



## Potentiometric and conductometric studies of binary and ternary complexes of sulphamethoxazole and glycine with metal ions

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**Abstract** Potentiometric and conductometric studies of binary and ternary complexes of sulphamethoxazole (SMZ) and glycine (Gly) with metal ions; Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Th(IV), Ti(II) and Zr(IV). In 0.1 M NaClO<sub>4</sub> and 25 % (v/v) ethanol–water mixture, stability constant of metal ions complexes with SMZ have been determined potentiometrically. The ionic strength effect on the formed complexes stability was studied. The stoichiometries of these complexes were determined conductometrically and indicated that the formation of 1: 1, 1: 2 and/or 1: 3 (metal: ligand) complexes. Also, the species distribution diagrams of SMZ and its metal ion complexes were reported. For ternary complex; M: SMZ: Gly = 1: 1: 1, the protonation constants were calculated. The order of stability of both binary and ternary complexes was examined.

**Keywords** Sulfamethoxazole, Glycine, Potentiometry, Conductometry, Stability Constants, Distribution Diagrams.

### 1 Introduction

Sulfamethoxazole (4-amino-N-(5-methyl-3-isoxazolyl)-benzenesulfonamide; (SMZ)) is the most predominant sulfonamide in human medicine. Sulfonamides are synthetic antimicrobial agents derived from sulfanilamide, whose antibacterial activity was discovered in the early 1930's by Domagk and Tréfouel [1–3]. Especially in the case of penicillin's hypersensitivity, sulfonamides were prescribed against a wide variety of bacterial infections. However, the widespread bacterial resistance to these compounds limits their application spectrum today. In monotherapy, sulfonamides lead to a bacteriostatic effect, while a combination with trimethoprim, a diaminopyridin derivative, results in a bactericidal effect [4]. SMZ is used often in combination with trimethoprim for the treatment of urinary tract infection and also prophylaxis of pneumocystis carinii pneumonia in AIDS patient [5–7]. Intrarenal distribution of trimethoprim and SMZ were studied by Trottier et al [8]. SMZ is metabolized to a varying extent in the human body (e.g. by N<sup>4</sup>-acetylation and hydroxylation) and are subsequently excreted mainly via the urine. Approximately 50 % of the administered dose is excreted as the inactive metabolite N<sup>4</sup>-acetylsulfamethoxazole [3].

The realization of the interaction between biologically active molecules and metals is extremely important. Such interactions occupy prominence in the field of medicinal inorganic chemistry where it is offer great possibilities in biomaterials preparation process, considering certain aspects of biocompatibility or even in design of therapeutic agents which are not readily available to organic compounds [9–11]. Actually, therapeutic value of the metal drug complexes has encouraged the researcher to improve on new alternative drugs [12, 13]. The use of metal complexes in medicine as chemotherapeutic agent, magnetic resonance imaging contrast agent and rheumatic drugs are well established [14–18]. In our case, the presence of donor atoms (N, S, O) at various positions in SMZ molecules enable them to behave as multidentate ligands and thus form chelates of diverse structural types with a wide range of metal ions [19]. It was found that the product of metal chelates of sulfa



drugs is more bacteriostatic than the drugs themselves [20–24]. In addition to sulfa drugs, other drugs show the same behavior when it chelate with metal ions studied in present work [24–31].

The study of model species such as the simple amino acids can assist in the interpretation of more complex system. Amino acids form complexes with metal atoms and exhibit significant biological and enzymatic activities [32]. Glycine (Gly) as a simple amino acid has the neutral donor N at one end and acidic replaceable H at the other end and is sufficient length to span two adjacent coordinating site and the resulting complexes is a non electrolyte chelate or inner complex compound [33]. Condensation of glycine metal complexes with glutaraldehyde can be used for the synthesis of coordination polymers [34].

This work reports the results of a potentiometric and conductometric investigations of binary and ternary complexes of sulfamethoxazole and glycine with the several important metal ions; Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Th(IV), Ti(II) and Zr(IV).

## 2 Experimental

### 2.1 Materials

Sulfamethoxazole (SMZ) (AL–Maya Pharmaceutical Factory, Tripoli, Libya), glycine (Gly) was Merck biochemical grade reagents. Other chemicals and solvents were obtained from commercial sources and were used as purchased. All syntheses were carried out under ambient atmosphere. Standard solution were prepared by using double–distilled CO<sub>2</sub>–free water and stored in the refrigerator.

### 2.2 Apparatus

All the potentiometric measurements were made using VWR Scientific Products Model 2000, USA. Before and after each titration, the electrode was calibrated using standard buffer pH ≈ 4.01, pH ≈ 7.00 and pH ≈ 9.00. Conductance TDS Engineered system, U.S.A, was employed for the conductometric titration.

### 2.3 Procedure

#### 2.3.1 pH–metric studies

This is based on Rossotti method [35, 36]. Generally, six sets of solutions; free acid, free acid + primary ligand (SMZ), free acid + primary ligand (SMZ) + metal ion, free acid + secondary ligand (Gly), free acid + secondary ligand (Gly) + metal ion, and finally solution of free acid + primary ligand (SMZ) + secondary ligand (Gly) + metal ion were prepared and titrated against standard carbonate–free NaOH solution at 25 ± 0.1 °C. In all titrations, the total volume was maintained constant at 50 mL and different ionic strength of NaClO<sub>4</sub>. Multiple titrations were carried out for each system.

#### 2.3.2 Conductometric titration

It was carried out at room temperature by titrating 25 mL of 0.001 M of each metal ion with 0.01 M of each ligand solution in 0.5 mL increment. Correction for the dilution effect is performed by multiplying the values of specific conductance by factor (25+V)/25, where V is the volume of the titrant added.

## 3 Results and discussion

### 3.1 Proton–ligand formation constants

Potentiometric titration of SMZ in the presence of 0.01 M HClO<sub>4</sub> was carried out. Ligand protonation constant and stability constants of complexes formed with some metal ions have been tabulated with different ionic strengths, I = 0.1, 0.2, 0.3, 0.4, and 0.5 M NaClO<sub>4</sub> aqueous solution adjusted by addition of NaClO<sub>4</sub> at 25 ± 0.1 °C and using carbonate–free NaOH as a titrant. The representative titration curves are shown in Fig. 1.

According to Irving and Rossotti [35, 36], calculations of proton–ligand formation constants was carried out by plotting  $\bar{n}H$  against pH (titration curves were a and b solutions) . The average number of proton attached per

ligand,  $\bar{n}H$  was calculated at different pH values using Irving and Rossotti [35, 36], as shown in Eq. 1:

$$\bar{n}H = Y + \frac{(V_1 - V_2)(N^\circ + E^\circ)}{(V_o + V_1)T_cL^\circ} \quad (1)$$

Where Y = 2 (number of dissociable protons in the ligand), V<sub>o</sub> is the initial volume, V<sub>1</sub> and V<sub>2</sub> are the alkali volume required to reach the same pH value either in mineral acid (HClO<sub>4</sub>) or (HClO<sub>4</sub>+SMZ) solutions, respectively. T<sub>c</sub>L<sup>o</sup> is the total concentration of the ligand, N<sup>o</sup> is the normality of the alkali and E<sup>o</sup> is the initial

concentration of free acid. Calculation of proton ligand dissociation constants were carried out by plotting  $\bar{n}H$  against pH at 0.1 M NaClO<sub>4</sub> ionic strength as shown in Fig. 2.



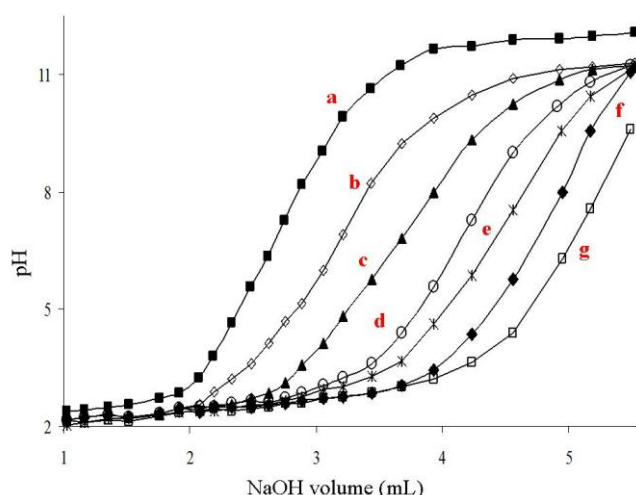


Figure 1: Representative potentiometric curves of SMZ in 0.1 M NaClO<sub>4</sub> at 25 ± 0.1 °C: (a) 0.01 M HClO<sub>4</sub>, (b) a + 0.001 M SMZ, (c) b + 0.001 M Sr (II), (d) b + 0.001 M Pb (II), (e) b + 0.001 M Co (II), (f) b + 0.001 M Fe (III) and (g) b + 0.001 M Al (III).

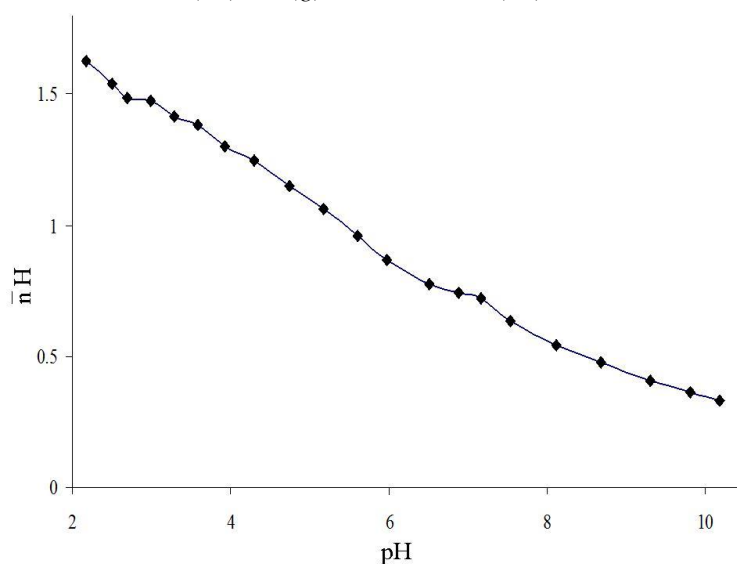
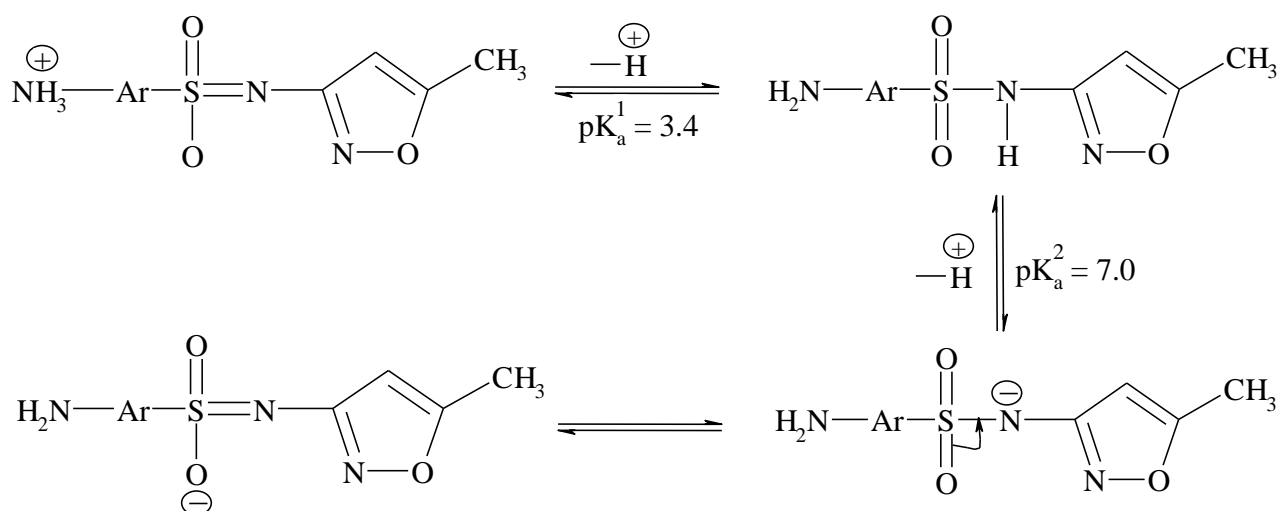


Figure 2: Representative protonation constant curve of SMZ in 0.1 M NaClO<sub>4</sub> at 25 ± 0.1 °C. SMZ undergoes two deprotonation steps up to pH 11.5, attributed to the  $-\text{NH}_3^+$  and  $-\text{NH}$  groups of the ligand, the values corresponding to  $\bar{nH}$  equal to 0.5 and 1.5. The values of  $\text{Log}K_1^H$  and  $\text{Log}K_2^H$  are 7.0 and 3.4 respectively. Under our condition, the protonation constant of amino group ( $-\text{NH}_2 \rightarrow -\text{NH}_3^+$ ) at  $\text{p}K_a = 1.83$  did not calculated [37]. However, the reaction mechanism is show as follow:





### 3.2 Metal–ligand formation constants of binary (1:1) systems

The pH–metric titration of ten metal salts solutions; Ti(II), Zr (IV), Sr(II), Al(III), Cr(III), Fe(III), Th(IV), Pb(II), La(III) and Co(II) were selected to elucidate their interaction with SMZ using potentiometric method. The protonation constant of the compound and stability constants of complexes formed were calculated using ionic strength,  $I = 0.1 \text{ M NaClO}_4$  in aqueous solutions at  $25 \pm 0.1 \text{ }^\circ\text{C}$  and using carbonate–free NaOH as a titrant.

In Fig. 1 the titration curves of the metal–ligand solutions (curves from *c* to *g*) are well separated from the curve of ligand solution (curve *b*). Thus replacement of  $\text{H}^+$  ion is due to complexation. From these titration curves,  $\bar{n}$  (average number of ligand molecules attached per metal ion) and  $pL$  (free ligand exponent) values were calculated using Irving and Rossotti equations [35, 36].

$$\bar{n} = \frac{(V_3 - V_2)(N^\circ + E^\circ)}{(V_0 + V_2)n_A T_c M^\circ} \quad (2)$$

$$pL = \text{Log} \left[ \frac{1 + \beta_1 [H^+] + \beta_2 [H^+]^2}{(T_c L^\circ - \bar{n} T_c M^\circ)} \times \frac{V_0 + V_3}{V_0} \right] \quad (3)$$

Where  $V_1$ ,  $V_2$  and  $V_3$  are the volume of alkali to reach the same pH in the free acid, free acid + ligand and free acid + ligand + metal ion curves, respectively.  $V_0$  is the original volume of the mixtures (50 ml).  $T_c M^\circ$  denotes the total concentration of metal present in the solution.

**Table 1:** Formation constants of SMZ and stability constants of metal ion complexes at  $0.1 \text{ M NaClO}_4$  and  $25 \pm 0.1 \text{ }^\circ\text{C}$ .

Metal ion	Log $K_1$ (M: L)*	Log $K_2$ (M: L)*	Log $K_3$ (M:L)*
$\text{H}^+$	7.0	3.4	-----
Al (III)	11.18 (1:1)	8.24 (1:2)	5.56 (1:3)
Pb (II)	11.09 (1:1)	8.44 (1:2)	-----
Zr (IV)	11.71 (1:1)	9.28 (1:2)	6.46 (1:3)
Ti (II)	11.39 (1:1)	8.75 (1:2)	-----
Co (II)	10.24 (1:1)	8.04 (1:2)	4.37 (1:3)
Fe (III)	10.53 (1:1)	7.83 (1:2)	-----
Cr (III)	10.84 (1:1)	8.38 (1:2)	5.98 (1:3)
Sr (II)	11.36 (1:1)	8.50 (1:2)	-----
Th (IV)	11.9 (1:1)	10.25 (1:2)	-----
La (III)	11.5 (1:1)	8.65 (1:2)	-----

\*These ratios are from potentiometric and conductometric methods



The  $n$  values were plotted against the corresponding pL values to get the formation curves of the metal complexation equilibria. The formation curves are shown in Fig. 3. From these formation curves, the values of stability constants at 0.1 M NaClO<sub>4</sub> ionic strength listed in Table 1 were determined using the half-integral method [35, 36].

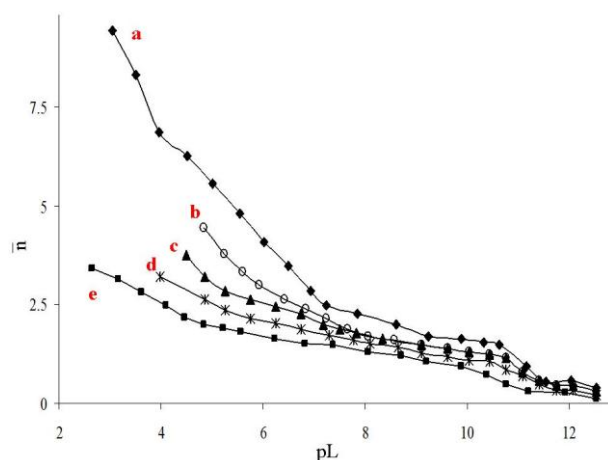
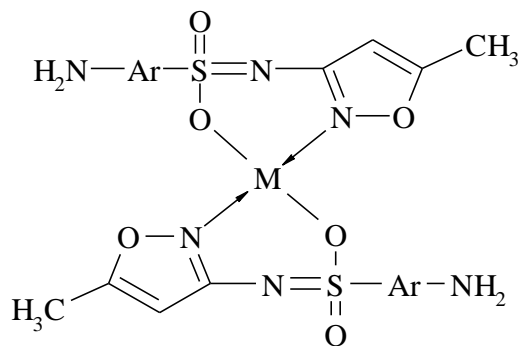


Figure 3: Representative formation curves of binary metal ion complexes with SMZ in 0.1 M NaClO<sub>4</sub> at 25 ± 0.1 °C: (a) Th (IV), (b) Ti (II), (c) La (III), (d) Sr (II) and (e) Co (II).

Looking at the Table 1 we can conclude that, some metal ions such as Zr(IV), Al(III), Cr(III) and Co(II) with SMZ forms three types of metal–ligand complexes; 1:1, 1:2 and 1:3 (metal : ligand) at the ionic strength under investigation. For the other metal ions (Sr(II), Pb(II), Ti(II), Fe(III), Th(IV) and La(III)) tend to form two types of metal–ligand complexes; 1:1 and 1:2 (metal : ligand). This may be due to the concentration of ligand, ionic strength and the nature of metal ion.

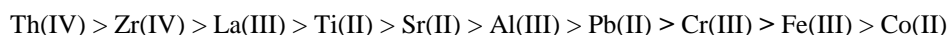
SMZ has two sites, the first site is the deprotonation of protonated amino group (NH<sub>3</sub><sup>+</sup>) and the other site is the dissociation of proton in the imino group (NH). These sites are shown as follow:



Ratio (1:2) (metal:ligand)

SMZ has two sites bearing protons. The first site is N–isoxazol ring and the second one is sulfonamido (–SO<sub>2</sub>NH–) group. The proton may be dissociated from these sites in proportions which vary with the degree of neutralization [38]. It is suggested that the structures of SMZ chelates are similar to Cu(II) chelates of some sulfa–drugs which supported by previous studies of metal–sulfa–drugs complexes [39].

The order of stability constants of the different binary complexes formed between SMZ and bivalent metal ions investigated in this study is in the expected Irving–Williams order [40, 41] for (1:1) metal to ligand at I = 0.1 M NaClO<sub>4</sub>:



Looking at our results it can be seen that, comparison of the formation constants of metal ions investigated with SMZ is difficult due to the lack of data concerning these systems. It is worth mentioning that the pH–metric determination of the formation constant for binuclear complex species was not possible. This is due to the formation of this type of complexes at high pH values, *i.e.* beyond the precipitation point for each system. On the other hand, the weak tendency of binuclear complex formation for this ligand can be attributed to the electron



drawing character of the six-membered chelate ring formed. This behavior can also be attributed to the steric effect which results from the electrostatic repulsions between the protonated metal complex and the metal ion. The effect of ionic strength on stability constant of SMZ with different metal ions; Zr(IV), Th(IV), Al(III), Cr(III) and Pb(II) has been discussed. The studied ionic strength's values were 0.1, 0.2, 0.3, 0.4 and 0.5 M NaClO<sub>4</sub> at 25 ± 0.1 °C. By plotting the relation between the ionic strength under investigation and the first stability constants  $\text{Log}K_1^H$ , we can conclude that the stability constants of metal–ligand complex (1:1) were decreased as the ionic strength increased (Fig. 4).

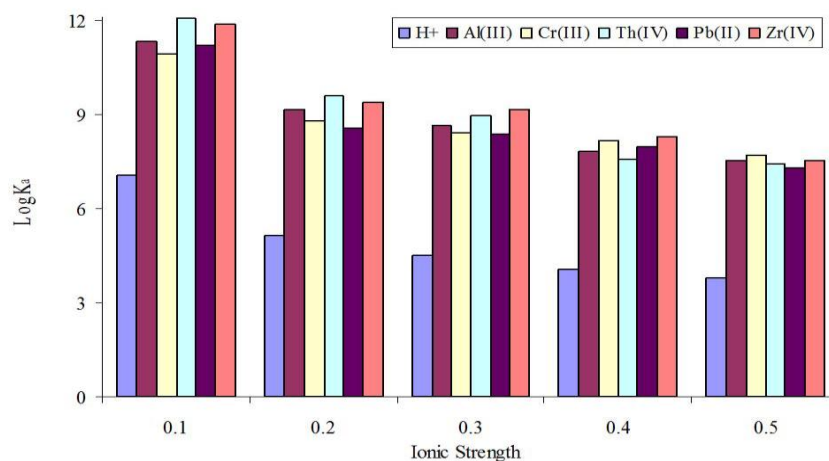


Figure 4: Effect of ionic strength on stability constants of SMZ with metal ions.

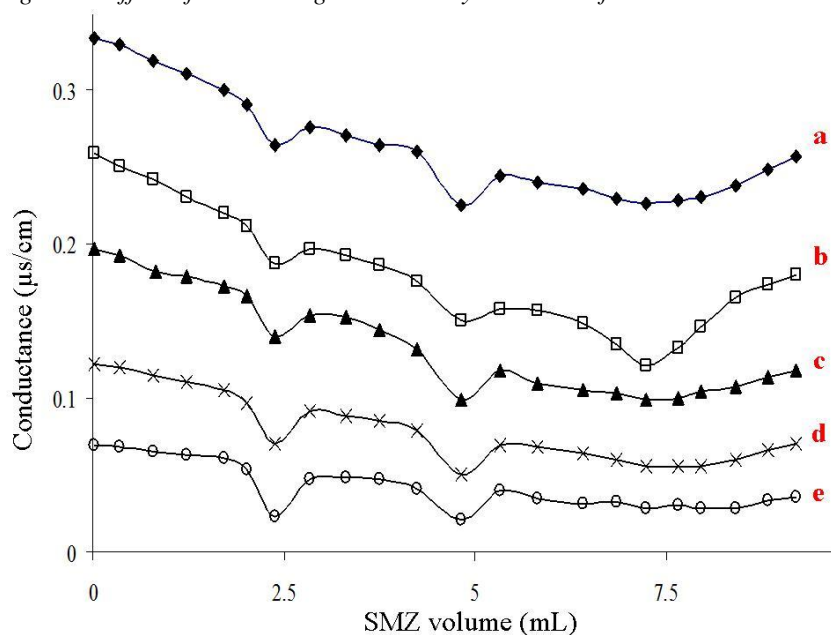


Figure 5: Representative conductometric titration curves of 25 mL 0.001 M metal ions with 0.01 M SMZ in 0.1 M NaClO<sub>4</sub> at 25 ± 0.1 °C: (a) Th (IV), (b) Cr (III), (c) La (III), (d) Co (II) and (e) Ti (II).

### 3.3 Conductometric studies on the metal complexes of SMZ

Conductometric measurements can be applied for tracing complex formation in solution. This method has useful application as a sensitive tool to test for decimal variations in ionic radii of investigated transition metal ions. The conductometric analysis is based on changes in the electrical conductivity values of solutions as a result of complex formation. These changes depend upon the number of ions present and their mobilities. In this work, conductivity measurements were employed to trace the different types of chelate species formed between Ti(II), Zr(IV), Sr(II), Al(III), Cr(III), Fe(III), Th(IV), Pb(II), La(III) and Co(II) in addition to SMZ.

The conductometric titrations were performed by titrating 25 mL of each metal ion ( $1 \times 10^{-3}$  M) with successive volumes of SMZ solution ( $1 \times 10^{-2}$  M). Plotting of the recorded specific conductance values as a function of the added volumes of SMZ is shown in Fig. 5. The obtained relationship show a well defined breaks corresponding



to the stoichiometric ratios 1:1, 1:2 and/or 1:3 (metal:ligand), these results are in agreement with those obtained by potentiometric method (Table 1). The observed increase in conductivity during the range titration of metal ion with SMZ ligand during the complex formation, clearly indicate liberation of high ionic mobile  $H^+$  ions. Thus chelation can take place through covalent bond between the metal ion and nitrogen atom of imino (NH) group and liberation of hydrogen ions.

### 3.4 Species distribution diagrams of SMZ

Looking at Fig. 6, we can see that, in the pH range from 2.2 to 5.0, the major species of the ligand is  $\alpha^0 = H_2L$  species, but in the pH from 5.0 to 5.8, the  $\alpha_1 = HL^-$  species is the major one, as well as, the  $\alpha_2 = L^{2-}$  species is the major in the pH range from 5.8 to 11.4.

The mole fraction  $\alpha_{ML}$  and  $\alpha_{ML_2}$  can be calculated from potentiometric data using the obtained stability constant for ML, and  $ML_2$  complexes and the initial concentrations of metal ions and ligand [42]. The species distribution curves can be obtained by plotting  $\alpha$  ( $\alpha$ = mole fraction of the species) vs. pH as depicted in Fig. 6. Representative closely related plots were obtained for other metal–SMZ complex is shown in Fig. 7.

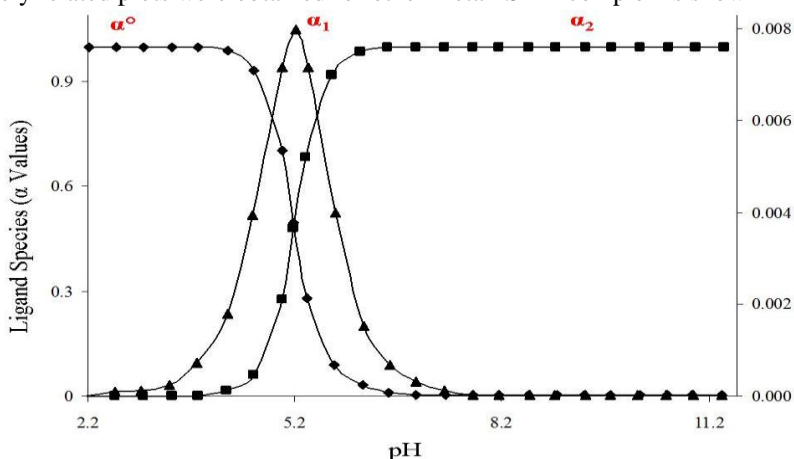


Figure 6: Ionic equilibria of SMZ in different pH ranges.

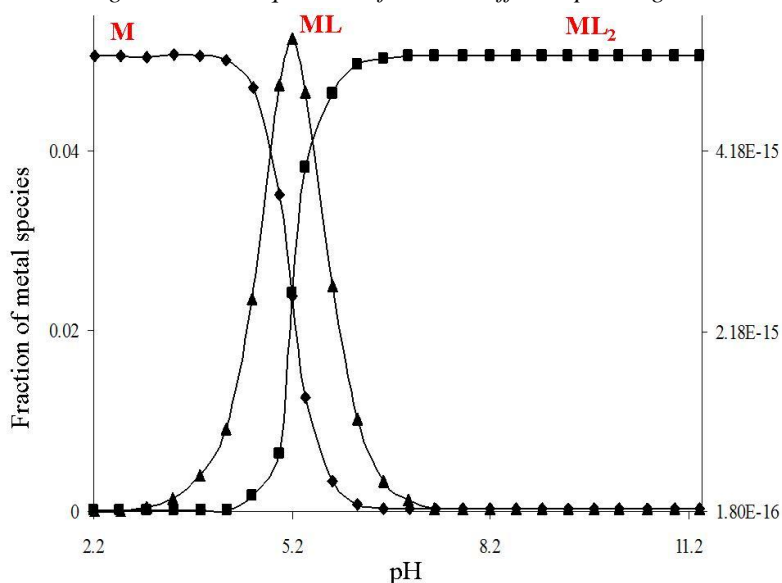


Figure 7: Representative ionic equilibria of Al–SMZ in different pH ranges.

On increasing the pH of medium, the concentration of metal ion tends to decrease, while that of ML species tends to increase at moderately acidic media (pH  $\approx$  2.8–3.5). The values of  $\alpha_M$ ,  $\alpha_{ML}$  and  $\alpha_{ML_2}$  present in solution depends mainly on the pH of the medium. The distribution curves show that complexation begins at pH values  $\approx$  2.4, 2.75, 2.79, 2.8, 2.81, 2.85, 2.9, 3.0, 3.1, and 3.25, for Pb(II), Fe(III), Co(II), Al(III), Zr(IV), Ti(II), La(III), Sr(III), Th(IV) and Cr(II), complexes respectively, as shown in Fig. 7.

At pH range of 4.4–11.6 the essential change is the increase in the concentration of  $ML_2$  with decrease in ML. Above this region, almost all of metal ion remains in the form of ML and  $ML_2$  species and their concentration





increases on increasing the pH of solution. This demonstrates clearly that ML species are much more stable than  $ML_2$  in their solutions. This behavior is in line with stability constant values obtained for the chelates (Table 1), with no significant  $\alpha_{ML_2}$  species of Th(IV) and Zr(IV) even at high values of pH.

### 3.5 Determination of formation constants of metal–SMZ–Gly complexes (Ternary system)

Ten metal ions viz; Ti(II), Zr(IV), Sr(II), Al(III), Cr(III), Fe(III), Th(IV), Pb(II), La(III) and Co(II) were selected to make further investigation to elucidate the interaction of these metal ions with mixtures of SMZ and Gly (mixed ligand complexes).

The potentiometric equilibrium measurements were made, at constant ionic strength  $I = 0.1 \text{ M NaClO}_4$  at  $25 \pm 0.1 \text{ }^\circ\text{C}$ , for the interaction of SMZ and the selected ten metal ions, with biologically important secondary ligand glycine (Gly) in a (1:1:1) molar ratio ( $1 \times 10^{-3} \text{ M}$  for each). The solutions were titrated pH–metrically against standard carbonate–free NaOH solution as illustrated in Fig. 8.

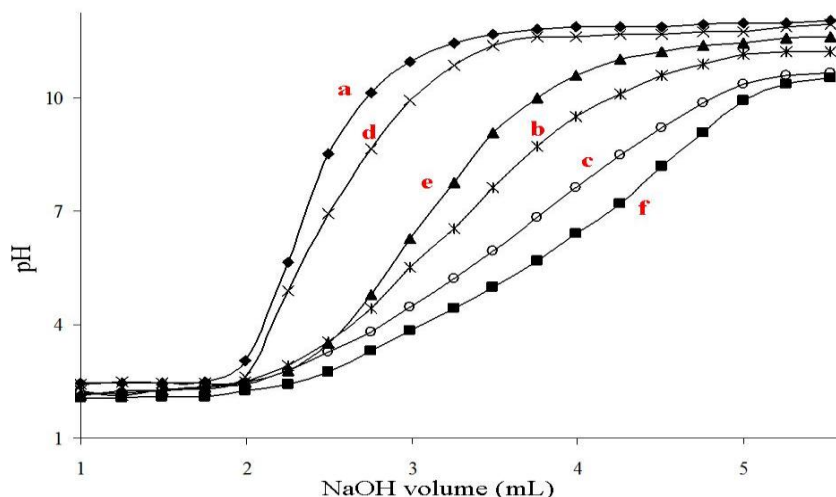


Figure 8: Representative potentiometric curves of Al(III)–SMZ–Gly system in  $0.1 \text{ M NaClO}_4$  at  $25 \pm 0.1 \text{ }^\circ\text{C}$ : (a)  $0.01 \text{ M HClO}_4$ , (b) a +  $0.001 \text{ M SMZ}$ , (c) b +  $0.001 \text{ M Al(III)}$ , (d) a +  $0.001 \text{ M Gly}$ , (e) d +  $0.001 \text{ M Al(III)}$  and (f) a +  $0.001 \text{ M SMZ} + 0.001 \text{ M Gly} + 0.001 \text{ M Al(III)}$ .

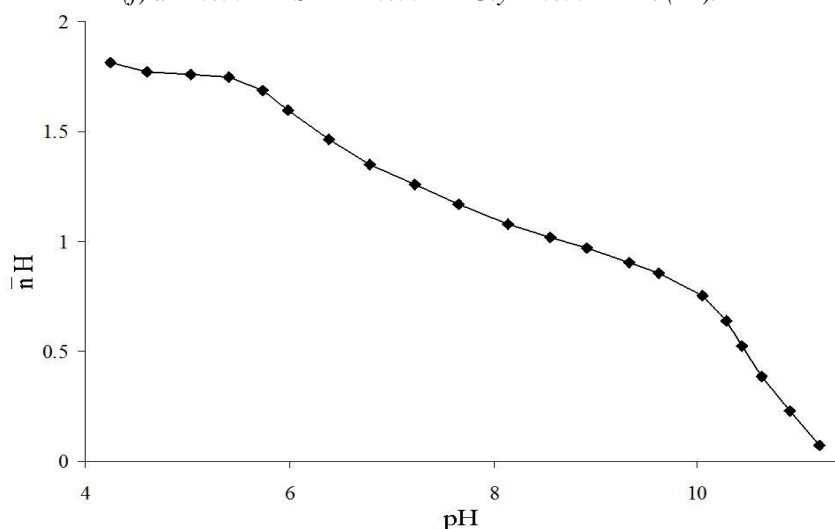


Figure 9: Representative protonation constant curve of Gly in  $0.1 \text{ M NaClO}_4$  at  $25 \pm 0.1 \text{ }^\circ\text{C}$ .

The proton ligand association constants for SMZ were calculated in the binary system from the titration curves as has already been mentioned in the previous section.

The proton–ligand stability constants for Gly were calculated from the titration curves (a and d) in Fig. 8 using equation of Irving and Rossotti [35, 36]. The proton–ligand formation curve was obtained by plotting  $\bar{nH}$  versus pH as shown in Fig. 9. The values of  $\text{Log}K_1^H$  and  $\text{Log}K_2^H$  proton–ligand association constants were





determined by interpolation at  $\bar{n}H$  values equal 0.5 and 1.5 are corresponding to the pH values of 10.3 and 5.5, respectively. The values are in a good agreement with the literature value [43]. It is worth mentioning that the first dissociation constant value is low. Accordingly this value is not used in the calculations.

In Fig. 8, the titration curve (e) which related to the metal–Gly solutions is well separated from the titration curve (d) which related to ligand solution. Thus, replacement of  $H^+$  ions is due to complexation. From these titration curves,  $\bar{n}$  (average number of ligand molecules attached per metal ion) and pL (free ligand exponent) values were calculated [35, 36]. The  $\bar{n}$  values were plotted against the corresponding pL values to get the formation curves of the metal complexation equilibria. The formation curves are shown in Fig. 10. From these formation curves, the values of stability constants which tabulated in Table 1 were calculated using the half-integral method [35, 36].

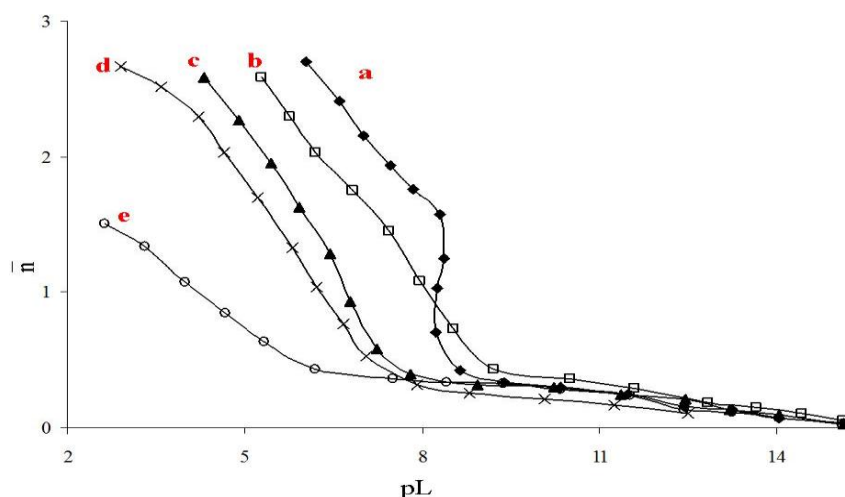


Figure 10: Representative formation curves of binary metal ion complexes with Gly in 0.1 M NaClO<sub>4</sub> at 25 ± 0.1 °C: (a) Zr (IV), (b) Pb (II), (c) Cr (III), (d) Co (II) and (e) Th (IV).

The second formation constant of Gly was determined from the titration curves and using Irving and Rossotti formula [35, 36]. The plot of  $\bar{n}$  values against pL as in Fig. 10, represents the formation curves of metal–Gly complexes. Only one complex was formed between each metal ion and Gly with stoichiometry of 1:1 (metal:Gly). The  $\text{Log}K_1$  for the metal–Gly complexes are illustrated in Table 2.

**Table 2:** Proton ligand formation constants of SMZ and stability constant of ternary complexes formed in this study at 0.1 M NaClO<sub>4</sub> and 25 ± 0.1 °C.

Metal ions	M (SMZ)	M (SMZ)	M (Gly)	$\text{Log} K_{M(\text{SMZ})(\text{Gly})}^{M(\text{SMZ})}$	$\Delta\text{Log}K$
	$\text{Log} K_1^H$	$\text{Log} K_2^H$	$\text{Log} K_1$		
H <sup>+</sup>	7.00	3.40	10.30	-----	---
Fe (III)	11.53	7.83	6.34	3.81	- 2.53
Al (III)	11.18	8.24	4.94	9.02	+ 4.08
Sr (II)	11.36	8.50	8.34	5.63	- 2.71
Th (IV)	11.90	10.25	5.94	4.42	- 1.52
Pb (II)	11.09	8.44	9.14	8.75	- 0.39
La (III)	11.50	8.65	6.94	7.13	+ 0.19
Ti (II)	11.39	8.75	9.54	3.65	- 5.89
Zr (IV)	11.71	9.28	8.53	6.22	- 2.31
Co (II)	10.24	8.04	7.14	9.33	+ 2.19
Cr (III)	10.84	8.38	7.54	8.94	+ 1.40



Fig. 8 represents typical titration curves for the metal–SMZ–Gly system studied. It is observed that the metal ion–SMZ titration curve (c) diverges from SMZ curve (b) at different pH values (pH  $\approx$  2.8 for Fe(III), pH  $\approx$  3.5 for La(III), pH  $\approx$  4.2 for Th(IV), pH  $\approx$  5.5 for Zr(IV), pH  $\approx$  4.5 for Al(III) and pH  $\approx$  6.06 for Co(II)) denoting the formation of metal ions–SMZ binary complexes. For the titration curves of the ternary systems studied, it can be observed that the curves (c) and (f) however overlap with each other at lower pH values in case of Fe(III) and La(III), while that for Sr(II), Pb(II), Cr(III) and Ti(II) are well separated. This indicates the formation of metal ions–SMZ–Gly ternary complexes at lower pH values which can be considered as an evidence for the formation of protonated SMZ mixed ligand complex.

The stability constants of the ternary metal ion complexes containing SMZ and Gly were calculated from Eqs. 4 and 5, using the data obtained from potentiometric titrations ( $I = 0.1M NaClO_4$  at  $25 \pm 0.1$  °C).



$$K_{M(SMZ)(Gly)}^{M(SMZ)} = \frac{[M(SMZ)(Gly)]}{[M(SMZ)][Gly]} \quad (5)$$

Similarly, the constants of the binary complexes (Eqs. 6–9) were also determined.



$$K_{M(SMZ)}^M = \frac{[M(SMZ)]}{[M][SMZ]} \quad (7)$$



$$K_{M(Gly)}^M = \frac{[M(Gly)]}{[M][Gly]} \quad (9)$$

It is assumed, for convenience that, complexation of the secondary ligand (Gly) starts after the complete formation of the metal ion–SMZ (1:1 complex). Thus, the overall stability constant  $K_{M(SMZ)(Gly)}^M$  can be calculated by Eq. 10:



$$K_{M(SMZ)(Gly)}^M = \frac{[M(SMZ)(Gly)]}{[M][SMZ][Gly]} = K_{M(SMZ)(Gly)}^{M(SMZ)} \cdot K_{M(SMZ)}^M \quad (11)$$

At the experimental pH values used in calculations in this work, the interfering effects of hydroxo complexes are negligible. Thus, the secondary ligand (Gly) combines with the binary metal:SMZ complex (1:1) in similar manner to its interaction with aquated metal ion in solutions. The horizontal distance between curves (c) and (f)

can be measured and used for the calculation of  $\bar{n}_{mix}$  (average number of secondary ligand molecules associated with one  $[M(SMZ)]$  ion) using the following equation [35, 36]:

$$\bar{n}_{mix} = \frac{(V_4 - V_3) - (V_2 - V_1)[(N^\circ + E^\circ) + T_c L^\circ (Y - \bar{n}_H)]}{(V_0 + V_3) \bar{n}_H T_c M^\circ} \quad (12)$$

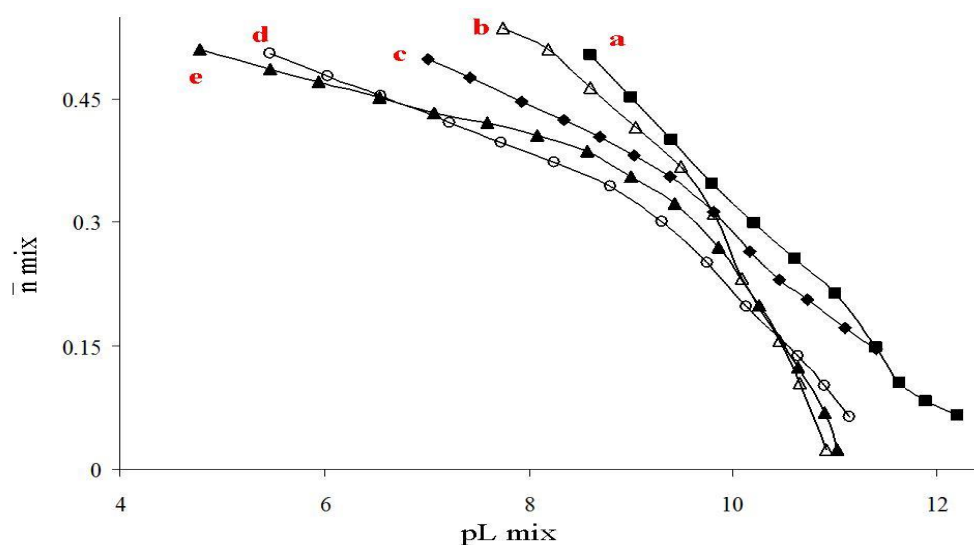
In Eq. 12,  $T_c M^\circ$  is referring to the concentration of  $[M(SMZ)]$  which is equal to the concentration of metal ion;  $Y$  = number of dissociable protons of Gly ( $Y = 1$ ),  $\bar{n}_H$  for the secondary ligand at different pH values were calculated from the amino acid formation curve. The difference  $(V_4 - V_3) - (V_2 - V_1)$ , where  $V_1$ ,  $V_2$ ,  $V_3$  and  $V_4$  are the volumes of NaOH required to reach the same pH values of free acid, free acid + SMZ, free acid + SMZ + metal ion and free acid + SMZ + metal ion + Gly, respectively. From the obtained values of  $\bar{n}_{mix}$ , free secondary ligand exponent;  $pL_{mix}$  was calculated using Eq. 13:



$$pL_{mix} = \text{Log} \left[ \frac{\sum_{n=0}^i \beta_n^H \left( \frac{1}{10^B} \right)^n}{T_c L^\circ - n_{mix} T_c M^\circ} \cdot \frac{V_o + V_4}{V_o} \right] \quad (13)$$

Where  $\beta$  is second formation constant value of Gly, B = the pH–meter reading. Formation curves corresponding to the various mixed ligand metal ion–SMZ–Gly system were obtained by plotting  $n_H$  vs.  $pL_{mix}$ . Representative results are shown in Fig. 11. The corresponding formation constants  $\text{Log}K_{M(SMZ)(Gly)}^{M(SMZ)}$  obtained by the average value method are reported in Table 2.  $\Delta\text{Log}K$  as defined by Eq. 14, is a measure of the stability of the ternary complexes with respect to the binary complexes.

$$\Delta\text{Log}K = \text{Log}K_{M(SMZ)(Gly)}^{M(SMZ)} - \text{Log}K_{M(Gly)}^M \quad (14)$$



**Figure 11:** Representative  $M$ –SMZ–Gly formation curves: (a) Co (II), (b) Cr (III), (c) La (III), (d) Sr (II) and (e) Th (IV).

#### 4 Conclusions

In this article, a potentiometric and conductometric studies of binary and ternary complexes of sulfamethoxazole and glycine with the several important metal ions; Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Th(IV), Ti(II) and Zr(IV) were achieved in aqueous medium. Based on conductometric measurements, for the binary complex (metal:SMZ), the chelation can take place through covalent bond between the metal ion and nitrogen atom of imino (NH) group and liberation of hydrogen ions. In case of ternary complexes, it was concluded that glycine combines with the binary complex (metal:SMZ) (1:1) in similar manner to its interaction with aquated metal ion in solutions. Stability constant of the ternary complexes was calculated with respect to the binary complexes.

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