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Synthesis, Structure and DNA-Binding Properties of Manganese(II) Complex with 1,3-*bis*(1-Benzylbenzimidazol-2-yl)-2-oxapropane

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A five-coordinated manganese(II) complex containing ligand 1,3-*bis*(1-benzylbenzimidazol-2-yl)-2-oxopropane (bobb), with composition Mn(bobb)(pic)$_2$ (pic = picrate), has been synthesized and characterized. The crystal structure of complex has been determined by single-crystal X-ray diffraction. The manganese(II) complex adopts a distorted square-pyramidal geometry. In addition, DNA-binding properties of the ligand bobb and its manganese(II) complex have been investigated by electronic absorption and viscosity measurements. The experimental results suggest that ligand and manganese(II) complex bind to DNA *via* an intercalation binding mode and their binding affinity to DNA follows the order of manganese(II) complex greater than ligand bobb.

Keywords: 1,3-*bis*(1-Benzylbenzimidazol-2-yl)-2-oxopropane, Manganese(II) complex, Crystal structure, DNA-binding property.

INTRODUCTION

Benzimidazoles have a wide variety of pharmacological applications including fungicides, anthelmintics, antiulcers, antivirals and antihistamines[1,2]. Recently, *bis*-benzimidazole ligands, which represent a class of aromatic N-donor organic linkers, are still less developed[3,4].

The interaction of transition metal complexes with DNA have been an active area of research at the interface of chemistry and biology[5,6]. Numerous biological experiments have demonstrated that DNA is the primary intracellular target of anticancer drugs; interaction between small molecules and DNA can cause damage in cancer cells, blocking the division and resulting in cell death[7,8]. Studies on the interaction of transition metal complexes with nucleic acid have gained prominence, because of their relevance in the development of new reagents for biotechnology and medicine[9]. However, transition metal complexes containing benzimidazole-based ligand are a subject of intensive researches not only owing to their rich coordination chemistry but also due to a number of established and potential application areas[10]. In this contribution, the synthesis, characterization and DNA-binding properties of Mn(II) complex were investigated.

EXPERIMENTAL

The C, H and N elemental analyses were determined using a Carlo Erba 1106 elemental analyzer. ^{1}H NMR spectra were obtained with a Mercury plus 400 MHz NMR spectrometer with TMS as internal standard and $CDCl_3$ as solvent. The IR spectra were recorded in the 4000-400 cm^{-1} region with a Nicolet FT-VERTEX 70 spectrometer using KBr pellets. Electronic spectra were taken on a Lab-Tech UV Bluestar spectrophotometer. Calf thymus DNA (CT-DNA) was obtained from Sigma-Aldrich and prepared CT-DNA stock solutions[11-13].

1,3-*bis*(1-Benzylbenzimidazol-2-yl)-2-oxopropane (bobb): This compound was synthesized according to literature methods[14]. Yield: 9 g (75 %); m.p. 177-178 °C. Anal. Calcd for $C_{30}H_{26}N_4O$ (%): C 78.58; H 5.71; N 12.22; found (%): C 78.51; H 5.73; N 12.24. ^{1}H NMR ($CDCl_3$-d_1, 400 MHz): δ = 7.78-7.80 (m, 4 H), 7.17-7.30 (m, 10 H), 6.94-6.96 (m, 4 H), 5.29 (s, 4 H), 4.80-4.82 (m, 4 H). FTIR (KBr, ν_{max}, cm^{-1}): 1078 ν(C-O-C), 1496 ν(C=N), 1463 ν(C=N-C=C). UV/visible (DMF): λ = 279, 287 nm.

Preparation of Mn(II) complex: To a stirred solution of 1,3-*bis*(1-benzylbenzimidazol-2-yl)-2-oxopropane (0.183 g, 0.40 mmol) in hot MeOH (5 mL) was added Mn(II) picrate (0.102 g, 0.20 mmol) in MeOH (5 mL). A deep yellow crystalline product formed rapidly. The precipitate was filtered off, washed with MeOH and absolute Et_2O and dried *in vacuo*. The dried precipitate was dissolved in DMF resulting in a brown solution. The brown crystals suitable for X-ray diffraction studies were obtained by ether diffusion into DMF after several days at room temperature. Anal. Calcd. for $C_{42}H_{30}N_{10}O_{15}Mn$ (%): C 52.02; H 3.12; N 14.44. Found (%): C 52.03; H 3.21; N 14.40. FTIR (KBr, ν_{max}, cm^{-1}): 713 $\nu_{(Ar-O)}$, 1066 $\nu_{(C-O)}$, 1483 $\nu_{(C=N)}$, 1610 $\nu_{(C=C)}$. UV/visible (DMF): λ = 280, 289 nm.

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR THE Mn(II) COMPLEX

Complex	$Mn(bobb)(pic)_2$
Molecular formula	$C_{42}H_{30}N_{10}O_{15}Mn$
Molecular weight	969.70
Crystal system	Orthorhombic
Space group	Pbca
a (Å)	22.323(6)
b (Å)	10.937(3)
c (Å)	34.130(9)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	8333(4)
Z	8
ρ_{cald} (mg m^{-3})	1.546
Absorption coefficient (mm^{-1})	0.404
F (000)	684
Crystal size (mm)	0.28 × 0.21 × 0.15
θ range for data collection (°)	2.16 to 28.39
h /k /l (max, min)	-18 < = h < = 29, -14 < = k < = 13, -45 < = l < = 45
Reflections collected	54714
Independent reflections	10276 [R(int) = 0.0595]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	10276/1/623
Goodness-of-fit on F^2	0.983
Final R_1,wR_2 indices [I>2σ(I)]	R_1 = 0.0583, wR_2 = 0.1181
R_1,wR_2 indices (all data)	R_1 = 0.1176, wR_2 = 0.1431
Largest differences peak and hole(eÅ^{-3})	0.530 and -0.422

X-Ray crystal structure determination: All data were collected on a Bruker Apex-II CCD diffractometer with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) at 296(2) K. Data reduction and cell refinement were performed using SAINT programs[15]. The absorption correction was carried out by empirical methods. The structure was solved by Direct Methods and refined by full-matrix least-squares against F^2 using SHELXTL software[16]. All H atoms were found in difference electron maps and were subsequently refined in a riding model approximation with C-H distances ranging from 0.93 to 0.97 Å. The crystal data and experimental parameters relevant to the structure determination are listed in Table-1. Selected bond distances and angles are presented in Table-2.

CCDC 849260 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif.

DNA-binding studies: According to the literature[11,12], we performed the absorption titration and viscosity experiments. From the absorption titration data, the binding constant (K_b) was determined using below equation[17]:

$$[DNA]/(\varepsilon_a-\varepsilon_f) = [DNA]/(\varepsilon_b-\varepsilon_f) + 1/ K_b (\varepsilon_b-\varepsilon_f)$$

The ratio of slope to intercept in the plot of $[DNA]/(\varepsilon_a-\varepsilon_f)$ *versus* [DNA] gave the value of K_b. Viscosity data were presented as $(\eta/\eta_0)^{1/3}$ *versus* the ratio of concentration of the compound to CT-DNA. Viscosity values were calculated from the observed flow time of CT-DNA containing solutions corrected from the flow time of buffer alone (t_0), $\eta = (t-t_0)$[5].

RESULTS AND DISCUSSION

The ligand bobb and Mn(II) complex are very stable in air. The ligand bobb is soluble in organic solvents but insoluble in water. Mn(II) complex is soluble in DMF and DMSO but insoluble in water and common organic solvents.

IR and electronic spectra: The free ligand bobb exhibits characteristic C=N stretching frequency at 1496 cm^{-1}, while the C=N stretching frequencies of Mn(II) complex is observed at 1483 cm^{-1}. The C=N stretching frequencies are shifted upon complexation[18]. The shift indicates that the nitrogen atoms of ligand are coordinated to Mn(II) atom. They are the preferred nitrogen atoms for coordination, as found in other metal complexes with benzimidazole open chain crown ether derivatives. Information regarding the possible bonding modes of the picrate and benzimidazole rings[19] may also be obtained from the IR spectra, such as 742, 1276, 1363, 1434, 1487 and 1550 cm^{-1}. This fact agrees with the result determined by X-ray diffraction. In UV/visible spectra, the band of free ligand are red-shifted in Mn(II) complex and show clear evidence of C=N coordination to the metal atom. The absorption band is assigned to π-π^* (imidazole) transition[20].

X-ray crystallography: Complex crystallizes in the orthorhombic space group Pbca and its structure along with the atomic numbering is shown in Fig. 1. The Mn(II) atom is coordinated by one tridentate 1,3-*bis*(1-benzylbenzimidazol-2-yl)-2-oxopropane ligand and two picric ions in a five-coordinated distorted square-pyramidal geometry. The distortion in the coordination polyhedron (τ)[21] from a perfect trigonal bipyramidal geometry (τ = 1) toward a regular tetragonal pyramid (τ = 0) has been calculated according to the method. For this treatment, O1, N1, O2 and N3 make up the basal plane, while the apical site is occupied by O9 and τ = 0.038. The parameter τ is defined as (β-α)/60 (where β = O(9)---Mn(1)--O(1), α = N(3)-Mn(1)-N(1)). The disorder of the O_4 atom being symmetry imposed.

TABLE-2
SELECTED BOND LENGTHS (Å) AND ANGLES (°) FOR $Mn(bobb)(pic)_2$

Bond lengths			
Mn(1)-O(2)	2.069(2)	Mn(1)-O(9)	2.102(2)
Mn(1)-N(1)	2.160(2)	Mn(1)-N(3)	2.169(2)
Mn(1)-O(1)	2.363(2)	–	–
Bond angles			
O(2)-Mn(1)-O(9)	84.88(9)	O(2)-Mn(1)-N(1)	103.94(9)
O(9)-Mn(1)-N(1)	111.67(9)	O(2)-Mn(1)-N(3)	104.43(9)
O(9)-Mn(1)-N(3)	99.28(9)	N(1)-Mn(1)-N(3)	139.39(9)
O(2)-Mn(1)-O(1)	133.05(9)	O(9)-Mn(1)-O(1)	141.67(8)
N(1)-Mn(1)-O(1)	69.75(8)	N(3)-Mn(1)-O(1)	69.66(8)

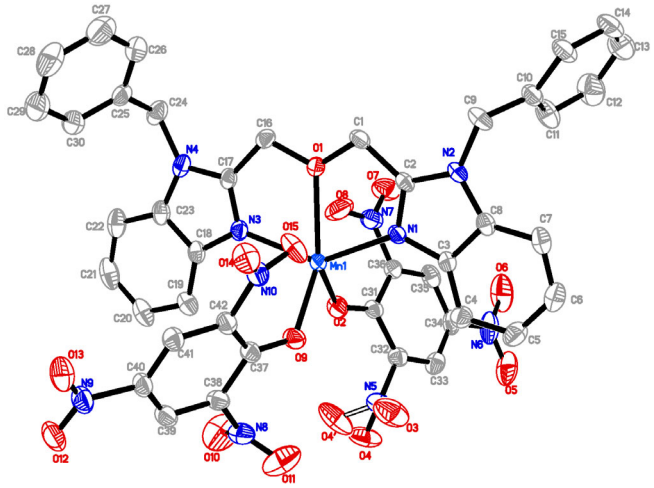

Fig. 1. Molecular structure of Mn(II) complex showing displacement ellipsoids at 30 % probability level. Hydrogen atoms have been omitted for clarity

CT-DNA binding studies: Electronic absorption spectroscopy is universally employed to determine the binding characteristics of metal complexes with DNA[22,23]. The absorption spectra of the ligand bobb and the Mn(II) complex in the absence and presence of CT-DNA are given in Fig. 2a and c, respectively. As for the ligand bobb with a well-resolved band at 287 nm in Fig. 2a, there is also a well-resolved band at about 286 nm in Fig. 2c for the complex. With increasing DNA concentrations, the hypochromism are 63.4 % at 287 nm for the ligand bobb and 50.7 % at 286 nm for the Mn(II) complex. The hypochromism suggest that the ligand bobb and the Mn(II) complex interact with DNA[24].

The binding constant K_b for the Mn(II) complex have been determined from the plot of [DNA]/(ε_a-ε_f) *vs.* [DNA] and found to be 1.5×10^5 M^{-1} (R = 0.996 for 16 points). K_b for the ligand (8.4×10^4 M^{-1}) (R = 0.995 for 16 points) is thus smaller than for the Mn(II) complex. Compared with the classic DNA-intercalative reagent[25], the binding constants (K_b) of the ligand bobb

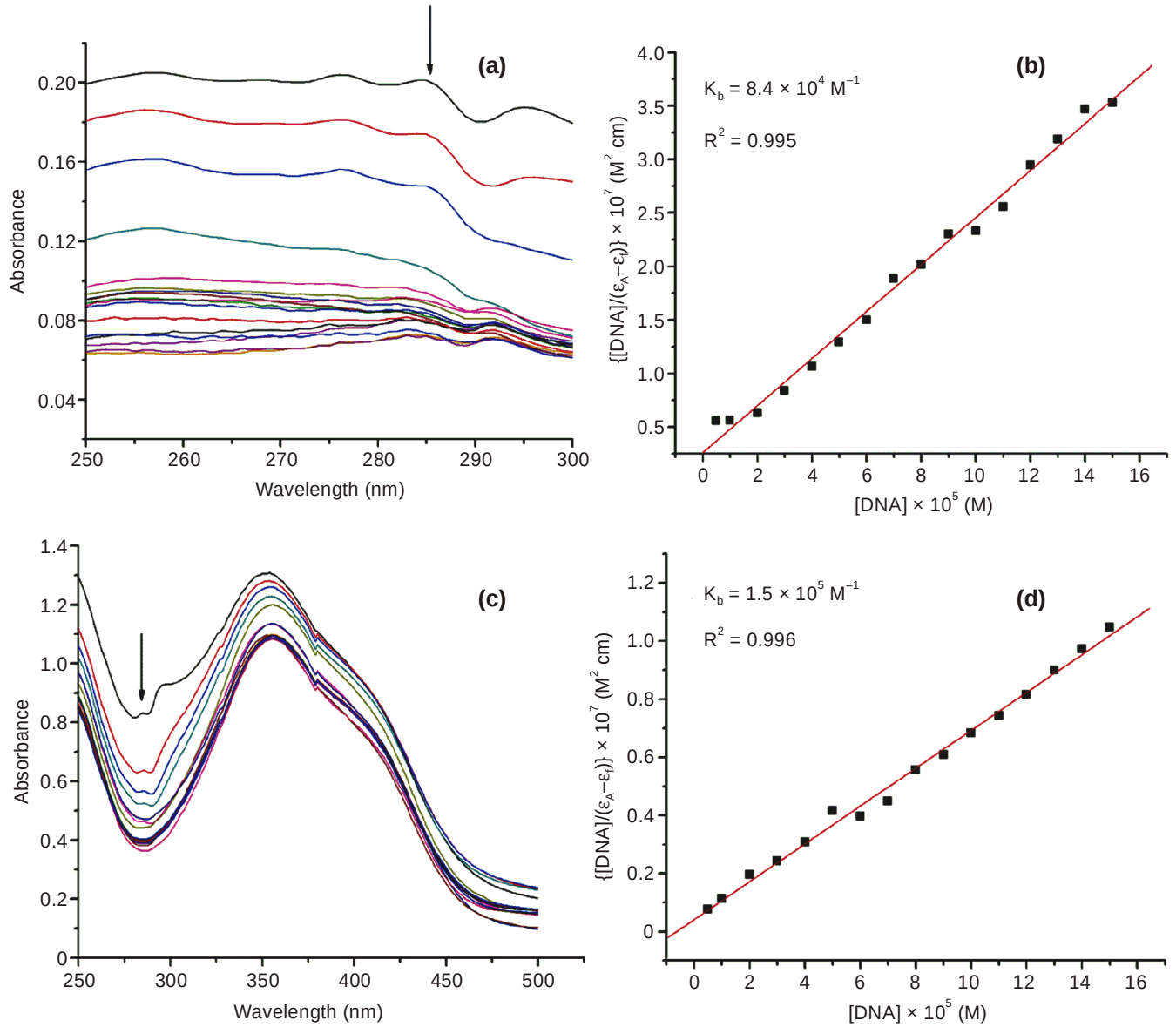

Fig. 2. Electronic spectra of free bobb (a) and Mn(II) complex (c) in *tris*-HCl buffer upon addition of CT-DNA. [DNA] = 1×10^{-5} - 16×10^{-5} M. The arrow shows the emission intensity changes upon increasing DNA concentration. [DNA]/(e_a-e_f) *versus* [DNA] for the titration of free ligand (b) and the Mn(II) complex (d) with CT-DNA

and Mn(II) complex suggest that the complex probably bind to DNA in an intercalation mode. The magnitude of K_b value is parallel to intercalative strength and the affinity of compound binding to DNA[26]. With the above intrinsic binding constant values, the binding affinity of Mn(II) complex is stronger than free ligand of bobb.

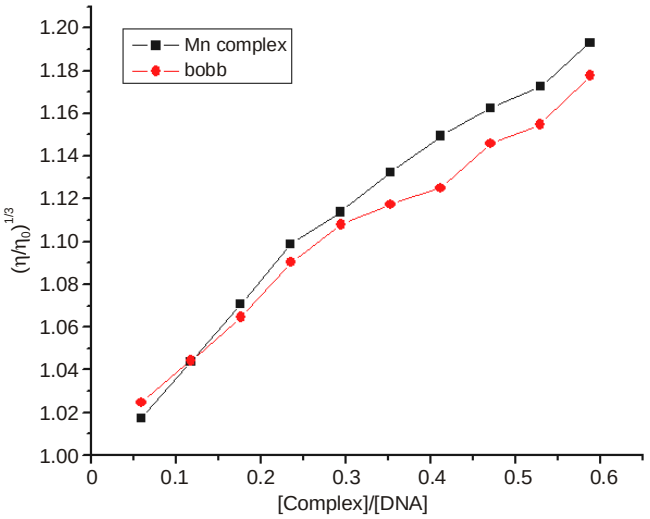

Fig. 3. Effect of increasing amounts of the compounds on the relative viscosity at 25 ± 0.1 °C

Optical photophysical probes generally provide necessary, but not sufficient clues to support a binding model. Measurements of DNA viscosity that is sensitive to DNA length are regarded as the least ambiguous and the most critical tests of binding in solution in the absence of crystallographic structural data[27]. Intercalating agents are expected to elongate the double helix to accommodate the ligands in between the bases leading to an increase in the viscosity of DNA. In contrast, complex that binds exclusively in the DNA grooves by partial and/or non-classical intercalation, under the same conditions, typically cause less pronounced (positive or negative) or no change in DNA solution viscosity. The values of $(\eta/\eta_0)^{1/3}$ were plotted against [compound]/[DNA] (Fig. 3). Upon addition of the ligand and Mn(II) complex the viscosity of rod-like CT-DNA increased significantly, indicating that the ligand bobb and Mn(II) complex can bind to DNA by intercalation mode[28], which may due to the large coplanar aromatic rings in two compounds that facilitate it intercalating to the base pairs of double helical DNA[29]. The results from the viscosity experiments confirm the mode of these compounds intercalating into DNA base pairs and already established through absorption spectroscopic studies.

Conclusion

We have reported the synthesis and structural characterization of a new Mn(II) complex. The DNA binding properties of the ligand bobb and the Mn(II) complex were studied *via* electronic absorption titration and viscosity experiment. All results suggested that the ligand bobb and the Mn(II) complex interacted with DNA in an intercalation mode. Moreover, their binding affinity to DNA follows the order of the Mn(II) complex greater than the ligand bobb. Results obtained from our present work would be useful to understand the mechanism of interactions of the small molecule compounds binding to DNA and helpful in the development of their potential biological, pharmaceutical and physiological implications in future.

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