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Synthesis, characterization, biological activity of Schiff bases derived from 2-bromo-4-methyl aniline and its potentiometric studies with Cu(II), Co(II) and Ni(II) ions

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ABSTRACT

Schiff bases namely, 2-bromo-4-methyl-N-(2-nitrobenzylidene)aniline; 2-bromo-4-methyl-N-(2,4,5-trimethoxybenzylidene)aniline; 2-bromo-N-(4-methoxybenzylidene)-4-methylaniline and N-((1H-indol-3-yl)methylene-2-bromo-4-methylaniline have been synthesized and characterized by elemental analysis, FT-IR, Mass and ^{1}H-NMR spectroscopy. Schiff bases have been screened for Antimicrobial activity against bacteria and fungi by using MIC determination. Binary complexes of Co(II), Ni(II) and Cu(II) with Schiff bases in solution have been studied potentiometrically in 60:40 % (V/V) 1,4-dioxane-water system at constant temperature 27 ±0.5 ºC and at an ionic strength of 0.1 M KNO_3. The order of stability constant of formed binary complexes in solution was examined.

***Keywords*:** Schiff base, 2-bromo-4-methyl aniline, Antimicrobial activity, Potentiometric studies, Stability constant, Irving-Rossotti

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1. INTRODUCTION

Schiff bases, named after Hugo Schiff [1], are derived from condensation reaction of aromatic primary amine with carbonyl compounds [2],[3]. Structurally, Schiff bases sustain imine or azomethine (-HC=N-) functional group and they coordinate to transition metal ion via azomethine nitrogen atom[4]. Various studies have shown that, azomethine group in Schiff base has considerable biological importance in fungicidal and insecticidal fields [5]. Schiff bases have been studied extensively and play very important and versatile role in industrial and biological field. They are utilized as starting material in the synthesis of industrial products [6]. Schiff bases have found significant importance in medicinal and pharmaceutical field due to expansive range of biological activities like anticancer [7], antituberculosis [8], antibacterial [9], antimicrobial [10], antispasmodic [11], antioxidants [12], analgesic [13],[14], plant growth inhibitors [15], anthelmintic [16] and anti-inflammatory activity [17]. In the recent years, schiff base and their metal complexes have receieved considerable interest in the chemistry. Literature review informed that metal complexes exhibit greater biological activity than free organic compound [5]. Schiff base and their metal complexes have wide applications in various fields like food industry, dyes industry, analytical chemistry [18],[19], catalysis[20] and also in clinicinal applications as enzyme inhibitors [21], antibacterial [22],[23], antiviral [24],[25],[26] and as anticancer [27],[28],[29]. Schiff bases readily form stable complexes with transition metals [30] and also these complexes are regarded as models for biological important species. Various calix systems [31-39], natural, naturally derived and non-natural compounds are having imine or azomethine groups have been shown various biological activities [40],[41].

Review of research work indicates that the pH-metric studies have received great response in the study of binary, ternary and quaternary complexes by pH-metric method [42],[43],[44],[45],[46] using biological molecules [47],[48],[49]. Potentiometric method has been used extensively for determination of stability constant and also used in many branches of solution chemistry. Coordination behaviour of Schiff base with transition metal ions may help in understanding the mode of chelation of ligand towards metal. The stability constant of a complex is useful in theoretical problems as well as in the practical application of complexation.

In the present investigation we have reported synthesis, characterization of schiff bases derived from 2-bromo-4-methyl aniline and their biological activity against two gram positive bacteria *S. aureus, B. subtilis* and two Gram negative bacteria *i.e. S. marcescens, E. coli* and fungal strains *Rhizopus* sp. and *A. Niger* in solvent DMF/$CHCl_3$. The present article brings a complete potentiometric study on binary complexes formed in solution with Schiff bases and different metal ions Co(II), Ni(II) and Cu(II). Potentiometric titration curves of binary complexes were used in calculating stability constant. Stability constant of the type M-Schiff base is calculated by using Calvin-Bjerrum [50] and pH-metric titration technique as adopted by Irving-Rossotti [51],[52].

2. EXPERIMENTAL

2. 1. Reagents and Solutions

Experimental procedure follows the preparation of amine (2-bromo-4-methyl aniline) by reported method [53]. All chemicals were of analytical grade and used as received without further purification. Metal nitrate salts, aldehyde and other chemicals were obtained from

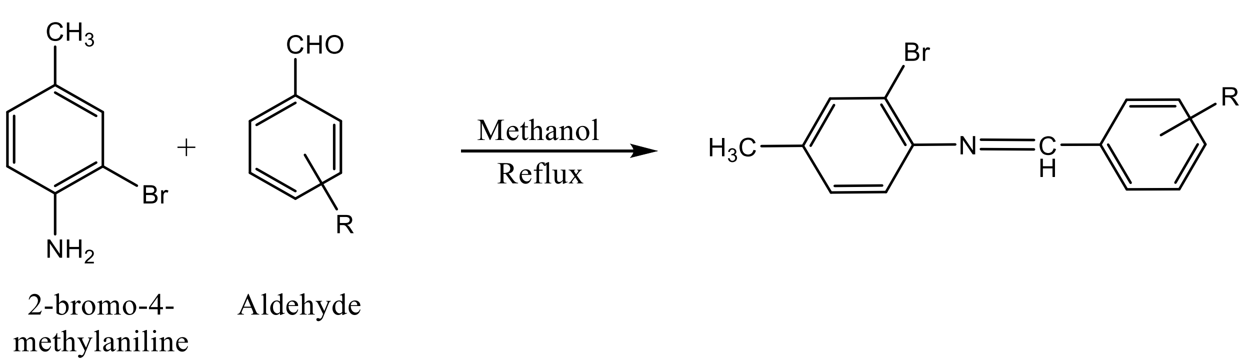
Sigma-Aldrich and E. Merck. All aqueous solutions were prepared with quartz distilled deionized water. The stock solutions of metal ions Cu(II), Co(II) and Ni(II) were prepared from their nitrate salts in double distilled water and concentrations of the metal ions were checked using the standard method [54]. Solutions of ligands were prepared in 1,4-dioxane. KOH solution was prepared and standardized by standard solution of (0.1M) oxalic acid and then standard alkali solution was used for standardization of HNO_3. A stock solution of KNO_3 (1.0M) was also prepared in CO_2-free double distilled water and used as a supporting electrolyte.

2. 2. Apparatus

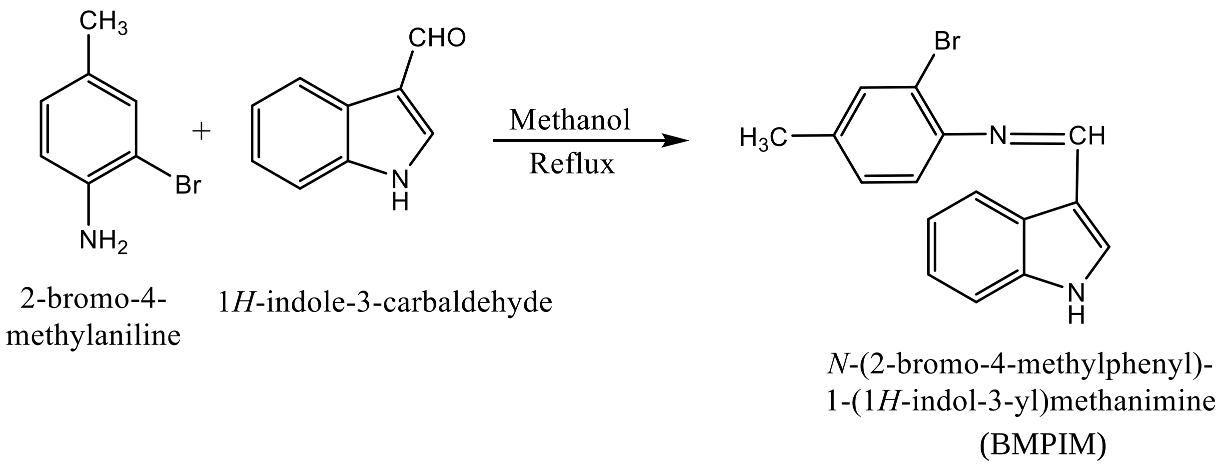
The melting points were determined using capillary and theils tubes filled with paraffin oil and are uncorrected. Infrared spectra were recorded on tensor Bruker 27 (Ettlingen, Germany) and expressed in cm^{-1}. Mass spectra (GC-MS) were determined using Jeol D-300 spectrometer. ^{1}H- NMR spectra were recorded in $CDCl_3$ on Bruker spectrophotometer (500 MHz) using TMS as an internal standard. Elemental analysis data are in accordance with the theoretically calculated percentage of C, H, N and O. The pH of the solution measured using with Equiptronics Micro Controller digital pH meter (model EQ 621) equipped with combined glass electrode having pH range 0-14 and temperature range 20-100 ºC (accuracy ±0.001 pH unit). The electrode was calibrated time to time before and after each titration against standard buffers (pH 4.02 and 9.18). The pH meter was started half an hour before the titration for the initial warm up of the instrument. The glass electrode washed with distilled water and dried by filter paper before taking pH readings.

2. 3. Synthesis of Schiff base general method

To a methanolic solution of 2-bromo-4-methyl aniline (0.001 mol) and 2-nitrobenzaldehyde / 2,4,5-trimethoxybenzaldehyde / 4-methoxybenzaldehyde / 1H-indole-3-carbaldehyde was mixed using catalytic amount of glaciel acetic acid.



1) R= *2*-NO2
2) R= *O*CH3 (*2, 4, & 5*)
3) R= *4*-*O*CH3



Scheme 1. Synthesis of Schiff bases 1) BMNBA, 2) BMTBA, 3) BMBMA and 4) BMPIM

The reaction mixture was refluxed with constant stirring at 60-80 ºC for 8-10 hrs. Schiff base was obtained by slow evaporation method at room temprature.

To remove excess aldehyde, the product was washed with sodium bisulphite and then washed with chilled methanol to remove other impurities. The product was isolated, dried by ether and recrystalized using hot methanol. (Scheme 1) The purity of ligands were checked by TLC and characterized by elemental analysis, FT-IR, mass and ^{1}H-NMR spectra.

2. 4. Characterization of ligands

2. 4. 1. 2-bromo-4-methyl-N-(2-nitrobenzylidene)aniline

Yellow, Yield: 82%. Melting point: 130 ºC. Molecular weight: 319.15. Elemental analysis calc.: ($C_{14}H_{11}BrN_2O_2$) (%): C, 52.69; H, 3.47; N, 8.78; O, 10.03; found: C, 52.55; H, 3.49; N, 8.70; O, 9.90. FT-IR (KBr) (cm^{-1}): $\nu_{(HC=N)}$ 1627, $\nu_{(C=C)}$ 1550, $\nu_{(C-H)}$ 3063, $\nu_{(C-Br)}$ 561, $\nu_{(C-CH3)}$ 2914, $\nu_{(N=O)}$ 1311,1516. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H, Ar-CH_3); 7.06-8.37 (m, 7H, Ar-H); 8.86 (s, 1H, N=CH). Mass spectra (GC-MS) m/z = 318 $[M-H]^+$.

2. 4. 2. 2-bromo-4-methyl-N-(2,4,5-trimethoxybenzylidene)aniline

White, Yield: 87%. Melting point: 146 ºC. Molecular weight: 364.23. Elemental analysis calc. ($C_{17}H_{18}BrNO_3$) (%): C, 56.06; H, 4.98; N 3.85; O, 13.18; found: C, 55.06; H, 5.01; N 3.78; O, 12.10. FT-IR (KBr) (cm^{-1}): $\nu_{(HC=N)}$ 1693, $\nu_{(C=C)}$ 1554, $\nu_{(C-H)}$ 3009, $\nu_{(C-Br)}$ 578, $\nu_{(C-CH3)}$ 2937. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H, Ar-CH_3); 3.88 (s, 3H, Ar-OCH_3), 3.97-3.93 (d, 6H, Ar-OCH_3); 6.52-7.75 (m, 5H, Ar-H); 8.71 (s, 1H, N=CH). Mass spectra (GC-MS): m/z = 363 $[M-H]^+$.

2. 4. 3. 2-bromo-N-(4-methoxybenzylidene)-4-methylaniline

Brown, Yield: 77%. Melting point: 58-60 ºC. Molecular weight: 304.18. Elemental analysis calc.: ($C_{15}H_{14}BrNO$) (%): C, 59.23; H, 4.64; N, 4.60; O, 5.26 found: C, 59.13; H, 4.66; N, 4.50; O, 5.06. FT-IR (KBr) (cm^{-1}): $\nu_{(HC=N)}$ 1629, $\nu_{(C=C)}$ 1591, $\nu_{(C-H)}$ 3190, $\nu_{(C-Br)}$ 586, $\nu_{(C-CH3)}$ 2966. ^{1}H-

NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H, Ar-CH_3); 3.85 (s, 3H, Ar-OCH_3); 6.88-7.89 (7H, Ar-H); 8.25 (s, 1H, N=CH). Mass spectra (GC-MS) *m/z* = 303 $[M-H]^+$.

2. 4. 4. N-((1H-indol-3-yl)methylene-2-bromo-4-methylaniline

Light orange, Yield: 70%. Melting point: 169-172 ºC. Molecular weight: 313.19. Elemental analysis calc.: ($C_{16}H_{13}BrN_2$) (%): C, 61.36; H, 4.18; N, 8.94; found: C, 61.26; H, 4.28; N, 8.84. FT-IR (KBr) (cm^{-1}): $\nu_{(HC=N)}$ 1643, $\nu_{(C=C)}$ 1573, $\nu_{(C-H)}$ 3149, $\nu_{(C-Br)}$ 532, $\nu_{(C-CH3)}$ 2928. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H, Ar-CH_3); 10.07 (s, 1H, NH); 7.02-8.70-8.65 (m, 8H, Ar-H); 8.59 (s, 1H, N=CH). Mass spectra (GC-MS): *m/z* = 312 $[M-H]^+$.

2. 5. Antimicrobial activity

MIC determination was employed to ascertain the antimicrobial activity of synthesized Schiff bases in suspended Luria Broth in sterile double distilled water as a media. The antibacterial activity of the ligands has been tested against *S. aureus, B. subtilis* (Gram-positive bacteria), *S. marcescens, E. coli* (Gram-negative bacteria) and antifungal activity was carried out against *Rhizopus* sp. and *A. niger*. Culture was incubated for 24 hrs at 35 ºC for gram positive and negative bacteria. MIC was determined using two fold serial dilution technique in liquid media containing varying concentration of tested compounds from 0.1–10,000 µM. Bacterial growth was measured by the turbidity of the culture after 15 h. All equipments and culture media employed during the process were sterile. The results were monitored by measuring inhibition zones in mm. DMF/$CHCl_3$ was used as a solvent. The growth of fungus was measured by recording the diameter of fungal colony. The following relation is used to calculate the fungal growth inhibition:

$$\text{Fungal growth inhibition (\%)} = [(A - B)/A] \times 100$$

where: A is the diameter of the fungal colony in the control plate and B is the diameter of the fungal colony in the test plate.

2. 6. Potentiometric measurement

Potentiometric studies can be used to determine the proton - ligand stability constant (pK_1^H) of the Schiff bases and metal-ligand stability constant of the formed complexes. In the present study, the proton-ligand stability constant and metal-ligand stability constants were determined by Calvin-Bjerrum titration technique adopted by Irving-Rossotti. All the pH-metric titrations were carried out in 60:40 % (V/V) 1,4-dioxane-water mixture at constant temprature 27 ±0.5 ºC at ionic strength = 0.1M. The following three sets (A-C) of solutions were prepared keeping the total volume is 50 ml before the titration:

Set-A: HNO_3 (0.2M, 5 ml) + KNO_3 (1M, 9.0 ml) + D.D.W. (6.0 ml) + 30 ml 1,4-dioxane.

Set-B: HNO_3 (0.2M, 5 ml) + KNO_3 (1M, 8.9 ml) + Ligand solution (0.02M, 5 ml) + D.D.W. (6.1 ml) + 25ml 1,4-dioxane.

Set-C: HNO_3 (0.2M, 5 ml) + KNO_3 (1M, 8.8 ml) + Ligand solution (0.02M, 5 ml) + Metal nitrate solution (0.02M, 5ml) + D.D.W. (1.2 ml) + 25 ml 1,4-dioxane.

The solutions were titrated potentiometrically against 0.2M KOH solution in this titration technique, the ratio of metal (M): ligand (L) was maintained at 1:1 in each of the binary system. The pH meter readings were taken after each addition of alkali and change in pH was obtained.

3. RESULTS AND DISCUSSION

3. 1. Characterization of ligand

The Schiff base compounds were synthesized according to scheme-1 to 4. The structures of all the compounds were established on the basis of elemental analysis, FT-IR, mass and ^{1}H NMR spectral data. The ligands were insoluble in water but soluble in methanol, ethanol, chloroform, 1,4-dioxane and DMF.

3. 1. 1. IR Spectral Studies

The IR spetra of four Schiff bases strong bands was observed at 1627-1693 cm^{-1} belong to (HC=N) vibration of azomethine group. The asymmetric C-H vibration for methyl group was occurred in the range 2914-2966 cm^{-1}. The C-Br stretching vibration appeared in the range 532-586 cm^{-1}. (ν C-NO_2) is appeared at 1311- 1516 cm^{-1} region in the BMNBA spectrum. Aromatic ν(C-H) stretching at 3063-3009 cm^{-1} and the C=C stretching vibrations of Schiff bases are strongly observed at 1550 cm^{-1}, 1554 cm^{-1}, 1591 cm^{-1} and 1573 cm^{-1} proved existence of aromatic rings.

3. 1. 2. Mass spectral studies

The mass spectra showed molecular ion peak at m/z: 318, 363, 303 and 312 corresponding to molecular weights of the BMNBA, BMTBA, BMBMA and IMBMA ligands, respectively.

3. 1. 3. ^{1}H NMR spectral studies

In the ^{1}H NMR spectra of Schiff base, The Chemical Shift of Aromatic protons are observed as multisignals within the range from 6.52-8.70 δppm. A sharp singlet is observed for Schiff bases within the 8.25-8.86 δppm region of spectrum which corresponds to the azomethine group proton. The methyl group protons appear as a singlet at 2.32-2.36 δppm. The methoxy group of compounds BMTBA and BMBMA were shown singlet at about 3.85-3.97ppm. The signal at δ (10.07) (s, 1H) was assigned to -NH group proton in the BMPIM ligand.

3. 2. Antimicrobial activity

All the synthesized compounds were screened for antimicrobial activity by MIC determination. MIC was determined by the comparision between the amount of growth in the tubes/wells containing antimicrobial agents and the growth in the growth-control wells/tubes (with no active ingredients) in each set of tests. For present study, antibiotics used were Ketoconazole and Ciprofloxacin. The results showed that among the tested compounds, BMBMA has been found very effective against Gram positive bacteria *B. subtilis* and Gram negative bacteria E.coli and IMBMA has exhibited maximum bactericidal activities against *S. aureus* and *S. marcescens*. BMNBA is less active against both gram-positive and gram-negative bacteria. BMTBA and BMBMA are moderate active against *S. aureus* and *S. marcescens*.

IMBMA is less active against *B. Subtilis* and showed moderate activity against *E. coli*. In the fungal studies, BMBMA exhibited moderate fungicidal activity against *Rhizopus* sp. and minimum against *A. niger*. Compound BMBMA and IMBMA are inactive against *A. Niger*. Remaining compounds are less active against *Rhizopus* sp. and *A. niger*. The column graph of Antibacterial and antifungal activities of Schiff bases are presented in Figure 1.

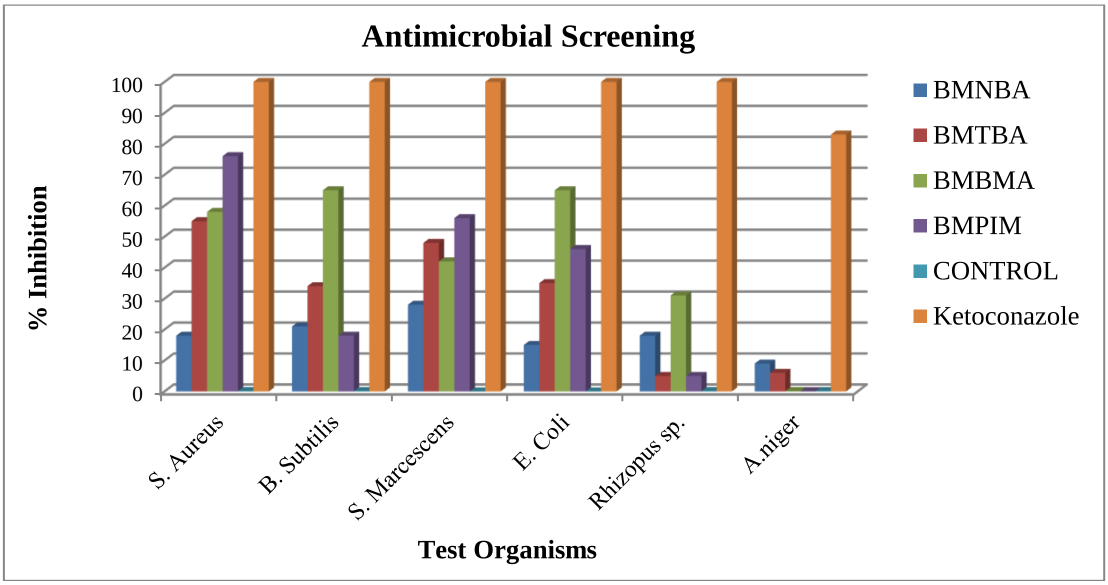


Figure 1. Antibacterial and antifungal activity of Schiff bases

3. 3. Potentiometric measurements

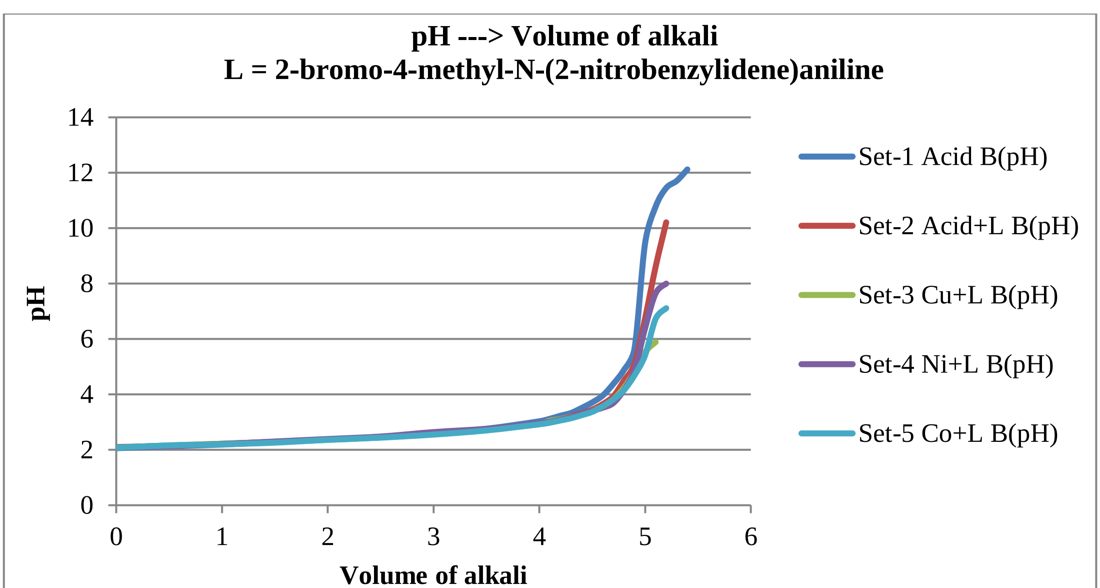


Figure 2. Potentiometric titration curve of BMNBA for acid, acid+ligand and acid+ligand+metal

In this research work, all pH measurements are obtained by Calvin-Bjerrum pH-metric titration technique as adopted by Irving - Rossotti. Evaluated values of stability constants show the behavior of ligands and their interaction with metal ion in solution. The stability constants derived are depended on experimental conditions of solvent system *i.e.* 60:40 % V/V dioxane-water system at 27 ±0.5 ºC. pH-metry data can be converted into stability constant using pointwise calculation method as given by Irving and Rossotti. The formation curves were obtained for acid, acid + ligand and acid + ligand + metal by the pH values plotted against the volume of alkali as given in fig.(2) for BMNBA Schiff base.

3. 3. 1. Proton-ligand stability constant

The ligand act as a base and the basicity of ligand is one of the important factor which is helpful in deciding the stability of resulting complex. So, if other factors are same the stability is propotional to the proton-ligand stability constant log pK_1^H. The plots of volume of alkali (KOH) against pH values were used to evaluate the proton-ligand stability constant of Schiff bases BMNBA, BMTBA BMBMA and BMPIM. The horizontal difference between ligand titration curve from the free acid titration curve was used to evaluate the formation constant $\bar{n}_H$, the average number of proton associated with the ligand molecule L at different pH values from the following equation – (1).

$$\bar{n}_H = y + \frac{(V'' - V')\,(N^\circ + E^\circ)}{(V^\circ + V')T_L^\circ} \qquad \text{................(1)}$$

$$\log pK_1^H = B + \log [\, \bar{n}_H/(1-\bar{n}_H)] \qquad \text{..................(2)}$$

where: V′, V′′ are the volumes of alkali required to reach the same pH in the acid and acid+ligand titration curves respectively, V^o and T^o_L are the initial volume of mixtures and initial concentration of the ligand respectively, N^0 and E^0 are the concentration of base and initial concentration of acid in the mixture respectively, Y is the number of dissociable protons from ligand and B is the pH meter readings. Values of proton-ligand stability constant (log pK_1^H) have been obtained by pointwise calculation method from linear plot of pH against log ($\bar{n}_H$/(1- $\bar{n}_H$)), as given in Fig.(3). Derived values of proton-ligand stability constant by equation-(2) are given in Table 1.

Table 1. Proton-Ligand Stability Constant of Schiff Base

Ligand	**Log pK_1^H**	**pK_1^H**
BMNBA	4.51	3.2359×10^4
BMTBA	4.94	8.7096×10^4
BMBMA	5.63	4.26580×10^5
BMPIM	5.16	1.44543×10^5

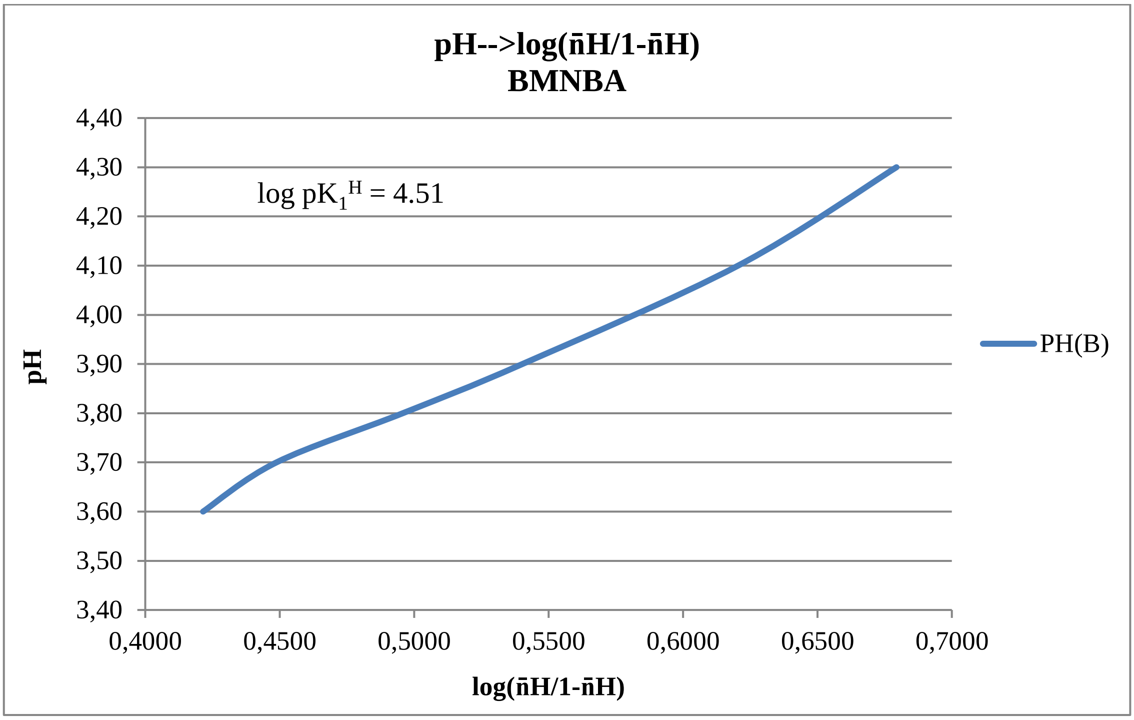


Figure 3. Plot of pH against log ($\bar{n}_H$/(1- $\bar{n}_H$)) of BMNBA

3. 3. 2. Metal-ligand stability constant for binary system

The metal-ligand stability constant of binary complexes were evaluated assuming that (i) metal complexes are formed in solution under the experimental conditions used, (ii) no hydrolysed products or polynuclear hydrogen bearing complexes are formed and absence of anion complexing of metal ion. In this study, the data of stability constant has been examined and it is evident that the metal – titration curve shows considerable deviation below the reagent titration curve along the volume axis and during the metal titrations, a distinct color appears at particular pH value is the reason of complex formation in solution. The stability constants are calculated between pH range 3.0 to 8.0 where precipitation is not observed for any system and metal hydroxides can also not be precipitated. The formation curve for metal-ligand stability constant is obtained by constructing a plot of pL → log ((1-n̄)/n̄) as given below in Fig. (4). From these formation curves, the values of stability constants were determined using pointwise calculation method. The $\bar{n}$ values and from that the values of free ligand exponent, pL are determined using these equations:

$$\bar{n} = \frac{(V''' - V'')[N^{\circ} + E^{o} + T_L^{o}\,(Y - \bar{n}_H)]}{(V^{o} + V'')\,\bar{n}_H\,T_M^{o}} \qquad \text{……..……..(3)}$$

$$pL = \log_{10}\left[\frac{\sum_{J=o}^{J} \beta_J^H \cdot \frac{1}{(antilog\ B)^J}}{T_L^{\circ} - \bar{n}\,.T_M^{\circ}} \times \frac{V^{\circ} + V'''}{V^{\circ}}\right] \qquad \text{…………….(4)}$$

where, $\bar{n}$ is average number of ligand bound per metal ion, T_M^o is initial total metal ion concentration and V'' and V''' are volumes of alkali required to attain the same pH in the (acid + ligand) and (acid+metal+ligand) curves respectively, $\beta_J{}^H$ is the overall proton ligand stability constant and the other terms have their same meaning as mentioned above. The values of $\bar{n}$ was found to be between 0.0 to 1.0 for binary complexes of Co(II), Ni(II) and Cu(II) metal ions which indicating the formation of 1:1complexes in solution. The values of $log\ K_{ML}^M$ were listed in Table 2. From the data of Log K_1, the order of metal – ligand stability constant in BMNBA and BMTBA is Co(II) > Cu(II) >Ni(II) and in BMBMA is Ni(II) > Cu(II) > Co(II) and in BMPIM is Cu(II) > Co(II) > Ni(II).

Table 2. Metal-Ligand Stability Constants for Binary (M- Schiff Base) Complex System

Sr. No.	**Ligand**	**Log K_1**		
		Co	Ni	Cu
1.	BMNBA	4.1129	3.2672	3.8709
2.	BMTBA	4.8722	4.1686	4.4865
3.	BMBMA	4.2559	4.7543	4.4515
4.	BMPIM	4.2064	4.1269	4.2086

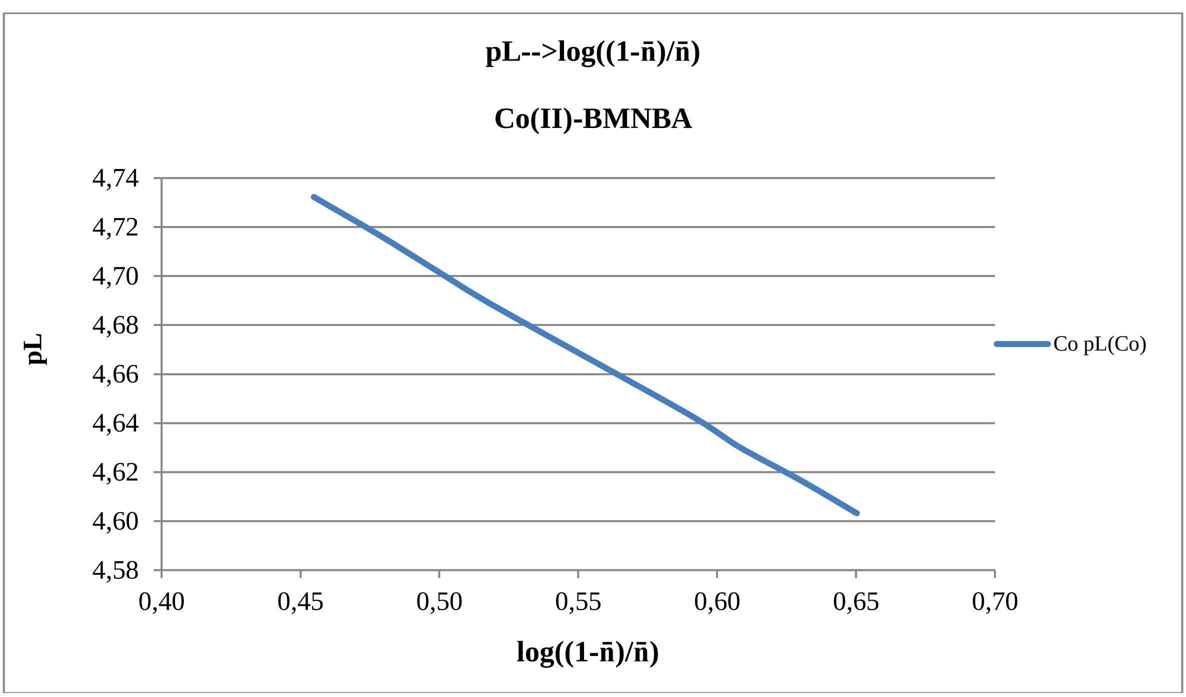


Figure 4. Graphs of pL vs log((1-n)/n) for schiff base BMNBA with Co metal ion

4. CONCLUSIONS

In this paper, we have described new Schiff base, synthesized by condensation of 2-bromo-4-methyl aniline with different aldehydes like 2-nitro benzaldehyde; 2,4,5-trimethoxy benzaldehyde; 4-methoxybenzaldehyde; 1H-indole-3-carbaldehyde in an alcoholic medium using glacial acetic acid with good yield give BMNBA, BMTBA, BMBMA and BMPIM respectively. The structure of Schiff bases have been confirmed by various physicochemical methods. In this study, these Schiff base derivatives are found active antimicrobial compound. Schiff base BMBMA and BMPIM were proved to have maximum antibacterial activity against both Gram-negative and Gram-positive bacteria and Schiff base BMBMA also exhibited moderate antifungal activity against Rhizopus sp. In the present article, the proton-ligand and metal-ligand stability constants of binary complexes of Schiff bases with different metal ions were calculated using potentiometric methods in 60:40 % (V/V) 1,4-dioxane-water mixture at constant temperature 27 ±0.5 ºC and at ionic strength μ = 0.1M. To determine the stability constant of Binary complexes in solution, pointwise calculation method were used. The order of stability of the formed binary complexes in solution was examined.

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