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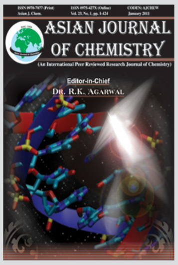

Synthesis and DNA-Binding of Transition Metal Complexes with 3,4-Dimethoxyphenylacetic Acid

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Three complexes with the general composition $[M(DMPA)_2(H_2O)_2]$ **1-3** (HDMPA = 3,4-dimethoxyphenylacetic acid, $C_{10}H_{12}O_4$; M = Ni, (**1**); Cu, (**2**); Zn, (**3**)) were synthesized from 3,4-dimethoxyphenylacetic acid and $Ni(OH)_2$, $Cu_2(OH)_2CO_3$, $Zn(OH)_2$. All these complexes were characterized by elemental analysis, molar conductance, IR spectroscopy, thermal analysis. The $DMPA^-$ ligand behaves as a bidentate ligand having a O,O donor sets towards the metal cations. In all the three metal complexes, the central M(II) ion coordinates with both two $DMPA^-$ ligands *via* four oxygen atoms of carboxylato groups and two water molecule *via* their two oxygen atoms. The coordination numbers are tentatively assigned as six. The interaction between these metal complexes and DNA were studied by EtBr fluoescent probe.

Key Words: Transition metal complex, 3,4-Dimethoxyphenylacetic acid, DNA.

INTRODUCTION

Transition metals are necessary for our life, especially Mn, Co, Ni, Cu and Zn[1,2]. Zinc is an important life element and some activity centers of enzyme[3]. The coordination ability of aromatic carboxylic acids towards transition metal complexes has received considerable attention, due to the strong coordination ability and varieties of the bridging modes of the carboxylate group with regard to the formation of extended frameworks[4-7]. Deoxyribonucleic acid (DNA) plays an important role in the life process since it contains all the genetic information for cellular function. However, DNA molecules are prone to be damaged under various conditions like interactions with some molecules. This damage may cause various pathological changes in living organisms, which is due to their possible application as new therapeutic agents and their photochemical properties which make them potential probes of DNA structure and conformation[8-12]. The binding interaction of transition metal complexes with DNA is of interest for both therapeutic and scientific reasons[13-15]. Many transition metal complexes are known to bind to DNA *via* both covalent and non-covalent interactions. In covalent binding the labile ligand of the complexes is replaced by a nitrogen base of DNA. On the other hand, the non-covalent DNA interactions include intercalative, electrostatic and groove (surface) binding of cationic metal complexes along outside of DNA helix, major or minor groove. In order to learn the relationship between the biological properties and the structures of metal complexes, it is necessary to study the interaction between them and DNA. In this work, the Ni, Cu and Zn complexes with 3,4-dimethoxyphenylacetic acid (HDMPA) have been synthesized and characterized by elemental analysis, molar conductance, IR spectroscopy, thermal analysis. The interactions of the three complexes and DNA were studied.

EXPERIMENTAL

3,4-Dimethoxyphenylacetic acid (HDMPA), $Cu_2(OH)_2CO_3$, $NiSO_4·6H_2O$, $ZnSO_4·7H_2O$, NaOH and other chemical reagents were obtained from commercial sources and used without further purification. $Ni(OH)_2$ and $Zn(OH)_2$ were prepared by reactions of NaOH and $NiSO_4·6H_2O$, $ZnSO_4·7H_2O$.

CT-DNA (Beijing Hua Mei Co., China): CT-DNA solution (200 μg mL^{-1}, c = 3.7 × 10^{-4} mol L^{-1}) was obtained by using 0.1 mol L^{-1} NaCl aqueous solution and reserved at 4 ºC; EB (EthBr) (Fluka Co. Sweden). The DNA concentrations were determined according to the absorbance ratio A_{260}/A_{280} was in the range 1.80-1.90 and the molarities of double stranded DNA solution were calculated by using ε_{DNA} = 6600 mol^{-1} cm^{-1} L. The stock solutions of 1.0 × 10^{-4} mol L^{-1} complexes were obtained by dissolving complexes **1-3** in DMF.

The metal contents were determined by EDTA complexometric titration after decomposition a known amount of the complexes with concentrated nitric acid. Elemental analyses for C, H were carried out on an Elementar Vario EL III elemental analyzer. IR spectra on KBr pellets were recorded on a Nicolet NEXUS 670 FTIR spectrophotometer in the range of 4000-400 cm^{-1}. Molar conductivity of the complexes were measured with a Shanghai DDS-11A conductivity meter in DMF (1.0×10^{-3} mol L^{-1}). Thermal analyses were carried out using Mettler-Toludo TGA/SDTA851e thermal analyzer with a heating rate of 10 ºC min^{-1} from 30-900 ºC in air atomsphere. Emission spectra were recorded on a Perkin-Elmer LS55 luminescence spectrometer.

Syntheses: $[Ni(DMPA)_2(H_2O)_2]$ (**1**): A solution (30 mL) of 3,4-dimethoxyphenylacetic acid (0.395 g, 2.0 mmol) and $Ni(OH)_2$ (0.093 g, 1 mmol) was constantly strirred and refluxed for 4 h and then filtrated. Light green powder were obtained from the filtrate after 2 months, yield 80 % (based on $Ni(OH)_2$).

Complex (**2**) was synthesized with the same method as (**1**) except for replacing $Cu_2(OH)_2CO_3$ with $Ni(OH)_2$, grass green powder were obtained after 50 d, yield 90 %.

Complex (**3**) was also prepared with the same method as (**1**) except for replacing $Zn(OH)_2$ with $Ni(OH)_2$, white powder were obtained after 45 d, yield 85 %.

Determining of emission spectra: To 10 mL test tube 2 mL *tris* buffer (pH = 7.4) was added, then 2 mL 1.0×10^{-5} mol L^{-1} complexes **1-3** solutions and different volume of DNA solution (200 μg mL^{-1}) was added and finally the solutions were diluted to the desired concentration. Fluorescence measurements were carried out at 251 nm excitation wavelength in the range of 520-700 nm. Relative fluorescence intensity (F/F_0), in which F_0 was the fluorescence data of the system without DNA solution, was calculated.

RESULTS AND DISCUSSION

The compositions of complexes are summarized in Table-1. The C, H, M contents both theoretically calculated values and actual values are in accordance with the formula $M(DMPA)_2(H_2O)_2$ and it shows that the complexes are consist of one central metal, two ligands($DMPA^-$), two water molecule. Their molar conductance in DMF (1.0×10^{-3} mol L^{-1}) solvent lie in the range of 1.7-4.4 S cm^2 mol^{-1}. The conductance value are in accordance with the non-electrolytic nature of the complexes[16], which clearly indicates that anions are coordinated with metal.

The most characteristic absorptions of IR spectra of the complexes are listed in Table-2. In the IR spectra of complexes **1-3**, the absorption of the ν(C=O) of the free HDMPA ligand at 1708 cm^{-1} has disappeared and has been replaced by two very strong characteristic band in the range of 1588-1565 and 1427-1409 cm^{-1} which can be assigned as asymmetric, $\nu_{as}(-COO^-)$ and symmetric, $\nu_s(-COO^-)$ strectching vibrations, respectively. The difference $\Delta = \nu_{as}(-COO^-)-\nu_s(-COO^-)$ is a useful characteristric for determining the coordination mode of the carboxylato group of the ligands. For complexes **1-3**, the Δ values fall in the range of 174-156 cm^{-1}, indicating a bidentate coordination mode of the carboxylato group[17]. Abroad band in the range of 3442-3415 cm^{-1} shows that water molecules is existed in the complexes. Two absorption band at around 931-927 cm^{-1} attributed to HOH stretching and at 616-607 cm^{-1} attributed to δ_{HOH}, indicating that H_2O coordinated with metal[17]. A band at 553-547 cm^{-1} attributed to ν(M-O) are observed in the spectra of all the complexes, which are not found in the spectrum of the free ligand. So the coordination bond were formed between mental ion and oxygen atoms of $DMPA^-$ ligands and water molecules.

The TG-DTG curves of complexes are very similar and the complex (**1**) was discussed for example. The TG-DTG curves of complex (**1**) are shown in Fig. 1. The DTG curves show mainly two stages for the decomposition process. The first stage decomposition temperature is in the range of 105-195 ºC with a mass loss 7.38 % which corresponds to the loss of two H_2O (calcd. 7.42 %). The second stage of decomposition in the 230-412 ºC temperature range, in which the two $DMPA^-$ anions are decomposed with mass loss 80.30 % (calcd. 80.42 %), the final products is metal oxide NiO 12.37 % (calcd. 12.16 %). These results are in good accordance with the composition of the comple.

From measuring of above, it is concluded that every central M(II) ion in the complexes coordinates with four oxygen atoms of two $DMPA^-$ anions ligands and two oxygen atoms of two coordinated water molecules. Their coordination numbers are six. The suggested structure of the complexes are shown in Fig. 2.

The binding of complexes **1-3** to CT-DNA can be studied by competitive binding experiments. Ethidium bromide (EB) is known to show fluorescence when bound to DNA, due to

TABLE-1
ELEMENTAL ANALYSIS, MOLAR CONDUCTANCE DATA OF COMPOUNDS

Complex	m.p. (ºC)	Colour	Elemental analysis (%) calcd./found			Λ_M (S cm^2 mol^{-1-})
			C	H	M	
1 $[Ni(DMPA)_2(H_2O)_2]$	> 260	Light-green	51.13 (51.21)	5.55 (5.59)	12.46 (12.51)	4.4
2 $[Cu(DMPA)_2(H_2O)_2]$	> 260	Green	50.73 (50.68)	5.50 (5.53)	13.47 (13.41)	3.6
3 $[Zn(DMPA)_2(H_2O)_2]$	> 260	White	50.38 (50.49)	5.45 (5.51)	13.69 (13.74)	1.1

*The data in the brackets are the calculated values.

TABLE-2
IR SPECTRA DATA OF COMPLEXES (cm^{-1})

Complex	$\nu_{as}(-COO^-)$	$\nu_s(-COO^-)$	Δν	H_2O	ν(M-O)	ν(O-H)
1 $[Ni(DMPA)_2(H_2O)_2]$	1565 (s)	1409 (s)	156	927 (w), 616 (w)	533 (w)	3278 (m)
2 $[Cu(DMPA)_2(H_2O)_2]$	1588 (s)	1427 (s)	161	930 (w), 615 (w)	537 (w)	3442 (m)
3 $[Zn(DMPA)_2(H_2O)_2]$	1588 (s)	1414 (s)	174	931 (w), 607 (w)	549 (w)	3415 (m)

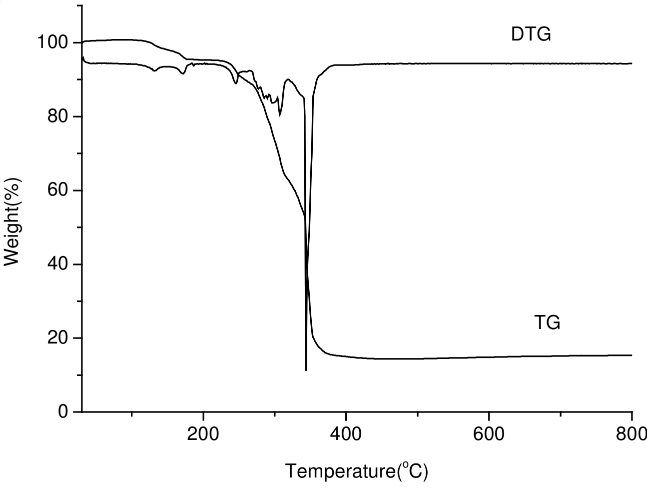


Fig. 1. TG-DTG curves of complex **1**

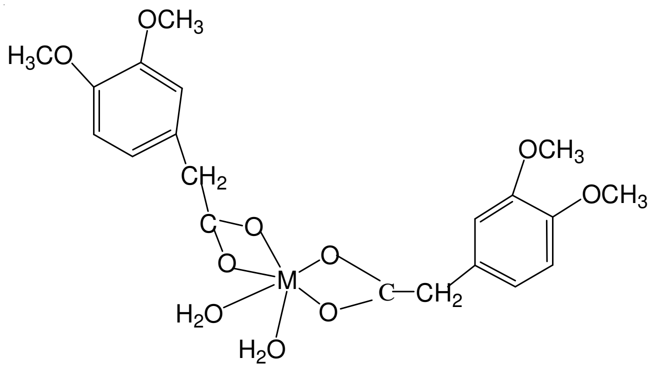
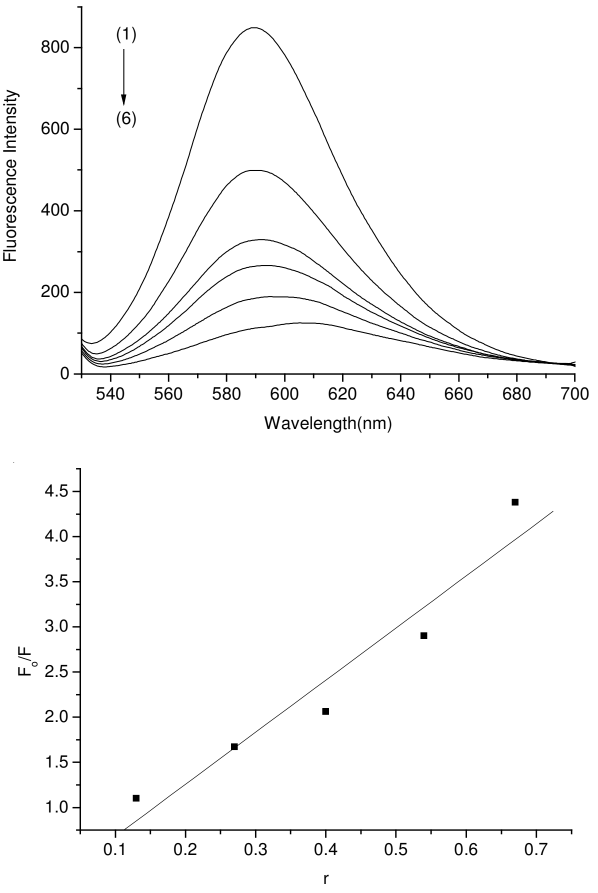
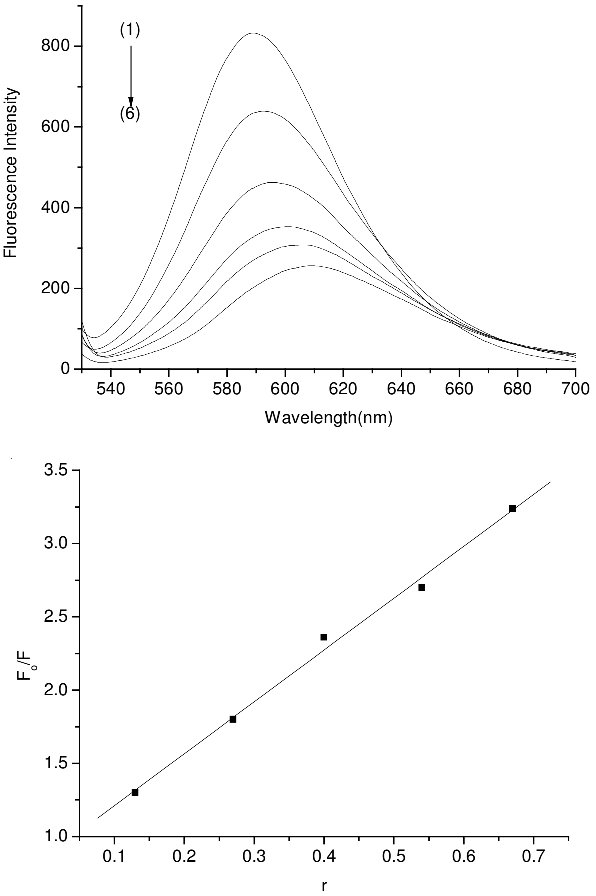


Fig. 2. Suggested structure of the complexes

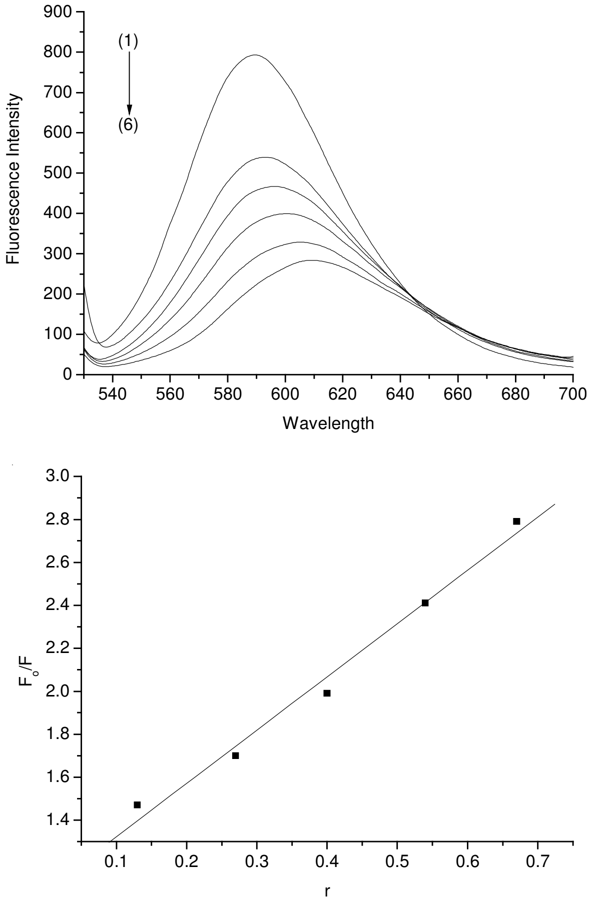
its strong intercalation between the adjacent DNA base pair. The fluorescent light is quenched by the addition of a second molecule[18,19]. The quenching extent of fluorescence of ethidium bromide binding to DNA is used to determine the extent of binding between the second molecule and DNA. The addition of the three complexes to DNA pretreated with ethidium bromide causes appreciable reduction in the emission intensity, indicating the replacement of the ethidium bromide fluorophore by the complexes results in a decrease of the binding constant of the ethidium to the DNA. According to the classical Stern-Volmer equation[19]: $I_0/I = 1 + Kr$, where I_0 and I are the fluorescence intensities in the absence and the presence of complexes, respectively. K is a linear Stern-Volmer quenching constant dependent on the ratio of rbe (the ratio of the bound concentration of ethidium bromide to the concentration DNA). r is the ratio of the total concentration of complexes to that of DNA. The fluorescence quenching curves of ethidium bromide bound to DNA by the three complexes are shown in Fig. 3. The quenching plots illustrate that the quenching of ethidium bromide bound to DNA by all the complexes are in good agreement with the linear Stern-Volmer equation, which also indicates that the three complexes binds to DNA. In the plot of I_0/I *versus* $C_{Complex}/C_{DNA}$, K is given by the ratio of the slope to intercept. The K values for **1-3** are 7.84, 3.33 and 2.52, respectively. The data suggest that the interaction of complex **1** with DNA is strongest, which is consistent with the above absorption spectral results. K values indicate that the interaction of the three complexes with DNA is a intercalative mode.



Complex **1**



Complex **2**



Complex **3**

Fig. 3. Fluorescence spectra of ethidium bromide-DNA system in the absence and presence of increasing amount of $C_{Complex}/C_{DNA}$ ($r_1 = 0$; $r_2 = 0.13$; $r_3 = 0.27$; $r_4 = 0.40$; $r_5 = 0.54$; $r_6 = 0.67$)

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