

A Study and Optimization of Complexation of Cobalt Ions with Dihydroquercetin in Aqueous Solutions

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Abstract—This work continues a series of studies devoted to complex formation of ions of biogenic metals with the flavonoid dihydroquercetin (DHQ). The interaction of Co^{2+} ions with DHQ in aqueous solutions has been investigated. It has been found that, at different pH of a solution, complex compounds (CC) with different stoichiometry are formed; a variation of the pH value of a solution from 6.0 to 7.0 results in the formation of compounds (1)–(3) with the metal : flavonoid ligand ratio (Met : L) from 1 : 2 at pH 6.0 (1), through 2 : 3 at pH 6.4–6.7 (2), to 1 : 1 at pH 6.8–7.0 (3). By using the thermogravimetric method and the data of the elemental analysis, the most probable composition of the compounds with the determination of the amount of bound water has been proposed: $[\text{CoL}_2(\text{H}_2\text{O})_4]$ for (1), $[\text{Co}_2\text{L}_3(\text{OH})(\text{H}_2\text{O})_4]$ for (2), and $[\text{CoL}(\text{OH})(\text{H}_2\text{O})_2]$ for (3). Conditions for the optimization of product yield in the complexation reaction of Co^{2+} ions with DHQ in an aqueous solution have been determined for compound (2): the pH value of solution 6.7; the reaction time 15 min; the temperature of the reaction solution 90°C ; the molar ratio of the initial reagents DHQ : Co^{2+} 1 : 1.5; the initial concentration of DHQ 0.020 mol/L and that of Co^{2+} 0.030 mol/L; and the use of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ as a source of cobalt ions. The yield of the product is 81.8%.

Keywords: dihydroquercetin, flavonoids, complex compounds, cobalt ions, optimization, product yield

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INTRODUCTION

In a continuation of systemic investigations of complex formation between the ions of biogenic metals and the flavonoid dihydroquercetin (DHQ) [1–6], the reaction of DHQ with Co^{2+} ions in aqueous solutions was studied. The choice of the metal as a complex-forming agent was dictated by the fact that it plays a key role in the normal functioning of the body.

Cobalt is one of the most important trace elements; it is involved in protein, carbohydrate, mineral, and fat metabolism and hemopoiesis; it stimulates the formation of hemoglobin and erythrocytes (erythropoiesis), maintains tissue respiration, and is a constituent of the molecule of vitamin B12 (cobalamin). Cobalt activates enzymes and comes into the composition of some enzymes; it provides the metabolism of folic acid and catecholamines, promotes the functioning of the central nervous system, regulates the function of the vegetative nervous system and the thyroid gland, and contributes to muscle weight gain. Along with magnesium, zinc, and manganese ions, cobalt ions prevent the formation of calculi in the urinary system. A deficiency of cobalt in the organism affects the reproductivity and causes both obstetric and gynecological pathologies [7–13].

The number of publications devoted to the complex formation of cobalt with flavonoids and the properties of these complexes is rather small. The biological activity of complexes of cobalt with quercetin has been studied [14]. It has been found that the antiradical action of CC obtained in water-ethanol medium with the ratio Met : L 1 : 2 toward the 2,2-diphenyl-1-picrylhydrazyl radical is more pronounced compared with the standard antioxidant butylhydroxyanisole. In addition, cobalt exhibits antibacterial activity toward the *Escherichia coli* phage and weak antimicrobial activity. The cobalt–quercetin complex with the stoichiometric ratio Met : L 1 : 1 obtained in ethanol shows antibacterial activity against *E. coli*, *Staphylococcus aureus*, and *Klebsiella Pneumoniae* bacterial strains, which is comparable with the activity of penicillin [15].

The formation of triple complexes of cobalt with glycosides and diglycosides of flavonoids of various types: the flavonol rutin; the flavanones hesperidin, neohesperidin, and naringin; the isoflavone genistein; and the flavones diosmin and neodiosmin with the addition of an auxiliary ligand (2,2'-bipyridine or 4,7-diphenyl-1,10-phenanthroline) has been studied by mass spectrometry [16–20]. Plausible structures of biligand complexes of cobalt with flavonoid monoglycosides based on flavones, flavonols, and flavanone have been suggested [21].

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The goal of the work was to study and optimize the complexation reaction of cobalt with DHQ in an aqueous solution. The performance of the reaction in aqueous solutions implies the ecological safety of the process, which is important in the development of technologies for the production of compounds promising for application in medicine.

EXPERIMENTAL

Complex compounds (CC) of cobalt with DHQ were synthesized using DHQ (OOO INPF Khimiya drevsiny) [22] and water-soluble salts of cobalt: $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ (chemically pure reagents).

Conditions for the synthesis of CC of cobalt with DHQ. Aqueous solutions of DHQ and cobalt salts were heated under constant stirring and control of pH values. The pH was brought to the required value by the addition of an aqueous NH_3 solution. The range of pH values of the reaction solution was varied from 5.4 to 7.0, the temperature of the solution was from 60 to 95°C, and the reaction time was from 5 to 60 min. The molar ratio of the initial components DHQ : Co^{2+} was from 1 : 1 to 1 : 3, and the concentration of DHQ was from 0.01 to 0.03 mol/L. After the termination of the synthesis, the precipitate was filtered under vacuum by washing it many times first with water to remove excessive salt and then with ethanol to eliminate the traces of initial DHQ. The precipitate was dried at 50°C to a humidity of not more than 7% and then at 105°C to a constant weight. Compounds (1)–(3) were obtained as grey-brown powders insoluble in water and ethanol and poorly soluble in DMSO [23].

Compound (1). Melting point 211°C. IR (ν , cm^{-1}): 3404, 3257 (O–H), 1604 (Ar), 1552 (C=O), 1449, 1373, 1260 (–C–O–C–), 614 (Met–O). Found, %: C 48.2; H 3.1; Co^{2+} 7.7. Calculated, %: C 48.9; H 4.1; Co^{2+} 8.0; M 737. The empirical formula: $\text{C}_{30}\text{H}_{30}\text{O}_{18}\text{Co}$.

Compound (2). Melting point 209°C. IR (ν , cm^{-1}): 3390, 3248 (O–H), 1603 (Ar), 1551 (C=O), 1448,

1373, 1260 (–C–O–C–), 612 (Met–O). Found, %: C 48.0; H 3.7; Co^{2+} 10.5. Calculated, %: C 48.4; H 3.8; Co^{2+} 10.6; M 1116. The empirical formula: $\text{C}_{45}\text{H}_{42}\text{O}_{26}\text{Co}_2$.

Compound (3). Melting point 205°C. IR (ν , cm^{-1}): 3428, 3244 (O–H), 1605 (Ar), 1553 (C=O), 1448, 1372, 1265 (–C–O–C–), 606 (Met–O). Found, %: C 43.4; H 3.8; Co^{2+} 14.1. Calculated, %: C 43.4; H 3.9; Co^{2+} 14.2; M 415. The empirical formula: $\text{C}_{15}\text{H}_{16}\text{O}_{10}\text{Co}$.

Measurements of pH values were performed on an Expert-pH device. IR spectra were recorded on a Varian 3100 FT-IR spectrometer in KBr pellets (2.5 mg/300 mg KBr). A thermogravimetric analysis was performed on an STA 449 F3 Jupiter simultaneous thermal analyzer (Netzsch Gabo, Germany) in a dynamic mode (the sample heating rate 10 deg/min) in the nitrogen flow (the rate of gas supply 30 mL/min).

RESULTS AND DISCUSSION

The interaction of cobalt ions with DHQ was studied in aqueous solutions at different pH values. To assess the effect of this parameter on the composition of the complex and the product yield, the reactions were performed in the pH range from 5.4 to 7.0 (Table 1). The pH value of a solution is one of the most important parameters of the reaction, which affects both the yield and the composition and structure of the reaction product. An analysis of studies devoted to complex formation of various flavonoids with metal ions shows that the complexation in an alkaline medium proceeds predominantly with the involvement of the hydroxyl groups of the catechol fragment of the B ring of the flavonoid molecule [24–28]. Because it is supposed that just these hydroxyl groups participate in reactions with superoxide anion radicals and hence free o-hydroxyl groups in the B ring contribute to the manifestation of high antioxidant activity of the flavonoid [29, 30], the complexation at pH values >7 was not performed. The reaction was carried out at 70°C

Table 1. Effect of the pH value on the composition of a complex and product yield

Compound	pH	Content in CC, %						Empirical formula, M, g/mol	Ratio Met : L in a CC	Yield of product, %
		found			calculated					
		C	H	Co^{2+}	C	H	Co^{2+}			
–	5.4	–	–	–	–	–	–	–	–	Traces
1	6.0	48.2	3.1	7.7	48.9	4.1	8.0	$\text{C}_{30}\text{H}_{30}\text{O}_{18}\text{Co}$	1 : 2	17.4
	6.4	47.6	3.7	10.9				737		50.2
2	6.6	47.2	3.4	10.6	48.4	3.8	10.6	$\text{C}_{45}\text{H}_{42}\text{O}_{26}\text{Co}_2$	2 : 3	55.1
	6.7	48.7	4.0	10.4				1116		71.5
3	6.8	44.3	3.9	13.8						64.1
	6.9	41.2	3.8	14.6	43.4	3.9	14.2	$\text{C}_{15}\text{H}_{16}\text{O}_{10}\text{Co}$	1 : 1	64.4
	7.0	45.6	3.6	13.5				415		64.4

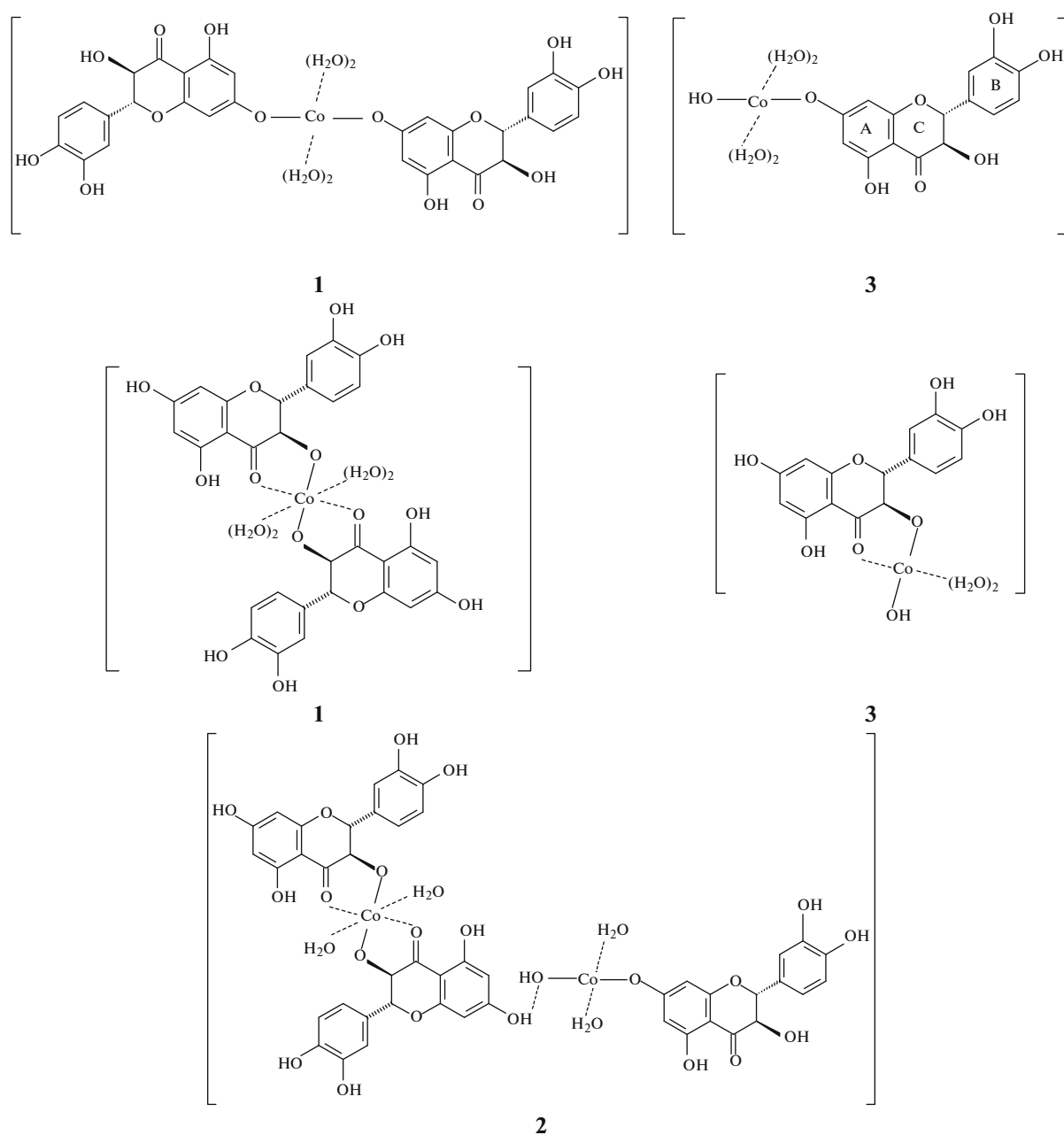


Fig. 1. Some possible structures of complex compounds of Co^{2+} with DHQ.

for 15 min with a small excess of cobalt ions (DHQ : Co^{2+} 1 : 1.5 mol).

An elemental analysis of each reaction product obtained indicates that, at different pH values of a reaction solution, compounds with different metal : flavonoid ligand ratios form. The reaction product, compound (1) begins to form at a pH value close to 6; it has a low yield (17.4%) and the Met : L ratio 1 : 2.

In the pH range 6.4–6.7, compound (2) with stoichiometry Met : L 2 : 3 forms; the yield of the product in this pH range increases almost 1.5 times (from 50.2 to 71.5%). Most typical is the formation of CC of metals with flavonoids with the stoichiometric ratios 1 : 1

and 1 : 2. However, there are examples of CC with the metal : ligand ratios 3 : 2, e.g., in the case of complexation of rutin with Al^{3+} , Zn^{2+} [24], and Sn^{2+} [31] in methanol, and 2 : 3 in the case of complexation of DHQ with silibinin, a product of oxidative condensation of DHQ with lignin and copper (II) ions in methanol [32].

The reaction performed at higher pH values (6.8–7.0) results in the formation of compound (3) with the Met : L ratio 1 : 1. The yield of the product is stable (64.1–64.4%). Figure 1 shows some possible structures of the resulting compounds.

Table 2. Temperature ranges characterizing weight losses at Mp for compounds (1)–(3)

Compound	Mp, °C	Peak of weight loss	
		ΔT , °C	Δm , %
1	211	100–230	9.20
2	209	105–215	6.83
3	205	105–215	8.45

Table 3. Effect of the temperature of the solution on the yield of compound (2)

Temperature, °C	Yield of product, %
60	55.1
70	71.5
80	72.3
90	75.0
95	73.9

The absence of complexation in acidic solutions at $\text{pH} < 6$ can be explained by the fact that DHQ exists predominantly in a protonated form, which is not prone to complexation. Increasing the pH of a solution decreases the extent of protonation of a flavonoid and converts it to the form in which it exhibits electron donor properties and is capable of interacting with metal ions. The minimal pK_a value of DHQ is 7.3 ± 0.1 [33], and the equilibrium between the dissociated and nondissociated forms of the flavonoid sets in at pH approximately equal to pK_a . This may explain an increase in the yield of compound (2) with increasing pH value from 6.0 to 6.7. Presumably, the change in the Met : L ratio in the composition of compounds (1)–(3) results from the partial hydrolysis of CC.

Polar functional (carbonyl and hydroxyl) groups present in flavonoid molecules determine intermolecular interactions with other polar molecules. Flavonoids tend to form crystalline hydrates with rigid hydrate forms. The presence of bound water in compounds can deteriorate the characteristics of an individual substance and affect biological activity. The content of bound water in various objects is determined by the widely used thermogravimetric method, which makes it possible to study the mode of thermal degradation of individual substances [34–36]. The content of bound water in CC and the most probable composition of compounds (1)–(3) were determined thermogravimetrically (Table 2) with the involvement of the data of elemental analysis.

It follows from the data of Table 2 that water that remains after drying samples at 105°C evaporates in temperature ranges 100–230 and 105–215°C, which are characterized by the removal of firmly bound water. These data suggest that compounds (1)–(3) are crystalline hydrates. The calculations indicated that the amount of bound water per 1 mol of the product of

complexation of cobalt ions with DHQ is 4, 4, and 2 mol for compounds (1), (2), and (3), respectively. The most probable composition of complexes is $[\text{CoL}_2(\text{H}_2\text{O})_4]$ for (1), $[\text{Co}_2\text{L}_3(\text{OH})(\text{H}_2\text{O})_4]$ for (2), and $[\text{CoL}(\text{OH})(\text{H}_2\text{O})_2]$ for (3).

An analysis of IR spectra of samples showed that, in the high-frequency region, there are broad absorption bands due to valence vibrations of hydroxyl groups bound by intramolecular ($3390\text{--}3428\text{ cm}^{-1}$) and intermolecular ($3225\text{--}3257\text{ cm}^{-1}$) hydrogen bonds, which suggests that the compound contains bound water [24]. The valence vibrations of the aromatic ring make themselves evident in the region of $1600\text{--}1605\text{ cm}^{-1}$. The presence of the band at 1260 cm^{-1} indicates the retention of the --C--O--C bond in the C ring of the basic flavonoid [24, 37]. A comparison of IR spectra of resulting samples with the spectrum of DHQ revealed some differences. The appearance of a new band at $606\text{--}614\text{ cm}^{-1}$, which is assigned to the valence vibrations of the Met–O bond, indicates the formation of a bond of the cobalt ion with the oxygen atom of the hydroxyl group of the flavonoid ligand. The significant shift of the maximum of the absorption band of valence vibrations of the carbonyl group C=O in the DHQ molecule (1640 cm^{-1}) is caused by the ionization of this group due to the introduction of the electron acceptor substituent into the DHQ molecule.

To optimize the yield of compound (2), the effect of the following reaction parameters on the yield was studied: the pH and temperature of the solution, the reaction time, the molar ratio, and the initial concentrations of starting components. The reaction was carried out at pH 6.7, which is the optimal pH value for product (2).

To provide a more complete conversion of DHQ, the reaction was carried out in the temperature range of $60\text{--}95^\circ\text{C}$ (Table 3), and the reaction time was varied from 5 to 60 min (Fig. 2). Increasing the temperature of the reaction mixture from 60 to 70°C increased the yield of the product almost by 30%, from 55 to 71.5%. On further heating the mixture to 95°C , the yield increased insignificantly, to 72–75%, with the greatest yield being obtained at 95°C .

The estimation of the effect of reaction time on the yield of compound (2) (Met : L 2 : 3) leads to the conclusion that the bulk of the product is formed within the first five minutes of the reaction. Increasing the reaction time to 10–15 min raises the product yield by 15–18% (from 63.7 to 75%). On further holding the reaction mixture to 60 min, no gain in the product yield occurs.

Further optimization of the reaction for compound (2) was carried out by varying the molar ratio of the initial components DHQ : Co^{2+} from the equimolar to a triple excess of cobalt ions (Table 4). The reaction was carried out at 90°C for 15 min; the initial concentration of DHQ was 0.02 mol/L.

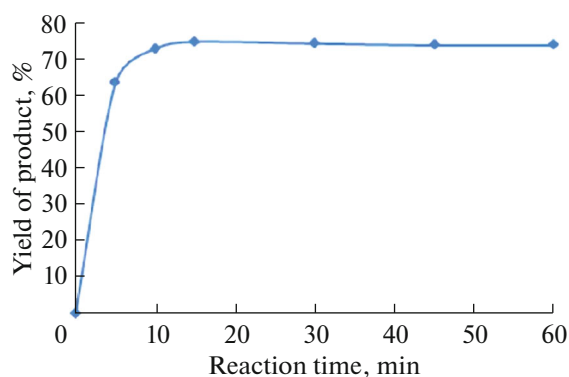


Fig. 2. Dependence of the yield of compound (2) on reaction time.

The highest yield of the reaction product (81.8%) was obtained with a small excess of cobalt ions at the initial molar ratio DHQ : Co^{2+} 1 : 1.5. The use of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ for the reaction increased the yield of the product throughout the range of molar ratios of initial reactants. The effect was enhanced as the frac-

tion of the metal in the reaction solution decreased (to 8.5–20% at the ratio of the reagents 1 : 1.5 and 1 : 1 mol). The content of the metal in the product did not significantly change and also characterized the compound with the stoichiometric ratio Met : L 2 : 3.

The effect of initial concentrations of reagents on the product yield was estimated in the range from 0.01 to 0.03 mol/L of a flavonoid at the molar ratio of initial reagents 1 : 1.5 (Table 5). The conditions (temperature, reaction time) were the same as in the preceding experiment.

The data presented in Table 4 show that increasing the concentration of DHQ from 0.010 to 0.020 mol/L and of Co^{2+} ions from 0.015 to 0.030 mol/L increases the yield of the product 1.7 times in the reaction of DHQ with cobalt chloride and about 1.4 times in the reaction with cobalt sulfate. Further increase in the concentration of the reactants decreases the product yield.

Thus, the study allows the conclusion that the highest yield of compound (2) is 81.8%; it is obtained when the reaction is carried out for 15 min at 90°C, at the pH value of the solution 6.7, the molar ratio of the initial reagents DHQ : Co^{2+} 1 : 1.5, and initial concen-

Table 4. Effect of the molar ratio of the initial components of the solution on the yield of compound (2)

Initial ratio DHQ : Co^{2+} , mol	Cobalt salt	Yield of product, %	Content of Co^{2+} in CC, %
1 : 1	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	63.2	9.6
	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	75.7	10.8
1 : 1.5	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	75.4	11.2
	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	81.8	10.2
1 : 2	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	58.6	10.9
	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	61.0	10.3
1 : 3	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	50.3	10.3
	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	50.9	12.7

Table 5. Effect of initial concentrations of reactants on the yield of compound (2)

Concentration of DHQ, mol/L	Concentration of Co^{2+} ions, mol/L	Cobalt salt used	Yield of product, %
0.010	0.015	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	43.5
		$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	58.8
0.015	0.023	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	71.9
		$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	67.2
0.020	0.030	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	75.4
		$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	81.8
0.025	0.038	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	71.8
		$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	68.8
0.030	0.045	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	42.2
		$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	50.0

trations 0.020 and 0.030 mol/L of DHQ and Co^{2+} , respectively, and with the use of cobalt sulfate as a source Co^{2+} ions.

CONCLUSIONS

The complexation of Co^{2+} ions with DHQ in aqueous solutions was studied. It was found that, at different pH values of the solution, CC with different stoichiometry are formed. Changing the pH value of the solution from 6.0 to 7.0 leads to the formation of compounds (1)–(3) with the metal : flavonoid ratio from 1 : 2 at pH 6.0 (1), through 2 : 3 at pH 6.4–6.7 (2), to 1 : 1 at pH 6.8–7.0 (3). Using the thermogravimetric method and the data of elemental analysis, the amount of bound water in CC was determined and the most probable composition of the compounds was proposed: $[\text{CoL}_2(\text{H}_2\text{O})_4]$ for (1), $[\text{Co}_2\text{L}_3(\text{OH})(\text{H}_2\text{O})_4]$ for (2), and $[\text{CoL}(\text{OH})(\text{H}_2\text{O})_2]$ for (3).

The following conditions were determined to optimize the yield of the product of complexation of Co^{2+} ions with DHQ in an aqueous solution for compound (2): the temperature of the reaction solution 90°C, the molar ratio of the initial reagents DHQ : Co^{2+} 1 : 1.5, the initial concentration of DHQ 0.020 mol/L and of Co^{2+} 0.030 mol/L, and the use of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ for the reaction. The yield of the product is 81.8%.

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COMPLIANCE WITH ETHICAL STANDARDS

The work does not involve experiments on animals or humans.

Conflict of Interests

Authors declare they have no conflicts of interests.

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