Electrochemical Study of Theophylline - Urea Interaction Using Square Wave Voltammetry

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ABSTRACT

In this work, the interaction between theophylline (TP) which gives a stable well-defined reduction peak at (1.07) V versus Ag/AgCl. Sat. KCl/ in phosphate buffer solution (pH=7) and urea was studied using square wave voltammetry (SWV) technique. Also, the binding constant and the thermodynamics parameters have been calculated. Different temperatures (288, 293, 298, 298, 303, 308 and 310) ºK were used to study the effect of temperature on binding constant (K). The results showed that the binding constant (K) decreased with increasing temperature. This is as a result of the negative value of enthalpy (-31.07)KJ.mol⁻¹. The negative value of Gibbs energy (-13.632 x 10²_-12.296 x 10²) KJ.mol⁻¹ indicates that the interaction is spontaneous and could be due to van der Waals forces or hydrogen bonds effect (weak interaction).

Keywords: Theophylline, Urea, Interaction, Modified electrode.

INTRODUCTION

Theophylline (1,3-dimethylxanthine) as a xanthine derivative has been commonly used as an additional treatment drug in the asthmatic acute phase in children and asthma and bronchospasm in adults (Fuyong Jiao et al., 2018; Igarashi and Iwakawa, 2009; Kanehara et al., 2008; Kawai and Kato, 2000). It is also used clinically as diuretic, cardiac stimulant and smooth muscle relaxant
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(Blake and Kamada, 1996; Weinberger and Hendelees, 1996; Minton and Henry, 1996). Thus, more and more scientists have paid increasing attention to the techniques for the quantitative determination of theophylline. The chemical structure of theophylline is shown in Fig. (1).

![Chemical structure of theophylline](image)

**Fig. 1: The chemical structure of theophylline**

At present, many methods have been employed for measuring theophylline quantitatively, such as liquid chromatography (Kalyani et al., 2017; Srdjenovic et al., 2008), UV spectrometry (Sujana et al., 2016; Culzoni et al., 2005), chemiluminescent immunoassay (Zhou et al., 2005), gas chromatography/mass spectrometry (GC–MS) and gas chromatography–isotope dilution mass spectrometry (GC–IDMS) (Arinobu et al., 2009; Kress et al., 2002). Nevertheless, some of these methods, such as chromatography and mass spectrometry, are time-consuming, expensive and need complicated preconcentration or multisolvent extraction as well as trained technicians. Instead, electrochemical methods are characterized by simplicity, high sensitivity, good stability, low-cost instrumentation on-site monitoring (Sadik et al., 2003). Thus, they are exploited for the determination of theophylline.

Urea [(NH2)2CO] is one of the chief human nitrogen-based metabolic wastes. The urea concentration in serum or urine indicates kidney diseases and diabetes, and its analysis in clinical laboratories is very frequent (Branzoi et al., 2011; Singh et al., 2008). However, the urea quantification uses conventional methods, such as spectrophotometric, potentiometry, and piezoelectricity (Singh et al., 2008), which are expensive and time consuming. Therefore, it is very important to develop simple, sensitive, and accurate methods for urea detecting. A variety of analytical methods have been developed and used to analyze urea in aqueous samples. As a result, voltammetric sensors have become an excellent alternative for detecting various analyses, including urea. Since urea is electroactive and most of the electroanalytical techniques are selective, highly sensitive, time-saving, inexpensive, have a wide dynamic range, and a quick response, electrochemical techniques have been used to determine urea as a strong alternative to the other methods. Various forms of modified electrodes have been used for electrochemical studies of urea because of their unusual characteristics (Harish et al., 2018; Branzoi et al., 2011; Singh et al., 2008; Hamilton, 2012; Yang et al., 2004).

**EXPERIMENT**

**Apparatus**

All the electrochemical experiments were performed using a 797VA Computrace instrument (Metrohm, Switzerland). The reference electrode was an Ag/AgCl with saturated KCl and a platinum wire was used as the auxiliary electrode and a glassy carbon electrode GC used as the working electrode.

pH measurements were performed by using a digital pH meter (HANNA, Italy, calibrated with standard buffers. The Haake Heated Water Bath Circulator is Model G, USA.
Chemicals and Reagents
All chemicals used in this work (urea, theophylline, dipotassium hydrogen phosphate $\text{K}_2\text{HPO}_4$, and potassium dihydrogen phosphate $\text{KH}_2\text{PO}_4$) were of analytical grade and used without further purification, and were purchased from Fluka, and BDH.

RESULTS AND DISCUSSION

Electrochemical Behaviour of Theophylline
The square wave voltammogram was recorded using $(9.090 \times 10^{-5})$ M theophylline (TP) in phosphate buffer solution under the default instrument. After that the optimum conditions of TP has been studied, and the voltammograms of $(9.090 \times 10^{-5})$ M of TP Fig. (2) were recorded under each effective parameter and the results obtained are summarized in (Table 1).

| Condition                              | Default conditions | Optimum conditions of TP |
|----------------------------------------|--------------------|--------------------------|
| Start Potential (V)                    | 0.4                | 0.4                      |
| End Potential (V)                      | 1.4                | 1.4                      |
| Deposition potential (V)              | -0.9               | -1.5                     |
| Deposition time (s)                    | 60                 | 50                       |
| Equilibration time (s)                | 5                  | 5                        |
| Voltage step (V)                       | 0.006              | 0.002                    |
| Amplitude (V)                         | 0.02               | 0.03                     |
| Frequency (Hz)                         | 50                 | 100                      |
| Sweep rate                             | 0.3                | 0.1984                   |

Effect of Urea on Theophylline Reduction Peak
The effect of urea on TP peak was studied by adding sequence additions of urea $(72.595 \times 10^{-3} - 79.915 \times 10^{-3})$ M on $(0.0002)$ M of TP; a decrease in the TP current peak was observed with the sequence additions of urea Fig. (3).
Fig. 3: The voltammograms of TP (0.0002) M (a) in the absence of urea (b) in the presence of urea (72.595 x10-3 - 79.915 x 10-3) M

Stability of Theophylline Reduction Peak in the Presence of Urea

The stability of TP voltammogram (8.84956x10⁻⁵) M in the presence of urea (2.654x10⁻³) M was measured at different times, using phosphate buffer solution (pH=7) under the previous optimum conditions of TP and the results are shown in (Table 2). The results indicate that the interaction peak was stable within the studied time (120) min.

Table 2: Stability of theophylline reduction peak in the presence of urea

| Time (min) | Ep.(V) | Ip. (µA) |
|-----------|--------|----------|
| 0         | 1.05   | 7.020    |
| 10        | 1.05   | 7.260    |
| 20        | 1.05   | 6.810    |
| 50        | 1.05   | 7.070    |
| 60        | 1.05   | 7.000    |
| 70        | 1.05   | 6.970    |
| 80        | 1.05   | 7.140    |
| 90        | 1.05   | 7.170    |
| 100       | 1.05   | 7.091    |
| 110       | 1.05   | 7.150    |
| 120       | 1.05   | 7.030    |

Thermodynamic Calculations

The binding constant of theophylline-urea was calculated according to the equation (1).

\[
\ln \left( \frac{I_p}{I_p^o - I_p} \right) = \ln \left( \frac{1}{[\text{Conc.}(M)]} \right) - \ln (K) \quad \ldots \ldots \ldots \quad (1)
\]

Where \(I_p^o\) is the reduction current of TP alone, \(I_p\) is the reduction current of TP-urea complex, Conc. is the molar concentration of TP, and \((K)\) is the binding constant of TP-urea complex.

The binding constant was calculated at different temperatures (288, 293, 298, 303, 308, 310) K°, and the results are shown in Fig. (4).
Thermodynamic parameters were calculated Fig. (5) according to the equations (2) for Van't Hoff eq. and (3), the binding constant at different temperatures are shown in (Table 3).

$$\ln K = \frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots
Table 3: The relation between binding constant and temperature

| T(Kº) | Ln Kb | The binding constant Kb (10²) M | ΔH (KJ.mol⁻¹) | ΔG (KJ.mol⁻¹) | ΔS (J.mol⁻¹.K⁻¹) |
|-------|-------|-------------------------------|----------------|----------------|------------------|
| 288   | 5.693 | 2.968                         | -31.070        | -13.632        | -60.6            |
| 293   | 5.463 | 2.358                         | -13.039        | -12.691        |
| 298   | 5.263 | 1.930                         | -13.039        | -12.691        |
| 303   | 5.038 | 1.541                         | -12.422        |
| 308   | 4.851 | 1.278                         | -12.422        |
| 310   | 4.771 | 1.180                         | -12.296        |

The negative value of ΔS indicates that the interaction is ordered. The negative value of ΔH means that the interaction is exothermic. From the values of ΔG, the spontaneity of interaction is decreased with increasing temperature. This agrees with negative value of ΔH showing that the type of interaction is hydrogen bonding or vander Waals forces. From the binding constant and thermodynamic results, we find that the interaction between TP and urea is week, exothermic, spontaneous and stable (Ross and Subramanian, 1981).

CONCLUSION

Square wave voltammetry technique is a good technique to study the interaction between TP and urea. Thermodynamics parameters give an idea about interaction type, negative value of enthalpy change means that the interaction was exothermic, negative value of entropy change indicates that the interaction became more ordered and the shifting of Gibss free energy value to more positive caused the spontaneus decrease. From the thermodynamics parameters we can conclude that the interaction between TP and urea is due to either hydrogen bond or vander Waals forces.

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