) [9.45] **(K)**	(38.24) **(NK)**
W	(2.71) **(K)**	(13.95) **(NK)**	(0.00) [13.60] **(K)**	(0.03) **(K)**	(34.26) **(NK)**
E					
G	(29.64) **(NK)**	(12.50) **(NK)**	(0.00) [23.21] **(K)**	(1.11) **(K)**	(13.48) **(K)**
W	(15.55) **(NK)**	(6.44) **(NK)**	(0.00) [26.48] **(K)**	(0.20) **(K)**	(12.86) **(K)**
F					
G	(2.41) **(K)**	(15.60) **(NK)**	(0.21) **(K)**	(0.00) [3.94] **(K)**	(55.72) **(NK)**
W	(1.73) **(K)**	(4.09) **(NK)**	(0.13) **(K)**	(0.00) [7.27] **(K)**	(49.40) **(NK)**

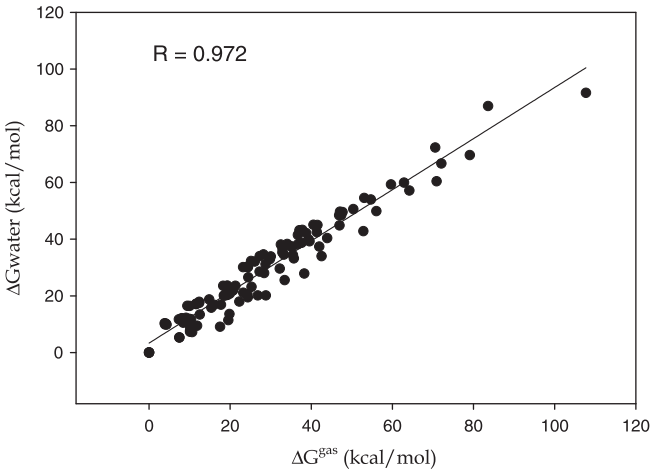


Fig. 2. Linear correlation between relative stability of the oxadiazolone derivatives in the gas phase and in water simulated by the IEF-PCM method. Gibbs free energies were calculated at the B3LYP/aug-cc-pVDZ level.

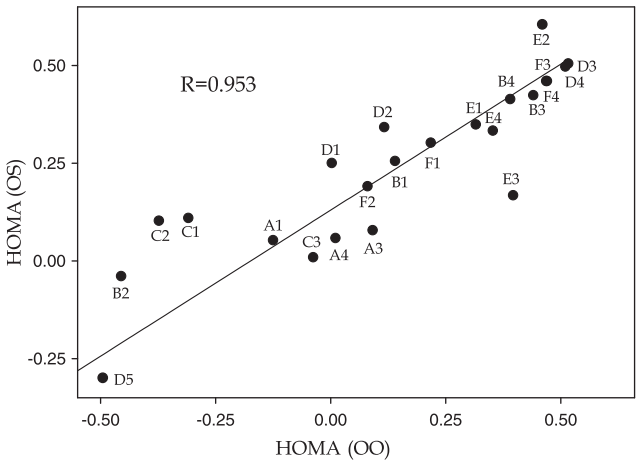


Fig. 3. Correlation between HOMA aromaticity indices of oxadiazolones and oxadiazolthiones.

are some changes maybe worth mention like D3 molecule which in the gas phase was separated from the most stable tautomer by over 3 kcal/mol and in water the energetic gap decreased more than 3-times. Similar situation occurs for E4 form which in water is separated by only 0.4 kcal/mol. In these two situations the gap in water suggests that the two form can be simultaneously observed.

For oxadiazolthiones, the D3 form in the gas phase is predicted to be less stable than D4 by ca. 0.7 kcal/mol, whereas in water it is practically as stable as D4 one (Table 2). On the other hand, C3 becomes separated from C4 in water by only 0.14 kcal/mol, while in the gas phase it is 0.9 kcal/mol. Similar comparisons can be made for E4 form. For thiadiazolones D3 and E4 gains significant stability in water and are predicted to coexist in water solution with D4 and E3 molecules, respectively (Table 3). However, the most interesting is the case of F1, F3, and F4 molecules. In the gas phase F3 and F4 are predicted to be found in almost equimolar content, whereas in water the two molecules are much less stable than F1 (a matter of 2.4 kcal/mol), which is predicted to definitely predominate. For thiadiazolthiones, the C1 gains additional stability in water and is predicted to be also observed in equilibria with C3 and C4. Finally, three pairs of compounds: D3 and D4, E3 and E4, and F3 and F4, are predicted to be found in water in ca. 1:1 ratio (Table 4). Generally, the water simulated by implicit IEF-PCM model suggest that special stabilization can occur for forms with external OH or OH groups of D, E, and F type.

3.6. A remark on aromaticity of the studied systems

Although the studied systems cannot exhibit significant aromatic character, the question about a contribution of aromatic factor into stability of the studied compounds was somehow intriguing. Therefore, we calculated the simplest but reliable structural HOMA aromaticity index [44–47] to check whether there are some correlations between the index and the relative stability of the compounds, or not. Unfortunately, we found no a regular dependence between these two variables. However, there is a linear correlation between HOMA indices of oxadiazolones and oxadiazolthiones (Fig. 3). This means that change of the external substituent ═O to ═S or from OH to SH does not significantly change the overall character of the pi-electronic system in the studied compounds. We did not perform the analogous analysis for the thiadiazolones and thiadiazolthiones because of lack of parameterization of the HOMA index for the S-atom incorporated into the ring.

Remark first that the upper limit of the indices is ca. 0.5 while HOMA = 1.0 denotes the perfect aromaticity of benzene molecule. This means that the studied compounds are not aromatic and cannot profit from this stabilization factor. Remark next that the lower limit is somehow below −1.0 (the outlying C5 point is neglected). This means, that some structures are indeed antiaromatic. The antiaromaticity means that the system exhibits alternating single and double bonds. This is not surprising that the systems denoted by number 5 have such alternations. The C═O and C═S groups enforce localization of the double bonds on these very moieties, and the presence of the CH_2 group incorporated into the ring enforces the localization of the single bonds around this group. As a result the double bond is also well localized at the N═N moiety and the systems exhibit antiaromaticity.

Aromaticity of the other type of compounds, neither denoted by letter from A to F, nor by the number from 1 to 4, cannot be summarized by a simple statement. The points of each group are spread out along the correlation straight-line from ca. −0.5 to ca. 0.5. The largest changeability exhibit non-Kekuléan structures denoted by number 2 in which the B2 is placed below 0.0 for two coordinates while E2 exhibit one of the highest aromaticity of ca. 0.5 with respect of the two axes. On the other hand, aromaticity of the structures denoted by number 1 does not exceed value of ca. 0.3 whereas aromaticity of the OH tautomers (labels 3 and 4) is not smaller than ca. 0.0.

Summing up this section we can state that the aromaticity is not an additional stabilization factor for oxadiazolones and oxadiazolthiones, and, the most probably it neither is for thiadiazolones and thiadiazolthiones. The pi-electron system in the studied systems is not sensitive to change of external chalcogen ═X atom or —XH group.

4. Conclusions

The constitutional isomers and tautomers of oxadiazolone, 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 cathegorized into six groups (from A to F) according to permutations of three heteroatoms in the five-membered ring. Each constitutional isomer was considered to have five tautomers conserving stable five-membered ring: two NH tautomers, two rotameric OH (or SH) form and one CH_2 tautomer.

It appeared that the largest difference between oxadiazolone O and S analogs 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 is incorporated. This is because of much larger van der Waals radius of S-atom than of O-atom. The external chalcogen is only modifying the general energetic factors. Therefore, the energetics of oxadiazole isomers was found to be similar to that of oxadiazolthione isomers and energetics of thiadiazolone isomers was found to be similar to that of thiadiazolthione isomers.

In oxadiazolones and oxadiazolthiones, the most stable appeared to be the 3H-[1,3,4]oxapyrazol-2-one and 3H-[1,3,4]oxapyrazol-2-thione molecule, respectively. In comparison to this molecule the constitutional isomers in which the three ring heteroatoms were separated by the CH group exhibited the relative Gibbs free energy not higher than ca. 12 kcal/mol. The oxadiazolone isomers with three neighboring heteroatoms were found to be very unstable with the relative free Gibbs energy higher by at least 35 kcal/mol. The cyclic urea analogues were found to be the least stable. It is important that systematic consideration of all constitutional isomers leaded to several non-Kekuléan molecules (for which there is no unequivocal match of the double bonds in the ring). For each type of constitutional isomers these non-Kekuléan molecules always appeared to be the least stable.

The energetics of oxadiazolthiones is similar to that of oxadiazolones. Some differences comes from intramolecular interactions produced by the OH and SH groups. The external OH or SH groups in the studied systems may interact with diverse neighboring heteroatoms. The intramolecular hydrogen bonds in oxadiazolone differentiate more the OH rotamers than does the SH group. This is because the OH is stronger proton donor, and also stronger proton acceptor. Moreover, the C—S(H) distance is much larger than the C—O(H) and the intramolecular interactions of the SH group are weaker. For thiadiazolone and thiadiazolthione isomers the most stable is the 4H-[1,2,4]thiaimidazol-5-one and 4H-[1,2,4]thiaimidazol-5-thione molecule, respectively. The thiadiazolthione isomers seem to be even more stable than the thiadiazolone isomers.

The studied compounds exhibit several proton-donor and proton-acceptor centers which can interact with water changing the tautomeric equilibria. The presence of water was mimicked with the IEF-PCM implicit water model. In general, the relative stabilities in the gas phase and in water solutions are in fair agreement shown by linear correlation of data ($R = 0.972$). Generally, the water simulated by implicit IEF-PCM model suggest that special stabilization can occur for forms with external OH or OH groups of D, E, and F type.

The aromaticity of the studied systems was checked by means of the structural HOMA aromaticity index. The aromaticity dos not exceeds ca. 0.5 therefore it is not an additional stabilization factor for oxadiazolones and oxadiazolthiones, and, the most probably, it neither is for thiadiazolones and thiadiazolthiones. The fair linear correlation between HOMA indices of oxadiazolones and oxadiazolthiones shows that the pi-electron system in the studied systems is not sensitive to change of the external chalcogen =X atom or —XH group.

Acknowlegments

A part of this study was granted by the Ministry of Science and Higher Education in Poland for statutory activity of the National Medicines Institute. The computational Grants G19-2 from the Interdisciplinary Center of Mathematical and Computer Modeling (ICM) at the Warsaw University are gratefully acknowledged.

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