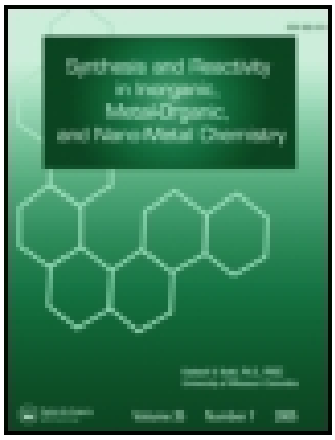

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Synthesis, Crystal Structure and DNA-Binding Studies of a Cadmium(II) Complex with the Bis(N-benzylbenzimidazol-2-ylmethyl)aniline

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ABSTRACT

A complex of cadmium (II) picrate (pic) with Bis(*N*-benzylbenzimidazol-2-ylmethyl)aniline (Bebba), with composition $[Cd(Bebba)_2](pic)_2$, was synthesized and characterized by elemental analysis, electrical conductivity and IR and UV/Vis spectral measurements. The crystal structure of the cadmium(II) complex has been determined by single-crystal X-ray diffraction. The cadmium(II) cation is bonded to two Bebba ligands through four benzimidazole nitrogen, resulting in a distorted octahedron geometry. The DNA-binding properties of the cadmium(II) complex were investigated by electronic absorption, fluorescence spectra and viscosity measurements. The experimental results suggest that the cadmium(II) complex binds to DNA in an intercalation mode.

Keywords: Bis(*N*-benzylbenzimidazol-2-ylmethyl)aniline; Cadmium(II) complex; Crystal structure; DNA binding property.

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INSTRODUCTION

Since the benzimidazole unit is the key building block for a variety of compounds which have crucial roles in the functions of biologically important molecules, there is a constant and growing interest over the past few years for the synthesis and biological studies of benzimidazole derivatives [1-3]. Benzimidazole compounds are environmentally friendly compounds with two high active nitrogen atoms in 1, 3-sites [4-6]. Benzimidazoles and their derivatives have a wide range of well-known biological activities such as anticancer [7-10], antimicrobial [11-12], antifungal [13], antiviral [14], etc. An interesting concept for finding a complex with distinct biological and pharmaceutical features, the bis(N-methylbenzimidazol-2-ylmethyl)aniline (Bebba) was selected as a ligand to chelate cadmium(II), which may enhance the interaction of the metal center(s) with DNA [15].

In this paper, we report the synthesis, crystal structure, and DNA-binding properties of the Cd(II) picrate complex with Bebba.

EXPERIMENTAL

Materials

All chemicals and solvents were reagent grade and used without further purification. Elemental analyses were determined using a Carlo Erba 1106 elemental analyzer. The IR spectra

were recorded on a BRUKER FT-IR VERTEX 70 spectrometer in the range of 4000-400 cm^{-1} using KBr pellets. ^{1}H-NMR spectra were obtained with a Mercury plus 400MHz NMR spectrometer with TMS as internal standard and DMSO-d_6 as solvent. Electronic spectra were taken on a LabTech UV Bluestar spectrophotometer. Fluorescence measurements were performed on a LS-45 spectrofluorophotometer. Electrolytic conductance measurements were made with a DDS-307 type conductivity bridge using 10^{-3} $mol \cdot L^{-1}$ solution in DMF at room temperature.

Calf thymus (CT-DNA) and ethidium bromide (EB) were obtained from Sigma-Aldrich Chemicals Co. (USA). Tris-HCl buffer solution containing 5 mM Tris-HCl / 50 mM NaCl (pH = 7.2) in double-distilled water was used to prepare all stock solutions for DNA binding studies. The stock solution of DNA (2.5×10^{-3} M) was prepared in Tris-HCl/NaCl buffer (pH = 7.2, stored at 4 °C and used when not more than 4 days). The solution of CT-DNA gave a ratio of UV absorbance at 260 nm and 280 nm, A_{260}/A_{280}, of 1.8-1.9, indicating that the DNA was sufficiently free of proteins [16]. The concentration of CT-DNA was determined from its absorption intensity at 260 nm with a molar extinction coefficient of 6600 $M^{-1}cm^{-1}$ [17]. The absorption spectra of complex binding of DNA was performed by increasing amounts of DNA to complex in 5 mM Tris-HCl/50 mM NaCl buffer (pH = 7.2). The stock solution of ligand and complex was dissolved in DMF at the concentration 3×10^{-3} M.

By the fluorescence spectral method, the relative binding of complex to CT-DNA was studied

with an EB-DNA complex solution in 5 mM Tris-HCl/50 mM NaCl buffer (pH = 7.2). Fluorescence intensities (520 nm excitation) were measured at different complex concentrations. The experiment was carried out by titrating complex into EB-DNA complex solution ([EB] = 2.2 × 10^{-3}M, [CT-DNA] = 2.5× 10^{-3} M).

Viscosity experiments were carried out using an Ubbelodhe viscometer maintained at a constant temperature at 25.0 ± 0.1 ºC in a thermostatic water-bath. Flow time was measured with a digital stopwatch, and each sample was measured three times, and an average flow time was calculated. Titrations were performed for the complex (3-30 μM) and complex was introduced into the CT-DNA solution (50 μM) present in the viscometer. Data were presented as $(\eta / \eta_0)^{1/3}$ versus the ratio of the concentration of the compound to CT-DNA, where η is the viscosity of CT-DNA in the presence of the complex, and η_0 is the viscosity of CT-DNA alone. Viscosity values were calculated from the observed flow time of CT-DNA containing solutions corrected for the flow time of the buffer alone (t_0) with the equation $\eta = (t - t_0) / t_0$ [18].

Preparation of bis(benzimidazol-2-ylmethyl)aniline(bba)

A mixture of phenylimiodiacetic acid (54.25 g, 0.25 mol) and o-phenylenediamine (54.00 g, 0.50 mol) in ethylene glycol (250 mL) was refluxed for 24 h. The yellow precipitate was filtered and washed with distill water. Yield 82.05 g (75.8 %). Anal. Calcd for $C_{22}H_{19}N_5$ (%): C, 74.77; H, 5.42; N, 19.82. Found (%): C, 74.79; H, 5.41; N, 19.83. Selected IR data (KBr ν/cm^{-1}): 1600m ν(C=C), 1445m ν(C=N), 1272m ν(C-N), 743mν(O-Ar). 1H NMR (400 MHz, DMSO-d6, δ /

ppm): 7.2-7.68(m, 10H, benzimidazole), 6.55-7.10(m, 5H, Ph), 5.14(s, 4H, CH_2). Λ_M. (DMF, 297 K): 3 $S \cdot cm^2 \cdot mol^{-1}$.

Preparation of bis(N-benzylbenzimidazol-2-ylmethyl)aniline (Bebba)

The synthesis of the ligand Bebba is displayed as scheme 1. 5.3 g (0.015mol) bis(benzimidazol-2-ylmethylene)aniline with 1.17 g (0.03mol) potassium in 150mL evaporated tetrahydrofuran was followed by adding 5.13 g (0.03mol) benzyl bromide. The resulting solution was concentrated and recrystallized from methanol which was given pale yellow block crystals of Bebba. Yield 6.14 g (75.8%). Anal. Calcd for $C_{34}H_{31}N_5$ (%): C, 80.13; H, 6.13; N, 13.74. Found (%): C, 80.27; H, 6.07 ; N, 13.66. Selected IR data (KBr ν/cm^{-1}): 1600m ν(C=C), 1454m ν(C=N), 1291m ν(C-N)，744mν(O-Ar). 1H NMR (400 MHz, DMSO-d_6, δ / ppm): 7.13-7.60(m, 8H, benzimidazole), 7.09-6.64(m, 5H, Ph), 5.019(s, 4H, CH_2), 3.78-3.21(s, 14H, benzyl). UV/Vis (DMF): λ = 282, 287 nm. Λ_M. (DMF, 297 K): 7 $S \cdot cm^2 \cdot mol^{-1}$.

Preparation of $[Cd(Bebba)_2](pic)_2$

To a stirred solution of Bebba (0.267 g, 0.5 mmol) in hot MeOH (10 mL) was added $Cd(pic)_2$ (0.143 g, 0.25 mmol) in MeOH (5 mL). A pale-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 to form a yellow solution into which Et_2O was allowed to diffuse in at r. t. Paleyellow crystals of $[Cd(Bebba)_2](pic)_2$ suitable for X-ray diffraction were obtained after five days. Anal. Calcd for $C_{84}H_{66}CdN_{16}O_{14}$ (%): C, 61.98; H, 3.59; N, 13.77.

Found: C, 61.83; H, 3.79; N, 13.61. Selected IR data (KBr ν/cm^{-1}): 1633m ν (C=C), 1495m ν(C=N), 1312m ν(C-N)，742m ν(O-Ar). Λ_M. (DMF, 297 K): 130 $S \cdot cm^2 \cdot mol^{-1}$.

X-Ray crystal structure determination

All data were obtained using a Bruker Smart CCD diffractometer with graphite Monochromated Mo-Ka radiation (λ = 0.71073 Å) at 296 K. Date reduction and cell refinement were performed using SAINT programs [19]. The absorption corrections were carried out by the empirical method. The structure was solved by Direct Methods and refined by full-matrix least-squares against F^2 of data using SHELXTL software [20].

The non-H atoms in the structure were subjected to anisotropic refinement. Hydrogen were located geometrically and treated with the riding model. Basic crystal data, description of the diffraction experiment, and details of the structure refinement are given in Table 1. Selected bond distances and angles are presented in Table 2.

RESULTS AND DISCUSSION

The synthetic route for the ligand Bebba is shown in Scheme 1. The Cd(II) complex $[Cd(Bebba)_2](pic)_2$ was prepared by reaction of Bebba with $Cd(pic)_2$ in methanol. It is soluble in polar aprotic solvents such as DMF, DMSO and MeCN, slightly soluble in ethanol, methanol, ethyl acetate, and chloroform, and insoluble in water, Et_2O and petroleum ether. The elemental analysis shows that its composition is $[Cd(Bebba)_2](pic)_2$ which was confirmed by the crystal

structure analysis.

Crystal structure of $[Cd(Bebba)_2](pic)_2$

The central Cd(II) is six-coordinate, by virtue of six nitrogen atoms from two tridentate Bebba(Fig. 1). The coordination geometry of Cd(II) is that of a distorted octahedron with (N1, N3, N4, and N1A) providing the equatorial plane. In the equatorial plane, the lengths of the bonds connected with Cd(II) range from 2.2285 to 3.031 Å , The ligand – metal – ligand angles vary from 62.82(6)° to 127.02(15)°, while the bond lengths between Cd(II) and the apical nitrogen atoms (N3A, N4A) are almost equal, average 2.255 Å . The bond angle of N3A – Cd – N4A in axial positions is 126.45(7)°. Therefore, compared with a regular octahedron, it reflects a relatively distorted coordination octahedron around Cd(II) [21—23] . Besides, In the crystal structure a parallel arrangement between the benzene rings is realized indicating π - π stacking of them with a distance between them of around 4.012Å (Fig. 2).

IR and UV spctra

The IR spectral data for the free ligand and the Cd(II) complex with their relative assignments have been studied to characterize their structures. The IR spectrum of the free ligand Bebba shows characteristic absorption bands of the benzimidazole group at 1600, 1447, and 1280 cm^{-1} assigned to ν(C=C), ν(C=N) and ν(C-N), respectively [24 – 25]. The bands are shifted by

around 30 cm^{-1} in the complex, which implies direct coordination of the metal ion to four benzimidazole nitrogen atoms and two nitrogen atoms, which are the preferred atoms for coordination as found for other metal complexes with benzimidazoles. Information regarding the possible bonding modes of the picrate and benzimidazole rings may also be obtained from the bands at 708, 1177, 1312, and 1633 cm^{-1}. The results agree with those determined by X-ray diffraction.

DMF solutions of the ligand Bebba and its cadmium(II) complex show, as expected, almost identical UV spectra. The UV bands of Bebba (287 nm) are only marginally blue-shifted (2 nm) in the complex, which is a clear evidence of C=N coordination to cadmium(II). The absorption band is assigned to $\pi \rightarrow \pi^*$ (benzimidazole) transitions.

DNA banding mode and affinity

Electronic absorption titration

Electronic absorption spectroscopy is universally employed to determine the binding characteristics of metal complexes with DNA. The absorption spectra of the ligand Bebba and the Cd(II) complex in the absence and presence of CT-DNA are given in Figs. 3 (a), (b) respectively. As for the ligand Bebba with two well-resolved bands at 276 and 282 nm (Fig. 3(a)), in Fig. 3(b) there are also two well-resolved bands at about 282, 287 nm for the complex (Fig. 3(c)), in Fig. 3(d). With increasing DNA concentrations, the hypochromism are 16.34 % at 287

nm for the ligand Bebba, and 24.25 % at 287nm for the Cd(II) complex. These spectral characteristics suggest that the Cd(II) complex interacts with DNA, most likely through a mode that involves a stacking interaction between the aromatic chromophore and the base pairs .

The binding constant K_b for the complex has been determined from the plot of [DNA] / ($\varepsilon_a - \varepsilon_f$) vs. [DNA] and found to be 6.26×10^4 M^{-1}. K_b for the ligand (1.41×10^5 M^{-1}) is larger than for the complex. Compared with those of a so-called DNA-intercalative ruthenium complexes , the binding constants (K_b) of Bebba and the Cd(II) complex suggest that the two compounds most probably bind to DNA in an intercalation mode. With the above intrinsic binding constant values, the binding affinity of the Cd(II) complex is stronger than that of Bebba.

However, the affinity for DNA is more strong in case of Cd(II) complex when compared with the ligand. For this difference, we attributed to three possible reasons. (i) By comparison of the molecular structure of the ligand and Cd(II) complex, we find the greater number of coplanar aromatic rings may lead to higher affinity for DNA [26]. (ii) The charge transfer of coordinated Bebba ligands caused by the coordination of the central Cd(II) atom, lead to the reduce of the charge density of the plane conjugate system, which is conducive to insert. (iii) This difference in their DNA binding ability also could be attributed to the presence of an electron deficient center in the charged Cd(II) complex where an additional interaction between the complex and phosphate rich DNA back bone may occur .

Competitive binding with EB

Ethidium bromide (EB) is one of the most sensitive fluorescent probes which can bind to DNA through intercalation [27, 28]. Competitive binding to DNA of the drugs with EB could provide rich information with regard to the DNA-binding affinity. As shown in Fig.4, the fluorescence intensity decrease obviously with the increasing concentration of the ligand Bebba and the Cd(II) complexes. The Ksv values for ligand are 7.31×10^{3} M^{-1} and the Cd(II) complex is 3.23×10^{3} M^{-1}, respectively. The quenching plots illustrate that the quenching of EB bound to DNA by the compounds are in good agreement with the linear Sterne-Volmer equation and the binding ability of two compounds follows the order Cd(II) complexes > Bebba. Furthermore, such quenching constants of the ligand and the Cd(II) complexes suggest that the interaction of all the compounds with DNA should be of intercalation.

Viscosity studies

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 [29]. 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, compounds that bind 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 [30]. The values of $(\eta / \eta_0)^{1/3}$ were plotted against [compound] / [DNA] (Fig. 5). Upon addition of the ligand, the Cd(II) complex the viscosity of rod-like CT-DNA increased significantly, which suggests that the ligand Bebba, the Cd(II) complex can bind to DNA by intercalation [31].

CONCLUSION

In summary, a complex $[Cd(Bebba)_2](pic)_2$ has been synthesized and characterized by elemental analysis, molar conductivity, IR spectra and UV–Vis spectra. DNA binding properties of the free ligand Bebba and its complex were investigated by ultraviolet absorption spectroscopy, fluorescence spectroscopy and viscosity measurements. The results support the fact that two compounds can bind to DNA via intercalation mode.

SUPPLEMENTARY MATERIALS

Supplemental data is for this article is available at the publisher's website. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC 837721. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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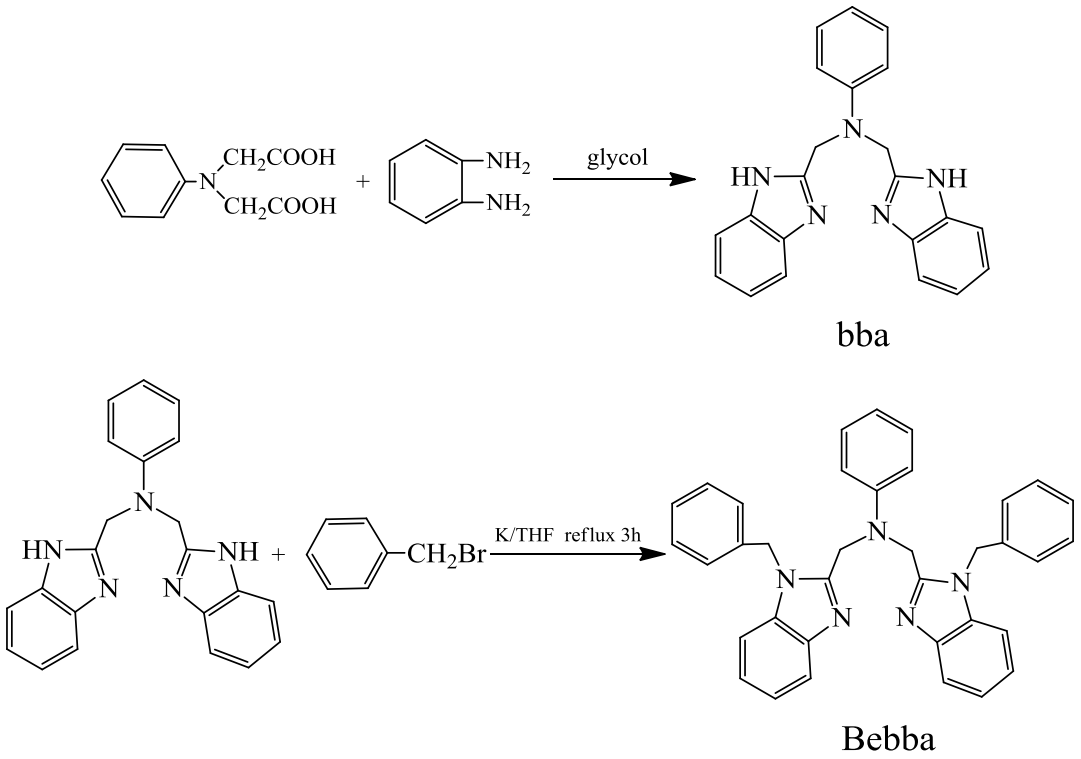

Scheme.1. The synthesis of the ligand Bebba .

TABLE 1 Crystal data and structure refinement for $[Cd(Bebba)_2](pic)_2$

formula	$C_{84}\ H_{66}\ Cd\ N_{16}\ O_{14}$
M	1635.93
Temperature (K)	293(2)
system	Monoclinic
space group	*P2/c*
a(Å)	11.8100(10)
b(Å)	13.7340(12)
c(Å)	22.809(2)
α/(°)	90
β/(°)	95.2900(10)
γ/(°)	90
V/Å^3	3683.8(6)
Z	2
ρ_{caled} g/cm^3	1.475
F(000)	1684
Limiting indices	-14<=h<=14, -16<=k<=16, -27<=l<=22
Crystal size mm	0.40 x 0.38 x 0.30

q range for data collection, deg	$1.73 < \theta < 25.50$
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.0955
R indices (all data)	R1 = 0.0425, wR2 = 0.1000
$\Delta\rho$(max) and $\Delta\rho$(min)	0.893 and 0.860

TABLE 2 Selected bond lengths (Å) and angles (°) for $[Cd(Bebba)_2](pic)_2$

Bond lengths	Cd(1)-N(3)#1	2.2285(18)	Cd(1)-N(3)	2.2285(18)
	Cd(1)-N(4)#1	2.2799(19)	Cd(1)-N(4)	2.2799(19)
	Cd(1)-N(1)	3.031(2)	Cd(1)-N(1)#1	3.031(2)
Bond angles	N(3)#1-Cd(1)-N(3)	110.92(10)	N(3)#1-Cd(1)-N(4)#1	126.45(7)
	N(3)-Cd(1)-N(4)#1	101.50(7)	N(3)#1-Cd(1)-N(4)	101.50(7)
	N(3)-Cd(1)-N(4)	126.45(7)	N(4)#1-Cd(1)-N(4)	91.21(10)
	C(23)-N(4)-Cd(1)	123.50(15)	C(36)-N(4)-Cd(1)	126.27(15)
	C(8)-N(3)-Cd(1)	127.02(15)	C(21)-N(3)-Cd(1)	126.07(15)
	N(3)#1-Cd(1)-N(1)	123.73(6)	N(3)-Cd(1)-N(1)	63.79(6)
	N(4)-Cd(1)-N(1)	62.82(6)	N(4)#1-Cd(1)-N(1)	108.45(6)

Symmetry transformations used to generate equivalent atoms: #1 -x,y,-z+1/2

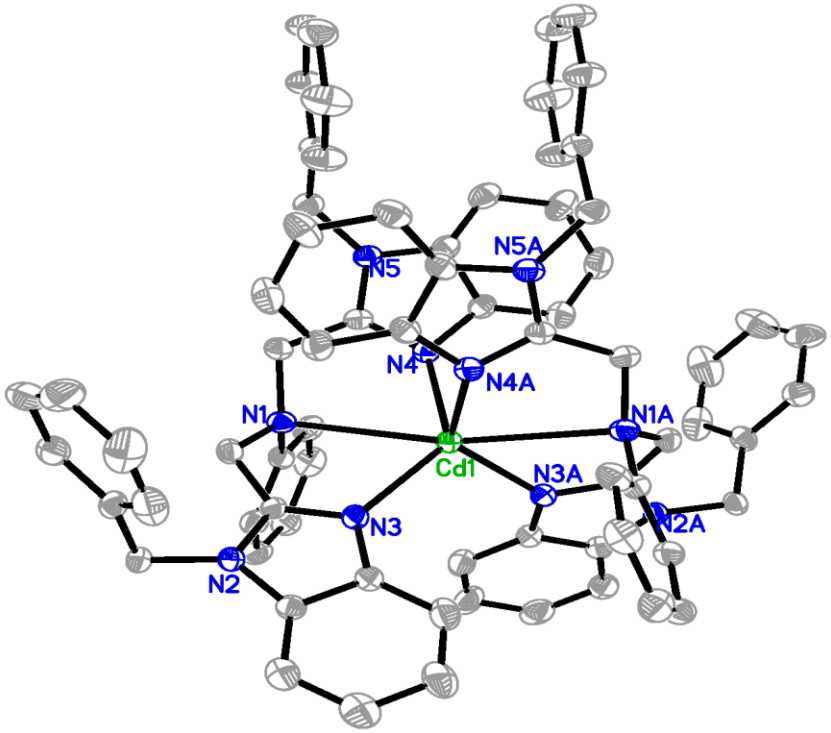

Fig. 1. Molecular structure and atom-numberings of $[Cd(Bebba)_2]^{2+}$ with hydrogen atoms omitted for clarity.

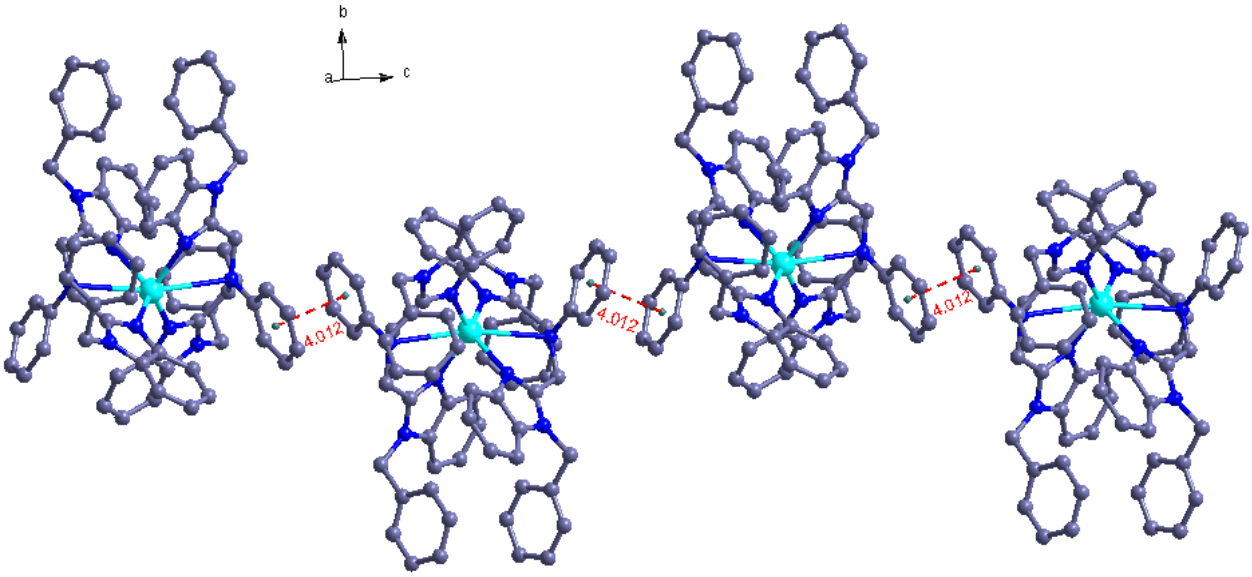

Fig.2. The structure of the Cd(II)complex linked via π - π stacking interaction

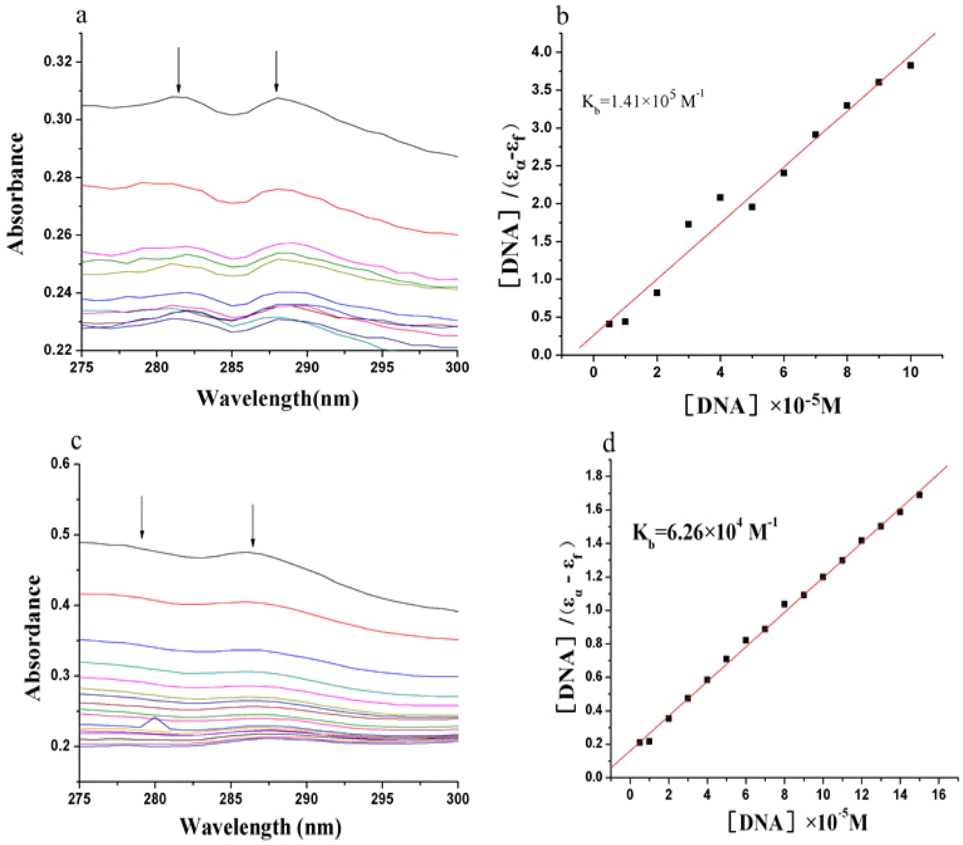

Fig. 3. Electronic spectra of the free ligand Bebba (a) and complex the Cd(II) complex (c) in Tris–HCl buffer upon addition of CT-DNA. [DNA] = 1×10^{-5} - 9×10^{-5} M. The arrow shows the emission intensity changes upon increasing DNA concentration. [DNA] / (εa−εf) versus. [DNA] for the titration of the free ligand Bebba (b) and the Cd(II) complex (d) with CT-DNA

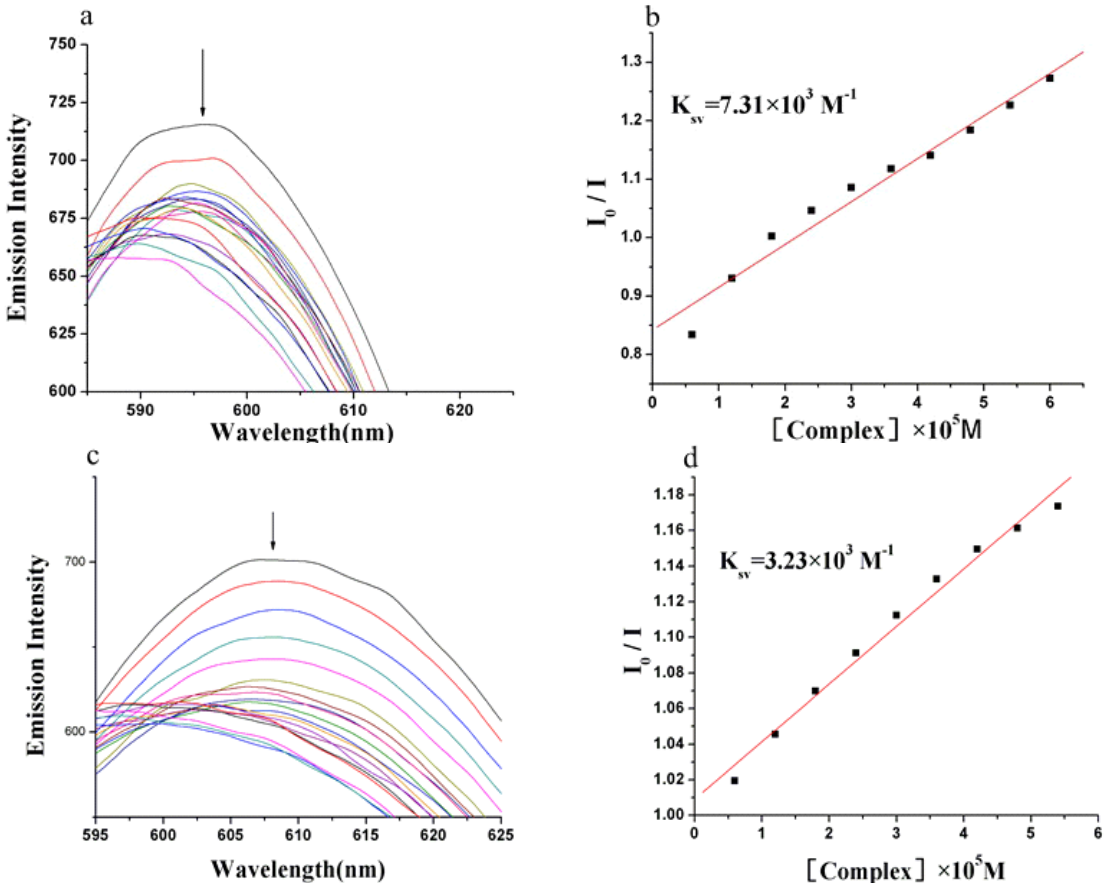

Fig. 4. Emission spectra of EB bound to CT-DNA in the presence of the free Bebba (a) and the Cd(II)complex (c), λ_{ex} = 520 nm., [Compound] = 0.6×10^{-5} – 6×10^{-5} M. The arrows show the intensity changes upon increasing con- centrations of the complexes. Fluorescence quenching curves of EB bound to CT-DNA by the free Bebba (b) and the Cd(II)complex (d). (Plots of I_0 / I versus. [Compound].)

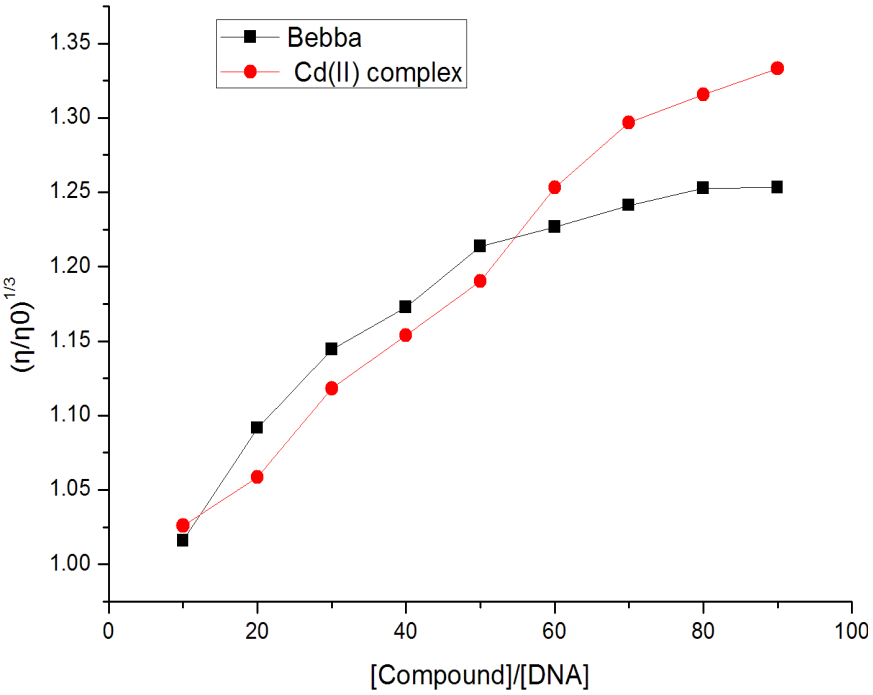

Fig. 5. Effect of increasing amounts of the compounds on the relative viscosity at 25.0 ± 0.1°C