Kinetics and Mechanism of Oxidation of β-Benzoyl Propionic Acids by Pyridinium Chlorochromate in Aqueous Acetic Acid Medium

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The kinetics of the oxidation of six substituted β-benzoyl propionic acids $X - C_6H_4 - \overset{\overset{O}{\|}}{C} - CH_2 - CH_2 - COOH$ (where X = –H, –OCH₃, –OC₂H₅, –CH₃, –Cl and –Br) by pyridinium chloro chromate (PCC) in aqueous acetic acid medium is reported here. The reaction rate shows first order dependence on [substrate], [PCC] and [H⁺]. The rate of the reaction increases with decrease in dielectric constant of the medium. Increase in the ionic strength of the medium has negligible effect on the rate of the reaction. The rates satisfactorily correlate with Hammet's equation and electron releasing substituents accelerate the rate of the reaction. Arrhenius and activation parameters have been calculated by studying the reaction rate at different temperatures (308-323 K). The major product of oxidation of the keto acids (KA) is the corresponding benzoic acid. A most probable mechanism is also proposed.

Key Words: Kinetics, Mechanism, Oxidation, β-Benzoyl propionic acids, Pyridinium chlorochromate.

INTRODUCTION

A great variety of compounds containing chromium(VI) have proved to be versatile reagents capable of oxidizing almost every oxidizable organic functional group. During oxidation, chromium(VI) is reduced to chromium(III). Among the variety of Cr(VI) reagents, pyridinium chloro chromate (PCC) has been used as a mild and selective oxidant in synthetic organic chemistry[1-5]. The oxidation by PCC takes place through hydride ion transfer. The readily available, easily and safely prepared reagent has been used with high efficiency to oxidize a wide variety of compounds such as aldehydes[6,7], cyclic alcohols[8], organic acids[9], methionine[10], diphenyl sulfide[11], dimethyl and dipropyl sulphides[12].

The study of the α and β keto acids is found widely in literature[13-17]. Branched chain organic keto acids play a major role in the pathogenesis[18] of the so called ketotic hypoglycemia. Infants, new borns and prematures children have higher urinary

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excretion of organic keto acids than older children. β-Keto acids are biologically formed in cell extracts of Xanthobacter strain Py2 by carboxylation of epoxides. Some literature about the kinetics and mechanism of oxidation of keto acids are reported in the literature[19,20,21]. However the kinetics of oxidation of β-benzoyl propionic acids by PCC has not been reported so far and hence need for the present investigation.

EXPERIMENTAL

The parent β-benzoyl propionic acid and the phenyl substituted β-keto acids were prepared by Friedel-crafts acylation of the substituted benzene with succinic anhydride[22]. Pyridinium chlorochromate (PCC) was prepared by adding pyridine (7.9 mL) to the homogeneous solution of chromium trioxide (100 g) in HCl (18 mL, 6M) at 0 ℃. Recooling to 0 ℃, PCC was obtained as yellow orange solid, which was filtered and dried. Acetic acid (AnalaR) was purified by known method[23]. Standard solutions of potassium dichromate, sodium thiosulphate, potassium iodide, starch and sodium perchlorate were prepared by using doubly distilled water. Standard solutions of substrate and oxidant were prepared by dissolving the required amount in distilled acetic acid.

Kinetic runs were carried out under pseudo first-order conditions ([KA] >> [PCC]). Rate studies were carried out at constant temperature. Requisite amounts of keto acid, perchloric acid, acetic acid and doubly distilled water were pipetted out into a reaction vessel at the temperature of 35 ℃. In another flask the oxidant was taken and it was also thermostated along with the reaction vessel at the same temperature. The reaction was started by the rapid addition of PCC solution and its progress was followed by estimating iodometrically, the amount of unreacted PCC at regular intervals of time.

Stoichiometry and product analysis: The reaction mixture containing excess of oxidant over the substrate in the presence of perchloric acid was prepared in aqueous acetic acid. The mixture was left at room temperature for about 24 h for the completion of the reaction. Estimation of unreacted PCC showed that one mole of substrate reacted with one mole of PCC.

Product study was made under mineral acid catalyzed condition in β-benzoyl propionic acid. Keeping concentration of β-benzoyl propionic acid in excess over PCC, the two solutions were mixed and perchloric acid was also added. The reaction was allowed to proceed to completion by keeping it in a thermostat at 45 ℃ for 3-4 h. The excess oxidant was decomposed by adding 2 N sulphuric acid, potassium iodide solution and sodium thiosulphate solution. The solution was then shaken with ether. The ethereal layer was washed with water many times to remove acetic acid. The ethereal layer was kept on a water bath for the evaporation of ether and cooled in an ice bath. The identification of the corresponding benzoic acid was made by comparing the R_f values with the authentic samples. The product was further confirmed by verifying the mixture melting point.

RESULTS AND DISCUSSION

Effect of oxidant: The kinetics of oxidation of β-benzoyl propionic acids by PCC has been investigated at several initial concentrations of the oxidant. The first order dependence of the rate on PCC is evident from the linear plot of log $[PCC]_t$ *versus* time (r = 0.997). The rate is not affected by the change in initial concentration of the oxidant (Table-1).

Effect of substrate: The first order dependence of the rate on substrate concentration is verified from the linear plot of log k_1 *versus* log [KA] at 35 ºC (r = 0.999), with the slope of unity (Table-1).

TABLE-1
EFFECT OF VARYING [SUBSTRATE] AND [OXIDANT] ON THE REACTION RATE
$[H^+]$ = 0.4 mol dm^{-3}, CH$_3$COOH = 70 % (v/v), μ = 0.4015 mol dm^{-3}, T = 308 K

$[PCC]10^3$ M (mol dm^{-3})	$[KA] \times 10^3$ (mol dm^{-3})	$k_1 \times 10^3$ (s^{-1})
0.5	15.0	1.22
1.0	15.0	1.19
1.5	15.0	1.20
2.0	15.0	1.21
1.0	7.50	1.80
1.0	10.0	2.35
1.0	12.5	2.90
1.0	15.0	3.55
1.0	17.5	4.20

KA = Keto acid.

Effect of perchloric acid: Effect of $[H^+]$ is investigated by varying [HClO$_4$] by keeping the [PCC], [substrate] constant (Table-2). The first order dependence of the rate on $[H^+]$ is verified from the linear plot of log k_1 *versus* log $[H^+]$ at 35 ºC (r = 0.996) with unit slope.

TABLE-2
EFFECT OF VARYING $[H^+]$ AND [HClO$_4$] ON THE REACTION RATE
[PCC] = .0015 mol dm^{-3}, [KA] = .015 mol dm^{-3}, T = 308 K

$[H^+] \times 10^2$ (mol dm^{-3})	$k_1 \times 10^3$ (s^{-1})	% HClO$_4$ (v/v)	D	$k_1 \times 10^3$ (s^{-1})
20	0.69	60	32.2	1.1
40	1.20	70	25.0	1.2
60	2.00	80	17.6	1.4
80	2.60	90	10.6	1.9

Effect of dielectric constant of medium: The oxidation of substrate is studied at different solvent polarities. The rate of the reaction increases with decrease in dielectric constant of the medium (Table-2). Plot of log k_2 *versus* 1/D (r = 0.986), where D is the dielectric constant of the medium gives straight line with positive slope.

Effect of ionic strength: The change in the ionic strength is effected by the addition of calculated volumes of sodium perchlorate solution of known strength. The rate is not affected by ionic strength (Table-2).

Effect of temperature on the rate: The oxidation of β-benzoyl propionic acids by pyridinium chloro chromate is carried out in the temperature range 308-323 K (Table-3). The Arrhenius plot of log k_2 *versus* 1/T is linear. The energy of activation, enthalpy of activation, entropy of activation and free energy of activation are calculated (Table-4). The oxidation reaction fails to induce the polymerization of added methylacrylate.

TABLE-3
TEMPERATURE DEPENDENCE OF THE OXIDATION OF
p-SUBSTITUTED KETO ACID (KA) BY PCC
[PCC] = 0.0015 mol dm^{-3}, [X-KA] = 0.015 mol dm^{-3}, [H$^+$] = 0.4 mol dm^{-3},
μ = 0.4015 mol dm^{-3}, CH$_3$COOH = 70 % (v/v)

Substrate X-KA	$k_2 \times 10$ (dm^6 mol^{-2} s^{-1})			
	Temperature (K)			
X	308	313	318	323
p-OCH$_3$	2.72	3.12	4.13	12.55
p-OC$_2$H$_5$	2.73	3.12	4.12	12.56
p-CH$_3$	2.36	2.86	3.40	3.49
p-H	1.98	2.78	3.05	3.17
p-Cl	1.18	1.77	2.13	2.43
p-Br	1.18	1.17	2.13	2.42

TABLE-4
KINETIC AND THERMODYNAMIC PARAMETERS FOR THE OXIDATION OF
β-(*p*-SUBSTITUTED BENZOYL) PROPIONIC ACIDS BY PCC
[PCC] = 0.0015 mol dm^{-3}, [X-KA] = 0.015 mol dm^{-3}, [H$^+$] = 0.4 mol dm^{-3},
μ = 0.4015 mol dm^{-3}, CH$_3$COOH = 70 % (v/v)

Substrate X-KA	Ea (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (kJ^{-1} mol^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})	log A
X					
p-OCH$_3$	72.3	69.8	-262.9	81.3	15.29
p-OC$_2$H$_5$	71.9	69.7	-260.7	81.2	15.29
p-CH$_3$	22.0	19.5	-193.7	79.1	6.05
p-H	27.2	24.6	-263.3	82.1	6.38
p-Cl	40.6	38.1	-139.1	80.9	8.55
p-Br	40.7	38.1	-138.6	80.5	8.55

Mechanism: The oxidation of 4-oxo acids by N-bromosuccinimide[21] involves the protonation of the substrate, where the electron donating substituents tend to delocalize the positive charge on protonated substrate and hence favours the formation of the positive species. In the present study, the substrate interacts with perchloric acid giving its protonated form in the first step. The protonated form of the substrate reacts with PCC forming the intermediate, which in turn gives the product.

Based on this, the following mechanism can be proposed.

$$C_6H_5-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-COOH + H^+ \;\underset{}{\overset{KA}{\rightleftharpoons}}\; C_6H_5-\underset{\underset{KAH^+}{\overset{\|}{\overset{+OH}{}}}}{C}-CH_2-CH_2-COOH$$

$$C_6H_5-\underset{\underset{KAH^+}{}}{\overset{\overset{+OH}{\|}}{C}}-CH_2-CH_2-COOH + PCC \;\xrightarrow[\text{slow}]{k_2}\; Intermediate \;\downarrow\; Products$$
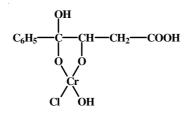
Applying equilibrium approximation to the protonated substrate, the rate law takes the form

Rate = k_2[PCC] [KAH$^+$]

The equilibrium constant K = [KAH$^+$]/[KA] [H$^+$]

[KAH$^+$] = K[KA] [H$^+$]

Substituting for [KAH$^+$] in the rate equation

Rate = k_2K[KA] [H$^+$] [PCC]

This rate law explains the first order dependence on oxidant, substrate and hydrogen ion concentration. The decrease of rate constant with increase in solvent permittivity (dielectric constant) shows the formation of a less polar transition state in the rate determining step. This agrees with the Westheimer[24] scheme of oxidation of alcohols.

The intermediate may be pictured as

$$C_6H_5-\underset{\underset{\underset{\underset{Cl \quad OH}{}}{\overset{/\;\backslash}{Cr}}}{\overset{O\;\;O}{\backslash\;\;/}}}{\overset{\overset{OH}{|}}{C}}-\overset{}{CH}-CH_2-COOH$$

Structure-reactivity correlations: The rate of oxidation of keto acids correlate well with Hammet's substituent constants (Table-5) with negative value of reaction constant. The value of ρ at 323 K and 318 K are -1.166 and -0.43, respectively. In the present investigation, the acceleration of reaction rate with the electron-releasing substituents and the negative value of the reaction constant indicate explicitly that the mechanism of oxidation involves the development of positive charge in the transition state[25,26]. The observed rate constant is composite of several terms. The rate constant k_2 depends on the concentration of protonated substrate and the electron

TABLE-5
RATE CONSTANTS FOR THE OXIDATION OF β-(*p*-SUBSTITUTED BENZOYL) PROPIONIC ACIDS BY PCC
[PCC] = 0.0015 moldm^{-3}, [X-KA] = 0.015 mol dm^{-3} , [H$^+$] = 0.4 mol dm^{-3},
μ = 0.4015 mol dm^{-3} CH$_3$COOH = 70 % (v/v), T = 308 K

Substrate X-KA	$k_2 \times 10^1$ (dm^6 mol^{-2} s^{-1})	σ_p
X		
p-OCH$_3$	2.72	-0.27
p-OC$_2$H$_5$	2.73	-0.25
p-CH$_3$	2.36	-0.17
p-H	1.98	0
p-Cl	1.18	0.230
p-Br	1.18	0.260

donating substituents tend to delocalize the positive charge on protonated substrate and hence favours the formation of this positive species. Near constancy of ΔG$^{\#}$ values implies that a common mechanism is operative for all the keto acids. The negative entropy of activation indicates that the transition state is highly solvated.

Isokinetic relationship: The genuine nature of the isokinetic relationship was verified by the Exner[27] criterion by plotting log k_2 at 308 K *vs.* log k_1 at 313 K. The value of β was calculated from the equation.

$$\beta = T_1(1 - q)/[(T_1/T_2) - q]$$

where q is the slope of Exner plot and $T_1 > T_2$. The value of is found to be 237 K which is less than the experimental temperature (308-323 K). This result indicates an increasing selectivity with the increase in temperature and the reaction series is characterized by compensation effect between[28] ΔH$^{\#}$ and ΔS$^{\#}$.

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