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Complexes of Palladium(II) and Platinum(II) with 6-*tert*-Butyl-2-thiouracil

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Abstract—*cis*-Dihalogeno complexes of platinum(II) and palladium(II) with 6-*tert*-butyl-2-thiouracil have been synthesized. The mode of coordination of the ligand to metal ions was established by IR and NMR spectroscopy.

Keywords: platinum(II), palladium(II), halogeno complexes, 6-*tert*-butyl-2-thiouracil

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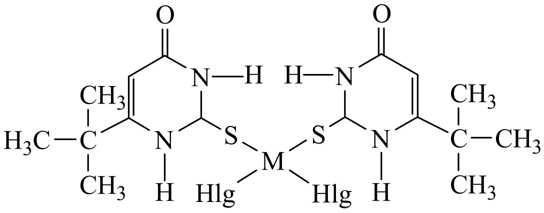
The interest to complexes of platinum and palladium is due to their high cytostatic activity. The search for new antitumor drugs, less toxic and more effective than *cis*-dichlorodiaminoplatinum, based on the Pt(II) and Pd(II) complex compounds is a state-of-the-art problem. The synthesis and investigation of complexes of platinum and palladium in which the ligands are represented by biologically active compounds seems to be the main direction of this search. One of the most promising compounds for this purpose, in our opinion, are thiouracils possessing high biological activity [1]. Some of thiouracil derivatives are widely used in medical practice [2], and the complexes with noble metals are promising as cancerostatics [3].

To date numerous metal complexes of thiouracil derivatives have been synthesized and their composition and structure with various metals like copper, iron, cobalt, nickel, manganese, cadmium, vanadium [3–5], as well as palladium, platinum and gold was studied [6]. However, the described chlorocomplexes of Pt(II) and Pd(II) with thiouracil derivatives have *trans*-configuration [7], while chlorocomplexes of *cis*-configuration were not reported until now.

The goal of the present study is the synthesis of *cis*-dichlorocomplexes of Pt(II) and Pd(II) with 6-*tert*-butyl-2-thiouracil and the investigation of their structure (Scheme 1).

Pt(II) and Pd(II) complexes with 6-*tert*-butyl-2-thiouracil (L) were synthesized using the method of ligand substitution of acetonitrile or benzonitrile by the molecules of ligand L at room temperature. The products are colored powders, insoluble in water, readily soluble in DMSO and moderately, in chloroform, ethanol, acetone, diethyl ether. The complexes, except $[PtCl_2L_2]$ (**1**), do not melt or decompose on heating to 300°C.

Scheme 1.



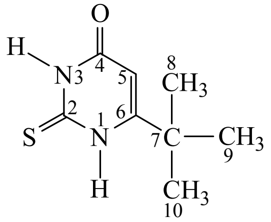
The results of elemental analysis and some physicochemical properties of the ligand and its halogenocomplexes with Pt(II) and Pd(II) are given in Table 1. As can be seen from these data, the ratio Pd(Pt) : L in the obtained complexes is equal to the ratio of the taken reagents. The data of ^{13}C NMR spectra of ligand L and its complexes with Pd(II) are presented in Table 2.

IR spectra of 6-*tert*-butyl-2-thiouracil, the precursors and halogenocomplexes are presented in Table 3. Full assignment of the IR absorption bands of 2-thiouracil is given in [8]. The spectrum contains strong bands in the range 3224–3029 cm^{-1} belonging to $\nu(N^1H)$ and $\nu(N^3H)$ stretching vibrations. A strong

Table 1. Elemental composition of 6-*tert*-butyl-2-thiouracil and its complexes

Comp. no.	M : L	Found, %						Formula	Calculated, %					
		C	H	S	N	M	Hlg		C	H	S	N	M	Hlg
L		52.6	6.6	17.3	15.1			$C_8H_{12}N_2OS$	52.2	6.6	17.4	15.2		
1	1:2	30.2	3.0	9.6	8.7	29.4	11.0	$C_{16}H_{24}Cl_2N_4O_2PtS_2$	30.3	3.8	10.1	8.8	30.7	11.2
2	1:2	35.0	4.2	11.7	10.3	26.6	14.7	$C_{16}H_{24}Cl_2N_4O_2PdS_2$	35.2	4.4	11.8	10.3	25.6	13.1
3	1:2	30.0	3.5	10.1	8.7	19.0	27.9	$C_{16}H_{24}Br_2N_4O_2PdS_2$	30.2	3.8	10.1	8.8	19.3	25.2

Table 2. ^{13}C NMR parameters (ppm) for 6-*tert*-butyl-2-thiouracil and its complexes with Pd(II)



Comp. no.	Parameter	C^8–C^{10}	C^7	C^2	C^4	C^5	C^6
L	δ	27.77	34.94	176.95	161.63	100.98	163.80
2	δ	27.23	34.68	174.00 (br)	160.34	102.41 (br)	163.03
	Δδ	0.54	0.26	2.95	1.29	–1.43	0.77
3	δ	27.23	34.65	175.09 (br)	160.42	103.12 (br)	163.14
	Δδ	0.54	0.29	1.86	1.21	–2.14	0.66

band at 1682 cm^{-1} corresponds to stretching vibrations ν(C^4=O), the band at 1542 cm^{-1}, to symmetric bending vibrations of the $N^3C^2N^1$ group of atoms. It is known that characteristic band of the C^2=S bond stretching vibrations appears at 1160 cm^{-1} [4]. However, our calculations of the vibrational spectrum of ligand L, consistent with calculations of other authors [9], suggest that this band comes from bending scissor vibrations δ($N^1C^2N^3$). The band at 952 cm^{-1} refers to complex vibrations ν(C^2=S) and planar bending vibrations δ($C^2N^1C^6$), and the band at 754 cm^{-1}, to the out-of-plane vibrations ν(C^2=S). The absence in the IR spectrum of ligand L of the absorption bands at 2600 cm^{-1} [ν(SH)] suggests that the compound exists in the thione form.

It is known that the synthesis of $PtCl_2(CH_3CN)_2$ by the method described in [10] without heating gives the complex of the *cis*-configuration, and with heating to 75°C, its *trans*-isomer [11]. The IR spectrum of the complex $PtCl_2(CH_3CN)_2$ which we synthesized at room temperature is similar to those described in [10]. The presence of two strong absorption bands in the far region at 362 and 354 cm^{-1} belonging to stretching vibrations of the Pt–Cl bond is indicative of the formation of the *cis*-isomer.

The obtained complex Pt(II) **1** is insoluble in solvents usually used for recording NMR spectra. It is soluble in DMSO-d_6, but in the solution the resolvation with liberation of ligand L occurs, therefore, the ^{13}C NMR spectrum of complex **1** could not be registered.

The absence of strong absorption band of the ν(C≡N) stretching vibrations at 2230 cm^{-1} in the spectrum of complex **1** as compared to the spectrum of its precursor $PtCl_2(CH_3CN)_2$ is indicative of complete substitution of acetonitrile molecules by the molecules of the ligand. The presence of two absorption bands at 336 and 322 cm^{-1} in the IR spectrum of complex **1**, lacking in the spectrum of the ligand points to the formation of chlorocomplex of Pt(II) of *cis*-configuration. These bands, according to the literature data for the spectra of chlorocomplexes of Pt(II) with neutral ligands (dialkyl sulfides, derivatives of pyridine, imidazole, benzotriazole, etc.) [12, 13], are due to the ν(Pt–Cl) stretching vibrations in complexes

Table 3. Characteristic absorption bands (cm^{-1}) in the IR spectra of 6-*tert*-butyl-2-thiouracil and its chlorocomplexes with Pt(II) and Pd(II)

Absorption band	L	**1**	**2**	**3**
ν(N^1H)	3224 v.s	3180 w	3200 sh	3253 v.s
ν(N^3H)	3136 v.s	3120 w	3121 w	3100 v.s
ν(C≡N)				
ν(C^4=O)	1682 s	1680 s	1689 v.s	1700 v.s
ν(C^5=C^6)	1622 s	1614 s	1623 s	1622 s 1615 s
δ($N^3C^2N^1$) in thioamide group	1542 s	1544 s	1547 s	1550 v.s
Scissor vibrations δ($N^1C^2N^3$) in thioamide group	1160 s	1166 s	1176 s	1163 s
Mixed vibrations ν(C^2=S) and δ($C^2N^1C^6$)	952 m	940 w	940 w	940 m
Out-of-plane vibrations ν(C^2=S)	754 m	735 w	759 w, br	735 w
ν(Pt–S) ν(Pd–S)		380 w	314 sh 310 sh	314
ν(Pt–Cl) ν(Pd–Cl)		336 m 322 m	348 m 320 m	
ν(Pd–Br)				266 s 244 m

of the *cis*-$PtCl_2L_2$ type of C_{2v} symmetry. A weak absorption band at 380 cm^{-1}, also absent in the spectrum of the ligand, corresponds to the ν(Pt–S) stretching vibrations, which proves coordination of the ligand to the metal ion via the sulfur atom of the thioamide group [14]. As compared to the IR spectrum of the ligand, in the spectrum of complex **1** due to the complex formation the combined absorption band ν(C^2=S) + δ($C^2N^1C^6$) at 952 cm^{-1} is shifted to the far region by 12 cm^{-1}, and the ν(C^2=S) band at 754 cm^{-1}, by 19 cm^{-1}.

As a starting reagent for the synthesis of Pd(II) complexes, (bis-benzonitrile)dichloropalladium(II) was employed. This compound is a classical labile complex in which the molecules of benzonitrile are easily replaced by the molecules of sulfur- and nitrogen-containing organic compounds. It is widely used as a precursor in coordination chemistry as well as in the synthesis of organopalladium complexes. Some researchers believe the complex to be the *trans*-isomer [15, 16] because of the presence of one strong absorption band of stretching vibrations ν(Pd–Cl) appearing, according to different authors, at 320 cm^{-1} [17], 368 cm^{-1} or 338 cm^{-1} [18]). In other works [19, 20] it is stated that the compound has the *cis*-configuration, since it shows in the IR spectrum two absorption bands ν(Pd–Cl): 388 and 358 cm^{-1} [19], 367 and 325 cm^{-1} [21], 334 and 315 cm^{-1} [22]. Therefore, there is no unambiguous assignment of absorption bands of the Pd–Cl stretching vibrations in the IR spectrum of *cis*-(bis-benzonitrile)dichloropalladium(II). The IR spectrum of its precursor shows strong absorption bands at 369 and 324 cm^{-1}. These bands can be assigned to the stretching vibrations ν(Pd–Cl), since in the spectrum of (bis-benzonitrile) dibromopalladium(II), which we also synthesized, they are lacking.

In the ^{13}C NMR spectra of Pd(II) complexes **2** and **3** the signals of atoms C^2, C^4, C^5 are shifted with respect to the spectrum of the ligand (Table 2), the largest shift being observed for the carbon atom of the thiocarbonyl group. The signals of all carbon atoms except atom C^5 are shifted upfield upon complex formation.

In the IR spectrum of complex **2**, the nitrile group absorption band, which in the spectrum of the precursor $PdCl_2(PhCN)_2$ appears at 2288 cm^{-1}, is lacking, thus indicating complete replacement of two molecules of benzonitrile by the molecules of the ligand. The absorption bands corresponding to the ν(N^1–H) and ν(N^3–H) vibration are shifted to the far region with respect to those in the spectrum of the ligand by 15–20 cm^{-1}, and the stretching and bending vibrations of the *tert*-butyl group ν(C^4=O), ν(C^5=C^6), δ($N^3C^2N^1$), and δ(CH_3), to the near region by 5–7 cm^{-1}. The bending vibrations band δ($N^1C^2N^3$) at the thioamide group is also shifted to high-frequency region by 16 cm^{-1}, the bands of combined vibrations ν(C^2=S) + δ($C^2N^1C^6$), to the far region by 12 cm^{-1}, and the absorption bands of the out-of-plane stretching vibrations ν(C^2=S) at 754 cm^{-1} broadened. The absorption bands at 348 and 320 cm^{-1} can be assigned, respectively, to asymmetric and symmetric stretching vibrations of the ν(Pd–Cl) band (complex of the *cis*-$PdCl_2L_2$ type, C_{2v} symmetry) [23].

For unambiguous assignment of the Pd–Cl absorption band in the spectrum of complex **2** we have synthesized its analog, $PdBr_2L_2$ (**3**). The IR spectrum of **3** in the range 4000–600 cm^{-1} is similar to that of chlorocomplex **2**. In the far region of the spectrum of **3** a strong absorption band appears at 265 cm^{-1} belonging to stretching vibrations ν(Pd–Br) [24].

The band at 314 cm^{-1} in the spectrum of complex **2** apparently corresponds to stretching vibrations ν(Pd–S). The whole set of the spectral data allows to assume that the formation of complex **2** is due to thecoordination of the ligand to Pd(II) via the sulfur atom of the thioamide group.

Therefore by the reaction of the Pd(II) and Pt(II) precursors with 6-*tert*-butyl-2-thiouracil we have first prepared chlorocomplexes of the *cis*-configuration. The formation of complexes was established to occur via the coordination of the thione sulfur atoms of the thiouracil ring to Pd(II) and Pt(II). Neither nitrogen nor oxygen atoms of the ligand are involved in the complex formation.

EXPERIMENTAL

IR spectrum was calculated by the M06-2X/MG3S method. IR spectra were recorded on a Specord M80 spectrophotometer in the range 4000–230 cm^{-1} (mineral oil, KRS-5). NMR spectra were registered on a Bruker Avance III spectrometer with working frequency 500.13 MHz (^{1}H), 125.47 MHz (^{13}C) and 50.58 MHz (^{15}N) in DMSO-d_6. Melting points were determined on a Boetius heating device.

5-*tert*-Butyl-2-thiouracil was obtained by the known procedure [25] from thiourea and ethyl ester of 4,4-dimethyl-3-oxopentanoic acid and purified by crystallization from 5% aqueous ethanol. Yield 46%, colorless needle crystals, mp 173°C. ^{1}H NMR spectrum, δ, ppm: 1.20 s (9H, CH_3), 5.62 s (1H, HC^5), 11.77 s (1H, HN^1), 12.34 s (1H, HN^3). $^{15}N\{^1H\}$ NMR spectrum (DMSO-d_6, 50 MHz), δ, ppm: 154.4 (N^1), 180.4 (N^3).

As a precursor for the synthesis of chlorocomplex of Pt(II) with 5-*tert*-butyl-2-thiouracil we used *cis*-bis-(acetonitrile)dichloroplatinum(II) $PtCl_2(CH_3CN)_2$, which was obtained by the known procedure [11]. Chloro- and bromocomplex of Pd(II) were synthesized from the preprepared (bis-benzonitrile)dichloropalladium(II) $PdCl_2(PhCN)_2$ and (bis-benzonitrile)dichloropalladium(II) $PdBr_2(PhCN)_2$ by the known procedures [19, 26].

As solvents, acetone (analytical purity grade), hexane (pure), ethanol and chloroform (both chemically pure), acetonitrile (analytically pure), acetonitrile (special purity) were used.

Complex 1, *cis*-[$PtCl_2L_2$]. 0.15 g (0.42 mmol) of *cis*-[$PtCl_2(CH_3CN)_2$] was dissolved at stirring in 25 mL of dry acetone. To the obtained solution, 10 mL of the solution of 0.1562 g (0.84 mmol) of the ligand in acetone was added. The formed transparent yellow solution was stirred for 2 h. To the reaction mixture 20 mL of hexane was added for complete precipitation of the complex. The formed yellow precipitate was filtered off, washed with hexane (3×20 mL), and dried at room temperature. Yield 0.28 g (97.0 %), mp 157°C.

Complex 2, *cis*-[$PdCl_2L_2$]. 0.1438 g (0.37 mmol) of *cis*-[$PdCl_2(PhCN)_2$] was dissolved in 10 mL of chloroform. To the obtained solution, 10 mL of the ethanol solution of 0.1382 g (0.75 mmol) of the ligand was added. After stirring for 1 h the formed bright-orange precipitate was filtered off, washed with hexane (3×20 mL) to remove the remained benzonitrile, and dried at room temperature. Yield 0.16 g (80.0 %).

Complex 3, *cis*-[$PdBr_2L_2$]. 0.2027 g (0.43 mmol) of [$PdBr_2(PhCN)_2$] was dissolved in 10 mL of chloroform at stirring. To the obtained solution, 10 mL of the ethanol solution of 0.1581 g (0.86 mmol) of the ligand was added. After stirring for 3 h, dark-red precipitate was gradually formed, which was filtered off, washed with hexane (3×20 mL), and dried at room temperature. Yield 0.23 g (96.0 %).

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