Research Paper

Kinetics and mechanism of the ligand substitution reaction of di-μ-hydroxobis(bipyridyl)dipalladium(II) ion with N,N'-diethylthiourea in aqueous solution

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Abstract- *The interaction of the title complex with N,N'-diethylthiourea (DETU) has been studied spectrophotometrically in aqueous medium as a function of [substrate complex], [ligand], and temperature at a particular pH (7.4), where the substrate complex exists predominantly as the dimeric dihydroxobridged species at constant ionic strength. The reaction has been monitored at 300 nm, the λ_{max} of the substituted complex, where the spectral difference between the reactant and the product is maximum. The reactions have been studied under pseudo-first order conditions. The reaction proceeds in a two-step-consecutive manner (A → B → C) where the first step is the ligand dependent and second step is the ligand independent and is assigned to formation of chelate ring. The reaction rate increases with increase in [ligand] before reaching a limiting value which is probably due to the completion of the outer-sphere association complex formation. At this stage the interchange of the ligands from the outer-sphere to the inner- sphere occurs. The activation parameters calculated from Eyring plots are: $\Delta H_1^{\neq} = 44.0 \pm 1.5$ kJ mol^{-1}, $\Delta S_1^{\neq} = -147 \pm 5$ JK^{-1}mol^{-1}, $\Delta H_2^{\neq} = 17.8 \pm 0.8$ kJ mol^{-1}, $\Delta S_2^{\neq} = -278 \pm 2$ JK^{-1} mol^{-1}. Based on the kinetic and activation parameters an associative interchange mechanism is proposed for the interaction processes. The product of the reaction has been characterized, as conductance measurement and IR spectroscopic analysis. Comparison of the kinetic and thermodynamic parameters of the interaction of N, N'-diethylthiourea and thiourea with the reactant complex, it is clear that steric effect plays an important role in determining the reactivity of the incoming nucleophile for an associative mode of activation.*

Introduction

Much work has been performed on the equilibrium studies of palladium(II) complexes with aliphatic amines[1- 4] and it is of interest to extend our work to the reactions of palladium(II) complexes with heterocycles, such as 2,2′-bipyridine. Aromatic heterocycles generally act as σ–donors and also function as fairly effective π-acceptors. In addition, heterocycles can be involved in π–π stacking with purine and pyrimidine bases. This can lead to complex formation with DNA subunits, which is an important target in cancer chemotherapy [5]. During the last decade it has become clear that platinum amine coordination compounds are very interesting from a biological point of view[6, 7]. It is generally accepted that the antitumour activity of various platinum containing drugs is related to the platination of DNA, most commonly via binding to guanine [8, 9]. Sulphur atom binds easily to platinum(II) and this binding might be important for biological systems[10 -13]. The kinetic lability of the platinum-sulphur bond is, however, much higher than that of platinum-nitrogen bonds, thus Pt-S bonded intermediates can play a significant role both in the transport and the toxicity of various platinum containing drugs [14]. As the kinetic and thermodynamic behaviors of Pt(II) and Pd(II) are very similar, it is expected that the μ-hydroxo-bridged dinuclear palladium(II) ion will behave similarly to the platinum(II) analogue.

Thiourea derivatives are potentially very versatile ligands, able to coordinate to a range of metal centres as neutral ligands, monoanions or dianions. The oxygen, nitrogen and sulphur donor atoms of thiourea derivatives provide a multitude of bonding possibilities. Both the free thioureas, and their metal complexes display a wide range of biological activity, including antibacterial, antifungal, antitubercular, antithyroid, antihelmintic, rodenticidal, insectidal, herbicidal, and plant-growth regulator properties [15 - 19].

In view of the above, we now describe the interaction of a palladium(II) complex towards N,N'-diethylthiourea at physiological pH which may throw some light on the bioinorganic chemistry of palladium(II).

Material and Methods

[Pd(bipy)Cl$_2$] (bipy =2,2′-bipyridine) was prepared by literature methods[20, 21]. The diaqua complex, [Pd(bipy)(H$_2$O)$_2$](ClO$_4$)$_2$ was prepared in solution by the method of Hay and Basak [22] by stirring the chlorocomplex with two mole equivalents of AgClO$_4$ followed by keeping overnight (with careful protection from light). The precipitated AgCl was removed by filtration and the filtrate made up to the requisite volume in a standard flask. The reactant complex, di-μ-hydroxobis(bipyridyl)dipalladium(II) ion (complex **1**), was obtained *in situ* by adjusting the pH to 7.4 with NaOH/HClO$_4$. The reaction product of DETU and complex **1** was prepared by mixing the reactants in different ratios, namely, 1:1, 1:2, 1:3, 1:5, and 1:10, and keeping at 60 °C for 24 h. The absorbance spectra of these mixtures (Fig. 1) all exhibited the same λ$_{max}$ with nearly identical intensities.

Product analysis

The composition of the product was determined by Job's method of continuous variation, which indicated a 2: 1 metal ligand ratio (Figure 2).

The IR spectra of free ligand display a sharp band at *ca* 3661 cm^{-1}, assignable to stretching frequency of –NH group. This remains at almost the same positions in the metal complex, suggesting that the nitrogen atom of the ligand is not involved in coordination. The band at 1020 cm^{-1} due to the C=S stretch are shifted towards lower frequencies in the complex, indicating coordination of sulphur to the metal. A sharp peak at *ca*. 472 cm^{-1} in the spectrum of the complex is assigned to the Pd(II)-S-Pd(II) stretch [23]. Broad and strong bands at *ca*. 1089 and 627 cm^{-1} are assigned to the of perchlorate salt of the complex.

Measurements

The pH of the solution was adjusted by adding NaOH/HClO$_4$ and the pH measurements were made with a Sartorius digital pH meter (model PB11 with an accuracy of ± 0.01 units). Doubly distilled water was used to prepare all the solutions. All other chemicals used were of AR grade. The reactions were carried out at constant ionic strength (0.1 mol dm^{-3} NaClO$_4$).

Spectroscopic measurements were made with a Shimadzu UV-VIS Spectrophotometer (UV-2101). IR Spectra (KBr disc, 4000 – 300 cm^{-1}) were measured on a Perkin-Elmer FTIR RX1 spectrophotometer. Conductance measurements were made with a Systronics conductivity meter (model 308) where the cell constant was calibrated with 0.01M KCl solution and water used as solvent. The kinetic studies were done on a Shimadzu UV 2101 PC Spectrophotometer attached to a thermoelectric cell temperature controller (Model Shimadzu TB 85 thermobath, accuracy ± 0.1 °C). The development of a characteristic peak of the product complex (complex **2**) at 300 nm was monitored with time at different fixed temperatures. The conventional mixing technique was followed and pseudo first order conditions were employed throughout
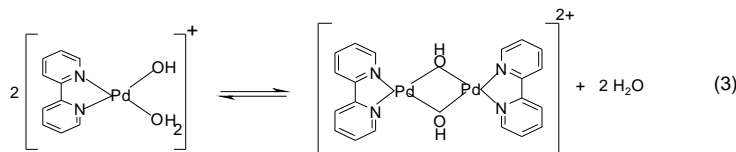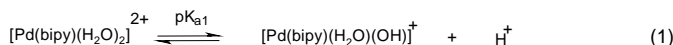
Results and Discussion

The plots of ln(A$_t$ - A$_\infty$), where A$_t$ and A$_\infty$ are absorbances at time t and after the completion of the reaction, against time were found to be non linear, being curved at the initial stage and subsequently of constant slope (Fig. 3).

The method of Weyh and Hamm[24] was adopted to calculate rate constants for two consecutive steps. From the linear second portion k$_2$ values were obtained. The k$_{1(obs)}$ values were obtained from the plot of lnΔ versus t. A typical plot is shown in Fig. 4. Rate data represented as an average of duplicate runs are reproducible within ±4 %.

The pKa values for [Pd(bipy)(H$_2$O)$_2$]$^{2+}$are 4.5 and 9.6 at 25 °C [25] . We can consider the following equilibria to be in operation:

From the above equilibria we can say that the dimerisation shown in eqn. (3) requires the prior formation of the aquo-hydroxy complex (eqn. (2)), which is the intermediate for dimerisation. Mononuclear hydroxo complexes of Pd may be destabilized because of repulsive interactions between filled d-orbitals from the metal and the two free electron pairs of hydroxide oxygen. These repulsions are reduced in the bridged complexes where the hydroxide takes part in bonding to two metal ions and there is only one free electrons pair left so the hydroxo aqua complex immediately dimerise. At pH 7.4, the first acid dissociation of the Pd-complex is already complete so the protonation state of the Pd-complex will be primarily the hydroxoaqua and this in turn leads to complete formation of the dimer [26 - 29] where as the ligand exists in the neutral form.

$$[Pd(bipy)(H_2O)_2]^{2+} \xrightarrow{pK_{a1}} [Pd(bipy)(H_2O)(OH)]^+ + H^+ \qquad (1)$$

$$[Pd(bipy)(H_2O)(OH)]^+ \xrightarrow{pK_{a2}} [Pd(bipy)(OH)_2] + H^+ \qquad (2)$$

The plot of $\ln(A_t - A_\infty)$ versus time indicates that the reaction is not a single step process. A two-step consecutive process may be assumed, the first step being dependent and the final step independent of the concentration of DETU.

The rate constant for such a process can be evaluated by assuming the Scheme1.

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$
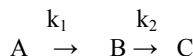
Scheme 1: Representation of reaction scheme.
Where A is the hydroxo-bridged dimer, B is as intermediate with DETU and C is the final product complex $[Pd_2(bipy)_2(OH)(DETU)]$.

Calculation of k_1 for A → B step
        The rate constant $k_{1(obs)}$ for the A→ B step can be evaluated by the method of Weyh and Hamm using the usual consecutive rate law:

$(A_\infty - A_t) - a_2 \exp(-k_2 t) = a_1 \exp(-k_{1(obs)}t)$ (4)

Where a_1 and a_2 are constants dependent upon the rate constants and extinction coefficient.

        Values of $[(A_\infty - A_t) - a_2 \exp(-k_2 t)]$ ware obtained from X -Y at different times (Fig. 3). Then,

$\ln \Delta = \text{constant} - k_{1(obs)} t.$ (5)

        The value of $k_{1(obs)}$ was derived from the slope of a plot of $\ln \Delta$ versus t (where t is small) (Fig. 4). A similar procedure was applied for each DETU concentration in the 2.85×10^{-3} to 8.55×10^{-3} mol dm^{-3} range, at constant [(**1**)] $(2.85 \times 10^{-4}$ mol dm$^{-3})$ and pH = 7.4, $\mu = 0.1$ mol dm^{-3} NaClO$_4$ and at different temperatures namely 45, 50, 55 and 60 ^{o}C . The $k_{1(obs)}$ values are collected in Table 1.

        The rate increases with increase in [DETU] before reaching a limiting value (Fig. 5), which is probably due to the completion of the outer-sphere association complex formation. At this stage the interchange of the ligands from the outer-sphere to the inner- sphere occurs, i.e., N,N'-diethylthiourea attacks one of the Pd(II) atoms of the dihydroxo-bridged dimer to give the intermediate complex.

From the experimental findings scheme 2 may be given for the A → B step

$$A + N, N'\text{-diethylthiourea} \xrightleftharpoons{K_E} A.N,N'\text{-diethylthiourea}$$

(Outer-sphere association complex)

$$A.N,N'\text{-diethylthiourea} \xrightarrow{k_1} B$$
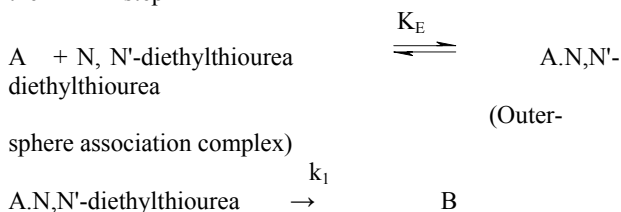
Scheme 2: Formation of intermediate complex

 Based on scheme 2 a rate expression can be derived for the A → B step;

$d[B]/dt = k_1 K_E[B][DETU] / (1 + K_E[DETU])$ (6)

$d[B]/dt = k_{1(obs)}[B]_T$

Where T stands for total concentration of Pd(II). Thus it can be written,

$k_{1(obs)} = k_1 K_E [DETU] / (1 + K_E[DETU])$ (7)

        Where k_1 is the rate constant for the formation of intermediate (B) from dihydroxy-dimer (A), K_E is the outer-sphere association equilibrium constant.
The equation can be written as

$1 / k_{1(obs)} = 1 / k_1 + 1 / k_1 K_E [DETU]$ (8)

A plot of $1/k_{1(obs)}$ versus $1/[DETU]$ should therefore be linear with an intercept of $1/k_1$ and slope $1/k_1 K_E$. This was found to be so at all temperatures studied (Figure 6)

The k_1 and K_E values obtained from the intercept and slope to intercept ratios are given in Table 2.

Calculation of k_2 for the step B → C
        The B → C step is intramolecular ring closure and is independent of ligand concentration. At a particular temperature the slope of $\ln(A_\infty - A_t)$ versus time plots at different DETU concentrations were found to be constant in the region where the plots are linear (Figure 3). For different temperatures the k_2 values were obtained directly from the limiting slopes and are collected in Table 3 and the average $10^5 k_2$ values were 2.23, 2.40, 2.80 and 3.15 s^{-1} at 45, 50, 55 and 60 ^{o}C respectively.

Effects of pH on the reaction rate
        The reaction was studied at five different pH values. At a fixed 2.85×10^{-4} mol dm^{-3} [complex **1**], 5.7×10^{-3} mol dm^{-3} [DETU] and 0.1 mol dm^{-3} NaClO$_4$ ionic strength, the $10^3 k_{1(obs)}$ values were 2.00, 1.91 1.85, 1.92 and 1.95 and $10^5 k_2$ values were 2.24, 2.23, 2.22, 2.24, and 2.23 at pH 5.5, 6.0, 6.5, 7.0 and 7.4 respectively at 45 ^{o}C. The change in rate may be explained based on two acid dissociation equilibria of the ligand and the complex, as follows. Firstly, within our studied pH range the ligand, DETU remain unchanged so the effects of pH on rate are therefore due to the change in reactive forms of the reacting complex. Above pH 5.5, the hydroxo-bridged dimer will be the predominant species. The effect of change in pH will be small, as observed experimentally. On the other hand the k_2 values are dependent only on the nature of the ligand during bridge formation. Hence, the k_2 values are independent of pH. In subsequent kinetic runs, the substitution reactions were followed at a constant pH of 7.4 to avoid complications from an additional parameter of $[H^+]$ to the rate equation.

Effects of temperature on the reaction rate
        Four different temperatures were chosen for study and the results are listed in Table 4. The activation parameters for the steps A → B and B → C were evaluated from the linear Eyring plots and the results are compared with analogous systems in Table 4.

Mechanism and conclusion
        The starting complex does not react well with azide, cytidine or with thymidine, but easily reacts with sulphur-containing molecules such as cysteine, thiosemicarbazide, methionine etc. So we may say that the sulphur atom of the ligand is involved in bonding with Pd(II) due to the soft nature of both the atoms.Our results

indicate that the first step, i.e. the attack by the incoming ligand (N,N'-diethylthiourea) proceeds by an associative interchange (I_a) mechanism. This proposition is supported by the following observations. First, with an increase in ligand concentration, saturation in the rate is observed. This indicates that an outer-sphere association complex is formed. Second, the low enthalpy of activation and large negative value of entropy of activation strongly suggest that the ligand participates in the transition state.

From the IR data, it is clear that –NH group is not participating in bonding. Hence, coordination of incoming ligand occurs through the sulphur This is consistent with the soft nature of both sulphur and palladium(II).

Thus, for N,N'-diethylthiourea to behave as a bridging ligand within a hydroxo bridged complex, the mono atom sulphur bridging seems the most likely possibility[32-33].

In the first step a rapid equilibrium is established, giving an outer-sphere complex between complex **1** and N,N'-diethylthiourea. The second step is the intramolecular ring closure which is independent on the incoming ligand concentration. Hence, the rate constant (k_2) for this step was independent of ligand concentration.The activation parameters for the first and second steps suggest an associative mode of activation for the substitution processes.

It was also found that after completion of the reaction, both the pH and conductance of the resulting solution had increased, which might be due to loss of one of the bridging OH groups, consequently ring closure occurs through sulphur bridging.

Based on the experimental results described above, we propose the reaction mechanism shown in Scheme 3.
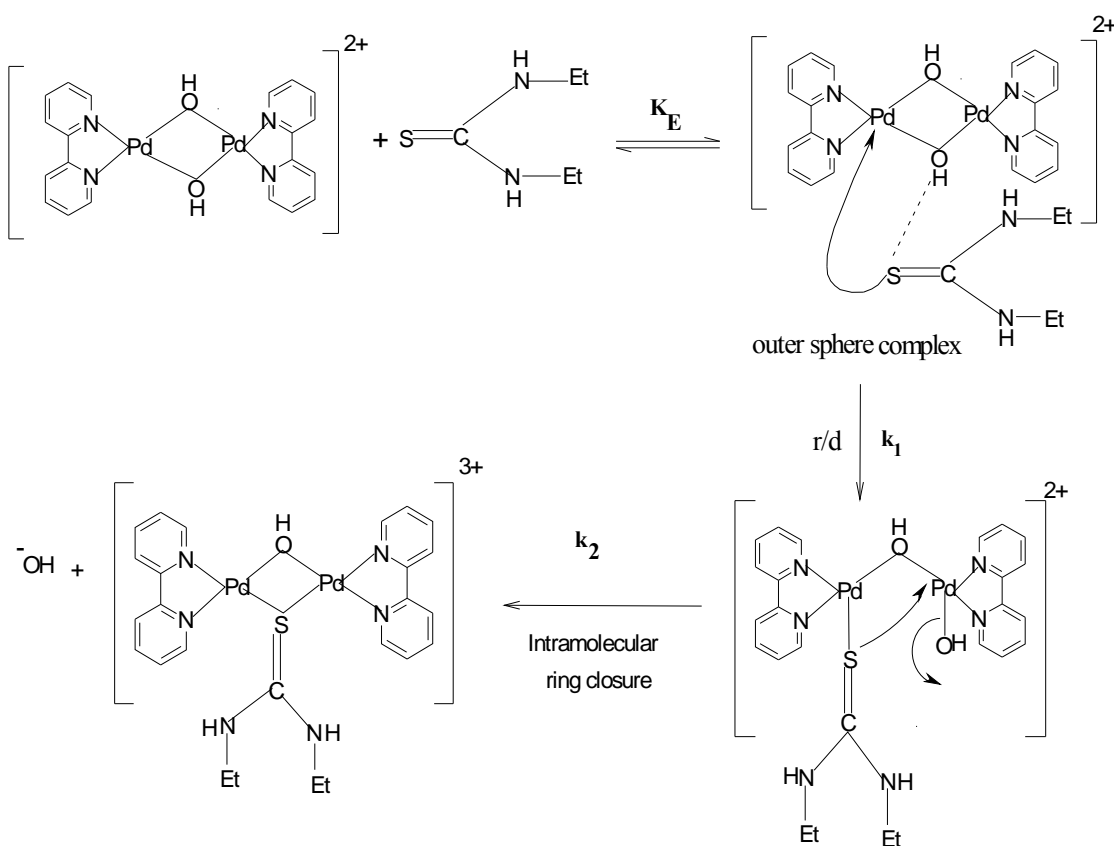
Scheme 3: **Proposed mechanism for the interaction of N,N'-diethylthiourea with complex 1.**

Table 1: 10^3 $k_{1(obs)}$ values for different DETU concentrations at different temperatures. [complex 1] = 2.85 × 10^{-4} mol dm^{-3}, pH = 7.4, ionic strength = 0.1 mol dm^{-3} NaClO$_4$

10^3 [DETU] (mol dm^{-3})	Temperature (^{o}C)			
	45	**50**	**55**	**60**
2.85	1.00	1.16	1.37	1.64
4.27	1.52	1.72	1.92	2.78
5.70	1.95	2.13	2.40	2.85
7.12	2.33	2.57	2.77	3.10
8.55	2.70	2.90	3.15	3.50

Table 2: k_1 and K_E values for the substitution reaction at different temperatures. [complex 1] = 2.85×10^{-4} mol dm^{-3}, pH = 7.4, ionic strength = 0.1 mol dm^{-3} NaClO$_4$.

Temperature (^oC)	$10^3 k_1$ (s^{-1})	K_E (dm^3 mol^{-1})
45	7.95	90
50	10.16	56
55	13.59	33
60	17.41	22

Table 3: $10^5 k_2$ values for different DETU concentrations at different temperatures. [complex 1] = 2.85×10^{-4} mol dm^{-3}, pH = 7.4, ionic strength = 0.1 mol dm^{-3} NaClO$_4$

10^3 [DETU] (mol dm^{-3})	Temperature (^oC)			
	45	50	55	60
2.85	2.23	2.40	2.78	3.13
4.27	2.24	2.38	2.80	3.14
5.70	2.23	2.41	2.80	3.15
7.12	2.22	2.40	2.81	3.15
8.55	2.21	2.41	2.82	3.18

**Table 4: Activation parameters for substitution of [complex 1] by various ligands in aqueous medium, pH = 7.4**

| Ligand	$\Delta H_1^{\neq}$ (kJ mol^{-1})	$\Delta S_1^{\neq}$ (J K^{-1} mol^{-1})	$\Delta H_2^{\neq}$ (kJ mol^{-1})	$\Delta S_2^{\neq}$ (J K^{-1} mol^{-1})	Ref.
Thiourea	24.2 ± 1.6	-210 ± 5	7.5 ± 1.0	-306 ± 6	[30]
Thioglycolic acid /	14.3 ± 1.6	-231 ± 5	2.0 ± 1.2	-320 ± 6	[31]
Glutathione /	15.4 ± 1.6	-233 ± 5	4.8 ± 1.0	-286 ± 6	
DL-penicillamine	30.3 ± 1.0	-195 ± 5	16.0 ± 1.5	-272 ± 6	
N,N'-diethylthiourea	44.0 ± 1.5	-147 ± 5	17.8 ± 0.8	-278 ± 2	this work
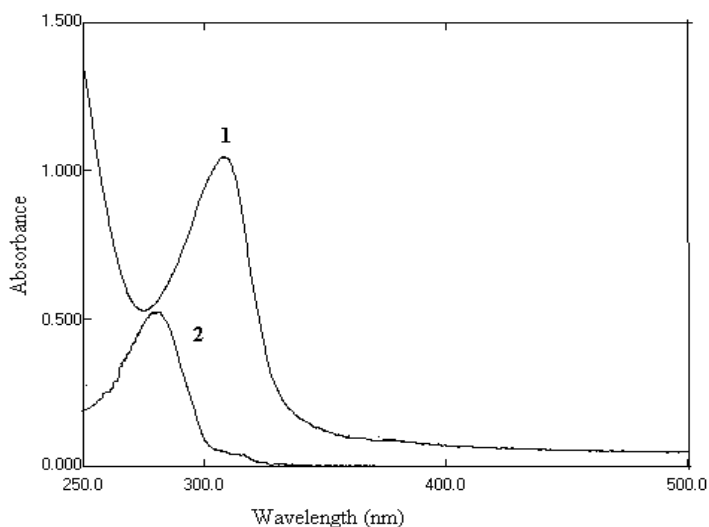
Figure 1: Spectra of the starting complex (1), and the ligand substituted complex (2); [complex 1] = 2.85×10^{-4} mol dm^{-3}, [DETU] = 5.7×10^{-3} mol dm^{-3}, pH = 7.4, cell used = 1 cm quartz.
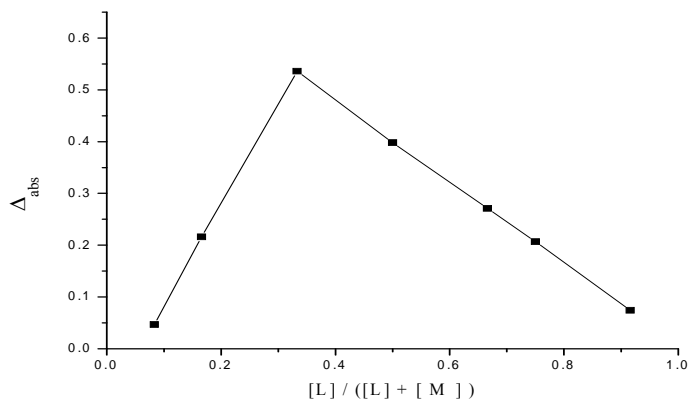
Figure 2: Job's plot for the reaction of complex 1 with DETU
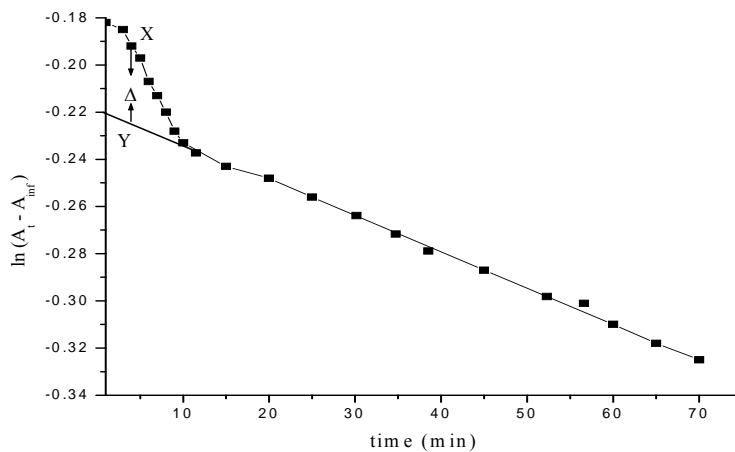
Figure 3: A typical plot of $\ln(A_t - A_\infty)$ versus time. [complex 1] = 2.85 ×10^{-4} mol dm^{-3},   [DETU] = 5.7 × 10^{-3} mol dm^{-3}, Δ = X – Y, indicates the difference in absorbances between two steps in different time interval. pH = 7.4, temp. = 50 ^{o}C.
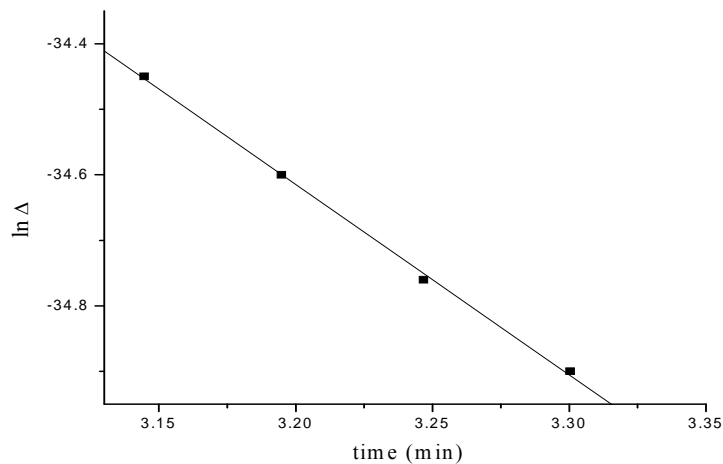
Figure 4: A typical plot of $\ln \Delta$ versus time. [complex 1] = 2.85 ×10^{-4} mol dm^{-3}, [DETU] = 5.7 × 10^{-3} mol dm^{-3}. pH = 7.4, temp = 50 ^{o}C.
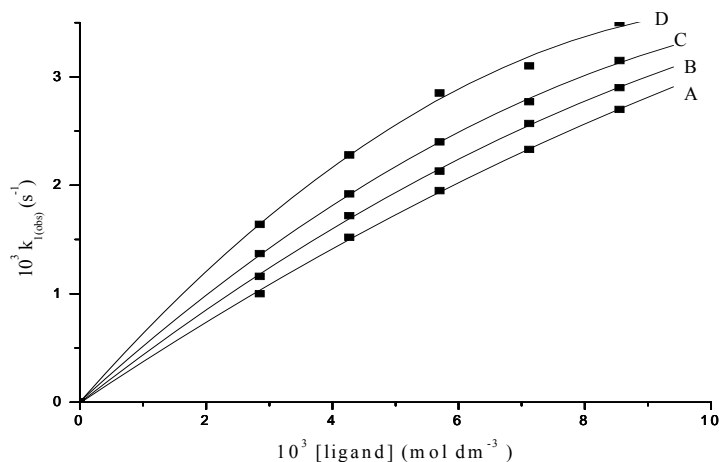
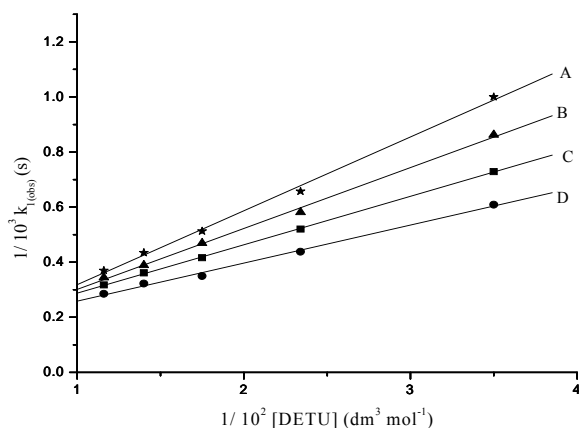**Figure 5: Plot of $k_{1(obs)}$ versus [DETU] at different temperatures. A = 45, B = 50, C = 55 and   D = 60 ^{o}C.**

Figure 6: Plot of $1/k_{1(obs)}$ versus 1/[DETU] at different temperatures at different temperatures.
A = 45, B = 50, C = 55 and D = 60 ^{o}C.

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