CHAPTER - I

Introduction
INTRODUCTION

1.0 HYDROXAMIC ACIDS: HISTORY AND NOMENCLATURE

The organic compound having paired carbonyl and hydroxylamino functional group (I) are known as hydroxamic acids

\[
\begin{align*}
- N - \text{OH} \\
\downarrow \\
- C = O
\end{align*}
\]

(I)

Hydroxamic acids, the versatile organic compound have exhibited many interesting facets of chemistry, since these were first reported by H. Lossen in 1869 [1]. Work on hydroxamic acids dates back many years and includes the pioneering studies of Exner [2-6], Crumbliss [7-11], Raymond [12-16], Farkas [17-20] and Tandon [21-27]. Hydroxamic acids and their metal hydroxamates are among the most studied compounds owing to their wide applicability in diverse areas and significance in various life processes. Due to which new works in the field of hydroxamic acid are constantly appearing in the literature [38-40,42-43,47-50,53-56,63,72,75].

Hydroxamic acids, (II) are the N-acyl derivatives of hydroxylamine, which can exist in tautomerism with enol form, named as Hydroximic acid, (III). Spectral evidence indicates that the keto form is predominant in an acidic medium and the enol of form in an alkaline medium [28]. Such keto-enol tautomerism provides a number of sites for chelation.

\[
\begin{align*}
\text{H} - \begin{align*}
N - \text{OH} \\
\downarrow \\
R - C = O
\end{align*} & \leftrightarrow & \begin{align*}
N - \text{OH} \\
\uparrow \\
R - C - \text{OH}
\end{align*} \\
\text{Unsubstituted Hydroxamic acid (II)} & \leftrightarrow & \text{Hydroximic acid (III)}
\end{align*}
\]
Structure (II) represents the unsubstituted hydroxamic acid. When alkyl or aryl group replaces the hydrogen atom attached to 'N' atom in (II), then N-substituted hydroxamic acids (IV) are formed. Substituted hydroxamic acids are incapable of exhibiting tautomerism.

\[ R' - N - OH \]
\[ \text{N-Substituted hydroxamic acid} \]

(IV)

If the hydrogen atom of \(-\text{OH}\) group is substituted by an alkyl or aryl group, these are regarded as ester (O-alkyl or O-aryl hydroxamates) which are having the following general formula (V)

\[ R' - N - OR'' \]
\[ \text{N-Substituted hydroxamic acid} \]

(V)

where \(R''\) = alkyl or aryl group

1.1 HETEROCYCLIC HYDROXAMIC ACIDS

The hydroxamic acids containing heteroatom in carbocyclic ring are known as heterocyclic hydroxamic acids. In structure (II) and (IV), when the substituent \(R\) is a heterocyclic ring then, these are known as unsubstituted (VI) and N-substituted (VII) heterocyclic hydroxamic acids.

Unsubstituted heterocyclic hydroxamic acids

(VI)

N-Substituted heterocyclic hydroxamic acid

(VII)
The heterocyclic hydroxamic acids containing oxygen heteroatom in the carbocyclic ring are known as furohydroxamic acids. Furohydroxamic acid is the trivial name assigned to these compounds. These are furoyl derivatives of hydroxylamines or N-alkyl or N-aryl hydroxylamines.

As from the survey of literature [29-43], it is evident that hydroxamic acids and their metal complexes have been studied in detailed but a scarce literature is available on oxygen containing heterocyclic hydroxamic acid[44-46]. Therefore, five oxygen containing heterocyclic hydroxamic acids has been chosen for present investigation. They are as follows:

(i) 2-Furohydroxamic acid [FHA]

\[ \text{H} - \text{N} - \text{OH} \]
\[ \text{O} - \text{\equiv} - \text{C} = \text{O} \]

(ii) N-Methyl-2-furohydroxamic acid [MFHA]

\[ \text{CH}_3 - \text{N} - \text{OH} \]
\[ \text{O} - \text{\equiv} - \text{C} = \text{O} \]

(iii) N-Phenyl-2-furohydroxamic acid [PFHA]

\[ \text{O} - \text{\equiv} - \text{N} - \text{OH} \]
\[ \text{O} - \text{\equiv} - \text{C} = \text{O} \]

(iv) N-p-Tolyl-2-furohydroxamic acid [p-TFHA]

\[ \text{CH}_3 - \text{O} - \text{\equiv} - \text{N} - \text{OH} \]
\[ \text{O} - \text{\equiv} - \text{C} = \text{O} \]

(v) N-p-Chlorophenyl-2-furohydroxamic acid [p-CIPFHA]

\[ \text{Cl} - \text{O} - \text{\equiv} - \text{N} - \text{OH} \]
\[ \text{O} - \text{\equiv} - \text{C} = \text{O} \]
1.2 APPLICATIONS OF HYDROXAMIC ACIDS

The chemistry of hydroxamic acids is complex but offers a fruitful area of research both from academic and practical consideration. These compounds have numerous application in various fields of agriculture, analytical, biological, technical and nuclear chemistry.

Hydroxamic acids and their metal complexes perform a broad spectrum of biological activities [47-53]. Most of them are antagonistic [54-56], antibacterial [57-63], antifungal [64-66], anticancer [67-72], antiviral [73-75], antineoplastic [76-78], antihistamine [79], antipsychotic [80], antitumour agent [81-84], whereas some exhibit mutagenic activity [85-86]. In medicine, these acids have been found to be of therapeutic potential in the treatment of cardiovascular disease, AIDS [87-88], Alzheimer's disease [89], Huntington's disease and Parkinson's disease [90]. One natural siderophore desferrioxamine is still the drug of choice for the treatment of iron overload associated with the transfusional treatment of β-thalassemia or cooley's anaemia [91-94]. They also display DNA cleavage properties [95-97] and used in carbohydrate metabolism [98-101]. Also, used in the treatment of connective tissue degradation [102-103] and act as insulin mimics [104-105]. They also show important role in inhibiting stone formation in urinary tract [106-109] and in controlling Helicobacter pylori induced gastritis [110-111]. Some hydroxamic acids are potentially useful for the removal of other toxic metals including plutonium from biological system [112].

A number of synthetic hydroxamic acids have been reported to be active as plant growth promoters [113-115], soil enhancers [116-117], herbicides [118] and as pesticides [119-120] in agriculture. These are also used as defence chemicals in graminæ [121-125] and as cultivators in corn seedlings to reduce water potentials before, during and after
germination [126] and in breeding for aphid resistance in wheat [127-128]. These are found to be present in roots of maize [129-130]. Extracts of certain Graminae such as rhye, wheat and maize contain hydroxamic acids [131-132] which inhibit growth and development of plant pathogens [133] and are involved in cereal resistance to various insects [134-135].

They have also rapt attention as specific enzyme inhibitors, such as peroxidase [136-137], urease [138-140], lipoxygenase, vasopeptidase [48,141], matrix metalloproteinase [142-143], elastase [144], thermolysin [145], aminopeptidase [146], ribonucleotide reductase with antineoplastic activity [147], cyclooxygenase [148], serine amidohydrolase [149] and siderophores for Iron (III) [150].

Hydroxamic acids have been used as excellent spectrophotometric, colorimetric and gravimetric reagents, with current interest focused on their reduction or complexation chemistry with transition metals [151-152]. As O,O donor ligands, they have a strong affinity for 'hard' metal ions, such as Fe^{3+}, Al^{3+} and Np^{4+} [153]. In industry hydroxamic acids are used as corrosion inhibitors [154], in commercial floatation in extractive metallurgy [155-156], in nuclear fuel reprocessing [157-158], in solvent extraction [159], in thermal power equipments [160], as stabilizers of photography developing solution [161] and as antioxidant [162]. Oxalohydroxamic acids is used in combustible compounds as primers for gun ammunition and other primary powders [163].

Hydroxamic acids with a low carbon backbone, such as FHA (formohydroxamic acid) and AHA (acetohydroxamic acid), have been shown to aid in the separation of tetravalent Np from hexavalent U through selective formation of a Np (IV) hydrophilic complex [164-166]. However, an additional property of these hydroxamic acids is that they can act as reducing agents for actinide ions [167]. As hydroxamic acids
are composed of only C, H, O and N atoms, they can be decomposed to gases so that their incorporation in industrial processes will not lead to increase in the waste volume [168]. Some hydroxamic acids show laser action and fluorescent properties [169-170]. Bis-hydroxamate complex of Rhodium (III) and oxidation of Rhodium (I) by hydroxamic acids have also been reported [171].

Such a broad spectrum of activity of hydroxamic acids is almost exclusively associated with only one type of chemical reactions, that is, their ability to bind a large variety of metal ions. In the vast majority of cases, O,O five membered chelate rings [172-175] are formed. (bridging [176] and monodenate [177] coordination modes are also known) and these complexes are often characterized by high stability constants [178-182].

It is evident from the above discussion that hydroxamic acids are important bioligands. The reactivity, acid-base equilibria and hydrolytic reactions of heterocyclic hydroxamic acids in comparison to mono-, di- and trihydroxamic acids are yet unexplored. Thus, it is the goal of this thesis to develop concise formulations of hydrolytic chemistry and metal-ion coordinating properties of some heterocyclic hydroxamic acids. Systematic studies are still lacking and deserve a greater attention, hoping to recognize and rationalize relationships between the electronic/structural properties of the binding metal centres and types of reactions. A detailed knowledge of the mechanism of reactions of these type of compounds can be of importance in planning their use as analytical reagents and in explaining their role in biological reactions.

1.4 BRIEF REVIEW OF EARLIER WORK

Extensive research [183-185] has been carried out on their synthesis, reactions and structures in the ground state. A review of these works
is far beyond the scope of the present investigation. Consequently, only major aspects of each area, directly related to present investigation are reviewed. The aim of the review is to put the present investigation in proper prospective.

1.41 Acid-Base Hydrolysis Of Hydroxamic Acids

The kinetics and mechanism of hydrolysis of esters [186-191], amides [192-194], anilides [195-197] and hydrazines [198-200] have been studied extensively.

This ubiquity of acid-base catalysis by protons and hydroxide ions makes the study of the pH dependence of reaction rates particularly important. The study of the dependence of the rate of the reaction on $H_3O^+$ or $OH^-$ concentration is of special significance because most of the reactions in aqueous media are involved directly or indirectly in equilibria which are influenced in some way by hydrogen or hydroxide ions can be varied, and their concentrations accurately detected. With such immense variation in proton concentration comes the possibility of a rich kinetic and mechanistic diversity. It has long been realized, however that catalysis by acids and bases usually involves one or more proton transfers, and the simple nature of the proton appears again in regularities which have been observed in the kinetics of catalysed reactions.

The interpretation of the variation in the rates of acid and base catalysed reactions with changing acidity and basicity has presented a considerable challenge to physical organic chemists, particularly as a guide to complete understanding of the detailed mechanism of such reactions.

The hydrolytic chemistry is one of the fundamental processes in organic chemistry and biochemistry. The chemical, physical and biological properties of hydroxamic acids are usually dictated by acidic or basic
groups that are present in it.

Hydroxamic acid are weak acids but also behave as weak bases due to the -NC=O moiety. Despite of their biological importance and rich chemistry there is only a few experimental contribution on their acid-base behaviour. Now, in most laboratories much work is being carried out on acid-base hydrolysis [201-203] and protonation equilibria of hydroxamic acids [204]. To evaluate the metal-ion binding properties of hydroxamic acid, it is necessary to study first their acid-base properties. The kinetic measurements of acid-base hydrolysis yield extremely valuable data for the elucidation of reaction mechanisms.

The kinetics of acid catalysed hydrolysis of benzohydroxamic acid in aqueous solution was studied for the first time by Berndt and Fuller [205] in 1966. They observed a first order dependence of rate on acid concentration for the hydrochloric acid catalysed hydrolysis of benzohydroxamic acid. This study, however only covered the low acidity range (0.1 M - 0.58 M acid) in which extensive protonation is not likely to occur. Tillett [206] and his group also examined the acid-catalysed hydrolysis of benzohydroxamic acid and five para substituted derivatives. The reaction was determined spectrophotometrically by following the decrease in characteristic absorption of the hydroxamic acid ferric chloride complex.

Hydrolysis of some aliphatic hydroxamic acids (acetohydroxamic acid, AHA) has been studied by Berndt and Sharp [207] in aqueous p-toluene sulphonic acids at 50.2°C. Mollin and Kucerova [208] measured hydrolysis rate of some different hydroxamic acids in perchloric acids in ethanol medium. The transition state polarity was studied by following the dependence of the rate constant on the dielectric constant of the solvent. This findings were in accord with the mechanism of the acid catalysed
hydrolysis of amides.

C.S. Rao [209] initiated the investigation on hydrolysis of N-phenyl-n-butyrohydroxamic acid in mineral acids. As part of broad programme on the hydrolysis reaction of hydroxamic acids Ghosh and Tandon studied hydrolysis of N-phenylbenzohydroxamic acid [210] and N-benzylbenzohydroxamic acid [26] in mineral acids over a wide range of acidity. Subsequent work opened up new vistas of chemistry and a fascinating broad field of chemistry on hydroxamic acids is developed [211-213]. Credit also goes to Professor D.C. Berndt and his coworkers of Western Michigan University, USA. Their work created a new dimension and continued to enrich this unexploited area of chemistry.

Little attention has been paid in the past to hydrolysis of hydroxamic acids in concentrated basic solutions. The pace of research in this field has been rather slow as evidenced by the small number of publications [214-215]. Although a few unsubstituted hydroxamic acids have been studied in NaOH solutions no systematic investigation has yet been made for N-substituted hydroxamic acids. The alkaline hydrolysis of esters [216-218], amides [219] and anilides [220-222] have been studied extensively. Most of the hydroxamic acids studied under this category are simple hydroxamic acid i.e. benzohydroxamic acid. Berndt and Fuller [205] studied rate of hydrolysis of benzohydroxamic acid as a function of hydroxide ion concentration. Both first and second order dependence on hydroxide ion is inferred in the base catalysed reactions. After this pioneering work of Berndt, Ahmed et. al [223] studied hydrolysis of benzohydroxamic acid in NaOH (0.0 to 6.0 mol dm\(^{-3}\)). No intermolecular general base catalysis was found in the reaction. However, intramolecular acid catalysis of hydroxyl ion attack on the substrate can be presumed with respect to suitable geometry. Further information about reaction
mechanism was drawn from hydrolysis kinetics of m- and p-substituted benzohydroxamic acids in NaOH. The substituent polar effects do not practically influence the hydrolysis rate in alkaline medium. An outstanding feature of these studies is the existence of a linear dependence of the pseudo-first order rate constant on concentration of NaOH.

Mane and Jagdale [215] examined the hydrolysis of aceto, isobutyro and hexanohydroxamic acids in aqueous NaOH. But no new information could be gathered from their studies. Bhuva and Buglass [214] studied the hydrolysis of phenyl hydroxamic acid in concentrated aqueous NaOH.

Hydrolysis of hydroxamic acids is a slow process even when catalysed by acid or base. A large number of research papers in this context have come up from various laboratory in last two decades [224-229] which usually describe the hydrolysis of simple mono- and dihydroxamic acids. But surprisingly scarce literature is available on acid-base catalysed hydrolysis of heterocyclic hydroxamic acids [230-231]. Studies on molecular structure, metal complexes, biological and analytical applications of hydroxamic acids requires a requisite knowledge of their acid-base hydrolytic chemistry. Thus, it was thought worthwhile to investigate kinetic studies of heterocyclic hydroxamic acids.

1.42 Chelating Properties Of Hydroxamic Acids

Hydroxamate molecules, one of the major classes of naturally occurring metal complexing agents, have been thoroughly studied as ligands [232-233]. Hydroxamic acids have tremendous capacity to form stable complexes with transition metal ions. Numerous papers showed that monohydroxamic acids adopts a typical binding mode due to the presence of reactive hydroxamic acid functional group, -N(OH). C(=O), which contains two functional group (i) the acidic group, -N-OH and (ii) the purely coordinating group, -C=O. In hydroxamic acids the acidic and coordinating
groups are so situated that they allow the formation of five membered ring with the metal ion as the closing member. Generally, the complex formation takes place by replacement of hydroxylamino hydrogen by the cation and ring closure through the carbonyl oxygen.

\[
n \left( \begin{array}{c} R' - N - OH \\ R - C = O \end{array} \right) + M^{n+} \xleftrightarrow{\text{reaction}} \left( \begin{array}{c} R' - N - O \\ R - C = O \end{array} \right) M + nH^+ n
\]

Each hydroxamate group acts as a bidentate oxygen ligands which has been proved by X-ray crystallographic studies [234]. Metal chelates represents a type of coordination compound in which a metal ion combines with a poly functional base, capable of occupying two or more positions of the coordination sphere of the metal ions, to form a cyclic compound.

The coordination chemistry of hydroxamic acid has received much attention due to its diverse coordination behaviour and its role in biological process. A large number of hydroxamic acid metal complexes have been synthesized and studied by various chemists [7-8, 10-11, 233, 235-240]. D. A. Brown et. al [241] have been proved that N-substituted mono- and dihydroxamic acids undergo oxygen abstraction on reaction with V (III), V(IV) and Mo(V) compounds to form hydroxamates of V(V) and Mo(VI) respectively together with the corresponding amides and diamides.

Farkas groups [232, 242-245] have been extremely active in the area of chelation properties of hydroxamic acids. They have studied the chelating properties of a series of monohydroxamic acids towards Cu(II), Ni(II), Zn(II), Ca(II), Mg(II) and Al (III) ions by pH metric, spectrophotometric and EPR methods. The solution properties of metal complexes of hydroxamic acids have been described in detail in a classic work by
Crumbliss et al. [11] estimate the dielectric constant at the reactive dinuclear Fe(III) site.

Among other elegant work relevant to the metal complexation of hydroxamic acids and other siderophores attention should be drawn to observations by Raymond et al. [246]. A series of dihydroxamic acid are reported and the coordination properties of their iron (III) complexes described by Raymond et al. The Fe(III), Al(III) and Cr(III) complexes of the fungal iron chelator, rhodotorulic acid (H₂RA), have been isolated and characterized by K.N. Raymond and C.J. Carrano [247].

Bell and Pratt [248] performed a series of qualitative and quantitative experiments, involving UV/VIS, ¹H NMR, ⁵¹V NMR spectroscopies and established that both 1:1 vanadate/hydroxamate complexes form at pH 7.5 with the former dominating at submillimolar concentrations. Formation constants for the complexes of several aryl and alkyl hydroxamic acids have been determined, e.g. for benzohydroxamic acid, the stepwise formation constants of the 1:1 and 1:2 complexes were 3000 and 400 M⁻¹ respectively.

Several crystal structures of Vanadium (V) hydroxamate complexes have now been described [249-250]. These show that in mononuclear complexes the hydroxamates interact with metal through the carbonyl and hydroxamate oxygen atoms [249-250], although additional coordination by nitrogen is also seen in a trinuclear complex [251-252].

The ligand is presumably bound to Vanadium through hydroxamic hydroxyl oxygen, but the hydroximic acid carbonyl oxygen interacts weakly with Vanadium. Vanadium (V) hydroxamates have been employed as insulin mimics [253], for example, the combinations of Vanadate with specific hydroxamic acid inhibit serin β-lactamases and proteases [254]. When all these recent observations and results are taken into account, it can
be assumed that hydroxamic acids are ideal metal chelators. These can be used according to structural requisites for their introduction in medicinal field. So, in the present study complexation of heterocyclic hydroxamic acid with Vanadium (V) is also one of the unexplored field of research work.

1.5 PRESENT INVESTIGATION

The chemical, physical and biological properties of hydroxamic acids are dictated by acidic or basic groups that are present in the molecules. In this regard it was, thought worthwhile to study the kinetics of hydrolysis, complexation and biological activity of some heterocyclic hydroxamic acids. The relationship between structure, hydrolysis behaviour and ion-coordinating properties have been investigated in order to understand fully the role of heterocyclic hydroxamic acids in biological and analytical systems. To achieve this goal the present investigation has been divided into following sections:


[C] Complexation of heterocyclic hydroxamic acid with Vanadium (V).

[D] Biological activity of some heterocyclic hydroxamic acids.

[A] SYNTHESIS AND CHARACTERIZATION OF SOME HETEROCYCLIC HYDROXAMIC ACIDS

Five heterocyclic hydroxamic acids have been synthesized and obtained in pure crystalline form for detailed investigation.
The purity of these heterocyclic hydroxamic acids were confirmed by elemental analysis, melting point determination, IR and NMR spectroscopic techniques.

[B] Kinetics And Thermodynamics Of Acidic Hydrolysis Of Some Heterocyclic Hydroxamic Acids

In present investigation the kinetics of acidic hydrolysis of four heterocyclic hydroxamic acids (FHA, PFHA, p-TFHA and p-Cl PFHA) has been studied in detail. Except FHA, rest of the heterocyclic hydroxamic acids are insoluble in water therefore, 20% (v/v) dioxane-water medium was chosen for all kinetic studies. Temperature, solvent, salt and surfactant effects have been studied to elucidate the reaction mechanism. Thermodynamic parameters have also been determined. The product of
hydrolysis reactions were identified to shed light on the mode of bond fission. Attempts have been made of study the effect of dielectric constant on rates of reaction for p-TFHA and p-CIPFHA by varying diverse solvent composition.

The kinetic data has been analysed by the application of rate-acidity correlations to establish the reaction mechanism. Empirical criteria of acid catalysed hydrolysis have been developed in terms of acidity function $H_0$ or $H_A$, the water activity $a_w$, total concentration of $H^+$ ions in acidic medium. Bunnett $\omega$ and $\omega^*$ treatment, Bunnett -Olsen $\phi$ LFER treatment and Cox-Yates excess acidity methods have been used to understand and establish the mechanism of acidic hydrolysis.

[C] Complexation Of Heterocyclic Hydroxamic Acid With Vanadium (V)

The chelating property of heterocyclic hydroxamic acid with metal ion, specially with Vanadium (V) have been studied. The heterocyclic hydroxamic acid FHA forms purple coloured complex with Vanadium (V) in acidic medium. The complex exhibits a wavelength of maximum absorption at 475nm. The coloured system obeys Beer's law and has been investigated to develop spectrophotometric method for the determination of Vanadium (V) in aqueous medium. The method has been used for the determination of Vanadium in steel, environmental and biological samples.

[D] Biological Activity Of Some Heterocyclic Hydroxamic Acids

Biological activity of five synthesized heterocyclic hydroxamic acids (FHA, MFHA, PFHA, p-TFHA and p-CIPFHA) has been studied in terms of their antibacterial and antifungal activity against certain bacteria and fungi. The antibacterial and antifungal activity of these compounds were
compared with standard antibiotics.

1.6 IMPORTANCE OF THE STUDY

The importance of present investigations are as follows:

a. Hydroxamic acids represents a specific class of organic bioligands, having functional group -CO-N(OH)- in their structure, hence the kinetic study of heterocyclic hydroxamic acids leads to understand their hydrolytic chemistry which help in predicting the mechanism.

b. The relationship between the structure, hydrolytic behaviour and metal ion-coordinating properties have been investigated inorder to understand fully the role of heterocyclic hydroxamic acid in industrial, biological and analytical system. To improve their biological performance this study will be very helpful.

c. In organic preparative reactions, several possible competing reactions can occur and the relative rates of these reactions usually influence the yield of each product. An understanding of the mechanism leads to improved yield of the desired chemical product. Moreover the kinetic data on the half life periods of hydrolysis reaction are of direct relevance for the yields and purity of synthesized heterocyclic hydroxamic acids.

d. The mechanism of hydroxamic acid is of fundamental importance in the context of its applicability in the nuclear fuel reprocessing, pharmaceuticals, solvent extraction and spectrophotometric determination of metals particularly using concentrated acid solutions. Particular attention has been devoted to the biological and chemical aspects of hydroxamic acids as well as to their potential clinical use as novel therapeutic agents. Information about hydrolysis reaction could be useful for understanding the biochemical production and degradation of hydroxamic acids.
e. From analytical considerations it will be very rewarding to kinetically investigate the hydrolytic stabilities of metal hydroxamic acid complexes. At present an analytical chemist normally examines the effect of time on coloured systems, empirically, the effort being tedious, time consuming and often irrational. Kinetic data for such systems will provide a rational basis for the choice of optimum range of acid concentration for maximum colour development.

f. Hydroxamic acids and their metal complexes have been implicated in a wide spectrum of biological activities. Most of them are antagonists, antibacterical, antifungal, anticancer, antiviral, antitumour agents and specific enzyme inhibitors. Some are found to be of therapeutic potential in the treatment of cardiovascular disease, HIV, Alzheimer's and Parkinson's disease. One natural siderophore desferrioxamine is used in the treatment of β-thalassemia or cooley's anaemia. Thus the combined use of hydrolytic chemistry and chelating properties of heterocyclic hydroxamic acids provide a better picture of application of heterocyclic hydroxamic acids. The insight gained from such attempt enable us to design more effective hydroxamic acids for biological and analytical applications.

1.7 ORDER OF PRESENTATION

The entire experimental work, observation and results have been presented in seven chapters. The following order of presentation has been adopted.

Chapter - I : It includes introduction of hydroxamic acids, heterocyclic hydroxamic acids, application of hydroxamic acids. The emphasis is given to highlight the biological, technical and analytical importance of hydroxamic acids. It provides a brief review of the work already done in the relevant field. It also outlines the objectives and importance of the study.
Chapter II: It incorporates the synthesis and characterization of five heterocyclic hydroxamic acids (FHA, MFHA, PFHA, p-TFHA, and p-CIPFHA). The physico-chemical properties of these heterocyclic hydroxamic acids have been studied by their melting point determination, elemental analysis, IR and NMR spectral analysis, which are discussed in this chapter.

Chapter III: The experimental details of kinetic measurements of acidic hydrolysis, effect of different organic solvents, salts and surfactants on the rate of acidic hydrolysis of heterocyclic hydroxamic acids, complexation with Vanadium (V) and biological activity of heterocyclic hydroxamic acids have been summarized.

Chapter IV: This chapter deals with detailed kinetic study of acid catalysed hydrolysis of four synthesized heterocyclic hydroxamic acids i.e. FHA, PFHA, p-TFHA and p-CIPFHA. The variation of reaction rate in presence of different mineral acids HCl, H$_2$SO$_4$, and HClO$_4$ has been studied. The effect of temperature on reaction rate has been described in terms of thermodynamic parameters. The Bunnett $\omega$, Bunnett-Olsen $\phi$ and Cox-Yates excess acidity correlations have been applied on kinetic data for mechanistic study.

Chapter V: It describes the effect of various organic co-solvents, salts and surfactants on the rate of hydrolysis of two heterocyclic hydroxamic acids i.e. p-TFHA and p-CIPFHA in acidic medium. Attempts have been made to study the dependence of rate of acidic hydrolysis of heterocyclic hydroxamic acids on reaction medium.

Chapter VI: This chapter deals with the complexation of heterocyclic hydroxamic acid (FHA) with Vanadium (V). This coloured reaction has been investigated to develop spectrophotometric method for determination of Vanadium (V) in aqueous medium, using 3M hydrochloric acid. The
colour system obeys Beer's law. The method has been successfully applied for determination of Vanadium in steel, environmental and biological samples.

**Chapter - VII:** This last chapter includes the study of biological activity of five synthesized heterocyclic hydroxamic acids (FHA, MFHA, PFHA, p-TFHA and p-CIFPHA) in terms of antibacterial and antifungal activity against some bacteria like Rhizobium, Lactobacillus, Pseudomonas, E.Coli and fungus like Alternaria, Curvularia and Rhizoctonia. Their antimicrobial activity has been compared with standard antibiotics.
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