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Protolytic and Complexation Properties of the Cyclic Thiosemicarbazone Ligand

L. D. Popov[a], G. A. Gazieva[b], A. N. Kravchenko[b], Yu. N. Tkachenko[a], O. I. Askalepova[a], S. I. Levchenkov[c], T. B. Karpova[b], Yu. P. Tupolova[a], V. A. Kogan[a†]

[a] *Southern Federal University, Chemical Department, Rostov-on-Don, Russia*

[b] *Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia*

[c] *Southern Scientific Center of the Russian Academy of Sciences, ul. Chekhova 41, Rostov-on-Don, 344022 Russia*
e-mail: s.levchenkov@gmail.com

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Abstract—The acid–base properties of the thiourea based cyclic thiosemicarbazone have been studied. The tautomerism and complex formation ability of the thiosemicarbazone were investigated by the methods of quantum chemistry and electronic spectroscopy. The complexes of copper(II), nickel(II), cobalt(II), and mercury(II) were synthesized and their structure suggested.

Keywords: thiosemicarbazones, tautomerism, density functional theory, electronic spectroscopy, complex formation

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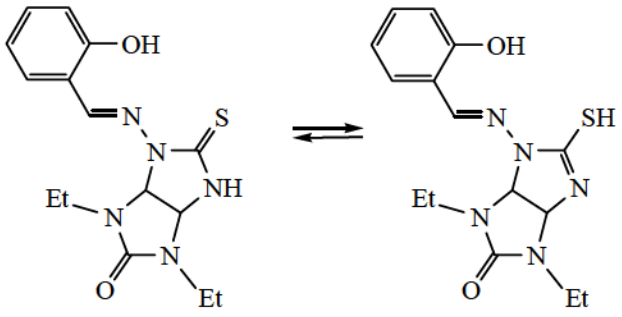
Thiosemicarbazones, products of condensation of carbonyl compounds with thiosemicarbazide derivatives, attract the attention of researchers due to their versatile biological activity [1–5] and high complex formation ability [6–11]. The anticancer [5, 12], antibacterial [4], antiviral [13] activity of thiosemicarbazones was reported. It is known that the introduction of metals into the molecule of thiosemicarbazones can enhance their biological activity [4, 14, 15]. In view of this, the search for new compounds of this type is a state-of-the-art problem. The goal of the present work was to investigate the protolytic and complexing properties of the cyclic analog of thiosemicarbazones, (*E*)-1,3-diethyl-4-[(2-hydroxybenzylidene)amino]-5-thioxohexahydroimidazo[4,5-*d*]-imidazol-2(1*H*)-one (**I**), which we had synthesized [16].

Due to the presence of several basic centers and acidic protons compound **I** can exist in various tautomeric forms, the main of which are the thione **Ia** and the thiol forms **Ib** (Scheme 1).

The ^{1}H NMR spectra and the results of X-ray diffraction (XRD) analysis of the analogs of compound **I** [16] allow the suggestion that the main tautomer is the thione form **Ia**. In order to determine the relative stability of possible forms we have performed calculations of the geometry and total energies of tautomers **Ia**–**Ib** in a vacuum and in ethanol solution.

The calculations of electronic and spatial structure were performed by the method of density functional theory (DFT). The solvent effect was taken into account using the polarizable continuum model (PCM) [17]. The hybrid exchange-correlation functional B3LYP [18–20] with the 6-311+G(d,p) valence-split basis set was employed. The geometry was fully optimized without symmetry restrictions. The minima on the potential energy surface (PES) were identified

Scheme 1.



Ia **Ib**

† Deceased.

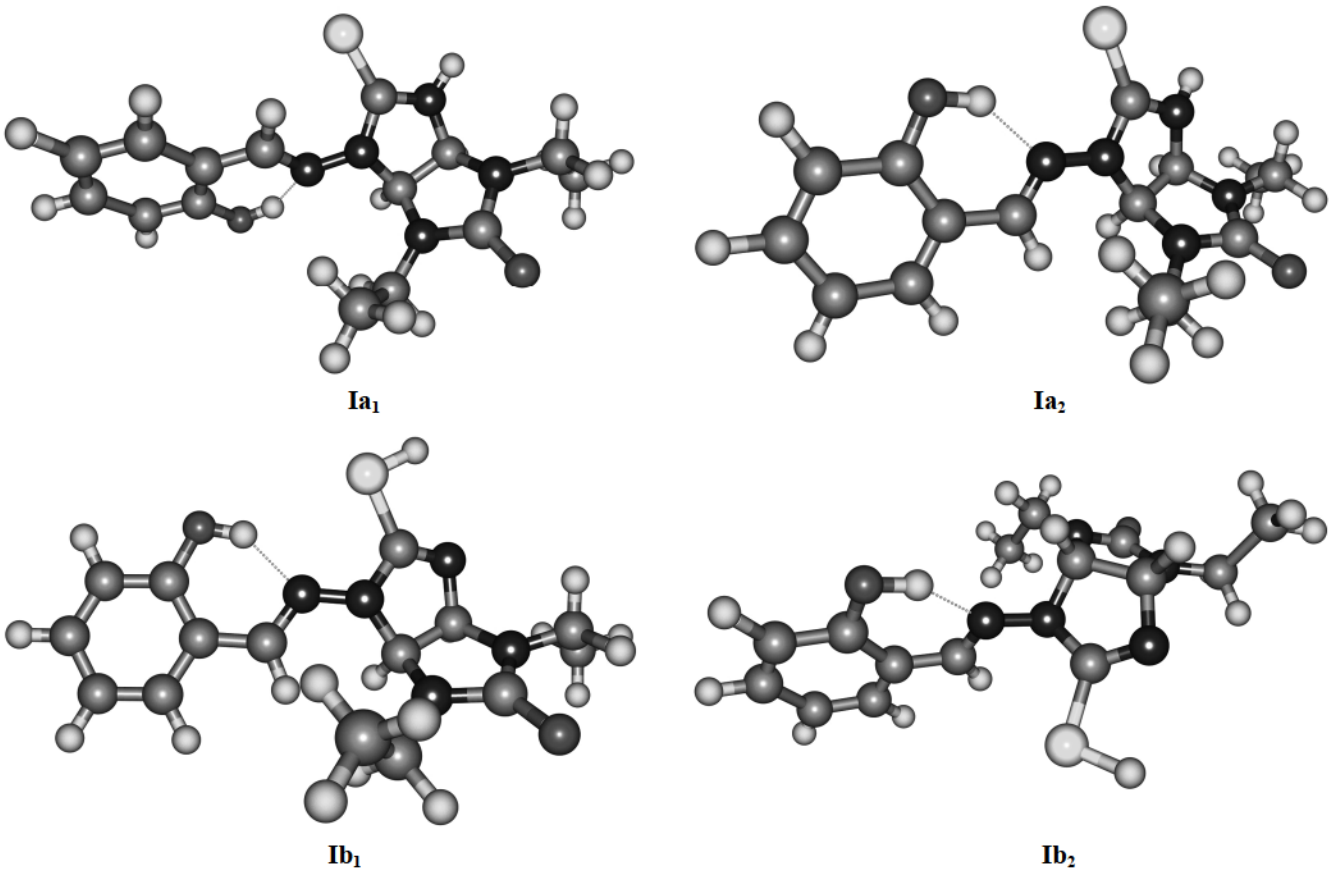


Fig. 1. General view of tautomeric forms of compound **I** in a vacuum.

for each structure by calculation of the force constants matrix and normal vibration modes. The calculated total energies of the isomeric structures (Fig. 1) of compound **I** in a vacuum and the relative energies are presented in Table 1.

According to calculations, the most stable form of compound **I** in a vacuum is the thione form **Ia**, for which two local minima were found corresponding to conformations $\mathbf{Ia_1}$ and $\mathbf{Ia_2}$, the latter (corresponding, according to XRD [16], to the structure of the dimethyl analog) being less stable by 2.52 kcal/mol. The most stable of the thiol forms $\mathbf{Ib_1}$ is destabilized by 13.8 kcal/mol with respect to $\mathbf{Ia_1}$.

In the ethanol solution the relative stability of the forms of compound **I** is changed. The total energies of the conformers of the thione form $\mathbf{Ia_1}$ and $\mathbf{Ia_2}$ become very close in energy, the $\mathbf{Ia_2}$ conformer being by 0.04 kcal/mol more stable than $\mathbf{Ia_1}$. At the same time, the total energy of the most stable conformation of the thiol tautomer $\mathbf{Ib_1}$ lies by 17.5 kcal/mol higher than $\mathbf{Ia_2}$. This allows to assume that in solution compound **I** also exists mainly in the thione form.

The structure of compound **I** predetermines the possibility for it to exist in the solution, depending on the pH, in the molecular, protonated or anionic forms. In the acidic medium the azomethine or the heterocyclic nitrogen atoms, or the sulfur atom can be protonated. In alkaline medium deprotonation of the phenolic hydroxyl or the NH group is possible.

Possible protolytic equilibria of compound **I** were studied by the method of potentiometric titration in aqueous-ethanol solution [21]. The obtained results suggest that in the pH interval 1–12 only one equilibrium is realized corresponding to elimination of one proton, with the pK_a constant of 10.54±0.06.

The electron absorption spectrum of the alcoholic solution of compound **I** contains the absorption bands at 225, 260, 299, and 327 nm. In aqueous-alcoholic solutions in the range of pH 1–8.5 the pattern of the spectrum does not change, which is indicative of the absence of protonation of compound **I**. In the alkaline medium a new absorption band appears at λ_{max} = 379 nm, and the intensity of the bands at λ_{max} 299 and 327 nm decreases (Fig. 2). The spectral characteristics

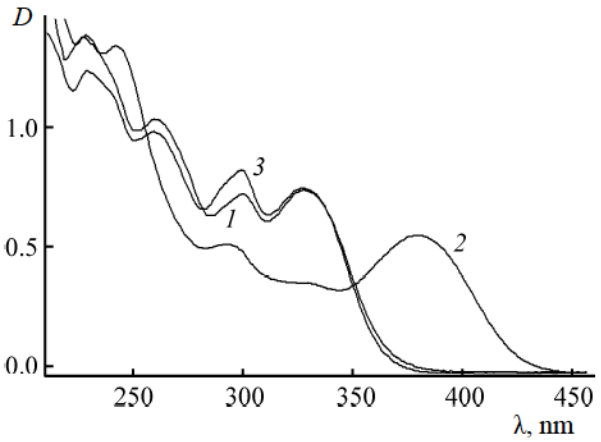


Fig. 2. Electronic spectra of the (*1*) molecular and (*2*) anionic forms of compound **I** in aqueous–ethanol (1 : 1) solutions and in (*3*) pure ethanol. $C = 2.8 \times 10^{-5}$ M.

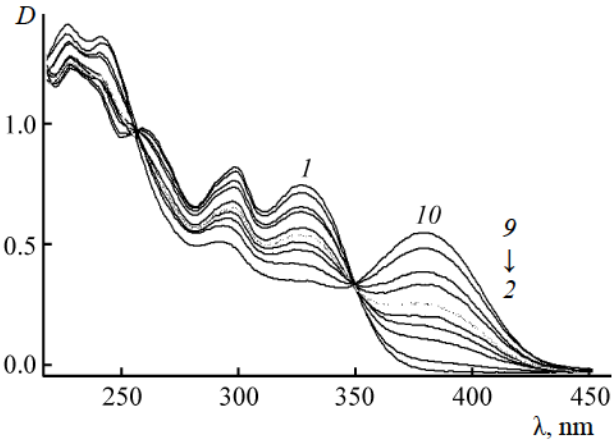


Fig. 3. Electron absorption spectra of aqueous–alcoholic (1 : 1) solutions of thiosemicarbazone **I** at the values of pH: (*1*) 6.11, (*2*) 9.42, (*3*) 10.06, (*4*) 10.22, (*5*) 10.48, (*6*) 10.57, (*7*) 10.85, (*8*) 10.99, (*9*) 11.4, and (*10*) 11.9. $C = 2.8 \times 10^{-5}$ M.

of the solutions of compound **I** are as follows, λ_{max} (ε_{max}), nm: molecular form, 299 (1.88×10^4), 327 (1.66×10^4); anionic form, 299 (1.36×10^4), 327 (1.07×10^4), 379 (7.95×10^3).

A substantial red shift of the long-wave absorption band in the alkaline medium allowed the spectrophotometric measurement of the dissociation constant ($pK_a = 10.5 \pm 0.1$), which practically coincides with that determined by potentiometric method. In Fig. 3 the spectra of aqueous-ethanolic solutions of compound **I** at different values of pH are shown.

The presence of several donor centers connected by the system of double bonds in the molecule of compound **I** allows a suggestion that it can act as an effective complexing agent. In order to investigate the complexing ability we have registered the electron absorption spectra of aqueous-alcoholic solutions of compound **I** in the presence of a series of metal cations. No changes were observed in the spectra in the presence of manganese(II) or iron(II) ions with respect to the solution of compound **I**, and for zinc(II) the spectral changes were negligible.

On the contrary, in the presence of copper(II), nickel(II), and cobalt(II) notable changes are observed in the spectra suggesting the formation of complexes of compound **I** with these ions. In the presence of cobalt(II), a long-wave absorption band with λ_{max} ~380 nm is observed, almost coinciding with the absorption band of the anionic form of compound **I** but more intense. In the presence of nickel(II) or copper(II) the long-wave band suffers even more pronounced shift to ~400 nm (Fig. 4).

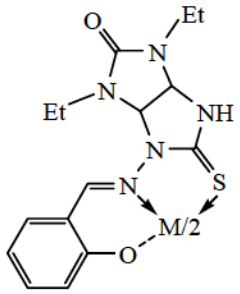
We were able to isolate preparatively the complexes of compound **I** with copper(II), nickel(II), cobalt(II), and mercury(II). All complexes were amorphous, high melting powders, poorly soluble in the main organic solvents except for DMF, DMSO. and pyridine. The composition of the obtained complexes corresponds to the general formula ML_2, where L is monodeprotonated residue of compound **I**.

In the ^{1}H NMR spectrum of the complex with mercury(II) as compared to the spectrum of the ligand the signal of the phenolic OH proton disappears, the signal of the azomethine proton is shifted upfield by 0.67 ppm, and the signal of the NH proton of the cyclic fragment is slightly shifted downfield by 0.15 ppm. The shifts of other protons are negligible.

Total and relative energies of tautomers of compound **I**

Structure	Total energy, au		ΔE, kcal/mol	
	vacuum	ethanol	vacuum	ethanol
Ia$_1$	–1405.7507262	–1405.7636784	0	0.04
Ia$_2$	–1405.7467035	–1405.7637471	2.52	0
Ib$_1$	–1405.7287865	–1405.7358891	13.8	17.5
Ib$_2$	–1405.7254390	–1405.7354056	15.9	17.8

The coordination of the ligand in the monodeprotonated form is confirmed by the absence of the absorption band of the phenolic fragment ν(OH) in the IR spectra of complexes, which was registered in the spectrum of compound **I** at 3350 cm^{-1}. A low-frequency shift of the absorption bands ν(C=N) (by 15–20 cm^{-1}) and ν(C=S) (by 5–10 cm^{-1}) is indicative of coordination of the azomethine nitrogen atom and the sulfur atom to the metal ions. The position of the absorption band corresponding to stretching vibrations ν(C=O) in the spectra of complexes remains practically unchanged. Based on these data, it is presumable that in the complexes the monodeprotonated residue of compound **I** acts as a tridentate O,N,S-donor ligand, and the complexes have the structure of the type **II** with octahedral arrangement of the metal ions.



II

The above structure is indirectly confirmed by the results of magnetochemical measurements. The values of effective magnetic moments of the Cu(II) and Ni(II) complexes are close to pure spin complexes (1.82 and 2.90 μB respectively), which points to the absence of a substantial orbital contribution, and is an indirect confirmation of the octahedral arrangement of the paramagnetic centers; the value of μ_{eff} for the Co(II) complex (4.60 μB) is significantly higher than the pure spin value due to spin-orbital interactions, which is characteristic of the hexacoordinate Co(II) complexes [22]. The values of μ_{eff} of the complexes are almost insensitive to temperature upon cooling to the boiling point of liquid nitrogen, which suggests a mononuclear structure of complexes of the type **II**.

EXPERIMENTAL

Elemental analysis was performed on a Perkin–Elmer 240C instrument. ^{1}H NMR spectra were registered in DMSO-d_6 on a Varian Unity 300 spectrometer (300 MHz), internal reference HMDS. IR spectra were recorded on a Varian Scimitar 1000 FT-IR instrument in the range 400–4000 cm^{-1} from

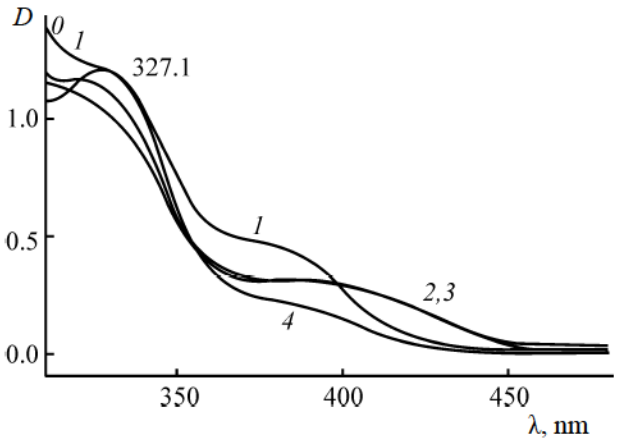


Fig. 4. Electron absorption spectra of aqueous-alcoholic solutions of complexes of thiosemicarbazone (I) with (*1*) Co^{2+}, (*2*) Ni^{2+}, (*3*) Cu^{2+}, and (*4*) of pure compound **I**. C_{Me} = 2×10^{-6} M, $C_R = 1 \times 10^{-4}$ M.

suspensions in mineral oil. Magnetic susceptibility was measured by the relative Faraday method in the temperature range 77.4–300 K; as a reference for calibration $Hg[Co(CNS)_4]$ was used. Electron absorption spectra were registered on a Varian Cary 50 Scan spectrophotometer in the range 200–800 nm. pH values were measured and ionization constants determined by potentiometric titration on a "Ecotest 2000 Ekoniks" pH-meter ionomer.

Quantum chemical calculations were performed on WSD and INFINI of the Computing Center of Southern Federal University using Gaussian'03 program [23]. For processing of the data and visualization of the results the ChemCraft program was used [24].

(*E*)-1,3-Diethyl-4-[(2-hydroxybenzylidene)amino]-5-thiooxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (I) was prepared by the earlier described procedure [16]. IR spectrum, ν, cm^{-1}: 3350 ν(OH), 3235 (NH), 1698 (C=O), 1620 (C=N), 1255 (C=S). ^{1}H NMR spectrum, δ, ppm: 1.02 t (3H, CH_3, J = 7.0 Hz), 1.09 t (3H, CH_3, J = 7.0 Hz,), 3.10–3.48 m (4H, CH_2), 5.58 d (1H, CH_{het}, J = 8.3 Hz), 6.18 d (1H, CH_{het}, J = 8.3 Hz), 6.92–6.95 m (2H, CH_{arom}), 7.33 t (1H, CH_{arom}, J = 7.6 Hz), 7.59 d (1H, CH_{arom}, J = 7.5 Hz), 8.91 s (1H, CH=N), 10.20 br. s (1H, NH), 10.91 br. s (1H, OH).

General procedure of the synthesis of metal complexes. To the boiling solution of 2 mmol of compound **I** in 15 mL of methanol the solution of 1 mmol of acetate of the corresponding metal in 5 mL of methanol was added, the solution was refluxed for 3–5 h until the precipitate was formed. The product

was filtered off, washed twice with boiling methanol, and dried in a vacuum.

Copper(II) complex. Yield 0.39 g (53%), fine-crystalline dark-green powder, mp > 250°C. IR spectrum, ν, cm^{-1}: 3225 (NH), 1699 (C=O), 1605 (C=N), 1250 (C=S). μ_{eff} (μB): 1.82 (298 K), 1.80 (77.4 K). Found, %: C 50.2; H 5.05; N 19.4; Cu 8.95. $C_{30}H_{36}CuN_{10}O_4S_2$. Calculated, %: C 49.5; H 4.98; N 19.2; Cu 8.72.

Nickel(II) complex. Yield 0.49 g (68%), amorphous light-green powder, mp > 250°C. IR spectrum, ν, cm^{-1}: 3119 (NH), 1690 (C=O), 1612 (C=N), 1246 (C=S). μ_{eff} (μB): 2.90 (298 K), 2.87 (77.4 K). Found, %: C 50.0; H 4.91; N 20.0. $C_{30}H_{36}NiN_{10}O_4S_2$. Calculated, %: C 49.8; H 5.02; N 19.4.

Cobalt(II) complex. Yield 0.43 g (60%), fine-crystalline wine-colored powder, mp > 250°C. IR spectrum, ν, cm^{-1}: 3215 (NH), 1690 (C=O), 1607 (C=N), 1245 (C=S). μ_{eff} (μB): 4.60 (298 K), 4.46 (77.4 K). Found, %: C 50.3; H 5.11; N 19.6. $C_{30}H_{36}CoN_{10}O_4S_2$. Calculated, %: C 49.8; H 5.01; N 19.4.

Mercury(II) complex. Yield 0.48 g (55%), amorphous white powder, mp >250°C. IR spectrum, ν, cm^{-1}: 3195 (NH), 1690 (C=O), 1610 (C=N), 1248 (C=S). ^1H NMR spectrum: 10.34 br.s (1H, NH,), 8.22 br.s (1H, CH=N), 7.60 d (1H, CH_{arom}, J = 7.8 Hz), 7.22 t (1H, CH_{arom}, J = 7.8 Hz), 6.90–6.82 m (2H, CH_{arom}), 5.96 d (1H, CH_{het}, J = 8.1 Hz,), 5.50 s (1H, CH_{het}), 3.52–3.15 m (4H, CH_2), 1.11–1.01 m (6H, CH_3). Found, %: C 42.1; H 4.16; N 16.0. $C_{30}H_{36}HgN_{10}O_4S_2$. Calculated, %: C 41.6; H 4.19; N 16.2.

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