Synthesis, Spectral Characterization, Crystal Structure, and Antioxidant Properties of novel Palladium(II) Complex from ONS Donor 1,5-bis(2-hydroxybenzylidene)thiocarbohydrazone

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Abstract: A new Pd(II) complex, [Pd(PPh$_3$)(L)] (L = 1,5-bis(2-hydroxybenzylidene)thiocarbohydrazone, PPh$_3$ = triphenylphosphine), was synthesized and characterized by FTIR, ^{1}H NMR and UV-Vis spectroscopies and elemental analysis. The molecular structure of [Pd(PPh$_3$)(L)] was confirmed by the single-crystal X-ray diffraction technique. Palladium ion has distorted square planar geometry according to X-ray diffraction studies. The free thiocarbohydrazone (L), potentially a pentadentate ONSNO donor, acted as a tridentate ONS donor. The antioxidant capacity of the free thiocarbohydrazone and Pd(II) complex was determined using the CUPRAC (cupric reducing antioxidant capacity) method. Also, the DPPH method was used to test the free radical scavenging activity of the free thiocarbohydrazone and Pd(II) complex. Antioxidant activity studies showed that free thiocarbohydrazone exhibited better activity than Pd(II) complex.

Keywords: Thiocarbohydrazone; Palladium(II) complex; Triphenylphosphine; Crystal structure; Antioxidant activity.

Submitted: October 25, 2022. **Accepted:** December 19, 2022.

Cite this: Kaya Y. Synthesis, Spectral Characterization, Crystal Structure, and Antioxidant Properties of novel Palladium(II) Complex from ONS Donor 1,5-bis(2-hydroxybenzylidene)thiocarbohydrazone. JOTCSA. 2023;10(1):129–38.

DOI: https://doi.org/10.18596/jotcsa.1194323.

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1. INTRODUCTION

Thiocarbohydrazide (NH$_2$-NH-C(S)-NH-NH$_2$) and its derivatives are a class of compounds that have applications in many fields and therefore attract great interest (1, 2). One or both of the hydrazine groups of thiocarbohydrazide can form Schiff bases called mono- or bisthiocarbohydrazone by reacting with aldehydes or ketones (3, 4). Thiocarbohydrazones are interesting ligand systems as they have a variety of potential donor sites; they can bind many transition metals through both azomethinic nitrogen and sulfur atoms in their structure and donor atoms originating from aldehyde or ketone (5). These compounds and their metal complexes show biological activities such as antimicrobial, antioxidant, anticancer, antiviral, antidiabetic, and hepatoprotective (5-17). In addition, there has been an increase in the use of thiocarbohydrazones as spectrophotometric reagents in metal determination in recent years (18-20).

Interest in phosphine-based ligands and their metal complexes increased after their roles were discovered in catalysis and stereoselective synthesis (21, 22). These compounds have also been shown to have significant bioactivities such as antitumor, antiviral, antifungal, antibacterial, and antioxidant (13, 23). Among these compounds, especially phosphine-based palladium(II) and nickel(II) complexes have been reported to have important bioactivities (22, 23). In addition, transition metal-phosphine complexes are very important for both industrial and laboratory scale catalytic applications (24).

Cisplatin, carboplatin, and oxaliplatin are effective metal-based anticancer agents (25, 26). Due to serious side effects, drug resistance and the limited spectrum of tumors, extensive attempts have been made to replace these drugs with more efficient, less toxic and targeted anticancer drugs (e.g. Pd, Ni, Ru and Au complexes) (26-28). Because their coordination geometry and complex forming processes are very similar to platinum(II) complexes, palladium(II) complexes have received special attention as metal-organic antitumor drugs (27-31). Palladium(II) complexes have also anti-microbial and antioxidant properties (32). Carbon-carbon bond formation reactions catalyzed by palladium, such as the Suzuki Miyaura, Heck, and Sonogashira coupling reactions, are significant synthetical transformations. These synthetic transformations are widely used to prepare a wide range of organic molecules and materials, including natural products, fine chemicals, drugs, agrochemicals, and polymers (33). Many catalytic systems have been improved using palladium catalysts such as $[Pd(PPh_3)_4]$ and $[PdCl_2(PPh_3)_2]$ (34-36). However, some palladium(II) complexes containing triphenylphosphine secondary ligand have been found to be inhibitors of enzymes such as alkaline phosphatase (ALP), topoisomerase-II, β-glucuronidase, carbonic anhydrase and acetylcholinesterase (37-41).

There are only very few reports concerning Pd(II) complexes containing both thiocarbohydrazone and triphenylphosphine in the literature (41, 42). Therefore, in this study, a new Pd(II) complex was synthesized using 1,5-bis(2-hydroxybenzylidene) thiocarbohydrazone (L) and $[PdCl_2(PPh_3)_2]$ to test its potential antioxidant activity. The characterization of free thiocarbohydrazone and Pd(II) complex were performed using elemental analysis, FTIR, ^{1}H NMR and UV-Vis spectroscopic techniques. The antioxidant activities of free thiocarbohydrazone and Pd(II) complex were also examined using DPPH• radical scavenging activity and CUPRAC method.

2. EXPERIMENTAL SECTION

2.1. Materials and Physical Measurements

Thiocarbohydrazide was obtained according to the published procedure (43). All other chemicals were purchased from chemical companies and used as received.

Elemental analyzes, IR and ^{1}H NMR spectra, UV-Vis data (in 4×10^{-5} M DMSO) and magnetic susceptibility measurements were performed using a Thermo Finnigan Flash EA 1112 elemental analyzer, an Agilent Cary 630 FTIR, a Varian UNITY INOVA 500 MHz NMR device, a Shimadzu 2600 UV-Vis spectrophotometer and a Sherwood Scientific MK I model device, respectively.

2.2. Synthesis of 1,5-bis(2-hydroxybenzylidene)thiocarbohydrazone (L)

Ligand (L) was prepared according to our reported article (44). Thiocarbohydrazide (0.01 mol, 1.06 g) and 2-hydroxybenzaldehyde (0.02 mol, 2.44 g) was mixed in methanol (25 mL). The mixture was refluxed for 4 h. The light-yellow colored product, which precipitated after a few days, was filtered and washed with methanol. Elemental analysis and spectroscopic data for L confirmed its synthesis (Figure 1).

Yield: 85%. Color: Light-yellow. M.p.: 190-191 °C. Calc. for $C_{15}H_{14}N_4O_2S$ (314.36 g mol^{-1}): C: 57.31, H: 4.49, N: 17.82, S: 10.20%; found: C: 57.50, H: 4.46, N: 17.84, S: 10.28%. ^{1}H NMR (500 MHz, DMSO-d$_6$, ppm): 11.70 (s, 2H, -OH), 11.62 (s, 1H, -NH), 10.62 (s, 1H, -NH), 8.67 (s, 2H, -CH=N-), 7.35-6.89 (m, 8H, aromatic H). IR (cm^{-1}): ν(OH) 3195, ν(NH) 3133, ν(C=N) 1613, ν(C=S) 1240. UV-Vis [λ_{max} (nm)]: 251 π→π*, 302 π→π*, 351 n→π*, 367 n→π*.

2.3. Synthesis of $[Pd(PPh_3)(L)]$

1 mmol of $[PdCl_2(PPh_3)_2]$ (0.71 g) dissolved in ethanol (5 mL) was mixed with 1 mmol of L (0.31 g) dissolved in ethanol (10 mL) and dichloromethane (5 mL). Then, Et_3N (1 drop) was added to the mixture and the mixture was stirred under reflux for 5 h to afford an orange precipitate. The obtained solid was filtered and washed with ethanol (Figure 1).

Yield: 52%. Color: Orange. M.p.: 271-273 °C. Calc. for $C_{33}H_{27}N_4O_2PPdS$ (681.05 g mol^{-1}): C: 58.20, H: 4.00, N: 8.23, S: 4.71%; found: C: 58.03, H: 3.96, N: 8.14, S: 4.57%. ^{1}H NMR (500 MHz, DMSO-d$_6$, ppm): 11.65 (s, 1H, -OH), 10.64 (s, 1H, -NH), 8.48 (s, 1H, -CH=N-), 8.11 (s, 1H, -CH=N-), 7.65-5.71 (m, 23H, aromatic H). IR (cm^{-1}): ν(OH) 3190, ν(NH) 3154, ν(C=N) 1618 and 1598, ν(PPh$_3$) 1432, 1099, 738, 690. UV-Vis [λ_{max} (nm)]: 256 π→π*, 280 π→π*, 313 π→π*, 339 n→π*, 355 n→π*, 410 n→π*, 424 LMCT.

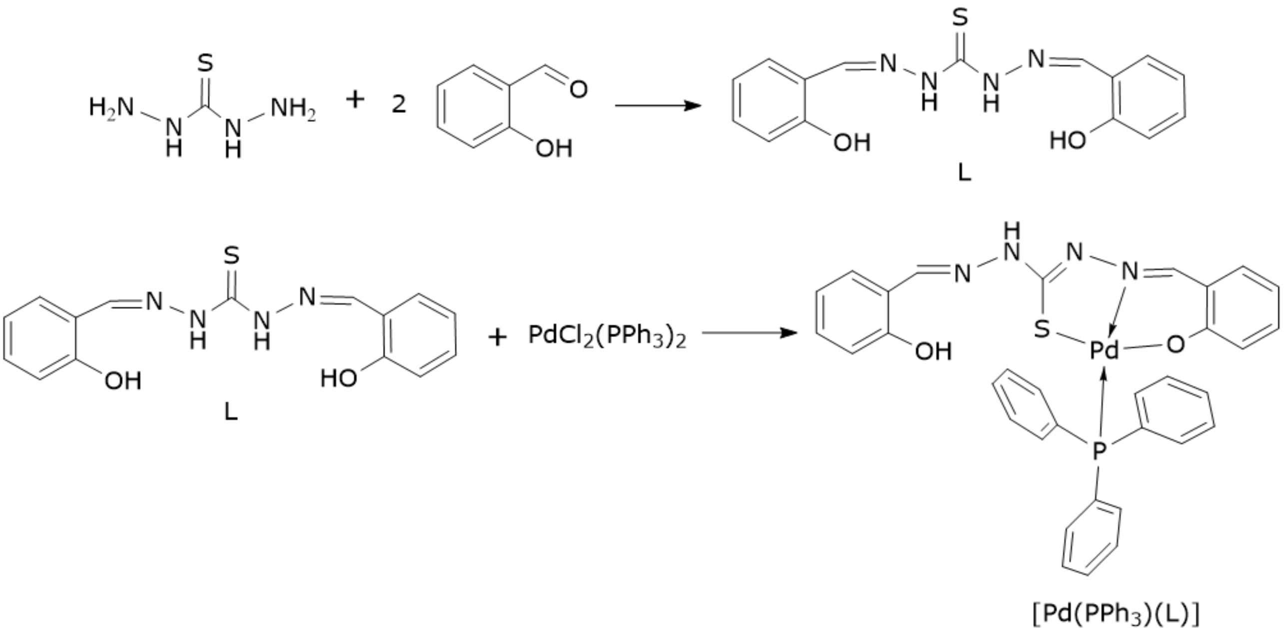

Figure 1: The general synthesis of the free thiocarbohydrazone and Pd(II) complex.

2.4. Determination of Crystal Structure

Slow evaporation of [Pd(PPh$_3$)(L)] in ethanol + DCM gave single crystals suitable for determining the molecular structure of the complex. A Bruker APEX II CCD three-circle diffractometer was used for X-ray diffraction data collection and unit cell determination at room temperature. Indexing, data reduction and integration were performed using APEX2 (45) and SAINT (46). Structure solution and refinement were performed with the SHELXT (47) and SHELXL (48) programs. The program Mercury was used to represent the molecular structure (49). Hydrogen atoms were positioned geometrically and treated with the riding model. The crystallographic data of [Pd(PPh$_3$)(L)] are given in Table 1. The selected bond distances and angles are listed in Table 2.

2.5. CUPRAC and DPPH Methods

The radical scavenging activities of free thiocarbohydrazone and Pd(II) complex were measured using the DPPH method according to the formerly declared method with minor changes (50). To a tube; 2 mL of 10^{-4} M DPPH in ethanol, 1 mL of 10^{-4} M of the sample in ethanol (containing 1% DMSO) and (1 - x) mL of ethanol were added. The mixture (4 mL) was incubated in a dark place at 25 ^{o}C. After 30 minutes, the absorbances of the sample and control solutions were measured against ethanol at 515 nm. The control solution was obtained by mixing DPPH solution (2 mL) and ethanol (2 mL). Trolox was used as the reference compound. The radical scavenging activity was computed from Equation (1) below.

$$\%\text{radical scavenging activity} = \left[\frac{A_{control} - A_{sample}}{A_{control}}\right] \times 100 \qquad \text{Equation (1)}$$

Antioxidant capacities of free thiocarbohydrazone and Pd(II) complex were determined by CUPRAC method (51). To a tube; 1 mL of 10^{-2} M $CuCl_2.2H_2O$ in water, 1 mL of 7.5 x 10^{-3} M neocuproine in ethanol, 1 mL of 1 M NH_4Ac in water, x mL of 10^{-4} M sample in ethanol (containing 1% DMSO) and (1.1 - x) mL of water were added and the total volume was adjusted to 4.1 mL. The mixture was incubated in a dark place for 30 minutes. Then, the absorbance values were recorded at 450 nm. The results were given as TEAC (trolox equivalent antioxidant capacity) coefficient. TEAC values were calculated by dividing the molar absorptivity (Ɛ) of the compounds by that of Trolox ($Ɛ_{trolox}$ = 1.67 x 10^4 L mol^{-1} cm^{-1}).

3. RESULTS AND DISCUSSION

3.1. Synthesis and Spectral Characterization

The ligand was prepared by the condensation of thiocarbohydazide (0.01 mol) with 2-hydroxybenzaldehyde (0.02 mol). The reaction of free thiocarbohydrazone (L) with an equimolar amount of [PdCl$_2$(PPh$_3$)$_2$] afforded the Pd(II) complex [Pd(PPh$_3$)(L)]. The complex is soluble in DCM, DMF and DMSO solvents. The μ_{eff} measurement showed that the complex is diamagnetic. The elemental analysis and spectroscopic data agreed with the proposed molecular formula of the free thiocarbohydrazone and Pd(II) complex.

In the IR spectrum of L, the characteristic peaks of OH, NH, C=N and C=S groups were seen at 3195, 3133, 1613 and 1240 cm^{-1}, respectively. The bands of OH and NH groups were observed at 3190 and 3154 cm^{-1} in the spectrum of [Pd(PPh$_3$)(L)]. This can be interpreted as one of the OH and NH groups of L did not participate in the formation of the complex. The absence of the band attributed to the ν(C=S) in the spectrum of [Pd(PPh$_3$)(L)] can be explained by the tautomerism of the C=S group with one NH group to form the C-SH in the molecule of L. One of the bands belonging to the azomethine groups in L shifted to lower wavenumber (1598 cm^{-1}) in the spectrum of [Pd(PPh$_3$)(L)]. This indicates the coordination of one of the azomethine nitrogen atoms of the ligand to the metal atom. [Pd(PPh$_3$)(L)] spectrum also includes the characteristic bands of the coordinated PPh$_3$ ligand at 1432, 1099, 738, 690 cm^{-1} (10, 41, 52).

^{1}H NMR spectrum of L exhibits two OH$_{\text{phenolic}}$ protons at 11.70 ppm whereas the spectrum of [Pd(PPh$_3$)(L)] adopts only one OH$_{\text{phenolic}}$ signal at 11.65 ppm since other OH proton is involved in bonding with palladium ion. Although the spectrum of L exhibits two NH signals at 11.62 and 10.62 ppm, the spectrum of [Pd(PPh$_3$)(L)] displays only one signal at 10.64 ppm. The disappearance of the proton in the NH group indicates the deprotonation in the NH group through the sulfur atom by tautomerism (NH-C=S↔N=C-SH). The spectrum of L shows signals belonging to two azomethine protons at 8.67 ppm, one of which undergoes a downfield shift by complexation (41, 44, 53).

The electronic spectrum of L exhibits two absorptions at 251 and 302 nm assigned to $\pi \rightarrow \pi^*$ transitions of phenyl rings. These bands were seen at 256, 280 and 313 nm in the spectrum of [Pd(PPh$_3$)(L)]. The absorption bands at 315 and 367 nm in the spectrum of L are due to $n \rightarrow \pi^*$ transitions of the C=N and C=S groups. The fact that these bands appear at 339, 355 and 410 nm in the spectrum of [Pd(PPh$_3$)(L)] can be interpreted as the metal atom being coordinated to the ligand via the azomethine nitrogen and sulfur atom. Also, different from the spectrum of L, the band attributed to the charge transfer transition (LMCT) was observed at 424 nm in the spectrum of [Pd(PPh$_3$)(L)] (26, 41, 54).

3.2. Crystal Structure Analysis

According to the results of the crystallographic analysis, [Pd(PPh$_3$)(L)] crystallizes in the P2$_1$/n space group and as a monoclinic crystal system. The molecular structure and atom labeling scheme of [Pd(PPh$_3$)(L)] is shown in Figure 2. There are two crystallographically independent [Pd(PPh$_3$)(L)] molecules with similar parameters in the asymmetric unit. The palladium ion displays a slightly distorted square planar geometry involving oxygen, nitrogen, sulfur and phosphorus atoms. Although free thiocarbohydrazone is a potential pentadentate, it acts as a dibasic tridentate ONS donor in [Pd(PPh$_3$)(L)]. In the complex, ligand is coordinated to Pd(II), forming six and five-membered chelate rings with O2-Pd1-N4, O4-Pd2-N8 and N4-Pd1-S1, N8-Pd2-S2 angles of 93.3(3)°, 92.9(3)° and 84.0(3)°, 85.0(3)° respectively, and these angles are similar to those observed in related Pd(II) complexes (26, 41, 55). The S1-Pd1-O2 [176.7(2)°], S2-Pd2-O4 [177.0(2)°] and N4-Pd1-P006 [178.4(3)°], N8-Pd2-P005 [178.8(3)°] bond angles are very close to the ideal angle of 180°. The binding parameters show that there is a slight distortion from ideal geometry around palladium ion. Pd-S [2.245(3) Å], Pd-O [2.013(8) Å and 2.014(8) Å], Pd-N [2.017(9) Å and 2.029(9) Å], and Pd-P [2.265(3) Å and 2.258(3) Å] bond distances are within normal ranges and are in good agreement with those found in four-coordinate Pd(II) complexes containing triphenylphosphine (26, 41, 56). C8-S1 [1.761(12) Å] and C41-S2 [1.764(12) Å] bond distances indicate that L is bound to palladium ion in the thiolate form (41, 42, 57). In addition, the molecular structure of [Pd(PPh$_3$)(L)] is stabilized by weak and moderately bound intermolecular and intramolecular hydrogen bonds (Table 3).

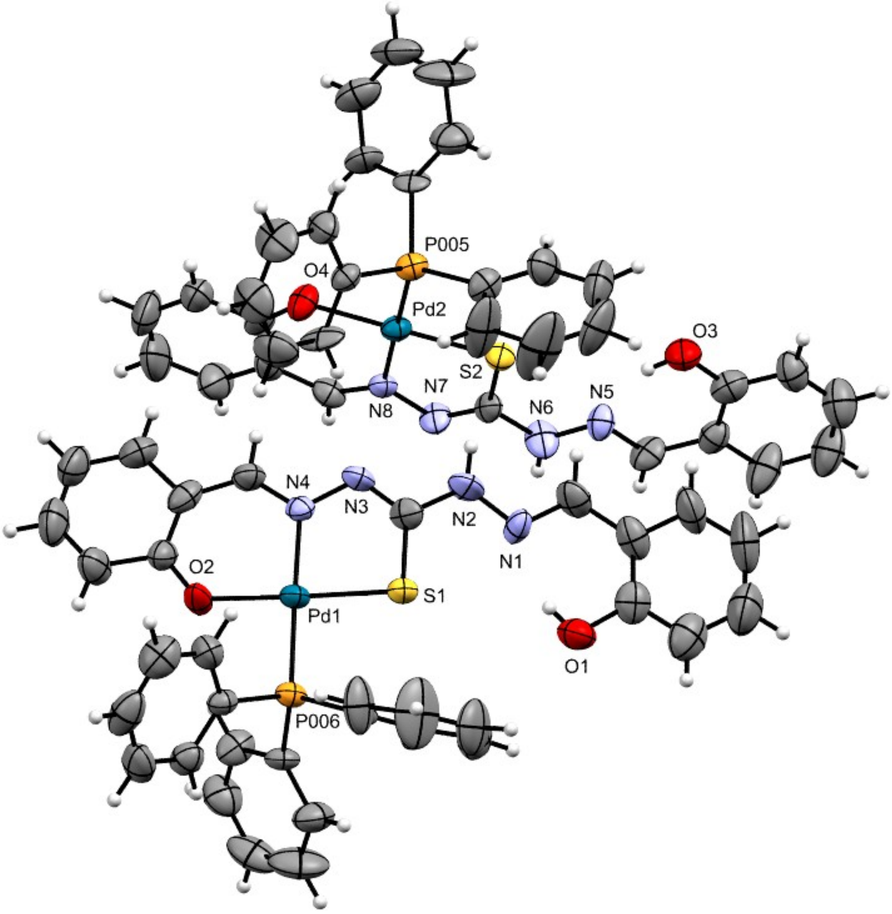

Figure 2: The molecular structure of $[Pd(PPh_3)(L)]$ with the atom numbering scheme excluding C and H.

Table 1: Crystal data and structure refinement parameters for $[Pd(PPh_3)(L)]$.

Name of the parameter	**Value**
CCDC	2196022
Empirical formula	$C_{33}H_{27}N_4O_2PPdS$
Formula weight	681.01
Temperature (K)	273.15
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	27.539(6)
b (Å)	8.765(2)
c (Å)	28.691(7)
α (°)	90
β (°)	110.690(4)
γ (°)	90

Crystal size (mm^3)	0.491 × 0.24 × 0.042
Wavelength (Å)	0.71073
Volume ($Å^3$)	6479(3)
Z	8
$D_{calc.}$ ($g.cm^{-3}$)	1.396
μ (mm^{-1})	0.721
F(000)	2768.0
θ range for data collection (°)	2.548 to 49.998
Index ranges	$-32 \leq h \leq 30$, $0 \leq k \leq 10$, $0 \leq l \leq 34$
Reflections collected	11398
Independent reflections	11398
Data/restraints/parameters	11398/0/760
Goodness-of-fit on F^2 (S)	1.115
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0991$, $wR_2 = 0.2255$
Final R indexes [all data]	$R_1 = 0.1328$, $wR_2 = 0.2368$
Largest diff. peak/hole ($e.Å^{-3}$)	1.15/-1.80

Table 2: The selected bond lengths (Å) and bond angles (°) for [$Pd(PPh_3)(L)$].

Bond lengths (Å)		**Bond angles (°)**	
Pd1—S1	2.245(3)	S1—Pd1—O2	176.7(2)
Pd2—S2	2.245(3)	S2—Pd2—O4	177.0(2)
Pd1—O2	2.013(8)	N4—Pd1—P006	178.4(3)
Pd2—O4	2.014(8)	N8—Pd2—P005	178.8(3)
Pd1—N4	2.017(9)	O2—Pd1—P006	87.9(2)
Pd2—N8	2.029(9)	O4—Pd2—P005	87.5(2)
Pd1—P006	2.265(3)	O2—Pd1—N4	93.3(3)
Pd2—P005	2.258(3)	O4—Pd2—N8	92.9(3)
N4—N3	1.384(12)	S1—Pd1—P006	94.78(11)
N8—N7	1.392(12)	S2—Pd2—P005	94.63(11)
N2—N1	1.359(14)	S1—Pd1—N4	84.0(3)
N6—N5	1.349(13)	S2—Pd2—N8	85.0(3)

Table 3: Geometric values for hydrogen bonds for [Pd(PPh_3)(L)].

D-H···A	D-H [Å]	H···A [Å]	D···A [Å]	D-H···A [°]
O1-H1···N1	0.821(8)	1.968(9)	2.617(12)	135.5(8)
O3-H3A···N5	0.819(10)	1.894(11)	2.617(15)	146.6(7)
N2-H2···S2	0.859(11)	2.709(3)	3.461(11)	146.8(8)
N6-H6A···S1^{i}	0.860(12)	2.787(3)	3.513(12)	143.2(7)
C66-H66···N3	0.930(11)	2.487(11)	3.393(15)	164.9(9)
C29-H29···N7^{ii}	0.931(16)	2.519(12)	3.440(2)	168.4(8)
C54-H54···O4	0.928(16)	2.471(9)	3.283(18)	146.2(8)
C52-H52···O3^{iii}	0.931(16)	2.518(7)	3.410(17)	160.6(11)

Symmetry codes: (i) +x, 1+y, +z; (ii) +x, -1+y, +z; (iii) 1-x, 3-y, 1-z.

3.3. Antioxidant Properties

The total antioxidant capacity of the free thiocarbohydrazone and Pd(II) complex was determined using the CUPRAC method. The TEAC values of the free thiocarbohydrazone and Pd(II) complex are given in Table 4. When the values are examined, it is seen that the total antioxidant capacity of both free thiocarbohydrazone and Pd(II) complex is better than Trolox ($TEAC_{trolox}$ = 1). It also appears that free thiocarbohydrazone shows higher activity than [Pd(PPh_3)(L)]. Similar to the antioxidant capacity, the antiradical activity of [Pd(PPh_3)(L)] is also lower than that of the free thiocarbohydrazone (Table 5). The degree of conjugation of the whole molecule and the number and position of the OH groups are substantial for electron transfer (58). This impacts the antioxidant activity of the tested compounds. The NH group in the thiocarbohydrazone also contributes to antioxidant activity (59). So, we can say that the decrease in the number of OH and NH groups in the free thiocarbohydrazone by complexation is the reason why the TEAC value and % radical scavenging activity of [Pd(PPh_3)(L)] are lower than that of free thiocarbohydrazone.

Table 4: The TEAC values of the compounds with regard to the CUPRAC assay.

Compounds	Molar absorptivity (L mol^{-1} cm^{-1})	TEAC	Correlation coeff. (r)
L	5.9089 x 10^4	3.54 ± 0.719	0.9939
[Pd(PPh_3)(L)]	2.5189 x 10^4	1.51 ± 0.087	0.9995

Table 5: % free radical scavenging activities of the compounds (initial concentration: 10^{-4} M, sample volume: 1 mL).

Compounds	Free Radical Scavenging Activity (%)
L	77.84 ± 0.19
[Pd(PPh_3)(L)]	55.07 ± 1.08
Trolox	82.33 ± 2.95

CONCLUSION

A new Pd(II) complex was synthesized from 1,5-bis(2-hydroxybenzylidene)thiocarbohydrazone (L) and structurally characterized. Crystal data showed that the complex had five- and six-membered chelate rings by the coordination of one oxygen, one nitrogen and one sulfur atom on the thiocarbohydrazone to the palladium ion. In the palladium ion with the distorted square planar geometry, the fourth coordination was completed with a phosphorus atom of triphenylphosphine co-ligand. Antioxidant activities of free thiocarbohydrazone and Pd(II) complex were studied using CUPRAC and DPPH methods. TEAC values determined according to the CUPRAC method showed that both free thiocarbohydrazone and Pd(II) complex had better antioxidant capacity than Trolox. Also, the DPPH radical scavenging ability of free thiocarbohydrazone was higher than that of the Pd(II) complex. In conclusion, free thiocarbohydrazone and Pd(II) complex with good antioxidant activity can be suggested as promising components for the prevention of oxidative stress-induced diseases.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGMENTS

I dedicate this paper to Prof. Dr. Ayşe ERÇAĞ, the mentor of my research career.

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