Oxidation of Cinacalcet Hydrochloride by Chloramine-B in Acid Medium: A Kinetic and Mechanistic Study

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Kinetic and mechanistic study of cinacalcet hydrochloride by chloramine-B (CAB) in HCl medium at 308 K was the aim of this work. Analyzed the reaction at five different temperatures and determined the thermodynamic parameters using Arrhenius plots. The reaction had a stoichiometry of 1:2 and characterized the oxidation product using chromatographic and spectroscopic methods. The rate law is deduced from the marked effects, which were accompanied by plausible mechanisms.

Keywords: Cinacalcet hydrochloride, Oxidation, Kinetics, Chloramine-B, Acidic medium.

INTRODUCTION

The chemistry of *N*-halo amines ability to act as halonium cations, hypo halites and *N*-anions that act as bases, nucleophiles, *N*-halo amines, also recognized as *N*-halo-aryl sulfonamides, is diverse in nature. As a result, these compounds react with a broad range of functional groups, influencing a wide range of molecular changes [1-4]. Monohaloamines experience a two-electron transition, while dihaloamines go through a four-electron change. The reduction products are sulfonamides and NaCl or HCl, respectively. Since the N-Cl bond in chloramine-T and chloramine-B is extremely polar, they are both strong electrophiles. Chloramine-B has been employed to probe a wide range of organic and inorganic compounds, as well as their kinetic mechanisms [5-9]. It is being exploited to explore the several organic and inorganic substrates and their oxidation mechanisms.

Cinacalcet hydrochloride (CNT) is a white powder with the molecular formula $C_{22}H_{23}NClF_3$ and a molecular weight of 393.90 g/mol. It is soluble in methanol, ethanol and water, but not ether or hexane [10]. Cinacalcet hydrochloride (CNT)

is an anti-parathyroid drug, which is used orally to treat secondary hyperparathyroidism caused by chronic kidney disease. Hyperparathyroidism (HPT) is a deficiency marked by excessive parathyroid hormone (PTH) secretion because of calcium receptor deficiency in the parathyroid glands. Calcimimetics are calcium-like compounds that enhance the sensitivity of these receptors to calcium, inhibiting the release of parathyroid hormone and rapidly lowering suppress parathyroid hormone levels [11-13].

EXPERIMENTAL

Chloramine-B, an ACS reagent with a purity of > 85.0% was purchased from TCI Chemicals Pvt. Ltd., India. A kind gift sample of cinacalcet hydrochloride (purity > 95.0%) from Jubilant Bioscience Ltd., India was received. Throughout the trial, analytical grade chemicals and double distilled water used as well as the desired strength of the compound. For HPLC analysis, Shimadzu LC-2010 which consist of Phenomenex C18, with a diameter of 250 mm, a thickness of 4.6 mm, 5 µm column was used.
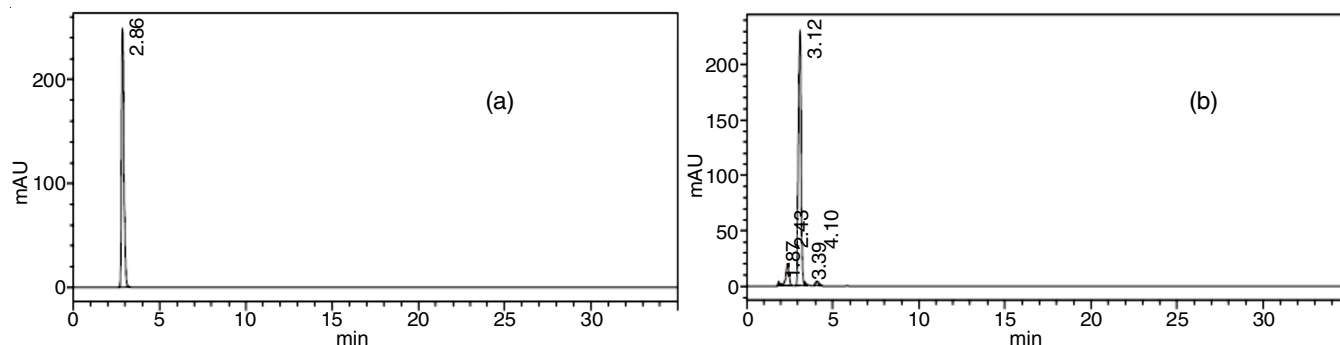
Fig. 1. HPLC chromatograms of cinacalcet hydrochloride at 2.86 min (a) and its oxidation product at 3.12 min (b)

General procedure: For kinetic runs, the reactions in pseudo-first-order conditions were carried out. To avoid the photochemical reaction, the [substrate]$_0$ > [oxidant]$_0$ required amount of cinacalcet hydrochloride was mixed and sealed in a brown-coloured container. To keep a steady overall volume, a measured quantity of water was added. For 30 min, the tube thermo specified (Techno-ST-405, India) was used to keep the target temperature of 308 K. The reaction was applied a precise volume of pre-equilibrated CAB to the mixture. Iodometric titration of unreacted CAB in calibrated aliquot 5.0 mL mixture at various time intervals was used to monitor the reaction's progress. The reaction took two half-lives and the rate constant was calculated using the linear plots.

Stoichiometry and product analysis: At 308 K, various ratios of CAB to CNT for 24 h were equilibrated. The residual oxidant measured by iodometric titration, which confirmed that in the presence of acid medium, one mole of CNT was consumed by two moles of CAB.

$$C_{22}H_{22}NF_3 + PhSO_2NClNa \longrightarrow$$
$$C_{22}H_{20}NF_3 + 2PhSO_2NH_2 + 2NaCl \quad (1)$$
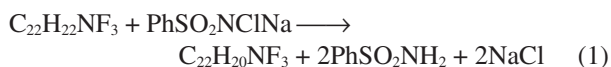
At 308 K, a stoichiometric ratio reaction mixture in the presence of acid media could proceed for 24 h under stirred conditions. Thin layer chromatography was used to monitor the reaction after the completion of the reaction [14,15]. TLC and HPLC (TLC; 5:4:1 acetonitrile/methanol/water) are often used to identify the reaction product after the separation with hexane (Fig. 1). A molecular ion peak of m/z 358 amu was revealed from the LC-MS technique, which shows a sharp peak of C=N stretching frequency at 1650 cm^{-1} (Fig. 2) confirmed the formation of an imine compound.

RESULTS AND DISCUSSION

Under pseudo-first-order conditions, the kinetic oxidation of cinacalcet hydrochloride (CNT) by chloramine-B (CAB) was investigated at various initial concentrations of reactants at 308 K. At constant [HCl] and temperature, plot log [CAB]$_0$ *versus* time was linear (R = 0.9926), showing that the reaction rate is first order dependent on [CAB]$_0$. Variations in [CAB]$_0$ have little impact on the values of the pseudo-first-order rate constant (k′) (Table-1).

The rate rises as [CNT]$_0$ rises and the plot of log k′ *versus* log [CNT]$_0$ was linear (R = 0.966) and had a first-order slope of 1.11, suggesting a first-order reaction on [CNT]$_0$ (Table-1
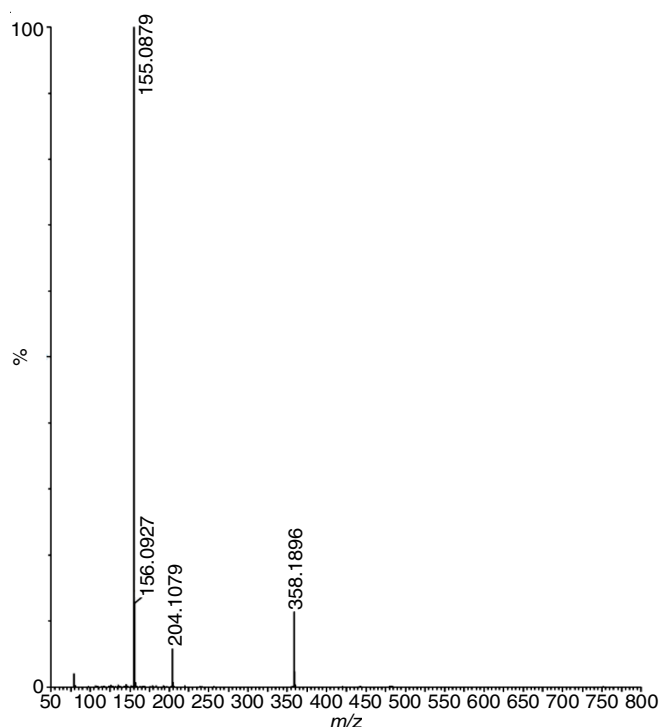

Fig. 2. LC-MS spectrum of imine its M + H molecular ion peak at 358.18 amu

TABLE-1			
EFFECT OF VARYING OXIDANT, SUBSTRATE AND HCl CONCENTRATIONS ON THE RATE OF REACTION AT 308 K			
10^4 [CAB] (mol dm^{-3})	10^3 [CNT] (mol dm^{-3})	10^2 [HCl] (mol dm^{-3})	10^4 k' (s^{-1})
2.0	6.0	3.0	5.55
4.0	6.0	3.0	5.62
6.0	6.0	3.0	5.88
8.0	6.0	3.0	5.69
4.0	2.0	3.0	3.94
4.0	4.0	3.0	4.50
4.0	6.0	3.0	5.62
4.0	8.0	3.0	6.18
4.0	10.0	3.0	6.71
4.0	6.0	1.0	3.83
4.0	6.0	2.0	4.35
4.0*	6.0	3.0	5.62
4.0	6.0	4.0	6.01
4.0	6.0	5.0	6.43
4.0**	6.0	3.0	5.69
*In presence of tolunesulfonamide; **At ionic strength 0.2 mol/dm^{-3}			

and Fig. 3). The rate of reaction increases as $[HCl]_0$ increases and the plot of log k′ versus log $[H^+]$ was linear (R = 0.9391) with a fractional slope of 0.309, indicating that the rate is fractionally dependent on $[H^+]$ (Table-1 and Fig. 4).
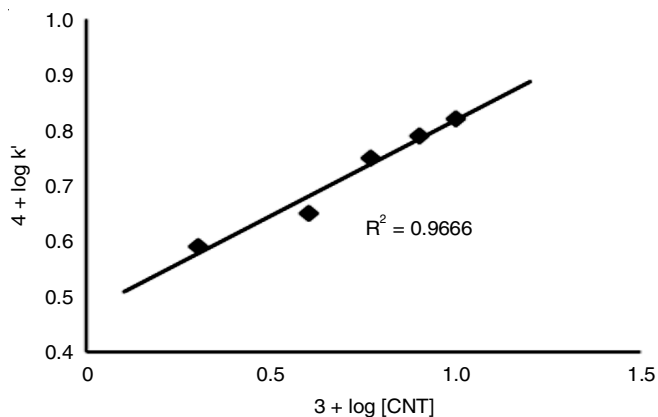

Fig. 3. Plot 4 + log k′ versus 3 + log [CNT]

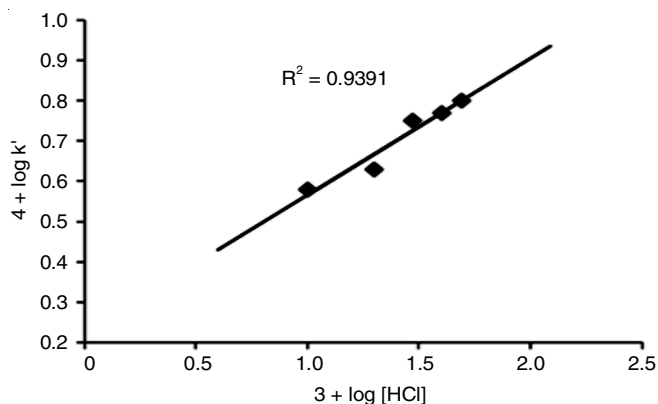Fig. 4. Plot 4 + log k′ versus 3 + log [HCl]

Varying the ionic strength of the medium by adding sodium perchlorate (0.1-0.2 mol dm⁻³) has little effect on the reaction rate, indicating that non-ionic species were involved in the rate-determining process as various concentrations of acetonitrile used (0-20%). The medium's dielectric permittivity changed, but there was no noticeable change in the rate (Table-2). The effect of halide ions (H^+ and Cl^-) were also investigated by varying the concentration of one ion while main-taining the concentration of the other ion steady. At a given $[H^+]$, adding NaCl had no significant effect on the intensity. As a result, the rate's dependency on [HCl] only mirrored the influence of $[H^+]$ and the rate of reaction is proportional to the concentration

TABLE-2
EFFECT OF VARYING DIELECTRIC CONSTANT OF THE MEDIUM

CH_3CN (%)	10^{-4} K (k' s⁻¹)	D
0	5.62	70.08
5	5.99	69.0
10	6.19	67.3
15	6.14	65.7
20	6.39	64.2

$[CAB]_0 = 4.0 \times 10^{-4}$ mol dm⁻³ ; $[CNT]_0 = 6.0 \times 10^{-3}$ mol dm⁻³; $[HCl]_0 = 3.0 \times 10^{-2}$ mol dm⁻³

of $[H^+]$ ions. The rate was unaffected by the addition of reactant and benzene sulfonamide (2.0×10^{-4} - 8.0×10^{-4} mol dm⁻³) to the mixture. Arrhenius plot log k′ vs. 1/T (R = 0.9508) (Fig. 5), values of activation parameters namely energy of activation (E_a), enthalpy of formation ($\Delta H^{\#}$), Gibbs free energy ($\Delta G^{\#}$) and entropy ($\Delta S^{\#}$), log A (Table-3).
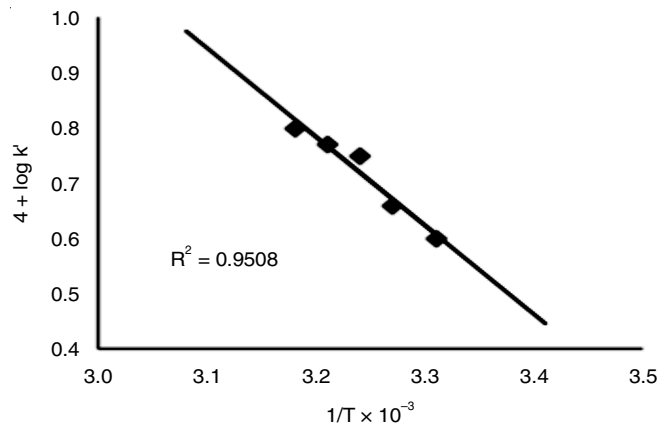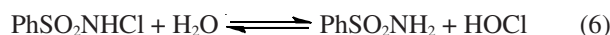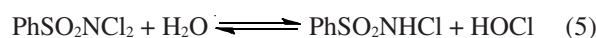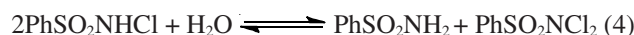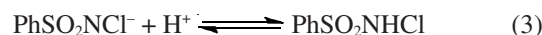

Fig. 5. Plot 4 + log k′ versus 1/T × 10³

TABLE-3
EFFECT OF VARYING TEMPERATURE ON THE RATE OF REACTION & ACTIVATION PARAMETERS FOR OXIDATION OF CNT BY CAB IN ACID MEDIUM

Temp. (K)	10^4 k' (s⁻¹)
302	4.02
305	4.60
308	5.62
311	5.99
314	6.43
E_a (kJ/mol⁻¹)	30.84
$\Delta H^{\#}$ (kJ/mol⁻¹)	28.27
$\Delta G^{\#}$ (kJ/mol⁻¹)	92.24
$\Delta S^{\#}$ (Jk⁻¹/mol⁻¹)	-231.31

$[CAB]_0 = 4.0 \times 10^{-4}$ mol dm⁻³ ; $[CNT]_0 = 6.0 \times 10^{-3}$ mol dm⁻³; $[HCl]_0 = 3.0 \times 10^{-2}$ mol dm⁻³

Reactive species of chloramine-B: Chloramine-B (CAB) has the same equilibrium in both acidic and basic aqueous solutions. In reactions, CAB undergoes a two-electron transi-tion, resulting in reduction products. The oxidation potential of CAB-BSA redox pair, which consists of benzene sulfonamide (BSA; $PhSO_2NH_2$) and NaCl, varies with the pH of medium in aqueous solutions. CAB is a strong electrolyte that produces a variety of reactive species based on pH [16,17].

$$PhSO_2NClNa \rightleftharpoons PhSO_2NCl^- + Na^+ \quad (2)$$

$$PhSO_2NCl^- + H^+ \rightleftharpoons PhSO_2NHCl \quad (3)$$

$$2PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + PhSO_2NCl_2 \quad (4)$$

$$PhSO_2NCl_2 + H_2O \rightleftharpoons PhSO_2NHCl + HOCl \quad (5)$$

$$PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + HOCl \quad (6)$$

$$HOCl \rightleftharpoons H^+ + OCl^- \quad (7)$$

$$HOCl + H^+ \rightleftharpoons H_2OCl^+ \quad (8)$$

As a result, in acidic CAB solutions, the potential oxidi-zing species were $PhSO_2NHCl$, $PhSO_2NCl_2$, HOCl and pre-

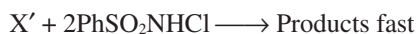sumably H_2OCl^+, while in alkaline CAB solutions, they are $PhSO_2NHCl$, $PhSO_2NCl\text{-}HOCl$ and OCl^- [18,19].

The first-order dependency of rate on $[CAB]_0$, as well as the fact that adding benzene sulfonamide has little effect on the rate of reaction, indicate that $PhSO_2NCl_2$ and $HOCl$ could not be reactive species (eqns. 4-6). And at the laboratory conditions, these species were found in very low concentrations.

The rate of reaction is virtually unaffected by changes in $[H^+]$, the ionic activity of the medium or the addition of reduction agent, benzene sulfonamide. The protonated conjugate acid $(PhSO_2NH_2Cl^+)$ has been suggested as a potential oxidizing species based on the experimental findings and we have proposed **Scheme-I** to describe the oxidation of CNT by CAB in an acid medium.
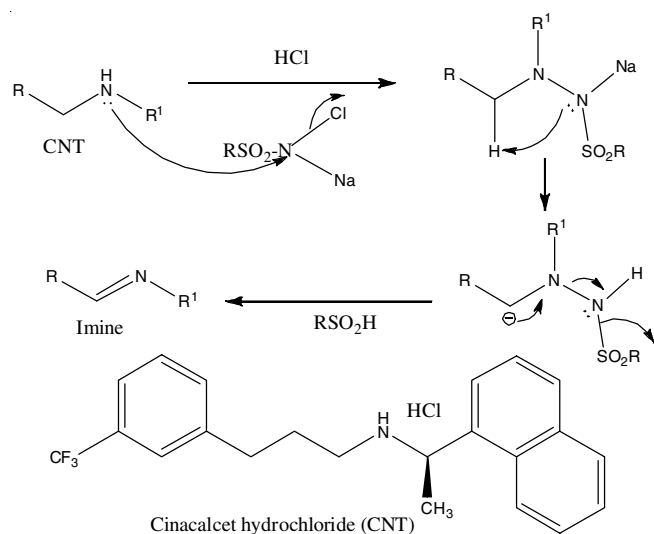
Scheme-I: Detailed mechanism of oxidation of cinacalcet hydrochloride (CNT) by chloramine-B (CAB) in acidic medium

Based on the above discussion and experimental findings, the following general reaction scheme involving the oxidizing species of CAB $(PhSO_2NHCl)$ reacts with substrate, the rate of reaction is first order dependency on $[substrate]_0$, prior equilibrium is shown and a rate-determining step follows.

$$PhSO_2NHCl + CNT \rightleftharpoons X \quad \text{fast}$$

$$X \longrightarrow X' \quad \text{slow and rate determining step}$$

$$X' + 2PhSO_2NHCl \longrightarrow \text{Products} \quad \text{fast}$$

Based on **Scheme-I**, the rate law has been derived as follows:

$$\text{Rate} = \frac{K_1K_2[CAB]_t[CNT][H^+]}{1+K_1[H^+]} \quad (9)$$

The mode of oxidation of cinacalcet hydrochloride (CNT) by CAB (**Scheme-I**) is in good agreement with the observed experimental results and rate law (eqn. 9) is in good agreement with the observed experimental results. Observed activation parameters affirm the suggested mechanism. Furthermore, high positive energy values of Gibbs free energy of activation and enthalpy of activation suggest a strongly solvated transition state, while a high negative value of entropy suggests the formation of a compact transition state of many degrees of freedom lost [20].

Conclusion

The kinetics and oxidation of cinacalcet hydrochloride by chloramine-B in acidic medium have been investigated. The reaction has a stoichiometry of 1:2. The oxidation products were established and the Arrhenius plot was used to calculate thermodynamic parameters. The observed results were accompanied by a valid mechanism and a rate law was proposed.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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