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Review Article

REVIEW ON OXIDATION OF PARACETAMOL

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ABSTRACT

This review paper deals with the study on oxidation of paracetamol by various oxidising agents in different media. The paper highlights about the involvement of various catalyst in the oxidation study of paracetamol. Kinetics and equivalence studies together with product analysis, observed effect of influence of the medium on the rate of the reaction and the activation parameters furnished in the various oxidation studies has been grouped together to evaluate paracetamol behavior towards other chemicals.

Key Words: Kinetics, Oxidation, Paracetamol, Oxidising agents, Diperiodatoargentate, Sodium N- chlorobenzenesulphonamide

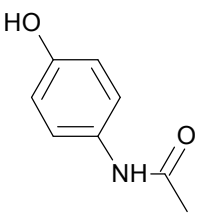
INTRODUCTION

The kinetics of paracetamol (PAM) oxidation has been studied both spectrophotometrically and iodometrically. Spectrophotometric determination of paracetamol in drug formulation has been a subject of several investigators.[1-9]

In this paper would like to consolidate the various work done on the well-known drug that finds extensive application in pharmaceutical industries in the last few decades.

The oxidation kinetics of this drug by oxidant like organic haloamines, metal ion oxidants, metal complex , use of catalyst, variation of media, product effect, we could understand the mechanism of metabolic conversion of paracetamol in biological systems and also identify the reactive species of the oxidant in aqueous acid/ base. The results of various studies are interpreted and consolidated.
Paracetamol or 4-hydroxy acetamide or Tylenol or 4-acetamide phenol is a well-known drug that finds wide application in pharmaceuticals industries, is a medication used to treat pain and fever. It is used for mild to moderate pain. Paracetamol has high analgesic properties.
Discovered in 1877.

Structure



Formula: $C_8H_9NO_2$
Molar mass: 151.163g/mol

It is also used as an intermediate for pharmaceutical (as a precursor in penicillin) and azo dye, stabilizer for hydrogen peroxide, photographic chemicals. It is used as an alternative for aspirin.

Till date the action of paracetamol at a molecular level is not completely understood but could be related the production of reactive metabolites by the peroxidase function of COX-2, which could deplete glutathione, a cofactor of enzymes such as PGE synthase[10] which has high therapeutic value.

Here are the list of oxidation of paracetamol done using UV/VIS Spectrophotometry/Iodometry.

1.Diperiodatoargentate (III) (DPA) Vs paracetamol in alkaline medium

The review on the above titled study gave a knowledge on the various steps to be followed in the kinetic study, about the different graph to be plotted and to interpret the relation between graph, rate constant value, order thus to arrive at rate law and to predict mechanism for the same. Kinetics of oxidation paracetamol using DPA in alkaline medium was done spectrophotometrically.
Ionic strength maintained was 0.01mol/dm^3. The reaction exhibits 1:2 stoichiometry.[11] The reaction is of first order with respect to concentration of DPA and less than unit order in both [PAM] and [alkali]. A decrease in the dielectric constant of the medium increases the rate of the reaction. The oxidation reaction in alkaline medium has been proceeding via DPA - PAM complex, which decomposes slow at the rate determining step, followed by a fast step to give the product.

About the oxidant
DPA is a powerful oxidising agent in alkaline medium with reduction potential value[12]1.74V. DPA has been used for study

Jaya Prakash Rao, *etal.*[13]for many organic species oxidation in which they proposed mechanism by generalizing the DPA as $[Ag(HL)L]^{(x+1)-}$.
Anil Kumar, *etal.*[14]gave a support for the reactive form of DPA in the alkaline medium. DPA is a metal complex with Ag in +3 oxidation state similar to Cu^{3+} in DPC (Diperiodatocuprate) and Fe^{3+} in Haemoglobin.
Ag (III) is a two electron oxidant. Among the various species of Ag (III), $Ag(OH)_4^-$, DPA and ethylenebis(biguanide), (EBS), silver (III) are of maximum attention to the researcher due to their relative stability. $Ag(OH)_4^-$ is rather unstable whereas others are considerably stable. DPA is used in highly alkaline medium and EBS is used in highly acidic medium.

Kinetic study
UV-VIS spectrophotometric study was done under pseudo first order condition [PAM]>[DPA]. Λ_{max} was kept at 360nm. Plot of the graph between log (absorbance) Vs time, k_{obs} were determined. Order are determined from the slopes of plots of log k_{obs} Vs respective concentration of species.

Product analysis
The product formed with 1mole of PAM and 2moles of DPA when reacted for 6hours in a closed vessel in presence of constant amount of OH^- and KNO_3 was identified as quinone oxime. (Confirmed by IR spectra)

Reaction orders
The reaction orders were determined by varying the concentration of one of the reactants in turn while keeping other conditions constant. Firstly, k_{obs} was determined by plotting log absorbance Vs time for the reaction that is 85% completed.

1. Linearity of the plots indicates a reaction order of unity.
2. The k_{obs} values increased with increase in concentration of the substance under study, indicates an apparent less than unit order dependence on the substance under study. This gets confirmed in the plots of k_{obs} Vs [PAM] in which it is linear.

In the oxidation study of paracetamol, using DPA it is observed a reaction order of unity with respect to DPA and less than unit order dependence with respect to PAM. The effect of alkali on the reaction was found to be less than unity.

Temperature effect
The influence of temperature in the kinetic study of PAM by DPA was studied at 25, 30, 35 and 40^oC.
Importance of temperature effect studies.
From the intercepts of $1/k_{obs}$ Vs 1/[PAM] gave the rate constant, k, of the slow step in scheme. The activation parameters required for prediction of the rate determining step is obtained by the least square method of plots of log k Vs 1/T.
Among various species of DPA in alkaline medium, $[Ag(H_2IO_6)(H_3IO_6)]^{2-}$ is considered as active species for the title reaction. It is notable that in carrying out this reaction, the role of the reaction medium is crucial. The $[OH^-]$ deprotonates the DPA to give a deprotonated diperiodatoargentate (III), followed by displacement of the ligand in the second step. Lower Ag (III) periodate species such as MPA (monoperiodateargentate) is more important in the reaction than DPA. MPA combines with a molecule of PAM to give an intermediate complex, which decomposes in a slow step to give the intermediate species by two equivalent change of Ag (III) in a single step. Then one more molecule of MPA further combines with intermediate in a fast step to give products.

2.Chloramine –T Vs paracetamol in aqueous acidic medium-by iodometric method.
The review done on oxidizing property of chloramine-T on paracetamol gave the application of iodometric titration in drug oxidation study. The usage of a catalyst was emphasized here.
Low concentration of paracetamol- shows first order dependence in the above titled study.[15] As the concentration increases, zeroth order. It is observed to be first-order dependence with respect to oxidant [CAT]. In addition, a negative fractional-order dependence on the rate for $[H^+]$ and [PAM].

About the oxidant
Chloramine-T (CAT), a byproduct in saccharin manufacture is well known as analytical reagent, and the mechanistic aspects of its reactions have been well-documented.[16-18]
Chloramine-T – a member in haloamine family is a good oxidising agent in both acidic and alkaline media. CAT undergoes a two-electron change in its reactions resulting in the formation of the reaction product p-toluenesulphonamide and sodium chloride. Depending on the reaction conditions, it can behave as both electrophile and nucleophiles.[19-20]

About the Catalyst
Many transition metal catalyst like Osmium, Iridium, Ruthenium either alone or as binary mixtures are preferred in redox processes.[21]
Ru (III) chloride as a non-toxic and homogenous catalyst has been known for its utility.[22-23] The study explored the catalytic role of Ru (III) with N-halo compounds as oxidant.

Kinetic study
A solution of Ruthenium (III) chloride was prepared by dissolving a known weight of $RuCl_3$ in HCl of known strength.
The kinetic study of oxidation of paracetamol using chloramine-T with the catalyst Ru (III) was done iodometrically. The rate of reaction –dc/dt is determined from the slope of tangent drawn at a fixed point (CAT) in each kinetic run.
The order of reaction in each reactant was calculated with the help of log (-dc/dt) Vs log concentration of reactants.

Stoichiometry and product analysis
The product formed when one mole of paracetamol and 2 moles of CAT reacted for 72hrs, 303K, in the presence of Ru (III), $HClO_4$ and excess CAT, was identified as quinone oxime which has been confirmed by IR spectrum, GC-MS analysis.

Reaction orders
Oxidation of paracetamol using CAT in presence of Ru (III) as catalyst was investigated. The slope of the tangent drawn at a fixed concentration of oxidant (CAT), gave the initial rate of the (-dc/dt) reaction.
The first order rate constant (k1) was calculated as k1=-(dc/dt)[CAT]
Under pseudo first-order conditions [[PAM]>>>[CAT]]with the other reaction conditions remaining constant, the order with respect to [CAT] was fixed to be unity as indicated by the linearity of the plots of (-dc/dt) Vs [CAT].
At lower concentration of [PAM] the rate of reaction k1 followed first order which shifted to zero order at its higher concentration.
Ru (III) concentration has direct influence or first order dependence on the rate of reaction, which has been proved by a linear graph passing through origin when rate constant k1 Vs [Ru(III)] was plotted. Whereas $[H^+]$ showed a negative effect on the rate of reaction of paracetamol.
Ru (III) with chloro complexes form $[RuCl_2(H_2O)_3OH]$ is the reactive species in the reaction of PAM with CAT.

In the absence of catalyst, oxidation of paracetamol oxidation is inactive and it becomes easy in the presence of Ru (III) catalyst.

3.Sodium N- chlorobenzenesulphonamide(CAB) Vs paracetamol in acid medium

Oxidation of PAM using the colourless oxidising agent was studied iodometrically using $HClO_4$.[24] The rate is first order in [CAB] and fractional order each in [PAM] and [H^+].

About the Oxidant

The chemistry centered N-metallo-N-arylhalosulphoamides generally known, as organic haloamines has been a topic of interest to many investigators because of their versatility and their behavior both as bases and nucleophiles. CAB one among them is easily prepared from benzenesulphonamide and chlorine and act as a mild oxidant.[25-27]

Kinetic measurements

Pseudo- first order conditions ([PAM]>> [CAB]) maintained. Kinetic study was performed and the progress of the reaction monitored by iodometric titrations for the determination of unreacted CAB. Pseudo first order rate constants (k') calculated from log [CAB] Vs time.

Stoichiometry and product analysis

The reaction stoichiometry was found to be 1:2. And the reduction product of CAB, benzenesulphonamide ($PhSO_2NH_2$), and oxidation product of paracetamol, 4-amino-2,6-dichlorophenol was confirmed by various spot tests, Beilstein's test, TLC.

Results

The kinetics of oxidation of PAM by CAB was studied at several initial concentration of the reactants in $HClO_4$ medium.

Under pseudo- first order conditions of [PAM] >> [CAB] at constant [H^+] and temperature, plots of log [CAB] Vs time is linear indicating first order dependence of rate on [CAB] values of rate constant increased with increase in [PAM]. Plot of log k' Vs log [PAM] is linear with slope of fraction, indicating fractional-order dependence of rate on [PAM]. The rate increased with increase in [$HClO_4$]. Similar plot with [H^+], also gave a fractional value indicating fractional –order dependence of rate on [H^+].

Temperature effect was studied at different temperatures and activation parameters were calculated from linear Arrhenius plot of log k' Vs 1/T. Rate constant value increased with increase in temperature.

Here, CAB undergoes a two-electron change in its reactions. The absence of ionic strength effects indicates the involvement of a neutral species in the rate-limiting step. It is $PhSO_2NHCl$, which gets protonated to give Substrate-CAB, complex that further decomposes to the products. Two moles of the oxidant is consumed to give the product.

4.By Chromium (VI) in absence and presence of Manganese (II) and Sodiumdodecyl Sulphate Vs Paracetamol in Acidic medium

Oxidising property of Chromium with paracetamol well reported and the paper highlights the catalytic behavior of manganese. Fast kinetic spectrophotometric method has been described for the determination of paracetamol.[28] Catalytic effect of manganese (II) on the oxidation of paracetamol by chromium (VI) in the presence of $HClO_4$(=0.23mol/dm3) is reviewed. In this paper the effects of anionic micelles of sodiumdodecyl sulphate (SDS) and complexing agents (ethylenediamine tetracetic acid, EDTA) and 2,2'-bipyridyl (bpy) were also studied and hence the decay of chromium(VI) absorbance at 350nm was possible.

About the oxidant

Chromium (VI) act as a good oxidising agent in acidic medium. This paper is in search for an alternative method, for high acid concentration and low temperature where catalyst comes in help.

Kinetic measurement

The kinetic studies of potassium dichromate, $HClO_4$ with paracetamol was followed by measuring the absorbance of the unreacted chromium (VI) ion from time to time at 350nm against water, using a spectronic 20-D spectrophotometer. The pseudo first order rate constants (k_{obs}, s^{-1}) were determined from the linear plots of log (absorbance) versus time with a fixed-time method. The same procedure was used to determine the rate constants in presence of Mn (II), EDTA, bpy and SDS.

Results

The slow reactions of PAM and dichromate in acidic conditions is sharply increased by the addition of trace amounts of Mn (II) and EDTA. The reaction follows the first, fractional and first - order kinetics with respect to [Cr(VI)], [PCM] and [Mn(II)] respectively. [EDTA] and [bpy] have zero-order dependence on reaction rate. Temperature effect showed the increase in reaction effect. Activation energy (E_a) calculated from Arrhenius plots was found to be higher showed that rate determining step was slow.

In the mechanism suggested we can understand that a chromate ester[29] is formed in the first step as PAM and Cr (VI) reacts. The chromate formed above undergoes oxidative decomposition (rate determining) to the formation of an intermediate and Cr (VI) which has been supported from product analysis. Spot test confirmed the products.

The positive catalytic effect of Mn (II) is due to one-step three electron oxidation of PAM directly to Cr (III). One electron from Mn (II) atom and other two from PAM. In the presence of Mn (II), the reaction proceeds through the formation of termolecular complex between Cr (VI), PAM and Mn (II).

When the reaction was studied in presence of small quantity of EDTA/bpy at similar conditions it is fairly fast. EDTA gives a higher rate than bpy for the same concentrations. Micelles increases rates of bimolecular reactions by concentrating both the reactants at their surfaces. Electrostatic-, approximation-, and medium effect are responsible for the incorporation of the reactants into or onto the micelle. The role of micelles on the PAM oxidation by Cr (VI) was studied by choosing an anionic micelle (SDS) and cationic micelle (CTAB).

5. Ruthenium (III)/Osmium (VIII)-catalysed oxidation of paracetamol by alkaline diperiodatoargentate(III) (Stopped flow technique)

Spectrophotometric method has been used to study the oxidation behavior of PAM using presence of diperiodatoargentate(III)(DPA) in presence of Ru(III)/Os(VIII)[30] as catalyst. The above titled paper concludes about the importance of catalyst in a kinetic study. The reaction between DPA and paracetamol in alkaline medium exhibits 2:1 stoichiometry in both catalyzed reactions (DPA: PAM). It is found that Osmium is more catalytic efficient than Ruthenium.

About the oxidant

(Oxidant information given in the earlier part of the paper)

In the recent years, the use of transition metal ions such as osmium, ruthenium and iridium has been used as catalyst in redox processes either alone or combined.[31] Mechanism of catalysis may be by different pathways: the formation of complexes with reactants or the oxidation of the substrate itself or the formation of free radicals.

In the present investigation, the evidence for the reactive species for DPA in alkaline medium has been clarified.

Kinetic measurements

Since the initial reaction was too fast to be monitored by usual methods, kinetic measurements were performed on a Hitachi 150-20 Spectrophotometer connected to a rapid kinetic accessory.

The kinetics was followed under pseudo-first-order conditions where [PAM]>>[DPA]. The reaction was initiated by mixing the DPA to PAM solution which contained required concentrations of Ru (III) or Os (VIII) and other required reagents, the progress of the reaction was monitored using spectrophotometer at 360nm.

k_t was found from the graph log(absorbance) Vs time, the plots were linear for the reaction which is 80% completion.

Results

For both Ru (III) and Os (VIII) catalyzed DPA oxidation with PAM, the stoichiometry was found to be 1:2(DPA:PAM). The reaction product was quinone oxime, which was confirmed by spot test, IR spectrum, NMR, GC-mass spectral analysis.

Reaction order

The reaction orders have been determined from the slopes of log k_c versus log (concentration) plots by varying the concentrations of PAM, Ru (III) or Os (VIII) and alkali in turn while keeping the others constant.

Effect of DPA. The linearity of the plots of log k_c Vs log [DPA] indicates a reaction order of unity in DPA.

Effect of PAM: The k_c increased with increase in concentration of PAM indicating fractional order dependence on [PAM].

Effect of [Ru(III)] or [Os(VIII)]: The order in [Ru(III)] and [Os(VIII)] is unity from the linearity plots of log k_c versus log[Ru(III)] or log[Os(VIII)].

Effect of alkali: The rate constant increased with increase in alkali concentration that is less than unit order dependence on alkali concentration.

Temperature effect: The rate constants, k, of the slow step were obtained from the intercepts of [Ru(III)] or [Os(VIII)]/k_C versus 1/[PAM] plots at four (25, 30, 35 and 40^{o}C) different temperatures. The activation parameters for the rate-determining step obtained by the least square method of plot of log k versus 1/T.

It has been pointed out by Moelwyn-Hughes[32]that, in the presence of the catalyst; the uncatalysed and catalysed reactions proceed simultaneously. Among various species of Ag (III) in alkaline medium, monoperiodatoargentate (III) is considered to be the active species for the title reaction. The active species of Ru (III) is found to be $[Ru(H_2O)_5OH]^{2+}$ and that for Os (VIII) is $[OsO_4(OH)_2]^{2-}$

CONCLUSION

The kinetic method of analysis are highly sensitive, selective, simple, accurate and less expensive.

Both spectrophotometric and iodometric studies can be done in the research laboratory with the minimum required apparatus but with accuracy and in presence of UV/VIS spectrophotometer. The time-consuming research study needs systematic, up to date updating of data recording and keen observation on the work.

The review done on the kinetic study on oxidation of paracetamol by various oxidant leads to the following conclusion

1) Media maintained plays an important role in the oxidation behavior of PAM. As seen in DPA oxidation, the crucial role-played by alkaline medium.
2) CAT oxidation of paracetamol suggested the application of catalyst in the reaction.
3) Cr (VI) oxidation study of paracetamol, is enhanced in the presence of complexing agents (Mn (II), EDTA and bpy) and surfactant.
4) Acidic medium maintained oxidation of paracetamol using N-metallo-N-arylhalosulphonamides like CAT and CAB are good oxidising agent.
5) The kinetic and mechanism study of organic drugs zeroes down on efficiency of catalytic property of various transistion metals. Osmium and Ruthenium studies confirms the efficiency of Os (VIII) in redox reactions.
6) Stoichiometry and product analysis were same in almost all studies. Quinone oxime was the major product in all paper.

Oxidation kinetics of the well-known antipyretic-analgesic drug, paracetamol, by various oxidation is studied to understand the mechanisms of metabolic conversion of paracetamol in biological systems and identify the intermediate of the oxidant in aqueous medium.

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