

Complexing Ability of *N*-[2-(2-Morpholinoacetyl)hydrazinocarbothioyl]benzamide Toward Iron(II) Ions

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Abstract—Qualitative and quantitative assessment of the complexing ability of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide toward iron(II) ions is given. Stability constants of iron(II) complexes are determined. Thermodynamics of the complex-formation processes is considered.

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Research on complex formation of biologically active compounds is focused on their reaction with low-molecular organic compounds, such as monosaccharides [1], or with high-molecular compounds, such as polymer derivatives of trypsin [2]. At the same time, complex formation with transition metal ions is generally studied in the presence of an additional agent (amino acid) [3], or with individual reactants [4] containing separately hydrazine, benzene, or heterocyclic fragments responsible for their biological activity. Works on the behavior of pharmaceuticals containing a complex of biologically active groups have been few in number [5–7]. Therefore, assessment of the complexing ability of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide (**I**) toward iron(II) ions is an actual problem both from the theoretical and practical viewpoints.

We made use of potentiometric titration in an aqueous alcoholic medium to determine the stability constants of iron(II) complexes (see figure).

The fact that the stability constants increase with ionic strength at high temperatures is due to the increasing activity of iron cations and ligand anions, as well as by hydrolysis of salts. As shown in [8], Fe(II) can form fairly stable five-membered complexes with ligands containing carbonyl and hydroxy groups. On

the other hand, if the ligand contains a sulfur atom, the probability that it will coordinate with a metal ion is much increased (analogs of ligand **I** which also contain the C=S group are thiourea and xanthate anion). It was found that in strongly acidic media the protonation to form a S–H bond takes place [9]. It should be noted that transition metal ions, in particular, Cu(II) and Fe(II) ions, exhibit a high affinity to chalcogen atoms because of the lower ionicity of the metal–chalcogen bond, as well as the possibility of formation of donor–

[I], M	0	0.05	0.1
$-\Delta_r H_{298}^0$, kJ mol ⁻¹	108.73	7.45	-93.83
$-\Delta_r H_{303}^0$, kJ mol ⁻¹	109.89	7.53	-94.83
$-\Delta_r H_{308}^0$, kJ mol ⁻¹	111.04	7.61	-95.82
$-\Delta_r H_{313}^0$, kJ mol ⁻¹	112.19	7.69	-96.82
$-\Delta_r H_{318}^0$, kJ mol ⁻¹	113.35	7.77	-97.81
$-\Delta_r S_{298}^0$, J mol ⁻¹ K ⁻¹	176.01	-157.14	-490.30
$-\Delta_r S_{303}^0$, J mol ⁻¹ K ⁻¹	186.03	-156.46	-498.95
$-\Delta_r S_{308}^0$, J mol ⁻¹ K ⁻¹	195.85	-155.79	-507.42
$-\Delta_r S_{313}^0$, J mol ⁻¹ K ⁻¹	205.47	-155.13	-515.72
$-\Delta_r S_{318}^0$, J mol ⁻¹ K ⁻¹	214.92	-154.48	-523.88

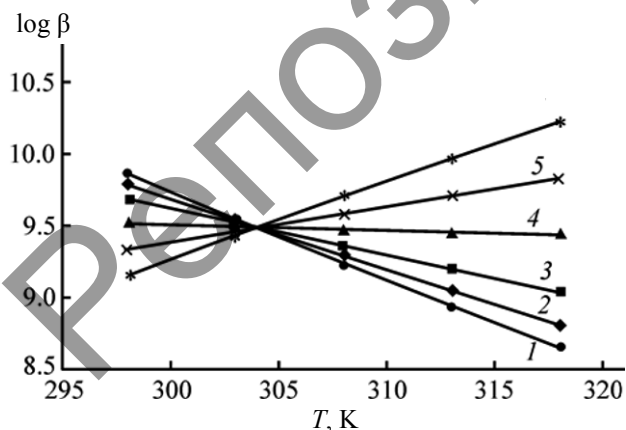
acceptor bonds which stabilize the whole molecule [10].

To obtain more information on the nature of binding between the metal ions and organic ligand we calculated thermodynamic parameters reported above.

The thermodynamic characteristics were found to be strongly affected by the background electrolyte. This is explained by the fact that the ligand contains no proton-donor or acid groups capable of forming stronger bonds with the metal, thereby neutralizing the positive charge. Here we deal with a salt effect which is manifested in the coordination of the complexing ion by nitrate ions. Further on we calculated the electrostatic and nonelectrostatic components of the Gibbs energies of complex formation.

[I], M	0	0.05	0.1
$-\Delta_r S_d$, kJ mol ⁻¹	174.96	-161.88	-498.71
$-\Delta_r H_d$, kJ mol ⁻¹	13.65	-12.63	-38.9
$-\Delta_r G_d$, kJ mol ⁻¹	-38.49	35.61	109.72
$-\Delta_r G_{id} = -\Delta_r H_{id}$, kJ mol ⁻¹	58.39	-15.76	-89.91

It was shown that the formation of the Fe(II) complex at a zero ionic strength involves the oxygen and sulfur atoms, and the mechanism is largely donor-acceptor. At the same time, at background electrolyte concentrations of 0.05 and 0.1 M, the binding mechanism changes from nonelectrostatic to electrostatic, on account of the involvement of nitrate ions.



Dependence of the stability constants of Fe(II) complexes of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide on ionic strength, M: (1) 0.01, (2) 0.025, (3) 0.05, (4) 0.075, and (5) 0.1.

On the other hand, positive or negative values of the temperature-dependent entropy contribution point to an increase or a decrease in the number of particles during complex formation. At a zero ionic strength, $\Delta_r S_d$ is negative, implying formation of the strongest complex. At the same time, the high positive values of $\Delta_r S_d$ at the ionic strengths 0.05 and 0.1 M correspond to the expulsion of solvent molecules due to metal-ligand association and increase of the concentration of the background electrolyte in the solution bulk [11].

Thus, in our study of complex formation between transition metals ions and *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide in an aqueous alcoholic medium we determined the stability constants of the complexes and the temperature-dependent and temperature-independent contributions in the Gibbs energy, enthalpy, and entropy. It was shown that Fe(II) complexes are fairly stable, and, therewith, a covalent metal-ligand bonding prevails in the absence of a background electrolyte, and it gives way to an electrostatic bonding in the presence of nitrate ions. These effects are important to be taken into account in the development of drugs for treatment of iron deficiency.

EXPERIMENTAL

Potentiometric study of complexing ability. In the work we used chemical grade FeSO₄·7H₂O and *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide (I). The compounds were dissolved in 70% aqueous ethanol. The reactions of compound I with *d*-metal cations were studied at 298–313 K (step 5 K) by potentiometry using FeS₂ electrodes whose selectivity with respect to transition metal ions was demonstrated in [10]. The reference electrode was a silver-silver chloride electrode, the measurements were performed with an I-500 pH meter. Potentiometric titration of a 0.001 M solution of a Fe(II) salt with compound I was performed by the procedure in [10]. The required temperature was maintained within ±0.1 K using a UTU-2/77 thermostat.

The IR spectrum was obtained on an Avatar-320 Nicolet FTIR spectrometer in KBr. The ¹H NMR spectrum was recorded on a Bruker DRX500 spectrometer at 500 MHz in DMSO, internal reference TMS. Compound I was synthesized by the procedure in [12].

***N*-[2-(2-Morpholinoacetyl)hydrazinocarbothioyl]benzamide (I).** Potassium thiocyanate, 0.31 g, was added to a magnetically stirred solution of 0.43 g of

benzoyl chloride in 5 ml of acetone. The mixture was stirred for 2 h, after which the KCl precipitate was filtered off. *N*-(Morpholinoacetyl)hydrazine, 0.5 g, in 5 ml of anhydrous isopropanol was then added to the filtrate, and the mixture was stirred at 60°C for 3 h. The solvent was removed by distillation, and the residue was recrystallized from isopropanol to obtain 0.74 g (74%) of compound **I** as white crystals, mp 187–188°C. Found, %: C 52.38; H 5.84; N 17.50. C₁₄H₁₈N₄O₃S. Calculated, %: C 52.16; H 5.63; N 17.38. *M* 322.

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