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) °K 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 $(-13.632 \times 10^2$ _ $-12.296 \times 10^2)$ 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.

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Ag/AgCl. Sat.   V (1.07)

(pH=7)   KCl

° (310   308   303   298   293   288)   .

(K)   (K)

/   (-31.07)

/ $(-12.296 \times 10^2$ _ $-13.632 \times 10^2)$

.(   )

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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

(Blake and Kamada, 1996; Weinberger and Hendeles,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).
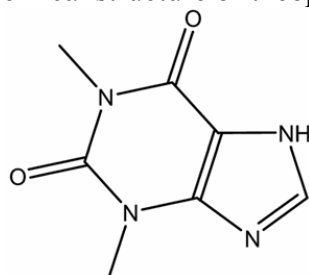
Fig. 1: The chemical structure of theophylline

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 chromatographymass 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 a797VA 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 K_2HPO_4, and potassumdihydrogen phosphate KH_2PO_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 (9.090×10^{-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 (9.090×10^{-5}) M of TP Fig. (2) were recorded under each effective parameter and the results obtained are summarized in (Table 1).

**Table 1: Default and the optimum conditions of TP**

Condition	Defaultconditions	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
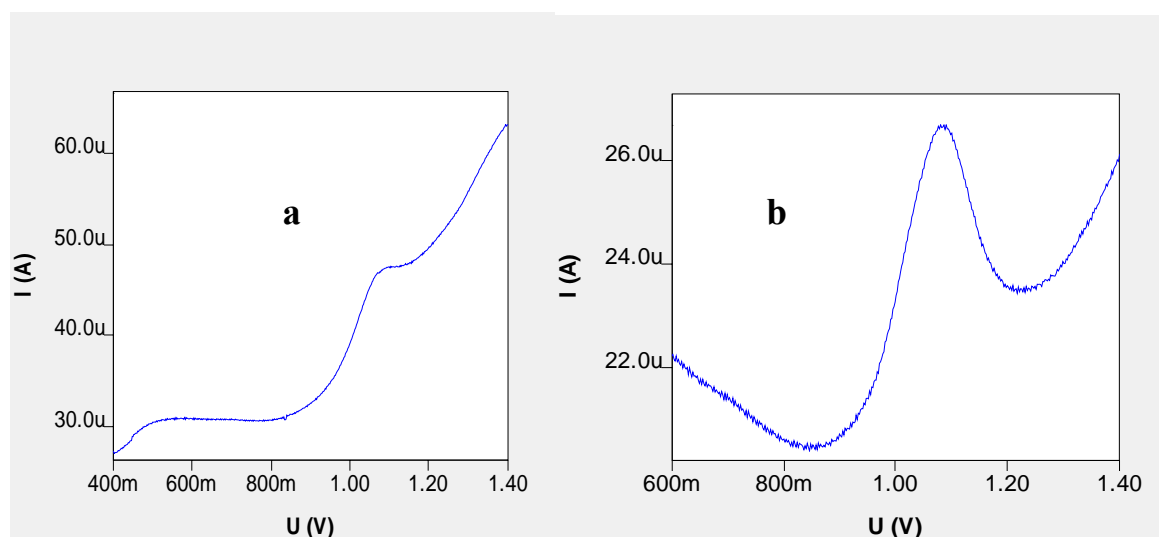
Fig. 2: The voltammogram of TP (9.090×10^{-5}) M (a)under the default conditions, (b) under the studied optimum conditions

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; adecrease in the TP current peek was observed with the sequence additions of urea Fig. (3).
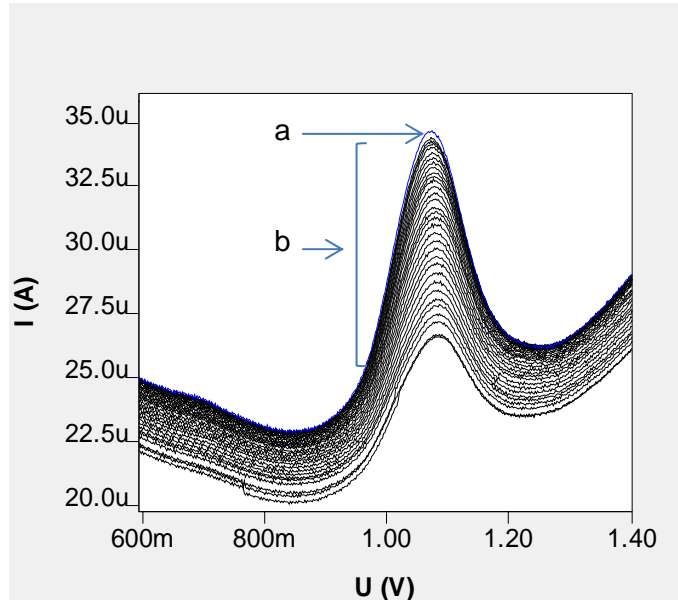
Fig. 3: The voltammograms of TP (0.0002) M (a) in the absence of urea (b) in the presence of urea (72.595 x10-3 - 79.915 x 10-3) M

Stability of Theophylline Reduction Peak in the Presence of Urea

The stability of TP voltammogram (8.84956×10^{-5}) M in the presence of urea (2.654×10^{-3}) M was measuredat 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	7000
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).

$$\ln (Ip/(Ip^o - Ip)) = \ln (1/[\text{Conc.(M)}]) - \ln (K) \quad \ldots\ldots\ldots\ldots \quad (1)$$

Where Ip^o is the reduction current of TP alone, Ip 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^o, and the results are shown in Fig. (4).
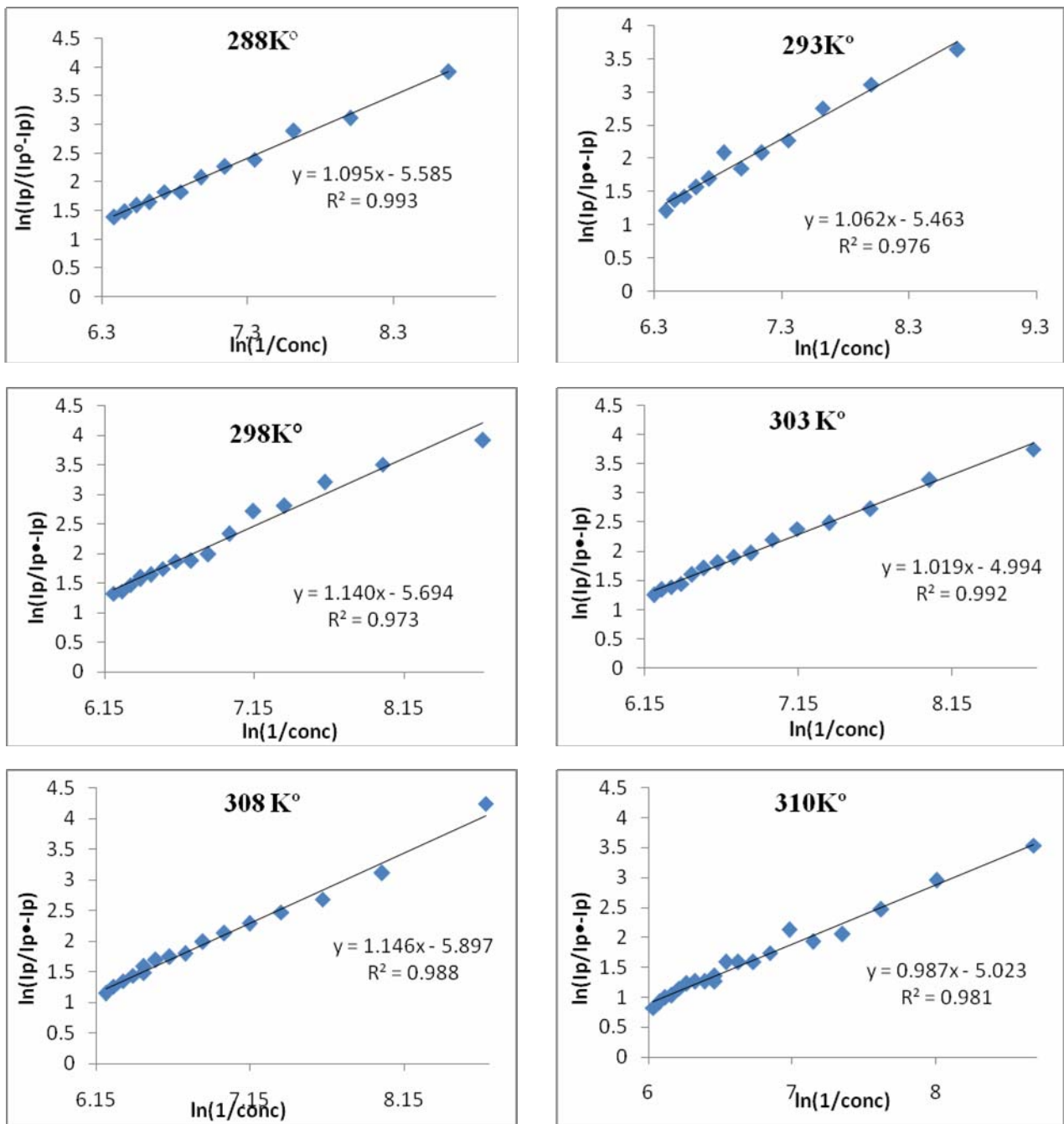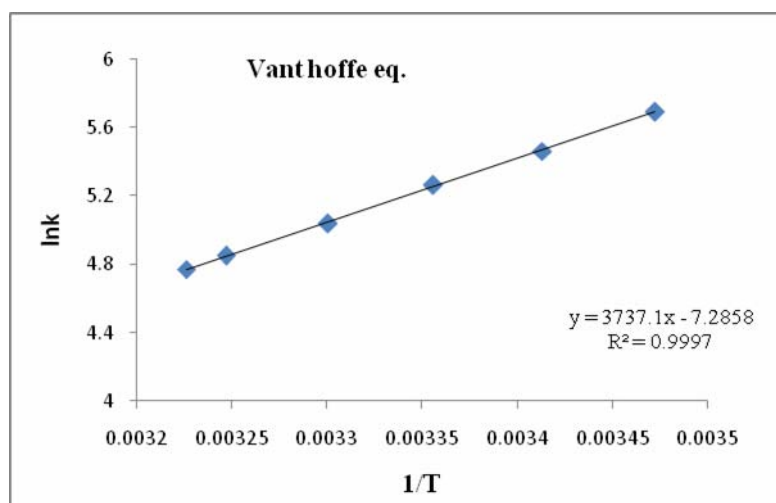
Fig. 4: Plot of ln (Ip/(Ipᵒ –Ip)) vsln (1/[Conc.(M)]) at (288, 293, 298, 298, 303, 308, 310)ᵒK

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).

$$\ln K = \frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad \ldots\ldots\ldots\ldots \quad (2)$$

$$\Delta G = - R\, T \ln K \quad \ldots\ldots\ldots\ldots \quad (3)$$

Fig. 5: Plot of ln K vs 1/T

Table 3: The relation between binding constant and temperature

T(Kº)	Ln K$_b$	The binding constant K$_b$ (10^2) M	ΔH (KJ.mol^{-1})	ΔG (KJ.mol^{-1})	ΔS (J.mol^{-1}.K^{-1})
288	5.693	2.968		-13.632	
293	5.463	2.358		-13.308	
298	5.263	1.930	-31.070	-13.039	-60.6
303	5.038	1.541		-12.691	
308	4.851	1.278		-12.422	
310	4.771	1.180		-12.296	

The negative value of ΔSindicates that the interaction is ordered. The negative value of ΔHmeans 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 changemeans 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 spontaneousdecrease. From the thermodynamics parameters we can conclude that the interaction between TP and urea is due to either hydrogen bonding or vander Waals forces.

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