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

Supplementary data

1. Computational part

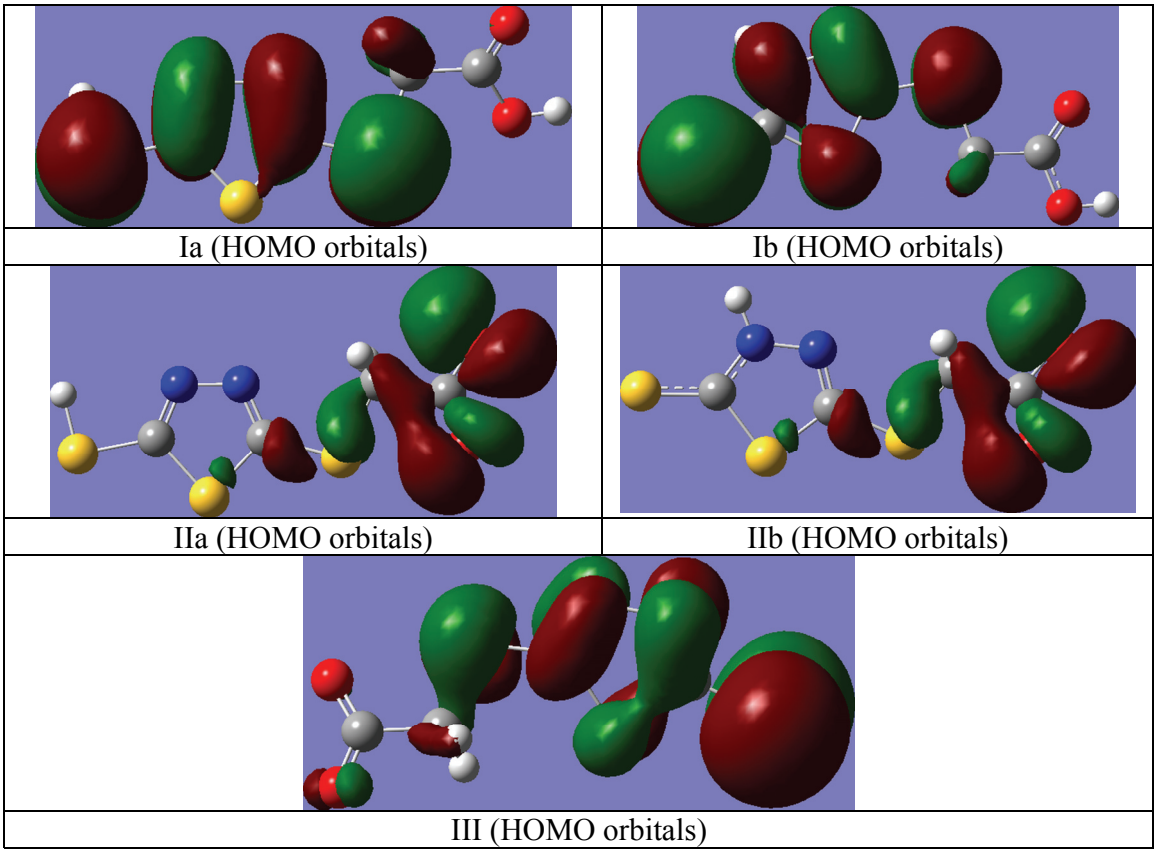


Figure 1. Graphical representation of HOMO orbitals

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

	ΔG_{solv} (kcal/mol)	
Compound	**IEFPCM**	**CPCM**
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. 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 ($K_{a1}/K_{a2}<10^4$).

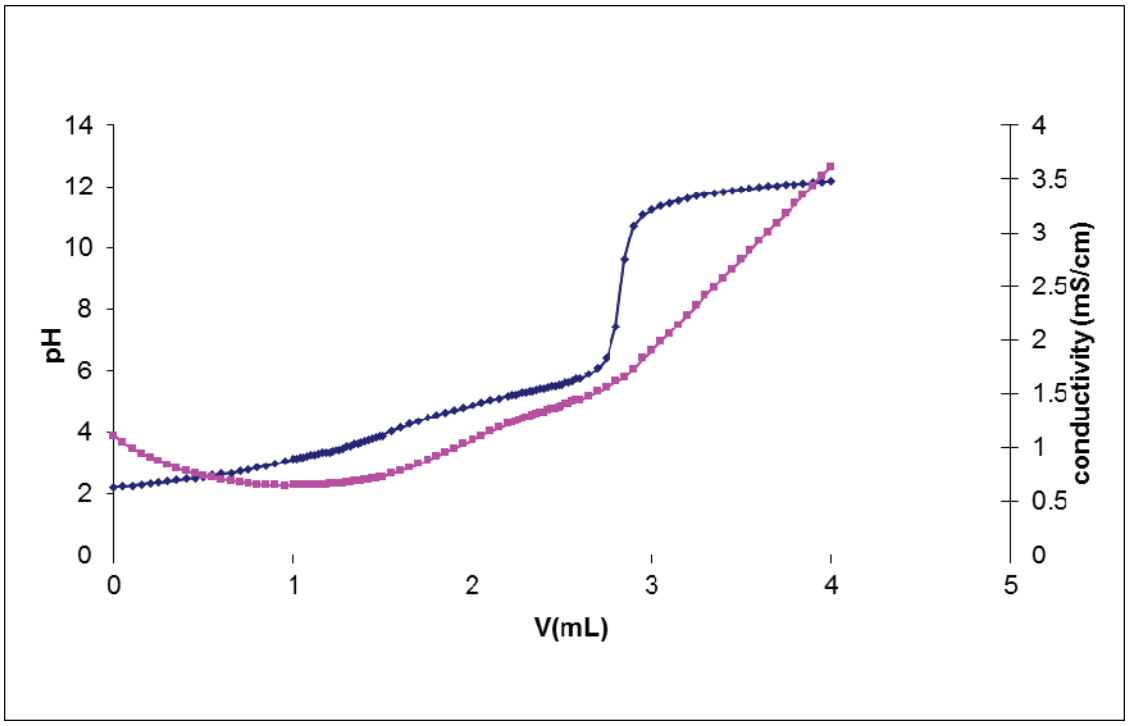
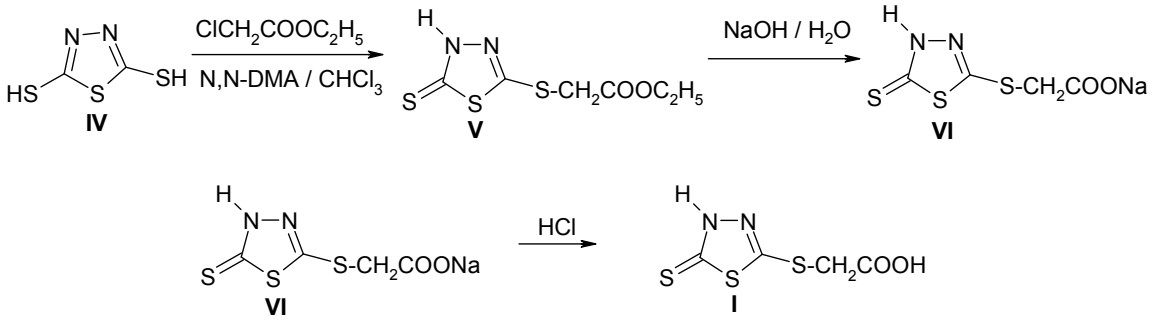


Figure 2. Conductometric (*) and acid-base titration (*) of 0.01M 2-mercapto-1,3,4-thiadiazol-5-yl thioacetic acid with 1M NaOH

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)

References

1. CarloErba SA, Dérivés thiéadiazolyliques d'acide 7-acylamido-3-cépheme-4-carboxylique et procédés de leur préparation, FR Patent Number 2,335,230, date of patent July 15, **1977.**

2. M. M. Venter, S. Cinta Pinzaru, V. Bercean, I. Haiduc, *Studia Univ. Babes-Bolyai*, *Physica* **2004,** *3*(XLIX), 285-288.