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Research Articles

Kinetics and mechanistic approach to the oxidation of Miglitol by N-Chlorophthalimide in acetic acid – water medium

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ABSTRACT

A kinetic study of oxidation of Miglitol (an oral anti-diabetic drug) with N-Chlorophthalimide (NCP) has been carried out in presence of $HClO_4$, in aqueous acetic acid medium, at 308 K. the reaction is fully $HClO_4$, acid catalyzed and negligible effect was observed when saccharin was added in reaction mixture. Variation of ionic strength of the medium shows negligible effect on rate of reaction. Increasing in dielectric permittivity of the medium; increases the rate oxidation. The stoichiometry of the reaction was found to be 1:1. The reported oxidation product of Miglitol was identified as the 3,4,5-trihydroxy-1-(2-oxoethyl)piperidine-2- carbaldehyde , which was detected by conventional methods and spot tests. Various activation parameters have been evaluated. The reaction constants involved in the proposed mechanisms were computed. The proposed mechanisms was good consistent with the observed experimental results.

Keywords: Kinetics, N-Chlorophthalimide, Miglitol, Hazard, eco-friendly.

INTRODUCTION

Chemistry is often cited as a style of chemical synthesis that is consistent with the goals of green chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry, which focuses on chemical phenomena in the environment. Environmental concern has forced the chemical industry to re-evaluate many of its processes to reduce or eliminate the formation of waste produced in the synthesis of organic products. This need is specially required in oxidation technology and can be addressed by the development of clean and safe oxidation Procedures. This is possible by establishment of green catalytic process by use of environmentally friendly oxidant or green catalysts. Chemists need to co-operate with other disciplines. In particular it is vital that chemists and engineers work together to develop new sustainable processes. Only by combining the best ideas from both areas will the required technological leaps be made. Concepts such as atom economy, energy efficient reactions, eco-friendly solvents and renewable feedstock's should be more prominent in basic chemistry education, and there should be less emphasis on the very narrow concept of immediate product yield[1].

In present paper, we have explored the kinetics of oxidation of Miglitol with N-Chlorophthalimide because it is an eco-friendly, cheap, non-hazardous and easily synthesized in chemical laboratories, available in the market. Miglitol is an oral anti-diabetic drug that acts by inhibiting the ability of the patient to break down complex carbohydrates into glucose. It is primarily used in diabetes mellitus type for establishing greater glycemic control by preventing the digestion of carbohydrates (such as disaccharides, oligosaccharides, and polysaccharides) into monosaccharides which can be absorbed by the body[2]. Miglitol, and other structurally-related iminosugars, inhibit glycoside hydrolase enzymes called alpha-glycosidase. Since miglitol works by preventing digestion of carbohydrates, it lowers the degree of postprandial hyperglycemia. It must be taken at the start of main meals to have maximal effect[3]. After reviewing the literature we found that there was only information available on the oxidation kinetics of Miglitol (MIG) by sodium -N-bromo - p- toluenesulphonamide (bromamine – T or BAT) in hydrochloric acid medium. Survey of revealed literature indicated that N-Chlorophthalimide is a source of positive halogen, and this reagent has been selectively used as an oxidant for a variety of substrates in both acid and alkaline media. N. Bhavani and K. Lily have employed NCP as an oxidant[4] for the oxidation of phenyl methyl sulphoxide. The psycho-economic activity of this oxidant is limited and scanty need to be explored widely. In the present work, the kinetics of oxidation of Miglitol with N-

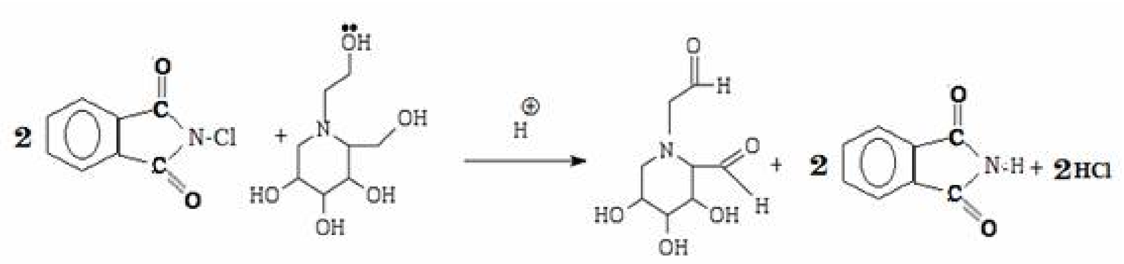
Chlorophthalimide in acid has been studied with a view to elucidate the mechanism of the reaction and to identify the reactive species of oxidant in acid media.

MATERIALS AND METHODS

The all the reagents employed in the kinetic investigations were analytical grade. The standard solution of Miglitol (Biocon Ltd.) was used as substrate for the preparation of solution. The solution of Miglitol was prepared in requisite volume of glacial acetic acid-water mixture. Double distilled water employed in all kinetic runs. To prevent photochemical effect, the freshly prepared solution of N-Chlorophthalimide was stored in an amber coloured bottle and its strength was checked iodometrically[5] using 1 % solution of freshly prepared starch as an indicator.

Kinetic measurements*:* All kinetic measurements made under pseudo first-order conditions, by keeping large excess of Miglitol over N-Chlorophthalimide. Mixture containing requisite amount of solutions of N-Chlorophthalimide, and $HClO_4$ in 30 % acetic acid equilibrated at 308 K. To this mixture added a measured amount of pre-equilibrated at 308 K., standard solution of N-Chlorophthalimide. To maintain the desired temperature (within ± 0.1^{o}C) the reaction mixture was kept in a thermo stated water bath and the progress of the reaction was monitored iodometrically by withdrawing aliquots of the reaction mixture at regular time of intervals.

Stoichiometry and Product Analysis: Stoichiometry of the reaction was ascertained by equilibrating the reaction mixture containing an excess of N-Chlorophthalimide over Miglitol and hydrochloric acid in 30 % acetic acid for 24 hrs. at 308 K. The un-reacted oxidant (N-Chlorophthalimide) was determined by iodometrically. The estimated amount of un-reacted N-Chlorophthalimide showed that one mole of Miglitol consumes two moles of N-Chlorophthalimide. The 3, 4, 5-trihydroxy-1-(2-oxoethyl) piperidine -2- carbaldehyde, was found as the end-product of oxidation. These product was identified by forming their 2,4-dinitrophenylhydrazone of 3,4,5-trihydroxy-1-(2-oxoethyl)piperidine-2- carbaldehyde, which was characterized by their melting point, spot test[6] and existing conventional methods[7].



RESULTS AND DISCUSSION

The oxidation of Miglitol with N-Chlorophthalimide was kinetically probed at several initial concentrations of the reactants in acid media. The salient feature obtained is discussed. Under pseudo-first-order conditions ([MIG] >> [NCP]) at constant [$HClO_4$], solvent composition and temperature, plots of log (a-x) vs. time were linear (r > 0.994) indicating a first-order dependence of rate on [NCP].

Table- 1: Effect of variation of reactants on pseudo first-order rate constant k_1 at 308K.

10^2 [MIG] (mol. dm.$^{-3}$)	10^3[NCP] (mol. dm.$^{-3}$)	10^3 [H^+] (mol. dm.$^{-3}$)	% HOAc-H_2O	k_1x10^5 (s^{-1})
1.25	1.00	1.25	30	10.29
1.25	1.25	1.25	30	10. 30
1.25	2.00	1.25	30	10.30
1.25	2.50	1.25	30	10.32
1.25	4.00	1.25	30	10.28
1.25	5.00	1.25	30	10.33
1.00	2.50	1.25	30	8.06
1.25	2.50	1.25	30	10.32
2.00	2.50	1.25	30	15.07
2.50	2.50	1.25	30	18.03
4.00	2.50	1.25	30	25.61
5.00	2.50	1.25	30	27.82
1.25	2.50	1.00	30	6.21
1.25	2.50	1.25	30	6.98
1.25	2.50	2.00	30	7.95
1.25	2.50	2.50	30	10.32
1.25	2.50	4.00	30	12.02

1.25	2.50	5.00	30	14.33
1.25	2.50	1.25	20	9.03
1.25	2.50	1.25	30	10.32
1.25	2.50	1.25	40	11.31
1.25	2.50	1.25	50	12.41
1.25	2.50	1.25	60	16.06

The pseudo-first-order rate constants (k_1) calculated is given in Table 1. Further, the values of k_1 calculated from these plots are unaltered with variation of [NCP], confirming the first-order dependence on [NCP]. The rate constant (k_1) have been found to increase with increase in the concentration of Miglitol and plot of k_1 Vs. [MIG] was linear with slope less than unity, indicating a fractional order dependence with respect to [MIG] (Fig.1-2, Table-1). Similarly, the reaction is fully acid catalyzed because, the rate of reaction increases with increase in [H^+] (Fig.3, Table 1).The effect of changing solvent composition on the reaction rate was studied by varying concentration of acetic acid from 20-60 %. The rate constants suggest that the rate of reaction increases with increase acetic acid content of the solvent mixture. The plot of log k_1Vs 1/D was found to be linear with positive slope indicating the involvement of two dipoles or an ion–dipole reaction.

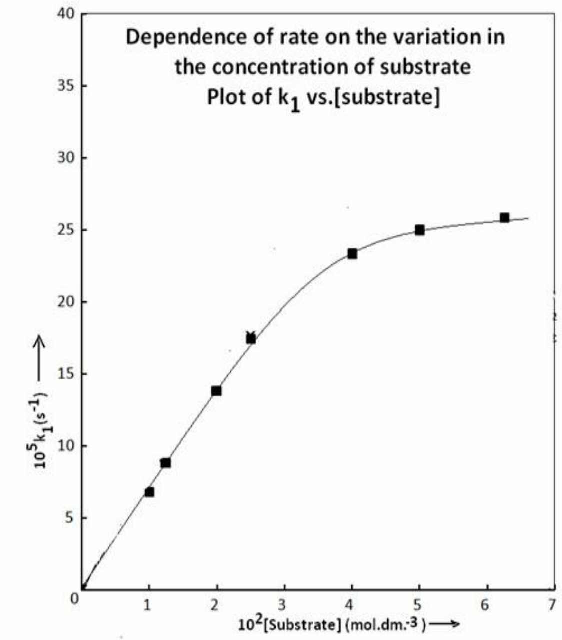


Fig.1 Effect of miglitol (substrate)

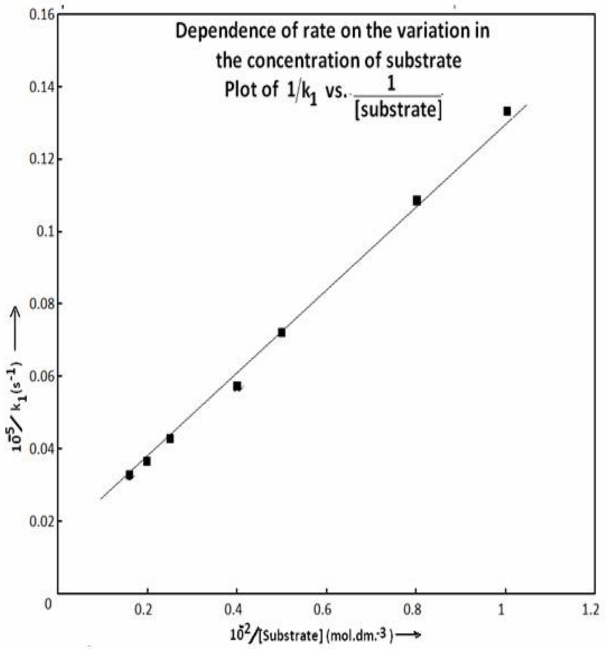


Fig.2 Effect of miglitol (substrate)

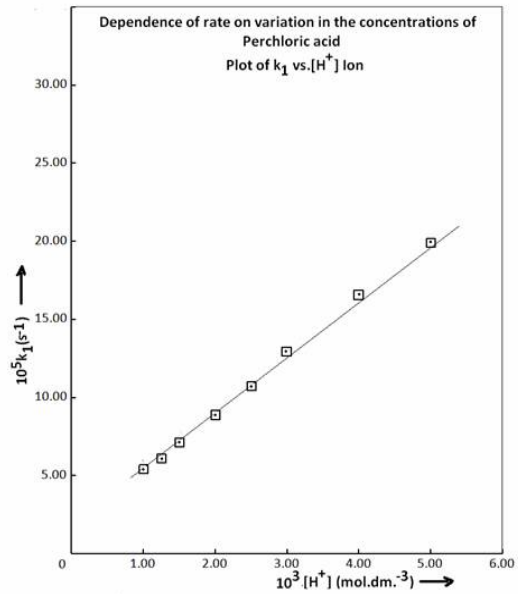


Fig. 3 Effect of Perchloric acid

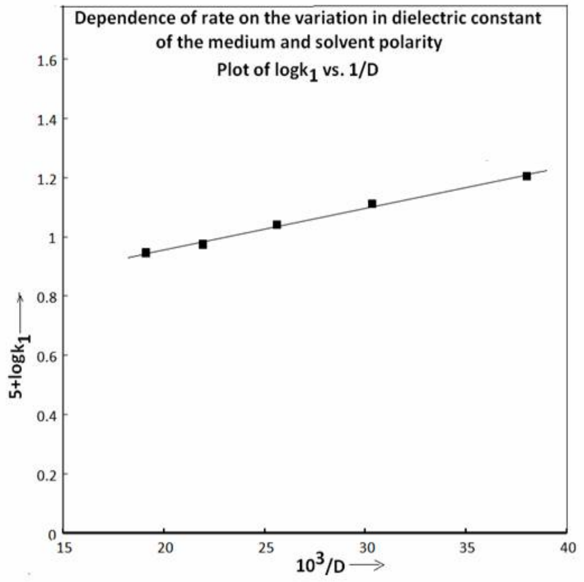
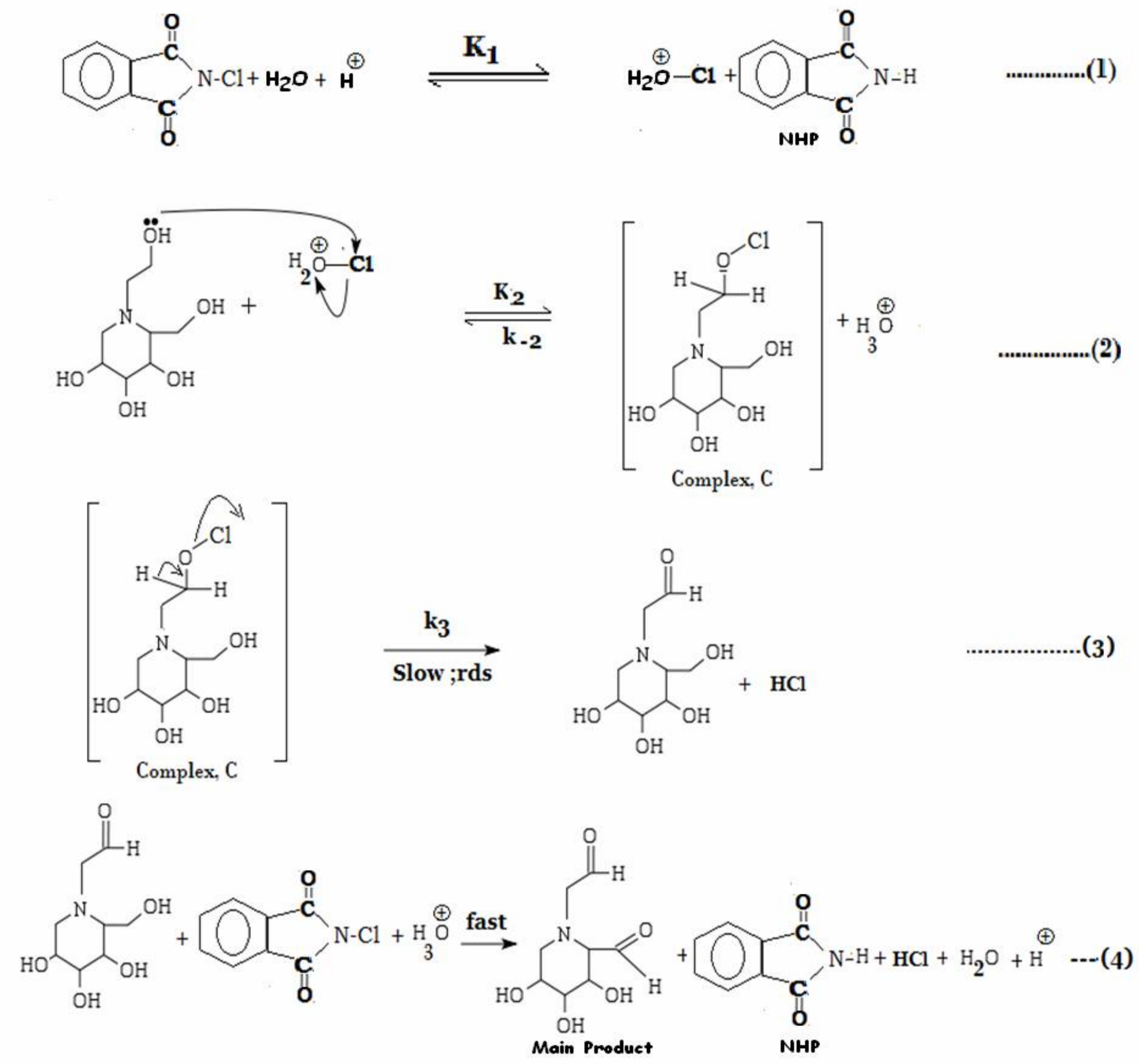


Fig. 4 Effect of Dielectric constant of the medium

Variation of added concentrations of Phthalimide, one of the products of oxidation, showed negative effect on the rate of reaction. The addition of acrylonitrile (monomer), reaction neither induces polymerization nor retards the reaction rate, which may be attributed to the inertness shown towards free radicals.

Reactive Species and Mechanism: It has been shown that probable reactive species of NCP in acid solution are NCP itself or Cl^+ or protonated NCP viz., $NCPH^+$, or (H_2O^+Cl) as active oxidizing species, and positive effect of the concentration of $HClO_4$,restricts us to take H_2O^+Cl as the oxidizing species. Based on the finding results and observed kinetic data, a probable mechanism is proposed for the Miglitol - NCP system.


N-Cl + H2O + H⊕
K1
H2O⊕—Cl + N-H
NHP
.............(1)
OH +
H2O⊕—Cl
K2
k-2
Complex, C
+ H3O⊕
...............(2)
k3
Slow ;rds
+ HCl
..................(3)
+ H3O⊕
fast
Main Product
NHP
N-H + HCl + H2O + H⊕
---(4)

The derived rate equation is:

$$k_{obs.} = \frac{K_1 k_2 k_3 [\mathrm{H}^+][\mathrm{MIG}]}{[\mathrm{NHP}]\{\mathrm{k}_{-2} + \mathrm{k}_3\}} \ldots\ldots\ldots\ldots (5)$$

The above rate equation is good agreement with the observed experimental data and results. Thus, mechanism is also in good agreement with the work reported by Patwari [8] and K. N. Mohana [9].

Table: 2

THERMODYNAMIC PARAMETER

Substrate	*Ea* (*kJ mol* $^{-1}$)	*A* (*s* $^{-1}$)	$\Delta H^{\#}$ (*kJ mol* $^{-1}$)	$-\Delta G^{\#}$ (*kJ mol* $^{-1}$)	$-\Delta S^{\#}$ *JK mol* $^{-1}$
Miglitol	60. 01 ±0. 44	2. 3 4x10^{5} ±0. 19	54. 94 ±0. 90	76. 93 ±0. 33	104. 21 ±0. 29

The Arrhenius plots of log *k* vs. 1/T were all linear From this plot, the activation and thermodynamic parameter for equilibrium step and rate determining step of the scheme was evaluated (**Table 2).** The observed $\Delta S^{\#}$ values are large and negative. It may be interpreted that the fraction of collisions become more stringent and decomposition of activation complex is a quite slow process. $\Delta H^{\#}$ indicates that the reaction is enthalpy controlled.

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