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OXIDATION OF N, N-DIMETHYLIMIDODICARBONIMIDIC DIAMIDE HYDROCHLORIDE WITH ALKALINE SODIUM N-CHORO-P-TOLUENE SULFONAMIDE

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ABSTRACT
The kinetics of oxidation of antidiabetic drug metformin by sodium N-chlorotoluenesulfonamide have been spectrophotometrically investigated in aqueous alkaline medium. The observed rate of oxidation is first order with respect to both [CAT] and [MET]. The stoichiometry of the reaction is set up to be in the 1:1 mole ratio. Effect of change in concentration of Substrate and Oxidant are also studied. The oxidation products are identified as metformin N-oxide by using GC-MS. Activation parameters and rate constant have been calculated. If concentration of alkali medium increased rate of reaction increased. Ionic strength (NaClO4) slightly affect rate of reaction. The Influence of halide ions and dielectric constant of the medium was studied on the rate of reaction. Thermodynamic parameters was also calculated and deliberated.

Keywords: Kinetics, Oxidation, Metformin hydrochloride, thermodynamic, Chloramine-T

INTRODUCTION
Metformin is used to lesser the blood glucose in those with type 2 diabetes. It fits to a class of compound known as biguanides which is identified as N,N-dimethyl imido diacarbonimide diamide. Metformin is the better option that improves and regulates glycemic activity. The chemistry of organic N-halo amines is of excessive concern owing to their different behavior. Sodium N-choro-p-toluene sulfonamide or Chloramine-T (CAT) and sodium N-chlorobenzene sulfonamide or Chloramine-B (CAB) are the main members of this class of compounds [1]. Metformin hydrochloride is white crystalline powder, hygroscopic and freely soluble in water, used as hypoglycemic drug. Chloramine-T is a famous analytical reagent, and the mechanistic characteristics in many of its reactions have been studied [2]. It is a mild, competent, stable, nontoxic and low-cost oxidant. However, scanty information is available in the literature on CAT reactions with MET. Chloramine-T (CAT) is the vital member of organic halo-amine family and acts as an oxidizing agent in both acidic and alkaline medium. It is adaptable oxidizing agent and has revealed a variety of kinetic. This is commercially available, cheap, water accepting, non-toxic and easy to handle [3]. Less report is available in the literature on the MET oxidation from the opinion of its kinetic characteristics. In sight of the above proofs, the present study has been started for studying the kinetics of oxidation of MET with CAT in alkaline medium.

Experiment:
The substrate metformin hydrochloride is of analar grade purity and was used as received from industry. Pharmaceutical grade substrate was kindly donated by Harman finochem. An aqueous solution of the required concentration of the substrate was prepared newly each time whenever required. Double distilled water was used every time through research work. Solution of CAT of required strength (Aldrich) was prepared afresh and preserved in bottles. All other chemicals used were of Analytical grade. Ionic strength was maintained at I= 1 mol dm−3 standardized NaClO4 solution.

Kinetic Measurements:
The kinetic of reactions between metformin hydrochloride and Sodium N-choro-p-toluene sulfonamide in aqueous medium were performed s with a large excess of substrate over oxidant at constant Ionic strength using UV–Vis spectrophotometer. All the kinetic of reactions were performed at room temperature. The progress of the reaction was monitored spectrophotometrically by mixing the required amount of solution of metformin

hydrochloride Sodium N-choro-p-toluene sulfonamide, NaOH and NaClO4. Necessary amounts of solutions of substrate, NaOH and sufficient water to keep the total volume constant (50 ml) for all kinetic runs were equilibrated at 303K. A required amount of CAT solution, also equilibrated at the same temperature was quickly added to the reaction mixture which was every so often shaken for uniform concentration. Instantly 5 mL of the reaction mixture was pipetted in to a cuvette placed in the UV Vis spectrophotometer, SHIMADZU UV-1800 and absorbance measurements were made (λmax of MET) for more than two half-lives. Plots of log absorbance ration vs. time were made to estimate the pseudo-first-order rate constants (k/ s−1).

Reaction Stoichiometry and Product Analysis:

stoichiometry was determined for varied ratios of Reaction mixtures CAT to MET: (i) $[CAT]_o = 5.0\times10^{-5}$ mol dm^{-3} and $[MET]_o = 5.0\times10^{-4}$ mol dm^{-3} and, in presence of 1.0 mol dm^{-3} NaOH for 48 h. Iodometric titrations of unreacted oxidant showed that one mole of MET consumed one moles of oxidant confirming the following stoichiometry.

After completion of the reaction, the reaction products were neutralized with HCl and extracted with ether. The reaction products were subjected to spot test and chromatographic analysis which discovered the formation of Metformin oxide in alkali medium. The oxidized product of MET was recognized as metformin *N*-oxide, which was established by GC-MS analysis. The mass spectrum showed a molecular ion peak at 145 amu, openly confirming metformin *N*-oxide. GC-MS data were obtained on a 17A Shimadzu gas chromatograph with a QP-5050A Shimadzu mass spectrometer. It was also observed that there was no further oxidation of product under present kinetic conditions.

$$CH_3C_6H_4SO_2NClNa + C_4H_{12}ClN_5 + H_2O \xrightarrow{NaOH} C_4H_{12}O + C_7H_7SO_2NH_2 + Na^+ + Cl^-$$

CAT Metformin HCL Metformin N-Oxide Toluene sulphonamide

Table 1: Effect of varying concentrations of [CAT], [MET] [NaOH] on reaction. $[CAT] = 2.0\times10^{-5}$ mol dm^{-3}; $[MET] = 5.0\times10^{-4}$ mol dm^{-3} ; $[NaOH] = 1.0\times10^{-4}$ mol dm^{-3} $[NaClO_4] = 1.0$ mol dm^{-3}

10^5[CAT] (mol dm-3)	10^4[MET] (mol dm-3)	10^4[NaOH] (mol dm-3)	10^2 k′ (s-1)
5	5	5	0.0413409
10	5	5	0.0462561
15	5	5	0.7450188
20	5	5	1.536140831
25	5	5	1.6721851
5	5	5	25.997142
5	10	5	0.0246867
5	15	5	0.4266101
5	20	5	2.004691331
5	25	5	3.1289154
5	5	5	1.6335893
5	5	10	1.5005005
5	5	15	1.360933516
5	5	20	1.2093385
5	5	25	1.1662911

RESULTS AND DISCUSSION:

The oxidation kinetics of metformin hydrochloride with chloramine t in occurrence of sodium hydroxide. Initially varying strength of metformin hydrochloride and kept all other component chloramine t and sodium hydroxide constant increases the rate of reaction. Under pseudo-first order conditions of [met] >> [cat], at constant [naoh]

naclo4 and temperature. Plots of log (absorbance) vs. Time were linear indicating a first-order dependence of rate on [met].

In next step varying concentration of [cat] and keeping concentration of all other component metformin hydrochloride, [naoh] and naclo4 constant. Result showing a first order dependence of the rate on [cat]. The values of pseudo-first order rate constants (k/ s -1) are reported in table 1. The values of k/ remain unaffected with a change in [cat].

Study of varying concentration of [naoh] and keeping concentration of all other component metformin hydrochloride, [cat] and naclo4 constant. The reaction rate reduced with increase in [naoh] concentration. A plot of log *k′* versus log [naoh] was linear with a slope of unity, founding an inverse-first order dependence of rate on [naoh**].**

The rate of the oxidation of met with cat was performed at altered temperature ranges from 308 to 318 ^{0}k at constant concentration of substrate, oxidant, alkali medium and ionic strength. Result observed that the rate constant of the reaction increases with increase in temperature. Using arrhenius equation plot of log k′ versus 1/t, values of activation parameters (ea, Δh≠, Δg≠, and Δs≠) were calculated. The results found are tabulated in table 2.

Table 2: temperature dependence on the rate of the oxidation reaction and values of activation parameters.

SR.NO.	TEMPERATURE IN ^{0}C	TEMPERATURE IN ^{0}K	10^{2} K′ (S-1)	ACTIVATION PARAMETER * 10^{3}
1	35	308 °K	6.5943387	Ea = 176.4498456 kJmol-1
2	40	313°K	0.279565	ΔH# = 176.441532 kJmol-1
3	45	318°K	4.6270089	ΔG# =2.310859166 kJmol-1
				ΔS# = −0.5559947302 KJ mol-1

[CAT] = 1.0×10^{-5} MOL DM^{-3}; [MET] = 1.0×10^{-4} MOL DM^{-3} ; [NAOH] = 1.0×10^{-4} MOL DM^{-3} [$NACLO_4$] = 1.0 MOL DM^{-3}

The effect of ionic strength (i) on the reaction rate was studied by adding 1 m naclo4 solution to the reaction mixture. It was established that the ionic strength has slight effect on the reaction rate. Value of rate constant is reported in table 3. The influence of salt on the reaction rate was performed by changing concentrations of salt. Keeping all other oxidant, substrate and alkali constant. It was detected that the rate of reaction was not changed by the addition of salts.

Table. 3: Effect of ionic strength on the oxidation reaction of met by cat

SR.NO.	[NACLO4] MOL DM-3	10^{3} K′ (S-1)
1	10	-1.108854
2	15	-3.532902
3	20	-2.42605
4	25	-1.0015608

[CAT] = 10×10^{-5} MOL DM-3; [MET] =$10\times^{10-4}$ MOL DM−3; [NAOH] = $10\times^{10-4}$ MOL DM−3; T = 303 ^{0}K

Effect Of Dielectric Constant: the dielectric constant of the medium was studied by the adding methanol to the reaction medium. The results obtained indicated that the increase in the concentration of methanol lowers the dielectric constant of the medium, resulting in the increase of rate of the reaction.

Table. 4 effect of changing dielectric constant on the reaction rate.

SR.NO.	[MEOH] % V/V	K′ (S-1)
1	0	-0.004010447
2	10	0.007543684

3	20	0.014873175
4	30	0.02108227

[CAT] = 10×10^{-5} MOL DM-3; [MET] =$10 \times 10-4$ MOL DM−3; [NAOH] = 10×10^{-4} MOL DM−3; T = 303 ^{0}K

CONCLUSION

In present work the kinetics study of metformin hydrochloride by chloramine - t in alkali medium. Followings are the conclusions from the above study.

The stoichiometry of oxidation reaction is to be 1:1. The reaction is established to be first order with respect to metformin and chloramine - t. The order of the reaction with respect to [naoh] is inverse-first order. The oxidation product identified was metformin n-oxide at is confirmed by gc-ms analysis. Thermodynamic parameters and rate constants are also calculated. The reaction is independent of ionic strength and dependence on dielectric constant of the medium.

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