



Synthesis, Spectroscopic, Thermal Studies of Palladium(II) Complex of SNO Donor Schiff Base and Their DNA Cleavage Activity

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Abstract: Palladium (II) complex of Schiff base ligand derived from the reaction of 5-chloro isatin with 4-methyl-3-thiosemicarbazid have been synthesized in absolute ethanol. The structures of the isolated solid compounds have been characterized by elemental analysis and spectral (FT-IR and UV-vis.) measurements. In addition, The synthesized compounds were subjected to the thermal study (TGA). The Schiff base ligand was further characterized by ¹H-NMR spectroscopy. It has been found that, the Schiff base ligand behaves as a bidentate ligand forming chelate 1:1 (metal: ligand). Square-planar geometry was suggested for the Pd(II) chelate. The synthesized compounds were tested against supercoiled pBR322 DNA. These compounds have been found to promote the cleavage of plasmid DNA pBR322 in the presence of H₂O₂.

Keywords: 5-chloro isatin, 4-methyl-3-thiosemicarbazid, square-planar, supercoiled pBR322.

تحضير ودراسة طيفية وحرارية لمعقد البلاتيوم (II) مع قاعدة شيف المعطية SNO وفعاليتها في انقسام DNA

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المخلص تم تحضير معقد البلاتيوم (II) مع قاعدة شيف المشتقة من تفاعل 5-كلورو ازاتين مع 4-ميثيل-3-ثاوسيميكاربازون في الإيثانول. تم توصيف بنية المركبان الصلبان المفصولان بواسطة قياسات التحاليل العنصرية والطيفية (الأشعة تحت الحمراء والأشعة فوق البنفسجية). قاعدة شيف تم تشخيصها كذلك بواسطة طيف الرنين النووي المغناطيسي للبروتون. التحليل الحراري (TG) لقاعدة شيف والمعقد المحضر تم لغرض تأكيد البنية الجزيئية ودراسة ثبات هذان المركبان. تم اختبار المركبان المحضران ضد الحمض النووي (supercoiled pBR322 DNA). أثبتت النتائج أن قاعدة شيف كان سلوكها كمرتبط ثنائي التسنن مكوناً معقد مخليبي بنسبة 1:1 (مرتبط:فلز) مع البلاتيوم واخذ الشكل الهندسي المربع المستوي. وجد أن هذان المركبان تعملان على إحداث شقوق في الحمض النووي plasmid DNA pBR322 في وجود بيروكسيد الهيدروجين.

الكلمات المفتاحية: 5-كلورو ازاتين ، 4-ميثيل-3-ثاوسيميكاربازون، مربع مستوي، plasmid DNA pBR322

1. Introduction

Metals bound to atoms such as N, O and S can form a chelate ring that binds the metal more tightly when compared to the non chelate form. Large biological molecules (proteins, enzymes, DNA... etc.) are electron-rich but metal ions are electron-deficient. Therefore, interactions occur between metal ions and many important biological molecules. Thiosemicarbazones are an important class of N and S donor ligands, and are strong chelating ligands which have considerable interest; because of their chemistry and biological activities, such as antitumor, antibacterial, antiviral, antiamebic and antimalarial activities (1,2). The deprotonated thiosemicarbazone ligands usually coordinate to transition ions through oxygen, nitrogen, and sulphur donor atoms in their (N and S) bidentate form or (N, N, S or O, N, S) tridentate form, to form complexes of different molecular geometry (3). These ligands are formed by the condensation reaction of an aldehyde or a

ketone with a thiosemicarbazide through a nucleophilic addition, which leads to formation of a hemi-aminal, and followed by dehydration to generate an imine. In numerous cases, this reaction is take place even in the absence of any catalyst either at room temperature or by heating for a few hours (4-6). Herein, in connection with our ongoing interest (7-9), we describe the synthesis, characterization and thermal study of Pd(II) complex with Schiff base derived from 5-chloro isatin with 4-methyl-3-thiosemicarbazid along with their DNA cleavage activity.

2. Experimental work

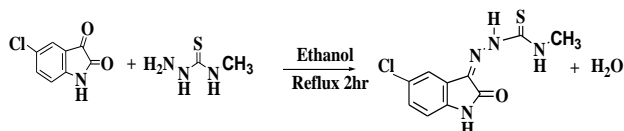
2.1. Materials and methods

The materials used in this study such as 5-chloroisatin, 4-methyl-3-thiosemicarbazide and palladium(II) chloride were purchased from Aldrich Chemicals. Commercial grade solvents and reagents were used as supplied without further purification. Supercoiled (SC) pBR322 DNA and loading dye were purchased from

Fermentas. Agarose (molecular biology grade), and ethidium bromide (EB) were from Sigma (St. Louis, MO, USA). The elemental analysis was carried out using Perkin-Elmer 2400 series-11 CHN/O analyzer (Waltham, MA, USA). Infrared, electronic and nuclear magnetic resonance were recorded on Perkin Elmer 2000, Perkin Elmer-Lambda 25, and Bruker 500MHz spectrometer at room temperature using *DMSO-d*⁶ as solvent and TMS as an internal standard, respectively. Thermal analysis was performed on 10-22 mg samples using a Mettler Toledo Star System. The samples was heated from 30 to 900 °C under nitrogen atmosphere flowing at 20 ml/min.

2.2. Synthesis of Schiff base ligand [(Z)-2-(5-Chloro-2-oxoindolin-3-ylidene)-N-methylthiosemicarbothioamide].

The Schiff base ligand was previously synthesized and reported as a single crystal⁽¹⁰⁾. Equimolar quantities of 5-chloro isatin and 4-methyl-3-thiosemicarbazid were refluxed in ethanol for 2 h. The precipitate that formed during reflux, was filtered and washed with cold ethanol (Scheme 1) and finally stored in a vacuum desiccator over P₂O₅.



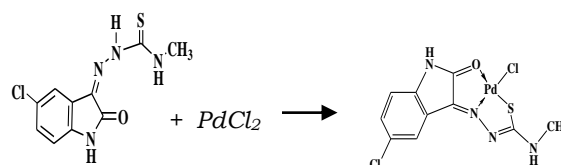
Scheme 1: Synthetic route and structure for the Schiff base ligand.

C₁₀H₉ClN₄OS: Yellow crystals; Mwt.: 268.72; MP: 268.4 °C to 268.8 °C; yield: 85%; analytical calculated values: C (44.70%), H (3.38%) and N (20.85%); analytical results (experimental values): C (44.23%), H (3.05%) and N (21.14%); selected IR data (KBr pellet, $\nu_{\text{max}}/\text{cm}^{-1}$): 3266 to 3248 (NH), 1697 (C=O), 1615 (C=N), 1561-1545 (C=C) and 1229/662 (C=S); ¹H NMR (500 MHz, *DMSO-d*⁶) [δ (ppm)]: 12.32 (s, 1 H, thiosemicarbazide N-NH), 11.80 (s, 1 H, indole N-H), 9.53 to 9.50 (q, 1 H, CS-NH, $J = 9.0, 4.5$ Hz), 8.50 (d, 1 H, indole C5-H, $J = 2.3$ Hz), 8.25 to 8.23 (dd, 1 H, indole C3-H, $J = 8.6, 2.5$ Hz), 7.10 (d, 1 H, indole C2-H, $J = 8.6$ Hz), 3.40 (d, 3H, thiosemicarbazide CH₃, $J = 4.6$ Hz).

2.3. Synthesis of palladium(II) complex

The Schiff base palladium(II) complex was synthesized by refluxing the reaction mixture of hot ethanolic solutions (30 ml each) of palladium(II) chloride (PdCl₂) (0.01 mol) and Schiff base ligand (0.01 mol) for 2 h. The precipitate that formed during reflux, was filtered and washed with cold ethanol (Scheme 2) and finally stored in a vacuum desiccator over P₂O₅.

C₁₀H₈Cl₂PdN₄OS (PdL): Brown powder; Mwt.: 407; MP: >300 °C; yield: 81%; analytical calculated values: C (29.32%), H (1.97%), N (13.68%) and Pd (25.98%); analytical results (experimental values): C (29.55%), H (1.76%), N (13.45%) and Pd (25.67%); selected IR data (KBr pellet, $\nu_{\text{ma}}/\text{cm}^{-1}$): 3321 to 3248 (NH), 1641 (C=O), 1609 (C=N), 1538 (C=C) and 656 (C-S).



Scheme 2: Synthetic route and structure of the palladium complex.

2.4. DNA cleavage studies

Cleavage experiments of supercoiled pBR322 DNA (0.5 $\mu\text{g}/\mu\text{l}$) were performed at pH 7.2 in Tris-HCl/NaCl (5:50 mM) buffer. Oxidative DNA cleavage was monitored by treating pBR322 DNA with varying concentrations of Schiff base ligand (1.0 to 6.0 mM) and Pd(II) complex (0.1 to 1 mM) and H₂O₂, followed by dilution with Tris-HCl/NaCl (5:50 mM) buffer to a total volume of 20 μl (Lanes 4 to 12). To investigate the mechanism of DNA cleavage promoted by these compounds, the experiment was carried out by adding scavenger for reactive oxygen species (ROS), DMSO to compound-DNA mixture (lane 3). The samples were incubated for 2 h at 37 °C. A loading dye was added, and electrophoresis was carried out at 50 V for 1 h in Tris-HCl buffer using 1% agarose gel. The resulting bands were stained with EB before being photographed under UV light.

3. Results and discussion

The palladium(II) complex was obtained in good yield from the reaction of palladium(II) with Schiff base ligand in 1:1 molar ratio in the ethanol medium with reflux for 2 h. This complex was slightly soluble in common organic solvents, but fully soluble in DMF and DMSO.

3.1. Spectroscopic properties

3.1.1. IR studies

IR spectrum of Schiff base (**Fig. 1**) showed absorption band at 1615 cm^{-1} can be assigned to (C=N) which confirms the formation of the Schiff base. The peak at 1561-1545 cm^{-1} may be assigned to (C=C) as reported for similar compounds⁽¹¹⁾. The peak at 1141 cm^{-1} regions resulting from $\nu(\text{N-N})$ stretching vibration band. The Schiff base contain a thione group (C=S) with protons adjacent to it. Although it has been noted that the thione group (C=S) is relatively unstable in the monomeric form and tends to convert to a stable C-SH single bond⁽¹²⁾. Absence of any bands in the 2800-2550 cm^{-1} region confirms the lack of -SH stretching frequencies in the molecule. The IR spectrum reveals the presence of only the thione tautomer in the solid state (strong bands at 1229 / 662 cm^{-1}). However, equilibrium with the thiole tautomeric form may be established in solution⁽¹²⁾.

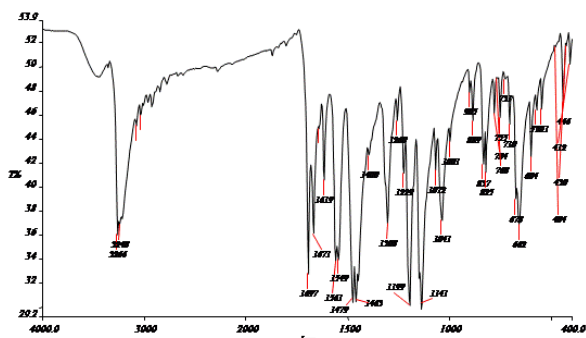


Fig. 1: FT-IR spectrum [(Z)-2-(5-Chloro-2-oxoindolin-3-ylidene)-N-methylhydrazinylidene]-N-methylthioamide in KBr.

The characteristic IR bands recorded for the free ligand differ from those of the related complex and provided significant indications of the bonding sites of thiosemicarbazone ligand. In comparison with the spectrum of the Schiff base, the Pd-complex (**Fig. 2**) exhibited the band of $\nu(\text{C}=\text{O})$ at 1641 cm^{-1} , showing a shift of the band to lower wavenumbers. This finding indicates that the carbonyl oxygen is coordinated to the metal ion. The band of $\nu(\text{C}=\text{N})$ at 1609 cm^{-1} in the metal complex shows a shift of the band to lower wavenumbers, which indicates that, the nitrogen atom of the azomethine group is coordinated to the metal ion. This finding is further supported by the band at around 656 cm^{-1} in the metal complex due to the $\nu(\text{C}-\text{S})$ (13).

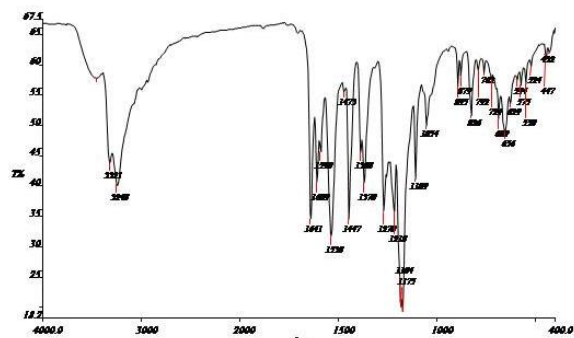


Fig. 2: FT-IR spectrum of chloro{N'-[5-Chloro-2-(oxo- κO)-1, 2-dihydro-3H-indol-3-ylidene]-N-methylcarbamohydrazonothioato- $\kappa^2\text{N}'$, S}palladium(II) in KBr.

Thus, the IR spectral results of the Pd(II) complex provide strong evidence for the complexation of Schiff base with metal ion in SNO tridentate mode.

3.1.2. UV-vis. studies

The UV-vis. spectra of the Schiff base and the Pd complex recorded in DMSO solution show similar pattern suggesting that, these compounds retain their structure in solution. The bands observed in the range 210-250 nm in the electronic spectrum of free ligand (**Fig. 3**) are probably due to the intra-ligand $\pi \rightarrow \pi^*$ transitions of the thiosemicarbazone ligand (14).

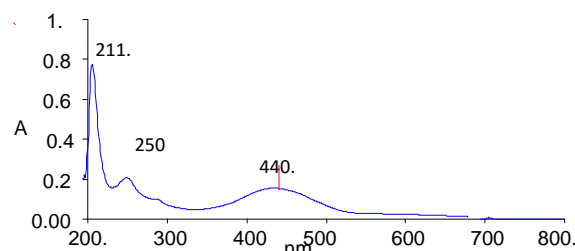


Fig. 3: Electronic spectrum of [(Z)-2-(5-Chloro-2-oxoindolin-3-ylidene)-N-methylhydrazinylidene]-N-methylthioamide in DMSO.

The electronic spectrum of palladium (II) complex (**Fig. 4**) showed bands in the region 220-468 nm. The appearance of bands below 470 nm suggests a square planar geometry around the Pd(II) in the complex (15). The band at 271 nm has been assigned to intra ligand transitions and the band appearing at of 368 nm has been assigned to ligand to metal charge transfer; LMCT (S d) transitions. The band at 468 nm is due to MLCT (metal to ligand charge transfer) (16).

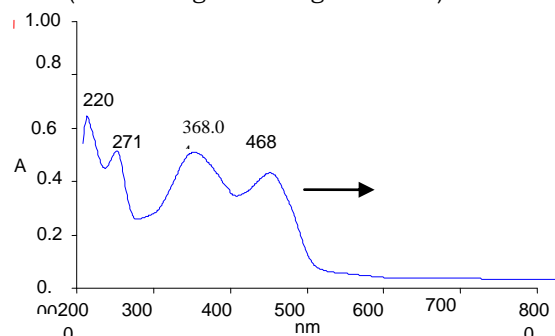


Fig. 4: Electronic spectrum of chloro{N'-[5-chloro-2-(oxo- κO)-1, 2-dihydro-3H-indol-3-ylidene]-N-phenylcarbamohydrazonothioato- $\kappa^2\text{N}'$, S}palladium(II) in DMSO.

3.1.3. ^1H NMR studies

The ^1H NMR spectrum of Schiff base ligand, (**Fig. 5**), which was recorded in d^6 -DMSO shows two singlet signals at 12.32 ppm (s, 1H) and 11.80 ppm (s, 1H) attributed to thiosemicarbazide N-NH and indole N-H, respectively. A characteristic proton signal at 11.28 ppm (s, 1H) is assigned to CS-NH proton of the thiosemicarbazide moiety as reported previously for similar compounds (17). The doublet signal observed at 3.40 ppm (s, 3H) due to CH_3 . Hence, NMR results support the IR inferences.

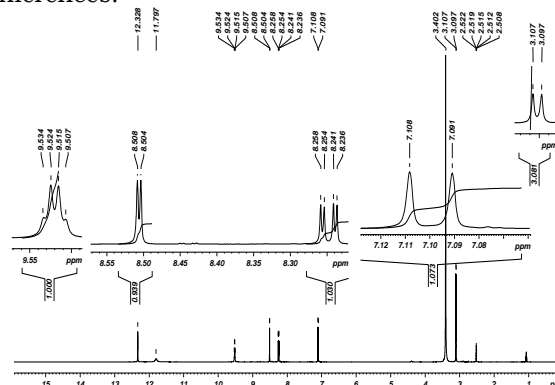


Fig. 5: ^1H NMR spectrum of [(Z)-2-(5-Chloro-2-oxoindolin-3-ylidene)-N-methylhydrazinecarbothioamide]in d₆-DMSO.

3.4. Thermogravimetric analysis of the Schiff base ligand and Pd(II) complexes

Thermogravimetric analysis of the Schiff base $\text{C}_{10}\text{H}_9\text{ClN}_4\text{OS}$ (Fig. 6) and the Pd(II) complex $\text{C}_{10}\text{H}_8\text{Cl}_2\text{PdN}_4\text{OS}$ (Fig. 7) were measured from the ambient temperature up to 800°C using heating rate of 10 °C /min. The TGA curve of Schiff base exhibits a first estimated mass loss of 59.06% (calcd: 59.05%) at 30-400 °C, which may be attributed to the liberation of $\text{C}_5\text{H}_9\text{N}_3\text{OS}$ as gases. In the 2nd and 3rd stages within the temperature range 400-900 °C, loses the remaining part with an estimated mass loss of 40.93% (calcd: 40.95%) with a complete decomposition as CO , CO_2 , NO , NO_2 , Cl_2 etc (18).

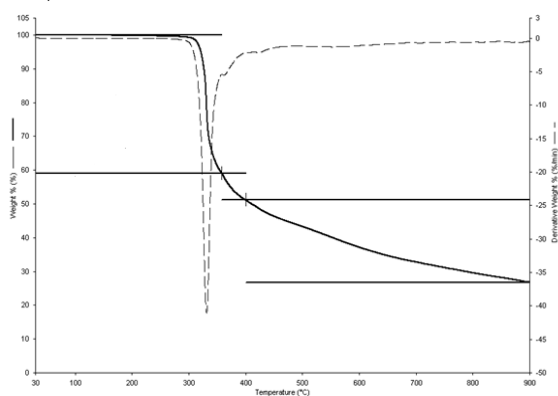


Fig.6: Thermogravimetric analysis of Schiff base ligand.

According to elemental analysis results, the complex does not have water molecules as coordinated or hydrated, and the stable line at the end of the curve is attributed to the existence of metal oxide as PdO which above 700°C. In the DTA analysis, the peak at 320 °C represents endothermic reaction (18-19).

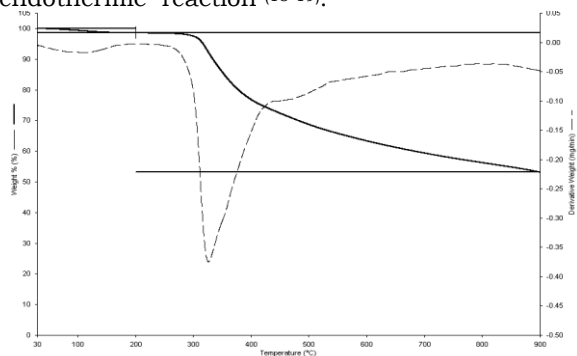


Fig.7: Thermogravimetric analysis of Pd(II) complex.

3. 5. DNA cleavage studies

The degree to which the compounds could function as DNA cleavage agent was examined using supercoiled pBR322 DNA (0.5 $\mu\text{g}/\mu\text{l}$) as the target. The efficiency of cleavage of these compounds was investigated through agarose gel electrophoresis using different concentrations of compounds in 1% DMSO/5 mM of Tris-HCl/50 mM and NaCl buffer at pH 7.2, with and without H_2O_2 , and for 2 h incubation. The activity of the compounds was estimated by the

conversion of DNA from Form(I) to Form (II) and Form(III). The fastest migration is detected in the supercoiled form (Form(I)). If only one strand is cleaved, the supercoils relax to convert into a slower-moving form (Form(II)). If both strands are cleaved, a linear form (Form(III)) is produced, which migrates between Forms(I) and Form(II) (20).

This experiment was evaluated in the presence of H_2O_2 as an oxidizing agent. The control experiment did not show any apparent cleavage of DNA (lane 2). In the presence of the compounds [Schiff base ligand, and Pd(II) complex] at different concentrations (lanes 4 to 12), the plasmid DNA was converted from Form I to Form II at 3.0 mM (lane 6 for Schiff base ligand; Fig. 8).

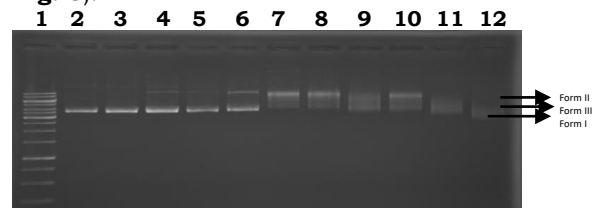


Fig. 8: Cleavage of supercoiled pBR322 (0.5 $\mu\text{g}/\mu\text{l}$) at different concentrations of Schiff base ligand in Tris-HCl buffer pH (7.2) for 2 h at 37 °C. Lane 1: DNA ladder; lane 2: DNA + H_2O_2 ; lane 3: DNA + Schiff base ligand + DMSO; lane (4-12): DNA with increasing the concentrations of Schiff base ligand (1-6 mM) + H_2O_2 + Buffer.

The DNA supercoiled was converted from Form(I) to Form(III) at 0.5 mM [lane 8 for Pd(II), (Fig. 9) complex.

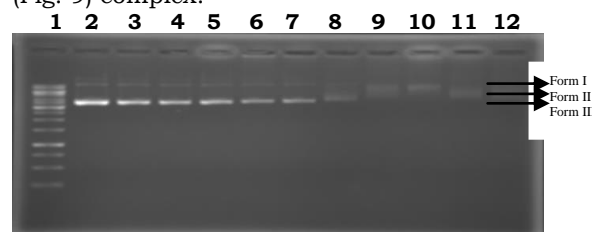


Fig. 9: Cleavage of supercoiled pBR322 (0.5 $\mu\text{g}/\mu\text{l}$) at different concentrations of Pd(II) complex in Tris-HCl buffer pH (7.2) for 2 h at 37 °C. Lane 1: DNA ladder; lane 2: DNA + H_2O_2 ; lane 3: DNA + Pd(II) complex (1 mM) + DMSO; Lanes: (4-12), DNA with increasing the concentrations of Pd(II) complex (0.1 to 1 mM)+ H_2O_2 + Buffer.

The supercoiled DNA was completely converted to Form(II) and Form(III) at (4.0 mM, lane 7 for Schiff base and at 0.6 mM, lane 9 for Pd(II) complex; Fig. 9).

To investigate the mechanism of DNA cleavage promoted by these compounds, the reactions were allowed to proceed in the presence of DMSO (lane 3) as hydroxyl radical scavengers (21). The addition of hydroxyl radical scavenger completely inhibits DNA cleavage activity (Schiff base ligand and Pd(II) complex, lane 3), which is induced by these compounds. This observation suggests the involvement of the hydroxyl radical in the cleavage, thereby confirming the oxidative pathways of these compounds toward DNA (22-23). The results revealed that the Pd(II) complex has more cleavage activity than the Schiff base ligand;

probably this may be due to the presence of Pd ion.

4. Conclusion

Mononuclear Pd(II) complex of tridentate Schiff base ligand were synthesized and characterized using elemental analysis and various spectroscopic techniques, their DNA cleavage abilities have been investigated. Results of gel electrophoresis experiments indicate that these compounds can induce cleavage of plasmid DNA. Cleavage of DNA by these compounds has been found to be concentration dependent. All compounds show nuclease activity in the presence of oxidant, which may be due to free radical reaction (OH^{*}) with DNA.

Abbreviations and Acronyms

DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
EB	Ethidium bromide
IR	Infrared
NMR	Nuclear Magnetic Resonance
pBR322 DNA	Is a 4361 bp double-stranded closed circular medium copyplasmid DNA commonly used for cloning.
TMS	Tetramethylsilane
UV-Vis	Ultraviolet-Visible

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