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Substitution reactions of [Pd(bipy)(malonate)] explored with a different set of ligands: Kinetic and mechanistic interpretation in aqueous medium and at pH 7.4

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Abstract. A brief overview of mechanistic studies of the reactions of Pd(II)-bipy-malonate complex with different set of ligands, *viz.*, (N, S), (S, O) and (S) donor molecules is reported here. The kinetics of complex-formation reactions of three sulphur containing bio-relevant ligands thioglycolic acid[L_1],thiourea[L_2] and thiosemicarbazide [L_3] were studied with innermetallic [Pd(bipy)(malonate)] complex at physiological condition. The effect of the nucleophilicity of the chosen nucleophiles was studied for the reactant complex under pseudo-first order conditions as a function of nucleophile concentration and temperature using stopped-flow technique. This article describes the results obtained for substitution reactions of bi-functional Pd(II) complex with different biomolecules, under varying experimental conditions. The kinetic studies showed that the malonate ring departs from the coordination zone of palladium centre *via* two-step mechanism. The first step depends on the concentration of the incoming ligand for all the ligands. But in the second step thiourea is ligand dependent where as other two are independent of the ligand concentration. Hence, it can be concluded that the second step is the chelation step for L_1 and L_3. The mechanism for the substitution of the coordinated malonate molecule is associative, as demonstrated by the negative values of $\Delta S^{\neq}$. Such type of complexes are less toxic than chloro-, which in turn hydrolyses to aqua or aqua complexes as they are prevented from oligomer formation at physiological pH.

Keywords. Pd(II); bipyridine; malonate; kinetics; mechanism

1. Introduction

The interaction of platinum group metal coordination complexes with DNA is now extensively accepted as the mechanism responsible for their anticancer activity.[1–4] Research in the area of the application of metal complexes in medicine began with the serendipitous discovery of the anti-tumour properties of cisplatin.[5,6] Despite a large number of complexes being synthesized, only the second and third generation platinum complexes such as carboplatin and oxaliplatin are broadly used for the treatment of different types of cancer. It is well known that the medicinal competence of cisplatin, *cis*- $[PtCl_2(NH_3)_2]$, is restricted by numerous toxic side effects, such as dose-limiting nephrotoxicity, drug resistance of the tumor cells and a narrow range of activities.[4,7,8] In the extended studies reported to date, more than 3000 complexes have been synthesized and studied with an expectation of better therapeutic activity with minimum toxic side effects. Among these huge number of reported potential drugs, a few namely, carboplatin, oxaliplatin, *etc.*, have shown some positive results.[9–11]

It has been conferred by scientists from all over the world that the Pd(II) complexes are usually good model compounds since they exhibit similar structural and equilibrium behaviour.[12] Now it is clear that bi-functional DNA-adduct of platinum complexes are exclusively responsible for its useful medicinal activity.[13,14] Most of the hazardous side effects arise due to hydrolysis of those well-known anticancer drugs at physiological conditions. These enlisted viewpoints enforced us to design the innermetallic, chelated malonate containing Pd(II)-bipy complex. The title complex exists as stable monomeric species at pH 7.4 since the chelated malonate ring is resistant to hydrolysis. Bi-functional nature of this reactant complex makes it competent to bind strongly to the nucleobases of DNA. Reactivity studies of this complex has not been reported earlier in the literature.

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Antitumor complexes bind with DNA constituents strongly but the adduct formation is quite a mammoth task as many other reactions with other bio-molecules (like, amino acids, peptides, inorganic anions) compete with this. In particular, sulphur-containing molecules, play a decisive character in drug distribution, thermodynamic and kinetic competition with nucleobase binding, and the mechanism of metabolism. In this context it was discovered that S-containing molecules play a twofold role in human physiology. First of all, the perilous side effects arise due to irreversible binding of anticancer drugs with sulphur present in proteins.[15] On the other hand, thiols and thioethers act as chemoprotectants which assist these drugs to reach nucleobases.[3]

We have chosen three 'S' containing molecule namely, thioglycolic acid (L_1), thiourea (L_2) and thiosemicarbazide (L_3), which contain thiol and thiocarbonyl groups respectively. Thioglycolic acid improves mucoadhesive properties of chitosan.[16] Thiourea is a well-known neutral, aqueous soluble inorganic species with good nucleophilic character. Thiourea commands attention for many years due to its multidimensional activity such as, antibacterial,[17] antifungal,[18] anti-HCV activity,[19] *etc.* Thiosemicarbazide has enthused considerable interest due to its pharmacological, antibacterial,[20] antitumor[21] and antifungal[22] activities and mimicking ability towards many bio-relevant molecules which help in better understanding of the mechanistic pathway.

In this work, we investigated the reactions of the above mentioned Pd(II)-bipy-malonato complex with thioglycolic acid, thiourea and thiosemicarbazide using stopped-flow technique to study the influence of electronic effects on reactions of potential biological importance. Significance of this work lies in the following reasons: (i) The inner-metallic palladium-malonate complex efficiently penetrates through cell membrane; (ii) Reactant complex is capable to prevent hydrolysis in physiological conditions; (iii) Less toxic because polymeric structures are not possible due to preclusion of hydrolysis.

2. Experimental

2.1 *Materials*

K_2PdCl_4, 2,2′-bipyridine (bipy) and disodiummalonate were purchased from Sigma-Aldrich. Thiourea, thioglycolic acid and thiosemicarbazide were purchased from Sisco Research Laboratory. All other reagents used in this research were sourced from commercial sources and used without purification. Solutions of the above-mentioned complex and other reagents used in this work were prepared in freshly prepared double-distilled water.

2.2 *Methods*

[Pd(bipy)Cl_2] was prepared by standard methods[23] and converted into the diaqua form by treating the chloro complex with two equiv. of $AgClO_4$ under light exclusion. Malonate complex was obtained for kinetic experiments from aqua complexes by adding one equiv. disodiummalonate at pH 7.0, and the mixture was stirred for 8 h at room temperature.[24] Desired complex was characterized and confirmed by UV-Vis (Figure 1), IR (Figure 2) and ESI MS (Figure 3) spectroscopic analyses. [Pd(bipy)(malonate)] [IR: $\nu_{C=N}$ 1633 cm^{-1}, $\nu_{C=O}$ 1595 cm^{-1} Mass: m/z = 387.04].

The products of the reaction between complex and ligands were separately prepared by mixing the reactants at pH 7.4 in different molar ratios, namely 1:1, 1:2, 1:3, 1:4.

The products of the reaction between complex and ligands were separately prepared by mixing the reactants at pH 7.4 in different molar ratios, namely 1:1, 1:2, 1:3, 1:4 and 1:5 and by thermostating the mixtures at 50°C for 48 h. The absorption spectra of the resulting solutions were recorded and each set were found to exhibit almost identical absorbance at the characteristic wavelengths irrespective of their different molar ratios. The difference in spectra between the product complexes and the substrate complex are shown in Figure 1. The pH of the solutions was adjusted by adding NaOH/$HClO_4$ at pH 7.4 so that reactant complex exists as malonate congener in the reaction mixture.

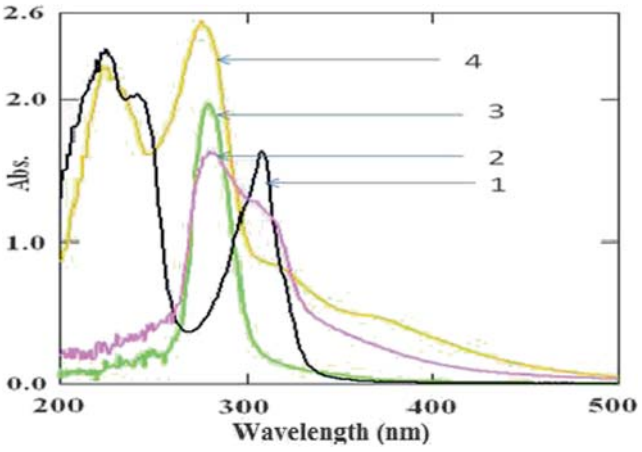


Figure 1. Absorption spectra of [Pd(2,2′-bipyridine)(malonate)] complex (1), thioglycolic acid (L_1) substituted product(2), thiourea (L_2) substituted product (3) and thiosemicarbazide (L_3) substituted product (4). [complex] = 2×10^{-4} mol dm^{-3}, [ligand] = 4×10^{-3} mol dm^{-3}, pH = 7.4, and quartz cell path length = 1 cm.

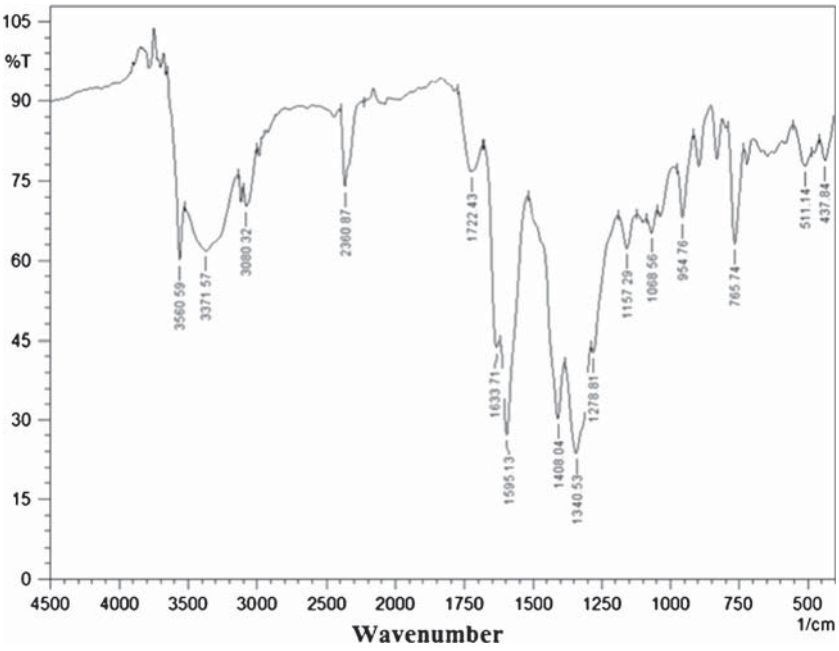


Figure 2. IR spectrum of the [Pd(2,2′-bipyridine)(malonate)] complex.

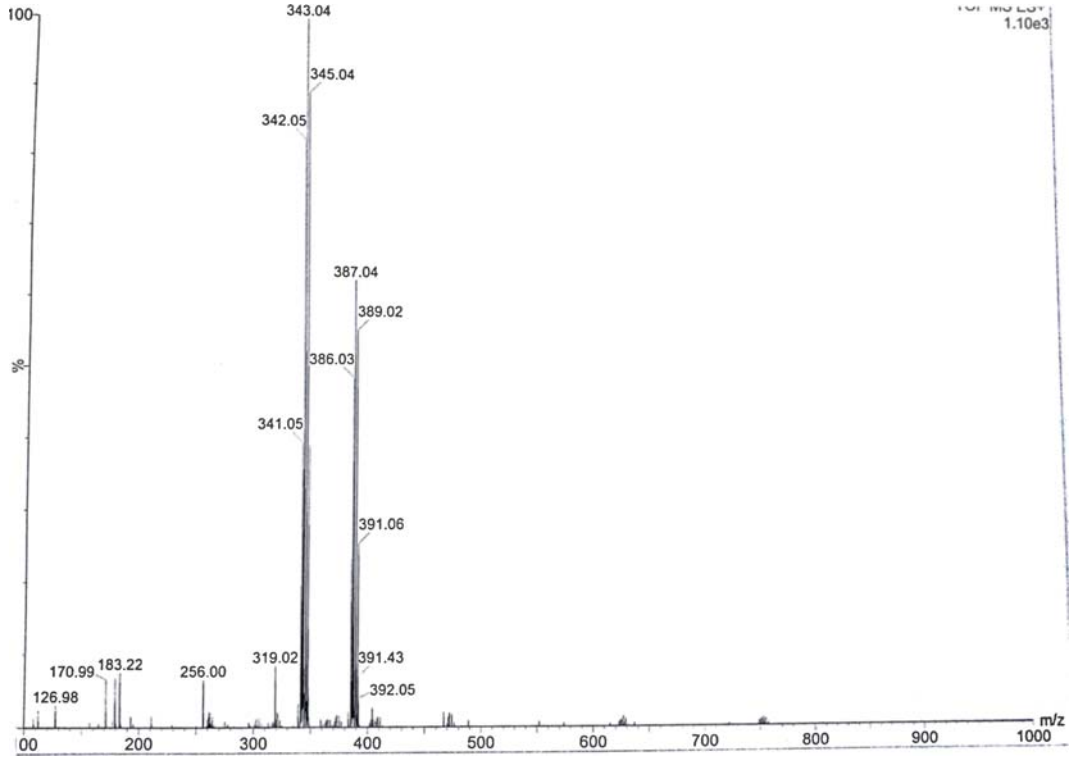


Figure 3. ESI Mass spectrum of the [Pd(2,2′-bipyridine)(malonate)] complex.

According to Job's method of continuous variation, metal–ligand compositions were found to be 1:1 for L_1 and L_3 (Figure 4) where as it is 1:2 for L_2 (Figure 4). L_1, L_2 and L_3 were separately mixed with complex in 1:1 (for L_1 and L_3) and 1:2 (for L_2) ratio at the experimental pH and three different products (Table 1) were formed and characterized by IR and mass spectroscopy in solution phase. To detect and characterize the correct forms of the products in solution phase, IR and mass spectroscopic analyses were done using concentrated aqueous solutions of the products in IR spectrophotometer coupled with ATR attachment and Q-ToF mass spectrophotometer in +ve ion mode respectively. The kinetic studies were done on a variable temperature stopped Flow

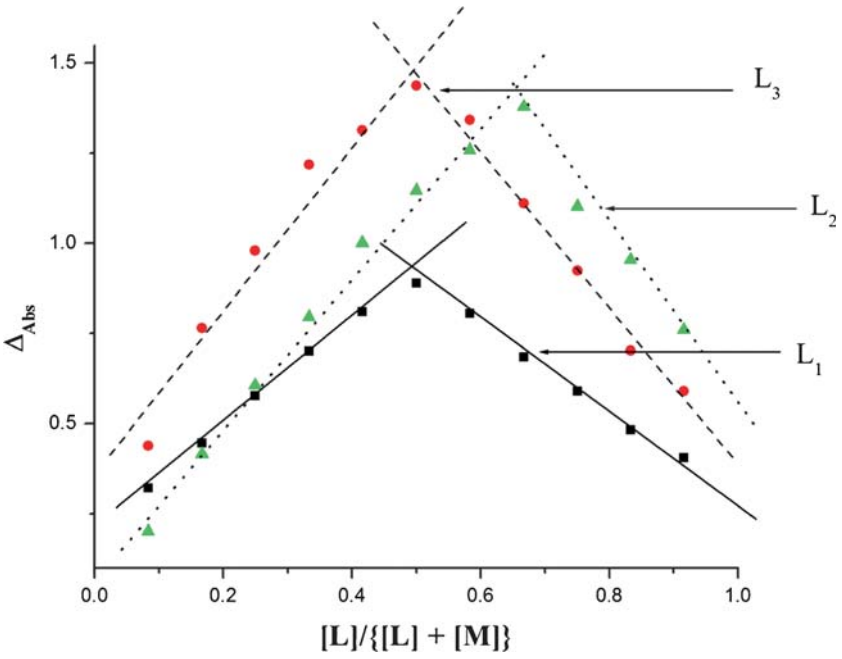
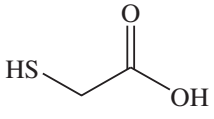
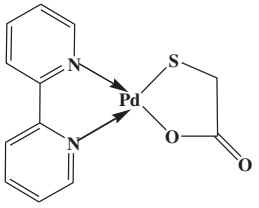
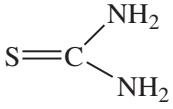
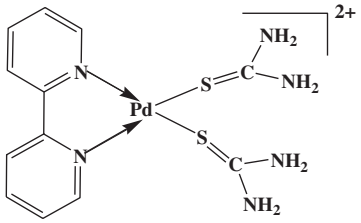
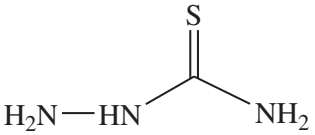
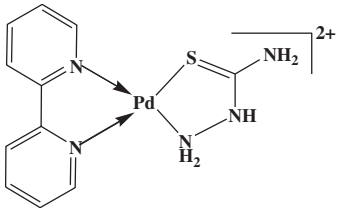


Figure 4. Typical Job's plots for the reaction between complex and ligands at pH =7.4 and ionic strength = 0.1 mol dm^{-3} $NaClO_4$.

Table 1. Metal-Ligand ratios and structures of the product complexes.

Ligand	Structure	Metal:Ligand ratio	Product complex
L_1 Thioglycolic acid		1:1	
L_2 Thiourea		1:2	
L_3 Thiosemicarbazide		1:1	

spectrophotometer. Pseudo-first order conditions with respect to metal ion concentration were maintained throughout the course of the reaction. Plots of $\ln(A_\infty - A_t)$ against time, where A_t and A_∞ are absorbances at time [t] and after completion of the reaction, were found to be nonlinear. Rate constant values were calculated as described in our previous work.[25] Origin software was used for computational analysis. Rate data, represented as an average of duplicate runs, were reproducible to within ±4%.

2.3 *Instrumentation*

All the uv-vis spectra of these reactions were recorded on a Shimadzu UV–VIS spectrophotometer (UV-2450) attached with TCC 240A temperature controller with accuracy (±0.1°C). Due to fast nature of the reactions, kinetic measurements were done in Hi-Tech stopped flow spectrophotometer (TGK Scietific UK). IR Spectra (4,000–400 cm^{-1}) were recorded with a Shimadzu IR Prestige-21 spectrophotometer. The pH of the solutions were adjusted by adding NaOH/$HClO_4$, and the measurements were carried using a Sartorius Digital pH meter (model PB11) with an accuracy of ±0.01 units. The reactions were carried out at constant ionic strength (0.1 mol dm^{-3} $NaClO_4$). ESI MS analyses were done in a Micromass Q-Tof Micro mass spectrometer in +ve ion mode.

3. Results and Discussion

3.1 *Product Analysis*

The electronic transitions observed from the UV-Vis spectroscopy were similar with what was expected for palladium(II) coordination complexes (Figure 1). UV-Vis spectra show λ_{max} values 281, 284 and 285 nm respectively. The IR spectra of the compounds were recorded in the region 4000–400 cm^{-1} (Figures S1, S2, and S3) and showed characteristic changes when compared to those of the free ligands. The palladium–ligand vibrations are expected to occur in a very low frequency range (below 600 cm^{-1}).[26]

For thioglycolic acid (L_1) substituted product (Figure S1 in Supplementary Information) bands observed at 3450 and 3200 cm^{-1} is due to ν_{OH}, which indicates the product is hydrated. Bands at 1629 and 1597 cm^{-1} observed due to C=O and C=N stretching respectively. Medium band at 1708 cm^{-1} will be considered as C-O bending vibration. Medium band at 1354 cm^{-1} region will be assigned as C-S stretching frequency.[27]

For thiourea(L_2) substituted product of complex (Figure S2), bands observed at 3400–3100 cm^{-1} were assigned to N-H stretching frequencies. The band observed at 1598 cm^{-1} in the substituted product of the Pd-complex can be marked to the NH_2 bending vibration and the medium band at 1462 cm^{-1} corresponds to the NH_2 rocking vibration respectively. The 1402 cm^{-1} medium band was assigned as N-C-N stretching vibration. A strong absorption band of thiourea at 1083 cm^{-1} corresponding to C=S stretching shifted to lower frequency region (1078 cm^{-1}) due to coordination with platinum metal. The bands observed at about 725 cm^{-1} in the spectra of the products correspond to the 730 cm^{-1} band of thiourea. The lowering of intensity can be attributed to the reduced double bond character of the C=S bond. The band at 433 cm^{-1} corresponds to the N-C-S deformation.[28]

For thiosemicarbazide(L_3) substituted product of reactant complex (Figure S3), the strong bands in the region 3500–3100 cm^{-1} is due to N-H stretching vibration.[29] The absorption bands at 1639–1616 cm^{-1} may be due to overlapping of the $\nu_{C=N}$ and δ_{NH2} bending motion coordinated to platinum.[30,31] The band observed at 1359 cm^{-1} was due to NH_2 rocking vibration. Medium band at 995 cm^{-1} represents the C=S stretching vibration. The medium band at 543 cm^{-1} is indicative of Pd-N and band at 499 cm^{-1} represents the Pd-S bond formation.[27]

ESI-MS of the resulting solutions, obtained from the (1:1) mixture (for L_1 and L_3) and (1:2) mixture (for L_2) of the substrate complex and ligands are shown in Figures S4, S5 and S6 in Supplementary Information. It is clear from these spectra that the ion at m/z 454.15 (Pd + bipy + thioglycolic acid + $HClO_4$), 419.82 (Pd + bipy + 2(thiourea) + Na^+) and 377.41(Pd + bipy + thiosemicarbazide + Na^+) (molecular ion peak), for L_1, L_2 and L_3 substituted product of reactant complex respectively, have become the precursor ion species in the mixture solutions and the relative abundance of isotope peaks match the predictable values.

3.2 *Kinetic and mechanistic studies*

The *pKa* values of the ligands L_1, L_2 and L_3 are $pK_1 =$ 3.58 (COOH), $pK_2 = 9.30$(SH) (for L_1),[32] 2.0 (NH_3^+) (for L_2)[33] 2.0 (NH_3^+) (for L_3)[33] respectively, at 25°C. From the *pKa* values of the ligands it can be concluded that at pH 7.4, among these S containing ligands L_1 remains in anionic form and other two exist as neutral species, which take part in the reactions. The reactions between complex and ligands involve a two-step consecutive route; we suggest that in the first step chelating malonate ring is opened from *cis*-[Pd(2,2′-bipyridine)(malonate)] by the L. The second step is slower, where chelate ring closure is occurring for L_1 and L_3. On the other hand, L_2 (thiourea) is not performing as a chelating ligand; here, in the second step, another thiourea molecule fills up the second coordination site. For thiourea, the second step is also ligand concentration dependent step. The rate constant for such a process can be evaluated by assuming the following scheme:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Table 2. $10^{-2}k_{1(obs)}(s^{-1})$ values for different concentrations of $\mathbf{L_1}$, $\mathbf{L_2}$ and $\mathbf{L_3}$ at different temperatures. [complex] = 2×10^{-4} mol dm^{-3}, pH = 7.4, μ = 0.1 mol dm^{-3} $NaClO_4$.

		Temperature	10^3 [**L**] (mol dm^{-3})				
Complex	Ligand	(±0.1°C)	2.00	3.00	4.00	6.00	10.00
[Pd(bipy) (malonate)]	$\mathbf{L_1}$	25	4.25 ± 0.01	6.23 ± 0.03	8.66 ± 0.02	12.59 ± 0.02	21.07 ± 0.01
		30	4.82 ± 0.02	7.31 ± 0.03	9.54 ± 0.04	14.28 ± 0.02	23.87 ± 0.02
		35	5.59 ± 0.01	8.32 ± 0.02	11.31 ± 0.03	16.92 ± 0.02	27.73 ± 0.03
		40	6.67 ± 0.02	10.03 ± 0.02	13.09 ± 0.01	19.87 ± 0.02	33.12 ± 0.01
		45	8.15 ± 0.01	12.36 ± 0.03	16.42 ± 0.04	24.19 ± 0.02	40.61 ± 0.03
	$\mathbf{L_2}$	25	2.35 ± 0.02	3.52 ± 0.03	4.85 ± 0.06	6.89 ± 0.02	11.61 ± 0.03
		30	2.82 ± 0.02	4.21 ± 0.04	5.69 ± 0.01	8.46 ± 0.05	13.74 ± 0.06
		35	3.45 ± 0.02	5.32 ± 0.02	6.81 ± 0.03	10.35 ± 0.06	17.02 ± 0.03
		40	4.33 ± 0.02	6.49 ± 0.03	8.51 ± 0.04	12.50 ± 0.06	21.32 ± 0.08
		45	5.62 ± 0.01	8.27 ± 0.05	11.12 ± 0.04	16.89 ± 0.07	27.75 ± 0.04
	$\mathbf{L_3}$	25	0.97 ± 0.02	1.48 ± 0.03	1.98 ± 0.05	2.79 ± 0.03	4.78 ± 0.03
		30	1.25 ± 0.02	1.82 ± 0.06	2.61 ± 0.09	3.68 ± 0.01	6.06 ± 0.03
		35	1.65 ± 0.02	2.47 ± 0.02	3.18 ± 0.04	5.07 ± 0.08	8.13 ± 0.06
		40	2.23 ± 0.02	3.36 ± 0.04	4.63 ± 0.10	6.82 ± 0.11	10.95 ± 0.08
		45	3.08 ± 0.02	4.62 ± 0.05	6.23 ± 0.06	8.91 ± 0.09	15.13 ± 0.05

Table 3. $10^3k_{2(obs)}$ (s^{-1}) values for different concentrations of (L_2) at different temperatures. [complex] = 2×10^{-4} mol dm^{-3}, pH = 7.4, μ = 0.1 mol dm^{-3} $NaClO_4$.

		Temperature	10^3 [$\mathbf{L_2}$] (mol dm^{-3})				
Complex	Ligand	(± 0.1°C)	2.00	3.00	4.00	6.00	10.00
[Pd(bipy) (malonate)]	$\mathbf{L_2}$	25	2.65 ± 0.02	3.73 ± 0.02	5.12 ± 0.03	7.97 ± 0.03	13.06 ± 0.04
		30	3.60 ± 0.03	5.36 ± 0.04	7.39 ± 0.10	10.61 ± 0.04	17.82 ± 0.02
		35	4.99 ± 0.02	7.59 ± 0.02	10.16 ± 0.09	14.83 ± 0.04	24.76 ± 0.08
		40	7.04 ± 0.01	10.28 ± 0.02	13.79 ± 0.05	21.02 ± 0.12	34.85 ± 0.06
		45	10.20 ± 0.02	15.09 ± 0.06	19.84 ± 0.11	30.82 ± 0.14	49.59 ± 0.03

Table 4. $10^{-5}k_1$ and k_2 values for the substitution reaction.

[Pd(bipy)		$\mathbf{L_1}$		$\mathbf{L_2}$		$\mathbf{L_3}$	
(malonate)]	Temperature (°C)	$10^{-5}k_1$ (mol^{-1} dm^3 s^{-1})	k_2 (s^{-1})	$10^{-5}k_1$ (mol^{-1} dm^3 s^{-1})	k_2 (mol^{-1} dm^3 s^{-1})	$10^{-5}k_1$ (mol^{-1} dm^3 s^{-1})	k_2 (s^{-1})
	25	2.11 ± 0.02	1.12 ± 0.02	1.15 ± 0.02	1.31 ± 0.02	0.47 ± 0.03	0.59 ± 0.02
	30	2.38 ± 0.02	1.54 ± 0.01	1.38 ± 0.05	1.77 ± 0.04	0.60 ± 0.05	0.87 ± 0.05
	35	2.74 ± 0.01	2.15 ± 0.03	1.70 ± 0.02	2.47 ± 0.08	0.82 ± 0.01	1.32 ± 0.05
	40	3.31 ± 0.03	3.08 ± 0.04	2.12 ± 0.03	3.48 ± 0.11	1.10 ± 0.08	2.05 ± 0.03
	45	4.05 ± 0.02	4.50 ± 0.01	2.78 ± 0.06	4.98 ± 0.05	1.50 ± 0.10	3.23 ± 0.04

where, A is the malonate species (1), B is the single substituted intermediate, and C is the final product. Formation of C from B is predominant after some time has elapsed.

3.2a *Calculation of* k_1: The rate constant for the first step of the reaction A → B was obtained from the absorbance records using the Origin 6.0 software. The $k_{1(obs)}$ values for different ligand concentrations at different temperatures are given in Table 2.

The following mechanism is proposed:

$$[\text{Pd}(2,2'\text{-bipyridine})(\text{malonate})] \longrightarrow [\text{Pd}(2,2'\text{-bipyridine})(\text{malonate})(\text{L})]^{y-} \quad (1)$$

Table 5. Activation parameters for complex by different ligand in aqueous medium, at pH 7.4.

Complex	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})
[Pd(bipy) (malonate)]	**L_1**	22.7 ± 1.6	−65 ± 4	55.1 ± 2.5	−69 ± 2
	L_2	31.8 ± 2.0	−41 ± 2	50 ± 3.4	−74 ± 3
	L_3	42.6 ± 3.4	−11 ± 1	65.2 ± 3.5	−30 ± 2

$$[\text{Pd}(2,2'\text{-bipyridine})(\text{malonate})(\text{L})]^{y-} \longrightarrow [\text{Pd}(2,2'\text{-bipyridine})(\text{L})_n]^{x+} \quad (2)$$

where L is the anionic variety of ligands. x, y and n are dependent on the nature of the ligand. Based on the above scheme, a rate expression (equation 4) can be derived for the

$$\text{A} \longrightarrow \text{B step}: \quad \text{dB/dt} = k_1[\text{Pd}(2,2'\text{-bipyridine})(\text{malonate})]_{\text{total}}[\text{L}] \quad (3)$$

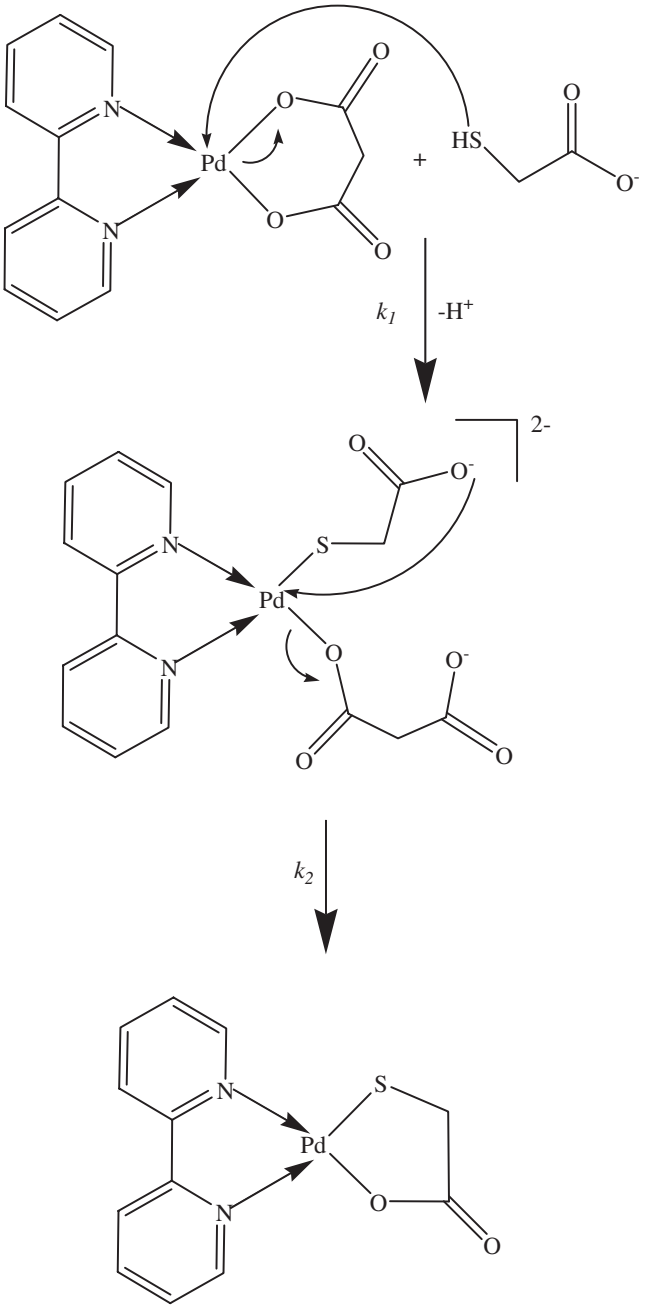
where $[\text{Pd}(2,2'\text{-bipyridine})(\text{malonate})]_{\text{total}}$ is the concentration of the unreacted complex. Hence, we can write

$$k_{1(obs)} = k_1[\text{L}] \quad (4)$$

where k_1 is the second-order rate constant for the malonate ring opening *via* ligand substitution. A plot of $k_{1(obs)}$ (s^{-1}) versus [L] should be linear, passing through the origin. This was found to be so at all temperatures studied (Figures S7, S8 and S9). The second-order rate constants (k_1) calculated from the slopes of the plots of $k_{1(obs)}$ (s^{-1}) versus [L] (mol dm^{-3}) at different temperatures are given in Table 4.

3.2b *Calculation of k_2*: The B ⟶ C step is allocated to ring closing for L_1 and L_3. This chelation step is independent of ligand concentration. Slower reaction rate seems to be due to the steric hindrance. At each temperature, the k_2 values were calculated from the limiting linear portion (when t is large) of the plots of $\ln(A_\infty - A_t)$ versus t are compiled in Table 4. Unlike k_1, k_2 was found to be independent of ligand concentration at each of the temperatures studied for L_1 and L_3. But for L_2, second step is found to be ligand concentration dependent and hence k_2 values are obtained from $k_{2(obs)}$ values (Table 3) by following the same calculation techniques as followed in case of k_1 and tabulated in Table 4.

The first step of this two-step process is ligand concentration dependent ring opening step and second step is relatively slow intramolecular chelation step for thioglycolic acid and thiosemicarbazide (Scheme 1). Thiourea was unable to form chelate, and here both the steps are ligand concentration dependent. Two thiourea molecules substitute the bidentate malonate in a consecutive fashion. Among the three sulphur donor ligands possible coordination sites are S, O for thioglycolic acid



Scheme 1. Plausible mechanistic pathway.

and S, N for thiourea and thiosemicarbazide. From IR studies it is clear that 'S' atom is a common ligating site due to soft-soft interaction. Job's study suggests that thiourea was unable to use 'N' donor centre through chelation as it generates strained four membered ring, so it acts as monodentate ligand. In the experimental pH thioglycolic acid exists as thioglycolate anion which increases its donor ability towards the metal centre whereas both thiourea and thiosemicarbazide exist as neutral species. On the other hand, when we took a quick look between these two neutral ligands it was very much clear that thiosemicarbazide is little bit more sterically hindered than thiourea and the small size with excellent donor ability make thiourea faster than thiosemicarbazide. For the second step the order of reactivity is different from the previous step. Here a new thiourea molecule attacks the metal atom whereas for the other two it is an intramolecular chelation process and chelation reactions are little bit slow which may be due to steric hindrance. That is why thiourea is the fastest in the second step.

3.3 *Effect of Temperature on the Reaction Rate*

These reactions were monitored at five different temperatures for diverse ligand concentrations and the substitution rate constants for both A $\longrightarrow$ B (k_1) and B $\longrightarrow$ C (k_2) steps are arranged in Table 4. The activation parameters calculated from Eyring plots are tabulated in Table 5.

From the large negative values of $\Delta S^{\neq}$ it can be concluded that these reactions proceed *via* associative mechanism.

4. Conclusions

The complex [Pd(bipy)(malonate)] reacts with sulphur containing biomolecules *via* direct substitution mechanism excluding the formation of reactive dichloro and/or diaqua products. The pharmacokinetic importance of the chelating malonate ligand originates mainly from its ability to form innermetallic complex with Pd(II), inertness to hydrolysis at pH 7.4 and its chelate effect. We have performed an extensive study on the ease of substitution of malonate group from first sphere of attraction of the palladium complex by using selective thiocarbonyls and thiol (*viz.*, Thioglycolic acid, Thiourea and Thiosemicarbazide). Generally, the chelate ring-opening reaction of a dicarboxylate such as the malonate ligand is associated with a large contribution of the back reaction but only strong nucleophiles like S containing molecules are able to restrict it due to greater soft-soft interaction.

This kinetic investigation has reported the rate constant values of substitution processes on [Pd(bipy)(malonate)] complex with biorelevant nucleophiles. A set of three biologically important nucleophiles were chosen and rate constants of substitution reaction of these nucleophiles in the complex were investigated. These ligands contain (S, O), (S) and (S, N) donor centres respectively. These Pd(II) complexes always demonstrated a higher reactivity towards the sulfur donor nucleophiles due to soft-soft interaction between Pd and S atoms. It was concluded that the reaction with these type of inner metallic complexes proceed *via* a direct substitution mechanism, since the reaction with chloride was too slow to account for an aqua or chloro complex as the reactive species, as observed in Pt(II) complexes.[34–37] The rate constant 'k_1' for the ligands thioglycolic acid (L_1), thiourea(L_2) and thiosemicarbazide (L_3) guided us to arrange them as, thioglycolic acid (L_1) > thiourea (L_2) > thiosemicarbazide (L_3). The second step follows a different reactivity order thiourea (L_2) > thioglycolic acid (L_1) > thiosemicarbazide (L_3).

Supplementary Information (SI)

All figures pertaining to the characterization of the product complexes such as IR spectra (Figures S1–S3) and ESI Mass spectra (Figures S4–S6) and figures related to rate constant values (Figures S7–S9) are given in the Supplementary Information, available at www.ias.ac.in/chemsci.

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References

1. Wong E and Giandomenico C M 1999 *Chem. Rev.* **99** 2451
2. Wheate N J and Collins J G 2003 *Coord. Chem. Rev.* **241** 133
3. Reedijk J 1999 *Chem. Rev.* **99** 2499
4. Jamieson E R and Lippard S J 1999 *Chem. Rev.* **99** 2467
5. Rosenberg B, Camp L V, Trosko J E and Mansour V H 1969 *Nature* **222** 385
6. Saha P, Descoteaux C, Brasseur K, Fortin S, Leblanc V, Parent S, Asselin E and Berube G 2012 *Eur. J. Med. Chem.* **48** 385
7. Wong E and Giandomenico C M 1999 *Chem. Rev.* **99** 2451

8. Kostova I 2006 *Recent Pat. Anti-Cancer Drug Discovery* **1** 1
9. Zhao J, Gou S, Liu F, Sun Y and Gao C 2013 *Inorg. Chem.* **52** 8163
10. Marques-Gallego P, Dulk H, Brouwer J, Kooijman H, Spek A L, Roubean O, Teat S J and Reedijk J 2008 *Inorg. Chem.* **47** 11171
11. Reedijk J 2009 *Eur. J. Inorg. Chem.* **10** 1303
12. Petrovic B, Bugarcic Z D and van Eldik R 2008 *Dalton Trans*. 807
13. Jakubec M A, Galanski M and Keppler B K 2003 *Rev. Physiol. Biochem. Pharmacol.* **146** 1
14. Lippert B 1999 In *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug* (Zürich, Switzerland: Wiley-VCH)
15. Takahara P M, Frederic C A and Lippard S J 1996 *J. Am. Chem. Soc.* **118** 12309
16. Constantia E K and Bernkop-Schnürch A 2001 *Biomaterials* **22** 2345
17. Khan S A, Singh N and Saleem K 2008 *Eur. J. Med. Chem.* **43** 2272
18. Saeed S, Rashid N, Jones P G, Hussain R and Bhatt M H 2010 *Cent. Eur. J. Chem.* **8** 550
19. Kang I J, Wang L W, Lee C C, Lee Y C, Chao Y S, Hsu T A and Chern J H 2009 *Bioorg. Med. Chem. Let.* **19** 1950
20. Siwek A, Stączek P and Stefanska 2011 *Eur. J. Med. Chem.* **46** 5717
21. Campbell M J M 1975 *Coord. Chem. Rev.* **15** 279
22. Pandeya S N, Nath S D and DeClercq E G 1999 *Eur. J. Pharm. Sci.* **9** 25
23. Al-Baker S and Dabrowiak J C 1987 *Inorg. Chem.* **26** 613
24. Kidani Y, Inagaki K, Iigo M, Hoshi A and Kuretani K 1978 *J. Med. Chem.* **21** 1315
25. Ray S, Nandi D, Chattopadhyay A, Sarkar R, Karmakar P and Ghosh A K 2014 *Monatsh. Chem.* **145** 1727
26. Williams R L and Pace R J 1957 *J. Chem. Soc.* 4131
27. Yamaguchi A, Penland R B, Mizushima S, Lane T J, Curran C and Quagliano J V 1958 *J. Am. Chem. Soc.* **80** 527
28. Chan S C, Chan M C W, Wang Y, Che C M, Cheung K K and Zhu N 2001 *Chem. Eur. J.* **7** 4180
29. Quiroga A G, Perez J M, Lopez-Solera I, Masaguer J R, Luque A, Roman P, Edwards A, Alonso C and Navarro-Ranninger C 1998 *J. Med. Chem.* **41** 1399
30. Kovala D, Demertzis M A, Miller J R, Papadopoulou C, Dodorou C and Filousis G 2001 *J. Inorg. Biochem.* **86** 555
31. Sengupta P S, Sinha R and De G S 2001 *Transition Met. Chem.* **26** 638
32. Sillen L G, Martell A E and Bjerrum J 1964 In *Stability Constants of metal-ion complexes*, Special publication by Royal Society of Chemistry London (London: The Chemical Society) **17** 376
33. Ajayi S O and Campbell M J M 1969 *J. Chem. Soc. A* 506
34. Barnham K J, Djuran M I, Murdoch P del S, Ranford J D and Sadler P J 1996 *Inorg. Chem.* **35** 1065
35. Guo Z, Hambley T W, Murdoch P del S, Sadler P J and Frey U 1997 *J. Chem. Soc. Dalton Trans.* 469
36. Canovese L, Cattalini L, Chess G and Tobe M L 1988 *J. Chem. Soc. Dalton Trans.* 2135
37. Allsopp M A, Sewell G J, Rowland C G, Riley C M and Schowen R L 1991 *Int. J. Pharm.* **69** 197