

Research Article

Determination of the Ionization Constants of Some Benzoyl Thiourea Derivatives in Dioxane-Water Mixture

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The stoichiometric ionization constants of *N,N*-dialkyl-*N'*-(4-substituted benzoyl) thiourea (Substitutes: H, Cl, and Br; alkyl groups: ethyl, *n*-propyl, *n*-butyl, and phenyl) derivatives have been determined potentiometrically in dioxane-water (*v:v*, 50:50) mixture at ionic strength of 0.1 M and $25.0 \pm 0.1^\circ\text{C}$. The ionization constants were calculated with the BEST computer program and the formation curves using the data obtained from the potentiometric titrations. The effects of substituents and alkyl groups on the ionization constants of the benzoyl thiourea derivatives have been investigated. A comparison of the basicities of ethyl, *n*-propyl, and *n*-butyl thiourea derivatives ($-\text{C}_2\text{H}_5 < -\text{C}_3\text{H}_7 < -\text{C}_4\text{H}_9$) shows that the *n*-butyl group is a more powerful electron-releasing group than the other groups in 50% dioxane-50% water mixture (*v:v*). So, the acidity of benzoyl thiourea derivative compounds decreases, while the length of alkyl chain increases. The orders of $\text{p}K_a$ values for all thiourea derivatives are as expected in the light of steric, resonance and inductive effects of substituents. Furthermore, when the basicities of halogen derivatives of the same substitution pattern are compared, orders obtained ($4\text{-Br} < 4\text{-Cl} < 4\text{-H}$) can be explained by considering the total electronic substituent effect (electron-withdrawing and electron-donating effects) except the 4-Br_Ph derivative.

1. Introduction

Thiourea derivatives and their transition metal complexes have been known since the beginning of the 20th century. The syntheses of the thiourea derivatives are easily with good yields [1]. Thiourea and its derivatives represent a well-known important group of organic compounds due to the diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry [2]. The benzoyl thiourea derivatives have a wide range of biological activities including antiviral [3], antibacterial [4–6], antifungal [7], antitubercular [8, 9], herbicidal [10], insecticidal [11], and pharmacological properties [12] and acting as chelating agents [13, 14].

Although the synthesis, characterization, and applications of many benzoyl thiourea derivatives were reported in the literature [15–25]; to the best of our knowledge, there

is no report on the determination of ionization constants of substitute benzoyl thiourea derivatives. On the continuation of our research on the determination of ionization constants of some industrial useful organic compounds in this study, we report the stoichiometric ionization constants of some substituted benzoyl thioureas in dioxane:water mixture (*v:v*, 50:50). Various techniques can be used to determine ionization constants, such as potentiometry, conductometry, and spectrophotometry [26]. For more benefit, in this research, we select the potentiometric titration technique. Since the solubility of these compounds in water is too low, dioxane-water mixtures were used as medium in the experiments. The stoichiometric ionization constants have been measured by the potentiometric titration, and calculations were performed by the BEST computer software [27, 28]. In addition, in this research, the effects of substituents and alkyl groups on the ionization constants of the benzoyl thiourea derivatives have been discussed.

2. Experimental

2.1. Chemicals and Standard Solutions. All of the reagent-grade quality chemicals and solvents (acetone, 1,4-dioxane, and dichloromethane) were purchased from Merck and used without further purification. Double-distilled deionized water free of CO₂ was used throughout the experimental.

The benzoyl thiourea derivatives were prepared by a procedure similar to that reported in the literature [29, 30]. The benzoyl thiourea derivatives were purified by recrystallization from ethanol:dichloromethane (1:2) mixture. The synthesized compounds were characterized by infrared spectroscopy, nuclear magnetic resonance, and elemental analysis. All the compounds were checked for purity by chromatography. The stock solutions of the synthesized compounds were prepared in dioxane. The standard substitute benzoyl thiourea solutions (0.030 M) were prepared in 50% dioxane-50% water mixture ($v:v$) [31].

Stock solutions of strong acid and strong base were prepared using analytical reagent-grade hydrochloric acid and sodium hydroxide, respectively. The solution of the sodium hydroxide (0.10 M) containing 0.10 M NaCl was prepared in 50% aqueous dioxane solutions ($v:v$) and was standardized by titration against primary standard potassium hydrogen phthalate. The hydrochloric acid (0.10 M) solution was prepared in water which was potentiometrically standardized against standard base solutions by the use of Gran's plot techniques, allowing the determination of dissolved carbonate impurities [32]. Chemically pure sodium chloride was used to maintain a constant ionic strength.

2.2. Potentiometric Apparatus and Procedure. All potentiometric experiments were carried out in an 80 mL jacketed titration cell thermostated at $25.0 \pm 0.1^\circ\text{C}$. The cell electromotive force (e.m.f.) was measured using an Orion 960 automatic titrator, equipped with a combined glass pH electrode (Ingold) containing a filling solution of 0.10 M NaCl. The potentiometric cell was calibrated before each experiment, so that the hydrogen ion concentration rather than the activity was measured [33, 34]. The reproducible values of the autoprotolysis constants K_w were calculated from several series of $[\text{H}^+]$ and $[\text{OH}^-]$ measurements at 0.10 M NaCl [35, 36]. The following solution prepared in water and each of the solvent mixtures studied (total volume = 50.0 mL) were titrated potentiometrically with carbonate-free standard 0.10 M sodium hydroxide dissolved in the corresponding solvents: (i) 2.00×10^{-3} M HCl (for cell calibration), (ii) 2.00×10^{-3} M HCl + 1.50×10^{-3} M benzoyl thiourea derivatives. During each titration, the ionic strength was maintained at 0.10 M NaCl, and the cell potential was read after waiting to establish the equilibrium throughout the titrations.

2.3. Calculation Techniques. The stoichiometric ionization constants of the benzoyl thiourea derivatives was calculated in two different ways. The first method were the computer program (BEST) developed by Motekaitis and Martell [27, 28]. The program BEST was used to minimize the standard

TABLE 1: Calibration constants for the potentiometric cell and pK_w values for various 50% dioxane-50% water ($v:v$) medium.

E_{cell}° (mV)	329.97 ± 3.58
k (slope)	59.14 ± 0.02
pK_w	15.17 ± 0.07

deviation of the fit (σ_{fit}) between the observed and calculated pH values for overall titration data.

The second method employed to calculate the ionization constants was formation curves (\bar{j} -pH) [28]. The experimental curves fit reasonably well to the theoretical curves, that is why the pH at $\bar{j} = 0.5$ was accepted as being equal to the negative logarithm of the ionization constant (pK_a) of each compound.

3. Results and Discussion

Substitute benzoyl thiourea derivatives were produced by the reaction of 4-substitute benzoyl chloride with an equimolar amount of potassium thiocyanate in dry acetone. Twelve benzoyl thiourea derivatives were synthesized from 4-substitute benzoyl isothiocyanate and secondary amines in dry acetone. Scheme 1 outlines the synthesis of the series of thiourea derivatives. The ligands were purified by recrystallization from an ethanol:dichloromethane mixture (1:2) and obtained in yields ranging from 70 to 95%. ¹H-NMR spectra, FT-IR spectra, and elemental analysis data of all synthesized compounds confirm the proposed structures.

Benzoyl thiourea derivatives were often used in analytical and biological applications [2–14, 37]. For an effective use of these compounds, the value of the ionization constants must be known, because this is an important parameter to determine the application fields.

The stoichiometric ionization constants were determined with an electrochemical cell calibrated in 50% dioxane-50% water ($v:v$) medium to measure the hydrogen ion concentration. For this purpose, the hydrochloric acid solutions prepared in each medium were titrated with sodium hydroxide solutions, and the potential values were plotted against the logarithm of the hydrogen ion concentration to determine calibration constants (E_{cell}° and k). The calibration constants obtained from these curves are tabulated in Table 1. The combined glass pH electrode has a slope of 59 mV, the same as the Nernstian value. It was therefore concluded that the electrode could be used to determine the potentiometric constants for 50% dioxane-50% water ($v:v$) media. The electrode which exhibited Nernstian behavior in acidic media was found to show the same behavior in alkaline media [38]. The ion products ($K_w = [\text{H}^+][\text{OH}^-]$) were also calculated at a constant ionic strength of 0.10 M with NaCl in 50% dioxane-50% water mixture, based on measurements of $[\text{OH}^-]$ and pH in several experiments. The pK_w value obtained is 15.17 ± 0.2 . These data are in agreement with previous studies [39].

The titration and formation curves (\bar{j} -pH) of *N,N*-dimetil-*N'*-(4-chloroethyl)benzoyl thiourea were shown in Figure 1 as an example. Considering the consumption of

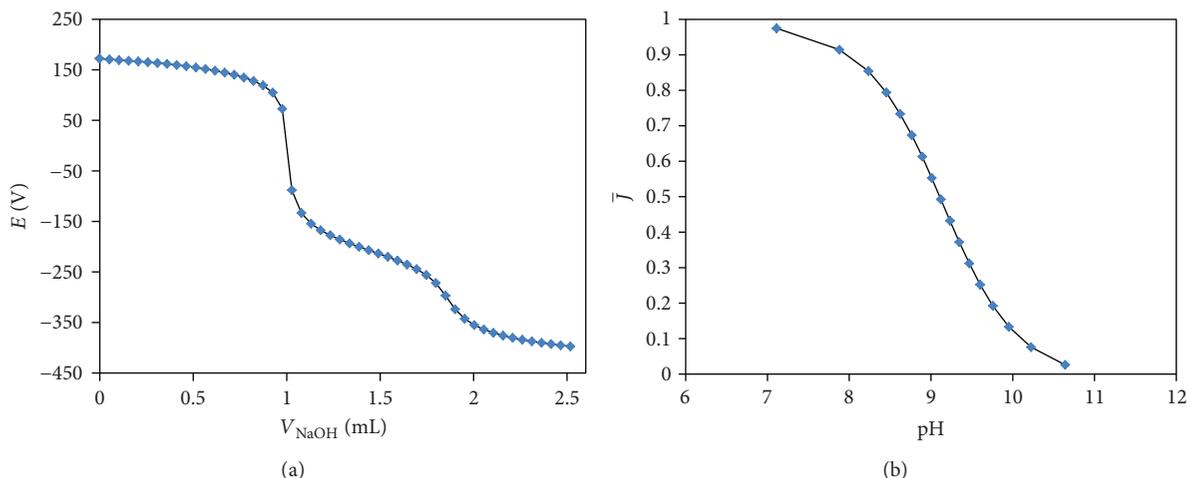
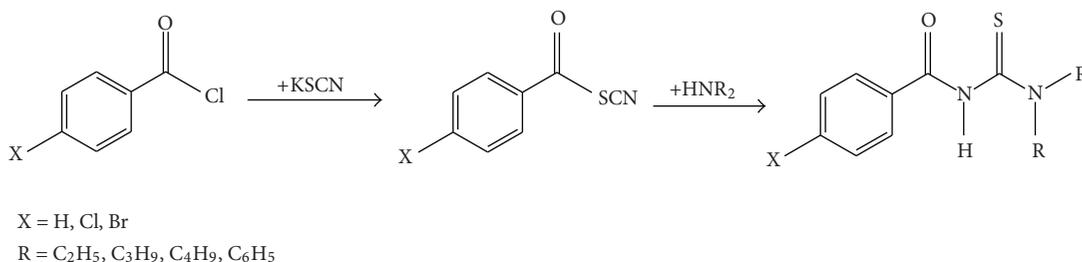


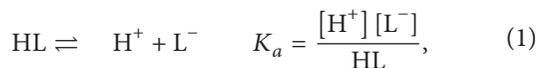
FIGURE 1: (a) The titration curve in presence of HCl and (b) the formation curve (\bar{j} -pH) of *N,N*-dimetil-*N'*-(4-chloroethyl)benzoyl thiourea) in 50% dioxan-50% water medium.



SCHEME 1

NaOH in the titration, two end points were observed in Figure 1(a); the first of them was corresponding to the added HCl in the medium. The second one is related with separation of one mole proton from the compound. This proton was considered to the N-H group. The stoichiometric calculations also show that only one mole proton per one mole benzoyl thiourea compound dissociates. The same case was also observed in other benzoyl thioureas studied. The formation curve (\bar{j} -pH) of *N,N*-dimetil-*N'*-(4-chloroethyl) benzoyl thiourea was given in Figure 1(b). The values of \bar{j} for the substituted benzoyl thiourea derivative compounds are between 0 and 1 and are related with the second end point. This means that these compounds have one dissociable proton (the hydrogen ion of the N-H group in structure).

The ionization equilibrium for the investigated derivatives is described by (1) and Scheme 2. Also, Scheme 2 shows the resonance structures of the ligand



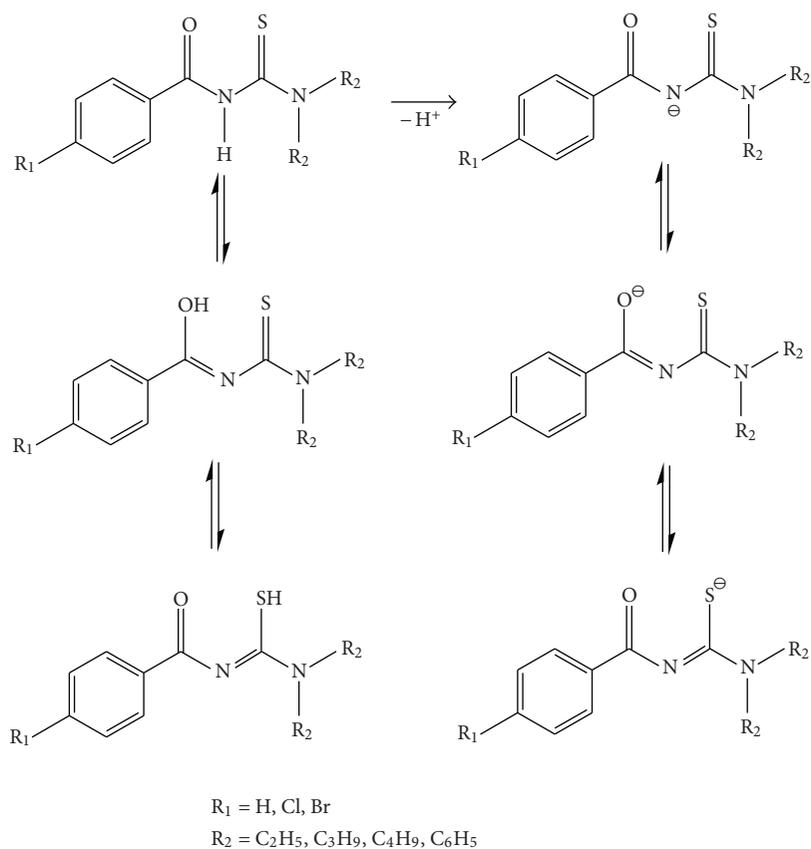
where HL is the ligand; K_a is the ionization constant; $[\text{H}^+]$ and $[\text{L}^-]$ are the ionic species.

Table 2 shows the stoichiometric ionization constant values determined using the BEST program and \bar{j} -pH plot for

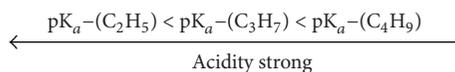
the substituted benzoyl thiourea derivatives in 50% dioxane-50% water mixture ($v:v$). The ones obtained by using the BEST software with the $\text{p}K_a$ values obtained from \bar{j} -pH plots are very close to each other. This shows to us that the use of \bar{j} -pH plots is suitable to calculate the ionization constants of this type of compounds. Each value given in Table 2 is the mean value of at least three experiments. The values given to the right of the \pm symbols are the deviations from the mean values.

The orders of $\text{p}K_a$ values for all thiourea derivatives are as expected in the light of steric, resonance and inductive effects of substituents. Furthermore, when the basicities of halogen derivatives of the same substitution pattern are compared, orders obtained ($4\text{-Br} < 4\text{-Cl} < 4\text{-H}$) can be explained by considering total electronic substituent effect (electron-withdrawing and electron-donating effects) except the 4-Br-Ph derivative [34, 40].

The effect of the substituents in benzoyl thiourea derivatives on ionization constants has been examined. The most important factor which affects the basicity and therefore the ionization constant of a compound is the structural effect. This effect can be explained by taking the electronic and steric effects of the alkyl groups investigated into account. Since alkyl groups are electron donating, one can expect



SCHEME 2



SCHEME 3

TABLE 2: Ionization constants ($\text{p}K_a$) determined by potentiometric method in 50% dioxane-50% water ($v:v$) mixture at $25.0 \pm 0.1^\circ\text{C}$ ($\mu = 0.10 \text{ M NaCl}$) of some benzoyl thiourea derivatives ($\sigma_{\text{fit}} \leq \pm 0.03$).

Group No	Sample No	Code	Compounds	BEST	$\bar{j} - \text{pH}$
I	1	4-H_Ph	<i>N,N</i> -diphenyl- <i>N'</i> -benzoylthiourea	9.23 ± 0.06	9.23 ± 0.08
	2	4-H_Et	<i>N,N</i> -diethyl- <i>N'</i> -benzoylthiourea	9.62 ± 0.05	9.62 ± 0.04
	3	4-H_Pr	<i>N,N</i> -di- <i>n</i> -propyl- <i>N'</i> -benzoylthiourea	9.80 ± 0.04	9.79 ± 0.09
	4	4-H_Bu	<i>N,N</i> -di- <i>n</i> -butyl- <i>N'</i> -benzoylthiourea	9.84 ± 0.06	9.84 ± 0.06
II	5	4-Cl_Ph	<i>N,N</i> -diphenyl- <i>N'</i> -(4-chlorobenzoyl)thiourea	8.79 ± 0.02	8.80 ± 0.07
	6	4-Cl_Et	<i>N,N</i> -diethyl- <i>N'</i> -(4-chlorobenzoyl)thiourea	9.10 ± 0.03	9.09 ± 0.03
	7	4-Cl_Pr	<i>N,N</i> -di- <i>n</i> -propyl- <i>N'</i> -(4-chlorobenzoyl)thiourea	9.33 ± 0.02	9.31 ± 0.02
	8	4-Cl_Bu	<i>N,N</i> -di- <i>n</i> -butyl- <i>N'</i> -(4-chlorobenzoyl)thiourea	9.39 ± 0.01	9.37 ± 0.01
III	9	4-Br_Ph	<i>N,N</i> -diphenyl- <i>N'</i> -(4-bromobenzoyl)thiourea	8.91 ± 0.02	8.93 ± 0.04
	10	4-Br_Et	<i>N,N</i> -diethyl- <i>N'</i> -(4-bromobenzoyl)thiourea	9.09 ± 0.01	9.08 ± 0.01
	11	4-Br_Pr	<i>N,N</i> -di- <i>n</i> -propyl- <i>N'</i> -(4-bromobenzoyl)thiourea	9.24 ± 0.01	9.23 ± 0.01
	12	4-Br_Bu	<i>N,N</i> -di- <i>n</i> -butyl- <i>N'</i> -(4-bromobenzoyl)thiourea	9.31 ± 0.01	9.30 ± 0.01

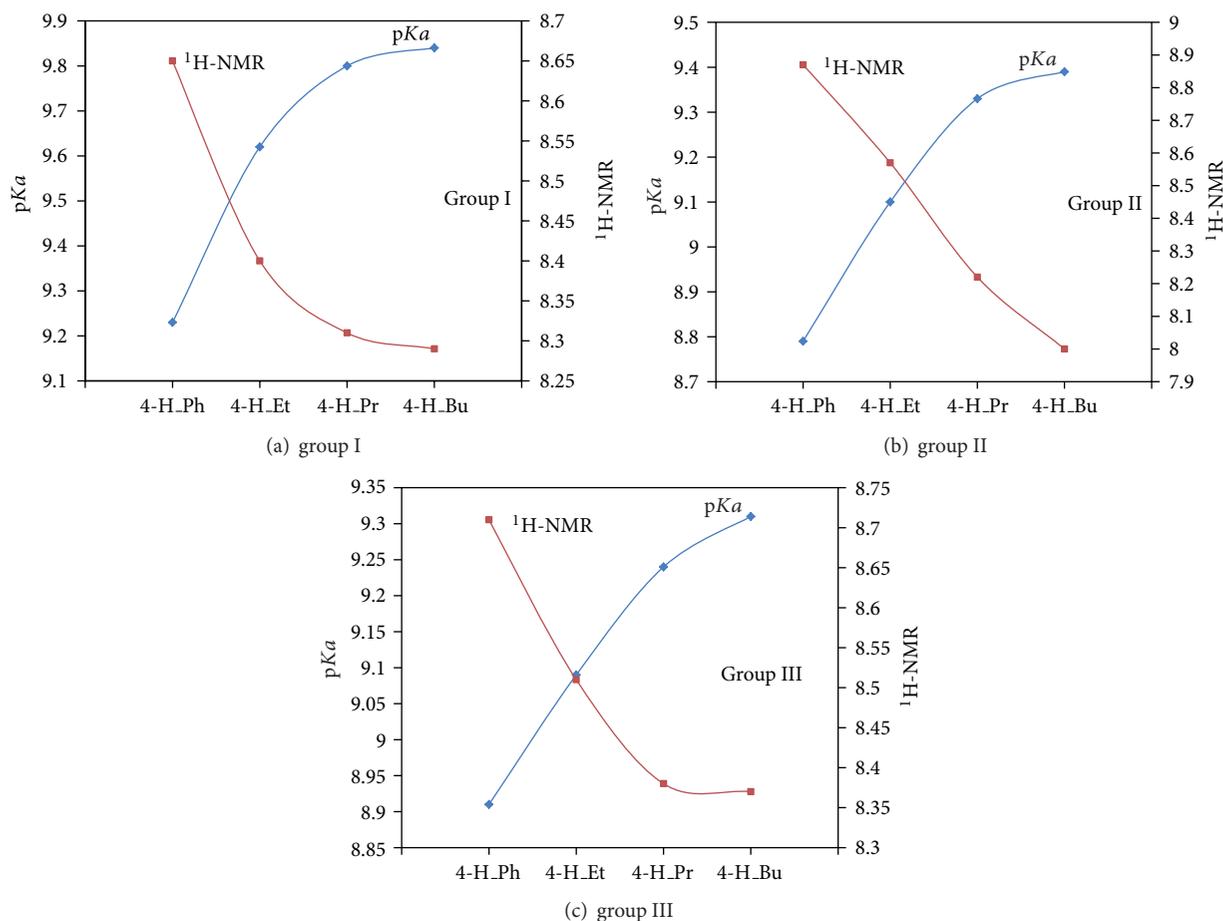


FIGURE 2: The relationship between the mean pK_a values calculated by using BEST software and $^1\text{H-NMR}$ chemical shift values of NH group for (a) group I, (b) group II and (c) group III (some benzoyl thiourea derivatives).

them to increase the ionization constant. As shown in Table 2, the acidity of the investigated compounds substituted with phenyl groups is greater than the other compounds attached with alkyl groups. A comparison of the basicities of ethyl, *n*-propyl, and *n*-butyl thiourea derivatives ($-\text{C}_2\text{H}_5 < -\text{C}_3\text{H}_7 < -\text{C}_4\text{H}_9$) (Scheme 3) shows that the *n*-butyl group is a more powerful electron-releasing group than the other groups in 50% dioxane-50% water mixture ($v:v$). This means that the acidity of benzoyl thiourea derivative compounds decreases, while the length of alkyl chain increases (Figure 2).

The variation of the acidity with chain length of alkyl groups can also be confirmed by $^1\text{H-NMR}$ spectra of the compounds because chemical shift value of N-H group gets greater if the alkyl chain gets shorter (see Figure 2).

4. Conclusion

Benzoyl thiourea derivatives are a class of compounds used for various analytical and biological applications. A good knowledge of the ionization of some benzoyl thiourea derivatives in dioxane-water media is highly desirable. For this reason, knowledge of the constants for the thiourea

derivatives is a prerequisite to gaining an understanding of their mechanisms of action in both chemical and biological processes. So, the ionization constants of some benzoyl thiourea derivatives were determined potentiometrically in 50% dioxane-50% water mixture. Also, the effect of structure on their ionization constants was discussed.

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