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Potentiometric Studies on Nickel(II), Copper(II) and Zinc(II) Metal Complexes with New Schiff Bases Containing Cyclobutane and Thiazole Groups in 60% Dioxane-Water Mixture

Yüksel Altun,,[a] Fitnat Köseoğlu,[a] Havva Demirelli,[a] İbrahim Yılmaz,[b] Alaattin Çukurovalı[b] and Nusret Kavak[a]*

[a]*Department of Chemistry, Faculty of Gazi Education, University of Gazi, Ankara, Turkey*

[b]*Department of Chemistry, Faculty of Arts and Sciences, University of Fırat, Elazığ, Turkey*

Neste estudo são investigados potenciometricamente os equilíbrios ácido-base de bases de Schiff contendo ciclobutano e tiazol como grupos funcionais e de seus complexos de cobre(II), níquel(II) e zinco(II) em dioxano-água, 60% em média, a 25,0 ± 0,1 °C e com I = 0,10 mol L^{-1} ($NaClO_4$). Os valores das constantes de protonação, $\log K_{OH}$, $\log K_{NH(1)}$ e $\log K_{NH(2)}$, determinados no presente estudo, estão relacionados com a protonação do átomo de oxigênio do fenolato, do átomo de nitrogênio no anel tiazólico e do átomo de nitrogênio imínico, respectivamente. A variação das constantes de protonação das bases de Schiff foi interpretada em função de fatores estruturais. Estas bases formam complexos estáveis com os íons cobre(II), níquel(II) e zinco(II). Não foi encontrada nenhuma correlação significativa entre a basicidade das bases de Schiff e as constantes de estabilidade dos seus complexos. As estabilidades dos complexos seguem a tendência: cobre(II) > níquel(II) > zinco(II), que está de acordo com a série de Irving-Williams.

The acid-base equilibria of Schiff bases containing cyclobutane and thiazole functional groups and their copper(II), nickel(II) and zinc(II) complexes were investigated potentiometrically in 60% dioxane-water media at 25.0 ± 0.1 °C and I = 0.10 mol L^{-1} $NaClO_4$. The values of the protonation constants determined in this study, $\log K_{OH}$, $\log K_{NH(1)}$ and $\log K_{NH(2)}$, are related to the protonation of the phenolate oxygen atom, the nitrogen atom on the thiazole ring and the imine nitrogen atom, respectively. The variation of the protonation constants of the Schiff bases was interpreted on the basis of structural factors. The Schiff bases form stable complexes with copper(II), nickel(II) and zinc(II) metal ions. There was not a meaningful correlation between the basicity of the Schiff bases and the stability constants of their complexes. Complex stabilities follow the trend copper(II) > nickel(II) > zinc(II), which is in agreement with the Irving-Williams series.

Keywords: cyclobutane, thiazole, protonation constants, stability constants

Introduction

The ligands used in this work have three different and important functionalities: Schiff base character, thiazole and cyclobutane. It has been shown that Schiff base complexes derived from 4-hydroxysalicylaldehyde and amines have strong anticancer activity, e.g. in Ehrlich ascites carcinoma (EAC).[1] The chemistry of thiazoles and their derivatives has attracted the attention of chemists, since they are of importance in biological systems as anti-inflammatory or analgesic agents and as inhibitors of lipoxygenase activities.[2-4] Furthermore, thiazole is found in vitamin B1 and in the cocarboxylase coenzyme. The penicillin molecule also contains a thiazolidine ring.[5] It is also well known that 3-substituted cyclobutane carboxylic acid derivatives exhibit anti-inflammatory and antidepressant activities,[6,7] as well as liquid crystal properties.[8]

The extensive synthetic possibilities of these Schiff bases, due to the presence of several reaction sites, hold promise for the preparation of new thiazole derivatives and determination of their acidity (or basicity) and the stability of their metal complexes. In the field of industrial pharmacy, perhaps the most important physicochemical characteristics of substances containing important functional groups are

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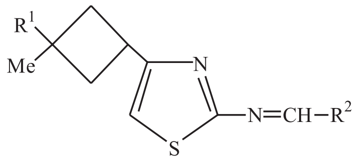
*e-mail: yukseloz@gazi.edu.tr

their protonation and stability constants. This knowledge may eventually help to throw some light on the inactivation of essential trace metals in biological systems.

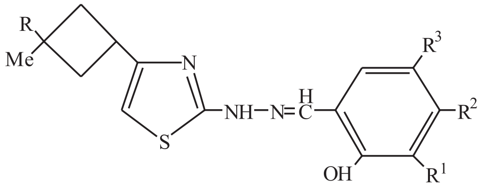
A survey of the literature shows no research on Schiff bases including cyclobutane, thiazole and azomethine functional groups in the same molecule, but there are many works concerning Schiff base derivatives including different functional groups.[9-24] We have previously examined the synthesis, antimicrobial activity and characterization (by IR, ^{1}H NMR, TGA, DSC and magnetic susceptibility) of the Schiff bases shown in Tables 1 and 2 and several of their transition metal complexes. These studies have already been reported.[25-36] The present work deals with the determination of the stoichiometric protonation constants of these Schiff bases and the stoichiometric stability constants of their Ni^{2+}, Cu^{2+} and Zn^{2+} complexes by the potentiometric titration method, employing 60% dioxane:water media and an ionic strength of 0.10 mol L^{-1} sodium perchlorate at 25.0 ± 0.1 °C. Data obtained from titrations were evaluated by the computer program BEST.[37] In addition, the effects of substituents on the protonation and stability constants of the Schiff bases have been investigated.

Table 1. First group Schiff bases studied in this work



Code	R^1	R^2	Schiff Bases
L^1	Phenyl	2-hydroxy-5-bromobenzaldehyde	4-(1-phenyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-5-bromobenzylideneimino) thiazole
L^2	Phenyl	2-hydroxy-1-naptalaldehyde	4-(1-phenyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-5-bromonaphtylideneimino) thiazole

Table 2. Second group Schiff bases studied in this work



Code	R	R^1	R^2	R^3	Schiff Bases
L^3	Phenyl	H	H	H	4-(1-phenyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxybenzylidenehydrazino) thiazole
L^4	*p*-Xylyl	H	H	H	4-(1-xylyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxybenzylidenehydrazino) thiazole
L^5	Mesityl	H	H	H	4-(1-mesityl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxybenzylidenehydrazino) thiazole
L^6	Phenyl	H	H	Br	4-(1-phenyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-5-bromobenzylidenehydrazino) thiazole
L^7	*p*-Xylyl	H	H	Br	4-(1-*p*-xylyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-5-bromobenzylidenehydrazino) thiazole
L^8	Mesityl	H	H	Br	4-(1-mesityl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-5-bromobenzylidenehydrazino) thiazole
L^9	Phenyl	OCH_3	H	H	4-(1-phenyl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-3-methoxybenzylidenehydrazino) thiazole
L^{10}	*p*-Xylyl	OCH_3	H	H	4-(1-*p*-xylyl-1-methylcyclobuthyl-3-yl)-2-(2-3-methoxybenzylidenehydrazino) thiazole
L^{11}	Mesityl	OCH_3	H	H	4-(1-mesityl-1-methylcyclobuthyl-3-yl)-2-(2-hydroxy-3-methoxybenzylidenehydrazino) thiazole
L^{12}	Phenyl	H	OH	H	4-(1-phenyl-1-methylcyclobuthyl-3-yl)-2-(2,4-dihydroxybenzylidenehydrazino) thiazole
L^{13}	*p*-Xylyl	H	OH	H	4-(1-*p*-xylyl-1-methylcyclobuthyl-3-yl)-2-(2,4-dihydroxybenzylidenehydrazino) thiazole
L^{14}	Mesityl	H	OH	H	4-(1-mesityl-1-methylcyclobuthyl-3-yl)-2-(2,4-dihydroxybenzylidenehydrazino) thiazole

Experimental

Reagents

2-Hydroxy-1-naphtaldehyde, thiourea, thiosemicarbazid and all substituted benzaldehydes were purchased from Merck and used as received. Approximately 0.03 mol L^{-1} Schiff base stock solutions were prepared in dioxane purified by a published method.[38] Ultra pure, freshly boiled water, whose conductivity did not exceed 0.05 µS cm^{-1}, was used as aqueous medium as well as for the preparation of dioxane-water mixtures. All stock solutions of $Cu(ClO_4)_2$, $Ni(ClO_4)_2$, $Zn(ClO_4)_2$, sodium perchlorate, perchloric acid and potassium hydrogen phthalate (analytical reagent grade, Merck) were prepared in water. Stock solutions of $Cu(ClO_4)_2$, $Ni(ClO_4)_2$ and $Zn(ClO_4)_2$ were standardized by EDTA titrations, using a suitable indicator.[39] Sodium perchlorate was used as a background electrolyte. Carbonate-free sodium hydroxide solutions were prepared under a nitrogen atmosphere in 60% (v/v) dioxane-water mixtures. The ionic strength of each NaOH solution was adjusted to 0.10 mol L^{-1} by addition of $NaClO_4$. The alkali titre and absence of carbonate were periodically checked by pH-metry, using the appropriate Gran function[40] against primary standard oven-dried potassium hydrogen phthalate. Acid solutions prepared from perchloric acid were titrated against standardized sodium hydroxide.[40]

Apparatus

The pH-metric measurements were made with an Orion 940 meter (resolution 0.1 mV, accuracy 0.2 µL), equipped with a Mettler Toledo Inlab 412 combined glass electrode and Orion 960 automatic titrator. The electrode was modified by replacing its aqueous KCl solution by the mixture of 0.01 mol L^{-1} NaCl + 0.09 mol L^{-1} $NaClO_4$. The temperature was maintained constant inside the cell, at 25.0 ± 0.1 °C, by circulating water from an external thermostat (Haake, precision ± 0.1 °). The apparatus is described in detail elsewhere.[41, 42]

Procedure

The protonation constants and the stability constants of the Schiff bases and their complexes were determined by means of the data obtained from potentiometric titrations in 60% (v/v) dioxane-water mixtures at 25.0 ± 0.1 °C and 0.1 mol L^{-1} ionic strength ($NaClO_4$). For this purpose, in the first step, the potentiometric cell was calibrated before each experiment to obtain pH ($-\log[H^+]$) values for the titration medium by measuring the emf of the cell ($E(mV) = E^o_{cell} + S\log[H^+] + E_j$, where S = electrode slope) in the course of the titrations. The standard potential in this cell, E^o_{cell}, was evaluated by means of series of emf measurements of $HClO_4$ solutions and the method of Gran from titrations of diluted $HClO_4$ solutions using NaOH solutions in 60% dioxane-water mixture as the titrant, and evaluation of the calibration parameters using multiparametric data fitting or Gran plots.[40,43] As the liquid junction potential value, E_j, depends only on the ionic strength, it can be considered constant in potentiometric titrations. The ion products ($K_w = [H^+][OH^-]$) were also calculated at constant ionic strength of 0.1 mol L^{-1} with $NaClO_4$ in 60% dioxane-water mixture, based on measurements of $[OH^-]$ and pH in several experiments. The pK_w value obtained is 15.37 (± 0.2) and is in agreement with literature values.[44]

In the second step, the potentiometric equilibrium measurements were made on 50 mL of the Schiff base solutions initially about 3×10^{-3} mol L^{-1}, firstly in the absence of metal ions and then in their presence. [M]:[L] ratios were about 1:1 and 1:2. For all the Schiff bases, an excess of $HClO_4$ solution was added, so that they were fully protonated at the beginning of the titrations. The potential values were measured after addition of 0.05 mL increments of standard NaOH solution. After each addition, the potential was allowed to stabilize and its value was used, in combination with the calibration parameters calculated in the calibration step, to determine the pH of the solution. Titrations for each set were carried out at least three times to check the reproducibility of the data.

Data treatment

The protonation and the stability constants of the Schiff bases and their complexes were evaluated by iterative non-linear least squares fit of potentiometric equilibrium curves through mass balance equations for all the components expressed in term of known and unknown equilibrium constants, using the computer program BEST.[37] All the models converged at $\sigma < 0.03$ pH units of the observed pH values, which is considered to be an acceptable fit. The equilibrium constants reported in this paper were obtained as average values of three titrations. The selection of the equilibrium models was based on critical evaluation of the least squares fitting results, namely analysis of the statistical parameters. Because of the low solubility of the samples and their possible hydrolysis in aqueous solutions, it was necessary to work in 60% dioxane-water media, at low concentrations, and pH values should be neither extremely low nor extremely high. Species distribution curves were calculated with the FORTRAN program SPE.[37]

Results and Discussions

Since all the Schiff bases and their metal complexes were found to be either insoluble or sparingly soluble in water, a reaction medium consisting of 60% (v/v) dioxane-water was used. Dioxane has the advantage of a very low dielectric constant (2.209 as compared to 78.30 for water at 25 °C), thus preventing decomposition of the metal chelates. Further, pure dioxane is very hygroscopic and controlling its water content is difficult.[45] On the other hand, 60% dioxane–water mixtures have only a small hygroscopic character. A further advantage is the compatibility with the standard glass electrode, so that the pH measurements may be carried out in a way similar to that employed in a purely aqueous solution.[45] Another advantage of this mixture is its large acidity range (pK_w = 15.37), which allows the investigation of protonation equilibria of weak bases which could hardly be studied in water.[44-47]

Protonation equilibria

The stoichiometric protonation constants of the L^1-L^2 and L^3-L^{14} Schiff bases (Tables 1 and 2) were determined potentiometrically in 60% dioxane-water mixture at 25.0 ± 0.1 °C. The values obtained for the protonation constants are reported in Table 3.

The titration profiles in Figures 1 and 2 show two end-points at m = 2 and m = 3 (m = number of moles of NaOH *per* mole of the Schiff base). It can thus be concluded that the Schiff bases studied here have only three protonation sites. In multiple protonation equilibriums, it is very important to know in which protonation region the first protonation occurs. The phenolic group is known to be weakly acidic, indicating strong bonding between the proton and the oxygen donor. This means that the protonation constants of the ligands containing a phenolic oxygen should be high.[42] These findings are in agreement with NMR and UV-Vis spectroscopic measurements.[48,49] Thus, the first protonation equilibrium refers to the phenolate ion ($\log K_{OH}$). The other protonation sequences of the Schiff bases are assigned as follows: the protonation at the phenolic oxygen, the nitrogen on the thiazole ring ($\log K_{NH(1)}$) and the azomethine nitrogen ($\log K_{NH(2)}$). The protonation constant values for the azomethine nitrogen are smaller than those for the nitrogen on the thiazole ring, due to the intramolecular hydrogen bonding between the phenolate oxygen and the nitrogen atom of the azomethine group.[50-53] The values of the protonation constants determined in the present study are in good agreement with the data reported in the literature.[9-14, 42, 54, 55] Differences are minor and expected, considering the distinct experimental conditions employed (solvent media, ionic strength and temperature) and the substituent effects. The protonation constants of NH in the L^3-L^{14} Schiff bases (which contain hydrazone) and of the S atom in the thiazole group in all Schiff bases could not be determined in this study. This can be explained by conjugation of the unpaired electrons on the NH and S atoms, which are added to the ring and establish aromaticity. Joule *et al.*[56] explained that the S atom on the thiazole ring is not protonated due to the resonance effect. The equilibrium reaction steps are shown in Scheme 1.

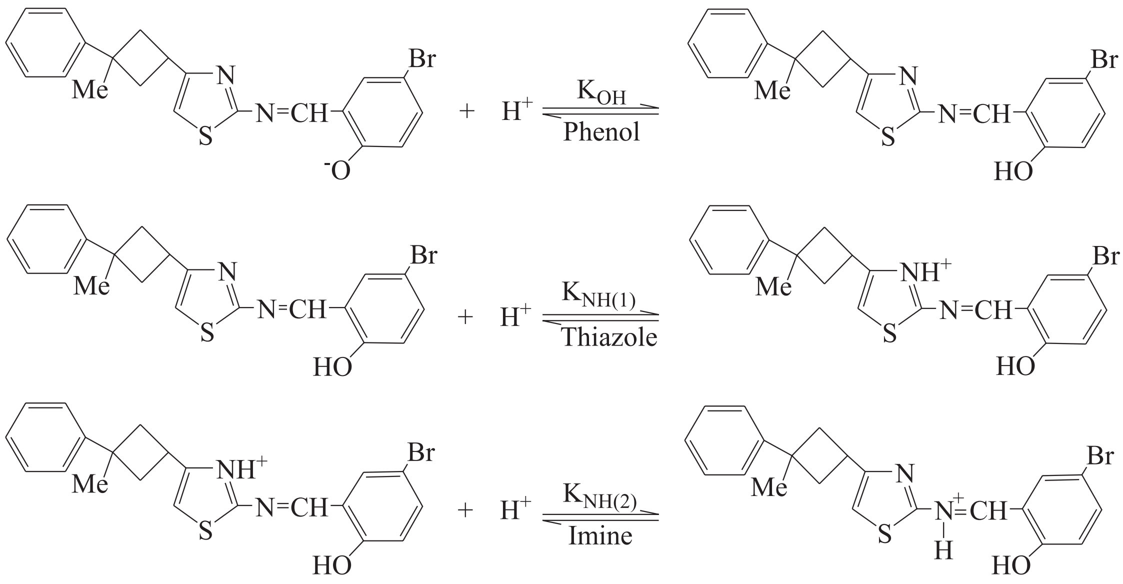
Table 3. The stoichiometric protonation constants of the Schiff bases (L^1-L^2 and L^3-L^{14}) in 60% dioxane-water mixture at 25.0 ± 0.1 °C and I = 0.10 mol L^{-1} ($NaClO_4$)

Schiff Bases	$\log K_{OH}$	$\log K_{NH(1)}$	$\log K_{NH(2)}$
L^1	8.89 ± 0.03	4.90 ± 0.02	2.72 ± 0.03
L^2	8.94 ± 0.04	4.92 ± 0.03	2.85 ± 0.02
L^3	11.59 ± 0.03	2.87 ± 0.01	2.46 ± 0.04
L^4	11.61 ± 0.05	2.86 ± 0.04	2.47 ± 0.04
L^5	11.51 ± 0.03	2.89 ± 0.02	2.53 ± 0.02
L^6	10.57 ± 0.05	2.90 ± 0.01	2.73 ± 0.03
L^7	10.67 ± 0.04	2.89 ± 0.02	2.71 ± 0.02
L^8	10.73 ± 0.03	2.90 ± 0.03	2.65 ± 0.04
L^9	11.40 ± 0.02	2.91 ± 0.02	2.56 ± 0.02
L^{10}	11.37 ± 0.05	2.93 ± 0.01	2.51 ± 0.03
L^{11}	11.36 ± 0.04	2.97 ± 0.04	2.52 ± 0.02
L^{12}	10.74 ± 0.03	2.99 ± 0.03	2.52 ± 0.02
L^{13}	10.83 ± 0.04	3.05 ± 0.01	2.48 ± 0.03
L^{14}	10.78 ± 0.03	3.08 ± 0.02	2.64 ± 0.04

The effect of substituents on the basicity of the Schiff bases is also discussed by using the data obtained in this study. The basicity orders of the phenolic oxygen were found to be as follows, for the media studied:

$L^6 < L^{12} < L^9 < L^3$ (reference compound) (phenyl group)
$L^7 < L^{13} < L^{10} < L^4$ (reference compound) (*p*-xylyl group)
$L^8 < L^{14} < L^{11} < L^5$ (reference compound) (mesityl group)

This order is as expected in the light of resonance and inductive effects of the substituents.[57,58] The absence of substantial differences in $\log K_{OH}$ values for the L^3, L^4 and L^5 Schiff bases (11.59, 11.61 and 11.51 respectively) can probably be attributed to the fact that the phenyl, xylyl and mesityl groups (R) are far from the phenolic oxygen. The reason why L^6, L^7 and L^8 Schiff bases including 5-bromosalicylaldehyde are less basic than the *para* derivatives can be explained on the ground that Br is an electron withdrawer group.[57, 58] When the $\log K_{OH}$ values



Scheme 1.

of the L^9, L^{10} and L^{11} Schiff bases, which have methoxy groups, are compared with the logK$_{OH}$ values for the L^3, L^4 and L^5 Schiff bases, it is seen that *ortho* derivatives have less basic character. This situation is explained by steric effects of *ortho* substituents. The comparison of the basicity orders obtained for the L^3, L^4 and L^5 Schiff bases with those obtained for L^{12}, L^{13} and L^{14} revealed that L^3, L^4 and L^5 are less basic. An explanation is that inductive electron attraction by oxygen is more pronounced in the *para* position.[57,58]

Little or no substituent effect is seen in the log K$_{NH(1)}$ and log K$_{NH(2)}$ values of all the Schiff bases. This result can be explained by the fact that substitution in the phenyl ring attached to the carbon atom does not affect the use of the lone pair of the nitrogen atom on the thiazole ring and imine nitrogen.

It is also interesting to compare the protonation constants (about 11.4) with those of substituted N-benzylidene-2-hydroxyanilines (BA) Schiff bases reported in our previous study for the same dioxane-water media.[59] It can be seen that, in general, the logK$_{OH}$ values of substituted benzylideneanilines (BA) for 60% dioxane-water mixtures are higher than those of the corresponding L^1-L^{14} salicylideneanilines (SA), while the logK$_{NH}$ values (BA) are smaller than those of SA. These results can be attributed to the fact that the electron densities of phenolate ions are different because of the substituents.[60,61] One can think that these values obtained for the protonation constants of the BA and SA can also be explained by comparing the conformational structures of these compounds. Spectroscopic studies show the existence of strong intramolecular hydrogen bonding in the Schiff bases such as salicylideneaniline (SA), but hydrogen bonding is not observed in the benzylideneanilines (BA) because of unfavourable steric conditions.[50-53] Thus, in the case of SA, the electron density of the hydrogen acceptor azomethine nitrogen decreases and the observation of lower logK$_{NH}$ values for the SA (L^3-L^{14}) derivatives can be explained in terms of stereochemistry.

It is also interesting to compare the protonation constants of the Schiff Bases studied with those of substituted *N*-benzylidene-2-hydroxyanilines (BA) Schiff bases reported in our previous studies for 60% ethanol-water media.[42] It can be seen that logK$_{OH}$ values of substituted L^3-L^{14} salicylideneanilines (SA) (except L^1-L^2) for 60% dioxane-water mixtures are higher than those of the corresponding benzylideneanilines (BA) (about 10.7) in ethanol-water mixture. However, logK$_{NH}$ values of SA are smaller than those (about 4.25) of BA. These facts suggest that solute-solvent interactions, as well as inductive effects, are also important in the determination of the numerical values of the Schiff base protonation constants. An increase on the solvation of the unprotonated phenolic oxygen by a hydrogen bond donor from a solvent such as ethanol is caused by an increase in the hydrogen bond donor capability of the solvent and therefore it decreases electrolyte ($SB^- + H^+ \rightarrow HSB$) protonation and logK$_{OH}$. There also exists a dipole-dipole interaction between the polar Schiff bases and the polar solvent, while an ion-dipole interaction is the important force between the polar solvent and unprotonated Schiff bases. Since the solute ion-solvent dipole interaction is stronger than the dipole-dipole interaction, increasing the polarity of the solvent (polarity and polarizability, π^* for 60% dioxane-water mixture and 60% ethanol-water mixture 0.57 and 0.91; 5.2 and 1.7, respectively)[62] causes the unprotonated form of the Schiff bases to become more stable than the protonated form, thus the degree of protonation of the phenolic oxygen decreases in ethanol-water mixtures.

An analysis of the various contributions to $\log K_{NH(1)}$ corresponding to the azomethine nitrogen shows (Table 3) that an increase in the polarity and the H-bond-donating acidity of the mixed solvent causes the $\log K_{NH}$ values to increase (bond-donating acidity for 60% dioxane-water mixture and 60% ethanol-water mixture, 0.57 and 0.91 respectively).[62] Also, both effects have the same sign and can be added, thus increasing the total effect upon the $\log K_{NH}$ values. This study confirms the usefulness of microscopic parameters, such as α (the H-bond donating acidity), β (the H-bond accepting basicity) and π (polarity and polarizability) in the explanation of microscopic processes, since the solvent properties in the cybotactic zone are the ones which directly affect the solutes. Preferential solvation by water occurs in dioxane-water mixtures, in the range of compositions studied here, for hydrogen ions.

The investigation of stability constants of metal(II) complexes of Schiff bases

A set of typical potentiometric titration curves for the 2:1 L^2 Schiff base-metal(II) and the 2:1 L^3 Schiff base-metal(II) systems is shown in Figures 1 and 2, respectively. Similar behaviours were observed for the other Schiff base derivatives. Analysis of the potentiometric titration curves (Figures 1 and 2) in the presence of metal ions indicates that the addition of these ions to the Schiff base solutions shifted the buffer region to lower pH values. The observed decrease in the curves of the complexes (□, △ and ▲) in comparison to the free Schiff base solution curve (■) indicates the formation of ML_2 species in solution. It can also be seen in Figures 1 and 2 that there is a break near m = 4 for the copper(II)-L and near m = 6 for nickel(II)-L and zinc(II)-L systems. It is very well known that Cu prefers complexing in a planar or distorted tetrahedral structure form due to Jahn-Teller distortion.[64] So, Cu^{2+} replaces four protons in the Schiff bases, and therefore there is a break near m = 4 in the titration curves. In contrast to copper(II), Zn^{2+} and Ni^{2+} ions form hexagonal complexes, and, as a result, there is a break near m = 6 in the titration curves. These findings are in agreement with recent reports in the literature.[25-30]

The stoichiometric stability constants of the Schiff bases complexes with copper(II), nickel(II) and zinc(II) obtained in this study are presented in Table 1. An inspection of the stability constant values of ML ($\log K_1$) and ML_2 ($\log K_2$) complexes in which the Schiff Bases have phenyl, *p*-xylyl and mesityl groups respectively in the cyclobutane ring reveals that the order is:

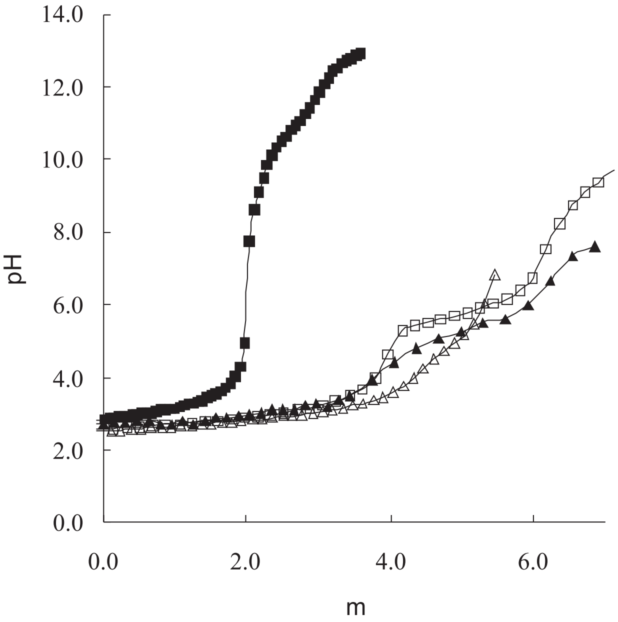


Figure 1. Potentiometric titration curves of binary (1:2) Schiff base (L^2) complexes (m = moles of base added *per* mole of metal ion (or Schiff base) present). ■: H_3L^2; □: ZnL^2_2; ▲: NiL^2_2; △: CuL^2_2.

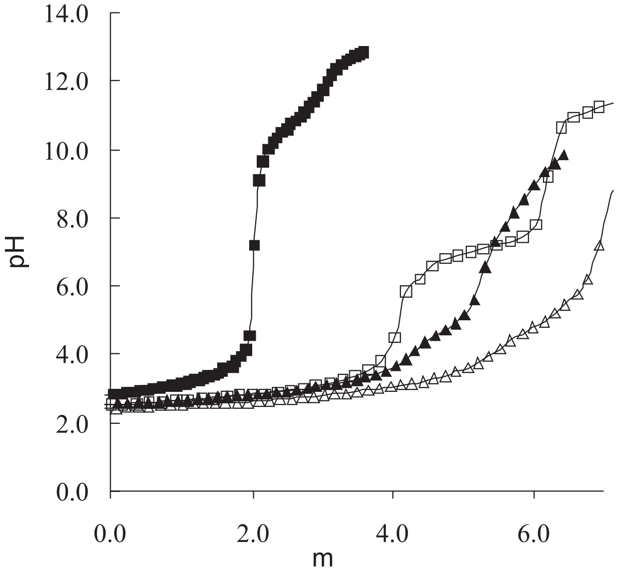


Figure 2. Potentiometric titration curves of binary (1:2) Schiff base (L^3) complexes (m = moles of base added per mole of metal ion (or Schiff base) present). ■: H_3L^3; □: ZnL^3_2; △: NiL^3_2; ▲: CuL^3_2.

For Cu^{2+};

$\log K_1$ values	$L^6 < L^3$ (ref. comp.) $< L^{12} < L^9$ (phenyl group)
	$L^7 < L^{13} < L^{10} < L^4$ (ref. comp.) (*p*-xylyl group)
	$L^8 < L^{14} < L^{11} < L^5$ (ref. comp.) (mesityl group)

Table 4. The stability constants of the Schiff base-metal(II) (Ni^{2+}, Cu^{2+} and Zn^{2+}) complexes in 60% dioxane-water mixture at 25.0 ± 0.1 °C and I = 0.10 mol L^{-1} ($NaClO_4$)

Schiff Bases	Ni^{2+}			Cu^{2+}			Zn^{2+}		
	$\log K_1$	$\log K_2$	$\log \beta_2$	$\log K_1$	$\log K_2$	$\log \beta_2$	$\log K_1$	$\log K_2$	$\log \beta_2$
L^1	4.52 ± 0.03	3.56 ± 0.02	8.08 ± 0.04	7.64 ± 0.03	5.10 ± 0.02	12.74 ± 0.03	4.05 ± 0.02	3.97 ± 0.03	8.02 ± 0.03
L^2	5.22 ± 0.02	3.65 ± 0.03	8.87 ± 0.02	7.86 ± 0.03	5.73 ± 0.03	13.59 ± 0.03	4.54 ± 0.03	3.61 ± 0.02	8.15 ± 0.02
L^3	10.23 ± 0.04	8.42 ± 0.02	18.65 ± 0.03	11.34 ± 0.02	8.77 ± 0.02	20.11 ± 0.02	8.73 ± 0.04	7.29 ± 0.04	16.02 ± 0.05
L^4	9.72 ± 0.03	9.17 ± 0.04	18.89 ± 0.02	11.95 ± 0.05	8.99 ± 0.04	20.94 ± 0.05	8.63 ± 0.03	8.02 ± 0.02	16.65 ± 0.02
L^5	9.45 ± 0.05	9.21 ± 0.02	18.66 ± 0.05	11.68 ± 0.02	8.90 ± 0.02	20.58 ± 0.02	8.76 ± 0.02	8.17 ± 0.02	16.93 ± 0.03
L^6	8.95 ± 0.04	7.87 ± 0.05	16.82 ± 0.04	11.33 ± 0.02	8.31 ± 0.02	19.64 ± 0.02	8.50 ± 0.04	7.65 ± 0.04	16.15 ± 0.02
L^7	9.03 ± 0.03	8.16 ± 0.03	17.19 ± 0.02	11.12 ± 0.05	8.54 ± 0.04	19.66 ± 0.04	8.58 ± 0.02	7.82 ± 0.02	16.40 ± 0.03
L^8	8.85 ± 0.03	8.35 ± 0.03	17.20 ± 0.02	11.00 ± 0.02	8.56 ± 0.02	19.56 ± 0.02	8.67 ± 0.03	7.91 ± 0.02	16.58 ± 0.03
L^9	9.05 ± 0.02	7.36 ± 0.04	16.41 ± 0.03	12.09 ± 0.02	9.02 ± 0.02	21.11 ± 0.02	8.33 ± 0.02	7.73 ± 0.03	16.06 ± 0.02
L^{10}	9.25 ± 0.05	7.45 ± 0.02	16.70 ± 0.05	11.68 ± 0.03	9.30 ± 0.02	20.98 ± 0.02	8.34 ± 0.04	7.88 ± 0.02	16.22 ± 0.03
L^{11}	9.17 ± 0.04	7.85 ± 0.04	17.02 ± 0.02	11.57 ± 0.04	9.12 ± 0.03	20.69 ± 0.04	8.31 ± 0.02	8.12 ± 0.02	16.43 ± 0.02
L^{12}	8.78 ± 0.03	7.69 ± 0.02	16.47 ± 0.04	11.36 ± 0.02	7.98 ± 0.02	19.34 ± 0.02	8.32 ± 0.03	8.06 ± 0.05	16.38 ± 0.04
L^{13}	8.86 ± 0.02	7.46 ± 0.03	16.32 ± 0.02	11.22 ± 0.04	7.96 ± 0.03	19.18 ± 0.03	8.21 ± 0.02	7.94 ± 0.02	16.15 ± 0.02
L^{14}	8.94 ± 0.02	7.70 ± 0.02	16.64 ± 0.03	11.12 ± 0.02	7.93 ± 0.02	19.05 ± 0.02	8.43 ± 0.04	8.08 ± 0.05	16.51 ± 0.05

$\log K_2$ values $L^{12} < L^6 < L^3$ (ref. comp.) $< L^9$ (phenyl group)
$L^{13} < L^7 < L^4$ (ref. comp.) $< L^{10}$ (*p*-xylyl group)
$L^{14} < L^8 < L^5$ (ref. comp.) $< L^{11}$ (mesityl group)

For Ni^{2+};
$\log K_1$ values $L^{12} < L^6 < L^9 < L^3$ (ref. comp.) (phenyl group)
$L^{13} < L^7 < L^{10} < L^4$ (ref. comp.) (*p*-xylyl group)
$L^8 < L^{14} < L^{11} < L^5$ (ref. comp.) (mesityl group)

$\log K_2$ values $L^9 < L^{12} < L^6 < L^3$ (ref. comp.) (phenyl group)
$L^{13} < L^{10} < L^7 < L^4$ (ref. comp.) (*p*-xylyl group)
$L^{14} < L^{11} < L^8 < L^5$ (ref. comp.) (mesityl group)

For Zn^{2+};
$\log K_1$ values $L^{12} < L^9 < L^6 < L^3$ (ref. comp.) (phenyl group)
$L^{13} < L^{10} < L^7 < L^4$ (ref. comp.) (*p*-xylyl group)
$L^{11} < L^{14} < L^8 < L^5$ (ref. comp.) (mesityl group)

$\log K_2$ values L^3 (ref. comp.) $< L^6 < L^9 < L^{12}$ (phenyl group)
$L^{10} < L^7 < L^{13} < L^4$ (ref. comp.) (*p*-xylyl group)
$L^8 < L^{14} < L^{11} < L^5$ (ref. comp.) (mesityl group)

When these orders obtained for stability constants of the second Schiff bases group (L^3-L^{14}) are compared with the order obtained for their protonation constants, it is seen that there is a correlation between the values of $\log K_1$ and protonation constants only for copper(II) and zinc(II) xylil and mesityl Schiff base derivatives, but there is not any correlation between $\log K_2$ and the protonation constants. This may be due to the fact that the stability of the complex is not dependent only upon the basic character of the Schiff base.[65] For the L^1 and L^2 Schiff bases, it is seen that there is correlation between the stability constants and the protonation constants.

When evaluating stability constants of Schiff base-metal(II) complexes for every metal ion separately, it is seen that the values in each group are close. This shows that the substituents added to phenyl ring do not affect the stability constant values too much. In terms of the nature of the metal ion, the complex stability follows the trend copper(II) > nickel(II) > zinc(II), which is in agreement with the Irving-Williams' order of metal ions.[66,67]

In order to investigate the change in the concentration of complexes, the species distribution curves (Figures 3-5) were established by the SPE program.[37] Obviously, the clear difference between metal(II)-L^1 and metal(II)-L^5 complex systems is that metal(II)-L^5 complexes form in lower pH. As seen in Figure 3, the NiL^1 complex does not form in the acidic region, but forms in neutral and basic regions. The NiL^1_2 complex is dominant above pH = 7.0. $Ni(OH)_2$ is formed above pH = 10 in the nickel(II)-L^1 system. In the species distribution curves, the nickel(II)-L^5 complex starts forming in the acidic region in contrast to the NiL^1 complex. While the NiL^5 complex is dominant in the pH range of 3.0-8.0, the NiL^5_2 complex starts forming above pH = 4 and is dominant in a wide pH range.

According to the distribution curves of copper(II)-L^1 in Figure 4, Cu^{2+} ion is dominant in pH < 4.5 and occurs in free

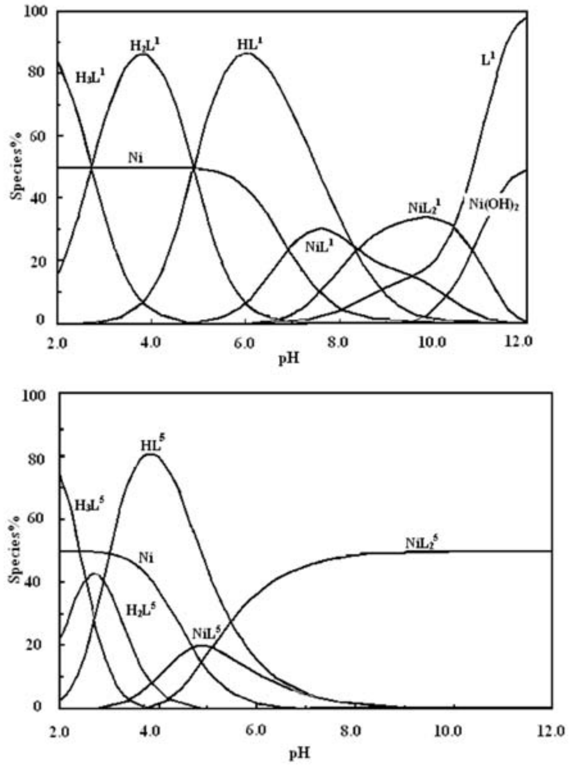


Figure 3. Species distribution diagram for the nickel(II):L^1 and nickel(II):L^5 Schiff base systems in 1:2 molar ratio as a function of pH ($I = 0.10$ mol L^{-1} $NaClO_4$, $T_L = 3.0 \times 10^{-3}$ mol L^{-1}, $T_{Ni} = 1.5 \times 10^{-3}$ mol L^{-1}, % = percentage concentration of species).

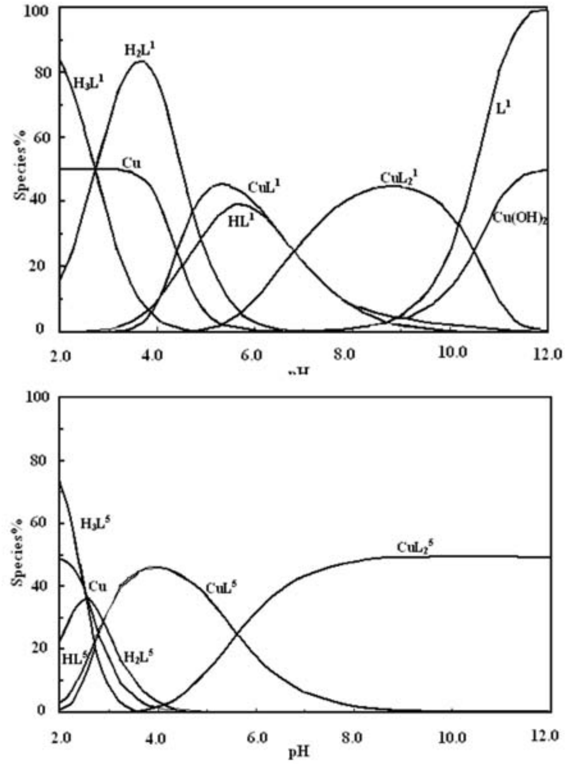


Figure 4. Species distribution diagram for the copper(II):L^1 and copper(II):L^5 Schiff base systems in 1:2 molar ratio as a function of pH ($I = 0.10$ mol L^{-1} $NaClO_4$, $T_L = 3.0 \times 10^{-3}$ mol L^{-1}, $T_{Cu} = 1.5 \times 10^{-3}$ mol L^{-1}, % = percentage concentration of species).

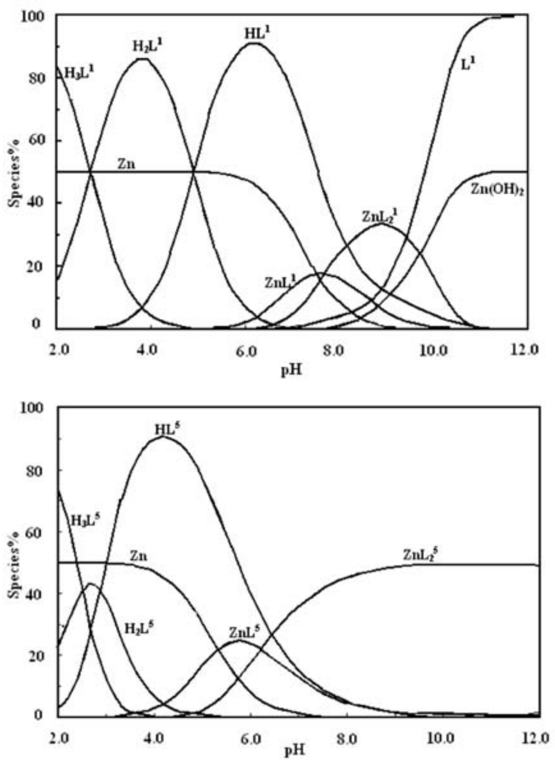


Figure 5. Species distribution diagram for the zinc(II):L^1 and zinc(II):L^5 Schiff base systems in 1:2 molar ratio as a function of pH ($I = 0.10$ mol L^{-1} $NaClO_4$, $T_L = 3.0 \times 10^{-3}$ mol L^{-1}, $T_{Zn} = 1.5 \times 10^{-3}$ mol L^{-1}, % = percentage concentration of species).

form till pH = 4.0. The CuL^1 complex forms in the pH range of 4-10 and reaches its maximum at pH = 5.5. The CuL_2^1 complex, in its turn, starts forming at pH 5.0 and reaches the maximum at pH = 9. In this system, Cu^{2+} is hydrolysed above pH = 7.5. In their distribution curve, copper(II)-L^5 complexes start forming in a very acidic region and CuL^5_2 complexes are dominant above pH = 6.0. When the species distribution curves of the zinc(II)-L^1 and zinc(II)-L^5 complex systems in Figure 5 are examined, it can be seen that they are similar to nickel(II)-L^1 and nickel(II)-L^5 systems. The species distribution curves are useful for indicating the conditions necessary to achieve maximum Schiff base-metal(II) (Ni^{2+}, Cu^{2+} and Zn^{2+}) complex formation.

Conclusion

To clarify activities in the biological systems involving the novel Schiff bases having three different and important functionalities such as phenolate oxygen, thiazole and azomethine nitrogen atoms, it is very important to have quantitative data such as the protonation and the stability constants of the Schiff bases and their metal complexes. In this study, based upon the detailed inspection of constants determined by a potentiometric study, it was demonstrated that, in every complex, one metal ion is coordinated to two azomethine nitrogen atoms and two oxygen atoms of two ligand molecules. These results indicate the high effectiveness of two functional groups of the ligands for the complexation with copper(II), nickel(II) and zinc(II) metal ions. Furthermore, the results obtained in this study should contribute to furthering our understanding of the acid-base behaviour of substances in the widely used dioxane-water mixtures and of the chemical factors which are involved in more complicated biological processes.

References

1. Zishen, W.; Zhipping, L.; Zhenhaun, Y.; *Transition Met. Chem.* **1993**, *18*, 291.
2. Hadjipavlou-Litina, D.; Geronikaki, A.; *Arzneim. Forsh./Drug Res.* **1996**, *46*, 805.
3. Holla, B. S.; Malini, K.V.; Rao, B. S.; Sarojini, B. K.; Kunari, N. S.; *Eur. J. Med. Chem.* **2003**, *38*, 313.
4. Çukurovalı, A.; Yılmaz, İ.; Gür, S.; Kazaz, C.; *Eur. J. Med. Chem.* **2006**, *41*, 201.
5. Beyer, H.; *Organic Chemistry*, Verlag Harry Deutsch: Frankfurt/Main, Zürich, 1963, p. 609.
6. Roger, E.; Pierre, C. J.; Pualette, V.; Gerard, G.; Chepat, J. P.; Robert, G.; *Eur. J. Med. Chem.* **1977**, *12*, 501.
7. Gerard, G.; *Eur. J. Med. Chem.* **1979**, *14*, 493.
8. Dehmion, E. V.; Schmidt, S. S.; *Liebigs Ann. Chem.* **1990**, 411.
9. Alarcón-Angeles, G.; Corona-Avendaño, S.; Rojas-Hernández, A.; Romero-Romo, M. A;. Ramírez-Silva, M. T.; *Spectrochim. Acta, Part A.* **2005**, *61*, 313.
10. El-Taher, M. A.; Gabr, A. A.; *Talanta* **1996**, *43*, 1511.
11. Öğretir, C.; Demirayak, S.; Tay, N. F.; *J. Chem. Eng. Data* **2006**, *51*, 946.
12. Öğretir, C.; Demirayak, S.; Tay, N. F.; Duran, M.; *J. Chem. Eng. Data* **2008**, *53*, 422.
13. Yarlıgan, S.; Öğretir, C.; Csizmadia, I. G.; Açıkkalp, E.; Berber, H.; Arslan, T.; *J. Mol. Struc. (Theochem)*, **2005**, *715*, 199.
14. Losada, J.; del Peso, I.; Beyer, L.; *Inorg. Chim. Acta* **2001**, *321*, 107.
15. Kaya, İ.; Yıldırım, M.; *J. Appl. Polym. Sci.* **2007**, *106*, 2282.
16. Temel, H.; Çakır, Ü.; Uğraş, H. İ; Şekerci, M.; *J. Coord. Chem.* **2003**, *56*, 943.
17. Chaviara, A. Th.; Cox, P. J.; Repana, K. H.; Papi, R. M.; Papazisis, K. T.; Zambouli, D.; Kortsaris, A. H.; Kyriakidis, D. A.; Bolos, C. A.; *J. Inorg. Biochem.* **2004**, *98*, 1271.
18. Pandeya, S. N.; Srirama, D.; Nath, G.; DeClercq, E.; *Eur. J. Pharm. Sci.* **1999**, *9*, 25.
19. Vicini, P.; Geronikaki, A.; Incerti, M.; Busonera, B.; Poni, G.; Cabras, C. A.; La Collac, P.; *Bioorg. Med. Chem.* **2003**, *11*, 4785.
20. Olszewski, T. K.; Boduszek, B.; Sobek, S.; Kozłowski, H.; *Tetrahedron* **2006**, *62*, 2183.
21. Sharma, C. I.; Mishra, V.; Narvi, S. S.; *Synth React. Inorg. Met.-Org. Chem.* **1986**, *16*, 243.
22. Mishra, V.; *J. Polym. Mater.* **1995**, *12*, 63.
23. Mishra, V.; Parmar, D. S.; *J. Indian Chem. Soc.* **1995**, *72*, 811.
24. More, P. G.; Muthal, B. N.; Lawand, A. S.; *J. Ind. Chem. Soc.* **2006**, *83*, 36.
25. Çukurovalı, A.; Yılmaz, İ.; *Polish. J. Chem.* **2000**, *74*, 147.
26. Çukurovalı, A.; Yılmaz, İ.; Ahmedzede, M.; Özmen, H.; *Synth. React. Inorg. Met.-Org. Chem.* **2001**, *31*, 255.
27. Çukurovalı, A.; Yılmaz, İ.; Özmen, H.; *Trans. Met. Chem.* **2001**, *26*, 619.
28. Çukurovalı, A.; Yılmaz, İ.; Özmen, H.; Ahmedzede, M.; *Trans. Met. Chem.* **2002**, *27*, 171.
29. Çukurovalı, A.; Yılmaz, İ.; Özmen, H.; Ahmedzede, M.; *Heteroat. Chem.*, **2001**, *12*, 42.
30. Çukurovalı, A.; Yılmaz, İ.*; J. Coord. Chem.* **2001**, *53*, 329.
31. Yakuphanoğlu, F.; Çukurovalı, A.; Yılmaz, İ.; *Opt. Mater.* **2005**, *27*, 1363.
32. Çukurovalı, A.; Yılmaz, İ.; Ahmedzede, M.; *Synth. React. Inorg. Met.-Org. Chem.* **2000**, *30*, 843.
33. Çukurovalı, A.; Yılmaz, İ.; *Synth. React. Inorg. Met.-Org. Chem.* **2003**, *33*, 657.
34. Yılmaz, İ.; Çukurovalı; A.; *Trans. Met. Chem.* **2003**, *28*, 399.
35. Öner, H.; Karatepe, H.; Karataş, F.; Öner, J.; Yılmaz, İ; Çukurovalı, A.; *Cell Biochem. Funct.* **2005**, *23*, 427.
36. Aksoy, İ.; Yılmaz, İ.; Sarı, U.; Güven, K.; Çukurovalı, A.; *Cryst. Res. Technol.* **2006**, *41*, 293.
37. Martell, A. E.; Motekaitis, R. J.; *The Determination and use of Stability Constants*, VCH: New York, 1988.
38. Perrin, D. D.; Armarego, W. L. F.; *Purification of Laboratory Chemicals*, Pergamon: Oxford, 1992.
39. Schwarzenbach, G.; Flaschka, H. A.; *Complexometric Titrations*, Barnes and Noble-Methuen: New York, 1957.
40. Serjeant, E. P. In *Potentiometry and Potentiometric Titrations*; in *a Series of Monographs on Analytical Chemistry and its Applications*; Elving, P. J.; Winefordner J. D., eds.; John Wiley & Sons: New York, 1984, vol. 69, ch. 5.
41. Altun, Y.; Köseoğlu, F.; *Monatsh. Chem.* **2006**, *137*, 703.
42. Altun, Y.; *J. Solution Chem.* **2004**, *33*, 477.
43. Gran, G.; *Analyst* **1952**, *7*, 661.
44. Barbosa, J.; Fonrodona, G.; Marques, I.; Sanz-Nebot, V.; Toro, I.; *Anal. Chim. Acta* **1997**, *351*, 397.
45. Ishiguro, S. I.; Ohtaki, H.; *J. Coord. Chem.* **1987**, *15*, 237.
46. Hernández-Molina, R.; Mederos, A.; Gili, P.; Domínquez, S.; Núñez, P.; Germain, G.; Debaerdemaeker, T.; *Inorg. Chim. Acta* **1997**, *256*, 319.
47. Lloret, F.; Molar, M.; Moratal, J.; Faus, J.; *Inorg. Chim. Acta* **1986**, *124*, 67.

48. Martin, R. P.; Petit-Ramel, M. M.; Scharff, J. P. In *Metal Ions in Biological Systems*; Sigel, H., eds.; Marcel Dekker: New York, 1976, p. 2.
49. Ireland, R. J.; Joy, K.W. In *Transaminases*; Christen, P.; Metzler, D. E., eds.; Wiley: New York, 1985.
50. Filarowski, A.; *J. Phys. Org. Chem.* **2005**, *18*, 686.
51. Ourari, A; Ouari, K.; Moumeni, W; Sibous, L.; *Trans. Met. Chem.* **2006**, *31*,169.
52. Sakagami, S.; Koga, T.; Nakamizo, M.; *Liq. Cryst.* **2001**, *28*, 347.
53. Sollenberger, P. Y.; Martin, R. B.; In *The Chemistry of Amino Group;* Patai, S., eds.; John Wiley & Sons: London, 1968.
54. Gölcü, A.; Tümer, M.; Demirelli, H.; Wheatley, R. A.; *Inorg. Chim. Acta* **2005**, *358*, 1785.
55. El-Sayed, M.; Müler, H.; Rheinwald, G.; Lang, H.; Spange, S.; *Monatsh. Chem.* **2003**, *134*, 361.
56. Joule, J. A.; Mills, K.; Smith, G. F.; *Heterocylic Chemistry*, 3rd ed., Chapman and Hall: London, 1998.
57. Isaacs, N. S.; *Physical Organic Chemistry*, Longman Scientific & Technical: New York, 1986.
58. Perrin, D. D.; Dempsey, B.; Serjeant, E. P.; *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall: London, 1981.
59. Demirelli, H.; Köseoğlu, F.; Kavak, N.; *J. Sol. Chem.* **2004**, *33*, 1467.
60. Badger, G. M.; *The Structure and Reactions of Aromatic Compounds*, Cambridge, University Press: UK, 1954, p. 202.
61. Morrison, R. T.; Boyd, R. N.; *Organic Chemistry*, 5th ed., Prentice Hall: New Delhi, 1990, p 203.
62. Barwick, V. J.; *TrAC, Trends Anal. Chem.* **1997**, *16*, 293.
63. Greenwood, N. N.; Earnshaw, A.; *Chemistry of the Elements*, 2nd ed., Butterworth Heinemann: 2001, vol. 28, p. 1192.
64. Figgis, B. N.; *Introduction to Ligand Fields*, John Wiley & Sons: New York, 1966.
65. Irving, H.; Pettit, L. D.; *J. Chem. Soc*. **1963**, 1546.
66. Irving, H.; Williams, R. J. P.; *Nature* **1948**, *162*, 746.
67. Irving, H.; Williams, R. J. P.; *J. Chem. Soc.* **1953**, 3192.

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