Acid Dissociation Constants of 5,5-Diphenylpyrrolidine N-Aroylthioureas and Stability Constants of their Pt(II) and Ni(II) Complexes in Acetonitrile-Water Hydroorganic Solvent

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Abstract
In this study, acid dissociation constants of 5,5-diphenylpyrrolidine N-aroylthiourea derivatives, exhibiting anti(myco)bacterial activity, were determined by potentiometric titration in 30% (v/v) acetonitrile-water hydroorganic solvent at 25 ± 0.1 °C, at an ionic background of 0.1 mol / L of NaCl using the HYPERQUAD computer program. Three acid dissociation constants were determined for each compound 1a-e and we suggest that these acid dissociation constants are related to the carboxyl, enol and enthiol groups. Stability constants of their Pt(II) and Ni(II) complexes were also determined by potentiometric titration under the same conditions stated above using the HYPERQUAD computer program. The ligands behave as bidentate and bind to the metal atom via the S and O atoms. In various pH conditions, the different complex forms were formulated as ML₂, MHL₂, MH₂L₂, MH₃L₂, MH₄L₂ and MH₅L₂ between Pt²⁺/Ni²⁺ ions and 5,5-diphenylpyrrolidine N-aroylthioureas. Stability constants of the complexes show that the ligands 1a-e form complexes with Pt(II) and Ni(II) metals as 2:1. The stability of the complexes formed by the ligands and platinum were found to follow the order: 3d > 3a > 3e > 3c > 3b. The stability of the complexes formed by the ligands and nickel were found to follow the order: 4d > 4c > 4a > 4b > 4e. As a result, generally the platinum complexes formed with these ligands are more stable than their nickel complexes.

Keywords—Acid dissociation constant, Aroylthiourea, 5,5-Diphenylpyrrolidine, Nickel, Platinum, Stability constant

1 Introduction
Physicochemical parameters contain critical information to understand the nature of molecules and one of them is the acid dissociation constant (pKₐ) [1]. pKₐ is an indispensable parameter for the pharmaceutical scientist because it provides information about many features of molecules such as acidity, solubility and hydrogen bonding capacity [2-4]. The majority of drugs are organic-based molecules and numerous new organic molecules containing acidic or basic groups have been synthesized for the determination of their pharmacological activities. Most of the pharmacologically active compounds contain one or more ionizable groups and are capable of gaining and/or losing a proton in aqueous media [2, 5-7]. pKₐ values help to predict the degree of ionization of pharmacologically active molecules in different pH regions of the living systems [2, 6]. Furthermore, pKₐ values are cru-
cial for drug design and molecular modeling studies [8, 9], selection of the optimum conditions for analysis methods [6] and understanding of the stereochemical structures of active centers of enzymes [10]. For these reasons, many studies have been reported about the determination of $pK_a$ values of pharmacological active compounds by using various analytical methods such as potentiometry [1, 11], spectroscopy [6, 12], chromatography [13, 14] and electrophoresis [15, 16] etc.

The stability constant is another physicochemical parameter which contains very critical information for drug development. The stability constant provides information to understand the formation of bonds in a complex, the bonding mechanisms and the stability of the complex in different pH conditions, to determine the concentration of the components present in a mixture in equilibrium and to reveal the presence of complexes in media [17, 18]. Furthermore, the mechanism of anticancer activity described by dissociation of the ligand and subsequent binding to DNA, resulting in antitumor activity, is also associated with the stability of the organometallic pharmaceuticals [19].

Transition metals play a vital role in living systems and many pharmaceuticals containing transition metals such as platinum, nickel, ruthenium, gold, copper, cobalt, zinc and iron are widely used in the clinical field. Moreover, transition metals have been intensively studied in bioorganometallic chemistry to develop new metal based drugs [20, 21]. Many studies have been reported in the literature about the determination of stability constants of transition metal complexes with various organic ligands with potential pharmacological activity [22-26]. The ability of complex formation between organic ligands and transition metals depends on a number of factors, such as the type of solvent, pH value of the solution and temperature [19, 27].

$N$-Substituted-$N'$-aryloyl(thiourea) derivatives with general formula $R_1C(O)NHC(S)NR_2R_3$ have been extensively studied as ligands in bioorganometallic and coordination chemistry [28], due to their wide range of pharmacological activities such as antibacterial, antifungal [29, 30], antitubercular [31] anticancer [32] and carbonic anhydrase inhibitor [33] activities, and due to the carbonyl and thio-carbonyl groups in their structures, which have a huge bonding potential [28]. Many metal complexes such as Ni(II) [34-36], Pd(II) [36-38], Pt(II) [31, 38], Cu(II) [35, 36] and Co(III) [39, 40] of $N$-aryloylthiourea derivatives have been synthesized within the scope of their wide range of pharmacological properties. Furthermore, these types of ligands have been studied in pharmaceutical chemistry as bioactive molecules [41] and intermediate molecules for the synthesis of potential bioactive heterocyclic compounds [42-44]. The pyrrolidine ring is an indispensable scaffold for drug research. The pyrrolidine ring is present in many drug molecules such as procyclidine [45] and bepridil [46]. Pyrrolidines bearing modifiable substituents can be easily synthesized regio- and stereospecifically via a 1,3-dipolar cycloaddition reaction [47-53]. Grigg et al. [47-50] and Najera et al [51-53] have published many studies about the synthesis of pyrrolidine derivatives with potential pharmacological properties.

In the previous work [54], we have reported the synthesis and antimicrobial activity of a series of 5,5-diphenylpyrrolidine $N$-aryloylthioureas. In this study, the determination of acid dissociation constants of 5,5-diphenylpyrrolidine $N$-aryloylthiourea derivatives and the stability constants of their Pt(II) and Ni(II) complexes in acetonitrile-water hydroorganic solvent are reported.

2 Materials and Methods

2.1 Apparatus and Materials. The ligands were prepared according to a literature method [54]. All reagents had analytical grade and were used without further purification. Potassium hydrogen phthalate (Fluka) and sodium tetraborate (Fluka), required for calibration of the electrode systems, were dried and used for the preparation of 0.05 mol / kg potassium hydrogen phthalate and 0.01 mol / kg sodium tetraborate solutions. The ligand solutions were prepared as $1.10^{-2}$ mol / L in acetonitrile and a 0.025 mol / L NaOH solution served as titrant. Solutions of Pt(II) and Ni(II) ions ($1.10^{-3}$ mol / L) in deionized water were prepared from K$_2$PtCl$_4$ and NiCl$_2$·6H$_2$O, respectively, and then standard-
ized with ethylenediaminetetraacetic acid (EDTA) [55]. 0.1 mol / L HCl (Titrisol® Merck) and 1.0 mol / L NaCl (Merck) stock solutions were also prepared. An aquaMAX™-Ultra water purification system (Young Lin Inst.) was used for obtaining deionized water with a resistance of 18.2 MΩ.cm.

Titration was performed by using set of the Molspin pH-mV-meter, with an Orion 8102BNUWP ROSS ultra combination pH electrode having an automatic micro burette, and the system was controlled by a PC computer. During the titrations, the temperature in the double-wall glass titration vessel was controlled using a thermostat (DIGITERM 100, SELECTA) and kept at 25.0 ± 0.1 °C, and the vessel solution was stirred. Calibration of the combination pH electrode was performed by using the buffer solutions of pH 4.005 (potassium hydrogen phthalate) and 9.018 (sodium tetraborate) at 25.0 ± 0.1 °C in water as required in the instructions of the Molspin Manual [56]. After then, the combination pH electrode was calibrated by using the buffer solution of pH 5.015 (potassium hydrogen phthalate) at 25.0 ± 0.1 °C in 30 % (w/w) acetonitrile-water [57]. During all of the titrations, the titration vessel was purged through nitrogen (99.9 %). In this study, HYPERQUAD, one of the most useful computer programs which are used to determine acid dissociation constants with high precision and accuracy from potentiometric data [58], was used for calculate the acid dissociation constants and stability constants from potentiometric data.

2.2 Procedure. As described in our previous study [59], the potentiometric titrations were performed in the double-wall glass titration vessel, kept at 25.0 ± 0.1 °C, the titration solution was magnetically stirred. Before and after each titration process, the double-wall glass titration vessel was rinsed and dried. The titration vessel was capped by a lid, containing three holes. Air bubbles were removed during dropwise addition of the alkali solution. The syringe was rinsed with deionized water and several times with the alkali solution before adding the alkali solution. In the first part of this study, to determine of the pKₐ values of 1a-e in 30% (v/v) acetonitrile-water mixture, added 10 mL of the ligand solution, 0.5 mL of the HCl solution and 5 mL of the NaCl solution from their stock solutions to the titration cell. After that, 5 mL acetonitrile added to titration cell and the titration cell was filled to 50.00 mL with deionized water. In the second part of this study, to determine of the stability constants of the Pt(II) and Ni(II) complexes of 1a-e ligands in 30% (v/v) acetonitrile-water mixture, added 10 mL of the ligand solution, 5 mL of the K₂PtCl₄ or NiCl₂-6H₂O solution, 0.5 mL of the HCl solution and 5 mL of the NaCl solution from their stock solutions to the titration cell. After that, 5 mL acetonitrile added to titration cell and the titration cell was filled to 50.00 mL with deionized water. The data were obtained by titrating 50.00 mL of the prepared titration cell with standardized NaOH solution and three titrations were performed for each compound. Standard deviations quoted only refer to random errors. Volume increment of the NaOH solution was 0.03 mL and for each titration process, 200 data points were obtained. The pKₐ value, defined as –log[H⁺][OH⁻] for the aqueous system was obtained as 13.98 at the ionic strength employed.

3 Results and Discussion

3.1 Protonation Constants of the Ligands

Acid dissociation constants of 5,5-diphenylpyrrolidine N-arylthioureas 1a-e were determined potentiometrically at 25.0 ± 0.1 °C in a 30% (v/v) acetonitrile-water hydroorganic solvent system. Solutions of the ligands were prepared in acidic media and NaCl solution was used to keep the ionic strength constant at 0.1. As a result of the calculations, three different pKₐ values were found for each ligand. pKₐa, pKₐb and pKₐc values were obtained in a range of 3.49 ± 0.07 - 5.19 ± 0.04, 6.96 ± 0.03 - 7.84 ± 0.04 and 8.29 ± 0.02 - 9.94 ± 0.08 respectively. We proposed that pKₐa values arise due to carboxylic acid formation by hydrolysis of the methyl ester of 1a-e in acidic aqueous media (Fig. 1) and the result for acidic aqueous media is consistent with the literature [60]. The formation of carboxylic acid derivatives 2a-e from hydrolysis of methyl esters of 1a-e in acidic media is shown in Fig. 1. According to the protonation of 2a-e in acidic aqueous media, given in Fig. 2, the 5,5-diphenylpyrrolidine N-arylthioureas containing...
carboxylic acid groups (2a-e) may have five ionizable centers as two carboxyl groups, enthiol, enol and amide NH groups.

According to the obtained $pK_a$ values, it can be suggested that $pK_1$ value is related to the carboxyl group, $pK_2$ and $pK_3$ values are related to the enol and enthiol group respectively. The expected $pK_a$ value range of the amide NH group of 2a-e is around 10-12. Difference in the structure of 2a-e originates from the substituent at the 4-position of the aromatic ring of the aroyl group and 2a-e, given alphabetically, have at that position $H$, $C(CH_3)_3$, $OCH_3$, $Cl$ and $Ph$ respectively. If we examine the changing $pK_a$ values of 1a-e and make comments about the $pK_a$ values among themselves; in the presence of $OCH_3$ group as substituent, the highest $pK_a$ value was obtained and decreased significantly the acidity of 1c with $5.19 \pm 0.04$. The lowest $pK_a$ value, $3.49 \pm 0.07$, was obtained for 2b containing a C(CH$_3$)$_3$ group as substituent. We can anticipate that the C(CH$_3$)$_3$ group should increase the $pK_a$ value. This unexpected result can be explained by the fact that the substituents are at a distance from the carboxyl groups, so the changing $pK_a$ values stem from intra(inter)-molecular interactions. It can be also said that the carboxyl groups interact with the solvent system as another explanation. When comparing the $pK_a$ values of 2a-e, the lowest $pK_a$ value, $6.96 \pm 0.03$, was obtained for 2d containing a Cl group as substituent as expected. The highest $pK_a$ value, $7.84 \pm 0.04$, was obtained in the presence of an $OCH_3$ group as substituent. When comparing the $pK_a$ values of 2a-e, the lowest $pK_a$ value was obtained for 2d with $8.29 \pm 0.02$ in the presence of a Cl group as substituent, and the highest $pK_a$ value was obtained for 2e with $9.94 \pm 0.08$ in the presence of a phenyl group as substituent. $pK_a$ values for each C(O)NHC(S)N type of ligands in a dioxane-water (50% (v/v)) mixture have been reported [61]. In the previous study [59], we reported that three acid dissociation constants exist for each fused ring thiohydantoin-pyrrolidine derivative having a C(O)NHC(S)N cyclic moiety and suggested that the $pK_a$ values were related to their carboxyl, enol and amide NH groups. Herein, we have reported that three $pK_a$ values for each 5,5-diphenylpyrroloidine N-aryltioureas were determined in acetonitrile-water hydroorganic solvent by using the HYPERQUAD computer programme.

\[ L_{H_n} \rightleftharpoons L_{H_{n+1}} + H \] (1)

and the deprotonation constants ($K_a$) are given by equation 2:

\[ K_n = \frac{[LH_{n+1}][H]}{[LH_n]} \] (2)
Fig. 2 A scheme showing the proposed mechanism for protonation of 5,5-diphenylpyrrolidine N-aryloxythioureas 2a-e.

The protonated ligand loses its protons with increasing pH and converts into another species of the ligand (see Fig. 3). The titration curves of 2a-e and the distribution curves of species H in a 30% (v/v) acetonitrile-water mixture are given in Fig. 3.
Acid dissociation constants of 2a-e were computed from data, obtained by potentiometric titrations in acidic media, by using the HYPERQUAD computer program. The determined acid dissociation constants of 2a-e are given in Table 1.

### Table 1 pKₐ values of the ligands (30% (v/v) acetonitrile-water mixture, 25.0 ±0.1 °C, I=0.1 mol / L by NaCl) (log⁰β is cumulative acid dissociation constants)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Species</th>
<th>log⁰β</th>
<th>pKₐ Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LH₁</td>
<td>19.88±0.03</td>
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<tr>
<td>2a</td>
<td>LH₂</td>
<td>16.33±0.03</td>
<td>7.43±0.03</td>
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<td></td>
<td>LH</td>
<td>8.90±0.03</td>
<td>8.90±0.03</td>
</tr>
<tr>
<td></td>
<td>LH₃</td>
<td>19.79±0.03</td>
<td>3.49±0.07</td>
</tr>
<tr>
<td>2b</td>
<td>LH₂</td>
<td>16.30±0.07</td>
<td>7.25±0.07</td>
</tr>
<tr>
<td></td>
<td>LH</td>
<td>9.05±0.05</td>
<td>9.05±0.05</td>
</tr>
<tr>
<td></td>
<td>LH₃</td>
<td>22.10±0.03</td>
<td>5.19±0.04</td>
</tr>
<tr>
<td>2c</td>
<td>LH₂</td>
<td>16.91±0.03</td>
<td>7.84±0.04</td>
</tr>
<tr>
<td></td>
<td>LH</td>
<td>9.07±0.04</td>
<td>9.07±0.04</td>
</tr>
<tr>
<td></td>
<td>LH₁</td>
<td>18.98±0.05</td>
<td>3.73±0.05</td>
</tr>
<tr>
<td>2d</td>
<td>LH₂</td>
<td>15.25±0.03</td>
<td>6.96±0.03</td>
</tr>
<tr>
<td></td>
<td>LH</td>
<td>8.29±0.02</td>
<td>8.29±0.02</td>
</tr>
</tbody>
</table>

3.2 Stability Constants

The stability constants of 5,5-diphenylpyrrolidine N-aryloxyurea 1a-e with the Pt(II) and Ni(II) ions in 30% (v/v) acetonitrile-water hydroorganic solution were interpreted with the HYPERQUAD computer program.

The cumulative stability constants (βₐmllh) are defined in the following equations 3 and 4 [62]:

\[ mM + IL + hH \rightarrow MmLHh \]  
(3)

\[ \beta_{mllh} = \frac{[M_mLHL_h]}{[M]^m[L]^l[H]^h} \]  
(4)

M, L and H denotes the metal ion, the ligand and H⁺ respectively. Respective stoichiometric coefficients are specified as m, l and h. Pt(II)-ligand and Ni(II)-ligand titration curves are given in Fig. 4 and Fig. 5, respectively.

A number of species formulated as PtH₅L₂, PtH₄L₂, PtH₃L₂, PtHL₂, PtL and PtL₃ of Pt(II)-2a-e are formed in acetonitrile-water solution at the different pH ranges. Three different species of 3a exist during the complexation of the Pt(II) ions with 2a. The first occurring type is PtH₅L₂ in acidic media and disappears around pH 6. During addition of base to the titration cell, PtH₃L₂ species also begin to exist in addition to PtH₂L₂ species in the solution and up to pH 6, where it reaches a maximal occurrence of about 95% and the species disappears around pH 10. PtL₂ species start to exist around pH 7 and reaches a maximal occurrence of about 100% over pH 10 and it is the only species in the solution at a pH above 10. During the complexation of the Pt(II) ions with 2b, six different species of 3b were observed. The first occurring type is PtH₅L₂ in acidic media and during addition of base to the titration cell, PtH₄L₂, PtH₃L₂, PtHL₂, PtL and PtL₂ species, respectively, exist and these species reach a maximal occurrence of about 40%, 95%, 80%, 35% and 100%, respectively, at the appropriate pH points. PtH₃L₂ and PtH₂L₂ species...
occur in acidic media and disappear before pH 6. PtH₃L₂ and PtH₄L₂ occur in both acidic and basic media, but PtHL₂ and PtL₂ species only occur in basic media. PtL₂ species is the only species in the solution at a pH above 11. During the complexation of the Pt(II) ions and 2c, six different complex species of 3c exist, by analogy with 3b. The first occurring type is also the PtH₃L₂ species in acidic media and during addition of base to the titration cell, PtH₄L₂, PtH₅L₂, PtHL₂ and PtL₂ species begin to exist, respectively, and the species reach a maximal occurrence of about 75%, 80%, 60%, 58% and 95%, respectively at the appropriate pH points. The PtL₂ species is also the only species in the solution at a pH above 11 in the complexation of the Pt(II) ions and 2c. The marked differences between complexation of Pt(II) ions with 2b or 2c are the maximal occurrence of the species, and the PtH₃L₂ species of 3c disappears around pH 7 instead of pH 6. Five species formulated as PtH₄L₂, PtH₅L₂, PtHL₂, PtL₂ and PtL₂ of 3d occur during the complexation of the Pt(II) ions and 2d. PtH₄L₂ and PtH₅L₂ species occur and disappear in acidic media. PtH₄L₂ and PtHL₂ occur in both acidic and basic media, but PtL₂ species only occur in basic media. Four different species of 3e occur during the complexation of the Pt(II) ions and 2e. The first occurring type is PtH₃L₂ in acidic media and disappears around pH 9. During addition of base to the titration cell, other species formulated as PtH₄L₂, PtHL₂ and PtL₂, having a maximal occurrence of about 75%, 15% and 95%, respectively, at the appropriate pH points, of 3e begin to exist in the media. All the species exist in basic media, but PtHL₂ and PtL₂ are never absent in acidic media. The PtL₂ is the only species in the solution at a pH above 10. According to the results, to obtain only PtL₂ species of Pt(II) complexes of the 5,5-diphenylpyrrolidine N-ary thioureas in 30% (v/v) acetonitrile-water hydroorganic solution, the pH value of the media must be higher than approximately pH 11 (Fig. 4).
A number of species, formulated as NiH₃L₂, NiH₄L₂, NiH₅L₂, NiH₆L₂, NiHL₂, NiL₂ and NiH₄L₂, of Ni(II)-2a-e are observed in the media at the different pH ranges. Six species, formulated as NiH₃L₂, NiH₄L₂, NiH₅L₂, NiH₆L₂, NiHL₂ and NiL₂, of 4a are observed during the complexation of the Ni(II) ions with 2a. The NiH₃L₂ species is observed only in acidic media and disappears around pH 6. During addition of base to the titration cell, NiH₄L₂, NiH₅L₂ and NiH₆L₂ species, respectively, are observed in both acidic and basic media and their maximal occurrence is around 95%, 35% and 90%, respectively, at the appropriate pH points. Additionally, NiHL₂ and NiL₂ species were observed only in basic media and these species reached a maximal occurrence of about 40% and 95%, respectively, at the pH value of approximately 9.5 and 11, respectively. During the complexation of the Ni(II) ions with 2b, 2c, 2d, seven species were observed, formulated as NiH₃L₂, NiH₄L₂, NiH₅L₂, NiH₆L₂, NiHL₂, NiL₂ and NiH₄L₂, related to 4b, 4c, 4d complexes, respectively. NiH₃L₂ species of 4b, 4c, 4d complexes run out around pH 7. NiH₄L₂ and NiH₅L₂ species of 4b, 4c, 4d complexes were observed both in the acidic and basic media. NiHL₂ and NiL₂ species of 4b, 4c, 4d complexes were observed only in the basic media and NiH₄L₂ species were observed for the three compounds above pH 11. Five different species of 4e occur during the complexation of the Ni(II) ions and 2e. The first occurring type is NiH₃L₂ in acidic media and disappears around pH 7. During addition of base to the titration cell, other species formulated as NiH₄L₂, NiH₅L₂, NiH₆L₂ and NiL₂, having a maximal occurrence of about 30%, 90%, 80% and 95%, respectively, at the appropriate pH points, of 4e begin to exist in the media. All the species exist in the basic media, but NiH₄L₂ and NiL₂ were never absent in acidic media (Fig. 5). Furthermore, the NiHL₂ species of 4e could not be determined in these conditions.
Fig. 5 Potentiometric titration curves (n) of Ni(II) complexes with the ligands and distribution curves of Ni(II) complexes with the ligands [(o) 4a, (p) 4b,
When we evaluated the stability constants of the Pt(II) and Ni(II) complexes (Table 2), the stability constants of the PtL₂ and NiL₂ species of 3a-e and 4a-e complexes, they can be sorted as 3d > 3a > 3e > 3c > 3b and 4d > 4c > 4a > 4b > 4e. These results show that bonding a Cl as substituent at the 4-position of the aromatic ring increased the stability of the complex more than other substituents. In other words, to bind electron-withdrawing groups to the aromatic ring of the N-aryloxythiourea moiety increases the stability of Pt(II) and Ni(II) complexes with 5,5-diphenylpyrrolidine N-aryloxythioureas.

<table>
<thead>
<tr>
<th>Complex</th>
<th>ML₂</th>
<th>MHL₂</th>
<th>MH₂L₂</th>
<th>MH₃L₂</th>
<th>MH₄L₂</th>
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<td>38.49±0.07</td>
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<tr>
<td>3b</td>
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<td>30.12±0.06</td>
<td>38.94±0.06</td>
<td>45.89±0.06</td>
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<td>3c</td>
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<td>3d</td>
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<td>35.56±0.03</td>
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<td>32.50±0.10</td>
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<td>50.86±0.18</td>
<td>56.99±0.21</td>
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</table>

4 Conclusion

In conclusion, the acid dissociation constants of a series of 5,5-diphenylpyrrolidine N-aryloxythioureas having anti(myco)bacterial activity and the stability constants of their Pt(II) and Ni(II) complexes were potentiometrically determined. Three acid dissociation constants, containing useful information for many different scientific areas, were interpreted with the HYPERQUAD computer program. The determination of the pKₐ values was carried out in 30% (v/v) acetonitrile-water hydroorganic solvent at 25 ± 0.1°C, at ionic strength of 0.1. Under these conditions, pKₐ values for 1a-e were calculated and determined three pKₐ values for the ionizable species of N-Substituted-N'-aryloxythiourea type compounds. Furthermore, the stability constants show that 5,5-diphenylpyrrolidine N-aryloxythiourea ligands form stable complexes with Pt(II) and Ni(II) as 2:1 and other protonated forms of Pt(II) and Ni(II) complexes in different range of the pH value.

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6 References


