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Synthesis, Spectroscopic Characterization, Crystal Structure, and DNA Docking Studies of A New Trans-Platinum Saccharinate Complex Containing Aqua and Dimethyl Sulfoxide Ligands

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Abstract: A new trans-platinum complex, trans-[Pt(sac)$_2$(H$_2$O)(DMSO)] (sac= saccharinate; DMSO= dimethyl sulfoxide), was synthesized and characterized by elemental analysis, UV, FTIR, NMR spectroscopy and X-ray single-crystal diffraction. In the mononuclear complex, the platinum(II) cation was coordinated by two N-coordinated sac ligands in the trans position, the sulfur atom of the DMSO ligand, and an aqua ligand, forming a distorted square planar coordination geometry. The interaction of the platinum(II) complex with DNA was studied using molecular docking. The complex successively docked into the minor groove of DNA via intermolecular hydrogen bonds with the adenine, cytosine, and guanine bases.

Keywords: Platinum(II) complex, saccharinate, X-ray crystallography, DNA docking.

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1. INTRODUCTION

Saccharin (sacH, 1,1-dioxo-1,2-benzothiazol-3-one or benzosulfimide) is an artificial sweetener and is commercially available in the forms of sodium or calcium salts. SacH is a weak acid with a pK_a of about 2 and readily loses the imine proton in aqueous solutions. The saccharinate anion (sac) acts as a polyfunctional ligand towards various metal ions through the imine N, carbonyl, and sulfonyl O donor groups, displaying mono-, bi-, and tridentate chelating and bridging coordination modes (1).

Platinum(II) complexes such as cisplatin, oxaliplatin, and carboplatin are extensively used in cancer chemotherapy. Since they display serious side effects and drug resistance, increasing attention was paid to the development of other platinum anticancer agents. Over the last two decades, many Pt(II) complexes were prepared and evaluated in vitro and in vivo anticancer activity (2–6). The first palladium(II) and platinum(II) complexes of sac were reported by Henderson et al. (7). *cis*-[Pt(sac)$_2$(NH$_3$)$_2$] (8) and {K[Pt(sac)$_3$(H$_2$O)]·H$_2$O}$_2$ (9) complexes were also reported by Al-Jibori et al. and Cavicchioli et al., respectively. In the last two decades, our research group prepared a number of palladium(II) and platinum(II) complexes of sac with polypyridyl ligands (10–17) and phosphine ligands (18–23). Some of these complexes displayed potent in vitro/in vivo anticancer activity and were documented in recent reviews (24–27).

Since DNA is one of the main targets of many drugs, the interaction of metal complexes with DNA has long been the subject of intensive research. The metal complexes bind to DNA through covalent and non-covalent modes (28,29). The anticancer platinum(II) drug, cisplatin, forms covalent bonds with the nitrogen of two adjacent guanine bases on the same DNA strand (30). On the other hand, the non-covalent modes of the metal complex–DNA interactions were classified as intercalative, groove binding, and electrostatic (31). The intercalation of metal complexes typically occurs via the insertion of planar aromatic rings of the coordinated ligands between the base pairs of DNA (32), while groove binding takes place at the grooves of DNA, and the electrostatic mode is associated with the attractive force between metal complex cations and the anionic sugar-phosphate backbone of DNA.

In this study, a new *trans*-platinum sac complex containing aqua and dimethyl sulfoxide ligands,

namely *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)], has been synthesized and characterized by elemental analysis, FTIR, NMR, and X-ray single-crystal diffraction methods. The platinum(II) aqua complexes usually exist in aqueous solutions and were rarely obtained in the solid state (33–38). Therefore, the present platinum(II) complex will be a new example containing aqua ligand in the crystalline state. In addition, the interaction of the new platinum(II) complex with DNA was studied using in silico methods such as molecular docking since platinum(II) aqua complexes display a high affinity towards DNA.

2. EXPERIMENTAL SECTION

2.1. Materials and Measurements

cis-[PtCl$_2$(DMSO)$_2$] was synthesized by following a method reported by Price et al. (39). All other chemicals were purchased and used as received. Elemental analyses (C, H, and N) were obtained using a Costech elemental analyzer. UV and IR spectra were recorded on a Perkin Elmer Lambda 35 and a Perkin Elmer Spectrum Two FT-IR spectrophotometer, respectively. NMR spectra were performed using a Bruker Ascend 400 MHz spectrometer in DMSO-d_6. Melting point was measured using a Thermo Scientific Electrothermal Digital Melting Point. The conductivity measurement was performed in MeOH using a HANNA HI 5521 pH/conductometer.

2.2. Synthesis of *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)]

The solid Na(sac)·2H$_2$O (120.6 mg, 0.5 mmol) was added to the aqueous solution (30 mL) of *cis*-[PtCl$_2$(DMSO)$_2$] (105.6 mg, 0.25 mmol) with stirring. 5 mL MeOH was added to the solution. After 6 h refluxing at 55 °C, the solution was filtrated and evaporated to remove the solvents. The solid was crystallized from a mixture of H$_2$O, MeOH, and DMSO (1:1:1).

Colorless crystals. Yield: 134.4 mg, 82%. M.p. 115–117 °C. Anal. Calcd. for $C_{16}H_{16}N_2O_8PtS_3$ (%): C, 29.31; H, 2.46; N, 4.27. Found C, 29.14; H, 2.60; N, 4.51. UV-vis (MeOH), λmax (nm) ε_{max} ($M^{-1}cm^{-1}$): 272 (6700), 283 (5900). IR (cm^{-1}) ν: 3437broad (OH-aqua), 3094w, 3019w (CH-Ph), 2925w (CH-DMSO), 1669m (C=O), 1594w (CN), 1461w, 1422vw, 1338w $(CNS)_{sym}$, 1289vs, 1250s $(SO_2)_{asym}$, 1174s, 1157vs $(SO_2)_{sym}$, 1123s, 1057w, 1027m, 972s $(CNS)_{asym}$, 798w, 752s (γCH), 718w, 677s γ(ring-Ph), 594vs, 563vs, 537s, 520vs. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.01–7.52 (m, 8H, sac), 3.45 (s, 6H, DMSO, $^3J_{Pt-H}$ = 36.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 162.9 (s, C_7-sac), 142.2 (s, C_1-sac), 133.9 (s, C_3-sac), 132.2 (s, C_6-sac), 131.6 (s, C_4-sac), 123.8 (s, C_5-sac), 120.5 (s, C_2-sac), 40.8 (s, DMSO). Molar conductivity, Λ_M (MeOH, 298 K, 1 mM) 44 S cm^2 mol^{-1} (nonelectrolyte).

2.3. X-ray Crystallography

Single crystal X-ray diffraction data of *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)] were collected on a Rigaku Xcalibur X-ray diffractometer with EOS CCD detector using Mo-Kα radiation (0.71073 Å) with ω-scan mode. The data collection, cell refinement, and data reduction were performed using CrysAlispro (40). Using Olex2 (41), the structure was solved with the ShelXT structure solution program (42) using Intrinsic Phasing and refined with the ShelXL refinement package (43) using Least-Squares minimization. Except for nitrogen atoms, all non-hydrogen atoms were refined with anisotropic thermal displacement parameters, while all hydrogen atoms were located at calculated positions and refined using the riding model. Since the two nitrogen atoms are disordered, they were refined isotropically to obtain better refinement results. The crystal structure of the complex was determined as a non-merohedral twin with a fractional contribution of 0.72 from the main twin component. Due to the very high mosaicity of the crystals of the complex, the crystal is of very low quality, causing the vibration amplitudes of the atoms to be quite large. To eliminate the problems arising from this, EADP constraints and a set of ISOR/SADI/RIGU restraints were applied to improve some disordered atoms or parts of the molecular structure.

The details of data collection and refinement are presented in Table S1. Crystallographic data are deposited at the Cambridge Crystallographic Data Centre with a CCDC number 2311770. Copy of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk.

2.4. Molecular Docking

The crystal structures of DNA (PDB ID: 1BNA and 1AIO) were obtained from the Protein Data Bank (PDB). The Autodock/Vina was employed for docking evaluations (44). The water molecules were removed from 1BNA, and cisplatin was removed from 1AIO together with water molecules. The binding site was centered on DNA, and a grid box was created with 60 × 60 × 60 points and a 0.375 Å grid spacing. For each docking calculation, 9 different poses were required within the energy range of 2 kcal mol$^{-1,}$ and then, the pose with the lowest energy and best docking was selected. All other parameters were kept at their default values. The docked molecules were visualized by Discovery Studio 3.5 software.

3. RESULTS AND DISCUSSION

3.1. Synthesis and Spectroscopic Characterization

trans-[Pt(sac)$_2$(H$_2$O)(DMSO)] was synthesized by the reaction of *cis*-[PtCl$_2$(DMSO)$_2$] with Na(sac)·2H$_2$O in aqueous solution. A DMSO ligand and the two chloride ligands in *cis*-[PtCl$_2$(DMSO)$_2$] were substituted by an aqua ligand and two sac ligands, yielding the title platinum(II) complex. The experimental elemental analyses agree well with the calculated values. The complex is air-stable and highly soluble in common organic solvents and moderately soluble in water. The complex is non-electrolyte as evidenced by the conductivity measurements.

The platinum(II) complex was characterized using UV-Vis, IR and NMR spectral data Figures (S1–S3). Two distinct absorption bands were observed in the

UV region at 272 and 283 nm, attributed to intraligand transitions. In the IR spectrum, the broad band centered at 3437 cm^{-1} is due to the OH stretching of the aqua ligand with hydrogen bonding. The aromatic and aliphatic CH vibrations were observed as weak bands at 3019 and 2925 cm^{-1}, respectively. The band at 1669 cm^{-1} is characteristic for the carbonyl group of sac. The antisymmetric and symmetric stretching vibrations of the sulfonyl group of sac occurred at 1250 and 1157 cm^{-1} as sharp bands. The ^{1}H NMR spectrum displayed the signals of the aromatic protons of sac as a multiplet in the range of 8.01-7.52 ppm. The protons of the Me groups of DMSO appeared as a singlet at 3.45 ppm. In the ^{13}C NMR spectrum, the signals appeared at 163 and 142 ppm were characteristic to the C=O and C–S groups of sac, respectively. The other C signals of the Ph ring occurred in the range of 134-120 ppm. and The signal of the Me groups of DMSO was observed at ca. 41 ppm.

3.2. Description of the X-ray Structure

trans-[Pt(sac)$_2$(H_2O)(DMSO)] crystallizes in the monoclinic crystal system with the $P2_1/n$ space group. The molecular structure of the platinum(II) complex is illustrated in Figure 1a, and selected bond distances and angles are given in Table 1. The bond angles suggest a distorted square planar coordination geometry around the platinum(II) cation. Two sac ligands are N-coordinated and occupy the *trans* positions, while DMSO is S-bonded in accord with the hard-soft acid-base definition. The Pt–N bond distances of 1.879(13) and 1.949(13) Å compares well with those in reported platinum(II) sac complexes (7–23, 45). On the other hand, the Pt–S bond distance of Pt–S bond distance of typical as observed in *cis*-[$PtCl_2(DMSO)_2$] (46). The Pt–OH_2 bond distance is 2.043(15) Å, being comparable with those found in aqua platinum complexes: 2.052(8) Å in *cis*-[$Pt(NH_3)_2(H_2O)$(1-methylcytosine)]$(NO_3)_2{\cdot}H_2O$ (33), 2.078(6) Å in [Pt(*N*,*N*'-dimethylethylenediamine)(H_2O)(SO_4)].H_2O (34) and 2.016(7) Å in *trans*-[Pt{HN=C(O)-Bu^t}$_2$(H_2O)$_2$]·1/3H_2O (35). Longer Pt–O bond distances were observed in other 2.099(5) Å in [Pt{1,1-bis(aminomethyl)cyclohexane}(H_2O)(SO_4)]·H_2O (36), 2.12(2) Å in *trans*-[$PtCl_2(H_2O)(PPh_3)$] (37) and 2.200(5) Å in [Pt{($CH(CH_2C_6F_5)(CH_2CH_2CH{=}CH_2)$}($C_6F_5$)($H_2O$)] (38).

In the crystalline state, two molecules of *trans*-[Pt(sac)$_2$(H_2O)(DMSO)] are doubly bridged through strong OH···O hydrogen bonds involving the aqua ligands in neighboring molecules (Figure 1b). The hydrogen bonded dimers are further connected via π···π stacking interactions (3.659(5) Å) between the phenyl rings of sac in the adjacent molecules (Figure 1b).

3.1. Docking of *trans*-[Pt(sac)$_2$(H_2O)(DMSO)] with DNA

The DNA binding of *trans*-[Pt(sac)$_2$(H_2O)(DMSO)] was studied using molecular docking modelling. The lowest energy docked pose showing interactions between the platinum(II) complex and DNA (PDB ID: 1BNA) is illustrated in Figure 2. The molecular docking analysis indicated that the platinum(II) complex binds to the minor groove of DNA through the non-covalent binding interactions, including relatively strong hydrogen bonds with adenine (A), cytosine (C) and guanine (G) bases of DNA (Table 2). Consequently, these interactions between the platinum(II) complex and DNA results in the binding energy of –36.40 $kJ.mol^{-1}$. The results suggest that the complex display a greater affinity towards DNA compared to the reported platinum(II) complexes of sac (19–21, 23).

Since the Pt–OH_2 bond was suggested to undergo the ligand substitution reactions (47), the possibility of the covalent binding of *trans*-[Pt(sac)$_2$(H_2O)(DMSO)] with DNA (PDB ID: 1AIO) after removal of the aqua ligand was also studied. The docking analysis showed that the approach of the [Pt(sac)$_2$(DMSO)] moiety to the N donor sites of the G base was sterically hindered by the two sac ligands, resulting in a Pt–N bond distance of 5.31 Å, which cancels the presence of any covalent bonding. The binding energy of the [Pt(sac)$_2$(DMSO)] moiety with DNA was computed as –33.47 $kJ.mol^{-1}$, being remarkably lower than that of the parent platinum(II) complex.

Table 1: Selected geometrical parameters for *trans*-[Pt(sac)$_2$(H_2O)(DMSO)].

Bond distances (Å)		Bond angles (°)	
Pt1–N1	1.879(13)	N1– Pt1–N2	177.8(5)
Pt1–N2	1.949(13)	N1– Pt1–O1W	88.1(6)
Pt1–O1W	2.043(15)	N1– Pt1–S3	92.4(4)
Pt1–S3	2.211(6)	N2– Pt1–O1W	89.9(7)
		N2– Pt1–S3	89.6(4)
		O1W– Pt1–S3	179.3(6)

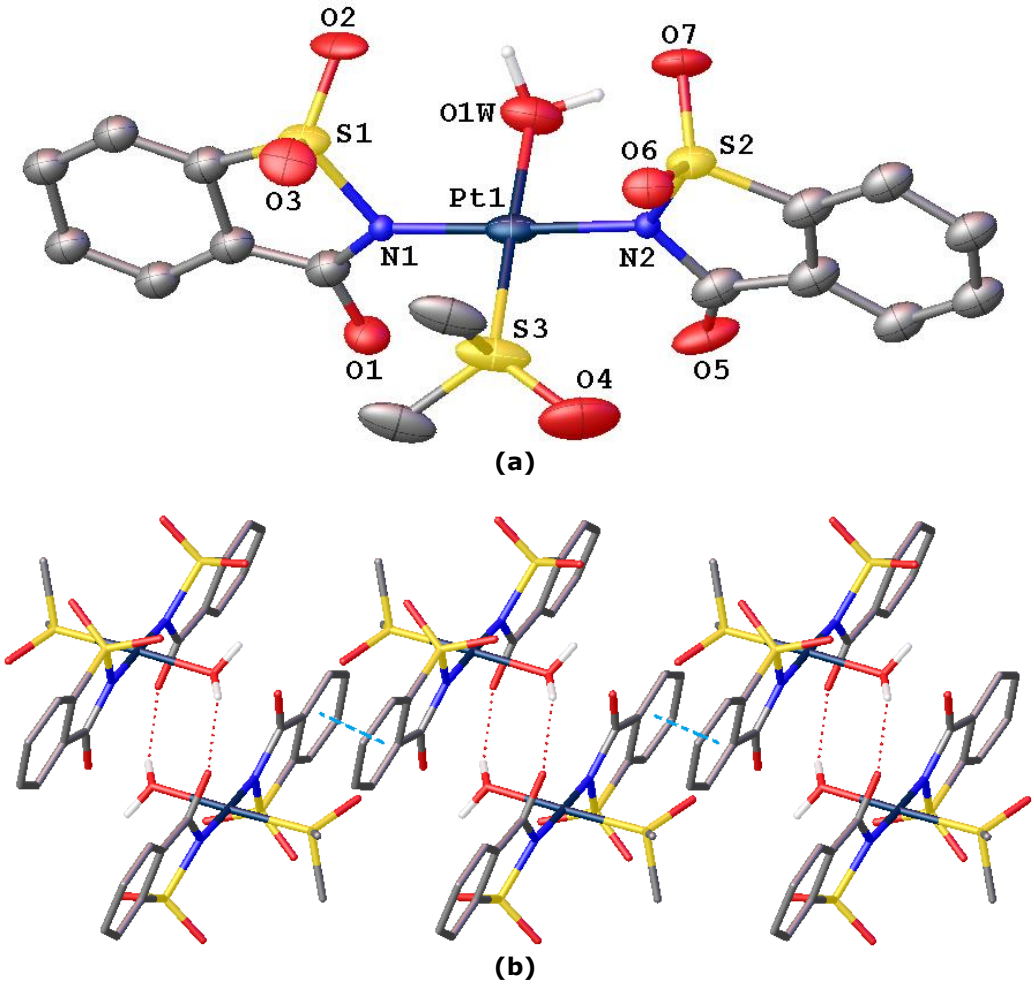

Figure 1: (a) The molecular structure of *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)] with the atom numbering. The CH hydrogens were omitted for clarity. **(b)** The hydrogen bonds and π–π stacking interactions between the molecules of *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)].

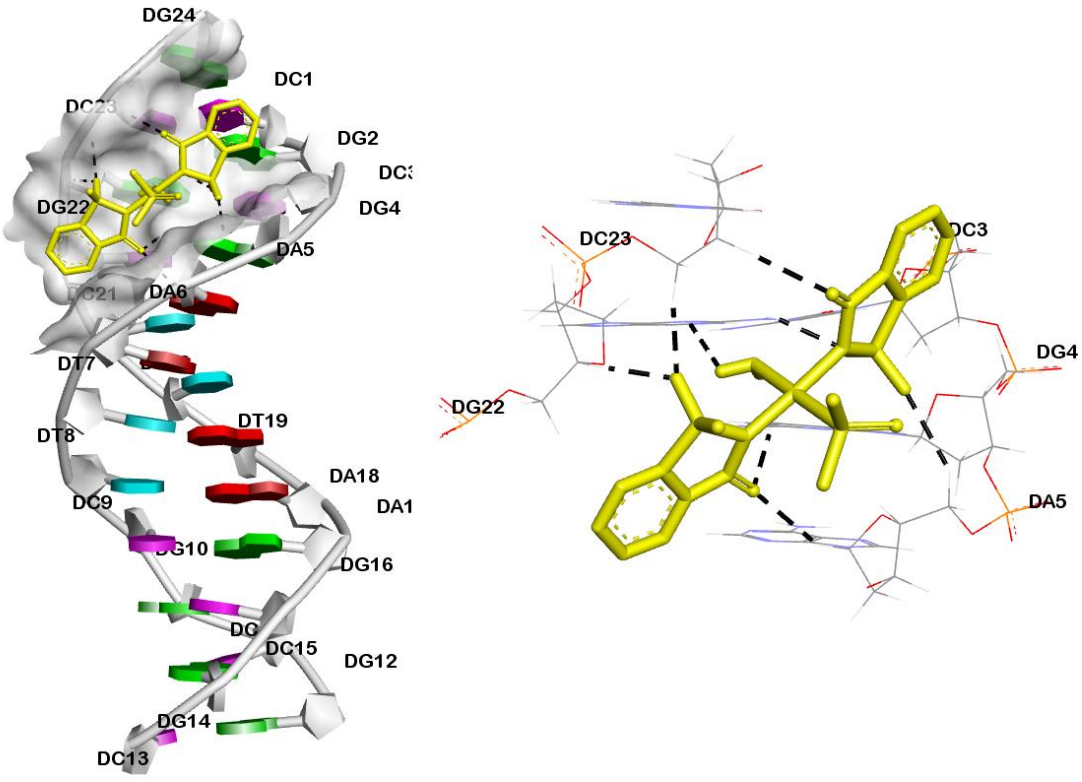

Figure 2: Docking of *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)] with DNA (1BNA), showing intermolecular interactions of the platinum(II) complex with DNA bases at the minor groove.

Table 2: The intermolecular interactions between *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)] and DNA (1BNA).

Hydrogen bonds	Distance (Å)	Binding energy (kJ mol^{-1})
G22(CH$_2$)···O (sac sulfonyl)	2.15; 2.44	−36.40
G4(NH$_2$)···O (sac carbonyl)	2.26	
C23(CH$_2$)···O (sac sulfonyl)	2.37	
A5(CH)···O (sac carbonyl)	2.54	
C23(CH)···O (sac carbonyl)	2.54	
A5(CH$_2$)···O (sac sulfonyl)	2.75	
OH$_2$··· N (G22)	2.76	

4. CONCLUSION

In this study, a new trans-configured complex, namely *trans*-[Pt(sac)$_2$(H$_2$O)(DMSO)], was synthesized and characterized by spectroscopic methods. The crystal structure of the platinum(II) complex was identified by single-crystal spectroscopy. The present complex is an interesting example of the rare platinum(II) complexes bearing the aqua ligand. The DNA binding of the complex was studied using molecular docking modeling. The results indicated that the complex shows a great binding affinity towards DNA with a binding preference for the minor groove.

5. CONFLICT OF INTEREST

There is no conflict of interest.

6. ACKNOWLEDGMENTS

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