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Triphenyl phosphine adducts of platinum(IV) and palladium(II) dithiocarbamates complexes: a spectral and in vitro study

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Abstract

Triphenyl phosphine adducts of dithiocarbamate complexes of platinum(IV) and palladium(II) of the type $[Pt(L)_2PPh_3Cl_2]$ and $[Pd(L)_2PPh_3]$ [L: morpholine dithiocarbamate (L^1), aniline dithiocarbamate (L^2) and *N*-(methyl, cyclohexyl) dithiocarbamate (L^3)] were prepared and characterized by elemental analysis, electronic, IR, ^1H NMR and ^{13}C NMR spectral studies. Thermal studies of the complexes were carried out. In vitro antitumor activity has been screened towards human adenocarcinoma cell lines and showed significant inhibition even at very low concentration.

Keywords: Dithiocarbamate complexes; Spectral, thermal and in vitro study; Triphenyl phosphine

1. Introduction

Platinum(IV) and palladium(II) complexes with tertiary phosphines have been poorly characterized [1–3]. The reaction of all M(S–S) compounds (M = Pt, Pd; $(S–S)^- = {}^-S_2CNR_2$ (R = Me, Et), ${}^-S_2COR$ (R = Et · $PhCH_2$), ${}^-S_2P(OEt)_2$ and ${}^-S_2PR_2$ (R = Me, Et, Ph)] with tertiary phosphines occurs by stepwise cleavage of metal–sulphur bonds to generate four-coordinate compounds of formulae $[M(S–S)_2PR_3']$ and $[M(S–S)(PR_3')_2]$ (S–S) with unidentate/bidentate and ionic/bidentate coordination respectively [4–7]. All the ionic compounds readily revert to the $[M(S–S)_2PR_3']$ complexes in the presence of non-polar solvents via nucleophilic attack by $(S–S)^-$ on the metal.

The investigation of platinum and palladium complexes is important for the treatment of human cancer [8–10]. Even at very low concentration these have been found to be active as revealed by in vitro studies. The general consensus is that they derived their activity through different adducts that they formed with DNA [11].

The synthesis of triphenyl phosphine adducts was planned after considering that square planar $[M(S–S)_2]$ complexes [M = Pd or Pt; $(S–S)^- = R_2NCS_2{}^-$, $ROCS_2{}^-$, $(RO)_2PS_2{}^-$ and $R_2PS_2{}^-$] easily form adducts with various tertiary phosphines [12–16].

2. Experimental

2.1. Dithiocarbamates L (L: L^1, L^2, L^3 and L^4)

The dithiocarbamates were prepared by the method described by Gilman and Blatt [17] with some modifications.

0.4 mol of corresponding amine was dissolved in methanol and chilled. To this a chilled solution of 2.24 g (0.04 mol) potassium hydroxide in aqueous methanol was mixed with constant stirring. The mixed solution was treated with an ice cold solution of 2.5 cm^3 (0.04 mol) carbon disulphide (density 1.27) in 4 cm^3 methanol keeping the temperature of the reaction mixture below 10 °C. During the process, desired crystalline precipitates separated. It was filtered and washed with ice cold aqueous methanol and recrystallized.

2.2. Mixed ligand complexes

2.2.1. $[Pt(L)_2(PPh_3)Cl_2]$, $[Pd(L)_2(PPh_3)]$ (where L = L^1, L^2 and L^3)

The complexes were prepared by taking $[Pt(L)_2Cl_2]$ and $[Pd(L)_2]$ as starting materials. $[Pt(L)_2Cl_2]$ and $[Pd(L)_2]$ was

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prepared by adding aqueous solution of the corresponding metal chloride (K_2PtCl_6 or $PdCl_2$) to the aqueous solution of desired dithiocarbamate L (where L = L^1, L^2 and L^3) in 1:2 ratio.

A suspension of corresponding dithiocarbamate complex X (X = $[Pt(L^1)_2Cl_2]$ (0.167 g, 0.25 mmol), $[Pt(L^2)_2Cl_2]$ (0.170 g, 0.25 mmol), $[Pt(L^3)_2Cl_2]$ (0.127 g, 0.25 mmol), $[Pd(L^1)_2]$ (0.095 g, 0.25 mmol), $[Pd(L^2)_2]$ (0.096 g, 0.25 mmol), $[Pd(L^3)_2]$ (0.097 g, 0.25 mmol)), in CS_2 was treated with triphenyl phosphine (0.065 g, 0.25 mmol) dissolved in toluene, the mixture was left under continuous magnetic stirring for 1 h. The resulting yellow coloured solution was filtered and after few hours yellow precipitate was formed and the precipitation was completed by addition of light petroleum ether. The yellow precipitates were filtered off, washed with diethyl ether and dried under vacuum.

2.3. Physical measurements

All the reagents used were of AR grade. IR and far IR spectra were recorded on a Perkin-Elmer Spectrum 2000 FTIR spectrometer. Electronic spectra were recorded on Beckman DU-64 UV-Vis spectrophotometer. Conductance measurements were carried out on a Elico conductivity Bridge Model CM-102, India. ^{1}H NMR and ^{13}C NMR were recorded on Bruker a spectrospin advance 300 spectrometer and BAS-CV 50 W voltammetric analyser was used to record the voltammograms of complexes. TG/DTA curves were simultaneously recorded on a Perkin-Elmer, Model TGA-7, USA in static air, DTA. curves were recorded on a Rigaku, model 8150 thermoanalyser in static air at a heating rate of 10 °C min^{-1}.

2.4. Antitumor screening

In vitro growth inhibitory assay; human color adenocarcinoma cell line was cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS), 100 μg cm^{-3} streptomycin. 100 μg cm^{-3} penicillin and 50 μg cm^{-3} gentamycine. For the assay, 10,000 cells were plated per well of a 96-well tissue culture plate and allowed to adhere overnight at 37 °C in a 5% CO_2 incubator. The following day, the medium was changed to RPMI 1640 containing 5% FCS. The compounds to be tested were dissolved in DMSO and subsequent serial dilutions were made in RPMI 1640 medium. The cells were treated with various concentrations of the compounds (10 μM–10 pM) and allowed to incubate at 37 °C in a CO_2 incubator. A second dose of the compounds was added to the cells after 24 h and, thereafter, the cells were incubated for a further 24 h. Appropriate controls for assessing cytotoxicity due to DMSO were included in the assay.

Cytotoxicity was assessed using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT). Briefly, MTT dissolved in 50 cm^3 phosphate buffered saline (PBS) (pH 7.4) was added to the cells at a final concentration of 0.5 mg cm^{-3}. The cells were incubated at 37 °C for 3 h. Thereafter, the medium was aspirated and the cells were analyzed with 150 μl DMSO added to each well. Absorbance was measured at 570 nm and percentage cytotoxicity was calculated:

$$\text{cytotoxicity (\%)} = 1 - \frac{\text{optical density in sample well}}{\text{optical density in control well}} \times 100$$

3. Results and discussion

Satisfactory results of elemental analysis (Table 1) and spectral studies reveal that the complexes are of good purity. The complexes obtained are microcrystalline or powder like and yellow to brown in color. Conductance measurements for these complexes are <10 Ω^{-1} mol^{-1} cm^2 indicating that these compounds are non electrolytes. These complexes are soluble in DMSO and insoluble in most of the organic solvents, so all the attempts to recrystallize platinum(IV) and palladium(II) complexes were unsuccessful.

3.1. Electronic spectra

In the present studies, all the complexes are found to be diamagnetic. The platinum(IV) complexes are octahedral and palladium(II) complexes are square planar in structure. The geometries are supported by their electronic spectra. Ground state of platinum(IV) which belong to d^6 system is $^1A_{1g}$. Four bands can be expected corresponding to $^1A_{1g} \rightarrow {}^3T_{1g}$ (23,900–24,200 cm^{-1}), $^1A_{1g} \rightarrow {}^3T_{2g}$ (17,200–18,250 cm^{-1}) $^1A_{1g} \rightarrow {}^1T_{1g}$ (38,300–28,000 cm^{-1})

Table 1
Elemental analysis of mixed ligand complexes

Complexes	Found (calculated) (%)					
	C	H	N	S	Cl	Metal
$[Pt(L^1)_2(PPh_3)Cl_2]$	40.3 (39.4)	3.9 (3.6)	4.1 (3.3)	15.1 (15.0)	8.0 (8.3)	22.9 (23.0)
$[Pd(L^1)_2(PPh_3)]$	40.0 (40.5)	4.4 (4.5)	3.9 (4.0)	18.3 (18.5)	–	15.3 (15.3)
$[Pt(L^2)_2(PPh_3)Cl_2]$	43.8 (44.4)	3.7 (3.1)	4.0 (3.2)	14.0 (14.8)	8.6 (8.2)	23.2 (22.7)
$[Pd(L^2)_2(PPh_3)]$	55.0 (54.5)	4.0 (3.8)	3.2 (3.4)	19.0 (18.2)	–	15.3 (15.0)
$[Pt(L^3)_2(PPh_3)Cl_2]$	45.0 (45.1)	4.1 (4.8)	3.9 (3.1)	14.8 (14.1)	8.3 (7.8)	21.1 (21.7)
$[Pd(L^3)_2(PPh_3)]$	55.2 (54.8)	6.2 (5.8)	3.1 (3.8)	17.3 (17.2)	–	14.3 (14.3)

Table 2
Electronic spectral data of mixed ligand complexes of Pt(IV) and Pd(II)

	λ_{max} (nm)	log(ε)
$[Pt(L^1)_2(PPh_3)Cl_2]$	275	4.0
	350	3.5
$[Pd(L^1)_2(PPh_3)]$	270	3.9
	380	3.2
$[Pt(L^2)_2(PPh_3)Cl_2]$	295	3.9
	340	3.6
$[Pd(L^2)_2(PPh_3)]$	285	3.6
	355	3.1
$[Pt(L^3)_2(PPh_3)Cl_2]$	280	4.0
	353	3.9
$[Pd(L^3)_2(PPh_3)]$	276	3.8
	360	3.6

and $^1A_{1g} \rightarrow ^1T_{2g}$ (27,500–25000 cm^{-1}) transitions [17]. Palladium(II) is d^8 system and three spin allowed singlet–singlet d–d transitions are predicted [18–20]. The ground state is $^1A_{1g}$ and three predicted transitions are $^1A_{1g} \rightarrow ^1A_{2g}$ (16,800–12000 cm^{-1}), $A_{1g} \rightarrow ^1B_{1g}$ (17,500–23,100 cm^{-1}) and $^1A_{1g} \rightarrow ^1E_g$ (21,000–26,500 cm^{-1}). These transitions are from the lower lying d orbitals to the empty $d_{x^2-y^2}$ orbital. Strong charge transfer transitions may interfere and prevent the observation of all the expected bands [18,21–24]. Strong bands between 26,000 and 28,000 cm^{-1} are assignable to a combination of M → LCT (metal–ligand charge transfer) and d–d bands. The very intense band at ca. 450 nm is assignable to combination of sulphur → metal charge transfer (Lπ → MCT) and d–d bands.

In electronic spectra of mixed ligand complexes, two bands are observed. Band I is due to $\pi \rightarrow \pi^*$ transition and band II is due to metal → ligand charge transfer. Electronic spectral data of mixed ligand complexes is presented in Table 2.

3.2. IR spectra

In the IR spectra of the complexes, the doublets in the region 1000 cm^{-1} separated by ca. 20 cm^{-1} was observed, as reported by Bonati and coworkers [25–27] it indicates that one dithiocarbamate ligand is bidentate and another is monodentate. Whereas in $(Pt(L_2)Cl_2]$ and $[PdL_2]$ complexes one singlet was observed ca. 1000 cm^{-1} indicating that both dithiocarbamate ligands are bidentately bound.

In far IR spectra contains the M–S stretching frequencies [28] in the region 390–320 cm^{-1}. The band at ∼390 cm^{-1} is assigned to $\nu_{(Pt-Cl)}$ vibrations. The IR and far IR bands of mixed ligand complexes of platinum(IV) and palladium(II) has been presented in Table 3.

Table 3
IR absorption frequencies (cm^{-1}) of mixed ligand complexes of Pt(IV) and Pd(II)

	$\nu_{(C=N)}$	$\nu_{(C=S)}$	$\nu_{(M-S)}$	$\nu_{(M-Cl)}$
$[Pt(L^1)_2(PPh_3)Cl_2]$	1510, 1490	1008, 998	400	295
$[Pd(L^1)_2PPh_3]$	1505, 1496	1003, 978	390	–
$[Pt(L^2)_2(PPh_3)Cl_2]$	1512, 1492	1012, 990	398	291
$[Pd(L^2)_2(PPh_3)]$	1509, 1497	1000, 978	392	–
$[Pt(L^3)_2(PPh_3)Cl_2]$	1520, 1498	998, 975	399	301
$[Pd(L^3)_2(PPh_3)]$	1515, 1500	1005, 982	389	–

Table 4
Percentage cytotoxicity (w.r.t. control) of the complexes

Concentration	$[Pt(L^1)_2(PPh_3)Cl_2]$	$[Pt(L^2)_2$ $PPh_3Cl_2]$
100 nM	74.30	67.30
10 nM	89.29	28.80
1 nM	87.50	+6.40
100 pM	66.62	+34.20
10 pM	45.60	+35.00
1 pM	38.40	+33.10

Symbol '+' denotes proliferation.

3.3. ^1H and ^{13}C NMR spectra

The ^1H NMR spectra of complexes were recorded in d_6-DMSO taking TMS as internal standard.

δ (ppm): 7.3−7.8 (m, 15H, $–C_6H_5$), 3.87 (m, 16H, $–CH_2$).
δ (ppm): 7.3−7.7 (m, 15H, $–C_6H_5$), 3.82 (m, 8H, $–CH_2$)
δ (ppm): 9.1 (s, br, 2H, –NH), 7.3−7.8 (m, 25H, $–C_6H_5$).
δ (ppm): 9.0 (s, br, 2H, –NH), 7.3−7.87 (m, 25H, $–C_6H_5$).
δ (ppm): 7.2–7.76 (m, 15H, $–C_6H_5$), 2.15 (s, 6H, $–CH_3$), 1.10–1.92 (m, 22H, $–C_6H_{11}$).
δ (ppm): 7.3–7.78 (m, 15H, $–C_6H_5$), 2.12 (s, 6H, $–CH_3$), 1.12–1.87 (m, 22H, $–C_6H_{11}$).

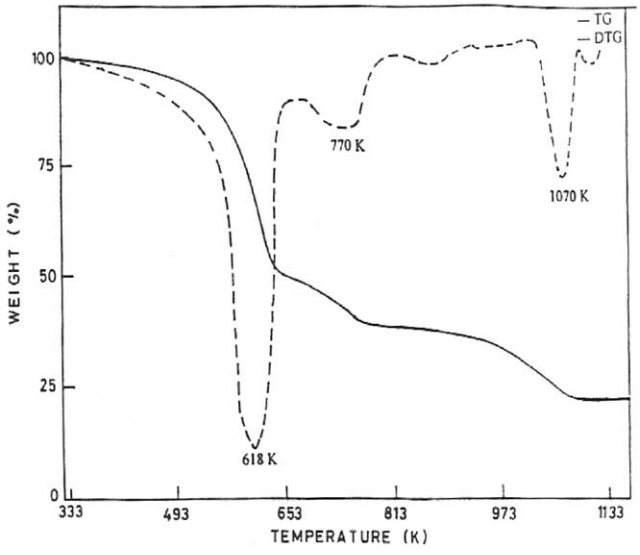

Fig. 1. TG and DTG curves of $[Pt(L^1)_2(PPh_3)Cl_3]$ complex.

On the basis of these spectroscopic studies, the probable structure of the complexes is:

3.4. Antitumor screening

Some complexes were tested for the in vitro antitumor activity. The complexes were tested on primary adenocarcinoma (color). Appropriate controls for DMSO (solvent) were included in the final values. The complexes showed good activity at 100 and 10 nM solutions. But proliferation started in complexes on further dilution. In $[Pt(L^1)PPh_3Cl_2]$

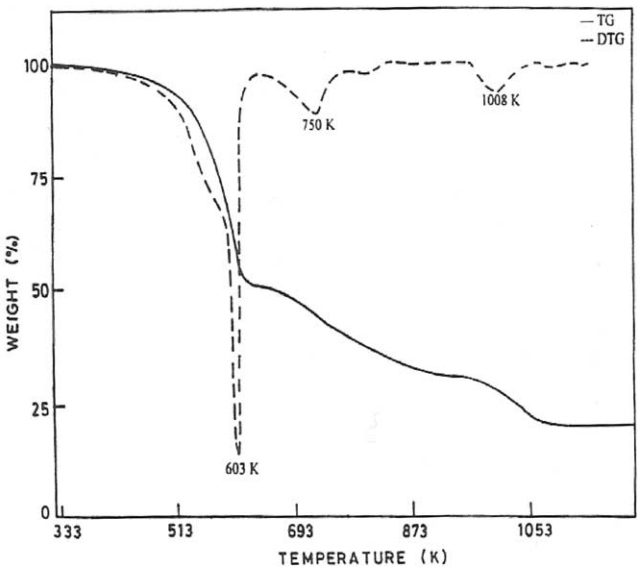

Fig. 2. TG and DTG curves of $[Pt(L^3)_2(PPh_3)Cl_3]$.

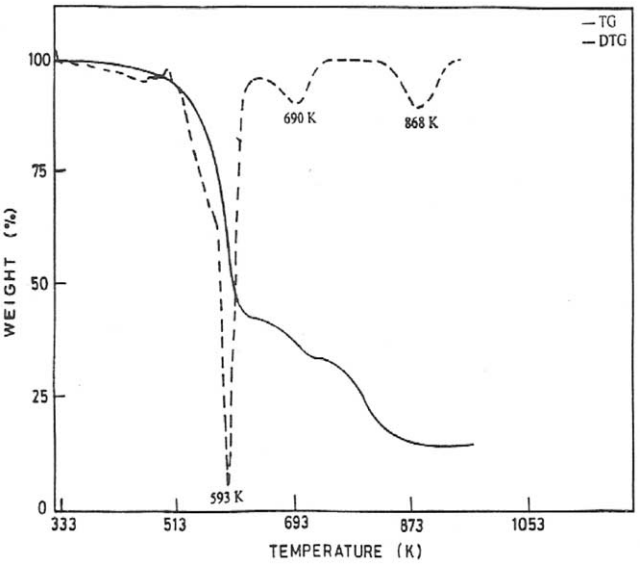

Fig. 3. TG and DTG curves of $[Pd(L^1)_2(PPh_3)Cl_3]$ complex.

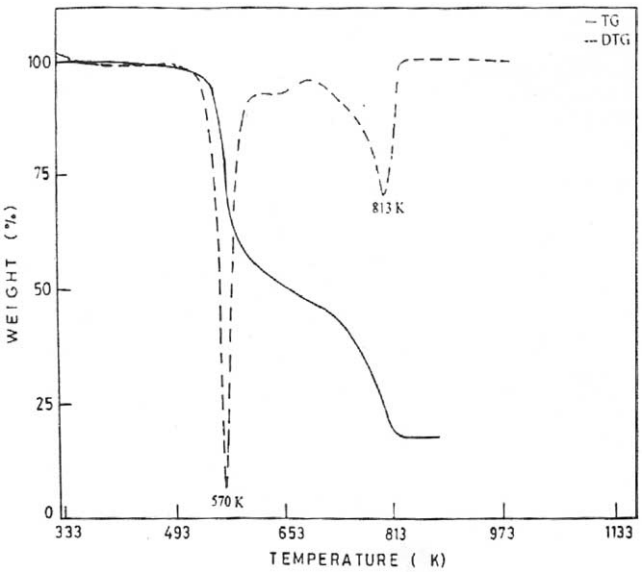

Fig. 4. TG and DTG curves of $[Pd(L^3)_2(PPh_3)Cl_3]$ complex.

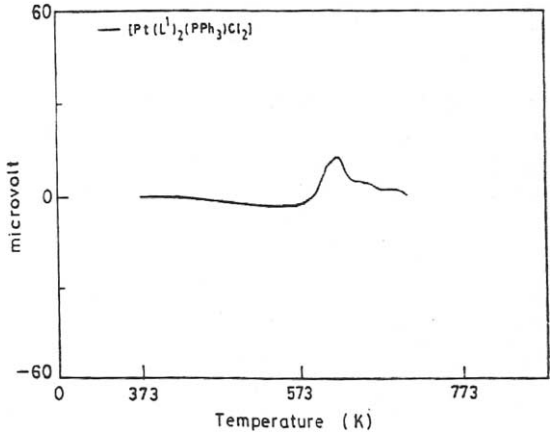

Fig. 5. DTA curves of $[Pt(L^1)_2(PPh_3)Cl_3]$.

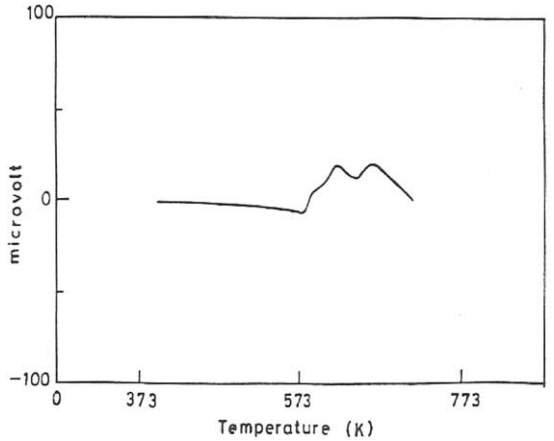

Fig. 6. DTA curves of $[Pd(L^1)_2(PPh_3)]$.

Table 5
Thermal data (TG and DTG) for mixed ligand complexes

Complex	Step no.	TG				DTG	DTA		
		Temperature range (K)	n	E_a (kJ mol^{-1})	$S^{\neq}$ (J K^{-1} mol^{-1})	Peak (K)	Thermal effect	T_{max}	ΔH (kJ g^{-1})
$[Pt(L^1)_2(PPh_3)Cl_2]$	I	354–678	1	91.1	36.2	618	Exotherm	621	55.0
	II	678–813	1	42.3	14.3	770			
	III	813–1083	1	41.1	13.6	1070			
$[Pd(L^1)_2(PPh_3)]$	I	396–644	1	86.5	34.2	593			
	II	644–734	1	42.1	14.3	690	Exotherm	663	115.0
	III	734–918	1	41.0	13.7	868			
$[Pt(L^3)_2(PPh_3)Cl_2]$	I	340–651	1	134.6	55.4	603			
	II	653–960	1	15.2	2.3	750			
	III	970–1070	1	70.1	26.2	1008			
$[Pd(L^3)_2(PPh_3)]$	I	413–686	1	153.8	63.8	570, 650			
	II	686–899	1	44.9	15.4	813			

complex, the activity found was significant enough at 1 pm concentration. Antitumor activity of the complexes is given in Table 4.

The complexes were further tested for any adverse effect on the various organs like liver, kidneys, brain and bladder of rabbits. The study was carried out by taking the rabbits weighing about 2–2.5 kg. Two sets of procedures were planned, one control and the other experimental. In the control rabbit ^{99m}Tc-labelled GHA was injected intravenously through the dorsal ear vein-whereas in the experimental rabbit platinum complex was injected (iv) followed by ^{99m}Tc-GHA injection (iv). Two hours after the first injection imaging was performed starting from 5 min to 4 h under the effect of selective using a planar gamma camera fitted with a paralleled collimater. In both the rabbits brain, kidneys and bladder were the organs which accumulated the activity. Liver was visualized in the very initial images but activity was cleared quickly from it. Administration of platinum complex did not change the pattern of localization of activity. It was concluded that the complex had no effect on the bioroutine of ^{99m}Tc-GHA, it did not reflect any additional information depicting its presence in the system.

3.5. Thermal studies

Thermal studies have been utilised for elucidation of a number of kinetic and thermodynamic parameters. From TG curves, the order (n), activation energy (E_a) and apparent activation entropy ($S^{\neq}$) have been enumerated by Coats–Redfern method [29]. From DTA curves, the heat of reaction has been calculated. The TG, DTG and DTA studies in static air atmosphere have been carried out for some complexes TG and DTG curves are shown in Figs. 1–4 while DTA curves are in Figs. 5 and 6. Thermal data of the complexes is given in Table 5.

TG and DTG curves indicate decomposition to be three step process. The first step corresponds to the loss of one dithiocarbamate ligand and triphenyl phosphine molecule. The second decomposition step corresponds to the formation of metal sulphide and after the third and final step the weight left corresponds to the metals as residue.

E_a values and $S^{\#}$ values are found to be higher for first step of decomposition than subsequent steps in all the complexes.

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