

Acid–Base Properties of Bis(hydrazinocarbonylmethyl) Sulfoxide and Its Complex Formation with Copper(II) and Nickel(II)

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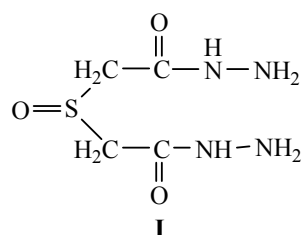
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Abstract—Behavior of physiologically active compound, bis(hydrazinocarbonylmethyl) sulfoxide, in aqueous solution has been studied by means of potentiometry, spectrophotometry, and mathematical simulation. Protolytic properties of bis(hydrazinocarbonylmethyl) sulfoxide have been described, and the formation of sodium salt has been confirmed. Composition and stability constants of bis(hydrazinocarbonylmethyl) sulfoxide complexes with copper(II) and nickel(II) have been determined, and the complexes structures have been simulated by molecular mechanics method.

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Bis(hydrazinocarbonylmethyl) sulfoxide **I** (2,2'-sulfinyldiacetohydrazide) and related hydrazides of some sulfur-containing acids are interesting due to their antitumor activity [1, 2]. Similar to other acid hydrazides, they can have antituberculous activity. However, properties of these compounds have not been studied in detail.



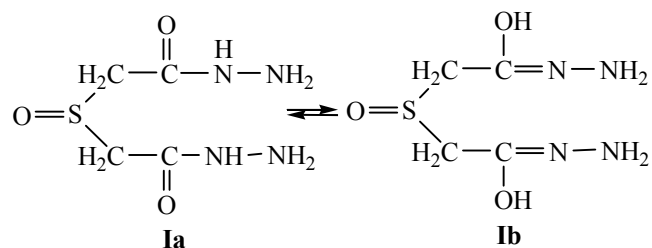
Some publications include the description of properties of compounds containing functional groups of **I**. In particular, complexes of copper, nickel, cobalt, iron, manganese, zinc, cadmium, lead, palladium, silver, and rhodium with dihydrazides of malonic and succinic acids have been prepared [3, 4], and their spectral, magnetic, and conductive properties have been studied in solid state as well as in solution. X-ray diffraction studies of metal coordination compounds with hydrazides have been reviewed in [5]. Complex formation of copper(II), nickel(II), and cobalt(II) with

dihydrazides of malonic and adipic acids in water as well as in aqueous-organic solvents have been described in [6].

The state of compound **I** in solution has not been studied so far; its acid-basic and complexing properties have been unknown as well. Yet being important *per se* this information assists in prediction of the compound properties in various media.

Here we report on protolytic properties of compound **I** and its complex formation ability towards copper(II) and nickel(II) in aqueous solutions. Furthermore, the structures of compound **I** and its complexes as simulated by means of molecular mechanics are presented.

Similarly to other acid hydrazides [7], compound **I** may be involved in the tautomerism **Ia** \rightleftharpoons **Ib**.



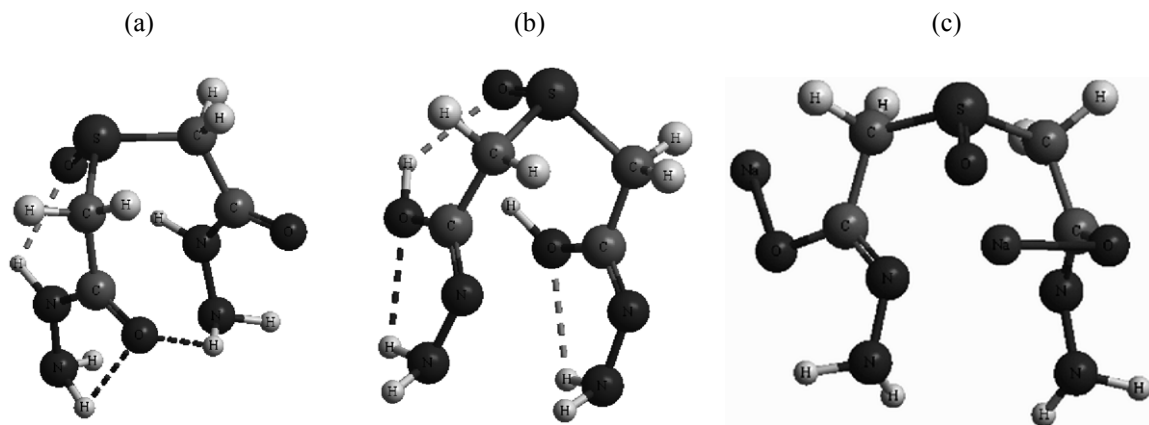


Fig. 1. Optimized spatial structures of (a) amide ($E = -12.33$ kcal/mol) and (b) imidol ($E = -13.14$ kcal/mol) forms of compound **I** and (c) of compound $[\text{Na}_2\text{D}_2]$ ($E = -146.9$ kcal/mol).

Figure 1 displays optimized structures of amide (**Ia**) and imidol (**Ib**) forms of compound **I**. Both forms possess a convolute conformation stabilized by intramolecular hydrogen bonds involving both hydrazide fragments and oxygen atoms of sulfoxide group. Potential energies of both forms were close, hence, both forms should be present in solutions, likely the imidol form being somewhat preferred.

^1H NMR spectrum of compound **I** in DMSO contained signals of hydrazide group at 4.37 ppm (NH_2) and at 9.38 ppm (NH) in the ratio of 2 : 1; the signal of hydroxy groups was absent. Therefore, compound **I** in DMSO existed in the amide form.

IR spectrum of compound **I** showed that it existed as well in the solid state in the hydrazide form [8]. The spectrum contained intense absorption bands of $\nu(\text{C}=\text{O})$ (amide I) at 1664 cm^{-1} , amide group vibrations (amide II): $\delta(\text{NH}_2)$ at 1600 cm^{-1} and $\delta(\text{NH})$ at 1544 cm^{-1} , $\nu(\text{S}=\text{O})$ at 1021 cm^{-1} as well as a broad band of $\nu(\text{N}-\text{H})$ with several maxima at 3188, 3312, and 3332 cm^{-1} .

Data of potentiometric titration of compound **I** in solution are given in Fig. 2 in the form of so-called formation curves: plots of Bjerrum function (n) versus pH [9].

The experimental data were further simulated using the mathematical model; below the deduced parameters of protolytic equilibria (1)–(3) are given (hereinafter D represents compound **I**, α_{max} stands for the highest ratio of the respective form at pH_{max}).

Equilibrium	$\log K$	α_{max}	pH_{max}
$\text{D} + \text{H}^+ \rightleftharpoons [\text{HD}]^+$ (1)	2.73 ± 0.01	0.50	2.43
$\text{D} + 2\text{H}^+ \rightleftharpoons [\text{H}_2\text{D}]^{2+}$ (2)	4.86 ± 0.06	0.36	2.25
$\text{D} + 2\text{Na}^+ \rightleftharpoons [\text{Na}_2\text{DH}_2] + 2\text{H}^+$ (3)	-6.55 ± 0.26	0.99	10.06

Under acidic conditions, two protonated forms of the compound existed, $[\text{HD}]^+$ and $[\text{H}_2\text{D}]^{2+}$, their formation constants being close to those of malonic acid dihydrazide (2.75 and 4.55, respectively, [3]). According to [6], $\log K$ of malonic acid dihydrazide were 3.13 ± 0.01 and 5.25 ± 0.03 at $I = 0.01$ (KNO_3), the corresponding values in the case of adipic acid

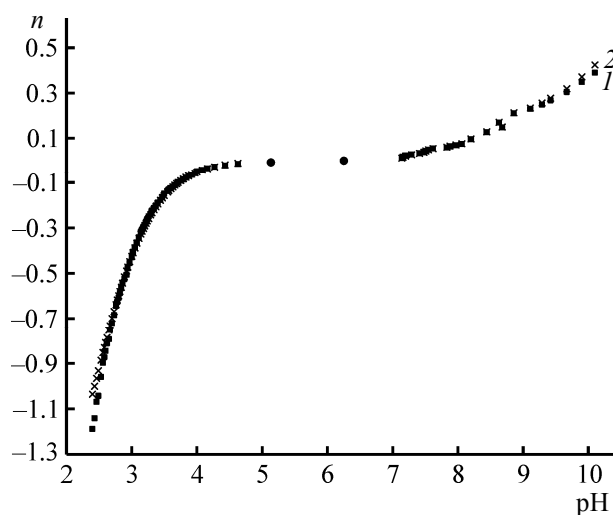


Fig. 2. (1) Experimental and (2) theoretical pH dependence of the Bjerrum function. $c_1 = 5 \times 10^{-3}$ mol/L.

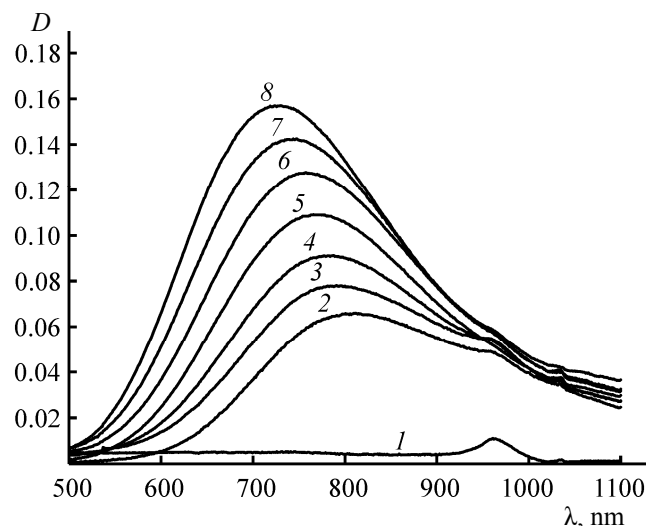


Fig. 3. Absorption spectra of solutions (1) of compound **I**, (2) Cu^{2+} and (3–8) Cu^{2+} in the presence of compound **I**. c_{I} , mol/L: (1) 2.3×10^{-3} , (3) 1.1×10^{-3} , (4) 2.5×10^{-3} , (5) 5.1×10^{-3} , (6) 8.0×10^{-3} , (7) 1.33×10^{-2} , (8) 2.12×10^{-2} ; $c_{\text{Cu}^{2+}}$ 4.9×10^{-3} (2–8). λ_{max} , nm: (2) 817, (3) 791, (4) 787, (5) 766, (6) 757, (7) 744, (8) 730; ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$: (2) ϵ_{817} 13.3, (3) ϵ_{791} 15.8, (4) ϵ_{787} 18.5, (5) ϵ_{766} 22.1, (6) ϵ_{757} 25.8, (7) ϵ_{744} 28.8, (8) ϵ_{730} 31.8; pH: (1) 6.00; (2) 5.00; (3) 4.11, (4) 4.00, (5) 3.85, (6) 3.85, (7) 3.90, (8) 3.90.

dihydrazide were 3.61 ± 0.01 and 6.54 ± 0.03 at $I = 0.01$ (NaNO_3).

Neutral form of compound **I** dominated at pH of 4.5–7.0. Deprotonated imidol forms of the compound were not detected. Dissociation of imidol form of acid dihydrazides has not been described in the literature so far.

In order to properly describe potentiometric experimental data under basic conditions ($\text{pH} > 7.5$), the formation of disodium salt of the dihydrazide imidol form should have been assumed; the convolute conformation of the compound was retained (Fig. 1c).

The changes of UV absorption spectrum of compound **I** ($c = 1.1 \times 10^{-4}$ mol/L) in the presence of two-fold quantity of NaOH (blue shift of the band maximum to $\lambda_{\text{max}} = 194$ nm accompanied with the intensity increase, $\Delta A_{194} = 0.17$) could be due to absorption of disodium salt of the imidol form **Ib**.

Interaction between compound **I** and copper(II) was confirmed by acidification of aqueous solution of the latter in the presence of **I** and by sharp increase of the solution absorbance ($\Delta A_{200} \approx 1.2$). Changes in the

visible part of the spectrum were less evident due to lower absorbance of both the complex and the metal ion in that spectral range. Nevertheless, in the presence of increasing amounts of **I**, the blue shift of copper(II) absorption band was evident (Fig. 3).

The decrease in the solution pH [$\Delta \text{pH} = 0.69$ at 5.6×10^{-5} mol/L of copper(II) and 1.18×10^{-4} mol/L of **I**; $\Delta \text{pH} = 1.29$ at 1.00×10^{-2} mol/L of copper(II) and 2.00×10^{-2} mol/L of **I**] may signify that the complex formation occurs with imidol form **Ib**. Equilibria (4)–(6) were established, giving three neutral complexes.

Equilibrium	$\log K$	α_{max}	ϵ_{290}	pH_{max}
$\text{Cu}^{2+} + \text{D} \rightleftharpoons [\text{CuDH}_2] + 2\text{H}^+$ (4)	7.82 ± 0.02	0.86	42	4.68
$2\text{Cu}^{2+} + 2\text{D} \rightleftharpoons [\text{Cu}_2(\text{DH}_2)_2] + 4\text{H}^+$ (5)	18.01 ± 0.04	0.51	254	3.85
$\text{Cu}^{2+} + 2\text{D} \rightleftharpoons [\text{Cu}(\text{DH}_1)_2] + 2\text{H}^+$ (6)	9.88 ± 0.08	0.48	741	3.90

In Eqs. (4)–(6), DH_2^- and DH_1^- are anions of the imidol form of compound **I**.

The combination of Eqs. (4) and (5) allowed the determination of dimerization equilibrium constant, K_7 .



$$\log K_7 = \log K_5 - 2\log K_4 \log K_7 2.37.$$

The complexes spatial structure was simulated under assumption of different types of the ligand coordination.

In the case of $[\text{CuDH}_2]$ complex (Fig. 4a) computed values of potential energy showed that bidentate coordination of both deprotonated imidol hydrazide fragments via oxygen atoms was preferential ($E = 7.32$ kcal/mol). As a result, the charge of the central ion (Cu^{2+}) was neutralized, and the eight-membered cycle was formed due to the favorable ligand geometry. The eight-membered ring containing copper(II) was non-planar (the dihedral angles θ and α were 120.97° and 113.5° , respectively) (Fig. 4b). The complex structure was likely additionally stabilized by the five-membered cycle formed due to hydrogen bonding at the hydrazide part.

Participation of the sulfoxide group oxygen in coordination (in that case the ligand was tridentate) was unfavorable by energy ($E = 46.66$ kcal/mol). Other

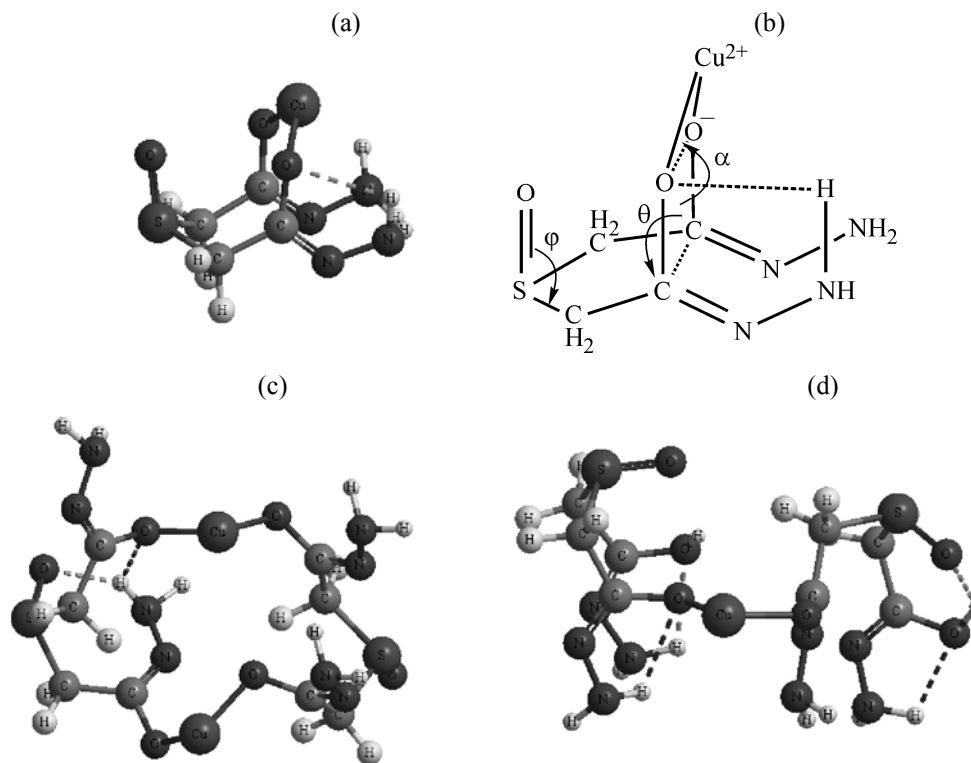


Fig. 4. Optimized spatial structures of copper(II) complexes with compound D (**I**). (a, b) $[\text{CuDH}_2]$ (θ 120.97°, α 151.0°, φ 113.5°), (c) $[\text{Cu}_2(\text{DH}_2)_2]$, and (d) $[\text{Cu}(\text{DHL}_1)_2]$.

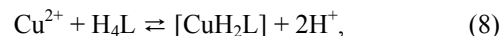
coordination types (tetradentate coordination via two oxygen atoms of anionic imidol fragments and two amino groups, $E = 283.59$ kcal/mol; bidentate coordination via one of two deprotonated imidol fragments to form five-membered metal cycle, $E = 55.93$ kcal/mol), were even less favorable.

In the case of $[\text{Cu}_2(\text{DH}_2)_2]$ dimer, the lowest potential energy corresponded to the structure with anionic imidol fragments coordinated via oxygen atoms bridging both metal ions (Fig. 4c; $E = 11.98$ kcal/mol). Under the assumption of additional coordination via two or four amino groups, potential energy of the corresponding structures was significantly higher (112.54 and 305.67 kcal/mol, respectively).

Similarly, in the case of $[\text{Cu}(\text{DHL}_1)_2]$ complex in the most favorable structure each monodentate ligand was bound to copper(II) via oxygen atom of deprotonated imidol form of hydrazide fragment. The non-coordinated hydrazide fragments were in imidol form as well (Fig. 4d, $E = -11.54$ kcal/mol). Bidentate coordination of one ($E = 69.25$ kcal/mol) or both ($E = 132.72$ kcal/mol) hydrazide fragments was less favorable due to ligand steric restrictions.

To conclude, in the cases of the three observed neutral complexes of copper(II), bidentate coordination of hydrazide parts of compound **I** via oxygen atoms of its anionic imidol form was operative.

Noteworthy, bidentate coordination via oxygen atoms of two phenolate groups of methylresorcinol with formation of eight-membered cycle was suggested in the case of $[\text{Cu}(\text{H}_2\text{L})]$ neutral complex in aqueous 2-propanol (80 vol % of the alcohol) [10].



$$\log K_8 = -5.54 \pm 0.09.$$

In Eq. (8), $(\text{H}_2\text{L})^{2-}$ designates dianion of 2,2-bis-[(2,4-dihydroxy-3-methylphenyl)ethyl]methylamine H_4L . The comparison of complex formation constants of Eqs. (4) and (8) [10] demonstrated the high stability of $[\text{CuDH}_2]$ complex.

Amorphous precipitate was formed upon incubation of solutions of compound **I** in the presence of copper(II). Further on, solutions with $c_{\text{Cu}^{2+}} = 4.9 \times 10^{-3}$ mol/L became viscous gel-like fluids. The gels formed at higher concentration of the ligand were

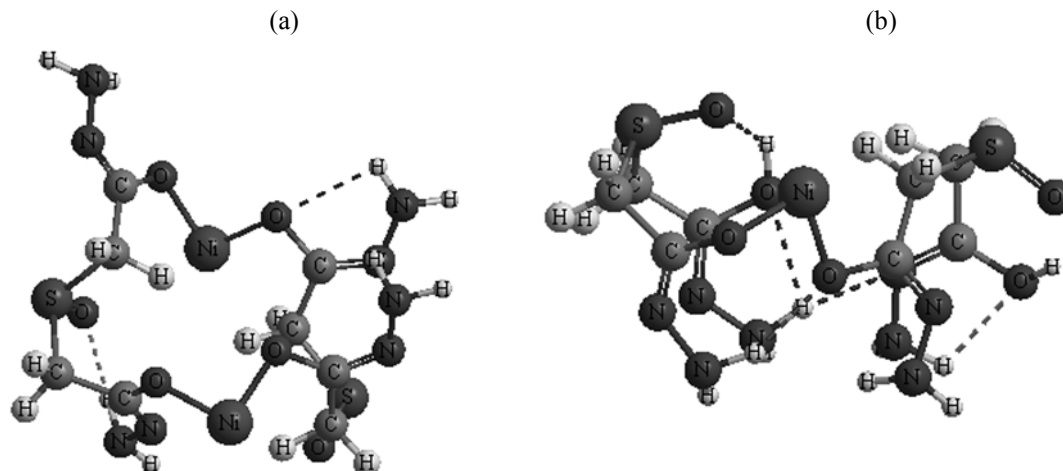


Fig. 5. Optimized spatial structures of nickel(II) complexes with compound D (**I**) (a) $[\text{Ni}_2(\text{DH}_2)_2]$ ($E = -6.28$ kcal/mol) and (b) $[\text{Ni}(\text{DH}_1)_2]$ ($E = -21.06$ kcal/mol).

stable over at least a month. Similar gel formation was observed in the case of Cu(II) – malonic acid systems in water or aqueous DMSO [6]; however, in the latter case, the gels were steadily disintegrated over several weeks due to slow Cu(II) reduction to elemental copper. No sign of copper(II) reduction was observed in this work in the presence of compound **I**.

Additionally, we studied complex formation between compound **I** and nickel(II). At pH of 5.53–6.21, neutral 2 : 2 $[\text{Ni}_2(\text{DH}_2)_2]$ [Eq. (9)] and 1 : 2 $[\text{Ni}(\text{DH}_1)_2]$ [Eq. (10)] complexes were formed.

Equilibrium	$\log K$	α_{\max}	ϵ_{252}	pH_{\max}
$2\text{Ni}^{2+} + 2\text{D}$ $\rightleftharpoons [\text{Ni}_2(\text{DH}_2)_2] + 4\text{H}^+$ (9)	19.07 ± 0.34	0.99	297	5.66
$\text{Ni}^{2+} + 2\text{D}$ $\rightleftharpoons [\text{Ni}(\text{DH}_1)_2] + 2\text{H}^+$ (10)	9.53 ± 0.27	0.09	999	5.61

No turbidity was observed in those solutions over prolonged incubation.

In contrast to the case of copper(II)-containing systems, $[\text{NiDH}_2]$ complex was not observed. The fraction of $[\text{Ni}(\text{DH}_1)_2]$ was no higher than 9%; the dimer form $[\text{Ni}_2(\text{DH}_2)_2]$ prevailed. From the equilibrium constants, the dimer nickel(II) complex was more stable than the corresponding copper(II) complex. In the nickel(II) complexes, similarly to those of copper(II), hydrazide fragments of compound **I** were coordinated to metal ions via oxygen atoms of anionic imidol form (Figs. 5a, 5b); thus, the ligand was bidentate.

Potential energy of dimer complexes revealed higher stability of nickel(II) complexes as well: $[\text{Ni}_2(\text{DH}_2)_2]$, $E = -6.28$ kcal/mol and $[\text{Cu}_2(\text{DH}_2)_2]$, $E = 11.98$ kcal/mol. Probably that could result from additional hydrogen bonding between amino group hydrogen and C–O oxygen forming a stable five-membered cycle.

EXPERIMENTAL

Electron absorption spectra were registered with the SHIMADZU UV mini-1240 spectrophotometer (quartz cells, $l = 1$ cm, pure solvent as reference). ^1H NMR spectra were recorded using the Bruker MSL-400 spectrometer with TMS as internal reference. IR spectra were recorded using the Vector 22 Fourier (Bruker) spectrometer (from mulls in mineral oil).

Solutions pH were measured with pH-673 M pH-meter using the ELS-43–07 glass electrode as indicator electrode and saturated silver chloride electrode as reference.

Solutions of compound **I** were prepared by weighing. Compound **I** was prepared and identified as described in [2]. Ionic strength of the solutions was supported by adding the components since the background electrolyte could decrease the compounds solubility and influence their association. Solutions of carbonate-free sodium hydroxide, copper(II) nitrate, and nickel(II) sulfate were prepared from chemically pure grade reagents. The concentration of the solutions was determined by titration.

The potentiometric titration of compound **I** solutions with HCl or NaOH was performed by continuous addition of the titrant, in a temperature-controlled glass cell (298 K) at stirring.

Experimental data were processed using CPESSP software [11]. Models reliability was estimated by calculation of *F* and *R* factors [12, 13]; the mean deviation of simulated data from experimental values (*R* factor [13]) was below 0.05.

Spatial structures optimization was performed using the MM2 molecular mechanics method implemented in ChemOffice 12.0 software package [14].

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