



Molecular docking, potentiometric and thermodynamic studies of some azo quinoline compounds



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ABSTRACT

The ligands of 5-(4-derivative phenyl azo)-8-hydroxyquinoline and its derivatives (**HL_n**) were synthesized from the coupling of the quinoline with diazonium salt derived from aniline and its *p*-derivatives and characterized by different spectroscopic techniques. Molecular docking was used to predict the binding between azo compounds with the receptor of breast cancer mutant 3hb5-oxidoreductase. The X-ray diffraction, XRD, pattern of the ligand (**HL₃**) is polycrystalline nature. The proton-ligand dissociation constant of the azo compounds (**HL_n**) and metal-ligand stability constants of their complexes with metal ions (Mn²⁺, Co²⁺, Ni²⁺ and Cu²⁺) have been determined by potentiometric technique in 0.1 M KCl and 50% (by volume) DMF–water mixture. For the same ligand at constant temperature, the stability constants of the formed complexes increase in the order Mn²⁺, Co²⁺, Ni²⁺ and Cu²⁺. The effect of temperature was studied at 298, 308 and 318 K and the corresponding thermodynamic parameters (ΔG , ΔH and ΔS) were derived and discussed. The dissociation process is non-spontaneous, endothermic and entropically unfavorable. The formation of the metal complexes has been found to be spontaneous, endothermic and entropically favorable.

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1. Introduction

Quinoline azodye and its derivatives are very important compounds and have attracted much attention in both academic and applied research used in many applications such as their biological relevance, coordination capacity, their use as metal extracting agent and their therapeutic properties [1–6]. Also the azo compounds based on quinoline play a central role as chelating agents for a large number of metal ions, as they form a stable six and/or five-membered ring after complexation with the metal ion [4,6]. The azo compounds are used in dyeing processes; some of them are used in analytical separation of many metal ions in a mixture. It is well-known that N atoms play a key role in the coordination of metals at the active sites of numerous metallobiomolecules [7].

The potentiometric study is one of the most convenient and successful technique employed for metal complex equilibrium measurements. Such applications are based on studying the influence of the pH on the equilibrium system components; metal ion, ligand and proton [8,9]. The use of protein–ligand docking has become a standard method in potentiometric studies [10]. The protein groups surrounding the ligand can highly influence the local pH, so that a different protonation could be favored in the bound state. The molecular docking is widely used to

predict protein–ligand [10,11] and to screen large libraries for molecules that will modulate the activity of a biological receptor.

In this paper, the potentiometric studies are used to determine the dissociation constants of 5-(4-derivative phenyl azo)-8-hydroxyquinoline (**HL_n**) and the stability constants of its complexes with some divalent transition metal ions such as Mn²⁺, Co²⁺, Ni²⁺ and Cu²⁺ at different temperatures. The corresponding thermodynamic functions are evaluated and discussed. Moreover, the molecular docking of the ligands (**HL_n**) is studied.

2. Materials and methods

All the compounds and solvents used were purchased from Aldrich and Sigma and used as received without further purification.

2.1. Preparation of the ligands

The ligands of 5-(4-derivative phenyl azo)-8-hydroxyquinoline and its derivatives (**HL_n**) were prepared by dissolving aniline or its *p*-substituted derivatives (10 mmol) in hydrochloric acid [12,13]. The compound was diazotized below –5 °C in an ice–salt bath with a solution of sodium nitrite (0.8 g, 10 mmol, 30 ml distilled H₂O). The diazonium salt was coupled with an alkaline solution of quinoline-8-ol (1.0 g, 10 mmol) in pyridine. The precipitate was filtered and dried after thorough washing with water and ethanol. The crude products were purified by recrystallization from hot ethanol and dried in vacuum

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desiccator over P₂O₅. Yield percent was 65–81%. The ligands are also characterized by IR and ¹H NMR spectroscopies (Fig. 1).

HL₁ = 5-(4-methoxyphenyl azo)-8-hydroxyquinoline.

HL₂ = 5-(4-methylphenyl azo)-8-hydroxyquinoline.

HL₃ = 5-(phenyl azo)-8-hydroxyquinoline.

HL₄ = 5-(4-chlorophenyl azo)-8-hydroxyquinoline.

2.2. Potentiometric studies

A ligand solution (0.001 M) was prepared by dissolving an accurately weighted amount of the solid in DMF. Metal ion solutions (0.0001 M) were prepared from metal chlorides in bidistilled water and standardized with EDTA [14]. Solutions of 0.001 M HCl and 1 M KCl were also prepared in bidistilled water. A carbonate-free NaOH solution in 50% (by volume) DMF–water mixture was used as titrant and standardized against oxalic acid.

The apparatus, general conditions and methods of calculation were the same as in previous work [15,16]. The following mixtures (i)–(iii) were prepared and titrated potentiometrically at 298 K against standard 0.002 M NaOH in a 50% (by volume) DMF–water mixture:

- 5 cm³ 0.001 M HCl + 5 cm³ 1 M KCl + 25 cm³ DMF.
- 5 cm³ 0.001 M HCl + 5 cm³ 1 M KCl + 20 cm³ DMF + 5 cm³ 0.001 M ligand.
- 5 cm³ 0.001 M HCl + 5 cm³ 1 M KCl + 20 cm³ DMF + 5 cm³ 0.001 M ligand + 10 cm³ 0.0001 M metal chloride.

For each mixture, the volume was made up to 50 cm³ with bidistilled water before the titration. These titrations were repeated for the temperatures of 308 and 318 K. All titrations have been carried out between pH 3.5 and 13.0 and under nitrogen atmosphere.

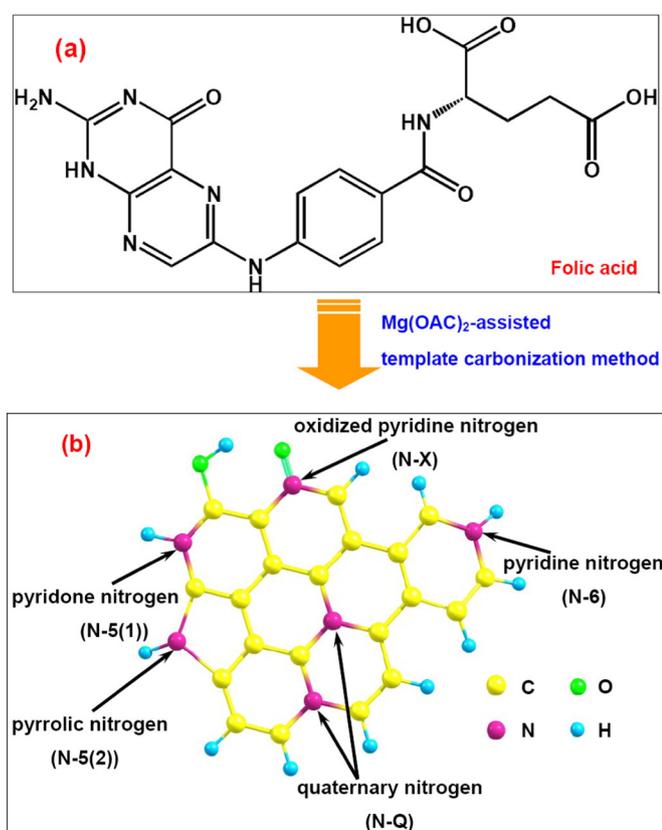


Fig. 1. The formation mechanism of azo quinoline derivatives (HL_n).

Table 1
Analytical data of the ligands (HL_n).

Compound	Exp. (Calc.) %		
	C	H	N
HL ₁	68.64 (68.82)	4.52 (4.66)	14.84 (15.05)
HL ₂	72.87 (73.00)	4.78 (4.94)	15.67 (15.97)
HL ₃	72.12 (72.29)	4.20 (4.42)	16.51 (16.87)
HL ₄	63.26 (63.49)	3.32 (3.53)	14.44 (14.82)

2.3. Measurements

Elemental microanalyses of the separated ligands for C, H and N were determined on Automatic Analyzer CHNS Vario ELIII, Germany. FT-IR spectra (KBr disks, 4000–400 cm⁻¹) by Jasco-4100 spectrophotometer. The ¹H NMR spectra by Bruker WP 300 MHz using DMSO-d₆ as a solvent containing TMS as the internal standard. X-ray diffraction measurement (XRD) is recorded on X-ray diffractometer in the range of diffraction angle 2θ = 5–80°. This analysis is carried out using CuK_{α1} radiation (λ = 1.540598 Å). The applied voltage and the tube current are 40 KV and 30 mA, respectively. The pH measurements were performed with a Metrohm 836 Titrand (KF & Potentiometric Titrator) equipped with a combined porolyte electrode. The temperature was controlled to within ±0.05 K by circulating thermostated water (Neslab 2 RTE 220) through the outer jacket of the vessel.

Docking calculations were carried out using a Docking Server [17–19]. The MMFF94 force field [20] was used for energy minimization of ligand molecule using Docking Server. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged and rotatable bonds were defined. Docking calculations were carried out on 3hb5-oxidoreductase protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools [21]. Affinity (grid) maps of 20 × 20 × 20 Å grid points and 0.375 Å spacing were generated using the Autogrid program [21]. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method [22]. Initial position, orientation and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

3. Results and discussion

3.1. Characterization of the ligands (HL_n)

The chemical structures of the ligands were elucidated by elemental analyses Table 1. The infrared spectra of ligands (HL_n) shows two bands in the range of 3266–3315 and 1570–1590 cm⁻¹ for stretching OH of quinoline at C₈-position and CN_{quin}. (nitrogen atom of azomethine of quinoline group), respectively. The aromatic C–H bands was observed at 3000–3120 cm⁻¹ as used and methyl C–H vibration of methoxy group was observed at 2990–2850 cm⁻¹ and exhibit band in the range of 1500–1504 cm⁻¹ which could be assigned to νN=N stretching vibration [23–27].

¹H NMR spectra of ligands (HL_n) were recorded in dimethylsulphoxide (DMSO-d₆) solution using tetramethylsilane (TMS) as internal standard. The ¹H NMR spectra of quinoline and benzene rings appeared in the range of 7.01–8.25 ppm. For the HL₁ has a singlet observed at 3.88 ppm is assigned to OCH₃ protons (the integration curve shows three protons). Also HL₂ has a singlet at 3.76 ppm which is assigned to the CH₃ protons. The ¹H NMR spectra show two

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