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Synthesis, crystal structures and biological evaluation of water-soluble zinc complexes of zwitterionic carboxylates

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ABSTRACT

Three water-soluble zinc complexes, $[Zn(Cbp)_2Br_2]$ (**1**) (Cbp = *N*-(4-carboxybenzyl)pyridinium), $\{[Zn(BCbpy)_2(H_2O)_4]_3Br_6{\cdot}2(BCbpy){\cdot}2(4,4'\text{-bipy})\}$ (**2**) (BCbpy = 1-(4-carboxybenzyl)-4,4′-bipyridinium) and $\{[Zn_4(Bpybc)_6(H_2O)_{12}](OH)_8{\cdot}9H_2O\}_{2n}$ (**3**) (Bpybc = 1,1′-bis(4-carboxybenzyl)-4,4′-bipyridinium), were synthesized and characterized by IR, elemental analysis and single-crystal X-ray crystallography. In complex **1**, the central Zn atom adopts a distorted tetrahedral coordination geometry that is formed from two unidentate Cbp ligands and two Br atoms. For complex **2**, the Zn atom in $[Zn(BCbpy)_2(H_2O)_4]^{2+}$ is strongly coordinated by four water molecules and two N atoms from two BCbpy ligands, hence forming an octahedral geometry. In complex **3**, each Bpybc ligand bridges two $[Zn(H_2O)_3]^{2+}$ units through two terminal carboxylate groups in a monodentate coordination mode, thus forming a flowerlike two-dimensional network. Agarose gel electrophoresis (GE) and ethidium bromide (EB) displacement experiments indicated that complex **3** was capable of converting pBR322 DNA into open circular (OC) and linear forms, and exhibited high binding affinity toward calf-thymus DNA. MTT assay showed that complex **3** displayed inhibitory activities toward the proliferation of lung adenocarcinoma A549 and mouse sarcoma S-180 cells, with the IC_{50} values being 27.3 and 48.8 μM, respectively.

1. Introduction

It is well known that many metalloenzymes contain one or more zinc(II) ions in the active sites [1–3]. These Zn(II) ions generally show high affinity toward the oxygen atom(s) of carboxyl groups from carboxypeptidase [4]. Such zinc-containing active sites play a crucial role in the catalytic processes and have been characterized for their multiple activities [5,6]. Therefore, the chemistry of zinc complexes of carboxylates has been receiving an increasing attention. To date, a wide variety of model compounds has been prepared with the aim to mimic the structures and functions of the active sites of zinc metalloenzymes [7]. Remarkable among them are the biologically active compounds that are synthesized from Zn^{2+} and amino acid derivatives, for example, as anticonvulsant and antitumor agents and as synthetic nucleases [8,9].

Because zinc complexes having good water-solubility can find wide potential applications [10], considerable efforts have been spurred to develop their synthetic approaches [11–13]. One viable approach to improve the water-solubility of the resulting zinc complexes, is to incorporate carboxylate ligands with highly hydrophilic groups [13,14]. Herein, we report the synthesis, crystal structures and biological evaluation of water-soluble zinc complexes **1**–**3** of three zwitterionic carboxylates having quaternary ammonium groups, including *N*-(4-carboxybenzyl)pyridinium bromide (HCbpBr), 1-(4-carboxybenzyl)-4,4′-bipyridinium bromide (HBCbpyBr) and 1,1′-bis(4-carboxybenzyl)-4,4′-bipyridinium bromide ($H_2BpybcBr_2$) (Chart 1). Among them, it is reported that HCbpBr and HBCbpyBr have diverse coordination modes (Chart 2) [15–21].

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. Electrospray ionization mass (ESI-MS) spectra

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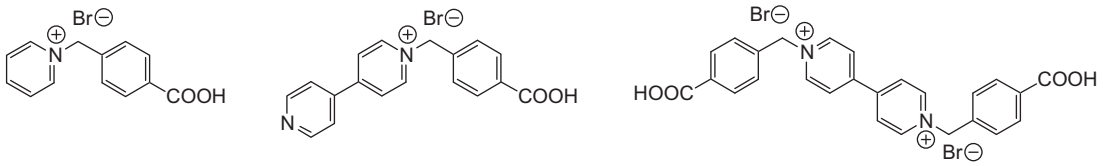

Chart 1. Chemical structures of HCbpBr, HBCbpyBr and $H_2BpybcBr_2$.

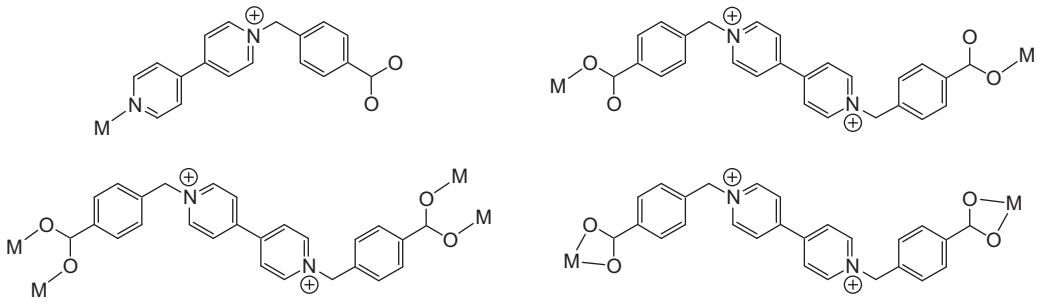

Chart 2. Reported coordination modes of HBCbpyBr and $H_2BpybcBr_2$.

were measured on an Applied Biosystems Sciex API 4000 Qtrap mass spectrometer. Agarose gel electrophoresis (GE) was conducted on DYY-8C electrophoresis apparatus and DYCP-31DN electrophoresis chamber, and detected on Alpha Hp 3400 fluorescence and visible light digital image analyzer. Fluorescence spectra were measured on a HITACHI F-2500 spectrofluorimeter.

Calf-thymus (CT) DNA and plasmid pBR322 DNA were obtained from Sigma–Aldrich and Takara Chemical Co., respectively. Their solutions were prepared in 5 mM Tris–HCl buffer (5 mM NaCl, pH 7.63). The concentration of CT DNA was determined spectrophotometrically using the molar extinction coefficient of 13 200 M^{-1} cm^{-1} per base pair (bp) at 260 nm [22]. HCbpBr, HBCbpyBr and H_2Bpy $bcBr_2$ were prepared according to the reported protocols [16,23,24]. 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. $[Zn(Cbp)_2Br_2]$ (**1**)

HCbpBr (118 mg, 0.4 mmol) was dissolved in H_2O (5 mL), and the pH was adjusted to 7 with 0.1 M NaOH solution. Then, a solution of $Zn(NO_3)_2{\cdot}6H_2O$ (59 mg, 0.2 mmol) in H_2O (5 mL) was added. The resulting mixture was stirred for 30 min to give a clear solution, and then allowed to stand for 1 month to produce colorless blocks. Subsequent washing with Et_2O and drying under vacuum yielded **1** (63 mg, 48% based on HCbpBr). Elemental *Anal.* Calc. for $C_{26}H_{22}Br_2ZnN_2O_4$: C, 47.92; H, 3.40; N, 4.30. Found: C, 47.45; H, 3.37; N, 4.45%. IR (KBr disc, cm^{-1}) ν 1632 (w), 1594 (m), 1548 (w), 1507 (w), 1488 (w), 1416 (w), 1390 (w), 1374 (m), 1178 (w), 770 (m).

2.2.2. $\{[Zn(BCbpy)_2(H_2O)_4]_3Br_6{\cdot}2(BCbpy){\cdot}2(4,4'\text{-bipy})\}$ (**2**)

To a solution of HBCbpyBr (149 mg, 0.4 mmol) in H_2O (5 mL) were added dropwise 0.1 M NaOH solution to adjust the pH 7, and then a solution of $Zn(NO_3)_2{\cdot}6H_2O$ (59 mg, 0.2 mmol) in H_2O (5 mL). The resulting mixture was stirred at room temperature for 1 h to give a clear solution, and then allowed to stand for 45 days to produce colorless blocks. Subsequent washing with Et_2O and drying under vacuum yielded **2** (133 mg, 76% based on HBCbpyBr). Elemental *Anal.* Calc. for $C_{164}H_{152}Br_6N_{20}O_{28}Zn_3{\cdot}26.7H_2O$: C, 49.15; H, 5.16; N, 6.99. Found: C, 49.78; H, 4.74; N, 6.82%. IR (KBr disc, cm^{-1}) ν 3446 (s), 3049 (w), 1614 (s), 1558 (w), 1456 (w), 1380 (s), 1158 (w), 811 (w), 744 (w).

2.2.3. $\{[Zn_4(Bpybc)_6(H_2O)_{12}](OH)_8{\cdot}9H_2O\}_{2n}$ (**3**)

Similar procedures for the synthesis of **2** were employed, except that $H_2BpybcBr_2$ (120 mg, 0.2 mmol) and $Zn(NO_3)_2{\cdot}6H_2O$ (59 mg, 0.2 mmol) in H_2O (5 mL) were used. Yield: 93 mg (82% based on $H_2BpybcBr_2$). Elemental *Anal.* Calc. for $C_{312}H_{340}N_{24}O_{106}Zn_8$: C, 56.39; H, 5.15; N, 5.06. Found: C, 55.91; H, 4.87; N, 4.92%. IR (KBr disc, cm^{-1}) ν 3400 (s), 3047 (s), 1616 (s), 1597 (s), 1556 (s), 1395 (s), 1374 (s), 1164 (m), 1019 (w), 1808 (m), 770 (w), 512 (w).

2.3. X-ray structures of complexes **1**–**3**

All the measurements were made on a Rigaku Mercury CCD X-ray diffractometer by using graphite monochromated Mo Kα (λ = 0.71070 Å). Crystals of **1**–**3** were mounted with grease at the top of a glass fiber, and cooled at 193 K in a liquid nitrogen stream. Cell parameters were refined by using the program CrystalClear (Rigaku and MSC, Ver. 1.3, 2001). The collected data were reduced by using the program CrystalStructure (Rigaku and MSC, Ver. 3.60, 2004) while an absorption correction (multiscan) was applied.

The crystal structures of **1**–**3** were solved by direct methods and refined on F^2 by full-matrix least square methods with SHELXTL-97 program [25]. All non-hydrogen atoms were refined anisotropically, and all the hydrogen atoms were placed in geometrically idealized positions. For **2**, free 4,4′-bipy was found to disorder over two sites with an occupancy factor of 0.5/0.5 for N9/N9A, N10/N10A, C73/C73A, C74/C74A, C75/C75A, C76/C76A, C77/C77A, C78/C78A, C79/C79A, C80/C80A, C81/C81A and C82/C82A. The solvent accessible void occupies a volume of 781.0 $Å^3$ (8.3% of the total cell volume) and is filled with highly disordered H_2O based on the FT-IR spectra. Because the disorder models did not give satisfactory results, the solvent contribution to the scattering factors was taken into account with PLATON/SQUEEZE [26]. As a result, a total of 267 electrons were found in each unit cell, corresponding to 26.7H_2O molecules per cell. Where relevant, the crystal data reported in this paper contained no contribution from the disordered