Kinetic Studies of Charge Transfer Formation of Erythromycin and 2, 3 Dichloro-5, 6-Dicyano -1,4-Benzoquinone

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Abstract

The kinetics of erythromycin with 2, 3 dichloro-5,6-dicyano-1,4-benzoquinone [DDQ] is described for the determination of erythromycin. It was carried in aqueous HClO4 (2M) medium at ionic strength of 0.01moldm-3. Kinetics of the reactions infer that the rate of formation of the charge transfer complex did not vary significantly with increase in concentration of erythromycin indicating likely zeroth order dependence of the rate with respect to concentration of the drug. However, the linearity of the pseudo-first order plot points to first order dependence of rate on [DDQ]. The overall rate equation for the reactions can be given as

- \( \frac{d[DDQ]}{dt} = k_{\text{obs}}[DDQ] \)

Keywords: Kinetic studies; Erythromycin; Charge transfer; DDQ

Introduction

The kinetic methods of analysis are highly sensitive, selective, simple, accurate and less expensive [1]. Erythromycin, 3R, 4S, 5S, 6R, 7R, 9R, 11R, 12R, 13R, 14R-4-[(2,6-diodicyclo-3-c-methyl-1,3-0-methyl-α-l-ribo-hexopyranosi) oxy]-14 ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-dimethyl-kmiro-P-D-xylo-hexopyranosi)-oxy] oxa-cyclofetradiene-2, 10-dione is a macrolide antibiotic used for the treatment of urinary tract infection. It targets at the ribosome and inhibits the protein synthesis of gram positive bacteria such as mycoplasma and Chlamydia [2]. In recent years, several kinetic catalytic techniques have been reported for the detection of biomolecules [3,4]. Literature revealed different techniques for the analysis of erythromycin as follows: spectrofluorimetry [5]. Capillary electrophoresis [6], HPLC [7], microbiological method [8] spectrophotometry [9,10]. Therefore, the aim of this research is to determine a kinetic method based on formation of charge transfer complex between erythromycin and DDQ that is simple, fast, economical and less laborious.

Materials and Methods

Equipment

All kinetic measurements were carried out using a UV-1800 Shidmazu and 752w UV – Vis grating with a silica glass cell of 1 cm thickness. All chemicals were of analytical grade and were used as such. Erythromycin powder was supplied by AC pharmaceutical limited, Enugu, Nigeria. The commercial erythromycin tablet (500mg per tablet) was purchased from the local market (Syncom formulations limited, India) 2,3 dichloro-5, 6-dicyano-1,4-benzoquinone (98% purity) was supplied by sigma Aldrich, Germany.

Kinetic Measurements

Kinetics of the reactions of DDQ with erythromycin was followed spectrophotometrically under pseudo-first order condition with one of the reactants (donor) in at least 10 fold in excess over the reactant (acceptor) at 29°C. The pseudo-first order rate constants were determined by using various concentrations of erythromycin (0.001 M to 0.0035 M) with fixed concentration of acceptor (2.5 x10-4 M). Effects of ionic strength, pH and hydrogen ion on the rates of reaction were also determined.

The pseudo-first order rates constant were obtained from a plot of log \( \frac{A-A_t}{A_0-A_t} \) versus time following equation 1.

\[
(A_\infty - A_t) = (A_\infty - A_0)e^{-k_{\text{obs}}t}
\]
where \( A_\alpha \) and \( A_\beta \) are the final and initial absorbencies respectively. \( A_t \) is absorbance at time \( t \) and \( K_{obs} \) is pseudo-first order rate constant.

### Effect of Hydrogen Ion Concentration on the Rate of Erythromycin and DDQ Reaction

Within the hydrogen ion concentration range 1.0 \( \times \) \( 10^{-2} \) to 1.0 mol dm\(^{-3} \), kinetic runs were carried out keeping the concentrations of the drug and reagent constant at \( I = 1.02 \) mol dm\(^{-3} \) and \( T = 30.0 \pm 0.2^\circ C \).

### Effect of Ionic Strength on the Rate of Erythromycin-DDQ Reaction

Within the range of ionic strength of the media 0.001-0.03 mol dm\(^{-3} \), the variation of rate of reaction with ionic strength was investigated for the reaction of erythromycin and DDQ. At \( T = 28^\circ C \) and keeping the concentrations of drug and reagent constant, the ionic strength was varied and the rate of reaction monitored.

### Results and Discussion

#### Reaction of Erythromycin with DDQ

The wavelength of maximum absorption spectrum was found to be 464 nm with a stoichiometric ratio of 1:1 of erythromycin - DDQ complex [11].

#### Kinetic Studies

The rate of the charge transfer reaction of erythromycin and DDQ was followed spectrophotometrically under pseudo - first order conditions by monitoring the rate of consumption of DDQ at 464 nm. Erythromycin was at least 10 fold in excess of DDQ and the reaction was carried out at pH 8. Kinetic decays were exponential and pseudo first rate constants were determined from the plots of log versus time according to equation 1. The plots were linear for more than 90 % extent of reaction. Typical

#### Table 1: Values of pseudo-first order and second order rate constants for the formation of erythromycin-DDQ reaction, [DDQ] =10 \(-3 \)M at 30°C.

| Vol of Erythromycin (10\(^{-2}\)M) | Vol of Methanol (cm\(^3\)) | \( k_{obs} \) (s\(^{-1}\)) | \( k_2 \) (dm\(^3\)mol\(^{-1}\)s\(^{-1}\)) |
|----------------------------------|-----------------------------|-----------------------------|-------------------------------------|
| 0.4                              | 1.2                         | 0.016                       | 0.2                                 |
| 0.6                              | 1.0                         | 0.016                       | 3.33                                |
| 0.8                              | 0.8                         | 0.0138                      | 1.0                                 |
| 1.0                              | 0.6                         | 0.0138                      | 2.0                                 |
| 1.2                              | 0.4                         | 0.0115                      | 0.67                                |
| 1.4                              | 0.2                         | 0.0115                      | 0.57                                |

\( \text{NaClO}_4 = 1.02 \text{M}, [\text{Erythromycin}] = 2.0 \times 10^{-4} \text{ M}, [\text{DDQ}] = 1 \times 10^{-6} \text{ M} \)

The second order rate constants were determined by dividing \( K_{obs} \) with [erythromycin]. The values of \( K_{obs} \) and \( k_2 \) are represented in Table 1. The result from table 1 shows that as concentration of erythromycin increased from 0.001 M to 0.0035 M, the \( K_{obs} \) values did not vary significantly indicating a zero order dependence on reaction rate with respect to the concentration of erythromycin. However, the linearity of the pseudo – first order plot points to first – order dependence of rate with respect to [DDQ].

#### Effect of Hydrogen Ion Concentration on Erythromycin – DDQ Complex

The \( H^+ \) concentration was varied from 0.08 M to 1 M while keeping other variables constant. Table 2 shows that \( K_{obs} \) increase from 0.08 M to 1 M. This infers that within this acid concentration range, protonation of the reactants played significant role in the charge transfer reaction. The second order rate constants were determined by dividing \( K_{obs} \) with [erythromycin]. Table 2 is a display of pseudo-first order and second order rate constants.
Table 2: Acid values for the pseudo-first order and second order rate constant of erythromycin-DDQ complex at $\lambda_{max} = 464$ nm, $T = 30^\circ$C NaClO$_4$ = 1.02M, [Erythromycin]=2.0x10$^{-5}$ M,[DDQ]=1 x 10$^{-6}$ M

| I (mold m$^{-3}$) | $k_{obs}$ (s$^{-1}$) | $k_2$ x10$^2$ (dm$^3$mol$^{-1}$s$^{-1}$) |
|------------------|---------------------|---------------------------------|
| 0.001            | 0.005               | 2.5                             |
| 0.005            | 0.005               | 2.5                             |
| 0.01             | 0.005               | 2.5                             |
| 0.015            | 0.002               | 1.0                             |
| 0.02             | 0.009               | 4.5                             |
| 0.025            | 0.009               | 4.5                             |
| 0.03             | 0.002               | 1.0                             |

Effect of Ionic Strength on Erythromycin – DDQ Complex

In addition, ionic strength medium was varied from 0.001M to 0.03M. Table 3 shows that $K_{obs}$ did not vary significantly at 0.001M-0.01M but increased from 0.015M to 0.025M of the varied ionic strength which indicates primary salt effect and likely involvement of charged partners at the rate determining step.

Table 3: Effect of ionic strength on the rate of erythromycin-DDQ reaction at $\lambda_{max} = 464$ nm, $T = 30^\circ$C, NaClO$_4$ = 0.1M, [Erythromycin] =2.0x10$^{-5}$ M, [DDQ] =1 x 10$^{-6}$ M.

| I (mold m$^{-3}$) | $k_{obs}$ (s$^{-1}$) | $k_2$ x10$^2$ (dm$^3$mol$^{-1}$s$^{-1}$) |
|------------------|---------------------|---------------------------------|
| 0.001            | 0.005               | 2.5                             |
| 0.005            | 0.005               | 2.5                             |
| 0.01             | 0.005               | 2.5                             |
| 0.015            | 0.002               | 1.0                             |
| 0.02             | 0.009               | 4.5                             |
| 0.025            | 0.009               | 4.5                             |
| 0.03             | 0.002               | 1.0                             |

Effect of Temperature on Erythromycin – DDQ Complex

Effect of temperature was studied between 303k - 333k. Result in (Table 4) shows a drop in $K_{obs}$ from 313k to 333k, this shows that as the temperature increases, the rate of reaction decreased. Also, Table 4 reveals a negative entropy, negative enthalpy change and positive Gibb’s free energy change which means that the reaction does not occur spontaneously.

Least square fit of $\log K_{obs}/T$ vs $1/T$ based on the Eyring – Polanyi [12] (equation 2) is represented in Figure 2.

$$k_r \left( \frac{KT}{h} \right) \exp \left( \frac{\Delta S^\#}{R} \right) \exp \left( -\frac{\Delta H^\#}{RT} \right)$$

Where, $k_r$ = rate constant, $k = $ Boltzmann’s constant, $h = $ Planck's constant, $\Delta S^\# = $ entropy of activation $\Delta H^\# = $ enthalpy of activation, $T = $ absolute temperature, $R = $ gas constant.

The rate determining steps of erythromycin-DDQ complex are as follows:

$$\frac{d[DDQ]}{dt} = k_{obs}[DDQ]$$

$$k_1 \begin{array}{c} \rightarrow & k_1 \end{array}$$

$$\begin{array}{c} \rightarrow & \end{array}$$

$$k_2$$

Table 4: Effect of temperature on the pseudo-first order rate constant and activation parameters for the formation of erythromycin-DDQ complex at $\lambda_{max} = 464$ nm, [Erythromycin] =10$^{-2}$ M, [DDQ] =10$^{-3}$ M.

| Temperature (oC) | $\Delta G^* \times 10^5$ (kJ mol$^{-1}$) | $K_{obs}$ (s$^{-1}$) | $k_2$ (dm$^3$mol$^{-1}$s$^{-1}$) |
|------------------|-----------------------------------|---------------------|---------------------------------|
| 30               | 7.25                              | 0.016               | 16                              |
| 35               | 7.37                              | 0.016               | 16                              |
| 40               | 7.49                              | 0.016               | 16                              |
| 45               | 7.61                              | 0.01375             | 13.75                           |
| 50               | 7.73                              | 0.0115              | 11.5                            |
| 55               | 7.84                              | 0.01035             | 10.35                           |
| 60               | 7.96                              | 0.0092              | 9.2                             |

$\Delta S^\# \ (kJk^{-1}/mol) = -2391$; $\Delta H^\# \ (kJ mol^{-1}) = -11$
Conclusion

The proposed kinetic method infer that the rate of formation of charge transfer complexes did not vary significantly with increase in concentration of erythromycin indicating a likely zeroth order dependence of the rate with respect to the concentration of erythromycin. However, the linearity of the pseudo – first order plot points to first order dependence of rate on [DDQ].

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