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Photoactivation of dichloro(ethylenediamine)platinum(II)

H. Christopher Fry, Cynthia Deal, Erin Barr, Scott D. Cummings*

Department of Chemistry, Kenyon College, Gambier, OH 43022-9623, USA

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Abstract

Photolysis of dimethylsulfoxide (dmso) solutions of the compound Pt(en)Cl_2, where en = ethylene-1,2-diamine, leads to solvolysis of the complex and formation of Pt(en)(dmso)Cl^+. The reaction follows clean pseudo-first-order kinetics with parallel photolytically activated and thermally activated paths. Both paths are first-order in both Pt(en)Cl_2 and solvent. Eyring analysis of the rate constants for $25\,^{\circ}C \leq T \leq 55\,^{\circ}C$ yielded a Gibbs energy of activation of $96\,kJ\,mol^{-1}$ for the thermal pathway and no measurable activation barrier for the photochemical pathway. The quantum yield for the photochemical path is 0.22, as determined using ferrioxalate actinometry.

Keywords: Platinum; Cisplatin; Photodissociation; Kinetics

1. Introduction

Cisplatin (*cis*-Pt$(NH_3)_2Cl_2$), a widely used anti-cancer drug, has been the subject of a large body of research focused on understanding the mechanism by which it destroys tumor cells [1,2]. In recent years, this mechanism has been shown to involve binding of platinum to guanine bases of DNA [3]. Detailed investigations into the kinetics of this process indicates that cisplatin hydrolysis precedes DNA binding [4,5]. Thousands of related compounds have been investigated for their anti-cancer action, with several reaching clinical trials [6].

The photoreactivity of cisplatin and related compounds has been receiving increased attention in recent years. Some of this research has addressed the need to better understand the photostability of solutions of the drug in clinical settings, where fluorescent lighting or ambient sunlight may lead to decomposition [7–14]. In addition, investigations into the photochemistry of related cisplatin compounds may lead to new routes for the synthesis of next generation drugs. The development of "photocisplatin reagents," metal complexes that bind to DNA upon irradiation, has also been pursued [15–20].

Photolysis of cisplatin in water, results in the formation of $[Pt(NH_3)_2(H_2O)Cl]^+$ [9]. However, one study [8] indicated that when a saline solution of cisplatin is exposed to daylight, one major ($[PtNH_3Cl_3]^-$) and one minor ($[Pt(NH_3)_2(H_2O)Cl]^+$) product form, whereas another study [7] identified as many as thirteen products. The photoreactivity of cisplatin derivatives may proceed by different routes, with the photochemistry of (2,2′-diamino-1,1′-binaphthyl)dichloroplatinum(II) proceeding by substitution of the diamine chelate rather the chloride ligands [18].

Because solvolysis of cisplatin and related second generation drugs is the primary step in the mechanism of anti-cancer action, some studies have explored solvolysis using other solvents.

Dimethylsulfoxide (dmso) is used extensively in biochemical studies of cisplatin reactivity due to its excellent solvating properties, although it is not a perfect analog to water [21]. Building off the work of Kerrison and Sadler, experiments by Sundquist et al. indicated that the reaction of *cis*-Pt$(NH_3)_2Cl_2$ in dmso to form *cis*-[Pt$(NH_3)_2$-(Me_2SO)Cl]Cl follows first-order kinetics during early reactions times, but five additional solvolysis products form after 3 h [21]. In addition to investigations of solvolyis reactions, platinum(II)dmso complexes have been prepared and studied for their potential as anti-tumor agents [22,23].

This paper reports on the cisplatin derivative Pt(en)Cl_2 (en = ethylene-1,2-diamine), known to be a potent anti-tumor agent [24]. Unlike cisplatin, its reactivity is greatly simplified, allowing for the determination of solvolysis rate constant and Gibbs energies of activation for both thermal and photochemical reactions.

* Corresponding author. Tel.: +1-740-427-5355; fax: +1-740-427-5731.
E-mail address: cummingss@kenyon.edu (S.D. Cummings).

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2. Experimental

The compound *cis*-dichloro(ethylenediamine)platinum(II) was prepared according to the literature [25], and gave satisfactory elemental analysis. Spectroscopic grade dmso (Aldrich) was dried using Linde 4 Å molecular sieves; although trace amount of water were certainly present in the solvent, this appeared to have no measurable effect on the kinetics.

Absorption spectra were measured on an Hewlett Packard 8453 diode array spectrophotometer, equipped with a temperature-controlled cuvette holder. All spectra were obtained in sealed 1 cm^2 quartz cuvettes. Proton NMR spectra were obtained using a 200 MHz Varian Gemini 2000 spectrometer. Solutions were prepared in dmso-d_6 (99.9% D, Aldrich, dried with Linde 4 Å molecular sieves) and chemical shifts are reported relative to tetramethylsilane. Irradiation experiments were performed using a Photon Technologies International photolysis lamp system, including a 200 W Hg–Xe lamp with an f/4.5 elliptical reflector, a circulating water IR filter assembly, grating monochromator (PT1 Model 102) and temperature-controlled sample compartment.

The kinetics of $Pt(en)Cl_2$ solvolysis were followed by measuring changes in the absorbance (A_t) at 310 nm until absorbance values became constant (A_{eq}). Initial absorbance values (A_0) were obtained within 1 min of dissolving the solid reagent in dmso to a concentration of 1.5–2 mM. Absorbance values were corrected for any baseline drift of the spectrophotometer. Rate constants were obtained by plotting absorbance and time data according to Eq. (1) and averaging over four or more trials:

$$\ln\left(\frac{A_0 - A_{eq}}{A_t - A_{eq}}\right) = kt. \quad (1)$$

Initial concentrations of $Pt(en)Cl_2$ in dmso were calculated using the molar absorptivity $\varepsilon_{310} = 270\,M^{-1}\,cm^{-1}$, as determined from a Beer's law analysis.

Chemical actinometry using ferrioxalate was carried out using a standard procedure described in the literature [26]. Absorbance values and photolysis times for the ferrioxalate and platinum solutions were kept close in value, and the quantum yield was determined by averaging the results of seven trials.

3. Results and discussion

In the dark, the compound $Pt(en)Cl_2$ undergoes a slow solvolysis reaction in dmso [27]:

$$Pt(en)Cl_2 + dmso \rightarrow Pt(en)Cl(dmso)^+ + Cl^-. \quad (2)$$

The reaction was monitored by UV–VIS spectroscopy and ^1H NMR spectroscopy, both of which indicate clean conversion to a single reaction product. UV–VIS spectra display a decrease in absorbance at 310 nm (maximum of d–d transition [28] of reactant), an increase at 275 nm and a sharp isosbestic point at 288 nm (Fig. 1). Proton NMR spectra indicate a complete conversion from $Pt(en)Cl_2$, having a resonance at 5.31 ppm for equivalent amine protons, to $Pt(en)(dmso)Cl^+$, having a set of resonances at 6.31 and 6.06 ppm due to inequivalent amine protons. In contrast, the reaction of

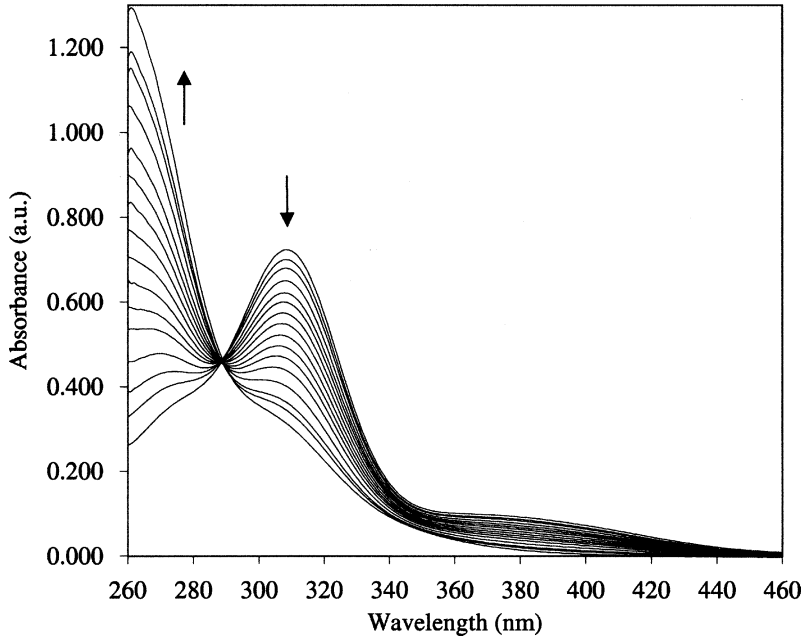

Fig. 1. Overlaid UV–VIS spectra of a 1.1 mM solution of $Pt(en)Cl_2$ in dmso during irradiation using $\lambda_{ex} = 310$ nm for 15 min.

cisplatin, *cis*-$Pt(NH_3)_2Cl_2$, in dmso yields more than one product, as evidenced by the lack of isosbestic points in the overlaid UV–VIS spectra. This results is consistent with other studies [7,8].

The kinetics of the thermal (dark) solvolysis reaction, measured by monitoring the decrease in absorbance at 310 nm, follow a first-order rate equation with a rate constant $k_{th} = 1.0 \times 10^{-4}\,s^{-1}$ at 25 °C. The reaction reaches completion after ~12 h. This rate constant agrees well with results of Fanizzi et al. ($k_{obs} = 1.53 \times 10^{-4}\,s^{-1}$ at 30 °C) [27] and our measurements of the temperature dependence of the rate constants, described later. In comparison, the rate constant for solvolysis of cisplatin by dmso is much slower, with rate constants of $6.24 \times 10^{-5}\,s^{-1}$ at 26 °C and $4.36 \times 10^{-5}\,s^{-1}$ at 23 °C reported by Sundquist et al. [21]. Addition of excess (10 mM) tetramethylammonium chloride inhibits the reaction rate, consistent with chloride displacement.

UV photolysis of dmso solutions of $Pt(en)Cl_2$ results in the same solvolysis reaction, as indicated by the identical changes in UV–VIS and ^1H NMR spectra as described before, but at a significantly faster rate. The reactant can be completely converted to $Pt(en)(dmso)Cl^+$ in ~15 min of photolysis, although a second product begins to form at longer reaction times, as indicated by a loss in the 288 nm isosbestic point. The photoreactivity appears to be completely independent from the thermal (dark) reaction described before. For example, in 4:1 dmso/CH_3CN at 9 °C, the complex reacts only photochemically and not thermally. In addition, the photoreaction requires continuous photolysis and does not depend on oxygen concentration, suggesting that the photoreaction does not involve photoinitiated catalysis or radical chain pathways.

The photochemical reaction follows first-order kinetics over several lifetimes. A consistent rate constant can be obtained for a particular selection of excitation wavelength, monochromator slits and sample position, with our conditions yielding a value of approximately $k_{obs} = 5 \times 10^{-3}\,s^{-1}$ at 25 °C. Knowing the thermal rate constant, a photochemical rate constant k_{ph} can be calculated for a given photolysis set-up using Eq. (3):

$$k_{ph} = k_{obs} - k_{th}. \quad (3)$$

This rate constant increases with increased light intensity reaching the sample solution, an effect that was investigated using a series of neutral density filters. Using ferrioxalate actinometry, a reaction quantum yield of $\phi = 0.22 \pm 0.03$ was calculated, which is close to values obtained by Perumareddi and Adamson for the solvolysis of cisplatin in water [29].

The observed kinetics are consistent with a mechanism involving two parallel and independent reaction paths, one photochemical and one thermal, leading irreversibly to the same product. A rate equation to describe this mechanism is:

$$\text{rate} = k_{th}[Pt(en)Cl_2] + k_{ph}[Pt(en)Cl_2]. \quad (4)$$

Both paths follow first-order kinetics due to the large excess of dmso in the system. Both the thermal and photochemical rate constants, k_{th} and k_{ph}, are pseudo-first-order rate constants which were found to decrease as the mole fraction of dmso (x_{dmso}) was reduced from 1 to 0.6 with acetonitrile. Kinetics analysis of the UV–VIS data was hampered at lower x_{dmso} due to the formation of other products, presumably through the displacement of chloride by acetonitrile. Further support for this rate equation comes from results,

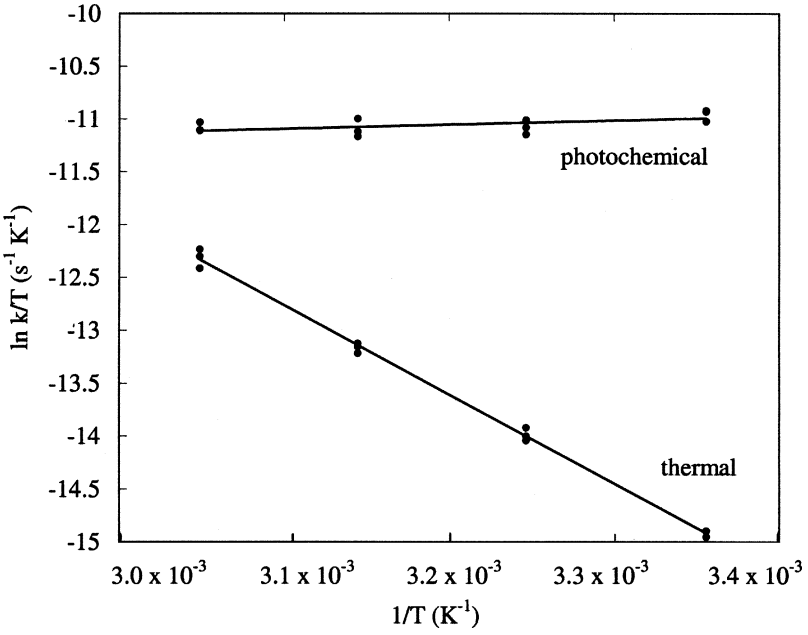

Fig. 2. Eyring plots for the determination of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the thermal and photochemical reaction of $Pt(en)Cl_2$ in dmso.

using the method of initial rates, indicating that both paths are first-order in Pt(en)Cl_2 in the range of 1.5–7.5 mM.

The temperature dependence of both reaction paths was explored in the range of 25–55 °C and plots of $\ln k/T$ versus T^{-1} (Fig. 2) were used to calculate activation parameters for each path. The enthalpy of activation $\Delta H^{\ddagger} = 70\,\mathrm{kJ\,mol^{-1}}$ and entropy of activation $\Delta S^{\ddagger} = -88\,\mathrm{J\,K^{-1}\,mol^{-1}}$ are consistent with an associative mechanism of chloride displacement by solvent [30]. A Gibbs energy of activation $\Delta G^{\ddagger} = 96\,\mathrm{kJ\,mol^{-1}}$ at 25 °C is significantly lower than the activation barrier for cisplatin solvolysis in water, as studied by Perumareddi and Adamson [29], but essentially the same values as obtained for solvolysis by dmso of cisplatin [21] and for an Pt(1,4-dit-butyl-ethylenediamine)Cl_2 [27]. The photochemical rate constants do not show any temperature dependence over the temperature range studied, suggesting that there is an insignificant activation barrier to solvolysis in the excited state. In contrast, Perumareddi and Adamson found that photochemical rates were thermally activated for cisplatin hydrolysis in water [29].

The simple photoreaction observed for Pt(en)Cl_2 was not found for the related compound Pt(bpy)Cl_2, where bpy is the diimine chelate 2,2′-bipyridine; instead more than one product was indicated by the lack of isosbestic points and the reaction was significantly slower in dmso.

4. Conclusion

The kinetic results for the photoreaction of Pt(en)Cl_2 in dmso provide an interesting compliment to the photoreactivity of other cisplatin compounds. With simple parallel photochemical and dark reactions paths, the reaction demonstrates how UV light can provide the necessary energy to surmount the activation energy of the dissociation reaction. Although the activation energy of $96\,\mathrm{kJ\,mol^{-1}}$ could be provided by visible light, Pt(en)Cl_2 does not absorb significantly in the visible region. Further work will investigate the use of visible light to drive chloride dissociation in platinum(II) complexes containing visible light-absorbing chromophores.

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