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SAR and DFI studies of supramolecular tetraammoniumplatinate + DNA matrix with UV/Vis spectrophotometry and physicochemical analysis at 298.15 K

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ABSTRACT

DNA binding activity of bis(benzyldimethylalkylazaniumyl) tetrachloroplatinumdiuide supramolecular complexes (MBKs) was studied at 298.15 K with UV/Vis spectrophotometric and physicochemical methods. In UV/Vis spectrophotometric method, absorbance at $\lambda_{max} = 260$ nm has inferred a hyperchromic effect for explaining intercalating nature of MBKs. DNA binding constant in spectrophotometric titrations for intercalating strength of complexes has shown stronger intercalating activities of MBK8 and MBK12. Density, sound velocity and refractive index of DNA have been studied before and after interaction with MBKs with their stronger interaction. Isentropic and apparent molal compressibilities have inferred that the supramolecular interactions cause distortion of DNA helix. The relative viscosity of DNA-MBKs inferred intercalation of MBKs with DNA due to an aromatic ring in MBKs. DFI relationship shows lowering in surface tension and increases in viscosity data of DNA-MBKs solution, and explained their interaction pattern. This DFI study explained their structure–activity relationship (SAR) as well as their anticancer nature.

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1. Introduction

Serendipitous discovery of cis-diamminedichloridoplatinum (II) is popularly known as cisplatin that has introduced platinum complexes in the field of chemotherapy. Later, many platinum based drugs have developed and undergone in vitro and in vivo analysis, reportedly, some of them reached upto clinical level[1]. Not only cisplatin analogous but also supramolecular platinum salts have significant historical importance in area of medicinal sciences [1,2]. Many platinum salts are being used to cure various categories of human cancers; however, their side-effects like nephrotoxicity and drug resistance restrict their wider uses [3,4]. Previously [5], we have reported metallosupramolecular ionic network of tetraammoniumplatinate $[(C_6H_5CH_2N(CH_3)_2(C_nH_{2n+1})]_2^+[PtCl_4]^{2-}$ (MBK8, MBK10, MBK12 and MBK14) depicted in Fig. 1, where benzalkonium chloride (BKC) was selected as cationic part of tetraammoniumplatinate complexes (TC), which has huge biological applications [6]. BKC is used as a cationic surfactant for rapid and prolonged incorporation into cell lipid membranes [7,8]. With its huge applicability in medicinal areas, it is considered at trials in transmission of HIV [9]. Apart from synthesis, the DNA binding study is a practical approach, through which, the medicinal applications of complexes are identified such as anticancer activity, because binding with DNA is a primary molecular target of any anticancer drugs [10]. Thereby, the DNA binding with platinum complexes have been widely examined during past several decades, due to, their use as potential anticancer drugs, DNA structural probes, DNA-dependent electron transfer probes, DNA foot printing, sequence-specific cleaving agents and so on have in hot discussion [10–12]. Thus, the DNA targeted metal based drugs involving non-covalent DNA binding; particularly metallointercalators have drawn attention in advancement of efficient anticancer drugs [13]. Considering such specification, the investigation of DNA binding activity of TC has been our main concern, and in the present study, we reported DNA binding study of TC which is analyzed with UV/Vis spectrophotometric and physicochemical method. Such contributions could be helpful in designing novel ionic complexes of platinum which could be an asset in medical or pharmaceutical progressions.

2. Experimental section

2.1. Materials and methods

Synthesized bis(benzyldimethyloctylazaniumyl) tetrachloroplatinumdiuide (MBK8), bis(benzyldimethyldecylazaniumyl) tetrachloroplatinumdiuide (MBK10), bis(benzyldimethyldodecylazaniumyl) tetrachloroplatinumdiuide (MBK12) and bis(benzyldimethyltetradecylazaniumyl) tetrachloroplatinumdiuide (MBK14) are studied for DNA interaction. Table 1 furnishes information about the chemicals used in this study whose purification was checked with chromatographic method and the water contents were checked with Karl Fischer. The Milli-Q water (Millipore SAS 67/20 Mosheim)

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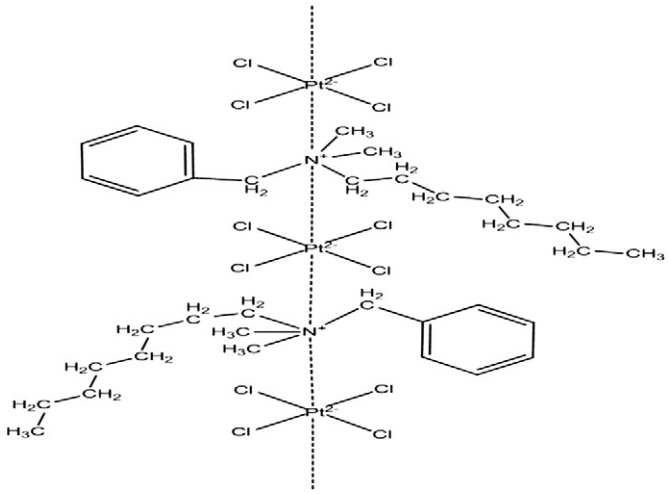

Fig. 1. General structure of supramolecular MBK.

Table 1
Materials.

Chemicals	Source	Cas no	%Purity
Tris–HCl buffer	Sigma	1185-53-1	>99
DMSO	Rankem	67-68-5	99.8

Table 2
Calibration of survismeter: density ($\rho^{Literature}$), PDN ($n^{Experimental}$), VFT ($t^{Experimental}$), viscosity ($\eta^{Literature}$), surface tension ($\gamma^{Literature}$), calibration constant for viscosity ($K\eta$) and surface tension ($K\gamma$) at 298.15 K. Standard uncertainties u are: $u(T) = 0.01$ K, $u(\rho) = 1 \times 10^{-5}$, $u(\ ) = 1 \times 10^{-4}$, and $u(\gamma) = 1 \times 10^{-2}$.

$10^3 \cdot \rho^{lit}$	n	t	η^{lit}	γ^{lit}	K_η	K_γ
kg m^{-3}		s	mPa·s	mN/m		
0.997044 [36]	121	90.81	0.8937 [37]	71.97 [38]	0.00987	8806.0448
	122	90.81			0.00987	8806.0448
	122	90.82			0.00987	8806.0448
	122	90.81			0.00987	8806.0448
	122	90.82			0.00987	8806.0448

of 10^{-7} S cm^{-1} was used for Tris–HCl buffer solution preparation. The ct-DNA (analytical grade) stock solution was prepared using aqueous Tris–HCl buffer (10 M, pH = 7.2) and then diluted with the same buffer twice. The complex solutions were prepared with 10% DMSO in buffer for absorption titrations and also for measurements of physicochemical properties. Absorption titrations of TC in DMSO-buffer were performed using variable complex concentrations (10, 30, 50, 70 and 90 μM) to which the DNA stock solution (50 μM) was added, (ri = [complex] / [DNA] = 0.2, 0.6, 1, 1.4 and 1.8 respectively). The TC–DNA solutions were incubated at room temperature for 0.5 h before absorption spectra were recorded. The glassware were cleaned with standard method and dried to absolute dryness that checked with the anhydrous $CuSO_4$. Few pinch of the $CuSO_4$ was spread inside the flasks, beakers and others which did not change the color from colorless to blue due to a level of absolute dryness.

2.2. Experimental measurements

Solutions were prepared w/v using Mettler Toledo electronic Kern balance ABS 220-4, with ±0.01 mg accuracy. Absorption spectra were recorded with Spectro 2060 plus model UV/Vis spectrophotometer over 200–600 nm using 1 cm path length cuvette. Densities and sound velocities were measured with $\pm 10^{-3}$ kg m^{-3} accuracy by Anton Paar Density and Sound velocity meter DSA 5000M [14]. The DSA meter was calibrated with water and dry air as per instructions (DMA instruction manual; Anton Paar, Graz, Austria). For each measurement, the tube was cleaned with acetone and dried by passing dry air through the tube by an inbuilt air pump. A drying process was continued till a constant oscillation period was obtained. The refractive index was measured with Rudolph Research analytical J series Refractometer model-57 having $\pm 10^{-4}$ accuracy. The surface of the Refractometer prism was cleaned with HPLC grade ethanol and a lens wiper, in the measurements. This process ensured complete cleaning with no stains or air bubbles left on the prism surface. Each measurement was repeated at least twice to check reproducibility. The pendent drop numbers (PDN) and viscous flow times (VFT) for surface tension and viscosity measurements respectively, were measured with Borosil Mansingh Survismeter (BMS) [15,16]. Before each measurement units of the BMS were cleaned with Milli-Q water and then washed with pure acetone and dried. Once a week, the BMS was kept with the chromic acid as a cleaning mixture for 24 h. The BMS is a three in one instrument, and thus, both the PDN and VFT were measured with this single instrument. For temperature control, an auto temperature Lauda Alpha RA 8 thermostat was used for 298.15 K with ±0.01 °C accuracy. About 15 to 20 measurements were made for precision. Calibration of instrument, accuracy in data with literature comparison are reported in Tables 2, 3 and 4 for density, surface tension, viscosity, sound velocity and refractive index measurements.

3. Results and discussion

3.1. Spectrophotometric analysis

The DNA concentration was determined by absorption spectroscopy using the molar absorptivity (6600 M^{-1} cm^{-1}) of DNA at 260 nm [17,18]. Ratio of UV absorbance at 260 and 280 nm for DNA in buffer was calculated, and found near about 1.8–1.9 which inferred that the

Table 3
Water densities (ρ), surface tensions (γ) and viscosities (η) for literature comparisons, and standard deviation with their values at 298.15 K. Standard uncertainties u are: $u(T) = 0.01$ K, $u(\rho) = 1 \times 10^{-5}$, $u(\gamma) = 1 \times 10^{-2}$, and $u(\ ) = 1 \times 10^{-4}$.

$10^3 \cdot \rho$ kg m^{-3}			γ mN/m			η mPa·s		
Lit [36]	Exp	St dv	Lit [38]	Exp	St dv	Lit [37]	Exp	St dv
0.997044	0.997044	8.36×10^{-7}	71.97	71.97	0.008	0.8937	0.8938	8.367×10^{-5}
	0.997045			71.98			0.8937	
	0.997045			71.99			0.8936	
	0.997044			71.97			0.8938	
	0.997043			71.98			0.8937	

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