

KINETIC AND MECHANISTIC ASPECT OF THE PERCHLORIC ACID CATALYSED OXIDATION OF MANDELIC ACIDS

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ABSTRACT: - The problems to be solved in any kinetic investigation are (i) the establishment of the relationship between the rate of the reaction and various factors such as concentrations of the reactants, temperature, reaction medium, solvent composition etc., and (ii) interpretations of the empirical rate law proposed in terms of the reaction mechanisms, incorporating the possible intermediate and the product (or) products formed in the reaction. In the present investigation the kinetics of perchloric acid catalyzed oxidation of mandelic acid in aqueous acetic acid medium has been investigated with a view to propose suitable mechanism

KEYWORDS: Oxidation kinetics, Perchloric acid, aqueous acetic acid medium, reaction rate, suitable mechanism.

INTRODUCTION

The study of oxidation of organic compounds is of immense importance both from mechanistic and synthetic points of view. A series of chemical reactions are the deciding factors of life cycle as we know that our life is depending upon chemicals in different forms of our fundamental need. A chemical reaction may have several aspects one of which being oxidation. Oxidation processes are commonly met within everyday life. Oxidation reactions are no less common in general chemistry and their importance has resulted in the accumulation of a large number of empirical observations and conclusions. The study of such oxidation reactions through elucidation of their mechanisms and hence the investigation of reaction kinetics in chemical reactions are important aspects in chemistry. The kinetics deals with the study of change in concentration of the components of the reaction system in the gas phase as well as liquid phase with the passage of time and the results are summarized in the form of rate expressions. Among oxo derivatives of valence metals, chromium compounds play a major role as oxidants. A number of chromium reagents are readily available.

Chemical kinetics is a branch of chemistry which deals with rate of reaction. A detail study of chemical kinetic along with other non-kinetic study enables us to understand thoroughly mechanism of reactions. There are some reactions which takes place very fast, within fraction of second (up to femto second level). Some reactions are extremely slow for example rusting of iron. In between these two extreme ends, there are reactions which take reasonable time for completion. These reactions can be studied conveniently with suitable methods. There are several researchers who contributed in the field of chemical kinetics. Ludwig Ferdinand Wilhelmy, Wilhelmy Ostward, C.F. Wenzel, Louis Jacques Thenard, Pierre Eugene Mareelin Berthelot, Leon Pean de Saint Gilles, Peter Waage and Harcourt etc. had made pioneering work in the field of chemical kinetics.

Mandelic acid is an aromatic alpha hydroxy acid with the molecular formula $C_6H_5CH(OH)CO_2H$. It is a white crystalline solid that is soluble in water and polar organic solvents. It is a useful precursor to various drugs. Since the molecule is chiral, it exists in either of two enantiomers as well as the racemic mixture, known as paramandelic acid. Kinetically isomers are different from each other with the same molecular formula, they can be classified as: "constitutional (structural) isomers" and "stereoisomers".

Mandelic acid was discovered while heating amygdalin, an extract of bitter almonds, with diluted hydrochloric acid. The name is derived from the German "Mandel" for "almond". Derivatives of mandelic acid are formed as a result of metabolism of adrenaline and noradrenaline by monoamine oxidase and catechol-O-methyl transferase.

Mandelic acid is usually prepared by the acid-catalysed hydrolysis of mandelonitrile, which is the cyanohydrin of benzaldehyde. Mandelonitrile can also be prepared by reacting benzaldehyde with sodium bisulfite to give the corresponding adduct, forming mandelonitrile with sodium cyanide, which is hydrolyzed:

In this study, the objective was the separation of racemic mandelic acid to its enantiomers by enzyme enhanced ultrafiltration method (EEUF). In order to develop a methodology, bovine serum albumin (BSA) was used as

the separating agent for PEUF experiments in the first part of the study. To achieve enzyme enhanced ultrafiltration, the enzyme S-mandelate dehydrogenase was produced. For this production, the gene which is responsible from the production of S-mandelate dehydrogenase (MDH) was isolated from *Pseudomonas putida* and expressed in *Escherichia coli*. For the batch ultrafiltration, regenerated cellulose membranes (MWCO=10 kDa) were used. Operation parameters which are relative concentrations and pH were manipulated.

MATERIALS AND METHODS

Pyridinium bromochromate prepared as reported by Dhar et al. Commercial samples of oxalic acid and substituted trans-cinnamic acids were collected (Merk) and used as such. All other chemicals were of AR grade. Acetic acid used as solvent was purified before use.

Kinetics measurements

The reactions were found under pseudo first order condition by maintaining always the substrate concentration in excess over that of PBC in presence of oxalic acid. Known volumes of substrate, water and acetic acid were mixed to bring the percentage of acetic acid to the desired volume and thermostated. The reaction was started by adding the oxidant to the mixture and aliquots were removed at definite time intervals and the unreacted PBC was estimated by standard iodometric titrations.

Stoichiometry and product analysis

The stoichiometry of the reaction was determined by carrying out several sets of experiments with varying amounts of PBC largely in excess over [CA]. The estimation of unreacted [PBC] showed that one mole of cinnamic acid react with one moles of PBC. The products were separated by column chromatography. An infrared spectrum exhibited a carbonyl band at 1705 cm^{-1} and certain other bands below 900 cm^{-1} characteristic of benzaldehyde. The IR spectrum of the other product sample have two sharp bands at 1680 and 1662 cm^{-1} indicating the presence of two carbonyl groups. Bands at 3620 cm^{-1} (OH stretching), 1360 cm^{-1} (C-O stretching) and 1152 cm^{-1} (OH bending) are characteristic of glyoxalic acid.

RESULTS AND DISCUSSION

Pyridinium Chlorochromate (PCC) (Corey 1975, Pandurangan 1995) has been used as a mild and selective oxidizing reagent in synthetic organic chemistry. Oxidations of α -hydroxy acid by other pyridinium and quiniolinium halochromate (Asopa 1991) have been reported. These seem to be no report on the oxidation of α -hydroxy acid by PCC and no report on its mechanism.

Hydroxy acid may be oxidized either as alcohol, yielding corresponding oxoacids (Banerji 1978) may undergo oxidative decarboxylation to yield a ketone (Leavesley 1995) The catalytic effect of some bidentate ligands on the oxidation of lactic acid by Cr(VI) (Hiran 2004) has also been reported.

The hydroxy acid was a commercial product of the highest purity available and used as such. PCC was prepared by reported method and its purity checked by iodometric method. Double distilled water used as a medium. The solution of perchloric acid is prepared by diluting known volume of acid in water and standardized by sodium hydroxide using phenolphthalein as an indicator.

Product analyses were carried out under kinetic condition *i.e.* with an excess of the reductant over PCC. For both the acid, reaction mixture was allowed to stand in a dark for » 24 h to ensure the completion of the reaction. It was then treated with an excess of a freshly prepared 2,4-dinitrophenylhydrazine (DNP). The hydroxy acids yielded the DNP of the corresponding oxoacids (85-91% yields) after crystallization. The oxidation state of chromium in completely reduced reaction mixture was 3.

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Mandelic acid has a long history of use in the medical community as an antibacterial, particularly in the treatment of urinary tract infections. It has also been used as an oral antibiotic, and as a component of 'chemical face peels', along with other alpha-hydroxy acids (AHAs). The drugs cyclandelate and homatropine are esters of mandelic acid.

Mandelic acid is a chiral molecule, an aromatic α -hydroxy acid with the molecular formula of $\text{C}_8\text{H}_8\text{O}_3$ and molecular weight of 152.14 g/mol. It is soluble in water. Mandelic acid and its derivatives are important products

for chemical and pharmaceutical industries. They are used in synthesis and investigations related to stereochemistry. Enantiomers of mandelic acid are used for the separation of racemic alcohols and amines. (*R*)-Mandelic acid is the key intermediate of semisynthetic penicillin, cephalosporin, anti-tumor and anti-obesity drugs whereas (*S*)-mandelic acid is used in the synthesis of substituted cyclopentenones and commercial drugs, including the nonsteroidal anti-inflammatory drugs (Ju et al., 2010). Figure 1.4 shows the enantiomers of mandelic acid.

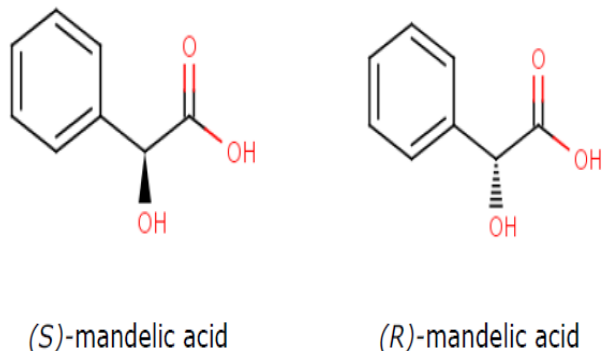


Figure 1. Structure of mandelic acid enantiomers

Therefore, production of enantiomerically pure products is an important task. It can be achieved by the synthesis of one of the enantiomers or by resolution of racemic mixtures.

Since the resolution is simple, reliable and practical when compared to asymmetric synthesis of enantiomers, it is the most widely applied method for the production of optically pure fine chemicals, pharmaceuticals and pharmaceutical intermediates. "Resolution and chirality are like twins until the day Louis Pasteur had separated crystals of salts of *D*-tartaric acid and *L*-tartaric acid under the microscope".

Retardation of rate was found when one of the products, nicotinamide was added to the reaction mixture. The addition of sodium perchlorate had no influence on rate. Its role was merely to keep the ionic strength constant. Mercuric acetate was added to the reaction mixture to suppress the formation of bromine which would vitiate the results. Added salts like BaCl₂, KCl, Na₂SO₄ and K₂SO₄ do not have any effect on the rate. No polymerization is observed when acrylonitrile is added to the reaction mixture.

Increase in temperature increased the rate of reaction. The effect of temperature has been studied from the plots of log *k*_{obs} Vs reciprocal of temperature. Arrhenius parameters and thermodynamic parameters have been evaluated. The entropy of activation is negative in all

cases. The free energy of activation of all the Aliphatic aldehydes is nearly the same. The correlation coefficient for the Exner plot was found to be 0.9999.

A suitable mechanism consistent with the experimental results was proposed. Linearity of Exner's plot and constancy in Δ*G*[‡] values imply the operation of a similar type of mechanism in all amino acids. A rate law deciphering all the observed experimental facts was derived.

In vitro antimicrobial activity of *N*-bromoisonicotinamide (NBIN) was conducted with the view that the study might throw light for further identification and synthesis of similar organic compounds which can be used as new antimicrobial agents. The following are salient findings of the present study:

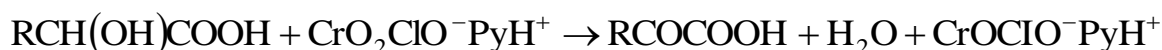
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The hydroxy acid was a commercial product of the highest purity available and used as such. PCC was prepared by reported method and its purity checked by iodometric method. Double distilled water used as a medium. The solution of perchloric acid is prepared by diluting known volume of acid in water and standardized by sodium hydroxide using phenolphthalein as an indicator.

Kinetic Experiments :

Keeping excess of the hydroxy acid over PCC attained the pseudo first order conditions. The temperature was kept constant to ± 0.1 K. The reaction was followed by monitoring the optical density of the reaction mixture spectrophotometrically at 354 nm up to 70% of the reaction by using a digital UV/ visible spectrophotometer model. No other reactant or product had any significant absorption at this wavelength.

The rate and other experimental data were obtained for both the hydroxy acids studied and similar results were obtained. The oxidation of hydroxy acids resulted in the formation of the corresponding oxoacids. Product analysis and stoichiometric determinations indicates that the overall reaction may be written as –



PCC undergoes a two electron change

Effect of substrate concentration :

The reaction increases linearly with an increase in the [hydroxy acids] (Table 1). The plot of $1/k_{obs}$ versus $1/[substrate]$ gave linear line passing through origin suggests that the rate does not obey Michaelis-Menten type kinetics. The hydroxy acids also show first order dependence over substrate in quinolinium bromochromate (QBC) and pyridinium hydrobromide perbromide .

Table 1. Variation of rate with substrate concentration
 [PCC] = 2×10^{-3} M; Temp = 303 K

[Substrate] x 10 ² M	Lactic acid, $K_1 \times 10^4, \text{sec}^{-1}$ at $[\text{H}^+] = 0.5\text{M}$	Mandelic acid, $k_1 \times 10^4, \text{sec}^{-1}$ at $[\text{H}^+] = 0.2\text{M}$
1.0	4.03	4.61
1.5	5.77	6.39
2.0	7.81	8.27
2.5	9.83	10.41
3.0	11.44	12.28
4.0	15.91	14.62
5.0	20.02	18.35

Test for polymerization :

The oxidation of hydroxy acids by PCC in an atmosphere of nitrogen failed to induce the polymerization of acrylonitrile.

Effect of ionic strength :

There was no effect of SO_4^{2-} and CH_3COO^- observed on the reaction rate in the Debye Huckle limit. It proves that interaction in rate determining step is not ion-ion type and one of the reactant molecules is neutral.

Effect of solvent composition :

The rate of oxidation of lactic and mandelic acid was determined in different solvent composition [1,4-dioxane]. The kinetics is similar for both the acids in the solvent. According to Scatchard the plot of $\log k_{obs}$ versus $1/D$ was liner and indicates ion dipole type of interaction (Table 2) in rate determining step.

Table 2. Variation of rate with solvent composition.
 [PCC] = 2×10^{-3} M; Temp = 303 K; [HA] = 2×10^{-2} M

[Substrate] x 10 ² M	Lactic acid, $K_1 \times 10^4, \text{sec}^{-1}$ at $[\text{H}^+] = 0.5\text{M}$	Mandelic acid, $k_1 \times 10^4, \text{sec}^{-1}$ at $[\text{H}^+] = 0.2\text{M}$
0	7.87	8.27
10	10.9	7.94
20	13.12	13.18
30	14.62	13.72

40	19.5	17.42
50	33.20	26.02

The rate of oxidation increased on increasing the concentration of hydroxy acid (HA). Plot of $1/k_{obs}$ versus $1/[\text{HA}]$ is linear and passing through origin means no Michaelis-Menten type kinetics were observed and no reversible complex formation between acids and PCC. The rate of reaction increases with increasing H^+ concentration. Plot of $\log k_{obs}$ Vs $\log [\text{H}^+]$ is straight line with slope ≈ 1 supports the idea that may be protonated PCC enhance the rate of oxidation.

There is no effect of ionic strength proves that in rate determining step ions are not involved. Increase in the percentage of 1,4-dioxane increase the rate, suggest that medium of low dielectric constant favors the reaction. Linear plots of $\log k_{obs}$ versus $1/D$ for both the acids confirm the ion-dipole type of interaction in rate determining step. $\log k$ versus $(D-1)/(2D+1)$ is a straight line (Laidler 1940), with negative slope indicates that activated state is less polar, while positive slope indicates more polar activated state. In our study we get negative slope indicate that activated state is less polar. Therefore, by increasing percentage of dioxane should increase which we have observed in both the acids. Rate of reaction was increased by increasing temperature. Various thermodynamic parameters are evaluated. Energy of activation and large and negative value of entropy suggest that $\alpha\text{-C-H}$ bond and formation of corresponding oxoacids as product. This fits in the criterion suggested by Narain and Bakore . The energy of activation ranges between 37 and 57 kJ mol^{-1} . Energy of activation does not correspond to carbon-carbon bond fission in the decomposition of organic substrates by Cr (VI) in rate-determining step. Calculation of activation parameters showed that these reactions are not enthalpy controlled. Lowest energy of activation is not associated with highest rate or vice versa. Vazirani *et al* also observed similar value of energy of activation for chronic acid oxidation of mandelic acid.

CONCLUSIONS

Chemical Kinetics is a part of science of dynamics. It plays a key role in elucidation of reaction mechanism. It deals with the rate of chemical reactions, at various conditions such as concentration, temperature, influencing the rate of reaction, and the explanation of all the rates in terms of the reaction mechanism. In this study, resolution of mandelic acid by enzyme enhanced ultrafiltration (EEUF) was studied.

- Membrane did not retain mandelic acid significantly and a diafiltration procedure was applied for BSA solutions before PEUF experiments.

- In PEUF experiments, pH was an important parameter for mandelic acid retention by ligand BSA and total retention of mandelic acid decreased while pH increased. At the unadjusted pH of 4.3, total retention was 74.4% which was a maximum. However, enantiomeric excess values were less than 10% and pH had no effect on enantioseparation of mandelic acid. Also, mandelic acid concentration had no significant effect on total mandelic acid retention.
- The enzyme *S*-mandelate dehydrogenase was produced to conduct the enantioseparation of racemic mandelic acid by EEUF. For this production, the gene which is responsible from the production of *S*-mandelate dehydrogenase was isolated from microorganism *Pseudomonas putida* and expressed in microorganism *Escherichia coli*. During the enzyme production by recombinant microorganism *E.coli* BL21 (DE3) pLySs pRSET A::mdIB, the highest cell concentration was achieved as 2.4 g dry cell/L at t=8 h where the cell growth was reached to the stationary phase. Also, at t=8h maximum enzyme activity was obtained and after that hour enzyme activity started to decrease significantly.
- In EEUF experiments, due to the existence of cofactor in the enzyme structure, the product benzoylformic acid was formed and existed in permeate solutions which obstructed the enantioseparation of mandelic acid. Increasing the pH of the feed solution increased the reaction efficiency.
- Enzyme conversion was prevented by sodium sulfite inhibition, but enzyme did not retain mandelic acid. By oxygen saturation of enzyme, conversion was prevented, binding was achieved but enzyme showed no enantioselectivity. By diafiltration of

enzyme at pH=3.0, conversion was prevented, binding was achieved but enantioselectivity values were very low. By diafiltration of enzyme at pH=10.0, conversion was only prevented to a certain degree but binding was achieved and enantioselectivity increased. When MDH was diafiltrated at pH=10, the highest total mandelic acid retention, enantiomeric excess and enantioselectivity were obtained as 77.2%, 38.9%, 2.27, respectively and enzyme selectivity was reversed as *R*selective.

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