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A Study of the thermodynamic parameters (functions) of complexes formation of Sulfanilamid with metal ions and DL-Alanine by potentiometric method

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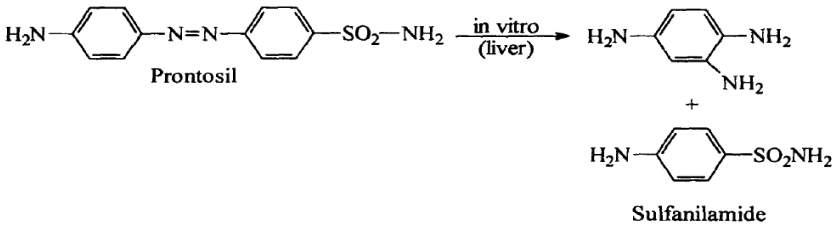
ABSTRACT

The current study deals with the preparation of disulfonalmide complexes composed of the sulfanilamid drug , the salt of chromium(III) and the trisulfonalmide complexes composed of the sulfonalmide drug , the metal salt and the amino acid (alanin), as well as study in the stability constant of each complex and making a comparison between them . The obtained results show that the tricomplex stability constant is higher than the dicomplex stability constant due to the existence of the amino acid in the tricomplex which makes greater stereo structure and eventually easier interaction. Besides the thermodynamic functions in this experiment have been studed since they cause a chemical spontaneous reaction and a random arrangement in system.

Introduction

Sulphonamide drugs have been used clinically since the 1930s in veterinary and human medicine [1]; [2] the sulphonamides commonly used to prevent bacterial growth by acting as a competitive inhibitor of dihydropteroate synthase (DHPS) during folate synthesis [3]; [4]; [5].

Prontosil was the first sulfa drug discovered by the German physician and chemist, [1]. He observed that prontosil protects mice against streptococcal infections. The sulfonamide is a generic name for derivatives of para - aminobenzenesulfonamide (sulfanilamide). In the liver it exists as follows:



Prontosil

Sulfanilamide

Sparingly soluble in water and white crystalline powder is characteristic of Sulfa drugs. They readily react with alkali and form salts which are more soluble than the parent drug.

The importance of potentiometric methods as the most accurate and widely applicable technique in studies related to the ionic equilibrium of different complexes[6]; [7]. It should be noted that the presence of metal ions in biological fluids could have a significant effect on the therapeutic action of such organic compounds [8].

The acute action of drug and their complex formation in complex media depends on metal ligands selectivity and stability constants [9]. The study of metal complexes with drugs shows that they are more potent than drugs [10].

The stability constants of metal complexes with drugs are important in order to know the proper dose of drugs and their adverse effect with all other components of blood streams [11]. The stability of complexes plays a major role in elucidation of mechanism of drug action.

The role of Cr in animals was reported almost four decades ago [12], and its essentiality in humans was documented in 1977 [13].

Large number chemotherapeutically significant sulfa drugs such as sulfanilamide, sulfamerazine, sulfamethoxazole and sulfapyridine have been used as antibacterial agents which can be used to treat many diseases caused by some types of bacterial such as treatment do urinary tract infections, throat and gum infections, eye infections and malaria [14]; [15].

At low concentrations, Cr is involved in natural human lipid and protein metabolism, so that very small amounts are needed for normal human life functions [16]. Much of the daily intake of chromium, typically about 100 μg, is from foods such as grains, fruits and vegetables, potatoes, seafood, mushrooms and egg yolk [17]; [18].

They kill bacteria and fungi by interfering with their metabolism. They were the "wonder drugs" before penicillin was discovered. They are used mainly for the treatment of urinary tract infections (UTI) [19].

Chromium ions in solution occur in two common forms, relatively safer Cr (III) and more toxic Cr (VI), and particularly the latter is not similarly biocompatible as solid chromium oxide in human contact [20]; [21].

In addition, low to modest amounts of chromium can appear in other potential sources such as type II anti-diabetic and dietary drugs [22]; [23], Chromium also occurs at much higher concentrations in industrial processes that can release potential pollutants to air and drinking water [24].

Amide of sulfonic acids are called sulfonamides. The sulfa drugs are a class of sulfonamides. An amide is composite of a carboxylic acid and ammonia or its derivatives. Amides are least reactive of all acid derivatives because of delocalization which reduces the electrophilicity of carbon (of $CONH_2$) [25].

Chromium (Cr) is a silvery white transition metal with atomic number of 24, relative atomic mass of 52.996 g/mol, and price between iron and nickel [26], Inherent brittleness sets the upper limit for its content in commercial alloys mostly to below 30-40% by weight. In medical and dental applications as tools, implants, bridges and other metallic appliances, chromium is a common alloying component.

Alanine is an aliphatic amino acid, because the side-chain connected to the α-carbon atom is a methyl group ($-CH_3$), making it the simplest α-amino acid except for glycine. The methyl side-chain of alanine is non-reactive and is, therefore, hardly ever directly involved in protein function [27].

designed, synthesized a series of *N*-aryl-β-alanine derivatives and diazobenzenesulfonamides containing aliphatic rings, and their binding to carbonic anhydrases (CA) I, II, VI, VII, XII, and XIII was studied by the fluorescent thermal shift assay and isothermal titration calorimetry[28]. Their results showed that 4-substituted diazobenzenesulfonamides were more potent CA binders than *N*-aryl-β-alanine derivatives. Most of the *N*-aryl-β-alanine derivatives showed better affinity for CA II while diazobenzenesulfonamides possessed nanomolar affinities towards CA I isozyme. X-ray crystallographic structures showed the modes of binding of both compound groups.

The drug forms harmless stable complexes during the detoxification of metal poisoning [29], Most of transition metal complexes are involved in storage, transport, and catalytic processes [30]; [31].

The L-isomer of alanine (left-handed) is the one that is incorporated into proteins. The right-handed form, D-Alanine occurs in polypeptides in some bacterial cell walls [32], and in some peptide antibiotics, and occurs in the tissues of many crustaceans and molluscs as an osmolyte [33].

The potentiometric method has been used extensively in many branches of solution chemistry. Great attention has been paid to the use of potentiometric methods in the study of binary and ternary complexes of transition metals with molecules of biological and pharmaceutical interest [34]; [35]; [36].

Either for the biological importance of the chrome metal. It is noticed that this metal exists with low rates in the human body and it is considered one of the factors used to treat diabetes , hypertension and poly cystic ovaries syndrome (PCOS) especially for patients suffering from problems in the heart and blood vessels because they contain beta bonds. Chrome can be taken via some drugs and foods such as meat , milk , vegetables and fruits[37].

The main benefit of this chemical element in these alloys is the inert protective oxide that forms on the surfaces in suitably oxidizing environments[38]. For full surface coverage by chromium oxide (Cr_2O_3), more than 10% of Cr is required, and typically the range of Cr content is 15 - 28%, for example in stainless steels[39].

This study deals with mixing complexes with the metal to form di complex and drug complexes with the metal and amino acid to obtain the tri complex[40]. These complexes are influenced by several factors such as crystal structure, the nature of the donating atoms, the exchange effect of the drug inside the complex and atomic number of the atom[41][42]. It is noticed in the study that there is a biological effect of the amino acid on the Chrome metal to remove or lessen the effect of the toxicity in the metal. This explains the reason behind studying tri complex[43][44].

The method of measurement used in the study is the potentiometric titration method which is used to calculate di complexes and tri complexes and is used through the process of forming complexes in the aquatic medium and changing colour through titration[45].

Experimental

Sulfanilamide was obtained in highly pure form from State Drug Industry (SDI), Samara-Iraq.

A-Preparation of primary ligand:

The primary ligand were prepared from 10 ml (0.002M Sulfanilamid) with 10 ml(0.002M metal nitrats (Cr^{+3}) and 10ml (0.1M HCl) then the volum become 50ml then titration with 0.1M NaOH at 306k°.

A) Free acid
B) Free acid + primary ligand
C) Free acid + primary ligand+ metal

The graph of volume between the NaOH against pH was plotted (Fig. 1)

B-Preparation of secondary ligand:

The secondary ligand were prepared from 10ml (0.002M Sulfanilamid) with 10ml(0.002M metal (Cr^{+3}) nitrats and 10ml (0.1M HCl) , 10ml (0.1M DL-Alanin), 10ml (0.1M KCl) then the volum become 50ml then titration with 0.1M NaOH at 306k.°

A) Free acid
B) Free acid + primary ligand
C) Free acid + primary ligand+ metal
D) Free acid+ KCl+ primary ligand + secondary ligand+ metal

The graph of volume between the NaOH against pH was plotted (Fig. 5)

Results and Discussion

The basic concern in this study is to deal with complexes to find the structural formula and their stability, so, the main object is to calculate the stability constant of the tri complexes and specify the type and nature of overlap between metals and drugs.

The adopted methods are Rosti and Irfink's since it is considal easy and suitable for the current study.

It is manipulated through titrating the drugs (di complex) composed of the drugs and the metal with a strong base (sodium hydroxide) in stable conditions of pH , temperatures and concentrations as will be shown in the subsequent figures and tables. Later in the study, the tri complexes composed of the drugs, metal and amino acid are investigated at a fixed temperature and concentration as shown in subsequent figures and tables. The dicomplexes and tricomplexes are also compared.

Effect of concentration:

Potentiometric (Sulfanilamid+Cr^{+3})+(Sulfanilamid) upon titration with 0.1M (NaOH) at 306k°.

As shown in subsequent figures(1) and tables(1,2,3,4), with change in the concentration of the di complex (drug and metal), that the complexity is in it's highest point at the 0.002 M concentration. This occurs due to the occurrence of symmetry at a specific pH and this ultimately indicates the dissolution or occurrence of a new hydroxidic complex different from the original one in formula and geometrical structure. It is noticed in the subsequent tables that the highest value of n is obtained through the concentration of 0.002 molari and that the stability constant is the highest at this concentration so the interaction is considered of the easy and not disabled type.

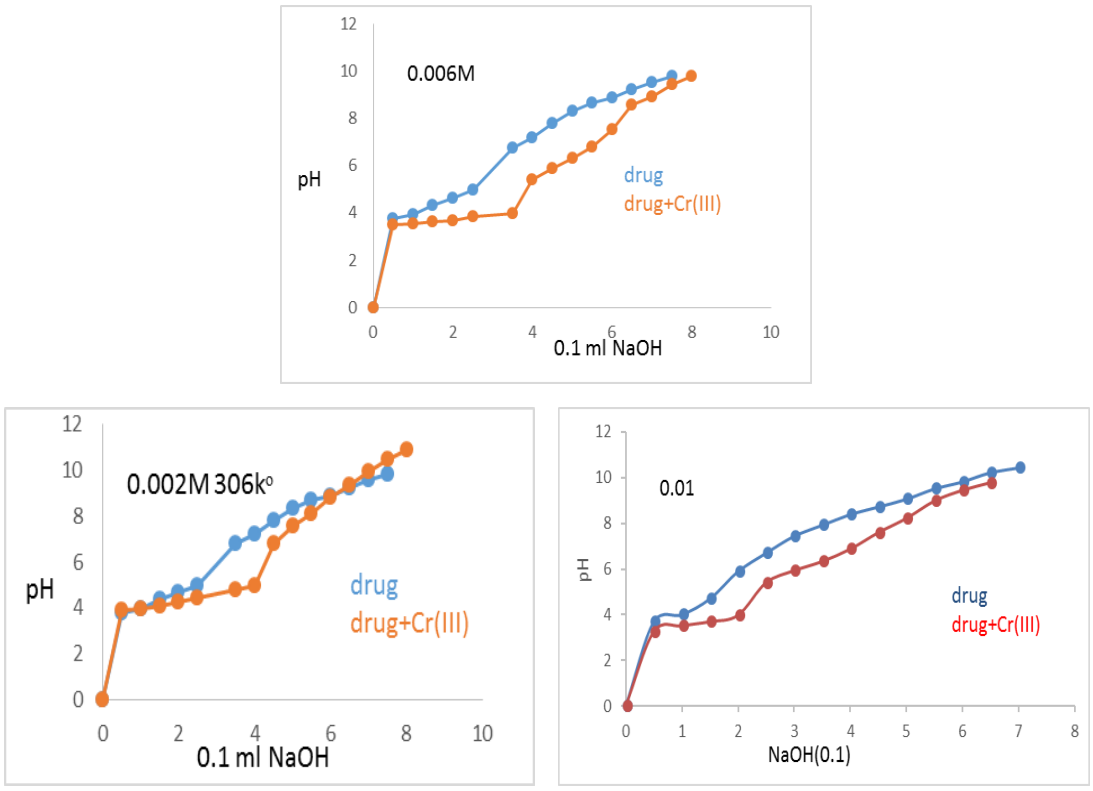


Fig (1) The volume of NaOH against pH at delf conc.(0.01,0.002,0.006)M.

Table(1,2,3) potentiometric (Sulfanilamid+Cr^{+3})+(Sulfanilamid) upon titration with 0.1M (NaOH) at 306k.

0.01M

pH	Δml NaOH* (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
3.70	0.1	0.0099	0.99	8.6901
3.98	0.1	0.0098	0.98	8.4102
5.4	0.1	0.0097	0.97	6.9903
5.93	0.3	0.0096	0.96	6.4604
6.33	0.2	0.0095	0.95	6.0605
6.87	0.1	0.0094	0.94	5.5206

0.002M

Ph	Δml NaOH (per 50 ml sample	Moles** OH- MA complexed (mole / litter)	n´	p[A]
4.45	0.3	0.0197	9.85	8.5304
4.77	0.1	0.0196	9.8	8.2104
4.95	0.2	0.0194	9.7	8.0306
6.77	0.2	0.0192	9.6	6.2108
7.56	0.1	0.0190	9.5	5.421
8.11	0.2	0.0188	9.4	4.8712

0.006M

Ph	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´***	p[A]****
3.64	0.2	0.059	9.8	8.901
3.7	0.1	0.057	9.5	8.843
3.88	0.4	0.056	9.3	8.664
5.43	0.1	0.055	9.1	7.115
5.88	0.3	0.0546	9.1	6.665
6.32	0.2	0.054	9.0	6.226

* The volume of NaOH.
**The moles of OH.
*** n´=totl lignd cnstration/ total metal constrtion
**** p[A]=pka acide – Ph – log [Oh] – [NaOH]

Table.4.The stability constant with change in the concentration of the di complex (drug and metal)

K_1*	concentration (M)	primary ligand
60.47	0.01	Sulfanilamid+Cr^{+3}
89.61	0.002	Sulfanilamid+ Cr^{+3}
34.55	0.006	Sulfanilamid+ Cr^{+3}

***K /** The stability constant frm the table (1,2,3).

Effect of temperature:
Potentiometric (Sulfanilamid+Cr^{+3}) + (Sulfanilamid) upon titration with 0.1M (NaOH) at (306,301,293,288,283)k°. Fig. 2. Table.(5,6,7,8,9).

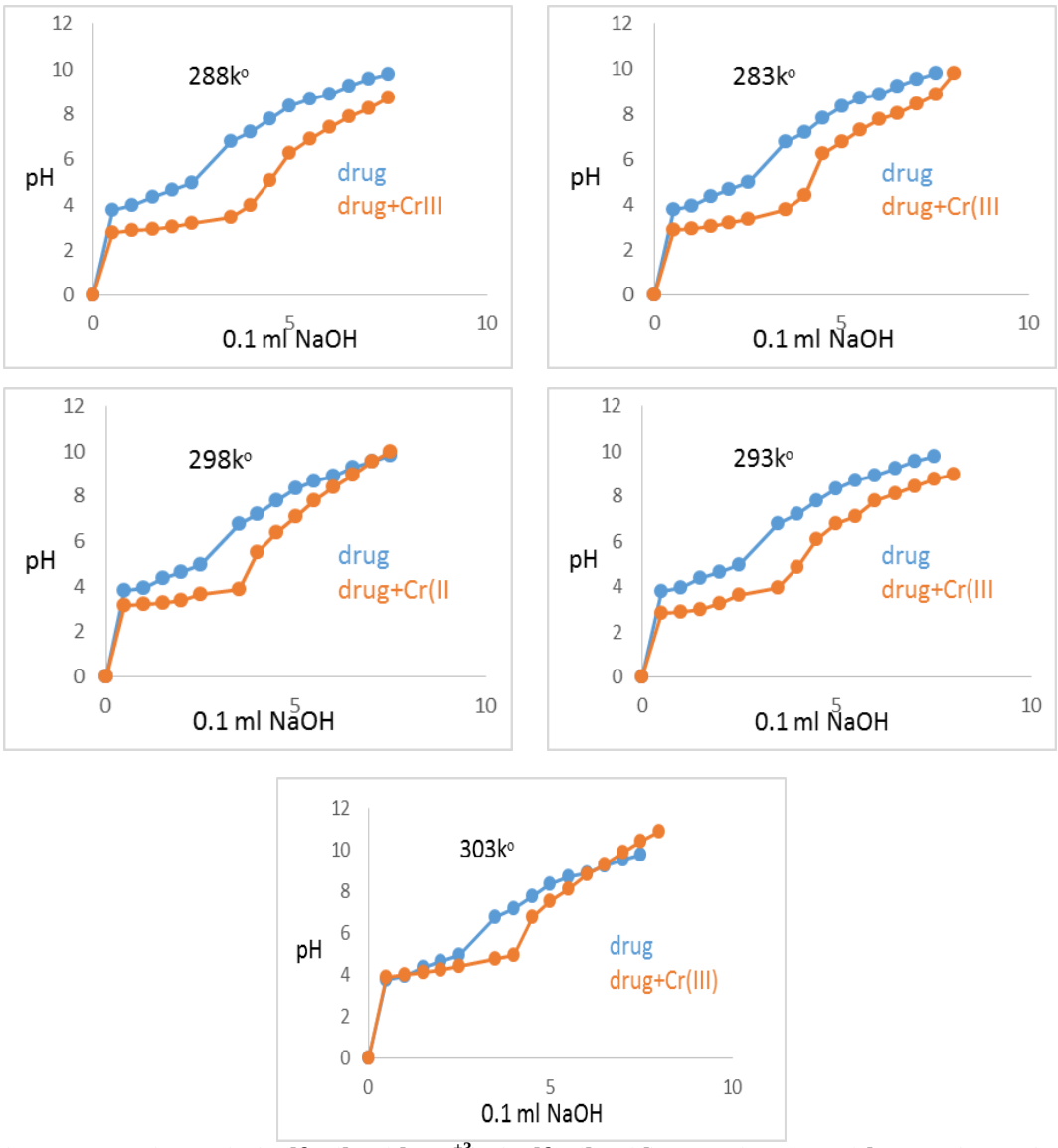


Fig. 2. Potentiometric (Sulfanilamid+Cr^{+3})+(Sulfanilamid) upon titration with 0.1M (NaOH) at (306,301,293,288,283)k°

Table.(5,6,7,8,9). Potentiometric (Sulfanilamid+Cr^{+3})+(Sulfanilamid) upon titration with 0.1M (NaOH) at (306,301,293,288,283)k°.

283k

pH	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
2.93	0.1	0.00192	0.96	10.068
3.03	0.2	0.00190	0.95	9.968
3.17	0.2	0.00188	0.94	9.828
3.33	0.3	0.00186	0.93	9.668
3.78	0.1	0.00185	0.92	9.218
4.4	0.1	0.00183	0.91	8.698

Table.6.

288k

pH	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
2.85	0.1	0.00196	0.98	10.148
2.94	0.1	0.00194	0.97	10.058
3.05	0.2	0.00192	0.96	9.948
3.2	0.1	0.00190	0.95	9.798
3.44	0.2	0.00188	0.94	9.558
3.97	0.1	0.00186	0.93	9.028

Table.7.
293k

pH	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
2.88	0.2	0.00194	0.97	10.118
3.1	0.1	0.00192	0.96	9.898
3.23	0.1	0.00190	0.95	9.678
3.65	0.1	0.00188	0.94	9.348
3.97	0.3	0.00186	0.93	9.028
4.83	0.4	0.00185	0.925	8.168

Table.8.
298k

pH	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
3.2	0.2	0.00192	0.96	9.7913
3.27	0.3	0.00190	0.95	9.7281
3.38	0.1	0.00188	0.94	9.6181
3.65	0.4	0.00186	0.93	9.3781
3.87	0.1	0.00185	0.92	9.1281
5.53	0.1	0.00183	0.91	7.4681

Table.9.
303k

pH	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
4.45	0.3	0.0197	9.85	8.5304
4.77	0.1	0.0196	9.8	8.2104
4.95	0.2	0.0194	9.7	8.0306
6.77	0.2	0.0192	9.6	6.2108
7.56	0.1	0.0190	9.5	5.421
8.11	0.2	0.0188	9.4	4.8712

The complexes investigated at different temperatures reveal that the complexity occurs at the highest temperature and that that ranges between 4.4 to 8.11 pH where the value of the stability constant is at it's highest points. The subsequent tables show that the value of n is the highest at the temperature that is equal to the human body temperature, so the interaction is considered easy and not disabled.

3- Thermodynamic Calculate*:*

The slope of the plot (log K vs. 1/T) was utilized to evaluate the enthalpy change (ΔH) for the complexation process. From Gibbs energy change (ΔG) and (ΔH) values one can deduce the entropy change (ΔS) using the well known relationships. The thermodynamic parameters ΔH, ΔG and ΔS were presented.

Table.10.

K	Log K	T k°	primary ligand
19.14	1.28	283	Sulfanilamid+Cr^{+3}
12.71	1.10	288	
31.74	1.50	293	
41.29	1.61	298	
89.61	1.95	303	

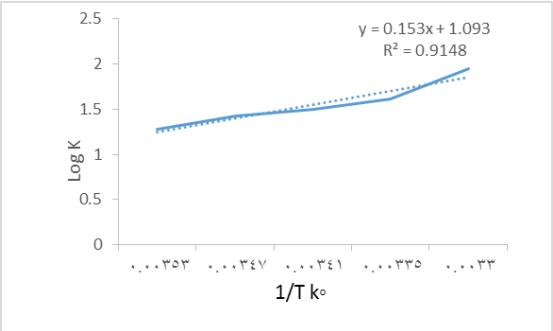


Fig.3. Van't Hoff plot of logk complexes with 1/T

Table.11.

Sulfanilamid+Cr^{+3}					
ΔH (K.J/mol)	ΔS° ($J.mol^{-}.K^{-1}$)	ΔG° (K.J/mol)	K	Log K	1/Tk°
-2.929	+4.001	-6.93	19.14	1.28	0.00353
	+3.131	-6.06	12.71	1.10	0.00347
	+5.481	-8.41	31.74	1.50	0.00341
	+6.251	-9.18	41.29	1.61	0.00335
	+8.381	-11.31	89.61	1.95	0.00330

After noticing the complex between the drug and the metal and after investigating the thermodynamic functions, the following result are obtained:

1- The system gives a positive value in the enthalpy and this means that endo them in reaction is heat absorbing and that interaction occurs.

2- It is noticed through change values in the entropy that they are positive, and this means that there is adecrease in randomness and eventually less freedom for water molecules

3- The negative values of free energy indicate that the complex occurs spontaneously.

4- Noticing the values of Vant-Hof equation, it is found that there is a good linear reaction that gives the bondage value 0.8972.

4- The secnadary Ligand:

The secnadary Ligand prepared from 10ml(0.002M matel nitrats (Cr^{+3}) and 10ml (0.1M HCl), 10ml (0.1M DL-Alanin) then the volume become 50ml then titration with 0.1M NaOH at 306k°. fig.4. table.12.

Table.12 The secnadary Ligand prepared from 10ml (0.002M matel nitrats (Cr^{+3}) and 10ml (0.1M HCl), 10ml (0.1M DL-Alanin) then the volum become 50ml then titration with 0.1M NaOH at 306k°

pH	Δml NaOH (per 50 ml sample	Moles OH- MA complexed (mole / litter)	n´	p[A]
7.13	0.1	0.00188	0.94	5.338
7.78	0.1	0.00186	0.93	4.688
8.42	0.05	0.00185	0.925	4.048
8.89	0.04	0.00183	0.915	3.578
9.37	0.1	0.00181	0.905	3.089
9.78	0.1	0.01880	0.9	2.688

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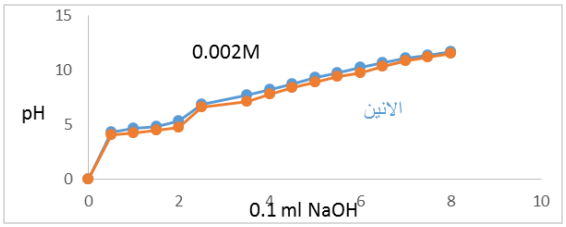

fig.4. The secnadary Ligand **prepared from 10ml(0.002M matel nitrats (Cr^{+3}) and 10ml (0.1M HCl), 10ml (0.1M DL-Alanin) then the volum become 50ml then titration with 0.1M NaOH at 306k°**

Table.13. The stability constant and secnadary Ligand .

K_2	$LogK_2$	secondary ligand
56.17	1.74	matel nitrats (Cr^{+3})+ DL-Alanin

Through complexity between the metal and the amino acid (alanin), it is noticed that the value of K is less than it is in the complex (drug and metal). This means that the ratio of the drugs is 1:1 due to the size of disability formed with the amino acid.

B-The secondary ligand:

This is prepared from 10ml (0.002M Sulfanilamid) with 10ml(0.002M matel nitrats (Cr^{+3}) and 10ml (0.1M HCl) , 10ml (0.1M DL-Alanin), 10ml (0.1M KCl) then the volume becomes 50ml and titration with 0.1M NaOH at 306k°. Fig.5. Table.13.

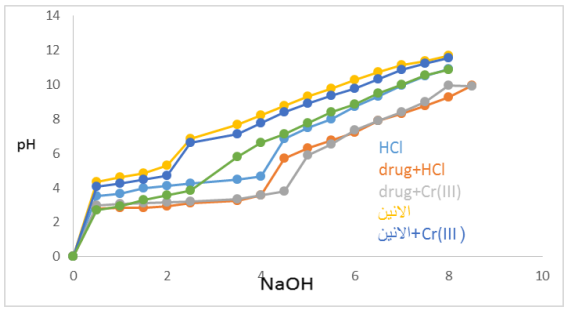

Fig.5.

Table.14

PH	(V_F-V_C)	$(V_F-V_C)(E^\circ+N^\circ)$	$\acute{n}_A$	$(V^\circ+V_C)\,\acute{n}_A\,Tc$	$\acute{n}_{mix}$
3.82	0.1	0.02095	0.8815	0.0934	0.0224
5.8	0.2	0.02089	0.5199	0.0556	0.0940
6.62	0.2	0.02088	0.4112	0.0444	0.0888
7.11	0.1	0.02087	0.3634	0.0396	0.0751
7.78	0.3	0.02086	0.6436	0.0707	0.03007
8.39	0.1	0.02085	0.6514	0.0723	0.0288
K	1/K	$\acute{n}_{mix}$. Tc	Tc-($\acute{n}_{mix}$. Tc)	$(V^\circ+V_F)\,/\,V^\circ$	PL_{mix}
99500	0.00001	0.000044	0.001956	1.06	0.00054
49500	0.00002	0.0001502	0.001849	1.07	0.00115
32833	0.00003	0.000188	0.001812	1.08	0.00178
19500	0.00005	0.0000604	0.001939	1.09	0.00281
13785	0.00007	0.0001776	0.001822	1.1	0.00422
10611	0.00009	0.0000576	0.001942	1.11	0.00514

Table.15.Comparison between Valuable Constants Stability for the system (sulfanilamide, metal ,amino acid).

ΔlogK=logß-$logK_2$ amino acid	ΔlogK= logß-logK1 Drug	logß	Triple Complex	$LogK_2$ amino acid	The dual Complex of amino acid	$logK_1$ Drug	Binary Complex of Drug
0.95	0.74	2.69	Sulpha nilamide +Cr(III)+Ala	1.74	Cr^{+3}+Ala.	1.95	Sulpha nilamide+Cr^{+3}

In this study, the tri complexes occurring between the di complex (drug and metal) and the tri complex (drug, metal and amino acid) are investigated. The interaction between them is large depending on the nature of the ligand and the metal ion in which several stages are required for the complexity to take place. Results indicate that the tri complex is more stable than the di complex because the Chrome metal exists in low rates with the drug to give a less log K than it is with the amino acid (alanine) that a high rate of the tri complex stability constant occur and because the nature of metal and this disagrees with Farghaly, et al (2017) as they conclude that the constants of nalidixic acid antibiotic with metal-ligand complex decrease as the concentration of medium increases.

Conclusion

The study depends on the potentiometric titration technique to get the highest values and suitable concentration in the human body .The experiment is undertaken in suitable conditions with very few concentration of the used metal because of its negative effects on the human body. The study comes up with the conclusion that the tri complex composed of the metal, the drug and the amino acid is more stable in the human body than the di complex (the drug and the metal) due to the existence of the alanine which gives a stereo structure and facilitates the reaction.

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دراسة تسحيحية وثرموديناميكية لمعقدات السلفانيلمايد مع الفلز الايوني والحامض الاميني بواسطة الطرق المجهادية

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الملخص

تم في هذا البحث تحضير معقدات السلفانيلمايد الثنائية المتكونة من دواء السلفانيلمايد وملح الفلز الكروم الثلاثي ومعقدات السلفانيلمايد الثلاثية المتكونه من دواء السلفانيلمايد وملح الفلز والحامض الاميني (الانين) ودراسة ثابت الاستقرار لكل مقعد والمقارنة بينهما حيث اظهرت النتائج ان ثابت استقرار المعقد الثلاثي اكبر من ثابت استقرار المعقد الثنائي وذلك لوجود الحامض الاميني في المعقد الثلاثي مما يجعل التركيب الفراغي اكبر وبالتالي يكون التداخل اسهل.

وتمت أيضا دراسة الدوال الثرمو داينميكيه في هذا البحث والتي أظهرت حدوث تفاعل كيميائي وتلقائي وعشوائية في النظام .