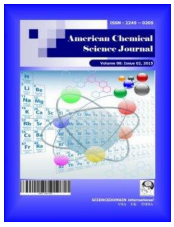

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Chemical Oxidation of Phthalmic Drug Timolol by Peroxodisulfate

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

The oxidation of morpholine-thiadiazol based structure ophthalmic beta blocker drug, Timolol, in the presence of Potassium Perxodisulfate (PDS) and 40% methanol-water has been studied using spectrophotometric method. It has been found that; oxidation reaction starts with electrophilic attack of PDS species on the protonated form of Timolol leading to produce three products (I,II and III) one of them retains the morpholne-thiadiazole structure (I). The products were characterized as (I) 4-morpholino-1,2,5-thiadiazol-3-ol, (II) 3-(carboxy diformylmethylamino)-2-hydroxypropanoic acid and (III) 2-(2-formyl-2-hydroxyethylamino)-2,2-diformylacetic acid. The detailed mechanism of the oxidation reaction was proposed, and thermodynamic parameters were obtained for different reaction steps.

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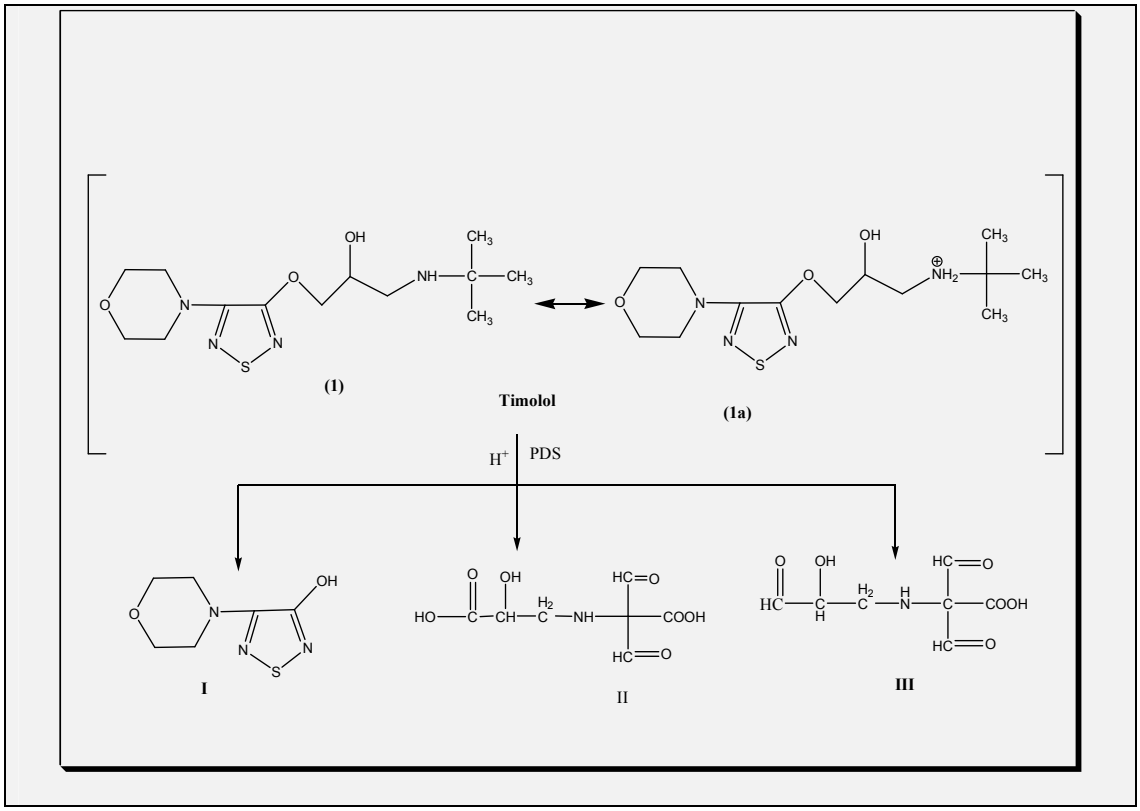


Keywords: Timolol; β– blockers; peroxodisulfate; kinetics; morpholine-thiadizaol; 3-hydroxy-4-morpholino-1,2,5-thiazole.

1. INTRODUCTION

Timolol (**1**) (1-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-3-(tert-butylamino)propan-2-ol) is β adrenergic receptors which is normally used as ophthalmic medication for the treatment of open-angle glaucoma and ocular hypertension [1,2]. From a chemical point of view; Timolol structure contains morpholino-thiadiazol as the main structural frame, however, presence of the aliphatic amine could also affect the chemistry of Timolol.

Timolol is very sensitive to light and oxidizing agents [1]. Light exposure could results in photo damage of this drug producing toxic products or at least lowering its therapeutic action [1,3].

Publications discussed the reactivity of Timolol mainly were mainly originated from the pharmaceutical industry, where most of them are mainly interested in development of new analytical methods to analyze Timolol in different dosage form or analysis of the photo-degradation products [3,4]. Recently, a few papers were published where the the mechanism of the photo-degradation of Timolol [1,5-7] were discussed. Criado et al. studied the photo-oxidation of the timolol using LC-MS; they found that the photo-oxidation occurs through singlet molecular oxygen and three products were obtained, one of them retains the morpholino-thiadiazol structure [6]. In fact, there is no studies correlate the photooxidation of Timolol with its chemical oxidation. As far as we know, there is no single study investigate the detailed mechanism of the chemical oxidation of the Timolol- β-blockers.

In the last years we are interest in the reactivity of the beta blockers drugs [8-14]. We have studied the kinetics and mechanism of the oxidation different beta blockers using different peroxides such as Peroxodisulfate, $H_2S_2O_8$, (PDS) and Peroxodiphosphate, $H_4P_2O_8$, (PDP) [12,15].

PDS is a known electrophilic reagent, which is widely used as an oxidizing agent [8-17]. In order to generalize this reaction mechanism and study the factors influencing the rate of the oxidation of

the different beta blocker drug with aims of controlling the formation of the reaction products and correlate the it to the photooxidation of these compounds, we carried out a new kinetic study of the oxidation of Timolol by peroxodisulfate (PDS) which is known to be a good electrophilic reagent [16,17].

2. EXPERIMENTAL SECTION

2.1 Materials

Timolol (**1**) (S-(−)-1-(t-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol, $C_{13}H_{24}N_4O_3S$, was purchased from Sigma-Aldrich (>98%), and were used as received without further purification. Potassium peroxodisulfate, $K_2S_2O_8$ (Sigma-Aldrich) was also used as received. The stock solutions of all reagents were freshly prepared and stored in the dark at 4°C to prevent light induction and hydrolytic composition.

Acidity of the solutions was adjusted by adding appropriate amounts of commercial standardized solutions of sulfuric acid (H_2SO_4).

2.2 Kinetic Experiments

Kinetic measurements were carried out under pseudo-first order reaction. The reactions were followed by monitoring the changes of absorbance at about 296 nm and 248 nm. This absorption corresponds to the maximum wavelength of Timolol (**1**) and the reaction product, respectively. The reaction rate constants were obtained by non-linear square fitting of the absorbance-time data to equation 1,

$$A_t = A_\infty + (A_0 - A_\infty)e^{-k_{obs}t} \quad (1)$$

At least two half-lives were followed. An excellent agreement between the experimental and calculated A_t values were obtained. All rate constants were averaged for at least three independent runs and standard deviations were smaller than 5%.

Neither the presence of external radical promoters nor radical traps have affected the oxidation rates, which excludes the involvement of radical species in the reaction steps. Possible interaction between different components of the reaction mixture was also investigated (i.e., possible interaction between methanol and sulfuric acid was tested and excluded; in fact no reaction was observed within the reaction time).

Kinetic measurements and evolution of the spectra of the reaction mixtures with time were carried out using a Specord, S– 600 Diode Array Spectrophotometer interfaced with an HP computer.

A stock solution of Timolol was prepared by dissolving appropriate amounts of Timolol in methanol.

3. RESULTS AND DISCUSSION

Fig. 1 shows the typical changes of the absorption spectra of Timolol (1) upon addition of PDS in 40% methanol-water mixture (the optimum experimental condition) as a function of time. It also shows a clear isosbestic points appeared at 264 nm.

The gradual disappearance at 296 nm (i.e., wavelength of maximum absorption of Timolol), leads to a spectrum corresponding to absorption spectra of the protonated Intermediate, Scheme 1. Once the intermediate is formed a second attack of PDS is expected and leads to the formation of the reaction products.

Under our experimental conditions of acidic media, three products were obtained and assigned to the **(I)** 4-morpholino-1,2,5-thiadiazol-3-ol, (**II**) 3-(carboxydiformylmethylamino)-2-hydroxypropanoic acid and (**III**) 2-(2-formyl-2-hydroxyethylamino)-2,2-diformylacetic acid. TLC analysis of the reaction products confirms that three products were obtained. TLC comparison of the reaction products with independently obtained samples of these compounds confirms [6] that these products are 4-morpholino-1,2,5-thiadiazol-3-ol, 3-(carboxydiformylmethylamino)-2-hydroxypropanoic acid and 2-(2-formyl-2-hydroxyethylamino)-2,2-diformylacetic acid [6]. Two of the obtained products are aliphatic acid and the third one retains morphino-Thiadiazole structure. The mass spectrum of the pure samples of the reaction products (**I, II and II**) MS (FAB): m/z were 187,219 and 203 respectivelly197.2 confirms these products are 4-morpholino-1,2,5-thiadiazol-3-ol, 3-(carboxy diformyl methyl amino)-2-hydroxypropanoic acid and 2-(2-formyl-2-hydroxy ethyl amino)-2,2-di formyl acetic acid, respectively [5,6]. A comparison of the spectral data of the obtained products with independently obtained product confirms that these products are 4-morpholino-1,2,5-thiadiazol-3-ol, 3-(carboxy diformyl methyl amino)-2-hydroxypropanoic acid and 2-(2-formyl-2-hydroxy ethyl amino)-2,2-di formyl acetic acid [5,6].

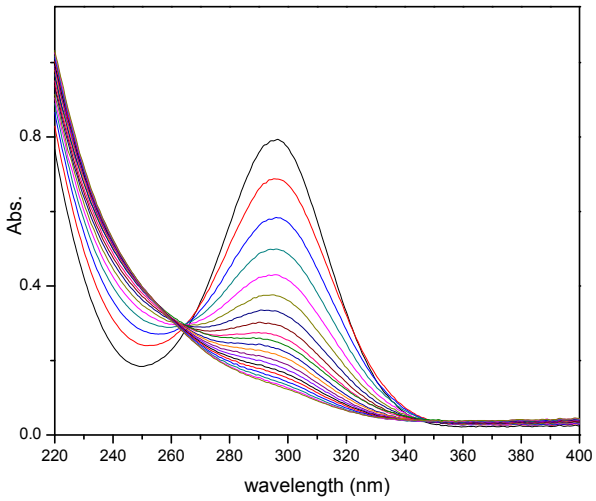
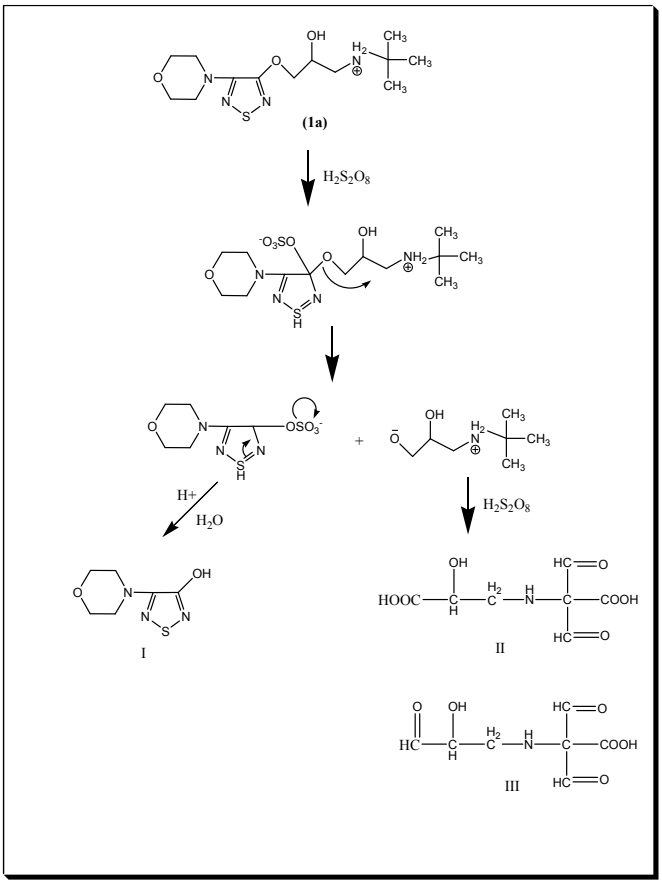


Fig. 1. Evolution with time of the reaction mixture of Carvedilol. [Timolol]= 1.278x10^{-4} mol.dm-3 mol.L^{-1}. [PDS] = 4.0 x10^{-5} mol.L^{-1} at 298 K in 40% methanol-water



Scheme 1. Reaction scheme of Chemical oxidation of Timolol in presence of PDS

The rate constants for both reaction steps: the disappearance of the Timolol ($k_{obs}.1$) and appearance of the reaction products ($k_{obs}.2$) were followed by monitoring the changes of the absorbance at 296 nm and 248 nm with time, respectively, under the condition of pseudo first order conditions with large excess of PDS. Absorbance-time data obtained for the two reaction steps are best fitted to first order exponential decay equation, equation 1, where values of the rate constants $k_{obs}1$ and $k_{obs.}2$ were estimated. In general the values of the rate constants $k_{obs}.1$ are larger than a first order rate constant of the product formation $k_{obs}.2$. Both rate constants $k_{obs.}1$ and $k_{obs.}2$ are found to be dependent on PDS concentrations. Values for both $k_{obs}.1$ and $k_{obs}.2$ at different PDS concentrations obtained under different acidic conditions are tabulated in Tables 1 and 2 and represented in Fig. 2.

For the first step of the reaction, data in Table 1 shows that; at fixed acid concentration, the rate constants $k_{obs}.1$ varies linearly with PDS concentrations with intercept at origin (**I1**) and slopes (**S1**). Both values (**I1 and S1**) are directly related to acid concentration, Table 1 and Fig. 2. The plot of the intercept at origin (**I1**) against the acidic concentrations is linear with zero intercept at origin and slope equal to (6.78±0.4) $x10^{-5}$.

On the other hand, at fixed PDS concentrations, values of $k_{obs.}1$ were also varies with proton concentrations. At fixed PDS concentrations, plot of the first rate constant ($kobs.1` = (kobs.1/[PDS])$) versus the acid concentrations is linear with zero intercept at origin and slopes equal to (S2). The plot of the slopes (S2), (of $k_{obs}1`$- $[H^+]$ curves) against the reciprocal concentration of PDS (1/PDS) concentrations is linear with intercept and slope equal to 0.09218±0.00158 and (6.20±0.3) $x10^{-5}$, respectively.

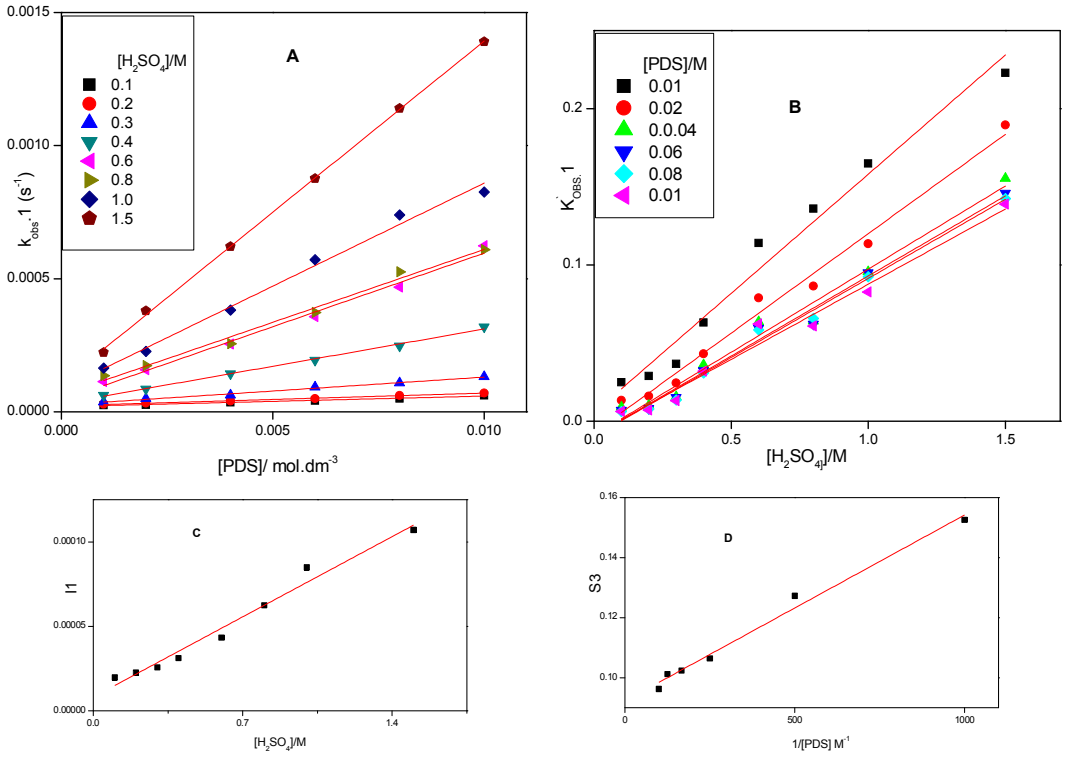


Fig. 2(A). Dependence of the rate constants $k_{obs.}1$ on the PDS concentrations at different acid concentrations. (B) Dependence of $k`_{obs.1}$ on the acid concentration at different concentration of PDS. (C) dependence of the intercept of $k_{obs.1}$-PDS plot on the acid concentrations. (D) Dependence of slopes (S3) of $k`_{obs.1}$-Acid plot against reciprocal of PDS concentrations. [Timolol] = 1.3 $x10^{-4}$ mol.L^{-1} at 298 K in 40% methanol-water

For the second step of the reaction; the appearance of the reaction product, values for the rate constants were reported in Table 2 and Fig. 3. Results could be summarized as follow: (i) At fixed acid concentrations; values of the second rate constant ($k_{obs}.2$) varies linearly with PDS concentrations with intercept at origin equal to (**I2**) and slopes equal to (S3). (ii) Both values of the intercept (**I2**) and slopes (S3) are acid dependence. (iii) The intercepts (**I2**) varies linearly with acid concentrations, the plot of the values of I2 against acid concentrations is linear with intercept at origin and slopes equal to $(4.78\pm0.7)x10^{-5}$ and $(1.558\pm0.1)x10^{-4}$, respectively. (iii)The slopes of these plots (**S3**) found also to increase with acid concentrations. The plot of the slopes (S3) against acid concentrations is linear with zero intercept at origin and slope equal to 0.1556±0.004.

The effects of ionic strength on both rate constants were studied using inert salt (NaCl). The variation of ionic strength was found to have a negligible effect on both rate constants ($k_{obs}.1$ and $k_{obs}.2$). From this result we can conclude that, both steps must involve neutral species. This information is important since PDS species could exist in different forms (i.e., different charge) under our experimental condition [16].

Finally, in order to obtain the thermodynamics parameters of the reaction; influence of temperature on both rate constants $k_{obs}.1$ and $k_{obs}.2$ were studied and the results were tabulated in Table 3. Experimental data were fitted according to the Eyring equation; from which the activation parameters were determined to be $\Delta H^{\#,1}$ = 46.0±1, $\Delta H^{\#,2}$ = 48.3±2 KJ/mol and $\Delta S^{\#,1}$ = -139.9±0.8 , $\Delta S^{\#,2}$ =-144.9±0.09 J/mol for the first and second step, respectively.

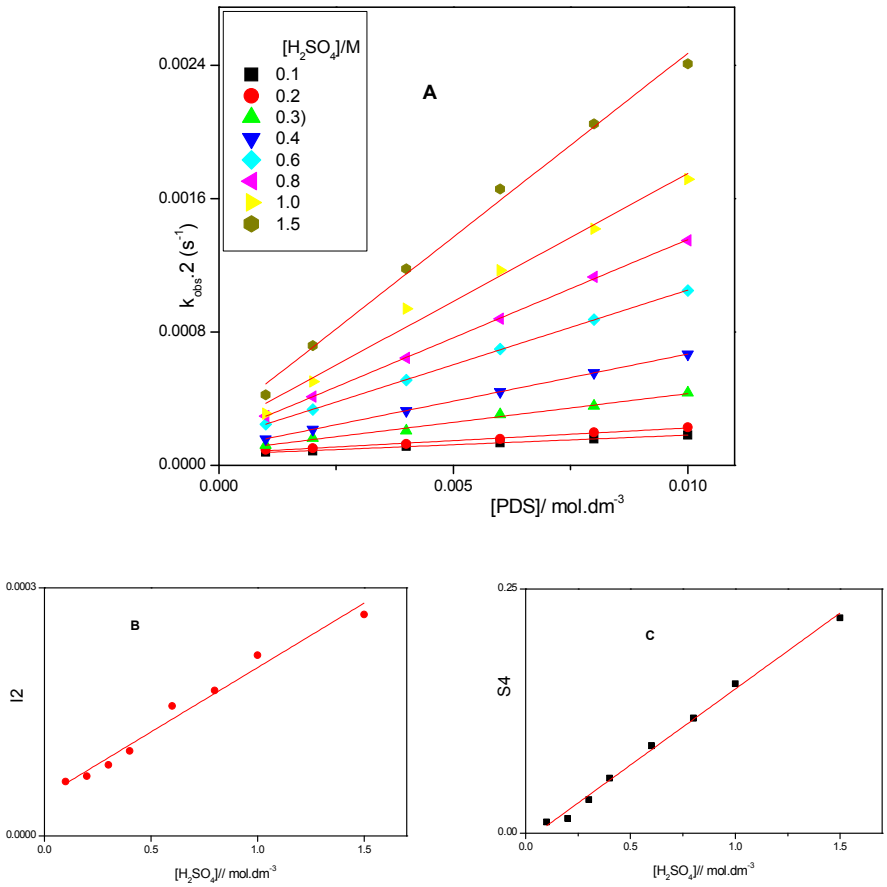


Fig. 3. Dependence of the rate constants $k_{obs}.2$ on the PDS concentrations, at different acid concentrations (A). (B) Dependence of the intercept (I2) of ($k_{obs.2}$-PDS plot) on the acid concentrations. (C) Dependence of slopes (S4) of $k_{obs.2}$-PDS plot against the acid concentrations. [Timolol]= 1.3 $x10^{-4}$ $mol.L^{-1}$ at 298 K in 40% methanol-water

Table 1. Pseudo-first-order rate constants $k_{obs}.1$ (s^{-1}) for the oxidation of Timolol by PDS in 40% methanol- water at different H_2SO_4 concentrations at 298 K: [Timolol] = $1.3x10^{-4}$ mol·L^{-1}

PDS	H_2SO_4 mol.L^{-1}/10^{-5} s^{-1}							
	0.1	**0.2**	**0.3**	**0.4**	**0.6**	**0.8**	**1.0**	**1.5**
0.001	2.49±0.04	2.91±0.02	3.66±0.08	6.32±0.09	11.4±0.3	13.6±0.8	16.5±0.2	22.3±0.9
0.002	2.66±0.01	3.22±0.03	4.91±0.05	8.62±0.05	15.8±0.8	17.3±0.9	22.7±0.3	37.9±0.8
0.004	3.57±0.07	3.99±0.04	6.25±0.07	14.4±0.4	25.4±0.2	25.6±0.2	38.2±0.5	62.1±0.4
0.006	4.22±0.01	4.99±0.02	9.24±0.01	19.5±0.3	35.1±0.8	37.3±0.8	57.1±0.9	87.6±0.6
0.008	4.95±0.06	6.15±0.05	10.8±0.3	24.8±0.6	46.5±0.3	52.6±0.5	75.9±0.7	113.6±0.9
0.01	6.20±0.05	7.14±0.06	13.1±0.4	31.9±0.2	62.3±0.4	60.9±0.4	82.6±0.5	139.0±0.8
10^{-3} /Slope	3.87±0.2	4.75±0.2	10.5±0.4	28.0 ±0.8	55.3±0.3	54.8±0.2	77.4±0.3	128.0±0.1
10^{-5} /Intercept	1.978±0.1	2.26±0.1	2.58±0.3	3.13±0.4	4.34±1	6.255±2	8.52±2	10.72±0.07
R^2	0.990	0.992	0.991	0.996	0.989	0.989	0.989	0.999

Table 2. Pseudo-first-order rate constants $k_{obs}.2$ (s^{-1}) for the oxidation of carvedilol by PDS in 40% methanol- water at different H_2SO_4 concentrations at 298 K: , [Timolol] = $1.3x10^{-4}$ mol·L^{-1}

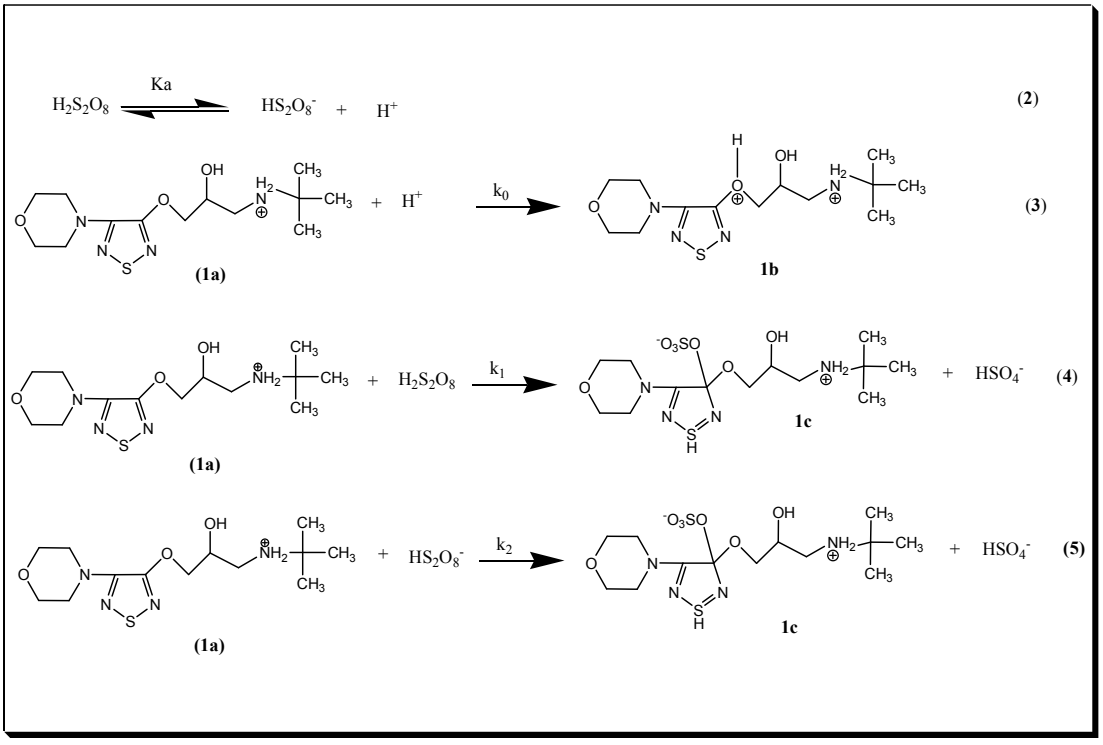
PDS	H_2SO_4 mol.L^{-1}/10^{-5} s^{-1}							
	0.1	**0.2**	**0.3**	**0.4**	**0.6**	**0.8**	**1.0**	**1.5**
0.001	0.797±0.006	0.928±0.005	1.21±0.09	1.59±0.02	2.47±0.06	2.96±0.03	3.1±0.01	4.24±0.04
0.002	0.851±0.003	1.029±0.0058	1.63±0.02	2.16±0.08	3.36±0.03	4.12±0.09	5.03±0.03	7.2±0.01
0.004	1.141±0.001	1.28±0.001	2.06±0.07	3.290±0.01	5.12±0.02	6.45±0.07	9.41±0.07	11.8±0.09
0.006	1.349±0.009	1.59±0.04	3.04±0.01	4.42±0.05	6.98±0.09	8.80±0.02	11.7±0.05	16.6±0.06
0.008	1.581±0.001	1.97±0.07	3.56±0.09	5.55±0.01	8.74±0.07	11.3±0.06	14.2±0.02	20.5±0.04
0.01	1.82±0.04	2.27±0.06	4.34±0.08	6.68±0.06	10.5±0.7	13.5±0.09	17.18±0.08	24.1±0.01
10^{-2} /Slope	1.16±0.2	1.52±0.06	3.45±0.02	5.65±0.02	8.98±0.05	11.74±0.05	15.32±0.09	22.05±0.07
10^{-5} /Intercept	6.57±0.02	7.29±0.04	8.67±0.09	10.27±0.01	15.7±0.2	17.6±0.05	21.86±0.5	26.78±0.5
R^2	0.996	0.992	0.990	0.996	0.986	0.990	0.984	0.994

3.1 Analysis of Kinetic Results

Taking into account the pKa value of Timolol (pKa = 9.21), we can assume that, under our experimental conditions, Timolol exists in a protonated form (**1a**). On the other hand, PDS could exist as monoanionic $H_2S_2O_8$ or $HS_2O_8^-$ species (pKa of $H_2S_2O_8$ was reasonably estimated to 2.45) [11-14]. Assuming that, the two species of PDS exist under experimental conditions, equation 2, and therefore both of them are involved in the first step of the reaction (i.e., $H_2S_2O_8$ *and* $HS_2O_8^-$ species), Scheme 2. The mechanism of the reaction could be mathematically expressed as proposed by equations 2-5:

Table 3. Pseudo-first-order rate constants $k_{obs.1}$ (s^{-1}) and $k_{obs.2}$ (s^{-1}) for the oxidation of Timolol by PDS in 40% methanol - water at different temperatures: [Timolol] = 1.3 × 10^{-4} M, [PDS] = 2.0 × 10^{-3} mol·L^{-1}, [H_2SO_4] =1 mol·L^{-1}

Temperature	10^{-3} / K_{obs}.1	10^{-3} /K_{obs}.2
15±0.1ºC	1.41±0.06	2.87±0.03
20±0.1ºC	2.06±0.01	4.31±0.04
25±0.1ºC	2.27±0.05	5.03±0.03
30±0.1ºC	3.68±0.07	8.01±0.03
35±0.1ºC	5.31±0.05	11.92±0.03
40±0.1ºC	6.66±0.04	14.57±0.08
45±0.1ºC	9.51±0.04	21.5±0.2



Scheme 2. Mechanism of the first step of the reaction of the oxidation of Timolol in presence of PDS

The total concentration of PDS is given equation 6

$$[PDS]_0 = [H_2S_2O_8] + [HS_2O_8^-] \quad (6)$$

From equation 6, the concentration of $[H_2S_2O_8]$ and $[HS_2O_8^-]$ could be expressed as

$$[H_2S_2O_8]=\left\{\frac{[H^+]}{[H^+]+Ka}\right\}[PDS]_0 \quad (7)$$

$$[HS_2O_8^-]=\left\{\frac{Ka}{[H^+]+Ka}\right\}[PDS]_0 \quad (8)$$

From the proposed mechanism on scheme 2, for the first step of the oxidation of Timolo by PDS, the rate law could be obtained as equation 9, the observed rate constant $k_{obs.}1$ and could be derived as appears in equation 11,

$$R=-\frac{d[Timolol]}{dt}=k_0[H^+][1a]+k_1[H_2S_2O_8][1a]+k_2[HS_2O_8^-][1a] \quad (9)$$

since Timolol concentation is constant $k_{obs.1}$ is expressed as

$$k_{obs.1}=k_0[H^+]+k_1[H_2S_2O_8]+k_2[HS_2O_8^-] \quad (10)$$

Taking into acount equations 6-8 equation 9, the oserved first rate constant is obtained as

$$k_{obs.1}=k_0[H^+]+\left(\frac{k_1[H^+]+k_2.K_a}{[H^+]+K_a}\right)[PDS]_0 \quad (11)$$

As it could be seen in equation 11, the observed rate constant, $k_{obs.}1$, is directly proportional to PDS concentrations. The plot of $k_{obs.}1$ against PDS concentrations, indeed, gives a straight line with an intercept at origin equal to ($k_0[H^+]$) and a slope equal to $\left(k_1[H^+]+k_2.K_a\right)/\left([H^+]+K_a\right)$.

Fig. 2 shows the plots of the experimental rate constants versus the PDS concentrations at fixed acid concentrations. As it is expected, straight lines with intercepts equal to (**I1**) and slopes equal to S2 were obtained, values of the intercepts (I1) are directly dependent on the acid concentrations, Values of the slopes and Intercepts under different acid concentrations are tabulated in Table 1.

The plot of the obtained values of the intercept (**I1**) against acid concentration is linear with zero intercept at origin and slope equal to (6.78±0.4) x 10^{-5} (R^2= 0.974). According to equation 11 the value of k_0 could be calculated from the value for the slope of the plot of the Intercept (**I1**) of the $k_{obs.}1$-PDS plot against acid concentrations, value of k_0 is estimated to (6.78±0.4) x 10^{-5} $M.s^{-1}$.

The effect of acidity on the rate constants could also be explained using the derived rate constant in equation 11. According to equation 11, at constant concentration of PDS, the observed rate constant is given in equation 12, assuming that under our experimental conditions Ka > $[H^+]$, then the observed rate constant can be expressed as Equation 13.

$$k'_{obs.1}=\frac{k_{obs.1}}{[PDS]_0}=\frac{k_0[H^+]}{[PDS]_0}+\left(\frac{k_1[H^+]+k_2.K_a}{[H^+]+K_a}\right) \quad (12)$$

Ka>$[H^+]$

$$k'_{obs.1}=\frac{k_{obs.1}}{[PDS]_0}=\frac{k_0[H^+]}{[PDS]_0}+\frac{k_1}{K_a}[H^+]+k_2 \quad (13)$$

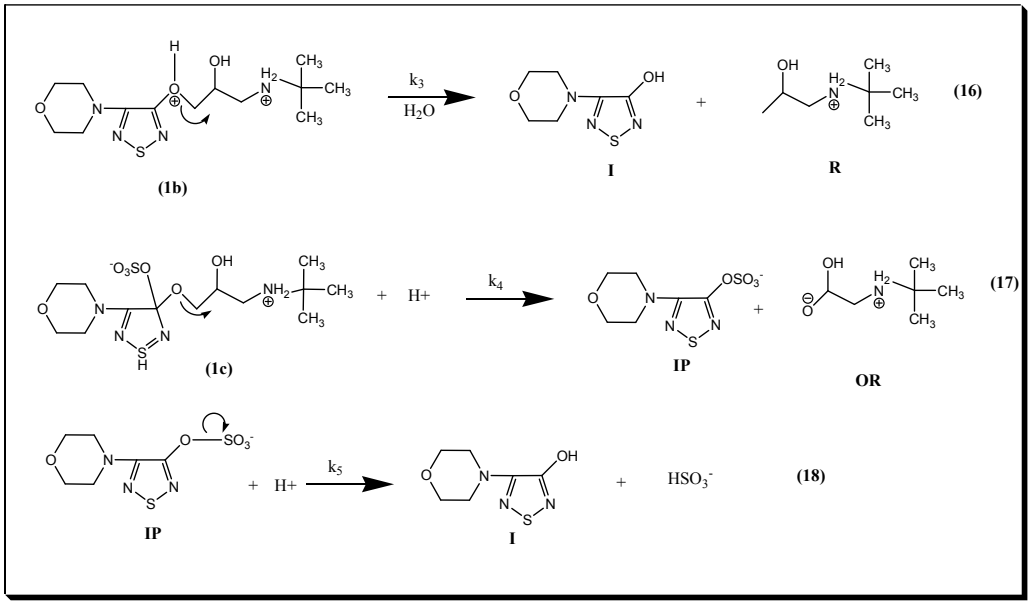
$$k'_{obs.1}=k_2+\left(\frac{k_1}{K_a}+\frac{k_0}{[PDS]_0}\right)[H^+] \quad (14)$$

According to equation 13 and 14, the plot of the observed rate constants versus acid concentration should be linear with intercept equal to $\mathbf{k_2}$ and a slope (S3) equal to (equation 15)

$$S3 = \frac{k_1}{K_a} + \frac{k_0}{\left[PDS\right]_0} \qquad (15)$$

The plot of $k^{/}_{obs.1}$ versus acid concentrations is indeed linear with zero intercept at origin (i.e., this means that values of $\mathbf{k_2}$ is equal to zero) and slopes directly depended on PDS concentrations, equation 15. The plot of the slopes S3 versus the inverse PDS concentrations (1/[PDS[) should be linear with a slope and an intercept equal to (k_0) and (k1/Ka), respectively, Fig. 2 (D). The parameters obtained allow us (i.e. by using value of 2.45 for the Ka of PDS) to calculate k0, k1 and k2 , values were found to be $6.49\times10^{-5}\pm5\times10^{-6}$ $M.s^{-1}$, 0.226±0.005 $M.s^{-1}$ and zero, respectively, at 298 K (It is important to highlight that the value of k_0 obtained from acid concentrations is equal to $6.20\times10^{-5}\pm 3\times10^{-6}$ $M.s^{-1}$ which is comparable to the value obtained according to equation 11, therefore the recorded value for k_0 is an average of the two values).

Results for the effect of ionic strength on the first rate constant (kobs.1) support our finding. The negligible effect of the ionic strength on the first rate constant ($k_{obs}1$) indicate that the rate determining step involve only the attack of the neutral form of the PDS ($H_2S_2O_8$) since the value of the k2 is zero.

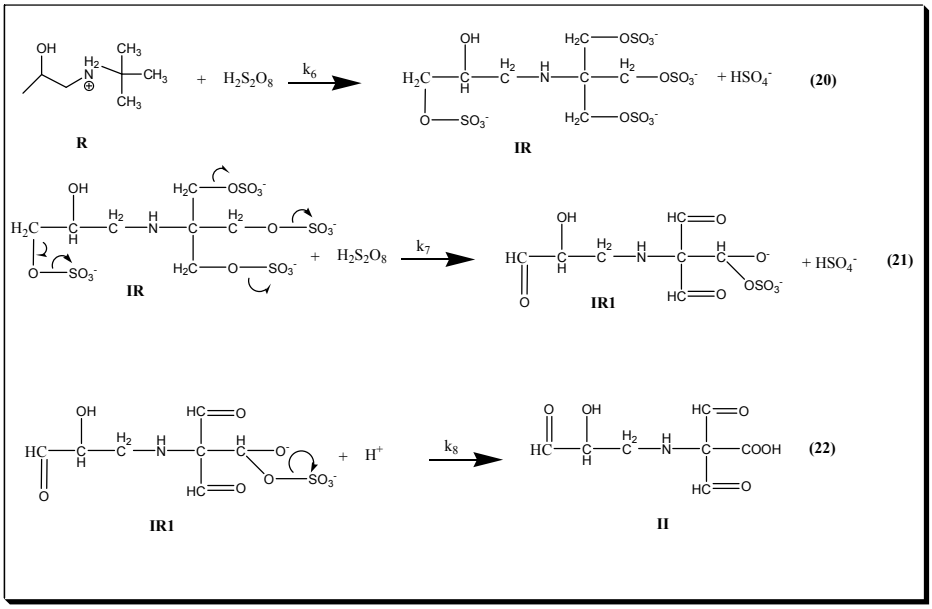


Scheme 3. Mechanism of the formation of 4-morpholino-1,2,5-thiadiazol-3-ol

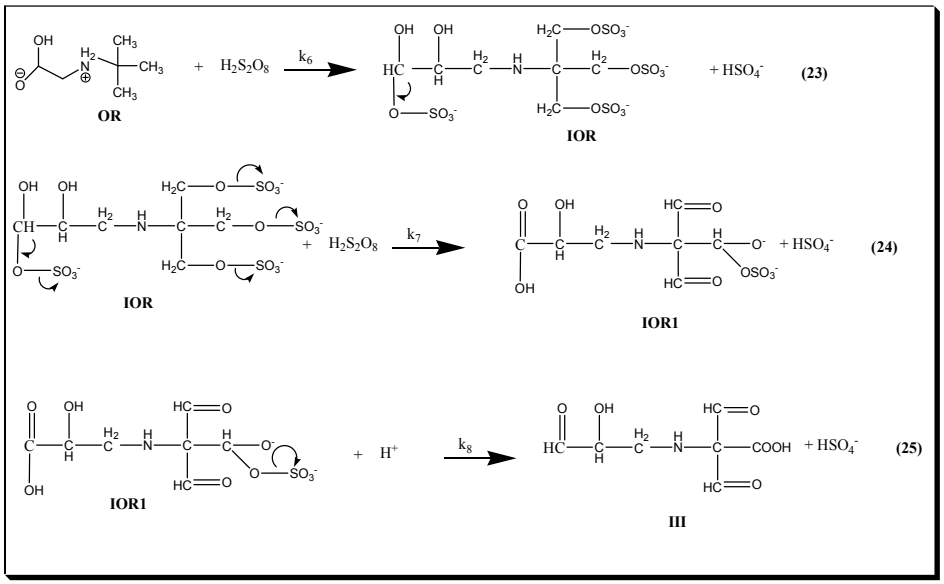
Once the intermediate is formed, (scheme 3) It is transformed into more stable species that can rearranged to produce the first product, 4-morpholino-1,2,5-thiadiazol-3-ol and two more aliphatic amide (R and OR in scheme 2), the rate law for the 4-morpholino-1,2,5-thiadiazol-3-ol formation is given by equation 19

$$k_{obs.2} = k_3 + k_4[H^+] \qquad (19)$$

Once the aliphatic amides (R and OR in scheme 2) are formed a second attack of PDS occurs leads to the formation of the reaction product **II** and **III** (2-(2-formyl-2-hydroxy ethyl amino)-2,2-di formyl acetic acid and 3-(carboxy diformyl methyl amino)-2-hydroxypropanoic acid) according to schemes 4 and 4a, respectively.



Scheme 4. Mechanism of the formation of 2-(2-formyl-2-hydroxy ethyl amino)-2,2-di formyl acetic acid



Scheme 4a. Mechanism of the formation of 2-(2-formyl-2-hydroxy ethyl amino)-2,2-di formyl acetic acid

On the other hand, the rate law for the formation of the other two products, II and III, scheme 4 and 4a) is described by equations 26-28

$$\frac{d[IIorIII]}{dt} = k_9[R/OR][H^+] \qquad (26)$$

Applying steady state approximation on the formation of IR or IOR

$$\frac{d[IR/IOR]}{dt} = zero = k_7[R/OR][H_2S_2O_8] - k_8[R/OR][H_2S_2O_8] \quad (27)$$

The rate law for the formation of products II and III is given by equation 28

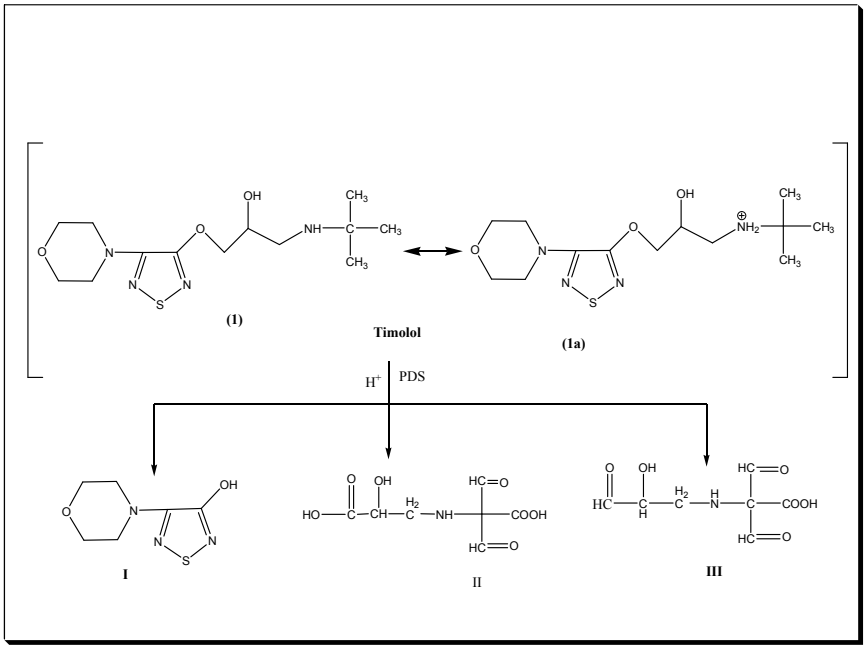
$$k_{obs.2}(II/III) = \frac{k_7[H^+]}{Ka + [H^+]}.[PDS]_0 \quad (28)$$

The observed rate constant, kobs.2, is represented by equations 29

$$k_{obs.2} = k_3 + k_4[H^+] + \frac{k_7[H^+]}{Ka + [H^+]}.[PDS]_0 \quad (29)$$

$$I2 = k_3 + k_4[H^+] \quad (30)$$

$$S4 = \frac{k_7[H^+]}{Ka + [H^+]} \quad (31)$$



Scheme 5. Oxidation of timolol in the presence of PDS

Again, taking into account the negligible effect of the ionic strength on the second rate constant, $k_{obs}.2$, we can conclude that the rate determining step involves a neutral molecule. Therefore, the second PDS attack involves attack of $H_2S_2O_8$ species, scheme 4 and 4a.

According to equation 29, the plot of the experimental data, Table 2, of $k_{obs}.2$ versus PDS concentrations at fixed acid concentration gives a straight line with intercept equal to I2 (equation 30) and slope S4 (equation 31), both of Intercept and slope are directly proportional to the acid concentrations. The value of K_{a2} for $H_2S_2O_8$ in equation 31 was previously estimated to 2.45 [11-14]. According to equation 30 a plot of the Intercept (I2) versus the acid concentration should be linear with intercept and slope equal to (k_3) and k_4, respectively; from which we can calculate the values of k3, and k4 to be (4.78±0.7)x10^{-6} M.s^{-1} and (1.558±0.09) x10^{-4} M.s^{-1} respectively, at 298 K.

According to equation 31 (assuming that under our experimental conditions $K_a > [H^+]$) a plot of the slope**s (S4)** versus the acid concentration should be linear with zero intercept at origin and slope equal to (k_7/ K_a); from which we can calculate the values of k7 to be 0.381±0.01 $M.s^{-1}$, at 298 K.

4. CONCLUSION

This paper summarize the results of the oxidation of one the β-blockers, Timolol in the presence of PDS in acidic solution of 40% methanol-water. According to scheme 5 above, the reaction consists of two steps; both of them involve electrophilic attack of PDS Species, where the reaction starts with electrophilic attack of monoanionic $H_2S_2O_8$ species of PDS to the protonated form of Timolol. Three products were obtained and assigned to the (**I**) 4-morpholino-1,2,5-thiadiazol-3-ol, (**II**) 3-(carboxydiformylmethylamino)-2-hydroxypropanoic acid and (**III**) 2-(2-formyl-2-hydroxyethylamino)-2,2-diformylacetic acid.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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