Palladium(II) complexes with R_2edda derived ligands. Part III.
Diisobutyl (S,S)-2,2’-(1,2-ethanediylidiimino)di(4-methylpenta
noate) and its palladium(II) complex:
synthesis and characterization

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Abstract: A new R_2edda-type ester, diisobutyl (S,S)-2,2’-(1,2-ethanediylidiimino)di(4-methylpentanoate) dihydrochloride, [(S,S)-H_2iBu_2eddl]Cl_2, 1, and its palladium(II) complex, dichloro(diisobutyl (S,S)-2,2’-(1,2-ethanediylidiimino)di(4-methylpentanoate))palladium(II), [PdCl_2{(S,S)-iBu_2eddl}], 2, were synthe
sized and characterized by elemental analysis, as well as IR and NMR spectroscopy. It was found that complex 2 was obtained as mixture of two diaste
eoisomers, observed in NMR spectra. The crystal structure of compound 1 was determined by X-ray diffraction studies and is described. The isolated
crystals consisted of one dicationic species [(S,S)-H_2iBu_2eddl]^2+ and two Cl^-.
The crystal system was tetragonal with the space group P4_2. Hydrogen bonds
significant for the manner of packing are N–H1N···Cl, 3.049(3) Å, 159(3)° and
N–H2N···Cl, 3.100(3) Å, 164(3)°. An infinite chain was formed building a one
layer structure, usual for these types of compounds. The C_2 symmetry axis of
the compound passes through the Cl–Cl’ bond vector and lies perpendicular to
the plane N_2Cl_2.

Keywords: palladium complexes; crystal structure; EDDP ligands; characteri
zation.

INTRODUCTION

The area of present research is of consequence to studies on Pt(II/IV) and
Pd(II) complexes with bis(carboxyalkylamino)ethane and -propane ligands and
their derivatives. Earlier, structural and antiproliferative investigations were per-
formed on complexes and esters from a family of similar compounds – H2edda- and R2edda-derived ligands and their transition metal complexes.1–8

Palladium(II) and platinum(II) have very similar chemistry and analogous coordination modes, however, palladium(II) complexes are kinetically less stable.9,10 Therefore, palladium(II) derivatives are quite often used in attempts to discover new cytotoxic compounds and to compare and determine the influence of the central metal atoms on antiproliferative activity and structure.11–17

Lately, our work has been focused on complexes with branch-chained esters of a chiral acid, (S,S)-ethylenediamine-N,N'-di-2-propanoic acid hydrochloride, [(S,S)-H3eddip]Cl (Fig. 1) and a large amount of structural information was obtained, as well as information on the antiproliferative activity of platinum(II/IV) and palladium(II) complexes.18–20

In these complexes, three diastereoisomers could be formed (R,R), (R,S ≡ S,R) and (S,S), due to the formation of chiral centers on the coordinated nitrogen atoms (Fig. 2). Experimental data and DFT calculations showed that in the case of platinum(IV) complexes with R2edda-type esters, a racemic mixture of (R,R) and (S,S) isomers is obtained.1 With chiral (S,S)-R2edda-type esters, only one diastereoisomer was isolated, the (R,R) isomer, which was determined by X-ray structure analysis18 (Fig. 1, A). All synthesized platinum(II) and palladium(II) complexes were obtained as a mixture of two diastereoismeric forms, i.e., as (R,R) and (R,S) isomers (Fig. 1, A and B), which was verified by 1H- and

Fig. 1. Platinum and palladium complexes containing R2edda-derived ligands.

A

B

C

D

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13C-NMR spectroscopy and supported by DFT calculations. In a recent study, a palladium(II) complex with a partially hydrolyzed isopropyl ester of \((S,S)\)-ethylenediamine-\(N,N'\)-di-2-propanoic acid (Fig. 1, C) was isolated and determined by X-ray structure analysis, and the \((R,R)\)-\(N,N'\) configured isomer with the \(\kappa^{2}N,N'\),\(\kappa O\) coordination mode was found. All the other complexes mentioned herein had the \(\kappa^{2}N,N'\) coordination mode of the ligand.

In this study, a new \(R_{2}\)edda-type ester di-isobutyl-\((S,S)\)-2,2'-\((1,2\text{-ethane-di-}
\text{yldiimino})\)di\((4\text{-methylpentanoate})\) dihydrochloride, \([\!(S,S)\text{-H}_{2}\text{iBu}_{2}\text{eddl}\!]\)Cl\(_{2}\), 1, and its palladium(II) complex, diisobutyl-\((S,S)\) 2,2'-\((1,2\text{-ethanediyl
}\text{diimino})\)di\((4\text{-methylpentanoate})\)palladium(II), \([\!\!\!\!\!\!\text{PdCl}_{2}\{\!(S,S)\text{-iBu}_{2}\text{eddl}\}!\!\!\!\!\!\!\!]\), 2 (Fig. 1, D) were synthesized and characterized by elemental analysis, as well as IR and NMR spectroscopy. The crystal structure of 1 is also described.

**EXPERIMENTAL**

**Materials and methods**

\((S,S)\)-2,2'-\((1,2\text{-ethanediylidiimino})\)di\((4\text{-methylpentanoic acid})\) dihydrochloride, \([\!(S,S)\text{-H}_{4}\text{eddl}\!]\)Cl\(_{2}\), was prepared using a similar method to that described in the literature. Thionyl chloride (4.0 cm\(^{3}\), 55 mmol) was introduced into a flask containing 50 ml of ice-cooled isobutanol (2-methyl-1-propanol) (anhydrous conditions) during 1 h. Subsequently, 2.0 g (5.5 mmol) of \((S,S)\)-2,2'-\((1,2\text{-ethanediylidiimino})\)di\((4\text{-methylpentanoic acid})\) dihydrochloride, \([\!(S,S)\text{-H}_{4}\text{eddl}\!]\)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, contaminated with acid, was recrystallized from methanol. Crystals suitable for X-ray diffraction studies were obtained from the mother liquor which was stored at room temperature for several days.

**Synthesis of [PdCl₂{(S,S)-iBu₂eddl}], 2**

K₂[PdCl₄] (0.200 g, 0.613 mmol) was dissolved in water (20 ml) and 0.290 g (0.613 mmol) of [(S,S)-H₂Bu₂eddl]Cl₂, 1, was added. After 2 h of stirring, 10.2 ml of a 0.12 M solution of LiOH was added in small portions to the reaction mixture. A pale yellow precipitate was obtained, which was filtered off, dissolved in 5 ml of CHCl₃ and filtered. A crystalline solid of the pure complex was obtained from the mother liquor.

**X-ray crystal structure determination**

Data of 1 were collected with a CCD Oxford Xcalibur S (λ(MoKα) = 0.71073 Å) using the ω and φ scans mode. Semi-empirical corrections for absorption were performed with SCALE3 ABSPACK. The structure was solved by direct methods. Structure refinement was realized with SHELXL-97. All non-hydrogen atoms were refined anisotropically. The crystallographic details are listed in Table I. Hydrogen atoms were refined isotropically. They were placed in the calculated positions with fixed displacement parameters \( U_{iso}(H) = 1.2 U_{eq}(C) \) and \( U_{iso}(H) = 1.5 U_{eq}(C) \) (riding model), except for the hydrogen atoms attached to the nitrogen atoms which were found in the difference Fourier map and refined freely. The ORTEP-3 program was used for the presentation of the structure.

The Cambridge Crystallographic Data Center, CCDC No. 723867, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

**TABLE I. Crystallographic data for 1**

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<th>Value</th>
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<td>( V / \text{Å}^3 )</td>
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<td>( D_{calc} / \text{g cm}^{-3} )</td>
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<td>( \mu(Mo-Kα) / \text{mm}^{-1} )</td>
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<tr>
<td>Refln. independent</td>
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</tr>
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<td>14178/3/106</td>
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<td>Goodness-of-fit on ( F^2 )</td>
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<tr>
<td>( R_1, wR_2 (I &gt; 2σ(I)) )</td>
<td>0.0588, 0.1414</td>
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<tr>
<td>( R_1, wR_2 ) (all data)</td>
<td>0.0725, 0.1446</td>
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<tr>
<td>Flack parameter, ( x )</td>
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<tr>
<td>Largest diff. peak and hole / ( e \text{ Å}^3 )</td>
<td>1.152/−1.018</td>
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</table>
RESULTS AND DISCUSSION

Synthesis and characterization

The ester, \([\{(S,S)\text{-H}_2\text{Bu}_2\text{eddll}\}]\text{Cl}_2\) (1), was synthesized using a previously described esterification reaction\(^{17,18}\). This compound is not soluble in chloroform and is poorly soluble in water. However, it is soluble in methanol and dimethyl sulfoxide.

The complex, \([\text{PdCl}_2\{(S,S)\text{-iBu}_2\text{eddll}\}]\), was synthesized by combining aqueous solutions of \(\text{K}_2\text{[PdCl}_4\text{]}\) and the ester. Under stirring, an aqueous solution of lithium hydroxide was added. The obtained complex is soluble in chloroform and dimethyl sulfoxide, but not soluble in water. The preparation routes of the ester and complex are shown in Scheme 1.

The analytic and spectral data for 1 and 2 are as follows (numbering as in Fig. 3):

1. \([\{(S,S)\text{-H}_2\text{Bu}_2\text{eddll}\}]\text{Cl}_2\) (1). Yield: 1.09 g (41.6 %). Anal. Calcd. for \(\text{C}_{22}\text{H}_{46}\text{Cl}_2\text{N}_2\text{O}_4\): C, 55.80; H, 9.79; N, 5.92 %. Found: C, 55.84; H, 9.41; N, 5.77 %. IR (cm\(^{-1}\)): 2965, 2592, 2523, 2398, 1735, 1535, 1468, 1206, 1063, 973, 802. \(^{1}\)H-NMR (200 MHz, DMSO-\(\text{d}_6\), \(\delta\) / ppm): 0.90–1.00 (24H, m, C5H, C6H, C10H, C11H), 1.77 (6H, m, C3H, C4H), 1.94 (2H, m, C9H), 3.42 (4H, m, C1H), 3.98 (4H, d, C8H), 4.13 (2H, t, C2H), 9.90–10.40 (4H, br, NH\(^2\)). \(^{13}\)C-NMR (50 MHz, DMSO-\(\text{d}_6\), \(\delta\) / ppm): 18.9 (C5,6), 21.4 (C10,11), 23.2 (C4), 24.5 (C9), 27.3 (C3), 41.7 (C1), 57.9 (C2), 71.8 (C8), 169.2 (C7).

2. \([\text{PdCl}_2\{(S,S)\text{-iBu}_2\text{eddll}\}]\) (2). Yield: 313 mg (88.4 %). Anal. Calcd. for \(\text{C}_{22}\text{H}_{44}\text{Cl}_2\text{N}_2\text{O}_4\text{Pd}\): C, 45.72; H, 7.67; N, 4.85. Found: C, 45.94; H, 7.36; N, 4.97 %. IR (cm\(^{-1}\)): 3130, 2959, 2873, 1735, 1467, 1370, 1237, 1194, 1141, 976, 737. Isomer A: \(^{1}\)H-NMR (200 MHz, DMSO-\(\text{d}_6\), \(\delta\) / ppm): 0.90–1.10 (24H, m, C5H, C6H, C10H, C11H), 1.68 (6H, m, C3H, C4H), 1.90 (2H, m, C9H), 2.23 and 2.61 (4H, m, C8H), 4.14 (2H, m, C2H), 6.50–6.80 (2H, br, NH). \(^{13}\)C-NMR (50 MHz, DMSO-\(\text{d}_6\), \(\delta\) / ppm): 19.0 (C5,6), 21.9 (C10,11), 23.8 (C4), 25.4 (C9), 27.3 (C3), 47.0 (C1), 58.4 (C2), 70.9 (C8), 170.1 (C7). Isomer B: \(^{1}\)H-NMR (200 MHz, DMSO-\(\text{d}_6\), \(\delta\) / ppm): 0.90–1.10 (24H, m, C5H, C6H,
C10H3, C11H3), 1.68 (6H, m, C3H2, C4H), 1.90 (2H, m, C9H), 2.40 and 2.85 (4H, m, C1H2), 3.88 (4H, m, C4H2), 4.14 (2H, m, C2H), 5.85–6.25 (2H, br, NH). 13C-NMR (50 MHz, DMSO-d6, δ / ppm): 19.0 (C5,6), 21.5 (C10,11), 22.9 (C4), 25.0 (C9), 27.3 (C3), 47.0 (C1), 59.1 (C2), 70.6 (C8), 171.2 (C7). Ratio of isomers A/B = 7/1.

The IR spectrum of [PdCl2{(S,S)-iBu2eddli}] showed specific absorption bands ν(C=O) at 1735 cm –1 (strong), (typical absorption for aliphatic esters), ν(C–O) at 1194 cm –1 (strong), ν(–CH3, –CH2, –CH) at 2959 and 2873 cm –1 (medium) (for comparison [(S,S)-H2iBu2eddli]Cl2: 1735, 1206, 2965 and 2871 cm–1, respectively). All of the mentioned bands including ν(C=O), were at similar positions to those in the spectrum of the free ligand, indicating that the oxygen atoms of the COOR moieties were not coordinated. As expected the ν(N–H) absorption bands were at 3130 cm –1, (typical absorptions for secondary amino groups) and may indicate that coordination occurred via the nitrogen atoms.

In the 1H-NMR spectrum of 2, the broad signal of hydrogen atoms belonging to secondary amino groups appeared in the range 5.8–6.8 ppm (compared with the ammonium groups of 1: 9.9–10.4 ppm). The signals of the protons between the nitrogen atoms of 2 showed coordination-induced shifts in comparison with those in the spectrum of 1 and also, two signals. The situation was different in the spectrum of 1, where only one signal was observed, which can also be confirmation of nitrogen coordination to the palladium atom. The signal for the hydrogen atom of the chiral carbon atom was observed at 4.13 ppm as a triplet for 1, and at 4.14 ppm as a multiplet for 2. The 13C-NMR spectra of 1 and 2 exhibited signals for the carbon atom of the COO moiety at similar positions, indicating that oxygen atoms were not coordinated. The chiral carbon atom showed a signal at 57.9 ppm for 1, but two signals at 58.4 and 59.1 for 2. Selected 1H- and 13C-NMR data of 1 and 2 are compared in Table II.

<table>
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<th>Compound</th>
<th>C5,6,10,11H3</th>
<th>C1H2</th>
<th>C2H</th>
<th>C10,11, C5,6</th>
<th>C1</th>
<th>C2</th>
<th>C7OO</th>
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<tr>
<td>1</td>
<td>0.90–1.00</td>
<td>3.42</td>
<td>4.13</td>
<td>18.9, 21.4</td>
<td>41.7</td>
<td>57.9</td>
<td>169.2</td>
</tr>
<tr>
<td>Isomer A</td>
<td>0.90–1.10</td>
<td>2.23 and 2.61</td>
<td>4.14</td>
<td>19.0, 21.9</td>
<td>47.0</td>
<td>58.4</td>
<td>170.1</td>
</tr>
<tr>
<td>Isomer B</td>
<td>0.90–1.10</td>
<td>2.40 and 2.85</td>
<td>4.14</td>
<td>19.0, 21.5</td>
<td>47.0</td>
<td>59.1</td>
<td>171.2</td>
</tr>
</tbody>
</table>

Crystal structure analysis of [(S,S)-H2iBu2eddli]Cl2, 1

The compound [(S,S)-H2iBu2eddli]Cl2 (1) crystallized in the tetragonal crystal system in the chiral space group P42. The molecular structure is shown in Fig. 3. Selected bond lengths and angles are given in Table III.

The isolated crystals consisted of one dicationic species [(S,S)-H2iBu2eddli]2+ and two Cl–. The most significant hydrogen bonds for the manner
of packing are N–H1N···Cl, 3.049(3) Å, 159(3)° and N–H2N···Cl, 3.100(3) Å, 164(3)° and these interactions form an infinite chain (Fig. 4). The compound has a $C_2$ symmetry. The axis passes through the C1–C1$^i$ bond vector and lies perpendicular to the plane N$_2$Cl$_2$.

![ORTEP presentation of the molecular structure of 1 with the atom labeling scheme (H-bonds shown by dashed lines). The displacement ellipsoids are plotted at the 50% probability level and the H atoms are shown as small spheres of arbitrary radii.](image)

TABLE III. Selected bond lengths and angles for 1

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length, Å</th>
<th>Bond</th>
<th>Angle, °</th>
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<td>N1–C2–C3</td>
<td>106.2(3)</td>
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<tr>
<td>O2–C7</td>
<td>1.334(5)</td>
<td>N1–C2–C7</td>
<td>110.8(3)</td>
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<tr>
<td>N1–H1N</td>
<td>0.99(2)</td>
<td>C3–C2–C7</td>
<td>109.9(3)</td>
</tr>
<tr>
<td>N1–H2N</td>
<td>0.99(2)</td>
<td>C7–O2–C8</td>
<td>115.9(4)</td>
</tr>
<tr>
<td>C3–C4</td>
<td>1.534(5)</td>
<td>C1–N1–C2</td>
<td>114.9(3)</td>
</tr>
<tr>
<td>C8–C9</td>
<td>1.507(7)</td>
<td>C1–N1–H1N</td>
<td>106(3)</td>
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</table>

Crystal structures of esters such as [(S,S)-H$_2$Pr$_2$eddip]Cl$_2$\textsuperscript{18} (H$_2$Me$_2$eddip)Cl$_2$\textsuperscript{28} and [(S,S)-H$_2$Cpe$_2$eddip]Cl$_2$\textsuperscript{20} were previously determined. These structures are very similar to each other and to [(S,S)-H$_2$Bu$_2$eddip]Cl$_2$ having bond lengths and angles in the same ranges, however the space groups are quite different ([(S,S)-H$_2$Pr$_2$eddip]Cl$_2$, orthorhombic, P2$_2_1_2_1$; (H$_2$Me$_2$eddip)Cl$_2$, monoclinic, P2$_1$/c; [(S,S)-H$_2$Cpe$_2$eddip]Cl$_2$, orthorhombic, P2$_1$2$_1$2). The mentioned compounds

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have a $C_2$ symmetry axis. All of these esters form layered structures via hydrogen bonding similar to that shown in Fig. 4.

Fig. 4. ORTEP presentation of the packing via intermolecular hydrogen bonding of 1 viewed along the $b$-axis.

CONCLUSIONS

Two novel compounds, the R$_2$edda-type ester [(S,S)-H$_2$iBu$_2$eddt]Cl$_2$, and its palladium(II) complex [PdCl$_2${(S,S)-iBu$_2$eddt}] were synthesized and characterized by IR, $^1$H-NMR and $^{13}$C-NMR spectroscopy and elemental analysis. The crystal structure of [(S,S)-H$_2$iBu$_2$eddt]Cl$_2$ was determined by X-ray analysis. Two diastereoisomers formed in the reaction of potassium tetrachloropalladate(II) and [(S,S)-H$_2$iBu$_2$eddt]Cl$_2$, as was deduced from the NMR spectra.

Acknowledgements. The authors are grateful to the Ministry of Science and Technological Development of the Republic of Serbia for financial support (Grant No. 142010).
ИЗЛОЗЕНА КРИСТАЛНИ И ЕТАНДИИЛДИИМИНО – ПАЛАДИЈУМ(II) КОМПЛЕКСИ СА ЛИГАНДИЈАМ(II) ДИЕТАНДИИЛДИИМИНО-ДИ(4-МЕТИЛПЕНТАНОАТ)-ДИХИДРОХЛОРИД И ЊЕГОВ КОМПЛЕКС СА ПАЛАДИЈУМОМ(II): СИНЕТЕЗА И КАРАКТЕРИЗАЦИЈА

БОЈАНА Б. ЗМЕЈКОВСКИ1, ГОРАН Н. КАЛУЂЕРОВИЋ1, САНТИГО ГОМЕЗ-РУИЗ2 И ТИБОР Ј. САБО3

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Нови естат R2edda-типа диизобутил-(S,S)-2,2’-(1,2-етанилдиимин)-дихидрохлорид [(S,S)-H2Bu2eddl]Cl2, 1 и његов комплекс паладијума(II), диизобутилдиизобутил-(S,S)-2,2’-(1,2-etанилдиимин)-дихихидрохлорид паладијум(II) [PdCl2{(S,S)-Bu2eddl}], 2, синтетисани су и охарактерисани уз помоћ елементалне анализе, IR и NMR спектроскопије. Нађено је да је комплекс 2 добијен као смешта два дијастереоизомера, што је примећено у NMR спектрима. Кристална структура 1 је решена и описана. Изоловани кристали се састојали из једне дијактановске врсте [(S,S)-H2Bu2eddl]2+ и два Cl−. Кристални систем је тетрагоналан са просторним групом P42. Значајне водоничне везе за начин паковања су N–H1N···Cl, 3,049(3) Å, 159(3)° и N–H2N···Cl, 3,100(3) Å, 164(3)°. Тиме се формира бесконачан ланац и једнослојна структура, који су уобичајени за ове типове структура. Оса симетрије C2 једињења пролази кроз C1–Cl вектор везе и лежи нормално на N2Cl2 раван.

(Примљено 3. априла, ревидирано 8. јуна 2009)

REFERENCES