Asian Journal of Chemistry; Vol. 26, No. 24 (2014), 8488-8496

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.18220

Kinetics Study of the Chemical Oxidation of Pindolol by Peroxodiphosphate

RAED GHANEM

Department of Chemistry. University of Al al-Bayt, P.O. Box 130040, Mafraq 25113, Jordan

Corresponding author: Tel: +962 795150054; E-mail: readsa@yahoo.com, raedag@aabu.edu.jo

Received: 30 May 2014; *Accepted*: 14 August 2014; *Published online*: 1 December 2014; AJC-16388

In order to analyze the selectivity of the oxidizing agent on the chemical oxidation of pindolol in methanol/acidic media, the reaction of pindolol by peroxodiphosphate [PDP] in acidic media was studied. It was found that the reaction mechanism is comparable with other peroxides, however, reaction products are different depending on the acidity condition, at low acid concentration, oxipindolol is formed through acid catalyzed transformation of the indonlonic intermediate while at high acid concentration, the intermediate can react through competing parallel reaction to produce three products (oxipindolol, dioxipindolol and indigo form of pindolol) for the 1-PDP reaction. It is also found that, under present experimental conditions, neutral $H_4P_2O_8$ is the active species involved in the oxidation process. Comparison of kinetics behaviour of the 1-PDP reaction with other peroxides were also investigated and we conclude that $H_4P_2O_8$ is more reactive than $H_2S_2O_8$ while $HS_2O_8^-$ is better electrophilic compared to the $H_3P_2O_8^-$.

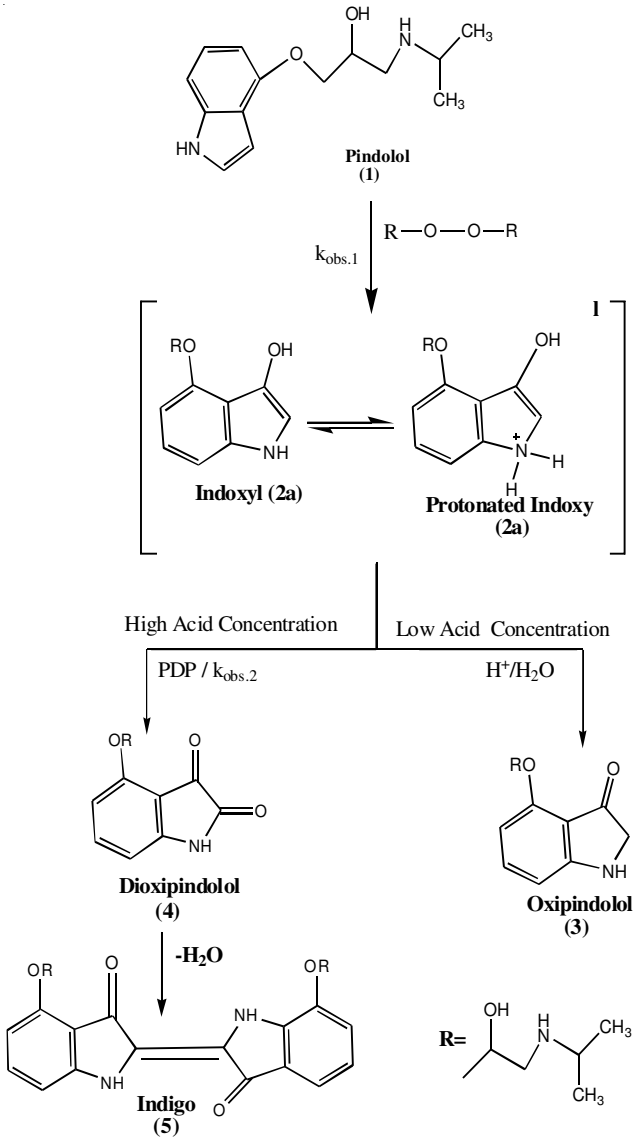
Keywords: Pindolol, Kinetic, Polar mechanism, Peroxodiphosphate.

INTRODUCTION

Pindolol (**1**) is a one of the non selective β-blocker drugs. Normally it prescribed as an efficient treatment for hypertension and angina pectoris. It is also used to enhance and/or accelerate selective serotonin specific reuptake inhibitors inducing antidepressant affects[1]. On the other hand pindolol is an example of indolic drug therefore it is very sensitive to light and oxidizing agents (*i.e.*, hydrogen peroxide, peroxodisulfate, ammonium persulfate, potassium ferricyanide and sodium periodate)[2]. It was reported that the indole ring in pindolole is readily oxidized by a variety of oxidants to produce indoxyl (**2**) species[3]. As indoxyl intermediate is formed it can goes under different reaction mechanism producing different products, depending on the acidity and oxidizing agents[3]. In low acid concentration, oxipindolol is formed while at high acid concentration dioxipindolol is formed; which could be dimerized to form indigo form of pindolol (**5**) **Scheme-I** [3-10].

Recently we studied the kinetics and mechanism of the oxidation of pindolol (**1**) to the corresponding oxi-product in methanol-water mixture in which peroxodisulfate ($H_2S_2O_8$), [PDS] (a known electrophillic regent used as oxidizing agent)[3,11-14]. It has been found that the 1-peroxodisulfate reaction proceeds only in acidic media. Thus as **Scheme-I** shows the reaction start by an electrophilic attack of the peroxodisulfate (PDS) at the indole ring in pindolol (**1**) to give the indolenine species (**2**), which are unstable intermediates[3]. Once indoleninic intermediate specie is formed, it can react according to two different mechanisms depending on the acidity and peroxodisulfate conentration. At low acidic conditions or in the absence of acid, the intermediate is transformed into the more stable indoxyl species, which could be rearranged to produce oxipindolol (**3**)[3]. At high acidic condition, a second electrophilic attack of peroxodisulfate against the indoxyl species occurred, the second attack of peroxodisulfate leads to the formation of dioxipindolol (DX) (**4**) form of pindolol. Dioxipindolol could be dimerized to form indigo (**5**) form of pindolol[3].

In order to analyze the generality of this reaction mechanism and study the role of the oxidizing agent and factors influencing the rate of the oxidation of the indolic β-blocker drug and then control the reaction products, we carried out a kinetic study of the oxidation of pindolol by peroxodiphosphate ($H_4P_2O_8$) which is known to be a good electrophilic reagent. Peroxodiphosphate (PDP) is isostructural and isoelectronic with peroxodisulfate, however, there is a fundamental differences between there reactivity; taking into account the pKa values of $H_4P_2O_8$ (*i.e.*, the first two pKa values are less than 1 and the second to around 5.2 and 7.7) we can conclude that pH can have a marked influence on peroxodiphosphate kinetics. Moreover, peroxodiphosphate shows an ability to act as chelate ligand to metal such as sodium and magnesium where peroxodisulfate does not do so. Finally, the behaviour of two peroxide was reported to be different, peroxodisulfate peroxide can act as outer sphere oxidant while peroxodiphosphate react by an inner sphere mechanism[11-14].



Scheme-I: Chemical reaction of pindolol

EXPERIMENTAL

Pindolol (**1**) [1-(1*H*-indol-4-yloxy)-3-(1-methylethylamino) propan-2-ol], > 98 % TLC, powder, $C_{14}H_{20}N_2O_2$, was purchased from Sigma-Aldrich and were used as received without further purification. Potassium peroxodiphosphate ($K_4P_2O_8$) (Sigma-Aldrich) was used as received. The stock solutions of all reagents were freshly prepared and stored on dark at 4 °C to prevent light induced and hydrolytic composition.

A stock solution of pindolol was prepared by dissolving appropriate amounts of pindolol in methanol (Sigma-Aldrich ≥ 99.9 %) and then several dilutions from the stock solution were made using distilled water, the final proportion of methanol in all mixture was kept constant to 40 % v/v methanol-water. Acidity of the solutions was adjusted by adding appropriate amounts of a commercial standardized solution of sulfuric acid (Merck, 95-97 %). In all experiments, the ionic strength, I, was kept constant at values of 6 mol L^{-1} by adding appropriate amount of sodium chloride (Sigma-Aldrich 99.0-100.5 %).

Spectrophotometric and kinetic measurements (*i.e.*, 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. In all reaction the temperature was controlled within ± 0.1 °C). Data were analyzed using origin software. The cuvette used has a path length of 1 cm.

Kinetic data analysis: Kinetic measurements were carried out under pseudo-first order reaction, the reactions were followed by monitoring the changes of absorbance at about 264 nm; the absorption corresponds to the maximum wavelength of pindolol (**1**), the rate constants were obtained by non-linear square fitting of the absorbance-time data to eqn. 1

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

where A_t is the absorbance at time *t* (in second), A_0 and A_∞ are initial and final absorbance, respectively and k_{obs} is the observed rate constant, A 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 %.

The possibility that hydrolysis of peroxodiphosphate could compete with the oxidation of pindolol, has been tested by independent measurements of the rate of the hydrolytic reaction under the same acidity conditions used in the oxidation reaction. These experiments demonstrated that hydrolytic reactions were slower than the oxidation reactions. Interference from the reaction products of this hydrolysis was not observed. Moreover, neither the presence of radical promoters nor radical traps affected the oxidation rates, which excludes the involvement of radical species in the reaction.

The influence of temperature on the rate constant of the release process was also studied. The obtained rate constants (k_{obs}) were fitted to Eyring equation., eqn. 2:

$$\ln\left(\frac{k_{obs}}{T}\right) = -\frac{\Delta H^*}{R}\cdot\frac{1}{T} + \ln\left(\frac{k_B}{h}\right) + \frac{\Delta S^*}{R} \quad (2)$$

where k_{obs} is observed rate constant of the release process at absolute temperature (T). R, k_B and h are gas constant, Boltzmann constant and Planck's constant, respectively, ΔH and ΔS are enthalpy and entropy of activation, respectively.

RESULTS AND DISCUSSION

Fig. 1 shows the spectral changes of typical reaction mixtures of pindolol (**1**) and peroxodiphosphate in the presence and absence of acidic media in 40 % methanol-water as a function of time. As Fig. 1a shows, two clear isosbestic points were appeared at 250 and 290 nm. These two isosbestic points clearly represents two distinguish steps. In first step, the gradual disappearance of the absorbance at the wavelength of maximum absorption of pindolol at 264 nm leads to a final spectrum corresponding to well-known absorption spectra of the protonated indoleninc chromophore (IP/IPH)[10-12]. As the indoleninic species were formed, they were instantaneously transformed into the more stable indoxyl species (**2**).

At conditions of low (or no) sulfuric acid concentration, chromatographic analysis of the reaction product (*i.e.*, TLC

and HPLC) confirm that there is a sole product which was assigned to be oxipindolol (**3**). The mass spectrum of the pure sample of the (**3**) MS (FAB): *m/z* (100 %): 264 confirmed this product is oxipindolol[10-14].

On the other hand, in the presence of sulfuric acid, (Fig. 1b), the gradual disappearance of the absorbance at the wave-length of the maximum absorption of pindolol at 260 nm is accompanied by the concomitance of new bands at around 400 and 570 nm. At the end of the reaction, three products were obtained, the reaction products were analyzed using TLC and HPLC apparatus with a nova-pack C18 (150 × 3.9 mm^2), results confirmed the formation of three distinguish products: (a) oxipindolol (**3**) (*i.e.*, MS (FAB): *m/z* (100 %): 264), (b), a blue product, ($\lambda_{max} \approx 570$ nm) with mass spectra of typical indigo form of pindolol (**5**). (MS(FAB): *m/z* (100 %): 524)[15] and (c) dioxipindolol (**4**) [with mass spectra of 278 (MS (FAB)]: *m/z* (100 %): 278)[3,15,16].

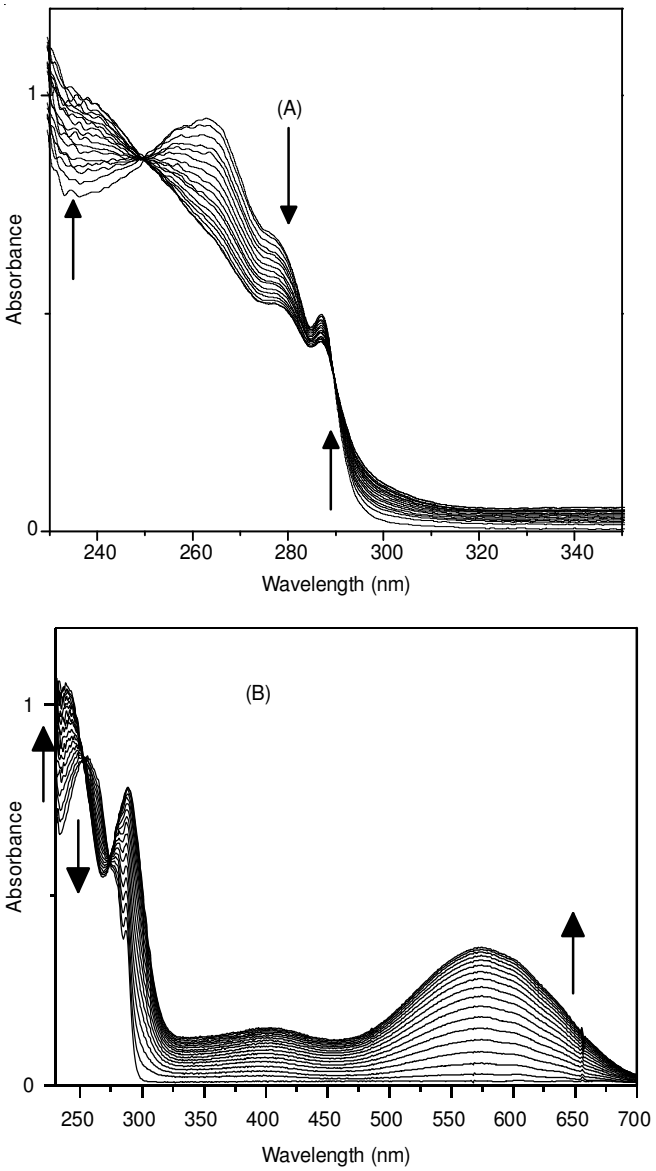


Fig. 1. Changes in UV-visible spectra for the reaction mixture: [Pindolol] =1.2 × 10^{-4} M. [PDP] = 6 × 10^{-3} M, at 25 °C ± 0.1, I = 6 mol L^{-1} and 40 % methanol-water at 10 min intervals in (A) 0.2 M H_2SO_4 and (B) in 1 M H_2SO_4

In fact these spectral changes and reaction product are comparable to these observed previously for the reaction between pindolol and peroxodisulfate[3], except that the oxipindolol was also detected under condition of high concentration of sulfuric acid, for all of the above it is concluded that pindolol-peroxodiphosphate reaction is comparable to the 1-peroxodisulfate. Thus we are going to analyze the kinetics of pindolol with peroxodiphosphate and compare the obtained results with those obtained previously with peroxodisulfate.

Kinetic results: The reaction steps under pseudo-first-order conditions (*i.e.*, with a large excess of peroxodiphosphate) were followed by monitoring the changes of absorbance at 264, 290 and 575 nm. These wavelengths correspond to the absorption maxima of the pindolol (**1**), indoxyl pindolol (**2**) and indigo (**5**) products, respectively.

Values of the pseudo-first-order rate constant $k_{obs.1}$ [*i.e.*, the electrophilic attack of the peroxodiphosphate at the indole ring in pindolol (**1**) to give the indolenine species (**2**)] were measured at the maximum absorption wavelength of pindolol (**1**) at 264 nm and values of the second rate constant $k_{obs.2}$, measured above 290 nm (*i.e.*, the formation of the final products according to acidity conditions)

The values of the experimental pseudo-first order rate constants, $k_{obs.1}$ and $k_{obs.2}$ for the first and second step, respectively, of 1-PDP reaction at different peroxodiphosphate and sulfuric acid concentration are tabulated in (Tables 1 and 2) under condition of low and high acid concentration, respectively.

Under condition of low sulfuric acid [0.1-0.4 M]; it was found that, the rate constant of the first step, $k_{obs.1}$ increase as peroxodiphosphate concentration increase. Plots of rate constants against peroxodiphosphate concentration are linear with intercept equal to zero. Moreover, the rate constants, $k_{obs.1}$ at constant concentration of peroxodiphosphate found to increase with sulfuric acid concentration, plots of $k_{obs.1}$ against acid concentration is linear with slopes and intercepts represented in Table-1. On the other hand, the rate constant for the second step $k_{obs.2}$ was found to be peroxodiphosphate independent, however, acid fund to have significant effect on the second rate constant (*i.e.*, Table-1 values of $k_{obs.2}$ for [PDP] = 6 × 10^{-3} M).

The influence of temperature on the rate constant $k_{obs.1}$ and $k_{obs.2}$ also studied, the experimental data fitted according to Eyring equation (eqn. 2), from which the activation parameters were determined to be $\Delta H^{\#,1}$ = 21.4 ± 0.9, $\Delta H^{\#,2}$ = 12.3 ± 0.6 kJ/mol and $\Delta S^{\#,1}$ = -244.3 ± 0.7, $\Delta S^{\#,2}$ = -270.4 ± 0.5 J/mol k for the first and second step, respectively. The low positive value of enthalpy and negative value of entropy indicates the polar values reaction mechanism[19].

The variation of ionic strength, using NaCl as inert salt was found to have negligible effect on both rate constants $k_{obs.1}$ and $k_{obs.2}$. Therefore the rate determining step of these reaction would involve at least one neutral molecules, this information is very important taken into account that both peroxodiphosphate and pindolol could exist with different charges under our experimental condition. At this point, it is important to compare the previous data of the reaction of pindolol with peroxodisulfate under these condition of low concentration of sulfuric acid, the major difference between 1-peroxodiphosphate and 1-peroxodisulfate is the salt effect, in 1-peroxodisulfate

TABLE-1
PSEUDO-FIRST ORDER RATE CONSTANTS $k_{obs.1}$ (s^{-1}) AND $k_{obs.2}$ (s^{-1}) FOR THE OXIDATION OF PINDOLOL BY PEROXO-DIPHOSPHATE AT 25 °C ± 0.1, I = 6 mol L^{-1} AND 40 % METHANOL-WATER. [PINDOLOL] = 1.5×10^{-4} M. UNDER LOW ACIDIC CONDITION (0.1-0.4 M)

	$k_{obs.1}$ (10^{-4} s^{-1})						
[PDP] (10^{-3} M)	$[H_2SO_4]$ M						
	0.1	0.2	0.3 $k^4_{obs.2}$ (10^{-4})	0.4	Intercept[2]	Slope[2]	R
3.0	0.311 ± 0.005	0.621 ± 0.01	0.91± 0.03 (2.39 ± 0.05)	1.11 ± 0.07	0.0022 ± 0.001	0.0895 ± 0.009	0.987
6.0	0.963 ± 0.08	1.242 ± 0.06	1.61± 0.04 (2.41 ± 0.05)	2.29 ± 0.01	0.0073 ± 0.002	0.0725 ± 0.008	0.935
$k^3_{obs.2}$ (10^{-4})	0.50 ± 0.08	2.23 ± 0.06	2.42± 0.04 (2.31 ± 0.6)	2.64 ± 0.07	(1.82 ± 0.03) 10^{-4}	(2.05 ± 0.08) 10^{-4}	0.996
9.0	1.52 ± 0.07	1.963 ± 0.04	2.463 ± 0.06 (2.41 ± 0.07)	3.17 ± 0.05	0.01018 ± 0.001	0.061 ± 0.002	0.982
12.0	2.17 ± 0.02	2.92 ± 0.07	3.34 ± 0.05 (2.29 ± 0.1)	4.42 ± 0.05	0.0118 ± 0.002	0.0626 ± 0.007	0.956
15.0	2.83 ± 0.03	3.52 ± 0.05	4.28 ± 0.09 (2.32 ± 0.04)	5.58. ± 0.01	0.012 ± 0.002	0.062 ± 0.006	0.982
20.0	3.63 ± 0.06	4.29 ± 0.09	5.82 ± 0.03 (2.42 ± 0.01)	7.04. ± 0.06	0.0113 ± 0.002	0.0588 ± 0.006	0.969
25	4.59 ± 0.02	5.275 ± 0.04	7.16 ± 0.07 (2.36 ± 0.09)	8.85 ± 0.02	0.0122 ± 0.002	0.0587 ± 0.007	0.952
Slope[1]	0.0194 ± 3.9×10^{-4}	0.0214 ± 1×10^{-3}	0.029 ± 4.4×10^{-4}	0.035 ± 6.3×10^{-4}			
R	0.9921	0.979	0.9986	0.998			

[1]Slope and intercepts were obtained for the plot of $k_{obs.1}$ versus PDP concentrations
[2]Slope and intercepts were obtained for the plot of ($k_{obs.1}$/[PDP] *versus* acid concentrations
[3]Pseudo-second order rate constants $k_{obs.2}$ (s^{-1}) at different acid concentration, [PDP] = 6×10^{-3} M
[4]Pseudo-second order rate constants $k_{obs.2}$ (s^{-1}) at different acid PDP concentrations $[H_2SO_4]$ = 0.3 M

TABLE-2
PSEUDO-FIRST ORDER RATE CONSTANTS $k_{obs.1}$ (s^{-1}) AND $k_{obs.2}$ (s^{-1}) FOR THE OXIDATION OF PINDOLOL BY PEROXO-DIPHOSPHATE IN 40 % METHANOL-WATER AT 25 °C ± 0.1, I = 6 mol L^{-1}AND. [PINDOLOL] = 1.5×10^{-4} M. UNDER HIGH ACIDIC CONDITIONS (0.7-2.0 M)

$[H_2SO_4]$/M	($k_{obs.1}$ or $k_{obs.2}$) (10^{-4}/s^{-1})									
[PDP] M	0.7		1.0		1.2		1.5		2.0	
	$k_{obs.1}$	$k_{obs.2}$	$k_{obs.1}$	$k_{obs.2}$	$k_{obs.1}$	$k_{obs.2}$	$k_{obs.1}$	$k_{obs.2}$	$k_{obs.1}$	$k_{obs.2}$
3.0×10^{-3} M	2.31 ± 0.02	2.45 ± 0.01	2.92 ± 0.05	4.19 ± 0.04	3.32 ± 0.05	4.39 ± 0.08	4.29 ± 0.05	4.95 ± 0.05	4.91 ± 0.04	5.46 ± 0.04
6.0×10^{-3} M	4.21 ± 0.01	4.87 ± 0.06	4.87 ± 0.03	5.99 ± 0.03	5.42 ± 0.02	6.99 ± 0.06	6.71 ± 0.04	8.35 ± 0.02	7.53 ± 0.03	9.95 ± 0.02
9.0×10^{-3} M	6.52 ± 0.07	6.93 ± 0.03	7.33 ± 0.05	8.63 ± 0.06	8.64 ± 0.07	10.26 ± 0.08	9.812 ± 0.06	11.36 ± 0.04	11.01 ± 0.01	13.45 ± 0.08
12.0×10^{-3} M	9.32 ± 0.02	10.14 ± 0.03	10.10 ± 0.01	12.02 ± 0.04	11.81 ± 0.01	13.57 ± 0.09	13.31 ± 0.02	15.49 ± 0.08	14.32 ± 0.03	17.23 ± 0.07
15.0×10^{-3} M	12.45 ± 0.05	12.45 ± 0.05	13.89 ± 0.08	14.21 ± 0.06	14.92 ± 0.06	16.52 ± 0.06	16.55 ± 0.07	18.25 ± 0.05	18.02 ± 0.04	20.45 ± 0.06
20.0×10^{-3} M	16.32 ± 0.04	17.14 ± 0.08	17.21 ± 0.05	18.24 ± 0.05	18.93 ± 0.08	20.21 ± 0.04	20.71 ± 0.08	23.64 ± 0.09	23.22 ± 0.05	26.43 ± 0.07
25.0×10^{-3} M	19.15 ± 0.02	20.92 ± 0.09	20.20 ± 0.03	21.91 ± 0.03	22.31 ± 0.07	24.41 ± 0.06	24.92 ± 0.06	27.32 ± 0.07	28.34 ± 0.01	31.31 ± 0.09

reaction; salt has negligible effects only on the first step and it strongly affect second step (*i.e.*, $k_{obs.2}$ and product yield formation), however, it has negligible effect on 1-peroxodiphosphate reaction. The difference in the two systems could be attributed to the different protonation of peroxodiphosphate and peroxodisulfate species involved in the reaction[13].

In this acidity range (0.0-0.4 M) peroxodiphosphate could exist as $H_4P_2O_8$ and $H_3P_2O_8^-$ species[17-20]. Therefore assuming that both peroxodiphosphate species contribute to the rate of the reaction, the mechanism for the first step of 1-peroxodiphosphate can be expressed as **Scheme-II.**

Using the above mechanism, **Scheme-II**, the rate law in eqn. 8 could be obtained for the first step of the oxidation of pindolol, from which the observed rate constant $k_{obs.1}$, eqn. 9 and eqn. 10, could be derived:

$$R = -\frac{d[P]}{dt} = \left(k_1[H_4P_2O_8] + k_2[H_3P_2O_8^-]\right)[P] \quad (8)$$

At constant pindolol concentration

$$k_{obs.1} = k_1[H_4P_2O_8] + k_2[H_3P_2O_8^-] \quad (9)$$

Taking into acount that equation 9a, 9b, 9c, 9d, 9e:

$$[PDP]_0 = [H_4P_2O_8] + [H_3P_2O_8^-] \quad (9a)$$

$$K_a = \frac{[H_3P_2O_8^-][H^+]}{[H_4P_2O_8]} \quad (9b)$$

$$[PDP]_0 = \left\{\frac{[H^+] + K_a}{[H^+]}\right\}[H_4P_2O_8] \quad (9c)$$

$$[H_4P_2O_8] = \left(\frac{[H^+][PDP]_0}{[H^+] + K_a}\right) \quad (9d)$$

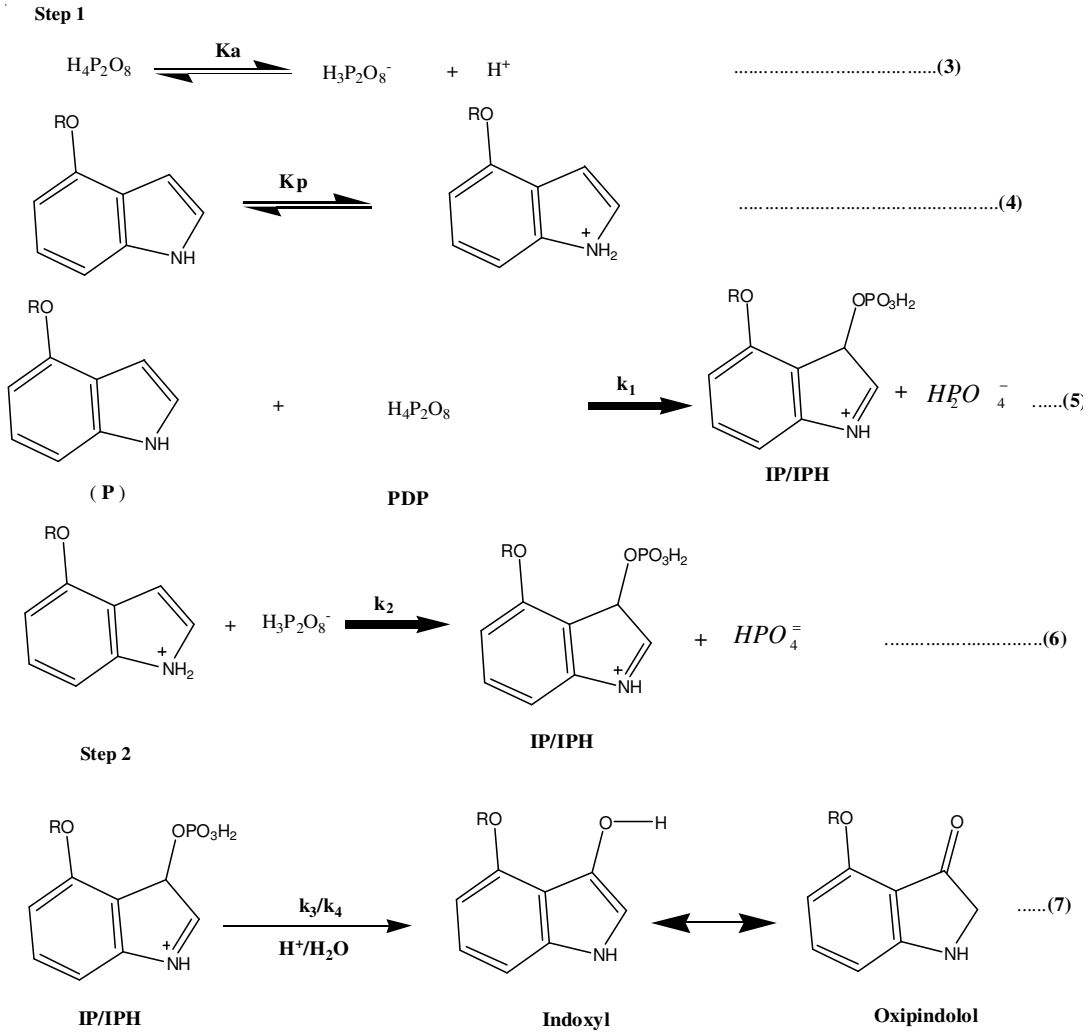
$$[H_3P_2O_8^-] = \left(\frac{K_a[PDP]_0}{[H^+] + K_a}\right) \quad (9e)$$

and thus

$$k_{obs.1} = \left(\frac{k_1[H^+] + k_2.K_a}{[H^+] + K_a}\right)[PDP]_0 \quad (10)$$

$$k'_{obs.1} = \frac{k_1}{K_a}[H^+] + k_2 \quad (10')$$

According to eqn. 10, $k_{obs.1}$ is directly proportional to the peroxodiphosphate concentration, plot of $k_{obs.1}$ against [PDP]



Scheme-II: Mechanism of 1-PDP under low acidic condition

give straight line with intercept at origin equal to zero and slopes equal $\left(k_i\left[H^+\right]+k_2.K_a\right)/\left(\left[H^+\right]+K_a\right)$ to which are found to be acid dependent.

On the other hand, acid dependent of the first rate constant $k_{obs.1}$ can also be explained using eqn. 10: at constant peroxodiphosphate, the observed rate constant $k_{obs.1}(k_{obs.1} = k_{obs.1})$/[PDP] is directly proportional to acid concentration, assuming that under our experimental condition that $K_a >> [H^+]$, eqn. 10 could rearranged into eqn. 10′, the parameters obtained (*i.e.*, from eqn. 10′) allows to calculate the mean values of k_2 and the ratio of k_1/K_a as 0.0088 ± 0.002 mol L^{-1} s^{-1} and 0.0673 ± 0.005 at 298 K.

Once indoleninic intermediate species are formed, eqn. 5 and eqn. 6, it reacts according to different pathways depending on the acidity and peroxodiphosphate concentration. Under condition of low or in the absence of sulfuric acid, intermediate is transformed into more stable indoxyl species that can produce oxipindolol, **Scheme-II**, from which the rate law for the second rate constant, $k_{obs.2}$, is shown in eqn. 10. As it excepted from eqn. 10, linear dependence of $k_{obs.2}$ with acid concentration with slopes and intercept allows to calculate the values of $k_3 = (2.05 \pm 0082) \times 10^{-4}$ mol L^{-1} $s^{-1}$and $k_4 = (1.82 \pm 0.03) \times 10^{-4}$ mol L^{-1} s^{-1}, respectively. Under these acidity condition, comparison of the rat constants obtained for the 1-peroxodiphosphate reaction compared to the 1-peroxodisulfate reaction reveals that: the corresponding value for k_1 (*i.e.*, k_1 calculated later to be 0.16 mol L^{-1} s^{-1}) for the 1-peroxodiphosphate reaction is slightly larger than the one for 1-peroxodisulfate system[10], however, the corresponding k_2 (k_2 = 0.0128 ± 0.003 mol L^{-1} s^{-1}) value for 1-PDP is smaller than the one previously obtained for 1-peroxodisulfate (*i.e.*, k_2 for 1-peroxodisulfate reaction was 0.0377 mol L^{-1} s^{-1}), these data indicate that peroxodiphosphate is better electrophile than peroxodisulfate. Moreover, recent results for the second step allowed us to obtain the values of k_3 and k_4, acid catalyzed and uncatalyzed transformation, eqn. 11 from which we conclude that: acid catalyzed transformation of the indonlonic intermediate is favored than the hydrolysis pathway.

$$k_{obs.2} = k_3[H^+] + k_4 \quad (11)$$

Under condition of relatively high sulfuric acid concentration [0.7-2.0 M]: A similar behaviour was observed for the first step in condition of low sulfuric acid concentration: the first rate constant, $k_{obs.1}$, was found to be directly related to both peroxodiphosphate and acid concentration. Moreover variation of ionic strength using inert salt was found to have negligible effect on the rate constant, $k_{obs.1}$. In general, under these conditions values of the observed rate constants $k_{obs.1}$ are higher than the one under low acidic condition which could

be attributed to acid concentration. According to eqn. 10, $k_{obs.1}$, exhibits, as observed, (Fig. 2), a linear dependence on peroxodiphosphate concentration with zero intercept at origin and the slopes (a_1) found to be acid dependent, at sufficiently high acid concentration, assuming $k_1[H^+] >> k_2K_a$ and, therefore, the double reciprocal plot of slopes (a_1) *versus* $[H^+]$ exhibit linear dependence as (Fig. 2) shows, this linearity is reached for $[H^+] > 0.7$. From the slope and intercept of this linear plot $k_1 = 0.16 \pm 0.008$ mol L^{-1} s^{-1} and $K_a = 6.093 \pm 0.5$ values can be calculated (the value for k_2 is previously calculated to equal 0.0128 ± 0.003). The calculated K_a value for peroxodiphosphate is reasonable compared to the value of 5.6 obtained earlier by Balon *et al.*[13] for the $H_4P_2O_8$.

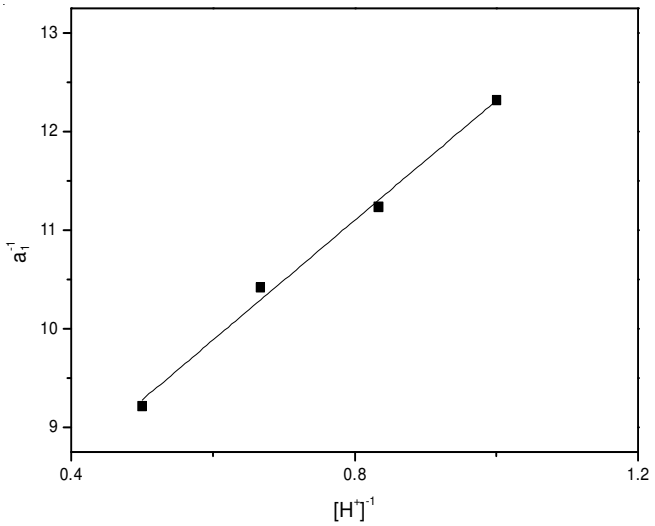


Fig. 2. Dependence of the reciprocal of the slopes a1 *versus* the reciprocal acid concentration for the first step of 1-PDP reaction under condition of high sulfuric acid

The rate constants for the second step, $k_{obs.2}$, were found to be dependent on both peroxodiphosphate and acid concentrations, however, variation of ionic strength, using NaCl as inert salt was also found to have a negligible effect on both rate constant under these acidity condition, which implies that the rate determining step involve at least one neutral species. Analysis of the reaction product, confirm the formation of three products: dioxipindolol (DX) which dimerizes to give the indigo form of pindolol and oxipindolol is also detected.

According to the obtained results, under experimental condition of high acid concentration, we can conclude that: once the intermediate is formed it reacts through competing parallel reactions in which the three reaction products obtained. As shown in **Scheme-III**, the intermediate (indoxyl) can react in two parallel reactions: (1) the first one in which a second peroxodiphosphate attack occurs and leads to the formation of dioxipindolol or (2) the second one, the intermediate could be transformed into oxipindolol (OX).

For the first pathway (*i.e.*, formation of dioxipindolol) and taking into account the influence of ionic strength under these experimental condition, we can assume that the second peroxodiphosphate attack involve species. The mechanisms for dioxipindolol and indogo formation at high acidic condition are described by eqn.[12-16].

Path (1)

$$\text{indoxyl} + H_4P_2O_8 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \text{indoxyl}^* + H_3PO_4 \quad (12)$$

$$\text{indoxyl}^* + H^+ \xrightarrow{k_6} DX \quad (13)$$

Dimerizaion

$$2DX \xrightarrow{K_D} \text{Indigo} \quad (14)$$

$$R = k_6[\text{indoxyl}^*][H^+] \quad (15)$$

$$k_{obs.2} = \frac{k_5 k_6 [H^+]}{k_{-5}[H_3PO_4] + k_6[H^+]} . [H_4P_2O_8] \quad (16)$$

path (2)

$$IP/IPH \xrightarrow{k_7} OX \quad (17)$$

$$IP/IPH + H^+ \xrightarrow{k_8} OX \quad (18)$$

$$k_{obs.2} = k_7 + k_8[H^+] \quad (19)$$

At this point it is important to summarize the main differences between 1-PDP and 1-PDP (I) in 1-PDP reaction, salt have a negligible effect on both rate constant ($k_{obs.1}$ and $k_{obs.2}$) under these acidity condition, while a positive effect of the ionic strength on the second rate constant was observed for the 1-PDP. (II) Once the intermediate is formed it reacts through competing parallel reactions in which the three reaction products were obtained for the 1-PDP reaction while for I-PDP reaction, dioxipindolol is the sole product, from which the indigo form of dioxipindolol is formed. (3) Finally, the second step of the reaction mechanism of dioxipindolol formation from 1-PDP involves the attack of one species ($H_4P_2O_8$ species) while for the 1-PDP, the second peroxodisulfate attack involves two negative charges species ($HS_2O_8^-$ and $S_2O_8^{2-}$).

By applying steady state approximation on the formation of the intermediate indoxyl*, the rate constant for the dioxipindolol/indigo production could be described by eqn. 16. On the other hand, the observed rate constant for the second path is represented by eqn. 19, taking into accounts eqn. 16 and eqn. 19, the overall observed rate constant $k_{obs.2}$ is shown in eqn. 20:

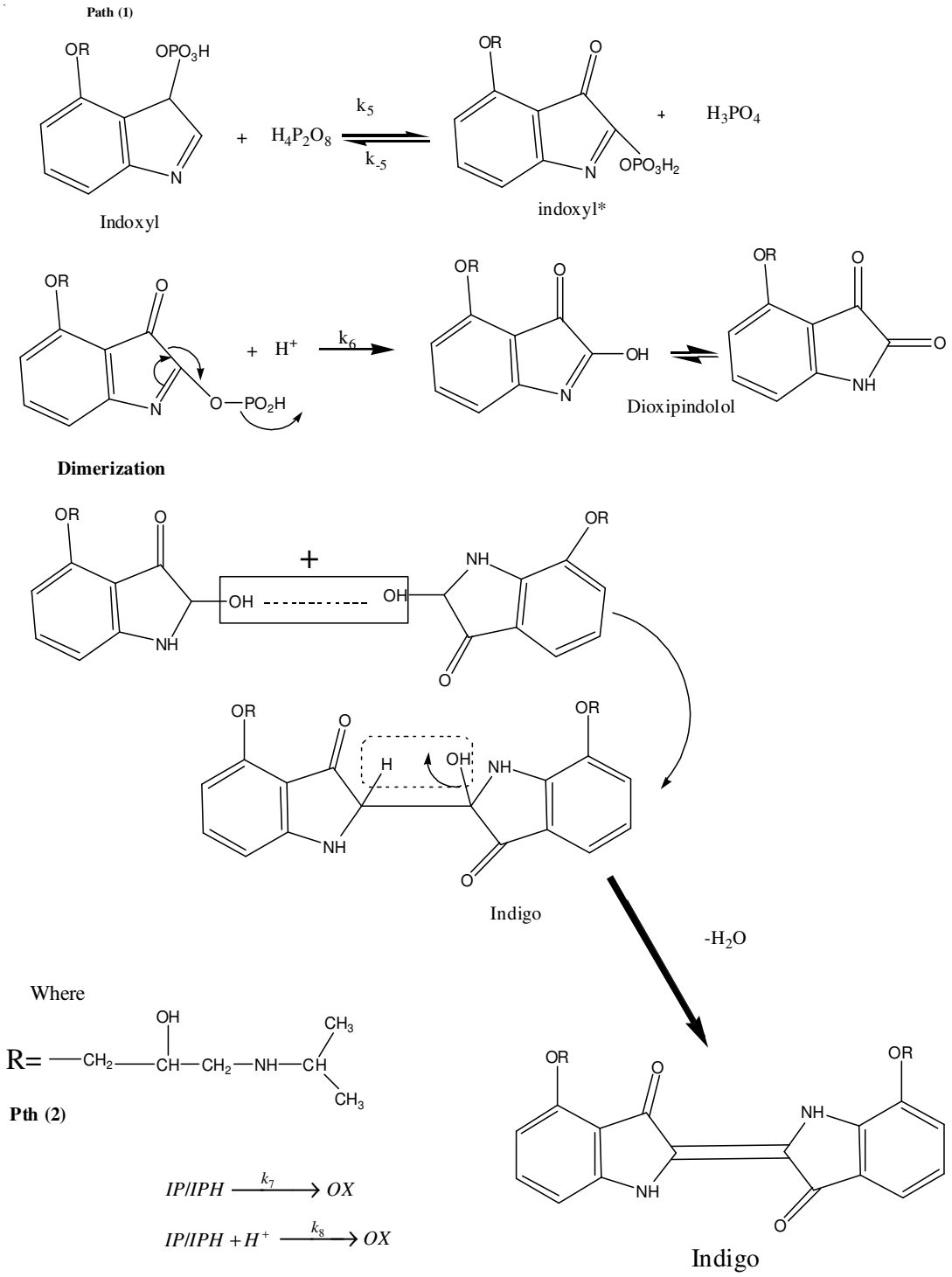
$$k_{obs.2} = k_7 + k_8[H^+] + \frac{k_5 k_6 [H^+]}{k_{-5}[H_3PO_4] + k_6[H^+]} . [H_4P_2O_8] \quad (20)$$

According to eqn. 20, at fixed $[H^+]$, as observed, the plot of the experimental rate constant $k_{obs.2}$ *versus* peroxodiphosphate concentration should be linear with intercept (b_2) and slope (a_2), represented in eqns. 21 and 22, respectively.

$$b_2 = k_7 + k_8[H^+] \quad (21)$$

$$a_2 = \frac{k_5 k_6 [H^+]}{k_{-5}[H_3PO_4] + k_6[H^+]} \quad (22)$$

As it shown in eqn. 21 and eqn. 22, both the slopes and intercepts are acid dependent. Both figures, (Fig. 3a) and (Fig. 3b) show that the plot of the intercept, b_2 *versus* $[H^+]$ is indeed linear with intercept and slopes equal to $(5.83 \pm 1) \times 10^{-5}$ mol L^{-1} s^{-1} and $(1.09 \pm 0.1) \times 10^{-4}$ mol L^{-1} s^{-1}, respectively, which allow us to calculate the values of k_7 and k_8 equals to $(5.83 \pm 1) \times 10^{-5}$ mol L^{-1} s^{-1} and $(1.09 \pm 0.1) \times 10^{-4}$ mol L^{-1} s^{-1},



Scheme-III: Mechanism of 1-PDP under high acidic condition

respectively. It is worth to mention that this step (*i.e.*, path 2 eqns. 17 and 18, transformation of indoxyl into oxipindolol) is the same step that take place under condition of low acidic conditions with k_3 and k_4 rate constants, eqn. 11, in general, values of rate constants of the of acid catalyzed transformation of indoxyl species k_3 and k_8 are higher than values of rate constants of the hydrolysis transformation of indoxyl into oxipindolol, k_4 and k_7. Moreover, rate constants of oxipindolol formation under low acidic conditions, k_3 and k_4 are two to three time larger than rate constants of the oxipindolol formation under high acidic condition which could be attributed the fact that oxipindolol is the sole product under low acidic condition.

On the other hand, the double reciprocal plot of slopes (a_2) *versus* [H^+] exhibit linear dependence as (Fig. 3b) shows, from the slope and intercept of this linear plot, $k_5 = 0.2 \pm 0.004$ mol L^{-1} s^{-1} and (k_{-5} [H_3PO_4])/(k_5 k_6) equal to 7.06 ± 0.15 values can be calculated (Table-3).

Under these condition of high acidic concentration, the influence of temperature on both rate constants, $k_{obs.1}$ and $k_{obs.2}$

TABLE-3
VALUES OF THE SLOPES, S1, AND S2 OF $k_{obs.1}$ AND $_{kobs.2}$ *VS* PDP CONCENTRATION AT DIFFERENT PROTON CONCENTRATION. UNDER HIGH ACIDIC CONDITIONS (0.7-2.0 M)

$[H_2SO_4]$ M	S1[a] (dm^3 mol^{-1} s^{-1})	S2 (dm^3 mol^{-1} s^{-1})	b_2 (s^{-1})
0.7	0.0781	0.0855	0.00
1.0	0.0812	0.082	1.61×10^{-4}
1.2	0.089	0.0920	1.94×10^{-4}
1.5	0.096	0.104	2.28×10^{-4}
2	0.1085	0.117	2.73×10^{-4}

[a]Intercept at origin b1 are independent of $[H^+]$ and equal to zero

TABLE-4
PSEUDO-FIRST ORDER RATE CONSTANT $k_{obs.1}$ (s^{-1}) AND $k_{obs.2}$ (s^{-1}) FOR THE OXIDATION OF PINDOLOL BY PDP IN 40 % METHANOL-WATER AT DIFFERENT TEMPERATURES AND UNDER DIFFERENT ACIDIC CONDITIONS. [PINDOLOL] = 1.5×10^{-4} M, [PDP] = 6×10^{-3} M

Temperature (°C)	25 ± 0.1 °C	30 ± 0.1 °C	35 ± 0.1 °C	40 ± 0.1 °C
$[H_2SO_4]$ = 0.2 M				
$k_{obs.1}$ (10^{-4})	1.88 ± 0.06	2.23 ± 0.03	2.55 ± 0.03	3.01 ± 0.05
$k_{obs.2}$ (10^{-4})	3.23 ± 0.06	3.53 ± 0.08	3.92 ± 0.01	4.29 ± 0.03
$[H_2SO_4]$ = 1.2 M				
$k_{obs.1}$ (10^{-4})	5.42 ± 0.02	5.91 ± 0.04	6.49 ± 0.09	7.22 ± 0.02
$k_{obs.2}$ (10^{-4})	6.99 ± 0.06	8.23 ± 0.07	9.41 ± 0.08	10.86 ± 0.05

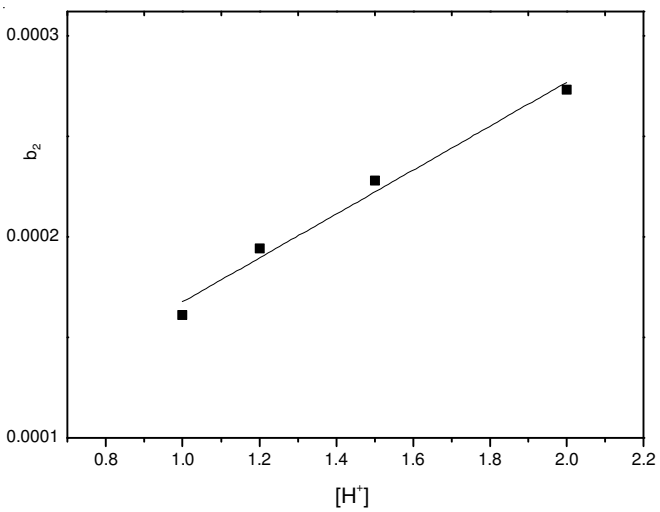


Fig. 3. (a) Plot of the intercept (b_2) *versus* the acid concentration $[H^+]$

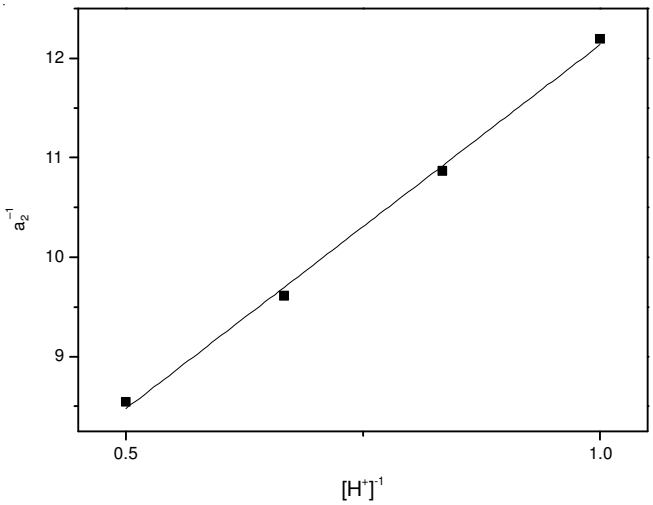


Fig. 3. (b) Dependence of the reciprocal of the slopes a_2 *versus* the reciprocal acid concentration. For the second step of 1-PDP reaction under condition of high sulfuric acid

also studied (Table-4) and the activation parameters were determined to be $\Delta H^{\#,1}$ = 13.21 ± 0.01, $\Delta H^{\#,2}$ = 20.1 ± 0.3 kJ/mol and $\Delta S^{\#,1}$ = -263.3 ± 0.3, $\Delta S^{\#,2}$ = -237.9 ± 0.4 J/mol k for the first and second step, respectively. Compared to the previously obtained results for the 1-peroxodisulfate reaction, the enthalpy is lowered than the one obtained for pindolol with peroxodisulfate, on the other hand, the entropy changes are more negative compared to the reaction with peroxodisulfate (*i.e.*, $\Delta S^{\#,1}$ = -208 , $\Delta S^{\#,2}$ = -83 J/mol k) which reflect the high disorder of the transition state compared to ground state.

Conclusion

From current and previous studies it is concluded that the reaction of **1** by perxodiphosphate and peroxdiosulfate has a comparable mechanism. However, reaction product is slightly different depend on the acidity condition, while dioxipindolol (DX) and its indogo form are the only product obtained for the reaction of 1-PDS under relatively high acidic condition, three products (oxipindolol (OX) dioxipindolol (DX) and its indogo form) were observed for the 1-PDP reaction.

From a kinetic point of view, the major difference could be summarized as follow: under our experimental conditions of low sulfuric acid concentration, (1) Variation of salt has a negligible effect on both reaction steps for 1-PDP reaction while it is strongly affect the second step of 1-PDS reaction which reflect type of the reactant species involved in the reaction, **Scheme-II**. (2) Moreover, from the rate constant k_2 and k_3, the electrophilic attack of the neutral $H_4P_2O_8$ towards the neutral form of pindolol is faster than the one in the 1-PDS reaction. (3) Finally, for the second step of 1-PDP reaction acid catalyzed transformation of the indolonic intermediate seems to be favored than the hydrolysis pathway for the OX formation.

On the other hand, under our experimental conditions of high sulfuric acid concentration, (1) variation of salt has a negligible effect on both reaction steps for 1-PDP reaction

while a positive effect was reported for the 1-PDS reaction, **Scheme-III**. (2) Once the intermediate is formed it can react through competing parallel reactions to produce three products for the 1-PDP reaction while for the 1-PDS, dioxipindolol is produced (3) Second step of the reaction mechanism of the 1-PDP involve electrophice attack of the neutral form of $H_4P_2O_8$ while for the 1-PDS, two negative species of peroxodisulfate (*i.e.*, $HS_2O_8^-$ and $S_2O_8^{=}$) attack the pindolole species. (4) Finally from the enthalpy change (ΔH) is reported to be lowered than the one obtained for 1-PDS.

Finally from the obtained results it is concluded that $H_4P_2O_8$ is more reactive than $H_2S_2O_8$ while $HS_2O_8^-$ is better electrophilic compared to the $H_3P_2O_8^-$, which could be attributed to the basicity of the leaving group; as the basicity of the leaving group decrease it become a better leaving group, thus increasing the reaction rate, which is characteristic of polar mechanism.

ACKNOWLEDGEMENTS

The author thank Syed Imran Hassan and Dr. Fatima Delmani for their critical reading and to the University of Al al Bayte, Deanship of Scientific Research, for providing the facilities to conduct this work.

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