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Antitumour and Thermogravimetric Studies of Transition Metal Complexes of the Schiff Base, Anthracene-9-Carboxaldehyde Thiosemicarbazone

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The complexes of transition metals with anthracene-9-carboxaldehyde thiosemicarbazone, (A9CTSC) have been prepared and characterized. Square-planar geometry has been assigned to all these complexes, although the Cu(II) chelate exists in a dimeric form. A9CTSC acts as a monovalent bidentate ligand in all these complexes using the donor sites azomethine nitrogen and thiolate sulphur atoms. The thermal decomposition kinetics and mechanism of these chelates were studied from thermogravimetric data. The kinetic parameters, namely activation energy, E, pre-exponential factor, A, and entropy of activation, ΔS, were calculated from the TG and DTA curves using mechanistic and nonmechanistic integral equations. The ligand and Cu(II) complex were screened for their possible antitumour activity and the chelate was appreciably active in reducing mice tumours. X-ray diffraction pattern of one of the chelate [CdL_2] was examined and successfully indexed.

Key Words: Transition metal, Complexes, Schiff Base, Antitumour, Thermogravimetric.

INTRODUCTION

The chemotherapeutic importance of thiosemicarbazones against tuberculosis, small pox, influenza and certain kinds of tumour are well documented[1,2]. Various thiosemicarbozone derivatives act as chelating agents for transition and inner transition metal ions and their ability to chelate trace metals has been considered as one of the reasons for their pharmacological[3,4] and microbiological[5,6] activity. Studies on thermal decomposition and kinetics of metal chelates with azomethine ligands, especially of thiosemicarbazones, have been reported extensively[7–9]. Non-isothermal methods have been widely used to study the kinetics and mechanism of thermal decomposition of solid chelates[10,11]. Further, it is becoming increasingly clear that certain transition metal complexes of Schiff bases play a vital role as antitumour agents[12–14]. However, little information is available on metal chelates of Schiff bases derived from anthracene-9-carboxaldehyde. Therefore, it was considered worthwhile and interesting to investigate the reactions of anthracene-9-carboxaldehyde thiosemicarbazone towards various transition metal

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salts so as to isolate and characterize the solid complexes formed. The thermal decomposition kinetics and mechanism of these chelates were studied by TG and DTG techniques. The X-ray powder diffraction pattern of one of the complexes [CdL_2] was also examined. The cytotoxic action of the ligand and the Cu(II) complex against different tumour cell lines were analyzed *in vitro* and *in vivo*.

EXPERIMENTAL

Anthracene-9-carboxaldehyde used was purchased from Sigma Company, USA. The acetates of Cu(II) and Zn(II) and cadmium chloride were of BDH AnalaR products. The reagent grade solvents were purified before use by the standard procedures[15]. The chemicals used for the antitumour studies were of E. Merck's reagent grade. Minimum essential medium and trypsin were obtained from Hi-Media Laboratories Pvt. Ltd., Bombay. Ehrlich Ascites (EA) and Dalton's Lymphoma Ascites (DLA) tumour cell lines were collected from Tata Memorial Hospital, Mumbai and propagated in the peritoneal cavity of mice. National Faculty for Cell and Tissue Culture, Pune, provided the lung fibrablast tumour cells, L929, for the cultural studies. Swiss Albino mice for *in vivo* studies were bought from Christian Medical College, Vellore.

Preparation of the thiosemicarbazone: Hot solution of thiosemicarbazide (0.91 g, 0.0l mol) in 80% EtOH (20 cm^3) was added dropwise to a refluxing solution of anthracene-9-carboxaldehyde (2.06 g, 0.01 mol) in ethanol (50 cm^3) and refluxed further for 3 h on a steam bath. The mixture was cooled to room temperature while brown coloured crystals of the thiosemicarbazone were separated which was suction filtered, washed with dilute EtOH and dried over P_4O_{10}, m.p. 178°C.

General method for preparing the complexes

To a hot solution of the thiosemicarbazone (0.004 mol) in DMF-EtOH mixture (1 : 20) was added slowly a hot solution of the metal acetate/chloride (0.002 mol) in EtOH and the mixture was refluxed for 1 h. Sodium acetate (1 g) was added and refluxed for further 1/2 h. The solid complex separated was removed by filtration, washed thoroughly with EtOH-H_2O mixture (1 : 1) and dried over P_4O_{10}. For the Cu(II) complex, 1 : 1 molar ratio of metal and ligand was used. Approximately 75% yield was obtained for all the complexes.

Metal contents of the complexes were estimated by standard procedures[16]. Gravimetric method was adopted for the estimation of sulphur. The IR spectra in the range 4000–200 cm^{-1} were recorded using KBr discs on a Perkin-Elmer 580 spectrophotometer. The solid state electronic spectra of the ligand and complexes were recorded using Hitachi-3200 UV-Vis spectrophotometer. Magnetic susceptibilities at room temperature were determined using a Gouy balance with $Hg[Co(NCS)_4]$ as the reference material and magnetic moments were calculated making the necessary diamagnetic corrections[17]. Microanalysis was performed using a Heraues CHN—O rapid analyzer. ESR spectrum of the Cu(II) complex was recorded on a Varian E-109 EPR spectrophotometer using DPPH as the internal standard. Conductivity measurements in nitrobenzene were conducted

using Toshniwal conductivity bridge with a dip type cell and platinum electrode. Thermogravimetric analysis in air were made on a Perkin-Elmer TGS-1 thermal balance with a heating rate of 10°C min^{-1} and a sample size of 1–5 mg. The X-ray powder diffraction pattern of Cd(II) complex was obtained on Philips XRD (PW. 1712) model (34 kW, 10MA) employing CuKα radiation with a scan speed 2°C min^{-1} and $\lambda = 1.5418$ Å

In vitro and *In vivo* experiments

The *in vitro* cytotoxicity studies were performed using Ehrlich ascites and Dalton's lymphoma ascites tumour cells. The drugs were incubated with 1×10^6 cells at 37°C for 3 h. After incubation the percentage of dead cells was determined by the trypan blue exclusion method using Neubauer haemocytometer[18].

For the study of growth inhibitory activity of the drugs on the tissue cultured cells, L929 tumour cell line was used. The cells were grown in culture flasks with minimum essential medium (MEM, 10 cm^3) containing 10% heat inactivated serum and some antibiotics. Drugs were added in different concentrations and incubated for 6 days at 37°C. After the incubation period, the medium was removed and the cells were detached by tripsinization. The number of live cells was counted using haemocytometer.

In vivo experiments were conducted in the peritoneal cavity of Swiss albino mice. The Ehrlich ascites tumour cells were transplanted in the peritoneal cavity of 12 female Swiss albino mice (two groups of six each) so that they may develop ascites tumour. The lyposomally encapsulated drug was then administrated intraperitoneally to one group, 24 h after the transplantation of tumour cells, as five doses (50μg/dose/animal) on alternate days and the survival of the animal was watched. The other group was kept as a control. The percentage increase of life span (ILS) was calculated using the formula (T-C) 100°C, where T and C are the average number of survival days of the treated and control animals respectively.

Thermal behaviour

Mathematical evaluation of the mechanism of decomposition reactions from non-isothermal methods has been discussed by Sestak *et al.*[19] and Satava[20]. The procedure is based on the assumption that the non-isothermal reaction proceeds isothermally in an infinitesimal time interval, so that the rate can be expressed by an Arrhenius type equation

$$\frac{d\alpha}{dt} = Ae^{-E/RT} f(\alpha) \qquad (1)$$

where A is the pre-exponential factor, t the time and $f(\alpha)$ depends on the mechanism of the process. For a linear heating rate (ϕ), $\frac{dT}{dt} = \phi$ and substitution into eq. (1) gives

$$\frac{d\alpha}{f(\alpha)} = \int_0^T \frac{A}{\phi} e^{-E/RT} dt \qquad (2)$$

Integration of the left hand side of eq. (2) gives

$$\int_0^{\alpha} \frac{d\alpha}{f(\alpha)} = g(\alpha) = \int_0^{T} \frac{A}{\phi} e^{-E/RT} dt \quad (3)$$

where $g(\alpha)$ is the integral form of $f(\alpha)$. A series of $f(\alpha)$ forms are proposed and the mechanism is obtained from that which gives the best representation of the experimental data. For evaluating kinetic parameters from the mechanistic equations given by Satava[20], Coats and Redfern[21] equation was used in the general forms

$$\ln \frac{g(\alpha)}{T^2} = \ln \frac{AR}{\phi E} - \frac{E}{RT} \quad (4)$$

and the various $g(\alpha)$ values were substituted. This has been recommended to be one of the best solutions by several authors[22].

Along with the mechanistic equations, two non-mechanistic methods suggested by Coats-Redfern[21] and Horowitz-Metzger[23] were also used for comparison. The reaction order can easily be estimated by comparing their values using n = 0.33, 0.5, 0.66 and 1 in equations (5) and (6).

$$1 - (1 - \alpha)^{1-n}/(1 - n)T^2 \quad vs. \quad 1/T \quad \text{for } n \neq 1 \quad (5)$$

$$\log [-\log (1 - \alpha)]/T^2 \quad vs. \quad 1/T \quad \text{for } n = 1 \quad (6)$$

RESULTS AND DISCUSSION

All the complexes are coloured, non-hygroscopic, stable and crystalline solids. They are insoluble in water and common organic solvents such as alcohols, ethers, etc. but are appreciably soluble in DMSO and DMF. The analytical data of the ligand and complexes (Table-1) show that the complexes have the formulae $[CuL(OAc)]_2$, $[ZnL_2]$ and $[CdL_2]$. The molar conductance values show that the complexes are non-electrolytic in nature. Magnetic susceptibility measurements

TABLE-1
COLOUR, MICROANALYTICAL, MAGNETIC AND CONDUCTANCE DATA OF THE LIGAND (LH) AND COMPLEXES

Compound (Colour)	Analysis %, found (calcd.)					μ_{eff} (B.M.)	Molar conductance (ohm^{-1} cm^2 mol^{-1})
	M	C	H	N	S		
LH (Brown)	—	67.58 (68.82)	5.17 (4.66)	15.52 (15.05)	11.98 (11.47)	—	—
$[CuL(OAc)]_2$ (Grey)	14.98 (15.86)	55.13 (53.93)	3.71 (3.75)	9.77 (10.49)	8.48 (7.98)	1.22	3.3
$[ZnL_2]$ (Yellow)	11.33 (10.52)	63.27 (61.79)	4.91 (3.86)	12.89 (13.52)	11.25 (10.30)	Diamag	2.8
$[CdL_2]$ (Orange)	18.03 (16.82)	56.68 (57.45)	4.31 (3.59)	10.99 (12.57)	8.47 (9.57)	Diamag	7.6

reveal that the complexes, except Cu(II) complex, are diamagnetic, suggesting square-planar geometry for Zn(II) and Cd(II) complexes. The Cu(II) chelate exhibits the magnetic moment 1.22 B.M. which is a very low value compared to the spin only value 1.73 B.M. This suggests a dimeric square-planar configuration facilitating antiferro-magnetic exchange.

Infrared spectral data of anthracene-9-carboxaldehyde thiosemicarbazone shows that the ligand exists in the thioketo form in the solid state. Bands attributable to S-H vibrations in the region 2650–2500 cm^{-1} are absent in the IR spectrum of the ligand. The bands observed at 3400, 3200 and 3170 cm^{-1} in the spectra of the ligand can be attributed to the asymmetric and symmetric stretching vibrations of the terminal NH_2 and NH groups. The sharp band observed at 1610 cm^{-1} may be assigned to the C=N stretching vibration which upon complexation undergoes red shift by *ca.* 30 cm^{-1} indicating the involvement of azomethine nitrogen in coordination. Most of the bands in the spectrum of ligand, especially in the lower frequency region, undergo frequency shift and intensity changes during complex formation. The most marked effect is that of the 880 cm^{-1} band which may be due to C=S vibration. In the spectra of chelates, this band disappears and instead a new band in the region 700–600 cm^{-1} is exhibited. The absence of band at 3170 cm^{-1} in the spectra of complexes illustrates that the hydrogen atom of the secondary NH group of the ligand takes part in the complex formation. All these observations may be attributed to the enolization of C=S and subsequent coordination through the thiolate (S^-). A band of medium intensity at about 1690 cm^{-1} exhibited only in the IR spectrum of Cu(II) complex can be assigned to the carbonyl stretching vibration of the acetate group.

Further evidence for the nature of the metal-ligand bonding is given by ν(M—N) and ν(M—S) bands observed in the spectra of the chelates at 450–410 cm^{-1} and 320–290 cm^{-1} respectively[24]. Thus, A9CTSC behaves as a potentially monovalent bidentate ligand during complex formation.

Electronic spectrum of the Cu(II) chelate shows a single broad and poorly resolved absorption band around 13888 cm^{-1} characteristic of Cu(II) with D_{4h} symmetry[25]. Since this complex exhibits relatively low magnetic moment value (near to spin only value) and are four-coordinate, the Cu(II) complex is assumed to have a square-planar geometry. Zn(II) and Cd(II) complexes exhibit strong charge transfer bands at about 25000 cm^{-1}.

The ESR spectrum of the crystalline Cu(II) complex, measured at room temperature and liquid nitrogen temperature, shows a broad intense signal with isotropic *g* value 2.11. This value indicates considerable covalent character of the metal-ligand bond in the complex[26]. The dimeric structure of the Cu(II) chelate is given in Fig. 1.

The X-ray powder diffraction pattern of one of the complexes [CdL_2] was examined and successfully indexed for the cubic system using Hesse and Lipson's procedure[27]. The diffractogram records 16 reflections for this chelate between 5 and 30° (2θ) with maximum at 6.6°. The 2θ values for the prominent peaks, the observed and calculated $\sin^2\theta$ values together with the hkl and relative intensities

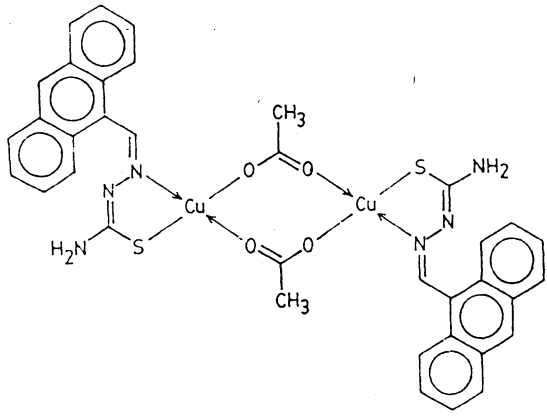

Fig. 1. Structure of Cu(II) chelate, $[CuL(OAc)]_2$

are given in Table-2. The observed data fit well in cubic system to give a unit cell with lattice constants a = b = c = 23.20 Å.

TABLE-2
OBSERVED AND CALCULATED $\sin^2\theta$ VALUES, hkl VALUES, RELATIVE INTENSITIES AND PLANE SPACING (d) OF $(CdL_2]$

Line	2θ	Plane spacing (d)	Relative intensity (I)	$\sin^2\theta$ (obs.)	$\sin^2\theta$ (calc.)	hkl
1	6.60	13.4930	100	0.0033	0.0033	111
2	9.45	9.3586	28	0.0067	0.0066	211
3	10.75	8.2296	99	0.0087	0.0088	220
4	11.75	7.5314	40	0.0104	0.0099	221
5	12.35	7.1668	40	0.0115	0.0110	310
6	14.43	6.1402	60	0.0157	0.0154	321
7	15.75	5.6265	98	0.0187	0.0187	410
8	17.85	4.9690	88	0.0240	0.0242	332
9	19.10	4.6465	30	0.0275	0.0276	500
10	20.65	4.3011	12	0.0321	0.0320	520
11	22.35	3.9777	20	0.0375	0.0375	530
12	24.15	3.6851	20	0.0437	0.0441	620
13	26.90	3.3143	75	0.0541	0.0540	632
14	27.90	3.1978	35	0.0581	0.0585	641
15	28.85	3.0946	68	0.0620	0.0618	642
16	29.70	3.0079	37	0.0656	0.0651	553

Thermal studies

The TG curves of all the chelates (Figs. 2–4) do not exhibit any detectable

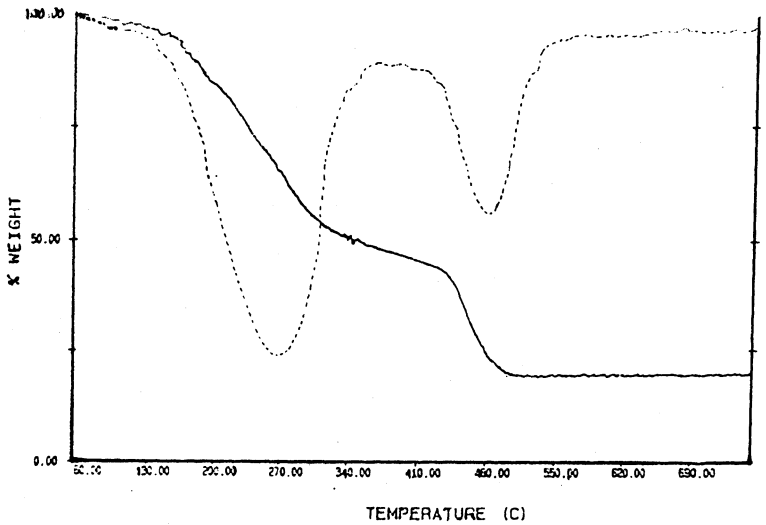

Fig. 2. TG and DTG traces of $[CuL(OAc)_2]_2$

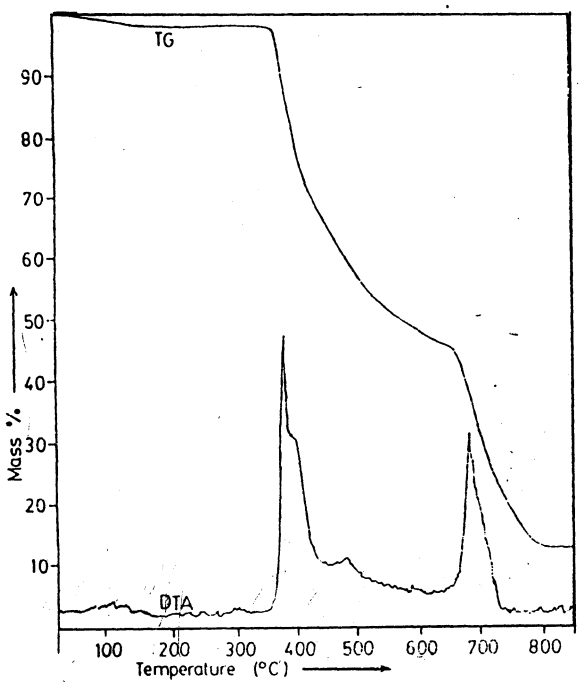

Fig. 3. TG and DTA traces of $[ZnL_2]$

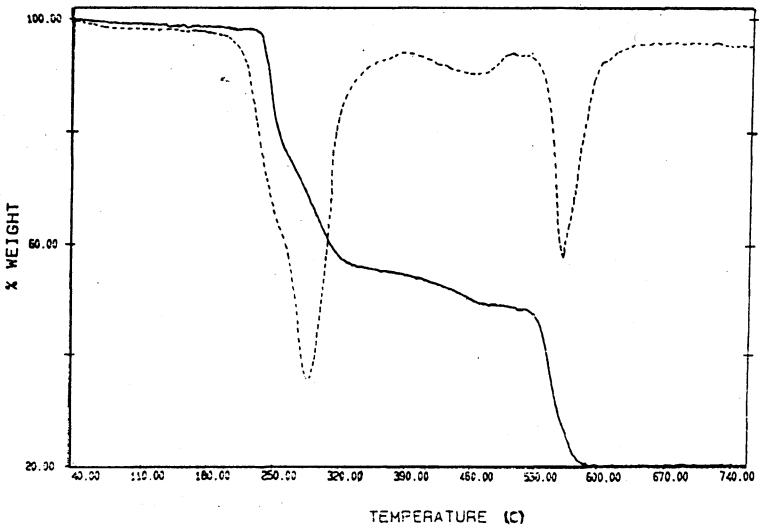

Fig. 4. TG and DTG traces of $[CdL_2]$

change up to 200°C, which suggests the absence of water of hydration as well as the coordinated water molecules. All these complexes show two clear-cut and non-overlapping stages of decomposition in their TG curves. The mass loss data of Zn(II) and Cd(II) complexes agree with the loss of two ligand moieties in two different steps. In the case of Cu(II) complex, $[CuL(OAc)]_2$, the first stage of decomposition can be assigned to the loss of aldehyde part of the ligand whereas the thiosemicarbazide part of the ligand molecule and the acetate group are removed in the second stage around 470°C. X-ray diffraction data and mass loss considerations confirmed the products to be the corresponding oxides, CuO, ZnO and CdO.

The thermal data for the metal complexes are given in Table-3. The kinetic parameters calculated from thermogravimetric data for the nine mechanistic equations are given in Table-4. The corresponding values E, A, ΔS and r from non-mechanistic equations (Coats-Redfern[21] and Horowitz-Metzger[23]) and the appropriate mechanistic equations are given in Table-5. The activation energies obtained for the different decomposition stages of the three complexes are also comparable to those of coordination compounds of transition metals having similar structures[28, 29].

Thermal stabilities of the metal complexes have been determined using initial decomposition temperatures and inflection temperatures. On the basis of our findings, the relative thermal stabilities of the present complexes can be given as $[CuL(OAc)]_2 < [ZnL_2] < [CdL_2]$

TABLE-3
THERMAL DECOMPOSITION DATA OF Cu(II), Zn(II) AND Cd(II) COMPLEXES OF ANTHRACENE-9-CARBOXALDEHYDE

Complex	Stage	Temp. ranges in TG (°C)	Peak temp. in TG (°C)	Peak temp. in DTA/DTG °C)	Loss of mass (%)			Probable assignments
					From TG	Calcd.	From pyrolysis (total mass loss)	
$[CuL(OAc)]_2$	I	100–320	290	290	48.00	47.44	—	Loss of aldehyde part
	II	320–490	470	475	32.00	32.71	—	Loss of thiosemicarbazide + acetate
					80.00	80.15	80.59	
$[ZnL_2]$	I	100–290	250	245	45.00	44.74	—	Loss of L
	II	290–650	570	560	42.00	42.17	—	Loss of L
					87.00	86.91	86.90	
$[CdL_2]$	I	100–310	290	290	42.70	41.59	—	Loss of L
	II	310–580	550	550	37.20	39.19	—	Loss of L
					79.90	80.78	81.22	

Decomposition kinetics

Data in the Tables 4 and 5 show that more than one equation gives good linear curves with a high value of correlation coefficient so that it may become difficult to assign the reaction mechanism unequivocally from the linearity of the curve alone. In such cases some authors have chosen the function $g(\alpha)$, which gives the kinetic parameters in agreement with those obtained by the numerical method. In the present case, it is observed that, for the second stage of decomposition of the Cd(II) complex and both stages of decomposition of Zn(II) complex, the E, A and ΔS values obtained from the Coats-Redfern[21] equations with n = 1 are in good agreement with E, A and ΔS values obtained from the Mampel equation which is based on random nucleation, one nucleus on each particle. The kinetic parameters obtained from Coats-Redfern[21] method with n = 1/3 and the R_2 mechanism based on a phase boundary reaction, cylindrical symmetry, was found to be in good agreement for the first stage of decomposition of the Cu(II) complex. The mechanistic equation followed during the first stage of decomposition of Cd(II) complex was found to be the D_1 mechanism with one dimensional diffusion.

TABLE -4

KINETIC PARAMETERS FOR THE DECOMPOSITION OF Cu(II), Zn(II) AND Cd(II) COMPLEXES OF ANTHRACENE-9-CARBOXALDEHYDE THIOSEMICARBAZONE FROM TG USING MECHANISTIC EQUATIONS

Complex	Parameter*	Mechanistic equations								
		1	2	3	4	5	6	7	8	9
$[CuL(OAc)]_2$										
Stage I	E	32.42	43.44	59.76	48.73	34.70	12.88	5.61	21.41	25.42
	A	1.57	1.76×10^{1}	3.17×10^{2}	1.65×10^{1}	7.34	1.82×10^{-2}	1.49×10^{-3}	8.35×10^{-2}	1.80×10^{-1}
	ΔS	-246.52	-226.45	-202.41	-227.01	-233.71	-283.62	-304.42	-270.95	-264.58
	r	0.9963	0.9978	0.9944	0.9971	0.9858	0.9758	0.9484	0.9950	0.9925
Stage II	E	213.40	261.57	338.41	285.93	209.32	98.53	61.59	144.07	163.07
	A	3.49×10^{12}	7.65×10^{15}	9.30×10^{20}	1.13×10^{17}	5.56×10^{12}	3.58×10^{4}	5.36×10^{1}	3.25×10^{7}	6.04×10^{8}
	ΔS	-12.38	51.59	148.97	74.01	-8.52	-165.38	-219.49	-108.74	-84.44
	r	0.9844	0.9931	0.9985	0.9962	0.9938	0.9931	0.9922	0.9972	0.9983
$[ZnL_2]$										
Stage I	E	189.24	200.55	213.33	204.79	108.85	50.01	30.38	99.08	102.24
	A	3.66×10^{15}	2.90×10^{16}	1.45×10^{17}	1.81×10^{16}	1.28×10^{8}	1.68×10^{2}	1.44	5.64×10^{6}	8.25×10^{6}
	ΔS	48.39	65.59	78.96	61.68	-99.44	-207.09	-246.62	-120.39	-117.22
	r	0.9341	0.9418	0.9496	0.9445	0.9530	0.9446	0.9339	0.9412	0.9453
Stage II	E	175.85	196.13	219.23	204.06	115.76	50.96	29.37	97.24	102.78
	A	9.55×10^{7}	1.21×10^{9}	1.05×10^{10}	9.47×10^{8}	3.49×10^{4}	1.75	4.90×10^{-2}	8.60×10^{2}	1.41×10^{3}
	ΔS	-100.82	-79.72	-61.76	-81.75	-166.65	-248.99	-278.74	-197.46	-193.36
	r	0.9727	0.9733	0.9734	0.9735	0.9705	0.9625	0.9507	0.9698	0.9683
$[CdL_2]$										
Stage I	E	60.05	76.89	101.10	84.77	59.52	25.12	11.16	39.98	45.92
	A	7.41×10^{2}	2.50×10^{4}	2.02×10^{6}	3.82×10^{4}	1.73×10^{3}	4.01×10^{-1}	1.46×10^{-2}	6.31	1.92×10^{1}
	ΔS	-195.34	-166.06	-129.53	-162.53	-188.27	-257.91	-285.48	-234.97	-225.72
	r	0.9947	0.9979	0.9986	0.9986	0.9963	0.9950	0.9928	0.9985	0.9984
Stage II	E	338.67	392.73	463.08	415.85	262.86	124.58	78.95	207.42	224.69
	A	8.87×10^{18}	1.83×10^{22}	1.93×10^{26}	1.40×10^{23}	3.19×10^{14}	2.75×10^{5}	2.11×10^{2}	2.97×10^{10}	2.90×10^{11}
	ΔS	109.43	172.89	249.93	189.84	24.31	-149.29	-208.93	-52.88	-33.94
	r	0.9650	0.9721	0.9793	0.9749	0.9833	0.9814	0.9791	0.9747	0.9780

*E in KJ mol^{-1}; A in S^{-1}; ΔS in J K^{-1} mol^{-1}; r = correlation coefficient

TABLE-5
KINETIC PARAMETERS FOR THE DECOMPOSITION OF Cu(II), Zn(II) AND Cd(II) COMPLEXES OF ANTHRACENE-9-CARBOXALDEHYDE THIOSEMICARBAZONE FROM TG USING NON-MECHANISTIC EQUATIONS

Complex	Parameter*	Coast-Redfern	Horowitz-metzger	Mechanistic	Equation followed	Order of reaction (n)
$[CuL(OAc)]_2$						
Stage I	E	17.83	29.52	21.42	Equation VIII:	1/3
	A	5.63×10^{-2}	1.13	8.35×10^{-2}	Phase	
	ΔS	-274.24	-249.25	270.96	boundary	
	r	0.9963	0.9992	0.9950	reaction, cylindrical symmetry	
Stage II	E	163.07	177.70	163.07	Equation IX:	2/3
	A	1.81×10^{9}	2.08×10^{10}	6.04×10^{8}	Phase	
	ΔS	-75.31	-55.02	-84.44	boundary	
	r	0.9983	0.9985	0.9983	reaction, spherical symmetry	
$[ZnL_2]$						
Stage I	E	108.86	112.5	108.86	Equation V:	1
	A	1.28×10^{8}	1.33×10^{8}	1.28×10^{8}	Mampel	
	ΔS	-94.45	-94.11	-94.45	equation	
	r	0.9530	0.9502	0.9530		
Stage II	E	115.76	133.31	115.76	Equation V:	1
	A	3.49×10^{4}	2.10×10^{5}	3.49×10^{4}	Mampel	
	ΔS	-166.66	-151.77	-166.66	equation	
	r	0.9705	0.9766	0.9705		
$[CdL_2]$						
Stage I	E	39.98	50.35	60.06	Equation I:	1/2
	A	1.26×10^{1}	1.44×10^{2}	7.41×10^{2}	One	
	ΔS	-229.22	-208.95	-195.34	dimensional	
	r	0.9985	0.9987	0.9947	diffusion	
Stage II	E	262.87	276.36	262.87	Equation V:	1
	A	3.19×10^{14}	1.03×10^{15}	3.19×10^{14}	Mampel	
	ΔS	24.32	34.03	4.32	equation	
	r	0.9833	0.9829	0.9833		

*E in KJ mol^{-1}, A in S^{-1}; ΔS in JK^{-1} mol^{-1}; r = Correlation coefficient

Antitumour studies

Based on the findings that the Cu(II) complexes exhibit marked antitumour activity[1, 13], the present Cu(II) complex was screened for its antitumour activity.

In vitro cytotoxic studies using Ehrlich ascites and Dalton's lymphoma ascites tumour cells (Table-6) reveal that the ligand has little or practically no cytotoxic action whereas the Cu(II) complex is remarkably active. A drug concentration of 10 $\mu g\ cm^{-3}$ produced 90% cell death towards both EA and DLA cell lines. Tissue culture studies using L929 tumour cells also show the same trend, where more than 85% growth inhibition was exhibited even with a concentration of 1 $\mu g\ cm^{-3}$. Further, *in vivo* studies were conducted with the Cu(II) complex, administration of which could considerably delay the onset of tumour development and increase the life span of the treated animals to 55.06% (Table-7).

TABLE-6
CYTOTOXIC ACTION OF THE LIGAND AND Cu(II) CHELATE ON EHRLICH ASCITES AND DALTON'S LYMPHOMA ASCITES TUMOUR CELLS

Compound	Tumour cell line	% Dead cell ($\mu g\ cm^{-3}$)				
		1	5	10	25	50
LH	EA	—	—	10	22	23
	DLA	—	—	05	17	19
$[CuL(OAc))]_2$	EA	63	76	90	100	100
	DLA	59	80	91	100	100

TABLE-7
EFFECT OF $[CuL(OAc)]_2$ ON SURVIVAL OF TUMOUR-BEARING MICE

Compound	Tumour model	Dose and mode of therapy	No. of mice survived after (days)					% ILS
			10	15	20	25	30	
$[CuL(OAc)]_2$	Ehrlich ascites	10 mg kg^{-1} b. wt Intraperitoneally	6	6	6	4	1	55.06
Control	Ehrlich ascites		6	6	0	0	0	—

From all these observations it is inferred that $[CuL(OAc)]_2$ possesses appreciable tumour reducing action. The significant activity of this compound may be due to its square-planar geometry, which is quite similar to the structure of *cis*-platin, a well known chemotherapeutic agent.

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