

Polarographic study of 1-chloro-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-2-ol (an antiprotozoal drug Ornidazole) at dropping mercury electrode

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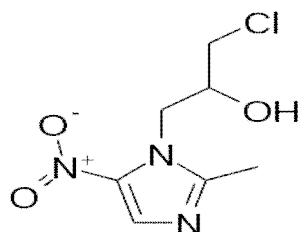
Abstract: The electrochemical reduction of antibacterial and antiprotozoal drug "Ornidazole" has been carried out in aqueous solution in the pH range 2.3 to 11.3 by Direct current (DC) polarography. Ornidazole exhibits one or two reduction peaks depending on pH. In acidic medium two reductions peak were observed while one in basic medium. Along with different pH, studies of drug have been carried out with different concentrations of drug and at different temperatures of medium. The reduction of ornidazole was found to be irreversible so kinetic parameters (K_{oh}^0 , αn) are evaluated using Meites-Israel and Gaur-Bhargava's methods. Thermodynamic parameters such as ΔH_p^\ddagger , ΔH_v^\ddagger , ΔG^\ddagger and ΔS^\ddagger are also evaluated.

Keywords: Ornidazole, direct current polarography, kinetic parameters, thermodynamic parameters.

Introduction

Ornidazole (5-nitroimidazole derivative) is a drug that cures protozoan infections. It has been investigated for use in Crohn's disease after bowel resection¹.

CAS number
16773-42-5
Formula
 $C_7H_{10}ClN_3O_3$
Molecular mass
219.625



The study of ornidazole (ORN) has been done by using different techniques like spectrophotometry²⁻⁵, ESR spectroscopy⁶, High performance thin layer chromatography⁷, Reversed-phase high performance liquid chromatography⁸⁻⁹, electrochemical¹⁰⁻¹² etc.

Present work is related to the electro-reduction of ORN at DME.

Experimental

1) 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.

[Ornidazole]

[IUPAC name: 1-chloro-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-2-ol]

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

2) Reagents

Ornidazole was obtained from “Vibha Enterprises, Amritsar (India)”.

Ornidazole was dissolved in 30% Ethanol.

All solutions were prepared freshly with doubly distilled water and analytical reagent grade chemicals (MERCK).

3) Proposed Procedure

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

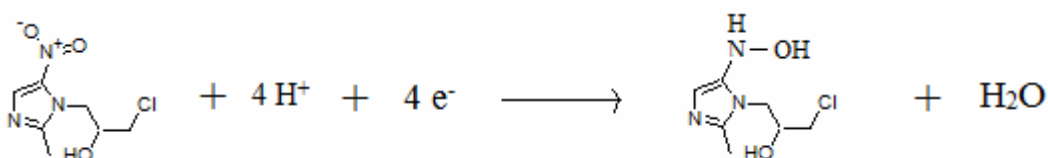
An aliquot (10 ml) of experimental solution which contains B.R. Buffer, Triton-X-100(Maxima Suppressor) and water was placed in a dry, clean polarographic cell and deoxygenated with nitrogen for 15 min. the current-voltage curves were measured manually.

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 ornidazole solution were added.

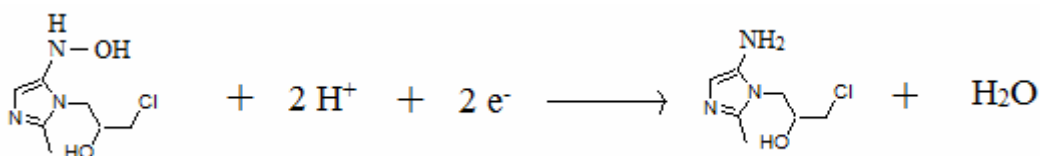
Result and Discussion

1) Effect of pH of medium:-

The effect of pH on the current-voltage curve at a concentration 4.5×10^{-3} M ornidazole was studied over the pH range 2.3 – 11.3. ORN gives rise to one or two reduction peaks depending on pH. In acidic medium ORN 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 electrons¹²⁻¹⁴ as following:



The second wave corresponds to the reduction of hydroxylamine to amine, transferring two electrons¹³⁻¹⁴.



In basic medium one reduction peak was obtained which refers to the six – electron reduction of nitro group to the corresponding amine.

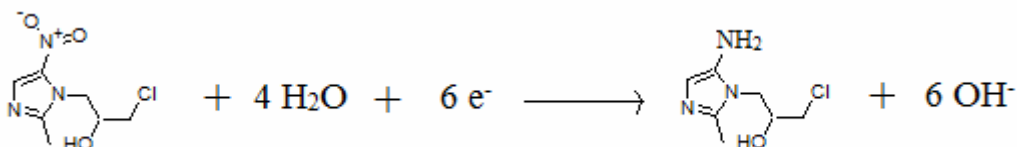


Table (1): Effect of pH on diffusion current and half wave potential of ornidazole wave in B.R. Buffer, ORN = 4.5×10^{-3} M, Triton-X-100 =0.001%

pH	$E_{1/2}$ (Volt)	$I_d \times 100$ nA
2.3	-0.5333	24
3.3	-0.6761	21.7
4.3	-0.7158	19.3
5.3	-0.7744	14.5
6.3	-0.7818	12
7.3	-0.7781	8.5
8.3	-0.7796	7.2
9.3	-0.7794	6.7
10.3	-0.7821	6.3
11.3	-0.7815	5.8

Where, i_d = Diffusion current
 $E_{1/2}$ = Half wave potential.

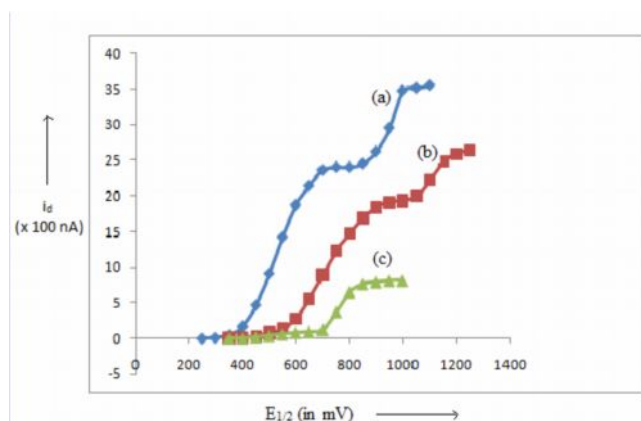


Figure (1):-[Effect of pH on Ornidazole Polarogram (a) at pH 2.3, (b) at pH 4.3 and (c) at pH 8.3]

The direct current polarogram (DCP) at different pH values for the reduction of ORN at a concentration of 4.5×10^{-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). 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 ORN 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), in basic medium half wave potentials ($E_{1/2}$) are remains 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 in basic medium, there is no effect of pH on reduction of NO₂ group. The polarogram at pH 5.3 was much sharper and well defined so this pH was chosen for subsequent work.

2) Effect of concentration of drug:-

The effects of concentration of ornidazole on polarogram are listed in table (2), the concentration of ORN was varied from 0.9×10^{-3} M to 8.1×10^{-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 ORN as expected. Fig (2) shows a linear relationship between i_d and concentration of drug. Since the reduction of ORN is irreversible hence kinetic parameters, like forward rate constant (K_{fh}^0) and transfer coefficient (αn) have been calculated using Meites-Israel and Gaur-Bhargava's methods.

Meites – Israel modification of Kotecky's method:-

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

$$E_{1/2} = \frac{0.0591}{\alpha n} \log \frac{1.349 K_{fh}^0 t^{1/2}}{D^{1/2}} \quad (2)$$

Gaur-Bhargava modification:-

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

$$E_{1/2} = \frac{0.05915}{\alpha n} \log \frac{K_{fh}^0 t^{1/2}}{(\text{antilog } C) D^{1/2}} \quad (4)$$

Where

K_{fh}^0 = formal rate constant for forward reaction

D = diffusion coefficient

αn = transfer coefficient

$E_{d.e.}$ and $E_{1/2}$ 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 values of K_{fh}^0 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.

$$(i_d)_{\max} = 706 n D^{1/2} C m^{2/3} t^{1/6} \quad (5)$$

All symbols have their usual meanings.

Table (2): Effect of Concentration of ORN on wave and hence on kinetic parameters in B.R. Buffer at pH =5.3, Triton-X-100 = 0.001%

Conc. (M)	$E_{1/2}$ (Volt)	$I_d \times 100$ nA	D ($\text{cm}^2 \text{sec}^{-1}$)	Slope (mV)	αn (M.I.) (V)	αn (G.B.) (V)	K^0_{fh} (M.I.) (cm sec^{-1})	K^0_{fh} (G.B.) (cm sec^{-1})
0.9×10^{-3}	-0.7881	3.2	0.3590	0.0822	0.6592	0.7194	4.63×10^{-10}	9.88×10^{-11}
1.8×10^{-3}	-0.7868	5.9	0.3051	0.0808	0.6702	0.7315	3.14×10^{-10}	6.53×10^{-11}
2.7×10^{-3}	-0.7852	8.4	0.2749	0.0772	0.7015	0.7655	1.2×10^{-10}	2.29×10^{-11}
3.6×10^{-3}	-0.7816	11.1	0.2700	0.0757	0.7155	0.7808	8.55×10^{-11}	1.59×10^{-11}
4.5×10^{-3}	-0.7846	13.6	0.2594	0.0731	0.7409	0.8086	3.55×10^{-11}	6.12×10^{-12}
5.4×10^{-3}	-0.7863	15.2	0.2250	0.0680	0.7964	0.8692	5.75×10^{-12}	8.48×10^{-13}
6.3×10^{-3}	-0.7781	17.8	0.2267	0.0627	0.8642	0.9432	9.53×10^{-13}	1.2×10^{-13}
7.2×10^{-3}	-0.7809	19.1	0.1998	0.0680	0.7961	0.8688	6.47×10^{-12}	9.74×10^{-13}
8.1×10^{-3}	-0.7844	21.3	0.1964	0.0585	0.9253	1.0099	1.11×10^{-13}	1.16×10^{-14}

Where

K^0_{fh} (M.I.) = Formal Rate Constant obtained from Meites & Israel's method
 K^0_{fh} (G.B.) = Formal Rate Constant obtained from Gaur & Bhargava's method

D = Diffusion coefficient,

αn = Transfer coefficient

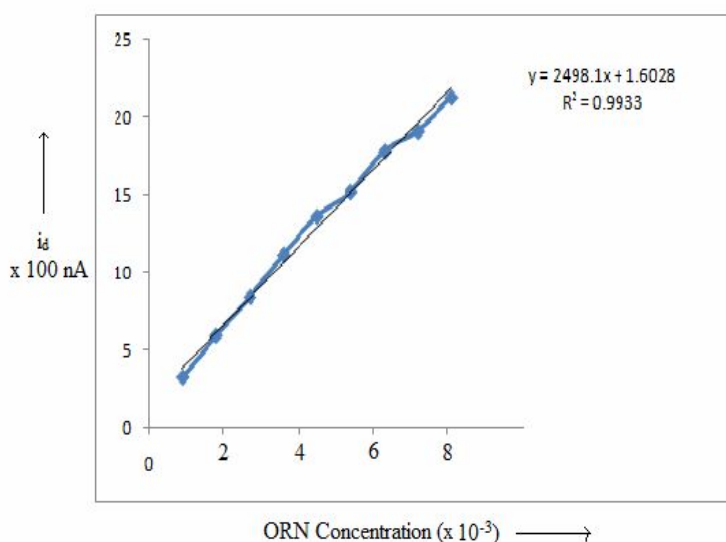


Figure (2):- [Effect of drug concentration on diffusion current]

3) Effect of temperature of medium:-

The effects of temperature on polarogram are listed in Table (3), temperature has a very little effect on $E_{1/2}$ but i_d increases with the temperature. The value of αn increases with temperature. A decrease in value of αn implies that transfer of electrons becomes difficult as temperature was elevated¹⁵, in present case transfer of electron becomes easier. Further the values of K^0_{fh} decreases with increase in temperature which suggests that irreversibility increases with increase in temperature; this implies that reduction products of ornidazole are stable at higher temperature.

At 35°C well defined and well shaped wave was observed.

Further, thermodynamic parameter (ΔH_p^\ddagger , ΔH_v^\ddagger , ΔG^\ddagger , ΔS^\ddagger) have been reported in Table (4). The enthalpy of

activation at constant pressure (ΔH_p^\ddagger) 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. Graph between $\log K^0_{fh}$ & $1/T$ is shown in Fig. (3).

$$\Delta H_p^\ddagger = 2.303R \times \text{Slope}$$

Where R= Gas constant.

The value of slope comes out to be 5.518×10^3 .

$$\Delta H_p^\ddagger = \Delta H_v^\ddagger + RT$$

From this relation ΔH_v^\ddagger (enthalpy change of activation at constant volume) was evaluated, the activation free energy change (ΔG^\ddagger) was determined by relationship.

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

Where K = Boltzmann constant,

h = Plank's constant,
 r_o = mean distance between depolarized ions in the bulk solution,
 R = Gas constant,
 T = absolute temperature.

In general value of r_o is taken as $2 \times 10^{-8} \text{ cm}^{16}$. The entropy of activation (ΔS^\ddagger) was calculated using following equation;
 $\Delta S^\ddagger = (\Delta H_v^\ddagger - \Delta G^\ddagger)/T$

The plot of $\log K_{\text{oh}}^0$ vs. $1/T$ is found to be linear from the slope of which the values of ΔH_p^\ddagger , ΔH_v^\ddagger , ΔG^\ddagger and ΔS^\ddagger have been evaluated and presented in Table (4).

A perusal of the values of various quantities presents in table (4) show that activation free energy change (ΔG^\ddagger) is positive at all the temperatures suggesting the non spontaneous nature of electrode process. Positive value of ΔS^\ddagger 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 ΔG^\ddagger increases and that of the ΔS^\ddagger decreases continuously, it shows that the non spontaneity of electrode process increases with temperature.

Table (4): Thermodynamic parameters at different temperatures

Temperature(°C)	ΔH_p^\ddagger (J/Mole)	ΔH_v^\ddagger (J/Mole)	ΔG^\ddagger (J/Mole)	ΔS^\ddagger (J/Kelvin)
20	10.57×10^4	10.322×10^4	63.713×10^3	134.82
25	10.57×10^4	10.318×10^4	66.544×10^3	122.92
30	10.57×10^4	10.313×10^4	70.068×10^3	109.13
35	10.57×10^4	10.309×10^4	72.707×10^3	98.65
40	10.57×10^4	10.305×10^4	75.303×10^3	88.65

ΔH_p^\ddagger = Enthalpy change for activation process at constant pressure.

ΔH_v^\ddagger = Enthalpy change for activation process at constant volume.

ΔG^\ddagger = Gibbs free energy change for activation process.

ΔS^\ddagger = Entropy change for activation process.

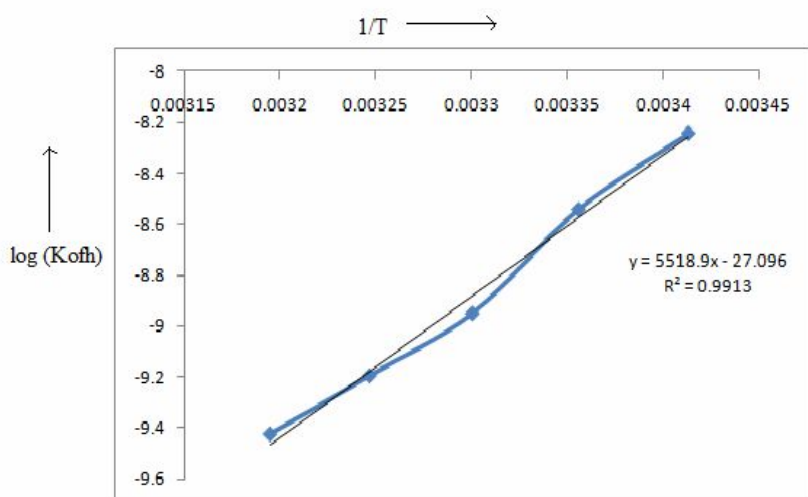


Figure (3):- [Graph between $\log K_{\text{oh}}^0$ & $1/T$]

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