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Studies on the behavior of the *bis*-complex of Pt(IV) with the tridentate ligand all-*cis*-2,4,6-triaminocyclohexane-1,3,5-triol in aqueous solutions

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NMR spectroscopy and high-resolution mass spectrometry were applied to study the stability of the complex cation $[Pt(taci)_2]^{4+}$ known as *ditaciplatin* in aqueous solutions at varying acidity and in the presence of monodentate ligands. *Ditaciplatin* is a cationic part of the *bis*-complex of Pt(IV) with the tridentate ligand all-*cis*-2,4,6-triaminocyclohexane-1,3,5-triol (taci) with a composition $[Pt(taci)_2](CO_3)_2 \cdot 6H_2O$ (2A). It was found that the *ditaciplatin* complex is stable in solution at all of the studied conditions within the period of 7 days. Three new compounds were isolated in the experiments in solution, namely: $[Pt(taci)_2](CO_3)_{1.5}(OH) \cdot 7H_2O$ (2B), $[Pt(taci)_2](Cl)_4 \cdot H_2O$ (2C) and $[Pt(taci)_2](NO_3)_4 \cdot 2H_2O$ (2D). 2B and 2C crystalize in triclinic crystal system P-1 and 2D – in monoclinic $P2_1/n$. The cationic part of the compounds is *ditaciplatin* and the counterions depend on the synthetic conditions.

Keywords: Pt(IV) complex, all-*cis*-2,4,6-triaminocyclohexane-1,3,5-triol (taci), solution behavior, NMR studies, high-resolution mass spectrometry, crystal structure

INTRODUCTION

Among the metal complexes with structures aimed at providing extended and sustained antitumor effects, as well as overcoming the drawbacks demonstrated by the classical platinum drugs [1–3], two octahedral Pt(IV) complexes of the tridentate ligand all-*cis*-2,4,6-triaminocyclohexane-1,3,5-triol (taci) deserve special attention [4]. These are the cationic 1:1 and 1:2 Pt(IV)-taci complexes known as *taciplatin* and *ditaciplatin* with a composition *fac*-$[Pt(taci)I_3]^+$, **1** and *bis*-$[Pt(taci)_2]^{4+}$, **2**, respectively. The ligand has a molecular structure consisting of a cyclohexane ring with three primary amino and three secondary hydroxy groups alternating as substituents [5]. Its two most stable chair conformers, namely those with *syn*-1,3,5-triaxial arrangements of OH- or of NH_2-groups, are of similar energy. In these conformations, the ligand provides four different modes of metal binding – two adamantane-type triaxial (N,N,N or O,O,O) called "symmetric" and two "asymmetric" axial-equatorial-axial (N,O,N or O,N,O) and all of them are performed by *facial* coordination. Thus, taci possesses six donor groups, but in all cases, it coordinates to the metal center as a tridentate ligand and the remaining uncoordinated donor groups are proper for H-bonding interactions and in some cases – for bridging with the next metal centers in polynuclear structures [6]. Furthermore, the amino and hydroxy groups of the tridentate ligand can serve for supramolecular construction [7], molecular recognition [8], and crystal engineering by forming a network of H-bonds [9].

The ligand, taci in the *taciplatin* and *ditaciplatin* complexes, is coordinated through the NH_2-groups, with each ligand occupying three coordination sites in the inner coordination sphere of Pt(IV). The complexes were isolated in solid state as *fac*-$[Pt(taci)I_3]I \cdot 3H_2O$ (**1A**) and *bis*-$[Pt(taci)_2](CO_3)_2 \cdot 6H_2O$ (**2A**), as the charge of the latter complex cation is neutralized by two CO_3^{2-}. The Pt(IV) in the PtN_3I_3-chromophore of **1A** and the PtN_6-chromophore of **2A** exhibits nearly regular octahedral coordination [4]. A thorough investigation of their *in vitro* antineoplastic activity compared to cisplatin showed a fundamentally different profile of chemosensitivity and spectrum of activity. Their main advantages derive from the proven overcoming of the inactivation mechanisms of cisplatin. The observed main differences in cytotoxicity compared to the cisplatin reference are related to the nature and arrangement of the ligands in their inner coordination sphere.

This study aims to investigate the behavior and stability of *ditaciplatin* in aqueous solutions at different media's acidities, as well as in the presence of an excess of monodentate ligands.

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EXPERIMENTAL

Materials and methods

The initial compound, *bis*-$[Pt(taci)_2](CO_3)_2 \cdot 6H_2O$, **2A** was synthesized as described by Velcheva *et al.* [4]. The reagents used in the synthesis: K_2PtI_6 was prepared by a method published by Thiele *et al.* [10] and the ligand taci·$2H_2O$ was freshly prepared from its trihydrochloride or sulfate precursors [11]. The compound **2A** was used after recrystallization: ^{1}H-NMR, δ [ppm] (*J* [Hz]): 3.02 (3H, t, $^3J_{HH}$: 4.14, (***H***-(C-NH_2)), $^3J_{PtH}$: 43.1 (I(^{195}Pt) = 1/2, 33.8%)), 4.29 (3H, t, $^3J_{HH}$: 4.12, ***H***-(C-OH)); HRMS (ESI+): $[Pt(taci)_2\text{-}3H]^+$ 546.1639 (calcd. 546.1641). All other chemicals and reagents were purchased from Sigma-Aldrich Chemie GmbH and Merck, Darmstadt, Germany, and were used without further purification. All solvents used were of analytical grade.

The ^{1}H-NMR spectra were obtained using Bruker Avance III HD spectrometer (500.13 M*Hz* for ^{1}H). The measurements were made of samples dissolved in D_2O using TSMP as an internal standard for ^{1}H (δ = 0 ppm).

The high-resolution mass spectrometry (HRMS) analysis was performed on a Waters SYNAPT G2-Si Q-ToF system at high-resolution mode (20 kDa). The samples of compound **2A** were dissolved in water (Optima, Fisher Chemical, MS-grade). The medium's acidity was adjusted using 0.1 M NaOH or 0.1 M HNO_3, and the obtained solutions were directly injected. The Electrospray ionization (ESI) source was used at the following conditions: capillary voltage 3.0 kV, sample cone voltage 40 V, source temperature 90 °C, desolvation temperature 250 °C and gas flow 350 L/h. A LockMass correction with leucine encephalin was applied for mass accuracy.

The pH measurements were made using a Mettler Toledo "Seven Compact" pH meter equipped with an InLab Micro Pro combination electrode.

Synthesis

bis-$[Pt(taci)_2](CO_3)_{1.5}(OH)\cdot 7H_2O$ *(2B):* Pale yellow crystals of **2B** were obtained from **2A** by dissolving 1 mg of the compound in 1 mL of aqueous solution at pH 11.5–12.0 by adding 0.1 mol/L NaOH.

bis-$[Pt(taci)_2](Cl)_4\cdot H_2O$ *(2C):* Crystals suitable for X-ray analysis of **2C** were obtained from an aqueous basic solution of **2A** (1 mL) at pH 11.0–12.0 (by adding 0.1 mol/L NaOH) in the presence of KCl (40 μL, 0.1 mol/L, molar ratio of KCl:**2A** = 6).

bis-$[Pt(taci)_2](NO_3)_4\cdot 2H_2O$ *(2D):* Yellow crystals of **2D** crystallized from an aqueous solution of **2A** (1 mg dissolved in 1 mL) after adding 0.1 mol/L HNO_3 to pH ~ 3.0.

*Studies on the stability of the complex **2A** in aqueous solutions at various acidity*

Samples of **2A**, 1 mg in 1 mL solution were analyzed in the pH 2–7 interval achieved by stepwise addition of 0.1 M HNO_3. Following the same procedure, the aqueous solutions of samples of **2A** were obtained in the pH range 10–12 with a stepwise addition of 0.1 M NaOH. To individual samples with pH ~ 11–12, a 0.1 mol/L solution of KCl was added at a molar ratio of Cl^- : Pt = 6. The samples were monitored by ^{1}H-NMR and HRMS [ESI+] at selected pH values in the studied interval over 7 days.

Single crystal X-ray diffraction (SCXRD) analysis

The most suitable single crystals from **2B**, **2C**, and **2D** were selected for data collection. The intensity data for **2B** and **2C** were collected on a Bruker Apex 2 Duo diffractometer with IμS Kα Cu X-ray source (λ = 1.54178 Å), Apex 2 CCD detector, and 4D Kappa goniometer. The intensity data for **2D** were collected on a Bruker SMART X2S benchtop system with an air-cooled micro-focus Mo Kα X-ray source (λ = 0.71073 Å) and a BREEZE CCD detector. The data were processed, including numerical absorption correction, with Apex 2 package [12]. The structures were solved by Intrinsic Phasing (SHELXT) [13], and non-hydrogen atoms were refined by a full-matrix least-squares procedure (SHELXL) [14] using anisotropic displacement parameters with graphical user interface software OLEX 2 [15]. All hydrogen atoms in the studied structures were placed in calculated positions and treated using a riding model with fixed isotropic thermal displacement parameters. **2B** exhibits substitutional disorder on one of the carbonate anions, which is located near an inversion center, resulting in each of its atoms having an image occupying 2 opposite positions with 0.50 occupancy. The exact positions of some water molecules are not determined due to various disorders. In the unit cell of **2C**, two pairs of Cl^- anions are refined as two positional disorders with total occupancy 1 for each pair. The Olex 2 [15] and Mercury [16] software were used to prepare publication materials, such as CIF files and pictures. Crystals' descriptions, data collection specifics, and refinement statistics for all compounds are given in Table 1. All crystallographic data were deposited at the Cambridge Crystallographic Data Centre with numbers: 1951498 (**2B**), 1951483 (**2C**), and 1951480 (**2D**).

Table 1. Data collection and refinement parameters for **2B**, **2C**, and **2D**.

Identification code	**2B**	**2C**	**2D**
Empirical formula	$C_{12}H_{30}N_6O_6Pt_1CO_{1.5}OH{\cdot}7H_2O$	$C_{12}H_{30}N_6O_6Pt4Cl{\cdot}H_2O$	$C_{12}H_{30}N_6O_6Pt4NO_3{\cdot}2H_2O$
Formula weight	774.58	709.32	833.58
Morphology, color	plate, yellow	plate, yellow	prism, yellow
Crystal size [mm^3]	0.19 × 0.10 × 0.07	0.22 × 0.14 × 0.05	0.45 × 0.3 × 0.14
Temperature [K]	110	273	300
Crystal system	Triclinic	Triclinic	Monoclinic
Space group, Z	P-1, 2	P-1, 2	$P2_1/n$, 2
a[Å]	8.8947(5)	9.0727(8)	9.2181(8)
b[Å]	9.1026(8)	9.0784(13)	14.3167(14)
c[Å]	17.4842(9)	14.3096(13)	10.4680(10)
α[°]	92.764(3)	82.830(2)	90
β[°]	92.172(2)	74.976(1)	111.688(3)
γ[°]	108.016(2)	71.530(1)	90
Volume [Å^3]	1342.6(2)	1078.5(2)	1283.7(2)
ρcalc[cm^3]	1.916	2.184	2.157
μ [mm^{-1}]	10.622	7.049	5.578
F(000)	772.0	696.0	828.0
X-ray source	CuKα (λ = 1.54178)	CuKα (λ = 1.54178)	MoKα (λ = 0.71073)
2Θ range [°]	5.07-133.56	4.74 to 54.36	5.062- 50.056
Reflection number	32595	22257	7982
R_{int} [%]	5.40	2.54	4.69
unique, refl.[I≥2σ]	4753, 4622	4790, 4597	2260, 1718
restraints, parameters	279, 388	0, 299	174, 220
Goodness of Fit, F^2	1.181	1.046	1.004
R_1, wR_2 [I≥2σ] [%]	5.81, 14.86	1.67, 3.96	1.98, 4.33
R_1 и wR_2 [%]	5.87, 14.94	1.81, 4.01	3.17, 4.67

RESULTS AND DISCUSSION

Stability in solution

Data on the structure of *ditaciplatin* in aqueous solutions, the molecule symmetry, and the mode of ligand coordination were investigated using ^{1}H-NMR spectroscopy. The identification of the chemical species in the solutions was confirmed by mass spectrometry. Compound **2A** is well soluble in water (conc. ~ 1.5×10^{-3} mol/L) and the pH value of its fresh aqueous solution is ~ 9.5. The characteristics of the ^{1}H-NMR spectrum of the fresh solution of *ditaciplatin* in D_2O were previously published [4] and it was demonstrated that no ligand substitution processes occurred during 5 days. HRMS (ESI+) experiments during this period showed a peak with a specific platinum isotopic pattern at m/z 546.1639, which corresponds to a cationic species with the composition $[Pt^{IV}(taci)_2\text{-}3H]^+$.

The expected stage of hydrolysis in the manifestation of neoplastic action of metal-based drugs, on the one hand, as well as the proven favorable antiproliferative and chemoselective effects of *ditaciplatin*, on the other, were the reasons to extend our research in solution to investigate the possible processes of ligand substitution. In the experiments, various approaches were applied, such as using a proper acidity of the medium to accelerate the hydrolytic processes, as well as the presence of monodentate ligands suitable for coordination. At each experiment, ^{1}H-NMR measurements and HRMS (ESI+) spectra recording were used to investigate the stability of *ditaciplatin*.

The recorded ^{1}H-NMR spectra of *ditaciplatin* aqueous solutions with an acidity of the medium in the pH range 2–12 and the presence of an excess of Cl^- were compared with these of the ^{1}H-NMR spectrum of the fresh *ditaciplatin* solution. All spectra are characterized by the same pattern of two signals belonging to *H*(C-OH) and *H*(C-NH_2) from the coordinated ligand and corresponding to the molecular D_{3d} symmetry of the complex species [4]. The determined constants accounting for the ligand spin system, and the *H*(C-NH_2) and ^{195}Pt couplings are almost identical. The observed downfield shift of the signals by ~ 0.4 ppm for *H*(C-NH_2) and ~ 0.3 ppm for *H*(C-OH) with increasing the acidity of the medium (between 12 and 2), Fig. 1, is explained by protonation processes of the coordinated ligand. No new signals belonging to other complex species were

detected in the spectra recorded in the studied pH range for 7 days.

An example of all observed mass spectrometry results during different investigation conditions, together with the theoretical characteristic patterns of the suggested structures is represented in Fig. 2. The heaviest molecular ion was observed at m/z = 546.1639 and corresponds to a cationic complex species with composition $[Pt^{IV}(taci)_2\text{-}3H]^+$. The molecular ion peak matches with the base peak. The fragment double-charged ion at m/z 273.5844 corresponds to $[Pt^{IV}(taci)_2\text{-}2H]^{2+}$ hence, to the double-deprotonated complex species. Fragmentation analysis showed the peaks that correspond to complex species based on Pt:taci = 1:2 with the deprotonated ligand OH-groups or loss of OH-groups substituted by H-atoms in the ligand cycle, for example $[Pt(taci)_2\text{-}2H\text{-}OH]^+$ (m/z 530.1677) and $[Pt(taci)_2\text{-}1H\text{-}1OH]^{2+}$ (265.5865), Fig. 2. Therefore, experiments in aqueous solutions performed with ^{1}H-NMR and HRMS prove that regardless of the medium's acidity, no change is observed in the inner coordination sphere of the platinum center of the *ditaciplatin* complex.

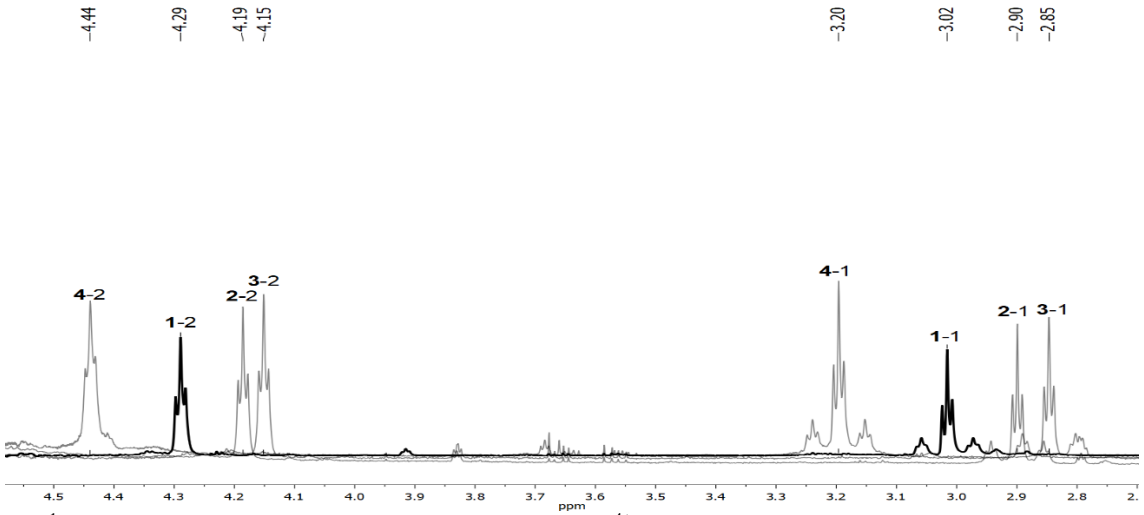


Fig. 1. ^{1}H-NMR spectra of aqueous *ditaciplatin* ($[Pt(taci)_2]^{4+}$) solutions at pH = 5 (**4**), 9 (**1**), 11 (**2**) and 12 (**3**), in H_2O/D_2O.

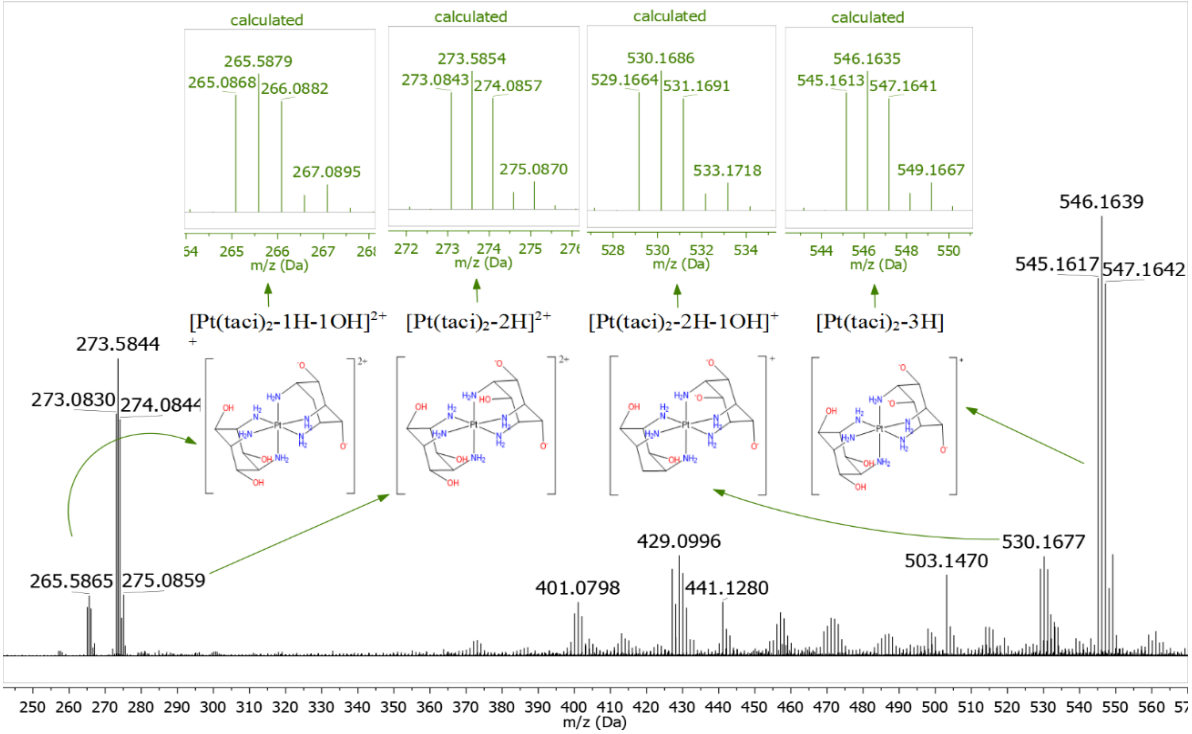


Fig. 2. A representative mass spectrum of an aqueous solution of *ditaciplatin* ($[Pt(taci)_2]^{4+}$).

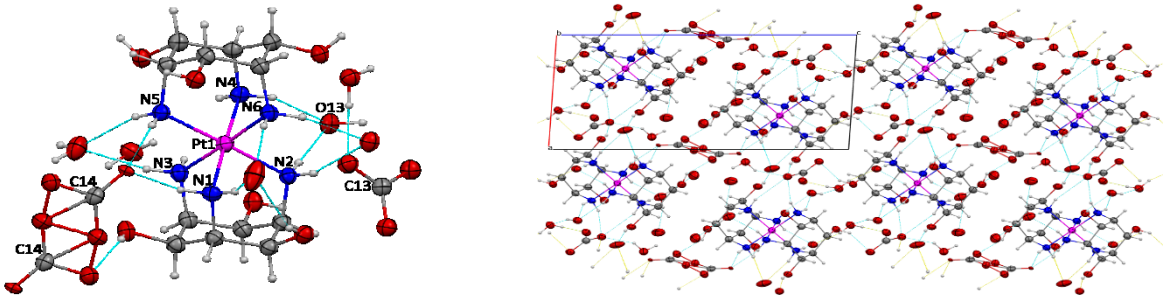
Crystal structure determination

Single crystals of three complex salts were isolated during the experiment in solution. The compounds **2B** and **2C** crystalize in triclinic crystal system P-1 (#2) and **2D** – in monoclinic $P2_1/n$ (#14). The cationic parts of the three compounds are identical and consist of Pt(IV) and two taci molecules each coordinated *via* three NH_2-groups. The inner coordination sphere of Pt(IV) in all three compounds is a nearly regular octahedron, subject in **2B** to very slight trigonal (N5-Pt1-N4 > 90 ° (92.0(2) °) and N5-Pt1-N2 < 90 ° (88.3(2) °)) and in **2C** to very slight tetragonal (for the two opposite Pt-N bonds (Pt1-N3 – 2.129(2) Å and Pt1-N6 – 2.041(2) Å)) distortions. All other Pt-N bond lengths are in the interval 2.065(2)–2.080(2) Å and the bond angles N-Pt-N (N and N from the same taci molecule) and N-Pt-N' (N and N' from the two coordinated taci molecules) are around 90 °. It is assumed that the anionic ligands from the outer coordination sphere of the new compounds are also responsible for the small deviations.

Depending on the synthetic conditions, the two carbonate anions of **2A** are partially or fully substituted in the new compounds. **2B** was synthesized at a high concentration of OH^- (pH ~ 11.5–12.0). Its asymmetric unit is built of a complex cation and two carbonate anions, one of which has an occupancy of 0.5, Fig. 3. Bearing in mind the +4 charge on the complex cation, it seems that the compound crystallizes with 1.5 carbonate anions and a hydroxide anion (assuming that the O13-atom belongs to OH^-). Thus, the partial substitution of carbonates with hydroxide anion leads to a composition of the compounds being $[Pt(taci)_2](CO_3)_{1.5}(OH)\cdot 7H_2O$ (**2B**). Under these conditions of high OH^- concentration, the coordinated ligand can be mono-deprotonated, hence the composition $[Pt(taci)(taci_{-1H})](CO_3)_{1.5}\cdot 8H_2O$ for **2B** is also possible, but the coordination polyhedron of the cationic complex of **2B** remains unchanged.

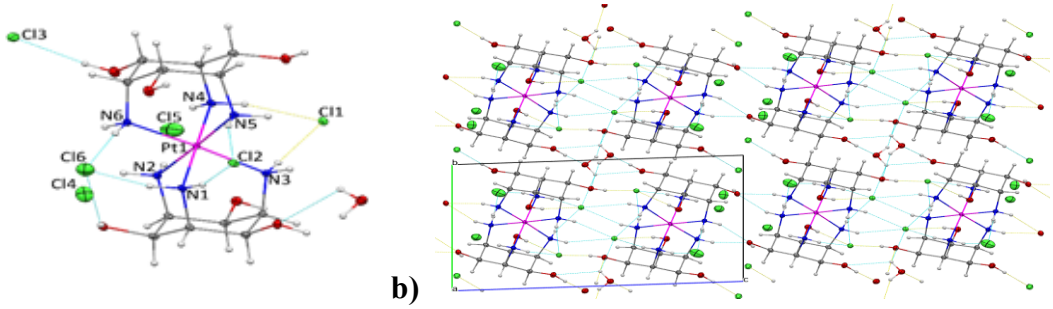
2C crystallizes from the basic aqueous solution of **2A** (pH = 10.0–12.0) in the presence of a six-fold excess of Cl^- anions. It was found that the carbonates of **2A** were fully substituted with four chloride anions in the outer coordination sphere. The asymmetric unit of **2C** consists of one Pt-complex, six chloride anions, four of which are disordered with total occupancy for two chlorides and one water molecule, Fig. 4. Thus, the composition of **2C** is $[Pt(taci)_2](Cl)_4\cdot H_2O$.

In acidic solutions, the carbonates of **2A** are easily separated as carbon dioxide and replaced by the anions of the added acid. The compound **2D** was synthesized from an aqueous solution of **2A** at pH ~ 3.0, obtained with HNO_3. In this compound, the outer-sphere carbonates are substituted by four NO_3^- anions, Fig. 5. The asymmetric unit of **2D** contains half of the complex cation, two NO_3^- anions, and one water molecule. After applying all symmetry elements for the $P2_1/n$ space group, the crystallographic cell of **2D** contains two Pt-complexes, eight NO_3^- anions, and four H_2O molecules, and thus the composition of **2D** is $[Pt(taci)_2](NO_3)_4\cdot 2H_2O$.



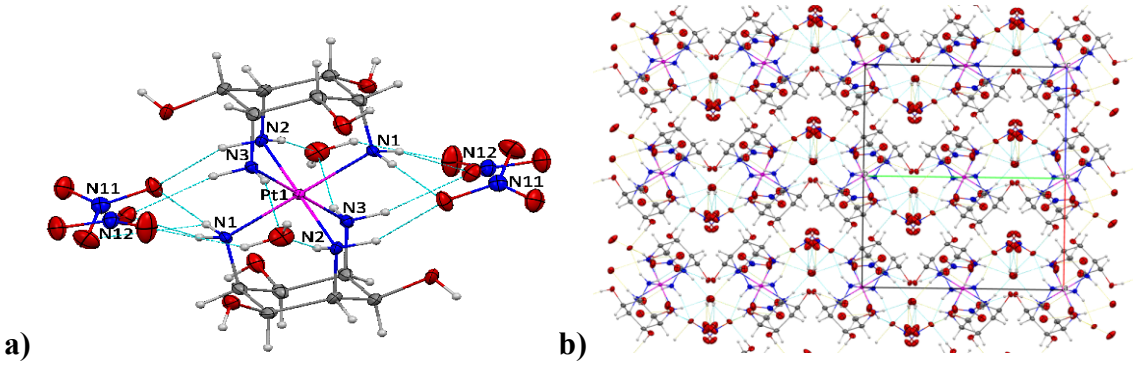
a) **b)**

Fig. 3. Crystal structure **a)** and crystal packing **b)** of **2B**.



a) **b)**

Fig. 4. Crystal structure **a)** and crystal packing **b)** of **2C**.



a) b)

Fig. 5. Crystal structure **a)** and crystal packing **b)** of **2D**.

Table 2. Selected H-bonds in **2B**, **2C,** and **2D**.

D	H	A	D(D-H)/ Å	D(H-A)/ Å	D(D-A)/ Å	D-H-A/°
			2B			
O2	H2	O9AA[1]	0.84	1.92	2.735(8)	164.6
O3	H3	O10	0.84	1.86	2.662(11)	158.7
O3	H3	O11[2]	0.84	1.82	2.562(11)	146.9
O5	H5	O9[3]	0.84	1.85	2.659(8)	161.6
O6	H6	O8[4]	0.84	1.90	2.663(8)	149.8
N1	H1A	O9AA	0.91	2.05	2.882(9)	151.6
N1	H1B	O12	0.91	1.96	2.839(9)	161.2
N2	H2A	O13	0.91	2.00	2.893(8)	166.5
N3	H3A	O3S	0.91	1.97	2.862(9)	166.9
N4	H4B	O9[5]	0.91	1.99	2.844(8)	156.3
N6	H6B	O6S	0.91	1.96	2.842(8)	164.2
[1]-1+X,-1+Y,+Z; [2]2-X,2-Y,2-Z; [3]+X,-1+Y,+Z; [4]2-X,2-Y,2-Z; [5]-1+X,+Y,+Z						
			2C			
O2	H2	O1S[1]	0.82	1.95	2.722(3)	156.2
N4	H4B	Cl5	0.89	2.02	2.870(3)	160.0
N6	H6A	Cl3[2]	0.89	1.86	2.720(3)	161.3
O1S	H1SB	O4[3]	0.85	2.12	2.895(3)	151.7
[1]1-X,-Y,1-Z; [2]1-X,1-Y,-Z; [3]+X,-1+Y,+Z						
			2D			
O1	H1	O13[1]	0.82	1.95	2.768(4)	171.5
O2	H2	O14[2]	0.82	2.01	2.827(4)	176.2
N1	H1B	O13[3]	0.89	1.99	2.868(4)	167.7
N2	H2B	O1S[4]	0.89	1.95	2.829(4)	169.6
[1]1/2-X,-1/2+Y,3/2-Z; [2]-X,2-Y,1-Z; [3]1-X,2-Y,1-Z; [4]1+X,+Y,+Z						

Networks of H-bonds formed with the participation of counterions, water molecules, and properly orientated donor groups of the taci ligand are formed in all structures, Table 2. A characteristic feature of the three structures is that some counterions and water molecules surround the platinum center, forming a second coordination sphere. The counterions CO_3^{2-} and OH^- (**2B**), Cl^- (**2C**), and NO_3^- (**2D**) occupy similar positions forming identical H-bonds with the amino groups of the two coordinated taci ligands: N-H---A---H-N (A ≡ counterions) and N-H---Ow---H-N (Ow ≡ water molecules). Chains of complex cations that form channels were observed in the 3D packing of **2C** and **2D** where the counterions and water molecules are located, Figs. 4, 5. One of the channels in **2C** is occupied by Cl^- and water molecules. Here, the Cl^- anions bridge every two opposite complex cations through intermolecular H-bonds with the participation of NH_2- and OH-groups of coordinated ligands: O-H---Cl---H-NH, O-H---Cl---H-O or HN-H---Cl---H-NH and the water molecules participate in the H-bonding network by formation of intermolecular H-bonds as H-O---Hw-Ow---Cl---H-NH or H-O---Hw-Ow---H-O. In the next channel, the Cl^- anions are disposed close to the complex cations, forming intramolecular H-bonds between the two coordinated taci molecules. In **2D**, an alternation of H-bonding nitrates and water molecules along [101] unit cell direction is observed, forming counterion chains, that further connect the neighboring complex cations (H-N---O(NO_2)---H-

N, H-N---O(NO_2)---H-O). It is accepted that the described interactions based on the H-bonding further stabilize the structures.

CONCLUSION

Here we presented three alternatives of the compound **2A**: [Pt(taci)$_2$](CO_3)$_{1.5}$(OH)·7H_2O (**2B**), [Pt(taci)$_2$]Cl_4·H_2O (**2C**), and [Pt(taci)$_2$](NO_3)$_4$·2H_2O (**2D**). The single crystal structure of the new compounds was solved by SCXRD analysis. The inner coordination sphere of Pt(IV) in these compounds is octahedrally constructed with six N-donors from two coordinated tridentate ligand taci. The complex cation, called *ditaciplatin*, remains unchanged in the compounds despite the different counterions. Single crystals of the compounds were grown from aqueous solutions of the parent compound **2A** ([Pt(taci)$_2$](CO_3)$_2$·6H_2O) during studies of the effects of medium acidity and presence of monodentate-suitable ligands on the ligand substitution and hydrolysis processes. It was shown that even in strongly basic media and in the presence of monodentate ligands, as well as in an acidic medium, *ditaciplatin* remains stable in solution within the investigated period. The structure in aqueous solutions corresponds to the structure in the solid state and the change in the composition of the solutions media reflects only on the outer-sphere ligands.

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