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PREDICTION OF STABILITY CONSTANTS FOR Cu^{2+} COMPLEXES WITH ORGANIC FLUORESCENT LIGANDS USING THERMODYNAMIC CYCLE IN COMBINATION WITH DFT THEORY AND SMD SOLVENT MODEL

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Abstract. Accurately predicting the stability constant (β) of the Cu^{2+} complex with organic fluorescent ligands provides an important basis to design molecular fluorescent sensors for selective detection of Cu^{2+}. With appropriate reference complexes, the calculated stability constants are in good agreement with experimental values. The logβ values of the predicted stability constants of Cu^{2+} complexes with Calcein blue (H_3Cb) and FluoZin-1 (H_2Fz) are 13.33 (exp. 14.27) and 6.59 (exp. 6.01), respectively. More importantly, the results could be applied to the investigation of complexes.

Keywords: fluorescent, stability constant, complex, thermodynamic cycle, DFT

1 Introduction

The complex interaction between metal ions and organic fluorescent ligands is one of the important approaches to design fluorescent sensors for the detection of metal ions as well as other analytical species, such as anions and biothiols through complex exchange reactions [1]. Besides a requirement of optical properties, a fluorescent sensor for detection of metal ions needs sufficiently strong interaction with the target metal ion, usually through complexation reactions [2]. Predicting this complex formation is very necessary for designing sensors [3].

Understanding the complexation characteristics of metal ions in aqueous solutions is the basis for predicting and controlling the behavior of metal ions in the environment, biological systems, and other industrial applications [4]. The key point of this problem is to estimate the affinity of metal ions with the ligands through the stability constant of complexes [5, 6]. By definition, the stability constant of complexes between metal ion M and ligand L (β_{ML_n}) in the solution is determined according to Eq. (1).

$$M_{(aq)} + nL_{(aq)} = ML_{n(aq)} \quad \beta_{ML_n} = \frac{a_{ML_n}}{a_M a_L^n} \qquad (1)$$

where "a" is the activity at equilibrium, and "aq" indicates the state in the aqueous solution. The stability constant can be approximately evaluated through concentration instead of activity; therefore, the stability constant can be expressed as in Eq. (2).

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$$\beta_{ML_n} \approx \frac{[ML_n]}{[M][L]^n} \tag{2}$$

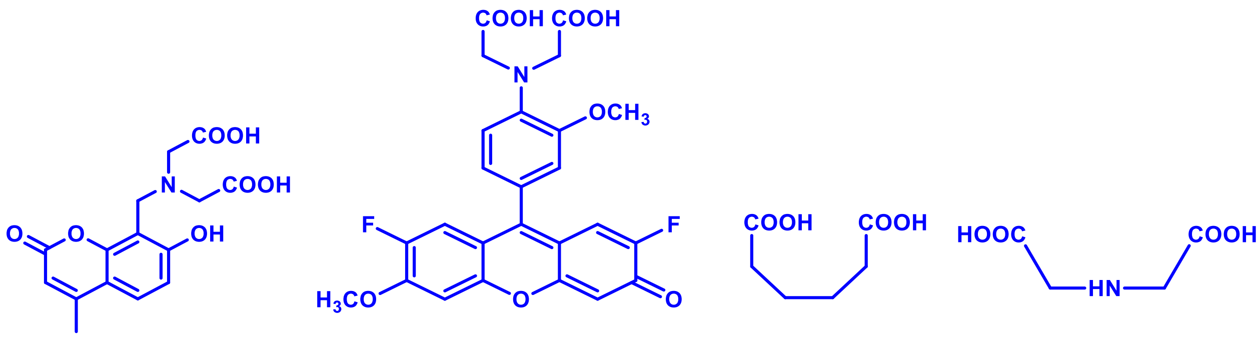
and the relationship between β_{ML_n} and Gibbs free energy of complex formation reaction (ΔG^0_{aq}) is expressed in Eq. (3).

$$\Delta G^0_{aq} = -RT \ln \beta_{ML_n} \tag{3}$$

In principle, it is possible to determine the stability constant of a complex by calculating the theoretical Gibbs energy of the reaction in solutions [6]. However, there are still various major obstacles in accurately assessing the Gibbs free energy value of reaction solutions [7]. This may be related to determining the true form of metal ions in aqueous solutions. For example, Cu^{2+} ions can exist in solution in possible stable forms such as $[Cu(H_2O)_4]^{2+}$, or $[Cu(H_2O)_5]^{2+}$, or $[Cu(H_2O)_6]^{2+}$ [8]. In addition, another difficulty is to assess the solvation energy of the substance in water. Especially for ions, when using common solvent models such as PCM (Polarizable Continuum Model) and COSMO (Conductor-like Screening Model), the calculated results are quite different from the experimental value [9].

A large number of stability constants for metal complexes have been experimentally determined, forming a database to serve relevant applications [10]. However, such data are not sufficient because numerous complexes exist between metal ions and ligands. There have been various attempts to theoretically predict the stability constants of metal complexes [6]. On the basis of the correlation between the stability constant and the properties of metal ions (i.e., ion radius, charge, electronegativity, and ionization potential), the equations for determining the stability constant from the empirical database are formulated [11, 12]. This approach is useful but requires a large amount of suitable empirical data that are suitable for the structure of the studied complex. So far, numerous research groups have made significant efforts in finding quantum computational methods to accurately predict the stability constants of metal complexes [13]. These studies show that a good control of the calculation models may lead to the results that are close to experimental values [14, 15].

In this study, we report an approach of using a thermodynamic cycle in a combination with the DFT theory and SMD solvent model to predict the stability constants of Cu^{2+} complexes with two organic fluorescent ligands, namely, Calcein blue (H_3Cb) and FluoZin-1 (H_2Fz) solutions. Two reference ligands, adipic acid (H_2A) and iminodiacetic acid (H_2Ia, are used. The chemical structure of the ligands is shown in Fig. 1.



(H_3Cb)
Calcein blue

H_2Fz
Fluozin-1

H_2Ad
Adipic acid

H_2Ia
Iminodiacetic acid

Fig. 1. Structural formula of fluorescent ligands and reference ligands

2 Methods

2.1 Thermodynamic methods

Because Cu^{2+} forms 1:1 stoichiometry complexes with the four selected ligands [16-19], the metal complexes with ligands in a 1:1 molar ratio with the presence of water molecules are considered in this study. Therefore, the complexation is modeled in solution according to Eq. (4).

$$[\mathrm{M(H_2O)_m}]^{x}_{(aq)} + \mathrm{L}^{y}_{(aq)} \xrightarrow{\Delta G^0_{\mathrm{aq,ML}}} [\mathrm{ML(H_2O)_n}]^{x+y}_{(aq)} + (m-n)\mathrm{H_2O}_{(aq)} \quad (4)$$

Similar complexation of reference ligands (L_{ref}) follows Eq. (5).

$$[\mathrm{M(H_2O)_m}]^{x}_{(aq)} + \mathrm{L}^{z}_{\mathrm{ref(aq)}} \xrightarrow{\Delta G^0_{\mathrm{aq,ML_{ref}}}} [\mathrm{ML_{ref}(H_2O)_k}]^{x+z}_{(aq)} + (m-k)\mathrm{H_2O}_{(aq)} \quad (5)$$

Eq. (4) and (5) are combined to give Eq. (6).

$$[\mathrm{ML_{ref}(H_2O)_k}]^{x+z}_{(aq)} + \mathrm{L}^{y}_{(aq)} \xrightarrow{\Delta G^0_{\mathrm{aq}}} [\mathrm{ML(H_2O)_n}]^{x+y}_{(aq)} + \mathrm{L}^{z}_{\mathrm{ref(aq)}} + (k-n)\mathrm{H_2O}_{(aq)} \quad (6)$$

Three Eqs. (4), (5), and (6) can be combined to obtain Eq. (7).

$$\Delta G^0_{\mathrm{aq}} = \Delta G^0_{\mathrm{aq,ML}} - \Delta G^0_{\mathrm{aq,ML_{ref}}} \quad (7)$$

According to thermodynamics, $\Delta G^0_{\mathrm{aq,ML}}$ is related to the equilibrium concentration of substances according to Eq. (8).

$$\Delta G^0_{\mathrm{aq,ML}} = -RT\ln\frac{[[\mathrm{ML(H_2O)_n}]][\mathrm{H_2O}]^{m-n}}{[\mathrm{M(H_2O)_m}][\mathrm{L}]} \quad (8)$$

Compared with the definition of stability constant, Eq. (9) is obtained.

$$\Delta G^0_{\mathrm{aq,ML}} = -RT\ln(\beta_{\mathrm{CuL}}\,[\mathrm{H_2O}]^{m-n}) \quad (9)$$

Similarly, for the reference complex, Eq. (10) is derived.

$$\Delta G^0_{\mathrm{aq,ML_{ref}}} = -RT\ln(\beta_{\mathrm{CuL_{ref}}}\,[\mathrm{H_2O}]^{m-k}) \quad (10)$$

Eqs. (7), (9), and (10) are combined to obtain Eq. (11).

$$\Delta G^0_{\mathrm{aq}} = -RT\ln\left(\frac{\beta_{\mathrm{CuL}}}{\beta_{\mathrm{CuL_{ref}}}}[\mathrm{H_2O}]^{k-n}\right) \quad (11)$$

Eq. (11) can be rewritten in the form of Eq. (12).

$$\log\beta_{\mathrm{CuL}} = -\frac{\Delta G^0_{aq}}{RT\ln(10)} + \log\beta_{\mathrm{CuL_{ref}}} - (k-n)\log[\mathrm{H_2O}] \quad (12)$$

The concentration of water under the standard state is 55.56 M [20, 21]. From Eq. (12), it can be seen that using a reference complex with known empirical stability constant value ($\beta_{\mathrm{CuL_{ref}}}$) can avoid estimating the existing form of metal ions in the water environment ($[\mathrm{M(H_2O)_m}]^{n+}$). Moreover, the choice of a complex reference structure that is more similar to the studied complex can partially eliminate the systematic error due to the calculation method [22]. β_{CuL} can be determined from Eq. (12) by using the Gibbs energy of reaction in Eq. (6), which can be found from the thermodynamic cycle in Fig. 2.

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$$\begin{tikzcd}
{[\mathrm{CuL_{ref}(H_2O)_k}]^{x+z}_{(g)}} \arrow[d, "\Delta G^0_{solv} + \Delta G^0_{g\to aq}"] & + & \mathrm{L}^{y}_{(g)} \arrow[r, "\Delta G^0_{g}"] \arrow[d] & {[\mathrm{CuL(H_2O)_n}]^{x+y}_{(g)}} \arrow[d] & + & \mathrm{L}^{z}_{\mathrm{ref}(g)} \arrow[d] & + & \mathrm{(k-n)H_2O_{(g)}} \arrow[d] \\
{[\mathrm{CuL_{ref}(H_2O)_k}]^{x+z}_{(aq)}} & + & \mathrm{L}^{y}_{(aq)} \arrow[r, "\Delta G^0_{aq}"] & {[\mathrm{CuL(H_2O)_n}]^{x+y}_{(aq)}} & + & \mathrm{L}^{z}_{\mathrm{ref}(aq)} & + & \mathrm{(k-n)H_2O_{(aq)}}
\end{tikzcd}$$

Fig. 2. The relationship between ΔG^0_{aq}, ΔG^0_{g}, $\Delta G^0_{\mathrm{solv}}$, and $\Delta G^0_{\mathrm{g\to aq}}$

where "g" indicates the gas phase; $\Delta G^0_{\mathrm{g\to aq}}$ is the Gibbs free energy change when transferring a mole of a substance from the standard condition in the gas phase (1 atm or $24.46\ \mathrm{L.mol^{-1}}$) into solution (1 L.mol^{-1}). This change is equivalent to the process of compressing one mole of an ideal gas with a volume of 24.46 L to 1 L at 298.15 K, and the change of Gibbs free energy is calculated according to Eq. (13).

$$\Delta G^0_{\mathrm{g\to aq}} = \int_{24.46}^{1} V\mathrm{d}p = -RT\int_{24.46}^{1}\frac{\mathrm{d}V}{V} = -RT\ln\frac{1}{24.46} = RT\ln 24.46 \quad (13)$$

Thus, for a substance transferred from the gas phase to the solution, the Gibbs free energy is calculated following Eq. (14).

$$G^0_{\mathrm{aq}} = G^0_{\mathrm{g}} + \Delta G^0_{\mathrm{solv}} + RT\ln 24.46 \quad (14)$$

And ΔG^0_{aq} of a complex exchange reaction is determined from the thermodynamic cycle according to Eqs. (15) and (16).

$$\Delta G^0_{\mathrm{aq}} = (k-n)G^0_{\mathrm{aq,H_2O}} + G^0_{\mathrm{aq,[CuL(H_2O)_n]}} + G^0_{\mathrm{aq,L_{ref}}} - G^0_{\mathrm{aq,[CuL_{ref}(H_2O)_k]}} - G^0_{\mathrm{aq,L}} \quad (15)$$

$$\Delta G^0_{\mathrm{aq}} = \Delta G^0_{\mathrm{g}} + \Delta\Delta G^0_{\mathrm{solv}} + \Delta\Delta G^0_{\mathrm{g\to aq}} \quad (16)$$

where ΔG^0_g is the Gibb free energy of reaction in the gas phase; $\Delta\Delta G^0_{\mathrm{solv}}$ is the solvation free energy of reaction, and $\Delta\Delta G^0_{\mathrm{g\to aq}}$ is the Gibbs free energy for standard state change of reaction.

2.2 Computational methods

All calculations were performed by using Gaussian16 software [23]. The optimized geometry of each substance is calculated at the theory level of PBE0/6-31+G(d) in the gas phase. Gibbs free energy in the solution of substances was calculated according to Eq. (17).

where ε_0 is the electronic structure energy obtained from the single-point energy calculation at PBE0/6311++G(d, p) from the corresponding optimized geometry at PBE0/6-31+G(d,p) in the gas phase. G_{corr} is the thermal correction to free energy, which includes zero-point energy correction, and is determined at the same level as the geometry at PBE0/6-31+G(d). ΔG_{solv} is the change of solvation free energy calculated according to the experimentally parameterized model by Truhlar at M052X/631G(d)/SMD [24].

$$G_{\mathrm{s}} = G_{\mathrm{g}} + \Delta G_{\mathrm{solv}} + RT\ln 24.46 = \varepsilon_0 + G_{\mathrm{corr}} + \Delta G_{solv} + RT\ln 24.46 \quad (17)$$

3 Results and discussion

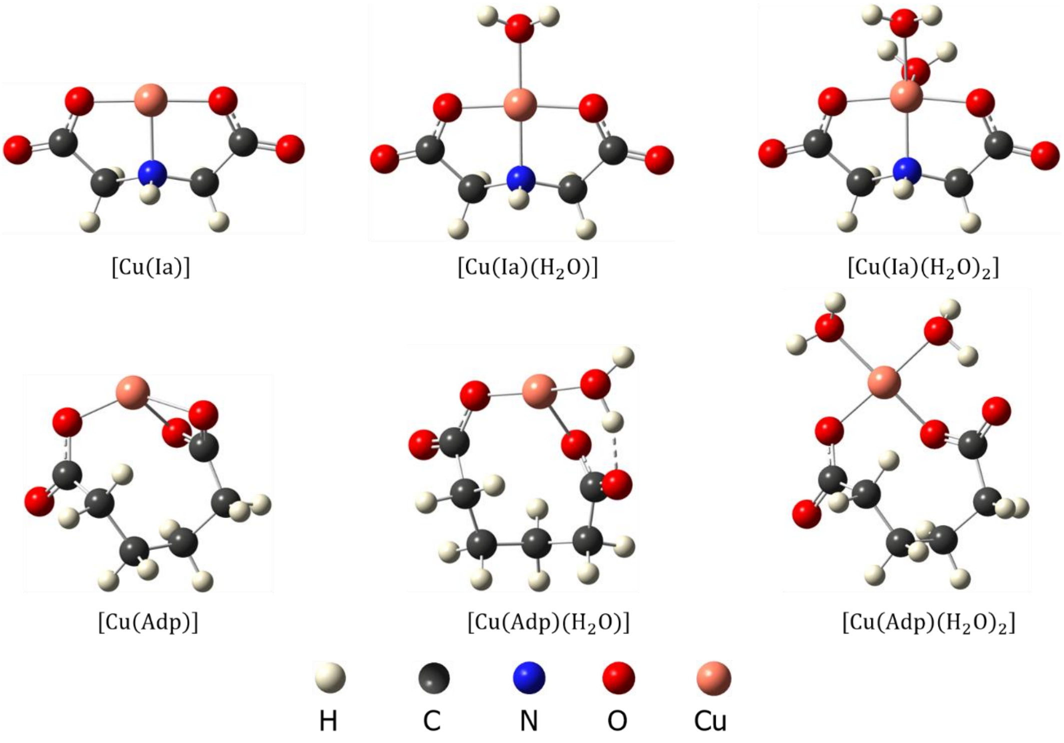
3.1 Determination of stable geometry for reference complexes

The value of logβ of the two reference complexes [Cu(Ia)] and [Cu(Adp)] is 10.54 and 3.35, respectively [16-18]. The geometric structure of these reference complexes is needed for the calculation models. It is possible to predict their stable geometric structures according to Gibbs free energy change of the conversion between the existing forms of complexes according to Eq. (18).

$$[CuL_{ref}]^{x+z}_{aq} + xH_2O_{aq} \xrightarrow{\Delta G^0_{aq}} [CuL_{ref}(H_2O)_x]^{x+z}_{aq} \quad (18)$$

The more thermodynamically favorable the conversion reaction, the more stable $[CuL_{ref}(H_2O)_x]$ complex (the more negative value of ΔG^0_{aq}). Possible stable geometries of the reference complexes are shown in Fig. 3.

The calculated results of Gibbs free energy change for the conversion reactions of different complexes (Table 1) show that [Cu(Ia)] and [Cu(Adp)(H2O)] are the most stable forms of the two reference complexes. Therefore, these two complexes are used in subsequent calculations.


$[Cu(Ia)]$ $[Cu(Ia)(H_2O)]$ $[Cu(Ia)(H_2O)_2]$

$[Cu(Adp)]$ $[Cu(Adp)(H_2O)]$ $[Cu(Adp)(H_2O)_2]$

Fig. 3. Stable geometry of the reference complexes

Table 1. Gibbs free energy change for the conversion reaction of the reference complex forms

Reaction	$\mathbf{\Delta G^0_{aq}}$ **(kcal. mol^{-1})**
$\mathbf{[Cu(Ia)]_{aq} + H_2O_{aq} \rightarrow [Cu(Ia)(H_2O)]_{aq}}$	1.35
$\mathbf{[Cu(Ia)]_{aq} + 2\ H_2O_{aq} \rightarrow [Cu(Ia)(H_2O)_2]_{aq}}$	8.58
$\mathbf{[Cu(Adp)]_{aq} + H_2O_{aq} \rightarrow [Cu(Adp)(H_2O)]_{aq}}$	–11.07
$\mathbf{[Cu(Adp)]_{aq} + 2\ H_2O_{aq} \rightarrow [Cu(Adp)(H_2O)_2]_{aq}}$	–6.22

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3.1 Determination of stability constant of Cu^{2+} complex with HCb^{2-} and Fz^{2-}

The complex forms that were chosen for the investigation include [Cu(HCb)], [Cu(HCb)(H_2O)], [Cu(HCb)(H_2O)$_2$], [Cu(Fz)], [Cu(Fz)(H_2O)], and Cu(Fz)(H_2O)$_2$]. The stable geometries of ligands and complexes are shown in Fig. 4 and 5.

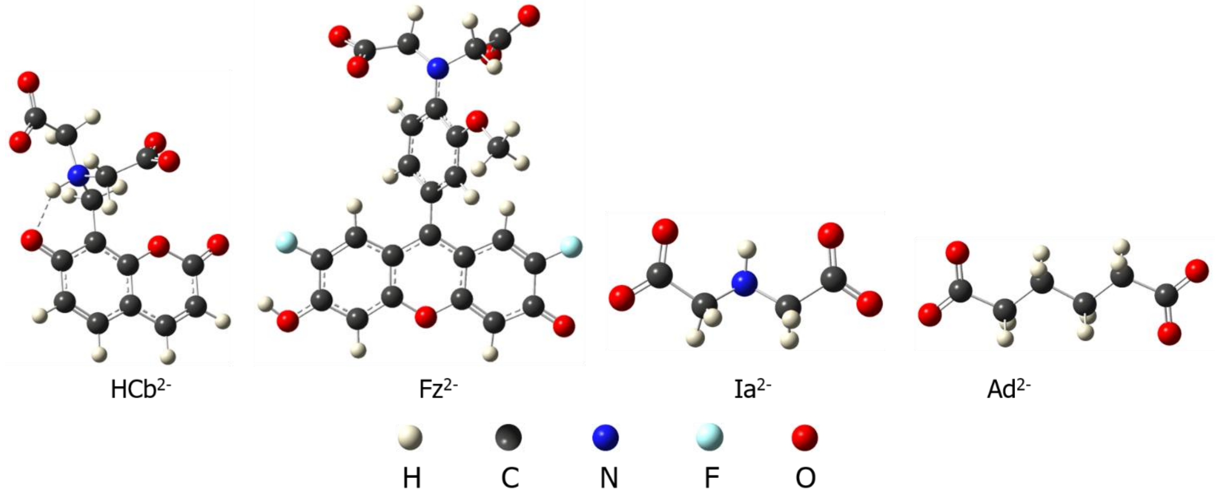
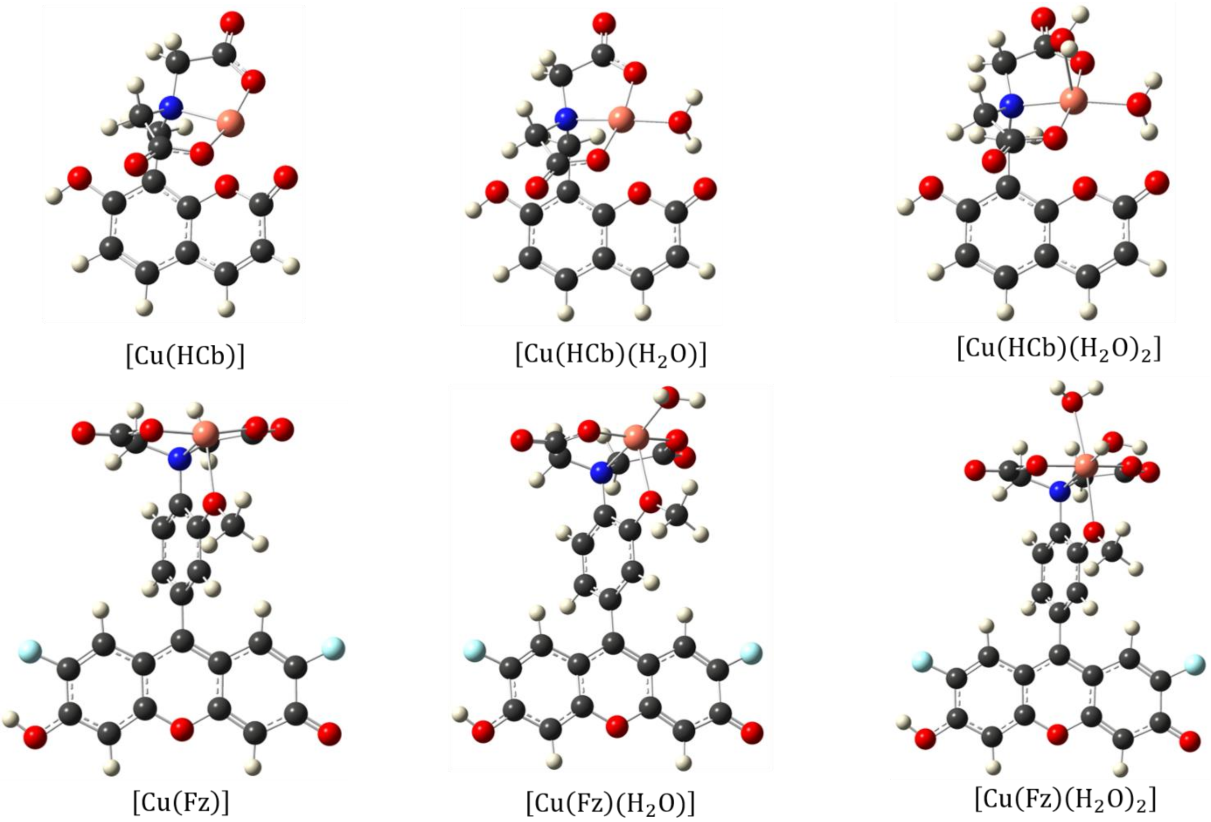

HCb^{2-} Fz^{2-} Ia^{2-} Ad^{2-}

Fig. 4. Stable geometries of fluorescent ligands and reference ligands


[Cu(HCb)] [Cu(HCb)(H_2O)] [Cu(HCb)(H_2O)$_2$]

[Cu(Fz)] [Cu(Fz)(H_2O)] [Cu(Fz)(H_2O)$_2$]

Fig. 5. Stable geometries of complex forms between Cu^{2+} and HCb^{2-} or Fz^{2-}

The calculated results in Table 2 indicate that the stability constants of Cu^{2+} complexes with HCb^{2-} and Fz^{2-} when using the reference complexes [Cu(Ia)] and [Cu(Adp)(H_2O)] decrease in the following order [Cu(HCb)(H_2O)] > [Cu(HCb)(H_2O)$_2$] > [Cu(HCb)] and [Cu(Fz)(H_2O)] > [Cu(Fz)] > [Cu(Fz)(H_2O)$_2$]. Therefore, the most stable complexes between Cu^{2+} and HCb^{2-} or Fz^{2-} are [Cu(HCb)(H_2O)] and [Cu(Fz)(H_2O)]. The calculated stability constants of these two complexes are then compared with the experimental values.

For the [Cu(HCb)(H_2O)] complex, the empirical $\log \beta_{\mathrm{exp}}$ is 14.27 [19] and the calculated $\log \beta_{\mathrm{calc}}$ when using the reference complexes [Cu(Ia)]) and [Cu(Adp)(H_2O)] are 13.33 and 11.39, respectively. The results show that when using the reference complex [Cu(Ia)], the predicted stability constant of the Cu^{2+} complex with HCb^{2-} is closer to the experimental value. This might be due to the similar structure of the chelating center [25]. Both ligands have a chelating center with three atoms containing nonbonding pairs of electrons on the two oxygen atoms in the two carboxyl groups (COO) and the nitrogen atom. For Adp^{2-} reference ligands, the similarity between the two chelating centers is lower due to the absence of nitrogen atom in Adp^{2-}. Hence, the calculated constant is less consistent with its experimental value.

For the [Cu(Fz)(H_2O)] complex, the empirical $\log \beta_{\mathrm{exp}}$ is 6.01 [19], and the calculated values of $\log \beta_{\mathrm{calc}}$ when using the reference complexes [Cu(Ia)]) and [Cu(Adp)(H_2O)] are 4.25 and 6.59, respectively. As a result, Adp^{2-} is a better reference ligand than Ia^{2-} for calculating the stability constant of the Cu^{2+} complex with Fz^{2-}. There is a similarity in the chelating center between the Adp^{2-} and Fz^{2-} ligands. The geometric structures of the complexes in Figures 3 and 5 show that the chelating center Adp^{2-} has three oxygen atoms containing nonbonding pairs of electrons in two carboxyl groups. Fz^{2-} also has three oxygen atoms containing nonbonding pairs of electrons in two carboxyl and methoxy groups (OCH_3), and a nonbonding pair of electrons in the nitrogen atom. However, unlike the nitrogen atom in Ia^{2-}, the nitrogen atom in Fz^{2-} is conjugated with the aromatic ring, reducing the density of the electron pair in nitrogen; therefore, it may reduce the ability to form a coordination bond between the nitrogen atom and Cu^{2+}.

Table 2. ΔG^0_{aq} (kcal.mol^{-1}) and predicted $\log \beta$ of different complex forms

Reference complex	**[Cu(Ia)]**			**[Cu(Adp)(H_2O)]**		
	ΔG^0_{aq}	$\log \beta_{\mathrm{ref}}$	$\log \beta_{\mathrm{calc}}$	ΔG^0_{aq}	$\log \beta_{\mathrm{ref}}$	$\log \beta_{\mathrm{calc}}$
[Cu(Cb)]	5.17	10.54	6.75	–4.31	3.35	4.77
[Cu(Cb)(H_2O)]	–1.43	10.54	13.33	–11.70	3.35	11.93
[Cu(Cb)(H_2O)$_2$]	6.37	10.54	9.35	–3.91	3.35	7.96
[Cu(Fz)]	10.07	10.54	3.17	–5.42	3.35	5.59
[Cu(Fz)(H_2O)]	10.95	10.54	4.25	–4.42	3.35	6.59
[Cu(Fz)(H_2O)$_2$]	20.47	10.54	–0.99	5.09	3.35	1.36

4 Conclusions

In this study, we propose an approach that uses a thermodynamic cycle in combination with the density functional function theory and the SMD solvent model to predict the stability constant of Cu^{2+} complexes with organic fluorescent ligands. The calculated results show that there is a good agreement between the theoretical stability constant and the experimental value. The predicted stability constants ($\log\beta$) of the Cu^{2+} complex with Calcein blue and FluoZin-1 are 13.33 (exp. 14.27) and 6.59 (exp. 6.01), respectively. The results also indicate that the selection of reference ligands is a very important task to calculate the stability constants of the target ligands. The more similar the reference and chelating center of a ligand are, the more accurate it is to predict the stability constant of complexes. The method for predicting stability constant presented in this work could be applied to many other complexes.

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