Synthesis, characterisation, nuclease and cytotoxic activity of phosphate-free and phosphate-containing copper 4'-(*N*-methylpyridinium)-2,2':6',2'' terpyridine complexes

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MS received 16 September 2017; revised 1 January 2018; accepted 1 January 2018; published online 7 February 2018

Abstract. Mononuclear Cu(II) pyridinium terpyridine based compounds, viz., [Cu(q-pytpy)(I)(CH₃COO)](I)·(2H₂O) (**1**) and [Cu(dipp)(dippH)(q-pytpy)]·(2H₂O)(DMF) (**2**) were isolated by reacting Cu(OAc)₂·H₂O with 4'-(*N*-methylpyridinium)-2,2':6',2''-terpyridine (q-pytpy) in the presence of 2,6 diisopropylphenyl phosphate (dippH₂). Both the new compounds were isolated as single crystals and characterised by spectroscopic (IR, ESI-MS, EPR, UV–Vis), thermogravimetric and microanalytical techniques. The molecular structures of both the compounds were determined in the solid-state by single crystal X-ray diffraction studies. Complexes **1** and **2** were evaluated for their nuclease and *in vitro* anti-tumor activities against human breast and colorectal cancer cell lines. The DNA cleavage and cytotoxic assays revealed that both **1** and **2** are effective in cleaving DNA, while the cytotoxic activity of **1** is better than **2** in both human colon and breast cancer cell lines.

Keywords. Pyridinium terpyridine; X-ray structures; DNA cleavage; cytotoxic activity.

1. Introduction

In the last few decades, a number of transition metal complexes have been investigated for nuclease and anti-cancer activities.^{1–4} Majority of these complexes show high affinity for nucleic acids and bind non-covalently to DNA either by intercalation or groove-face binding.^{3,5–7} This binding of metal complexes to the genomic DNA creates double-stranded nicks which are more dangerous and apparently less readily repaired inside a cell.⁵ Moreover, under *in vivo* conditions, these metal complexes lead to severe oxidative damage which ultimately trigger apoptosis in tumour cells.^{8–11} In this perspective, platinum-based drug, cisplatin has gained tremendous popularity and has proven to be an effective chemotherapeutic agent for the treatment of ovarian, lung, testicular, colon, and neck and head cancers.^{12,13} Other natural products with antitumour activities like bleomycins are also known to cause both single-strand and double-strand breaks in DNA duplex leading to death of cancer cells.^{14,15} However, despite the use of

these drugs as effective anti-cancer entities they have posed some serious limitations like drug resistance in certain cancers,¹⁶ damage to hair follicle, bone marrow and lining of the gastro-intestinal tract.^{17,18} To overcome these clinical problems many efforts have been made to synthesize several transition metal complexes of Cu(II), Fe(III), Ru(II), Co(III), Zn(II) and Ni(II) which could act as substitute to anti-cancer drugs with lesser side effects.^{19–24} Among all these metals, the biocompatible nature of Cu(II) complexes makes them better candidates as pharmacological agents in biological systems.²⁵ Also, the level of copper in the serum correlates with tumor incidence, tumor volume, degree of malignancy and recurrence in various human cancers including sarcoma, leukemia, Hodgkin's lymphoma, brain tumours and cancer of the cervix, breast, liver and lung; supporting the hypothesis that copper could be used as a potential cancer-specific target.^{3,26} A number of copper complexes with potent anticancer activity but lesser toxicity than platinum complexes have been reported.^{2,9,27} This anti-cancer activity of Cu complexes is due to their

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ability to generate reactive oxygen species along with the cleavage of genomic DNA and the activity can vary depending on type of ligand(s) present on the metal.¹

Structurally and electronically diverse ligands have been employed for the synthesis of copper-based anticancer agents, since the nature of ligand/s plays a crucial role in determining the binding characteristics and properties of the resulting complex.^{1,3,28} For instance, [Cu(tpy)(dppz)]²⁺ has been shown to bind and cleave genomic DNA and is effective against the breast cancer cell line- MCF-7, whereas other terpyridine-based copper complexes interact with G-quadruplex DNA.²⁵ In the field of anticancer drug design, the utilization of pytpy containing systems has come under spotlight due to their recently recognized propensity to stabilize G-quadruplex structures.^{29–33} The first proof of metal-terpyridines as G-quadruplex binders was reported by Teulade-Fichou *et al.*, who demonstrated that square-planar and square-based pyramidal metal complexes containing substituted terpyridines are efficient G-quadruplex binders.^{34,35} The metal chemistry of pytpy is well-established in the literature yielding complexes ranging from discrete to polymers.^{36–41} The use of pytpy as an ancillary ligand in metal phosphates and phosphonates was limited until recently when terpyridine was used as an auxillary ligand along with a bisphosphonate for the rational synthesis of phosphonate containing bimetallic wave structure.^{42,43}

In our laboratory, we have shown that di-*tert*butyl phosphate, [(*t*BuO)₂P(O)(OH)] (dtbph) on reaction with copper precursors leads to the formation of monomeric, dimeric as well as polymeric copper phosphate complexes.⁴⁴ These compounds were utilized as single source precursors for the facile synthesis of fine particle ceramics.⁴⁴ In the presence of chelating ancillary ligand such as 1,10-phenanthroline, monomeric complex [Cu(dtbp)₂(phen)(OH₂)] was isolated to demonstrate the mechanism of phosphate diester hydrolysis assisted by intramolecular H-bonding interactions between the coordinated water and the phosphate ligands.⁴⁵ Besides, it has also been shown by us that the nuclearity of the resultant copper phosphates can be fine-tuned by altering the bulkiness of the ortho-substituents on the aryl ring of arylphosphate monoesters.⁴⁶ Recently, we have reported on the selective formation of dimeric and polymeric copper organophosphates, while the methanol soluble dimeric complexes have also been assessed for their *in vitro* anti-tumour properties.⁴⁷ As a part of ongoing investigations in our research group on molecular phosphates,^{48–50} we report here on two new mononuclear copper complexes that contain N-alkylated pendant pyridyl terpyridine as the ancillary ligand. We also

report on the DNA cleavage and cytotoxic activity of these complexes.

2. Experimental

2.1 Instruments and methods

Since the starting materials and the products of this study were found to be stable, no specific precautions were taken to exclude both air and moisture. Infrared spectra were obtained on a Perkin–Elmer Spectrum One FT-IR spectrometer as KBr diluted discs. Microanalyses were performed on a Thermo Finnigan (FLASH EA 1112) microanalyzer. TGA were carried out on a Perkin–Elmer Pyris thermal analysis system under a stream of nitrogen gas at a heating rate of 10 °C/min. The ESI-MS studies were carried out on Bruker MaXis impact mass spectrometer. Solvents were purified according to standard procedures prior to their use. Commercially available starting materials [Cu(OAc)₂].H₂O (S.D. Fine), and 2,6-diisopropylphenol (Sigma Aldrich) were used as procured. The q-pytpy and dippH₂ were synthesized by following reported literature procedures.^{51,52}

2.2 Synthesis and characterization of 1 and 2

To a solution of [Cu(OAc)₂.H₂O] (0.039 g, 0.20 mmol) in methanol (30 mL), a solution of q-pytpy (0.092 g, 0.2 mmol) and dippH₂ (0.051 g, 0.2 mmol) in methanol and chloroform (10 mL) (1:1 v/v) was slowly added to yield a clear green solution. After stirring for 3 h, the solution was filtered and kept for crystallisation at room temperature. After 24 h, brown needle shaped crystals of **1** were obtained. After the separation of compound **1**, the remaining green colour filtrate was again kept for crystallisation on a bench top. After few days, green block-shaped crystals of **2** grew from this solution.

1: Yield: 35% (based on Cu). M.p.: > 250 °C. Elem. anal. Calcd.(%) for C₂₃H₂₅CuI₂O₄N₄ (Mr = 737.92): C, 37.39; H, 3.41; N, 7.58 Found(%): C, 37.90; H, 3.01; N, 7.30 IR (KBr, cm^{−1}): 3044 (s), 2928 (w), 1583 (s), 1395 (s), 1390 (s), 1086 (s), 843(s), 801(s), 626(s) TGA: temperature range (weight loss): 30–300 °C (~13%); 300–800 °C (~45%); 800–1000 °C (~20%).

2: Yield: 45% (based on Cu). M.p.: > 250 °C. Elem. anal. Calcd. (%) for C₄₈H₆₃CuN₅O₁₁P₂ (Mr = 1011): C, 56.99; H, 6.28; N, 6.92 Found(%): C, 55.89; H, 6.55; N, 6.92. IR (KBr, cm^{−1}): 3444 (Br), 3048 (m), 2924 (w), 1587 (s), 1106 (s), 1089 (w), 1019 (s), 842 (s), 797 (s). TGA: temperature range (weight loss): 30–150 °C (~10%); 160–750 °C (~43%); 780–870 °C (~10%). ESI-MS: m/z calcd. 902.2802, found 902.2629 [M + H]⁺.

2.3 Single crystal X-ray diffraction studies

Single crystals of **1** and **2** were directly obtained from methanol and chloroform solvent mixture (1:1 v/v) at room temperature as described above. Crystals suitable for

Table 1. Crystallographic refinement details of compounds **1** and **2**.

Compound	1	2
Identification code	GB-628	GB-628-A
Empirical formula	C ₂₃ H ₂₀ CuI ₂ N ₄ O ₂	C ₄₈ H ₆₃ CuN ₅ O ₁₁ P ₂
FW	701.77	1011.51
Temp, [K]	150(2)	150(2)
Crystal system	Monoclinic	Tetragonal
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>I</i> 4 ₁ / <i>a</i>
<i>a</i> , [Å]	8.170(4)	33.1952(3)
<i>b</i> , [Å]	23.470(9)	33.1952(3)
<i>c</i> , [Å]	13.168(5)	20.9005(3)
α , [°]	90	90
β , [°]	94.394	90
γ , [°]	90	90
<i>V</i> , [Å ³]	1415.81(9)	23030.7
<i>Z</i>	4	16
<i>D</i> (calcd), [Mg/cm ³]	1.852	1.167
μ [mm ⁻¹]	3.346	0.490
Θ range, [°]	2.647 to 24.999	1.683 to 24.998
No. of reflections collected	18732	247219
Independent reflections	4413	10152
GOF	1.051	1.120
<i>R</i> 1(<i>I</i> ₀ > 2 σ (<i>I</i> ₀))	0.0521	0.0585
<i>wR</i> 2 (all data)	0.1444	0.1718

diffraction studies were mounted on a Rigaku Saturn 724+ ccd diffractometer using Paratone oil for unit cell determination and three-dimensional intensity data collection. Data integration and indexing was carried out using *CrystalClear-SM Expert* and structures were solved using direct methods (SIR-92).⁵³ The structure refinement and other calculations were carried out using programmes implemented in WinGX.⁵⁴ Final refinement was carried out using full least square methods on *F*² using SHELXL-97.⁵⁵ SQUEEZE was applied for disordered solvent molecules in the crystal lattice of **1** by using PLATON. Crystal data and details of the structure refinement are given in Table 1. CCDC 1571740 (**1**) and 1571741(**2**) contain the supplementary crystallographic data for this paper.

2.4 Anti-cancer activity

2.4a DNA cleavage studies: Nuclease activities of complexes **1** and **2** were determined by using plasmid pcDNA-3.1 as template. The pcDNA 3.1(-) DNA (Promega, US) (30 μ M) was incubated with various concentrations of complex **1** or **2** (10 μ M - 200 μ M) at 37 °C for 4 h in 5 mM Tris-HCl/50 mM NaCl buffer (pH = 7.1). To stop this reaction, DNA loading dye (25% bromophenol blue, 0.25% xylene cyanol, 30% glycerol and 0.61% Tris) was added and electrophoresis was carried out in 1% agarose gel containing ethidium bromide (1 μ g/mL) for 2 h at a potential of 80 V in a tris-acetate EDTA buffer. Control reaction (pcDNA 3.1, 30 μ M in Tris-HCl/NaCl, with 4 h incubation at 37 °C, but without complex **1** or **2**) was also run in parallel to ensure that the cleavage in

DNA occurred only due to the addition of complex **1** or **2**. The gel images were captured by BIORAD Gel DocTM (Biorad Instruments Inc.).

2.4b Cell culture: Human colon cancer cell line, HCT-116 and Human breast cancer cell line, MCF-7 were obtained from National Centre for Cell Science, Pune (India). Both the cell lines were grown in DMEM (Sigma-Aldrich, MA, USA) supplemented with 10% fetal bovine albumin (Sigma-Aldrich, MO, USA) and 100 units of penicillin/mL and 100 μ g of streptomycin/mL (Hyclone, South Logan, Utah). The cell lines were incubated at 37 °C in a humidified chamber supplemented with 5% CO₂ (Eppendorf Brunswick, USA).

2.4c Cell proliferation assay (MTT Assay): The effect of **1** and **2** on proliferation of human breast cancer cell line MCF-7 and human colon cancer HCT-116 cells was quantified using the MTT colorimetric assay. 2×10^4 cells/well were seeded in 24-well plates followed by treatment with different concentrations (10 μ M–200 μ M) of complex **1** or **2**. Plates were kept in a humidified incubator at 37 °C and 5% CO₂ for 24 h along with media and cell controls. MTT solution (5 mg/mL, Invitrogen, US) was added to all wells and the plates were incubated at 37 °C for 3 h. The reaction was stopped by discarding the supernatants followed by addition of 200 μ L of MTT solvent (0.1% NP-40 and 4 mM HCl in isopropanol) to each well and thorough mixing to dissolve the blue formazan crystals. Plates were again incubated at 37 °C for 20 min in dark, after ensuring that all crystals were dissolved, the plates

were read on a ELISA plate reader (BioRad Instruments Inc.) within 10 min at a wavelength of 570 nm.

3. Results and Discussion

3.1 Synthesis and characterisation of $\{[Cu(q-pytpy)(I)(CH_3COO)] \cdot (I)(2H_2O)\}$ (**1**) and $\{[Cu(dipp)(dippH)(q-pytpy)] \cdot (2H_2O)(DMF)\}$ (**2**)

Addition of $[Cu(OAc)_2 \cdot H_2O]$ to a solution of 4'-(*N*-methylpyridinium)-2,2':6',2''-terpyridine (*q*-pytpy) and *dippH*₂ in methanol and chloroform solvent mixture (1:1 v/v) at room temperature resulted in the formation of clear green solution. Slow evaporation of this reaction mixture over 24 h led to the formation of brown needle shaped crystals of $\{[Cu(q-pytpy)(I)(CH_3COO)] \cdot (I)(2H_2O)\}$ (**1**). The green filtrate was again kept for slow evaporation to yield $\{[Cu(dipp)(dippH)(q-pytpy)] \cdot (2H_2O)(DMF)\}$ (**2**) as green block shaped single crystals within one week (Scheme 1). Compound **1** is insoluble in methanol while compound **2** was found to be highly soluble in methanol, aiding an efficient separation of these two products from each other. Complexes **1** and **2** were characterized by spectroscopic and analytical methods.

The presence of a broad IR absorption band at around 2360 cm^{-1} in FT-IR spectrum of **2** suggests that there are residual (unreacted) P-OH groups in the product. FT-IR spectrum of **1** on the other hand did not show any absorption in this region indicating the absence of phosphate ligands in this complex. The broad absorption band at 1086 cm^{-1} for **1**, and absorption bands at 1179 cm^{-1} for **2** can be assigned to $M-O-C$ vibrations. Further absorption bands around 1090 and 927 cm^{-1} for **2** can be assigned to $P=O$ stretching vibrations and $M-O-P$ asymmetric and symmetric stretching vibrations, respectively (Figure S1 in Supplementary Information). The TGA curve of **1** shows first weight loss of around 13.0% in the temperature range of $100-300^\circ\text{C}$ due to the loss of lattice water and coordinated acetate ions. On further heating, the observed major weight loss of around 45% is assigned to the removal of organic moiety (*q*-pytpy), finally resulting in the formation of copper oxides at higher temperature (Figure S2 in Supplementary Information). On the other hand, the TGA curve of compound **2** shows an initial weight loss of around 10% due to the loss of coordinated DMF and water molecules. On further heating, a weight loss of around 42% occurs due to the decomposition of organic moieties of *pytpy* and *dippH*₂ in the temperature range of $150-450^\circ\text{C}$ resulting in the formation of

Scheme 1. Synthesis of **1** and **2**.

Figure 1. Selective portion of ESI-MS spectrum of **2** (positive ion mode) showing simulated and experimental isotopic pattern in agreement with each other.

Figure 2. X-band (9.42 GHz) EPR spectra of **1** at 100 K and RT.

[Cu(O₃POH)], which undergoes further condensation at higher temperature through the removal of water leading to the formation of Cu₂P₂O₇. This phase is found to be stable up to 800 °C (Figure S3 in Supplementary Information).

While the ESI-MS spectrum of **1** did not yield the molecular ion peak, compound **2** shows [M+H]⁺ peak at *m/z* 902, suggesting structural integrity of this complex in solution under mass spectral conditions. The simulated and experimental isotopic patterns are in good agreement with each other (Figure 1).

To understand the electronic structure and geometrical properties of **1** and **2**, their X-band EPR spectra were measured at room temperature and 100 K (Figures 2 and 3). The EPR spectra of both **1** and **2** were found to be axial and well-resolved at a lower temperature (100 K) whereas the hyperfine splitting was not observed at the room temperature. Thus, the 100 K spectra of

Figure 3. X-band (9.42 GHz) EPR spectra of **2** at 100 K and RT.

1 and **2** show hyperfine splitting of four bands for $g_{\parallel}$ corresponding to a (N₃O₂)Cu(II) ($I = 3/2$) centre. The $g_{\parallel}$ and $g_{\perp}$ values for **1** are 2.34 and 2.08, whereas for **2** the values are 2.27 and 2.06, respectively. In compound **1** $g_{\parallel} > g_{\perp} > 2.0$ and $G = (g_{\parallel} - 2)/(g_{\perp} - 2) = 4.5$ suggests a distorted square pyramidal geometry with d_{x-y}^2 as ground state.^{56–60} Moreover, the value of $g_{\parallel}/A_{\parallel}$ quotient (132 cm) lies in the range that is normally observed for such complexes. As in the case of **1**, the EPR spectrum of **2** also shows hyperfine splitting due to Cu(II) ions with $g_{\parallel} > g_{\perp} > 2.0$ and $G = (g_{\parallel} - 2)/(g_{\perp} - 2) = 4.25$, suggesting a square-pyramidal geometry with d_{x-y}^2 as ground state. Further, the value of $g_{\parallel}/A_{\parallel}$ quotient (171 cm) also lies in the expected range for distorted square pyramidal complexes (for an ideal square-planar geometry, $g_{\parallel}/A_{\parallel} = 105–135$ cm).^{56,57,60} Kivelson and Neiman have shown that $g_{\parallel}$ is a judiciously sensitive function for the estimation of ionic versus covalent character of M-L bond. If the values are higher than 2.3, it is inferred that M-L bond is ionic; values lower than 2.3 normally predominantly covalent M-L bonds.⁶¹ Since the observed values are less than 2.3 for both **1** and **2**, the M-L bonds in these complexes can be termed predominantly covalent.

Due to solubility reasons, the absorption spectrum for **1** was obtained in acetonitrile while that of **2** was recorded in methanol. The absorption spectrum of **1** exhibits four bands at 229, 248, 272 and 351 nm whereas the absorption spectra of **2** shows bands at 209, 279 and 348 nm (Figure 4). The molar extinction coefficient along with absorbance for these bands are listed in Table 2. These absorption bands are assignable to $\pi - \pi^*$ transitions of the pyridyl rings of terpyridine. These bands exhibit a small red or blue shift with respect to the free q-terpy ligand.⁶²

Figure 4. UV-Vis spectra of **1** in acetonitrile (2.5×10^{-5} M) and **2** in methanol (1.6×10^{-5} M).

Table 2. UV-Vis spectral data for **1** and **2**.

Compound	$\lambda_{\max}$ (nm)	Abs.	ϵ ($\text{M}^{-1}\text{cm}^{-1}$)
1	351	0.1809	7.2×10^3
	272	0.9071	3.6×10^4
	248	0.8884	3.5×10^4
	229	0.7921	3.1×10^4
2	348	0.1485	9.2×10^3
	279	0.7306	4.5×10^4
	209	0.9147	3.1×10^4

3.2 Molecular structure of **1**

Compound **1** crystallizes in the monoclinic space group $P2_1/n$. Molecular structure diagram of **1** is shown in Figure 5. In the mononuclear copper complex **1**, the metal centre is surrounded by one q-pytpy, one acetate, one coordinated iodide ion, besides a lattice iodide ion and two disordered water molecules. The geometry around the Cu(II) ions is distorted square-pyramidal; three nitrogen atoms of q-pytpy (N1, N2 and N3) and one oxygen atom (O1) of the acetate ion occupy the equatorial plane while the apical coordination is occupied by an iodide. The central Cu-N pytpy distance (Cu(1)-N(2) 1.958(6) Å) is slightly shorter than the peripheral Cu-N bonds (Cu(1)-N(1), Cu(1)-N(3)), which are 2.022(6) and 2.037(6) Å, respectively, as has been observed in many chelating terpyridine complexes.⁶³ While one of the acetate oxygen atoms O(1) is tightly bound to the metal (Cu(1)-O(1) 1.909(5) Å), the other acetate oxygen atom O(2) shows a weak interaction with the metal centre (Cu(1)-O(2) 2.719 Å). Similar weak interactions in the range of 2.441–3.240 Å has been reported for analogous acetate coordinated terpy-based compounds.⁶⁴ The Cu(1)-I(1) bond distance (2.9544(13) Å) is comparable with those found in similar complexes.⁶⁵ The N-M-N bond angles originating from the CuN3 coordination of q-pytpy (79.2(2) and 80.2(2)°) deviate from the ideal value of 90°, being a consequence of geometrical constraints imposed by the q-terpy ligand.⁶³ The

Figure 5. Molecular structure of **1** (Hydrogen atoms, lattice iodide ion and two water molecules are omitted for clarity). Selected bond distances (Å) and angles (°) for **1**: Cu(1)-N(1) 2.022(6), Cu(1)-N(2) 1.958(6), Cu(1)-N(3) 2.037(6), Cu(1)-O(1) 1.909(5), Cu(1)-I(1) 2.121(2) Å, N(2)-Cu(1)-N(1) 79.2(2), N(2)-Cu(1)-N(3) 80.2(2), O(1)-Cu(1)-N(2) 173.4(2), O(1)-Cu(1)-N(1) 101.2(2), O(1)-Cu(1)-I(1) 101.95(16), N(2)-Cu(1)-I(1) 84.66(16)°.

Figure 6. Molecular structure of **2**; Hydrogen atoms except H3 and two lattice water molecules and one DMF molecule are omitted for clarity. Selected bond distances (Å) and angles (°) for **2**: Cu(1)-N(1) 2.058(3), Cu(1)-N(2) 1.949(3), Cu(1)-N(3) 2.048(3), Cu(1)-O(1) 2.147(2), Cu(1)-O(5) 1.895(2) Å; N(2)-Cu(1)-N(1) 79.20(10), N(2)-Cu(1)-N(3) 79.46(10), O(5)-Cu(1)-N(1) 99.82(10), N(2)-Cu(1)-O(1) 94.93(10), O(5)-Cu(1)-O(1) 106.61(9), O(5)-Cu(1)-N(2) 158.46(11)°.

pendant pyridine is twisted from the rest of the ligand framework by a dihedral angle of 11.52°.

3.3 Molecular structure of **2**

Compound **2** crystallises in the tetragonal space group $I4_1/a$. The final refined structure is shown in Figure 6. The asymmetric unit of the unit cell contains one Cu(II) ion, two diisopropylphenyl phosphate ligands (one doubly deprotonated and one singly deprotonated) and one q-pytpy besides lattice water and DMF solvent molecules. The distorted square pyramidal Cu(II) ion in **2** is surrounded by the terpyridine by its three nitrogen centres (N1, N2 and N3) and one oxygen atom O5 of the doubly deprotonated dipp ligand in the equatorial plane. The apical position is occupied by the oxygen atom O1 of a mono deprotonated phosphate ligand (dippH) (Scheme 1 and Figure 6). Both the phosphates coordinate to the metal centre in a monodentate fashion (1.100] Harris notation)],⁶⁶ leaving free uncoordinated P=O and P-OH groups on the mono deprotonated phosphate (dippH) and P=O and P-O⁻ on the doubly deprotonated phosphate ligand. In the CuN3 coordination, the central Cu-N distance (Cu(1)-N(2) 1.949(3) Å) is slightly shorter than the

peripheral ones (Cu(1)-N(1) 2.058(3) and Cu(1)-N(3) 2.048(3) Å), due to geometrical constraints imposed by the tris-chelation of the ligand.⁶³ The Cu(1)-O(5) bond (1.895(2) Å) is slightly shorter than the apical Cu(1)-O(1) bond (2.147(2) Å) due to the Jahn-Teller distortion. Thus, the Cu-N and Cu-O distances are comparable with the distances reported for similar type of complexes.⁴³ The bond angles subtended by the terpyridyl unit in the equatorial plane N(2)-Cu(1)-N(1) 79.20(10)°, N(2)-Cu(1)-N(3) 79.46(10)° deviates considerably from the ideal square pyramidal angle of 90°, as has been commonly observed in terpyridyl complexes.³⁶ The phosphoryl oxygen atoms (P=O) and free P-OH of phosphate ligand are involved in strong intermolecular hydrogen bonding interactions with the adjacent water and DMF molecules to yield a dimeric structure as shown in Figure 7. This dimeric structure is involved in further secondary interactions, leading to the formation of 2D polymeric structure (Figure 8).

3.4 DNA cleavage activity of complexes **1** and **2**

Numerous metal-based complexes have been successfully employed as anti-proliferative drugs. Apart from

Figure 7. Formation of dimeric units through O – H $\cdots$ O hydrogen bonding interactions in **2**.

Figure 8. Interactions in dimeric structures of **2** leading to the formation of 2-D polymeric structures.

platinum, one metal that is of special importance is the copper. Copper(II) complexes, because of their biocompatibility and intrinsic nuclease activity, show significant anti-proliferative activity. These metal complexes

target either the genomic DNA or some specific proteins inside the cancer cells. To evaluate the scope of complexes **1** and **2** in anti-cancer therapeutics, we first checked their effect on the cleavage of the nucleic acids.

Figure 9. DNA cleaving activity of complex 1 and complex 2. (A) Agarose gel image showing the cleavage of pcDNA3.1(-) by 1 and 2 (10–200 μ M) in Tris-HCl/NaCl buffer (PH = 7.4) at 37 $^{\circ}$ C for 4 h; Lane 1-DNA; Lane 2-DNA + Complex 1(10 μ M); Lane 3-DNA + Complex 1(30 μ M); Lane 4-DNA + Complex 1(50 μ M); Lane 5-DNA+Complex 1(100 μ M); Lane 6-DNA+Complex 1(200 μ M). (B) Lane 1-DNA; Lane 2-DNA+Complex 2(10 μ M); Lane 3-DNA+Complex 2(30 μ M); Lane 4-DNA+Complex 2 (50 μ M); Lane 5-DNA+Complex 2(100 μ M); Lane 6-DNA+Complex 2(200 μ M). SC = Supercoiled form, L = Linear form.

For this purpose we choose plasmid DNA pcDNA.3.1(-) (30 μ M) and incubated it with varying concentrations of compounds 1 and 2 (10–200 μ M) in 5 mM Tris-HCl/50 mM NaCl (pH = 7.4) buffer at 37 $^{\circ}$ C for 4 h followed by agarose gel electrophoresis. After visualization under UV, it was observed that both complexes were able to create nicks in the double stranded DNA as evidenced by the conversion of the supercoiled form (SC) of plasmid into linear form (L) (Figure 9). Moreover, the cleavage of DNA by complexes 1 and 2 follow first order kinetics since increasing the concentration of either 1 or 2 led to increase in cleavage of plasmid DNA. This was proved by the increase in the L form of plasmid DNA and subsequent decrease in SC form (Figure 9, A and B). Moreover, the gel results also infer that complex 1 cleaves DNA efficiently than complex 2. At 200 μ M concentration of complex 1, ~70% of supercoiled DNA (SC) form was present as linear (L) DNA when compared to control DNA (without complex 1) (Figure 9A, compare Lane 1 and Lane 6; Figure 10). In contrast, under similar reaction conditions, complex 2 (200 μ M) shows only 20% cleavage of SC-DNA into L-DNA (Figure 9B, compare Lane 1 and Lane 6, and Figure 10). Thus, the intrinsic nuclease property of complex 1 is significantly higher than complex 2. Control experiments with ligands or DNA alone did not exhibit any significant cleavage of DNA, validating the intrinsic DNA cleavage potential of complexes 1 and 2.

Figure 10. Plot showing % cleavage of SC DNA as a function of concentration of compounds 1 and 2.

Figure 11. Cell cytotoxicity in human colon and breast cancer cell lines by complexes 1 and 2. Breast cancer cells, MCF-7 cells and HCT-116 cells were treated with different concentrations of complex 1 or 2. After 24 h post-transfection, cell viability was assayed using MTT assay. (A) MTT cell viability assay showing that compounds 1 and 2 decrease the overall cell proliferation in treated human colon cancer, HCT-116 cells in comparison to untreated HCT-116 cells. IC₅₀ of complex 1 in HCT-116 is 50 μ M and complex 2 is 200 μ M. (B) MTT cell viability assay showing that complexes 1 and 2 decrease the overall cell proliferation in human breast cancer, MCF-7 cells as compared to control. IC₅₀ for complex 1 in MCF-7 is 100 μ M and for complex 2 remains undetermined. The data shown represent three independent experiments performed in triplicates.

3.5 Effect of complex 1 and 2 on proliferation of human colon and breast cancer cell lines

Most of the anti-cancer drugs act by restraining the proliferation of the cancer cells or by increasing the cancer cell apoptosis. In order to evaluate the effect

of complexes **1** and **2** on proliferation of human breast cancer (MCF-7) and human colon cancer (HCT-116) cell lines, cell viability assay was performed. Cells were treated with complexes **1** and **2** over a concentration range of 10 μM –200 μM and incubated for 24 h along with untreated cell and medium control. The proliferation of both cancer cell lines decreased on treatment with complexes **1** and **2** in a concentration dependent manner, compared to the control (Figure 11). However, IC_{50} was different for these complexes and even varied in these two cell lines. For complex **1**, IC_{50} value for HCT-116 was 50 μM and in case of MCF-7, IC_{50} was 100 μM (Figure 11A and B). However, in case of complex **2**, $\text{IC}_{50} = 200 \mu\text{M}$ in HCT-116 and in MCF-7, it was not determined even at a concentration of 200 μM ; approximately 70% of the cells were live at this concentration (Figure 11A and B) thus inferring that HCT-116 are more sensitive than MCF-7 to both **1** and **2**, as it requires higher concentrations to cause death of 50% of MCF-7 cells as compared to HCT-116 cells. In addition, these viability assay results suggest that complex **1** is a good cytotoxic agent than complex **2**, and could prove as a good candidate for cancer treatment since lower doses of complex **1** are needed to cause death of greater than 50% of cancer cells. This is in accordance with the high DNA cleavage ability of complex **1**.

4. Conclusions

We have demonstrated that two new mononuclear Cu(II) complexes viz., $[\text{Cu}(\text{q-pytpy})(\text{I})(\text{CH}_3\text{COO})](\text{I}).(2\text{H}_2\text{O})$ (**1**) and $[\text{Cu}(\text{dipp})(\text{dippH})(\text{q-pytpy})].(2\text{H}_2\text{O})(\text{DMF})$ (**2**) can be isolated as single crystals from the same reaction mixture in high purity by exploiting their solubility differences. The new compounds were characterised by various spectroscopic and analytical methods and the molecular structures were confirmed by single crystal X-ray diffraction studies. Compounds **1** and **2** were evaluated for their *in vitro* anticancer activity against human breast and colorectal cancer cell lines and these assays revealed that both **1** and **2** are potent cytotoxic agents but the activity of **1** is better than **2** under all conditions. Thus, copper terpyridine complexes may prove as good candidates in cancer therapy but further *in vivo* studies are imperative to support their application as anti-cancer drugs.

Supplementary Information (SI)

Tables of bond lengths and angles, H-bonding table, TGA graphs, FT-IR spectra are available as supplementary information. CCDC 1574745 (**1**) and 1574746 (**2**) contain the

supplementary crystallographic data for this paper. Supplementary Information is available at www.ias.ac.in/chemsci.

Acknowledgements

This work was supported by (1) DST Nanomission (SR/NM/NS-1119/2011), (2) SERB, New Delhi (SB/S1/IC-48/2013) and (3) IIT-Bombay Bridge Funding. R. M. thanks SERB (SB/S2/JCB-85/2014), New Delhi for a J. C. Bose Fellowship, G.A.B thanks UGC New Delhi for a research fellowship. The authors thank Dr. Sandeep Kumar Gupta for help in solving one crystal structure.

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