

Potentiometric and Conductometric Studies on the Binary and Ternary Complexes of Tolbutamide with Some Metal Ions

Hussein M.El-Sagher¹ and Othman. A. Farghaly²

¹Department of Chemistry, College of Science, Sohag University, Sohag, Egypt

²Department of Chemistry, College of Science, Al-Azhar University, Assiut, 71524, Egypt

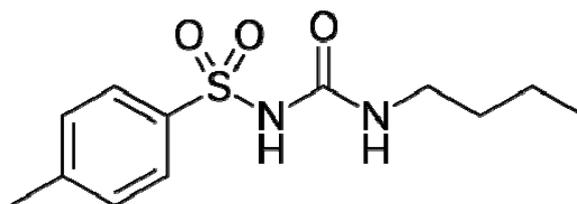
*E-mail: omran1st@yahoo.com

Abstract: The interaction of Fe (III), Pb (II), Co (II), Al (III), La (III), Sr (II), Cr (III), Th (IV), Ti (II) and Zr (IV) ions with tolbutamide (TA) as primary ligand was investigated potentiometrically. The formation constants were determined for a ligand : metal ratio of 1:1 at $25 \pm 0.1^\circ \text{C}$ and $I = 0.1 \text{ M NaClO}_4$. The stoichiometry of the formed complexes was confirmed by conductometric method. Also, the ionic equilibria of ligand and its complexes with different metal ions in solution were investigated. For ternary complexes, where glycine (Gly) was used as secondary ligand, the protonation constants of the complexes were evaluated for the system $\text{M: TA: Gly} = 1: 1: 1$. The order of stability of the binary and ternary complexes was examined. It was found that glycine adds preferably $[\text{M(II)-TA}]$ rather than to the aqueous complexes of M(II) . In all cases 1: 1: 1 complex was formed.

Keywords: Potentiometry; glycine; tolbutamide; chelates; Heterometallic

1. INTRODUCTION

Tolbutamide (TA) is chemically known as 1-butyl-3-(4-methylphenyl) sulfonylurea and has the following structure:



Importance of sulfonylurea compounds arises primarily from their ability to reduce blood sugar levels without affecting glucose tolerance [1]. Currently in the United States, three sulfonylureas are in use clinically for the management of maturity onset or stable diabetes [2]. These are tolbutamide, chlorpropamide, and acetohexamide. In addition to these, hundreds of (arylsulfonyl) ureas and related compounds have been synthesized and tested for hypoglycemic activity. The principal mechanism of the hypoglycemic action of the sulfonylureas in stimulation of insulin release by the β -cells of the pancreas [3]. Generally these drugs induce increase in the insulin levels. In some cases, however, decrease has been observed [4, 5].

However, ten metal ions; Cu (II), Mn (II), Zn (II), Pb (II), UO_2 (II), Th (IV), Al (III), Fe (III) and Mg (II) were selected to elucidate the interaction of these metal ions with TA using potentiometric method. The protonation constant of TA and stability constants of the formed complexes have been calculated at $25 \pm 0.1^\circ \text{C}$, $I = 0.1 \text{ M NaClO}_4$ in 25 % (v/v) aqueous ethanol solution. Complexes of 1:1 and/or 1:2 metal to ligand ratios were formed depending on the nature of the ligand or metal ion [6].

Also, the complexes of sulfamethazine (SMZ), sulfathiazole (STZ) and tolbutamide (TA) with Cu (II) and Fe (III) have been investigated. The formation of 1:1 and 1:2 species were inferred from electronic spectra and conductivity measurements. The bonding sites are the oxygen of sulphonamide group and heterocyclic nitrogen atom of aryl moiety. Interaction of Cu (II) and Fe (III) ions with salicylaldehyde as the primary ligand and with SMZ, STZ, and TA as secondary ligands has been studied spectrophotometrically. The data indicate the formation of ternary complexes with stoichiometric ratio of (1:1:1). Stability of binary and ternary complexes was found to be in the order $\text{SMZ} > \text{STZ} > \text{TA}$ [7].

The potentiometric method has been used extensively in many branches of solution chemistry. Great attention has been paid to use potentiometric methods in study of binary and ternary complexes of transition metals with molecules of biological and pharmaceutical interest [8–16]. The significance of potentiometric methods as the most accurate and widely applicable technique in studies related to ionic equilibria of different complexes [17].

Recently, much attention has been paid to the study of binary and ternary complexes of transition metals with molecules of biological and pharmaceutical interest [9, 18,19]. Furthermore, it has been suggested that the presence of metal ions in biological fluids could have a significant effect on the therapeutic action of drugs [20].

The interaction of tolbutamide with metal ions has attracted considerable interest not only for the development of analytical methods, but also to provide information about the action mechanism of the pharmaceutical compound.

Several types of analytical procedures have been proposed for the determination of stability constants of tolbutamide with metal ions, but these procedures are not simple for routine analysis and required expensive or sophisticated instruments. In this work, we will investigate the possibility of binary and ternary complexes of tolbutamide (TA) as primary ligand and glycine (Gly) as secondary ligand; with ten metal ions; Fe (III), Pb (II), Co (II), Al (III), La (III), Sr (II), Cr (III), Th (IV), Ti (II) and Zr (IV) using simple potentiometric and conductometric methods.

2. EXPERIMENTAL

2.1. Apparatus:

All pH measurements were carried out on pH-meter model ELE international, using combined glass electrode (accurate total 0.01 pH units). Conductometric titration measurements were carried out using conductivity meter model 4320, Jenway, using an immersion cell. The electrode system was calibrated in terms of hydrogen ion concentrations instead of activities; thus all constants determined in this work are concentration constants.

Calvin-Bjerrum is technique as adopted by Irving and Rossoti [21, 22] or Kather and Munshi [20] were used to determine the dissociation constants of the ligand (TA) and the formation constants of TA-metal complexes at 25 ± 0.1 °C in dilute acidic solution.

2.2 Materials and Solutions:

Tolbutamide (TA) (AL-Maya Pharmaceutical Factory, Tripoli, Libya), sodium nitrate (BDH), nitric acid (CALO-ERBA) and sodium hydroxide (BDH), were used as such. All other chemicals were of salts with analytical grade (BDH, UK, GENEVA or INDIA) and were used as purchased.

A stock standard solutions of tolbutamide and glycine were prepared by dissolving suitable amounts of each substance, in mg, in double distilled water. The mixture was warmed at 40 °C in a water-bath for 5 min, sonicated in an ultrasonic bath for 5 min, cooled to room temperature and diluted to volume using double-distilled CO₂-free water and stored in the refrigerator.

Working standard solutions were prepared from the stock solution by appropriate dilution with water. Also, the solutions of metal ions (A.R; B.D.H) were standardized before used.

2.3. Procedures:

2.3.1. pH-metric studies:

This is based on the Rossotti method [17]. Generally, the following solutions were prepared:

- (a) 0.01 M HClO₄ + 0.09 M NaClO₄.
- (b) Solution (a) + 0.001 M TA.
- (c) Solution (b) + 0.001 M metal ion.
- (d) Solution (a) + 0.001 M secondary ligand.
- (e) Solution (d) + 0.001 M metal ion.
- (f) Solution (a) + 0.001 M TA + 0.001 M Gly + 0.001 M metal ion.

All the prepared solution was titrated individually against standard CO₂-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 NaClO₄. Multiple titrations were carried out for each system. The pH-meter was calibrated before and after each titration using three standard buffers at pH 4.01, 7.00 and 9.00.

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:

The pH–metric titration of TA with the metal ions that mentioned previously was carried out in 25 % (v/v) aqueous EtOH medium at ionic strengths ($I = 0.1, 0.2, 0.3, 0.4$ and 0.5) M NaClO_4 and using 0.1 M carbonate–free sodium hydroxide as titrant. The titration curves are shown in Fig. 1.

$$\bar{n}A = Y + \frac{(V_1 - V_2)(N^\circ + E^\circ)}{(V_0 + V_1)TcL^\circ} \dots \dots \dots (1)$$

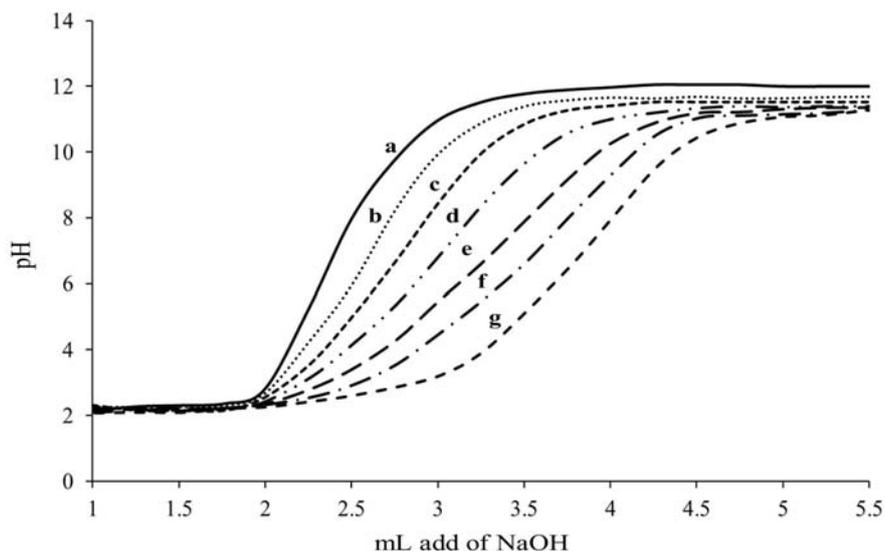


Figure 1. Representative potentiometric titration curves of TA at 0.1 M NaClO_4 and 25 ± 0.1 °C: (a) 0.01 M HClO_4 , (b) a + 0.001 M TA, (c) b + 0.001 M Sr (II), (d) b + 0.001 M Pb (II), (e) b + 0.001 M La (III), (f) b + 0.001 M Al (III) and (g) b + 0.001 M Co (II).

Fig. 2 shows the plot of $\bar{n}H$ against pH. The one proton–ligand association constants was determined by interpolation at $\bar{n}H$ values. The value of formation constants for TA is in agreements with the value reported in the literature [6], but the metal ions such Al (III), Fe (III), Pb (II) and Th (IV) are in disagreements with those values reported in the literature mentioned above with TA, in which they demonstrated that TA has one association constant with proton. This is due to the difference in the medium and ionic strength used.

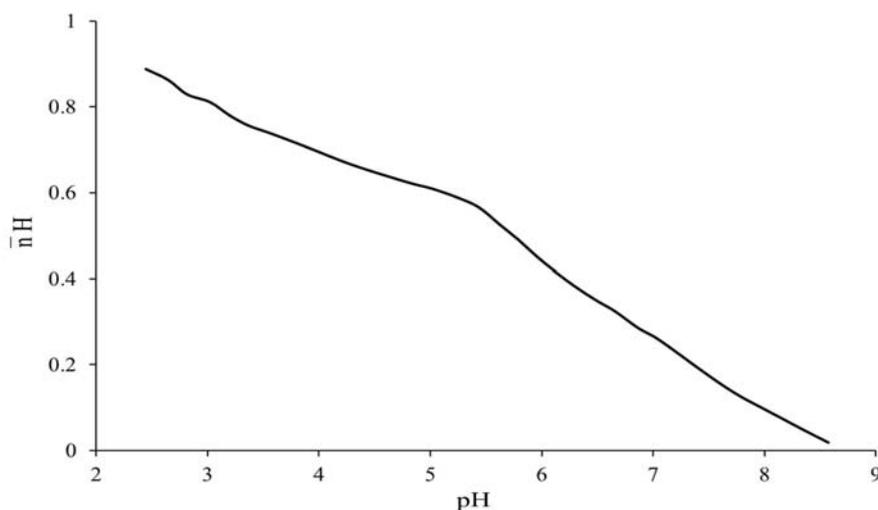
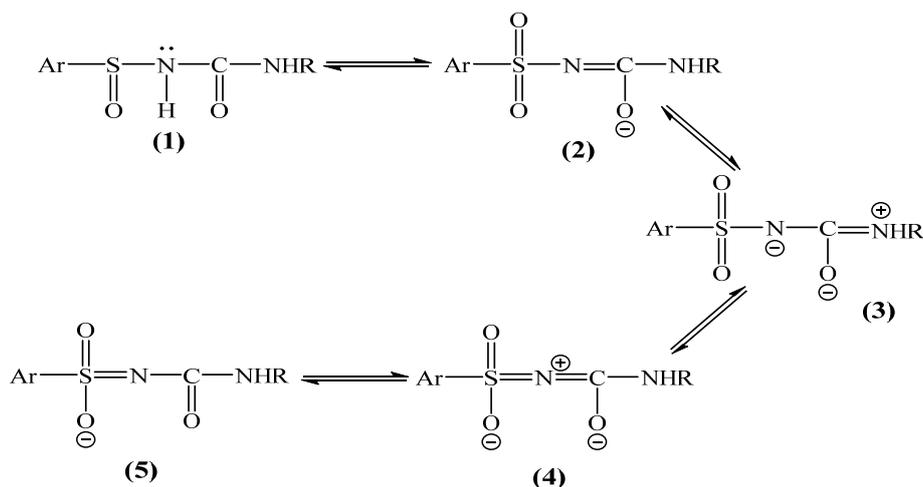


Figure 2. Representative protonation constant curve of TA at 0.1 M NaClO_4 and 25 ± 0.1 °C.

The value of $\log K_1^H$ (the first proton association constant of TA) is the pH value corresponding to $\bar{n}H = 0.5$. TA has only one site and the proton may be dissociated from these sites in proportion, which vary with the degree of neutralization. However, similar suggesting reveals that, upon deprotonation of the sulfonyl–bonded nitrogen atom, delocalization of the negative charge on least five possible resonance forms:



It is obvious that, formula (4) is very similar to our suggesting. Also from other earlier report, indicated that TA is bounded to Hg (II) and Cd (II) via SO_2 oxygen atoms and carbonyl oxygen atoms [21]. **From the reported IR spectra [22], the N–H stretch of the SO_2NHCO group, present in the spectra of the free ligand, is missing as expected upon coordination through that deprotonated nitrogen atom. The proton of this moiety is the most acidic and therefore the first to be deprotonated by base. The major characteristic of the IR spectra is the position of the $\text{C}=\text{O}$ stretching vibration. The energy of this band depends upon the coordination mode of the sulfonamide ligand. Therefore, our suggestion is indicated.**

3.2. Binary metal–ligand systems:

In this part the ten metal ions were selected viz; Ti (II), Zr (IV), Sr (II), Al (III), Cr (III), Fe (III), Th (IV), Pb (II), La (III) and Co (II), to investigate the complex formation with TA. The pH–metric titrations of these metal ions in the presence of TA at constant ionic strength 0.1 M and temperature $25 \pm 0.1^\circ\text{C}$ was investigated. The titration curves obtained are well separated as shown in Fig. 1 indicating that complexes are formed between these metal ions and TA. The stability constants of the complexes formed are determined using the half- \bar{n} values method [23]. The values of $\bar{n}A$, \bar{n} and pL at various pH values were calculated using an appropriate forms of the equations 1, 2 and 3 mentioned before. Fig. 3 represents the \bar{n} versus pL plots.

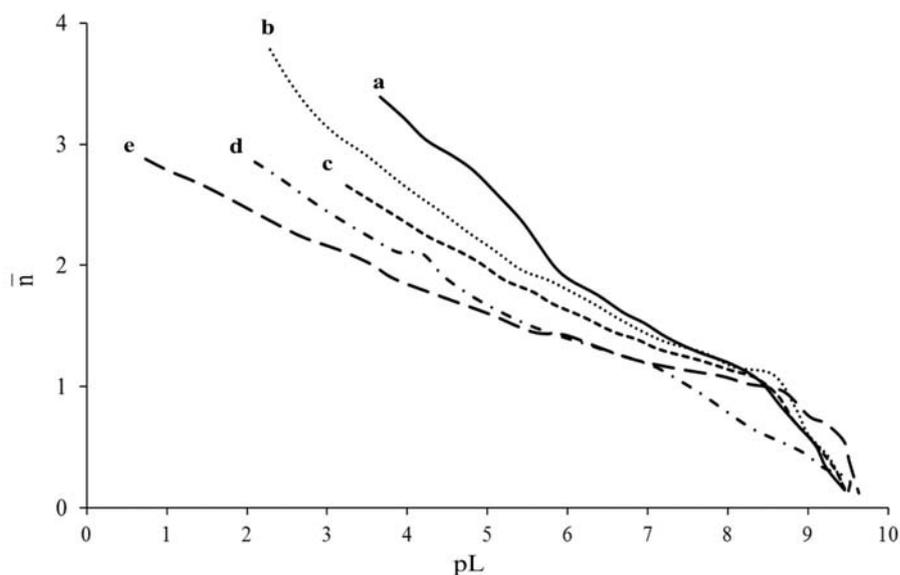


Figure 3. Representative formation curves of binary metal ion complexes with TA at $I = 0.1 \text{ M NaClO}_4$: (a) Zr (IV), (b) Th (IV), (c) Cr (III), (d) Co (II), and (e) Sr (II).

Table 1. Formation constants of TA and stability constants of metal ion complexes at 0.1 M NaClO₄ and 25±0.1 °C.

Metal ion	Log K ₁ (M: L)*	Log K ₂ (M: L)*	Log K ₃ (M:L)*	References
H ⁺	5.4 (6.35)	-----	-----	Home work [6]
Al (III)	9.23 4.90 (1:1)	6.34 4.73 (1:2)	4.29 (1:3)	Home work [6]
Pb (II)	8.83 3.01 (1:1)	6.58 (1:2)	-----	Home work [6]
Co (II)	8.63 (1:1)	-----	-----	
Fe (III)	9.79 (1:1)	8.204 6.63 (1:2)	-----	Home work [6]
Ti (II)	8.73 (1:1)	6.15 (1:2)	-----	
Cr (III)	8.82 (1:1)	6.38 (1:2)	-----	
Sr (II)	9.42 (1:1)	-----	-----	
Th (IV)	9.02 6.65 (1:1)	6.78 6.01 (1:2)	-----	Home work [6]
La (III)	8.43 (1:1)	-----	-----	
Zr (IV)	9.03 (1:1)	6.99 (1:2)	-----	

(*) These ratios are from potentiometric and conductometric methods
The metal ions form 1:1, 1:2 and/or 1:3 metal/ligand complexes.

$$\bar{n} = \frac{(V_3 - V_2)(N^\circ + E^\circ)}{(V_0 + V_2)\bar{n}_A T c M^\circ} \dots\dots\dots(2)$$

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

Looking at the Table 1, Al (III) ion form (1:1), (1:2) and (1:3) metal to ligand complexes. Also, Zr (IV), Fe (III), Ti (II), Cr (III) and Pb (II) ions forms (1:1) and (1:2) metal to ligand complexes, but in the case of Co (II), Sr (II) and La (III) only one complex (1:1) metal to ligand was formed. This is may be due to the nature of metal ion, concentration of ligand and ionic strength.

The stability constants of the complexes formed with TA decrease in the order for (1:1) metal to ligand at I = 0.1 M NaClO₄:

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

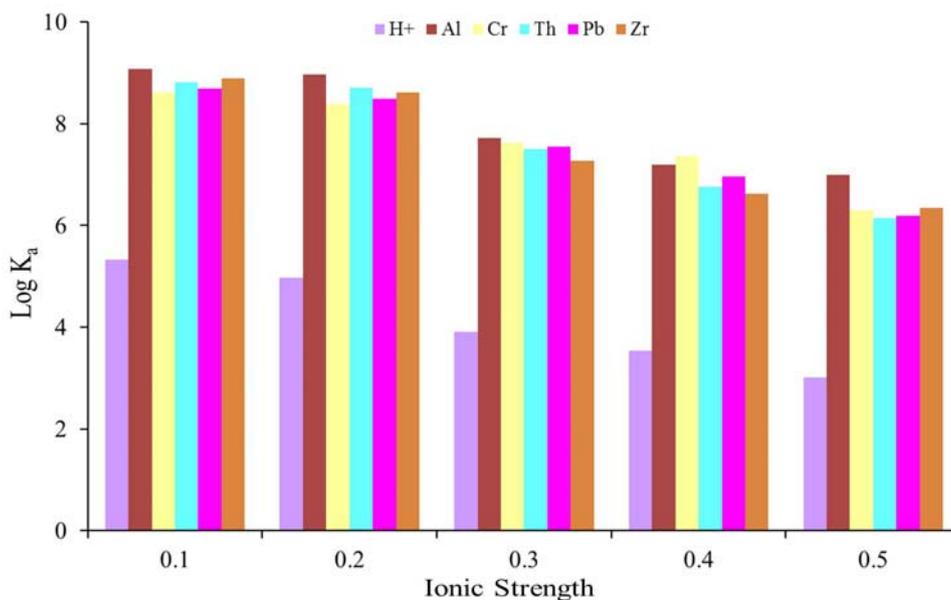
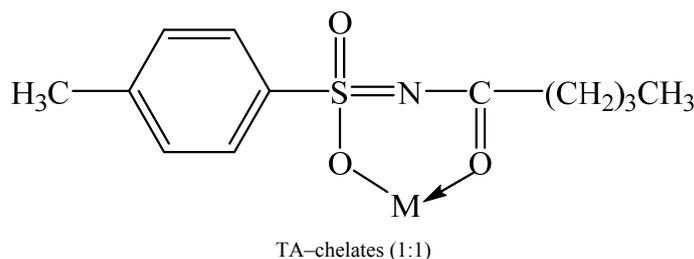


Figure 4. Effect of Ionic strength on the stability constant of TA with metal ions

This is in agreement with the decrease in the ionic potential (charge per ionic radius) of metal ions [24]. The values of $\log K_1$, $\log K_2$ and $\log K_3$ for the all systems are gathered in Table 1. The potentiometric data could be fitted by assuming the formation of 1:1 complexes with the formation of six membered ring via oxygen of sulfanilamide and oxygen of carbonyl group. This site is shown as follow:



The effect of concentration of medium (ionic strength) on stability constant of TA with metal ions; Pb (II), Al (III), Zr (IV), Cr (III) and Th (IV) was studied viz; $I = 0.1, 0.2, 0.3, 0.4,$ and 0.5 M NaClO_4 at 25 ± 0.1 °C. From this study it can concluded that the stability constant of metal ligand complex (1:1) decreased as the concentration of medium increased, as we can seen in Fig. 4.

3.3. Conductometric titration of TA:

Conductometric measurement can be applied for tracing complex formation in solution. This method has useful application as sensitive tool to test for decimal variation in ionic radii of transition metal ions investigated. The conductometric analysis is based on changes in the electrical conductivity values of solution as result of complex formation. These changes depend upon the number of ions present, and their mobility's. In this work, the conductometric titrations are performed by titrating of 25 mL (1×10^{-3} M) of each metal ion with successive volume of 1×10^{-2} M ligand solution. Conductivity measurements are employed to trace the different types of chelate species formed between metal ions and the ligand. Generally, on plotting the specific conductance values as function of the volume of each ligand added, the graphs shown in Fig. 5 are gathered.

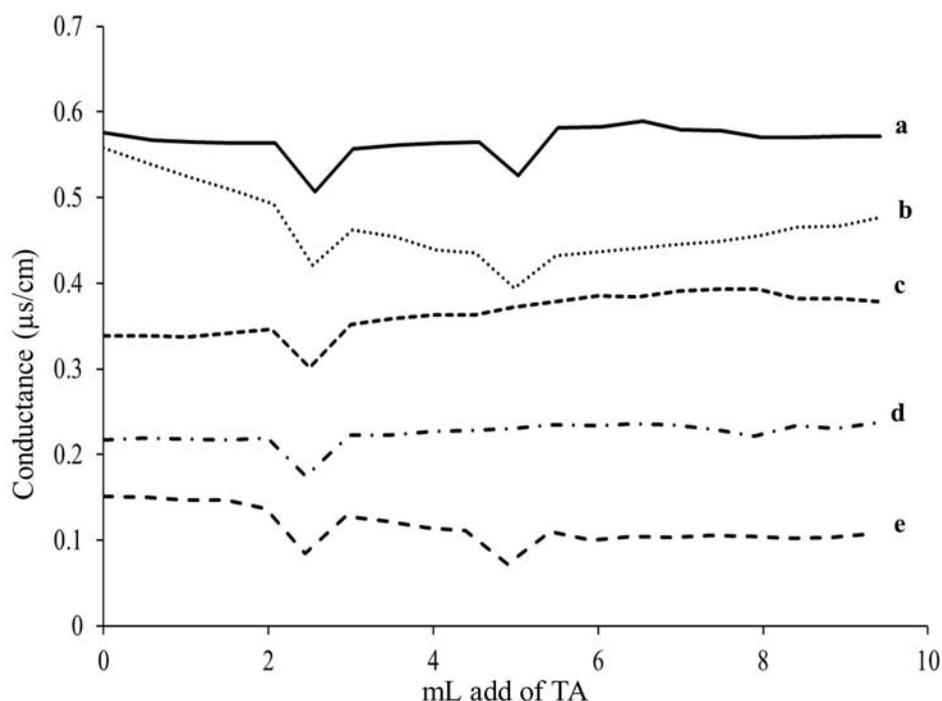


Figure 5. Representative conductometric titration curves of 25 mL (1×10^{-3} M) metal ions with 1×10^{-2} M of TA: (a) Zr (II), (b) Th (IV), (c) La (III), (d) Sr (II) and (e) Ti (II).

The relationships show a well-defined breaks corresponding to the stoichiometric ratios 1:1, 1:2 and/or 1:3, M:L, these results are in agree with those obtained by potentiometric method (Table 1).

The small increase in specific conductance of metal ions on addition of TA is attributed to the non-liberation of hydrogen ions, which should exhibit a higher conductivity values than the ions originally existing in solution. Furthermore, a continuous little increase in conductance is observed. This confirms the electrolytic nature of the anion of the metal salt, which can migrate freely and act as charge carriers for current flow. The observed increase in conductivity during titration of metal ion with ligand, clearly indicate liberation of high ionic mobile H^+ ions. Thus chelation can take place through covalent bond between the metal ions and oxygen atom of O-SO- group and nitrogen of oxazole range.

3.4. Species distribution diagrams of TA:

The mole fraction α_{ML} and α_{ML_2} can be calculated from potentiometric data using the obtained stability constants for ML, and ML_2 complexes and the pH [25]. The species distribution curves can be obtained by plotting α (α = mole fraction of the species) vs. pH. The values of α_M , α_{ML} and α_{ML_2} present in solution depends mainly on the pH of the medium. The species distribution curves for the ligand were obtained from the curve draw between α and pH ranges (Fig. 6), where: α^0 represents the (H-TA) species, which is major in pH range from (2.2-4.2), then it starts to decrease at $pH \approx 4.5$. In the same time, the species $\alpha_1 = (TA)^-$, tend to start and increased gradually in pH range (4.2-8.2). However, α^0 species is intersecting with α_1 species at pH value (5.5), which corresponding to the dissociation constant of TA.

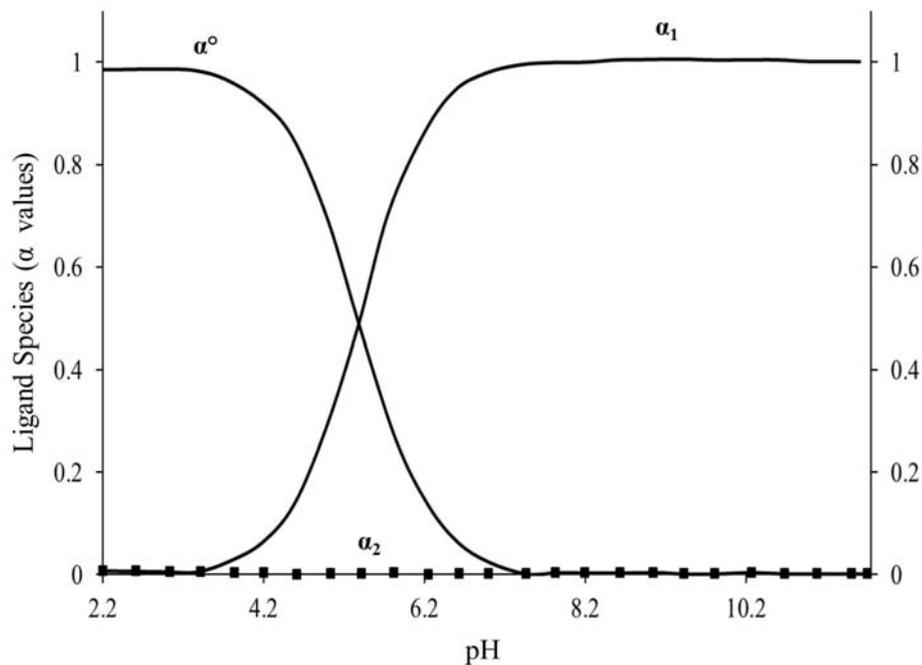


Figure 6. Ionic equilibria of TA in different pH's range

The interactions of M with L (1:1) and (1:2) lead to forms ML and ML₂ type complexes. The data obtained from M-TA titrations have been evaluated using Excel program and the species distribution curves obtained from calculations [12], as given in Fig. 7. Various complexes formulated as ML, ML₂ between the ligand and the metal ions are formed depending on pH. The main metal ions viz; Ti (II), Pb (II), La (III), Cr (III), Fe (III) and Th (IV) complexes are starts at pH (2.6–2.8) range. But the other metal ions such as Al (III), Co (II), Zr (IV) and Sr (II) complexes are formed after pH (3.0–3.2) range. For all metal ions investigated with TA, the ML species (1: 1) are the major species and the species ML₂ (1:2) is the minor one in the entire pH ranges. Finally, the species distribution of ligands and its metal complexes under investigated are variables during the pH's ranges.

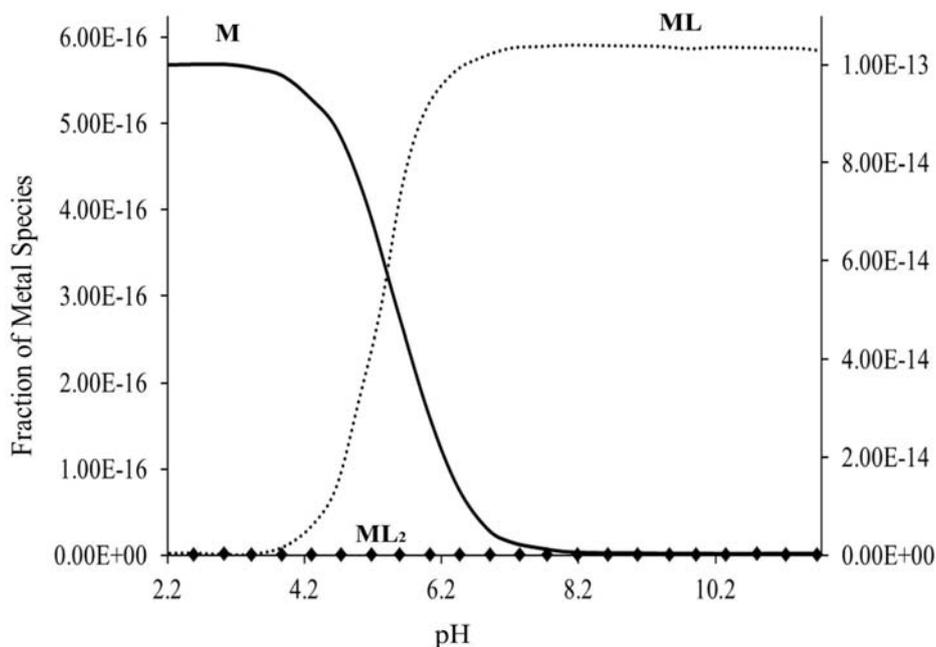


Figure 7. Representative ionic equilibria of Al-TA in different pH's range

3.5. Determination of formation constants of metal-TA-Gly complexes (Ternary system):

The potentiometric titration curves of the metal ions-TA-Gly system in NaClO₄ (I = 0.1 M) at 25±0.1 °C are shown in Fig. 8.

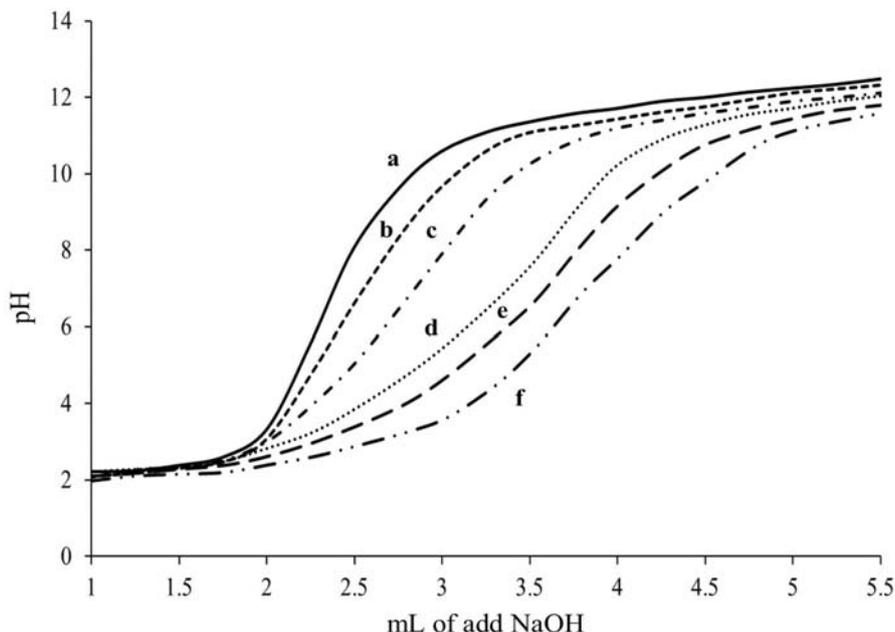
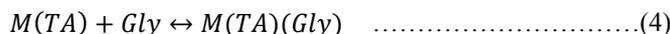


Figure 8. Representative potentiometric titration curves for Al(III)-TA-Gly system at 0.1 M NaClO₄ and 25±0.1 °C: (a) 0.01 M HClO₄, (b) a + 0.001 M TA, (c) b + 0.001 M Al(III), (d) a + 0.001 M Gly, (e) d + 0.001 M Al(III), and (f) a + 0.001 M TA + 0.001 M Gly + 0.001 M Al(III).

The stability constants of the ternary complexes containing TA and Gly were calculated from the data obtained from pH-metric titrations according to Eq. 4:



$$K_{M(TA)(Gly)}^{M(TA)} = \frac{[M(TA)(Gly)]}{[M(TA)][Gly]} \dots\dots\dots(5)$$

Similarly, the constants of the binary complexes were also determined using Eqs. 6 and 8.



$$K_{M(TA)}^M = \frac{[M(TA)]}{[M][TA]} \dots\dots\dots(7)$$



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

It is assumed, for convenience, that complexation of the secondary ligand; glycine (Gly) starts after formation of the metal ions-Gly (1:1) complex. Thus, the overall stability constant $K_{M(TA)(Gly)}^M$ may be represented as given in Eq. 10:



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

Formation curves corresponding to the various metal ions-TA-Gly systems were obtained by plotting \bar{n}_{mix} vs. PL_{mix}, the results are shown in Fig. 9.

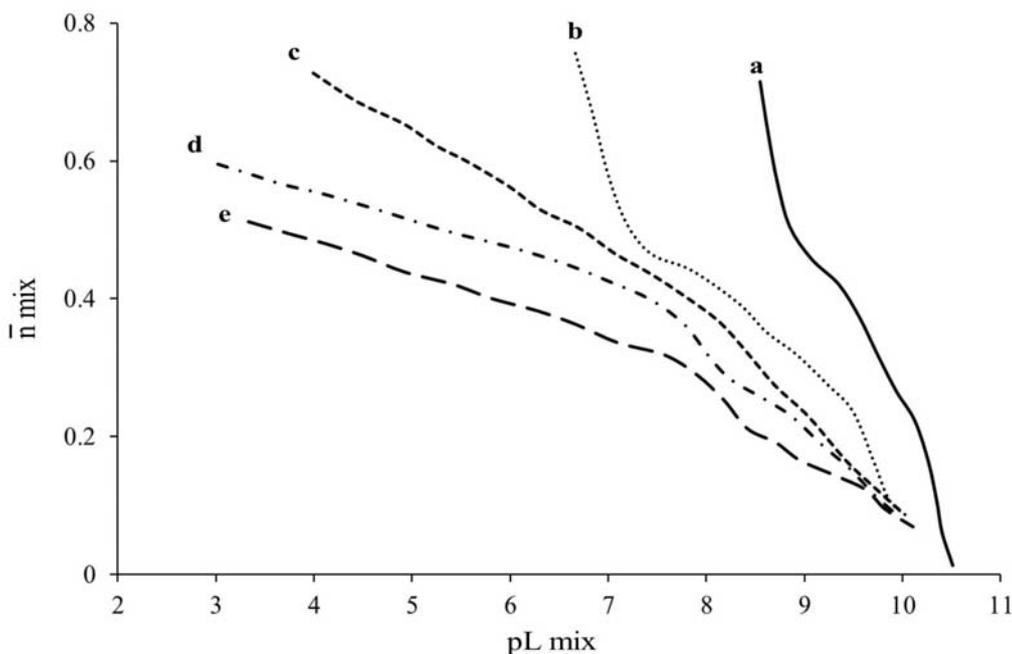


Figure 9. Representative M-TA-Gly formation curves: (a) Fe (III), (b) Pb (II), (c) Ti (II), (d) Co (II), and (e) Sr (II).

\bar{n}_{mix} (The average number of secondary ligand molecules associated with one $[M(SMZ)]$ ion, which can be calculated using Eq. 12 [22]:

$$\bar{n}_{mix} = \frac{(V_4 - V_3) - (V_2 - V_1)[N^\circ + E^\circ] + TcL^\circ(Y - \bar{n}H)}{(V_0 + N_3)\bar{n}HTcM^\circ} \dots\dots\dots(12)$$

Where TcM° is the concentration of $[M(SMZ)]$ which is equal the concentration of metal ion used; Y is the 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 a, b, c and f, respectively.

The free secondary ligand exponent pL_{mix} was calculated using Eq. 13:

$$pL_{mix} = \log \left[\frac{\sum_{n=0}^i \beta_n^H \left(\frac{1}{10^B}\right)^n \cdot \frac{V_0 + V_4}{V_0}}{TcL^\circ - \bar{n}_{mix}TcM^\circ} \right] \dots\dots\dots(13)$$

Where β is the second formation constant of Gly and B is the pH-meter reading. The second dissociation constant of Gly was determined from the titration curves a and d using the formula of Rossotti and Irving [24]. The obtained value (10.3) is in good agreement with literature data [26].

The corresponding formations constants $\log K_{M(TA)(Gly)}^M$ obtained by the average value method are reported in **Table 2**. $\Delta \log K$ as defined by Eq. 14 is a measure of the stability of the ternary complexes relative to the binary complexes and was interpreted on the basis of statistical considerations and the nature of species formed in solution. It was found that Sr (II), Co (II), Zr (IV), Pb (II), Cr (III), Ti (II), Th (IV), La (III), Fe (III) and Al (III), each form a single mixed complex (1:1:1) with TA. The importance of such mixed complexes can be ascribed to their application as models for metallo-enzyme substrate complexes and also as components of multi metal-multi ligand systems in biological fluids. Accordingly, the study of such mixed ligand complexes is considered as an effort to understand the nature of metal-ion complexation in biological systems.

$$\Delta \log K = \log K_{M(TA)(Gly)}^{M(TA)} - \log K_{M(Gly)}^M \quad (14)$$

Table 2: Proton ligand formation constants of TA and stability constant of ternary complexes formed in this study at 0.1M NaClO₄ and 25±0.1 °C.

Metal ions	M (TA) $\log k_1^H$	M (TA) $\log k_2^H$	M (Gly) $\log k_1$	$\log K_{M(TA)(Gly)}^{M(TA)}$	$\Delta \log k$
H ⁺	5.4	---	10.3	---	---
Fe (III)	9.79	8.204	6.34	8.83	+ 2.49
Al (III)	9.23	6.34	4.94	7.23	+ 2.29
Sr (II)	9.42	---	8.34	3.42	4.92
Th (IV)	9.02	6.78	5.94	7.63	+ 1.69
Pb (II)	8.83	6.58	9.14	6.83	- 2.31
La (III)	11.5	8.65	6.94	4.48	- 2.46
Ti (II)	8.73	6.15	9.54	6.76	- 2.78
Zr (IV)	9.03	6.99	8.53	3.37	- 5.16
Co (II)	8.63	---	7.14	4.96	- 2.18
Cr (III)	8.82	6.38	7.54	5.64	- 1.9

4. Conclusion:

From this study it can be concluded that potentiometric and conductometric methods are excellent methods for calculation of stability constant of metal ligand complexes. It was found that TA has only one site and the proton may be dissociated from this site in proportion, which varies with the degree of neutralization. The stability constant of metal ligand complex (1:1) decreased as the concentration of medium increased.

However, Al (III) ion forms (1:1), (1:2) and (1:3) metal to ligand complexes. Also, Zr (IV), Fe (III), Ti (II), Cr (III) and Pb (II) ions form (1:1) and (1:2) metal to ligand complexes, but in the case of Co (II), Sr (II) and La (III) only one complex (1:1) metal to ligand was formed. The stoichiometric ratio that was obtained from the potentiometric method is in agreement with the results of the conductometric method. For all metal ions investigated with TA, the ML species (1:1) are the major species and the species ML₂ (1:2) is the minor one in the entire pH range.

Ternary complexes formed between TA, Gly and the studied metal ions prove that all studied metal ions form a single mixed complex (1:1:1) with TA.

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