



Molecular docking, theoretical calculations and potentiometric studies of some azo phenols



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ABSTRACT

The ligands 5-amino-2-(phenyldiazenyl)phenol and its derivatives (**HL_n**) were synthesized from the coupling of 3-aminophenol with aniline and its *p*-derivatives and characterized by different spectroscopic techniques. The molecular and electronic structures of the investigated compounds (**HL_n**) were also studied using quantum chemical calculations. Molecular docking was used to predict the binding between azo compounds with the receptor of prostate cancer 2q7k-Hormone and 3hb5-oxidoreductase receptor of breast cancer. 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 40% (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 303, 313 and 323 K and the corresponding thermodynamic parameters (ΔG , ΔH and ΔS) were derived and discussed. The dissociation process is non-spontaneous, endothermic and entropic ally unfavorable. The formation of the metal complexes has been found to be spontaneous, endothermic and entropic ally favorable.

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1. Introduction

Aminophenols have aroused interest owing to their utility as starting materials for many azodyes [1], corrosion inhibitors [2], bactericides [3] and anti-inflammatory agent [4]. From the complexing point of view, many have taken interest in studying aminophenol as potential ligands [5]. Azo colorings are the most versatile class of dyes [6]. The dyes have been most widely used in fields such as dyeing textile fibers, biomedical studies, advanced applications in organic synthesis and high technology areas like lasers, liquid crystalline displays, electro-optical devices and ink-jet printer [7]. The presence of —N=N— group can lead to increase the solubility of low valent metal oxidation states due to its π acidity and presence of low lying azo centered π^* molecular orbitals [8].

Potentiometry is one of the most convenient and successful techniques employed for metal complex equilibrium measurements. In recent years the use of protein–ligand docking has become a standard method in potentiometric studies. The protein groups surrounding the ligand can highly influence the local pH, so that a different protonation could be favored in the bound state. To account for this effect, the ideal case would be to use multiple protonations in the docking and have the algorithm automatically pick the correct state. Molecular docking is

widely used to predict protein–ligand [9,10] and to screen large libraries for molecules that will modulate the activity of a biological receptor. In continuation of our previous work [11–15], we report herein the dissociation constant of (**HL_n**) and the stability constants of their complexes with Mn²⁺, Co²⁺, Ni²⁺ and Cu²⁺ at different temperatures. The corresponding thermodynamic functions are evaluated and discussed. Moreover, the molecular and electronic structures of the investigated compounds (**HL_n**) are also studied using quantum chemical calculations. Molecular docking was used to predict the binding between azo compounds and the receptors of prostate cancer and breast cancer.

2. Materials and methods

2.1. Measurements

All the compounds and solvents used were purchased from Aldrich and Sigma and used as received without further purification. Elemental microanalyses of the separated ligands for C, H, and N were determined on Automatic Analyzer CHNS Vario ELIII, Germany. FT-IR spectra (KBr discs, 4000–400 cm^{−1}) by Jasco-4100 spectrophotometer. The calculations of geometry optimization were performed using Perkin Elmer ChemBio 3D software by HF method with 3-21G basis set [16,17]. Geometry optimization option was employed to obtain the most stable structure. The pH measurements were performed with a Metrohm 836 Titrand (KF & Potentiometric Titrator) equipped with a combined porolyte electrode. The pH-meter readings in the non-aqueous medium

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were corrected [18]. The electrode system was calibrated according to the method of Irving et al. [19]. The temperature was controlled to within ± 0.05 K by circulating thermostated water (Neslab 2 RTE 220) through the outer jacket of the vessel.

2.2. Preparation of the ligands

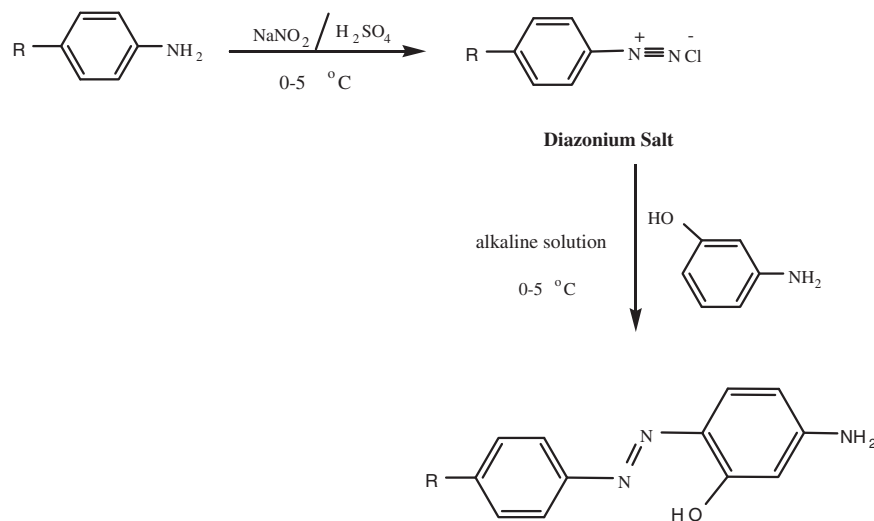
The ligands 5-amino-2-(phenyldiazenyl)phenol and its derivatives (**HL_n**) were prepared by dissolving aniline or its *p*-substituted derivatives (10 mmol) in conc. H₂SO₄. The compound was diazotized below -5 °C in an ice-salt bath with a solution of sodium nitrite (0.8 g, 10 mmol, 30 ml distilled H₂O). The diazonium salt was coupled with an alkaline solution of 3-aminophenol (1.0 g, 10 mmol) in 20 ml of ethanol. The precipitate was filtered and dried after through washing with water and ethanol. The crude product was recrystallized from ethanol and the microcrystals were obtained in a yield of 94–97% (Fig. 1). The resulting formed ligands are 5-amino-2-((4-methylphenyl)diazenyl)phenol (**HL₁**), 5-amino-2-(phenyldiazenyl)phenol (**HL₂**) and 5-amino-2-((4-chlorophenyl)diazenyl)phenol (**HL₃**).

2.3. Potentiometric studies

A ligand solution (0.01 M) was prepared by dissolving an accurately weighted amount of the solid in DMF. Metal ion solutions (0.001 M) were prepared from metal chlorides in bidistilled water and standardized with EDTA [20]. Solutions of 0.01 M HCl and 1 M KCl were also prepared in bidistilled water. A carbonate-free NaOH solution in 40% (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 [11–15]. The following mixtures (i)–(iii) were prepared and titrated potentiometrically at 298 K against standard 0.02 M NaOH in a 40% (by volume) DMF–water mixture:

- i) 5 cm³ 0.01 M HCl + 5 cm³ 1 M KCl + 20 cm³ DMF.
- ii) 5 cm³ 0.01 M HCl + 5 cm³ 1 M KCl + 15 cm³ DMF + 5 cm³ 0.01 M ligand.
- iii) 5 cm³ 0.01 M HCl + 5 cm³ 1 M KCl + 15 cm³ DMF + 5 cm³ 0.01 M ligand + 10 cm³ 0.001 M metal chloride.



R = -CH₃ (**HL₁**), -H (**HL₂**) and -Cl (**HL₃**).

Fig. 1. Structure of the azo phenols (**HL_n**).

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 4.0–11.0 and under nitrogen atmosphere.

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 shows a broad band located at the region 2946–3158 cm⁻¹ due to $\nu(\text{OH})$ group. The two bands appear at the region 3320–3359 cm⁻¹ are due to $\nu(\text{NH}_2)$. The $\nu(\text{N}=\text{N})$ group appeared at 1481–1623 cm⁻¹ region. The bands at 2603–2711 cm⁻¹ region are assigned to $\nu(\text{C}-\text{H})$ vibrations of the aromatic system.

3.2. Molecular structure

The optimized structures, bond length and bond angles of the (**HL_n**) ligands are presented in Fig. 2 and Tables 2 and 3. Both the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are the main orbital which take part in chemical stability. The HOMO represents the ability to donate an electron; LUMO as an electron acceptor represents the ability to obtain an electron as shown in Fig. 3. Quantum chemical parameters of the ligands (**HL_n**) are obtained from calculations such as energies of the highest occupied molecular orbital (E_{HOMO}) and the lowest unoccupied molecular orbital (E_{LUMO}) as listed in Table 4. Additional parameters such as HOMO–LUMO energy gap, ΔE , absolute electronegativities, χ , chemical potentials, μ , absolute hardness, η , absolute softness, σ , global electrophilicity, ω , global softness, S , and additional electronic charge, ΔN_{max} , are calculated using the following equations [15,21–23]:

$$\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}} \quad (1)$$

$$\chi = \frac{-(E_{\text{HOMO}} + E_{\text{LUMO}})}{2} \quad (2)$$

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