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Thermodynamic and Kinetic Evaluation of Ampicillin Complexation with Nickel(II) and Copper(II) Ions

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Abstract

This study examined the apparent thermodynamic and kinetic behavior of ampicillin complexation with Ni(II) and Cu(II) in a water–ethanol medium at 25 and 35 °C. Potentiometric titration curves for an acid blank, free ampicillin, and equimolar metal–ampicillin mixtures were compared, and apparent formation constants were estimated from the reported half-neutralization treatment. At 25 °C, the apparent log β values were 7.19 for Ni(II)–ampicillin and 4.07 for Cu(II)–ampicillin. Both systems had negative standard Gibbs energy changes at the two temperatures studied. The Ni(II) system was exothermic and entropically unfavorable ($\Delta H^\circ = -59.80$ kJ mol^{-1}; $\Delta S^\circ = -62.93$ J mol^{-1} K^{-1}), whereas the Cu(II) system was exothermic with a favorable entropy contribution ($\Delta H^\circ = -14.07$ kJ mol^{-1}; $\Delta S^\circ = 30.72$ J mol^{-1} K^{-1}). Time-dependent pH measurements yielded linear plots of ln[H$^+$] against time under the selected experimental conditions. The apparent first-order rate constant increased slightly with temperature for Cu(II) but decreased for Ni(II). Consequently, the Ni(II) data show anti-Arrhenius behavior over this narrow temperature interval and should not be interpreted as a conventional positive activation energy. The results indicate stronger apparent binding of Ni(II) than Cu(II), but rigorous publication-level formation constants require nonlinear speciation fitting, replicate titrations, and uncertainty estimates. This revised interpretation distinguishes observations supported by the data from mechanistic hypotheses.

Keywords: Ampicillin, Nickel(II), Copper(II), Potentiometric Titration, Apparent Formation Constant, Thermodynamics, Kinetics

1. Introduction

Interactions between metal ions and β-lactam antibiotics are relevant to coordination chemistry, pharmaceutical analysis, and medicinal inorganic chemistry. Coordination can alter solubility, acid–base behavior, chemical stability, and biological activity relative to the unbound drug. Ampicillin contains several potential donor sites, particularly the amino and carboxylate groups, while carbonyl and thioether functions may also participate depending on pH, metal identity, and solution composition. Because protonation and metal binding are coupled, meaningful equilibrium measurements require careful control of ionic strength, temperature, solvent composition, and electrode calibration (Martell & Motekaitis, 1992; Rossotti & Rossotti, 1961) [6, 8].

Ni(II) and Cu(II) are first-row transition-metal ions with distinct ligand-field preferences and hydration behavior. Both interact readily with nitrogen- and oxygen-donor ligands, but their observed affinities depend strongly on ligand protonation and competing hydrolysis. The well-known Irving–Williams series describes a general trend for high-spin divalent first-row transition-metal complexes, but comparisons are valid only when the complexes have comparable stoichiometry, donor sets, and experimental conditions (Irving & Williams, 1953) [4].

Thermodynamic quantities provide complementary information. The formation constant describes the position of equilibrium under defined conditions; ΔG° follows directly from that constant, whereas ΔH° and ΔS° may be estimated from its temperature dependence. Kinetic measurements address how rapidly the monitored signal approaches equilibrium. A linear integrated-rate plot establishes an empirical order for the monitored variable under the chosen conditions, but it does not by itself establish the overall molecular reaction order or substitution mechanism (Atkins *et al*., 2018; Laidler, 1987) [1, 5].

The objectives of this work were to estimate apparent formation constants for Ni(II)–ampicillin and Cu(II)–ampicillin at 25 and 35 °C, calculate the corresponding thermodynamic quantities, evaluate the time dependence of hydrogen-ion concentration after mixing, and interpret the kinetic parameters within the limitations of a two-temperature data set.

2. Materials and Methods

2.1 Reagents and Solutions

Ampicillin sodium (reported purity ≥98%) was obtained commercially and recrystallized before use. A fresh 0.100 mol L^{-1} solution was prepared in doubly distilled water to limit β-lactam hydrolysis. Nickel(II) chloride hexahydrate and copper(II) chloride dihydrate (analytical grade, reported purity ≥99%) were used to prepare 0.100 mol L^{-1} metal-ion solutions; their concentrations were checked by EDTA complexometric titration (Mendham *et al*., 2000) [7]. Sodium chloride, hydrochloric acid, sodium hydroxide, and ethanol were of analytical grade. Sodium hydroxide (0.500 mol L^{-1}) was standardized against potassium hydrogen phthalate. Solutions were prepared with doubly distilled, CO_2-free water.

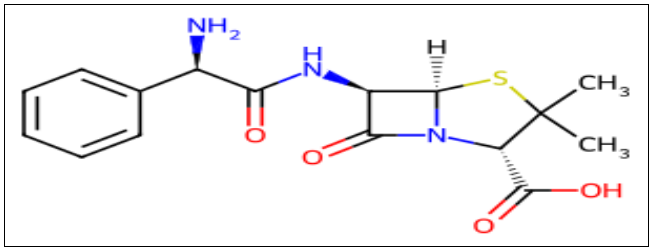

Fig 1: Structural formula of ampicillin

2.2 Potentiometric Titration

For each metal ion and temperature, three 50 mL solutions were prepared: (A) 5 mL of 0.100 mol L^{-1} HCl, 5 mL of 1.00 mol L^{-1} NaCl, 15 mL ethanol, and 25 mL water; (B) solution A with 5 mL of 0.100 mol L^{-1} ampicillin replacing 5 mL water; and (C) solution B with 5 mL of 0.100 mol L^{-1} metal solution replacing a further 5 mL water. The final medium therefore contained 30% (v/v) ethanol and nominally 0.100 mol L^{-1} NaCl before titrant addition. Solutions were stirred under nitrogen and maintained at 25.0 or 35.0 °C. A combined glass electrode was calibrated at the working temperature using pH 4.00, 7.00, and 9.00 buffers. Standardized NaOH was added incrementally, and pH was recorded after stabilization.

Fig 2: Potentiometric titration assembly used for NaOH delivery and pH monitoring

2.3 Estimation of Apparent Formation Constants

The supplied data were originally treated by reading the pH at a reported half-neutralization volume and assigning that value to log β. This procedure is analogous to estimating a pKa for a simple monoprotic acid, but it is not a rigorous general method for determining a metal–ligand formation constant in a coupled, multiequilibrium system. Accordingly, the values are reported here as apparent formation estimates (log βapp) specific to the experimental medium and data treatment. A publication-grade equilibrium analysis should fit the complete titration data by mass-balance and charge-balance equations, including ligand protonation, metal hydrolysis, activity-coefficient treatment, and plausible complex stoichiometries, using software such as SUPERQUAD or an equivalent validated program (Gans *et al*., 1985; Martell & Motekaitis, 1992) [3, 6].

2.4 Thermodynamic Calculations

For each reported apparent constant, ΔG° was calculated from $\Delta G^\circ = -2.303RT \log \beta app$. The two-point van't Hoff relationship was used to estimate ΔH°: $\Delta H^\circ = -2.303R(\log \beta_2 - \log \beta_1)/(1/T_2 - 1/T_1)$. Entropy was then calculated from $\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T$. R was 8.314 J mol^{-1} K^{-1}. Because only two temperatures were available, ΔH° and ΔS° are two-point estimates without regression-based uncertainty and assume that heat-capacity effects are negligible over the 10 K interval.

2.5 Kinetic Treatment

After mixing the reactants under the potentiometric conditions, pH was monitored with time and converted to $[H^+] = 10^{-}pH$. Zero-, first-, and second-order linearizations were compared. The reported first-order model was $\ln[H^+] = \ln[H^+]_0 - kobst$, with $t½ = \ln 2/kobs$. The two-temperature Arrhenius expression was used to calculate an apparent slope parameter, $Ea,app = -R \ln(k_2/k_1)/(1/T_2 - 1/T_1)$. Activation free energies were calculated from transition-state theory, $\Delta G‡ = RT \ln(kBT/hkobs)$, and $\Delta H‡$ and $\Delta S‡$ were estimated from the two-temperature Eyring relationship. These quantities are conditional on the empirical pH-response model and are not evidence by themselves for a unique elementary mechanism.

3. Results and Discussion

3.1 Apparent Equilibrium and Thermodynamic Results

3.1.1 Ni(II)–ampicillin

The Ni(II) titration curves at 25 and 35 °C are shown in Figures 3 and 4. The estimated log βapp decreased from 7.19 to 6.85 as temperature increased, corresponding to ΔG° values of −41.04 and −40.41 kJ mol^{-1}, respectively (Table 1). Within the adopted model, negative ΔG° indicates favorable complex formation at both temperatures. The temperature dependence gives $\Delta H^\circ = -59.80$ kJ mol^{-1} and $\Delta S^\circ = -62.93$ J mol^{-1} K^{-1} (Table 2). Thus, the apparent driving force is predominantly enthalpic, while the negative entropy term opposes complexation. This pattern is consistent with favorable metal–donor interactions accompanied by increased organization and/or incomplete compensation for the loss of translational and conformational freedom. Because the constants are method-dependent estimates, this interpretation should be regarded as provisional rather than a definitive structural assignment.

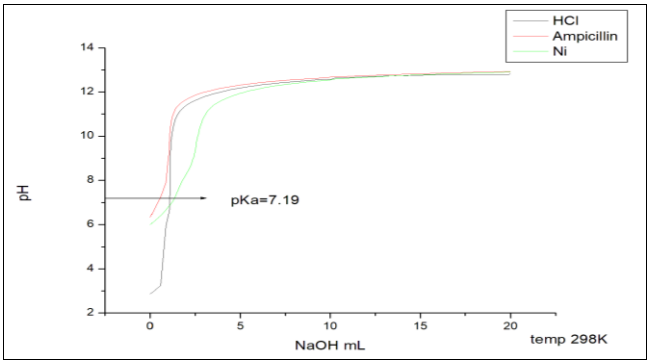

Fig 3: Potentiometric titration curves for the acid blank, ampicillin, and Ni(II)–ampicillin mixture at 25 °C

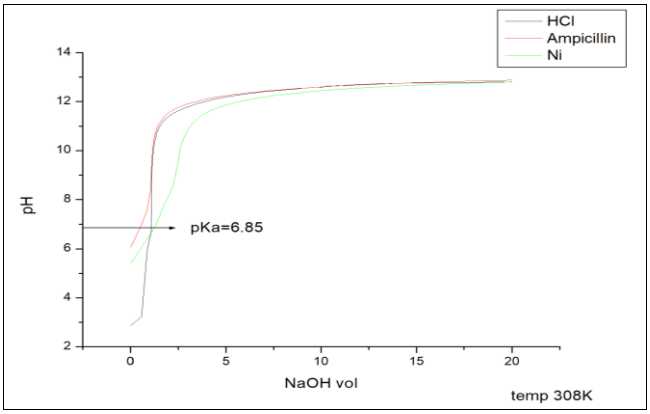

Fig 4: Potentiometric titration curves for the acid blank, ampicillin, and Ni(II)–ampicillin mixture at 35 °C

Table 1: Apparent formation constant and Gibbs energy for Ni(II)–ampicillin

Parameter	25 °C (298.15 K)	35 °C (308.15 K)
log βapp	7.19	6.85
βapp (L mol⁻¹)	1.55×10^7	7.08×10^6
ΔG° (kJ mol⁻¹)	−41.04	−40.41

Table 2: Two-point van't Hoff parameters for Ni(II)–ampicillin

ΔH° (kJ mol⁻¹)	ΔS° (J mol⁻¹ K⁻¹)
−59.80	−62.93

3.1.2 Cu(II)–ampicillin

For Cu(II), log βapp changed only slightly, from 4.07 at 25 °C to 3.99 at 35 °C (Figures 5 and 6; Table 3). The corresponding ΔG° values were −23.23 and −23.54 kJ mol⁻¹. The two-point estimates, ΔH° = −14.07 kJ mol⁻¹ and ΔS° = 30.72 J mol⁻¹ K⁻¹, indicate favorable enthalpic and entropic contributions (Table 4). A positive entropy change may reflect solvent release and reorganization during binding, but the present measurements do not independently quantify solvation or coordination geometry. The small difference between the two log βapp values also means that ΔH° and ΔS° are particularly sensitive to experimental error.

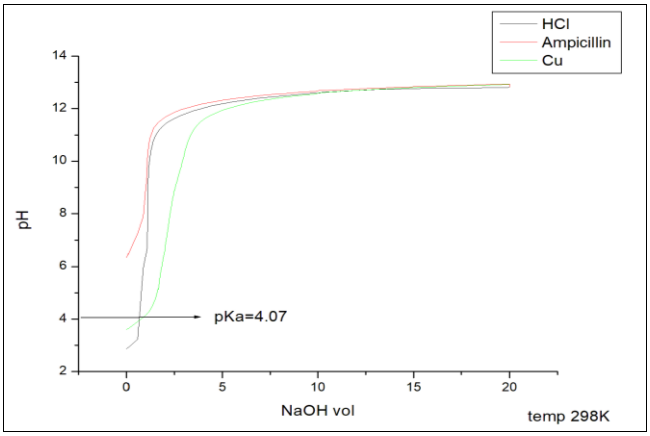

Fig 5: Potentiometric titration curves for the acid blank, ampicillin, and Cu(II)–ampicillin mixture at 25 °C

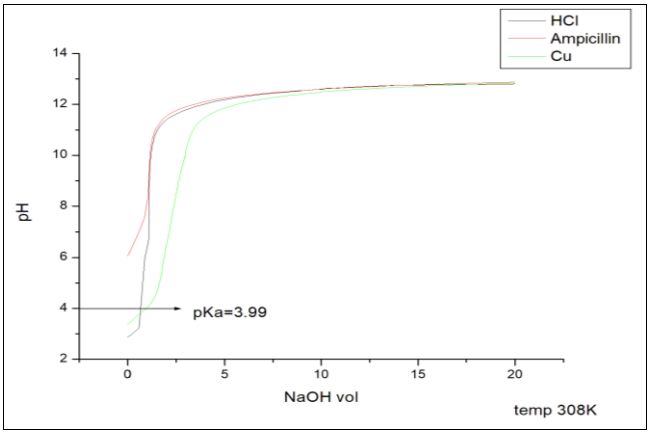

Fig 6: Potentiometric titration curves for the acid blank, ampicillin, and Cu(II)–ampicillin mixture at 35 °C

Table 3: Apparent formation constant and Gibbs energy for Cu(II)–ampicillin

Parameter	25 °C (298.15 K)	35 °C (308.15 K)
log βapp	4.07	3.99
βapp (L mol⁻¹)	1.17×10^4	9.77×10^3
ΔG° (kJ mol⁻¹)	−23.23	−23.54

Table 4: Two-point van't Hoff parameters for Cu(II)–ampicillin

ΔH° (kJ mol⁻¹)	ΔS° (J mol⁻¹ K⁻¹)
−14.07	30.72

At 25 °C, the apparent stability order was Ni(II) > Cu(II). This order should not be presented as a contradiction of the Irving–Williams series because the values were not obtained through full speciation analysis and may include different contributions from protonation, hydrolysis, solvent composition, and conditional activity effects. Reliable comparison with literature constants requires matched ionic medium, temperature, ligand protonation model, and defined complex stoichiometry.

3.2 Kinetic Results

3.2.1 Ni(II)–ampicillin

The plots of ln[H⁺] against time were treated as linear under the selected conditions (Figures 7 and 8). The apparent first-order rate constant decreased from 0.07688 s^{-1} at 25 °C to 0.06987 s^{-1} at 35 °C, and the half-life increased from 9.02 to 9.92 s (Table 5). This inverse temperature dependence produces Ea,app = −7.30 kJ mol^{-1} and ΔH‡ = −9.82 kJ mol^{-1} (Table 6). A negative apparent Arrhenius parameter can occur when the monitored response reflects pre-equilibria, competing pathways, changes in speciation, or instrumental equilibration rather than a single elementary step. It must not be interpreted as a conventional energy barrier. The calculated ΔS‡ is strongly negative, but assigning an associative interchange mechanism from this value alone would be unjustified without concentration-dependent kinetic data and an independently established rate law.

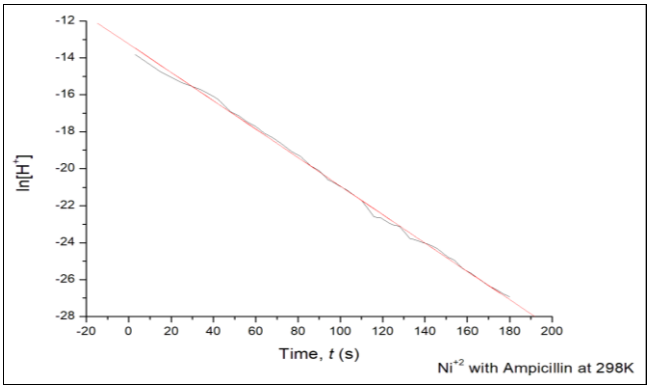

Fig 7: Reported first-order kinetic plot for Ni(II)–ampicillin at 25 °C

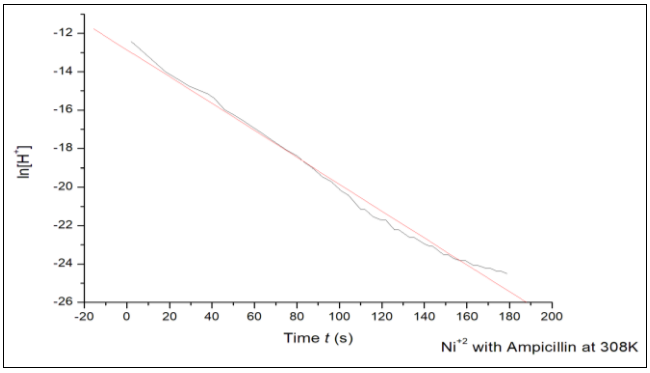

Fig 8: Reported first-order kinetic plot for Ni(II)–ampicillin at 35 °C

Table 5: Apparent kinetic quantities for Ni(II)–ampicillin

Parameter	25 °C	35 °C
kobs (s^{-1})	0.07688	0.06987
t½ (s)	9.02	9.92
ΔG‡ (kJ mol^{-1})	79.38	82.37

Table 6: Two-temperature apparent activation parameters for Ni(II)–ampicillin

Ea,app (kJ mol^{-1})	Aapp (s^{-1})	ΔH‡ (kJ mol^{-1})	ΔS‡ (J mol^{-1} K^{-1})
−7.30	4.04×10^{-3}	−9.82	−299.19

3.2.2 Cu(II)–ampicillin

For Cu(II), kobs increased slightly from 0.07642 s^{-1} at 25 °C to 0.07809 s^{-1} at 35 °C (Figures 9 and 10; Table 7), giving Ea,app = 1.65 kJ mol^{-1}. The small temperature response leads to ΔH‡ = −0.87 kJ mol^{-1} and ΔS‡ = −269.20 J mol^{-1} K^{-1} (Table 8). The large negative entropy estimate indicates that the activated-state calculation is dominated by a small observed rate relative to kBT/h; however, it does not uniquely diagnose an associative pathway. Replicate measurements at several temperatures and reactant concentrations are needed to distinguish chemical kinetics from mixing, electrode response, buffer effects, and coupled acid–base equilibria.

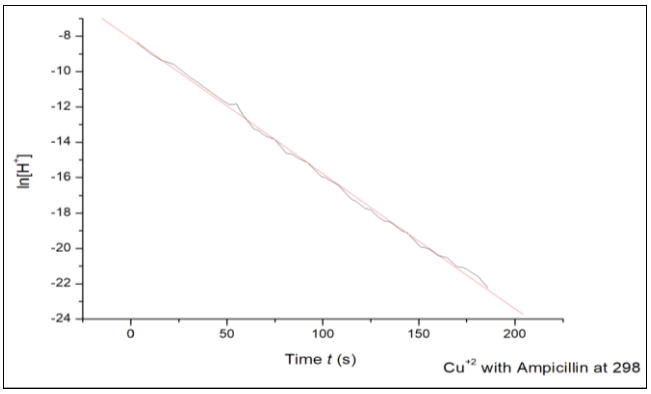

Fig 9: First-order kinetic plot for Cu(II)–ampicillin at 25 °C

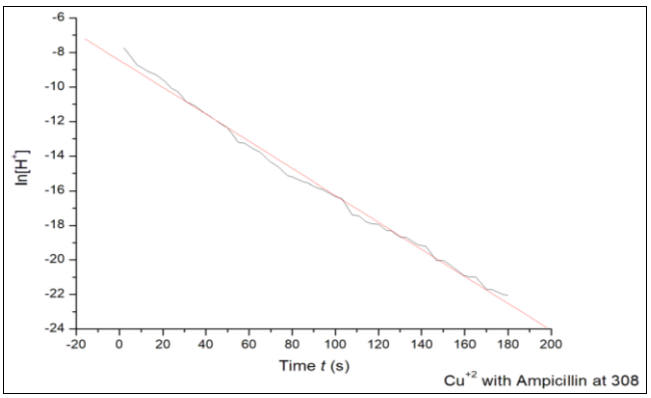

Fig 10: First-order kinetic plot for Cu(II)–ampicillin at 35 °C

Table 7: Apparent kinetic quantities for Cu(II)–ampicillin

Parameter	25 °C	35 °C
kobs (s^{-1})	0.07642	0.07809
t½ (s)	9.07	8.88
ΔG‡ (kJ mol^{-1})	79.39	82.09

Table 8: Two-temperature apparent activation parameters for Cu(II)–ampicillin

Ea,app (kJ mol^{-1})	Aapp (s^{-1})	ΔH‡ (kJ mol^{-1})	ΔS‡ (J mol^{-1} K^{-1})
1.65	1.49×10^{-1}	−0.87	−269.20

3.3 Study limitations and requirements for journal submission

The numerical trends are internally reproducible from the reported values, but several limitations should be addressed before the work is submitted to a selective journal. First, complete titration datasets should be fitted globally to chemically plausible speciation models rather than converting a half-neutralization pH directly to log β. Second, replicate titrations and kinetic runs are needed so that standard deviations, confidence intervals, and goodness-of-fit statistics can be reported. Third, metal hydrolysis and ampicillin degradation should be evaluated under the experimental pH range. Fourth, complex stoichiometry and

donor-site assignments require independent evidence, for example Job plots or mole-ratio analysis supported by UV–visible, FTIR, NMR, conductivity, elemental analysis, or mass spectrometry as appropriate. Finally, kinetic measurements should include several metal and ligand concentrations, more than two temperatures, electrode-response controls, and residual analysis for competing rate models.

4. Conclusions

Under the reported water–ethanol conditions, the estimated apparent formation constants indicate stronger conditional association of ampicillin with Ni(II) than with Cu(II). Both complexes have negative calculated ΔG° values at 25 and 35 °C. Ni(II) complexation appears enthalpy-driven with an unfavorable entropy contribution, whereas the Cu(II) estimates contain favorable enthalpic and entropic terms. The pH-time traces were consistent with an empirical first-order model for $[H^+]$ over the measured interval. Cu(II) showed a small positive temperature dependence, while Ni(II) showed anti-Arrhenius behavior. The present data therefore support comparative conditional trends, but they do not yet establish absolute formation constants, a unique coordination structure, an overall molecular reaction order, or an associative substitution mechanism. Global equilibrium fitting, replication, uncertainty analysis, and independent structural characterization are required to substantiate those claims.

5. Declarations

Conflict of Interest: The authors should insert the journal-required conflict-of-interest statement before submission.

Funding: The authors should state the funding source or declare that no specific funding was received.

Data Availability: The authors should specify where the raw titration and kinetic data can be accessed.

Author Contributions: The authors should provide contribution statements using the journal's required taxonomy.

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