Synergistic catalytic activity of RuCl$_3$ and OsO$_4$ on the selective oxidation of pregabalin drug molecule: Exploration of scope, reaction mechanism and kinetic modeling

S. Dakshayani, Puttaswamy *

Department of Chemistry, Bangalore University, Central College Campus, Bangalore 560 001, India

ABSTRACT

The kinetics and mechanism of (RuCl$_3$ + OsO$_4$) in combination and, RuCl$_3$ and OsO$_4$ alone catalyzed oxidation of pregabalin (PGB) drug with chloramine-T have been investigated at 313 K in aqueous alkaline medium. The kinetic characteristics were found to be varied for each catalyzed reactions. In all the three catalyzed reactions, the reaction rate shows a first-order dependence of rate on [CAT]$_0$ and a negative-fractional-order on [NaOH]. The order of [PGB]$_0$ is found to be unity incase of [OsO$_4$], but it is fractional in both RuCl$_3$ and [RuCl3 + OsO4] catalyzed reactions. The orders with respect to [RuCl$_3$] and [OsO$_4$] are less than one whereas it is unity in case of [RuCl$_3$ + OsO$_4$]. Activation parameters have been evaluated. 2-isobutylsuccinic acid was identified as the oxidation product of PGB. Under identical set of experimental conditions, the reaction rates revealed that all the three catalyzed reactions are about 25 to 71-fold faster than the uncatalyzed reactions. The catalytic efficiency of these catalysts follows the order (RuCl$_3$ + OsO$_4$) > OsO$_4$ > RuCl$_3$. The observed reactivity sequence may be attributed to the different d-electronic configuration of the catalysts. Most noteworthy is the significant catalytic activity of 71-fold in case of (RuCl$_3$ + OsO$_4$) catalyst. It justifies the synergistic effect of (RuCl$_3$ + OsO$_4$) catalyst on the oxidation of PGB drug. An isokinetic relationship is observed with β = 366 K, indicating that enthalpy factors are controlling the rate. The reaction mechanisms put forward and rigorous kinetic models deduced, give the best fit to the experimental results for each catalyzed reactions.

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1. Introduction

Epilepsy is a group of neurological diseases characterized by epileptic seizures. Anti-epileptic drugs (AEDs) are outstanding drugs to treat people suffering from epileptic seizures. Pregabalin (PGB) is an important anti-epileptic drug, which is chemically known as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. It is commonly used as an adjunctant to cure partial seizures (focal seizures) in adults and also in the treatment of generalized anxiety disorder, and diabetic neuropathy [1]. An extensive literature survey reveals that there are no reports so far on the oxidation of PGB by any of the oxidants in the light of its kinetic behavior and mechanistic aspects. Also, no one has examined the impact of platinum group metal ions as catalysts in the oxidation-kinetics of this drug. Further, amines find wide applications in dye, polymer and pharmaceutical industries [2]. Conversion of amines to carboxylic acids

is an important synthetic route in organic chemistry. Carboxylic acids are also useful reagents in the production of polymers, solvents and pharmaceuticals [3,4]. Consequently, the present redox system is of great significance as the amine group of the PGB is transformed into the corresponding carboxylic acid.

The chemistry of organic *N*-haloamines is of great interest due to their diverse behavior [5]. Consequently, these compounds react with a wide variety of functional groups and affect several molecular changes [6–9]. The most significant member of this class of compounds is sodium *N*-chloro-4-methylbenzenesulfonamide commonly known as chloramine-T (CAT) and considerable literature exists on the kinetic and mechanistic aspects of the same [6–12]. The catalytic studies using platinum group metal ions as catalysts in a number of redox reactions have gained enormous interest and plays an important role in understanding the mechanism of redox reactions [13–16]. Ruthenium trichloride (RuCl$_3$) and Osmium tetroxide (OsO$_4$) have been extensively used as homogeneous catalysts in various redox reactions both in acid and alkaline media [15–21]. The kinetic and mechanistic picture of these reactions have been clarified to a large extent. But similar information

* Fax: +91 80 22961331.
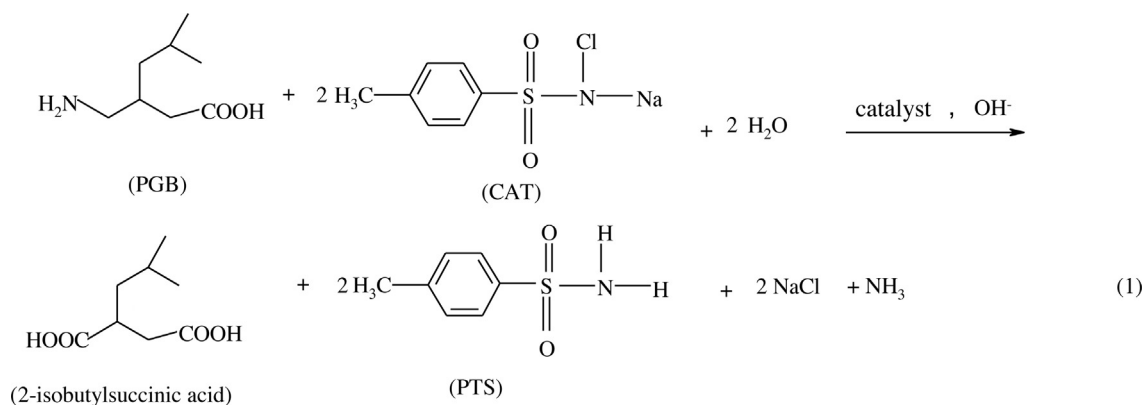*E-mail address:* pswamy_chem@yahoo.com (Puttaswamy).

on the ($RuCl_3 + OsO_4$) bimetallic catalyst is meager [22,23]. This bimetallic catalyst is expected to improve its properties and reactivities than each one alone, and hence synergistic effect is expected.

Our preliminary experiments revealed that the reaction rate between PGB and CAT was too slow to be measured kinetically in both acid ($k^{/} = 0.19 \times 10^{-4}\,s^{-1}$) and alkaline ($k^{/} = 0.28 \times 10^{-4}\,s^{-1}$) media under the present set of standard experimental conditions: ($[CAT]_0 = 1.0 \times 10^{-4}\,mol\,dm^{-3}$; $[PGB]_0 = 2.0 \times 10^{-3}\,mol\,dm^{-3}$; $[NaOH] = 5.0 \times 10^{-3}\,mol\,dm^{-3}$; $T = 313\,K$). However, the PGB-CAT reaction was potentially catalyzed in the presence of a trace concentrations (Ca. $10^{-5}\,mol\,dm^{-3}$) of $RuCl_3$ and OsO_4 alone, and ($RuCl_3 + OsO_4$) in combination in alkaline medium. This backdrop instigated us to carry out the detailed kinetic study on the oxidation of PGB with CAT in alkaline medium in the presence of $RuCl_3$, OsO_4 and ($RuCl_3 + OsO_4$) catalysts at 313 K. The main goals of this research were: (i) to accumulate all the possible kinetic data, (ii) to unfold the mechanistic picture of these redox systems, (iii) to put forward appropriate rate laws, (iv) to characterize the oxidation products, (v) to ascertain the various reactive species, (vi) to evince the formation of complexes, (vii) to establish isokinetic temperature, and (viii) to explore the catalytic efficiency of $RuCl_3$ and OsO_4, alone, and ($RuCl_3 + OsO_4$) in combination catalysts and also to probe the synergistic effect of ($RuCl_3 + OsO_4$) catalyst towards this redox system.

2. Experimental

2.1. Materials

Chloramine-T was purchased from Merck and purified by the method of Morris et al. [24]. An aqueous solution of CAT was prepared afresh, standardized by iodometric method and preserved in brown bottles to prevent any of its photochemical deterioration. Analytical grade of PGB was gifted from Apotex Pharmachem India Pvt., Ltd, Bangalore, India and was used as received. An aqueous solution of PGB was freshly prepared whenever required. Solutions of $RuCl_3$ (E-Merck) and OsO_4 (Thomas Baker) were prepared in 20 mM HCl and 20 mM NaOH, respectively and were used as catalysts in alkaline medium. The combination of ($RuCl_3 + OsO_4$) catalyst was prepared by taking equimolar ratio of each. Allowance was made for the amount of HCl/NaOH present in catalyst solution, while preparing for kinetic runs in alkaline medium. Analytical grade chemicals and doubly distilled water were used throughout the work.

2.2. Kinetic measurements

Detailed kinetic runs were performed under pseudo-first-order conditions of $[PGB]_0 \gg [CAT]_0$ at 313 K. Raagaa Ultra Cold Chamber with digital temperature control (Chennai, India) was used to maintain the desired temperature with an accuracy of $\pm 0.1\,°C$. Reactions were carried out in glass stoppered pyrex boiling tubes whose outer surfaces were coated black to prevent photochemical effects. For each kinetic run, the oxidant as well as the requisite amounts of PGB, NaOH, catalyst solutions ($RuCl_3$, OsO_4 and ($RuCl_3 + OsO_4$)) and water (to keep the total volume constant for all kinetic runs) were taken in separate tubes and thermostated at 313 K for thermal equilibrium. The reaction was initiated by the rapid addition of a known amount of CAT solution to the stirred reaction mixture. The progress of the reaction was monitored by withdrawing measured aliquots (5 mL each) from the reaction mixture at regular time intervals and determining the unreacted CAT iodometrically. The course of the reaction was studied for at least two half-lives. The pseudo-first-order rate constants ($k^{/}$, s^{-1}) were calculated from the linear plots of log $[CAT]_0$ versus time. Duplicate kinetic runs performed revealed that the rate constants were reproducible within $\pm 5\%$. The regression coefficients (R^2) for all the plots were performed using a fx-100z scientific calculator.

3. Results

3.1. Reaction stoichiometry

Reaction mixtures containing varying ratios of CAT to PGB in presence of $5.0 \times 10^{-3}\,mol\,dm^{-3}$ NaOH and $3.2 \times 10^{-5}\,mol\,dm^{-3}$ catalyst solutions were equilibrated separately at 313 K for 24 h. Iodometric titrations of unreacted CAT indicated that one mole of PGB consumed two moles of CAT in all the three catalyzed reactions, which can be stoichiometrically represented as,

$$(1)$$

3.2. Product characterization

The PGB-CAT reactions were allowed to proceed for 24 h at 313 K under stirred conditions in the presence of NaOH and $RuCl_3$, OsO_4 and ($RuCl_3 + OsO_4$) catalysts separately. After completion of the reaction (monitored by TLC), the reaction products were neutralized with acid and extracted with ether. The organic products were subjected to spot tests and chromatographic analysis (TLC technique). 2-isobutylsuccinic acid was identified as the oxidation product of PGB and p-toluenesulfonamide (PTS) as the reduction product of CAT for all the three catalyzed reactions. The separation of these products were achieved using column chromatography. The oxidation product was confirmed by GC-MS analysis. The GC-MS data was obtained by Agilent technologies mass spectrometer. The mass spectrum exhibited a molecular ion peak at 174(M-1) amu, clearly confirming 2-isobutylsuccinic acid (Fig. 1). It was also observed that this product does not undergo further oxidation under the present set of experimental conditions. PTS was also