

Review On Kinetics Of Oxidation Of Atenolol

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Abstract

Recent review article deals with the study on oxidation of the anti-anginal and antihypertensive drug, atenolol. The paper highlights about the involvement of various catalyst in the oxidation study of atenolol. Kinetics and equivalence studies together with product analysis, observed effect of influence of the medium on the rate of the reaction and the effect various oxidants. Media maintained plays an important role in the oxidation behavior of atenolol. Kinetics studies together with product analysis, observed effect of medium on the rate of reaction, role of catalyst in the various oxidation studies are interpreted and consolidated to evaluate atenolol behavior towards different oxidants by using spectroscopic and iodometric methods with high accuracy. The derivative of oxidation products of atenolol find its importance in biological systems.

Introduction

Atenolol is most preferred antianginal and antihypertensive drug prescribed for regulating blood pressure because of its cardiovascular action as beta blocker [1]. It is used in management of alcohol withdrawal, in anxiety states, migraine prophylaxis, hyperthyroidism and tremor. It is a medication used to prevent angina and improve survival after a heart attack. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decreases blood pressure [2-4]. The kinetics of atenolol oxidation has been studied spectrophotometrically and iodometrically in last few decades.

Literature survey reveals that the kinetics of atenolol oxidation have been studied using oxidants like Ce(IV)[5], 12-Tugstocobaltate(III)[6] Chloramine-T[7] in acidic medium and potassium permanganate[7], Chloramine-B[8], Chloramine-T[9], Hexacyanoferrate(III)[10], Diperoargentate(III)[11], diperidonickel(IV)[12], diperidocuprate(II)[13] in alkaline medium.

In this article would like to consolidate the various researches on the well known antihypertensive drug, atenolol that finds extensive application in pharmaceutical industries in the last few decades. The oxidation kinetics of atenolol drug by oxidants like organic haloamine, metal ion oxidants, use of catalyst, variation in media, become useful to understand the mechanism of metabolic

conversion of atenolol in biological system. It is also helpful to identify the reactive species of the oxidant in aqueous acid/base. The derivative of oxidation products of atenolol find its importance in biological systems[6].

1. Ru(III) catalysed and uncatalysed Oxidation by Chloramine-T in acidic medium

The review focuses on the oxidising property of Chloramine-T (CAT) on atenolol gave the application of iodometric titration in acidic medium. Kinetics of atenolol oxidation by CAT in perchloric acid medium was studied with and without Ru(III) catalyst at 299 K. The use of catalyst was emphasized in reported study.

About the oxidant:- Chloramine-T is the member of haloamine family. It is good oxidizing agent in both acidic and alkaline media. CAT, a byproduct in saccharin manufacture is well known as analytical reagent, and the mechanistic aspects of its reaction have been well documented[14-16]. CAT is capable of affecting an array of molecular transformations, including limited oxidation of specific groups[7]. CAT undergoes two-electron change in its reactions resulting in the formation of the product p-toluene sulphonamide and sodium chloride. Depending on the reaction conditions, CAT can behave as both electrophile or nucleophile. Based on kinetic data, the conjugate acid $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCl}$, is assumed to be the reactive oxidizing species.

About the catalyst:- Ruthenium(III) chloride is well known non-toxic and homogenous catalyst [17,18]. It is widely used as catalyst due to strong catalytic influence in the various reactions. The study explored the catalytic role of Ru(III) with N-halo compounds as oxidant.

Kinetic study:- The progress of the reaction was followed iodometrically at 299 K in acidic medium under pseudo-first order condition at constant ionic strength. The reaction shows a first order dependence on [CAT], a zero order dependence on [atenolol] and an inverse fractional order dependence on $[H^+]$ for both Ru(III) catalysed and uncatalysed reactions. The order with respect to Ru(III) catalyst is unity. Ru(III) catalysed reactions are 2-3 times faster than the uncatalysed reactions.

Stoichiometry and Product Analysis- The main oxidation product is 4-acetamidobenzeneoxyacetic acid and isopropyl amine. Determination of unconsumed CAT in the reaction mixture shows 1:4 (Atenolol:CAT) stoichiometry.

2. Ru(III) catalysed oxidation by alkaline diperidatonickelate(IV).

The kinetics of Ru(III) catalysed oxidation of atenolol by diperidatonickelate(IV) in alkaline medium at a constant ionic strength has been studied spectrophotometrically. The use of catalyst was emphasized in reported study [12].

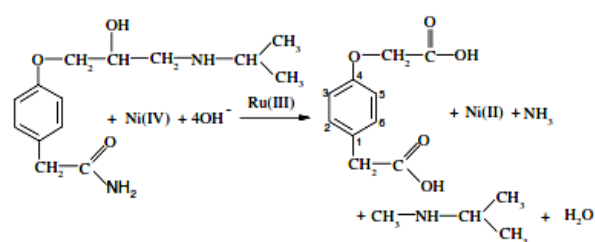
About the oxidant:- The use of diperidatonickelate(IV) in alkaline medium is new and restricted to a few cases due to limited solubility and stability of oxidant in aqueous solution.

About the catalyst:- Ruthenium(III) chloride is well known non-toxic and homogenous catalyst [17,18]. Ru(III) acts as an efficient catalyst in many redox reactions particularly in an alkaline medium [12]. The study explored the catalytic role of Ru(III) with N-halo compounds as oxidant.

Kinetic study:- The progress of the reaction was followed spectrophotometrically. in alkaline medium under pseudo-first order condition at constant ionic strength. The reaction shows a first order dependence on [oxidant] and apparent less than unit order dependence each in [atenolol] and [alkali]. The order with respect to Ru(III) catalyst is unity.

Addition of periodate has no effect on the rate of reaction.

Stoichiometry and Product Analysis- The oxidation of atenolol by diperidatonickelate(IV) exhibits 1:1 stoichiometry. The main oxidation product (4-carboxy methoxy phenyl acetic acid) were identified by IR, NMR, fluorimetry and mass spectral studies. The results suggest the formation of a complex between the atenolol and Ruthenium(III) species which reacts with one mole of oxidant species is a RDS, resulting in the formation of a free radical, which in a subsequent fast step to yield the products.



3. Oxidation by diperidatoargentatete(III) in alkaline medium.

The kinetics of oxidation of atenolol by diperidatoargentatete(III) (DPA) at a constant ionic strength has been studied spectrophotometrically in wide range alkaline medium. The hydrolysed species of atenolol was found to be the active form of atenolol. The study aims to know the oxidative behaviour of atenolol in alkaline medium [11].

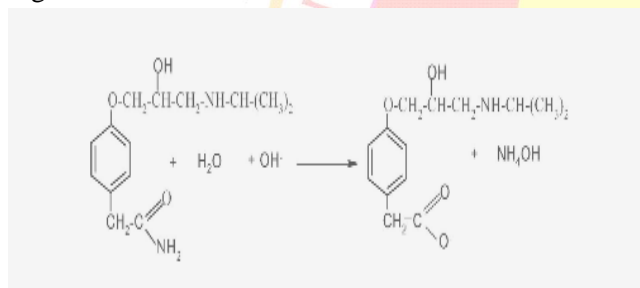
About the oxidant:- Diperidatoargentatete(III) is powerful oxidising agent in alkaline medium with reduction potential 1.74V [19]. It is widely used as a volumetric reagent for the determination of various organic and inorganic species [20]. Rao and coworkers [21,22] used DPA as an oxidising agent to determine the kinetics of oxidation of various organic substrates.

Kinetic study:- The progress of the reaction was followed spectrophotometrically in alkaline medium under pseudo-first order condition at constant ionic strength. The kinetics were studied at 360 nm by monitoring decrease in absorbance due to DPA.

The pseudo first order rate constants were determined from the graph of log O. D. versus time. The plots were linear upto 90% of reaction under the

lower concentration range of OH^- and linear upto 50 % completion of the reaction at higher concentration range of OH^- . The constancy in pseudo first order rate constants for higher and lower concentration range of OH^- revealed that the kinetics followed unit order in [DPA]. The rate constants were increased with increase in [atenolol] for both higher and lower concentration range of OH^- . The order in [atenolol] was found to be 0.6. The rate of reaction increased with increase in $[\text{OH}^-]$ and become optimum at $4.0 \times 10^{-3} \text{ mol dm}^{-3}$. A further increase in $[\text{OH}^-]$ from 4.0×10^{-3} to 4.0×10^{-2} caused the rate of reaction to decrease. The order in $[\text{OH}^-]$ was found to be 0.35.

Product-The main oxidation product of hydrolysed atenolol were found to be 4-(hydroxyl carboxy methoxy phenyl) acetic acid (characterized by IR spectrum) and N-isopropyl methylamine. The product is found to be the same in both lower and higher alkali concentration.



Mechanism- In low $[\text{OH}^-]$, the rate of reaction is gradually increased but after reaching a particular pH the rate of reaction decreased gradually due to existence of DPA as mono peridoargentate(III) (MPA) in the low alkali concentration. In higher alkali concentration, the hydroxylated monoperidoargentate(III) (HMPA). In both mechanisms, the reactive species of DPA forms a complex by combining with a single molecule of atenolol followed by decomposition to give products in a fast step.

4. Oxidative degradation and deamination of atenolol by aqueous alkaline permanganate

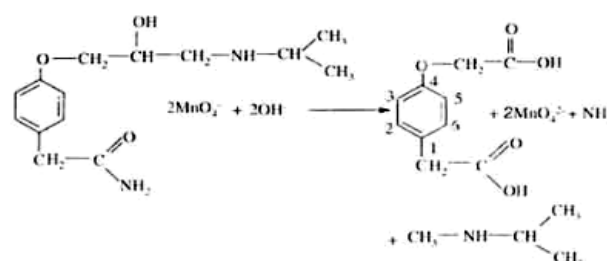
The kinetics of oxidative degradation and deamination of atenolol by permanganate in alkaline medium at constant ionic strength has been studied spectrophotometrically

About the oxidant:- Permanganate is unique oxidizing agent in neutral, alkaline and acidic medium. During oxidation by permanganate, it is

evident that permanganate is reduced to various oxidation states in neutral, alkaline and acidic medium. The expected oxidizing species of permanganate in acid media are MnO_4^- , H_2MnO_4^+ , HMnO_3 , Mn_2O_7 . Among them MnO_4^- ion is powerful oxidizing agent in aqueous alkaline as well as acidic medium[23]. The mechanism by which permanganate oxidises a substrate depends not only on the substrate but also on the medium used for the study[24]. In strongly alkaline medium, the stable reduction product is the manganate ion MnO_4^{2-} .

Kinetic study:- The progress of the reaction was followed spectrophotometrically at 339 nm in alkaline medium under pseudo-first order condition at constant ionic strength. The reaction is first order in [permanganate ion] and has less than unit order each in [atenolol] and [alkali].

Stoichiometry and Product Analysis- The reaction between atenolol and permanganate has a stoichiometry of 1:2. The oxidation in alkaline medium has been shown to proceed via permanganate-atenolol complex, which decomposes slowly in a RDS followed by a fast reaction between a free radical of atenolol and another molecule of permanganate species to give the products. The main oxidation product, 4-carboxymethoxy phenyl acetic acid was identified by IR, NMR, fluorimetry and mass spectral studies. N-isopropyl methylamine was identified by spot test.



5. Oxidation by 12-Tungstocobaltate(III) in acidic medium

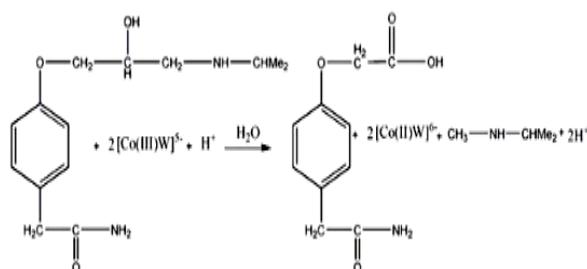
The kinetics of oxidation of atenolol by 12-Tungstocobaltate(III) was followed under pseudo-first order condition in acidic medium at constant ionic strength[6].

Kinetic study:- The progress of the reaction was followed spectrophotometrically by measuring the absorbance of formation of $[\text{Co}^{\text{II}}\text{W}_{12}\text{O}_{40}]^{6-}$ at 624 nm.

About the oxidant:- Due to high thermal stability, solubilities in various media (aqueous as well as organic), strong acidity and strong oxidizing ability Keggin type polyoxometalates are widely used for organic transformations [25]. The Keggin structure of 12-tungstocobaltate(III) anion is substitution inert and precluded inner sphere mechanism because the central Co^{III} atom is protected by a sheath of chemically inert oxygen atoms. Electron exchange between the Co^{III} and Co^{II} compounds in solution is relatively rapid which support outer-sphere electron transfer. $[\text{Co}^{\text{III}}\text{W}_{12}\text{O}_{40}]^{5-}$ is powerful oxidizing agent in acidic medium.

Kinetic study:- In acidic medium, atenolol exist in the protonated form. The reaction shows a first order dependance on $[\text{Co}^{\text{III}}\text{W}_{12}\text{O}_{40}]^{5-}$ and apparent less than unit order dependence each in [atenolol] and [acid]. The rate constant progressively increased with increase in the concentration of acid.

Stoichiometry and Product Analysis- The reaction between atenolol and $[\text{Co}^{\text{III}}\text{W}_{12}\text{O}_{40}]^{5-}$ has a stoichiometry of 1:2. The H^+ combines with atenolol to give protonated atenolol species $[\text{ATNH}^+]$ in prior equilibrium step which is supported by the observed less than unit order in $[\text{H}^+]$ and the Michal-Menton plot which is linear with positive intercept. The reaction occurs in single step, with one electrons transferred and involving free radical formation. The main oxidation products (4-acetamidobenzeneoxyacetic acid and isopropyl methylamine) were identified by TLC, spot test and FT-IR studies.



Conclusion

The kinetic methods of analysis are highly sensitive selective, simple, accurate and less expensive. Both spectrophotometric and iodometric studies can be done in research laboratory with the minimum required apparatus but with accuracy and in presence of UV/VIS spectrophotometer. The

reviews done on the kinetic study on oxidation of atenolol by various oxidant leads to following conclusions

1] Media maintained plays an important role in the oxidation behavior of atenolol. As seen in DPA oxidation, the crucial role played by alkaline medium.

2] Oxidation by CAT and diperidonickelate(IV) suggested the application of catalyst in the reaction.

3] Oxidation of atenolol by CAT and 12-Tungstocobaltate(III) requires acidic medium. The main oxidation products were 4-acetamidobenzeneoxyacetic acid and isopropyl methylamine in both cases.

4] The main oxidation product in alkaline medium, 4-carboxymethoxy phenyl acetic acid) was identified by IR, NMR, fluorimetry and mass spectral studies. N-isopropyl methylamine was identified by spot test.

Oxidation kinetics of the well known hypertensive drug, atenolol by various oxidant is studied to understand the mechanisms of metabolic conversion of atenolol in biological systems and identify the intermediates of the oxidant in aqueous medium. The derivative of oxidation products of atenolol find its importance in biological systems.

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