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Potentiometric and Conductometric studies of Sulfathiazole: Glycine Binary and Ternary Complexes

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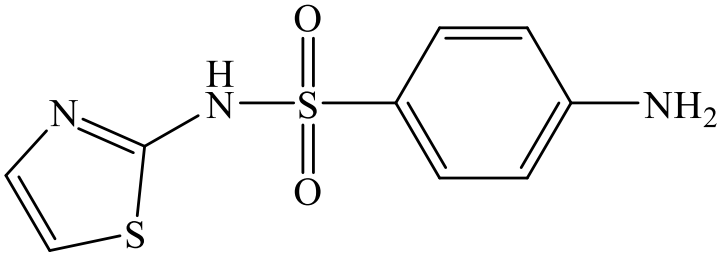
The binary and ternary complex systems of Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Ti(II), Zr(IV) and Th(IV) with sulfathiazole (as the primary ligand) and the amino acid glycine (as the secondary ligand) have been assessed potentiometrically at a temperature of 25.0±0.1ºC and a concentration of 0.1 M $NaClO_4$ in a 25% (v/v) ethanol–water solution. To investigate the effect of the secondary ligand on the formation of 1:1 M:Sulfathiazole, the stoichiometries and stability constants of binary complexes consisting of the above metal ions in a 1:1, 1:2 and/or 1:3 ratio were assessed. The protonation constants of the complexes were measured for the m M:Sulfathiazole:Glycine system at a 1:1:1 ratio. In the case of Al(III) and Th(IV), glycine as a secondary ligand prefers to bind with a [M–Sulfathiazole] binary complex rather than to the metal ion complex in an aqueous solution. In all cases, the stability order of the binary (M:Sulfathiazole) and ternary (M:Sulfathiazole:Glycine) complexes was examined.

Keywords: potentiometry, glycine, sulfathiazole, binary complexes, ternary complexes

1. INTRODUCTION

Since the 1930s, sulfonamides have been used in human and livestock drug production[1, 2]. During folate synthesis, sulfonamides inhibit bacterial growth by acting as an aggressive inhibitor of dihydropteroate synthase (DHPS)[3-5]. It was found that the metal complexes with sulfonamides as ligands were found to be more efficient in resisting bacteria than the original drugs[6]. Sulfathiazole (STZ) (4–amino–N–(1,3–thiazol–2–yl)benzenesulfonamide) is one member of the sulfa drug class that has been used widely; its structure is shown below:



STZ is a highly toxic compound, even at low levels; therefore, it is used only in combination with other sulfonamides, such as sulfabenzamide or sulfacetamide, in topical drug formulations for the treatment of bacterial vaginitis infections. STZ is also used in a mixture with other medicines for the treatment of skin inflammation disorders [7, 8]. A variety of STZ metal complexes have been studied, and the results have been reported in the literature. Some examples of these include the Co(II)–STZ[9, 10], Pt(II)–STZ[11], Hg(II)–STZ[12], and Ag(I)–STZ[13] complexes. The investigation of the binary and ternary complexes of STZ may, therefore, further the understanding of the influential forces that are responsible for mixed ligand complex formation in biological systems.

Potentiometric methods have been widely used in the different branches of solution chemistry to study the binary and ternary complexes of transition elements with molecules of biological and pharmaceutical importance[14-16]. Potentiometric methods are among the most accurate and widely applicable techniques used in studies related to the ionic equilibrium of different complexes[17]. It is important to note that the presence of metal ions in complex biosynthesis may have a significant impact on the therapeutic effects of these biological compounds[18].

As a continuation of our research into complexes containing organic compounds of biological significance[19-25], the present paper shows a complete study of binary and ternary complexes with STZ as the primary ligand and the amino acid glycine (Gly) as the secondary ligand with different metal ions (Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Th(IV), Ti(II) and Zr(IV)) based on potentiometric and conductometric methods. All studied metal ions are heavy metals with the exception of Sr(II), which may exist in medicinal products as an impurity. Heavy metals that are likely to be present in pharmaceutical products can come from the raw materials or reagents that are used in pharmaceutical preparation, from the leaching of equipment or vessels used during the manufacturing process, or even from catalysts that are deliberately added to the process[26]. Among the studied heavy metals, Fe(III) is required in very low concentrations for the survival of all forms of life[27]. Pb(II) is considered a toxic heavy metal[26], and Th(IV) is considered a radioactive element, both of which are used as catalysts in the synthesis of N-methylamphetamine[28]. Therefore, the suggested complexes in the current work can be used for in situ determination of studied heavy metals in the final pharmaceutical form or even in humans who have been exposed to the natural sources of such heavy metals. Moreover, the prepared complexes can be used in the removal of studied heavy metals from pharmaceutical production lines.

The potentiometric and conductometric titration and distribution curves of the aforementioned complexes were constructed. The curves obtained were used to calculate the stability constants of the formed complexes.

2. EXPERIMENTAL PROCEDURE

2.1. Apparatus

All potentiometric and pH measurements were carried out using a pH meter (model: ELE international, Jenway, UK) with a combined glass electrode (accurate total 0.01 pH units). The conductometric titration measurements were carried out using a conductivity meter (model: 4320, Jenway, UK) with an immersion cell. Before and after each titration, the electrode was calibrated using standard buffer solutions of pH ~4.01, pH ~ 7.00, and pH ~9.00. The stoichiometry and stability constants were calculated using numerical and computerized programs (Excel) [19-25].

2.2. Materials and Methods

Analytical grade reagents were used in this study. All solutions were prepared using pure ethanol or double-deionized water.

2.2.1. Sulfathiazole (STZ):

STZ was purchased from Sigma Chemical Company (USA) and used as received without any purification. A stock solution of STZ (0.1 M) was prepared in pure ethanol. The solution was stored in the dark at 4 °C. The working solutions of 1×10^{-3} M were prepared by successive dilutions from the stock solution with ethanol.

2.2.2. Glycine (Gly):

Gly was purchased from Sigma Chemical Company (USA) and used as received without any purification. A solution of 1×10^{-3} M Gly was prepared in double–distilled CO_2–free water and stored in the refrigerator

2.2.3. Metal Ion solution:

The salts with the metal ions (Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Ti(II), Zr(IV) and Th(IV)) were purchased as nitrates (BDH, U.K, GENEVA or INDIA), and solutions were prepared in the laboratory. Standard aqueous solutions of the studied metal ions were prepared according to a well-known method [29].

2.2.4. Sodium Hydroxide and Sodium Perchlorate:

The standard aqueous solutions of 0.1 M NaOH and 0.09 M $NaClO_4$ were prepared by dissolving their salts in appropriate amounts of double-deionized CO_2–free water.

2.3. Procedure

2.3.1. Potentiometric Studies

The studies were based on the method of Irving and Rossoti equations[30]. For binary and ternary systems, the following solutions were prepared and calibrated using a standard NaOH solution at 25.0±0.1ºC:

(a) 0.01 M $HClO_4$ + 0.09 M $NaClO_4$.

(b) Solution (a) + 1×10^{-3}M STZ.

(c) Solution (b) + 1×10^{-3} M metal ion solution.

(d) Solution (a) + 1×10^{-3} M Gly.

(e) Solution (d) + 1×10^{-3} M metal ion solution.

(f) Solution (a) + 1×10^{-3} M STZ + 1×10^{-3} M Gly + 1×10^{-3} M metal ion solution.

In all the titrations, the total volume was kept constant at 50 mL and different ionic strengths of $NaClO_4$ in 25% (v/v) aqueous ethanol solution.

2.3.2. Conductometric Titration

Conductometric titration was performed at 25.0±0.1ºC by titrating 25 mL of 0.001 M of each metal ion solution with 0.001 M of each ligand solution at an increment of 0.5 mL. The specific conductance values were multiplied by a factor of (25+V)/25, where V is the volume of the titrant added for correction purposes.

3. RESULTS AND DISCUSSION

3.1. Proton–STZ System

All pH measurements were performed at 25.0±0.1ºC. The medium was aqueous acid with an ionic strength of 0.1 M $NaClO_4$. To study the binary complexes, three types of mixtures (each with total volume of 50 mL) were used including: (a) free acid, (b) STZ (as ligand) and (c) chelate produced from individual complexation of STZ with different metal ions of Ti(II),Zr(IV),Sr(II), Al(III), Cr(III), Fe(III), Th(IV), Pb(II), La(III), and Co(II). As shown in Fig. 1, the potentiometric titration curves of the STZ complexes with different metal ions are plotted as pH versus the added volume of alkali. The average number of protons linked with STZ ($\bar{n}$H) were calculated by the following equation:

$$\bar{n}H = Y + \frac{(V_1 - V_2)(N^\circ + E^\circ)}{(V_\circ + V_1)TcL^\circ} \qquad (1)$$

Where Y = 2 (number of dissociable protons in the ligand), V_o is the initial volume, V_1 and V_2 are the alkali volume required to reach the same pH value either in a mineral acid ($HClO_4$) or ($HClO_4$+STZ) solutions, respectively. T_cL° is the total concentration of the STZ, N° is the normality of the alkali and E° is the initial concentration of free STZ.

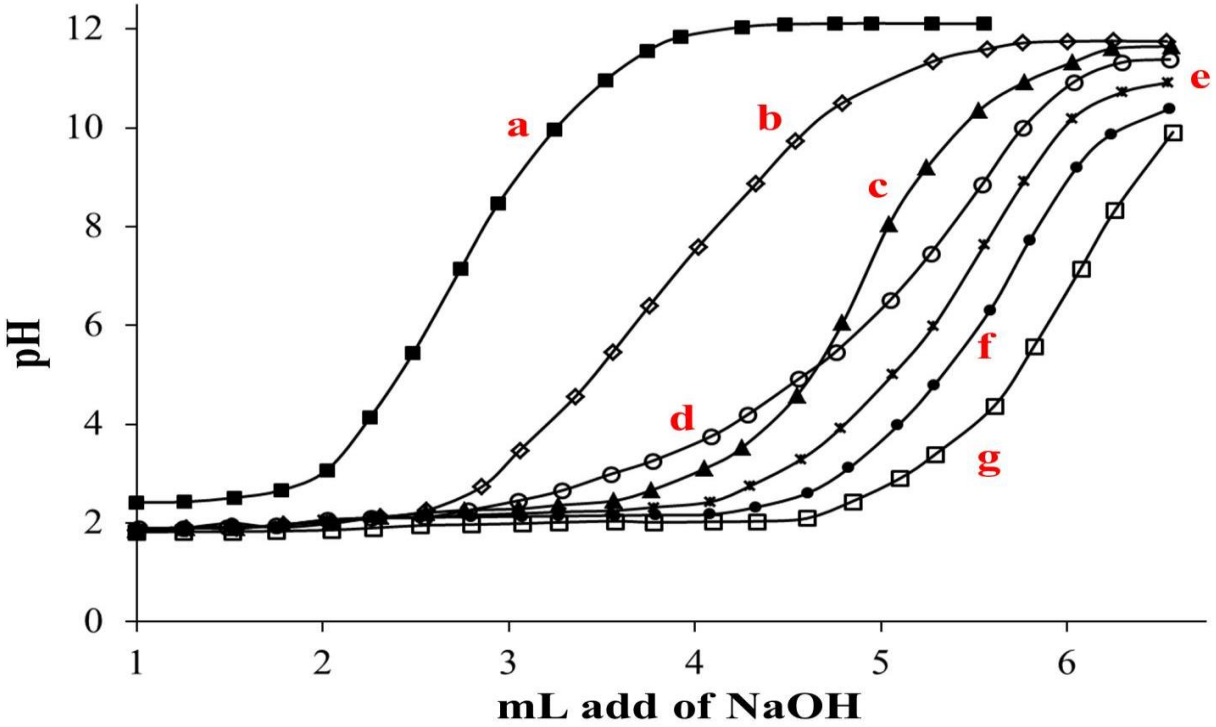


Figure 1. Representative potentiometric titration curves of STZ at 0.1 M $NaClO_4$ (25.0±0.1ºC): (a) 0.01 M $HClO_4$, (b) a + 0.001 M STZ, (c) b + 0.001 M Sr(II), (d) b + 0.001 M Pb(II), (e) b + 0.001 M Co(II), (f) b + 0.001 M Al(III), and (g) b + 0.001 M Fe(III).

The titration curves were used to assess $\bar{n}$H (the average number of protons connected with STZ). The proton ligand association constants were calculated based on the relationship between the $\bar{n}$H and pH values (Fig. 2).

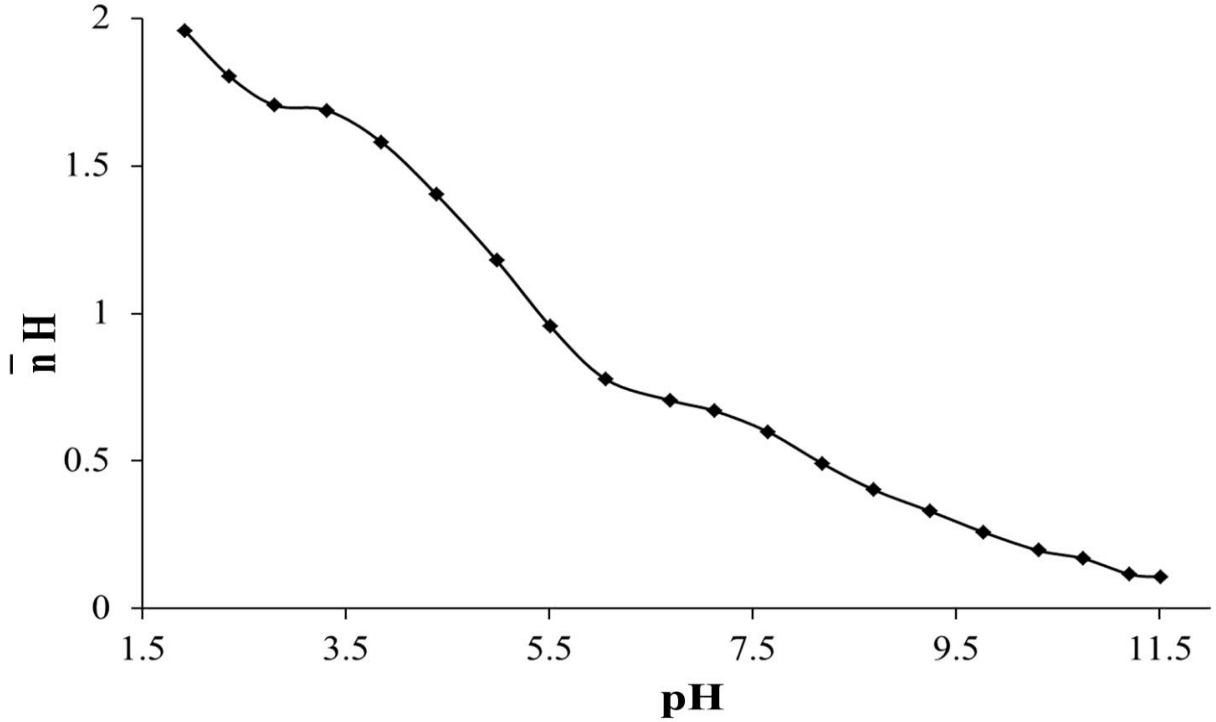


Figure 2. Representative potentiometric constant curve of STZ at 0.1 M $NaClO_4$ (25.0±0.1ºC).

The concentrations used were TcL°= 0.001 M and TcM°= 0.001 M. The stability constants of the proton-ligand and metal-ligand interactions were calculated and are presented in Table 1.

Table 1. Formation constants of STZ and stability constants of metal ion complexes at 0.1 M $NaClO_4$ and 25.0±0.1ºC. The listed data are based on measurements from three replicates.

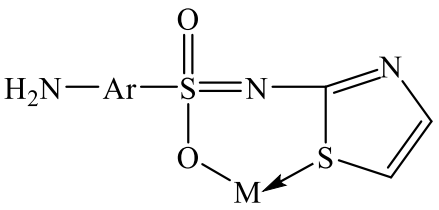
Metal Ion	$log\ K_1$ (M: L)*	$log\ K_2$ (M: L)*	$log\ K_3$ (M:L)*
H^+	7.20	3.80	– – –
Al(III)	6.85 (1:1)	4.82 (1:2)	1.61 (1:3)
Pb(II)	4.85 (1:1)	2.85 (1:2)	– – –
Co(II)	7.65 (1:1)	– – –	– – –
Fe(III)	8.85 (1:1)	6.45 (1:2)	– – –
Ti(II)	7.25 (1:1)	– – –	– – –
La(III)	6.05 (1:1)	– – –	– – –
Cr(III)	5.64 (1:1)	– – –	– – –
Sr(II)	5.45 (1:1)	3.49 (1:2)	– – –
Th(IV)	4.47 (1:1)	3.24 (1:2)	– – –
Zr(IV)	7.05 (1:1)	4.93 (1:2)	2.50 (1:3)

* These ratios are from potentiometric and conductometric methods

Table 1 shows the stability constants of the binary complexes formed between STZ and the metal ions. The order of their stabilities, which was in the expected Irving–Williams[30] order, is as follows:

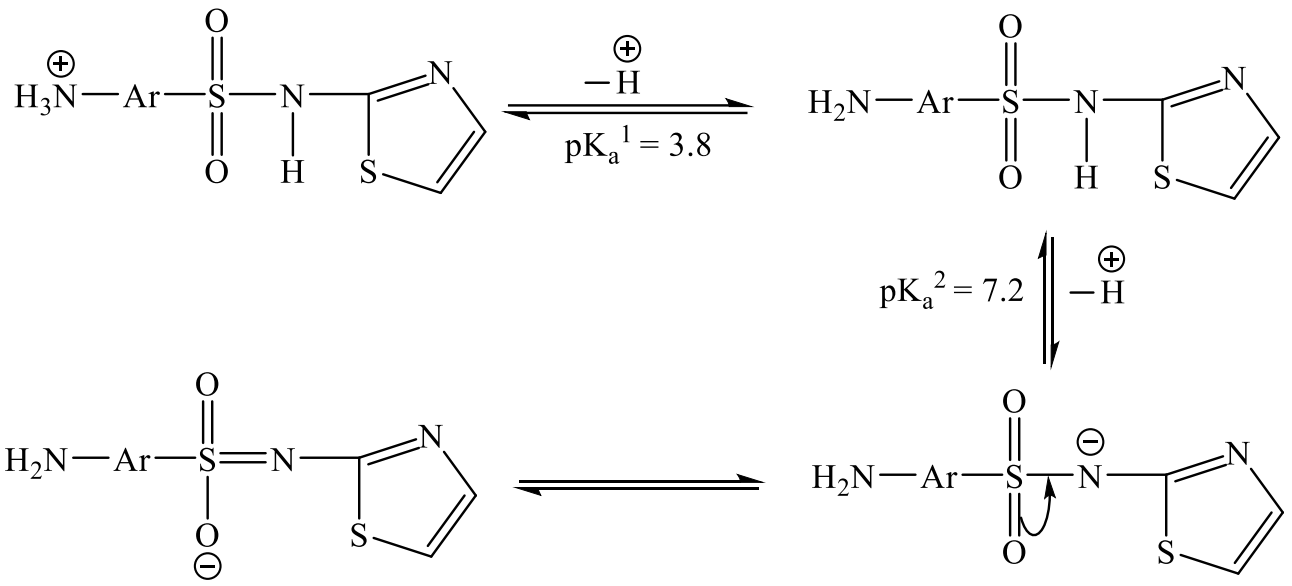
Fe(III) >Co(II) >Ti(II) >Zr(IV) > Al(III) > La(III)> Cr(III) >Sr(II) >Pb(II) >Th(IV)

Such behavior of STZ may be due to its bidentate structure that coordinates through the oxygen atom of sulfonamide group and a sulfur atom in the thiazole ring, forming a stable six-membered chelate ring as illustrated below:



Ratio (1:1) metal: ligand

During the titration of the STZ-metal complexes with a diluted base (0.1 M) in the range of pH 2.20-11.20, a maximum of two protons can be released from STZ. STZ behaves as dibasic acid [H_2–STZ]. The acid-base properties of STZ in a 25% (v/v) EtOH medium at different ionic strengths of $NaClO_4$ (I =0.1, 0.2, 0.3, 0.4 and 0.5 M) showed that one proton from the protonated amino group ($NH_2 \rightarrow NH_3^+$) was deprotonated in the lower pH range (3.63–4.95). The second site was the dissociation of the amino group proton (NH) in a pH range of 7.10–9.40. The values of $logK_1^H$ and $logK_2^H$ refer to the first and second proton formation constants of STZ, respectively, were the pH values equivalent to $\bar{n}H$ = 0.5 and 1.5, respectively. The values of $logK_1^H$ (7.20) and $logK_2^H$ (3.80) are calculated using the half-integral method[30], which are presented in Table 1. The reaction mechanism was as follows:



3.2. Binary Metal–STZ Systems

The formation curves of the complex equilibriums were obtained by plotting the degree of the complex formation ($\bar{n}$; average number of ligand molecules attached per metal ion) against the negative logarithm of the concentration of the non–protonated ligand (pL; free ligand exponent) (Fig. 3) and calculated using the Irving and Williams[30] equations:

$$\bar{n} = \frac{(V_3 - V_2)(N^\circ + E^\circ)}{(V_\circ + V_2)\bar{n}_A TcM^\circ} \qquad (2)$$

$$pL = Log\left[\frac{1 + \beta_1[H^+] + \beta_2[H^+]^2}{(TcL^\circ - \bar{n}TcM^\circ)} \times \frac{V_\circ + V_3}{V_\circ}\right] \qquad (3)$$

Where V_1, V_2 and V_3 are the volume of alkali needed to reach the same pH in the free acid, free acid + ligand and free acid + ligand + metal ion curves, respectively. V_o is the original volume of the mixture (50 mL). T_cM^o denotes the total concentration of metal present in the solution.

The obtained results showed that both Al(III) and Zr(IV)ions formed (1:1), (1:2) and (1:3) metal to ligand complexes. Additionally, some of the metal ions, including Sr(II), Fe(III), Th(IV) and Pb(II), formed (1:1) and (1:2) metal to ligand complexes, but in the case of Co(II), Cr(III), Ti(II) and La(III), only (1:1) metal to ligand complexes were formed. The data obtained are in good agreement with previously published work [31-39]. This result could be due to the nature of the metal ion, the concentration of the ligand or the ionic strength.

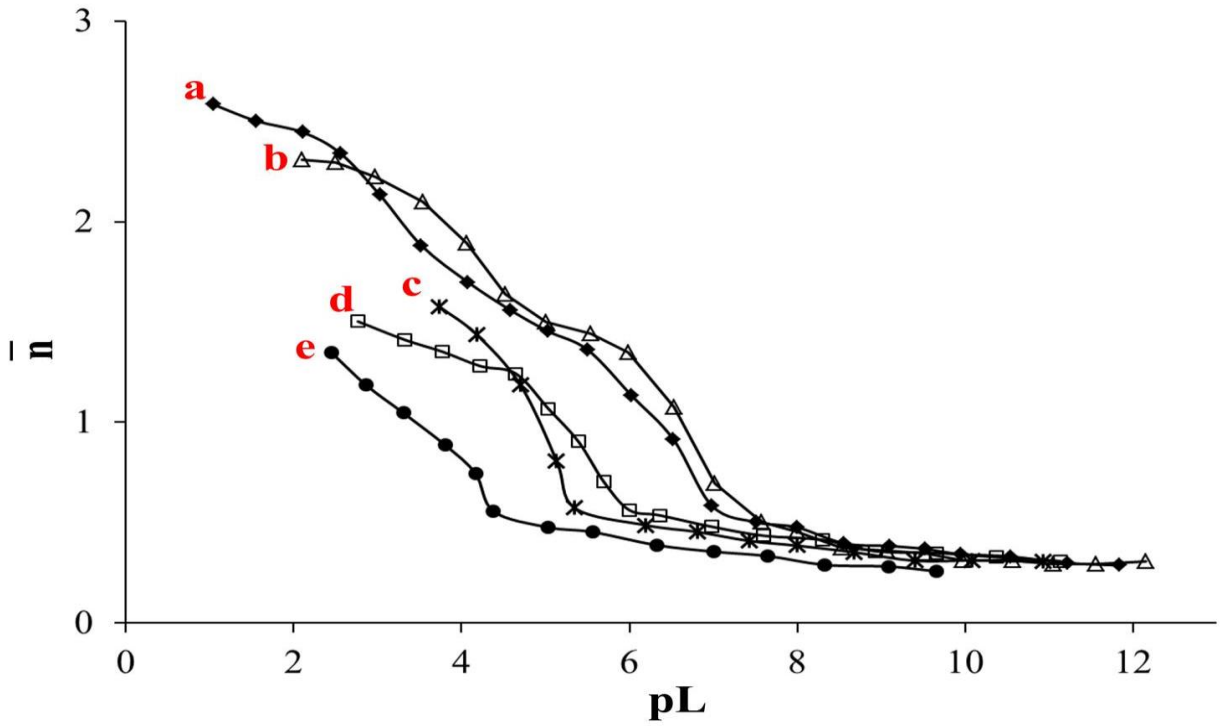


Figure 3. Representative formation curves of binary metal ion complexes with STZ at I = 0.1 $MNaClO_4$: (a) Zr(IV), (b) Ti(II), (c) Sr(II), (d) La(III) and (e) Th(IV).

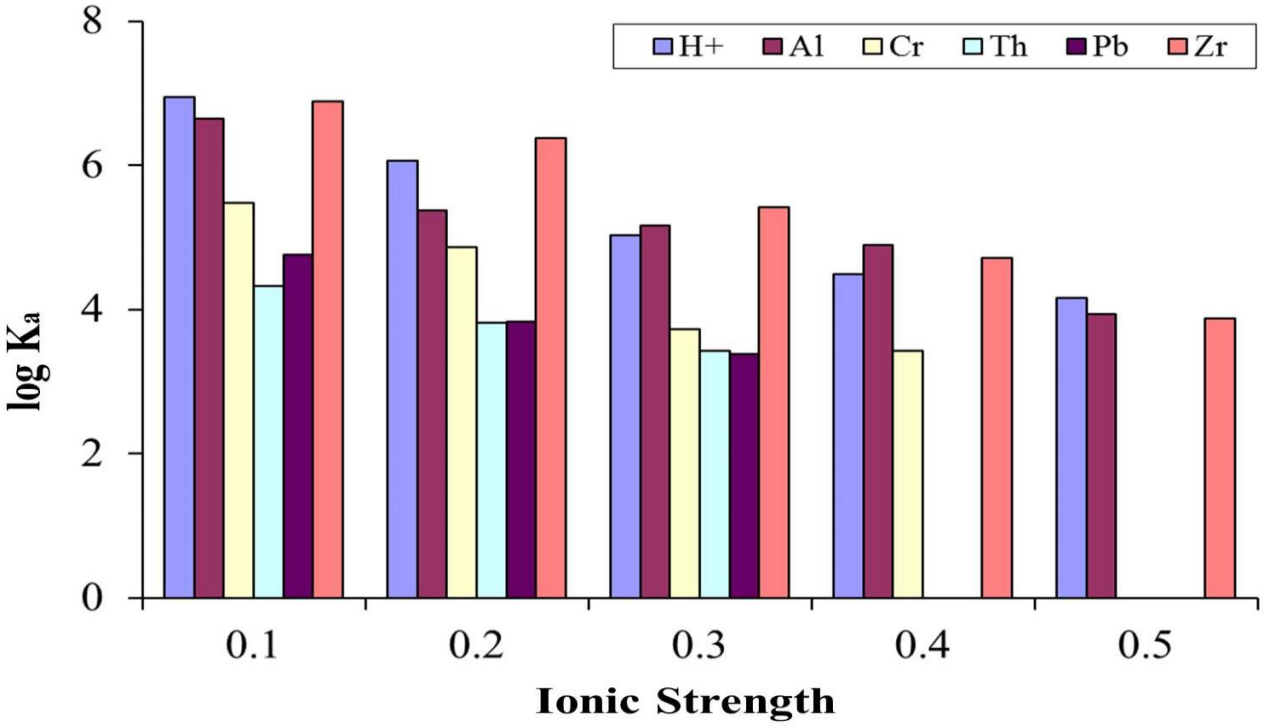


Figure 4. The effect of ionic strength on the stability constants of STZ with metal ions.

The effect of ionic force values on the stability constants of STZ with Al(III), Th(IV), Cr(III), Pb(II) and Zr(IV) metal ions in aqueous solutions at 25.0±0.1ºC were investigated. The relationship between $\boldsymbol{logK_1}$ and the ionic strength is shown in Fig. 4. The figure indicates that the stability constants for STZ complexes with metal ions in a 1:1 ratio were reduced by increasing the ionic strength. These findings are compatible with the explanations given by *Bazzicalupi et. al* [40-43].

3.3. Conductometric Titration of STZ

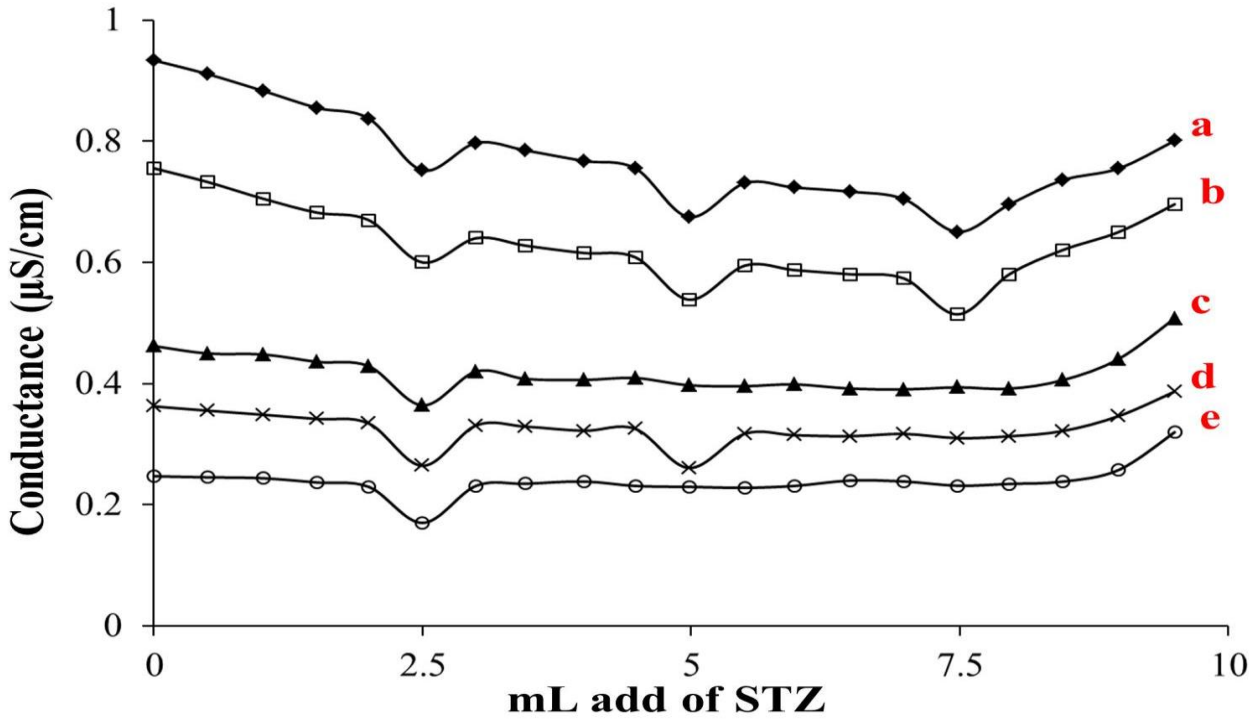


Figure 5. Representative conductometric titration curves of 25 mL 0.001 M metal ions with 0.001 M STZ: (a) Al(III), (b) Zr(IV), (c) Co(II), (d) Pb(II) and (e) Cr(III).

Conductometric analysis can be used to trace the formation of a complex. Generally, measuring conductivity is considered a sensitive tool to test the decimal differences in the ionic radii of transition metal ions[44]. This measurement is based on changes in the electrical conductivity values of solutions with complex formation. These changes depend on the number of ions present in solution and their mobility. The conductivity measurements are employed to trace the different types of chelate species formed between metal ions and STZ. Fig. 5 shows the conductometric titration curve for the binary ligand system containing Ti(II), Zr(IV), Sr(II), Al(III), Cr(III), Fe(III), Th(IV), Pb(II), La(III) and Co(II) ions. The results presented in Fig. 5 show an initial decrease in the conductance values and a minimum at a 1:1 ratio. The conductance increased slightly between 1:1, 1:2 and 1:3, which may be the result of binary ligand complex formation and H^+ release from STZ.

3.4. Species Distribution Diagrams of STZ

The distribution curves of STZ at I =0.1 M $NaClO_4$ are shown in Figure 6. It can be observed from these curves that, the major species was sα_o (H_2–STZ) in the pH range of 2.20–4.80, the major species was α_1 (H–STZ^{-1}) in the pH range of 4.80–6.00, and α_2 (STZ^{-2}) was the major species in the pH range of 6.00– 11.40. Similar results were observed by Naciye *et al.* [45].

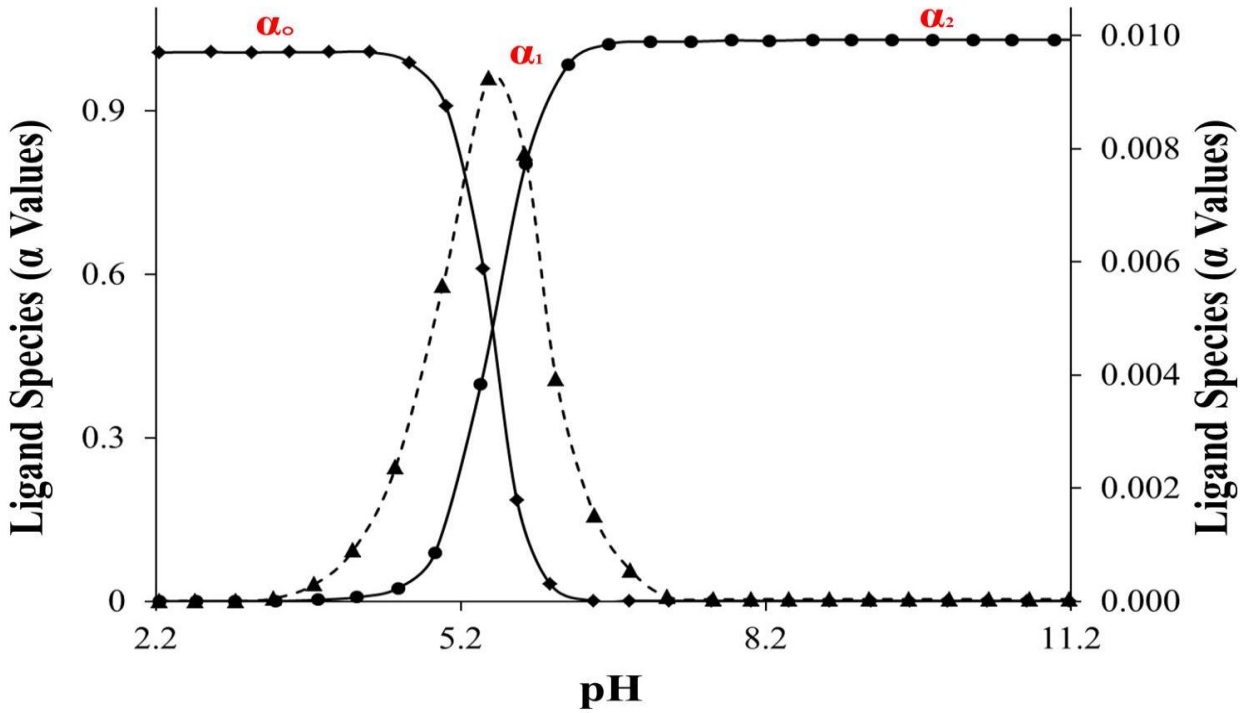


Figure 6. Ionic equilibria of STZ in different pH ranges.

The species distribution curves obtained by plotting the relationships of the mole fractions of metal species versus pH values are shown in Figure 7. The analysis of these curves revealed that at low pH values, most of the metal ions are found in the form of free ions. This result indicated that no complex formation occurred in the acidic medium. During titration, when the ligand concentration increased upon increasing pH of the solution, the mole fraction of the free metal ion decreased while that of the STZ:metal species (ML) tended to rise in moderately acidic media; however, the value of $\boldsymbol{logK_1}$>$\boldsymbol{logK_2}$ indicated that there will be a noticeable concentration of ML species in this pH region. Upon further solution pH increases, the essential change observed was an increase in the ML_2 concentration with a decrease in ML. Above this region, almost the entire metal ion remains in the form of ML or ML_2 with increasing pH values. At some of the fraction species at the intersection points and maximum pH, complexes are represented.

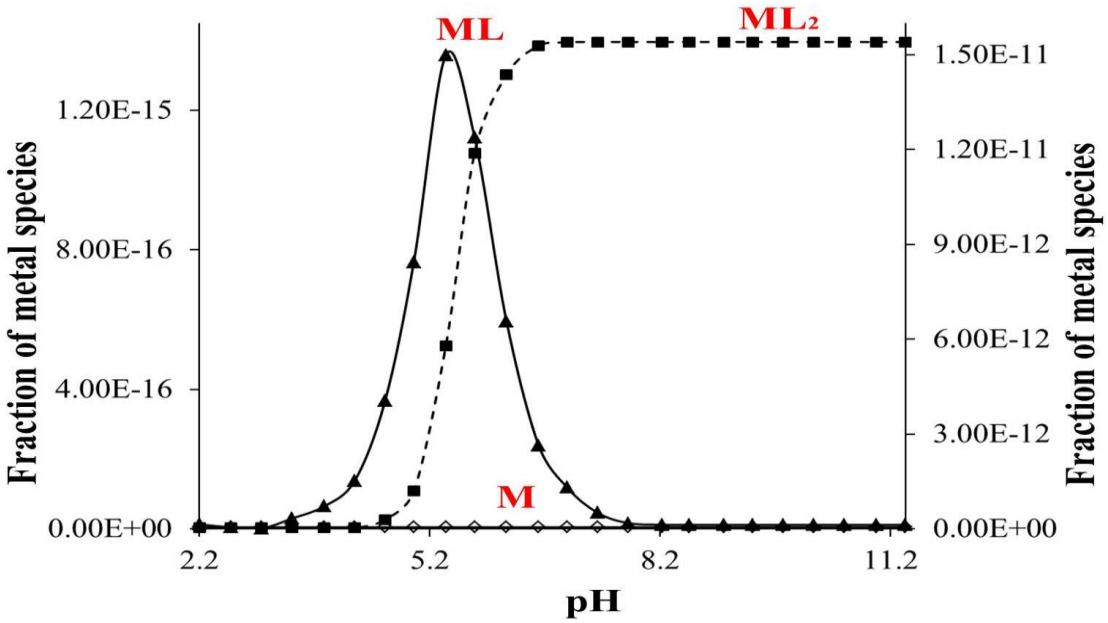


Figure 7. Representative ionic equilibria of Al(III)–STZ in different pH ranges.

3.5. Ternary Systems

Table 2. Proton ligand formation constants of STZ and stability constants of ternary complexes formed in this study at 0.1 M $NaClO_4$ and 25.0±0.1ºC.

Metal Ions	M (STZ)	M (STZ)	M (Gly)	$log\ K^{M(STZ)}_{M(STZ)(Gly)}$	$\Delta logK$
	$log\ K_1$	$log\ K_2$	$log\ K_3$		
H^+	7.20	3.80	10.30	– – –	– – –
Fe(III)	8.85	6.45	6.34	3.35	– 2.99
Al(III)	6.85	4.82	4.94	9.23	+ 4.29
Sr(II)	5.45	3.49	8.34	6.09	– 2.25
Th(IV)	4.47	3.24	5.94	8.15	+ 2.21
Pb(II)	4.85	2.85	9.14	8.93	– 0.21
La(III)	6.05	– – –	6.94	5.76	– 1.18
Ti(II)	7.25	– – –	9.54	9.13	– 0.41
Zr(IV)	7.05	4.93	8.53	7.47	– 1.06
Co(II)	7.65	– – –	7.14	4.04	– 3.10
Cr(III)	5.64	– – –	7.54	4.72	– 2.82

The stability constants for the ternary complexes were calculated by keeping the concentrations of the metal ions:STZ:Gly at a 1:1:1 ratio. All measurement parameters are presented in Table 2.

The production of the M-STZ-Gly ternary complexes was investigated. The results in Figure 8 show that the production of the ternary complex M (STZ) (Gly) results in the transfer the pH values from the acidic to alkali region, in which the ternary complex systems were more stable than the that of the binary complexes.

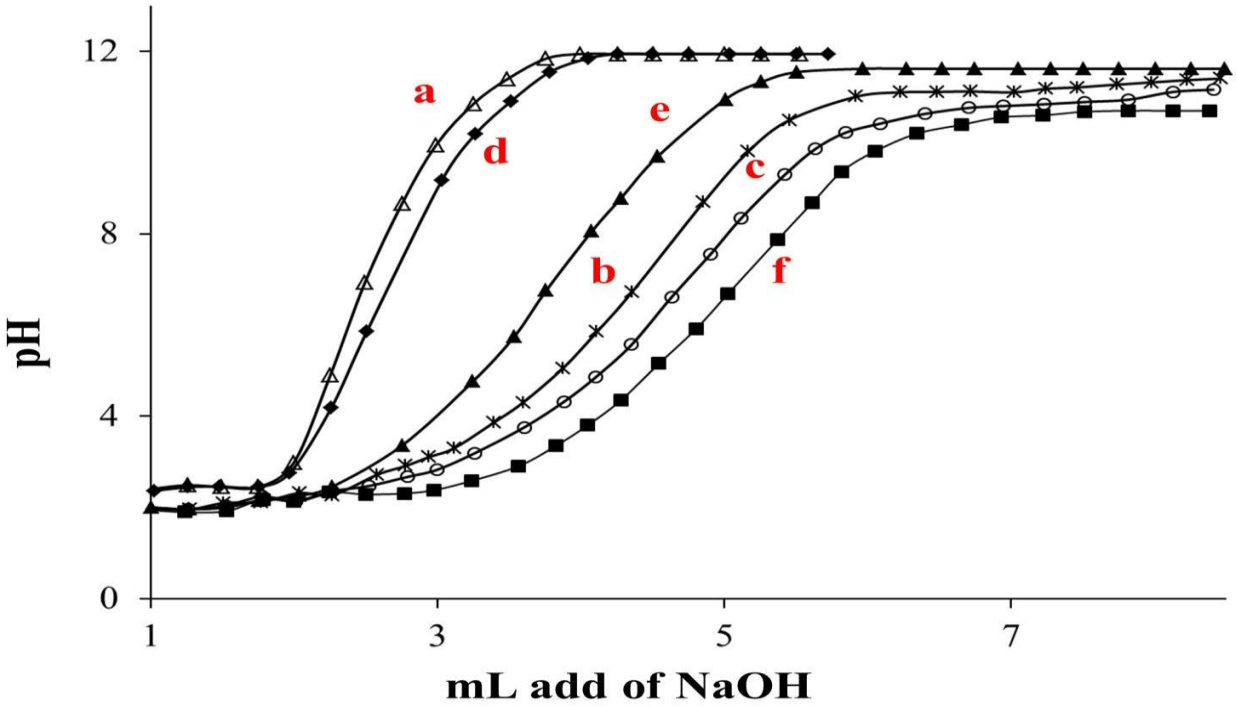


Figure 8. Representative potentiometric titration curves for the Al(III)-STZ-Gly system at 0.1 M $NaClO_4$ (25.0±0.1ºC): (a) 0.01 M $HClO_4$, (b) a + 0.001 M STZ, (c) b + 0.001 M Al(III), (d) a + 0.001 M Gly, (e) d + 0.001 M Al(III) and (f) a + 0.001 M STZ + 0.001 M Gly + 0.001 M Al(III).

The horizontal gap between the curves *e* and *f* was calculated and used for the estimation of $\bar{n}_{mix}$ (average number of secondary ligand (L) molecules attached per (M–STZ) binary complex) using Eq. 4:

$$\bar{n}_{mix} = \frac{(V_4 - V_3) - (V_2 - V_1)[(N^\circ + E^\circ) + TcL^\circ(Y - \bar{n}H)]}{(V_\circ + V_3)\bar{n}H\ TcM^\circ} \qquad (4)$$

where V_1, V_2, V_3, and V_4 are the volumes of NaOH required to reach similar pH values for solutions of free acid, free acid +STZ, free acid + STZ + metal ion and free acid + STZ + metal ion + Gly, respectively. The difference $(V_4–V_3)–(V_2–V_1)$ can be used for the computation of $\bar{n}_{mix}$(average number of secondary ligands connected to one $[M(STZ]_n^+$ion. The free secondary ligand exponent, pL_{mix}, was computed using Eq. 5:

$$pL_{mix} = Log\left[\frac{\sum_{n=0}^{i}\beta_n^H\left(\frac{1}{10^B}\right)^n}{TcL^\circ - \bar{n}_{mix}\,TcM^\circ}.\frac{V_\circ + V_4}{V_\circ}\right] \qquad (5)$$

From the obtained results, the equilibrium complexation of M-STZ-Gly can be calculated using the equilibrium equations as follows:

$$M + STZ \leftrightarrow M(STZ) \qquad (6)$$

$$M(STZ) + Gly \leftrightarrow M(STZ)(Gly) \qquad (7)$$

$$K^{M(STZ)}_{M(STZ)(Gly)} = \frac{[M(STZ)(Gly)]}{[M(STZ)][Gly]} \qquad (8)$$

The most suitable comparison for the stabilities of the ternary complex species with those of the original binary complexes is in terms of ΔlogK, which was carried out by calculating the ΔlogK values (the variation of the stabilities of the binary and the ternary complexes). The ΔlogK values are given by Eq. 9:

$$\Delta \log K = \log K^{M(STZ)}_{M(STZ)(Gly)} - \log K^{M}_{M(Gly)} \qquad (9)$$

Only in the case of Al(III) and Th(IV) was the difference found to be positive in terms of stability and were the stability constants of the mixed ligand complexes found to raise markedly. The results in Table 2 show $logK^{M(STZ)}_{M(STZ)(Gly)}$, where the stability constants of the ternary complexes decreased in this direction according to the following order:

Al(III)>Ti(II)>Pb(II)>Th(IV)>Zr(IV)>Sr(II)> La(III)> Cr(III)> Co(II)> Fe(III)

The obtained curves that match the different metal ion-STZ-Gly systems were determined by plotting $\bar{n}_{mix}$ *vs.* pL_{mix}. The results are shown in Figure 9.

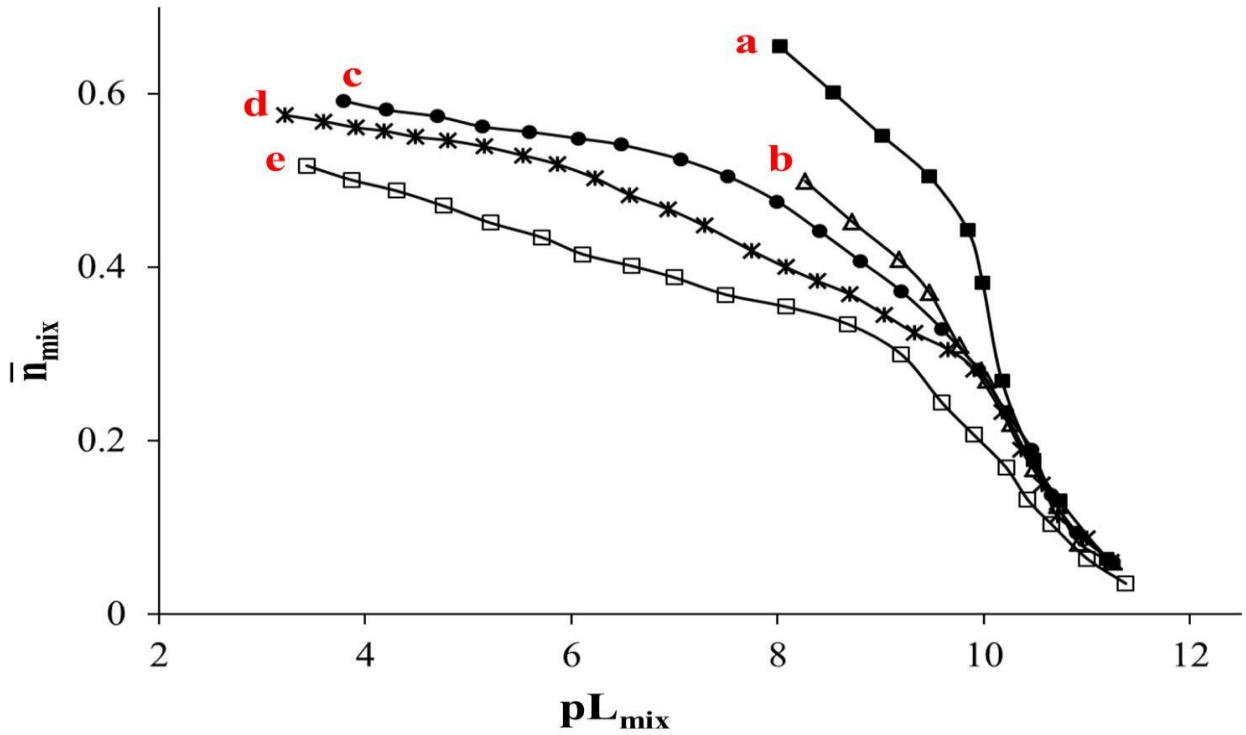


Figure 9. Representative M-STZ-Gly formation curves: (a) Al(III), (b) Pb(II), (c) Zr(IV), (d) Th(IV) and (e) Sr(II).

The formation constant values for the STZ ternary complexes (Table 2) show that the metal ions such as Al(III)and Th(IV) used in M-STZ-Gly ternary complexes are more stable than the (1:1) M–STZ binary complex and the (1:1) M–Gly binary complexes. Thus, only in the cases of Al(III) and Th(IV), the formed M–STZ complexes (1:1) have stronger affinities to combine with Gly molecules to form ternary complexes; however, some metal ions, including Fe(III), Cr(III), La(III)and Co(II), form less stable ternary complexes with STZ and Gly than the corresponding binary complexes with STZ.

Therefore, in the case of Fe(III), Cr(III), La(III) and Co(II), the formed binary complexes with STZ may be at odds with and combine with Gly molecule to form ternary complexes. On the other hand, some metal ions, including Pb(II), Sr(II), Ti(II) and Zr(IV) have higher-than-normal values; the formation constant higher values with negative ΔlogK values, which is the opposite in the case of Al(III) and Th(IV). This behavior can be explained based on the nature of the complex species produced in the solution. Our findings are in agreement with previously published results [46-50].

4. CONCLUSION

In the present study, the protonation and formation of binary and ternary complexes of STZ and Gly with different metal ions were computed using potentiometric and conductometric methods at 25.0±0.1ºC and I = 0.1 M $NaClO_4$ in a 25% (v/v) ethanol-water medium. The order of the formation constants of the produced binary and ternary complexes was presented. The experimental data of ΔlogK values were calculated and shown to influence the primary ligand bound toward the formation of the secondary ligand. Based on the positive values of the ΔlogK, the ternary complex systems were found to be more stable than those of the corresponding binary systems. We believe that the results obtained in this study will provide a better understanding of how binary and ternary complexes form and their stabilities.

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