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Synthesis and DNA photocleaving activities of ancillary ligand-containing zinc complexes of quaternized carboxylates

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ABSTRACT

Three zinc complexes, that is, $\{[Zn_2(Cbp)_2(BDC)_2(H_2O)_2]\cdot 4H_2O\cdot MeOH\}_n$ (**1**) (Cbp = N-(4-carboxybenzyl)pyridinium, BDC = 1,4-benzenedicarboxylate), $[Zn(BCbpy)_2(H_2O)_4]_2(BDC)_2\cdot 13H_2O$ (**2**) (BCbpy = 1-(4-carboxybenzyl)-4,4′-bipyridinium) and $\{[Zn_2(Bpybc)_3(BDC)_2]\cdot 4H_2O\}_n$ (**3**) (Bpybc = 1,1′-bis(4-carboxybenzyl)-4,4′-bipyridinium), were synthesized and characterized on the basis of IR, elemental analysis and single-crystal X-ray crystallography data. Complexes **1** and **3** possess polynuclear structures, whereas complex **2** has a mononuclear structure. Agarose gel electrophoresis studies indicated that, under the irradiation of UV-A at 365 nm, complex **2** showed negligible DNA-cleaving activity, whereas complexes **1** and **3** were capable of efficiently converting pBR322 DNA into OC forms, most probably *via* an oxidative mechanism. Kinetic assay on complexes **1** and **3** afforded the catalytic efficiency (k_{max}/K_M) of 0.63 and 10.8 h^{-1} mM^{-1}, respectively. The higher cleaving efficacy of complex **3** is a likely consequence of its polynuclear structure and one more quaternary ammonium center.

1. Introduction

During the past decades, transition metal complexes that are capable of cleaving DNA have been receiving considerable attentions. This is because such complexes have wide applications, for example, in the development of structural probes for DNA and novel chemotherapeutic agents [1–12]. Among those complexes, the ones that are able to specifically bind to and cleave DNA under light irradiation and physiological conditions, are of particular interest because they have great potentials in photodynamic therapy (PDT) to cancers [13–16]. The DNA-binding and photocleaving properties of ruthenium(II), copper(II) and related other transition metal complexes have been extensively studied [17–20]. In contrast, zinc-based metal complexes as photodynamic therapeutic agents have been far less developed, though zinc(II) ion is a bioessential element and thought to be less toxic than many other transition metal ions. In addition, many enzymes rely on zinc(II) ion to exert their activities [21–24]. As a consequence, considerable efforts have been made to identify zinc(II) complexes showing DNA photocleaving activity.

In previous studies, we have reported the copper complex of 4-carboxy-1-(4-carboxybenzyl) pyridinium bromide (HCcbpBr), $\{[Cu(Ccbp)_2]\cdot 4H_2O\}_n$ [25], and the zinc complex of 1,1′-bis(4-carboxybenzyl)-4,4′-bipyridinium) bromide ($H_2BpybcBr_2$, Chart 1), $\{[Zn_4(Bpybc)_6(H_2O)_{12}](OH)_8\cdot 9H_2O\}_{2n}$ [26]. Both complexes showed high DNA-cleaving activities. More importantly, the latter complex exhibited moderate cytotoxicities toward lung adenocarcinoma A549 and mouse sarcoma S180 cells. We assume that these activities are a likely consequence of their polynuclear structures. On the other hand, recent studies have shown that metal complexes bearing cationic ammonium groups could act as effective photosensitizers and photocleavers [27,28]. These findings inspired us to synthesize the polynuclear metal complexes of quaternized carboxylates and to conduct a detailed investigation into their DNA photocleaving activities.

With this background in mind and with the aim to obtain polynuclear zinc complexes having potential interesting bioactivities, we prepared the Zinc(II) complexes of *N*-(4-carboxybenzyl) pyridinium bromide (HCbpBr), 1-(4-carboxybenzyl)-4,4′-bipyridinium bromide (HBCbpyBr) and $H_2BpybcBr_2$ in the presence of 1,4-benzenedicarboxylate disodium (Na_2BDC) [29–31] (Chart 1). This is based on the fact that Na_2BDC is well recognized as a bridging ligand that is deliberately included for dimension upgrade. Consequently, we obtained three new zinc complexes, that is, $\{[Zn_2(Cbp)_2(BDC)_2(H_2O)_2]\cdot 4H_2O\cdot MeOH\}_n$ (**1**), $[Zn(BCbpy)_2(H_2O)_4]_2(BDC)_2\cdot 13H_2O$ (**2**) and $\{[Zn_2(Bpybc)_3(BDC)_2]\cdot 4H_2O\}_n$ (**3**) (Chart 1). Of these three complexes, complexes **1** and **3** have polynuclear structures. Herein we report the synthesis, crystal structures and photo-induced DNA-cleaving activities of complexes **1**–**3**.

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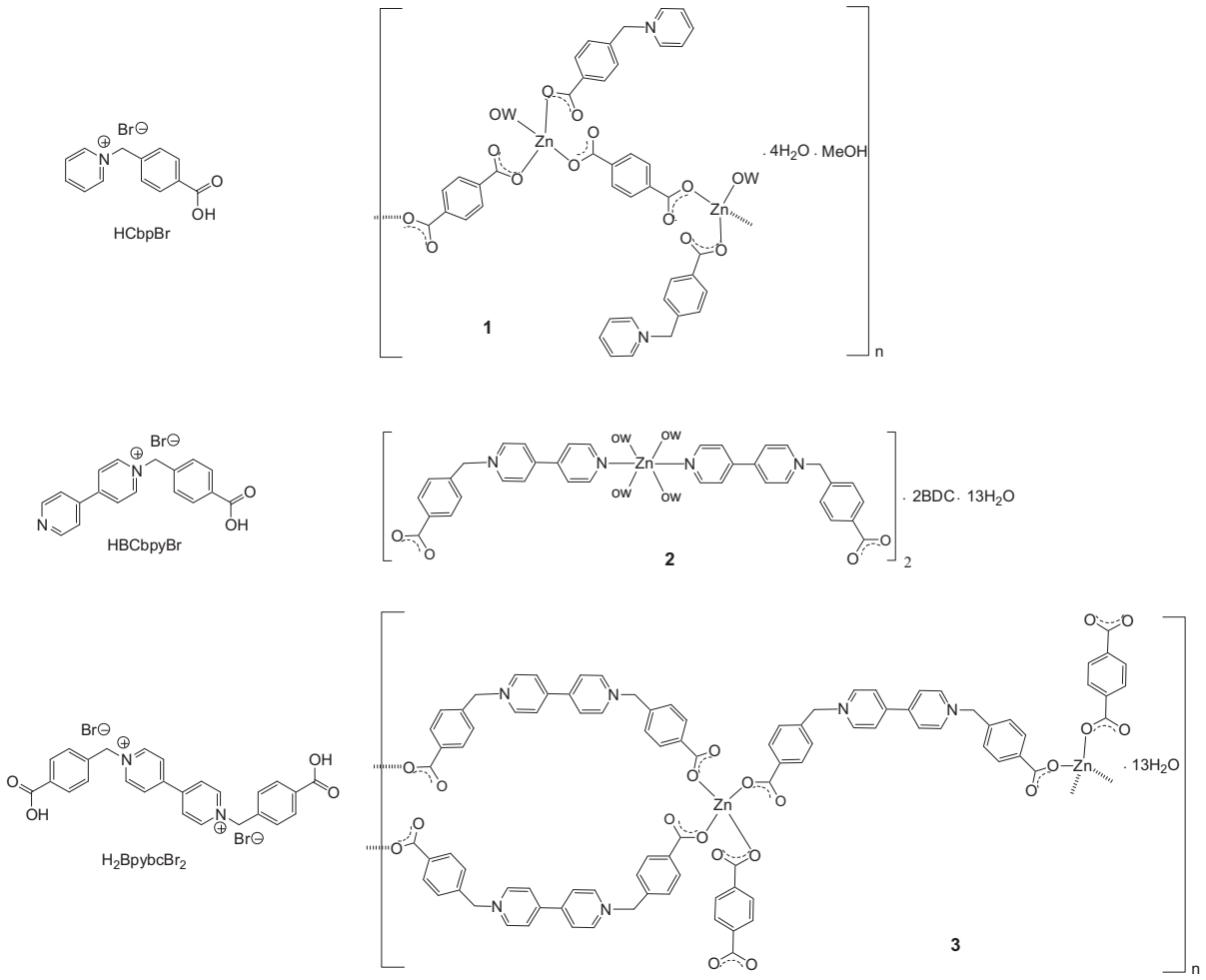

Chart 1. HCbpBr, HBCbpyBr, $H_2BpybcBr_2$ and their zinc complexes **1**–**3**.

2. Experimental

2.1. General

IR spectra were recorded on a Nicolet MagNa-IR 550. Elemental analyses for C, H, and N were performed on an EA1110 CHNS elemental analyzer. ESI MS spectra were measured on a Waters UPLC/Quattro Premier XE mass spectrometer. The reaction of metal complexes with plasmid pBR322 DNA was conducted in a JHG-9023A oven with 2F-20D UV analyzer. Agarose gel electrophoresis (GE) was conducted on a DYY-8C electrophoresis apparatus and a DYCP-31DN electrophoresis chamber, and detected on an Alpha Hp 3400 fluorescence and visible light digital image analyzer. Fluorescence spectra were measured on a HITACHI F-2500 spectrofluorimeter.

Calf-thymus (CT) DNA, ethidium bromide (EB) and plasmid pBR322 DNA were obtained from Takara Chemical Co. The solution of plasmid pBR322 DNA was prepared in 5 mM Tris–HCl buffer (5 mM NaCl, pH 7.0). The concentration of CT DNA was determined spectrophotometrically using the molar extinction coefficient of 6600 $M^{-1}\,cm^{-1}$/base at 260 nm [32]. HCbpBr, HBCbpyBr and $H_2BpybcBr_2$ were prepared according to the reported protocols [33–35]. All the other chemicals and reagents were obtained from commercial sources and used without further purification. Buffer solutions were prepared in triply distilled deionized water.

2.2. Synthesis of complexes *1*–*3*

2.2.1. $\{[Zn_2(Cbp)_2(BDC)_2(H_2O)_2]\cdot 4H_2O\cdot MeOH\}_n$ (*1*)

A solution of HCbpBr (236 mg, 0.8 mmol) in H_2O (5 mL) was adjusted to pH 7.0 with 0.1 M NaOH solution. Then, a solution of $Zn(NO_3)_2\cdot 6H_2O$ (118 mg, 0.4 mmol) in H_2O (5 mL) was added. The resulting mixture was stirred at 100 °C for 0.5 h to give a clear solution. The resulting colorless solution was then treated with a solution of Na_2BDC (88 mg, 0.4 mmol) in H_2O (5 mL). The mixture was stirred for 0.5 h and filtered. The filtrate was cooled to room temperature and allowed to stand for one week to give the block crystals of complex **1** (189 mg, 92%). IR (KBr disc) *v* 3405 (s), 3121 (s), 1638 (m), 1555 (s), 1379 (s), 1220 (w), 1076 (w), 808 (w), 748 (m). *Anal.* Calc. for $C_{43}H_{46}N_2O_{19}Zn_2$: C, 50.35; H, 4.52; N, 2.73. Found: C, 50.69; H, 4.96; N, 2.92%.

2.2.2. $[Zn(BCbpy)_2(H_2O)_4]_2(BDC)_2\cdot 13H_2O$ (*2*)

Complex **2** (320 mg, 80%) was prepared from HBCbpyBr (298 mg, 0.8 mmol), $Zn(NO_3)_2\cdot 6H_2O$ (118 mg, 0.4 mmol) and Na_2BDC (88 mg, 0.4 mmol), using similar procedures as described for complex **1**. IR (KBr disc) *v* 3408 (s), 3121 (s), 1640 (m), 1555 (s), 1379 (s), 1210 (w), 1079 (w), 808 (w), 748 (m). *Anal.* Calc. for $C_{88}H_{106}N_8O_{37}Zn_2$: C, 52.88; H, 5.35; N, 5.61. Found: C, 52.53; H, 4.91; N, 5.33%.