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Neutral Mixed-Ligand Complexes of 2,2'-Bipyridinedichloroplatinum(II) with Dianionic Aromatic Chelating Ligands as Potential Photosensitizers

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Six mixed-ligand complexes of the formula [Pt(bipy)(LL)], where bipy is 2,2'-bipyridine and LL is dianion of phthalic acid, salicylic acid, thiosalicylic acid, catechol, 4-tert-butylcatechol or 3,4-dimercaptotoluene, were prepared by interaction of [Pt(bipy)Cl$_2$] with an appropriate dianionic chelating ligand. The conductivity data in dimethylformamide confirm that these complexes are non-electrolytes. The ultra-violet spectra of these complexes show the charge-transfer transitions from platinum d-orbital to π-antibonding orbitals of bipy and $\pi-\pi^*$ transitions of bipy ligand. In addition, a strong band is observed between 16–23 kK (ϵ_{max} = 2000 to 3000 l mol^{-1} cm^{-1}) in all complexes except the phthalate derivative. This band is solvent-dependent and is assigned to ligand-to-ligand charge transfer. The ^{1}H NMR spectra of the complexes suggest the binding of LL to platinum through their deprotonated functional groups. The infrared data further confirm the above mode of binding of LL to platinum(II). The catechol,4-tert-butylcatechol, thiosalicylic acid, 3,4-dimercaptotoluene derivatives photosensitized $^3O_2$ to $^1O_2$ in presence of light. The $^1O_2$ thus produced combines with 2,2,6,6-tetramethyl-4-piperidinol molecules, and gives EPR-detected nitroxide free radicals.

Introduction

Recently the platinum(II) complexes containing heterocyclic ligands such as 2,2'-bipyridine, 1,10-phenanthroline and 2,2',2''-terpyridine have been shown to bind non-covalently to DNA through intercalation [1]. Several mixed-ligand complexes of Be(II), Zn(II), Ni(II) and Pt(II) having 2,2'-bipyridine, 1,10-phenanthroline and related ligands show absorption bands corresponding to ligand-to-ligand charge transfer (LLCT) transitions at low energies if one ligand has high-lying filled orbitals and other low-lying empty orbitals [2–5]. The Pt(II) complex such as [Pt(bipy)(DMT)] (where DMT is 3,4-dimercaptotoluene) can be photo-oxidized when its chloroform solution is irradiated at 557 nm. This photo-oxidation seems to involve the triplet state of LLCT transition in the electron transfer process [5]. In view of the importance of mixed ligand platinum(II) complexes as metallointercalating reagents and in inorganic photochemistry, we report here the synthesis and characterization of [Pt(bipy)(LL)], where LL is the dianion of phthalic acid (PTH), salicylic acid (SAL), thiosalicylic acid (TSAL), catechol (CAT), 4-tert-butylcatechol (BCAT) or 3,4-dimercaptotoluene (DMT). Some of these complexes have been found to photosensitize $^3O_2$ to $^1O_2$ in the presence of light.

Experimental

Starting materials

Potassium tetrachloroplatinate(II), K$_2$[PtCl$_4$], was purchased from the Strem Chemical Co. (U.S.A.), 2,2,6,6-Tetramethyl-4-piperidinol was purchased from the Aldrich Chemical Co. (U.S.A.). 2,2'-Bipyridine (bipy) was bought from SISCO (India). Phthalic acid, salicylic acid, thiosalicylic acid, catechol, 4-tert-butylcatechol and 3,4-dimercaptotoluene were purchased from B.D.H. (England). The solvents were of reagent grade and were purified by standard methods [6] before use.

Synthetic Procedures

[Pt(bipy)Cl$_2$]

This complex was prepared according to the method given in [7].

[Pt(bipy)(PTH)]

[Pt(bipy)Cl$_2$] (422 mg, 1 mmol) was dissolved in 50 ml of dimethylformamide (DMF) and an appropriate quantity of AgNO$_3$ (320 mg, 1.9 mmol) was added. The mixture was heated on a water bath for one hour in the dark. The white precipitate of AgCl was removed by filtration through Whatman 42 filter paper. The traces of AgCl in the filtrate were finally removed by centrifugation at 4000 rpm for about 30 minutes. The clear yellow supernatant liquid was mixed with 250 ml of benzene and kept overnight in a refrigerator. A yellow precipitate was

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TABLE I. Colour, Yield and Chemical Analysis Data of [Pt(bipy)(LL)] Complexes.

Compound	Colour	Yield %	Calculated			Found		
			%C	%H	%N	%C	%H	%N
[Pt(bipy)(PTH)]	Yellow	60	41.94	2.33	5.44	41.92	2.98	5.35
[Pt(bipy)(SAL)]	Orange	50	41.89	2.46	5.75	41.50	2.31	5.19
[Pt(bipy)(TSAL)]	Orange	60	40.56	2.39	5.57	40.39	3.06	5.38
[Pt(bipy)(CAT)]	Violet	40	41.83	2.61	6.10	41.30	3.05	5.86
[Pt(bipy)(BCAT)]	Violet	40	44.27	3.30	5.44	44.77	3.90	5.57
[Pt(bipy)(DMT)]	Violet	40	40.40	2.77	5.54	40.33	2.87	4.97

obtained, which was filtered. This precipitate was dissolved in 50 ml of distilled water.

To the above solution an aqueous solution of disodium salt of phthalic acid (1.1 mol) was added in slight excess. The precipitate of the desired compound was obtained. This precipitate was filtered, washed several times with distilled water, and dried in vacuum at room temperature.

[Pt(bipy)(SAL)]

This compound was synthesized by the preparative method of [Pt(bipy)(PTH)] except that the disodium salt of salicylic acid was used in place of the disodium salt of phthalic acid. The resulting compound was recrystallized from a 1:1 mixture of methanol and chloroform.

[Pt(bipy)(TSAL)]

[Pt(bipy)Cl_2] (422 mg, 1 mmol) was dissolved in 50 ml of dimethyl sulphoxide (DMSO). 1 mmol of disodium salt of thiosalicylic acid in small quantity of water was added to the above solution. The reaction mixture was stirred for 4–5 hours. The compound was precipitated by adding water to the above solution. The precipitate was filtered, washed several times with distilled water, and dried in air. The compound was recrystallized by use of a chloroform–acetone mixture (1:1). The orange-red crystals were filtered, washed with cold acetone, and dried in vacuum at room temperature.

[Pt(bipy)(CAT)]

The preparative method of this compound was the same as that given for [Pt(bipy)(TSAL)], except that the disodium salt of catechol was used in place of the disodium salt of thiosalicylic acid.

[Pt(bipy)(BCAT]

This compound was prepared by following the synthetic method of [Pt(bipy)(TSAL)], except that the disodium salt of 4-tert-butylcatechol was used in place of the disodium salt of thiosalicylic acid. The resulting compound was recrystallized from ethanol. The crystals were filtered, washed with a small quantity of cold ethanol, and finally with diethyl ether. The compound was dried in vacuum at room temperature.

[Pt(bipy)(DMT)]

This compound was prepared by following the synthetic procedure given for [Pt(bipy)(TSAL)] except that the disodium salt of 3,4-dimercaptotoluene was used in place of the disodium salt of thiosalicylic acid. The resulting compound was recrystallized from ethanol. All the operations for synthesizing this compound were carried out in the dark.

Chemical analyses of carbon, hydrogen and nitrogen were carried out by standard methods.

Photochemical Measurements

The photoproduction of $^1O_2$ by [Pt(bipy)(LL)], where LL is TSAL, CAT, BCAT or DMT, was measured by EPR method using 2,2,6,6-tetramethyl-4-piperidinol as a singlet oxygen acceptor [8, 9]. Typically 25 ml of 200 μM solution of the above complexes in dimethylformamide (spectroscopic grade) were bubbled for 15 minutes with solvent saturated oxygen. Then the 2,2,6,6-tetramethyl-4-piperidinol was added to a final concentration of 10 mM, and the mixture was irradiated by light under one atmosphere of air in a double-jacketed pyrex vessel which was thermostatted at 25 ± 1 °C by circulating water through the jacket. The light source was a stabilized 150 watt tungsten-halogen lamp operating at 18 volts.

Physical Measurements

The electron paramagnetic resonance (EPR) spectra of the nitroxide free radicals formed by reaction of 2,2,6,6-tetramethyl-4-piperidinol with singlet oxygen were recorded at room temperature in EPR aqueous cell at different irradiation times on a Varian E-112 ESR spectrometer (X-band) using TCNE as g marker (g = 2.00277). Other physical measurements were carried out as described earlier [10, 11].

TABLE II. Electronic Absorption Spectra of [Pt(bipy)(LL)] Complexes in DMF.

Compound	Band Maxima (ϵ_{max}) in kK[a]					
	Band 1	Band 2	Band 3	Band 4	Band 5	
[Pt(bipy)Cl$_2$]	–	25.38	30.49	31.60	35.34	
[Pt(bipy)(PTH)]	–	26.74	30.67	31.85	36.50	
		(0.26)[b]	(0.98)	(0.88)	(1.66)	
[Pt(bipy)SAL)]	22.32	27.10	30.77	32.15	35.97	
	(0.19)	(0.29)	(0.84)	(1.04)	(1.38)	
[Pt(bipy)(TSAL)]	20.16	27.47	30.96	32.26	35.21	37.17
	(0.28)	(0.47)	(1.08)	(1.42)	(2.40)	(1.74)
[Pt(bipy)(CAT)]	18.18	26.88	30.58	33.78	37.59	
	(0.50)	(0.17)	(0.41)	(2.61)	(1.17)	
[Pt(bipy)(BCAT)]	17.54	26.33	30.40	33.45	37.18	
	(0.27)	(0.19)	(0.63)	(1.62)	(1.31)	
[Pt(bipy)(DMT)]	17.64	27.17	32.36	34.48	37.31	
	(0.74)	(0.15)	(2.60)	(1.99)	(2.60)	

[a] kK is 1×10^3 cm^{-1}. [b] Extinction coefficients in l mol^{-1} cm^{-1} cm^{-1} $\times 10^{-4}$ are given in parentheses.

TABLE III. Solvent Effect on Band 1 of [Pt(bipy)(LL)] Complexes.

Compound	λ_{max} in kK			
	Methanol	DMSO	DMF	Chloroform
[Pt(bipy)(SAL)]	22.47	22.47	22.32	20.41
[Pt(bipy)(TSAL)]	20.70	20.53	20.16	18.87
[Pt(bipy)(CAT)]	20.20	18.52	18.18	17.30
[Pt(bipy)(BCAT)]	19.76	17.92	17.54	16.53
[Pt(bipy)(DMT)]	18.52	18.02	17.64	16.23

Results and Discussion

Six neutral mixed-ligand complexes of general formula [Pt(bipy)(LL)] were prepared, where LL are dianions of phthalic acid, salicylic acid, thiosalicylic acid, catechol, 4-tert-butylcatechol and 3,4-dimercaptotoluene. The colour, yield and chemical analysis of these complexes are given in Table 1. The molar conductance values of these complexes in dimethylformamide solution (10^{-3} *M*) vary in the range of 2.6 to 21.5 cm^2 ohm^{-1} mol^{-1}. These small values of molar conductance indicate them to be non-electrolytes [12].

The ultraviolet–visible spectra of the platinum(II) complexes in dimethylformamide show several band maxima. The positions of these band maxima and their extinction coefficients are given in Table II. The bands in the ultraviolet region are assigned following band assignments of [Pt(bipy)Cl$_2$] [13]. The band 2 between 25 to 29 kK is due to a charge-transfer transition from platinum d-orbital to π-antibonding orbital of 2,2′-bipyridine. The band 4 is due to charge-transfer transition from the same platinum orbital to a higher π-antibonding orbital of 2,2′-bipyridine. The bands 3 and 5 are assigned to the first and second internal π–π^* type transitions of 2,2′-bipyridine respectively. In the visible region one strong band is observed between 16 to 23 kK (ϵ_{max} = 2000 to 3000 l mol^{-1} cm^{-1}) in all complexes except [Pt(bipy)(PTH)]. This band has comparable intensity to the charge-transfer band 2 and is highly solvent dependent. The maxima of this band in methanol, dimethyl sulphoxide, dimethylformamide and chloroform are given in Table III. In chloroform solution, this band shows maximum red shift. The large extinction coefficient of this band suggests it to be a LLCT band as assigned earlier for [Pt(bipy)(DMT)] [5]. The requirement for showing ligand-to-ligand charge transfer band in the mixed-ligand platinum(II) complexes is that the LL ligand must have at least one $-O^-$ or $-S^-$ group.

The selective bands in the infrared spectra of the mixed-ligand platinum(II) complexes in the range 4000 to 200 cm^{-1} have not been discussed before. The infrared spectrum of [Pt(bipy)Cl$_2$] shows two vibrational bands at 340 cm^{-1} (shoulder) and 337 cm^{-1} due to ν(Pt–Cl) vibrations [14]. However, these bands disappear in the infrared spectra of

TABLE IV. ^{1}H NMR Spectral Data of [Pt(bipy)(LL)] Complexes in DMSO-d_6.

Compound	2,2′-bipyridine protons			Ligand (LL) protons			
	$\delta_{H\text{-}6,6'}$[a]	$\delta_{H\text{-}5,5'}$	$^3J_{Pt-H(6,6')}$ (Hz)	δ_{H_A}	δ_{H_B}	δ_{H_C}	δ_{H_D}
[Pt(bipy)Cl$_2$]	9.52	7.86	42.0	–	–	–	–
[Pt(bipy)(PTH)]	9.16	7.84	–	7.42 (7.69)[b]	7.24 (7.69)	7.24 (7.69)	7.42 (7.69)
[Pt(bipy)(SAL)]	8.94	7.85	32.0	7.14 (7.50)	6.59 (7.00)	6.86 (7.00)	7.14 (7.96)
[Pt(bipy)(TSAL)]	8.96	7.98	–	7.42 (7.32)	7.04 (7.32)	7.20 (7.32)	7.64 (8.16)
[Pt(bipy)(CAT)]	–	7.75	–	6.49 (6.75)	6.24 (6.75)	6.24 (6.75)	6.49 (6.75)
[Pt(bipy)(BCAT)]	9.13	7.74	–	7.24 (7.92)	6.41 (6.81)	1.26 (1.20)	6.41 (6.81)
[Pt(bipy)(DMT)]	9.12	7.80	–	7.11 (7.30)	6.56 (6.89)	2.22 (2.25)	7.05 (7.27)

[a]Chemical shifts are given in δ, ppm. [b]Chemical shifts of free ligands are given in parentheses.

[Pt(bipy)(LL)] complexes. This suggests that the LL ligands have displaced the chloride ions from the coordination sphere of platinum.

The infrared spectrum of [Pt(bipy)(PTH)] shows a strong band at 1650 cm^{-1} which is due to coordinating –COO$^-$ groups to platinum(II) [15]. In the [Pt(bipy)(SAL)] complex, the ν(COO$^-$) vibration is observed at 1622 cm^{-1} as a strong band. This confirms the binding of the –COO$^-$ group of salicylic acid to platinum(II). In addition, the two strong bands at 1483 and 1300 cm^{-1} confirm the binding of salicylic acid to platinum(II) through the ionized hydroxyl group [16]. In the [Pt(bipy)(TSAL)] complex, the ν(COO$^-$) vibration is observed at 1680 cm^{-1}, which indicates the binding of –COO$^-$ group to platinum(II).

In addition, the ν(S–H) vibration present at 2520 cm^{-1} in free thiosalicylic acid was absent in the complex. The infrared spectrum of [Pt(bipy)(CAT)] complex shows strong bands at 1480 and 1273 cm^{-1}, which suggests the binding of ionized hydroxyl groups of catechol to platinum(II) [16]. In the [Pt(bipy)(BCAT)] complex, bands at 1480 and 1280 cm^{-1} have also been observed and they again suggest the binding of ionized hydroxyl groups coordinated to platinum(II). The infrared spectrum of free 3,4-dimercaptotoluene shows ν(S–H) vibration at 2540 cm^{-1} which is absent in the spectrum of the [Pt(bipy)(DMT)] complex. This suggests that –SH groups are ionized in the complex.

The ^{1}H NMR spectral data of [Pt(bipy)(LL)] complexes in deuterated dimethyl sulphoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal standard are given in Table IV. The coordination of platinum(II) normally produces downfield shifts for ligand protons, and the extent of the shifts of the ligand protons to lower fields decreases with increasing distance from the coordination site [17]. The chemical shifts of H-6,6′ and H-5,5′ protons of 2,2′-bipyridine molecule appear at 9.52 ppm and 7.86 ppm respectively in [Pt(bipy)Cl$_2$], whereas these protons invariably show upfield shifts in [Pt(bipy)(LL)]. These upfield shifts are more dominant in H-6,6′ protons and can be interpreted in terms of stronger binding of LL ligands to platinum(II) as compared to the binding of chloride ions to platinum(II) [18]. The $^3J_{Pt-H\text{-}6}$ for ^{195}Pt–H–C–H fragments are also observed in a few complexes (see Table IV).

The numbering scheme of protons of ligands is given in Fig. 1. The ^{1}H NMR spectrum of free phthalic acid in D_2O gives a multiplet at 7.69 ppm, which corresponds to four protons of the benzene ring. The [Pt(bipy)(PTH)] complex in DMSO-d_6 shows H_A and H_D protons at 7.42 ppm, and H_B and H_C protons at 7.24 ppm (see Table IV). The presence of lower field signals of H_A and H_D protons as compared with the signals of H_B and H_C protons indicates that –COO$^-$ groups are coordinated to platinum(II). The presence of proton signals of free phthalic acid at lower field than the proton signals of phthalate dianion in the complex may be due to stronger bonding of protons to –COO$^-$ groups of free phthalic acid.

The H_D and H_A protons of [Pt(bipy)(SAL)] appear at 7.14 ppm. The H_C proton appears at 6.86 ppm and the H_B proton at 6.59 ppm. These protons are upfield-shifted as compared to corresponding protons of free ligand. These upfield shifts are due to liberation of protons from –OH and –COOH groups and coordination of –O$^-$ and –COO$^-$ groups to platinum(II). The chemical shifts

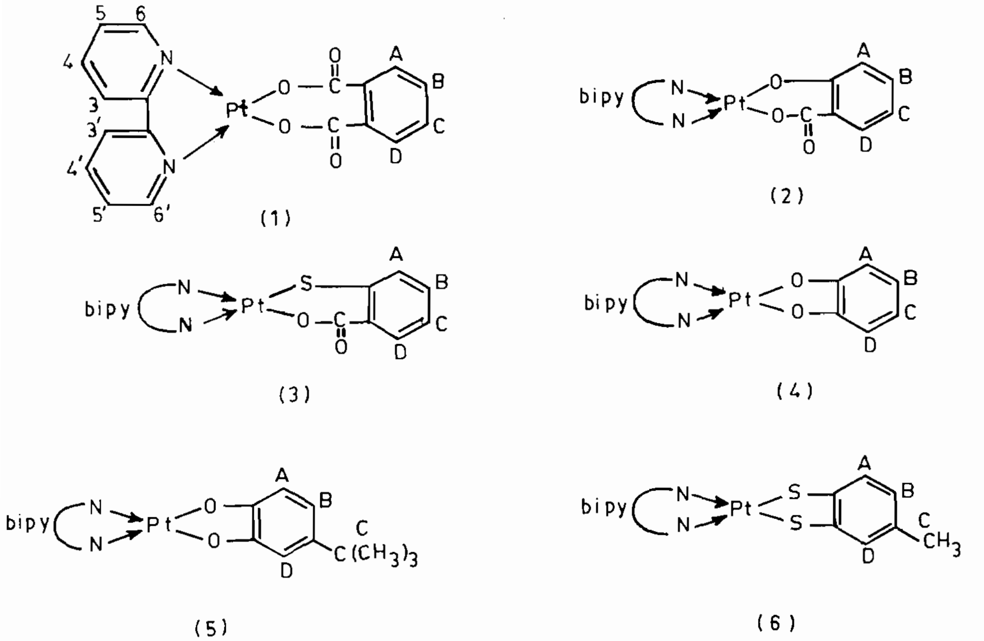

Fig. 1. Structure and numbering scheme of protons of [Pt(bipy)(LL)] complexes: LL is PTH in (1), SAL in (2), TSAL in (3), CAT in (4), SCAT in (5) and DMT in (6).

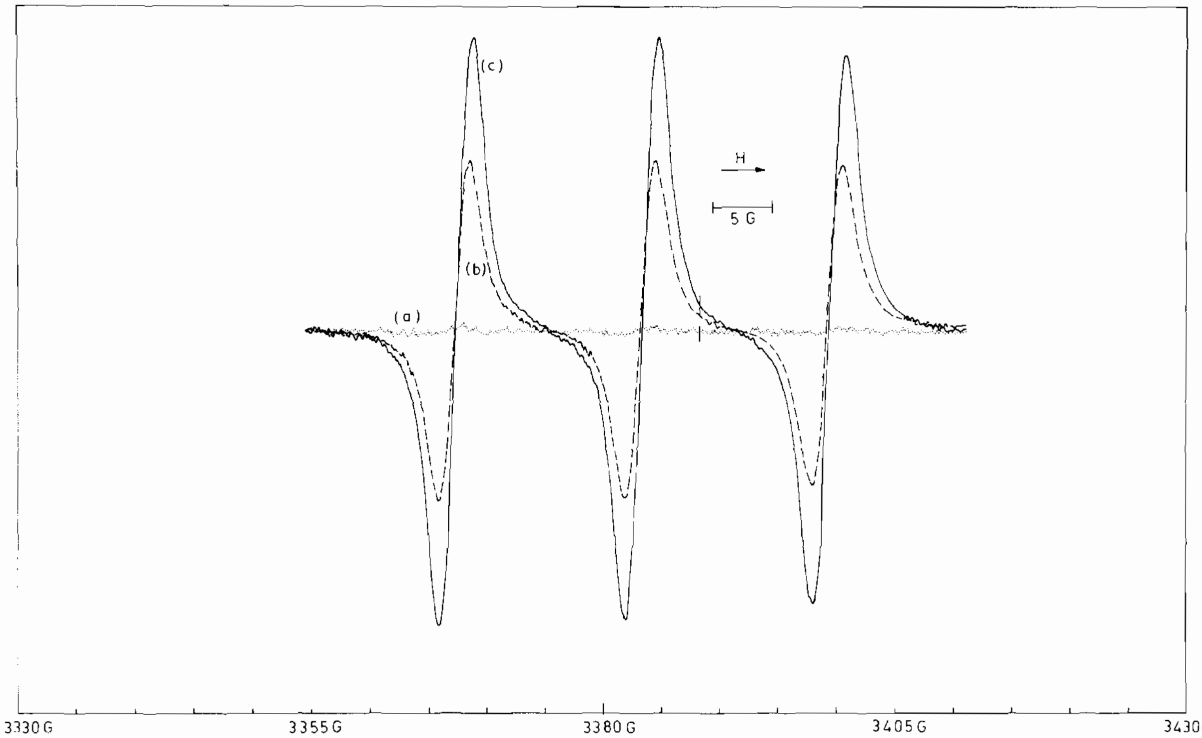

Fig. 2. EPR spectra of the aerated DMF solution of [Pt(bipy)(BCAT)] (200 μM) and 2,2,6,6-tetramethyl-4-piperidinol (10 mM) at different times of irradiation: (a) 0 min, (b) 45 min, and (c) 90 min.

of protons of TSAL in [Pt(bipy)(TSAL)] follow the trend similar to [Pt(bipy)(SAL)] (see Table IV) and confirm the binding of thiosalicylic acid to platinum(II) through $-S^-$ and $-COO^-$ groups. Here again the dianionic ligands bind more strongly with protons than with platinum(II).

The [Pt(bipy)(CAT)] shows two sets of multiplets of two protons at 6.49 ppm (H_A and H_D) and 6.24

ppm (H_B and H_C). The low field shift of H_A and H_D protons as compared to H_B and H_C protons is due to bonding of catechol to platinum(II) through $-O^-$ groups. However, the [Pt(bipy)(BCAT)] complex has a substitution of 4-tert-butyl group in the benzene ring of BCAT and the [Pt(bipy)(DMT)] complex has methyl group substitution in the benzene ring of DMT (see Fig. 1). These side chains have electron-donating character and the proton H_B is expected to be at the highest field. Thus, the H_B proton is present at 6.41 ppm in [Pt(bipy)(BCAT)] and at 6.56 ppm in [Pt(bipy)(DMT)]. The H_D proton of these two complexes is observed at lower field and the H_A proton at still lower field than the H_B proton. The nine protons of 4-tert-butyl group in [Pt(bipy)(BCAT)] appear at 1.26 ppm and three protons of methyl group in [Pt(bipy)(DMT)] appear at 2.22 ppm. These data suggest that BCAT and DMT are coordinating to platinum(II) by $-O^-$, O^- and $-S^-$, S^- groups respectively. Again, all these dianionic ligands bind protons more tightly than platinum(II).

The aerated DMF solutions of [Pt(bipy)(CAT)], [Pt(bipy)(BCAT)], [Pt(bipy)(TSAL)] and [Pt(bipy)(DMT)] were irradiated by light at different times. The singlet oxygen ($^1O_2$) thus formed combines with 2,2,6,6-tetramethyl-4-piperidinol molecules giving nitroxide free radicals, detected by EPR spectroscopy [8, 9]. Figure 2 gives the spectra of light exposed aerated solution of [Pt(bipy)(BCAT)] in DMF during 0, 45 and 90 minutes. The amount of nitroxide free radical measured by the EPR method bears a direct relationship to the $^1O_2$ produced, possibly via energy transfer from triplet of above platinum(II) complexes [8]. The relative ability of these complexes to yield $^1O_2$ has shown the order, [Pt(bipy)(DMT)] > [Pt(bipy)(TSAL)] ≫ [Pt(bipy)(BCAT)] > [Pt(bipy)(CAT)]. The yield of $^1O_2$ produced by [Pt(bipy)(DMT)] is comparable to its yield produced by hematoporphyrin IX [20]. Thus, these complexes behave as potential photosensitizers of $^3O_2$ to $^1O_2$.

Neutral mixed-ligand [Pt(bipy)(LL)] complexes should have good cell membrane permeability and are possibly anti-cancer agents [19]. Some of these complexes are potential photosensitizers of $^3O_2$ to $^1O_2$, and are expected to show possible antitumor activity similar to the hematoporphyrin derivative [21, 22].

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