

Research Article

Complex Formation of Nickel(II) and Copper(II) with Barbituric Acid

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Equilibrium studies have been carried out on complex formation of M^{2+} ions ($M = \text{Ni}$ and Cu) with $L = \text{barbituric acid (BA)}$ in aqueous solution at $25.0 \pm 0.1^\circ\text{C}$ and with an ionic strength of $I = 0.10 \text{ M (KNO}_3\text{)}$ in aqueous medium. The basicity of the ligand was also assessed by the determination of the dissociation constants of the ligand. The experimental pH titration data were analyzed with the help of the BEST computer program in order to evaluate the stability constants of the various species formed. The stability constants of the binary systems decrease in the order of $\text{Cu(II)} > \text{Ni(II)}$. Distribution diagrams for the species were drawn showing the concentrations of individual species as a function of pH by the SPE software program.

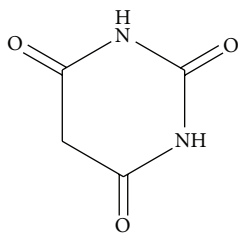
1. Introduction

Organotransition-metal complexes formed with biologically active ligands have attracted great attention in recent years. Studies of such complexes in biological systems can lead to a better understanding of the roles of these ligands and can also contribute to the development of metal-based chemotherapeutic agents. Pyrimidine ring-containing compounds can be found in nucleic acids, various vitamins, and coenzymes and they play an important role in many biological systems [1, 2]. In nucleic acids, they are related to anticancer chemotherapeutic antimetabolites [3]. Pyrimidine metal complexes have been studied in recent years because of their great variety of biological activities such as antimalarial, antibacterial, antitumoral, antiviral activities, and so forth [4–10]. Despite the multitude of coordination complexes of pyrimidines, the organometallic chemistry of these ligands received little attention, mostly from Beck and coworkers [11, 12].

Barbiturates are the derivatives of barbituric acid (2,4,6-trioxypyrimidine) (Scheme 1). These drugs are used for many reasons such as hypnotics, sedatives, or anesthetics [13, 14]. They also affect the motor and sensory functions, and they

are used as cures for anxiety, epilepsy, and other psychiatric disorders [15, 16]. The production process of plastics and pharmaceuticals requires the uses of barbituric acid. Introduced as one of the first medical use of barbiturates, barbital diethylbarbituric acid is known as veronal, or diemal [17]. The first psychologically active drug, barbital or veronal was introduced in 1903 by E. Fischer [18]. Only a few barbiturates have anticonvulsant properties, although many of them have sedative-hypnotic attributes. However, most barbiturates cause convulsions at large doses. Phenobarbital (5 ethyl-5 phenyl barbituric acid) is used for the treatment of convulsive disorders [19]. 5,5-Diethylbarbituric acid (H_2debarb) is a sedative-hypnotic, and even as a discontinued chemical, its low oil, water partition coefficient as a result of biological processes makes it interesting [18]. Because of their ability to coordinate with transition metals through carbonyl oxygen and one or both deprotonated oxygen atoms, and also because of their wide use in medicine, the synthesis of their metal complexes has received great interest.

Furthermore, it has been suggested that the presence of the metal ions in biological fluids could have a significant effect on the therapeutic action of drugs. Many diverse applications of metal species are aimed at understanding the



SCHEME 1: Structure of the barbituric acid (BA).

natural roles of metal ions or exploiting the unique properties of metal centers in the study of the biology or biochemistry of nucleic acid and nucleic acid constitutes [2].

The literature review indicated that no work has been done on complex formation equilibria of this ligand in aqueous medium. There is only one study [20] of this ligand with Cu(II) and no work on the barbituric acid with Ni(II). They studied Cu(II) and Fe(II) complexation with the barbiturate ion by the solubility method, potentiometric titration, spectroscopy, and photometry. But they decided that the barbiturate anion was a monodentate ligand and calculated that Cubar^+ , stability constants was $\log \beta_1 = 3.07 \pm 0.01$ by potentiometry [20]. So the objective of this work was to determine the stability constants of barbituric acid complexes with Ni(II) and Cu(II) metallic ions.

2. Experimental

2.1. Chemicals. Barbituric acid (BA) was obtained from Merck Chem. Co. $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ was provided by Aldrich Chem. Co. and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ was provided by Merck Chem. Co. All reagents were of analytical quality and were used without further purification. For the solutions, CO_2 -free double-distilled deionized water was obtained through the ultrawater purification system.

2.2. Titration Procedure. Solutions of metal ions (0.01 M) were prepared from $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ received and standardized with ethylenediaminetetraacetic acid (EDTA) [21]. HCl stock solution was prepared from concentrated HCl and their concentration was determined with standardized NaOH. All potentiometric titrations were carried out on solutions in a 100 mL double-walled glass vessel using titroline automatic titration system, which interfaces to a PC, with a 10 mL syringe, a Schott pH combination electrode, the temperature was controlled at $25.0 \pm 0.1^\circ\text{C}$ by circulating water from a constant-temperature bath. The cell was equipped with a magnetic stirrer and a tightly fitting cap, which contained three holes for the combined electrode, nitrogen gas, and automatic burette. The emf was measured under nitrogen atmosphere. The ligand concentrations varied in 2×10^{-3} – 6×10^{-3} M. The cell was standardized with two primary buffers. The buffer solutions were pH = 4.0 and pH = 7.0. The electrode was calibrated on the $-\log_{10} [\text{H}^+]$ scale by titration of a 0.01 M HCl solution (adjusted to $I = 0.1$ M by adding KNO_3) with carbonate free 0.1 M NaOH at $25 \pm 0.1^\circ\text{C}$. The electrode slope calculated from the formula

$K = (E_{\text{pH1}} - E_{\text{pH2}})/(\text{pH2} - \text{pH1})$ was close to the Nernstian value $59.16 \text{ mV (pHunit)}^{-1}$ within >99%. The emf readings were converted into hydrogen concentration. The $\text{p}K_w$ of water was calculated at ionic strength of 0.1 M to be 13.97.

The acid dissociation constants of the ligands were determined potentiometrically by titrating the ligand (50 mL) solution (2×10^{-3} – 6×10^{-3} M) of constant ionic strength 0.1 M, adjusted with KNO_3 . The stability constants of the binary complexes were determined by titrating 50 mL of a solution mixture of metal(II) (Ni(II) or Cu(II)) (2×10^{-3} M), the ligand (2×10^{-3} – 6×10^{-3} M), and 0.1 M KNO_3 . One hundred titration points were collected at one titration. All titrations were performed in a purified N_2 atmosphere, using aqueous 0.1 M NaOH as titrant.

The overall stability constants (β_{pqr}) are defined as follows (charges are omitted for simplicity):

$$p\text{M} + q\text{L} + r\text{H} \rightleftharpoons [\text{M}_p\text{L}_q\text{H}_r] \quad (1)$$

$$\beta_{pqr} = \frac{[\text{M}_p\text{L}_q\text{H}_r]}{[\text{M}]^p [\text{L}]^q [\text{H}]^r}, \quad (2)$$

where M is a metal ion, L is the ligand, H is the proton, and r is the respective stoichiometric coefficient. Calculations were performed using the computer program BEST [22] on a personal computer.

The stoichiometries and the stability constants of the complexes formed were determined by trying various possible composition models for the system studied. The concentration distribution diagrams were obtained using the program SPE [22].

3. Result and Discussion

Although the dissociation constants of barbituric acid have already been reported, we determined them under our experimental conditions by potentiometric titration in the pH range 1.8–12.0. The BEST computer program was used for calculations [22]. The obtained values are listed in Table 1 together with the literature data for comparison. A good agreement with earlier published data for BA is obtained [23] considering the differences in an ionic strength. The BA forms three species in aqueous solution, denoted by H_2L , HL , and L . Consider

$$\text{H}_2\text{L} \rightleftharpoons \text{HL}^- + \text{H}^+ \quad K_{a1} = \frac{[\text{HL}^-][\text{H}^+]}{[\text{H}_2\text{L}]} \quad (3)$$

$$\text{HL}^- \rightleftharpoons \text{L}^- + \text{H}^+ \quad K_{a2} = \frac{[\text{L}^-][\text{H}^+]}{[\text{HL}^-]}. \quad (4)$$

3.1. Stability Constants of Ni(II)-BA Complexes. Potentiometric pH titrations of Ni(II) were performed at 1:1, 1:2, and 1:3 metal/ligand molar ratios at $25.0 \pm 0.1^\circ\text{C}$ in an 0.10 M KNO_3 ionic medium. BA acid (solid) was added to the Ni(II) solutions with a metal/ligand molar ratio of 1:1, 1:2, and 1:3. Representative potentiometric titration curves for the Ni(II)-BA complexes with 1:1, 1:2 and 1:3 stoichiometry are shown

TABLE 1: Acid dissociation constants of Barbituric acid (BA) and the stability constants of the Ni(II), Cu(II)-BA complexes ($25.0 \pm 0.1^\circ\text{C}$, $I = 0.1\text{ M KNO}_3$).

Equilibrium	Constant	BA	Ni(II)	Cu(II)
$\text{H}_2\text{L} \rightleftharpoons \text{HL}^- + \text{H}^+$	$\log K_{\text{H}_2\text{L}}$	3.89 ± 0.04 (3.78) [23]		
$\text{HL}^- \rightleftharpoons \text{L}^{2-} + \text{H}^+$	$\log K_{\text{HL}}$	11.90 ± 0.04 (12.30) [23]		
$p\text{M} + q\text{L} + r\text{H}^+ \rightleftharpoons [\text{M}_p\text{L}_q\text{H}_r]$	$\log \beta_{110}$		6.62 ± 0.09	8.39 ± 0.05
	$\log \beta_{120}$		11.65 ± 0.03	14.16 ± 0.06
	$\log \beta_{131}$		17.94 ± 0.04	19.20 ± 0.04

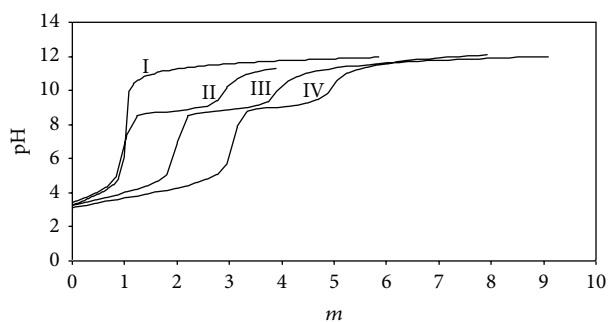


FIGURE 1: Potentiometric pH profiles for solutions containing (I) BA, $T_{\text{BA}} = 2.0 \times 10^{-3}\text{ M}$ and Ni(II) and BA in the ratios, (II) 1:1 ($T_{\text{Ni}} = 2.0 \times 10^{-3}\text{ M}$ and $T_{\text{BA}} = 2.0 \times 10^{-3}\text{ M}$), (III) 1:2 ($T_{\text{Ni}} = 2.0 \times 10^{-3}\text{ M}$ and $T_{\text{BA}} = 4.0 \times 10^{-3}\text{ M}$), and (IV) 1:3 ($T_{\text{Ni}} = 2.0 \times 10^{-3}\text{ M}$ and $T_{\text{Ni}} = 6.0 \times 10^{-3}\text{ M}$), respectively, $T = 25.0 \pm 0.1^\circ\text{C}$ and $I = 0.1\text{ MKNO}_3$.

in Figure 1 for BA systems together with the titration curve for the free ligand (BA). Analysis of the complexed ligand curves (Figure 1) indicates that the addition of metal ion to the free ligand solutions shifts region of the ligand to lower pH values. This shows that complex formation reactions proceed by releasing protons from BA. Two inflection points were observed at $m = 1.0$ and $m \sim 2.2$ on the titration curves of the 1:1 Ni(II)-BA systems (Curve 2 in Figure 1), where m is the number of moles of base added per mole of the metal (Figure 1). Experimental data has shown that, in the $m = 0$ to ~ 2.2 , the NiL complex forms between $\text{pH} = 6.0\text{--}11.0$. BA ligand acts as a bidentate chelating ligand via the negatively charged imino N atom and one of the carbonyl O atoms, adjacent to the imino N atom.

The potentiometric titrations of the 1:2 Ni(II)-BA systems were carried out under the same experimental conditions. In these curves, two inflection points were observed at $m = 1.8$ and $m = 3.8$. The titration of these protons in each of these systems indicates that the NiL_2 complex forms gradually. The second BA was bound as the same first BA.

The potentiometric titrations of the 1:3 Ni(II)-BA systems were carried out under the same experimental conditions. The titration of these protons in each of these systems indicates that the NiL_3H complex forms gradually. But in the third BA molecule it was bound only once via the negatively charged imino N atom or one of the carbonyl O atoms. In

the 1:3 molar ratio potentiometric titrations, the stability constants of the complexes NiL , NiL_2 , and NiL_3H were calculated by the BEST computer program [22]. The stability constants of their complexes are given in Table 1.

The distribution diagrams were drawn in the titration where the metal to ligand mole ratio was 1:3. They were obtained with the aid of SPE program [22] and the concentration of total metal ion present $\sim 2 \times 10^{-3}\text{ M}$ set at 100%. In Figure 3 the species NiL_3H for the system BA and metal ion Ni(II) reaches a maximum of 100% at $\text{pH } 10.0$. The second species NiL_2 reaches a maximum of 10% at $\text{pH } 7.0\text{--}12.0$ and NiL complex species in the mole ratio of 1 moles of ligand to one mole metal, presents a maximum of 70% near $\text{pH } 6.0$.

3.2. Stability Constants of Cu(II)-BA Complexes. The potentiometric titrations of the Cu(II):BA systems were performed at $25.0 \pm 0.1^\circ\text{C}$ in an 0.10 M KNO_3 ionic medium. BA acid was added to the Cu(II) solutions with a molar ratio of 1:1, 1:2, and 1:3. Two inflection points were observed at $m = 1.0$ and $m \sim 2.2$ on the titration curves of the 1:1 Cu(II)-BA systems (Curve 2 in Figure 2), where m is the number of moles of base added per mole of the metal (Figure 2). In addition, the titration curve of the Cu(II) complex is different from that of the free BA curve. Experimental data has shown that, in the $m = 0$ to ~ 2.2 buffer zone, the CuL complex forms between $\text{pH} = 6.0\text{--}11.0$.

The potentiometric titrations of the 1:2 Cu(II)-BA systems were carried out under the same experimental conditions. In these curves, two inflection points were observed at $m = 3.0$ and $m = 5.0$. The titration of these protons in each of these systems indicates that the CuL_2 complex forms gradually.

The potentiometric titrations of the 1:3 Cu(II)-BA systems were carried out under the same experimental conditions. In these curves, two inflection points were observed at $m = 4.0$ and $m = 5.0$. The titration of these protons in each of these systems indicates that the CuL_3H complex forms gradually. In the 1:3 molar ratio potentiometric titrations, the stability constants of the complexes CuL , CuL_2 , and CuL_3H were calculated by the BEST computer program [22]. The stability constants of their complexes are given in Table 1.

The distribution diagrams were drawn in the titration where the metal to ligand mole ratio was 1:3. They were obtained with the aid of SPE program [22] and the concentration of total metal ion presents $\sim 2 \times 10^{-3}\text{ M}$ set at 100%.

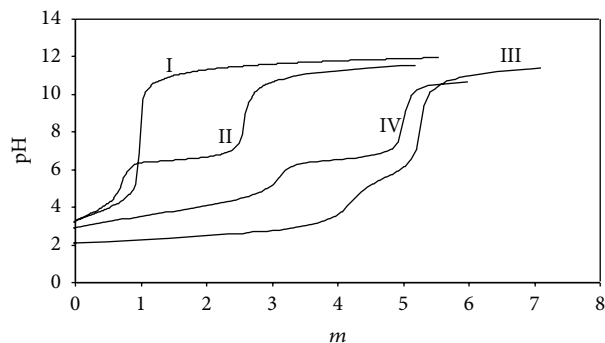


FIGURE 2: Potentiometric pH profiles for solutions containing (I) BA, $T_{BA} = 2.0 \times 10^{-3}$ M and Cu(II) and BA in the ratios, (II) 1:1 ($T_{Cu} = 2.0 \times 10^{-3}$ M and $T_{BA} = 2.0 \times 10^{-3}$ M), (III) 1:2 ($T_{Cu} = 2.0 \times 10^{-3}$ M and $T_{BA} = 4.0 \times 10^{-3}$ M), and (IV) 1:3 ($T_{Cu} = 2.0 \times 10^{-3}$ M and $T_{BA} = 6.0 \times 10^{-3}$ M), respectively, $T = 25.0 \pm 0.1^\circ\text{C}$ and $I = 0.1$ MKNO₃.

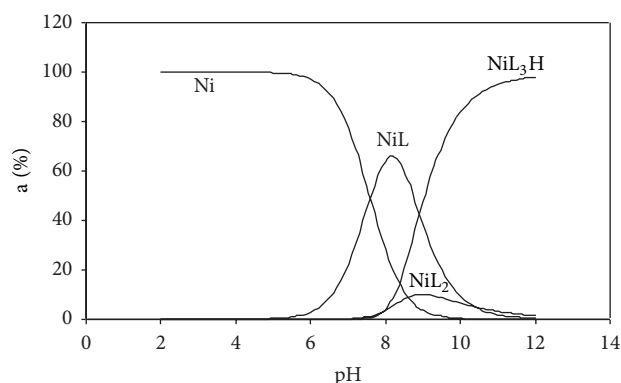


FIGURE 3: Species distribution curves of the metal ion Ni(II) and the BA as a function of pH, for a solution initially containing $T_{Ni} = 2.0 \times 10^{-3}$ M metal ion and $T_{BA} = 6.0 \times 10^{-3}$ M BA. $T = 25.0 \pm 0.1^\circ\text{C}$ and $I = 0.1$ MKNO₃. % a is the percentage of a species present, with the concentration of the metal set at 100%; NiL, NiL₂, and NiL₃H are the complexed species with one, two, and three ligand molecules.

In Figure 4, the species CuL₃H for the system BA and metal ion Cu(II) reaches a maximum of 90% at pH 12.0. The second species CuL₂ reaches a maximum of 60% at pH 6.0–12.0 and the CuL complex species in the ratio of 1 moles of ligand to one mole metal presents a maximum of 90% near pH 4.0–10.0.

It can be observed that the stability constants of the Ni(II)-BA complexes are lower than Cu(II)-BA complexes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

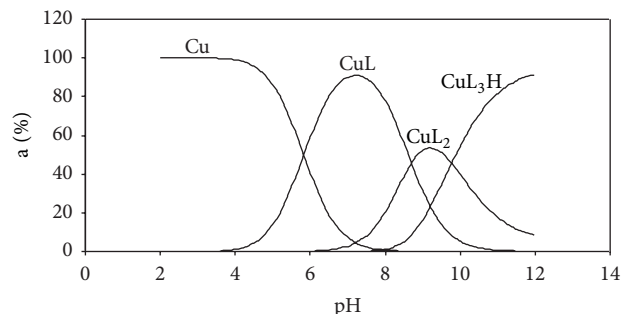


FIGURE 4: Species distribution curves of the metal ion Cu(II) and the BA as a function of pH, for a solution initially containing $T_{Cu} = 2.0 \times 10^{-3}$ M metal ion and $T_{BA} = 6.0 \times 10^{-3}$ M BA. $T = 25.0 \pm 0.1^\circ\text{C}$ and $I = 0.1$ MKNO₃. % a is the percentage of a species present, with the concentration of the metal set at 100%; CuL, and CuL₂, CuL₃H are the complexed species with one, two, and three ligand molecules.

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