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Chain photosolvation of *trans,trans,trans*-[$Pt^{IV}(py)_2(N_3)_2(OH)_2$] complex prospective as a light-activated antitumor agent

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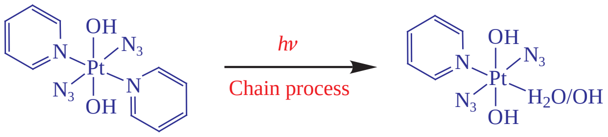
The photochemistry of a potential light-activated anticancer complex, *trans,trans,trans*-[$Pt^{IV}(py)_2(N_3)_2(OH)_2$], was explored by steady-state and laser flash photolysis. The photolysis was a multistage process with the formation of complexes *trans*-[$Pt^{IV}(py)_2(N_3)(OH)_2(H_2O)$]$^+$ and/or *trans*-[$Pt^{IV}(py)_2(N_3)(OH)_3$] due to chain photoaquation at the first stage.



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Photochemotherapy or photoactivated chemotherapy (PACT) is a prospective method of anticancer treatment based on photoinduced transformations of platinum metal complexes.[1–9] In PACT, a biologically active compound is protected against interaction with the cell environment by a light-cleavable protecting group and unprotected by light irradiation.[8] In comparison with traditional photodynamic therapy (PDT), PACT does not need dissolved oxygen, and this is important because many tumors are hypoxic.[3,10] In the case of platinum, prodrugs are photoactive Pt^{IV} complexes providing cytotoxic Pt^{II} species upon photolysis.[11–16] The target photochemical reaction is inner-sphere electron transfer in a light-excited complex,[16–21] which is typical for Pt^{IV}.[22]

Diazido complexes of Pt^{IV} are promising as prodrugs for PACT.[3,9,23,24] For example, complex *trans,trans,trans*-[$Pt^{IV}(py)_2(N_3)_2(OH)_2$] **1**, Figure 1)[13] demonstrated light-induced cytotoxicity comparable with the thermal cytotoxicity of the well-known anticancer drug cisplatin.[14,25] The anticancer effect of irradiated complex **1** is related to (i) the platination of DNA by reduced Pt^{II} products similar to the case of cisplatin and its analogues[14,26] and (ii) an attack of cancer cells by $N_3^{\bullet}$ radicals released by light-excited complexes.[27] Additionally, light-induced cytotoxicity can be related to an attack of photolysis products on peptides.[28,29]

In spite of practical importance, mechanistic aspects of the photochemistry of complex **1** were not studied in detail. Complexes *trans*-[$Pt^{II}(py)_2$ $(N_3)(OH/H_2O)$] **2**; (OH^- and H_2O can be the ligands) and *trans*-[$Pt^{II}(py)_2(OH/H_2O)_2$] **3** were reported[30] as intermediates and final products of two-electron photoreduction, respectively. However, primary stages of the photolysis of complex **1** in aqueous solutions were not studied by direct time-resolved methods. Conclusions on the mechanism of photolysis were based on an analysis of final products. For example, the idea that both $N_3^{\bullet}$ and $^{\bullet}OH$ radicals can be released upon photolysis, which was put forward by Vernooij *et al*.[30] based on the formation of complexes **2,** seems doubtful and needs verification. As an alternative, complexes **2** can be formed as a result of the disproportionation of Pt^{III} intermediates, which is typical in the photochemistry of Pt^{IV} complexes.[31,32,16] Vernooij *et al*.[30] applied ultrafast transient absorption (TA) spectroscopy to study the photophysics of complex **1** in acetonitrlile. However, the results obtained in MeCN should be used with caution in the case of aqueous solutions because the solvent effect on the photochemistry of Pt^{IV} complexes can be dramatic.[33]

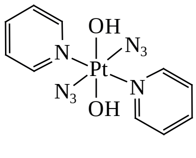

Figure 1 *trans,trans,trans*-[$Pt^{IV}(py)_2(N_3)_2(OH)_2$] (complex **1**).

Here we report preliminary results of a mechanistic study of the photochemistry of complex **1** by steady-state photolysis and nanosecond laser flash photolysis. Intermediate absorption was detected in the microsecond time domain.

The setups of the steady-state photolysis[34,35] and nanosecond laser flash photolysis[36,37] experiments are described in Online Supplementary Materials (OSM, Item S1). Complex **1** was synthesized as described elsewhere[13] and characterized by elemental analysis and NMR and UV spectroscopy (OSM, Item S2, Figures S1, S2). Solutions were prepared with deionized water.

Figure 2(*a*) shows the electronic absorption spectrum of complex **1** (curve *1*). The two absorption bands in the UV region were previously assigned to dissociative ^{1}LMCT ($N_3 \rightarrow Pt$, maximum at 296 nm) and mixed ^{1}LMCT/^{1}LC (OH → Pt, N3; LC is ligand-centered, maximum at 260 nm) transitions.[13] Irradiation in the region of the lower energy LMCT band (308 nm) resulted in a two-step photochemical process (Figure 2).

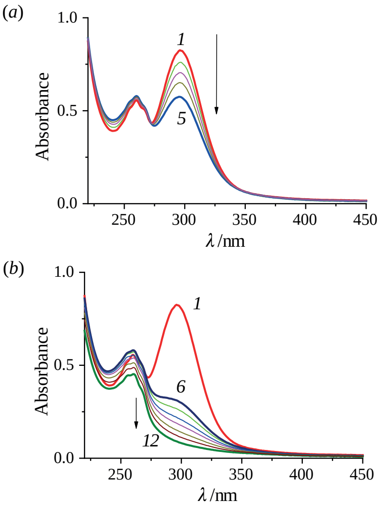

Figure 2 Changes in the UV spectrum of complex **1** (4.3×10^{-5} M, 1 cm cell, air-saturated aqueous solution) in the course of steady-state photolysis (308 nm): (***a***) initial stage (photoaquation) and (***b***) deep photolysis [photoreduction of Pt^{IV} to Pt^{II}]. Curves *1–12* correspond to irradiation for 0, 12, 23, 33, 52, 212, 272, 352, 432, 592, 812, and 1412 s, respectively.

The first stage [Figure 2(*a*)] is characterized by conservation of an isosbestic point at 272 nm and an increase in absorption at 241 nm. These spectral changes of light-irradiated Pt^{IV} complexes are typical of ligand photoexchange.[32] In our case, the formation of either *trans*-$[Pt^{IV}(py)_2(N_3)(OH)_2(H_2O)]^+$ or *trans*-$[Pt^{IV}(Py)_2(N_3)(OH)_3]$ is possible. Prolonged irradiation [Figure 2(*b*)] resulted in a decrease in absorption in the whole spectral region, which is typical of the $Pt^{IV} \rightarrow Pt^{III}$ photoreduction.[32] According to Vernooij *et al.*,[30] the final product of photoreduction is *trans*-$[Pt^{II}(py)_2(OH/H_2O)_2]$; the ratio between OH^- and H_2O ligands was not determined.

The determination of the quantum yield of the first stage is described in the OSM (Item S3 and Figure S3). The quantum yield was a linear function of the initial complex concentration (Figure 3). This is typical of a photochemical chain process. For the case of quadratic chain termination, the concentration dependence of quantum yield is described by the equation[31]

$$\varphi = \varphi_0 + \frac{k_p\sqrt{\varphi_0}\,c_0}{\sqrt{k_d I_{abs}}}, \qquad \text{(I)}$$

where $I_{abs} = I_0(1-10)^{-D_{abs}}/V$ is the rate of light absorption in the sample (concentration of light quanta absorbed in the sample per second); I_0 is the amount of incident light quanta (mole quanta per second); D_{abs} is the absorption of the sample at the excitation wavelength; V is the sample volume; φ_0 is the quantum yield of chain initiation; k_p and k_d are the rate constants of chain propagation and chain termination, respectively; and c_0 is the initial concentration of complex **1**. In the case of linear or mixed linear/quadratic chain termination, the linearity of $\varphi(c_0)$ functions is conserved.

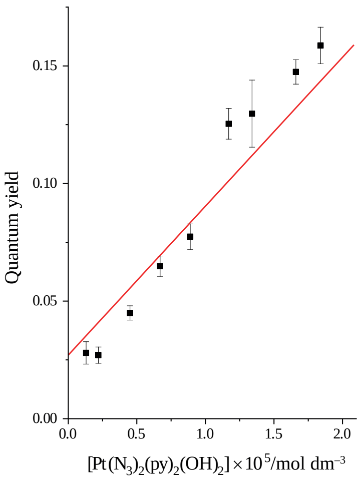

Figure 3 Steady-state photolysis (308 nm; incident light flux, 2.7×10^{-6} mol of quanta per second) of complex **1** (1 cm cell; sample volume, 3 cm^3; air-saturated aqueous solutions). Dependence of the quantum yield of photoaquation on the initial complex concentration.

The quantum yield of the second stage (see Item S3 and Figure S4 of the OSM) was estimated at $\sim1.2\times10^{-2}$ for an initial complex concentration of 5.3×10^{-5} M; that is, it was an order of magnitude lower than the quantum yield of the first stage (a detailed study of prolonged photolysis is out of the scope of this communication).

The laser flash photolysis (266 nm) of complex **1** demonstrated the occurrence and decay of intermediate absorption (Figure 4). Figures 4(*a*) and 4(*b*) show typical kinetic curves and intermediate absorption spectra at different time delays after exciting laser pulses. The intermediate absorption spectra indicate that bleaching in a wavelength range of 270–350 nm corresponds to the disappearance of the initial complex, and intermediate absorption has a maximum at 400 nm, which is typical of Pt^{III} intermediates.[32,16]

The initially formed intermediate absorption partially decayed by a first-order kinetic law [Figure 4(*a*)] with the appropriate rate constant $k_1 = (3.2 \pm 0.5)\times10^4$ s^{-1}. The residual of the fitting curves is nonzero. Because the absorbance of the final photolysis products in the visible spectral range is negligible (see Figure 2), we concluded that the residual corresponds to the absorption of second Pt^{III} species. The molar absorption coefficient of the second Pt^{III} intermediate is several times lower than that of the first one. The second intermediate decays in the millisecond time domain.

The laser flash photolysis experiment was described in Item S4 of the OSM. The dependence of the initial intermediate absorption on laser pulse energy (OSM, Figure S5) is typical of one-quantum processes. Therefore, two-quantum processes may not occur under pulsed laser irradiation. The molar absorption coefficient of the initial Pt^{III} intermediate $\varepsilon_{max} = 4200 \pm 1100$ dm^3 mol^{-1} cm^{-1} (at 400 nm) was determined according to a published procedure[38,39] (see Item S4 in the OSM).

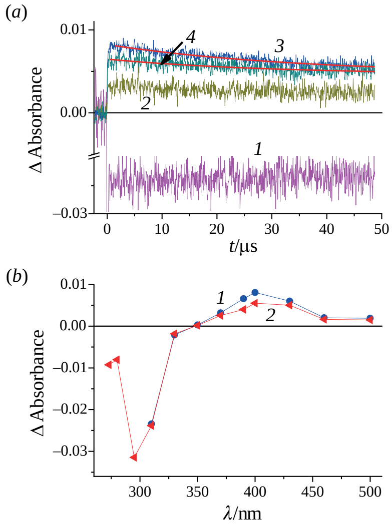

Figure 4 Laser flash photolysis (266 nm) of complex **1** in aqueous solutions (1.8×10^{-5} M, 1 cm cell, air-saturated solutions): (*a*) experimental kinetic curves and the best 1-exponential fits (red lines); curves *1–4* correspond to detection wavelengths of 310, 370, 400, and 430 nm, respectively; (*b*) intermediate absorption spectra 1.2 (curve *1*) and 46 μs (curve *2*) after a laser pulse.

Combining the data of stationary and laser flash photolysis, we proposed the following mechanism of the chain photoaquation of complex **1**:

chain initiation

$$[\mathrm{Pt^{IV}(py)_2(N_3)_2(OH)_2}] \xrightarrow{h\nu} [\mathrm{Pt^{III}(py)_2(N_3)(OH)_2}] + \mathrm{N_3^{\bullet}}, \quad (1)$$

chain propagation

$$[\mathrm{Pt^{III}(py)_2(N_3)(OH)_2}] \rightarrow [\mathrm{Pt^{III}(py)_2(OH)_2}]^{+} + \mathrm{N_3^{-}}, \quad (2)$$

$$[\mathrm{Pt^{III}(py)_2(OH)_2}]^{+} + [\mathrm{Pt^{IV}(py)_2(N_3)_2(OH)_2}] \xrightarrow{\mathrm{H_2O}}$$

$$[\mathrm{Pt^{III}(py)_2(N_3)(OH)_2}] + [\mathrm{Pt^{IV}(py)_2(N_3)(OH)_2(H_2O)}]^{+} \quad (3)$$

chain termination

$$\mathrm{Pt^{III}} + \mathrm{Pt^{III}} \rightarrow \mathrm{Pt^{IV}} + \mathrm{Pt^{II}}, \quad (4)$$

$$\mathrm{Pt^{III}} + \mathrm{N_3^{\bullet}} \rightarrow \mathrm{Pt^{IV}} + \mathrm{N_3^{-}}, \quad (5)$$

$$\mathrm{Pt^{III}} \xrightarrow{k_{\mathrm{1app}}} \mathrm{Pt^{II}} \text{ and/or } \mathrm{Pt^{IV}}. \quad (6)$$

The proposed mechanism is consistent with both the concentration dependence of the quantum yield and the existence of two $\mathrm{Pt^{III}}$ intermediates. Primary photoinduced process (1) is inner-sphere electron transfer from an azide ligand to the $\mathrm{Pt^{IV}}$ cation with the release of an azidyl radical to the bulk of solution. Our attempts to experimentally detect the $\mathrm{N_3^{\bullet}}$ radical were unsuccessful. The $\mathrm{N_3^{\bullet}}$ radical absorbs with a sharp maximum at 274 nm; the molar absorption coefficient is 2025 $\mathrm{dm^3\ mol^{-1}\ cm^{-1}}$, and the FWHM is about 20 nm.[40] Therefore, it is a problem to detect $\mathrm{N_3^{\bullet}}$ when the absorption of this radical is masked by the absorption of the initial compound. However, the azidyl radical was detected upon the photolysis of complex **1** using a spin trap method.[27]

Two intermediates, $[\mathrm{Pt^{III}(py)_2(N_3)(OH)_2}]$ and $[\mathrm{Pt^{III}(py)_2(OH)_2}]$ complexes, are involved into the chain propagation process. However, other sets of ligands (*e.g.*, $\mathrm{H_2O}$ instead of one of the $\mathrm{OH^-}$ ligands) cannot be ruled out based on the available experimental data.

Chain termination includes second-order reactions (4) and (5). However, pseudo-first-order reactions (*e.g.*, oxidation of $\mathrm{Pt^{III}}$ by dissolved oxygen and impurities) also cannot be excluded. Finally, we found that chain photoaquation is the first stage of photolysis of potential light-activated anticancer complex **1**.

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Online Supplementary Materials

Supplementary data associated with this article (experimental details, data of elemental analysis, NMR and UV spectra, details of quantum yields determination, estimation of molar absorption coefficient of $\mathrm{Pt^{III}}$ intermediate in the laser flash photolysis experiments) could be found in the online version at doi: 10.1016/j.mencom.2023.01.019.

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