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SHORT COMMUNICATION

Palladium(II) complexes with R_2edda derived ligands. Part VI. *O,O′*-Diisopropyl ester of *N,N′*-1,2-ethanediylbis-L-leucine, dihydrochloride dihydrate and its palladium(II) complex: synthesis and characterization

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Abstract: A new R_2edda-type ester, *O,O′*-diisopropyl ester of *N,N′*-1,2-ethanediylbis-L-leucine, dihydrochloride dihydrate, [(*S,S*)-H_2*i*Pr_2eddl]Cl_2·$2H_2O$, **1**, and its palladium(II) complex, dichlorido(*O,O′*-diisopropyl-*N,N′*-1,2-ethanediylbis-L-leucinate)palladium(II) hemihydrate, [$PdCl_2${(*S,S*)-*i*Pr_2eddl}]·$0.5H_2O$, **2**, were synthesized and characterized by elemental analysis, and IR and NMR spectroscopy. As expected, the palladium(II) complex was found in two from three possible diastereoisomeric forms (*R,R*), (*S,S*) and (*R,S*) ≡ (*S,R*).

Keywords: palladium complexes; R_2edda-type ligands; diastereoisomers.

INTRODUCTION

Palladium(II) complexes containing the EDTA ligand represent interesting fields in terms of synthesis and characterization.[1–3] In these complexes, the potentially hexadentate EDTA acts as a tetradentate or a bidentate ligand when competing ligands are present (*e.g.*, chlorides), forming mono- or even dimeric species. A significant part of previous research was focused on complexes with branched-chain esters of chiral edda-type acids, *N,N′*-1,2-ethanediylbis-L-alanine hydrochloride, [(*S,S*)-H_3eddip]Cl, and *N,N′*-1,2-ethanediylbis-L-leucine dihydrochloride, [(*S,S*)-H_4eddl]Cl_2, and a large amount of structural information was obtained, as well as interesting findings related to the antiproliferative activity of platinum(II), platinum(IV) and palladium(II) complexes.[4–10]

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Palladium(II) complexes with branched-chain R_2edda-type esters, previously described in literature,[7–9] are represented in Fig. 1, including the complex **2** from the present study (Fig. 1, complex **C**).

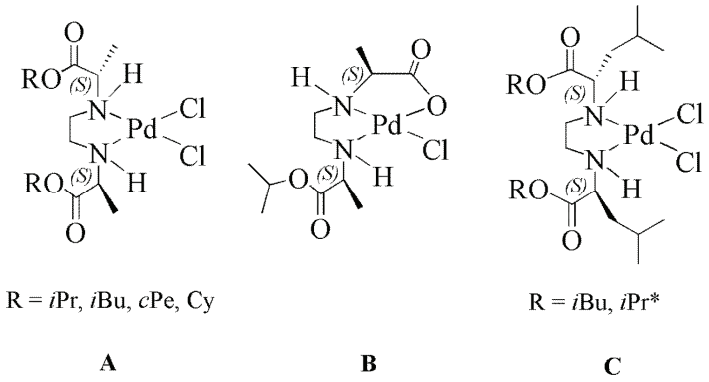


Fig. 1. Palladium(II) complexes with branch-chained R_2edda-type esters (* – complex **2** reported in this work).

Palladium(II) complexes **A** presented in Fig. 1 were obtained as a mixture of two diasteroisomers, as (*R*,*R*) and (*R*,*S*) isomers, as verified by ^{1}H- and ^{13}C--NMR spectroscopy and supported by DFT calculations.[7,8] However, three diastereoisomers can be formed in theory, (*R*,*R*), (*S*,*S*) and (*R*,*S*) ≡ (*S*,*R*), due to the formation of chiral centers on the coordinated nitrogen atoms. In a recent study a palladium(II) complex with a partially hydrolized isopropyl ester of *N*,*N*′-1,2-ethanediylbis-L-alanine (Fig. 1, **B**) was isolated and its structure was confirmed by X-ray analysis. It was found that the (*R*,*R*)–*N*,*N*′ configured isomer with a κ^2*N*,*N*′,κ*O* coordination mode was obtained, and that this is the most stable isomer of four theoretically possible ones.[7] All of the other complexes mentioned here have a κ^2*N*,*N*′ coordination mode of the ligand.

Herein, the synthesis and characterization of two new compounds, branched-chain R_2edda-type ester [(*S*,*S*)-H_2*i*Pr$_2$eddl]$Cl_2\cdot 2H_2O$, **1**, and corresponding palladium(II) complex [$PdCl_2${(*S*,*S*)-*i*Pr$_2$eddl}]$\cdot 0.5H_2O$, **2**, (Fig. 1, **C**, complex **2**) are described.

EXPERIMENTAL

Materials and methods

[(*S*,*S*)-H_4eddl]Cl_2 was prepared using a method described in the literature.[11] $K_2[PdCl_4]$ was purchased from Merck and used without further purification. The infrared spectra were recorded on a Nicolet 6700 FT-IR spectrophotometer using the ATR technique (4000–400 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Gemini 2000 (200 MHz) spectrometer in DMSO-d_6 using tetramethylsilane as an internal standard. Elemental analyses for C, H and N were realized on a Vario EL III C, H, N, S elemental analyzer.

*Synthesis of [(S,S)-H$_2$iPr$_2$eddl]Cl$_2$·2H$_2$O (**1**)*

The ligand **1** was prepared using a modified previously described esterification reaction.[9,10,12,13] Thionyl chloride (4.0 cm^3, 55 mmol) was introduced into a flask containing 50 ml of ice cooled 2-propanol (anhydrous conditions) during 1 h. Then, 2 g (5.54 mmol) of *N*,*N*´-1,2-ethanediylbis-L-leucine dihydrochloride, [(*S*,*S*)-H$_4$eddl]Cl$_2$, was added into the flask and the suspension was refluxed for 16 h. The mixture was filtered and the filtrate was stored for a few days at 4 °C. A white crystalline solid was obtained. The ester was purified by recrystallization from methanol.

*Synthesis of [PdCl$_2${(S,S)-iPr$_2$eddl}]·0.5H$_2$O (**2**)*

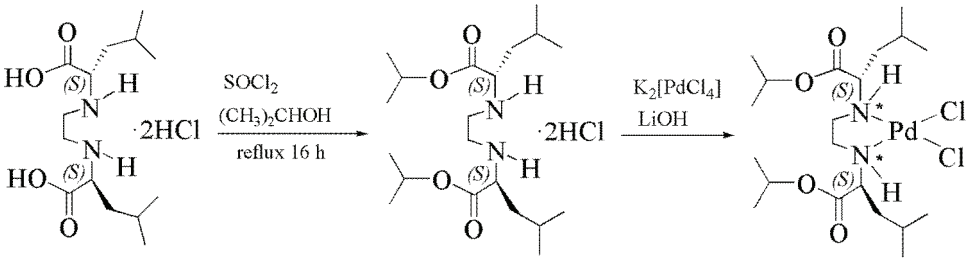
Complex **2** was prepared by dissolving K$_2$[PdCl$_4$] (0.167 g, 0.512 mmol) in water (10 ml) and 0.247 g (0.512 mmol) of [(*S*,*S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O (**1**) was added. During 2 h of stirring, 10 ml of a 0.1 M solution of LiOH (1.02 mmol) was added in small portions to the reaction mixture. A pale yellow precipitate was obtained, which was filtered off, and the crude product dissolved in 5 ml of CHCl$_3$ and filtered. A crystalline solid of the pure complex was obtained from the CHCl$_3$ solution.

RESULTS AND DISCUSSION

Synthesis and characterization

[(*S*,*S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O (**1**) was prepared using an appropriate modification of known methods.[5–10,12,13] This compound is not soluble in chloroform, poorly soluble in water, but fairly soluble in methanol and dimethyl sulfoxide.

[PdCl$_2${(*S*,*S*)-*i*Pr$_2$eddl}]·0.5H$_2$O (**2**) was synthesized by combining aqueous solutions of K$_2$[PdCl$_4$] and **1**. The obtained complex is soluble in chloroform and dimethyl sulfoxide, partially soluble in methanol, but not soluble in water. The preparations of the ester and the complex are shown in Scheme 1.



1 **2**

Scheme 1. Synthesis of the ester **1** and the palladium complex **2** (✶ – N atoms configured (*R*,*R*) or (*S*,*S*) or (*S*,*R*) ≡ (*R*,*S*)).

The analytic and spectral data for **1** and **2** are as follows:

Compound **1**. Yield: 1.25 g (47 %); Anal. Calcd. for C$_{20}$H$_{42}$Cl$_2$N$_2$O$_4$·2H$_2$O: C, 49.89; H, 9.13; N, 5.82 %. Found: C, 49.56; H, 8.86; N, 6.17 %; IR (cm^{-1}): 3395, 2959, 2620, 2404, 1728, 1468, 1217, 1103, 913, 802; ^{1}H-NMR (200 MHz,

DMSO-d_6, δ / ppm): 0.92 (12H, *d*, $^3J_{H,H}$ = 4.40 Hz, 4 C**H**$_3$–*i*Pr), 1.26 (12H, *d*, $^3J_{H,H}$ = 6.20 Hz, 4 C**H**$_3$), 1.75 (6H, *m*, 2 C**H**$_2$, 2 C**H**(CH$_3$)$_2$), 3.42 (4H, *m*, 2 C**H**$_2$–(en)), 4.05 (2H, *m*, 2 C**H**), 5.04 (2H, *m*, 2 C**H**–*i*Pr), 9.80–10.40 (4H, *s*, 2 N**H**$_2^+$); ^{13}C-NMR (50 MHz, DMSO-d_6, δ / ppm): 21.5 (**C**H$_3$), 21.6 (**C**H$_3$–*i*Pr), 23.2 (**C**H(CH$_3$)$_2$), 24.5 (**C**H$_2$), 41.6 (C**H**$_2$–(en)), 57.9 (**C**H), 70.4 (**C**H–*i*Pr), 168.5 (**C**OO–*i*Pr).

Compound **2**. Yield: 0.145 g (51 %); Anal. Calcd. for $C_{20}H_{40}Cl_2N_2O_4Pd{\cdot}0.5H_2O$: C, 42.98; H, 7.39; N, 5.01 %. Found: C, 42.80; H, 7.32; N, 5.23 %; IR (cm^{-1}): 3086, 2958, 2873, 1733, 1371, 1198, 1104, 936, 824; ^{1}H-NMR (200 MHz, DMSO-d_6, δ / ppm): Isomer **A**: 0.93 (12H, *d*, $^3J_{H,H}$ = 6.60 Hz, 4 C**H**$_3$–*i*Pr), 1.21 (12H, *d*, $^3J_{H,H}$ = 5.60 Hz, 4 C**H**$_3$), 1.68 (2H, *m*, 2 C**H**(CH$_3$)$_2$), 2.24 (4H, *m*, 2 C**H**$_2$), 2.58 and 2.77 (4H, *m*, 2 C**H**$_2$–(en)), 4.03 (2H, *m*, 2 C**H**), 4.92 (2H, *m*, 2 C**H**–*i*Pr), 6.20–6.80 (2H, *bs*, 2 N**H**); Isomer **B**: 0.88 (12H, *d*, $^3J_{H,H}$ = 6.00 Hz, 4 C**H**$_3$–*i*Pr), 1.28 (12H, *d*, $^3J_{H,H}$ = 6.60 Hz, 4 C**H**$_3$), 1.88 (2H, *m*, 2 C**H**(CH$_3$)$_2$), 2.34 (4H, *m*, 2 C**H**$_2$), 2.69 and 2.85 (4H, *m*, 2 C**H**$_2$–(en)), 3.72 (2H, *m*, CH), 5.02 (2H, *m*, 2 C**H**–*i*Pr), 5.80–6.10 (2H, *bs*, 2 N**H**); ^{13}C-NMR (50 MHz, DMSO-d_6, δ / ppm): Isomer **A**: 21.6 (**C**H$_3$), 22.1 (**C**H$_3$–*i*Pr), 23.1 (**C**H(CH$_3$)$_2$), 25.6 (**C**H$_2$), 38.2 and 47.0 (**C**H$_2$–(en)), 58.6 (**C**H), 68.6 (**C**H–*i*Pr), 169.3 (**C**OO–*i*Pr); Isomer **B**: 22.3 (**C**H$_3$), 22.6 (**C**H$_3$–*i*Pr), 23.7 (**C**H(CH$_3$)$_2$), 24.6 (**C**H$_2$), 40.9 and 50.0 (**C**H$_2$–(en)), 53.3 (**C**H), 63.8 (**C**H–*i*Pr), 170.5 (**C**OO–*i*Pr); Ratio of isomers: A/B = 5/1.

IR spectrum of **2** shows specific absorption bands: ν(C=O) at 1733 cm^{-1} (strong), ν(C–O) at 1198 cm^{-1} (strong), and ν(CH$_3$) at 2958 cm^{-1} (medium); (for comparison, **1** shows: ν(C=O) at 1728 cm^{-1} (strong), ν(C–O) at 1217 cm^{-1} (strong), and ν(CH$_3$) at 2959 cm^{-1} (medium)). Indication of nitrogen coordination was proved by the presence of a band for secondary amino group (3086 cm^{-1}), contrary to the IR spectrum of **1**, for which the absorption of the secondary ammonium group was observed at 3395 cm^{-1}.

In ^{1}H-NMR spectrum of **2**, the chemical shifts of hydrogen atoms belonging to secondary amino groups appeared at 8.55 ppm (compared with the ammonium groups of **1** at 9.9–10.4 ppm).[7–9] Coordination induced shifts in **2** related to the proton atoms from the ethylenediamine moiety were observed (≈0.7 ppm upfield), thus confirming nitrogen coordination to the palladium atom. Chemical shifts for the hydrogen atom bonded to the chiral carbon atom of **1** and **2** were observed at 4.05 ppm as a multiplet.

The ^{13}C-NMR spectra of **1** and **2** have resonances for the carbon atom of the COO moiety at similar positions, indicating that oxygen atoms did not coordinate and that the ester function remained intact.[7–9] The chiral carbon atom shows a chemical shift at 57.9 ppm for **1**, but two signals for the same carbon atom in corresponding palladium(II) complex were observed at 58.3 and 58.8 ppm, indi-

cating the presence of two isomers. Selected ^{1}H- and ^{13}C-NMR data for **1** and **2** are given in Table I.

TABLE I. Selected ^{1}H- and ^{13}C-NMR data (δ in ppm) of [(*S,S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O (**1**) and [PdCl$_2${(*S,S*)-*i*Pr$_2$eddl}]·0.5H$_2$O (**2**)

Compound		C**H**$_3$ [*i*Pr]	C**H**$_3$ [Leu]	C**H** [*i*Pr]	**C**H$_3$ [Leu]	**C**H$_3$ [*i*Pr]	**C**OO–*i*Pr	**C**H [*i*Pr]
1	[(*S,S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O	0.92	1.26	5.04	21.5	21.6	168.5	70.4
2	[PdCl$_2${(*S,S*)-*i*Pr$_2$eddl}]·0.5H$_2$O							
	Isomer **A**	0.93	1.21	4.92	21.6	22.1/	169.3	68.6
	Isomer **B**	0.88	1.28	5.02	22.3	22.6	170.5	63.8

As expected,[5–8] two sets of signals were found upon coordination of the ligand to the PdCl$_2$ moiety because of the formation of two extra chiral centers at the ligating *N* atoms. Thus, at least two from three diastereoisomers might be formed in the reaction of K$_2$[PdCl$_4$] and **1**. This is in agreement with earlier performed DFT calculations for similar compounds.[7,8]

CONCLUSION

Two novel compounds, R$_2$edda-type ester [(*S,S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O, and its corresponding palladium(II) complex [PdCl$_2${(*S,S*)-*i*Pr$_2$eddl}]·0.5H$_2$O, were synthesized and characterized by IR and NMR spectroscopy and elemental analysis. Potassium tetrachloridopalladate(II) reacts with [(*S,S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O forming two out of three possible diasteroisomers (*R,R*), (*S,S*) and (*R,S*) ≡ (*S,R*), as evidenced by NMR spectroscopy, which is in agreement with previous DFT calculations.

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ИЗВОД

КОМПЛЕКСИ ПАЛАДИЈУМА(II) СА ЛИГАНДИМА R$_2$EDDA ТИПА. ДЕО VI. *O,O′*-ДИИЗОПРОПИЛ ЕСТАР *N,N′*-1,2-ЕТАНДИИЛБИС-L-ЛЕУЦИНА, ДИХИДРОХЛОРИД ДИХИДРАТ И ЊЕГОВ КОМПЛЕКС СА ПАЛАДИЈУМОМ(II): СИНТЕЗА И КАРАКТЕРИЗАЦИЈА

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Нов естар R$_2$edda-типа *O,O′*-диизопропил естар *N,N′*-1,2-етандиилбис-L-леуцина, дихидрохлорид дихидрат [(*S,S*)-H$_2$*i*Pr$_2$eddl]Cl$_2$·2H$_2$O (**1**) и његов комплекс паладијума(II), дихлоридо(*O,O′*-диизопропил-*N,N′*-1,2-етандиилбис-L-леуцинат)паладијум(II)-

-хемихидрат $[PdCl_2\{(S,S)\text{-}iPr_2eddl\}]\cdot 0.5H_2O$ (**2**) су синтетисани и окарактерисани уз помоћ елементалне анализе, IR и NMR спектроскопије. Калијум-тетрахлоридопаладат(II), реагујући са $[(S,S)\text{-}H_2iPr_2eddl]Cl_2\cdot 2H_2O$, очекивано даје паладијумов комплекс **2** у облику два од могућа три дијастереоизомера, (*R*,*R*), (*S*,*S*) и (*R*,*S*) ≡ (*S*,*R*), што је потврђено уз помоћ NMR спектроскопије, а у сагласности је са раније урађеним DFT прорачунима.

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