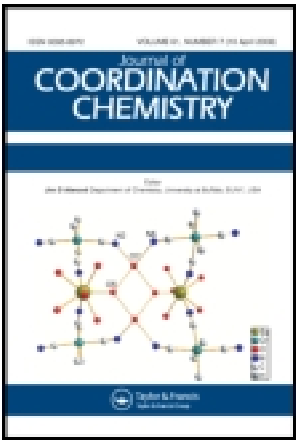

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Dibromido[(S,S)-ethylenediamine-*N*,*N*′-di-2-(3-cyclohexyl)propanoato]platinum(IV): synthesis, characterization, and DFT calculations

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Bromido complex of platinum(IV) with (*S,S*)-ethylenediamine-*N,N*′-di-2-(3-cyclohexyl) propanoic acid was synthesized. The reaction was performed in water solution in the presence of lithium hydroxide. In this reaction system, (*S,S*)-ethylenediamine-*N,N*′-di-2-(3-cyclohexyl) propanoic acid exists as the dicarboxylato anion and coordinates as a tetradentate ONNO ligand. The complex was characterized by ^{1}H and ^{13}C NMR, IR and UV-Vis spectroscopy. The *sym-cis* configuration has been elucidated using DFT calculations.

Keywords: Platinum(IV) complexes; edda-Type ligand; DFT calculation

1. Introduction

Since Chaberek and Martell [1] described chelating ability of ethylendiamine-*N,N*′-diacetic acid (H_2edda), the mode of coordination of this type of ligand to various metal ions has been of interest. Attention for platinum(IV) complexes with diamine ligands and *trans* dihalogenido ligands has grown [2, 3]. Synthesis of dihalogenido(ethylenediamine-*N,N*′-diacetato)platinum(IV) complex and similar complexes was a starting point. Stability of these complexes depends on the coordination mode of ligands to platinum(IV); these ligands can coordinate to platinum(IV) as tetradentate ONNO donors. Three geometrical isomers of edda-platinum(IV) complexes with two monodentate ligands are theoretically possible: *sym-cis*, *unsym-cis*, and *trans* (figure 1).

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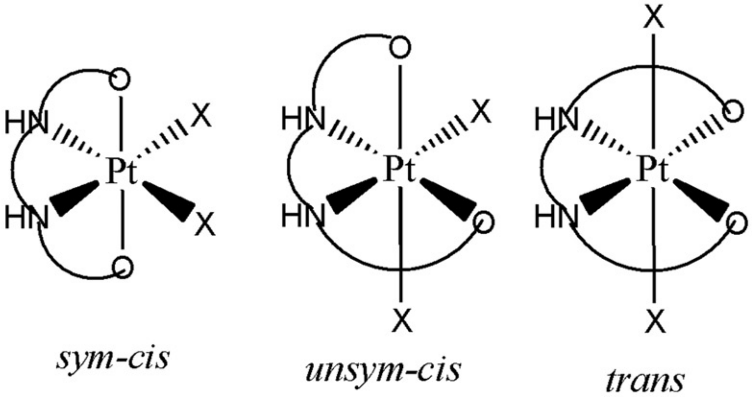


Figure 1. Geometrical isomers of platinum(IV) complexes with tetradentate ONNO ligands.

Liu [4] showed that edda coordinates as a tetradentate and the *sym-cis* arrangement of chelate in platinum(IV) complex was preferred. The edda-platinum(IV) complexes were synthesized by two methods: (1) direct reaction of potassium-hexachloroplatinate(IV) and H_2edda, and (2) oxidation of edda-platinum(II) complex. Both synthetic routes gave *sym-cis*-[Pt(edda)Cl_2] proving that *sym-cis* geometry is preferred. Therefore, it was supposed that all other edda-type ligands show the same coordination. However, the reaction of potassium hexachloroplatinate(IV) with ethylenediamine-*N,N′*-dipropanoic acid (H_2eddp) yields exclusively the platinum(IV) complexes with *trans* geometry [5]. *Trans* isomer of platinum(IV) complex with 1,3-propylenediamine-*N,N′*-diacetate (1,3-H_2pdda) was also found to be most stable [6].

Along with the structure of these complexes, their anticancer activity was examined. Structurally similar to the first potential orally available anticancer agent, satraplatin, these complexes and their analogues also showed significant or at least moderate anticancer activity [7, 8].

In this article we report the synthesis and characterization of platinum(IV)-dibromido complex with (*S,S*)-ethylenediamine-*N,N′*-di-2-(3-cyclohexyl)propanoic acid. This ligand is tetradentate and dianionic with aliphatic cyclohexyl substituent. Due to the bulky ligand and its conformation, it was supposed that the complex has octahedral, *sym-cis* geometry. The coordination mode was proposed on the basis of ^{1}H and ^{13}C NMR spectroscopy, comparing with already described analogue complexes and ligands [7]. DFT calculations were used to interpret the spectroscopic data and the calculated result is consistent with experimental results and indicates the *sym-cis* geometry of the synthesized complex.

2. Experimental

2.1. *Materials and methods*

(*S*)-2-Amino-3-cyclohexyl-propanoic acid hydrochloride was purchased from Senn Chemicals (Dielsdorf, Switzerland). $K_2[PtBr_6]$ was obtained as described [9]. Solvents were obtained commercially and used without purification.

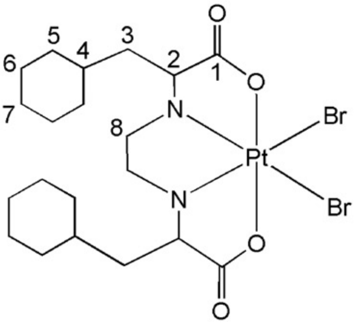


Figure 2. Numbering of the carbons in $[Pt(L)Br_2]$.

Elemental analyses were carried out with an Elemental Vario EL III microanalyser. Infrared (IR) spectra were recorded on a Nicolet 6700 FT–IR spectrometer using ATR technique. NMR spectra were recorded on a Varian Gemini 200 instrument. Chemical shifts for ^1H and ^{13}C spectra were referenced to residual ^1H and ^{13}C presented in deuterated DMSO. Electronic spectrum was carried out on a GBC UV-Visible Cintra 6 spectrometer, in DMSO, 2×10^{-4} mol dm^{-3} solution of complex. Melting points were determined on an electrothermal melting point apparatus.

2.2. *Synthesis*

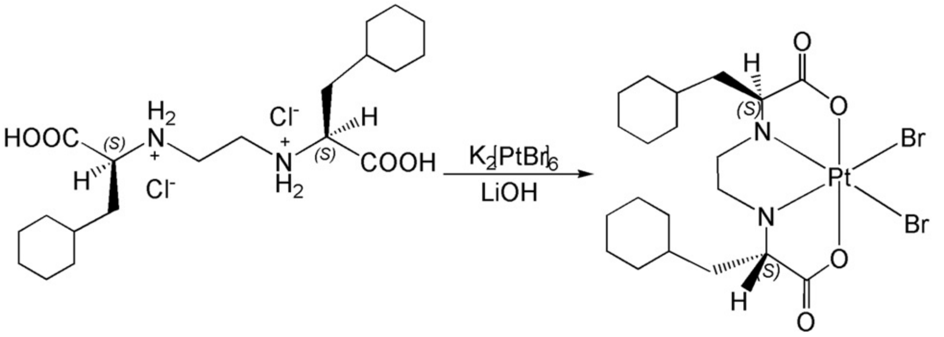
2.2.1. Preparation of L·2HCl. The (*S,S*)-ethylenediamine-*N,N′*-di-2-(3-cyclohexyl)-propanoic acid dihydrochloride was prepared by an already described procedure with reaction of (*S*)-2-amino-3-cyclohexyl-propanoic acid with 1,2-dibromethane [10]. The ^1H and ^{13}C NMR spectra of ligand proved its structure.

2.2.2. Synthesis of platinum(IV) complex, $[Pt(L)Br_2]$. To a solution of $K_2[PtBr_6]$ (0.20 g, 0.41 mmol) in 15 mL of water at 80°C, the (*S,S*)-ethylenediamine-*N,N′*-di-2-(3-cyclohexyl)propanoic acid dihydrochloride (0.18 g, 0.41 mmol) was added. The mixture was stirred for 8 h at 80°C, while in small portions a solution of LiOH (16.5 mL, 0.19 mol L^{-1}) was added. The yellow-orange precipitate was washed with water and dried *in vacuum* (figure 2).

Yield: 47.32%, m.p. = 266°C, Anal. Calcd for $C_{20}H_{34}O_4N_2Br_2Pt$ (%): C, 33.30; H, 4.75; N, 3.88. Found (%): C, 33.44; H, 5.13; N, 4.16. IR (cm^{-1}): 3442.1, 2932.9, 2851.1, 1667, 1448.4, 1261.4, 1071.7, 888.1. ^1H NMR (200 MHz, DMSO-d$_6$, δ (ppm)) 0.89 (8H, m, $C_{5,6}$), 1.17 (8H, m, $C_{6,7}$), 1.65 (4H, m, CH_2–Cy; 2H, m, C_4; 4H, m, C_5), 3.42 (4H, m, NH_2–CH_2CH_2–NH_2), 3.46 (2H, m, OOC–CH–NH_2). ^{13}C NMR (50 MHz, DMSO-d$_6$, δ (ppm)) 22.0 (C_6), 25.6 (C_4), 27.7 (C_7), 31.6 (C_5), 33.3 (C_3), 57.6 (C_8), 66.2 (C_2), 170.2 (C_1). Electronic spectrum: λ_{max}/nm ($\varepsilon_{max}/10^4$ (mol L^{-1})$^{-1}$ cm^{-1}) 260.25 (1.10).

2.3. *Theoretical calculations*

Geometry optimization was performed with the Gaussian 03 software package [11]. All structures were optimized using the B3LYP functional [12–15]. The 6-311++G** basis



Scheme 1. Synthesis of $[Pt(L)Br_2]$.

set was used for all atoms, with the exception of a Stuttgart basis set for Br and Pt [16–22]. All systems have been optimized without symmetry restrictions. The resulting geometries were characterized as equilibrium structures by analysis of the force constants of normal vibrations. The usefulness and correctness of the four theoretical methods available in the Gaussian package, namely GIAO [23], were tested. Theoretical chemical shifts were calculated with respect to tetramethylsilane (TMS).

3. Results and discussion

$[Pt(L)Br_2]$ was synthesized by the reaction of $K_2[PtBr_6]$ and $H_2L \cdot 2HCl$ in the presence of four eqvivalents of LiOH (scheme 1). The compound is soluble in DMSO but not in water, ethanol, acetonitrile, or chloroform.

3.1. *Spectroscopic characterization*

In the IR spectrum a strong broad band at 3400 cm^{-1}, typical for NH vibrations of secondary amines, was observed. In the range 2900–3190 cm^{-1} strong band corresponding to CH/CH_2 vibrations were found. The spectrum of the free ligand precursor ($H_2L \cdot 2HCl$) was compared with the corresponding spectrum of platinum(IV) complex $[Pt(L)Br_2]$ to confirm supposed coordination to the metal ion. The C=O vibration shifts from 1733 ($H_2L \cdot 2HCl$) to 1667 cm^{-1} ($[Pt(L)Br_2]$) confirming involvement of carboxylic oxygen in coordination. In addition, the change of value of asymmetric C–N vibration from 829 to 888 cm^{-1} indicates that ligand coordinates *via* nitrogen [24]. IR spectrum can indicate geometry of this type of complex as the shapes of absorption bands for COO^- (1600–1670 cm^{-1}) for the three geometrical isomers are different. *Trans* isomers have two very strong bands, *unsym-cis* one broad band, while *sym-cis* isomers have one sharp band [25, 26]. According to this, one sharp band at 1667 cm^{-1} indicates *sym-cis* geometry for $[Pt(L)Br_2]$.

The assumption that this complex has octahedral geometry is supported by its electronic spectrum with peak at 260 nm (38,424 cm^{-1}), which corresponds to ${}^1A_{1g}$–${}^1T_{1g}$

Table 1. ^{13}C NMR chemical shifts calculated for all three geometrical isomers of platinum(IV) complexes and correspond found shifts in [Pt(L)Br_2].

	Found	Calculated		
^{13}C NMR	[Pt(L)Br_2]	*sym-cis*	*unsym-cis*	*trans*
C1	170.2	180.0	182.2 178.1	177.9
C2	66.2	62.1	69.2 64.8	62.1
C3	33.3	41.8	42.8 41.0	38.2
C4	25.6	37.0	41.0 37.4	35.1
C5	31.6	38.4 33.7 (31.05)	38.0 37.8 34.3 34.0	36.8 34.8 (35.80)
C6	22.0	29.7 28.8 (29.25)	30.0 29.7 29.5 28.8	29.0 28.9 (29.95)
C7	27.8	29.2	29.1 28.3	29.8
C8	57.6	47.3	52.1 51.6	51.9

d–d transition. This transition is in the range of bands for the d^6 system and $^1A_{1g}$ ground state for octahedral platinum(IV) complexes [27].

^{13}C NMR and ^{1}H NMR spectra of metal-edda type complexes were very useful for explanation of precise structure and geometry [6]. In ^{1}H NMR spectrum of our complex, the absence of the proton signal from carboxylate indicates coordination of deprotonated ligand *via* oxygen [10]. It was shown that in octahedral metal-edda-type complexes with *trans* geometry, N–CH_2–CH_2–N protons are found between 2.6 and 3.5 ppm, with an AA′BB′ pattern from different signals for axial and equatorial protons. A broad band for *cis* complexes was found in this area. For this geometry there is also a characteristic sharp band at 3.8 ppm for methyne protons between NH and COO groups [28, 29]. In ^{1}H NMR spectrum there is a broad band from 3.0 to 3.6 ppm, which corresponds to methyne and methylene protons, indicating that the geometry is *cis*. Broadness of this band derives from coupling of methyne protons and methylene protons from –CH_2–Cy groups. This group of protons, the methylene protons from ethylendiamine moiety and methyne proton between COO and NH groups are slightly shifted downfield in comparison to the $H_2L{\cdot}2HCl$, indicating coordination through nitrogen and carboxylate to platinum(IV).

Corresponding carbon atoms bearing mentioned protons also showed chemically induced shifts (table 1) as a consequence of coordination to platinum(IV). The chemical shift of the carbon from carboxylate in complex is found at 170 ppm, indicating coordination to platinum(IV). The simple ^{13}C NMR spectrum of synthesized complex indicates high molecular symmetry and corresponds to the *sym-cis* geometry. This was explained on familiar complexes where ^{13}C NMR spectrum of complexes with *sym-cis* geometry has a simpler spectrum than that of *unsym-cis* geometry [6]. Theoretical calculations showed that complex of *unsym-cis* geometry would have two different chemical shifts for carboxylic carbon. In our structure there is one signal for this carbon in agreement with calculated shifts. This is also in agreement with IR and ^{1}H NMR spectra.

3.2. *Quantum chemical calculations*

To deal with structural feasibility, DFT calculations were conducted for the isomers of [Pt(L)Br_2]. In the synthesis of [Pt(L)Br_2] only one isomer has been formed as observed

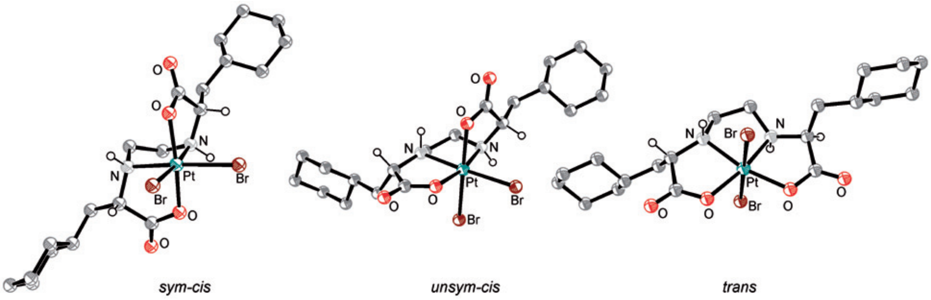


Figure 3. Optimized structures of *sym-cis*, *unsym-cis*, and *trans*-[Pt(L)Br_2] isomers.

by ^{1}H and ^{13}C NMR and IR spectroscopy. In order to investigate the reason of the selectivity, the differences in the energies (ΔE) between the *sym-cis*, *unsym-cis*, and *trans* isomers have been investigated by chemical calculations using the DFT method. Optimized structures are presented in figure 3. The most stable is the *sym-cis* isomer. The *unsym-cis* and *trans* isomers are less stable by 7.3 and 13.2 kcal mol^{-1} than the *sym-cis* isomer. The results from DFT calculations indicate that the *sym-cis* form is more stable, explaining the selectivity of the reaction.

4. Conclusions

[Pt(L)Br_2], where L is (*S,S*)-ethylenediamine-*N,N′*-di-2-(3-cyclohexyl)propanoic acid, has been characterized by ^{1}H and ^{13}C NMR, IR and UV-Vis spectroscopies. This complex crystallizes as yellow-orange powder, soluble only in DMSO. The tetradentate ligand is coordinated to achieve *sym-cis* configuration, confirmed on the basis of the IR, ^{1}H NMR, and ^{13}C NMR spectroscopies and DFT calculations.

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