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UV-Visible spectroscopic and DFT studies of the binding of ciprofloxacin hydrochloride antibiotic drug with metal ions at numerous temperatures

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Abstract−Ciprofloxacin hydrochloride (CPFH) is a very common antibiotic drug for the treatment of different types of bacterial infections. The activity of the drug depends on the complexation of the employed drug with different metals present in the body. In the current investigation, the complexation behavior of CPFH drug with numerous metal ions was explored by means of UV-Visible spectroscopic and density functional theory (DFT) techniques at various temperatures. The binding constants (K_f) of CPFH+metal ions complexes were determined from the Benesi-Hildebrand equation. The K_f values experience an alteration with the nature of metal ions employed and the change of temperature. The binding of CPFH with alkali earth metals decreases with the increase of metal size and increases with the increase of temperature, while the opposite effect of temperature was observed for transition metals. The Gibbs free energy of binding (ΔG^o) for the complexation between CPFH and metal ions was negative in all cases, which reveals that the complexation phenomenon is spontaneous. The values of enthalpy and entropy connote the presence of both hydrophobic and electrostatic interactions. The complexation of CPFH was observed to be endothermic in the case of alkali earth metals while exothermic for transition metals. The intrinsic enthalpy gain ($\Delta H^{o,*}$) values signify the higher stability of metal-drug complexes. The compensation temperature (T_C) values were found to be comparable to the biological systems. DFT studies show the formulation of 1 : 1 complexes with transition metals as well as the square planar geometry of the complexes. HOMO and LUMO analyses reveal that the stability of CPFH-Ni complexes is higher than that of CPFH-Co/CPFH-Zn complexes.

Keywords: Ciprofloxacin Hydrochloride, Metal Ion, Binding Constant, DFT Studies, Complexation

INTRODUCTION

Studies involving the complexation between ligands (including drugs, biomolecules) and metal ions have received much attention due to their significant importance in the fields of medicine, biomedical, technological, and biological processes [1-10]. Since the complexation of drugs with metals may significantly alter the physicochemical properties of drugs, probably, the in vitro stability as well as in vivo distribution, storage, biotransformation, and exclusion of drugs may be influenced in the occurrence of metals. It is reported that complexes of antibiotic drugs and metal ions exhibit a greater therapeutic effect compared to their pure drug [11-14]. Therefore, it appears that a quantitative knowledge of the complexation metal ion with antibiotic drug is of significant value. Knowledge of the formation constant has many applications in various fields of chemistry (analytical chemistry especially in pharmacy). The formation constant is an important physicochemical quantity that determines the biological effects of many drugs, vitamins, and other biomolecules. Metal ions present in the living system interact with the biomolecules and transport them to the physiologically active sites. The determination of formation constants and thermodynamics of complexation of drugs with metal ions has many biochemical interests. The complexes of metals have usages in numerous biological processes such as in the photosynthesis, transportation of O_2 in blood, enzymatic reactions; nevertheless, the extent of metal ions is simply 3% among the entire body composition. Amino acids, peptides, carboxylic acids, etc., are the biomolecules that have the tendency to create metal complexes of dissimilar stabilities having biomedical significance. Certain drugs show therapeutic consequence owing to the formation of complexes with metal ions (such as copper, zinc, iron, magnesium ions) [15]. In addition, the reaction of metal ions in our living systems commences the reduction of toxicity [16]. Therefore, for the active exclusion of poisonous metals from our bodies, it is compulsory for these metal complexes to have high thermodynamic stability. However, elimination of the unsafe metals from a living system involves numerous additional properties which are not entirely implied and measured [17]. To eliminate extra poisonous metals from the human body, the chelation process has been precisely established, though this method is not absolutely threat-free [18]. A thorough under-

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standing of the binding of an antibiotic with metal ions might help in the drug-design study. It is reported that the complexes of NSAIDS drugs with copper (II) ions have improved anti-cancer activity than naked drugs [19]. Heavy metals/minerals are eliminated from the body in the circumstances of autism by the chelation concept using certain chemical materials [20]. The literature study reveals the presence of interaction of various metals with antibiotics [21-24]. There are many coordination complexes of metals such as Pt, Au, Rh, Ru, Co, Li, Bi, Ca, Cu, Zn, that are utilized as medicine [25,26].

Ciprofloxacin hydrochloride (CPFH; Fig. S1 (Supplementary materials)), a synthetic fluorinated antibacterial agent that belongs to the quinolone group, has been reported to exhibit broad-spectrum activity against both gram-positive and gram-negative microorganisms [27,28]. It has been employed for the treatment of diverse bacterial diseases, for example, skin, respiratory/sinus, bone and joint as well as urinary tract infections. Also, it has usage in the cases of gonorrhea and anthrax or plague treatment. Fluoroquinolone drugs possess F atom and piperazine ring at C-6 and C-7, respectively. The improved affinity of this class of drugs for DNA has been described due to their intercalation with the purine/pyrimidine bases of the nucleic acid [28,29]. The enhanced solubility of CPFH in solvents containing metal ions like Fe^{2+}, Fe^{3+}, Ca^{2+}, Al^{3+}, Na^{+}, K^{+}, has been reported by Eboka and Okeri [30]. The improved solubility behavior has also been observed for the metal CPFH complexes by Chohan et al. in H_2O and ethanol solution where the metal ions were Co^{2+}, Cu^{2+}, Ni^{2+} and Zn^{2+} [32]. Panda et al. studied the ternary system of CPFH, metal ion, and glycine mixture and reported a similar activity toward bacteria compared to uncomplexed CPFH. They also observed some advantages of the CPFH, metal ion, and glycine ternary mixture over that of CPFH only [32]. The complexation between CPFH with sodium dodecyl sulfate and sodium deoxycholate has been reported to exhibit enriched payload effectiveness and promising for extended maintenance with enhanced efficacy against microorganisms by disclosing positively charged exterior part, which may be applied as a possible drug delivery tool for contemporary and parenteral uses [33].

Metal ions are necessary to preserve the human body in proper condition since numerous acute living purposes in humans can be governed upon their attendance, and their nonexistence or shortage possibly will be the cause of ailments. Iron is known to bind with the proteins such as hemoglobin and myoglobin and acts as the means of carrying O_2 to the different parts of the body. The lack of Fe and Co causes anemia, that of copper leads to illness of brain and heart [34]. Delay of growth happens due to the deficiency of Zn and the shortage of calcium is accountable for bone deterioration, while the scarcity of Cr lessens glucose acceptance [35-37]. Metal ions have their utmost important usages in drug discovery. Metal ions such as Zn^{2+}, Ca^{2+}, and Mg^{2+} have the ability to stop cytotoxicity [38]. In addition, iron deficiency is most familiar in the cases of cancer patients, and it is connected with difficulties in the surgical procedure.

Keeping all the above-mentioned factors in consideration, in the current study an investigation of the binding of ciprofloxacin antibiotic drug with the numerous divalent metal ions was performed using UV-visible spectroscopic and DFT studies. The binding constants and thermodynamic parameters of the drug-metal complexes were evaluated from the analysis of the experimental data obtained from the UV-visible spectroscopic technique. The bond length, bond angles, bandgap between HOMO and LUMO orbitals; molar absorptivity (ε), and highest wavelength (λ_{max}) of ligand and complexes were estimated from the DFT studies.

EXPERIMENTAL

1. Materials

Analytical grade materials were used throughout the study. Ciprofloxacin hydrochloride (CPFH, 98%) was provided by the ACME Laboratories, BD. Magnesium nitrate, 99% (BDH, England), calcium nitrate, 99% (BDH, England), strontium nitrate, 98% (LOBA, Mumbai, India), barium nitrate >99% (E. MERCK, India), cobalt (II) nitrate, 97% (LOBA, Mumbai, India), Nickel (II) nitrate, 99% (E. MERCK, India), cupric nitrate, >95% (LOBA, Mumbai, India), and zinc nitrate, 99% (E. MERCK, India) were selected and used as metal salts. Distilled deionized water was used in the entire solution preparation.

2. Procedure for the UV-visible Spectroscopic Technique

A computerized UV-visible spectrophotometer (Shimadzu UV-1601PC, Japan) having a thermostatic cell holder was utilized to carry out the investigation. The cell holder was connected to a Shimadzu TCC-240A electrical temperature controller spanning the range of 7-60 °C. The temperature controller had a setting accuracy of ±0.5 °C. The path length of the UV cell was 1 cm. Before each measurement, the baseline of the spectrophotometer was calibrated with the desired solvent (water). Primarily, 4×10^{-5} M ligand (CPFH) and metal solutions having numerous concentrations solution were prepared. Then six clean and dried 10 mL volumetric flasks were taken and filled with 5 mL 4×10^{-5} M CPFH solution. Then 5 mL of 0.004, 0.008, 0.01, 0.012, 0.016, and 0.02 M desired metal solutions (which were also prepared by deionized water) respectively were added to the volumetric flask containing CPFH solution. The selected metals were of alkaline earth metals (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and transition metals (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}). In the mixtures, the resultant concentration of CPFH was 2×10^{-5} M and the concentration of metal was 0.002 M, 0.004 M, 0.005 M, 0.006 M, 0.008 M, and 0.01 M respectively. The mixtures were then kept at constant temperature in a shaking incubator (GFL 3031, USA) for about one hour with constant shaking (80 rpm) to prepare a metal-ligand complex solution. The experiments were carried out at 298.15, 303.15, 308.15, and 313.15 K. The absorbances of the CPFH+metal ion complexes were then measured at the maximum wavelength of absorption (λ_{max}=276.4 nm) for CPFH was obtained as 276.4 nm. The detailed experimental procedure is also available in the literature [39-41].

3. Computational Method

Gaussian 09 program package was utilized to carry out all the calculations [40]. The complexation behavior along with some properties such as structural analysis, HOMO-LUMO energies, chemical hardness, and UV-Vis spectral analysis of the Ciprofloxacin ligand with transition metals such as Co(II), Ni(II), and Zn(II) was investigated by using the DFT method with the B3LYP functional and LANL2DZ basis sets [43].

RESULTS AND DISCUSSION

1. Absorption Spectrum of the Binding of CPFH Drug with Metal Ions

The studied drug, CPFH, exhibits maximum absorption at 275 nm in an aqueous medium [44]. The spectra of pure CPFH and CPFH in the presence of different divalent metal salts are provided in Figs. S2-S3 (Supplementary materials). From the absorption spectra (Fig. S2 and Fig. S3) of CPFH, the red shift with a strong absorption peak around at 278 nm along with a blue shift having a small absorption peak at 328 nm was detected due to the addition of the divalent cations. The possible resonating structures of the CPFH drug are given in Fig. S1 (Supplementary materials) in which it can be seen that quinolone nitrogen, in addition to the carboxylate group, is also involved in conjugation with the keto group. In addition, piperazinyl nitrogen is also in conjugation with the keto group. Therefore, these two nitrogen atoms have a positive resonant effect (+R) and increase the electron density on oxygen atoms. The significance of the resonance structures decreases in the following sequence: R1=R2>R4>R3. During the complexation of divalent cations with carboxylate ion and 4-keto oxygen of quinolones, more effective conjugation is experienced, which consequences the stabilized energy levels for both the ground and excited states. The excited state may experience greater stabilization during complexation, which lowers the energy differences, and thus a significant red shift, as well as a strong absorption band at 278 nm, was observed. The ground state energy level of a chromophore may experience greater stabilization than that of the excited state, due to the addition of divalent cations, because a stable 6-membered ring is formed amongst the keto and the carbonyl oxygen of CPFH [45]. Thus, a small blue shift along with a small absorption peak at 328 nm was observed. So, the quinolone-divalent cation complexes are the result of the effective involvement of both the 4-keto oxygen and the carboxylate ions of quinolones. Since two different chromophores (keto and carboxylate) are involved in complexation, a change in the two absorption bands was observed.

2. Determination of Binding Constant (K_f) of Metal-ligand Complexes

Absorption spectroscopy in the visible and ultraviolet region of the spectrum can be used to investigate electron donor-acceptor or charge transfer complexation [46]. The binding constant of the metal-ligand complex, K_f, was obtained by using a UV-visible spectroscopic tool. The association between the metal and ligand can be represented as

$$M + L \rightleftharpoons ML \tag{1}$$

In which binding constant $K_f = k_1/k_{-1}$ is the equilibrium constant for complexation between metal (M) and ligand (L), while k_1 and k_{-1} are the interaction rate constants for forward and backward reaction, respectively. When two molecules associate according to this scheme and absorbance (A) of the complex is measured at a definite wavelength, K_f is readily obtained from Benesi-Hildebrand equation [40,47,48]:

$$\frac{[D]}{A} = \frac{1}{K_f \in [C]} + \frac{1}{\in} \tag{2}$$

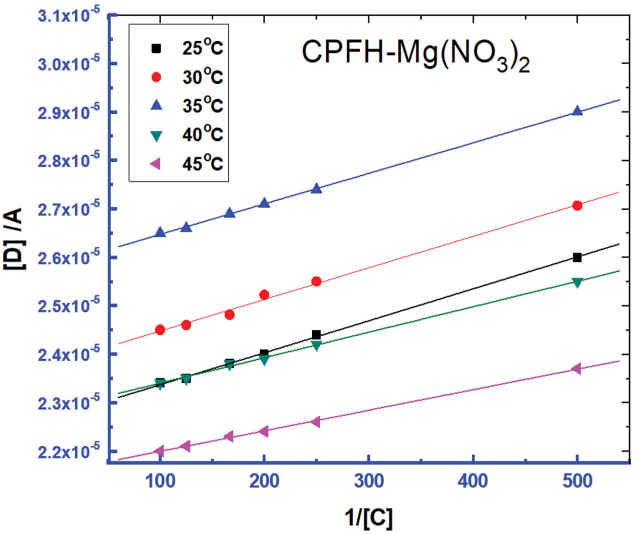


Fig. 1. A plot of (concentration of antibiotic)/absorbance vs. 1/(concentration of metal ion) in water at 25 °C, 30 °C, 35 °C, 40 °C and 45 °C; where λ_{max}=276.4 nm.

In Eq. (2), [D] and [C] are the initial concentration of ligand (antibiotic) and metal, respectively, in mole/liter, ∈ is the molar absorptivity of the metal-ligand complex at its given particular wavelength, and K_f, the binding constant is given in liter/mole. A plot of [D]/A versus 1/[C] results in a straight line with a slope of $1/(K_f\in)$ and an intercept of $1/\in$. The linear Benesi-Hildebrand plots exhibit the formation of 1 : 1 drug-metal ion complexes. Siddiqi et al. [49] also achieved the formation of 1 : 1 complexes between cefpodoxime drug and metal ions (Ca^{2+}, Mg^{2+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}). A representative plot of [D]/A vs 1/[C] for the CPFH-$Mg(NO_3)_2$ system is given in Fig. 1. The values of logK_f were found to be decreased with the increase of the ionic size of alkaline earth metal ions. The charge density of metal cations is decreased with the increase of cationic radii going down a group. On moving downwards, the size of the atoms having similar charges is increased in a group and thus the charge density is decreased [50].

The Mg^{2+} ion is relatively smaller, which enables it to form a stronger bond with ligand [50]. From Mg^{2+} to Ba^{2+} ionic size gets increased, which results in weaker interaction with ligand. Therefore, the ion-ion/ion-dipole interaction between CPFH and metal ions gets effectively reduced with the increase of ionic radius. Again, for certain alkaline earth metal ions, the values of logK_f were found to be increased with the increase of temperature in all cases. The higher values of logK_f for all the alkaline earth metal-ligand (antibiotic) complexes at higher temperatures indicate that stronger complexes are formed at the higher temperature. The increase of experimental temperature may enhance the free energy of metal-drug complexes as compared to the free drug and metal ions and, consequently, the logK_f values experience an enhancement with the escalation of temperature.

3. Thermodynamics of Metal-drug Complexation

To insight into the metal-drug complexation in a precious way, the thermodynamics of metal-drug complexation was analyzed from the K_f values at different temperatures. Different thermody-

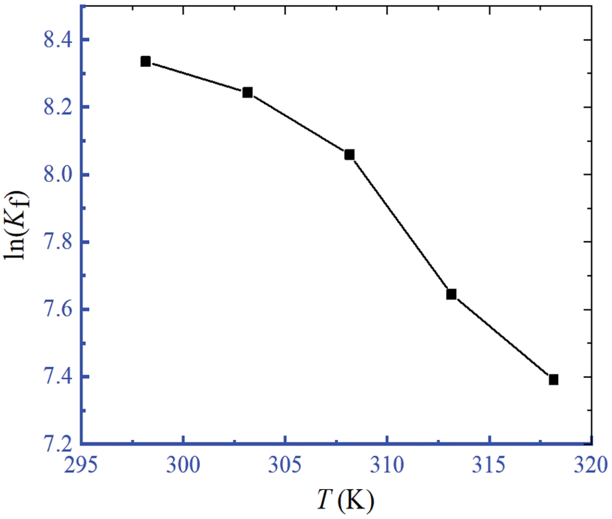


Fig. 2. $\ln K_f$ versus T plot of CPFH-$Co(NO_3)_2$ complex (concentration of CPFH is 4×10^{-5} M).

namic parameters, e.g., Gibbs free energy (ΔG^o), enthalpy change (ΔH^o), and entropy change (ΔS^o) were estimated solving the subsequent equations [48,51]:

$$\Delta G^o = -RT\ln K_f \quad (3)$$

$$\Delta H^o = RT^2\, \partial\ln(K_f)/\partial T \quad (4)$$

$$\Delta S^o = (\Delta H^o - \Delta G^o)/T \quad (5)$$

In the Eq. (3)-(5), R and T are molar gas constant and temperature in Kelvin scale.

The value of $\ln K_f$ varies non-linearly with T (Fig. 2) and can be presented by following relation [52,53]:

$$\ln(K_f) = A + BT + CT^2 \quad (6)$$

Here, A, B, and C are regression analyzed constants which are presented in Table S1 (Supplementary materials). The derivative of Eq. (6) with temperature gives the value of $\partial\ln(K_f)/\partial T$ equal to (B+2CT) and thus Eq. (4) takes a new form given below [52,53]:

$$\Delta H^o = RT^2(B+2CT) \quad (7)$$

The values of ΔG^o for the complexation of CPFH with metal ions were negative at all temperatures for each metal studied, which reveals the spontaneous metal-drug complexation. During the metal-CPFH complexation, a six-membered ring is formed which stabilizes the complex and causes the negative ΔG^o values. The negative ΔG^o values for alkali earth metal-CPFH complexation increase with the increase of temperature (Table 1), which reveals that complexation experiences more spontaneity at a higher temperature. The negative ΔG^o values for transition metal ions-CPFH complexation exhibit the opposite trend of alkali earth metal ions, i.e., decrease with the increase of temperature with few exceptions (Table 2), which reveals that spontaneity of complexation of CPFH with transition metal ions studied herein decreases with the increase of temperature. The negative ΔG^o values imply that the complexation of CPFH with alkali earth metals is slightly more spontaneous than that with transition metals investigated herein. The values of ΔH^o and ΔS^o for complexation of CPFH with alkali earth metals were obtained to be positive for all metals except the values of ΔH^o at

Table 1. Values of the logarithm of binding constant ($\log K_f$), free energy (ΔG^o), enthalpy (ΔH^o), and entropy change (ΔS^o) for CPFH+alkaline earth metal ions complexes at various temperatures in water at wavelength 276.4 nm (concentration of CPFH is 4×10^{-5} M)

System	T (K)	$\log K_f$	ΔG^o kJ mol^{-1}	ΔH^o kJ mol^{-1}	ΔS^o J $mol^{-1}K^{-1}$
CPFH-$Mg(NO_3)_2$	298.15	3.54	−20.21	−5.43	49.55
	303.15	3.56	−20.66	−1.80	62.23
	308.15	3.61	−21.30	2.09	75.90
	313.15	3.64	−21.82	6.24	89.60
	318.15	3.71	−22.60	10.65	104.5
CPFH-$Ca(NO_3)_2$	298.15	3.36	−19.18	47.93	225.1
	303.15	3.43	−19.91	45.73	216.5
	308.15	3.57	−21.06	43.30	208.9
	313.15	3.61	−21.64	40.64	198.9
	318.15	3.69	−22.47	37.74	189.3
CPFH-$Sr(NO_3)_2$	298.15	3.32	−18.95	5.27	81.23
	303.15	3.37	−19.56	6.21	85.01
	308.15	3.43	−20.23	7.21	89.05
	313.15	3.51	−21.04	8.26	93.57
	318.15	3.56	−21.68	9.37	97.59
CPFH-$Ba(NO_3)_2$	298.15	3.16	−18.04	59.89	261.4
	303.15	3.35	−19.44	47.39	220.5
	308.15	3.40	−20.06	33.97	175.3
	313.15	3.48	−20.86	19.59	129.2
	318.15	3.51	−21.38	4.23	80.50

Table 2. Values of the logarithm of binding constant ($\log K_f$), free energy (ΔG^o), enthalpy (ΔH^o), and entropy change (ΔS^o) for CPFH+transition metal ions complexes at various temperatures in water at wavelength 276.4 nm (concentration of CPFH is 4×10^{-5} M)

System	T (K)	$\log K_f$	ΔG^o kJ mol^{-1}	ΔH^o kJ mol^{-1}	ΔS^o J mol^{-1}K^{-1}
CPFH-Co(NO_3)$_2$	298.15	3.62	−20.66	−22.67	−6.750
	303.15	3.58	−20.78	−35.67	−49.12
	308.15	3.50	−20.65	−49.48	−93.58
	313.15	3.32	−19.90	−64.15	−141.3
	318.15	3.21	−19.55	−79.68	−189.0
CPFH-Ni(NO_3)$_2$	298.15	3.71	−21.18	−30.27	−30.51
	303.15	3.64	−21.12	−40.46	−63.80
	308.15	3.51	−20.71	−51.28	−99.23
	313.15	3.40	−20.38	−62.75	−135.3
	318.15	3.23	−19.67	−74.86	−173.5
CPFH-Cu(NO_3)$_2$	298.15	3.83	−21.86	−55.65	−113.3
	303.15	3.64	−21.12	−42.25	−69.69
	308.15	3.53	−20.82	−27.87	−22.86
	313.15	3.42	−20.50	−12.47	25.64
	318.15	3.38	−20.59	3.955	77.14
CPFH-Zn(NO_3)$_2$	298.15	3.59	−20.49	−11.08	31.57
	303.15	3.53	−20.49	−21.39	−2.968
	308.15	3.42	−20.18	−32.36	−39.54
	313.15	3.31	−19.84	−44.02	−77.20
	318.15	3.15	−19.19	−56.37	−116.9

298.15 and 303.15 K for complexation of CPFH with Mg^{2+}, which reveals that the complexation of CPFH with alkali earth metals is mostly endothermic. The $+\Delta H^o$ indicates that complexation phenomenon is accompanied by the absorption of heat, and higher $-\Delta G^o$ values reveal that complexation is more spontaneous at higher temperature and therefore formation constants are higher at a higher temperature for the complexation of alkali earth metal ions with CPFH (Table 1). The $+\Delta H^o$ and $+\Delta S^o$ values reveal that complexation is controlled by entropy as well as the presence of hydrophobic interaction. Again, low $+\Delta H^o$ or $-\Delta H^o$ values along with $+\Delta S^o$ values are reported to be the responsible for electrostatic interaction [54]. Banipal et al. studied the binding of caffeine and theophylline with BSA using the calorimetric technique. They obtained negative enthalpy and positive entropy changes of binding and described the existence of both hydrophobic and electrostatic interaction [55]. Therefore, the complexation of CPFH with alkali earth metals may be accompanied by both hydrophobic and electrostatic interactions. The values of ΔH^o and ΔS^o for complexation of CPFH with transition metals investigated herein were obtained negative for each metal (with a few exceptions), which reveals that complexation of CPFH with transition metals is enthalpy controlled. The $-\Delta H^o$ and $-\Delta S^o$ values connote the existence of dipole-dipole/ion-dipole/electrostatic interaction during complexation between CPFH and transition metals [56,57]. The metal ions interact elec-

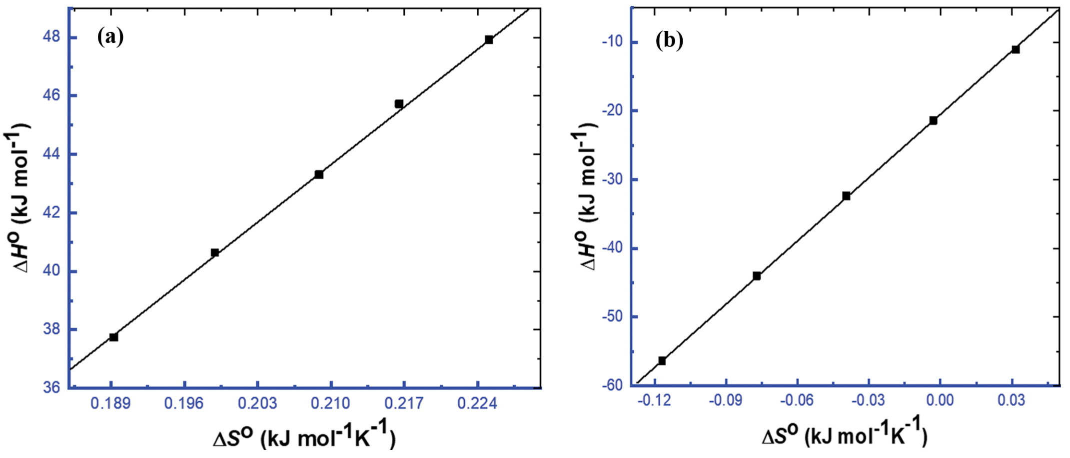


Fig. 3. Plot of enthalpy-entropy compensation for (a) CPFH-Ca(NO_3)$_2$ and (b) CPFH-Zn(NO_3)$_2$ systems in water.

Table 3. Enthalpy-entropy compensation parameters for CPFH+Metal ion complexes having constant CPFH concentration of 4×10^{-5} (M)

System	$\Delta H^{o,*}$ (kJ mol^{-1})	T_c (K)	R^2
CPFH-Mg$(NO_3)_2$	−20.01	292.9	0.9998
CPFH-Ca$(NO_3)_2$	−16.19	285.3	0.9989
CPFH-Sr$(NO_3)_2$	−14.88	248.0	0.9992
CPFH-Ba$(NO_3)_2$	−20.24	307.2	0.9998
CPFH-Co$(NO_3)_2$	−20.39	312.1	0.9998
CPFH-Ni$(NO_3)_2$	−20.59	311.9	0.9999
CPFH-Cu$(NO_3)_2$	−20.40	312.9	0.9999
CPFH-Zn$(NO_3)_2$	−20.53	305.1	0.9999

trostatically with the carboxylate ion and the negative pole of the CO group of CPFH and form a six-membered stable ring.

The estimated values of ΔH^o and ΔS^o exhibit excellent linearity (with correlation coefficient very close to 1) and hence enthalpy-entropy compensation parameters were estimated solving the following equation [58-61]:

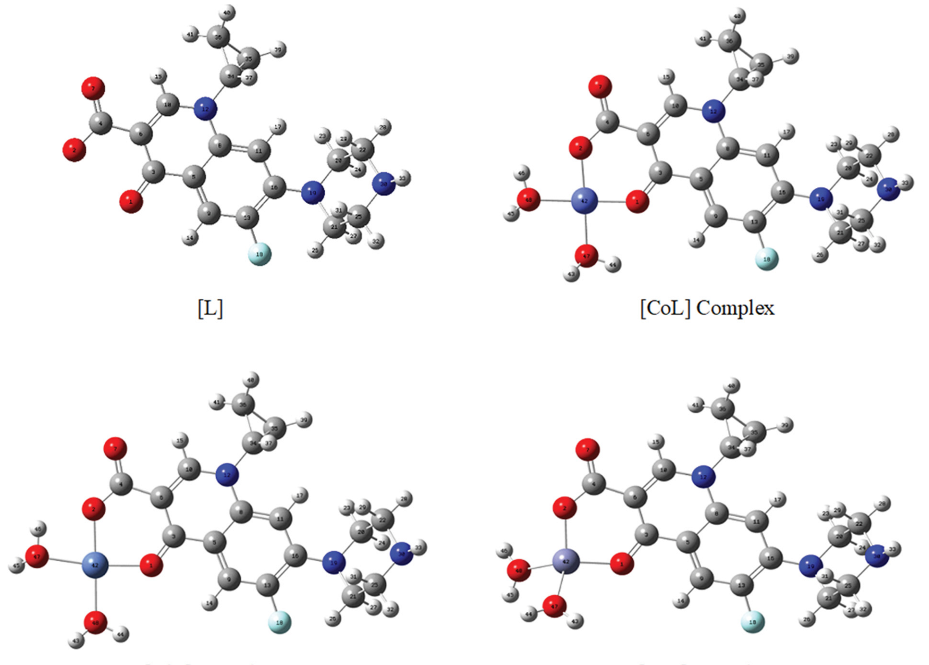
$$\Delta H^o=\Delta H^{o,*}+T_c\Delta S^o \tag{8}$$

A plot of ΔH^o as a function of ΔS^o is depicted in Fig. 3. The terms, $\Delta H^{o,*}$ and T_c in Eq. (8) stand for intrinsic enthalpy and compensation temperature. Again, the values of $\Delta H^{o,*}$ and T_c disclose the interaction of the solute with solute and solvent, respectively. The estimated values of $\Delta H^{o,*}$ and T_c are provided in Table 3. The values of $\Delta H^{o,*}$ were reported to be negative for all systems studied herein, which reveals the higher stability of CPFH-metal complexes. The $-\Delta H^{o,*}$ values are higher for CPFH-transition metal complexation than that of CPFH-alkali earth metal complexation, which implies that CPFH-transition metal complexes are more stable than that of CPFH-alkali earth metal complexes. The $-\Delta H^{o,*}$ values for CPFH-alkali earth metal complexation reduce with the size of alkali earth metal, but the highest value was observed for CPFH-Ba complexation, and this result indicates that stability of CPFH-metal complex is reduced with the increase of metal size. The $-\Delta H^{o,*}$ values reveal that all CPFH-transition metal complexes are almost of equal stability. The estimated values of T_c were in the range of 248.0 to 312.1 K (Table 3). In our earlier study, we observed T_c values of 296.4-301.9 K for the CPFH+surfactants (anionic/nonionic) mixtures in acidic/basic aqueous and alcoholic media [40]. Zheng et al. reported the T_c values of 310.2-312.2 K for a mixture of amphiphilic materials [62]. Jolicoeur and Philip [63] obtained T_c values for their studied systems. They proposed that T_c values can also be used to describe the characteristic property for hydrophobic interactions amid the hydrophobic/inert solutes [63]. The T_c value in the range of 270 to 330 K can be utilized to investigate the effect of water in the protein solution [64], and thus our results are comparable with the biological vicinity.

4. DFT Study for the Complexation between CPFH and Metal Ions

4-1. DFT Optimized Structures

We optimized the metals (M; Co(II), Ni(II), Zn(II)), and ciprofloxacin (L) ligand complexes in 1 : 1 ratio basis. The ML complexes and ciprofloxacin ligand [L] were optimized by DFT/B3LYP level with LANL2DZ basis set. The optimized molecular structures of the metal complexes and ligand [L] along with the number labeling scheme are shown in Fig. 4. The results of the DFT study of 1 : 1 complex (ML) formation are also supported by the experimental results (the linear behavior of the Benesi-Hildebrand plots). Uiva-



[L]

[CoL] Complex

[NiL] Complex

[ZnL] Complex

Fig. 4. Perspective view of [L], [CoL], [NiL], and [ZnL] complexes with atom labeling scheme.

Table 4. The significant bond lengths (Å) of the optimized ligand [L] and metal complexes

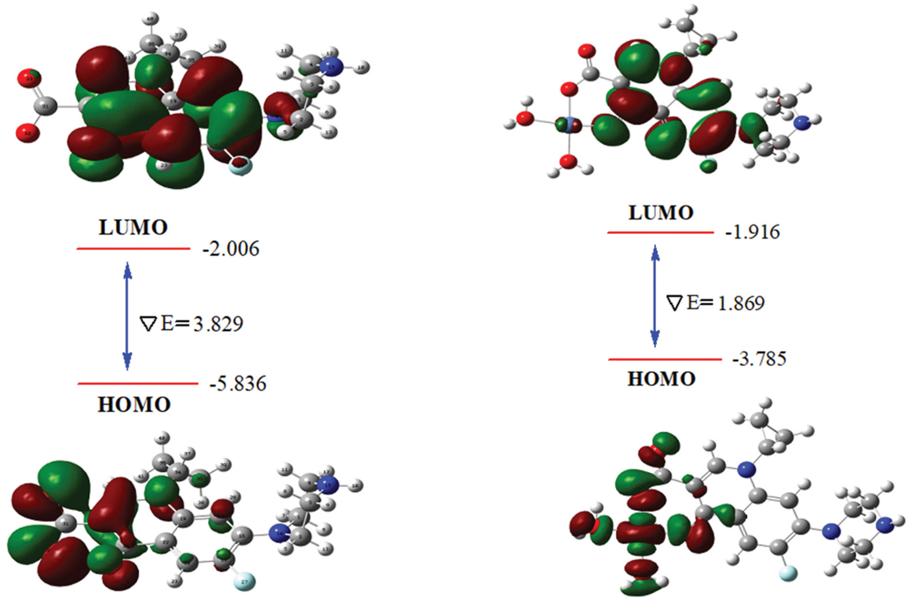
Bond lengths	[L]	[CoL]	[NiL]	[ZnL]
C(3)=O(1)	1.290	1.307	1.300	1.360
C(4)-O(2)	1.278	1.319	1.313	1.329
M-O(1)		1.869	1.989	1.944
M-O(2)		1.892	1.998	1.967

rosi reported that quinolone drugs have a tendency to form complexes with alkaline earth and transition metal (having positive charges of two) with 1 : 1 or 1 : 2 stoichiometry [65]. The molecular structure of [CoL] and [NiL] are planar, whereas [ZnL] complex is found to be non-planar. The selected bond length and bond angles of the complexes are shown in Tables 4 and 5, respectively.

Table 5. The evaluated bond angles (°) of the optimized metal complexes

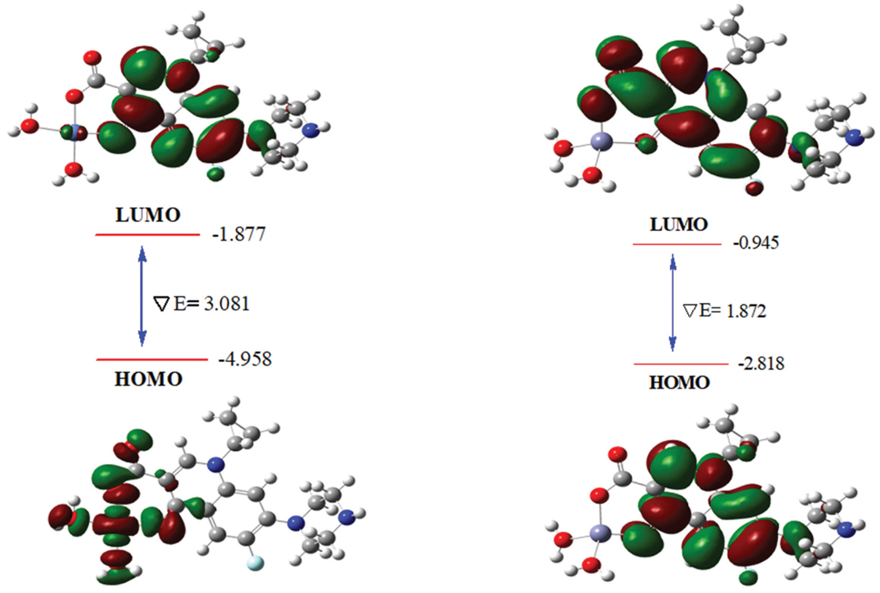
Bond angles	[CoL]	[NiL]	[ZnL]
O(1)-M-O(2)	95.66	92.135	95.376

As seen from the table, the C-O and C=O bonds are increased in all the complexes compared to the free ligands. All the M-O bonds have almost similar values in [ZnL] and [NiL] but slightly decreased in the [CoL]. Similar M-O bond is also found in the Schiff base ligand coordinated Co(II), Ni(II), Zn(II) complexes [66].



[L]

[CoL] Complex



[NiL] Complex

[ZnL] Complex

Fig. 5. HOMO-LUMO orbitals of the [L], [CoL], [NiL], and [ZnL] complexes.

Table 6. HOMO, LUMO energies, band gap, and hardness of the ligand and complexes

Complex	HOMO (ev)	LUMO (ev)	Band gap (ΔE) (ev)	Hardness (η)
Ciprofloxacin (L)	−5.836	−2.006	3.829	1.914
[CoL]	−3.785	−1.916	1.869	0.935
[NiL]	−4.958	−2.242	3.081	1.540
[ZnL]	−2.818	−0.945	1.872	0.9364

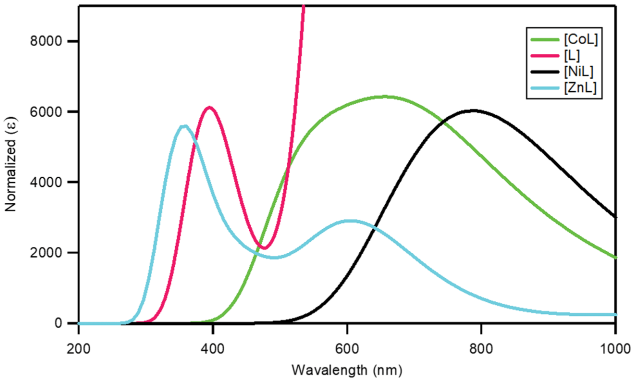


Fig. 6. Normalized UV-Vis spectra of [L] as well as [CoL], [NiL] & [ZnL] complexes.

Table 7. Molar absorptivity (ε) and highest wavelength (λ_{max}) of ligand and complexes

Complex	Highest wavelength (λ_{max}) (nm)	Molar absorptivity (ε) ($dm^3mol^{-1}cm^{-1}$)
[L]	395	765
[CoL]	656	6,430
[NiL]	785	1,005
[ZnL]	360, 608	5,594, 2,914

All the metal complexes have similar O(1)-M-O(2) bond angles. However, the dihedral angles for [CoL] and [NiL] are 178.78 and 175.59, respectively, similar for square planar geometry [67]. However, the dihedral angle for [ZnL] complex is 136.91, which shows the non-planar geometry.

4-2. HOMO and LUMO Analysis

A study of the frontier molecular orbital energies provides useful information of electronic structure and chemical stability. To do so the energy of HOMO and LUMO orbital are calculated by DFT/B3LYP level with LANL2DZ basis set. Schematic representation of frontier molecular orbitals of the metal complexes is shown in Fig. 5. The entire frontier molecular orbital has similar symmetry, which is (a) symmetry point group. The HOMO-LUMO gap, also called band gap (ΔE), represents the stability of the complex. The large band gap indicates more stability and less reactivity of the complexes [68]. The values of energy of HOMO and LUMO orbital and band gap (ΔE) are listed in Table 5. The calculation result shows that the band gap of [NiL] is much higher than [CoL] and [ZnL]. On the other hand, the band gap of [CoL] and [ZnL] is almost the same. Therefore, [NiL] complex is the most stable and less reactive. The stability of complexes follows the sequence as [NiL]>[ZnL]>[CoL]. This stability sequence follows our experimental results.

Another important parameter that can be obtained from the band gap is absolute hardness (η). It also demonstrates the stability of the complex. Absolute hardness is half of the HOMO-LUMO gap. According to the absolute hardness rule, the harder the complex, more stable is the complex [69]. From Table 6, it is found that the hardness value of [NiL] is higher than the other two complexes.

4-3. UV-Vis Spectra Analysis

To investigate the electronic properties of the metal complexes, a quantum chemical calculation has been carried out by the TD-DFT/B3LYP method using the LanL2DZ basis set [70]. The normalized UV-Vis spectra of the ligand [L] and the metal complexes [CoL], [NiL], and [ZnL] are shown in Fig. 6. The value of molar absorptivity (ε) and highest wavelength (λ_{max}) of ligand and complexes are summarized in Table 7. The band gap of the complexes and wavelength are inversely related to each other and it is reflected in our calculation. As the band gap of the [NiL] complex is higher than [CoL] and [ZnL], the value of λ_{max} is lower than the other two complexes. The value of molar absorptivity coefficient (ε) is higher for [CoL] and [ZnL] complexes, but it is much lower for the [NiL] complexes.

CONCLUSION

The complexation behavior of CPFH drug with numerous metal ions has been exposed using UV-Visible spectroscopic and DFT techniques at several temperatures. The binding constant (K_f) of CPFH+metal ion complexes was computed applying the Benesi-Hildebrand equation. The K_f values undergo a variation with the types of metal ions and temperature alteration. The achieved negative free energy (ΔG^o) for the complexation dictates the spontaneous complex formation between CPFH and metal ions. The ΔH^o & ΔS^o values suggest the existence of hydrophobic, electrostatic, and ion-dipole interactions. The complexation of CPFH was observed to be endothermic in the case of alkali earth metals, while the process became exothermic in the case of transition metals. The compensation parameters ($\Delta H^{o,*}$ & T_c) indicate the greater stability of metal-drug complexes and the results exhibit a good similarity with the solutions of protein and small solutes. DFT studies show the formulation of 1 : 1 complexes. Also, the molecular structure of [CoL] and [NiL] complexes are guessed to be planar, whereas [ZnL] complex is obtained to be non-planar. HOMO- LUMO band gap reveals that the stability of Ni complexes is higher than that of Co/Zn complexes with CPFH drug. The knowledge acquired from the current study will be helpful for the drug development, biology, and research-based arena.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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SUPPORTING INFORMATION

Additional information as noted in the text. This information is available via the Internet at http://www.springer.com/chemistry/journal/11814.

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Supporting Information

UV-Visible spectroscopic and DFT studies of the binding of ciprofloxacin hydrochloride antibiotic drug with metal ions at numerous temperatures

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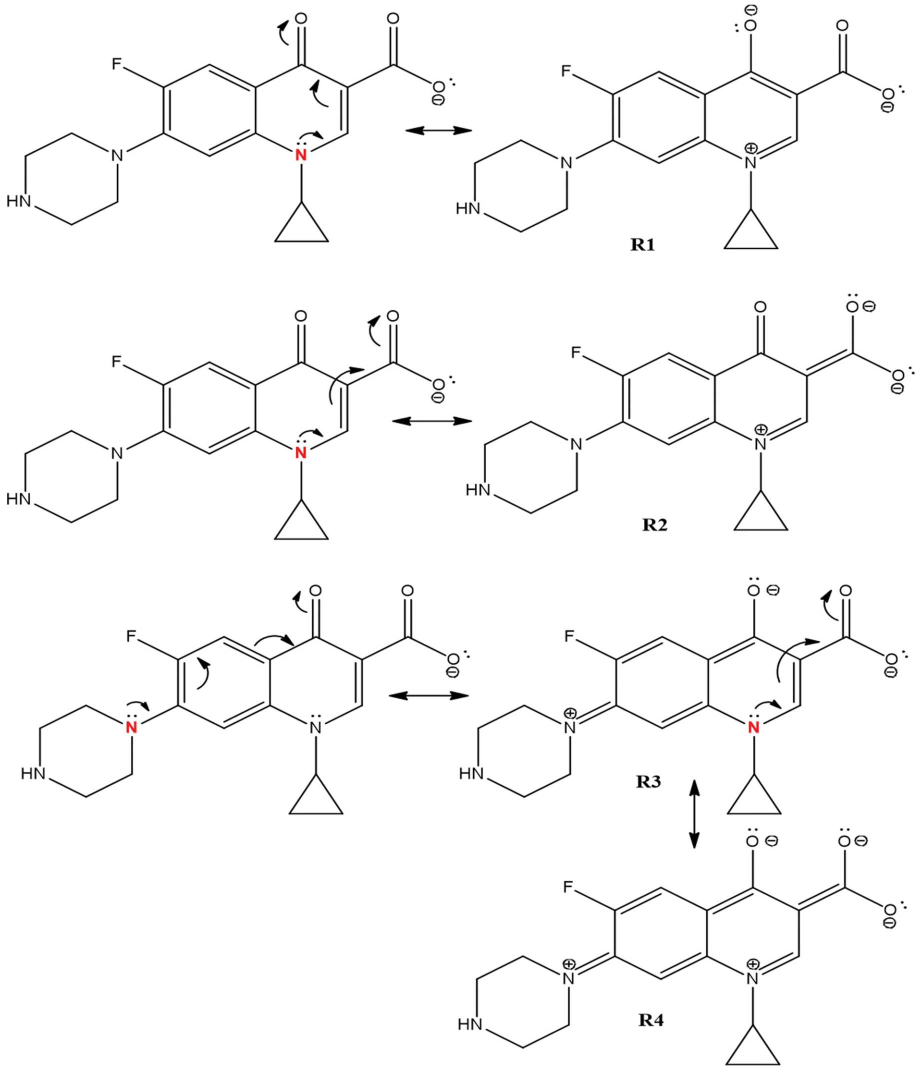

Fig. S1. Possible Resonance structures of CPFH drug.

Table S1. The values of different constants utilized for the calculation of the enthalpy change

System	A	B	C
CPFH-Mg(NO_3)$_2$	52.3800	−0.3055	0.0005
CPFH-Ca(NO_3)$_2$	−53.7370	0.3630	−0.0005
CPFH-Sr(NO_3)$_2$	11.6060	−0.0525	0.0001
CPFH-Ba(NO_3)$_2$	−185.0600	1.2140	−0.0019
CPFH-Co(NO_3)$_2$	−126.0600	0.9234	−0.0016
CPFH-Ni(NO_3)$_2$	−87.3070	0.6746	−0.0012
CPFH-Cu(NO_3)$_2$	211.4000	−1.2679	0.0020
CPFH-Zn(NO_3)$_2$	−101.4300	0.7602	−0.0013

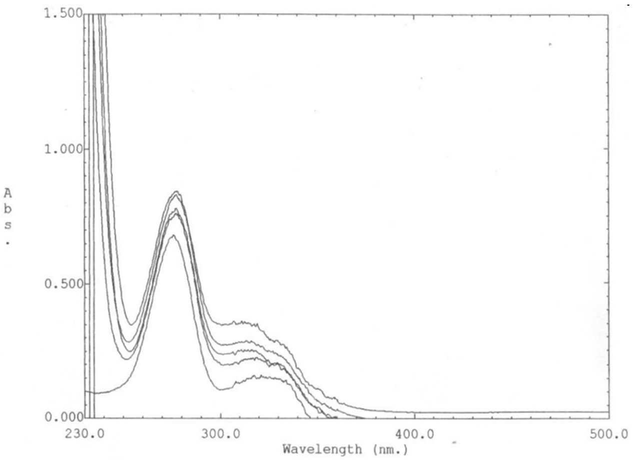

Fig. S2. **The absorption spectra of ciprofloxacin-alkaline earth metal complexes (from bottom to top- CPFH, CPFH -Ba^{2+}, CPFH -Ca^{2+}, CPFH -Sr^{2+}, CPFH -Mg^{2+}).**

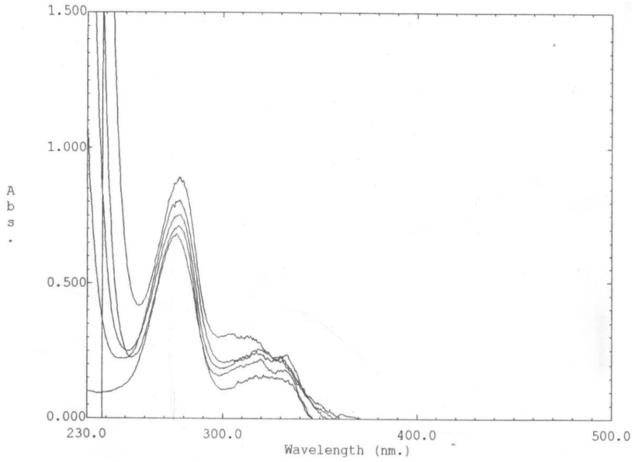

Fig. S3. **The absorption spectra of ciprofloxacin-transition metal complexes (from bottom to top- CPFH, CPFH -Zn^{2+}, CPFH -Co^{2+}, CPFH -Ni^{2+}, CPFH -Cu^{2+}).**