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Short Communication

Solution Behaviour of Ternary Complexes of Cobalt (II) Involving Sulfanilamide and Dicarboxylic acids

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Stability constants and complex formation equilibria between Co(II) and sulfanilamide (SM) with dicarboxylic acids (L) were studied pH-metrically at 25 ± 0.1 °C and ionic strength *I*= 0.1 mol/L $NaClO_4$ in aqueous solutions. The stepwise method is responsible for the formation of [Co(II)-SM-L] complexes, while dicarboxylic acid ligation follows sulphanilamide-Co(II) binding. Stability constants were obtained by applying the potentiometric data in HYPERQUAD computer program. The stoichiometry of the formed complexes was confirmed by conductometric method. A comparison between binary and ternary complexes' relative stabilities was conducted.

Keywords: Stability constant, Co(II), Sulfanilamide, Dicarboxylic acids, pH-metrically.

1. INTRODUCTION

Sulfanilamide (4-Aminobenzenesulfonamide) is an antibiotic, which has been used for decades for the treatment of vulvovaginal candidiasis. The drug blocks folic acid synthesis in bacterias by inhibiting the enzyme dihydropteroate synthase, which consists of aniline derivative with a sulfonamide group. Studies suggest that the administration of sulfa compounds as metal complexes results in an increased biological activity [1, 2]. The unique bioactivity of antibiotics and metals is attributed to their interactive nature, particularly with a variety of biomolecules, including lipids, protein receptors and genetic material (RNA, DNA) [3, 4]. These metal-based sulfa drugs; in addition to their use as antibiotics, have anti-diabetic, anti-parasitic, anti-viral, antibacterial and radio-sensitizing properties. Additionally, they are treatment options in cancer therapy.[5]. Several methods and techniques have been frequently used for investigating the stabilities of the metal-sulfa complexes. These methods

include spectrophotometry [6], polarography [7], and solvent extraction [8]. Research on metal ions and their complex equilibrium in association to drugs are beneficial for establishing drugs' action mechanism [9]. The determination of the stability constants of Co(II) complexes was achieved via a potentiometric technique with a primary ligand (sulphanilamide) and secondary ligands (a selection of dicarboxylic acids). The determination of the complexes' formation constants was done in an aqueous solution (ionic strength 0.1 mol/L $NaClO_4$), (T= 25 ± 0.1 °C). Values of Δ log *K* and the percentage of relative stabilization (% R.S.) were evaluated following a discussion. Additionally, a discussion of in solution-complex species took place; in addition to their concentration distribution. The chemical structure of ligands was depicted in Fig.1.

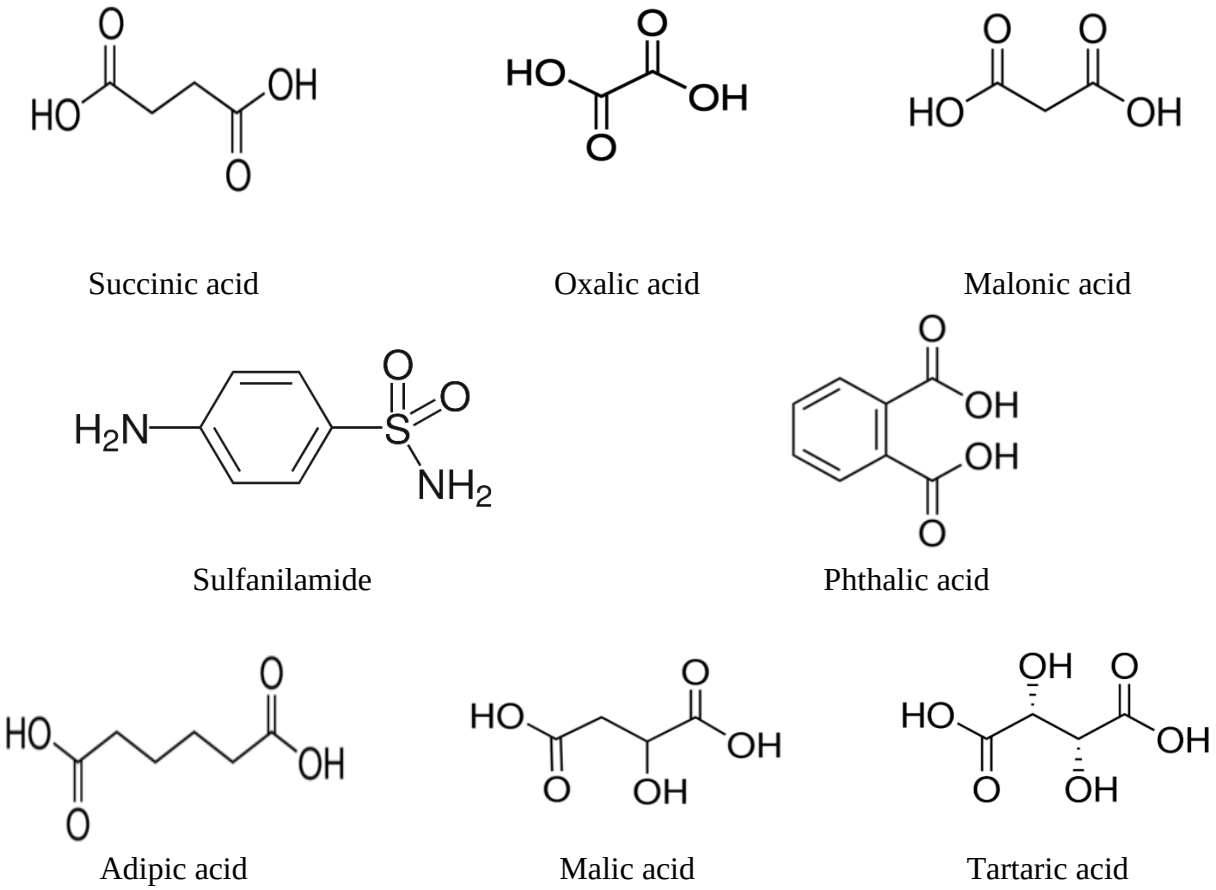

Figure 1. Structural formulas of investigated ligands.

2. EXPERIMENTAL

2.1. Materials and reagents

In order to prepare solution, double distilled water was used. Sulfanilamide (98%) and dicarboxylic acids (L), succinic (99%), oxalic (98%), malonic (99%), adipic (99%), malic (99%), tartaric (99.5%) and phthalic acids (98%) were provided by Sigma-Aldrich. For preventing metal hydrolysis,

HCl was added to the cobalt's stock solution (0.01 mol/L) to acidify it. For standardization of the titrant carbonate-free sodium hydroxide, potassium hydrogen phthalate was used.

2.3. pH-Metric measurements.

A Metrohm 211 microprocessor was utilised to produce potentiometric measurements (Hanna, Romania). To stir solutions, a magnetic stirrer was used and the performance of titrations was in triplicate (ionic strength = of 0.1 mol/L ($NaClO_4$)). The potentiometric determination of ligand (drug and dicarboxylic acids) dissociation constants was achieved by 40 cm^3 ligand solution titration (1.25×10^{-3} mol /L) of constant ionic strength 0.1 mol/L, adjusted with $NaClO_4$. The stability constant of the binary complexes were determined by titrating 40 $cm^3$of a solution mixture of Co (II)(1.25×10^{-3} mol/L) and ligands with (1:3), (1:2) and (1:1), ratios. For determining ternary complexes' formation constant, a titration of solution mixtures that contain equal amounts of (SM), Co(II)(1.25×10^{-3} mol/L) and different ligands with (1:1:1) concentration ratio was performed. Titrations were carried out in a purified N_2 environment with the use of the aqueous titrant NaOH (0.05 mol/L).

The equilibrium equation of the general four components is (To simplify, charges were eliminated):

$$m(Co) + s(SM) + l(L) + h(H) \rightleftharpoons [(Co)_m(SM)_s(L)_l(H)_h] \quad (1)$$

$$\beta_{mslh} = \frac{[Co_m SM_s L_l H_h]}{[Co]^m\,[SM]^s[L]^l\,[H]^h} \quad (2)$$

The complexes species are simply referred to as the combination of mslh and the formation constant is expressed as β_{mslh}.

2.4. Data processing

HYPERQUAD was employed to use Ca. 110 data points for obtaining the calculations of all titrations [10]. A trial of multiple composition models took place to determine the formed complexes' stability constants and stoichiometry. The selected model was in agreement with the titration data and gave the best statistical fit. Tables 1, 2 and 3 contain the results determined. HYSS was used to obtain the concentration distribution diagrams [11].

2.5. Conductometric titrations

At room temperature, conductometric titrations of ternary complexes in solution were performed and 25 cm^3 of cobalt ion (1×10^{-2} mol/L), 25 cm^3 of dicarboxylic acids (L) (1×10^{-2} mol\L) and 25 cm^3 of SM (1×10^{-2} mol/L) were titrated against a solution of NaOH (0.20 mol/L) at an increment of 0.5 cm^3 by Jenway, conductivity meter model 4320. A dilution effect correction was conducted via factor (25+V)/25 multiplication by specific conductance values, (V = volume of an added titrant).

3. RESULTS AND DISCUSSION

Under experiment conditions, dicarboxylic acids' dissociation constants and the formation constants of their binary complexes were determined and in the same manner as the mixed-ligand complexes' stability constants were found. Final findings match the literature data [12-14].

3.1. Acid dissociation constant of Sulfanilamide (SM)

The acid dissociation constant of Sulfanilamide (SM), *Table 1* was determined pH metrically using the computer program named "HYPERQUAD" (T= 25 ± 0.1 °C), (ionic strength *I*= 0.1 mol/L $NaClO_4$) in aqueous solutions. The *pKa* value of Sulfanilamide is 10.36 making it a weak acid, which is explained by $–SO_2$ potent electron attracting effect and the resulting anion's resonance stabilization [15]. Sulfanilamide ionization (Figure 2).

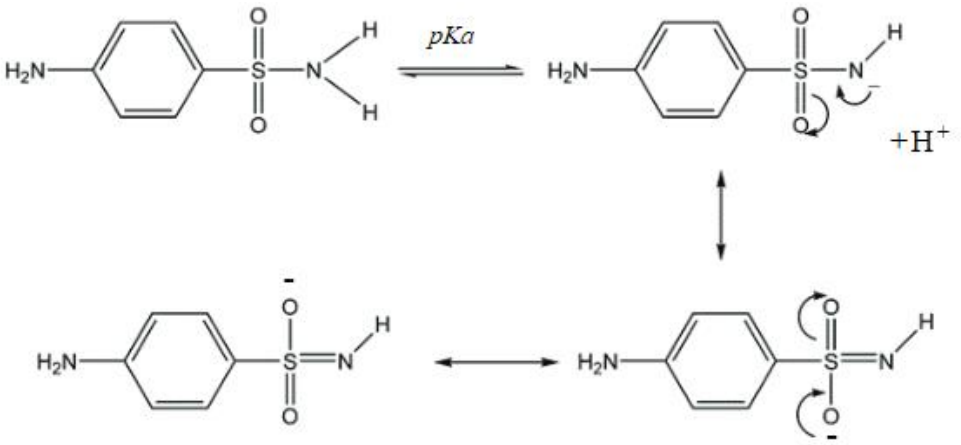

Figure 2. Sulfanilamide ionization

Table 1. Sulfanilamide (SM) and dicarboxylic acids (L) dissociation constants in aqueous solutions (T= 25 ± 0.1 °C), (I = 0.1 mol/L $NaClO_4$).

Ligands	**Ligands' pK_a**	
	pK_{a1}	**pK_{a2}**
Sulfanilamide	10.36 (0.01)	-
Succinic acid	4.22 (0.01)	5.87 (0.02)
Oxalic acid	1.35 (0.03)	4.19 (0.01)
Malonic acid	1.95(0.05)	5.97(0.01)
Adipic acid	4.57 (0.01)	5.93 (0.01)
Malic acid	3.32 (0.04)	5.44 (0.01)
Tartaric acid	2.88(0.02)	4.21(0.01)
Phthalic acid	2.88(0.01)	4.79(0.01)

Note. pK_{a1}: corresponds to 11 species (i.e., $L^- + H^+ \rightleftharpoons LH$); pK_{a2} corresponds to 12 species (i.e., $LH + H^+ \rightleftharpoons LH_2^+$). Standard deviations are given in parentheses.

3.2. Cobalt (II) - sulfanilamide equilibria

The Co(II)-drug interaction resulted in a complex, and in order to establish the complex stoichiometry, the proton displacement magnitude was determined. The ligand-containing titrating solutions were used against standard NaOH to find the proton displacement magnitude when Co(II) was present and absent. Co(II) complex titration curve is lower than the free ligand titration curve, which implies that hydrogen ions were released in association to complex formation. $[CO(II)(SM)_2]$ and [Co(II)(SM)] complexes were present in the best statistical model. Table 2 shows the stability constants determined in this study, while species' concentration distribution diagram as a function of pH. Are found in Fig. 3

Table 2. Binary systems Co(II) - SM , Co (II) stability constants - L in aqueous solutions (T= 25 ± 0.1 °C) , (I = 0.1 mol/L $NaClO_4$).

System	**$\log_{10} K_1$**	**$\log_{10} K_2$**
Sulfanilamide	8.23(0.01)	4.97(0.004)
Succinic acid	2.66(0.01)	-
Oxalic acid	3.01(0.06)	3.10(0.01)
Malonic acid	2.55(0.01)	2.01(0.01)
Adipic acid	2.91(0.03)	-
Malic acid	3.98 (0.01)	2.89(0.01)
Tartaric acid	4.22(0.03)	2.12(0.001)
Phthalic acid	4.82(0.04)	-

Standard deviations are given in parentheses.

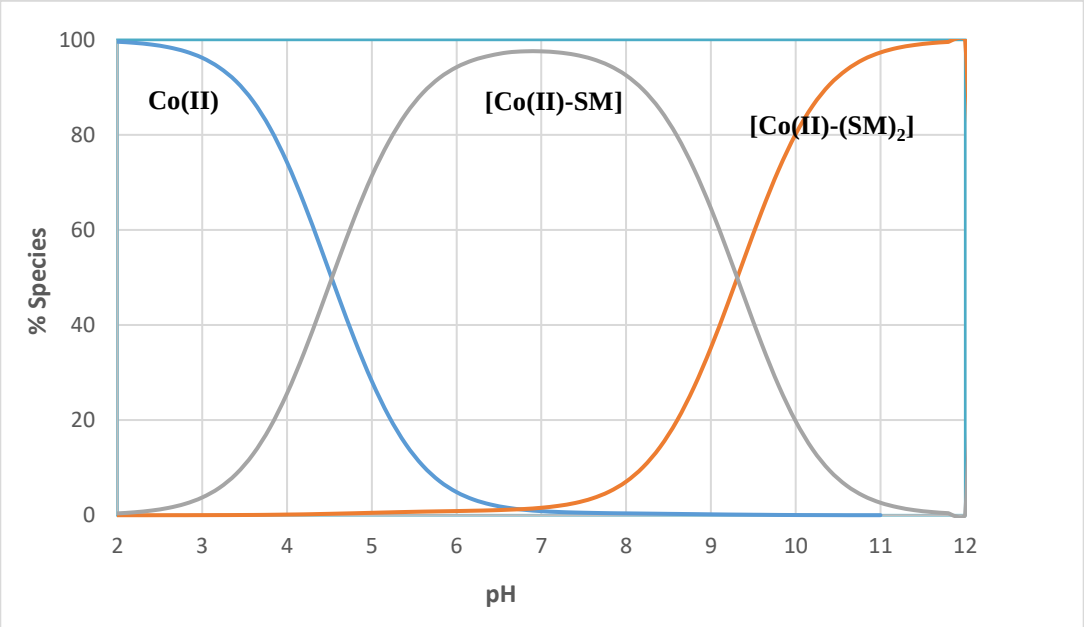

Figure 3. Concentration distribution curves as a function of pH determined for Co(II)-SM system in aqueous solutions at 25 ± 0.1 °C and I = 0.1 mol/L $NaClO_4$.

3.3. Cobalt (II)-sulfanilamide-dicarboxylic acids equilibria

Dicarboxylic acids and sulphanilamide chelating ability determines the process of forming a ternary complex, which can occur via a simultaneous or a stepwise mechanism. The formation constant stability of the 1:1 Co(II)complex with sulfanilamide is higher than that of the dicarboxylic acids binary complexes (*see* Table1). As a consequence, sulfanilamide is primarily ligated to Co(II) when both ligands are present. The coordination positions remaining are occupied as a result of dicarboxylic acids (L) ligation, which means that stepwise equilibrium is utilized to express ternary complex formation.

$$Co + SM \rightleftharpoons Co(SM) \quad (3)$$

$$Co(SM) + L \rightleftharpoons Co(SM)\,(L) \quad (4)$$

Fig 4 shows Co(II)-SM-Adipic ternary system, which represents the species of dicarboxylic acids and their potentiometeric titration curves. The composite curve obtained by the graphical addition of the titration data of adipic acid to that of Co(II)-SM titration curve compared with the titration curve of the mixed-ligand confirms ternary complex formation. Mixed ligand system deviation was observed in the composite curve, which implies that a ternary complex was formed. Species of the Co(SM)(L) complex are predominant in physiological pH as demonstrated by the Co(II)-SM-adipic acid complex concentration distribution diagram in Fig. 5.

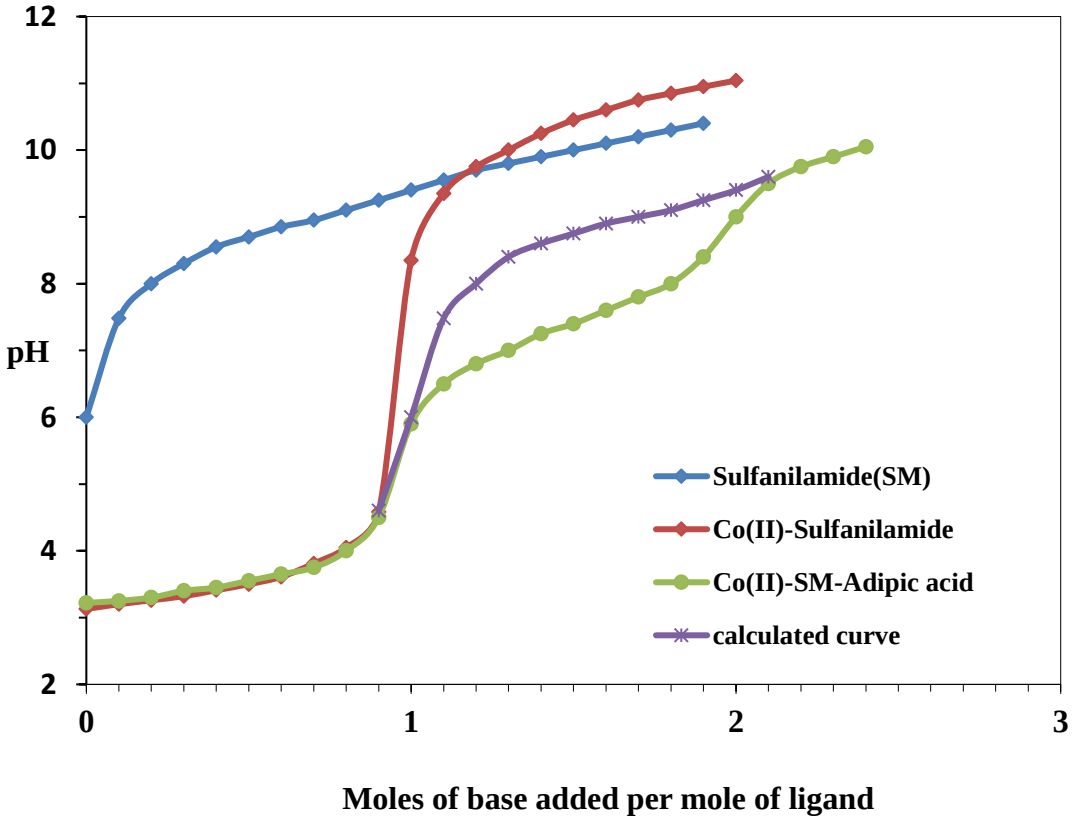

Figure 4. Co(II)-SM-adipic acid system potentiometric titration curve in aqueous solutions (T= 25 ± 0.1 °C), (*I* = 0.1 mol/L $NaClO_4$).

Table 3. Co(II)-SM-L systems' ternary species and their stability constants in aqueous solutions (T= 25 ± 0.1 °C), (I = 0.1 mol/L $NaClO_4$).

System	$\log_{10}\beta_{Co(MS)L}$	$\log_{10} K^{Co(SM)}_{Co(SM)(L)}$	$\log_{10} K^{Co(L)}_{Co(SM)(L)}$	$\Delta\log_{10} K$	% R.S.
Succinic acid	12.15 (0.01)	3.92	9.49	1.26	47.37
Oxalic acid	13.09 (0.006)	4.86	10.08	1.85	61.46
Malonic acid	13.21 (0.01)	4.98	10.66	2.43	95.29
Adipic acid	12.34 (0.005)	4.11	9.43	1.21	41.24
Malic acid	14.77 (0.02)	6.47	10.79	2.49	62.56
Tartaric acid	14.10 (0.04)	5.87	9.88	1.65	39.19
Phthalic acid	15.10(0.007)	6.87	10.28	2.05	42.53

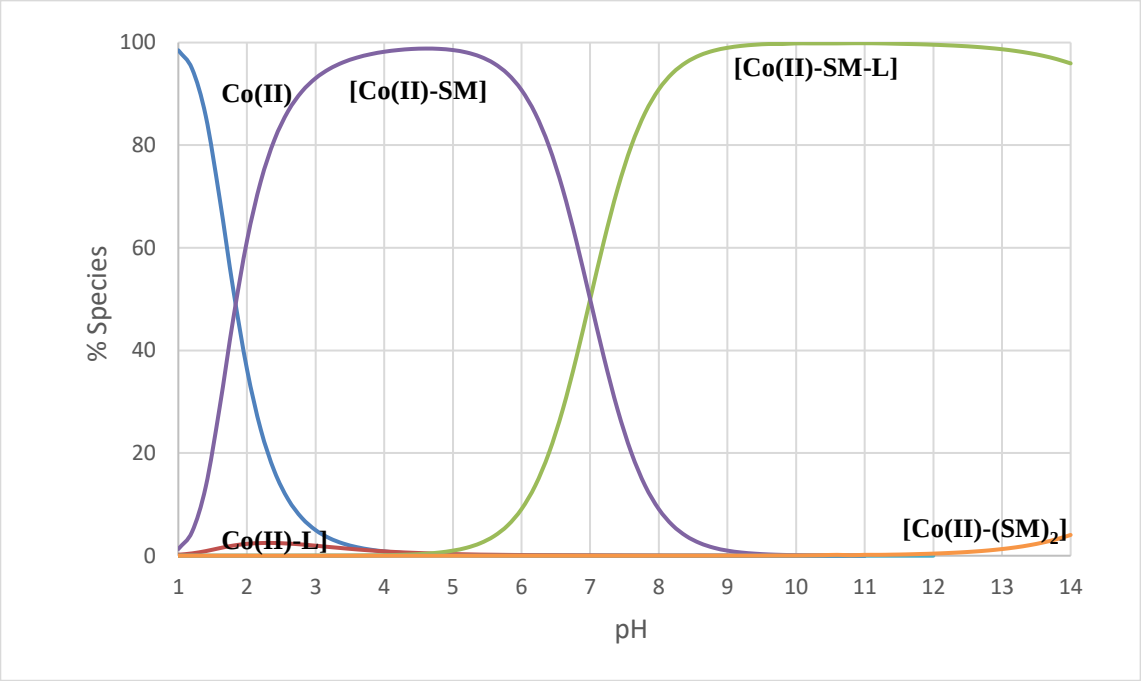

Figure 5. Co(II)-SM- adipic acid system and their concentration distribution curves as a function of pH in aqueous solutions (T= 25 ± 0.1 °C), (I = 0.1 mol/L $NaClO_4$).

Table 3 contains:

$\log_{10} K^{Co(SM)}_{Co(SM)(L)}$ $\log_{10}$ and $\log_{10} K^{Co(L)}_{Co(SM)(L)}$ calculations for ternary complexes. Sulfanilamide is the primary ligand and dicarboxylic acids are the secondary ligands as shown. The higher stability of the complex in the presence of phthalic acid is proven by a stacking interaction between the aromatic moiety of phthalic acid and that of sulfanilamide.

The formed ternary complexes (formation by a stepwise method) and their relative stability in comparison to the relative stability of binary complexes is formulated in regards to $\Delta\log_{10}K$ as:

$$\Delta\, log_{10}K = log_{10}\, K^{Co(MS)}_{Co(MS)L} - log_{10}\, K^{Co}_{Co(L)} \qquad (5)$$

Table 3 shows positive Δ log K values, which indicates that complexes formed from dicarboxylic

acids have a higher stability with Co(SM) in comparison to the complexes they form with free Co(II). Therefore, and by considering this information, a proof of dicarboxylic acids-drug stacking interactions is established.

(% RS) or percent relative stabilization is an additional factor used to quantify ternary complex stability, which is defined by [16]:

$$\%\ \text{R.S.}=\left[\frac{\left(log_{10}K^{Co(SM)}_{Co(SM)L}-log_{10}K^{Co}_{Co(L)}\right)}{log_{10}K^{Co}_{Co(L)}}\right]\times 100 \qquad (6)$$

Table 3 shows an agreement between the calculated values and Δlog10 *K* values.

3.4. Conductometric measurements

Conductometric analysis can be used to trace the formation of a complex by evaluating the measurements resulting from the change in values of the electrical conductivity of complex-forming solutions. Changes are dependent on solution mobility and the number of present ions. Fig. 6 shows Co(II)-SM-L ternary complexes' conductometric titration curves. An initial inflection and decrease at a=1 (a= moles of added base/moles of ligand) are shown on the titration curve, which might be a consequence of the release of H+ associated with SM and binary ligand complex formation. On the other hand, ternary complex formation, which is linked to the release of dicarboxylic acids' proton, explains the slight increase in conductance between 1 < a < 3. As a result of excess at a > 3, a further increase in conductance is observed.

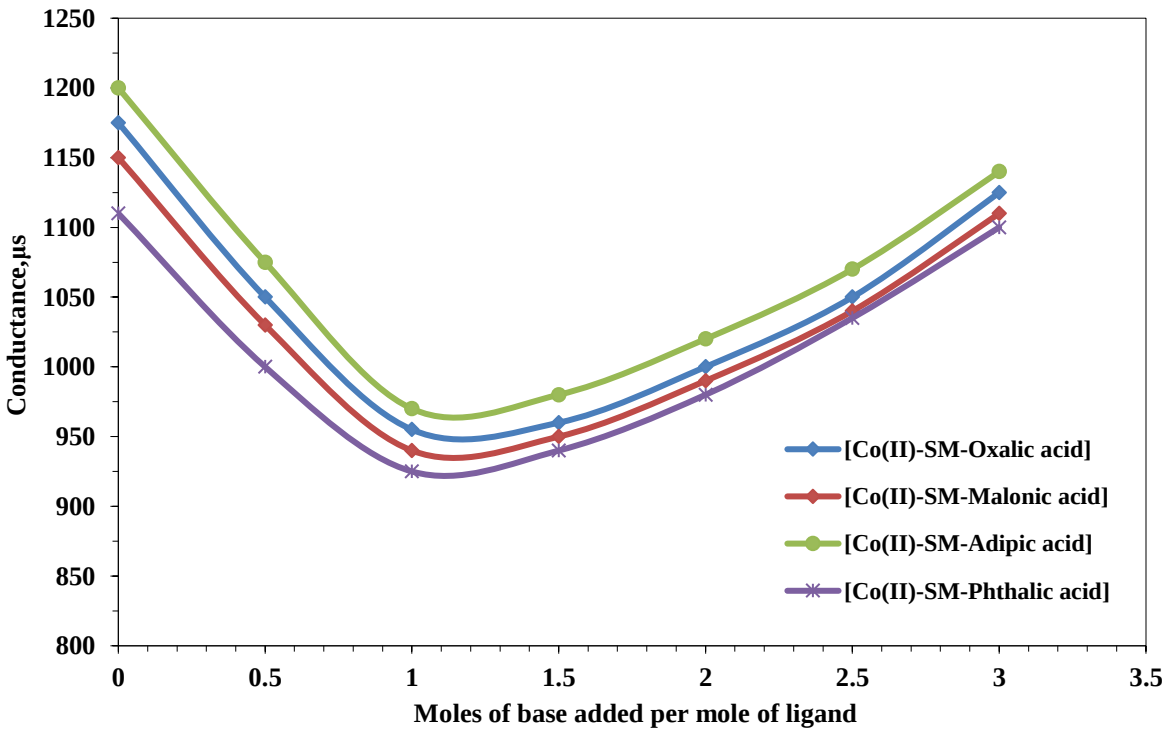

Figure 6. Conductometric titration curves of Co-MS- L system.

4. CONCLUSION

This study demonstrates the conductometric and potentiometrica investigation of the tendencies of Co (II) complexes' formation in dicarboxylic acids (phthalic, malonic, malic, tartaric, succinic, adipic, oxalic acids) and sulfanilamide drug (T= 25 ± 0.1 °C) and (*I*= 0.1 mol/L $NaClO_4$) in aqueous solutions. Co(II) ternary and binary complexes form with dicarboxylic acids and sulfanilamide, which is shown by measurements of the potentiometric equilibrium. Co(II)-SM-L ternary complexes form via stepwise mechanisms. The values of $\Delta\log_{10}K$ are positive, indicating that the the ternary complex systems were found to be more stable than those of the corresponding binary systems.

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References

1. V. Singh, N. K. Kaushik and R. Singh, *Asian J Res Chem*., 4(2011)339.
2. M. J. Thun, S. J. Henley and C. Patrono, *J Natl Cancer Inst*., 94(2002)252.
3. M.T. Zaworotko, H.H.Hammud, G.Mc- Manus, A.M. Ghannoum, A. Kabbani and M.S. Masoud, *J. Chemical Crystallography*, 39 (2009) 853.
4. M.S. Masoud, M. Awad, M. Shaker and M. M. T. El-Tahawy, *Corros. Sci*., 52 (2010) 2387.
5. C. Zhao, K.P. Rakesh, L. Ravidar, W.Y. Fang, and H.L. Qin. *Eur J Med Chem*. 15 (2019) 679.
6. G.P. Sengupta and C.R. Bera, *J. Inorg. and Nuclear Chem*., 43 (1981) 2139.
7. M. S. Parihar, F. Khan, *Eclet. Quím.,* 33 (2008) 345.
8. D. Marin, F. Mendicuti, *J. Chem. Educ*., 65 (1988) 916.
9. D Wang and S.J. Lippard, *Nat. Rev. Drug. Disc.*, 4 (2005) 307.
10. P. Gans, A. Sabatini and A. Vacca, *Talanta,* 43 (1996) 1739.
11. P. Gans, A. Ienco, D. Peters, A. Sabatini and A. Vacca, *Coord. Chem. Rev*., 184 (1999)311.
12. A. A. El-Sherif, *J Solution Chem*., 39 (2010) 1562.
13. A. M. Radalla, *Beni-Suef univ. j. basic appl. sci*., 4(2015) 174.
14. A.M. Radalla, M.M. Khalil and, N.M. Abd Elnaby, *J Solution Chem.*, 42 (2013)113.
15. D. Cairns, Essentials of Pharmaceutical Chemistry, Third edition, Pharmaceutical Press, London, Chicago, 2008, p. 69.
16. M. M. Khalil, A.-E. Radalla, F. Qasem, and R. Khaled, *Korean J Chem. Eng.*, 31 (2014) 109.