Conductance Studies on Complex Formation between CaCl$_2$ and Ampicillin as Ligand in Water and In Methanol Solvent at Different Temperatures.

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ABSTRACT

The complexation reactions between the metal cation (Ca$^{2+}$) and ligand (ampicillin) was studied in water and in pure MeOH solvent at 293.15, 298.15, 303.15 and 308.15K by applying the conductometric method. Consequently, we will study the effect of solvent properties on stoichiometry, the selectivity between ligand and ions in various systems and thermodynamic parameters of complexation. On drawing the relation between molar conductance and the ratio of metal to ligand concentrations, different lines are obtained indicating the formation of 1:1, and 2:1 (M:L) stoichiometric complexes. The stability constant of the complexes were obtained from fitting the molar conductivity curves using a computer program. This research focused on the study of thermodynamic complexation reactions between the ligand, ampicillin, with Ca$^{2+}$ metal cation in water and pure MeOH solvent.

INTRODUCTION

The study of the interactions involved in the complexation of different cations with ligand in solvent mixtures is important for a better understanding of the mechanism of biological transport, molecular recognition, and other analytical applications.

Recently, there has been much research on complex formation. There are a number of physico-chemical techniques that can be used in the study of these complexation reactions, for example, spectrophotometry, polarography, NMR spectrometry, calorimetry, potentiometry and conductometry [1]. Nevertheless of all these techniques, conductometric techniques are the most useful for studying this complexation of complexes. This is because conductometric techniques are highly sensitive and inexpensive, with a simple design of experimental arrangement for such investigations [2]. Therefore, it offers more benefits than the other methods.

Transition metal ions have a strong role in bio-inorganic chemistry and redox enzyme systems and may provide the basis of models for active sites of biological systems [3]. The chemistry of β-lactam antibiotic is of interest due to their versatile application in medicine and biology. Ampicillin is a penicillin β-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive organisms. [4]. The pharmacology and clinical efficiency of ampicillin and amoxicillin were extensively studied by many worker [5].

In this study, we discuss the complexation reaction between ampicillin that acts as a ligand with divalent cations in water and in methanol at different temperatures (293.15, 298.15, 303.15 and 308.15K). This study has been conducted at different temperatures by applying the conductometric
method. Consequently, we will study the effect of solvent properties on stoichiometry of complexes formation between ligand and ions in various systems.

**EXPERIMENTAL**

**Material and methods**

All chemicals used were of the highest purity available and were purchased from Merck.

**The ligand**

Molecular Structure of Ampicillin sodium salt:

![Molecular Structure of Ampicillin sodium salt](image)

6-[[Aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3,2,0]heptane-2-carboxylic acid sodium salt

Molecular Formula: C₁₆H₁₈N₃NaO₄S

**Conductometric titration**

In a typical experiment, 10 m; of the ampicillin solution (1.0 x 10⁻⁴ M) was placed in the titration cell, thermostated at the preset temperature and the conductance of the solution was measured after the solution reached thermal equilibrium. Then, a known amount of the CaCl₂ solution (1.0 x 10⁻³ M) was added in a stepwise manner using a calibrated micropipette. The conductance of the solution was measured after each addition until the desired cation-to-ligand mole ratio was achieved. The specific conductance values were recorded using conductivity bridge HANNA, H1 8819N with a cell constant equal to 1. The conductometer was conducted with a thermostat of the type the Kottermann 4130 ultra thermostat. The temperature was adjusted at 293.15, 298.15, 303.15 and 308.15 K.

**RESULT AND DISCUSSION**

The molar conductance (Λₘ) values were calculated using equation (1):

\[
Λₘ = \frac{(Kₘ - Kₘ^{solv})K_{cell} \times 1000}{C}
\]

(1)

Where \(Kₘ\) and \(Kₘ^{solv}\) are the specific conductance of the solution and the solvent, respectively; \(K_{cell}\) is the cell constant and \(C\) is the molar concentration of the CaCl₂ solution.

By drawing the relation between molar conductance (Λₘ) and the molar ratio of metal to ligand \([M]/[L]\) concentrations different lines are obtained with sharp breaks indicating the formation of 1:1 and 2:1 \([M : L]\) stoichiometric complexes, Fig. (1-4).

As is obvious from Fig. (1-4), in all cases studied, addition of the CaCl₂ solution to the ligand (ampicillin) solutions caused a continuous decrease in the molar conductance of the solutions, indicating the lower mobility of the complexed cations compared to the solvated ones. In all cases, the slope of the molar conductance-mole ratio plots change sharply at the point where the ligand to cation mole ratio indicate the formation of stoichiometric complexes, indicating the formation of a relatively stable 1:1 and 2:1 \([M : L]\) complex between the ligand and the cation solutions used.

The 1:1 binding of the Ca²⁺ cations with ampicillin ligand can be expressed by equilibrium:

\[
M^{2+} + L \rightleftharpoons ML^{2+}
\]
and the corresponding formation constants ($K_f$) for Ca$^{2+}$-ampicillin complexes were calculated by using equation:

$$K_f = \frac{[ML^{2+}]f_{ML^{2+}}}{[M^{2+}][L]f_{M^{2+}}f_L}$$  \hspace{1cm} (2)

where $[ML^{2+}]$, $[M^{2+}]$, $[L]$ and $f$ represents the equilibrium molar concentrations of complex, free cation, free ligand and the activity coefficients of the species indicated, respectively.

Under the dilute conditions used, the activity coefficient of the uncharged ligand, $f_L$ can be reasonably assumed to as unity $^{6,7}$. The use of Debye-Hückel limiting law of electrolytes $^{8}$ leads to the conclusion that $f_{M^{2+}} = f_{ML^{2+}}$, so that the activity coefficients in Eq. 2 cancel out.

Thus, the complex formation constant in terms of the molar conductance can be expressed as $^{9-11}$:

$$K_f = \frac{[ML]}{[M][L]} = \frac{\Lambda_M - \Lambda_{obs}}{(\Lambda_{obs} - \Lambda_{ML})[L]}$$  \hspace{1cm} (3)

$$[L] = C_L - \left\{ C_M + \frac{\Lambda_M - \Lambda_{obs}}{(\Lambda_M - \Lambda_{ML})} \right\}$$  \hspace{1cm} (4)

here, $\Lambda_M$ is the molar conductance of the CaCl$_2$ solution before addition of the ligand, $\Lambda_{ML}$ the molar conductance of the complex, $\Lambda_{obs}$ the molar conductance of the solution during titration, $C_L$ the analytical concentration of the ligand, $C_{M^{2+}}$ the analytical concentration of the CaCl$_2$ solution. The complex formation constant, $K_f$, and the molar conductance of the complex, $\Lambda_{ML}$, were obtained by computer fitting of Eqs. (3) and (4) to the molar conductance-mole ratio data using a nonlinear least-squares $^{12}$.

The stability constants of the resulting 1:1 and 2:1 [M:L] complexes were determined from the computer fitting of Eqs. 3 and 4 to the molar conductance-mole ratio data. A sample computer fit of the mole ratio data is shown in Fig. (1-4) and all $K_f$ values are summarized in Table 1.

The Gibbs free energies of formation for each stoichiometric complex were calculated by:

$$\Delta G_f = -RT \ln K_f$$ \hspace{1cm} (5)

The calculated $\Delta G_f$ values are presented in tables (2).

The enthalpy changes of complexation ($\Delta H_f$) were calculated from the plots of log $K_f$ against 1/T, (slope $= -\Delta H/2.303$ R) (Fig. 5) using Van’t Hoff eqn $^{6}$:

$$\log K_f = \frac{-\Delta H}{2.303R} \left( \frac{1}{T} \right) + \text{constant}$$ \hspace{1cm} (6)

Where R is the gas constant and T is the absolute temperature.

Entropy change $\Delta S$ were for complexes calculated $^{13-85}$ by using Gibbs-Helmholtz equation (6)

$$\Delta G_f = \Delta H_f - T\Delta S_f$$ \hspace{1cm} (7)

The calculated values of ($\Delta H_f$) and ($\Delta S_f$) for CaCl$_2$-ampicillin stoichiometric complexes are presented in Table (3).

In order to obtain a better understanding of the thermodynamics of the complexation reactions, it is useful to consider the enthalpic and entropic contributions to these reactions. The enthalpy and entropy of the complexation reactions were determined by measuring the formation constants as a function of temperature. Enthalpies and entropies of complexation reactions show that, in most cases, the reaction is entropic controlled although, in all cases, a negative value of enthalpic change is also obtained.
Comparison of $\Delta H_f$ values of complexation (Table 3) clearly revealed that the steric hindrance in organic ligand is an important factor in enthalpy changes in the process of complexation reactions. On the other hand, in most cases, the entropy changes during complexation reactions are quite favorable. The entropic change during the complex formation is in fact affected by several factors including the change in flexibility of the reactants in the course of complexation reaction and the differences between the extent of solvation-desolvation of the uncomplexed and complexed species. In the case of the complexation reactions of ligand with Ca$^{2+}$ cations, a large positive $\Delta S_f$ was obtained. This observation seems to be due to strong solvation of ligand by solvent alike MeOH [13–32]; during the process of complex formation with the ligand, these solvent molecules are liberated, causing a favorable entropic change. Interestingly to note, a comparison between the $\Delta S_f$, $\Delta H_f$ and $\Delta G_f$ values reported in Table 2&3 reveals that generally a decrease in $\Delta H_f$ value is accompanied with an increase in $\Delta S_f$ in such a way that the free energy change $\Delta G_f$ will remain more or less constant. Such enthalpy-entropy compensation effect was observed earlier in the case of complexation reactions of ligands with cation and inorganic guest species [33-85].

Since the conductance of an ion depends mainly on its mobility, it is quite reasonable to treat the rate process taking place with the change of temperature on the basis of equation (8):

$$\Lambda_o = A e^{-E_a/RT}$$  \hspace{1cm} (8)

$$\log \Lambda_o = \log A - \frac{E_a}{2.303RT}$$  \hspace{1cm} (9)

where $A$ is the frequency factor, $R$ is the gas constant and $E_a$ is the Arrhenius activation energy of the transfer process. Consequently, from the plot of $\log (\Lambda_o)$ vs. $1/T$, the $E_a$ values can be evaluated [80-85] as shown in Fig (5&6) for (1:1) M to L stoichiometric complexes of CaCl$_2$ and ampicillin in water and in methanol, giving high activation energy value due to solvation behavior.

**Figure 1:** The relation between molar conductance ($\Lambda_m$) and the [M]/[L] molar ratio of CaCl$_2$ to ampicillin in water at different temperatures.

**Figure 2:** The relation between molar conductance ($\Lambda_m$) and the [M]/[L] molar ratio of CaCl$_2$ to ampicillin in methanol at different temperatures.
Figure 3: The relation between (log $K_f$) and (1/T) for (1:1) and (1:2) M to L stoichiometric complexes of CaCl$_2$ and ampicillin in water.

Figure 4: The relation between (log $K_f$) and (1/T) for (1:1) and (1:2) M to L stoichiometric complexes of CaCl$_2$ and ampicillin in methanol.

Figure 5: The relation between (log $\Lambda_0$) and (1/T) for (1:1) M to L stoichiometric complexes of CaCl$_2$ and ampicillin in water.
Figure 6: The relation between \( \log \Lambda \) and \( 1/T \) for \((1:1) \) M to L stoichiometric complexes of \( \text{CaCl}_2 \) and ampicillin in methanol.

Table 1: The formation constants \( (\log K) \) of formation of \( \text{CaCl}_2 \) and ampicillin complexes in water and in methanol at different temperatures.

<table>
<thead>
<tr>
<th>Temp. (K)</th>
<th>( \log K ) in H(_2)O</th>
<th>( \log K ) in MeOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>293.15</td>
<td>6.693</td>
<td>5.755</td>
</tr>
<tr>
<td>298.15</td>
<td>5.045</td>
<td>5.770</td>
</tr>
<tr>
<td>303.15</td>
<td>5.004</td>
<td>6.101</td>
</tr>
<tr>
<td>308.15</td>
<td>4.815</td>
<td>5.684</td>
</tr>
</tbody>
</table>

Table 2: The Gibbs free energies \( (\Delta G) \) of formation of \( \text{CaCl}_2 \) and ampicillin complexes in water and in methanol at different temperatures.

<table>
<thead>
<tr>
<th>Temp. (K)</th>
<th>( \Delta G ) in H(_2)O (kJ mol(^{-1}))</th>
<th>( \Delta G ) in MeOH (kJ mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>293.15</td>
<td>-37.560</td>
<td>-28.160</td>
</tr>
<tr>
<td>298.15</td>
<td>-28.922</td>
<td>-27.943</td>
</tr>
<tr>
<td>303.15</td>
<td>-29.039</td>
<td>-28.035</td>
</tr>
<tr>
<td>308.15</td>
<td>-28.401</td>
<td>-28.503</td>
</tr>
</tbody>
</table>

Table 3: The enthalpies \((\Delta H)\) and entropies \((\Delta S)\) of formation of \( \text{CaCl}_2 \) and ampicillin complexes in water at different temperatures.

<table>
<thead>
<tr>
<th>M:L</th>
<th>( \Delta S ) (kJ mol(^{-1}) K(^{-1}))</th>
<th>( \Delta H ) (kJ mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>-0.5931</td>
<td>-211.416</td>
</tr>
<tr>
<td>2:1</td>
<td>-0.1319</td>
<td>-66.8204</td>
</tr>
</tbody>
</table>

Table 4: The enthalpies \((\Delta H)\) and entropies \((\Delta S)\) of formation of \( \text{CaCl}_2 \) and ampicillin complexes in methanol at different temperatures.

<table>
<thead>
<tr>
<th>M:L</th>
<th>( \Delta S ) (kJ mol(^{-1}) K(^{-1}))</th>
<th>( \Delta H ) (kJ mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>-0.00379</td>
<td>-31.186</td>
</tr>
<tr>
<td>2:1</td>
<td>-0.1197</td>
<td>-63.602</td>
</tr>
</tbody>
</table>
This research focused on the study of thermodynamic complexation reactions between the ligand, ampicillin, with Ca$^{2+}$ metal cation. The stability constants of the complex formation between ligand and metal cations was investigated by applying the conductometric method at different temperatures. Based on the results, the stability constant for the complexation reaction of Ca$^{2+}$–ampicillin shows a decrease with increasing temperatures.

In this thermodynamic study, the negative sign of the $\Delta G_r$ shows that the ligand is capable of forming stable complexes and that the process will proceed spontaneously, while the positive sign of the entropy shows that $\Delta S_r$ is the driving force of the complexation reaction in this complex formation. These facts mean that $\Delta G_r$ is always negative and $\Delta S_r$ is always positive.

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