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Sulfanilamide Copper(II) Chelates with 2-[(2-Hydroxyphenyl-imino)methyl]phenolom and 1-[(2-Hydroxyphenylimino)-methyl]naphthalen-2-ol

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Abstract—2-[(2-Hydroxyphenylimino)methyl]phenol (H_2L^1) and 1-[(2-hydroxyphenylimino)methyl]naphthalen-2-ol (H_2L^2) reacted with copper(II) acetate hydrate and sulfanilamide (Sf^1), sulfathiazole (Sf^2), sulfaethidole (Sf^3), sulfadiazine (Sf^4), and sulfadimidine (Sf^5) in ethanol to give mixed-ligand copper chelates with the composition $Cu(Sf^{1–5})(L^{1–2})\cdot n H_2O$ (n = 1, 2). All these complexes are monomeric. Salicylaldehyde imines (H_2L^1 and H_2L^2) behave as doubly deprotonated tridentate *O*,*N*,*O* ligands, whereas sulfanilamides ($Sf^{1–5}$) are unidentate ligands. Thermolysis of the synthesized complexes includes dehydration at 70–90°C, followed by complete thermal decomposition (290–380°C). The complexes $[Cu(Sf^1)(L^1)]\cdot 2H_2O$ and $[Cu(Sf^3)(L^1)]\cdot H_2O$ at a concentration of 10^{-4} M inhibited growth and reproduction of 100% of human myeloid leukemia cells (HL-60). The inhibitory effect was 90 and 75%, respectively, at a concentration of 10^{-5} M, whereas no antitumor activity was observed at a concentration of 10^{-6} M.

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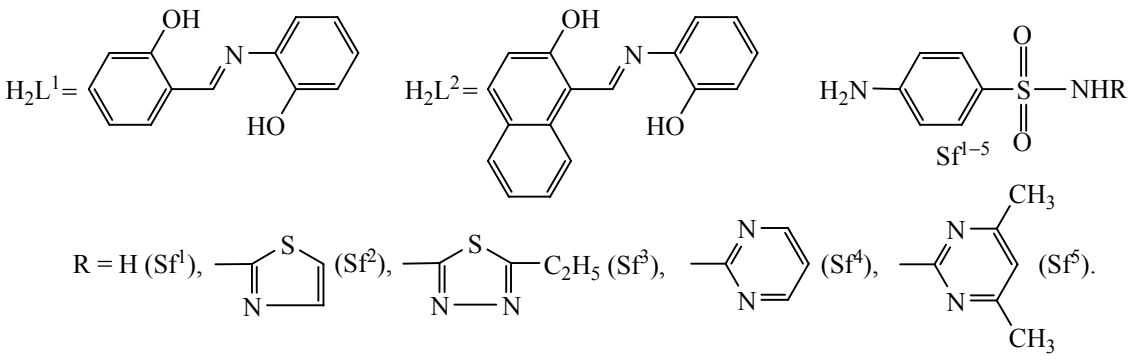
Transition metal salts with Schiff bases derived from 2-aminophenol give rise to biologically active coordination compounds with various compositions and structures [1–3]. The structure and physicochemical and biological properties of these compounds are determined by the nature of the central metal ion and its inner-sphere ligand environment [4, 5]. Taking the above stated into account, accumulation of experimental data on the synthesis and properties of new coordination compounds of biometals with such ligands is important from both theoretical and practical viewpoints.

The goal of the present work was to synthesize mixed-ligand copper chelates containing 2-[(2-hydroxyphenylimino)methyl]phenol (H_2L^1) and 1-[(2-hydroxyphenylimino)methyl]naphthalen-2-ol (H_2L^2) ligands together with sulfanilamide ligands, namely sulfanilamide (Sf^1), sulfathiazole (Sf^2), sulfaethidole (Sf^3), sulfadiazine (Sf^4), and sulfadimidine (Sf^5), and study their structure and physicochemical properties.



By reaction of a hot (50–55°C) ethanol suspension of copper(II) acetate hydrate with salicylaldehyde imines H_2L^1 and H_2L^2 and sulfanilamides Sf^{1-5} at a molar ratio of 1:1:1 we obtained finely crystalline substances **I–X**. On the basis of their elemental analyses (Table 1), the products were assigned the composition $Cu(Sf^{1-5})(L^{1-2})\cdot n H_2O$ (**I**, **VI**, Sf^1; **II**, **VII**, Sf^2; **III**, **VIII**, Sf^3; **IV**, **IX**, Sf^4; **V**, **X**, Sf^5; **I–V**, H_2L^1; **VI–X**, H_2L^2; **II**, **III**, **V**, **VII**, **VIII**, **X**, n = 1; **I**, **IV**, **VI**, **IX**, n = 2). Coordination compounds **I–X** are insoluble in diethyl ether, poorly soluble in water and alcohols, and readily soluble in *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and acetonitrile. Their yields and physical constants are given in Table 1.

Microscopic study of compounds **I–X** showed that they are homogeneous powders. Their purity and structure were determined by elemental and thermal gravimetric analysis, magnetochemistry, and IR spectroscopy. Determination of molar electric conductivity æ of complexes **I–X** in DMF (Table 1) revealed that they are nonelectrolytes. Magnetochemical parameters of coordination compounds **I–X** corresponded to a spin value for one unpaired electrone (Table 1) and indicated their monomeric structure.

The results of thermal gravimetric analysis of complexes **I–X** are collected in Table 2. Thermolysis of compounds **I–X** includes two steps. The DTA curves for all complexes displayed an endothermic effect at 70–95°C. Judging by the relatively low temperature, this effect corresponds to their dehydration. The next peak on the DTA curve is observed in the temperature range from 290 to 360°C and is exothermic. It reflects oxidative decomposition of the coordinated sulfanilamide (Sf^{1-5}) and salicylaldehyde imine ligands (H_2L^1 and N_2L^2). The temperature of complete decomposition (T_{dec}) depends on the nature of the inner-sphere ligands: it increases upon replacement of naphthalenylidene fragment in the Schiff base ligand by salicylidene. For complexes with the same Schiff base ligand, the temperature of complete decomposition decreases in the sulfanilamide series $Sf^5 \geq Sf^4 > Sf^3 \geq Sf^2 > Sf^1$.

Using the Horowitz–Metzger method [6] supplemented by Topor [7], we estimated the kinetic parameters for dehydration of coordination compounds **I–X**. The results are presented in Table 2. Judging by the energies of activation E_a and preexponential factors Z, the process is analogous to previously reported reactions [8, 9].

The mode of ligand coordination to the central copper ion was determined by analysis of the IR spectra of complexes **I–X** and initial Schiff bases H_2L^1 and H_2L^2 and sulfanilamides Sf^{1-5}, as well as of previously described [1–5] coordination compounds of

Table 1. Yields, effective magnetic moments, molar electric conductivities, and elemental analyses of sulfanilamide-containing copper(II) chelates with 2-[(2-hydroxyphenylimino)methyl]phenol and 1-[(2-hydroxyphenylimino)methyl] naphthalen-2-ol

Comp. no.	Yield, %	μ_{ef},[a] B. M.	æ,[a] Ω^{-1} cm^2 mol^{-1}	Found, %			Formula	Calculated, %		
				Cu	N	S		Cu	S	N
I	68	1.80	3	12.96	8.92	6.39	$C_{19}H_{21}CuN_3O_6S$	6.63	8.70	13.25
II	75	1.82	2	11.40	9.97	11.45	$C_{22}H_{20}CuN_4O_5S_2$	11.68	10.22	11.68
III	80	1.89	3	10.85	11.88	10.91	$C_{23}H_{23}CuN_5O_5S_2$	11.09	12.13	11.09
IV	65	1.76	4	11.17	12.32	5.47	$C_{23}H_{23}CuN_5O_6S$	5.70	12.48	11.41
V	72	1.77	2	11.01	11.97	5.33	$C_{25}H_{25}CuN_5O_5S$	5.60	12.26	11.21
VI	85	1.88	2	11.77	7.60	5.80	$C_{23}H_{23}CuN_3O_6S$	6.00	7.88	12.01
VII	67	1.84	3	10.46	9.08	10.61	$C_{26}H_{22}CuN_4O_5S_2$	10.70	9.36	10.70
VIII	70	1.82	3	10.03	10.91	10.06	$C_{27}H_{25}CuN_5O_5S_2$	10.21	11.16	10.21
IX	78	1.76	3	10.20	11.34	5.02	$C_{27}H_{25}CuN_5O_6S$	5.24	11.46	10.47
X	82	1.78	2	10.07	11.09	4.94	$C_{29}H_{27}CuN_5O_5S$	5.15	11.27	10.31

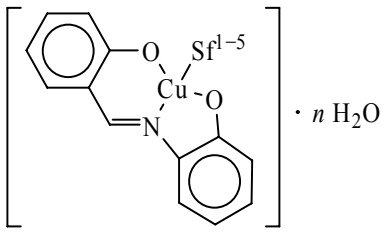
[a] At 293 K.

Table 2. Thermal gravimetric analysis of sulfanilamide-containing copper(II) chelates with 2-[(2-hydroxyphenylimino)-methyl]phenol and 1-[(2-hydroxyphenylimino)methyl]naphthalen-2-ol

Comp. no.	Dehydration temperature, °C	Weight loss			Kinetic parameters		Complete decomposition temperature, °C
		found, %	calculated, %	lost fragment	E_a, kJ mol^{-1}	log Z	
I	75	7.3	7.5	$2H_2O$	34.2	4.0	320
II	80	3.5	3.3	H_2O	43.5	4.7	350
III	85	3.0	3.1	H_2O	31.4	3.9	360
IV	70	6.5	6.4	$2H_2O$	31.0	3.8	360
V	95	3.5	3.2	H_3O	41.2	4.5	380
VI	80	7.0	6.8	$2H_2O$	27.3	2.8	290
VII	75	2.7	3.0	H_2O	31.2	3.6	320
VIII	80	3.0	2.9	H_2O	38.7	4.3	330
IX	75	6.2	5.9	$2H_2O$	36.5	4.2	350
X	85	3.1	2.9	H_2O	36.9	4.2	350

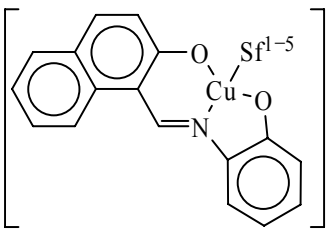
transition metals with structurally related Schiff bases. We found that aldehyde imines H_2L^1 and N_2L^2 act as doubly deprotonated tridentate *O*,*N*,*O*-ligands which are coordinated to the copper ion through phenolic oxygen atoms and nitrogen atom of the C=N group with formation of five- and six-membered chelate rings. The IR spectra of the complexes lack ν(OH) bands typical of initial Schiff bases H_2L^1 and H_2L^2 (3530–3520 cm^{-1}). In addition, the ν(C=N) band is displaced by 25–20 cm^{-1} toward higher frequencies, indicating coordination of the nitrogen atom in the ligand to the metal atom. All complexes displayed in the IR spectra a series of new absorption bands which were assigned to ν(Cu–N) (525–505, 430–405 cm^{-1}) and ν(Cu–O) vibrations (490–460 cm^{-1}). Participation of the other functional groups in H_2L^1 and H_2L^2 in coordination with the central metal ion may be ruled out, for the corresponding characteristic absorption bands appear in the same regions as in the spectra of the free Schiff bases. The IR data also indicated that sulfanilamide is coordinated through the nitrogen atom in the amino group and that coordination of sulfathiazole, sulfaethidole, sulfadiazine, and sulfadimidine involves nitrogen atom in the heteroring (thiazole, thiadiazole, or pyrimidine). This follows from splitting and low-frequency shift (by 25–15 cm^{-1}) of the ν(NH_2) and ν(NH) absorption bands in the IR spectra of complexes **I** and **VI**. In the spectra of coordination compounds **II**–**V** and **VII**–**X** we observed splitting and low-frequency shift (by 15–20 cm^{-1}) of the ν(C=N) band.

Thus, the data of elemental analyses and physicochemical studies allowed us to assign structures **A** and **B** to coordination compounds **I**–**X**.



· *n* H_2O

A



· *n* H_2O

B

Sf^1 = 4-aminobenzenesulfonamide, Sf^2 = 4-amino-*N*-(1,3-thiazol-2-yl)benzenesulfonamide, Sf^3 = 4-amino-*N*-(1,3,4-thiadiazol-2-yl)benzenesulfonamide, Sf^4 = 4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide, Sf^5 = 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide; *n* = 1, 2.

As shown in [10–12], many coordination compounds of 3*d* elements with *O*,*N*,*O*- and *O*,*N*,*S*-ligands selectively inhibit growth of malignant tumor cells (human myeloid leukemia HL-60). We examined the activity of complexes **I** and **III** against HL-60 cells *in vitro*. Compounds **I** and **III** at a concentration of 10^{-4} M) inhibited growth and reproduction of 100% of HL-60 cells. The inhibitory effect of **I** and **III** activity at a concentration of 10^{-5} M was estimated at 90 and 75%, respectively, whereas no antitumor activity was observed at a concentration of 10^{-6} M.

EXPERIMENTAL

The resistance of solutions of complexes **I**–**X** in DMF (20°C, c = 0.001 M) was measured with the aid of an R-38 rheochord bridge. The IR spectra were recorded on a Specord M-80 spectrometer from samples preliminarily dried in a drying box at 105°C until constant weight and dispersed in mineral oil. The effective magnetic moments of compounds **I**–**X** were determined by the Gouy method. The molar magnetic susceptibilities were calculated with correction for diamagnetism from the theoretical magnetic susceptibilities of organic compounds. Thermal gravimetric analysis of complexes **I**–**X** was performed on a Paulik–Paulik–Erdey instrument in the temperature range from 20 to 1000°C in air using a corundum crucible and Al_2O_3 as reference.

Salicylaldehyde imines H_2L^1 and H_2L^2 were synthesized by condensation of equimolar amounts of 2-aminophenol and salicylaldehyde or 2-hydroxynaphthalene-1-carbaldehyde in ethanol.

The antitumor activity of complexes **I** and **III** against human myeloid leukemia HL-60 was studied *in vitro* according to standard procedure [12, 13].

{2-[(2-Oxidophenylimino)methyl]phenolato-*O*,*O*,*N*}-(4-aminobenzenesulfonamide)copper(II) dihydrate (I). A solution of 10 mmol of 2-[(2-hydroxyphenylimino)methyl]phenol (H_2L^1) in 20 ml of ethanol was heated to 50–55°C, a suspension of 10 mmol of copper(II) acetate hydrate in 30 ml of ethanol was added, the mixture was stirred for 20–30 min, and 10 mmol of 4-aminobenzenesulfonamide was added. The mixture was stirred using a magnetic stirrer for 60–90 min at 50–55°C and cooled, and the green precipitate was filtered off through a glass filter, washed with a small amount of alcohol and diethyl ether, and dried in air until constant weight.

Complexes **II**–**X** were synthesized in a similar way using as starting compounds 2-[(2-hydroxyphenylimino)methyl]phenol (H_2L^1) or 1-[(2-hydroxyphenylimino)methyl]naphthalen-2-ol (H_2L^2), copper(II) acetate hydrate, and 4-aminobenzenesulfonamide, 2-(4-aminophenylsulfonylamino)-1,3-thiazole, 2-(4-aminophenylsulfonylamino-5-ethyl-1,3,4-thiadiazole, 2-(4-aminophenylsulfonylamino)pyrimidine, or 2-(4-aminophenylsulfonylamino)-4,6-dimethylpyrimidine, taken at a molar ratio of 1:1:1. The yields of compounds **I**–**X** and their elemental analyses and some physicochemical parameters are given in Tables 1 and 2.

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