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Tuning the π-backbonding and *σ-trans* effect of N^C^N coordinated Pt(II) complexes. *Kinetic and computational study*

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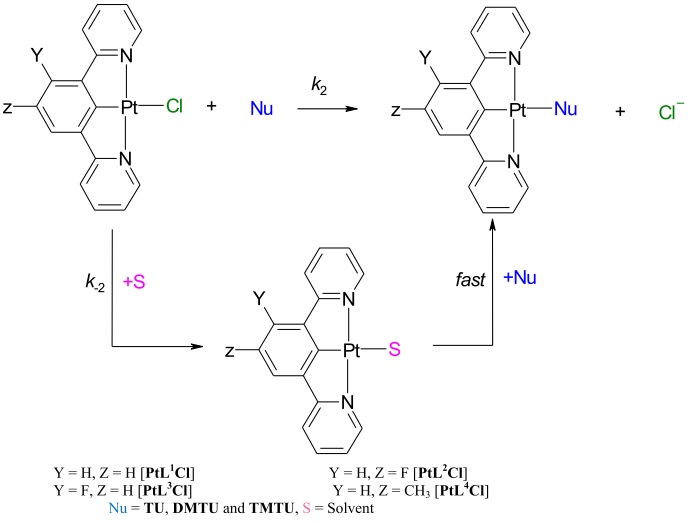

The mechanistic pathway for the substitution reaction of a strong *trans* labilizing phenyl of N^C^N platinum(II) complexes by biorelevant thiourea nucleophiles go through the solvent associated pathway.

The nucleophilic substitution reaction of cyclometallated complexes; [PtL^{2}Cl] (L^2 = 3,5-di(2-pyridinyl)-fluorobenzene), [PtL^{3}Cl] (L^3 = 2,4-di(2-pyridinyl)-fluorobenzene), and [PtL^{4}Cl] (L^4 = 3,5-di(2-pyridinyl)-toluene) with a series of neutral nucleophiles with different steric properties, thiourea (TU), *N,N*-dimethylthiourea (DMTU), and *N,N,N′,N′*-tetramethylthiourea (TMTU), was studied under *pseudo*-first-order conditions in methanol solution of an ionic strength of 0.1 M (0.09 M $LiCF_3SO_3$ and 0.01 M LiCl). The rate of substitution of the chloro ligand was studied as a function of nucleophile concentration and temperature using UV–visible and stopped-flow spectrophotometric techniques. The observed *pseudo*-first-order rate constants for the substitution reactions obey the rate law $k_{obs} = k_2[Nu] + k_{-2}$. The reactivity of the investigated complexes when [PtL^{1}Cl] is used as a reference follows the order [PtL^{2}Cl] > [PtL^{3}Cl] > [PtL^{4}Cl] > [PtL^{1}Cl]. The lability of the chloro group is dependent on the extent of π-backbonding and the *σ-trans* effect of the ligand backbone. [PtL^{2}Cl] and [PtL^{3}Cl], which have a common electron-withdrawing fluoride on the ligand *trans* to the leaving

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group, have a higher reaction rate compared to [PtL^{4}Cl], which has an electron-donating methyl group attached to the ligand backbone. The position of the substituent on the phenyl group *trans* to the leaving group also influences the overlap of frontier molecular orbitals which result in controlling the reactivity of the fluoro complexes. In general, the results show that the nature of the substituent, either electron withdrawing or electron donating, results in an increase in the rate of substitution. Second-order kinetics and large negative activation entropies ($\Delta S^{\#}$) support an associative substitution mechanism. The experimental data are supported by DFT calculations.

Keywords: Kinetics; Mechanistic; Platinum; Substitution

Introduction

Square planar platinum(II) complexes have been given much attention due to their application in many areas such as organic light-emitting diodes [1], photovoltaic devices [2], photocatalysts [3], chemosensors [4], phosphorescent emitters for displays, lighting applications [5], and as anticancer drugs due to the slow ligand exchange kinetics [6]. Thousands of platinum complexes have been synthesized and tested as potential antitumor drugs following the discovery of the antitumor properties of *cis*-diamminedichloro-platinum (II) more commonly known as cisplatin in the late 1960s [7]. These new platinum(II) complexes were synthesized to improve activity, reduce toxicity, and increase solubility [8]. This has led to interest in the substitution behavior of square planar d^8 platinum(II) complexes as the mechanism of action of cisplatin involves the formation of adducts with DNA [9].

Kinetic and mechanistic studies involving square planar complexes with one or more Pt–C bonds [10–14] have also been given much attention due to the ability of the Pt–C bond to stabilize the square planar geometry through the kinetic *trans* effect [14, 15]. The *trans* effect can accelerate the substitution rate by up to six orders of magnitude for complexes with a single Pt–C bond *trans* to the leaving group [16]. In addition, two *cis* Pt–C bonds have been reported to induce a mechanistic change over from the common associative substitution pathway [10] to a dissociative mechanism [12, 17]. Two Pt–C bonds have been found to weaken the leaving group through stabilization of the three coordinate (14-electron) intermediate in which the leaving group is dissociated from the platinum(II) [12, 14, 18]. A strong π-acceptor non-leaving ligand stabilizes the trigonal bipyramidal transition state by accepting π-back donation of electron density from the platinum(II) [16].

Kinetic studies have shown that for cyclometallated complexes with aliphatic carbon donors, the reaction rate is in minutes, but, in the case of a phenyl acting as a carbon donor, the reaction rate is 10^2 times faster; this is due to the in-plane configuration of the phenyl ring which enables effective π-backbonding as the electrophilicity of the metal center is enhanced. The π-acceptor effects of in-plane pyridine donors showed that π-backbonding in the *cis* position enhances the electrophilicity of the metal center more than in the *tran*s position [19], as observed in [Pt(bipy)(Ph)Cl], where the electrophilicity of the metal is influenced by the in-plane phenyl ring when the 6-phenyl-2,2′-bipyridine ligand becomes part of an extensive π-acceptor system and the strong π-electron withdrawal of the 2,2′-bipyridine fragment [13].

In a study carried out to investigate the lability of chloride in Pt(II) complexes of the type [Pt(N^N^N)Cl], [Pt(N^N^C)Cl], and [Pt(N^C^N)Cl], it was found that when a carbon was introduced *cis* to the leaving group, the reactivity of the complex reduced due to

accumulation of electron density around the metal center, while the introduction of carbon *trans* to the leaving group increased the reactivity due to the kinetic *trans* effect [20].

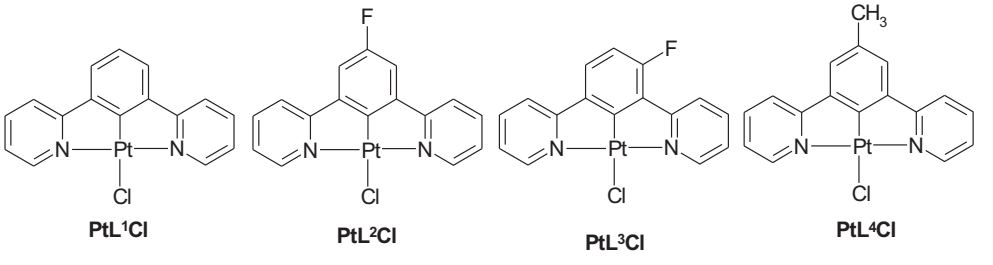
In order to tune the reactivity of a strong *trans* labilizing phenyl of N^C^N platinum(II) complexes with different substituents (electron-withdrawing and electron-donating groups) on the phenyl moiety *trans* to the leaving group on the Pt(II) complexes [PtL^2Cl], [PtL^3Cl], and [PtL^4Cl] were synthesized, characterized and their ligand substitution reactions were investigated. This study sheds light on the role of increasing π-backbonding through electron-withdrawing effect relative to increasing *trans* σ-effect. The substitution reactions were monitored using sulfur containing nucleophiles of different steric effects, *viz*. thiourea (TU), *N,N*-dimethylthiourea (DMTU), and *N,N,N′,N′*-tetramethylthiourea (TMTU). Literature data for [PtL^1Cl] were included for comparison purposes. The structures of the investigated complexes are shown in scheme 1.

Experimental

All reactions involving the synthesis of ligands and coordination of ligands to platinum(II) were carried out under nitrogen using standard Schlenk techniques. Organic solvents (toluene, methanol, hexane, dichloromethane, diethyl ether, acetic acid, and ethanol) used in the synthesis were purchased from Merck. Toluene, methanol, hexane, and ethanol were purified by standard distillation methods prior to use [21]. K_2PtCl_4 was obtained from Strem. 1,3-Dibromobenzene, 1,3-dibromo-5-fluorobenzene, 1,3-dibromo-4-fluorobenzene, 3,5-dibromo-toluene, tri-n-butylstannylpyridine, bis(triphenylphosphine)-palladium dichloride, lithium chloride, potassium fluoride, sodium bicarbonate, and sodium sulfate were obtained from Aldrich and used as received. The thiourea nucleophiles TU, DMTU, and TMTU were also obtained from Aldrich and used as supplied.

Synthesis of ligands

The ligands 3,5-di(2-pyridinyl)-fluorobenzene, 2,4-di(2-pyridinyl)-fluorobenzene, and 3,5-di (2-pyridinyl)-toluene were synthesized according to published methods [22], with minor modifications.



Scheme 1. Structures of the investigated platinum(II) complexes. [PtL^1Cl] was taken from the literature.

3,5-Di(2-pyridinyl)-fluorobenzene, L^2

To a mixture of 1,3-dibromo-5-fluorobenzene (1.39 g, 5.51 mM), 2-tri-n-butylstannylpyridine (5.00 g, 13.6 mM), bis(triphenylphosphine)palladium dichloride (1.00 g, 1.43 mM), and lithium chloride (0.37 g, 8.84 mM) in an oven dried Schlenk tube, distilled toluene (40 mL) was added. The mixture was degassed via the freeze-pump-thaw method until no gas bubbles were observed and refluxed at 110 °C under nitrogen for 48 h. After cooling the reaction mixture to room temperature, an aqueous solution of potassium fluoride (40 mL) was added and the insoluble black residue was filtered and washed with toluene. The toluene was removed under reduced pressure. Dichloromethane (100 mL) and aqueous sodium bicarbonate (100 mL) were added to the remaining residue. The organic phase was separated, washed with sodium bicarbonate (2 × 100 mL), then dried over anhydrous sodium sulfate and evaporated to obtain a yellow residue. This residue was then purified over silica with a mixture of 90% hexane: 10% diethyl ether, whose mole fraction was measured to 50% hexane: 50% diethyl ether to obtain a pale yellow solid (0.8078 g, 58%). Anal. Calcd for $C_{16}H_{11}N_2F$: C, 76.83; H, 4.43; N, 11.25. Found: C, 76.84; H, 4.82; N, 10.86. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 8.73 (ddd, 2H), 8.44 (t, 1H), 7.79–7.89 (m, 6H), 7.29 (ddd, 2H), TOF MS-ES$^+$, *m/z*: 251.0989.

2,4-Di(2-pyridinyl)-fluorobenzene, L^3

This ligand was prepared by a procedure similar to the one described above for synthesis of 3,5-di(2-pyridinyl)-fluorobenzene, starting from 2,4-dibromo-1-fluorobenzene (1.39 g, 5.5 mM) instead of 1,3-dibromo-5-fluorobenzene, together with 2-tri-n-butylstannylpyridine (5.00 g, 14 mM), bis(triphenylphosphine)palladium dichloride (1.00 g, 1.43 mM), and lithium chloride (0.38 g, 8.8 mM) in 40 mL toluene. After refluxing the reaction mixture for 48 h under nitrogen, the mixture was worked up as before and an oily yellow liquid which later solidified was obtained (0.8647 g, 62%). Anal. Calcd for $C_{16}H_{11}N_2F$: C, 76.83; H, 4.43; N, 11.25. Found: C, 76.33; H, 4.22; N, 11.01. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 8.75 (dd, 1H), 8.68 (dd, 1H), 8.58 (dd, 1H), 8.09 (ddd, 1H), 7.20 – 7.82 (m, 4H), 7.18 – 7.29 (m, 3H), TOF MS-ES$^+$, *m/z*: 273.0803 (M + Na^+).

3,5-Di(2-pyridinyl)-toluene, L^4

This ligand was also prepared by a procedure similar to the one described above for synthesis of 3,5-di(2-pyridinyl)-fluorobenzene, starting from 3,5-dibromo-toluene (1.38 g, 5.5 mM) instead of 1,3-dibromo-5-fluorobenzene, together with 2-tri-n-butylstannylpyridine (5.38 g, 15 mM), *bis*(triphenylphosphine)palladium dichloride (312 mg, 0.444 mM) and lithium chloride (2.38 g, 55 mM) in 30 mL toluene. After refluxing the reaction mixture for 48 h under nitrogen, the mixture was worked up as before and an oily yellow liquid which later solidified was obtained (0.7041 g, 51%). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.89; H, 5.73; N, 11.38. Found: C, 82.78; H, 5.61; N, 11.82. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 8.74 (ddd, 2H), 8.41 (t, 1H), 7.96 (dd, 2H), 7.86 (dd, 2H), 7.78 (ddd, 2H), 7.24 (ddd, 2H), 2.53 (s, 3H), TOF MS-ES$^+$, *m/z*: 243.3045.

Synthesis of complexes

[PtL^2Cl], [PtL^3Cl], and [PtL^4Cl] were prepared by reacting the corresponding ligand with K_2PtCl_4 in acetic acid at reflux under nitrogen, as reported for [PtL^1Cl] [23]. The purity of the complexes was analyzed using CHN analysis, ^{1}H NMR spectroscopy, and mass spectra.

[**PtL^2Cl**]: Yield: (80.6 mg, 49.4%). Anal. Calcd for $C_{16}H_{10}N_2PtF$: C, 39.97; H, 2.31; N, 5.83. Found: C, 39.72; H, 1.83; N, 5.58. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 9.39 (d, 2H), 7.99 (t, 2H), 7.67 (d, 2H), 7.35 (t, 2H), 7.23 (s, 2H). TOF MS-ES$^+$, *m/z*: 444.0482.

[**PtL^3Cl**]: Yield: (84.9 mg, 51.4%). Anal. Calcd for $C_{16}H_{10}N_2PtF$: C, 39.97; H, 2.31; N, 5.83. Found: C, 39.57; H, 1.96; N, 5.42. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 9.34 (dd, 1H), 9.24 (dd, 1H), 7.92 (m, 3H), 7.58 (d, 1H), 7.40 (ddd, 1H), 7.29 (m, 1H), 7.22 (m, 1H), 6.84 (m, 1H). TOF MS-ES$^+$, *m/z*: 444.0476.

[**PtL^4Cl**]: Yield: (106.8 mg, 53.0%). Anal. Calcd for $C_{17}H_{13}N_2Pt$: C, 42.91; H, 2.75; N, 5.89. Found: C, 42.88; H, 2.72; N, 5.83. ^{1}H NMR (400 MHz, DMSO-d_6) δ, 9.09 (d, 2H), 8.18 (t, 2H), 8.07 (d, 2H), 7.58 (s, 2H), 7.57 (t, 2H), 2.32 (s, 3H). TOF MS-ES$^+$, *m/z*: 444.0476. TOF MS-ES$^+$, *m/z*: 440.2834.

Physical measurements and instrumentation

NMR spectra for the ligands and the complexes were recorded on a Bruker Avance DPX 400 using a 5 mm BBOZ probe at 30 °C, with chemical shifts referenced to the relevant solvent signal. Low resolution electron-spray ionization (ESI$^+$) mass spectra of the samples were recorded on a TOF Micromass LCT Premier spectrometer operated in positive ion mode. Spectra for wavelength selection for the kinetic investigations were recorded on a Cary 100 Bio UV–visible spectrophotometer with a cell compartment thermostated by a Varian Peltier temperature controller having an accuracy of ±0.05 °C. All kinetic measurements were performed under *pseudo*-first-order conditions and were carried out on an Applied Photophysics SX 20 stopped-flow analyzer coupled to an online data acquisition system. The temperature was maintained within a range of ±0.1 °C using a coupled temperature control system. All kinetic data were analyzed using the Origin 7.5® graphical analysis software package [24].

Preparation of complex and nucleophile solutions for kinetic analysis

Stock solutions of platinum(II) complexes and the nucleophiles used in the kinetic analysis were prepared by dissolving known amount in methanol solution with an ionic strength of 0.1 M. The 0.1 M ionic strength solution of the methanol was made up by dissolving the required amount of $LiCF_3SO_3$ (0.09 M) and LiCl (0.01 M) in methanol, as $CF_3SO_3^-$ does not coordinate to Pt(II) [25]. Lithium chloride was added to suppress spontaneous solvolysis reactions.

The complex concentrations were maintained at 0.05 mM and the solutions of the nucleophiles *viz.* TU, DMTU, and TMTU were prepared fresh by dissolving a known amount of the required nucleophile in methanol solution (0.1 M ionic strength) to afford a final

concentration 50 times higher than that of the metal complex. Subsequent dilutions of the stock nucleophile solution afforded solutions of 10, 20, 30, and 40 times the concentration of the metal complex to assure *pseudo*-first order conditions.

Computational modeling

In an effort to understand the electronic differences of the complexes studied, calculations were performed. Ground-state electronic structures of [PtL^1Cl], [PtL^2Cl], [PtL^3Cl], and [PtL^4Cl] were optimized in the gas phase by density functional theoretical (DFT) calculations to identify the energy-minimized structures based on B3LYP/LANL2Z [26] (Los Alamos National Laboratory 2 double ζ) level theory, with inner core electrons of platinum replaced by relativistic effective core potential. In addition, composite basis sets

Table 1. DFT calculated structures showing HOMO and LUMO frontier molecular orbitals for the studied Pt(II) complexes.

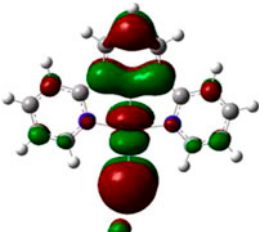
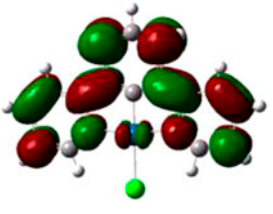
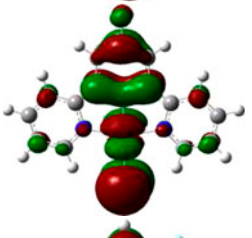
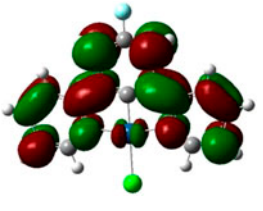
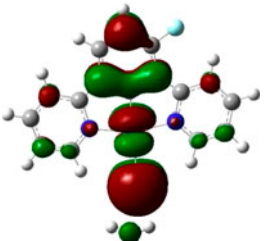
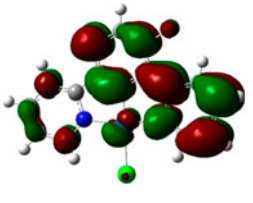
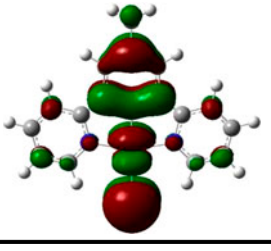
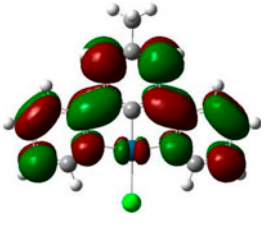
Complex structure	HOMO	LUMO
PtL^1Cl		
PtL^2Cl		
PtL^3Cl		
PtL^4Cl		

Table 2. Computational analysis of Pt(II) complexes showing bond lengths, bond angles, and electronic data obtained from DFT calculations.

Parameter	[PtL^{1}Cl]	[PtL^{2}Cl]	[PtL^{3}Cl]	[PtL^{4}Cl]
Bond lengths (Å)				
Pt–Cl	2.505	2.500	2.498	2.506
Bond angles (°)				
C–Pt–Cl	179.99	180.00	179.96	179.98
N_1–Pt–N_2	161.51	161.46	161.69	161.29
NBO charges				
Pt	0.426	0.429	0.430	0.425
Cl	−0.560	−0.554	−0.552	−0.561
C	−0.101	−0.114	−0.090	−0.106
HOMO (eV)	−5.57	−5.73	−5.76	−5.48
LUMO (eV)	−2.17	−2.45	−2.32	−2.14
ΔE (eV)	3.40	3.28	3.44	3.35
ω	4.410	5.096	4.742	4.335

Note: ω = Electrophilicity index.

[27] 6-31G*(C and H), 6-311+G (N, S, Cl), and LANL2DZ (Pt) were applied to [PtL^{1}Cl] to confirm minimized structure (zero imaginary frequency) and (one imaginary frequency) transition state [28]. The synchronous transit-guided quasi-Newton method [29], in this article for instance, QST2 was employed to locate the transition state. Singlet states were used due to the low electronic spin of Pt(II) complexes. The Gaussian 09 set of programs was used for all computational analysis [30]. Table 1 shows a summary of DFT calculated HOMOs and LUMOs, and table 2 is a representation of the data calculated for the complexes.

Results

Substitution of the coordinated chloride from the three Pt(II) complexes by thiourea nucleophiles of different nucleophilicities and steric hindrance were investigated under *pseudo*-first-order kinetics. The kinetic reactions of coordinated chloride were followed spectrophotometrically by following the change in absorbance at suitable wavelengths as a function of time using the stopped-flow technique and UV–visible spectrophotometry. The selected wavelengths are indicated in table SI 1 (see online supplemental material at http://dx.doi.org/10.1080/00958972.2014.1001752). The kinetic traces gave excellent fits to a single exponential decay function to generate the observed *pseudo*-first-order rate constant, k_{obs}. Figure 1 shows a typical kinetic trace obtained using the stopped-flow technique for the reaction between [PtL^{3}Cl] and TU nucleophile at an ionic strength of 0.1 M ($CF_3SO_3^-$) from which the k_{obs} was calculated.

The k_{obs} were calculated from the kinetic traces using the online non-linear least-squares fit of exponential data [31] to equation (1) using Origin 7.5 graphical analysis software [24],

$$A_t = A_o + (A_o - A_\infty)\exp(-k_{obs}t) \quad (1)$$

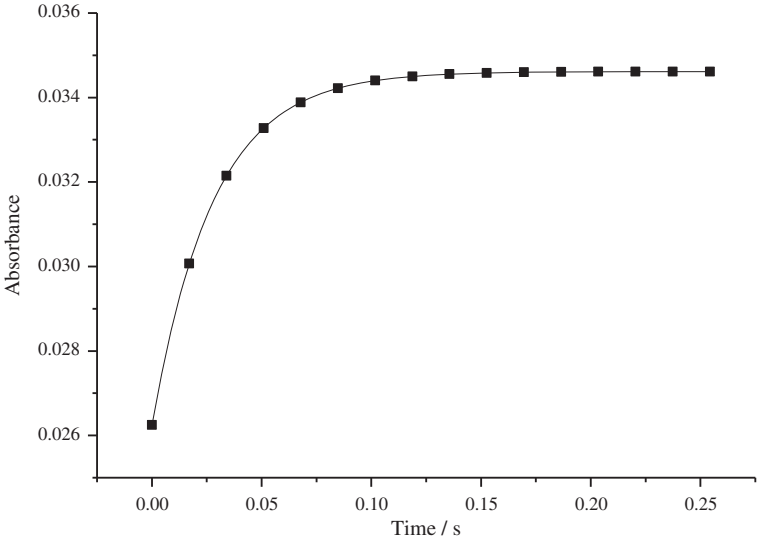


Figure 1. Kinetic trace obtained from the stopped-flow spectrophotometer showing a single exponential fit for the reaction between [PtL^{3}Cl] (0.049 mM) with TU (0.98 mM) in methanol monitored at 282 nm, I = 0.1 M at 298 K.

where A_o, A_t, and A_∞ represent the absorbance of the reaction mixture initially, at time t and at the end of the reaction, respectively. The obtained k_{obs} were plotted against the concentration of the entering nucleophile. A linear dependence on the nucleophile concentration was observed for all reactions with a non-zero intercept. This indicates that the addition of 10 mM LiCl was not sufficient to completely prevent the solvolysis pathway.

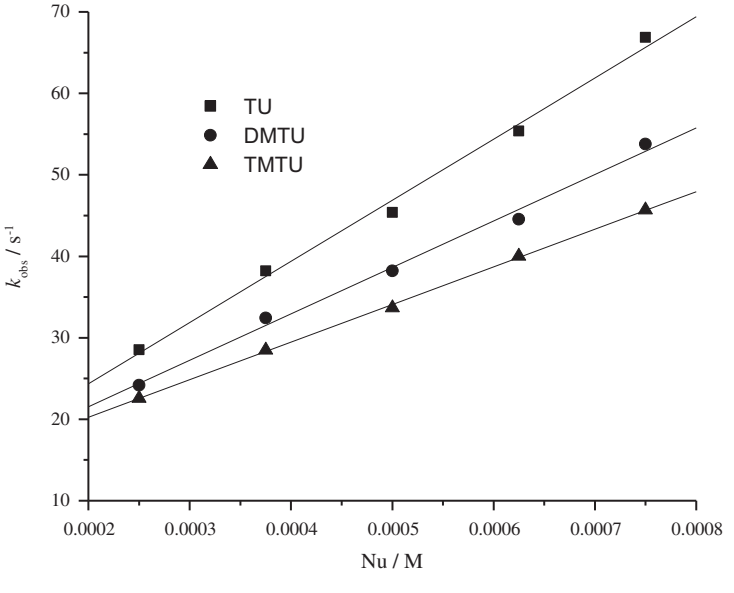


Figure 2. Dependence of k_{obs} on the entering nucleophile concentration for the displacement of chloride on [PtL^{2}Cl] in methanol, I = 0.1 M ($LiSO_3CF_3$), T = 298 K.

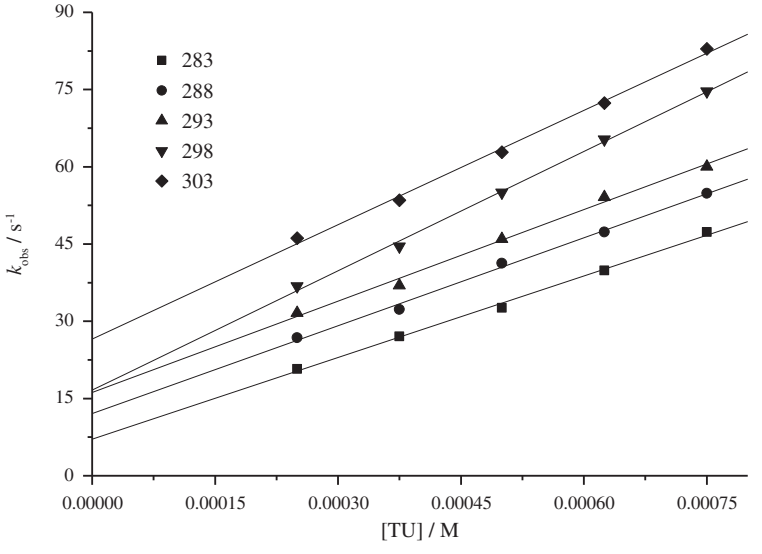
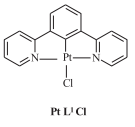
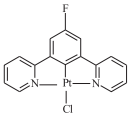
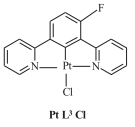
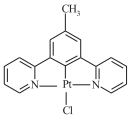


Figure 3. Dependence of k_{obs} on the entering TU concentration for the displacement of chloride on [PtL^3Cl] in methanol (I = 0.1 M) at various temperatures from 283 to 303 K.

Table 3. Summary of reaction rates at 25 °C and activation parameters for the substitution reactions of platinum (II) complexes with nucleophiles (Nu) in methanol (ionic strength of 0.09 M $LiSO_3CF_3$ and 0.01 M LiCl).

Complex	Nu	k_2 ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ M^{-1})	$\Delta S^{\#}$ (JK^{-1} M^{-1})	k_{-2} (s^{-1})
 Pt L^1 Cl	TU[a]	44,500 ± 2000	21 ± 1	−85 ± 5	*
	DMTU[a]	18,400 ± 500	16 ± 1	−109 ± 4	*
	TMTU[a]	7400 ± 300	10 ± 1	−135 ± 3	*
 Pt L^2 Cl	TU	89,203 ± 1540	20 ± 1	−145 ± 5	11.0 ± 0.4
	DMTU	57,050 ± 2661	10 ± 1	−150 ± 3	10 ± 1
	TMTU	46,176 ± 699	14 ± 1	−109 ± 3	9 ± 2
 Pt L^3 Cl	TU	73,985 ± 2623	12 ± 1	−111 ± 3	17 ± 1
	DMTU	53,140 ± 1541	12 ± 1	−172 ± 3	16.4 ± 0.3
	TMTU	26,552 ± 966	16 ± 1	−113 ± 4	15.9 ± 0.8
 Pt L^4 Cl	TU	51,858 ± 1210	14 ± 1	−109 ± 5	6.9 ± 0.1
	DMTU	26,860 ± 1024	5.6 ± 0.4	−142 ± 1	6.9 ± 0.5
	TMTU	23,158 ± 1099	15 ± 1	−93 ± 4	3.8 ± 0.6

[a]Values extracted from reference [20].
*Reported solvolytic path, with no calculated parameters.

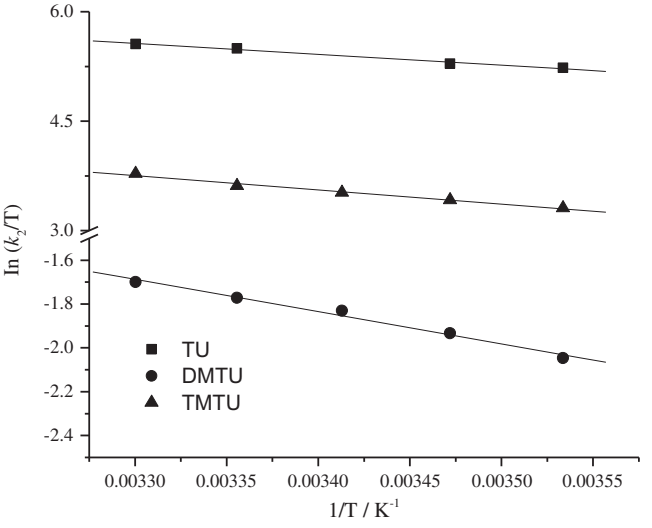
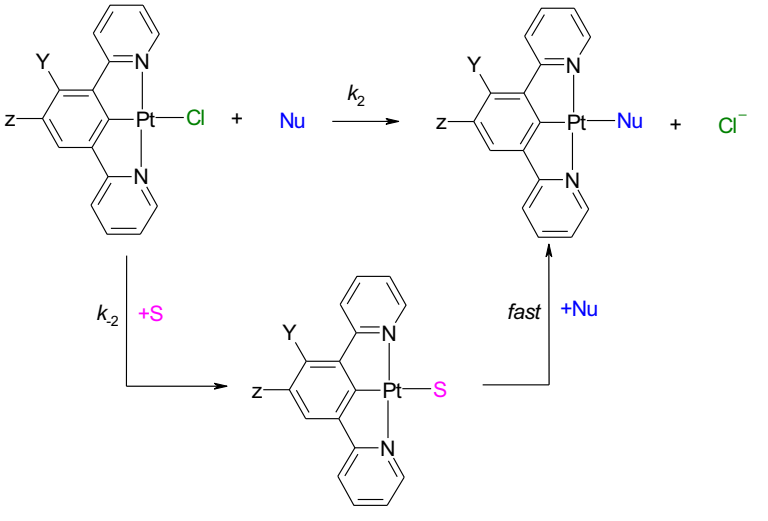


Figure 4. Plot of In $\left(\frac{k_2}{T}\right)$ against $\frac{1}{T}$ for reaction of [PtL^{3}Cl] with TU, DMTU, and TMTU at various temperatures from 283 to 303 K.

The parallel solvolysis reaction pathway is well known in Pt(II) chemistry [32]. Typical plots for the concentration dependence of the observed first-order rate constants are shown in figures 2 and 3, and the rate law can be expressed by equation (2). The second-order rate constant k_2 for the reaction of each metal complex with a particular nucleophile was obtained from the slope of linear regression of plot of k_{obs}*versus* nucleophile concentration using the software Origin 7.5 package® [24] and are summarized in table 3.



Y = H, Z = H [**PtL^{1}Cl**] Y = H, Z = F [**PtL^{2}Cl**]
Y = F, Z = H [**PtL^{3}Cl**] Y = H, Z = CH_3 [**PtL^{4}Cl**]
Nu = **TU**, **DMTU** and **TMTU**, S = Solvent

Scheme 2. Proposed mechanism of substitution from the investigated complexes by a series of thiourea nucleophiles.

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

The temperature dependence of the second-order rate constants was investigated over a temperature range of 10–30 °C at an interval of 5 °C. Typical Eyring plots obtained for [PtL^{3}Cl] for the three nucleophiles are shown in figure 4. Using the Eyring equation [31], the enthalpy of activation ($\Delta H^{\#}$) and entropy of activation ($\Delta S^{\#}$) were determined from the slope and the *y*-intercept, respectively. These activation parameters are summarized in table 3.

Experimental data in table 3 shows that the mechanism of substitution can be represented by scheme 2. One pathway involves the direct attack by the nucleophile (k_2) while the other involves formation of a solvent-complex (k_{-2}) followed by rapid substitution of the coordinated solvent. The second step is independent of concentration of the nucleophile.

Discussion

Three platinum(II) complexes, [PtL^{2}Cl], [PtL^{3}Cl], and [PtL^{4}Cl], were synthesized using literature methods and characterized. The three complexes have a common coordinated phenyl ring *trans* to the leaving group but differ by substituting electron-withdrawing or electron-donating groups on the ligand framework. We describe the substitution behavior of these Pt(II) complexes with thiourea-based nucleophiles. [PtL^{1}Cl] was included for comparison, and thus was taken from the literature [20].

The introduction of either electron-withdrawing or donating group has little or no significant effect on the Pt–Cl bond length or NBO charge on the platinum based on the computational data summarized in table 2. However, the substituents impact the overall electrophilicity of the whole complex showing an increase in case of electron-withdrawing atoms and a decrease for electron-donating atom when [PtL^{1}Cl] is used as reference. This shows that the ability of the complexes with electron-withdrawing substituents to accept electrons is enhanced through stabilization of HOMO–LUMO energy. This results in enhanced reactivity as seen in table 3.

The general reactivity trend for chloride substitution by the thiourea nucleophiles follows the order [PtL^{2}Cl] > [PtL^{3}Cl] > [PtL^{4}Cl] > [PtL^{1}Cl] for all nucleophiles. The trend in reactivity can be explained by electronic effects. There is no specific trend for the solvolysis path, k_{-2}, and these values are small, contributing very little to the observed rate.

In previous studies, results have been reported for substitution reactions of Pt(II) complexes containing metal–carbon bonds, with a single Pt–C bond located *trans* to the leaving group. These studies generally reported high substitution reactivity due to the σ-bound carbon ligands, that have a large kinetic *trans* effect and back-bonding in the case of the in plane aryl ligand [33].

Using [PtL^{1}Cl] as the basis for comparison, it can be seen from table 3 that the reactivity increases when an electron-withdrawing as well as electron-donating group is attached to the phenyl *trans* to the leaving group. Using the rate constants for TU to compare the reactivity of the complexes, [PtL^{2}Cl] and [PtL^{3}Cl] react about two times faster than [PtL^{1}Cl]. The fluoro group in both [PtL^{2}Cl] and [PtL^{3}Cl] withdraws electrons from the phenyl ligand *trans* to the leaving group which causes the ligand moiety to lose electron density to fluorine, increasing the electrophilicity of the system as supported by DFT calculations. The

withdrawal of electron density destabilizes the ground state but stabilizes the transition state due to increase in π-backbonding in [PtL^{2}Cl] and [PtL^{3}Cl] when compared to the unsubstituted [PtL^{1}Cl] complex. This leads to an increase in the reactivity of these complexes. The overlap of electron density affects reactivity when comparing [PtL^{2}Cl] and [PtL^{3}Cl]. For [PtL^{2}Cl] there is uniform distribution of LUMO with the *trans* carbon having a more negative NBO charge (−0.114) in comparison to that of [PtL^{3}Cl] whose LUMO is concentrated on the side of the cyclometallated ligand to which fluorine is attached. This results in the *trans* atom having a less negative NBO charge (−0.090). The orbital overlap influences the overall electrophilicity of the complex with [PtL^{2}Cl] (5.096) showing a better ability of accepting electrons in the transition state through π-backbonding in comparison to [PtL^{3}Cl] (4.742). This difference accounts for the observed reactivity between [PtL^{2}Cl] and [PtL^{3}Cl].

The phenyl group can withdraw or donate electrons through resonance [34]. When it acts as an electron withdrawer, one would have expected the σ-*trans* effect to decrease due to the introduction of an electron-drawing atom such as fluoro, with a net decrease in reactivity. In contrast, the reactivity increases and the DFT calculations show no significant change in Pt–NBO charges or the Pt–Cl bond lengths. The DFT calculations reveal the change in the electrophilicity of the whole complex, upon introduction of electron-withdrawing fluoro group on the phenyl ring. This observation can be understood by looking at the delocalization of the phenyl's π-electrons around the ring. This facilitates distribution of electron density from the attached group around the complex making the complex more electrophilic. The electron-withdrawing fluoro group increases the electron-withdrawing capabilities of the phenyl ring through π-backbonding, which enhances the formation of a new bond by stabilizing the 18-electron, five-coordinate transition state (figure SI 13, Supplementary Material). Previous studies involving π-backbonding [19, 21, 35] of a coordinated terpyridine ligand reported similar results for electron-withdrawing group attached to the ancillary position of terpyridine [20, 36].

In the case of the electron-donating methyl in [PtL^{4}Cl] the ability of the phenyl ligand to accept electrons from the metal center is reduced as compared to electron-withdrawing groups in [PtL^{2}Cl] and [PtL^{3}Cl]. Earlier work carried out using terpyridine demonstrated that electron-donating groups attached in the ancillary positions of the ligand backbone decrease the substitution reaction [33, 34, 37], due to the decrease in electrophilicity of the complex. This reduces the π-backbonding effect, destabilizing the five-coordinate transition state resulting in a slower reaction rate [38]. This was also observed by Schmülling *et al.* [15]. In the present study, the introduction of an electron-donating group did not slow the rate of reaction when compared to the parent complex [PtL^{1}Cl], in fact the introduction of a methyl group on the phenyl ring in [PtL^{4}Cl] resulted in an increase in the reaction rate by a small margin with all the nucleophiles when compared to [PtL^{1}Cl]. This result can be explained to be due to a marginal increase in *trans* σ-effect. It is clear from looking at the current results and what has been reported in literature that both π-backbonding and *trans* σ-effect play roles in influencing the rate of reaction. In the current study, the slight acceleration of the substitution process for electron-donating group is linked to the ground state destabilization due to strong σ-electron donation along the C–Pt–Cl axis.

The results in table 3 shows that reactivity of complexes with electron-withdrawing substituents is much higher than that of complexes with electron-donating groups; [PtL^{2}Cl] and [PtL^{3}Cl] react at a faster rate than [PtL^{4}Cl]. This is because, for electron-withdrawing substituents, there is an increase in π-backbonding which together with a strong σ-*trans* effect enhances the substitution reaction, while for electron-donating the π-backbonding is weak. The results also show that the position of the substituent on the coordinated phenyl in the

case of fluoro has no significant difference, as the rate constants are practically the same within the experimental error.

The kinetic results shown in table 3 clearly indicate that substitution of chloride by the nucleophiles TU, DMTU, and TMTU depends on the steric hindrance of the nucleophiles. The reactivity decreases according to the increase in steric hindrance of the nucleophiles for all the complexes, i.e. the most sterically hindered TMTU reacts significantly slower than the other nucleophiles. Thus, the rate of substitution for the nucleophiles is as follows: TU > DMTU > TMTU.

The values of the activation enthalpies are small and positive ($\Delta H^{\#}$) while the activation entropies ($\Delta S^{\#}$) are large and negative (table 3). The sensitivity of the second-order rate constants to different nucleophiles and the significantly negative intrinsic entropies of activation ($\Delta S^{\#}$) values are in line with the associative substitution mechanism and a net increase in the bond order in the transition state which is common for d^8 square-planar metal complexes [10, 39, 40].

Conclusion

The results in this study have shown that the lability of coordinated chloride depends on the electronic properties of the Pt(II) complexes, and the general reactivity trend for the complexes is $[PtL^2Cl] > [PtL^3Cl] > [PtL^4Cl] > [PtL^1Cl]$. Changing the nature (electron-withdrawing or electron-donating group) of the substituents on the phenyl ligand *trans* to the leaving group in Pt(II) complexes affects the π-backbonding and the *σ-trans* effect of the complex system and, thus, the reactivity of the complexes is influenced. Complexes with fluoro substituents, $[PtL^2Cl]$ and $[PtL^3Cl]$, have higher reaction rates due to the enhanced π-backbonding as compared to the parent complex, $[PtL^1Cl]$. In $[PtL^4Cl]$, the π-backbonding is weakened by the presence of an electron-donating group, but the *σ-trans* effect is enhanced resulting in an increase in the reactivity. The results show that irrespective of the nature of the substituent on phenyl, the reactivity increases. It can therefore be concluded that attaching a substituent (electron-donating or -withdrawing) *trans* to the leaving group in a strong *σ-trans* system such as N^C^N results in an increase in the substitution reaction. The reactivity of the nucleophiles is dependent on their steric effects. The mode of activation remains associative for all the studied complexes.

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