Polish J. Chem., **75**, 623–632 (2001)

Metal Complexes of C-Functionalized Macrocyclic Dioxotetraamines Bearing 8-Hydroxyquinoline: Stability in Aqueous Solutions

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(Received September 14th, 2000; revised manuscript December 11th, 2000)

Two novel 8-hydroxyquinoline connected dioxotetraamines have been designed and synthesized, and have been characterized by elemental analysis, IR, mass spectra and ^{1}H NMR. The two ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ have two chelating groups. Each can react with a transition metal ion forming complexes. Potentiometric titrations have been performed in 0.1 mol/L $NaNO_3$ at 25°C giving the 1:1 stability constants. Coupled with UV spectroscopy the affinity of 8-hydroxyquinoline and dioxotetraamines to transition metal ions were compared and the possible structure of the metal complex species in solution was discussed. The results show that as to Mn^{2+}, Zn^{2+} and Co^{2+}, 8-hydroxyquinoline is a stronger chelating reagent than dioxo[13] or [14]tetraamine macrocycles and at 1:1 molar ratio (M:L), the former binds in 100% to the metal ions, while the dioxotetraamines can be only partially or not coordinated.

Key words: dioxotetraamine, 8-hydroxyquinoline, metal ions, stability constants

Much attention has been focused on polyamine macrocyclic molecules during the past few decades [1]. As unique chelators for some transition metal ions, dioxotetramines have been discussed extensively [1a]. In recent years, new methods on the synthesis of dioxopolyamines have been reported [2]. However, the pendant-arm groups introduced into the parent macrocycles have only one or no donor atom, their role in such coordination compounds can only be axial or steric effect to the central metal ion. Moreover, the pendants to the macrocyclic molecules are mostly the N-functionalized due to the easier reaction with pendant group by the strong nucleophilic properties of the amine group. While for the C-functionalized macrocycles, there are fewer reports [3], let alone the pendant arm which containing chelating group. 8-Hydroxyquinoline is known to be a good chelating reagent and its derivatives have been studied actively [4], and we first introduced 8-hydroxyquinoline group into the dioxotetraamines through a simple method. The stability of their metal complexes in aqueous solution has been determined and possible structures are discussed in this paper. The related compounds are listed in Figure 1. The results show that as to Mn^{2+}, Zn^{2+} and Co^{2+}, 8-hydroxyquinoline is a stronger chelating reagent than dioxo[13] or [14]tetraamine macrocycles.

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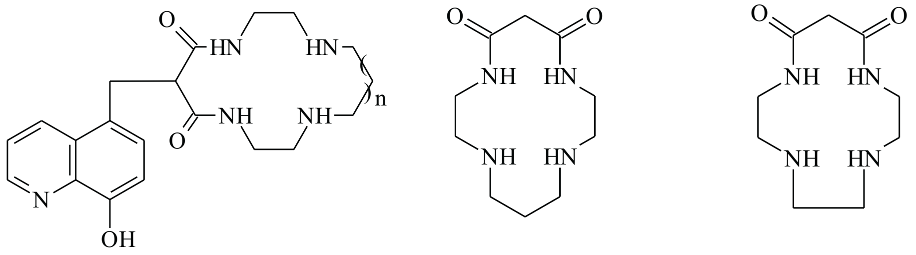


L₁(n = 0), **L₂**(n = 1) dioxo[14]aneN$_4$ dioxo[13]aneN$_4$

Figure 1. The structures of the ligands.

At 1:1 molar ratio (M:L) 8-hydroxyquinoline entirely binds to the metal ions, while the dioxotetraamine can only be partially or not coordinated.

EXPERIMENTAL

All chemicals were reagent grade, and were used without further purification. The Fourier-transform IR spectra were taken on a FT-IR 170SX (Nicolet) spectrometer and elemental analyses were made on Perkin-Elmer 240 C analyzer. MS was conducted on VG ZAB-HS instrument. Proton NMR spectra were recorded on a Bruker AC-P200 spectrometer 200 MHz at 25°C in $CDCl_3$ or DMSO-d6 solution with tetramethylsilane as the internal standard; electronic absorption spectra were obtained from a Shimadzu UV-240 spectrophotometer. The compound 5-chloromethyl-8-hydroxyquinoline was prepared according to literature [5].

5-[2,2-Bisethoxycarbonyl]ethyl]-8-hydroxyquinoline: A mixture of 5-chloro-methyl-8-hydroxyquinoline (6.8 mmol), diethyl malonate (8.2 mmol), and anhydrous K_2CO_3 (17 mmol) in dry DMF (30 mL) was stirred at room temperature under nitrogen atmosphere. After 3 days, the mixture was filtered, and the residue was thoroughly washed with DMF. The combined organic extract was concentrated in vacuum to give light yellow oil, which was chromatographed on silica gel eluted with EtOAc-C_6H_{12} (1:4) to give the pure product as colourless crystals (yield about 40%), m.p. 77.5–78.0°C. ^{1}H NMR ($CDCl_3$): δ 1.12~1.19 (s, 6H), 3.54~3.68 (m, 3H), 4.07~4.14 (m, 4H), 7.03~8.77 (m, 6H). IR (KBr pellet): 3356.7, 1729.5 ($\nu_{C=O}$), 1256 and 1202 cm^{-1}. The chemical analyses confirm the composition expected.

Synthesis of 1. 5-[2,2-Bis(ethoxycarbonyl)ethyl]-8-quinolinol (8 mmol) was dissolved in 300 mL absolute ethanol, the equivalent triethylenetetramine was added dropwise with constant stirring. The resulting mixture was refluxed under N_2 for about two weeks. The volume was reduced to about 20 mL on a rotary evaporator to give yellow oil. The pure product was precipitated in refrigerator, filtered and washed with cold ethanol three times to give the product in 14% yield as light yellow solid (pure product can also be obtained after column chromatography on silica gel using $CHCl_3/CH_3OH$, NH_4OH in drop). ^{1}H NMR (DMSO-d6): δ 2.39~2.49 (s, overlapped by DMSO), 3.32~3.50 (m, mixed with H_2O), 6.93 (m, H), 7.17 (m, H), 7.63 (m, H), 7.80 (m, H), 8.42 (m, H), 8.81 (m, H). IR (KBr pellet): 3330.7, 2941.9, 1673.1 ($\nu_{C=O}$), 1630.1 and 1474.0 cm^{-1}. CI-Ms: $(M+1)^+$: 372.2 (calcd.), 372.3 (found). The chemical analyses confirmed the composition expected.

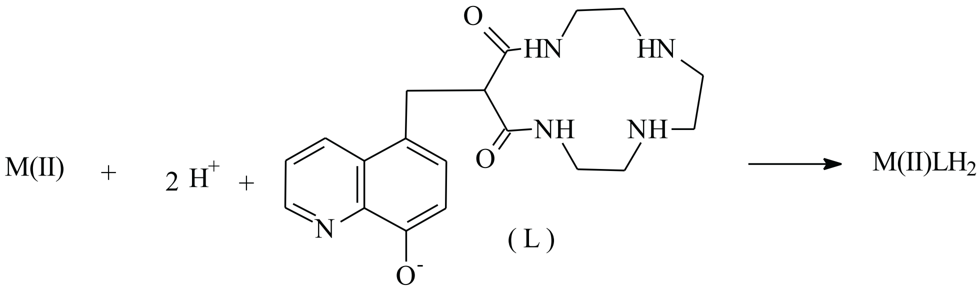
The synthesis of **L₂** was similar to that of **L₁** and N,N′-bis(2-aminoethyl)-1,3-propanediamine was used instead. The product is light yellow solid with a higher 21% yield. ^{1}H NMR (DMSO-d6): δ 1.50 (m, 2H), 2.49~2.83 (s, overlapped by DMSO), 3.33~3.60 (s, mixed with H_2O), 6.95 (m, H), 7.18 (m, H), 7.54 (m, 2H), 8.42 (m, H), 8.80 (m, H). IR (KBr pellet): 3340.5, 2931.2, 1672.1($\nu_{C=O}$), 1624.7 and 1473.9 cm^{-1}. $(M+1)^+$: 386.2 (calcd.), 386.3 (found). The chemical analyses confirmed the composition expected.

Potentiometric equilibrium measurements of the ligands in the presence of M^{2+} (Mn^{2+}, Co^{2+}, Zn^{2+}) ions were carried out with a Beckman pH meter (Model Φ71) equipped with a type 39841 combination electrode. Typical concentrations of experimental solutions were 1×10^{-3} mol·dm^{-3} for both the ligand and metal ions. Doubly distilled (in quartz equipment) H_2O was used for preparing all the solutions. $NaNO_3$, $Mn(NO_3)_2$, $Co(NO_3)_2$ and $Zn(NO_3)_2$ were recrystallized from H_2O before use. The concentrations of Mn^{2+}, $Co^{2+}$and Zn^{2+} in the stock solution were analyzed by EDTA titration methods. The ionic strength was adjusted to 0.1 mol·dm^{-3} $NaNO_3$. All titrations were carried out under N_2 at 25°C. Computation of equilibrium constants was made using the program based on the improved TITFIT technique [6]. For each system, at least two titrations were performed and each titration contained at least 45 experimental points.

RESULTS AND DISCUSSION

The titration curves have been plotted and the species present in the equilibrium systems are chosen and their equilibrium constants are refined to the best curve fitting according the TITFIT technique. In the following text, each species will be denoted by (p, q, r), where p is the stoichiometric coefficient of the metal in the complex, q that of the ligand and r that of the hydrogen ions. A negative value of r indicates that the complex has released a proton (for instance from the amide group of the ligand or the coordinated H_2O). The reaction scheme is shown below, where $\beta_{112} = [M(II)LH_2]/([Mn(II)][H^+]^2[L])$ (Scheme 1).

The stability constants are listed in Tables 1–3. Distribution curves are shown in Figures 2 and 3, while UV absorptions are given in Figures 4–6.



Scheme 1. Schematic illustration of the formation of MLH_2.

It has been demonstrated that in aqueous solution it was difficult to obtain the ML association constants of 8-hydroxyquinoline metal complexes due to the insolubility of ML_2 that causes the equilibrium to shift to the right [7]. However, as to the new ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ in the 1:1 (L:M material molar ratio) system, ML_2 type species could not have been obtained probably due to the introduction of dioxotetraamine in the new ligands $\mathbf{L_1}$ and $\mathbf{L_2}$. So it can be regarded that in the 1:1 system the amount of ML_2 could be neglected in the above titration situation.

From Tables 1–3 it can be found that the constants of β_{110} follow Irving-Williams stability sequence [8]: $Mn^{2+} < Co^{2+}$, Zn^{2+}. Considering the different coordination structures in (112), which are to be discussed consequently, we cannot get a sequence order from the β_{112} among the Mn^{2+}, Co^{2+} and Zn^{2+} complexes.

Table 1. The stability constants of Mn(II) with L.

	L_1	**L_2**
$Lg\beta_{112}$	22.15 ± 0.07	22.06 ± 0.08
$Lg\beta_{111}$	16.29 ± 0.07	16.11 ± 0.05
$Lg\beta_{110}$	7.39 ± 0.09	6.81 ± 0.06
$Lg\beta_{11\text{-}1}$	–2.15 ± 0.11	–2.65 ± 0.08
pH	3.1~9.8	3.5~9.8

Table 2. The stability constants of Co(II) with L.

	L_1	**L_2**
$Lg\beta_{112}$	21.91 ± 0.07	23.82 ± 0.03
$Lg\beta_{111}$	17.98 ± 0.02	18.50 ± 0.04
$Lg\beta_{110}$	9.32 ± 0.02	10.64 ± 0.07
$Lg\beta_{11\text{-}1}$	0.20 ± 0.03	3.13 ± 0.07
$Lg\beta_{11\text{-}2}$	–10.62 ± 0.14	–6.26 ± 0.13
pH	3.1~9.8	3.5~9.8

Table 3. The stability constants of Zn(II) with L.

	L_1	**L_2**
$Lg\beta_{112}$	21.12 ± 0.07	23.56 ± 0.04
$Lg\beta_{111}$	17.71 ± 0.03	18.35 ± 0.04
$Lg\beta_{110}$	9.40 ± 0.05	10.26 ± 0.07
$Lg\beta_{11\text{-}1}$	1.36 ± 0.05	2.25 ± 0.07
pH	3.1~8.7	3.5~8.8

As for the Mn(II) system, there will be four species through pH 3–10 and the model (112) constant of **L_1** is similar to that of **L_2**; as for Co(II) and Zn(II) this is not the case at all. In fact, the process from model (112) to model (111) indicates the system will release one proton. In order to interpret the results we compare the variations between (112) and (111) and list the results in Table 4.

Table 4. Comparison of $\lg\beta_{112}$ and $\lg\beta_{111}$ of Mn(II) complexes.

	L_1	**L_2**	dioxo[13]aneN_4	dioxo[14]aneN_4
$\Delta\lg\beta'$*	5.86	5.95		
$\Delta\lg\beta$*	2.87	4.55	3.82 ([ref. 1a)]	5.97 ([ref. 1a)]

*$\Delta\lg\beta'$ represents value of $[\lg\beta_{112} - \lg\beta_{111}]$ in complex; $\Delta\lg\beta$ represents the second protonation constants of dioxo[13] or [14]aneN_4.

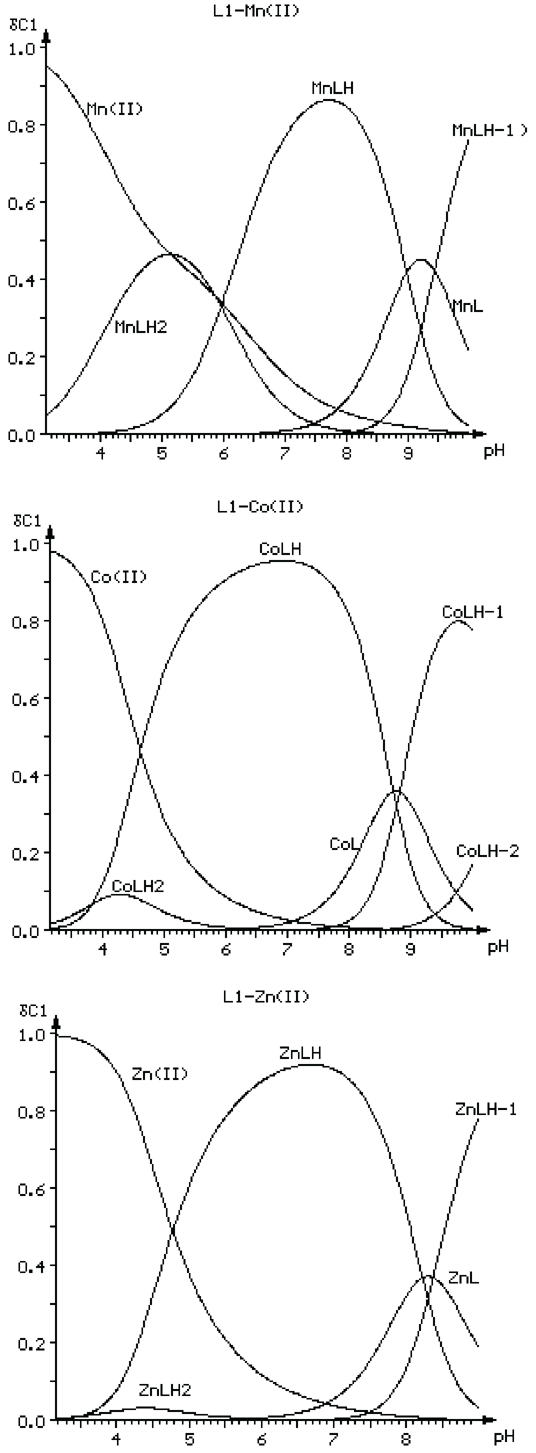


Figure 2. Distribution curves for M-$\mathbf{L}_1$ (molar ratio 1:1) system as a function of pH in 0.1 mol/L $NaNO_3$ solution at 298.15 K.

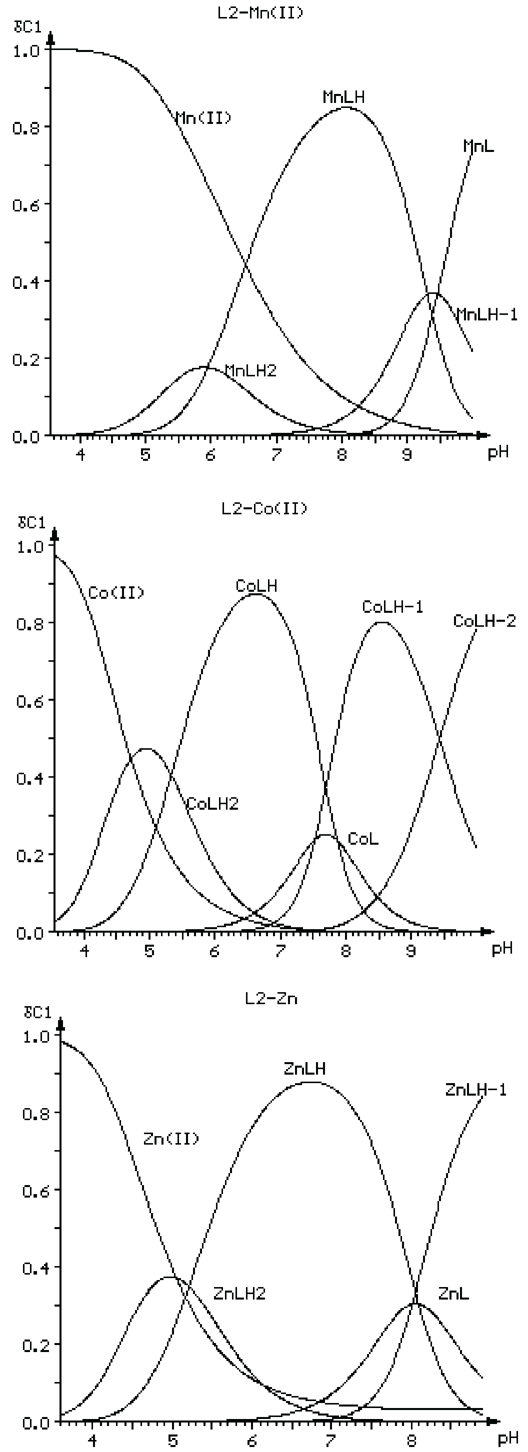


Figure 3. Distribution curves for M-$\mathbf{L}_2$ (molar ratio 1:1) system as a function of pH in 0.1 mol/L $NaNO_3$ solution at 298.15 K.

In Table 4 as for **L**$_1$, Δlgβ′ is larger than Δlgβ and dioxo[13]aneN$_4$, while **L**$_2$ Δlgβ′ is greater than Δlgβ and similar to that of dioxo[14]aneN$_4$. We also find that Δlgβ′ of the **L**$_1$ and **L**$_2$ systems are almost identical, which are possibly formed from a similar process, the deprotonation of (112) to (111). As for **L**$_2$, it is difficult to make certain whether the deprotonation is from amine group or from the hydroxyl group in 8-hydroxyquinoline only from data from potential titration data, since the Δlgβ′ is similar to Δlgβ of dioxo[14]aneN$_4$ from the titration curve data. In principle, if the hydroxyl group is coordinated to the metal ion, the UV absorption would be expected to change greatly [9]. Therefore, the UV absorption spectroscopy was conducted to investigate whether the hydroxyl in 8-hydroxyquinoline deprotonates to act as donor group in the range of pH under the same titration conditions (Figure 4).

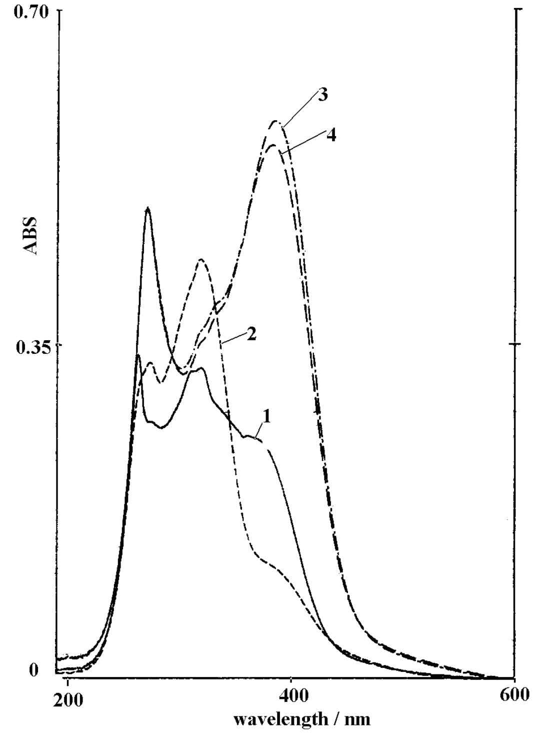


Figure 4. UV visible absorption spectra of the system of 1.982×10^{-4} mol/L **L**$_2$ and 1.982×10^{-4} mol/L Mn(II) at different pH (25°C, I = 0.1 mol·dm^{-3} NaNO$_3$): (1) pH 3.72, (2) pH 5.42, (3) pH 7.17, (4) pH 8.72.

In Figure 4, we find that at pH 5.42, the shape of the curve is similar to that of free 8-hydroxyquinoline in neutral solution, indicating that the hydroxyl group apparently is not deprotonated to chelate to metal ion. As pH increases, the characteristic absorption of the 8-hydroxyquinoline complex [9] is formed and rarely changes with the variation of pH, indicating that 8-hydroxyquinoline is entirely coordinated to Mn(II). Similar results between Δlgβ and Δlgβ′ in **L**$_1$ and **L**$_2$ can be ascribed to the following reaction.

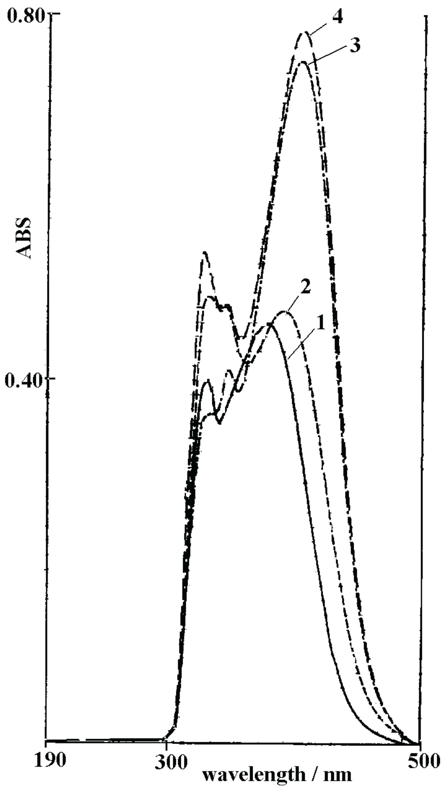


Figure 5. UV visible absorption spectra of the system of 2.975×10^{-4} mol/L $\mathbf{L_2}$ and 2.975×10^{-4} mol/L Co(II) at different pH (25°C, I = 0.1 mol·dm^{-3} $NaNO_3$): (1) pH 3.31, (2) pH 4.68, (3) pH 6.02, (4) pH 8.38.

Since Mn(II) is a harder acid and the amine is a base, the affinity of Mn(II) to amine is much weaker than that of Cu(II). The difference between $\lg\beta_{111}$ and $\lg\beta_{110}$ (8.90, 9.30) is very similar to the second protonation of free ligand (8.86, 9.35). We suggest that the dioxoaneN_4 does not take part in coordination. As the pH increases, the coordinated water will release one proton to give rise to the presence of model (11–1).

The properties of Co(II) and Zn(II) are alike and we have obtained similar results. From the UV absorptions (Figs. 5 and 6) and distribution curves of species (Fig. 3) we consider the structures of species as following: in (112) 8-hydroxyquinoline are coordinated and dioxoaneN_4 are entirely protonated. As pH increases, the dioxoaneN_4 will release a proton to take part in coordination. Due to the intrinsic tense in such systems, the dioxoaneN_4 can only be partly coordinated and could not release the proton of the amide group. As pH reaches a certain value (about 8), the coordinated water will dissociate its proton and species (11-1) comes into being.

In conclusion, 8-hydroxyquinoline is the stronger chelating reagent than dioxoane[13] or [14]N_4, which is evidenced from the two facts. Firstly, as pH increases the main absorption of the metal complexes does not change substantially with the characteristic absorption of 8-hydroxyquinoline metal complexes, which could be as-

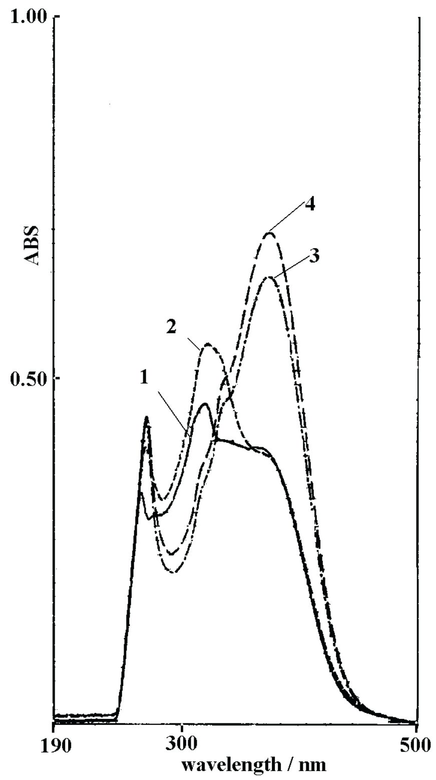


Figure 6. UV visible absorption spectra of the system of 2.975×10^{-4} mol·dm^{-3} $\mathbf{L}_2$ and 2.975×10^{-4} mol/L Zn(II) at different pH (25°C, I = 0.1 mol/L $NaNO_3$): (1) pH 3.74, (2) pH 4.95, (3) pH 6.74, (4) pH 8.11.

cribed to the 8-hydroxyquinoline 100% coordinated to the metal ions. Secondly, considering the intrinsic intense in the ligand, the macrocycle and 8-hydroxyquinoline could not chelate the same metal ion at the same time.

As to the difference between $\lg\beta_{110}$ and $\lg\beta_{11\text{-}1}$ constants we find the coordinated water's dissociation constant of Co$\mathbf{L}_2$ much lower than that of Co$\mathbf{L}_1$, Zn$\mathbf{L}_1$ and Zn$\mathbf{L}_2$, under which condition the hydrolytic metalloenzyme acts as an efficient catalyst. The surprising result reflects how the participation of dioxo[14]aneN_4 or 8-hydroxyquinoline changes the hard-soft property of Co(II) more greatly than those of other metal ions. As a result, the deprotonation is accomplished much more easily in Co(II). In fact, many metal complexes efficiently hydrolyze esters such as phosphate ester and RNA [10]. Further work is under investigation.

Acknowledgment

This project 2997/0/8 was supported by the National Natural Science Foundation of China, the Nature Science Foundation of Tianjin and the National Key Laboratory of the Coordination Chemistry, Nanjing University.

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