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Aqua substitution by biologically relevant nucleophiles in dinuclear platinum(II) complexes linked by diamino linkers with cyclohexyl groups

Mathias Chipangura · Allen Mambanda · Deogratius Jaganyi

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Abstract Substitution of the aqua ligand from three platinum(II) complexes, namely [Pt(H_2O)(*N,N*-bis(2-pyridylmethyl)cyclohexylamine](ClO_4)$_2$ (**Pt1**); [{Pt(H_2O)}$_2$-(*N,N,N′,N′*-tetrakis(2-pyridylmethyl)-*trans*-1,4-cyclohexyl diamine)](ClO_4)$_4$ (**Pt2**); and [{Pt(H_2O)}$_2$(*N,N,N′,N′*-tetrakis(2-pyridylmethyl)-4,4′-ethylenedicyclohexyldiamine)](ClO_4)$_4$ **(Pt3)**, by three biologically relevant nucleophiles [viz., glutathione (Glu); *DL*-penicillamine (Pen); and L-histidine (His)] was studied in aqueous 0.1 M perchloric acid medium. The substitutions were investigated under pseudo-first-order conditions as a function of nucleophile concentration and temperature using UV–visible spectrophotometry. The reactions of these complexes with the nucleophiles proceeded via a single step whose reactivity decreased in the order: **Pt1** > **Pt3** > **Pt2** and was controlled by steric and electronic influences of the complexes. Sulfur donor nucleophiles (Glu and Pen) reacted much faster than the nitrogen bearing His, with Glu appearing to be more nucleophilic than Pen. The large and negative activation entropies and low but positive enthalpies of activation affirm an associative mode of activation.

Introduction

Although cisplatin remains the prescribed regimen for treating testicular and ovarian cancers in the clinic [1–3], its widespread use has been limited by acute toxicity and resistance. Cisplatin is non-specific and can bind to non-cancerous cells as well [2, 3]. Binding to unintended targets alters key proteomic and enzymatic functions leading to toxicity, especially in the kidneys [4]. In addition, the drug is refractory to some tumor cell lines. In some cases, it may acquire resistance after an initial positive response. This has been ascribed to reduced cellular uptake, increased efflux from the cells and/or deactivation by glutathione, cysteinyl residues and albumins [4–9]. This has prompted much work to synthesize and screen thousands of cisplatin derivatives and other new platinum(II) complexes but with only a few showing improved efficacy compared with parent drug [5].

One of the mechanisms underlying cancer treatment by platinum-based drugs is induction of helical instability of DNA via covalent bonding at the nucleobases or intercalation between the nucleobases [6–9]. However, platinum(II) compounds may react with numerous other biomolecules (vide supra), chief among them being sulfur-containing proteins. Platinum(II) exhibits a high substitutional affinity for sulfur donor sites [10, 11]. As such, the study of substitution reactions of platinum(II) complexes by nitrogen- and sulfur-containing nucleophiles provides a fundamental basis for understanding toxicity and development of resistance in biological systems [12, 13].

Apart from the negative side effects resulting from the reactions of platinum(II) complexes with sulfur donor biomolecules, coadministration of cisplatin with so-called sulfur donor rescue agents has been demonstrated to ameliorate renal damage by the drug [10, 11]. It is also thought that sulfur biomolecules in blood plasma can reserve platinum complexes as inert species which can subsequently react with the nucleobases of DNA. For

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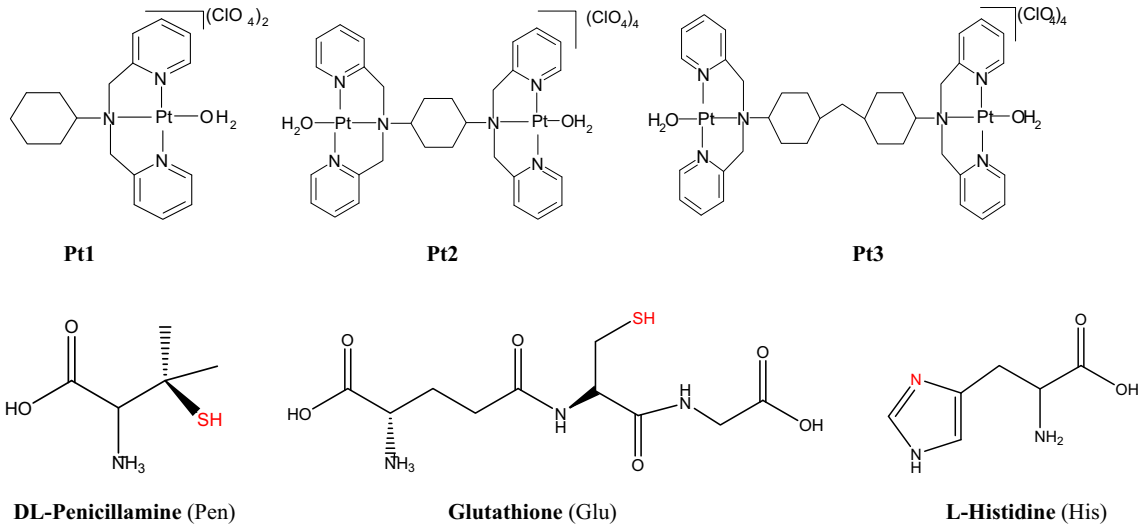

Fig. 1 Structures of the platinum(II) complexes (**Pt1**, **Pt2** and **Pt3**) and the nucleophiles (Pen, Glu and His) used for the substitution of the aqua ligands from complexes

instance, competition studies of the reactions of platinum(II) complexes with L-methionine and guanosine-5-monophosphate confirm the formation of persistent Pt–S(thioether) products which increase the bio-availability of the drugs at the target DNA sites [14–16]. The intermediate Pt–S(thioether) complexes are subsequently substituted by the DNA bases, in thermodynamically favoured reactions, forming cross-links that distort the helical structure.

As an extension to previous work from our laboratory [17–21], we studied the mechanism and reactivity of platinum(II) complexes linked by diamines bridges containing cyclohexyl moieties with three biologically nucleophiles bearing sulfur and nitrogen donor atoms. We now report on the effect of the cyclohexyl groups of the diamino linker on the reactivity of the platinum(II) dinuclear complexes. The two dinuclear platinum(II) complexes in this study are bridged by 1,4-*trans*-cyclohexyldiamine (**Pt2**), or 4,4′-dicyclohexylmethanediamine (**Pt3**), respectively. Included for comparative purposes is the mononuclear complex (**Pt1**) which has a cyclohexylamine pendant. The structures of these complexes are shown in Fig. 1 along with the structures of nucleophiles used in this work.

Experimental

Materials and procedures

The free ligands and their complexes were all synthesised under an inert atmosphere of nitrogen using the standard Schlenk methods. Organic solvents used in the syntheses were purchased from Merck and used without further purification. The diamines were procured from FLUKA, 2-Picolylchloride hydrochloride; the biological nucleophiles [viz, glutathione; *DL*-penicillamine; and L-histidine] as well as $NaClO_4{\cdot}H_2O$ and $AgClO_4$ (99 %) were purchased from Sigma-Aldrich and used as supplied. K_2PtCl_4 (99.99 %) was procured from Strem Chemicals. Ultrapure water (ELGA, Pure-laboratory Ultra-system) was used to prepare all aqueous solutions. The procedure reported by Mambanda [17] was followed for synthesizing both the ligands and complexes, and the results were in good agreement with those in the literature. Representative characterization data are presented in the supporting information (Figs. SI4–S23).

Preparation of complexes and nucleophile solutions for kinetics

The chloro complexes were converted into their aqua analogues in solution following a procedure described by Bugarčić et al. [22]. An accurately weighed amount of the dinuclear platinum(II) complex was suspended in 25 mL of 0.001 M $HClO_4$ containing $AgClO_4$ (1.98 mol equivalent). The mixture was left to stir in the dark for 24 h at 50 °C. The silver chloride precipitate was removed with a 0.45-μm Millipore filtration membrane, and the filtrate was diluted to 100 mL with 0.1 M $HClO_4$ to afford a solution of the di-aqua Pt(II) complex with a final concentration of 0.1 mM and ionic strength of approximately 0.1 M. Following the same procedure, the mononuclear analogue was prepared using 0.99 mol equivalent of $AgClO_4$.

Stock solutions of Glu, Pen and His were prepared shortly before each kinetic analysis by dissolving the

appropriate amount of each nucleophile in 0.1 M ionic strength ($HClO_4$) solution. The nucleophile concentration was provided in at least 10-fold excess over the concentration of each active platinum(II) center in the complexes which simplified the resulting kinetics to pseudo-first-order.

Kinetic measurements and instrumentation

A Thermo Scientific Flash 2000 Elemental Analyser and a Bruker Avance DPX 400 instrument were used for elemental and NMR analysis, respectively. Mass spectral data was obtained on a Micro-mass LCT Premier coupled to an ESI^+-TOF mass spectrometer. All kinetic measurements were performed on a Cary 100 UV–visible spectrophotometer (Varian), equipped with a Varian Peltier thermostatted cell holder. The temperature of the instrument was controlled within ±0.1 °C throughout all kinetic measurements.

The timescales of the substitution reactions and the wavelengths at which the kinetics could be performed were predetermined on the UV–visible spectrophotometer. Before the reactants were mixed, their neat solutions were each allowed to pre-equilibrate for about 10 min in the instrument cell holder, after which their spectra (pre-mix) were recorded over the entire 200–800 nm wavelength range. The solutions were then quickly mixed before subsequent spectral scans were acquired. The spectral acquisition was continued until no changes in the absorbance of the reaction mixture could be observed. Pseudo-first-order rate constants, $k_{obs.}$, were determined by a nonlinear least-squares fit of the absorbance-time data to Eq. (1) using Origin 7.5® graphical analysis software [23].

$$A_t = A_0 + (A_0 - A_\infty)e^{(-k_{obs.})t} \quad (1)$$

In Eq. (1), A_0, A_t and A_∞ represent absorbance of the reaction mixture at the onset of the reaction, at time t and at the end of the reaction, respectively. All kinetic traces gave perfect fits to a single exponential function.

Computational modeling

Cyclohexyl groups in the diamine linker have been reported to play a conformational role in tuning the reactivity of dinuclear platinum(II) complexes [18, 21]. In order to explain the observed experimental trends, quantum chemical calculations on the ground-state geometries of the three aqua complexes were carried out, in which the complexes were optimized as cations of +4 charge for the dinuclear complexes and +2 charge for the mononuclear complex. The calculations were performed in the gas phase with the density functional theory (DFT) [24, 25], utilizing the B3LYP/LACVP** method [26, 27] run on the Spartan 10 for Windows® program. Partial charges were calculated using the natural population analysis (NPA) method [28, 29]. A summary of some key selected data extracted from the calculation results is presented in Table SI 3 (Supporting Information).

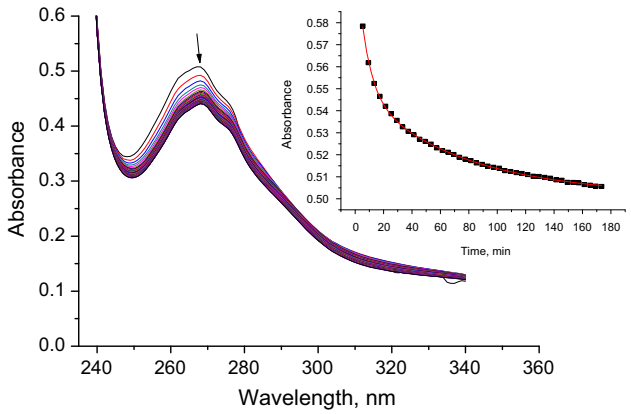

Fig. 2 UV–visible spectra recorded for the reaction of 0.1 mM **Pt2** with 5 mM His at pH = 1, T = 298 K and I = 0.1 M. *Inset* is a time-resolved kinetic trace of the data taken at 267 nm

Results

The kinetics of the aqua ligand substitution from the platinum complexes by the three nucleophiles was monitored spectrophotometrically by following the absorbance changes at a suitable wavelength as a function of time. A summary of the wavelengths used for each nucleophile is given in Table SI 1. Figure 2 depicts exemplary absorbance changes recorded during the course of the reaction between **Pt2** (0.1 mM) and His (5 mM) at 298 K.

The aqua substitution from all the three platinum(II) complexes follows second-order kinetics, according to the rate law given by Eq. (2):

$$-(\mathrm{d}[\text{complex}])/\mathrm{d}t = k_2[\text{platinum(II)}][\text{Nu}] \quad (2)$$

Under conditions where the concentration of the nucleophile, [Nu] ≫ [platinum(II)], the second-order rate constant, k_2, can be calculated from the slope of the plot of the observed first-order rate constant, $k_{obs.}$, versus concentration of the nucleophile according to Eq. (3):

$$k_{obs.} = k_2[Nu], \quad (3)$$

where Nu = Glu, Pen or His. A linear regression of data according to Eq. (3) resulted in plots passing through the origin, illustrating that the parallel solvolysis or reverse

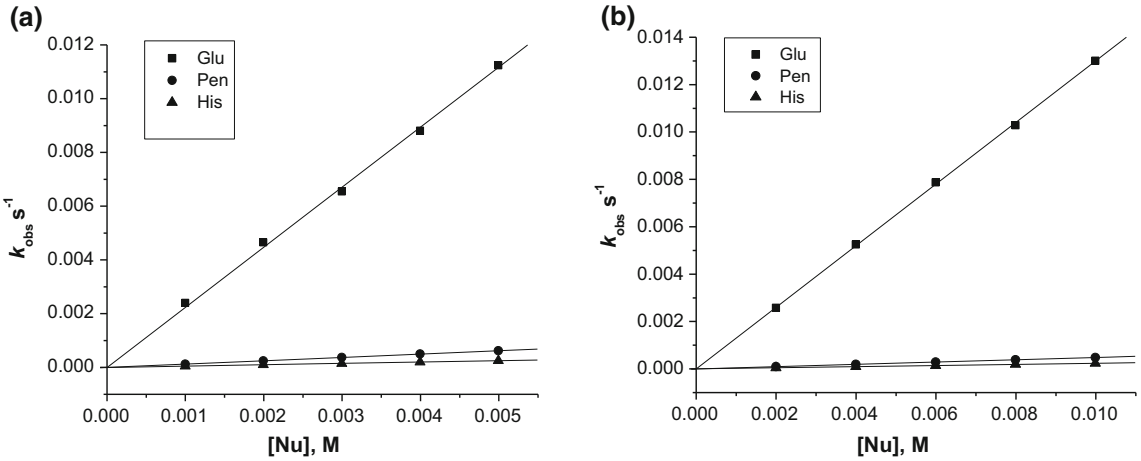

Fig. 3 Concentration dependence of $k_{obs,}$ s^{-1}, for the substitution of aqua ligands from **a Pt1** and **b Pt2** by Glu, Pen and His (pH = 1, T = 298 K, I = 0.1 M $HClO_4$)

reactions are insignificant or absent. A typical plot is shown in Fig. 3.

The second-order rate constants, k_2, obtained from the slopes of the plots are summarized in Table 1.

The temperature dependence of k_2 was studied in the temperature range of 288–308 K. The data were fitted to the Eyring equation, and representative plots are given in Fig. 4.

The enthalpy of activation, $\Delta H^{\neq}$ and entropy of activation, $\Delta S^{\neq}$ were calculated from the slopes and y-intercept of the plots, respectively, and their values are summarized in Table 1.

A pH of 1 was maintained throughout all kinetic reactions to ensure that all the platinum(II) complexes remained in the aqua form, considering their pK_a values reported in literature [18]. Also, at pH 1, the amine groups in the three nucleophiles are fully protonated, and their participation in the nucleophilic substitution of the aqua ligands is negligible, making sulfur the only available donor atom in Glu and Pen and the pyridinic nitrogen in His [30, 31].

Table 1 Second-order rate constants, k_2, and activation parameters for the substitution reactions of platinum(II) dinuclear complexes and their mononuclear analogue with Glu, Pen and His at a pH of 1 and ionic strength of 0.1 M

Complex	Nucleophile	K_2, M^{-1} s^{-1}	$\Delta H^{\neq}$, kJ mol^{-1}	$\Delta S^{\neq}$, J K^{-1} mol^{-1}
Pt1	Glu	2.22 ± 0.02	50 ± 3	−70 ± 9
	Pen	0.120 ± 0.002	45 ± 5	−110 ± 10
	His	0.050 ± 0.001	51 ± 2	−98 ± 6
Pt2	Glu	1.30 ± 0.01	55 ± 4	−57 ± 10
	Pen	0.048 ± 0.001	48 ± 3	−108 ± 9
	His	0.020 ± 0.001	51 ± 2	−124 ± 7
Pt3	Glu	1.50 ± 0.01	50 ± 2	−74 ± 6
	Pen	0.097 ± 0.004	51 ± 2	−94 ± 6
	His	0.040 ± 0.003	54 ± 6	−88 ± 20

Discussion

The substitution reactions of the two dinuclear platinum(II) complexes together with their mononuclear analogue using His, Pen and Glu as nucleophiles, were studied under pseudo-first-order conditions as a function of both concentration and temperature using UV–visible spectroscopy. The results obtained in this study do not support stepwise substitution as reported in similar reactions [32–35]. Due to the symmetrical nature of the dinuclear complexes, the two aqua ligands are equally susceptible to substitution which occurs simultaneously.

To test this assumption, we modeled the substitution of the aqua ligands of **Pt2** using thioglycolic acid (TGA) as a model thiol nucleophile. Complex **Pt2**, dissolved in heptadeutero-*N,N*-dimethylformamide (DMF-d_7), was reacted with two mole equivalents of **TGA** at 303 K, and the reaction was monitored kinetically for over 17 h using ^{1}H NMR spectroscopy. The evolution of the ^{1}H NMR spectrum during the substitution process is presented in Fig. 5.

The two insets to Fig. 5 show the ^{1}H NMR spectrum of **Pt2** before mixing with two equivalents of TGA and an expanded view of proton resonances labeled c and c', both appearing within the chemical shift range of 8.62–8.66 ppm. The pyridyl proton resonance (labeled c), appearing as a triplet centered at 8.62 ppm and whose subsequent integrals decrease with the progression of the reaction is assigned to **Pt2**, while the new set of triplets (labeled c'), appearing at 8.65 ppm and which builds up

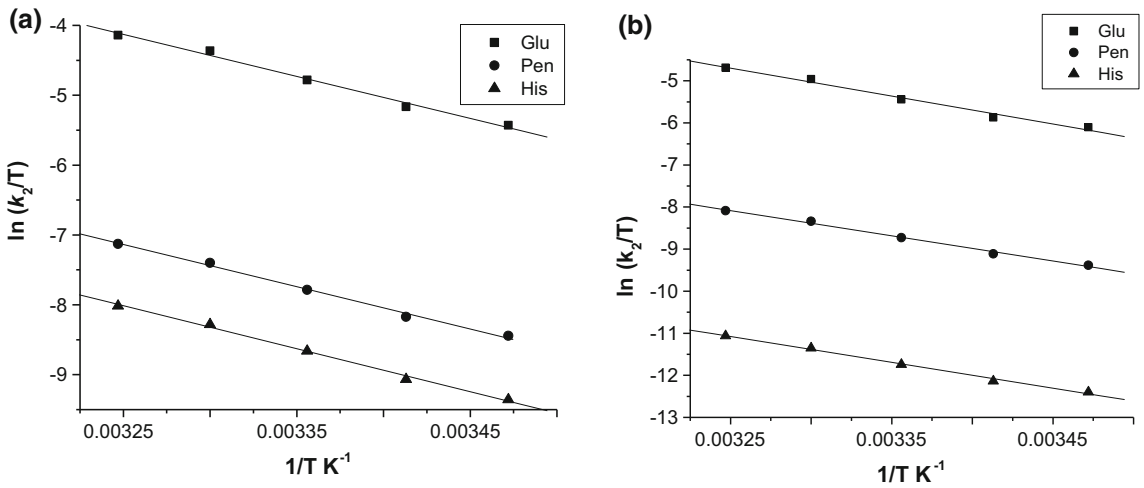

Fig. 4 Eyring plots for the simultaneous substitution of the aqua ligands from complexes: **a Pt1** and **b Pt2** by Glu, Pen and His

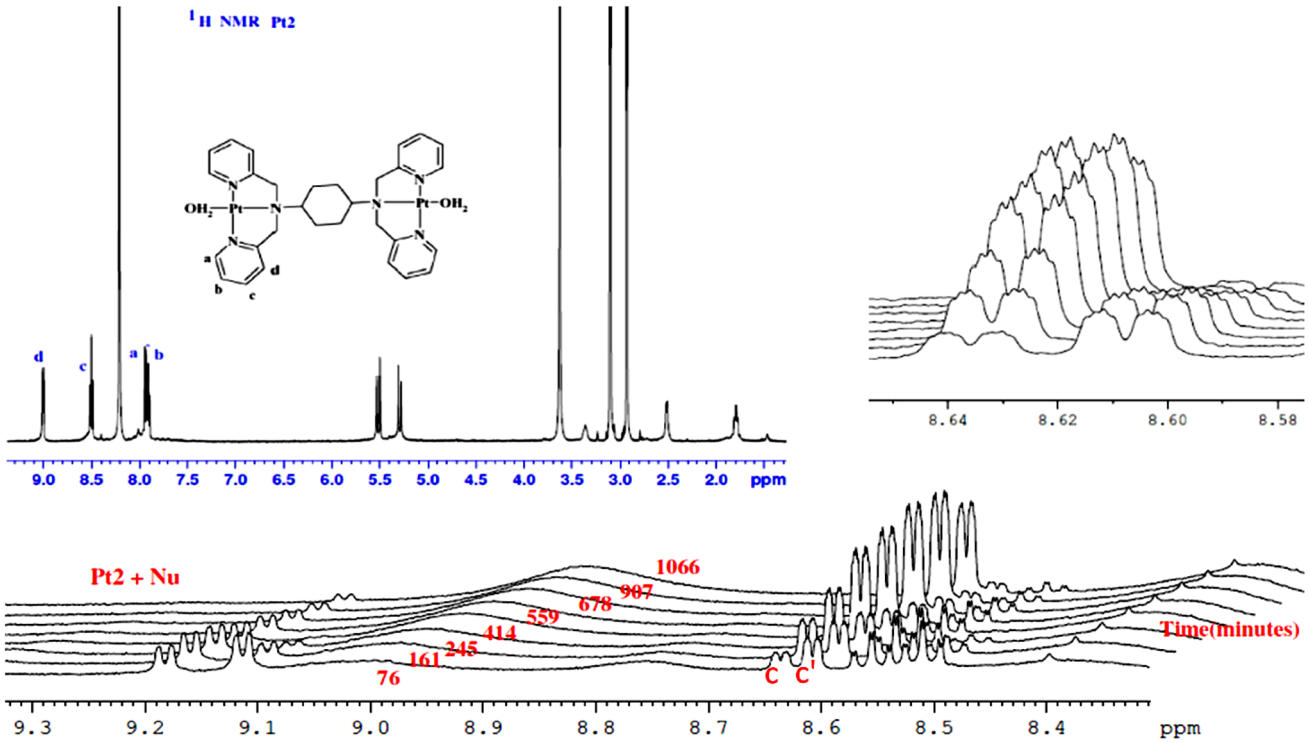

Fig. 5 ^{1}H NMR spectral array (shown for the aromatic resonance only) for simultaneous substitution of the aqua ligands of **Pt2** by thioglycolic acid (TGA) in DMF-d_7 at 303 K. The reaction was monitored for over 17 h

with time is assigned to the **Pt2**-TGA_2, substituted product. Within the timeframe of the experiment, we observe only one set of new pyridyl proton resonances for each of the four different types of proton resonances (a–d), which clearly confirms that the substitution of aqua ligands of **Pt2** and **Pt3** by TGA and other thiol nucleophiles such as Glu and Pen occurs simultaneously. The same can be assumed of the substitution reactions of His with **Pt2** and **Pt3**.

Substitution reactions in square-planar complexes usually proceed either by direct nucleophilic attack characterized by a second-order rate constant k_2 or via formation of a highly labile solvent complex in the rate-determining step, with a first-order rate constant k_{-1} [36]. The two rate constants can be calculated from the slope and intercept of a linear fit of the kinetic data to Eq. (1), which reduces to $k_{obs.} = k_2[Nu]$ in the absence of a meaningful intercept.

This is the case with these reactions, as exemplified by Fig. 3.

In Table 1, the rates of substitution of the aqua ligands from **Pt1**, **Pt3** and **Pt2** by Glu are (2.22 ± 0.02) M^{-1} s^{-1}, (1.50 ± 0.01) M^{-1} s^{-1}, and 1.30 ± 0.01 M^{-1} s^{-1}, respectively. This represents a decreasing ratio of 1.7 (**Pt1**):1.2 (**Pt3**):1 (**Pt2**) in the reactivity, and a similar trend is maintained when Pen or His are the incoming nucleophiles. The differences in reactivity of these complexes indicate an important steric effect (vide supra) on the metal chelates originating from the structural constraints of the cyclohexyl groups of the diamine linker. As previously reported [18] for the same complexes with strong thiourea nucleophiles, **Pt2** has a C_{2h} conformation which confers steric control over approaching nucleophiles. This steric effect becomes weaker as the chain length of the linker increases. The results of the DFT calculations [18] clearly show that the bridging ligand in **Pt3** (Pt–Pt distance 14.2 Å) is longer than in **Pt2** (8.8 Å) resulting in reduced steric hindrance at each platinum(II) center, in agreement with the observed reactivity trend when the two dinuclear complexes are compared. Inclusion of a methylene spacer in **Pt3** also introduces some flexibility to the complex resulting in the conformation switching to a C_{2v} structure. This may favorably contribute to an entrapment of the incoming nucleophile, thereby increasing reactivity of the complex relative to **Pt2**. For the mononuclear analogue (**Pt1**), for which steric influences are largely absent, the rate of aqua substitution from this complex is significantly higher than for either of the two dinuclear complexes. The reactivity trend follows the order: mononuclear complex (**Pt1**) > dinuclear with a cycloxyl diamine linker (**Pt3**) > dinuclear with the elongated 4,4′-methylenedicyclohexyl diamine linker (**Pt2**).

Another contributing factor is the σ-inductive effect of the ligand *trans* to the leaving group. In **Pt1**, the cyclohexyl group of the amine pendant has a strong positive inductive effect toward the platinum(II) metal center, resulting in stabilization of the transition state with the substituting nucleophiles and therefore to higher reactivity. In **Pt2**, the cyclohexyl group exerts a weaker σ-inductive donation since it is shared among two Pt(II) metal centers. The methylene spacer in **Pt3**, however, increases the number of functional groups which donate electron density toward each metal center, resulting in a slightly increased inductive effect. The result of this *trans* influence at the platinum(II) metal centers is to strengthen the Pt–N bond at the expense of the *trans*-configured Pt–OH_2 bond. This results in an increase in substitutional reactivity when the inductive donation increases.

Reactivities of nucleophiles

The data in Table 1 indicate that the order of nucleophilic attack at the platinum(II) centers is Glu > Pen > His. The sulfur donor nucleophiles, Glu and Pen are considered more easily polarized toward the platinum(II) center than His which is a hard and an intrinsically weaker nucleophile since it substitutes through a pyridinic nitrogen atom. Considering the reactivity of the mononuclear complex (**Pt1**), where steric influences on the platinum chelate are absent, Glu and Pen, respectively, substitute the aqua ligand from the metal center about 44 and two times faster than His. Despite the greater size of Glu relative to Pen, the former reacts about 18.5 times faster than the latter. This is contrary to expectation if one considers the relative bulks of the two nucleophiles in a bimolecular substitution encounter at the transition state. However, the results can be explained in terms of the anchimeric effect [37–41] where neighboring groups (hydrogen-bonding donors and acceptors) around the sulfur donor atom of Glu and the aqua leaving group of the complex interact non-covalently, resulting in a more structured transition state of lower energy [37, 38]. This stabilization is stronger for Glu than for Pen due to steric hindrance from the two methyl groups on the carbon to which the sulfur donor atom is bonded in Pen. However, the substitution reactions are still sensitive to the steric bulk of the nucleophiles. This is true if, for example, one compares the rates of aqua substitution by either Glu or Pen to those reported for thiourea (Tu) [18–21]. Reported k_2 values for reactions with Tu are $k_2 = 942 \pm 4$ M^{-1} s^{-1} (**Pt1**); 602 ± 9 M^{-1} s^{-1} (**Pt2**); and 774 ± 3 M^{-1} s^{-1} (**Pt3**), respectively. Hence for **Pt1**, the rates of aqua substitution by Glu and Pen are 270 and 5,000 times lower than those reported for Tu, respectively. This clearly underlines the role of steric effects for both Glu and Pen relative to the smaller thiourea, as expected for associatively activated reactions.

Activation parameters

The values of the enthalpy of activation, $\Delta H^{\neq}$, are all low and show a slight dependence on the steric bulk of the nucleophiles in some of the reactions. For example, reactions involving **Pt3** have enthalpy values which decrease in the order His > Pen > Glu in line with the decreasing size of the nucleophiles. This can be attributed to the destabilization of the transition state as the size of the incoming nucleophiles increases leading to increase in enthalpy of activation. The significantly negative activation entropies as well as low and positive enthalpies of activation affirm an associative mode of activation, as reported for substitutions in other square-planar complexes [39–41].

Conclusions

Based on the results of this study, the steric influences within the diamine linker are dominant in controlling the substitutional reactivity of these two dinuclear platinum(II) complexes. An increase in the chain length of the cyclohexyl diamine linker results in a notable decrease in steric influence at the platinum(II) centers. Weaker σ-inductive donation of electron density toward the metal center also influences the reactivity of the complexes. Substitution of aqua ligands in dinuclear platinum(II) complexes by the nucleophiles occurs via a single step which is slower than that reported for thiourea. This may imply that under biological conditions, the complexes should be moderately toxic due to their sluggish bio-transformation by biological thiol and nitrogen donor molecules. His, as a weaker nitrogen donor reacts much slower than either of the sulfur-containing nucleophiles. The order of nucleophilicity is Glu > Pen > His. Both the shielding effect of the methyl groups on the carbon atom attached to the sulfur donor atom in Pen and the neighboring group effects of H, O and N containing groups attached to Glu are the main reasons for the variation in reactivity of Glu and Pen. The magnitude of the activation parameters affirms an associative reaction mechanism. There is no dechelation evident in the substitution reactions with these biologically relevant nucleophiles.

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