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Research paper

The reactivity of 4′-substituted terpy platinum(II) complexes with bio-relevant azole nucleophiles. A kinetic and mechanistic study

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ABSTRACT

The rate of Chloride substitution from [Pt{(4′-ethylglycoxyl)-2,2′:6′,2″-terpyridine}Cl]Cl([**PtCl(tpy)eg]Cl**), [Pt{(4′-diethylglycoxyl)-2,2′:6′,2″-terpyridine}Cl]Cl([**PtCl(tpy)deg]Cl**) and [Pt{(4′-triethylglycoxyl)-2,2′:6′,2″-terpyridine}Cl]Cl([**PtCl(tpy)teg]Cl**), by a series of biological nitrogen donor nucleophiles, *viz.* pyrazole (**Pz**), triazole (**Tz**), imidazole (**Im**), 1-methylimidazole (**MIm**) and 1,2-dimethylimidazole (**DIm**) under *pseudo* first-order conditions as a function of concentration and temperature in methanol using UV/Visible spectrophotometry were investigated. The analysis of kinetic trend on the candidate complexes show that only the first carbon-oxygen pendant bond plays a crucial role in regulating the electron density donated by the polyethyleneglycoxyl fragment. This is reflected in the insignificant change in the reactivity as the polyethyleneglycoxyl chain increases. The obtained kinetic data are supported by the DFT calculations that reveal a less electrophilic Pt(II) metal centre for complexes bearing the 4′-substituent. The temperature dependent studies support an associative mode of activation where bond formation in the transition state is favoured.

1. Introduction

The voluminous number of Pt(II) complexes synthesised in the preceding decades informs of continuing research with the focus on tuning reactivity and other properties of Pt(II) complexes with a view to widen the biological spectrum of cisplatin [1]. Among the many synthesised compounds is 2,2′:6″,2″-terpyridine (tpy) whose derivatives are known to be good models for DNA intercalation [2]. 2,2′:6″,2″-Terpyridine (tpy) first synthesised by Morgan in 1932 [3], readily reacts with M^{n+} octahedral metal ions to give $[M(tpy)_2]^{n+}$ complexes [4]. For $[M(tpy)Cl]^+$ only the chloride ligand is labile due to the stable π-conjugated terpy ligand backbone [5], thus π-conjugation explains the greater reactivity of platinum (II) terpyridine complexes relative to the less conjugated Platinum (II) ethylenediamine [6,7]. DNA-Cisplatin adducts replication result to different strands of DNA with mutations leading to resistance which has elicited unmatched interest in substitution reactions of Pt(II) centre with nucleosides and other related compounds lately [1,8] unlikeearlier research that focused on knowing the mechanism of ligand substitution and binding mode of complexes with sulphur and nitrogen donor nucleophiles [9].

Research has shown that increasing the number pyridine ligands on the platinum(II) ethylenediamine increases its lability because the π-acceptor ability of subsequent complexes is enhanced [7]. The π-back-bonding of the terpy ligand enables the additional electron density from the incoming nucleophile to the π-acceptor orbitals of the pyridine groups to be stabilized in the transition state compared to the ground state [6], a significant property of the terpy complexes. Recent attention has been paid to the mechanistic investigations into the substitution behaviour of platinum(II) terpy complexes with regard to the electronic tuning and the reactivity of the metal centre by changing the structure of the ligand [10,11]. Constable and Housecroft [12–15] have reported a variety of terpy ligands containing different functional groups at the 4′-position. Inclusion of these substituents alters the electronic as well as steric properties of the complexes. It is reported that different electron-withdrawing and donating groups change the electronic properties of the ruthenium complexes [16]. Lowe et al. reported alteration of the electronic property of the terpy ligand on addition of substituents at the 4′ position [17]. A check in literature reveals that lability of the chloride ligand depends on the strength of π-back-bonding properties of the spectator terpy ligand backbone [18]. Substitution kinetics of $[Pd(bpma)(H_2O)]^{2+}$, $[Pd(dien)(H_2O)]^{2+}$ and $[Pd(dien)Cl]^+$ (bpma-bis(2-pyridylmethyl)amine and dien-diethylenetriamine) with azoles were reported by Bugarcic et al. Pitteri et al. also reported on the

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kinetics of reversible displacement of the chloride from [Pt(terpy)Cl] by some pyridines and heterocyclic compounds [19]. The common feature on the kinetics reported by these authors is that reactivity is dependent on basicity of entering azole nucleophile [19,20].

From a bioinorganic standpoint, azoles are essential given that the ligand histidine that binds to haemoproteins through its imidazole group is responsible for uptake of oxygen and electron transfer via cytochromes in plants and animals, hence the need to probe the substitution behaviour of azole nucleophiles [21]. Furthermore, coordination chemists have a keen interest in imidazole and its derivatives because information on their ability to coordinate to metal complexes is linked to that of proton affinities in gaseous phase, aqueous solutions, aprotic solvents and hydrogen binding abilities [22–24].

Data concerning the role of the π-acceptor ligands in the substitution reactions of square-planar platinum(II) complexes and the influence exerted by the substituents on the ancillary terpy ligand on the reactivity of these types of complexes [25,26] in the literature has no mention on the kinetics of these complexes with biorelevant azole nucleophiles. It is on this basis that we extended the research to explore the effect the polyglycoxyl substituents at the 4′-position on the terpy ligand system will have on the rate of chloride substitution using azoles as the incoming nucleophiles. DFT calculations were used to aid in the interpretation of kinetic results. It is envisaged that this paper will throw more light on the mechanism and kinetics of these complexes with azoles given their relevance in biological systems. The structural formulae of the platinum(II) complexes investigated and the respective azole nucleophiles are shown in Figs. 1 and 2 respectively.

2. Experimental

The Pt(II) complexes were synthesised according to modified literature procedures by our group [27–30]. The chemical analysis, UV–vis spectra and ^{1}H NMR spectra data were in good agreement with those obtained in previous preparations. The purity of the ligands was confirmed by ^{1}H NMR and mass spectroscopy. The ^{1}H NMR spectra obtained are similar in the aromatic region for the ligands. The identity and the purity of the final complexes were confirmed by using ^{1}H NMR, ^{13}C NMR, ^{195}Pt NMR, elemental analyses, IR and mass spectroscopy. The ^{1}H NMR spectra obtained show similarity in the aromatic region. Presence of a peak at about −2700 ppm on the ^{195}Pt NMR spectra confirms the Pt(NNN) coordination [30b–d]. Corresponding ^{1}H NMR, ^{13}C NMR, ^{195}Pt NMR and IR are given in Figs. SI 1–9 in the supporting information. The peak due to the OH proton is not seen in any of the ^{1}H NMR spectra due to the proton exchange with the solvent, methanol [31a]. Furthermore, the IR spectra of the complexes show distinct broad bands at around 3200–3300 cm^{-1} due to the O—H stretches along with the C-Hpeaks at around 3000 cm^{-1} [31b–d].

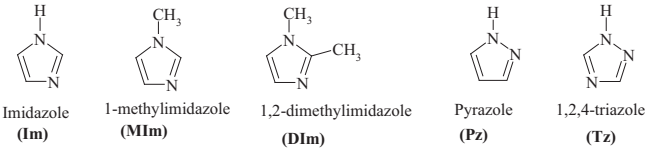


Fig. 2. Structural formulae of the azole nucleophiles.

2.1. Materials

Methanol bought from Merck was distilled over magnesium [30a] prior to use for kinetic analysis. Dimethylsulfoxide (99.9%) from Aldrich was used without any further purification. Ethylene glycol (99.8%), diethylene glycol (99%) and triethylene glycol (99%) werebought from Sigma Aldrich. The ligand, 4′-chloro,2,2′:6′,2″-terpyridine (97%), tetraethylene glycol (99%), and the platinum salt, potassium tetrachloroplatinate (II) (99.9%) were bought from Aldrich. All other chemicals were purchased from SigmaAldrich and were used without further purification.

2.2. Synthesis of ligands

The syntheses of ligands were carried out by literature procedures [27]. To a suspension of KOH in dry DMSO at 50 °C was added the ethylene glycol and its respective polymer (n = 2, 3, 4) in excess to avoid the formation of the di-terpyridine ligand [27a]. After stirring for 30 min, 4′-chloro-2,2′:6′,2″-terpyridine was added and the reaction mixture stirred for 20 h at this temperature. Upon cooling to room temperature, the reacting mixture was treated with deionised water and filtered. The crude product was extracted from the filtrate in dichloromethane (3 × 30 mL) dried over anhydrous magnesium sulfate and the solvent removed. 4′-[2-(2-Hydroxyethoxy)ethoxy]-2,2′:6′,2″-terpyridine (**tpy(eg)**) and 4′-[2-(2-Hydroxyethoxy)ethoxy]-2,2′:6′,2″-terpyridine (**tpy(deg)**) gave a white paste and a white powder respectively. Crude products were purified in THF to give white solids. 4′-{2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy-2,2′:6′,2″-terpyridine (**tpy(teg)**) yielded pale yellow oil, pure enough for platination.

2.2.1. tpy(eg)

Yield: 250 mg, (70%), off white paste. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.63(d, 2H, 6 6″), 8.55 (2H, d, 3 3″), 7.99 (2H, s, 3′ 5′), 7.79 (dt, 2H, 4 4″), 7.29 (dt, 2H, 5 5″), 4.23 (t, 2H, CH_2), 3.97 (t, 2H, CH_2). ^{13}C NMR (77 MHz, $CDCl_3$, ppm), δ = 61.1, 69.6, 107.6, 121.5, 123.8, 136.9, 148.9, 155.6, 157.2, 167.1. TOF MS-ES^{+}, *m/z*: 316.1062, $(M+Na)^{+}$.

2.2.2. tpy(deg)

Yield: 190 mg, (80%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.69(d, 2H, 6 6″), 8.62 (d, 2H, 3 3″), 8.13 (s, 2H, 3′ 5′),

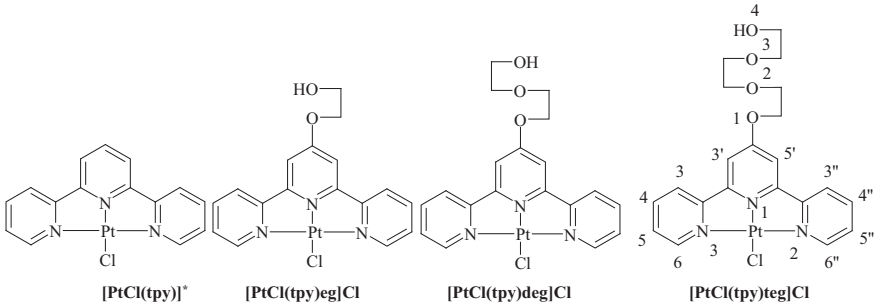


Fig. 1. Structural formulae of the platinum(II) complexes.

7.87 (t, 2H, 4 4″), 7.35 (t, 2H, 5 5″), 4.46 (t, 2H, CH_2), 3.94 (t, 2H, CH_2), 3.77 (t, 2H, CH_2), 3.69 (t, 2H, CH_2). ^{13}C NMR (400 MHz, $CDCl_3$, ppm), δ = 61.7, 68.1, 69.9, 72.8, 108.3, 121.6, 124.0, 137.1, 148.9, 155.7, 156.7, 167.3. *Anal.* Calc. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. *Found*: C, 68.00; H, 5.81; N, 11.97. TOF MS-ES$^+$, *m*/*z*: 360.1324, $(M+Na)^+$.

2.2.3. tpy(teg)

Yield: 175 mg, colourless oil (70%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.66(d, 2H, 6 6″), 8.59 (d, 2H, 3 3″), 8.03 (s, 2H, 3′ 5′), 7.83 (t, 2H, 4 4″), 7.31 (t, 2H, 5 5″), 4.40 (t, 2H, CH_2), 3.92 (t, 2H, CH_2), 3.73 (m, 4H, CH_2), 3.69 (t, 2H, CH_2), 3.60 (t, 2H, CH_2). ^{13}C NMR (400 MHz, $CDCl_3$, ppm), δ = 61.7, 67.9, 69.8, 70.4, 71.0, 72.9, 107.8, 121.4, 123.9, 136.9, 148.9, 155.9, 157.0, 167.1. TOF MS-ES$^+$, *m*/*z*: 404.1580, $(M+Na)^+$.

2.3. Synthesis of platinum(II) complexes

The synthesis of the complexes was carried out using the following procedure: To a stirred solution of $[Pt(cod)Cl_2]$ [43a] in dry methanol at room temperature, a suspension ofthe ligand in dry methanol was added at 55 °C. The reaction mixture was stirred for 24hours at the same temperature, after which the solution was cooled and filtered. Whenthe bright yellow filtrate was concentrated under *vacuo*, the desired compoundprecipitated as pale yellow solid. The compound was filtered, washed with chloroform (20 mL), cold methanol (1 × 5 mL), diethylether (2 × 15 mL) and dried and stored in a desicator.

2.3.1. [PtCl(tpy)eg]Cl

Yield: 35 mg, (55%), pale yellow powder. ^{1}H NMR (400 MHz, CD_3OH, ppm) δ = 10.23 (2H, d, 6 6″), 9.79 (2H, d, 3 3″), 9.78 (t, 2H, 4 4″), 9.39 (2H, s, 3′ 5′), 9.20(t, 2H, 5 5″), 5.88 (t, 2H, CH_2), 5.44 (t, 2H, CH_2). ^{195}Pt NMR (CD_3OH, ppm) δ = −2715. IR (4000–650 cm^{-1}) υ: 3237 (O—H), 3062 (C—H stretch), 1607 (C=H, pyridine), 1476–1423(C—H stretch), 1222.43 (C—O), 788 (C—H stretch). *Anal.* Calc. for $C_{17}H_{15}Cl_2N_3O_2$: C, 36.51; H, 2.70; N, 7.51. *Found*: C, 36.38; H, 3.20; N, 7.92. TOF MS-ES$^+$, *m*/*z*: 524.0482, $(M+1)^+$.

2.3.2. [PtCl(tpy)deg]Cl

Yield: 46 mg, (64%), crystalline yellow powder. ^{1}H NMR (400 MHz, CD_3OH, ppm) δ = 9.76 (d, 2H, 6 6″), 9.67 (d, 4H, 3 3″), 9.65 (t, 2H, 4 4″), 9.17 (s, 2H, 3′ 5′), 9.07(t, 2H, 5 5″), 5.87 (t, 2H, CH_2), 5.38 (t, 2H, CH_2), 5.21 (t, 2H, CH_2), 5.11 (t, 2H, CH_2). ^{13}C NMR (400 MHz, CD_3OH, ppm), δ = 62.26, 69.93, 72.01, 74.07, 112.07, 126.95, 130.28, 142.73, 152.27, 156.70, 159.58, 170.89. ^{195}Pt NMR (CD_3OH) δ = −2705. IR (4000–650 cm^{-1}) υ: 3338 (O—H), 3071 (C—H stretch), 1607 (C=H, pyridine), 1476–1430 (C-Hstretch), 1219 (C—O), 773(C—H stretch). *Anal.* Calc. for $C_{19}H_{21}Cl_2N_3O_4$: C, 37.73; H, 3.41; N, 6.76. *Found*: C, 37.35; H, 3.75; N, 6.34. TOF MS-ES$^+$, *m*/*z*: 568.0847, $(M+1)^+$.

2.3.3. [PtCl(tpy)teg]Cl

Yield: 38 mg, dark orange powder (60%). ^{1}H NMR (400 MHz, CD_3OH, ppm) δ = 9.98 (dd, 2H, 6 6″), 9.73 (s, 2H, 3′ 5′), 9.71 (d, 2H, 3 3″), 9.29 (t, 2H, 4 4″), 9.13(t, 2H, 5 5″), 5.90 (t, 2H, CH_2), 5.40 (t, 2H, CH_2), 5.22 (m, 2H, CH_2), 5.14 (t, 2H, CH_2), 5.11 (t, 2H, CH_2), 5.04 (t, 2H, CH_2). ^{195}Pt NMR (CD_3OH, ppm) δ = −2708. IR (4000–650 cm^{-1}) υ: 3332 (O—H), 3071 (C—H stretch), 1607 (C = H, pyridine), 1448 – 1429 (C-Hstretch), 1220 (C-O), 774 (C—H stretch). *Anal.* Calc. for $C_{21}H_{23}Cl_2N_3O_4$: C, 38.96; H, 3.58; *N*, 6.49; *Found*: C, 38.48; H, 3.41; *N*, 6.32. TOF MS-ES$^+$, *m*/*z*: 612.1027, $(M+1)^+$.

2.4. Chemicals and solutions

Solutions of chloro-complexes were prepared by dissolving known amount of the complex in methanol solution of constant ionic strength (*I* = 0.01 M, (0.009 M $LiCF_3SO_3$ + 0.01 M LiCl)). Solutions of **[PtCl(tpy)eg]Cl**, **[PtCl(tpy)deg]Cl** and **[PtCl(tpy)teg]Cl** were dissolved to give platinum(II) complexes concentrations of 5.00×10^{-5} M each. The 0.01 M ionic strength solution used to prepare complex and nucleophile solutions was made up of required amounts of $LiCF_3SO_3$ (0.009 M) and LiCl (0.01 M) dissolved in dry methanol since $CF_3SO_3^-$ does not coordinate to Pt(II) [31]. Lithium chloride was added to suppress spontaneous solvolytic reactions. Nucleophile solutions were prepared by dissolving a known amount of the required nucleophile in 50 mL of methanol solution of constant ionic strength to afford a concentration of *ca.* 100 times that of the metal complex. Subsequent dilutions of the stock solution were done to afford a series of standards of 80, 60, 40 and 20 times that of the platinum complex.

2.5. Physical measurements and instrumentation

Kinetic measurements were done using a Varian Carry 100 Bio UV–vis spectrophotometer with an attached Varian Peltier temperature control unit with online kinetics application. All the UV–vis spectrophotometric measurements were thermostatically controlled to within ±0.1 °C. All kinetic measurements were performed under *pseudo*-first-order conditions i.e., at least 20-fold excess of nucleophile concentration was used. The spectral changes resulting from mixing of complex and ligand solutions were recorded over the wavelength range of 200–800 nm and a suitable wavelength at which kinetic measurements could be performed was found. Reactions were initiated by mixing equal volumes of metal complex and azole solutions in a tandem cuvette on the UV–visible spectrophotometer and the rate of complex formation was followed by monitoring the decrease in absorbance at 310 nm. All the kinetic measurements are reproducible within the limits of error of ±0.5%. The quoted values are the average of a number of runs under identical experimental conditions. Fig. 3 shows an absorbance spectrum for the reaction of **[PtCl(tpy)eg]Cl** and **Im** at 298 K and *inset* is a kinetic trace obtained for the reaction of **[PtCl(tpy)eg]Cl** and **Im** at 298 K. Other kinetic traces are presented in the Supplementary Information Figs. SI 16–21. Data for **[PtCl(tpy)]Cl*** [43] is incorporated for comparison purposes.

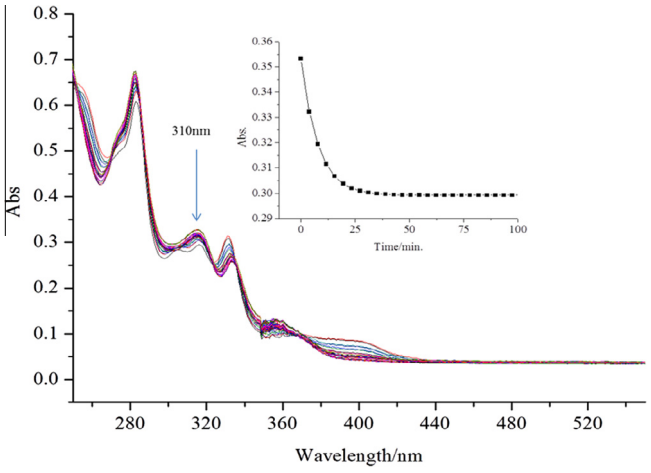


Fig. 3. Absorbance spectra of [PtCl(tpy)eg]Cl (5.0×10^{-5} M) and **MIm** (5.0×10^{-3} M) at 298 K.

The observed *pseudo* first-order rate constants, k_{obs}, were obtained from kinetic traces applying the online non-linear least-squares fit using Eq. (1)

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

where A_0 is initial absorbance of the mixture, A_t is absorbance of the reaction mixture at time, t and A_∞ is final absorbance. Second order rate constants, k_2, for the forward reaction and the solvolytic rate constants, k_s, were obtained from the graph of k_{obs} verses nucleophile concentration using, Origin 7.5® software [32]. Eq. (2) illustrates this relationship

$$k_{obs} = k_2[Nu] + k_s \approx k_2[Nu] \quad (2)$$

A typical plot of k_{obs} verses $[Nu]$ is shown by Fig. 4 for the substitution reactions of **Im** with [**PtCl(tpy)eg]Cl**. Other concentration dependence plots are presented in the Supplementary Information Figs. SI 10, 12 and 14. Data forplots of k_{obs} verses nucleophile concentration is presented in Supplementary Information Tables SI 1–3.

The temperature dependence of the rate constants were studied over the temperature range of 20–40 °C in increments of 5 °C. Graphs of $\ln(k_2/T)$ verses $1/T$ were plotted using Origin 7.5® [32] from which activation parameters, enthalpy of activation, $\Delta H^{\neq}$ and entropy of activation, $\Delta S^{\neq}$ were obtained from the slope and the intercept respectively from the Eyring Eq. (3). Where the letters represent their usual meaning.

$$\ln k_2/T = -\left(\frac{\Delta H^{\neq}}{R}\right)\frac{1}{T} + \left(23.8 + \frac{\Delta S^{\neq}}{R}\right) \quad (3)$$

A typical Eyring plot is shown in Fig. 5 for the reaction of [**PtCl(tpy)eg]Cl** with **Im**, **Pz** and **Tz** and other Eyring plots are presented in the Supplementary Information Figs. SI 11, 13 and 15. Respective data for Eyring plots are presented in the Supplementary Information Tables SI 4–6.

3. Computational details

To gain further insight on the structural and electronic differences among the complexes in this study, computational calculations were carried at the DFT level of theory [33,34]. DFT calculation data in systems that contain transition metals have shown better agreement with experimental data than that obtained from Hartree–Fock (HF) calculations [35]. The LANL2DZ basis set was employed in the current case because it provides reliable results in systems of this nature [34,36–39]. Singlet states were used due to the low electronic spin of Pt(II) complexes. The frontier molecular orbitals of the complexes were generated in Gauss view 5.0 applying the same level of theory. The Gaussian09 suite of programs was used for all DFT computations [40]. A summary ofthe DFT calculated frontier HOMO and LUMO molecular orbitals of the complexes in the study are shown in Table 1. Thecalculated angles and distances around the oxygen atoms on the polyglycoxyl group are illustrated in Fig. 6 while the processed data for the complexes are included in Table 2.

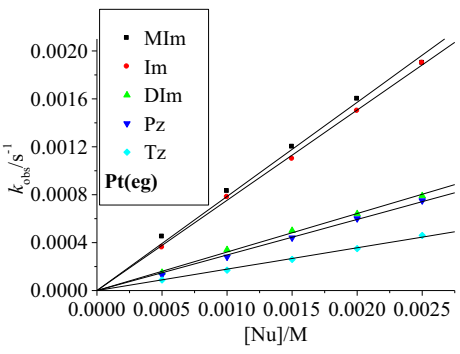


Fig. 4. Plots of k_{obs} verses nucleophile concentration for the reaction of [PtCl(tpy)eg]Cl with the azole nucleophilesat 298 K.

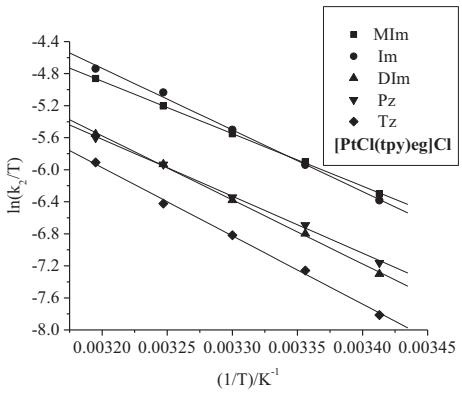


Fig. 5. Eyring plots for the reaction of [PtCl(tpy)eg]Cl with **MIm**, **DIm** and **Tz** in the temperature range of 20–40 °C.

4. Results

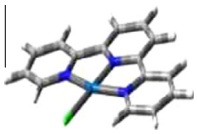
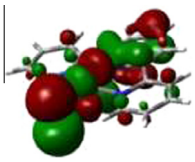
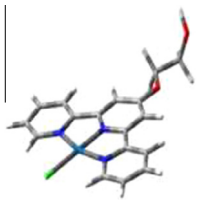
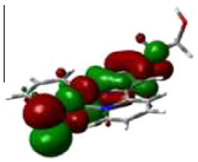
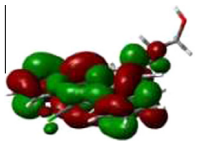
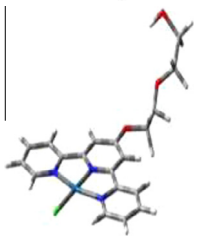
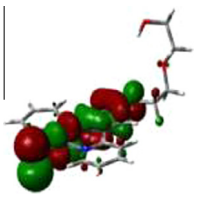
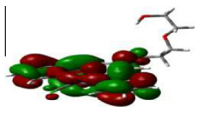
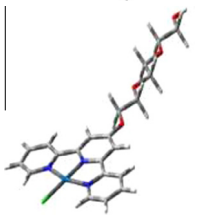
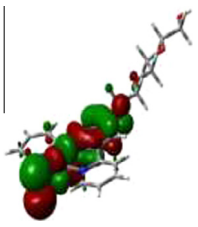
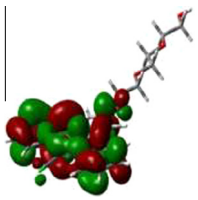
4.1. Kinetic analysis

Substitution of the coordinated chloride from [**PtCl(tpy)eg]Cl**, [**PtCl(tpy)deg]Cl** and [**PtCl(tpy)teg]Cl** by the azole nucleophiles *viz* imidazole, 1,2-dimethylimidazole, pyrazole, 1,2,4-triazole and 1-methylimidazole was investigated. UV–visible spectrophotometry was used to track the progress of the reaction. All the kinetic traces were described by single exponentials with the *pseudo* first order rate constants calculated from the traces plotted against the concentration of incoming nucleophiles giving straight lines with negligible intercepts (Fig. 4). Values of second order rate constant, k_2, representing direct attack by nucleophile according to Equation2 are shown in Table 3.

5. Discussion

The data in Table 3 indicate higher reactivity for [**PtCl(tpy)]Cl*** complex than [**PtCl(tpy)eg]Cl**, [**PtCl(tpy)deg]Cl** and [**PtCl(tpy)teg]Cl.** There is about six fold drop in the reactivity for most studied nucleophiles when the ethylene glycoxy unit is added in the 4′-position. This decrease can be attributed to the presence of the lone pair of electrons on the first oxygen atom, O21 which is in close proximity to the extended π-conjugation of the terpyridyl unit allowing greater delocalization of the electrons into the pyridyl rings [41]. This donation of the electrons towards the Pt(II) centre is explained by the higher enthalpy of activation of the complexes bearing the substituent compared with that of [**PtCl(tpy)]Cl*** as shown in Table 3. This means higher energy is needed to form the transition state complex for the substituted complexes. The π-donation along with σ-electron donation of the oxygen atom of the ethylene glycoxy increases the negative charge on the *trans* nitrogen atom of the complexes compared to[**PtCl(tpy)]Cl*** as shown in Table 2. This is responsible for the lowering of the chargeon the Pt(II) centre from 0.605 to 0.591 (Table 2) as well as the electrophilicity of the complex which changes from 7.31 to 6.94 for the substituted complexes. All these observations support the observation that there is electron flow from the oxygen atom of the substituent towards the metal centre.

Table 1
DFT-calculated frontier molecular orbitals of the investigated Pt(II) complexes.

Complex	Lowest energy structure	Map	
		HOMO	LUMO
[PtCl(tpy)]Cl*			
[PtCl(tpy)eg]Cl			
[PtCl(tpy)deg]Cl			
[PtCl(tpy)teg]Cl			

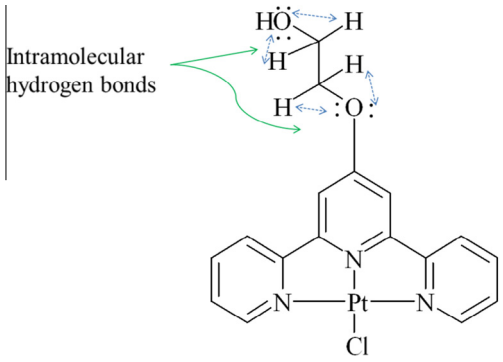


Fig. 6. Hydrogen bonding interactions in the polyglycoxyl pendant.

In addition the C7–O21 bond length, (1.369 Å) (Table 2) is shorter than the normal C-O bonds (range 1.456–1.467 Å) (Table 2) a fact reported in literature [42], which illustrates the conjugation of the p-type orbital of the oxygen atom in the 4-position. Further, angles of about 120° around the oxygen atom indicate that the atom has sp^2 character supporting the delocalization of the lone pair of electron into the π-system of the terpy. The donation of electron-density to the terpyridyl rings reduces the π-accepter capabilities of terpy bearing the polyglycoxyl substituents causing the platinum centre and the whole complex to be less electropositive hence less reactive [41]. The dipole moments of the Pt(II) complexes (Table 2) corroborate the fact that the terpy unit of **[PtCl(tpy)]Cl*** has the highest extended π-withdrawing character hence most electropositive platinum centre [41]. Platinum(II) complexes with substituents experience steric hinderance by the inclined substituent at the 4-position. The inclined pendant hinders the nucleophiles approaching the complex from the axial position an additional contribution to the reduction in the reactivity.

The reactivity remains fairly constant on increasing the length of the substituents in the 4′-position for the studied complexes. A trend that is observed for all the incoming nucleophiles. The reactivity was expected to decrease due to increased electron donation as the chain length increases but DFT calculations show that the charges on Pt(II) centre and on the *trans* nitrogen atom remain constant for the complexes indicating that there is no further electronic effects beyond the first glycol unit. Even the global electrophilicity indices are consistence with the results. It can then be concluded that after the first glycol unit, both electronic and steric hindrance reaches a limit such that any additional units of the ethylene glycol have minimal or no influence on the reactivity of the complexes. This is despite the angles of inclination, of the pendants in the 4-position decreasing as its length increases, an effect that would have increased steric hinderance and lowered reactivity**.** Very weak intra-molecular hydrogen bonding interactions between the lone pairs of electrons on the oxygen atoms and neighbouring hydrogen atoms as illustrated by Fig. 6 could account for minimal or no effect on steric hinderance among the complexes. The H···O, Fig. 6, length measured is 2.1 Å typical of hydrogen bond length range 1.5–2.5 Å [41] which supports the idea of existence of intra-molecular hydrogen bonds.

It is worth noting that while the electron density in the chain increases with the increase in the chain length of the appended group; the donation of electron density towards the Pt atom is less

Table 2
Computational data of the complexes investigated.

Property	[PtCl(tpy)]Cl*	[PtCl(tpy)eg]Cl	[PtCl(tpy)deg]Cl	[PtCl(tpy)teg]Cl
Bond lengths (Å)				
Trans N-Pt	1.961	1.960	1.960	1.960
Cis N-Pt	2.049	2.048	2.051	2.048
Pt-Cl	2.443	2.444	2.444	2.442
Angles (°)				
Angle of elevation, β, of the ethylene glycoxy pendant (°)	–	37.55	36.44	19.38
Energy (eV)				
LUMO	−3.35	−3.23	−3.23	−3.23
HOMO	−7.04	−6.89	−6.89	−6.89
$\Delta E_{LUMO-HOMO}$	3.69	3.66	3.66	3.66
NBO charges				
Pt^+	0.605	0.591	0.591	0.590
Dipole moment (D)	13.30	11.51	10.72	6.83
Electrophilicity index (ω)	7.31	6.94	6.97	7.00

Table 3
Rate constants and activation parameters for Pt(II) complexes with the azole nucleophiles.

Complex + Nu	$k_2(M^{-1}\,s^{-1}) \times 10^{-3}$	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})
[PtCl(tpy)]Cl*			
Im	3980 ± 50	41 ± 3	−96 ± 10
Pz	2200 ± 100	42 ± 1	−96 ± 5
Tz	1040 ± 70	40 ± 2	−107 ± 6
MIm	3840 ± 40	42 ± 2	−91 ± 5
DIm	1620 ± 40	46 ± 1	−88 ± 3
[PtCl(tpy)eg]Cl			
Im	753 ± 6	64 ± 3	−33 ± 10
Pz	297 ± 4	59 ± 2	−55 ± 6
Tz	178 ± 3	71 ± 1	−21 ± 3
MIm	790 ± 10	54 ± 1	−64 ± 3
DIm	321 ± 4	67 ± 3	−31 ± 9
[PtCl(tpy)deg]Cl			
Im	767 ± 10	69 ± 3	−16 ± 1
Pz	307 ± 3	59 ± 1	−57 ± 3
Tz	186 ± 3	62 ± 1	−50 ± 5
MIm	803 ± 5	57 ± 1	−56 ± 3
DIm	325 ± 5	61 ± 3	−49 ± 9
[PtCl(tpy)teg]Cl			
Im	790 ± 20	62 ± 1	−40 ± 4
Pz	323 ± 4	58 ± 2	−59 ± 5
Tz	197 ± 2	63 ± 2	−47 ± 5
MIm	1028 ± 15	65 ± 2	−28 ± 5
DIm	333 ± 2	55 ± 1	−69 ± 3

* Data extracted from Ref. [43a].

effective or non-existentas the chain length of the pendant increases [42]. The geometry of the platinum centres remains distorted square-planar withbite angles of 160–161° showing a slight deviation from planaritytypical of Pt(II) square planar complexes [6,43]. It is also observed that the introduction of the ethylene glycoxyl units has negligible influence on the structural differences which has also been observed by others workingwith similar compounds having a 4′-substituted 2,2′:6″,2″-terpyridine ligand [43,9,44–46].

The trend in the reactivity of the nucleophiles investigated is **Im** > **Pz** > **Tz** also observed in other reports [36]. The decrease in the reactivity correlates with their basicities; 7.00, 2.52 and 2.19 respectively though the trend is non-linear because **Tz** exhibits tautomerism even though the 1H form is predominant [47]. The reactivity of the otherset of nucleophilesfollows the order; **MIm** > **Im** > **DIm** having basicities of 7.30, 7.00 and 7.85 respectively [47]. The reactivity does not correlate with the basicities in the second set of nucleophiles because of steric hindrance brought about by the presence of methyl groups on **DIm** [26]. The overall trend in reactivity for the nucleophiles is **MIm** > **Im** > **DIm** > **Py** > **Tz** [26] consistent with their respective basicities except for **DIm** because of its steric bulk.

The observed trend agrees with previous studies on [Pd(terpy)Cl]$^+$ and [Pt(terpy)Cl]$^+$ complexes with pyridines [48,49] and [Pt(terpy)Cl]$^+$ complex with five membered N-donor heterocyclic ligands [19]. The magnitude of steric effects is attributed to the free rotation of the ligand around the Pt-N (azole) bond [19]. In the associative mode of reaction, the Pt-N (azole) bond is well formed and Pt-Cl bond weakened at the transition state, the trigonal bipyramidal intermediate contains pyridine rings on either side of the terpy in axial positions where the pyridyl protons sterically interact with α-methyl protons of the incoming nucleophiles which impede free rotation of the just formed Pt-N (azole) bond [50] effectively retarding the reaction. The effects of bulky azoles affect the energy of the transition state complexes hence the observed reaction rate as tabulated in Table 3 [51]. Steric hindrance due to interaction between α-substituted methyl with solvent causes charge dispersion through hydrogen bonding with solvent. This reduces basicity of the nucleophile in solution which plays a role in slowing the reaction involving **DIm** [51]. The higher reactivity of **MIm** is dueto the inductive effects of the methyl group attached to N1 of the imidazole ring that results in the donation of electrons from the methyl group to N3 making it more basic. Since the methyl in **MIm** is further from the pyridyl rings on the terpy, steric congestion in the transition state is unlikely or minimal. For **DIm**, steric effects prevail over inductive effects of the methyl groups [50], accounting for the difference in reactivity.

The intercepts of plots k_{obs} verses concentration of were insignificantly small indicating that the reverse reactions are very slow or absent the reason being that the Pt-N (azole) bond formed is stabilized by the π-back-bonding with the Pt(II) centre [19]. Values of enthalpy of activation, $\Delta H^{\neq}$, are relatively low while those of entropy of activation, $\Delta S^{\neq}$, are large and negative confirming an associative mode of substitution typical of Pt(II) square planar complexes [52,53].

6. Conclusions

This study clearly reveals that electron donation towards the terpy chelate by the 4′-substituted polyglycoxyl units decreases the π-accepter ability of the chelatemaking the platinum centre of these complexes less electrophilic retarding theirligand substitutions reactions whencompared to that of **Pt**. The electron donation is only effective up to the first oxygen atom, beyond which there is no significant electronic effect on the Pt(II) centre. The overall decrease in reactivity from **Pt** to **Pt(eg)** ismostly due to the electronic effect and to a minimal extent the steric factor. The reactivity of the nucleophiles is controlled by the basicity

and steric hindrance, with the more basic nucleophiles being more reactive but steric factors come into play for the bulky nucleophiles.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2016.08.044.

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