COMPOSITION AND STABILITY OF CHROMIUM METAL COMPLEXES WITH DRUG SALBUTAMOL AND AMINO ACIDS

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ABSTRACT
The equilibrium studies of the mixed ligand complexes of chromium (III) ion with drug salbutamol as primary ligand and the amino acids viz. glycine, arginine, tryptophan, leucine, glutamic acid, glutamine, valine, methionine, phenylalanine and alanine as secondary ligand were determined pH metrically at 27 °C and an ionic strength of 0.1 M NaClO\textsubscript{4} in 80\% (v/v) ethanol-water medium. The calculations have been made using the stability constant of generalized species computer programme.

Key Word: Equilibrium constant; ΔlogK; mixed ligand complexes.

INTRODUCTION
Salbutamol is β-adrenoeceptor agonists\textsuperscript{[1-3]}. It is available in oral dosage forms as well as in inhalers. It is used primarily as bronchodilators in asthma and other constrictive pulmonary conditions.

Glycine is the neutral, aliphatic, optically inactive non-essential, glycogenic aminoacid\textsuperscript{[4-9]}. It can be synthesized from CO\textsubscript{2} and NH\textsubscript{3} by glycine synthase or transamination of glyoxylate and in metabolism of serine and choline. It plays an important role in haeme synthesis. Haeme is a tetra pyrrole ring system with transition metal iron. The nitrogen from each pyrrole is denied from glycine. It can form serine, creatine and purine. It is essential constituent of glutathione and also takes part in detoxication mechanism. There are several abnormalities in glycine metabolism such as primary hyperoxaluria, due to diversion of more glycine to oxalate formation glycinuria, urine contain large amounts of oxalates as well as less reabsorption of glycine in the kidney.
Arginine is essential amino acids. It is basic and in addition to the amino group in the α-position, arginine has a guanido group. It is glycogenic amino acid. Arginine is required for polyamine biosynthesis\[^{10,11}\] in bacteria, fungi and higher eukaryotes. Arginine is an important source for the formation of nitric oxide (NO). Nitric oxide synthase is the enzyme, which cleaves the guanido group of arginine to form NO. Nitric oxide serves important functions. Nitric oxide is a vasodilator\[^{12}\] and smooth muscle relaxant. It regulates blood flow and blood pressure\[^{13-14}\]. It inhibits platelet aggregation and adhesion. It is neurotransmitter and helps macrophages in the bactericidal action.

\[
\text{NH}
\]

The formamido group (– \(\text{C} – \text{NH}_2\)) can be transferred to glycine to form guanidoacetic acid (glycocyamine) which can be methylated to form creatine. It is the immediate precursor in the formation of urea by the liver\[^{15-20}\]. Arginine, by the action of aggregase, is converted to ornithine and urea. The ornithine, on transamination, is converted to glutamic acid semialdehyde, which can be oxidized to glutamate. Thus, it is glycogenic. Ornithine, in conjunction with methionine, serves as a precursor for the synthesis of polyamine spermidine and spermine. These polyamines are growth factors and are required for cell proliferation. Since, they carry a high positive charge, readily associate themselves with polyanions like DNA and RNA and help in stabilizing those structures and may also stimulate their synthesis. They also act as inhibitors of certain enzyme synthesis, particularly the kinases. In pharmacological doses, they act as hypothermic and sedatives\[^{21}\]. Spermidine and spermine are oxidized to putrescine and other products by the enzyme, ‘polyamine oxidase’ which is present in the liver peroxisomes. Large amounts of putrescine and spermidine are excreted in urine\[^{22}\] in a acetylated form.

Tryptophan\[^{23}\] is aromatic essential glycogenic and ketogenic amino acid. In tryptophan metabolism, anthranilic acid finally converted to glutaric acid, which gives two molecules of acetate. Tryptophan can form vitamin Niacin. Serotonin is a decarboxylation product of tryptophan, which is a vasoconstrictor, smooth muscle constrictor and cerebral stimulant. Serotonin is formed by intestinal epithelial cells, blood platelets and in the brain. ‘Argentaffinomas’ is a tumor of intestine produces large amounts of serotonin. Its metabolite product 5-Hydroxyindole acetic acid is excreted in
urine in very large quantity. The enzyme monoamine oxidase convert serotonia to 5-HIAA. Reserpine drug used in the treatment of hypertention. It promotes action by monoamine oxidase and depresses cerebral function.

The defect in the renal and intestinal transport of tryptophan lead to Hartnup disease. The disease similar with pellagra. Large amounts of the amino acid are excreted in the urine and feces. Melatonin hormone is synthesized from serotonin.

Leucine\textsuperscript{[24]} is neutral essential ketogenic amino acid and forms an acetoacetate and acetate. It is branched chain amino acid and taken up by brain and muscle. In leucine metabolism, transamination gives $\alpha$-keto isocaproic acid, which is converted into corresponding CoA, this is similar to oxidative decarboxylation of alfa-ketoglutarate and pyruvate. The enzyme complex is very important in the body of living organism. A deficiency of the enzyme causes maple syrup urine disease. In this disease the urine gives odor of maple syrup or burnt sugar, deterioration is rapid and results in mental retardation.

Glutamic acid\textsuperscript{[25]} is acidic non-essential glycogenic amino acid with one amino group and two carboxylic groups. It takes part in transamination, transamidation and interconversion of amino acids and also participate in ammonia transport and urea formation. Glutamic acid involve in glycogenic function, on deamination it form oxaloacetate and $\alpha$-ketoglutarate and form glycogen. Its wide range contribution in urea formation, purine, pyrimidine rings synthesis. Glutamic acid on decarboxylation gives rise to gamma aminobutyric acid. It controls the neuronal activity. Glutamic acid is one of the constituent of glutathione which is important in the activity of sulphadryl enzyme system.

Glutamine is acidic non-essential glycogenic amino acid\textsuperscript{[26]}. It is a constituent of folic acid. Basically it is used in higher animal for conjugation, detoxification of phenyl acetic acid.

Valine is essential amino acid\textsuperscript{[27]} widely distributed but rarely occurs in amount exceeding 10%. It is branched chain amino acid and can be derived from alanine by the introduction of two methyl group present on $\alpha$-carbon atom. This is glycogenic. On deamination, it forms methyl-malonyl-CoA which can be converted to succinyl-CoA in place of two H atoms of the methyl group.
Methionine\textsuperscript{[28]} is essential glycogenic amino acid. It is the only common amino acid possessing an ether linkage. Cereals have sufficient quantity of methionine whereas pulses lack in it. It is methylation product of homocysteine. Apart from its role as a protein constituent and as an essential amino acid, methionine is also important as a donor of active methyl groups. Methionine is particularly important as a donor of methyl group in reaction known as transmethylation reactions. To act as a methyl donor, the methionine has to be first activated by ATP.

The S-methyl bond is a high energy bond. The methyl group is hence labile and can be readily transferred to an acceptor. The activating enzyme is known as methionine adenosyl transferase. The enzymes, which bring about transmethylation are called methyl transferases or methylferases.

Phenylalanine\textsuperscript{[29]} is aromatic essential glucogenic and ketogenic amino acid. In metabolism phenylalanine is converted into tyrosine. In metabolism homogenstic acid is formed which undergoes cleavage and form fumarate and acetoacetate. The hormones such as adrenaline, noradrenaline, thyrosine and melanin pigment formed from tyroxine. Several abnormalities observed in phenylalanine metabolism such as phenylketonuria and alkaptonuria. In phenylketonuria, there is a black in hydroxylation of phenyl alanine to form tyrosine, this leads to mental retardation. Alkeptanaria, in this homogenstic acid is not further oxidised and excreted in urine, which lead to black coloration of urine.

Alanine\textsuperscript{[30]} is a non-essential, glycogenic amino acid. It was first isolated in 1888 from silk fibrin where it occurs in abundance along with glycine and serine. It is the parent substance of all the amino acids except glycine. The various amino acids may be derived from alanine by replacement of one or two H atoms of the methyl group present on \(\alpha\)-carbon atom. Alanine is the least hydrophobic of the 8 non-polar aminoacids because of its small methyl side chain.

Deamination or transamination produces pyruvic acid, which can be readily converted to glucose or oxidised in citric acid cycle. \(\beta\)-alanine is a constituent of pantothenic acid.

Glucose is released from liver by glycogenolysis and gluconeogenesis during muscular contraction. Glucose is utilized by muscle by glycolysis, producing pyruvate. While part of this pyruvate is converted to lactate, the rest is aminated to form alanine.
Both are returned to the liver and can participate in gluconeogenesis, to form fresh glucose.

Formation of alanine from pyruvate in muscle also helps in removing some of the NH$_3$ formed in that tissue during amino acid metabolism. The cycle of transport of glucose from liver to muscle and of alanine from muscle to liver is known as glucose-alanine cycle$^{31,32}$

β-alanine is a component of pantothenic acid. Anserine and carnosine are dipeptides containing beta alanine and histidine. They have important functions in the skeletal muscle and activate myosin ATP Phase Chromium is a transition metal ion and is widely distributed throughout the body.$^{33}$ Infants have a higher chromium concentration than adults. Brewer’s yeast is rich in chromium and most grains and cereal products contain significant quantities. Significant amount of chromium is obtained in the diet by cooking foods in stainless steel cookware.

Chromium is absorbed poorly in the diet. It is absorbed mainly in the small intestine by pathways. It appears to share with zinc. It is transported to tissues, bound to ‘transferrin’ and appears in the liver mitochondria, microsomes and cytosol.

Chromium is essential ultra trace metal and needed for potentiation of insulin action on carbohydrate and lipids; active as a bioorganic chromium complex. The deficiency of chromium causes insulin resistance. Chromium plays an important role in carbohydrate, lipid and protein metabolism. It is a true potentiator of insulin and is known as glucose tolerance factor (GTF). Trivalent chromium has been claimed to be a constituent of glucose tolerance factor.

Chromium supplementation in deficient diets decreases serum cholesterol levels and prevents atheromatous plaque formation in aorta. When given with insulin in chromium deficiency state, it improves amino acid incorporation mainly with α- amino isobutyric acid, glycine, serine and methionine. In protein energy malnutrition (PEM) states, chromium supplementation is beneficial for weight gain. Chromium functions in vivo as an organic chromium complex and biological role to potentiate insulin activity.

Survey of literature reveals that no work has been reported on complex tendencies of drug salbutamol with transition metal ion chromium (III) in ethanol-water solution. Therefore in order to understand the complex formation tendencies of salbutamol it was
though worthwhile to determine the formation constant 1:1:1 ternary complexes of salbutamol with chromium (III) in the presence of amino acids in 80%(v/v) ethanol-water medium at 27 °C at a fixed ionic strength 0.1 M NaClO₄.

**MATERIALS AND METHODS**

Drug sample of salbutamol in pure form were obtained from pharma industries and used as received. Ethanol was purified as described in literature[^34]. Double distilled water was used for the preparation of ethanol-water mixture and stock solution of salbutamol.

All chemicals used were AnalAr grade. NaClO₄ (0.1M) and NaOH solution was prepared in carbondioxide free double distilled water. Carbonate free NaOH was standardized by titrating with oxalic acid. HClO₄ Reidal (Germany) was used for the preparation of the stock solutions of chromium (III) to prevent hydrolysis and standardized by using standard EDTA solution[^35].

The experimental procedure, in the study of ternary chelated by the potentiometric titration technique, involves the titration of carbonate free solution of

- Free HClO₄(A)
- Free HClO₄ + Ligand salbutamol Drug
- Free HClO₄ + Ligand salbutamol + Metal ion
- Free HClO₄ + Ligand Aminoacids
- Free HClO₄ + Ligand Aminoacids + Metal Ion
- Free HClO₄ + Ligand Drug + Ligand Aminoacids + Metal Ion

Against standard solution of sodium hydroxide, were drug salbutamol and aminoacid are two ligands. The ionic strength of the solutions was maintained constant i.e. 0.1M by adding appropriate amount of 1M sodium perchlorate solution. The titration were carried out at 27 °C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO₂. pH meter reading in 80% (v/v) ethanol-water were corrected by method of Vanuitert and Hass[^36]. The formation constant of ternary complexes were determined by computational programme SCOGS[^37] to minimize the standard derivation.
RESULTS AND DISCUSSION

Binary Metal Complexes

The proton ligand constant and metal ligand stability constant of salbutamol and amino acids with chromium (III) determined in 80% (v/v) ethanol-water mixture at 27 °C and ionic strength \( \mu = 0.1 \text{M NaClO}_4 \) are already published\(^{[38,39]}\).

Ternary Metal Complexes

In the ternary systems, the mixed ligand titration curve coincide with acid + drug complex curve up to the pH \( \sim 2.5 \) and after this pH, it deviates. Theoretical composition curve remains toward left to the mixed ligand titration complex curve. After pH \( \sim 2.5 \), the mixed ligand curve drift towards X axis, indicating the formation of hydroxide species. Since the mixed ligand curve coincide with individual metal complex titration curves, the formation of 1:1:1 complex by involving stepwise equilibria.

The Primary ligand salbutamol form 1:1 and secondary ligand amino acids such as glycine, arginine, tryptophan, leucine, glutamic acid, glutamine, valine, methionine, phenylalanine and alanine form 1:1 and 1:2 complexes with chromium (III). It is evident from the figure of the percentage concentration species Cr(III)-salbutamol-aminoacids system, that the percentage distribution curve of free metal decreases sharply with increasing pH. This indicates involvement of metal ion in the complex formation process. Percentage concentration of free ligand salbutamol and amino acids increases and this increase may be due to the dissociation of excess ligand present in the system, as a function of pH.

Species Distribution Studies

To visualize the nature of the equilibria and to evaluate the calculated stability constant of ternary complexes Cr(III)-salbutamol-glycine, species distribution curves have been plotted as a function of pH at temperature 27 °C and \( \mu = 0.1 \text{ M NaClO}_4 \) using SCOG program.

It can be seen that, the concentration of Cr(III)-salbutamol-glycine increases from pH~2.8, whereas the concentration for the formation of D (drug) and HR (amino acid) represented by \( C_1 \) and \( C_2 \) show continuous decrease with increasing pH which indicates
the formation of Cr(III)-salbutamol-glycine and represented by $C_7$. The concentration of this species continuously increases; confirm the formation of ternary complexes.

SCOG distribution curve of ternary system Cr(III)-salbutamol-glycine showed that the formation of ternary complex started at pH ~ 2.8 when Cr(III) at pH ~ 4.8. Ternary complexes attain their maximum concentration in the pH ~4.2. From the SCOG distribution curve it is concluded that the formation of ternary complex started only after the metal-primary ligand complex has attained its maximum concentration. This indicates that the metal-primary ligand complex Cr(III)-salbutamol is formed first and then the secondary ligand Cr(III)- glycine coordinated to it, resulting the formation of ternary complex.

According to this method in this system ternary complex of salbutamol with glycine, arginine, tryptophan, leucine, glutamic acid, glutamine, valine, phenylalanine and alanine show the following types of the concentration species distribution.

$$C_1 = HD \xrightleftharpoons{D+H}$$
$$C_2 = H_2R \xrightleftharpoons{HR+H}$$
$$C_3 = HR \xrightleftharpoons{R+H}$$
$$C_4 = M+R \xrightleftharpoons{MR}$$
$$C_5 = MR+R \xrightleftharpoons{MR_2}$$
$$C_6 = M+D \xrightleftharpoons{MD}$$
$$C_7 = M+R+D \xrightleftharpoons{MDR}$$

According to this method in this system ternary complex of salbutamol with methionine show the following types of the concentration species distribution.

$$C_1 = HD \xrightleftharpoons{D+H}$$
$$C_2 = H_2R \xrightleftharpoons{HR+H}$$
$$C_3 = HR \xrightleftharpoons{R+H}$$
$$C_4 = M+R \xrightleftharpoons{MR}$$
$$C_5 = M+D \xrightleftharpoons{MD}$$
$$C_6 = M+R+D \xrightleftharpoons{MDR}$$

Where $M = $ Metal, $R = $ Aminoacids and $D =$ drug salbutamol.

Moreover, the maximum percentage of the formation of ternary complexes is less than that of the Cr(III)- glycine binary complex; and more than Cr(III)-salbutamol binary...
complex, this indicates that the ternary complex is less stable as compared to Cr(III)-glycine binary complex and more stable than Cr(III)-salbutamol binary complex.

The Stability Constant of Ternary Complexes

The relative stabilities of the binary and ternary complexes are quantitatively expressed in term of $\beta_{11}$, $\beta_{20}$, $K_{\text{D}}$, $K_{\text{R}}$, $K_{\text{r}}$ and $\Delta \log K$ value which are represented in Table. The stability constants of ternary systems are represented in Table.

The stability of ternary complexes is conveniently characterizes by two ways, one based on difference of stability constant $\Delta \log K$ and second disproportion constant.

\[
\begin{align*}
\text{MR}+\text{D} & \rightleftharpoons \text{MRD} & \text{(I)} \\
\text{M}+\text{D} & \rightleftharpoons \text{MD} & \text{(II)}
\end{align*}
\]

\[\Delta \log k = \log K_{\text{ML2}} - \log K_{\text{ML1}}\]

The first equation mentioned above is similar to the reaction

\[\text{MD} + \text{D} \rightleftharpoons \text{MD}_2\]

With respect to the availability of coordination sites for ligand D in MR or MD. Generally $K_{\text{ML1}} > K_{\text{ML2}}$ because more coordination positions are normally available for bonding first ligand to a metal ion than the second ligand. Evidently $K_{\text{ML1}} > K_{\text{ML2}}$ or $\Delta \log K$ is negative. $\Delta \log K$ can be calculated by the expression.

\[\Delta \log K = \log \beta_{\text{MRL}} - (\log K_{\text{MR1}} + \log K_{\text{MD1}})\]

The negative $\Delta \log K$ for ternary systems indicates that the primary ligand anion and secondary ligand anions preferentially form ternary complexes to their binary ones. It follows from above expression that the difference, $\Delta \log K$ results from the subtraction of two constants and therefore, a constant which corresponds the equation,

\[\text{MR} + \text{MD} \rightleftharpoons \text{MRD} + \text{M}\]

The positive value of $\Delta \log K$ indicates the equilibrium is more on its right side. The other characterization is based on the disproportion reaction represented by the following equilibrium;

\[\text{MR}_2 + \text{MD}_2 \rightleftharpoons 2\text{MRD}\]

The disproportion reactions for the system containing the ligands which form 1:1 and 1:2 complexes individually with the metal ion are as
Above two reactions are for the system containing one ligand which form only 1:1 and other form both 1:1 and 1:2 binary complexes. The last reaction is for the system containing ligands which form only 1:1 binary complexes. The magnitude of the constant is the measure of stability of mixed ligand complexes. Watter and Kida calculated statistically expected value 0.6 log unit by considering with probabilities for a variety of reason discussed by Sigel. \Delta \log K value can be calculated by using first or second approach. The calculated $\Delta \log K$ values for all systems are given in Table 1.

Table 1: Parameters based on some relationship between the formation of ternary complexes of chromium (III) metal ion with salbutamol in the presence of amino acids (1:1:1) system

Temp = 27°C  I = 0.1 M NaClO₄  Medium = 80% (V/V) Ethanol-Water

<table>
<thead>
<tr>
<th>AMINOACIDS</th>
<th>$\beta_{11}$</th>
<th>$\beta_{02}$</th>
<th>$\beta_{20}$</th>
<th>$K_D$</th>
<th>$K_R$</th>
<th>$K_r$</th>
<th>$\Delta \log K$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLYCINE</td>
<td>9.0867</td>
<td>10.4500</td>
<td>2.8309</td>
<td>6.2258</td>
<td>2.5767</td>
<td>1.3683</td>
<td>-0.2542</td>
</tr>
<tr>
<td>ARGinine</td>
<td>11.7685</td>
<td>8.5166</td>
<td>2.8309</td>
<td>8.9376</td>
<td>3.2519</td>
<td>2.0742</td>
<td>0.4210</td>
</tr>
<tr>
<td>TRYPTOPHAN</td>
<td>10.2610</td>
<td>14.8835</td>
<td>2.8309</td>
<td>7.4201</td>
<td>1.7969</td>
<td>1.1584</td>
<td>-1.0400</td>
</tr>
<tr>
<td>LEUCINE</td>
<td>9.7692</td>
<td>12.0578</td>
<td>2.8309</td>
<td>6.9383</td>
<td>2.0614</td>
<td>1.3122</td>
<td>-0.7695</td>
</tr>
<tr>
<td>GLUTAMIC ACID</td>
<td>6.0746</td>
<td>6.5506</td>
<td>2.8309</td>
<td>3.2437</td>
<td>2.4659</td>
<td>1.2950</td>
<td>-0.2650</td>
</tr>
<tr>
<td>GLUTAMINE</td>
<td>10.0287</td>
<td>13.3302</td>
<td>2.8309</td>
<td>7.1978</td>
<td>2.7801</td>
<td>1.2410</td>
<td>-0.0508</td>
</tr>
<tr>
<td>VALINE</td>
<td>8.4417</td>
<td>9.2023</td>
<td>2.8309</td>
<td>5.6108</td>
<td>2.8295</td>
<td>1.4030</td>
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</tr>
<tr>
<td>METHIONINE</td>
<td>4.5864</td>
<td>3.1000</td>
<td>2.8309</td>
<td>1.7555</td>
<td>1.4864</td>
<td>1.5466</td>
<td>-1.3445</td>
</tr>
<tr>
<td>PHENYL ALANINE</td>
<td>8.9830</td>
<td>11.8021</td>
<td>2.8309</td>
<td>6.1521</td>
<td>2.5425</td>
<td>1.2277</td>
<td>-0.2884</td>
</tr>
<tr>
<td>ALANINE</td>
<td>13.0300</td>
<td>19.4190</td>
<td>2.8309</td>
<td>10.1991</td>
<td>2.3310</td>
<td>1.92610</td>
<td>-0.4999</td>
</tr>
</tbody>
</table>
In Cr (III)-salbutamol-aminoacids, primary ligand salbutamol form only 1:1 and secondary ligand form both 1:1 and 1:2 binary complexes. Therefore these systems favour the following disproportion reactions.

\[
\begin{align*}
MR_2 + MD & \rightleftharpoons MRD + MR \\
MR_2 + MR & \rightleftharpoons MRD + MD
\end{align*}
\]

The Comparison of \(\beta_{11}\) with \(\beta_{20}\) and \(\beta_{02}\) of this system show that preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The considerably low value of \(K_D\) and \(K_R\) indicates less stability of ternary complexes with respect to that of primary as well as secondary ligands. The \(K_r\) value of this complex is positive but less which indicates lower stability of ternary complexes.

Results of the present investigations show that the stability constant of ternary complexes formed are less stable. The negative \(\Delta \log K\) value of this system indicates that the ternary complex is less stable than the binary 1:1 metal–salbutamol and metal–aminoacids complex. This is in accordance with statistical considerations. The negative value of \(\Delta \log K\) does not mean that the complex is not formed. The negative value may be due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance\([40-44]\), electronic consideration\([45-46]\), difference in bond type, geometrical structure etc.

Sigel concluded that in the case of bidentate ligand Salbutamol and amino acid, there are twelve edges of a regular octahedron available to the first entering ligand but only five for the second. Then the statistical factor would be 5/12 and accordingly \(\Delta \log K = -0.4, -0.6\) and \(-0.9\) for square planer and distorted octahedral complexes. Hence the experimentally determined value \(\Delta \log K < -0.6\) indicate less stabilization in ternary complexes.

The larger size of salbutamol may be responsible in decreasing the stability of ternary complexes as indicted by more negative\(\Delta \log K\) value.

The conclusion drawn from the pattern of the different species distribution curves for glycine, similarly for other amino acids. The stability of ternary complexes are governed by the nature of both, the primary and secondary ligand. The ligand first bound
to metal ion influence the bonding properties of secondary ligands to be bound. The stabilization of ternary can be governed by binding properties of secondary ligand.

The order of stability of ternary of ternary complexes of Cr(III) with respect to secondary ligands for salbutamol are;

Salbutamol = Arginine > Valine > Glutamine > Glycine > Gluta. acid > Phenylalanine > Alanine > Leucine > Tryptophan > Methionine.

The values of $K_r$ (Statistical relationship) is presented in Table, which indicates the measure of relative stability of a mixed-ligand complexes with respect over all stabilities of binary complexes. From Table it is observed that $\Delta \log K$ values for all the systems are negative, as already discussed that the negative $\Delta \log K$ values for ternary systems indicates less stability of complexes.

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