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Micro concentrations of Ru(III) used as homogenous catalyst in the oxidation of levothyroxine by N-bromosuccinimide and the mechanistic pathway

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ABSTRACT

In this paper, we report the micro concentration of Ru(III) used as homogenous catalysis in the oxidation of levothyroxine by N-bromosuccinimide and the results of a spectrophotometric investigation of the mechanistic pathway. Such studies are helpful in gaining an insight into the interaction of metal ions through the investigation of the mechanistic pathway of levothyroxine in redox reaction.The reaction stoichiometry is 1:1 in the presence of catalyst. The oxidation products of levothyroxine have been identified as 2-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetaldehyde and succinimide by TLC, UV and FTIR. The reaction rate was examined with reference to variations in ionic strength, solvent polarity, free radicals, halides ions, mercuric acetate for the sequestration of Br^- in the reaction mixture and the addition of the product succinimide (RNH). The reaction constants involved in the mechanism were computed. The overall activation parameters have been evaluated from the Arrhenius plot. The observed results have been explored by proposed mechanisms, and the relative rate laws have been evaluated further.

1. Introduction

Levothyroxine (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoic acid (LVT) (Fig. 1) is the sodium salt of the levo-isomer of thyroxine, the primary hormone secreted by the thyroid gland [1]. It has been used for the treatment of hypothyroidism, as a thyroid stimulating hormone (TSH) suppressant, and as treatment for various types of euthyroid goiters [2]. LVT is a white to pale, odorless, tasteless, hygroscopic, crystalline powder. It is insoluble in acetone, chloroform, and ether [3]. The aqueous solubility of levothyroxine is pH dependent [4]. It contains three ionizable moieties, including carboxyl, phenolic and amino groups; therefore, it can exist as a cation, zwitterion, or anion [5].

Several methods have been reported for the analysis of levothyroxine, including enzyme immunoassay [6], fluorescence [7–9], radioimmunoassay [10], HPLC [11–13], chemiluminescence [14,15], cyclic-voltammetry [16], and spectrophotometry [17].

The chemistry of N-bromosuccinimide (NBS), a source of positive halogen, is well understood. In particular, it is known for its capacity to oxidize a variety of substrates in both acidic and alkaline solutions [18–21]. Of the compounds for which NBS has been used as an oxidant, the majority has been in conjunction with platinum metals or Fe(II) groups, examining their roles in homogenous catalysis [22–30]. To our knowledge, our efforts described in this work constitute the first report of a novel, efficient procedure utilizing micro-concentrations of Ru(III) in homogenous catalysis of the oxidation of LVT by NBS and elucidation of the mechanistic pathway of oxidation. A literature survey revealed no mention of the mechanistic details of the oxidation of LVT with N-bromosuccinimide. Likewise, the catalytic role of platinum-group metals, such as ruthenium, in the oxidation of LVT has received no attention. The objectives of the present work are to elucidate plausible reaction mechanisms, synthesize a complex that decomposes at the slow step in the mechanism, obtain and identify the reaction products, evaluate the efficiency of catalysis and compare the reaction behavior at different temperatures to determine the activation energy.

2. Experimental

2.1. Materials and reagents

Appropriate amounts of levothyroxine (Sigma-aldrich, New Delhi, India) were dissolved in alkali media and neutralized by adding concentrated acid. N-bromosuccinimide was prepared fresh before each experiment. The catalyst solution, ruthenium(III)

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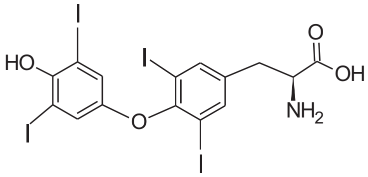


Fig. 1. Chemical structure of LVT.

chloride (Sigma), was prepared in HCl and standardized against EDTA [31]. Acetonitrile and acrylonitrile (Sigma-aldrich, Mumbai, India), were used as received and employed in varying proportions (v/v) of water–acetonitrile mixtures to study the effects of solvent polarity on the reaction medium and free radical formation. Potassium nitrate and mercury (II) acetate were used without further purification to study the effect of ionic strength and sequester Br^- in the reaction mixtures.

2.2. Procedure

All measurements were completed in glass-stoppered Pyrex boiling tubes, coated black to eliminate any unwanted photochemical reactivity. The reaction was initiated by mixing previously thermo-stated solutions of NBS and LVT containing the desired amounts of ruthenium(III) chloride, HCl, KNO_3 and mercuric acetate. Kinetic monitoring of these reactions took place at 25 °C. The progress of the reaction was monitored by estimating the amount of unconsumed NBS through measurement of the absorbance at 267 nm on a UVD-2960 Double beam UV–vis spectrophotometer connected to a PC.

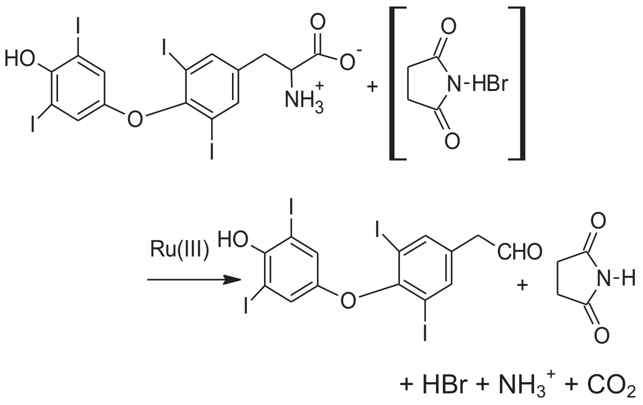
All potentiometric measurements were performed on an EL20 Education Line pH meter from Mettle Toledo Inc. The progression of each reaction was studied for at least two half-lives. The first order rate constants (k_{obs}) were evaluated from a plot of log [NBS] versus time and were reproducible within ±4%. Regression analysis of the experimental data to obtain the regression co-efficient (r) was performed using Origin Software.

3. Results and discussion

3.1. Stoichiometry and products

Reaction mixtures containing LVT, an excess of NBS, and $RuCl_3$ at constant ionic strength and acidity were left to stand for 72 h in an inert atmosphere at 25 °C. Substrates were completely converted to products. The unconsumed oxidant was identified by iodometry, which showed a 1:1 ratio of LVT consumed per mole of NBS in the presence of $RuCl_3$ catalysts, indicating that a stoichiometric ratio of LVT–NBS was satisfactory for stirred, 24 h experiments at 25 °C. After completion of the stirred reaction, the products were checked by TLC and extracted with ether.

The main reaction products, 2-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetaldehyde and succinimide, were identified and characterized by FT-IR. The ν(C=O) band appeared at 1638 cm^{-1}, which is the characteristic of aldehydes, while another broadband at 3380 cm^{-1} was indicative of the N–H stretch in succinimide. The product does not undergo further oxidation. Ammonia was identified by Nessler's reagent. Liberated CO_2 was detected by passage into limewater. The proposed pathway of the reaction is given below.



3.2. Effects of varying ionic strength and relative permittivity of the medium

Experiments in which the KNO_3 concentration varied in the range of 6.0×10^{-5} to 6.0×10^{-4} mol/dm^3 while other parameters were held constant indicated that the reaction was negligibly affected by changes in ionic strength. The effect of the relative permittivity of the medium (D) was studied by varying the CH_3CN–H_2O content (v/v) with all other factors held constant. The rate of reaction decreased with increasing CH_3CN volume. The plot of log k_{obs} versus $1/D$ was linear and had a negative slope (Fig. 2).

The values of D for various CH_3CN–H_2O mixtures were calculated from the following equation:

$$D = D_W V_W + D_A V_A$$

In this equation, D_W and D_A are the dielectric permittivities of H_2O and CH_3CN and V_W and V_A are the volume fractions of H_2O and CH_3CN. Blank experiments in which NBS and LVT were reacted in pure CH_3CN did not affect the reaction rate.

3.3. Test for free radicals

The Ru(III) catalyzed oxidation of LVT by NBS is expected to occur by free radicals generated in reaction mixture. Initially, free radical formation was observed by the addition of a monomer,

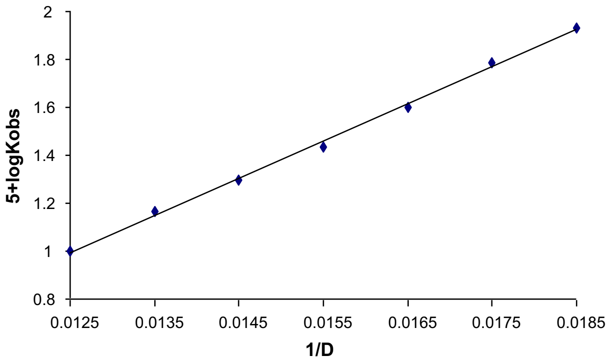


Fig. 2. Effect of relative permittivity of the medium on the Ru(III) catalyzed oxidation of LVT by NBS at 25.0 °C.