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Scientific paper

Theoretical Considerations Regarding the Thione-thiol Tautomerism in 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic Acid

Raluca Pop,[1,*] Maria Ilici,[2,*] Mihaiela Andoni,[1] Vasile N. Bercean,[2] Cornelia Muntean,[2] Monica M. Venter,[3] and Ilie Julean[2]

[1] *University of Medicine and Pharmacy "Victor Babeş" Timisoara, Faculty of Pharmacy, Eftimie Murgu Square 2, 300041 Timişoara, Romania*

[2] *University POLITEHNICA Timisoara, Faculty of Industrial Chemistry and Environmental Engineering, 300006 Timisoara, Romania*

[3] *Babeş-Bolyai" University, Faculty of Chemistry and Chemical Engineering, 11 Arany Janos Str., 400028 Cluj-Napoca, Romania.*

** Corresponding author: E-mail: ralucapop24@gmail.com; ilici2011@gmail.com*

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Abstract

The acidity constants K_{a1} and K_{a2} of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid have been determined both by experimental and theoretical methods. pK_a computations at B3LYP/6-311+G(d,p) level of theory were carried out for the two tautomeric forms, thiol and thione, of the above-mentioned acid. Comparisons between the experimental and theoretical values led to the establishing of the most stable tautomer of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid in aqueous solution. Also, a DFT study regarding the reactivity, aromaticity and population analysis of the two tautomers has been performed.

Keywords: thiadiazole, pK_a, thiol-thione tautomerism, theoretical computations, DFT.

1. Introduction

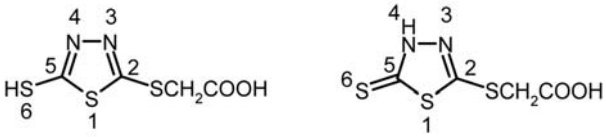
Together with the other 5-membered heterocycles, thiadiazoles have gained an increased popularity during the last decades. Their importance is due to their versatility and their biologic activity as antitumor, antifungal and antiviral agents.[1,2] The presence of the sulfur atom within the cyclic structure confers them, compared to the 5-membered nitrogen heterocycles, an improved liposolubility and better penetration of the cellular membranes.[2] Also, the 5-imino-1,2,4-thiadiazole derivatives are found to be inhibitors of glycogen synthase kinase 3 (GSK3), a protein kinase with active role in diabetes, cancer and Alzheimer's disease.[3,4]

In the case of heterocyclic moieties that show biologic activity and where the possibility of the co-existence of two tautomeric forms appears, it becomes very important to determine the most stable tautomer. Nowadays, computational chemistry techniques allow the prediction of the tautomeric behavior prior to the experimental studies.[5] There are numerous papers that where published in the last years regarding theoretical studies of the thiol-thione,[6–9] keto-enol,[10] formamide-formamidic acid,[11] nucleic acid bases,[12,13] heterocyclic rings –pyrazoles, triazoles[14–17] tautomerism.

The 5-membered mercapto-aza heterocyclic derivatives (like Bismuthiol – dimercaptothiadiazole) were used with good results for the preparation of new metal complexes.[18] Within our research group, there has been reported the obtaining of various metal complexes of the dimercaptothiadiazole derivatives.[18–19] A derivative of 1,3,4-thiadiazol-2-yl-thioacetic acid, which can exist both in thiol (2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid) or thione (2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetic acid) form, has been used for the preparation of metal complexes with various transitional metals.[19]

Previous studies of our research group have highlighted two possible tautomeric forms: thiol (5SH, **Ia**) and thione (5S, **Ib**).[19,20] In this regard, the pK_a values for the two deprotonation stages of each tautomer may offer valuable data regarding the stability of both tautomer species in aqueous solution.

The present study deals with the evaluation, both by theoretical and experimental methods, of the pK_a of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid. This way, an estimation of the pK_a values by theoretical means –using both thermodynamic cycles[21–24] and isodesmic reactions[25] – may also result in clarifying the issues regarding the dominant tautomer in aqueous solution.

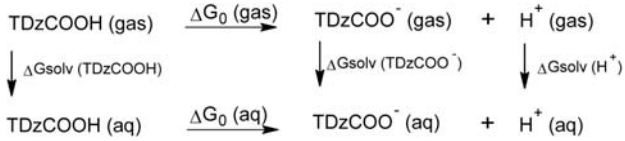


Ia **Ib**

Scheme 1. Tautomeric structures of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid **I** ($C_4H_4S_3N_2O_2$) (**Ia** – thiol form; **Ib** – thione form).

In order to estimate the theoretical pK_a value of the 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid, two thermodynamic cycles and one isodesmic reaction scheme have been employed.

Method 1: Thermodynamic cycle 1

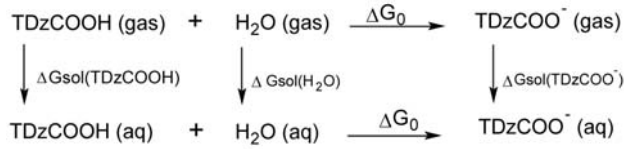


Scheme 2. Thermodynamic cycle (1) used for the pK_a computation.

The value of pK_a was calculated by means of the thermodynamic cycle presented in Figure 1. According to literature data, one of the main challenges in pK_a computations consists in determining the appropriate value of the free energy of solvation of H^+, as it is well known that an error of 1.36 kcal/mol leads to an 1 unit of pK_a error.[22,24] The experimental data range within –254 and –265.9 kcal/mol,[21–24] but two of the most often used values are –264.0 kcal/mol[24] and –265.9 kcal/mol,[22] respectively. Within the present study, the values of –265.9 kcal/mol (solvation) and –6.28 kcal/mol (gas-phase) of the free energy of H^+ were considered. Also, the correction to the gas-phase free energy of the deprotonating reaction (RTln24.46, representing 1.895 kcal/mol) was added. The correction factor is required for transforming the gas-phase free energy of the deprotonation reaction, computed to a reference state of 1 atm, in a value computed for a reference state of 1M (specific to the aqueous phase computations).

Method 2: Thermodymanic cycle 2

The second thermodynamic cycle is based on the reaction with a water molecule, when the corresponding anion of the thiadiazole derivative, along with the hydronium ion, is obtained. This way, the source of errors consisting in the thermodynamic parameters of H^+ is avoided. Within the following computations, the accepted values of the $\Delta G_{sol}H_3O^+$ and $\Delta G_{sol}H_2O$ were considered –110.3 kcal/mol and –6.32 kcal/mol, respectively.



Scheme 3. Thermodynamic cycle (2) used for the pK_a computation.

The equations that were used for the computation of pK_a are the following:

$$pKa = \frac{\Delta Gaq}{RT\ln 10} \quad (1),$$

where:

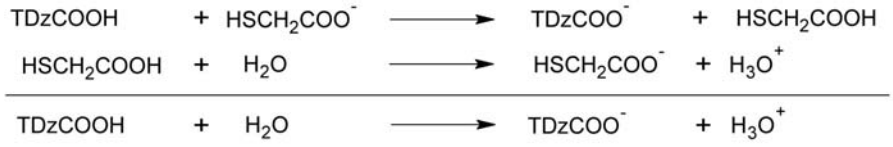
$$\Delta G_{aq} = \Delta G_{gas} + \Delta\Delta G_{sol} \quad (2)$$

$$\Delta G_{gas} = G_{gas}(products) - G_{gas}(reagents) \quad (3)$$

$$\Delta\Delta G_{sol} = \Delta G_{sol}(products) - \Delta G_{sol}(reagents) \quad (4)$$

Method 3: Isodesmic reaction scheme with thioglycolate

The isodesmic reactions are characterized by the conservation of the type of broken/formed bonds. Namazian and Heidary[25] proposed an isodesmic reaction sche-



Scheme 4. Isodesmic reactions used for pK_a computations

me with acetate/acetic acid for the computation of pK_a for a number of carboxylic acids with similar structure. In this regard, the thioglycolate ion and the thioglycolic acid were chosen as references for the pK_a computation of the 2-mercapto-1,3,4-thiadiazol-5-yl thioacetic acid.

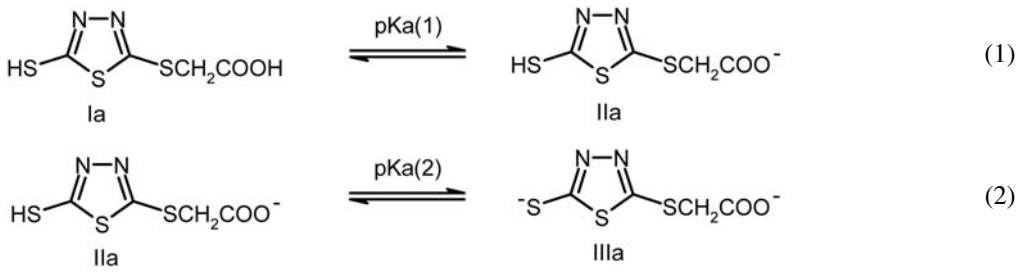
2. Experimental

The geometric optimization of compounds **Ia** and **Ib** and their corresponding anions has been performed at B3LYP/6-311+G(d,p) level of theory. Vibrational analysis, carried out at the same level of theory, showed that no imaginary frequency was obtained. In order to quantify the effects of the aqueous environment, two solvation models -conductor-like polarizable continuum model (CPCM) and integral equation formalism polarizable continuum model (IEFPCM – with the solute characterized by the electronic density) – have been employed.[26] The geometric optimization of the two tautomers (and of the corresponding anions) in aqueous environment have been also performed at B3LYP/6-311+G(d,p) level of theory, using both CPCM and IEFPCM solvation models. Geometry optimizations, frequency computations, thermochemistry data and reactivity indices (the condensed Fukui functions[27]) have been performed using the Gaussian 09W package.[28] Also, for the NICS(0) and NICS(1) computations (NICS – Nucleus-Independent Chemical Shift), the GIAO (Gauge Independent Atomic Orbitals) approach within Gaussian 09W program has been employed. For the experimental determination of K_a values, conductometric and potentiometric titrations have been performed using a MM 41 Crison multimeter, fitted with a conductivity cell and a glass electrode. For the determination of the equivalence points of potentiometric titration and for the calculation of K_{a1} and K_{a2} values, software applications developed by the authors (I. Julean and C. Muntean) have been used.

3. Results and Discussions

3. 1. Theoretical Calculation of pKa

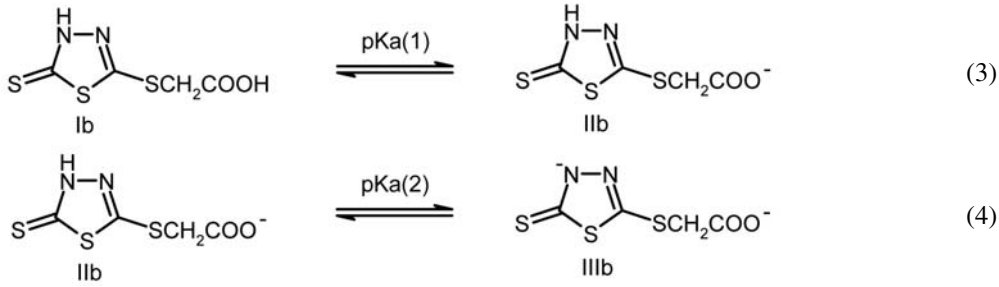
First ionization stage of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid consists in the removal of the H atom from the carboxyl group (reactions (1) and (3), respectively). The reaction is very similar for both tautomeric forms, leading to the obtaining of the thioacetate anion. Instead, significant differences appear during the second ionization stage, that involves H^+ removal from the –SH group (tautomer **Ia**) and the H^+ removal of the –NH group, a (tautomer **Ib**). One can approximate that a more "acidic" character is expected for the proton removal from the –SH group, which is directly bonded to the aromatic skeleton of 1,3,4-thiadiazole. In the case of the second ionization stage of the thione tautomer **Ib**, the hydrogen atom that has to be removed belongs to a secondary amino group (also, the cyclic delocalization of the electrons within the heterocyclic ring is affected).



(1)

(2)

Scheme 5. The heterocyclic species involved in the first and second ionization of the thiol tautomer (**Ia**) of the 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid.



(3)

(4)

Scheme 6. The heterocyclic species involved in the first and second ionization of the thione tautomer (**Ib**) of the 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid.

The experimental results (see detailed information in *Appendix*) are presented in Table 1 and show a 3rd order difference between the K_a values (and, corresponding, 3 pK_a units) that were obtained for the two stages of the ionization process.

Table 1. Experimental values of K_a and pK_a, determined for the first and second ionization stages of compound **I**

Compound	K_{a1} (pK_{a1})	K_{a2} (pK_{a2})
I ($C_4H_4S_3N_2O_2$)	$8.72 \cdot 10^{-3}$ (2.06)	$8.632 \cdot 10^{-6}$ (5.06)

The theoretical computations of pK_a values allow the evaluation of the acid character of both tautomeric forms. Similarities with the experimental results will be used for the prediction of the dominant tautomer in aqueous solution).

Several conclusions can be drawn regarding the results presented in Table 2 and Table 3; pK_{a1} values are very similar, regardless of the chosen method of computation. As expected, loosing the H atom of the carboxyl group (namely, the pK_{a1} value) is only slightly influenced from the thiol-thione tautomerism. The computed values show a difference of 0.65 pK_a units between the two tautomers, the more acidic being the thione form (**Ib**). Significant differences appear between the pK_{a2} values (almost 7 pK_a units is the difference between the thiol and thione tautomers). These results lead to the conclusion that, in aqueous solution, the dominant tautomer is **Ia** (the thiol form of the 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid). The results presented in Table 2 show a ΔpK_a value around 3, in good correlation with the experimental one. The results seem to illustrate the Gustafson's paradox: the most acidic tautomer is also the less abundant.[5]

As regards the accuracy of the results, it is obvious that the theoretical calculations of pK_a, regardless the chosen method, overestimate the pK_a values. A possible explanation for the lower values of experimental pK_a (when compared to the calculated ones) can be attributed to the undervaluing of the energies of the compounds when carrying PCM computations. Among the three variants that were used for the estimation of pK_a, differences appear only for the pK_{a2} values computed by means of the first thermodynamic cycle. As the pK_{a1} calculations (by means of all of the three methods) led to insignificant differences among the obtained values, it may be assumed that the underestimation of the pK_{a2} value, when using the first thermodynamic cycle, cannot be caused by the free energy of solvation of H^+ (considered –265.9 kcal/mol within the present study).

3. 2. Similarities and Differences Between the Thiol-thione Tautomers Ia and Ib

3. 2. 1. Aromatic Character of the Thiol- and Thione- Derivatives of the 2-(5-mercapto-1,3,4-thiadiazol-2-yl-thio)acetic acid

The magnetic criterion was chosen in order to evaluate the aromaticity of the two tautomers. In this regard, NICS(0) and NICS(1) computations were performed; the results are presented in Table 4.

Table 4. NICS(0) and NICS(1) values, computed at B3LYP/6-311+G(d,p) level of theory

$C_4H_4S_3N_2O_2$	NICS(0) (ppm)	NICS(1) (ppm)
Tautomer **Ia**	–10.156	–8.994
Tautomer **Ib**	–7.310	–5.194

The results confirm that the thiol form of the 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid is more aromatic than the thione one; given that in the case of the thione tautomer, formation of the exocyclic C=S bond disrupts the π-electron conjugation and leads to a decrease of the aromatic character.

Table 2. Theoretical pK_a values calculated for the two ionization stages of the thiol tautomer (**Ia**)

$C_4H_4S_3N_2O_2$	pK_{a1}		pK_{a2}		$\Delta pK_a = pK_{a(2)} - pK_{a(1)}$	
Ia	IEFPCM	CPCM	IEFPCM	CPCM	IEFPCM	CPCM
Method 1	4.63	4.63	6.08	6.12	1.45	1.49
Method 2	4.64	4.64	7.82	7.80	3.18	3.16
Method 3	4.63	4.56	7.82	7.62	3.26	3.06

Table 3. Theoretical pK_a values calculated for the two ionization stages of the thiol tautomer (**Ib**)

$C_4H_4S_3N_2O_2$	pK_{a1}		pK_{a2}		$\Delta pK_a = pK_{a(2)} - pK_{a(1)}$	
Ib	IEFPCM	CPCM	IEFPCM	CPCM	IEFPCM	CPCM
Method 1	3.98	3.97	12.30	12.28	8.32	8.31
Method 2	3.98	3.99	14.00	14.05	10.02	10.06
Method 3	3.94	3.86	13.99	13.80	10.05	9.94

In addition to the magnetic index of aromaticity (NICS), the global stability of the six species involved in the ionization process (the two tautomers **Ia** and **Ib** and their corresponding monoanions and dianions) was evaluated. As well as in the case of other aromatic compounds, HOMO-LUMO gap computation represents an useful tool for comparisons among the stability of various species.[29]

Table 5. HOMO-LUMO gap of the **Ia–IIIa** and **Ib–IIIb** species (B3LYP/6311+G(d,p))

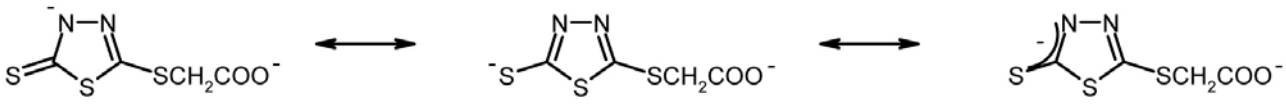
	Ia	**IIa**	**IIIa**
HOMO-LUMO gap	5.11	3.38	4.26
(eV)	**Ib**	**IIb**	**IIIb**
	4.59	3.21	4.26

According to the results presented in Table 5, the most stable specie is the tautomer **Ia**, whereas at the opposite side the monoanions **IIa** and **IIb** are found. The identic value obtained for the dianionic species **IIIa** and **IIIb** suggests that a delocalization of both the negative charge and the double bond appears among the N-C-S atoms, leading to the same specie (see Scheme 7).

3. 2. 2. NBO (Natural Bond Orbitals) Analysis

The evaluation of the donor-acceptor interactions and their energetic contributions to the stability of the compounds is performed by means of the 2nd order perturbation theory within NBO analysis. The stabilization energy E2, as difference between the localized-delocalized structures, is reported in tables below:

The results presented in Table 6 and Table 7 emphasize the differences among the thione and thiol form (namely between the neutral and monoanionic species, **Ia–Ib** and **IIa–IIb**). The lone pair of the nitrogen atom N4 has an exclusive p character in the thione form, leading to stronger stabilization interactions. Regarding the S6 atom hybridization, it results that the content in s and p orbitals is changing when transition to the thiol to the thione form occurs. The dianionic species **IIIa–IIIb** are characterized by the same hybridization -as obtained for the thiol tautomer- for N4, while S6 has the same character as in the case of the thione tautomer, leading to the structure of the mesomeric form **III**. The specific donor-acceptor interactions of the 5SH- and 5S- tautomers are preserved within the dianionic form **III**.



IIIb IIIa III

Scheme 7. Mesomeric species IIIa and IIIb.

Table 6. NBO analysis of the 6SH tautomer

Thiol tautomer	**LP N3 hybridization**	**Donor-acceptor interactions**	**E2 (kJ/mol)**
Ia	36.34% s, 63.54% p	LP N4 ↔ σ* C5-S6	14.58
IIa	35.76% s, 64.13% p	LP N4 ↔ σ* C5-S6	14.54
IIIa	36.43% s, 63.52% p	LP N4 ↔ σ* C5-S6	14.79
	LP S6 hybridization		
Ia	68.91% s, 31.07% p	LP S6 ↔ π* C5-N4	24.52
IIa	68.25% s, 31.73% p	LP S6 ↔ π* C5-N4	21.56
IIIa	81.17% s, 18.82% p	LP S6 ↔ π* C5-N4	39.22

Table 7. NBO analysis of the 6S tautomer

Thione tautomer	**LP N4 hybridization**	**Donor-acceptor interactions**	**E2 (kJ/mol)**
Ib	99.99% p	LP N4 ↔ σ* C5-S6	74.37
		LP N4 ↔ π* C2-N3	32.36
IIb	99.99% p	LP N4 ↔ σ* C5-S6	80.22
		LP N4 ↔ π* C2-N3	28.47
IIIb	36.40% s, 63.50% p	LP N4 ↔ σ* C5-S6	14.91
	LP S6 hybridization		
Ib	81.39% s, 18.59% p	LP S6 ↔ π* C5-N4	11.94
IIb	81.02% s, 18.95% p	LP S6 ↔ π* C5-N4	11.62
IIIb	81.17% s, 18.81% p	LP S6 ↔ π* C5-N4	39.80

3. 2. 3. Reactivity Indices

Condensed Fukui functions have been computed for the N4, N3 and S6 heteroatoms, in order to assess their reactivity during a reaction with an electrophile.[26]

Table 8. Condensed Fukui functions computed for the 6SH tautomer (B3LYP/6-311+G(d,p))

Atom	f^- (Ia)	f^- (IIa)	f^- (IIIa)
N4	0.064	0.111	0.091
N3	0.068	0.072	0.034
S6	0.171	0.028	0.356

Table 9. Condensed Fukui functions computed for the 6S tautomer (B3LYP/6-311+G(d,p))

Atom	f^- (Ib)	f^- (IIb)	f^- (IIIb)
N4	0.109	0.048	0.091
N3	0.056	0.028	0.034
S6	0.335	0.021	0.353

The condensed Fukui functions computed for the neutral forms **Ia** and **Ib** show that the S6 atom has the largest electrophilic character (higher for the thione tautomer). The two N atoms of the thiadiazole heterocycle have similar reactivity in the case of the tautomer **Ia** (see Table 8); the reactivity difference between the two N atoms of the tautomer **Ib** is outlined by the almost double value obtained for the N4 atom. The S6 atoms within the monoanionic species present the lowest reactivity; the graphical presentation of the HOMO orbitals of the thioglycolate anions clearly shows that the highest electrophilic character appears at the thyoglycolate residue, not within the heterocyclic ring (*see Appendix*). The dianion **III** shows a similar reactivity of the S6 atom as in the case of the thione form, whereas the reactivity of the N4 atom is between (almost the mean value) the values of Fukui function f^- of the N4 atom in the thiol and thione tautomers.

4. Conclusions

Theoretical evaluation of the pK_a for the two ionization stages of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio) acetic acid (both tautomeric forms) have been performed, in order to predict the more stable tautomer in aqueous solution. Two solvation models, IEFPCM and CPCM, have led to similar results for the solvation free energies of all the species involved in the ionization process. Two thermodynamic cycles and one isodesmic reaction scheme have been used for the theoretical computation of pK_a. Compared with the experimental results, theoretical calculations tend to overestimate the pK_a values; instead, the computed difference ΔpK_a has the same value for both theoretical and experimental results obtained for the thiol tautomer **Ia**. The results led to the conclusion that, in aqueous solution, the thiol form is the more stable tautomer. Also, NBO analysis for the 6SH and 6S tautomers has been carried out and the donor-acceptor interactions that lead to the stabilization of the compounds have been identified. The reactivity differences between the two tautomers are outlined by the values of the condensed Fukui functions, computed for the heteroatoms involved in the tautomeric equilibrium.

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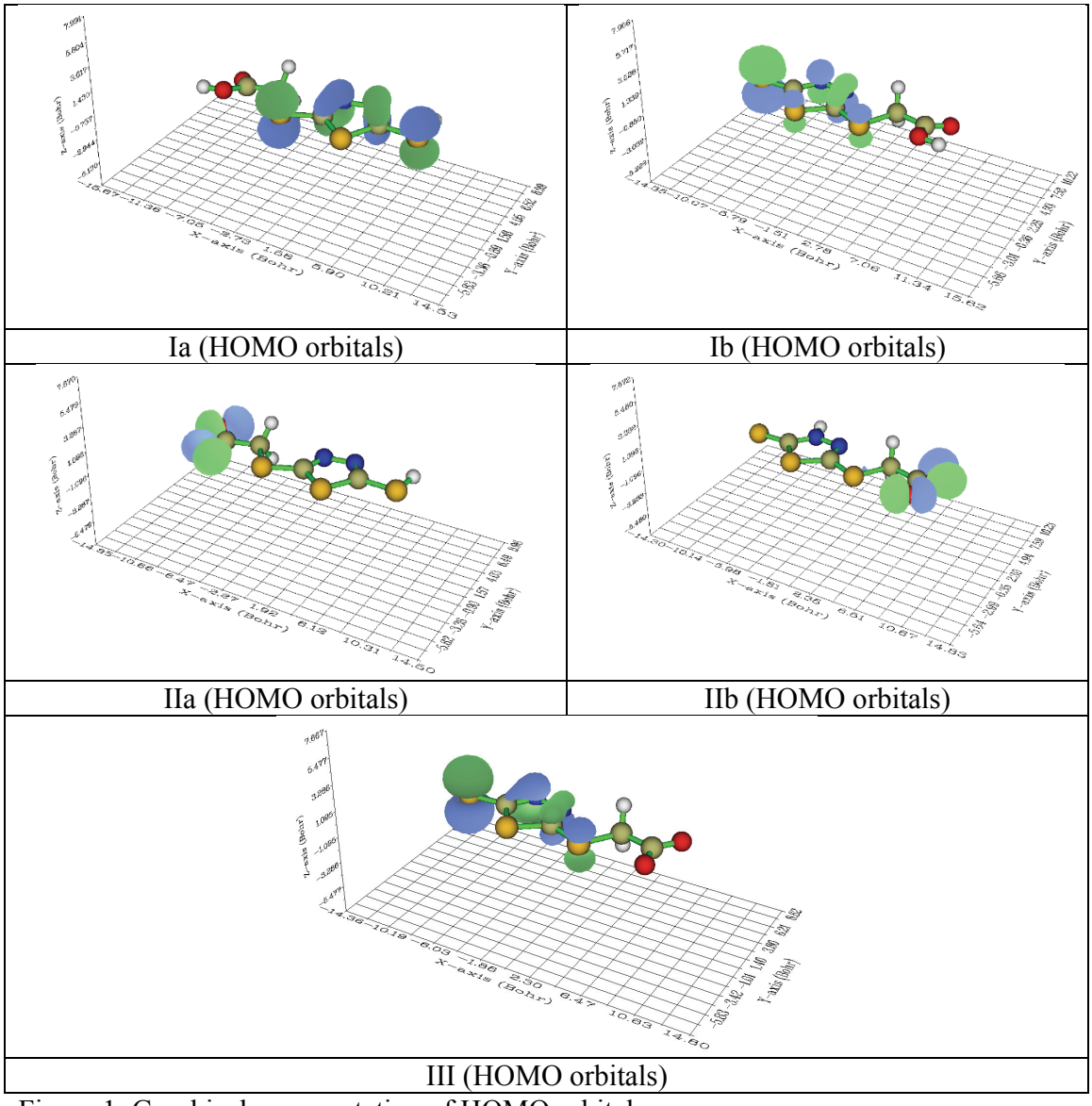
Povzetek

Za 2-(5-merkapto-1,3,4-tiadiazol-2-iltio)ocetno kislino smo določili eksperimentalne in teoretične vrednosti konstant K_{a1} in K_{a2}. Izračune pK_a smo za dve tavtomerni obliki izvedli na B3LYP/6-311+G(d,p) nivoju. S primerjavo eksperimentalnih in izračunanih vrednosti smo določili najbolj stabilno tavtomero preiskovane kisline v vodni raztopini. Dodatno smo izvedli smo še DFT analize reaktivnosti, aromatskega značaja in populacije obeh tavtomer.

Theoretical considerations regarding the thione-thiol tautomerism in 2-mercapto-1,3,4-thiadiazol-5-yl thioacetic acid

Supplementary data

1. Computational part



Ia (HOMO orbitals) | Ib (HOMO orbitals)

IIa (HOMO orbitals) | IIb (HOMO orbitals)

III (HOMO orbitals)

Figure 1. Graphical representation of HOMO orbitals

Free energies of solvation, computed at B3LYP/6-311+G(d,p), are presented in table below:

	ΔGsolv (kcal/mol)	
Compound	**IEFPCM**	**CPCM**
Ia	-9.194	-9.270
IIa	-58.119	-58.192
IIIa	-158.131	-158.158
Ib	-9.740	-9.810
IIb	-55.228	-55.300
IIIb	-158.143	-158.159
Thioglycolic acid	-5.962	-6.021
Thioglycolate	-58.523	-58.420

Table 1. ΔGsolv (kcal/mol) (B3LYP/6-311+G(d,p) level of theory)

2. Experimental part

The acid-base titration data that have been used to determine the equivalence volume and pH and to calculate the acidity constants Ka_1 and Ka_2 by means of software applications (Visual Basic) developed by the authors (I. Julean and C. Muntean):

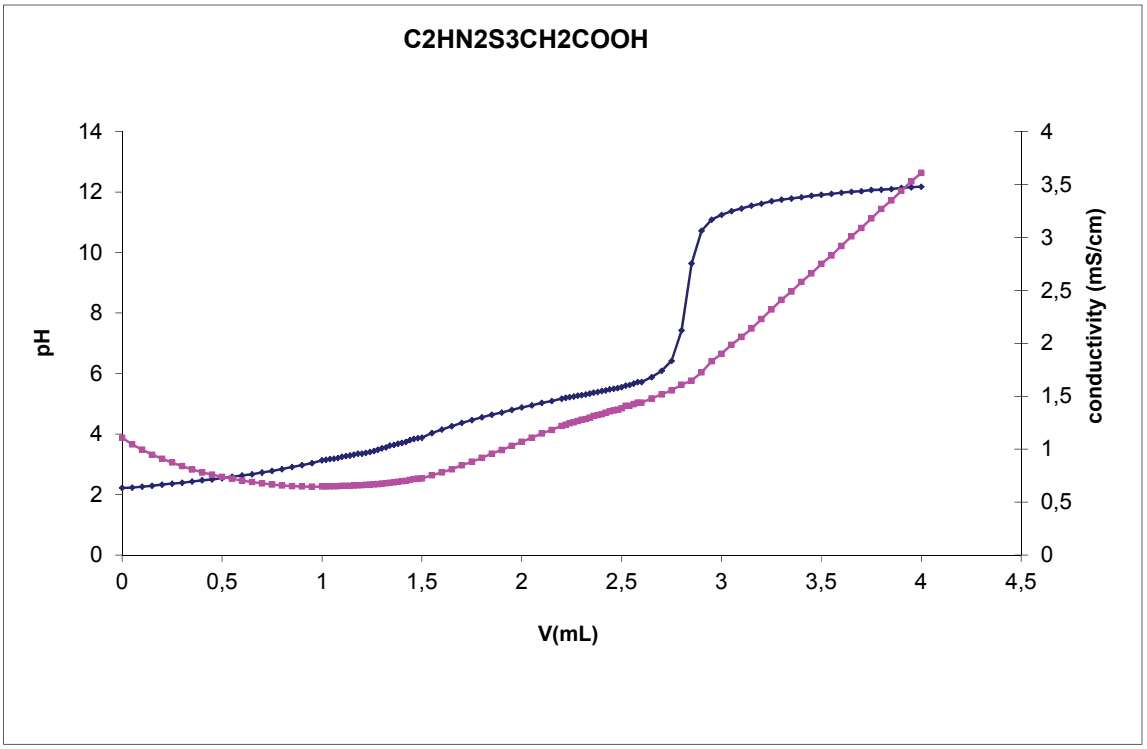


Figure 2. Conductometric (*) and acid-base titration (*) of 0.01M $C_4H_4S_3N_2O_2$ with 1M NaOH

Theoretical considerations regarding the thione-thiol tautomerism in 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid

Supplementary data

1. Computational part

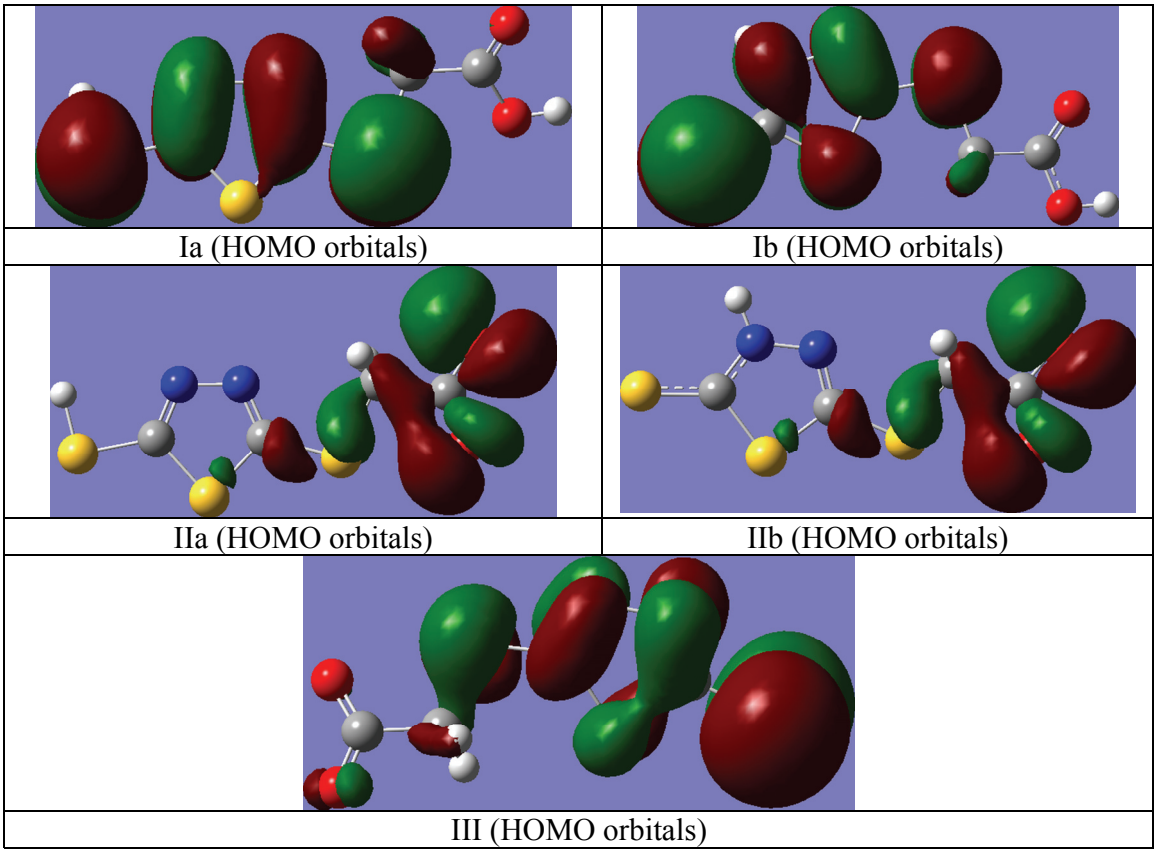


Figure 1. Graphical representation of HOMO orbitals

Free energies of solvation, computed at B3LYP/6-311+G(d,p), are presented in table below:

	ΔG_{solv} (kcal/mol)	
Compound	**IEFPCM**	**CPCM**
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Table 1. ΔG_{solv} (kcal/mol) (B3LYP/6-311+G(d,p) level of theory)

2. Experimental part

In order to evaluate the acidity constants of 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid, both potentiometric and conductometric titration were performed. Five identical samples of acid were employed, for obtaining the averaged value for each of the two acidity constants.

For each of the five samples, the pH at the equivalence point and the volume at the second equivalence point were determined by using the experimental data obtained during the potentiometric titration. The experimental data have been used for determining the acidity constants K_{a1} and K_{a2} by means of software applications (Visual Basic) developed by the authors (I. Julean and C. Muntean).

Figure 2 depicts the titration curves of the 2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)acetic acid. It can be observed the inflection of the curve at the first equivalence point, while the second equivalence point is characterized by a larger jump of pH. This behavior is usual for diprotic acids with similar values of the two acidity constants ($K_{a1}/K_{a2}<10^4$).

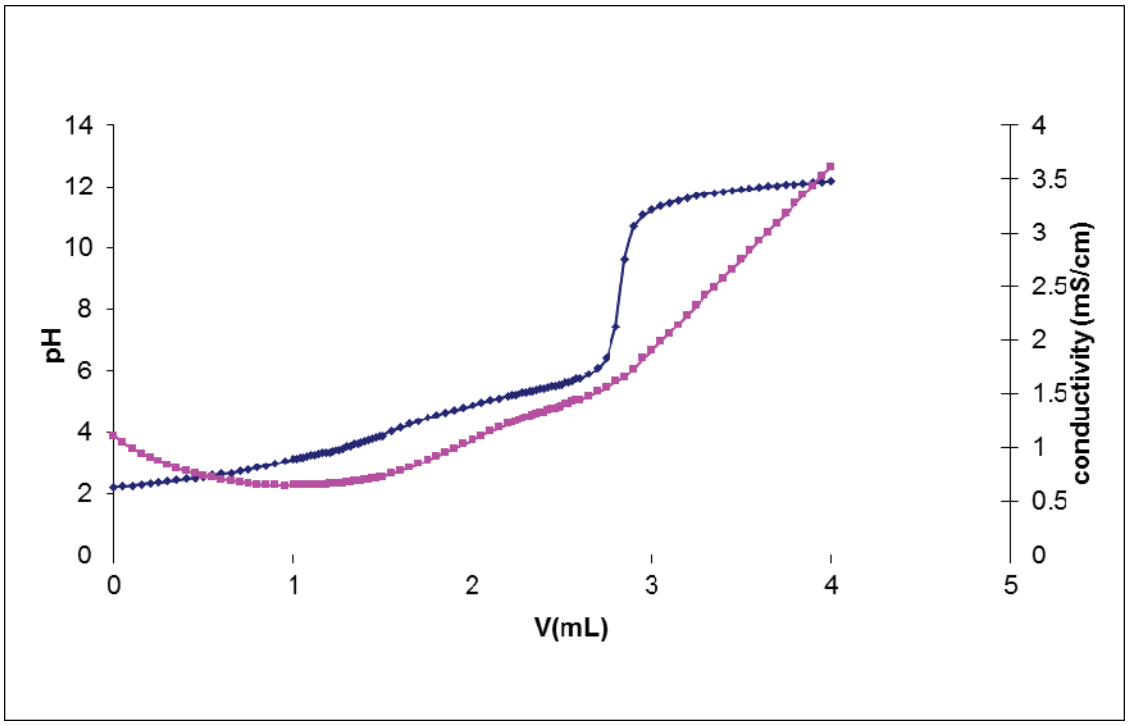
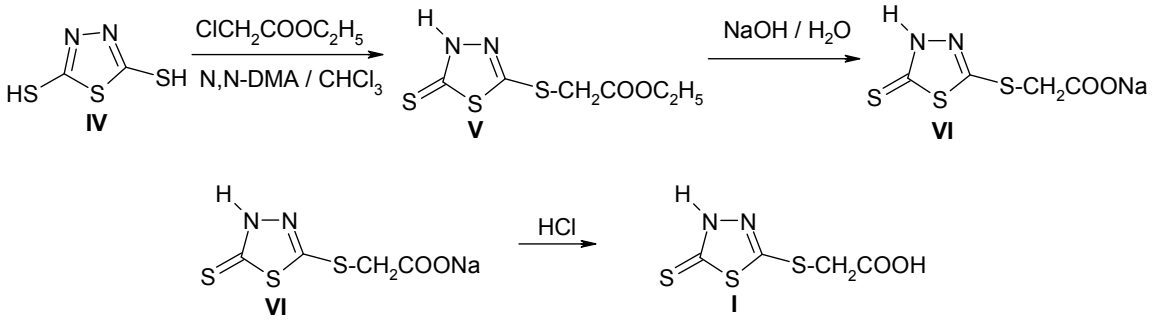


Figure 2. Conductometric (*) and acid-base titration (*) of 0.01M 2-mercapto-1,3,4-thiadiazol-5-yl thioacetic acid with 1M NaOH

Synthesis of 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetic acid

2-(5-Thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetic acid (**I**) was prepared according to **Scheme 1.** The alkylation of 2,5-dimercapto-thiadiazole (**IV**) was carried out with ethylchloroacetate in chloroform in the presence of N,N-dimethylaniline, followed by the hydrolysis of the raw ethyl 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio) acetate (**V**) with aqueous NaOH, which afforded the sodium salt (**VI**) of 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetic acid (**I**). Compound **VI** was transformed in the free acid (**I**) with diluted HCl.



Scheme 1. Synthesis of 3*H*-2-thioxo-1,3,4-thiadiazole-5-il) thioacetic acid (**I**).

Method: To a suspension of 0.04 moles of 2.5-dimercapto-thiadiazole and 0.044 moles of N,N-dimethylaniline in 25 mL $CHCl_3$ was added, without cooling, a solution of 0.041 moles ethylchloroacetate in 10 mL $CHCl_3$. After refluxing 90 min. and repeated washings at room temperature with water, diluted HCl, the solution was treated with anhydrous Na_2SO_4. After the solvent removal, the row product (**V**) was suspended at reflux in a solution of 0.044 mol NaOH in 30 mL water. The obtained solution was washed out by active charcoal, hot filtered and then cooled. After water recrystallization, the obtained product (VI) has a m.p.=268-270ºC. Compound VI was characterized by FT-IR-Raman spectroscopy and by single-crystal X-ray diffraction which prove its molecular structure as hydrate, $[Na(C_2HN_2S_3CH_2COO)(H_2O)_4]_2 \cdot 2H_2O$.

A water solution of sodium salt (VI) was treated with diluted HCl, and the precipitated acid (I) was recrystallized from water. The product was characterized by m.p.=160-162°C (lit[1] 164-166°C, FT-IR and Raman spectroscopy[2], ^{1}H-NMR and ^{13}C-NMR spectra recorded on a Bruker Avance 300MHz Spectrometer.

^{1}H-NMR: [DMSO-d_6, δ(ppm)]: 4.01 (s, 2H, CH_2)

^{13}C-NMR [DMSO-d_6, δ(ppm)]: 188.24 (C=S), 169.40(C-S), 157.88 (C=O), 35.43 (CH_2)

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