Section 1.1

INTRODUCTION TO ORGANIC N-HALOAMINES

The chemistry of N-halo-N-sodio (or potassio) and N, N-dihalo aromatic sulfonamides,

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{S} & \quad \text{N} \\
\text{O} & \quad \text{M (or X)} \\
\end{align*}
\]

\( R = \text{CH}_3 \text{ or } H \)  
\( M = \text{Na or K} \)  
\( X = \text{Cl, Br or I} \)

...has evinced considerable interest because they act as sources of both halonium cations and N-anions which act as both bases and nucleophiles [1]. Amongst these, N-metallo-N-haloaryl sulfonamides have received significant attention. Organic sulfonyl-N-haloamines (organic N-haloamines) are mild oxidants containing a strongly polarized N-bonded halogen in its +1 oxidation state. Kinetics and mechanism of oxidation by these reagents have attracted the attention of chemists due to their diverse properties [2-7]. These compounds resemble hypohalites in their oxidative behavior and, although less familiar, they are more stable than hypohalites [8]. Consequently, these reagents react with a wide range of functional groups effecting an array of molecular transformations [2-7]. The prominent members of organic N-haloamines are chloramine-T (p-\( \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NClNa.3H}_2\text{O} \) or CAT) and chloramine-B (\( \text{C}_6\text{H}_5\text{SO}_2\text{NClNa.1.5H}_2\text{O} \) or CAB), and their corresponding bromine analogues are bromamine-T (p-\( \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NBrNa.3H}_2\text{O} \) or BAT), bromamine-B (\( \text{C}_6\text{H}_5\text{SO}_2\text{NBrNa.1.5H}_2\text{O} \) or BAB), respectively. Generally, these mono-haloamines undergo a two electron change in their reactions, the products being p-toluenesulfonamide / benzenesulfonamide and NaCl / NaBr [9]. The redox potential of haloamine-sulfonamide couple is pH dependent, and decreases with an increase in the pH of the medium (for CAT \( E_{\text{redox}} 1.138, 0.778, 0.614 \) and 0.5 V at pH 0.65, 7.0, 9.7 and 12, respectively). Since organic haloamines have the same chemical properties, it is expected that similar equilibria exist in solutions of these compounds [8].
Aqueous solutions of haloamines behave as strong electrolytes and, depending on the pH, they furnish following types of reactive species [10-13].

\[
\begin{align*}
\text{RNXNa} & \rightleftharpoons \text{RN}^-\text{X} + \text{Na}^+ \\
\text{RN}^-\text{X} + \text{H}^+ & \rightleftharpoons \text{RNHX} \\
2 \text{RNHX} & \rightleftharpoons \text{RNH}_2 + \text{RNX}_2 \\
\text{RNHX} + \text{H}_2\text{O} & \rightleftharpoons \text{RNH}_2 + \text{HOX} \\
\text{RNX}_2 + \text{H}_2\text{O} & \rightleftharpoons \text{RNHX} + \text{HOX} \\
\text{RNHX} + \text{H}^+ & \rightleftharpoons \text{RN}^+\text{H}_2\text{X} \\
\text{RN}^+\text{H}_2\text{X} + \text{H}_2\text{O} & \rightleftharpoons \text{RNH}_2 + \text{H}_2\text{O}^+\text{X} \\
\text{HOX} & \rightleftharpoons \text{H}^+ + \text{XO}^- \\
\text{HOX} + \text{H}^+ & \rightleftharpoons \text{H}_2\text{O}^+\text{X}
\end{align*}
\]

(Here R= p-CH₃C₆H₄SO₂⁻ for CAT and BAT and C₆H₅SO₂⁻ for CAB and BAB; X= Cl or Br)

Therefore, the possible oxidizing reactive species in acidified monohaloamine solutions are RNHX, RNX₂, HOX, and possibly H₂O⁺X, and in alkaline solutions RNHX, HOX, RN X and O’X. Out of these possible oxidizing species of N-haloamines, the reactive species shall be decided by the observed kinetic data. These are mild and efficient oxidizing agents in the kinetic and mechanistic studies of oxidation of different functional groups. Therefore, the mechanisms of oxidation of several substrates have been extensively investigated kinetically using these reagents by many researchers [2-7]. Chloramines are commercially available whereas BAT and BAB can be easily prepared from bromination of their chloramines. These reagents are inexpensive, water tolerant, non-toxic and easy to handle [6]. For these reasons, further studies are warranted for a better understanding of oxidation-kinetic behavior of aforesaid reagents towards various substrates under different experimental conditions. Consequently, these N-haloamines have been used as oxidizing agents in the present kinetic study.
**Chloramine T:** Chloramine T was first prepared by Chattaway [14] by treating toluene with chlorosulphonic acid when ortho and para isomers of toluenesulphonylchloride are formed. The para compound on treatment with ammonia gives sulfanamide which with aqueous sodium hypochlorite (1.3 – 2.0 mol dm⁻³) produces CAT. The colourless compound can be crystallized out and can be purified by recrystallization from warm water, and drying in air subsequently. The maximum purity obtainable is 99.5% with successive crystallizations. Hence, CAT cannot be used as a primary standard. It is soluble in water to an extent of 14 g / 100 ml at 298 K. It is also soluble in alcohol and acetone, but insoluble in benzene, chloroform and ether. Bishop and Jennings [8] have calculated the concentrations of different species in 0.05 mol dm⁻³ CAT solutions at different pH. As seen from Table 1.1, TsNHCl and TsNCl₂ predominate at low pH but as the acidity decreases, the anion TSN⁺Cl becomes important and is present in a reasonable high concentration even in weakly acidic solutions. In alkaline medium, the acid anion predominates over HOCl.

**Table 1.1 Concentrations of various species present in a 0.05 mol dm⁻³ CAT solution over a range of pH values.**

<table>
<thead>
<tr>
<th>pH</th>
<th>[TsNCl]</th>
<th>[TsNHCl]</th>
<th>[TsNCl₂] = [TsNH₂]</th>
<th>[HOCI]</th>
<th>[OCl⁻]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.60 x 10⁻⁵</td>
<td>4.01 x 10⁻²</td>
<td>9.90 x 10⁻³</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻¹⁴</td>
</tr>
<tr>
<td>1</td>
<td>9.60 x 10⁻⁴</td>
<td>4.01 x 10⁻²</td>
<td>9.90 x 10⁻³</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻¹³</td>
</tr>
<tr>
<td>2</td>
<td>7.80 x 10⁻³</td>
<td>3.24 x 10⁻²</td>
<td>7.98 x 10⁻³</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻¹²</td>
</tr>
<tr>
<td>3</td>
<td>2.83 x 10⁻²</td>
<td>1.18 x 10⁻²</td>
<td>2.92 x 10⁻³</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻¹¹</td>
</tr>
<tr>
<td>4</td>
<td>3.84 x 10⁻²</td>
<td>1.60 x 10⁻³</td>
<td>3.95 x 10⁻⁴</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻¹⁰</td>
</tr>
<tr>
<td>5</td>
<td>4.00 x 10⁻²</td>
<td>1.67 x 10⁻⁴</td>
<td>4.10 x 10⁻⁵</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻⁹</td>
</tr>
<tr>
<td>6</td>
<td>4.00 x 10⁻²</td>
<td>1.67 x 10⁻⁵</td>
<td>4.10 x 10⁻⁶</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻⁸</td>
</tr>
<tr>
<td>7</td>
<td>4.00 x 10⁻²</td>
<td>1.67 x 10⁻⁶</td>
<td>4.10 x 10⁻⁷</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻⁷</td>
</tr>
<tr>
<td>8</td>
<td>4.00 x 10⁻²</td>
<td>1.67 x 10⁻⁷</td>
<td>4.10 x 10⁻⁸</td>
<td>3.95 x 10⁻⁷</td>
<td>1.3 x 10⁻⁶</td>
</tr>
</tbody>
</table>

Chloramine-T can be used as a useful oxidant since it liberates iodine from acidified iodide solution. TsNClNa + 2I⁻ + 2H⁺ → TsNH₂ + I₂ + Na⁺ + Cl⁻
**Chloramine B:** Chloramine-B was first proposed by Afanas’ev [15] as a substitute for chloramine-T for volumetric reagent. It was prepared by the action of chlorine on benzenesulfonamide in the presence of NaOH. Benzenesulfonamide (1 mole) was added gradually to 4-5 mol dm$^{-3}$ NaOH solution (2-3 moles), at 298 K with stirring. When the solution became homogenous, it was filtered and the filtrate was heated to 338 – 343 K and chlorine was bubbled slowly over a period of 1 h. The mass separated was stirred for 1 h at the same temperature, then heated to 358 K and filtered through a Schott’s funnel. A 99 % yield was obtained. If chlorine is passed more rapidly, dichloramine-B is formed along with CAB as an intermediate product.

Chloramine-B is water and alcohol soluble. The active chlorine content in CAB has been estimated by iodometric method and was found to be 28-29.5%. It is observed that CAB does not liberate chlorine in acid solution. On acidifying an aqueous solution of CAB with HCl or H$_2$SO$_4$, a white precipitate of dichloramine-B (DCB) is formed. The reaction involves a two electron change and hence the equivalent weight of CAB is equal to half its molecular weight. Chloramine-B is found to be fairly stable when preserved in colored glass stoppered bottles at room temperature. In the present research, we have used commercially available CAT and CAB. The purity of these compounds was checked frequently by iodometric method. Like CAT, CAB is an oxidant in volumetric analysis and is also used for the purification of drinking water.

**Bromamine-T:** Bromamine-T is an addition to the class of haloamines and was used as an oxidimetric titrant in aqueous medium by Nair *et al* [16]. The compound can be prepared by the partial debromination of dibromamine-T (p-CH$_3$C$_6$H$_4$SO$_2$NBr$_2$ or DBT) which is obtained by the bromination of CAT. Chloramine-T (10 g) is dissolved in water and liquid bromine (2 ml) is added from a burette to the solution with constant stirring. The golden yellow precipitate of DBT obtained is thoroughly washed with water, filtered under suction and dried in vacuum desiccators for 24 h. About 33 g of DBT thus prepared was dissolved in 50 ml of aqueous 4 mol dm$^{-3}$ NaOH in small quantities at a time with stirring and the solution was cooled in ice. Pale yellow crystals of BAT separated out. These were filtered under suction,
washed quickly with the minimum quantity of water and dried over P₂O₅. The yield was ~ 28 g. The available bromine was determined by iodometric method: found 24.3%, required for BAT 24.5%.

The purity of compound was checked iodometrically and also from IR spectral data. The IR spectrum of the compound was recorded on a Perkin-Elmer 298 grating infrared spectrophotometer (KBr pellets). The spectrum shows characteristic bands (cm⁻¹) at 3500 (strong γ-OH), 2150 (weak, γC=C), 1656 (medium, γ-OH), 1235 (strong, γ_{asym-SO₂}), 1120 (strong, shoulder, γ_{sym-SO₂}), 1075, 1015 (medium, aromatic in plane δ,CH), 915 (strong, γ, N-N), 802 (strong, 1,4 disubstituted phenyl ring), 665 (medium, γ_N-Br) and 615 (medium, out of plane ring deformation). Here γ = stretch, γ_{sym} = symmetric stretch, γ_{asym} = asymmetric stretch, δ = bending.

**Bromamine-B:** Bromamine-B was prepared [17] by the partial debromination of dibromamine-B (C₆H₅SO₂NBr₂ or DBB), which in turn was obtained by the bromination of CAB. Chloramine-B (30 g) was dissolved in 560 ml of water, and then 6 ml of liquid bromine was added dropwise from a burette with constant stirring. The yellow precipitate of DBB formed was thoroughly washed with water, filtered under suction and dried in a vacuum dessicator. The yield was about 35 g indicating ~ 100% recovery. Dibromamine-B (31.5 g) was added in small quantities at a time and with constant stirring to 50 ml of 4 mol dm⁻³ NaOH. The pale yellow mass obtained was cooled in ice, filtered under suction and the product was dried over anhydrous calcium chloride. The yield was about 25.6 g (~ 90%). The compound was recrystallized from hot water (323 K) and stored in brown bottles. The available bromine was determined by iodometry: found 27.95%; required for BAB, 28.04%. Bromamine-B is highly soluble in water (374.3 g / kg at 302 K). Approximately 0.1 N (0.05 M) stock solution was prepared by dissolving 14.3 g in 1 litre of water was kept in amber colored bottles. It was standardized by the addition of 2 N H₂SO₄ and a slight excess of KI solution and titration of the liberated iodine (two equivalents per mole of BAB) with thiosulphate. The solution is moderately stable for a fortnight, but should be standardized
whenever required. The pH of 0.05 mol dm\(^{-3}\) BAB is 9.25. The conditional redox potential determined by the extrapolation procedure is +0.80 V at 297 K and pH 7.9.

Bromamine-B was characterized by IR spectrum data. Infra-red spectral data of BAB (KBr pellet) shows a characteristic absorption band at 561 cm\(^{-1}\) (strong, out of plane ring deformation), 578 cm\(^{-1}\) (strong \(\gamma_{N-Br}\)), 656 cm\(^{-1}\) (strong, in plane ring deformation), 689 cm\(^{-1}\) (strong, in plane ring deformation), 723 cm\(^{-1}\) (medium, out of plane CH bending of two adjacent aromatic H atoms), 753 cm\(^{-1}\) (medium, out of plane CH bending of two adjacent aromatic H atoms), 934 cm\(^{-1}\) (strong, \(\gamma_{sym-N}\)), 1044 cm\(^{-1}\) (weak in plane \(\delta_{CH}\)), 1106 cm\(^{-1}\) (strong, in plane \(\delta_{CH}\)), 1150 cm\(^{-1}\) (strong, \(\gamma_{asym-SO2}\)), 1262 cm\(^{-1}\) (very strong, \(\gamma_{sym-SO2}\)), 1075 cm\(^{-1}\), 1450 cm\(^{-1}\) (strong \(\gamma_{cnc}\)), 1489 cm\(^{-1}\) (weak \(\gamma_{cnc}\)), 1653 cm\(^{-1}\) (strong, \(\gamma_{cnc}\)), 3500 cm\(^{-1}\) (broad, -OH stretch).

**Structures of organic N-haloamines used in the present work.**

![Structures of organic N-haloamines](image-url)
Section 1.2

OXIDATION-KINETICS AND MECHANISTIC INVESTIGATIONS WITH ORGANIC N-HALOAMINES

Chloramine-T, chloramine-B, bromamine-T and bromamine-B are mild and potential oxidizing agents in acid and alkaline media. Review articles of Campbell and Johnson [1], Bremner [2], Banerji et al [3], Agarwal and Upadhyay [4], Amesto et al [5], Geetanjali [6] and Kolvari [7] comprehensively covered almost all the research work pertaining to the kinetic and mechanistic aspects of oxidation reactions of diverse group of substrates with N-haloamines up to the year 2007. Therefore, a brief summary of the relevant work carried out with these reagents has been given below from the year 2008 to till date.

Oxidation-kinetics of chloramine-T

Kinetics of oxidation of Os(VIII)-catalyzed oxidation of benzimidazole (BzI) and 2-substituted benzimidazoles viz., 2-methylbenzimidazole (2-MeBzI), 2-hydroxybenzimidazole (2-HyBzI), 2-aminobenzimidazole (2-AmBzI) and 2-phenylbenzimidazole (2-PhBzI) with CAT in alkaline medium have been investigated by Ramalingaiah et al [18]. The five oxidation reactions follow identical kinetics with first-order dependence each on [CAT]₀ and [substrate]₀, and fractional-order dependence each on [OH⁻] and [Os(VIII)]. The rate of oxidation of benzimidazoles follows the order: 2-MeBzI > 2-HyBzI > 2-PhBzI > 2-AmBzI > BzI > 2-PhBzI. This trend can be attributed to electronic factors. The rates of catalyzed reactions were found to be 10 - 15 fold times faster than the uncatalyzed ones. A suitable mechanism and the related rate law have been deduced. Shukla and co-workers [19] have reported the kinetics of oxidation of vitamin B1 (thiamine hydrochloride) and vitamin B₆ (pyridoxine hydrochloride) by CAT in perchloric acid medium in presence and absence of a non ionic surfactant (Triton x-100). The reaction rate shows identical kinetic behavior with a first-order dependence on [CAT]₀, fractional-order dependence on [substrate]₀ and zero-order dependence on [H⁺], respectively in absence as
well as in presence of Triton x-100. The binding between the oxidant and surfactant micelle was evidenced by spectroscopic data. The binding parameters were evaluated using a pseudo-phase kinetic model.

Puttaswamy and Suresha [20] have reported the kinetics of Ru(III) catalyzed and uncatalyzed oxidation of atenolol (ATN) with CAT in acid medium. The reaction shows a first-order dependence each on [CAT], [Ru(III)], a zero-order dependence on [ATN], and an inverse fractional-order dependence on [H+] for both the Ru(III) catalyzed and uncatalyzed reactions. Activation parameters have been computed. The stoichiometry of the reaction was found to be 1:4 and the oxidation products were characterized. Suitable mechanisms and related rate laws were deduced. Sharma et al. [21] have studied the kinetics and mechanism of oxidation of triethylene glycol with CAT catalyzed by cetyltrimethylammonium bromide in acetic acid medium. The rate shows a first-order with respect to [CAT], and fractional-order with respect to [triethylene glycol]. The salt effect was noticed. The reaction rate increased with increase in dielectric constant of the medium. Effect of chloride ion and p-toluenesulfonamide on the reaction rate was studied. A suitable mechanism and rate law consistent with the experimental results have been proposed.

The kinetics of Pd(II) catalyzed oxidation of D-fructose with CAT in acidic solution in the presence of Hg(II) acetate was studied by Srivastava and Singh [22] in the temperature range of 203 – 318 K. The rate shows first-order in case of oxidant, zero-order with respect to substrate and first-order with respect to catalyst. The rate is independent of [H+]. The positive effect of [Cl−] and almost negligible effect of [Hg(II)] were noticed. There was no effect of rate on the ionic strength of the medium. The formation of transient complex takes place between Pd(II) and CAT. Activation parameters were deduced. The observed results are in conformity with the proposed reaction mechanism. Mohan and Jagadeesh [23] have investigated the oxidation-kinetic study of gabapentin (GP) by CAT in perchloric acid medium. The rate exhibits a first-order dependence on [CAT], and a fractional-order on [GP]. The rate was retarded with an increase in [H+]. There was no pronounced effect by the addition of p-toluenesulfonamide, halide ions and ionic strength of the medium on the
reaction rate. Activation parameters have been calculated. Stoichiometry of the reaction and the oxidation products were identified. A suitable mechanism has been suggested.

Shukla and Upadhyay [24] have narrated the kinetics of oxidation of vitamins B₁ and B₆ by CAT in presence of polyoxyethylene(23)laurylether (Brij-350) micelle. The orders with respect to oxidant are first, substrate is fractional and acid is zero. The binding or association between oxidant and surfactant was supported by the spectrophotometric evidence. Menger and Portnoy’s kinetic model was adopted and the binding parameters have been calculated. Platinum group metal ions catalyzed oxidation-kinetics of glycyl-glycine (Gly-Gly) by CAT in alkaline medium was investigated by Puttaswamy and Jagadeesh [25]. The stoichiometry and oxidation products were same for all the catalyzed reactions but the kinetic patterns were different. The relative trend reactivity of the catalysts in the oxidation of Gly-Gly by CAT are as follows: Os(VIII) > Ru(III) > Pt (IV) > Pd(II). This may be attributed due to d-electronic configuration of the catalysts. The rates of oxidation of catalyzed reactions are found to be 7 to 24 fold times faster than the uncatalyzed reactions. The comprehensive mechanistic interpretation and the related kinetic modeling have been worked out for each catalyzed reaction. Vinod et al [26] have investigated the kinetics and mechanism of oxidation of an azo dye amaranth by CAT in perchloric acid medium spectrophotometrically at 293 K. The kinetic data exhibits first-order dependence of rate both on [CAT]₀ and [Dye]₀, and an inverse fractional-order on [H⁺]. The stoichiometry of the reaction was found to be 1:1. The oxidation products of the dye were identified. The derived rate law was in consistent with the experimental results.

Singh et al [27] have reported the systematic kinetic and mechanistic study of paracetamol with CAT catalyzed by iridium (III) chloride in acid medium. The orders with respect to [oxidant]₀, [substrate]₀ and [Cl⁻] are first-order each at lower concentrations but changes to zero-order at higher concentrations. The reaction rate showed first-order kinetics with respect to catalyst. The rate was retarded with increase in acid concentration. Addition of p-toluenesulphonamide decreased the rate. The rate increased with increase in dielectric constant of the medium. Activation parameters were evaluated. A plausible mechanism was
elucidated based on kinetic results, stoichiometric ratio and products. The kinetics and 
mechanism of Pd(II) catalyzed oxidative decolorization of p-rosaniline, crystal violet and 
ethyl violet dyes by CAT in alkaline medium have been investigated by Vinod et al [28]. The 
oxidation reaction shows similar kinetic behavior for all the three dyes. The reaction kinetics 
obey the rate law, rate = k [CAT]_o^a [Dye]_o^b [OH]_o^c [Pd(II)]_o^d where a and b are unity, and c 
and d are less than unity. The rate was retarded by the addition of p-toluenesulfonamide. The 
rate of the reaction increases with increase in ionic strength of the medium. The reactivity rate 
follows the order: p-rosaniline > crystal violet > ethyl violet. This reactivity trend may be due 
to inductive effect of the substituents present in the dye. Further, it was found that the 
catalyzed oxidation reactions are around four-times faster than the uncatalyzed reactions. A 
mechanistic scheme and the rate law have been worked out based on the kinetic observations.

Shubha and puttaswamy [29] have reported results obtained on the kinetics of 
oxidation of thiourea and N-substituted thioureas namely: N-methylthiourea, N-allylthiourea, 
N-phenylthiourea and N-tolylthiourea by CAT in presence of HClO₄ at 278 K. The reactions 
follow identical kinetics for all thioureas, being first-order each with respect to [CAT]_o, 
[Thiourea]_o and [H^+]. Ionic strength of the medium and addition of p-toluenesulfonamide or 
halide ions have negligible influence on the rate. The solvent isotope effect has been studied 
using D₂O in the case of the oxidation of thiourea. Decrease in dielectric constant of the 
medium by adding methanol decreases the rate. Composite activation parameters have been 
computed. An isokinetic relationship observed with β = 314 K, indicating that enthalpy 
factors control the reaction rate. Under comparable experimental conditions, the rate of 
oxidation of thioureas increases in the order: N-allylthiourea > N-phenylthiourea > 
N-methylthiourea > thiourea > N-tolylthiourea. A mechanism involving the interaction of 
conjugate acid (CH₃C₆H₄SO₂NHCl) and substrate giving an intermediate complex, in a slow 
step, has been suggested. The derived rate law is in agreement with the observed kinetics. 
Oxidation mechanism of metochlopramide hydrochloride (MCP) by CAT in acid medium has 
been kinetically studied by Meenakshi and Pai [30]. The reaction rate exhibits first-order 
dependence on [oxidant]_o, and fractional-order on [MCP]_o. The rate was retarded by [H^+]. 
Reaction constants have been computed. Michaelis-Menten type of kinetics was proposed.
Stoichiometric ratio was found to be 1:2 and oxidation products were characterized. A suitable mechanism has been suggested. Related rate law has been derived.

Singh and Raghuveer [31] have carried out the oxidation - kinetic study of D-ribose and D-arabinose by acidic solution of CAT catalyzed by Pd(II) in the presence of mercuric acetate, as a scavenger. The rate shows a first-order dependence with respect to [CAT] and [Pd(II)] and zero order with respect to the [substrate]. The rate increases with an increase in [Cl⁻] but it is independent of [H⁺]. There is no pronounced effect of mercuric acetate on the rate of the reaction. Activation parameters have been calculated. A suitable mechanism in consistent with observed kinetics has been proposed. A detailed oxidative decolorization kinetics study of methylene blue (MB) by CAT in alkaline medium catalyzed by Os(VIII) have been studied [32] spectrophotometrically at 664 nm (λmax of the dye). The reaction rate exhibited a first-order dependence each on [CAT], and [MB], a fractional-order dependence on [Os(VIII)], and an inverse-fractional-order dependence on [NaOH]. The dielectric constant is negative. The solvent isotope effect k'(H₂O) / k' (D₂O) was equal to 1.37. Activation parameters were computed. The kinetics of oxidation of MB by CAT in alkaline medium was also studied with other platinum metal ions. The relative reactivity of these catalysts are in the order Os(VIII) > Ru(III) > Ir(III) > Rh(III) > Pt(IV) > Pd(II). This trend may be attributed to the different d-electronic configurations of the metal ions. It was found that the catalyzed reactions are about 3 to 10-fold times faster than the uncatalyzed reactions. The mechanism proposed and the derived rate law are in agreement with the observed kinetics.

Singh and co-workers [33] have investigated the kinetics and mechanism of Os(VIII) catalyzed oxidation of 2-methyl cyclohexanol by alkaline CAT. The results indicate zero-order kinetics with respect to 2-methyl cyclohexanol and first-order kinetics with respect to CAT, OH⁻ and Os(VIII) concentrations. There is insignificant effect of ionic strength, p-toluene sulphonamide and KCl on the reaction rate. The dielectric effect is positive. Elevation of temperature increases the rate of reaction in oxidation of 2-methyl cyclohexanol. A suitable mechanism in conformity with the above observation has been proposed. Decolorization
kinetics of indigo carmine (IC) by oxidation process using CAT as oxidant and Co(II) as catalyst in acidic buffer media (pH 5.8) has been investigated at 300 K spectrophotometrically [34]. The Co(II)-catalyzed reaction shows first-order dependence of the rate each on [CAT] and [IC]. It also shows fractional-order dependence both on [Co(II)] and [H⁺]. Addition of halide ions and p-toluenesulfonamide, and variation of ionic strength and dielectric constant of the medium do not have any significant effect on the reaction rate. Activation parameters are evaluated from the Arrhenius plot. A plausible mechanism is proposed for the reaction. Related rate law has been derived.

The kinetics of oxidation of dulcitol by alkaline solution of CAT in the presence of iridium (III) chloride catalyst has been studied [35]. The results show first-order kinetics with respect to each on [CAT]₀, [Ir(III)] and [OH⁻]. First-order kinetics with respect to dulcitol at its low concentration tends to zero-order at its higher concentration range. Addition of potassium chloride decreases the rate constant. Zero effects of rate upon addition of p-toluenesulfonamide and also variation of ionic strength of the medium have been observed. A suitable mechanism with all experimental results has been proposed. Khan et al [36] have studied the kinetics and mechanism of oxidation of levofloxacin (LF) with CAT in aqueous perchloric acid medium at 298 K. The reaction followed a first-order kinetics each on [CAT]₀, [LF]₀, and [H⁺] in their lower concentrations range, but the reaction shows zero-order at their higher concentrations. The effect of added products, ionic strength and dielectric constant of the medium was studied on the rate of reaction. The activation parameters with respect to the slow step of the mechanism were evaluated. A suitable mechanism has been suggested.

The kinetic and mechanistic study of oxidative conversion of Lactic acid (LA) by CAT in acid medium have been reported by Kolachana et al [37]. The oxidation-kinetics of LA by CAT in acid solutions at 323 K has been spectrophotometrically investigated at λₘₐₓ = 255 nm. The reaction, studied under pseudo-first-order conditions of [LA]₀ >> [CAT]₀, follows a first-order dependence of the rate on [CAT]₀ and a fractional-order on [LA]₀. Variations of the [PTS], [H⁺], [SO₄²⁻], dielectric constant, and ionic strength of the reaction medium have no significant effect on the rate. Activation parameters are evaluated. A
mechanism consistent with the observed kinetics and activation data has been proposed leading to the derived rate law. Shubha and Puttaswamy [38] have carried out the oxidative decolorization kinetics of carmosine dye with acidic CAT spectrophotometrically. The experimental results reveals that reaction rate exhibits a first-order dependence each on [oxidant]₀ and [dye]₀ and a fractional-order dependence on [H⁺]. Activation parameters have been deduced. Effects of added p-toluenesulfonamide and halide ions and variation of ionic strength and dielectric constant of the medium on the rate of the reaction have been investigated. Suitable mechanism and related rate law have been worked out.

**Oxidation-kinetics of chloramine-B**

Oxidative cleavage of Vitamin B₁ (thiamine hydrochloride, THM) with CAB in presence of HCl and Ru(III) catalyst have been investigated kinetically by Mohana et al [39]. The rate law obtained is : rate = k [CAB]₀[Ru(III)][H⁺][THM]₀ᵃ[Cl⁻]ᵇ, where a and b are less than unity. Addition of benzenesulfonamide and variation of ionic strength does not have any significant effect on the rate. Dielectric effect was studied by changing the solvent composition with acetonitrile. The stoichiometric ratio was found to be 1:1. Oxidation products were characterized. Activation parameters and the reaction constants were evaluated. A suitable mechanism and relative rate law has been deduced. The kinetics of oxidation of phenyl propanolamine hydrochloride (PPA) with CAB catalyzed by Ru(III) has been carried out in HCl medium [40]. The reaction rate follows the order: -d [CAB] / dt = k [CAB]₀[H⁺]ʸ [PPA]₀ᶻ[Ru(III)]ᵣ, where x, y, z < 1. The stoichiometry of the reaction was found to be 1:1. Benzaldehyde and acetaldehyde were characterized as the oxidation products of PPA. Solvent isotope effect k⁺ (H₂O) / k⁺ (D₂O) was found to be 2.39. Activation parameters have been calculated. Proton inventory studies were carried out in H₂O-D₂O mixtures. The conjugate acid is postulated as the reactive species of CAB. A suitable mechanism is proposed based on the experimental observation.

Puttaswamy and Shubha [41] have investigated the kinetics of oxidation of coumarin and four substituted coumarins viz., 7-methoxycoumarin, 7-ethoxycoumarin,
7-hydroxycoumarin and 7-nitrocoumarin with CAB in HCl medium at 298 K. Under comparable experimental conditions, the reaction rate shows a first order dependence each upon [CAB]₀ and [coumarin]₀, and individually less than unit order dependence on [H⁺] and [Cl⁻]. Addition of benzenesulfonamide retards the reaction rate and the dielectric effect is positive. The solvent isotope effect for coumarin and 7-hydroxy coumarin is \( k' / k'' (\text{D}_2\text{O}) = 0.81 \) and 0.83, respectively. Activation parameters have been evaluated. The stoichiometry of the reaction was found to be 1:1 and the oxidation products of coumarins were identified as their corresponding o-hydroxy cinnamic acids. The rate of oxidation of coumarins increases in the order: 7-hydroxycoumarin > 7-ethoxycoumarin > 7-methoxycoumarin > coumarin > 7-nitrocoumarin. The rates satisfactorily correlate with the Hammett \( \sigma \) relationship and the reaction constant \( \rho \) is -0.04, signifies that electron donating groups enhance the rate and the electron withdrawing group retards the rate. An isokinetic relationship was observed with \( \beta = 348 \) K, which showed the reaction to be enthalpy controlled. A mechanism consistent with the experimental results is proposed and the related rate law has been deduced. The kinetics of oxidation of aliphatic primary amines, n-propylamine (PA) and butylamine (BA), by CAB and CAT in aqueous alkaline medium has been studied at 318 K by Veeraiah et al [42]. The reaction follows the experimental rate law: 
\[ k' [\text{oxidant}][\text{amine}]_0[\text{OH}^-]^x, \] 
where oxidant is CAT or CAB and \( x \) is fractional. Additions of chloride ions, p-toluenesulfonamide or benzenesulfonamide, and sodium perchlorate, which are used for varying the ionic strength of the solvent medium, have no effect on the reaction rate. However, the rate alters with change in dielectric constant of the medium. Activation parameters have been evaluated. A suitable mechanism consistent with the observed kinetic data has been proposed and the rate law derived.

Nirmala Vaz et al [43] have reported the kinetics and mechanism of oxidative conversion of 5-hydroxyindole to 2-oxo-hydroxyindole by CAB in alkaline medium. Under pseudo first-order conditions of \([\text{Indole}]_0 \gg [\text{CAB}]_0\), the oxidation reaction follows the experimental rate law: 
\[ \text{rate} = k'[\text{CAB}]_0[\text{Indole}]_0[\text{OH}^-]^x / [\text{BSA}]^y, \] 
where BSA represents benzenesulfonamide and \( x \) and \( y \) are fractional orders. The retarding effect of BSA on the rate indicates its involvement in a fast pre-equilibrium in the mechanism of oxidation. Activation
parameters have been determined. The variation of [OH⁻] at constant [BSA] was performed to evaluate the equilibrium and decomposition constants. Based on the mechanism proposed, a rate law has been derived. Furthermore, the methodology developed could be adopted in the synthesis of 2-oxo-5-hydroxyindole. The results obtained on the kinetics of oxidation of etamsylate (ETM) by CAB in NaOH medium at 303K has been reported [44]. The reaction rate shows a first order dependence on [CAB]₀ and fractional-order with respect to both [ETM]₀ and [OH⁻]. Effects of added benzenesulphonamide and halide ions have been investigated. The effect of dielectric constant of the medium by varying [MeOH] shows an inverse effect. The Michaelis – Menten type of kinetics has been proposed. The reaction was studied at different temperatures and the values of thermodynamic parameters were computed. The reaction stoichiometry and oxidation products have been identified and a suitable mechanism has been proposed.

**Oxidation-kinetics of bromamine-T**

Kinetic and mechanistic studies of the oxidation of ethylenediamine tetraacetic acid (EDTA) by BAT in acetic buffer of pH 5 have been investigated by Obeid [45]. The reaction showed first-order kinetics on [BAT] and fractional order each on [EDTA]₀ and [H⁺]. Addition of reaction p-toluenesulfonamide or varying the ionic strength of medium has no effect on the rate. A mechanism involving electrophilic attack by positive halogen of BAT at neutral nitrogen of EDTA was proposed. A rate law has been derived. The kinetics and mechanism of oxidation of diclofenac by CAT and BAT in NaOH medium have been studied at 293 K [46]. Under comparable experimental conditions, reactions with both the oxidants follow identical kinetics with a first-order dependence on each [oxidant]₀ and a fractional-order dependence each on [diclofenac]₀ and [NaOH]. Activation parameters have been computed. Solvent isotope effect was studied using D₂O. N-hydroxydiclofenac is identified as the oxidation product of diclofenac by GC-MS. Michaelis-Menten type of mechanism has been suggested. The rate of oxidation of diclofenac is about four-fold times faster with BAT as compared to CAT. This may be attributed to the difference in electrophilicities of Cl⁻ and Br⁻ ions and also the vander Waal’s radii of chlorine and bromine. A general mechanism involving the
formation of a complex between the substrate and the anion of the oxidant, which decomposes in the rate-determining step, has been proposed. A relevant rate law has been deduced.

Jagadeesh et al [47] have carried out the oxidation kinetics of folic acid (FA) with BAT in alkaline medium catalyzed by Ru(III), Os(VIII), Pd(II) and Pt(IV) at 313 K. The stoichiometries and oxidation products of the four catalyzed reactions were found to be the same, but their kinetic patterns and oxidation mechanisms were different. Oxidation products of folic acid are pterin-6-carboxylic acid, p-aminobenzoic acid and glutamic acid. Activation parameters were evaluated for each catalyzed reaction. Under identical sets of experimental conditions, the kinetics of all the four catalyzed reactions were compared with those of uncatalyzed reactions, revealing that the catalyzed reactions are 6–22 times faster. The catalytic efficiency of these catalysts follows the order: Os(VIII) > Ru(III) > Pt(IV) > Pd(II). This trend can be attributed to the different electronic configuration of the catalysts. Based on the observed experimental results, a detailed mechanistic interpretation and the related kinetic model were worked out for each catalyst.

The kinetics of oxidation of Cetirizine dihydrochloride [2-(2-{4-[[4-chlorophenyl](phenyl)methyl]-1-piperazino}ethoxy)acetic acid dihydrochloride, CTZ] with BAT in HCl medium has been studied by Rangaraju et al [48]. The reaction rate shows a first-order dependence each on [BAT]o, [CTZ]o and negative fractional-order dependence on [HCl]. The dielectric constant effect is negative. Thermodynamic parameters have been computed. The Michaelis-Menten type of kinetics has been proposed. A mechanism consistent with observed kinetics is proposed. Diwya et al [49] have carried out the kinetics and oxidation of tranexamic acid (TA) by BAT in hydrochloric acid medium using RuCl3 as catalyst at 303K. The rate was first-order both on [BAT]o and [RuCl3], and fractional-order each on [TX], [H+] and [PTS]. Dielectric effect is positive. From the linear Arrhenius plot, activation parameters were computed. Oxidation products were identified. Protonated oxidant H2O2Br has been postulated as the reactive species which reacts with the substrate. Based on kinetic results, a reaction stoichiometry and oxidation product, a suitable mechanism has been proposed.
Oxidation-kinetics of bromamine-B

The kinetics of oxidation of phenylpropanol amine with BAB in NaOH medium has been reported by Prasad and Mohana [50]. The reaction exhibits first-order dependence each on [BAB]₀ and [OH⁻], and fractional-order dependence on [substrate]₀. Rate increased with an increase in dielectric constant of the medium. Oxidation products were identified as benzaldehyde and ethyldeneamine. Proton inventory studies were made. Reaction constants and activation parameters have been calculated. Appropriate rate law has been deduced. Suitable mechanism has been worked out. Shubha and Puttaswamy [51] have reported the N-oxidation of pyrazines and substituted pyrazines by BAB kinetically in perchloric acid medium. The reaction shows identical kinetics being first-order each on [BAB]₀ and [Pyrazine]₀, and a fractional-order dependence on [H⁺]. There is no pronounced effect on the reaction rate by the variation of ionic strength of the medium and also addition of halide ion or benzenesulfonamide to the reaction mixture. The dielectric effect is positive. Stoichiometry of the reaction was found to be 1:1. The products were characterized as respective N-oxides. Hammett relationship was observed and the reaction constant ρ was found to be -0.8 indicating electron donating groups enhance the reaction rate. An isokinetic temperature of β = 333 K indicated that the reaction was enthalpy controlled. The mechanism and the related rate law are in consistent with the observed experimental results.

An efficient platinum (IV) catalyzed oxidation process has been developed for the facile conversion of benzoazoles to aminophenols using sodium salt of N-haloamines in an alkaline pH [52]. Under similar experimental conditions, the common oxidation mechanism which operates in all the reactions has been proposed and the related identical kinetic model was designed. Solvent isotope studies made in a mixture of H₂O-D₂O indicate the participation of OH⁻ ion in the formation of transition states. The reactions have also been carried out in the absence of platinum catalysts and the studies imply that the catalyst accelerates the reaction rates with about 10 to 12 fold times faster. An isokinetic temperature was observed with β = 370 K indicates that the reactions are under enthalpy control. Spectroscopic studies have been made for an intermediate complex formation between N-
haloamine and Pt(IV). The catalytic method developed for the oxidation process was found to be very efficient and the involvement of cost-effective reagents makes the reaction simple and convenient for scaling the method for the industrial / technological operations with suitable modification.

Karthikeyan and co-workers [53] have explained the Ru(III), Os(VIII) and Ru(III) + Os(VIII) catalyzed methodology for the synthesis of anthralinic acids from indoles using BAB in alkaline acetonitrile-water (1:1) at 313 K through kinetic and mechanistic studies. The positive synergistic catalytic activity of Ru(III) + Os (VIII) was observed to a large extent with the activity greater than the sum of their individual catalytic activities. Detailed kinetic and mechanistic investigations for each catalyzed reactions were carried out. Activation parameters were evaluated for each catalyzed reaction. The rates of oxidation reactions were compared with the uncatalyzed reaction. The catalytic efficiency of aforementioned catalysts follows the order: Ru(III) +Os(VIII) > Os(VIII) > Ru(III). This trend may be attributed to the different d-electronic configuration of the catalysts.
Section 1.3

INTRODUCTION TO DRUGS

In the present research, the following pharmacologically important organic compounds of diverse categories have been chosen for our oxidation-kinetic and mechanistic studies with N-haloamines under various experimental conditions:

<table>
<thead>
<tr>
<th>SL.No.</th>
<th>Category of the drug</th>
<th>Name of the drug</th>
<th>Structure of the drug</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tricyclic antidepressants</td>
<td>(i) Imipramine HCl</td>
<td><img src="image" alt="Imipramine HCl Structure" /></td>
<td>Used in the treatment of psychiatric disorders.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ii) Clomipramine HCl</td>
<td><img src="image" alt="Clomipramine HCl Structure" /></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Antiparasitic</td>
<td>(i) Ornidazole</td>
<td><img src="image" alt="Ornidazole Structure" /></td>
<td>Used to treat amoebiasis, trichomoniasis, giardiasis and anaerobic infections</td>
</tr>
<tr>
<td>3.</td>
<td>Skeletal muscular relaxants</td>
<td>(i) Mephenesin</td>
<td><img src="image" alt="Mephenesin Structure" /></td>
<td>Used as skeletal muscle relaxant</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscular relaxant and expectorant</td>
<td>(ii) Guaifenesin</td>
<td><img src="image" alt="Guaifenesin Structure" /></td>
<td>Used as expectorant. Derivatives of guaifenesin is methocarbamol, which is widely used for the relief of skeletal muscle spasm</td>
</tr>
<tr>
<td></td>
<td>Antifibrinolytic</td>
<td>(i) Tranexamic acid</td>
<td>It prevents excess loss of blood in hyperfibrinolytic conditions. It is also used in skin-whitening agent (recently)</td>
<td></td>
</tr>
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<td>----------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>β- lactam antibiotics</td>
<td>(i) Cephalexin</td>
<td>Widely used to treat respiratory and urinary tract infections, bronchitis, pneumonia, prostatitis, soft tissues infections that are often caused by sensitive bacteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ii) Cephradine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(iii) cefadroxil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Antimalarial</td>
<td>(i) amodiaquine HCl</td>
<td>It is useful as a first line drug for treating chloroquine resistant malaria.</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7.</td>
<td>Antiallergic</td>
<td>(i) Cetrizine 2HCl</td>
<td>It is used in the treatment of perennial and seasonal allergic rhinitis and also for chronic hives</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Antiulcer</td>
<td>(i) Ranitidine HCl</td>
<td>It is used in the treatment of ulcer</td>
<td></td>
</tr>
</tbody>
</table>

In view of the importance of the aforesaid drugs, it is very essential to know their oxidative mechanistic chemistry kinetically. An extensive literature survey reveals that only sporadic references are available on the kinetic and mechanistic aspects of oxidation of these drugs. Consequently, in the present research, these compounds have been oxidized with N-haloamines under different experimental conditions to unfold the kinetic and mechanistic aspects of the redox systems. The current research knowledge would be very beneficial to kineticists who are working on the kinetic and mechanistic chemistry of these drugs in biological systems.
Section 1.4

REACTION KINETICS, MECHANISM AND CATALYSIS

*Reaction kinetics:* Chemical kinetics is the branch of chemistry that deals with the reaction rates and their dependence with various factors such as reactant concentrations, temperature, catalyst, reaction medium etc [54]. The experimental data of chemical kinetics are records of concentration of reactants and products at different time intervals usually at constant temperature. How fast a reaction occurs is a determinative factor in its practical utilization. Besides, kinetics assist in the determination of the yield of the products, the relative reactivities of molecules and also the possibility of whether or not a reaction will take place under certain experimental conditions. Therefore, it is essential to know the rate at which the given reaction will take place under given conditions and what changes must be brought about for the reaction to proceed at the desired speed. From a theoretical stand point, the importance of kinetics to chemistry is its aid in the elucidation of many important aspects of reactions and in obtaining a deeper insight into their mechanism. The rate laws are of practical importance since they provide concise expressions for the course of the reaction and can be applied in calculating reaction times, yields and optimum economic conditions. Also, the rate laws often afford an insight into the mechanism by which the reaction proceeds. On the molecular scale, the course of the reaction may be complex, and sometimes the form of the empirical rate law will suggest the particular path via which the reaction takes place. Hence, the fundamental objective of study of the kinetics of chemical reactions is to unfold the mysteries of chemical processes. Hence, kinetic studies of reactions in solution have achieved commendable importance in explaining the mechanisms of the reactions.

*Rate of reaction:* The rate of a chemical reaction is measured by following the change in the concentration of the components of the reaction mixture at suitable intervals of time. It may thus be defined as the rate of change of concentration as a function of time and may be expressed either in the form of disappearance of reactants or the appearance of products [55]. Reaction rates can be measured by a number of methods depending on the nature of the
reaction anticipated. For reactions which proceed at appreciable rates both physical and chemical methods can be employed for the rate determination. The chemical methods for analysis include acid-base titration, potentiometric titration or gravimetric method. Physical methods of analysis involve the measurement of some physical property viz. change in conductivity, emf, optical, rotation etc of the components of the reaction mixture. In spectrometric method (UV, IR, NMR etc), measure the concentration of reactants or the products in terms of a physical parameter such as absorbance, chemical shift, spin-spin coupling etc. during a reaction. Special techniques are needed to measure the kinetics of very fast reactions ie., having a half-life of the order of approximately $10^{-7}$ s, such as those occurring during acid-base, explosive, enzyme catalysis, and also many organic reactions. A number of methods viz. flash photolysis, flow methods, relaxation methods and spectroscopic techniques are being used for this purpose.

**Molecularity and order:** Chemical reactions are classified either according to their molecularity or order. Molecularity is a theoretical concept whereas the order of a reaction is empirical. The order and molecularity for a reaction may be equal numerically but this is not always true for instance the decomposition of acetaldehyde ($\text{CH}_3\text{CHO} \rightarrow \text{CH}_4\text{CO}$) is unimolecular but the rate of the reaction is proportional to the square of the concentration of the acetaldehyde. Therefore it is a second order reaction. The molecularity of a reaction is defined as the total number of molecules of all the substances taking part in a chemical reaction, as represented by a simple equation. Accordingly, reactions having molecularity one, two and three are known as unimolecular, bimolecular and trimolecular reactions, respectively. The order of a reaction equals the sum of the exponents of the concentrations in the equation for the dependence of the rate on the concentrations of the reactants. A reaction is said to be zero-order if its rate is entirely independent of the concentration of the reactants. A first-order reaction is that in which the concentration of only one reactant changes with time or in which the rate of the reaction is proportional to the first power of concentration of the reactant. Reactions which are not unimolecular but obey the first-order rate expression are known as pseudo-unimolecular reactions. Such reactions involve more than one molecule in the chemical reaction. A second order reaction is one in which the reaction velocity is
proportional to the product of concentration of two substances or the second power of the concentration of a single substance. A third order reaction is one in which the rate depends on three variable concentration terms. Rate expressions for different orders [54] are reported in Table 1.2.

**Table 1.2 Rate laws for different orders**

<table>
<thead>
<tr>
<th>Order</th>
<th>Rate equation</th>
<th>Integrated form</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>( \frac{dx}{dt} = k )</td>
<td>( k = \frac{x}{t} )</td>
<td>Moles liter(^{-1}) sec(^{-1})</td>
</tr>
<tr>
<td>1/2</td>
<td>( \frac{dx}{dt} = k (a-x)^{1/2} )</td>
<td>( k = \frac{1}{t} \ln[a / (a-x)] )</td>
<td>Sec(^{-1})</td>
</tr>
<tr>
<td>1</td>
<td>( \frac{dx}{dt} = k (a-x) )</td>
<td>( k = \frac{1}{t} \ln[a / (a-x)] )</td>
<td>Sec(^{-1})</td>
</tr>
<tr>
<td>3/2</td>
<td>( \frac{dx}{dt} = k (a-x)^{3/2} )</td>
<td>( k = \frac{2}{t} \left[ 1/(a-x)^{1/2} - 1/a^{1/2} \right] )</td>
<td>Liters(^{1/2}) mole(^{-1/2}) sec(^{-1})</td>
</tr>
<tr>
<td>2</td>
<td>( \frac{dx}{dt} = k (a-x)^2 )</td>
<td>( k = \frac{1}{t} \ln[x / a(a-x)] )</td>
<td>Liters mole(^{-1}) sec(^{-1})</td>
</tr>
<tr>
<td>3</td>
<td>( \frac{dx}{dt} = k (a-x)^3 )</td>
<td>( k = \frac{2ax - x^2}{2t} \frac{1}{a^2 (a-x)^2} )</td>
<td>Liters(^2) mole(^{-2}) sec(^{-1})</td>
</tr>
</tbody>
</table>

Several methods have employed to determine the order of a chemical reaction. The various methods of determining the order of a reaction are (i) Vant Hoff’s differential method (ii) Integration method (iii) Graphical method (iv) Half-life method, (v) Ostwald’s isolation method (vi) Fractional change method (vii) Ratio variation method and (viii) Guggenheim’s method of analysis.
**Complicating factors:** In a number of simple reactions, complication arises due to several reactions take place along with the main reactions [54]. The factors affecting the rate of the reactions are: (i) Parallel reactions- these are reactions in which the reacting molecules react or decompose in more than one way yielding different sets of products. The reaction yielding maximum amount of the product is known as main reaction and the other reactions are referred as parallel or side reactions. To calculate the overall rate constant in such cases, the rate of the side reactions should also be taken into account, (ii) Opposing reactions - when a process is reversible in the chemical sense, the direct and the reverse reactions must occur simultaneously. The latter reaction is said to be an opposing or a reversible reaction. Then the alternatively opposing reactions must also be included in analyzing the kinetic data, (iii) Consecutive reactions - it often happens that the product of one reaction becomes itself the reactant of a following reaction. There may be a series of consecutive steps. All the steps should be considered in the calculation of overall rate constants, and (iv) Chain reactions - in chain reactions highly reactive species are produced as intermediates which carry on the reaction at a rapid rate for a long time. The concentrations of the reactive species are usually very small. However, these concentrations acquire small but steady values soon after the reaction is initiated and for a long time, the chain of reaction steps continues. This is known in reaction kinetics as steady state approximation. This is very useful in accounting for the rate laws of chain reactions.

**Rate-determining step:** Chemical reactions are not kinetically simple; they proceed through a number of steps between initial reactants and final products. Each of individual steps is called as an elementary reaction. Complex reactions are made up of a sequence of elementary reactions, each proceeds in a single step. In systems of consecutive reactions it may sometimes occur that there is one step which is very much slower than all the subsequent steps leading to product. Then the rate of production of product may depend on the rates of all the steps preceding the least slow step but will not depend on any of the subsequent steps, all of which are rapid compared to the last slow step. Such a last slow step is called the rate-determining step (rds) of the reaction.
**Arrhenius theory:** Increase in temperature leads to an increase in reaction velocity and hence in rate constants. Arrhenius first pointed out that the variation of rate constants with temperature can be represented by an equation similar to that used for equilibrium constants [56], namely,

\[
\frac{d\ln k}{dt} = \frac{E_a}{RT^2}
\]  

(1.10)

In this equation, \(k\) is the reaction rate constant, \(T\) the absolute temperature, \(R\) the gas constant and \(E_a\) is the energy of activation which is a quantity characteristic of the reaction with the dimensions of an energy. Energy of activation plays a very important role in chemical kinetics. When Eq. (1.10) is integrated on the supposition that \(E_a\) is a constant, we obtain

\[
\ln k = -\frac{E_a}{RT} + C
\]  

(1.11)

\[
\log k = -\left(\frac{E_a}{2.303R}\right) \frac{1}{T} + C
\]  

(1.12)

where \(C\) is the integration constant. However, if we integrate the above equation between the limits \(k = k_1\) at \(T = T_1\) and \(k = k_2\) at \(T = T_2\), then

\[
\log \frac{k_2}{k_1} = \frac{E_a}{2.303R} \left(\frac{T_2 - T_1}{T_1T_2}\right)
\]  

(1.13)

From Eq. (1.13) it is evident that as soon as two values of \(k\) are available at two different temperatures \(E_a\) may be evaluated; or, when \(E_a\) and a value of \(k\) at some temperature are known, \(k\) at another temperature may be calculated. Further, according to Eq. (1.12), a plot of \(\log k\) against \(1/T\) should be a straight line with a slope equal to \(-E_a/2.303R\) and \(y\) intercept equal to \(C\). Consequently, if such a plot is found to be linear the equation is confirmed. Furthermore, by taking the slope of the line, \(E_a\) may be calculated through the Eq. (1.12). Equation (1.12) can also be written as

\[
k = A e^{-E_a/RT}
\]  

(1.14)
In Eq. (1.14), A is called as frequency factor or pre-exponential factor. Equation (1.14) is known as integrated form of Arrhenius equation. Thus, Eq. (1.14) expresses the temperature dependence of k in terms of A and E_a. Both A and E_a are characteristics of the reaction.

According to the concept of activation energy, all the molecules cannot take part in the chemical reaction. It is only certain number of molecules that may be called active molecules which could take part in a chemical reaction. Thus the reactants do not pass directly to the products but must first acquire necessary energy to pass over an energy barrier known as the activated state or transition state. The minimum energy which the reacting molecules possess before the reaction to occur is known as energy of activation. It is to be noted that only those molecules which has sufficient energy to cross the energy barrier will take part in the reaction and not all the molecules. After reaction, the products lose their energy and the energy of activation released by the products is greater than the E_a absorbed by the reactants. The net effect is an evolution of heat, which would be the heat of reaction.

After calculating E_a, the important thermodynamic parameters can be calculated using the following equations:

(a) Enthalpy of activation, $\Delta H^\ddagger = E_a - RT$  \hspace{1cm} (1.15)
(b) Entropy of activation, $\Delta S^\ddagger = (\Delta H^\ddagger / T) - 4.576 \left( \log \frac{T}{k} \right) - 47.22$  \hspace{1cm} (1.16)
(c) Free energy of activation, $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$  \hspace{1cm} (1.17)
(d) Specific reaction rate constant
$$k_{sp} = \frac{k'}{[\text{substrate}]^l [\text{catalyst}]^m [\text{medium}]^n}$$ \hspace{1cm} (1.18)

where l, m and n are the orders with respect to substrate, catalyst and H^+ or OH^- (depending on the medium), respectively. Further, Arrhenius theory introduces the frequency factor (A), which can be calculated using the relation,

$$\log A = \log k_{sp} + \frac{E_a}{2.303 RT}$$ \hspace{1cm} (1.19)

Dimensions of A are the same as those of $k_{sp}$ from which it is derived.

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*Theories of reaction rates:* Arrhenius theory gives the information about the reaction process, but neither has it given any information about the frequency factor, nor does it predict the value of energy of activation. The following two theories [54] have been proposed to predict the reaction rates in terms of molecular collisions which allow a better interpretation of $A$ and $E_a$. (i) collision theory and (ii) transition state theory. These theories provide us a greater insight into the energetic and mechanistic aspects of the rate.

*Collision theory:* The collision theory attempts to account for the observed kinetics of reactions in terms of kinetic molecular theory. This theory has been found to be satisfactory for gaseous bimolecular reactions and postulates that the reacting molecules must collide. According to collision theory, for a chemical reaction to occur, the reacting molecules must collide each other. On collision, they must acquire sufficient energy to get themselves activated. This idea forms the basis of the collision theory of reaction rates. The collision theory predicts the value of the rate constant fairly accurately for reactions that involve atomic species or simple molecules if the activation energy is known. Significant deviations were found, however, for reactions involving complex molecules, wherein, the experimental rates are quite different from the calculated values. The reason is that the simple kinetic theory counts every sufficiently energetic collision as an effective one but in reality the molecules may not approach each other in the right orientation for the reaction to occur, even if ample of energy is available. Thus, in order to account for the observed discrepancy, an addition term called probability or steric factor is introduced in the rate expression:

$$k = P Z e^{-E_a/RT} \quad \quad (1.20)$$

where $P$ is the probability or steric factor and is related to the geometry of the molecule, $Z$ is the number of collisions. It takes into account of the fact in collision complex; molecules must be properly oriented to undergo reaction. This modification is an improvement, but the evaluation of steric factor is rather difficult.
**Transition state theory:** Although the collision theory is intuitively appealing and does not involve complicated mathematics, it suffers from the following drawbacks: (i) It is difficult to calculate the steric factor from molecular geometry for complex molecules, and (ii) the theory is applicable essentially to gaseous reactions. An alternative theory called the transition state theory of reaction rates frequently also called as activated complex theory, was developed by Eyring in 1935 to provide greater insight into the details of a reaction on the molecular level. The approach of the transition state theory helps us to understand not only the molecular features of gas phase reactions, but also some of the molecular features that operate on reactions in solutions. This theory attempts to treat the reaction rates from thermodynamic consideration and based on statistical mechanics. The basic tenet in this theory is that reactant molecules are in chemical equilibrium with the activated complex at the top of the activation energy barrier. Consider a simple bimolecular reaction:

\[
A + B \rightleftharpoons [AB^\#] \rightarrow \text{Products} \quad (1.21)
\]

In transition state theory, the reactants are assumed to combine together forming an energy rich activated complex which is in equilibrium with the reactant molecules. The activated complex then disproportionates at certain rate to give the products. It is this rate that determines the overall rate of the reaction. The thermodynamic formulation of transition state theory is given by the equation,

\[
k = k_B T / h e^{\Delta S^\# / R} e^{-\Delta H^\# / RT} \quad (1.22)
\]

Where \(k\) is the rate constant of the reaction, \(k_B\) is the Boltzmann constant, \(h\) is Planck’s constant, \(T\) is temperature in absolute, \(R\) is gas constant, and \(\Delta S^\#\) and \(\Delta H^\#\) are the standard molar entropy and standard molar enthalpy of activation, respectively. The probability factor ‘\(p\)’ introduced in the collision theory of reaction rate can be now explained in terms of entropy of activation. Equation (1.22) is an empirical one, both \(A\) and \(Ea\) must be determined experimentally. Equation (1.20) is based on collision theory, the value of \(Z\) can be calculated
from the kinetic theory of gases. In general, it is very difficult to estimate the magnitude of P accurately. Equation (1.22) provides us with the thermodynamic formulation of the reaction rate constant and is the most reliable of the three approaches. Equation (1.22), neither involves in the concentration terms nor the time factor, and has only thermodynamic terms which depend upon absolute values of potential energy and bond distances. For this reason transition state theory is also known as theory of absolute reaction rates.

**Effect of ionic strength:** Polar solvents are the best media for studying the ionic reactions. The rate constants of ionic reactions depend upon the charges carried by the ions and also upon the ionic strength of the solution. The effects of ions (ie., electrolytes) in solution can be divided into two types: the primary salt effect is the influence of electrolyte concentration on the rate of reaction, whereas the secondary salt effect is the actual change in the concentration of the reacting ions resulting from the addition of the electrolytes. For primary salt effect, Bronsted has given a relation between the reaction rate constant k and the ionic strength (\(\mu\)) in a reaction involving ions of charges \(Z_A\) and \(Z_B\), and later on it was modified by Bjerrum [54] as:

\[
\log k = \log k_o + 1.018 \ Z_A Z_B \sqrt{\mu}
\]  

(1.23)

here \(k\) and \(k_o\) are the rate constants at ionic strength \(\mu\) (of an added inert salt) and at infinitely dilute concentration (\(\mu = 0\)), respectively. This equation has been tested experimentally. According to this equation, a plot of \(\log k\) versus \(\sqrt{\mu}\) is a straight line with a slope equal to 1.018 \(Z_A Z_B\). The sign of \(Z_A Z_B\) determines the direction of slope. If the reacting ions are oppositely charged, raising ionic strength reduces the effective rate constant because the ions are shielded from each other to a greater extent. When the ions are of same charge, an increase in the ionic strength increases the reaction rate because the solvated ions change the dielectric behavior of the solution so that ions of like charge do not repel each other as greatly. For the reactions that involve uncharged reactants, the rate constant is expected to be independent of ionic strength. The secondary salt effect can be written as \(\log k = \log k_o + 1.018 \sqrt{\mu}\). When \(\mu\) is increased, the rate of the reaction also increases. The validity of this equation has been proved in a number of reactions.
**Effect of dielectric constant:** Most organic reactions are carried out in solution and hence it is essential to be aware of the effect of solvents on the course and rates of reactions. Solvent effects provide information on the nature of the reacting species in the rate-determining step as well as the structure of the activated complex. The relative permittivity or dielectric constant (D) of a dielectric is defined as the ratio of the capacitance (C_d) of the capacitor filled with dielectric to the capacitance (C) when the capacitance is evacuated i.e., \( D = C_d / C \). Many models are advanced to explain the dielectric constant on the rate of the reaction. Amongst, double sphere model is a simple model for reaction between two ions in solution and it is widely studied and well accepted. Scatchard [57] has given a relation between the velocity constant \( k_{1=0} \) for a reaction at temperature ‘T’ and zero ionic strength, and the dielectric constant (D), if the standard reference state of dielectric constant is taken as infinity for ion-ion reaction. The equation is in the form:

\[
\log k' = \log k'_{1=0,D=\infty} - \left( Z_A Z_B e^2 \right) / 2.303 r_\# k T
\]

(1.24)

here \( Z_A \) and \( Z_B \) are ionic charges of the reactants A and B, \( e = \) electronic charge,
\( k = \) Boltzmann constant, \( r_\# = \) radius of the activated complex (\( r_\# = r_A + r_B \)), D = dielectric constant of medium. Here a plot of \( \log k'_{1=0,D=\infty} \) versus 1/D must be linear with a slope of \(-Z_A Z_B e^2 / 2.303\ r_\# k T\). This is found to be true in a large number of cases. By allowing a reaction to occur in a series of mixed solvents of varying dielectric constants, it is possible to compare the values of \( r_\# \) from the observed slopes and infer on the size and charge of the transition state.

For the interaction between an ion and dipolar molecule, Amis and Jaffe [58] have derived a relation (1.25) for the variation of the rate constant as a function of the dielectric constant of the medium.

\[
\log k'_D = \log k' + (Z e \mu / 2.303 k T r^2 D)
\]

(1.25)
here $\mu$ is the dipole moment of the dipole and $r$ is the distance of approach between the ion and the dipole. It is evident from Eq. (1.25) that the rate constant will increase or decrease on increasing ‘D’, depending on whether the transition state bears a negative or positive charge. The slope of the line will be positive for a reaction between a positive ion and a dipole, whilst a negative slope is obtained for negative-dipole or dipole-dipole interactions. The treatment adopted for reactions between dipolar molecules and ions is based on an expression derived by Kirkwood [59]. The theory of Kirkwood was further developed by Laidler and Landskroner [60], Tanford and Kirkwood [61] and Hiromi [62]. A good account of this and other theories has been given by Entelis and Tiger [63]. From all these observations, it can be concluded that an ion-dipole or a dipole-dipole step is involved in the reaction sequence. Hence in order to find out the nature of the reactive species, the solvent isotope effect study with varying solvents is very important.

**Effect of solvent isotope:** Isotopic substitution most often involves replacing protium by deuterium or tritium, but is applicable to nuclei other than hydrogen. Since hydrogen isotopes have the largest relative mass differences, the quantitative differences are largest for hydrogen. Isotopic substitution usually has no effect on the qualitative chemical reactivity of the substrates, but it often has an easily measured effect on the rate, which is known as kinetic isotope effect [64-65]. On account of greater mass of deuterium, the vibrations associated with a C-D bond contribute less to the zero-point energy than the corresponding C-H bond. Consequently, substitution of protium by deuterium lowers the zero-point energy of a molecule. The transition state has the same energy for the protonated and deuterated species for a reaction involving cleavage of H or D bond. This is because the deuterated molecule has the lower zero-point energy; it has a higher $E_a$ to reach the transition state.

Primary kinetic isotope effects are those in which a bond to the isotopically substituted atom is broken in the rate-determining step. These effects can provide a couple of useful information about a reaction mechanism. First, the existence of a substantial isotope effect i.e., $k_H / k_D > 2$, is strong evidence that the bond to that particular hydrogen is being broken in the rate-determining step. Second, the magnitude of the isotope effect provides a
qualitative indication of where the transition state lies with regard to product and reactant. Secondary isotope effects are those in which the substituted hydrogen atom is not directly involved in the reaction but they occur due to the change in strength of the C-H bond at the transition state. These effects are usually smaller than primary effects. Secondary isotope effects are normal when \( k_H / k_D > 1 \) and inverse when \( k_H / k_D < 1 \). Hence, the detailed analysis of kinetic isotope effects provides valuable information about transition states.

The creation of a file of the contributing hydrogenic sites and the magnitude of the isotope effect for each site is called proton inventory [66-68]. The variation of the rate of reaction as a function of the mole fraction of D_2O in isotopic mixtures of H_2O and D_2O can be expressed by the equation:

\[
(k_n' / k_o') = (1 - n + n\phi_T) / (1 - n + n\phi_R)
\]

where \( k_n' \) is the rate constant in a number of isotopic water mixtures of deuterium atom fraction \( n \), \( k_o' \) is the rate constant in pure H_2O, \( \phi_R \) is the fractionation factor for the exchangeable reactant state and \( \phi_T \) is that for the transition state. In simplest cases, the reactant and the transition state will have only one and the same exchangeable site for hydrogen or deuterium. According to Eq. (1.26), a plot of \( (k_n' / k_o') \) versus \( n \) is usually a curve. On the other hand, a molecule contains a large number of exchangeable hydrogens and if all of them exchange independently, the effects of all the different hydrogens are multiplicative [66]. Then the Eq. (1.26) can be generalized as:

\[
k_n' / k_o' = \pi_i^{TS} (1 - n + n \phi_i) / \pi_j^{RS} (1 - n + n \phi_j)
\]

Equation (1.27) is the Kresge equation [67] and that describes the functional dependence of \( k_n' \) on the isotopic composition, \( n \), of the solvent. Here \( \phi_i \) and \( \phi_j \) are isotopic factors for isotopically exchangeable hydrogenic sites in the transition state (TS) and reactant state (RS), respectively. If it is assumed that the reaction proceeds through a single transition state [66], Eq. (1.27) takes the forms shown by Eqs. (1.28) and (1.29):
\[ k'_n = k'_o (1 - n + n \phi) \]  
\[ (k'_o / k'_n)^{1/2} = [1 + n (\phi - 1)] \]  

A plot of \((k'_o / k'_n)^{1/2}\) versus \(n\) should then be expected to be linear. Such studies have been made for the determination of fractionation factors by several workers [69-71].

**Linear free energy relationship:** The term linear free energy relationship (LFER) applies to a variety of relationships between kinetic and thermodynamic quantities that are important in both organic and inorganic reactions. Out of a number of empirical models proposed for the explanation of relationships between structure and reactivity, the most successful and widely investigated and, accepted are the linear free energy relationships (LFER) with the Hammett equation [72-73] being the most prominent example:

\[ \log k = \log k_o + \rho \sigma \]  
\[ \log K = \log K_o + \rho \sigma \]  

here \(k\) and \(K\) are the rate and equilibrium constants of a substituted derivative respectively; \(k_o\) and \(K_o\) denote the statistical quantity approximating to \(k\) and \(K\) for unsubstituted or parent compound; \(\sigma\), the substitution constant, which is the characteristic of the substituent and is independent of the nature of the reaction; and \(\rho\), the reaction constant, which is a quantitative measure of the susceptibility of the reaction to the influence of the substituents. Hammett has made use of ionization of benzoic acids as the model and it is believed that the interaction mechanism involved is of electronic origin. Excellent monographs are available which deal with the importance of Hammett equation and its modifications [72].

The Hammett equation does not apply well to the reactions of aliphatic compounds partly due to some steric interference between the substituents and reaction site. For aliphatic compounds, Taft has proposed the following equation [74]:

---

34
\[
\log \left( \frac{k}{k_0} \right) = \rho^* \sigma^* + \delta E_s
\]  
(1.32)

This is the same form as the Hammett equation, except one term has been added. The polar parameter \( \sigma^* \) is a measure of the polar effect of a substituent while \( \rho^* \) measure the sensitivity of the reaction to the polar effect. \( E_s \) is a measure of the steric effect introduced by the presence of a substituent while \( \delta \) measures the sensitivity of the reaction to this steric effect. If the Taft Eq. (1.32) is employed for a series of kinetic data, for the ortho substituted benzene derivatives or aliphatic compounds, a four parameter correlation [75] or single parameter correlation can be attempted. Much of the details of LFER have not been discussed here, since such relationships have not been studied in the present kinetic investigations.

**Isokinetic relationship:** Linear free energy relationships are empirical relationships between thermodynamic quantities. Isokinetic relationship [76] is a linear relationship between enthalpy and entropy contributions implies that the change in enthalpy in proceeding from reaction or to reaction in a series accompanied by a parallel change in enthalpy. Variation in rate within a reaction series may be caused by changes in either or both the enthalpy and the entropy of activation. Four categories can be recognized here and they are: i) Changes in rate are caused chiefly by changes in \( \Delta H^\phi \) when \( \Delta S^\phi \) is substantially constant. Many reaction series that follow the Hamnett \( \rho \sigma \) relationship fall within this category; ii) Changes in rate are caused chiefly by changes in \( \Delta S^\phi \), when \( \Delta H^\phi \) is substantially constant; iii) Changes in rate are caused by random changes in both \( \Delta H^\phi \) and \( \Delta S^\phi \); and iv) Changes in rate are caused by changes in both \( \Delta H^\phi \) and \( \Delta S^\phi \), but these quantities vary in a parallel fashion. In the last category, \( \Delta H^\phi \) and \( \Delta S^\phi \) are correlated by a linear relationship:

\[
\Delta H^\phi = \Delta H^\phi_o + \beta \Delta S^\phi
\]  
(1.33)

Equation (1.33) is called the isokinetic relationship and here \( \beta \) is the isokinetic temperature. Using the relation: \( \Delta G^\phi = \Delta H^\phi - T\Delta S^\phi \), it can be shown that, \( \delta \Delta G^\phi = (1 - T/\beta) \delta \Delta S^\phi \), where \( T \) is the experimental temperature. When \( \beta = T \), \( \Delta G^\phi = 0 \), and no variation of equilibrium or rate can be expected when substituents or media are changed. All members of a series will then
react at the same rate. When $T < \beta$, the reaction rate or equilibrium is mainly by the enthalpy change. In this region, the reaction with the lowest activation energy will react fastest and interpretation involving potential energy surface can be made. This is very common case. At temperatures above $\beta$, however, the controlling factor is $\delta \Delta S^f$ and interpretations based upon potential energy surfaces would obviously be in error. In general, it is found that electronic effects are contained in the enthalpy factor and that many solvent effects are due to the entropy factor.

The isokinetic temperature $\beta$ can be calculated from an enthalpy-entropy plot and it can also be obtained from a log-log plot of rate constants at the two extreme temperatures of the investigation as advanced by Exner [77] by employing the simple Eq. (1.34):

$$\log k_2 = a + b \log k_1$$

(1.34)

where $k_2$ and $k_1$ are the rate constants at the temperatures $T_2$ and $T_1$, respectively, and with $T_2 > T_1$. The isokinetic temperature $\beta$ can be evaluated from the expression:

$$\beta = T_1 T_2 (b-1) / (bT_2 - T_1)$$

(1.35)

Hence Exner’s method has been used to calculate $\beta$ by plotting $\log k_{T_2}$ against $\log k_{T_1}$ and the value of the isokinetic temperature for the reaction series can be obtained. The existence of isokinetic relationship and linear free energy relations are of considerable importance and are valuable tools to the mechanistic chemist when used as supporting evidence along with other types of information.

**Reaction mechanism:** Reaction mechanism means the particular sequence of elementary reactions that leads to the overall chemical change whose kinetics is under study. In chemical reactions some bonds are broken and new ones are formed. Usually, these processes are complicated and may involve a series of reactions step by step. A reaction mechanism describes exactly how the various bonds are broken and made involving one or more steps in
the reaction. During the course of a chemical reaction molecules come closer, atoms change their positions, electron-shifts take place and as a result new compounds are formed. A complete description of such a path is termed as the reaction mechanism [78]. A mechanism is a concept derived from experimental data obtained both by the use of physical and chemical methods. It is possible that more than one mechanism can be assigned to a particular reaction but the one which explains all the experimental results is taken to be a plausible one. Kinetics is apparently the first step in a study of reaction mechanisms because of the wealth of information it gives about the nature and the course of the reaction. Hence the application of reaction kinetics in organic chemistry is the most important step in the investigation of reaction mechanisms. Deciphering a reaction mechanism is the most enabling knowledge that a chemist has to conclude the consequence of a reaction. This is true in almost all industries, where optimization of the reaction condition in order to get maximum yield within a short interval of time is a primary goal.

**Platinum group metal ion catalysis:** The process of catalysis plays an important role in the production of chemicals and growth of chemical industries. Research into catalysis is a major field in applied, environmental and medicinal science. Many chemical reactions are very slow at ambient temperature, usually because they have relatively high activation energies and are nevertheless found to occur very rapidly due to the action of catalyst. A catalyst is a substance that alters the rate of a reaction by introducing a new, faster pathway without itself involving chemically in the reaction. Homogenous catalysis is one of the most interesting fields of chemistry, especially for its mechanism and kinetics. It provides excellent opportunities for the study of the molecular causes of reactivity, of what makes reactions to go. A thorough understanding of the molecular effects in homogenous catalysis can serve as a guide in the development of new and more efficient metal ion catalysts and their support. For these reasons, the number of homogenously catalyzed processes has been steadily growing. Platinum group metal ion catalyzed reactions from its use in many important industrial processes such as carboxylation, hydrogenation, alkynation and redox reactions [79-82] have generated an interesting among researchers due to its significance in understanding the mechanistic chemistry of a particular redox system. Oxidizing and catalytic activities of these
metal ions are due to the existence of variable oxidation states, as a consequence of partly filled d or f orbitals. Most d block elements effect inter ligand migration reactions and such a process forms one of the most important type of reaction in homogenous catalysis. Kinetic modeling of such catalytic reaction systems plays a critical role in the design and optimization of chemical processes. The mechanism of catalysis is quite complicated due to the formation of different intermediate complexes, free radicals and different oxidizing states. Consequently, in recent years Os(VIII), Ru(III), Rh(III), Pd(II), Pt(IV) and Ir(III) have been widely employed as catalyst because these elements demonstrates strong catalytic influence in many reactions. Some of these systems have proved suitable for kinetic analysis [83-86]. We expect that such studies will highlight the interactions and relative reactivities of metal ions in some of the redox systems and also the process is very important from the technological point of view in order to optimize the reaction condition.
Section 1.5

MATERIALS AND METHODS

Reagents:

**Chloramine-T:** Chloramine-T (E-Merck) was purified by the method of Morris *et al* [11]. An aqueous solution of 0.1 mol dm\(^{-3}\) CAT was prepared, standardized periodically by the iodometric method and stored in brown bottles to prevent any of its photochemical deterioration.

**Chloramine-B:** Chloramine-B (Fluka) was purified by the method of Verger and Perlin [87]. An aqueous solution of preferred strength was prepared afresh, standardized by iodometric procedure and preserved in brown bottles.

**Bromamine-T:** Bromamine-T was prepared [16] as described in section 1.1 of Chapter 1. An aqueous solution of BAT was freshly prepared whenever needed, standardized by iodometric method and kept in brown bottles.

**Bromamine-B:** Bromamine-B was prepared [17] as indicated in section 1.1 of Chapter 1. An aqueous solution of BAB was prepared, standardized iodometrically and stored in amber colored stoppered bottles to prevent any of its photochemical deterioration.

**p-toluenesulfonamide:** p-toluenesulfonamide (E-Merck) was used without further purification. The aqueous solution of the required strength was prepared and used whenever needed.

**Benzenesulfonamide:** Benzenesulfonamide (E-Merck) was used without further purification. The aqueous solution of desired strength was prepared by dissolving intended quantity of the compound.
**Ruthenium trichloride:** Ru(III) chloride was purchased by E-merck. The required strength of RuCl₃ solution was prepared in 0.20 mol dm⁻³ HCl and was used as a catalyst in some of the redox systems studied. Allowance was made for the amount of HCl present in catalyst solution, while preparing for kinetic runs in acid and alkaline medium.

**Osmium tetroxide:** A solution of Os(VIII) oxide (Aldrich) was prepared in 0.20 mol dm⁻³ NaOH and was used as catalyst in alkaline medium. Allowance for the amount of NaOH present in the catalyst solution was made while preparing the reaction mixtures for kinetic runs.

**Palladium dichloride:** A solution of Palladium(II) chloride (Arora-Matthey) was prepared in 0.20 mol dm⁻³ HCl and was used as a catalyst in alkaline medium. The acid present in the catalyst solution is also taken into account in the calculation of the total alkali present while preparing the reaction mixtures for kinetic runs.

**Rhodium trichloride:** Rhodium (III) chloride (SD. Fine Chemicals Ltd) solution was prepared in minimum quantity of HCl. Aqueous solutions of desired strength were prepared whenever required. Allowance for the amount of acid present in the catalyst solutions was made while preparing the reaction mixtures for kinetic runs.

**Buffer solution:** Phosphate buffer [88] was prepared by mixing different volumes of 0.1 mol dm⁻³ Na₂HPO₄ and 0.1 mol dm⁻³ KH₂PO₄ to get the desired pH and employed.

**Tricyclic antidepressants:** Imipramine hydrochloride and Clomipramine hydrochloride (R.L.Fine chemicals Ltd, Bengaluru, India) were used as received. A desired strength of the compound was freshly prepared in double distilled water whenever required.

**Antiparasitic drug:** Ornidazole is of pharmaceutical grade of purity was kindly provided by Bio-Organics and Applied Materials Pvt. Ltd. Bangalore, India and of assigned purity of
99.8%. It was used as received and an aqueous solution of compound was prepared fresh, just before use.

**Skeletal muscle relaxants:** Mephenesin (99.64% assay) and guaifenesin (99.61% assay) of analytical grade were gifted by Synthokem Lab Pvt. Ltd, Hyderabad, India and were used as received. Aqueous solutions of these substrates were prepared and employed.

**Antifibrinolytic drug:** Tranexamic acid (Aldrich) was used as received. An aqueous solution of the desired strength of the substrate was freshly prepared whenever required.

**β- lactam antibiotics:** Cephalexin, cefadroxil and cephradine were of analytical grade of purity, and were gifted by Orchid Chemicals Pvt. Ltd, Chennai, India. These compounds were used as received and aqueous solutions of desired strength were prepared and employed.

**Antimalarial drug:** Amodiaquine hydrochloride of analytical grade gifted by Medreich Lab Pvt. Ltd, Bangalore, India was used as received. Required quantity of the compound was accurately weighed and dissolved in double distilled water and used.

**Antiallergic drug:** Cetirizine dihydrochloride is of analytical grade of purity, was provided from University of Mysore, Mysore, India. It was used as received and aqueous solution of the desired strength of the substrate was prepared freshly each time whenever required.

**Antiulcer drug:** Ranitidine hydrochloride is of analytical grade of purity was gifted by Medreich Pharma Ltd, Bangalore, India. It was used without further purification and fresh aqueous solution of the desired compound was prepared every time required.

**Heavy water (D\textsubscript{2}O):** Heavy water (99.4 % purity) supplied by Bhabha Atomic Research Center, Mumbai, India, was employed for the solvent isotope effect investigations in the redox systems studied.
**Other reagents:** Perchloric acid, hydrochloric acid, sulfuric acid, sodium thiosulphate, potassium iodide, sodium perchlorate, sodium hydroxide, liquid bromine, sodium chloride, methanol, potassium hydrogen phthalate, potassium dichromate, ether, ethyl acetate, butanol, vanillin, starch indicator and other chemicals used in the present research work were of acceptable grade of purity. Double distilled water was used throughout the work.

**Reaction vessel:** The reaction was carried out in glass stoppered pyrex boiling tubes (1.5” x 7” and capacity 200 ml) with a standard B-34 interchangeable joints.

**Thermostat:** In the present redox systems, the kinetics of the reactions were followed between 280-333K. For this purpose Raagaa Ultra Cold Chamber with Digital Temperature Controller (Chennai, India) was used. The desired temperature within ± 0.1°C was maintained with the help of this thermostatic water bath.

**Spectrophotometer:** In the oxidation of amodiaquine hydrochloride, kinetic measurements were carried out using a UV-visible spectrophotometer (Digital Spectrophotometer 166, Systronics, India). Complex formation was evidenced by UV-visible spectrophotometer (UV-Visible spectra are recorded on UV-3101PC, UV-VIS-NIR Scanning Spectrophotometer, Shimadzu). Oxidation products were characterized by GC-MS spectrum which were obtained from 17A Shimadzu gas chromatograph with a QP-5050 Shimadzu mass spectrometer and also by LC-MS data which was obtained on a LC-MSD-Trap-XCT plus.

**Kinetic Procedure:** All kinetic runs were performed under pseudo-first-order conditions with a known excess of [substrate]₀ >>> [oxidant]₀ (except in case of amodiaquine hydrochloride, where the [oxidant]₀ was in excess over that of [substrate]₀). Kinetics of all the redox systems have been carried out by iodometry except in case of amodiaquine-CAT system wherein UV-visible spectrophotometry was used as a basic analytical approach.

**Iodometric method [25]:** Reactions were carried out in glass stoppered Pyrex boiling tubes whose outer surfaces were coated black to eliminate any photochemical effects. In a characteristic experiment, solutions containing suitable amounts of substrate, acid / alkali,
(RuCl₃, OsO₄, PdCl₂ or RhCl₃, in case of catalyzed reactions) solutions and water (to keep the constant total volume 50 ml for all runs) were taken in the boiling tube and thermostated at desired temperature until thermal equilibrium was attained (about 30 min). A measured amount of oxidant solution, which was also thermostated at the same temperature, was quickly added to the reaction mixture in the tube. The progress of the reaction was monitored by withdrawing known aliquots from the reaction mixture at regular intervals of time. The unreacted oxidant was determined iodometrically. The iodometric titration was carried out by pipetting 5 mL aliquots of the reaction mixture at regular intervals and run into a conical flask containing a quenching mixture (50 mL, ice-cold water, 10 mL of 10% KI and 10mL of 2N H₂SO₄). The liberated iodine was then titrated against standard sodium thiosulfate, using starch as an internal indicator near the end point. The course of the reaction was studied for at least two half-lives. The titre at t=0 gives the value of ‘a’ and the titre at any instant denotes (a-x). Plots of log (a-x) or log [oxidant] versus time were made and values of pseudo-first-order rate constants (k⁻¹s⁻¹) were calculated from these plots.

Spectrophotometric method [26]: In case of amodiaquine hydrochloride, kinetic measurements were carried out using a UV-visible spectrophotometer (Digital Spectrophotometer 166, Sytronics, India). Appropriate amounts of the amodiaquine hydrochloride, alkaline buffer solution, catalyst (in case of catalyzed reactions) solutions and water (to keep the total volume constant for all runs) were taken in the tube and thermostated at desired temperatures for thermal equilibrium. A measured amount of CAT solution, also thermostatted at the same temperature, was rapidly added to the mixture in the boiling tube. The mixture was periodically shaken to ensure uniform concentration. Immediately, 4 ml of the reaction mixture was pipetted into a cuvette placed in the spectrophotometer. Absorbance measurements were made at its λₘₐₓ (342 nm) of amodiaquine hydrochloride for more than two half-lives. The absorbance readings D₀ and D₁ are at the beginning of the reaction and at any time interval, respectively. The pseudo first-order rate constants (k' s⁻¹) calculated from the linear plots of log D₀/ D₁ versus time. All the kinetic runs were carried out twice to check the reproducibility. The values are found to be reproducible within ± 2-6 % error. An fx-100Z scientific calculator was used to obtain the regression coefficient, R².
The following experiments were designed for investigating the mechanisms of the present redox systems through kinetic studies:

(i) Determination of rate constants for all the reactions.

(ii) Determination of order of reaction with respect to oxidant, substrate, medium (acid, alkali, pH) and the catalyst wherever applicable.

(iii) Studying the effects of reduction product of oxidant (PTS or BSA), ionic strength, dielectric constant, halide ions and solvent isotope on the rate of the reaction.

(iv) Evaluating activation parameters for the reaction by studying the reaction at different temperatures.

(v) Determination of stoichiometry of the reaction and characterization of oxidation products.

(vi) Providing evidence for the formation of intermediate complexes in the catalyzed reactions.
Section 1.6

SCOPE AND OBJECTIVE OF THE PRESENT WORK

In chemical analysis and synthesis, redox reactions are most commonly encountered. Oxidation is a foremost transformation in organic synthesis. Hence, these reactions have been the topic of interest in detailed kinetic and mechanistic studies. The substrates selected in the present research are pharmacologically important compounds with different categories of biological activities. Additionally, in some of the redox systems wherever the reactions are slow, platinum group metal ions were used as catalyst in order to provide an insight to the interaction and reactivity of these catalysts in the redox reactions. The current research knowledge is very beneficial for the kineticists who are working on the mechanistic chemistry of the present drugs in biological systems. This kind of study helps to understand the mode of action of the drug at the molecular level and also to follow the solution behaviour of the drugs under study. This type of kinetic modeling plays a significant role in the design and optimization of chemical process.

An extensive literature survey reveals that there are no reports / very limited reports on the oxidation- kinetics of the following redox systems from the view point of their kinetic and mechanistic aspects. The following are the oxidation-kinetic and mechanistic studies of our interest:

(i) Oxidation-kinetics and mechanism of tricyclic antidepressants (imipramine hydrochloride and clomipramine hydrochloride) with chloramine-T in presence of perchloric acid.

(ii) Oxidation-kinetics and mechanism of antiprotozoal drug (ornidazole) with chloramine-T catalyzed by ruthenium(III) chloride in presence of hydrochloric acid and osmium tetroxide catalyzed reaction in sodium hydroxide medium.

(iii) Oxidation-kinetics and mechanism of skeletal muscle relaxants (mephinesin and guaifenesin) with chloramine-B in presence of perchloric acid.
(iv) Oxidation-kinetics and mechanism of antifibrinolytic drug (tranexamic acid) with bromamine-B in presence of perchloric acid and palladium(II) chloride catalyzed reaction in sodium hydroxide medium.

(v) Oxidation-kinetics and mechanism of β-lactam antibiotics (cephalexin, cephradine and cefadroxil) with chloramine-T in presence of sodium hydroxide.

(vi) Oxidation-kinetics and mechanism of antimalarial drug (amodiaquine hydrochloride) with chloramine-T in alkaline buffer medium with and without rhodium(III) chloride catalyst.

(vii) Oxidation-kinetics and mechanism of cetrizine dihydrochloride with bromamine-T in presence of perchloric acid and sodium hydroxide

(viii) Oxidation-kinetics and mechanism of ranitidine hydrochloride with chloramine-T in presence of perchloric acid and sodium hydroxide.
The following are the objectives of the present research:

(i) to accumulate all the possible kinetic data,
(ii) to identify the stoichiometry of the reaction and to characterize the oxidation products by spectral analysis,
(iii) to elucidate probable reaction mechanisms,
(iv) to deduce appropriate kinetic rate laws,
(v) to evaluate activation parameters,
(vi) to ascertain various reactive species,
(vii) to study the solvent isotope effect,
(viii) to establish iso-kinetic relationship, wherever possible,
(ix) to compare relative rates of some of the redox systems in acid and alkaline media,
(x) to inspect the role of platinum group metal ions as catalysts for some redox systems, wherever required,
(xi) to provide spectroscopic evidence for the formation of intermediate complexes in the case of catalyzed reactions.