BHARATHIDASAN UNIVERSITY, TIRUCHIRAPPALLI – 620 024

Format for Annual Progress Report of Ph.D, Candidates

Name of Candidate	**A. PERIYASAMI**
University Registration Number	**BDU2020192778534**
Name of the institution/college	Thanthai Periyar Government Arts and Science College, Tiruchirappalli – 620 023.
Topic of the Research	**Kinetic Study of Oxidation of 3-Methylindole by Potassium bromate: Comparative Investigation Using Various Solvents and Characterization of the Product**
Name of Research Supervisor (Convener of the Doctoral Committee)	**Dr. N. KUMARAGURU, Ph.D.** Associate Professor Department of Chemistry Thanthai Periyar Government Arts and Science College Tiruchirappalli – 620 023
Name of the Co-Guide. If applicable	-
Venue, Date and Time of the Doctoral Committee Meeting	Department of Chemistry Thanthai Periyar Government Arts and Science College Tiruchirappalli – 620 023. Date:05.10.2023 Time: 2:00 pm
Name and address of the Doctoral Committee Members	**1. Dr. K. THARINI, Ph.D.** Associate Professor Department of Chemistry Government Arts College Tiruchirappalli – 620 022 **2. Dr. K. RAJASEKAR, Ph.D.** Assistant Professor Department of Chemistry, Government Arts College Ariyalur-621713

1. N. KUMARAGURU
Dr. N. KUMARAGURU, Ph.D,
Associate Professor
Department of Chemistry
Thanthai Periyar Government Arts
and Science College (Autonomous)
TIRUCHIRAPPALLI - 620 023.

2. K. THARINI
Dr. K. THARINI
M.Sc. M.Ed. Ph.D. M.Phil. PGDCA
Associate Professor
P.G & Research Department of Chemistry
Government Arts College
Tiruchirappalli - 620 022.

3. K. RAJASEKAR
Dr. K. RAJASEKAR, M.Sc, M.Phil. B.Ed, Ph.D.
Asst. Professor & Research Advisor
PG & Research Department of Chemistry
Govt. Arts College, Ariyalur-621 713.

KINETIC STUDY OF OXIDATION OF 3-METHYLINDOLE BY POTASSIUM BROMATE: COMPARATIVE INVESTIGATION USING VARIOUS SOLVENTS AND CHARACTERIZATION OF THE PRODUCT

Annual Progress Report for the Year 2022-2023
To be submitted to the
Bharathidasan University, Tiruchirappalli-620 024
for the award of Degree of
**DOCTOR OF PHILOSOPHY
IN CHEMISTRY**

Submitted by

A. PERIYASAMI
(Ref. No. BDU2020192778534)

Under the Guidance of

**Dr. N. KUMARAGURU, Ph.D.,
Associate Professor**

DEPARTMENT OF CHEMISTRY

THANTHAI PERIYAR GOVERNMENT ARTS AND SCIENCE COLLEGE

TIRUCHIRAPPALLI - 620 023

1. INTRODUCTION

Indole occurs in coal-tar, jasmine flowers and orange blossoms. Indole is an electron rich hetero-atomic, nitrogen containing compound which appears in various naturally occurring compounds such as alkaloids and tryptophan metabolites [1]. Tryptophan is an essential amino acid and as such is a constituent of most proteins; it also serves as a biosynthetic precursor for a wide variety of indole-containing metabolites, which are involved in a large and essential number of physiological functions.

Indoles and bromo indoles are compounds with high potential for applications in various domains, especially in the electrochemical industry as electro catalysts, anode materials in batteries, anticorrosion coating, and fast response potentiometric sensors [2]. These compounds have also attracted considerable attention in pharmacology, mainly because of their ability to develop antifungal and antibacterial agents. They also act as candidates for direct oxidation/reduction of biomolecules, and other biological activities [3]. Because of the very potent and diverse biological activity exhibited by various indole derivatives, this heterocyclic system has attracted considerable attention in chemistry, biology and medicine. Hence, it is not surprising that indoles act as lead compounds and are key building blocks in numerous pharmaceuticals. Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including antihypertensive, antiproliferative, antiviral, antitumor, analgesic, anti-inflammatory, antimicrobial activities, etc. Although indole moiety is very small but is fascinated by scientists because of the diverse biological activities by not only indole but its various substituted derivatives as well. The indole moiety is present in many substances of biological occurrence. Its metabolism, in most cases, involves an oxidative pathway.

Among the various substituted indoles, Skatole or 3-Methylindole [3-MI] is taken for investigation. 3-Methylindole is also known as Skatole, a microbial fermentation product of tryptophan in the rumen cattle. The word skatole is derived from the Greek word skato, which means dung. This compound can be found in mammalian feces and has a sharp odour. Ironically, in low

concentration, skatole has a flowery scent and is used in the manufacturing of perfumes. Another interesting fact about this molecule is that it has been found to cause pulmonary edema in goats, sheep and several rodents, such as mice and rats.

The oxidation of 3-Methylindole into 3-Methyloxindole was carried out by peracetic acid. The oxidation of skatole by brominating agent gave bromo substituted 3-methyloxindole [4]. Oxidation of 3-Methylindole to indole-3-carboxaldehyde via indole-3-Methanol was carried out using an enzyme called Pseudomonas [5]. Oxidation of Indole-3-acetic acid (IAA) by PMS into 2-hydroxy indole-3-Methanol in aqueous acetonitrile medium was carried out by Chandramohan et al [6]. Muniyappan et al., investigated the kinetic study of oxidation of indole by PMS using various solvent medium like ethanol [7], acetonitrile [8] and acetone [9]. Skatole is a mildly toxic compound occurs naturally in 10 feces and coal tar. It is found in several flowers and essential oils, including those of orange blossoms, jasmine and Ziziphus mauritiana. Skatole is also used by U. S. military in its non-lethal weaponry, as malodorants [10]. Although the oxidation of certain substituted indoles such as 2,3-dialkyl indoles by peroxodisulphate [11], PMS [11], peroxomonophosphoric [12], peroxodiphosphoric [12] acids has been already reported in the literature and oxidation of indoles by tetrabutylammoniumtribromide (TBATB) has been already reported.

SCOPE OF THE RESEARCH WORK

Kinetic study

Kinetics of oxidation of 3-Methylindole by $KBrO_3$ in aqueous acetic acid medium has been investigated. The reaction follows a total second order, first order each with respect to [3-Methylindole] and [$KBrO_3$]. The rate of the reaction was not affected by added [H^+]. Variation of ionic strength (μ) had no influence on the rate. Increase of percentage of acetic acid decreased the rate. Absence of any polymerization indicated a no radical pathway. Activation and thermodynamic parameters have been computed. A suitable kinetic mechanism based on these observations is proposed. The reactivity of $KBrO_3$ towards 3-Methylindole was found to be higher than that with peroxomonosulphate and peroxodisulphate. The corrosive studies are

performed using weight lose method by dipping the mild steel panels in 1M HCl solution.

Computational chemistry

These oxidation reactions are verified by quantum chemical calculations using Gaussian program. The optimized structures of the compounds by B3LYP/6-311++G(d,p) present in rate determining steps give more supportive information for the proposed mechanism. The optimized structures are subjected to frequency calculations. The activation free energy change ($\Delta G\#$) has been calculated and the rate constant determined theoretically using Eyring equation compared with the experimental values of $KBrO_3$.

The optimization of the product 3-methyloxindole was done by HF and B3LYP/6-311++G(d,p) and subjected to vibrational studies. FT-IR and FT-Raman spectra of the product have been obtained from HF and B3LYP methods with 6-311G++(d,p) as basis set and compared with the frequencies obtained from the experimental values. A study of electronic properties such as excitation energies, wavelengths, HOMO and LUMO energies are performed by time-dependent DFT approach. Molecular electrostatic potential (ESP) and the thermodynamic properties (heat capacity, enthalpy, entropy and activation free energy) of the oxidized compound at different temperatures are calculated in gas phase.

EXPERIMANTAL

Kinetic Measurements

Kinetic studies were carried out in 50% (v/v) aqueous acetic acid medium under pseudo first-order conditions with a large excess of 3-Methylindole over potassium bromate in the temperature range of 293–303 K. The reaction was followed by estimating the unreacted PMS as a function of time by using the iodometric method. The liberated iodine was titrated against standard sodium thiosulphate solution by using starch as indicator. From the titre values, plots of log [$KBrO_3$] vs time were made and from the slope of such plots, the pseudofirst order rate constants, k (s^{-1}) were obtained. It was checked that the results were reproducible within ± 5% error.

Computational Chemistry

In chapter also deals with procedure of the different stages involved in quantum chemical calculations are discussed. An overview of density functional theory and the different basis sets are outlined. Quantum mechanical procedure for the description of potential energy surface, single point energy calculations, normal co-ordinate analysis, TD/DFT for electronic spectra, HOMO-LUMO Parameters, Mulliken Charge analysis, molecular electrostatic potential (MEP) and NMR spectra are discussed. Hence, this chapter serves to update the scientific information's on Quantum chemical calculation of   3-Methylindole, $KBrO_3$, 3-methylene oxindole. and biological importance of 3-Methylindole, 3-methylene oxindole and the corrosion inhibition properties studied.

RESULTS AND DISCUSSION (3-MI-Bromate-Acetic acid medium)

Factors influencing the rate of oxidation of 3-Methylindole by potassium bromate in acetic acid solvent medium such as effects by

(i) $[3\text{-}MI]_0$ (ii) $[KBrO_3]_0$ (iii) $[H^+]$ (iv) Ionic strength (μ) and (v) Dielectric constant has been studied. Rate and activation parameters were evaluated.

Effect of $[3\text{-}MI]_0$:

At constant $[KBrO_3]$, $[H+]$ and fixed percentage of acetic acid, kinetic runs were carried out with concentrations (2×10^{-2} to 4×10^{-2} mol/dm^3) of 3-Methylindole which yielded rate constants whose value depend on [3-MI]. The pseudo first order rate constants $K'(s^{-1})$ thus obtained were found to increase with [3-MI]. This shows the reaction obeys first order with respect to [3-MI] used. This was confirmed by the linear plots of $K'(s^{-1})$ Vs [3-MI] passing through the origin (r2 ≤ 0.99)
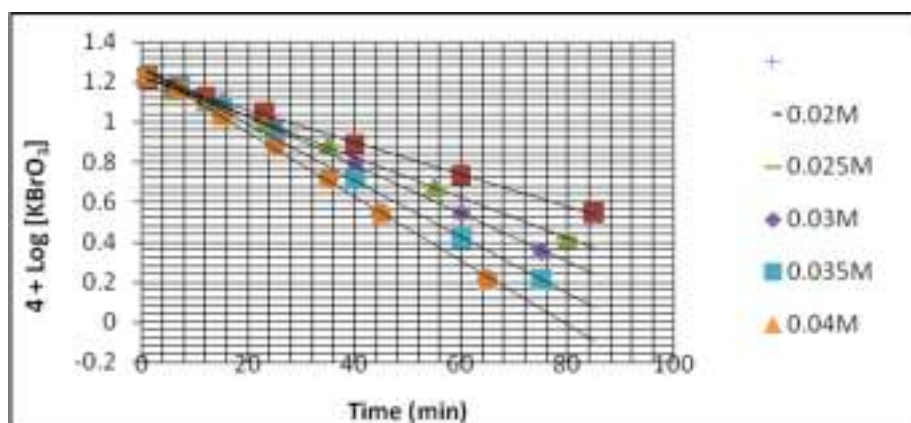
(Fig. 1). Such kinetic behaviour indicates the absence of any self-decomposition of $KBrO_3$.

Effect of [KBrO₃]₀:

The rate was found to be increased for various [KBrO₃] at fixed [3-MI], [H⁺] and the fixed percentage of acetic acid. This is due to the insitu formation of Br₂ and this was confirmed by the formation of precipitate on adding silver nitrate to the reaction mixture. This confirms there action obeys first order with respect to [KBrO₃] [3].
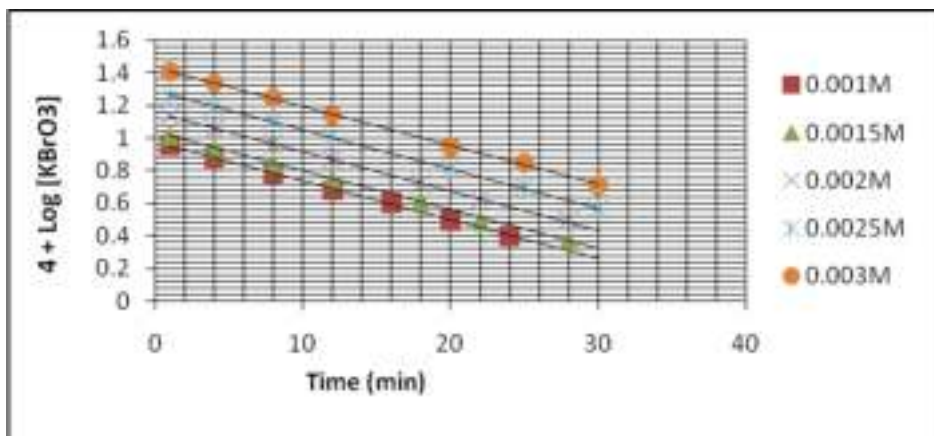

Fig. 1. Evaluation of K_2 at 303 K, 308 K and 313 K

Effect of [H+] ion:

This is an acid catalysed reaction in a narrow range of acidity (0.005 to 0.01 moldm-3). The rate depends nearly on the first powder of [H+] in the lowest range and it was calculated by ignoring the dissociation of[HSO₄⁻] and assuming [H⁺] ≈ [HSO₄⁻] at constant ionic strength. The dissociation of BrO3- is considerable at higher concentration, hence investigation of acid dependence is difficult [2, 4].

Effect of μ:

The influence of ionic strength (μ) maintained by the addition of sodium per chlorate on the reaction rate was found to be negligible (Table 1) indicating that the reaction occurs between neutral species namely the indole-3-aceticacid and the negative ion BrO₃⁻ the active species of the oxidant under experimental condition.

Effect of dielectric constant:

In order to determine the effect of dielectric constant (polarity) of the medium of rate, the oxidation of 3-Methylindole by KBrO₃ was studied in aqueous acetic acid of various compositions (Table 1). The data clearly reveal that the rate increase with decrease in the percentage of acetic acid (i.e) with increasing the dielectric constant of the medium leads to the charge

development in the transition state involving a more polar-activated complex than the reactants a neutral molecule (3-MI) and a negative ion (BrO_3^-), suggesting a polar mechanism [1]. Thus with decrease in concentration of acetic acid the ΔS# more and more negative hinting electrostriction due to more charge development at the activated complex.

Stoichiometry:

Solutions of 3-Methylindole containing an excess of $KBrO_3$ were kept overnight at room temperature. Titrimetric estimation of the concentration of potassium bromate unconsumed and assuming that all the indole-3-acetic acid taken reacted shows the stoichiometry of indole-3-acetic acid, potassium bromate to be 1:2.

Test of free radicals:

The observed total second order dependence of rate, first order on [3-MI] and [$KBrO_3$] shows that the reaction involves non-radical pathway. Moreover no polymer formation was observed when a freshly distilled acrylonitrile monomer was added to the deaerated reaction mixture indicating the absence of free radical intermediates [5-7].

Rate law:

In accordance with above observations, the rate law for the disappearance of potassium bromate is given as

$$-d \, [Br \, (V)] \, / \, dt \quad = K_2 \, [Br \, (V)] \, [3\text{-MI}]$$
$$Rate \, / \, [Br \, (V)] \quad = K's\text{-}1 = K_2[3\text{-MI}]$$
$$K' \quad = K_2[3\text{-MI}]$$

K'- Pseudo first order rate constant

K_2-Second order rate constant

Rate of activation parameters:

The effect of temperature on K'(s-1) was studied in the range 303-313 K and the results are shown in Table 1. From Arrhenius plot, the value of energy of activation (Ea) was calculated (Fig. 2). Hence the value of ΔS# was computed from the Eyring equation (Fig. 3). The large negative value of entropy of activation (ΔS#) obtained is attributed to severe restriction of solvent molecules around the transition state of higher charge and the cyclic nature of the intermediate. The values are indicated in Table 2.

Product analysis:

The final product obtained was isolated and characterised. To the solution of 3-MI in acetic acid (0.06 moldm^{-3}) was added to KBrO$_3$ (0.125 moldm^{-3}) in water. The [H$^+$] and percentage of acetic acid was maintained as in the regular kinetic runs. The reaction mixture was kept aside at room temperature for a day, so that the substrate was completely converted into product. The reaction mixture was poured into ice cold water. A solid mass obtained was filtered and washed several times with doubly distilled water dried and chromatographed on Whatmann No:1 filter paper. After drying the chromatogram was developed in water isopropanol system (19:1) as the developing solvent. The product was identified as 3-methylene oxindole with RF =0.35. The identity of the product was further confirmed from its HMNR and FT-IR spectra. FT-IR (KBr) 3412, 1710 and 1619cm-1, HNMR (DMSO) ppm = 6.0-8.0 (m, 5H, ArH, NH), 2.5 (S,2H, C-H).

Mechanism:

Based on the above observations such as first order rate dependence of the rate each on [3-MI], [KBrO$_3$], [H+] and negligible effect of μ and the stoichiometry, the following mechanism has been proposed. The reaction proceeds through an electrophilic attack of the oxidant (KBrO$_3$) at the neucleophilic site C-3 of 3-Methylindole by nucleophilic displacement of the bromate ion. Further HBrO$_2$ is a two equivalent oxidant strong enough to consume many more organic substrates and HBrO$_2$ oxidises the intermediates substrate in fast steps and finally converts to Br- ion. There is evidence for the similar formation HBrO$_2$inthe oxidation of malonic and 4-oxoacids [1, 5].

COMPUTATIONAL CHEMISTRY

These oxidation reactions are verified by quantum chemical calculations using Gaussian program. The optimized structures of the compounds by B3LYP/6-311++G(d,p) present in rate determining steps give more supportive information for the proposed mechanism. The optimized structures are subjected to frequency calculations. The activation free energy change ($\Delta G\#$) has been calculated and the rate constant determined theoretically using Eyring equation compared with the experimental values of KBrO$_3$.

The optimization of the product 3-methyloxindole was done by HF and B3LYP/6-311++G(d,p) and subjected to vibrational studies. FT-IR and FT-

Raman spectra of the product have been obtained from HF and B3LYP methods with 6-311G++(d,p) as basis set and compared with the frequencies obtained from the experimental values. A study of electronic properties such as excitation energies, wavelengths, HOMO and LUMO energies are performed by time-dependent DFT approach. Molecular electrostatic potential (ESP) and the thermodynamic properties (heat capacity, enthalpy, entropy and activation free energy) of the oxidized compound at different temperatures are calculated in gas phase.

CONCLUSION

3-MI-bromate reaction in the presence of bromo complexing metal ions, does not route through the mechanism suggested in oscillation reactions. Acid bromate oxidises the cyclic intermediate, which subsequently decomposes into the product 3-methylene oxindole. It is supported by the results obtained from the 3-MI bromate system in the presence of mercuric acetate. The deadliest infectious diseases like pneumonia, diarrhoeal diseases, and respiratory tract infections are more difficult to control now-a-days due to the emerging antimicrobial drug resistance. The present study concludes with the antifungal and antibacterial assay of 3-methylene oxindole. It was found to have significant inhibitory effect against *proteus sp*. And *vibrio sp*. Also their cytotoxicity, mode of action and its fate inside biological system need to be assessed before its use.

Future Work

Kinetic Study

Factors influencing the rate of oxidation of 3-Methylindole by potassium bromate in various solvent (acetonitrile, methanol and acetone) medium such as effects by $[3\text{-MI}]_0$ $[KBrO_3]_0$ $[H^+]$ Ionic strength (μ) and Dielectric constant will be study. Rate and activation parameters will be evaluated. $3\text{-MI} - KBrO_3$-Acetic acid system has been studied, $3\text{-MI} - KBrO_3$- Methanol system will be study. $3\text{-MI} - KBrO_3$-Acetonitrile system will be study. $3\text{-MI} - KBrO_3$- Acetone system will be study.

Computational Chemistry

These oxidation reactions are verified by quantum chemical calculations using Gaussian program. The optimized structures of the compounds by

B3LYP/6-311++G(d,p) present in rate determining steps give more supportive information for the proposed mechanism. The optimized structures are subjected to frequency calculations. The activation free energy change ($\Delta G\#$) has been calculated and the rate constant determined theoretically using Eyring equation compared with the experimental values of KBrO3.

The optimization of the product 3-methylene oxindole was done by HF and B3LYP/6-311++G(d,p) and subjected to vibrational studies. FT-IR and FT-Raman spectra of   the product have been obtained from HF and B3LYP methods with 6-311G++(d,p) as basis set and compared with the frequencies obtained from the experimental values. A study of electronic properties such as excitation energies, wavelengths, HOMO and LUMO energies are performed by time-dependent DFT approach. Molecular electrostatic potential (ESP) and the thermodynamic properties (heat capacity, enthalpy, entropy and activation free energy) of the oxidized compound at different temperatures are calculated in gas phase.

Anticorrosive study

The anticorrosive studies are performed using weight loss method by dipping the mild steel panels in 1M HCl solution. The values of percentage inhibition efficiency (η %) and corrosion rate (C_R) at 293 K are obtained at different concentrations of 3-Methylindole and its oxidized product 3-methylene oxindole.

References

1.   R. N. Goyal; Aditisangal, *ElectrochemActa,* 50, 2135 (1994).

2.   J. Xu, J. Hou, W. Zhou, G. Nie, S. Pu, S. Zhang; *Spectrochim Acta A* 63, 723 (2006).

3.   O. R. Suárez-Castilho, L. Beiza-Granados, M. Meléndez-Rodri´guez, A. Alvarez-Hernández; *J. Nat. Prod.*, 69, 1596 (2006).

4.   William B. Lawson, Abraham Patchornik, Bernhard Witkop,; *J. Am. Chem. Soc.*, 80 (17), 4748–4749 (1958).

5.   Hiroshi Ushiro, Katsuji Takai, Yoichi Noda, Shuh Narumiya, Takashi Tokuyama, Osamu Hayaishi; *J. Biol. Chem.*, 253, 9002-9008 (1978).

6.   G. Chandramohan, S. Kalyanasundharam, R. Renganathan; *Int J Chem Kinet.*, 34, 569–574 (2002).

7. Muniyappan Kavery, Chandramohan Govindasamy, Stephen Johnson, Kiruthikajothi Kannan; *Chem. Sci. Rev Lett.,* 3 (11), 345-352 (2014).

8. Muniyappan Kavery, Chandramohan Govindasamy, Stephen Johnson; *Journal of the Korean Chemical Society,* 57 (2), 210 – 215 (2013).

9. K. Muniyappan, G. Chandramohan, J. Stephen, A. Peiyasami; *Research Journal of Chemical Sciences*, 4(8), 7-11, (2014)

10. Virginia Ruth Pinney; *United States Patent 6,386,113 B1-* "Non-lethal weapon systems" (2002).

11. Ghamem, R.; Carmona, C.; Munoz, M. A.; Guardado,P.; Balon, M. *J. Chem. Soc., Perkin Trans 2* 1996, 2197

12. Carmona, C.; Balon, M.; Munoz, M. A.; Guardado,P.; Hidalgo, J. *J. Chem. Soc., Perkin Trans 2* 1995**,** 331.

Course work completed

1. **Research and Publication Ethics**

   (Prescribed for Ph.D., Course Work, Department Of Chemistry, Thanthai Periyar Government Arts and Science College, Tiruchirappalli-620 023)

2. **Advance in physical chemistry**

   (Prescribed for Ph.D., Course Work, Department Of Chemistry, Thanthai Periyar Government Arts and Science College, Tiruchirappalli-620 023)

3. **Advance in organic chemistry**

   (Prescribed for Ph.D., Course Work, Department Of Chemistry, Thanthai Periyar Government Arts and Science College, Tiruchirappalli-620 023)
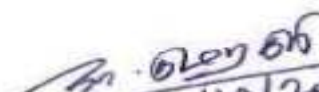
List of conference Participation

1. Computational Chemistry using Guassian workshop-2021, Centre for Advanced computational chemistry studies, AIMS Institute,Delhi as Professional Training Program, held from 8th Nov-12th Nov.2021.

2. " Solving Challenging Problems in Chemistry Using Computational Chemistry and Machine Learning" organized by Department of Chemistry , The American College, Madurai on 14th June 2021

List of publication:

1. A. Periyasami, N. Kumaraguru, Oxidation of 3-Methylindole by Potassium bromate in Acetic acid Medium – A Kinetic and Corrosion Investigation, **Eur. Chem. Bull**. 2023,12(12), 2613-2621.

Signature of Research Supervisor
with date
Dr. N. KUMARAGURU. Ph.D.
Associate Professor
Department of Chemistry
Thanthai Periyar Government Arts
and Science College (Autonomous)
TIRUCHIRAPPALLI-620 023.

Signature of the Candidate with date

Signature of DC - member - 1
with date
Dr. K. THARINI
M.Sc., M.Ed., Ph.D., M.Phil(Ed)., PGDCA,
Associate Professor
P.G & Research Department of Chemistry
Government Arts College
Tiruchirappalli - 620

Signature of DC - member - 2
with date
Dr. K. RAJASEKAR, M.Sc., M.Phil, B.Ed., Ph.D.
Asst. Professor & Research Advisor
PG & Research Department of Chemistry
Govt. Arts College, Ariyalur-621 713.