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STUDY OF ELECTRODE KINETICS AND THERMODYNAMIC PARAMETERS OF TINIDAZOLE POLAROGRAPHYCALLY

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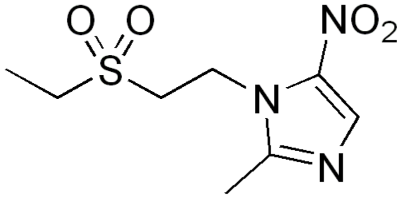
ABSTRACT

The electrochemical reduction of anti- parasitic drug “Tinidazole” has been carried out in aqueous solution in the pH range 2.3 to 11.3 by Direct current (DC) polarography. Tinidazole exhibits one or two reduction peaks depending on pH. In basic medium one reduction peak was observed. Along with different pH, studies of drug have been carried out with different concentrations of drug and at different temperatures. The reduction of tinidazole was found to be irreversible so kinetic parameters (K^{o}_{fh}, αn) are evaluated using Meites-Israel and Gaur-Bhargava’s methods. Thermodynamic parameters such as $\Delta H_p^{\neq}$, $\Delta H_v^{\neq}$, $\Delta G^{\neq}$ and $\Delta S^{\neq}$ are also evaluated.

INTRODUCTION: Tinidazole (TNZ) [1- (2-ethyl sulfonylethyl) - 2- methyl- 5- nitro- imidazole] is an anti- parasitic drug used against protozoan infections. It is highly effective for the treatment of trichomoniasis [1], giardiasis and amoebiasis. The oral single dose of TNZ is equivalent to a 3- day therapy with metronidazole without substantial side effects [2]. Outside the United States, it has been widely used to treat bacterial vaginosis [3-4].

TNZ has molecular weight 247.273 g/mol and melting point 125-128°C.



Tinidazole [1- (2- ethylsulfonylethyl)- 2- methyl- 5- nitro-imidazole]: Several methods have been reported for the determination of TNZ, including spectrophotometery [5-8] and Chromatography [9-11]. Little attention has been paid to the determination of TNZ using the electrochemical techniques [12-15]. But unfortunately no one paid attention about kinetic and thermodynamic parameters of TNZ. So in present paper I worked out this. Kinetic parameters (K^{o}_{fh}, αn) are calculated by Meites-Israel [16] and Gaur-Bhargava's methods [17].

MATERIALS AND METHODS:

Apparatus: The digital D. C. Polarograph (CL-357) of Elico Limited was used to record current-voltage data. This equipment has the three electrode assembly, dropping mercury electrode as working electrode, calomel as reference electrode and platinum electrode as counter electrode. Dropping mercury electrode had the characteristics m = 2.422 mg/sec, t = 2.5 sec and h = 60 cm.

The Elico digital pH meter model 111E was used to measure the pH of the analytes.

Reagents: Tinidazole was obtained from Aaray Drugs & Pharmaceuticals Ltd., Mumbai, Maharashtra, India. Tinidazole was dissolved in 30% Ethanol. All solutions were prepared freshly with doubly distilled water and analytical reagent grade chemicals (MERCK).

Proposed Procedure: The general procedure used to produce DC polarograms was as follows;

An aliquot (10 ml) of experimental solution which contains B.R. Buffer, Triton-X-100(Maxima Suppresser) and water was placed in a dry, clean polarographic cell and deoxygenated with nitrogen for 15 min. the current-voltage curves were measured manually. The negative potential was applied to the working electrode with 150 mV/min span rate and 100 nA/div sensitivity of current measurement. After the background polarogram had been obtained, aliquots of the required amounts of TNZ solution were added.

RESULTS AND DISCUSSION: The effect of pH on the current-voltage curve at a concentration 1.6×10^{-3} M TNZ was studied over the pH range 2.3- 11.3. TNZ gives rise to one or two reduction peaks depending on pH. In basic medium one reduction peak was obtained which refers to the six – electron reduction of nitro group to the corresponding amine. In acidic medium TNZ exhibits two reduction peaks. The height of the first wave is twice that of the second. The first wave corresponds to the reduction of the nitro group to form intermediate hydroxylamine, transferring four electrons while the second wave corresponds to the reduction of hydroxylamine to amine, transferring two electrons [18-19].

The direct current polarogram (DCP) at different pH values for the reduction of TNZ at a concentration of 1.6×10^{-3}M are shown in **fig. 1**. The values of the diffusion current and half wave potential for the first wave are shown in **table 1**.

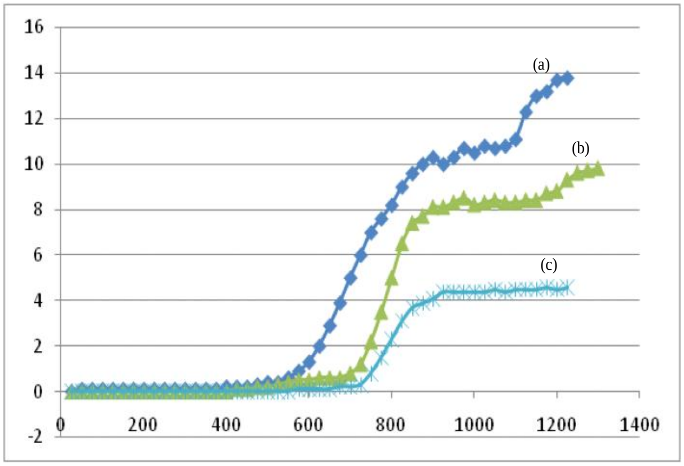


FIG. 1: EFFECT OF pH ON TNZ POLAROGRAM (a) at pH 3.3, (b) at pH 6.3 and (c) at pH 9.3

TABLE 1: EFFECT OF PH ON DIFFUSION CURRENT AND HALF WAVE POTENTIAL OF TNZ WAVE IN B.R. BUFFER, TINIDAZOLE = 1.6 × 10^{-3}M, TRITON-X-100 =0.001%

pH	E ½ (Volt)	I_d × 100 nA
2.3	-0.683	11.6
3.3	-0.716	10.7
4.3	-0.753	8.9
5.3	-0.778	7.8
6.3	-0.779	7.6
7.3	-0.776	6.6
8.3	-0.773	5.6
9.3	-0.795	4.3
10.3	-0.796	4.1
11.3	-0.797	3.9

Where id = Diffusion current; $E_{1/2}$ = Half wave potential

When we increase the pH of the solution from 2.3 to 11.3, i_d of the first wave decreases continuously; in acidic medium i_d of the second wave also decreases but in basic medium second wave collapses with the first wave. Hence it shows TNZ gives two reduction waves in acidic medium and only one in basic medium. The half wave potentials ($E_{1/2}$) of the polarographic waves gets shifted towards more negative potential with an increase in pH from 2.3 to 6.3 (acidic medium), near pH 7.0, values of $E_{1/2}$ are almost constant and in basic medium $E_{1/2}$ increases abruptly from pH 8.3 to 9.3 and then it becomes almost constant. These results show that in strong acidic medium the reduction of nitro group is easier, with increase in the pH, its reduction becomes difficult and near pH 7.0, there is no effect of pH on reduction of NO_2 group but in strong basic medium reduction of NO_2 group becomes most difficult and then there is no effect of pH on reduction of NO_2 group.

The polarogram at pH 11.3 was much sharper and well defined so this pH was chosen for subsequent work. The effects of concentration of TNZ on polarogram are listed in **table 2**; the concentration of TNZ was varied from 0.8 × 10^{-3}M to 4.0 × 10^{-3}M. The plots of log $[i/(i_d-i)]$ Vs $E_{d.e.}$ were linear with slope values much higher than expected for reversible reaction which suggest that electrode reaction is irreversible. The values of $E_{1/2}$ are almost constant and i_d increases with increasing concentration of TNZ as expected. Since the reduction of TNZ is irreversible hence kinetic parameters, like forward rate constant ($K^o{}_{fh}$) and transfer coefficient (αn) have been calculated using Meites-Israel and Gaur-Bhargava's methods.

Meites- Israel modification of Kotecky's method:

$$E_{d.e.} = E_{1/2} - \frac{0.0542}{\alpha n} \log \frac{i}{(i_d - i)} \qquad \text{……………… (1)}$$

$$E_{1/2} = \frac{0.0591}{\alpha\ n} \log \frac{1.349\ K^o_{fh}\ t^{1/2}}{D^{1/2}} \qquad \text{………………. (2)}$$

Gaur-Bhargava's modification:

$$E_{d.e.} = E_{1/2} - \frac{0.05915}{\alpha n} \log \frac{i}{(i_d - i)} \qquad \text{………………… (3)}$$

$$E_{1/2} = \frac{0.05915}{\alpha\ n} \log \frac{K^o_{fh}\ t^{1/2}}{(\text{antilog } C)\ D^{1/2}} \qquad \text{………… (4)}$$

Where; $K^o{}_{fh}$ = formal rate constant for forward reaction; D = diffusion coefficient; αn = transfer coefficient.

$E_{d.e.}$ and $E_{½}$ were determined with respect to calomel electrode. The values of αn were obtained by equation-1 (Meites-Israel method) and equation-3 (Gaur-Bhargava method). The value of K^o_{fh} was determined by equation-2 (Meites- Israel method) and equation-4 (Gaur-Bhargava method). The values of diffusion coefficient (D) were determined by using Ilkovic equation.

$(i_d)_{max}= 706nD^{1/2}Cm^{2/3}t^{1/6}$………………………………… (5)

All symbols have their usual meanings. The effect of concentration of tnz on wave and hence on kinetic parameters is given in table 2. The effects of temperature on polarogram are listed in **table 3**, at 35°C well defined and well shaped wave was observed.

TABLE 2: EFFECT OF CONCENTRATION OF TNZ ON WAVE AND HENCE ON KINETIC PARAMETERS IN B.R. BUFFER AT pH 11.3, TRITON-X-100 = 0.001%

Conc. (M)	E ½ (Volt)	I_d × 100 nA	D ($cm^2 sec^{-1}$) (× 10^{-2})	Slope(mV) (× 10^{-2})	αn (M.I.) (V)	αn (G.B.) (V)	K^ofh (M.I) (cm sec^{-1})	K^ofh(G.B.) (cm sec^{-1})
0.8 × 10^{-3}	-0.805	2.2	9.5419	6.6766	0.8118	0.8859	1.296× 10^{-12}	1.719× 10^{-13}
1.2× 10^{-3}	-0.798	2.9	7.3712	6.5525	0.8272	0.9027	8.818× 10^{-13}	1.142× 10^{-13}
1.6× 10^{-3}	-0.797	3.9	7.4966	6.3367	0.8553	0.9334	3.836× 10^{-13}	4.608× 10^{-14}
2.0× 10^{-3}	-0.796	4.8	7.2684	6.0895	0.8901	0.9713	1.330× 10^{-13}	1.455× 10^{-14}
2.4× 10^{-3}	-0.797	5.5	6.6306	6.8430	0.7921	0.8644	2.567× 10^{-12}	3.693× 10^{-13}
2.8× 10^{-3}	-0.796	6.6	7.0119	6.4871	0.8355	0.9118	7.084× 10^{-13}	9.050× 10^{-14}
3.2× 10^{-3}	-0.794	8.0	7.8905	5.4587	0.9929	1.0836	6.183× 10^{-15}	5.097× 10^{-16}
3.6× 10^{-3}	-0.794	8.6	7.2039	5.7278	0.9463	1.0327	2.498× 10^{-14}	2.351× 10^{-15}
4.0× 10^{-3}	-0.791	9.7	7.4256	5.5270	0.9806	1.0702	9.836× 10^{-15}	8.494× 10^{-16}

Where K^0_{fh} (M.I.) = Formal Rate Constant obtained from Meites & Israel's method; K^0_{fh} (M.I.) = Formal Rate Constant obtained from Gaur & Bhargava's method; D = Diffusion coefficient; αn = Transfer coefficient

TABLE 3: EFFECT OF TEMPERATURE ON TINIDAZOLE WAVE AND HENCE ON KINETIC PARAMETERS IN B.R. BUFFER AT pH 11.3, TINIDAZOLE = 4× 10^{-2} M, TRITON-X-100 = 0.001%

Temp (°C)	E ½ (Volt)	i_d× 100 nA	D ($cm^2 sec^{-1}$) (× 10^{-2})	Slope (mV) (× 10^{-2})	αn (M.I.) (V)	αn (G.B.) (V)	K^ofh (M.I) (cm sec^{-1})	K^ofh (G.B.) (cm sec^{-1})
25	-0.790	8.5	5.7025	7.072	0.7664	0.8364	6.502× 10^{-12}	1.029× 10^{-12}
30	-0.796	9.2	6.6771	6.960	0.7787	0.8498	4.014× 10^{-12}	6.048× 10^{-13}
35	-0.796	10.0	7.8905	6.691	0.8101	0.8841	1.652× 10^{-12}	2.271× 10^{-13}
40	-0.793	10.7	9.0360	6.173	0.8780	0.9581	4.015× 10^{-13}	2.744× 10^{-14}

Further, thermodynamic parameter ($\Delta H^\#_p$, $\Delta H^\#_v$, $\Delta G^\#$, $\Delta S^\#$) have been reported in Table (4). The enthalpy of activation at constant pressure ($\Delta H^\#_p$) has been calculated by substituting the value of slope of the plot (log K^0_{fh} v/s 1/T) in the Vant Hoff equation.

$$\Delta H^\#_p = 2.303R \times \text{Slope}$$

Where R= Gas constant.
The value of slope comes out to be 8.7 × 10^3.

$$\Delta H^\#_p = \Delta H^\#_v + RT$$

From this relation $\Delta H^\#_v$ (enthalpy change of activation at constant volume) was evaluated, the activation free energy change ($\Delta G^\#$) was determined by relationship.

$$K^0_{fh} = (KT/h)r_o\exp^{-\Delta G\#//RT}$$

Where K= Boltzmann constant, h= Plank's constant, r_0= mean distance between depolarized ions in the bulk solution, R= Gas constant, T= absolute temperature. In general value of r_0 is taken as 2 X 10^{-8}cm [20]. The entropy of activation ($\Delta S^\#$) was calculated using following equation;

$$\Delta S^{\#} = (\Delta H^{\#}_{v} - \Delta G^{\#})/T$$

The plot of log K^{0}_{fh} vs. 1/T is found to be linear from the slope of which the values of $\Delta H^{\#}_{p}$, $\Delta H^{\#}_{v}$, $\Delta G^{\#}$ and $\Delta S^{\#}$ have been evaluated and presented in **Table 4**.

TABLE 4: THERMODYNAMIC PARAMETERS AT DIFFERENT TEMPERATURES

Temperature (°C)	$\Delta H_{P}^{\neq}$ (J/Mole)	$\Delta H_{V}^{\neq}$ (J/Mole)	$\Delta G^{\neq}$ (J/Mole)	$\Delta S^{\neq}$ (J/Kelvin)
25	166.58×10^{3}	16.4102×10^{4}	2.2567×10^{4}	4.7495×10^{2}
30	166.58×10^{3}	16.4060×10^{4}	2.3294×10^{4}	4.6457×10^{2}
35	166.58×10^{3}	16.4019×10^{4}	2.4320×10^{4}	4.5357×10^{2}
40	166.58×10^{3}	16.3977×10^{4}	2.6119×10^{4}	4.4044×10^{2}

$\Delta H_{P}^{\neq}$ = Enthalpy change for activation process at constant pressure; $\Delta H_{V}^{\neq}$ = Enthalpy change for activation process at constant volume; $\Delta G^{\neq}$ = Gibbs free energy change for activation process; $\Delta S^{\neq}$ = Entropy change for activation process

A perusal of the values of various quantities presents in table 4 show that activation free energy change ($\Delta G^{\#}$) is positive at all the temperatures suggesting the non spontaneous nature of electrode process. Positive value of $\Delta S^{\#}$ suggests that formation of activated state is accompanied by increase of entropy. From table 4, it can be concluded that as we increase the temperature values of the $\Delta G^{\#}$ increases and that of the $\Delta S^{\#}$ decreases continuously, it shows that the non spontaneity of electrode process increases with temperature.

CONCLUSION: The advantages of this method lie in the rapid qualitative determination of TNZ in pharmaceutical formulations, easy preparation of the sample, fair enough reproducibility and use of inexpensive instrumentation. On the other hand, the suggested method is cheap and fast, accurate and highly reproducible and more simple and practical than the voltammetric methods using the pretreated glassy carbon electrode [12]. Therefore, the presented method can be recommended for routine analysis of TNZ in pharmaceutical formulations and may be adopted in the pharmacopoeias.

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