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Synthesis and Complexing Ability of *N*-[2-(2-Morpholinoacetyl)hydrazinocarbothioyl]benzamide

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Abstract—The synthesis and identification of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide were performed. A qualitative and quantitative evaluation of its complexing ability to the Ni(II) and Co(II) ions was done. The stability constants of the Ni- and Co-complexes were determined. The thermodynamic aspects of the complexing process were discussed.

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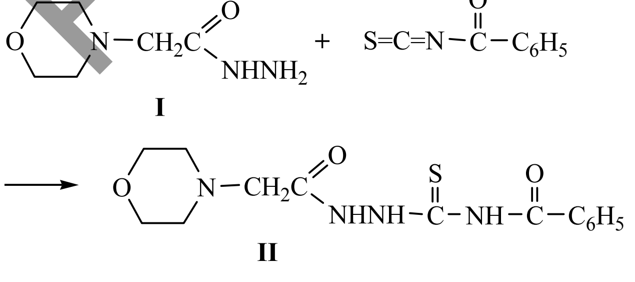
One of the known applications of hydrazides is the synthesis of thiosemicarbazide derivatives which possess a broad spectrum of biological activity [1, 2].

The isothiocyanate method allows introducing the thioamide group into the hydrazide structure to obtain thiosemicarbazides. This method not only extends the modification of these compounds, but also may lead to the compounds with new types of bioactivity.

In this connection, it is interesting to synthesize new thiosemicarbazide derivatives based on the *N*-morpholinylacetic acid hydrazide **I** and to study their complexing ability. Thus, the condensation of benzoyl isothiocyanate, obtained *in situ* by heating benzoyl chloride with potassium thiocyanate in an acetone medium, with *N*-morpholinylacetic acid hydrazide **I** in an alcohol solution at equimolar ratio of the reagents results in the thiosemicarbazide derivative **II** in a 74% yield. The resulting compound **II** is a white crystalline substance soluble in polar organic solvents when heated.



I

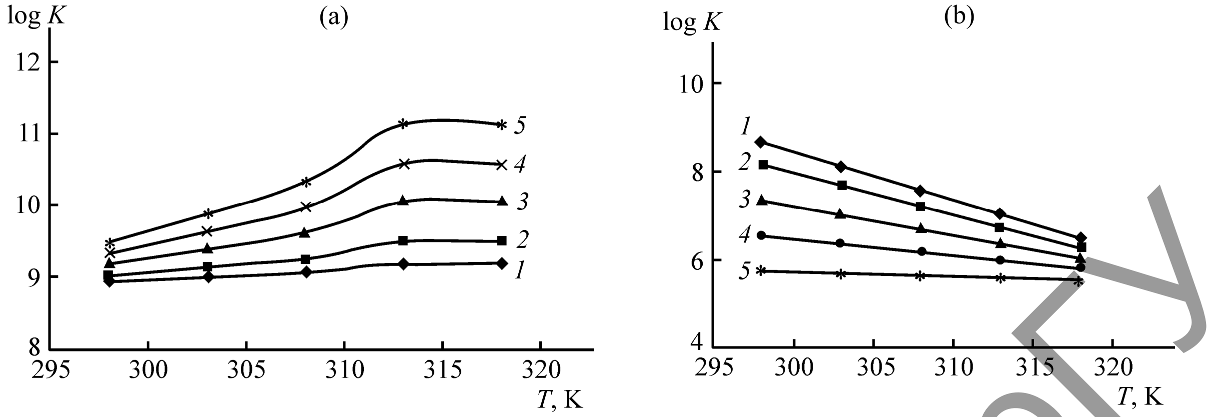
II

In the IR spectrum of compound **II** there is an absorption band in the range of 1332–1314 cm^{-1} belonging to the C=S bond of the thiosemicarbazide fragment. The absorption band of the amide group appears at 1692–1675 cm^{-1}. An absorption band at 3386–3362 cm^{-1} corresponds to the NH group.

The ^{1}H NMR spectrum of **II** in DMSO-d_6 contains a complex multiplet of the aromatic protons at 7.52 ppm. The amide and thioamide NH-protons are observed as three broadened singlets at 12.72, 11.80, and 10.65 ppm. Two triplets at 3.25–3.40 and 3.62–3.70 ppm correspond to the morpholine protons.

As indicated above, compound **II** is soluble in some polar organic solvents including alcohols, amides and other compounds containing polar functional groups. In this work we used a mixture of ethanol and water, because the solubility of the transition metal salts in pure polar organic solvents is lower than in water. On the other hand, this mixture should be regerded as a two-component solution of water in the amphiprotic solvents. According to [3], in a solution the primary structure of water dissociates into the small fragments and monomers that associate with the alcohol molecules. Therefore, in a solution there are no free molecules of H_2O. Thus, the hydration degree of the metal ions at the complex formation is very low.

Based on the results of potentiometric titration in an aqueous-alcoholic medium we determined the stability constants of the *d*-metal complexes (see the figure).



The dependence of the stability constants on the temperature and ionic strength of the complex of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide with the (a) Co^{2+} and (b) Ni^{2+} ions in an aqueous-alcoholic medium. Ionic strength, mol l^{-1}: (*1*) 0.01, (*2*) 0.025, (*3*) 0.05, (*4*) 0.075, and (*5*) 0.1.

Analysis of the data showed that the increasing temperature and ionic strength have a stabilizing effect on the complexes of cobalt with *N*-[2-(2-morpholylacetyl)hydrazinocarbothioyl]benzamide. However, in the case of the nickel complexes there is the opposite effect, due to the low complexing ability and the destructive effect of the above factors on the structure of the hydration sphere of the complexing metal ion.

In a solution the metal ion is surrounded by the solvent molecules, which form the inner and outer spheres [4]. In the temperature range of 298–318 K the stability constants increase as the concentration of the supporting electrolyte increases. The maximal effect of the ionic strength is observed at 318 K. This suggests that the nitrate ions complete the construction of the solvation shell of the complex, stabilizing the complexing metal ion. The stability constants increase as the temperature increases. This indicates the necessity of an additional energy for the more stable complex formation compensated by an increase in the entropy, which is responsible for the change in the structure.

When the temperature increases, the stability constants of the nickel complexes decrease. In this case the dehydration of the complex takes place, where the solvent molecules have played a stabilizing role. The complex stability decreases in the temperature range of 298–318 K as the concentration of supporting electrolyte increases. The ionic strength dependence of the stability constants indicates that the nitrate ions are involved into the complex formation and form the bonds directly with the metal ions. The main thermodynamic parameters of complex formation are given in Tables 1 and 2.

According to [5], for a binary solvent system in the first solvation shell of the ion the component dominates, in which the change in the Gibbs energy of the solvation has a negative value. Since the donor number of ethanol is lower than that of water, the inner sphere of the metal ion will contain water, while ethanol will occupy the outer sphere, or the metal ion is solvated with the water-ethanol associates. The nearest solvation is directly connected with the complex formation process. On the other hand, the behavior of the ions in a solution is influenced by their geometric characteristics, such as the ion radius and the value of the hydration entropy ($-\Delta_hS^0$, J mol^{-1} K^{-1}) [6]. According to the data on the hydration entropy of the ions [277.2 (Ni^{2+}), 257.6 (Co^{2+})], the nickel ion has a maximal structuring effect on the water molecules, whereas the cobalt ion has a minimal impact on the solvent molecules in the near hydrate shell.

For the cobalt(II) ions the ionic strength and temperature contribute to increasing the endothermicity, which explains the associates formation between the molecules of water and alcohol, i. e., the solvent has a stabilizing character in relation to the complex. The increase in ionic strength reduces the enthalpy. Therefore, the nitrate ions are inserted into the outer solvation shell of the complex and the coordination of water molecules occurs, which is the cause of the weakening of the donor-acceptor bonds between the solvent and the metal ion and of the strengthening of the metal-ligand complex.

This fact is connected with the presence of the weaker electrostatic field of the Co^{2+} ion and as a result, the occurrence of hydrogen bonds with the solvent molecules. In the case of high temperature, the

Table 1. The thermodynamic parameters [$\Delta_r H^0$ (kJ mol^{-1}), $\Delta_r S^0$ (J mol^{-1} K^{-1})] of the complex formation processes of the Co^{2+} ions with *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide in an aqueous-alcoholic medium

I	$-\Delta_h H^0_{298}$	$-\Delta_h H^0_{303}$	$-\Delta_h H^0_{308}$	$-\Delta_h H^0_{313}$	$-\Delta_h H^0_{318}$	$-\Delta_h S^0_{298}$	$-\Delta_h S^0_{303}$	$-\Delta_h S^0_{308}$	$-\Delta_h S^0_{313}$	$-\Delta_h S^0_{318}$
0.075	–19.73	–20.64	–21.55	–22.46	–23.37	237.62	241.80	245.99	251.30	254.35
0.1	–39.15	–40.95	–42.75	–44.56	–46.36	304.53	312.83	321.12	331.67	337.72
0.25	–71.52	–74.81	–78.10	–81.39	–84.68	416.04	431.20	446.35	465.62	476.66
0.5	–103.88	–108.66	–113.44	–118.22	–123.00	527.55	549.57	571.58	599.57	615.60
0.75	–136.25	–142.52	–148.78	–155.05	–161.32	639.06	667.94	696.81	733.51	754.55

Table 2. The thermodynamic parameters [$\Delta_r H^0$ (kJ mol^{-1}), $\Delta_r S^0$(J mol^{-1} K^{-1})] of the complex formation processes of the Ni^{2+} ions with *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide in an aqueous-alcoholic medium

I	$-\Delta_h H^0_{298}$	$-\Delta_h H^0_{303}$	$-\Delta_h H^0_{308}$	$-\Delta_h H^0_{313}$	$-\Delta_h H^0_{318}$	$-\Delta_h S^0_{298}$	$-\Delta_h S^0_{303}$	$-\Delta_h S^0_{308}$	$-\Delta_h S^0_{313}$	$-\Delta_h S^0_{318}$
0.075	183.79	192.26	200.73	209.2	217.68	–451.55	–490.54	–529.54	–568.54	–607.54
0.1	155.82	163.01	170.19	177.37	184.56	–366.90	–399.97	–433.04	–466.11	–499.18
0.25	109.21	114.24	119.28	124.32	129.36	–225.83	–249.02	–272.21	–295.4	–318.59
0.5	62.59	65.48	68.37	71.267	74.159	–84.76	–98.06	–111.38	–124.68	–137.99
0.75	15.97	16.72	17.46	18.21	18.96	56.30	52.88	49.45	46.03	42.60

entropy change is associated with reduction of the processes of loss of water of its spatial structure at the distribution of the water molecules in the matrix of an organic solvent, and also with the strength of the aggregates with more dense packing of the molecules [3]. This leads to the complex stabilization.

In the case of nickel(II) ions, an increase in the temperature contributes to increasing the exothermic process, i. e., the decrease in the complex stability is accompanied by changing the solvate environment, in particular, the release of the water molecules from the first and second solvation shell of the complexing metal ion or the rearrangement of water and an organic solvent in the inner and outer solvation shells of the complex. Since the nickel ion has a high polarizing power, the change in the composition of the near solvation sphere via the temperature increase or the introduction of the nitrate ions leads to destabilizing the structure of the complex. In the first case, it is due to the formation of the complexes with the covalent bonding, and in the second, of the complexes of the electrostatic nature.

EXPERIMENTAL

The potentiometric study of the complexing ability. We used in the study $Co(NO_3)_2$ and $NiCl_2$ of chemically pure grade, and *N*-[2-(2-morpholinoacetyl)-hydrazinocarbothioyl]benzamide. The compounds were dissolved in 70% aqueous solution of ethanol. The interaction of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide with the *d*-metals cations was studied at 298–313 K (the step of 5 K) by the potentiometric method using the NiS and FeS_2 electrodes. Their selectivity relative to the transition metal ions was determined in [7]. The reference electrode was a silver chloride electrode. The electromotive force was measured on an I-500 pH metermillivoltmeter. The potentiometric titration of 0.001 M. solutions of the *d*-metals salts with 0.001 M solution of *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide was carried out by the known method [7]. In order to maintain the desired temperature we used an UTU-2/77 thermostat with an accuracy of ±0.1 K.

The IR spectra were recorded on an Avatar-320 Nicolet FT-spectrometer (KBr). The ^1H NMR spectra were registered on a Bruker DRX500 spectrometer (500 MHz) in DMSO-d_6 relative to the internal TMS. The synthesis of compound **I** was performed by procedure [8].

***N*-[2-(2-Morpholinoacetyl)hydrazinocarbothioyl]-benzamide (II).** To a solution of 0.43 g of benzoyl chloride in 5 ml of acetone was added under stirring 0.31 g of potassium thiocyanate. The reaction mixture was stirred for 2 h and filtered through a paper filter. Then to the filtrate was added 0.5 g of *N*-morpholylacetic acid hydrazide in 5 ml of anhydrous isopropyl alcohol. The mixture was stirred at 60°C for 3 h. After the solvent removal, the residue was recrystallized from 2-propanol on cooling. Yield 0.74 g (74%), white crystalline solid, mp 187–188°C. Found, %: C 52.38, H 5.84; N 17.50. $C_{14}H_{18}N_4O_3S$. Calculated,%: C 52.16; H 5.63; N 17.38. *M* 322.

Thus, *N*-[2-(2-morpholinoacetyl)hydrazinocarbothioyl]benzamide, a representative of a large class of the nitrogen- and sulfur-containing organic compounds such as thiosemicarbazide with a wide range of useful properties, was synthesized. The studies of the complex formation of the transition metal ions with an organic component in a water-alcohol mixture revealed a linear relationship between the stability constants of the complexes and thermodynamic characteristics of the ions in the solution. According to the data on the thermodynamics of the complex formation, the degree of structuring of the solvent along with the nature of the complexing metal ion has a significant influence on the complex formation in a solution. At high temperatures this leads to an increase in the hydration number. Therefore, the introduction of the cobalt(II) ion not only increases the stability of the structure of the organic ligand in an aqueous-alcoholic medium, but also helps to increase the complex solubility, which can be used in the synthesis of the biologically active drugs or enzyme systems.

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