Chapter 1

Introduction
INTRODUCTION

During the past decade a substantial number of natural products which contain one or more oxidized peptide (amide) bonds, −CON(OH)− have been found mainly in microbial sources. These substances are assigned as hydroxamic acids. This hydroxamic acid bond has the outstanding chemical feature and it can be expected to play an important role in their biological action. These substances act variously as potent growth factors, antibiotics, antibiotic antagonists, tumor inhibitors and cell division factors. For this reason various properties of N-arylsubstituted hydroxamic acids are surveyed here.

NOMENCLATURE AND STRUCTURE

In 1869 H. Lossen(1) treated hydroxylamine with diethyl oxalate and obtained a derivative, which he called oxalohydroxamic acid. Since then N-acylderivatives of hydroxylamine are called hydroxamic acids (I). Compounds of structure (I) were recognised

\[
\begin{align*}
\text{H} & \quad \text{N} \quad \text{OH} \\
\text{R} & \quad \text{C}=\text{O} \\
\end{align*}
\]

(I)

as unsubstituted hydroxamic acids with the introduction of a new functional group in the field of organic chemistry, known as hydroxamic acid functional group (II). Later, more

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{C}=\text{O} \\
\end{align*}
\]

(II)

detailed studies have shown that these reagents are able to give a number of functional derivatives. A major difficulty has been the structure from several possible tautomeric forms –
Possibilities of geometrical isomerism and internal hydrogen bonding have added to the complexity. The controversy has been resolved by the application of UV and IR spectroscopy. Results of $^{17}$O NMR studies support the "amide" structure of hydroxamic acid with the internal hydrogen bonding in the syn-configuration.

Substituted hydroxamic acids are derived from N-substituted hydroxylamine, which has two nucleophilic centres and hence yields two series of derivatives by substitution on nitrogen and oxygen respectively. As to the structure of hydroxamic acids, these were recognised as N-acyl derivatives already by H.Lossen and exclusive N-acylation.
occurred in all cases under a variety of conditions and with a variety of acylating agents. The most widely used compound of structure (VIII) is N-phenylbenzo hydroxamic acid (IX), trivial name PBHA, which was synthesized in 1919 by Bamberger and has come into prominence because of its versatility as analytical reagent. Substituted hydroxamic acids are incapable of exhibiting tautomerism.

Hydroxamic acids have exhibited many interesting facets of chemistry since they were reported. Extensive work has been carried out on their formation, reactions and structure in the ground state. Various aspects of hydroxamic acid chemistry have been reviewed (5-13).

**ANALYTICAL APPLICATIONS**

Hydroxamic acids and their N-aryl substituted derivatives (X) serve as bidentate ligands towards many metal ions. The resultant complexes are highly coloured and, therefore

useful in colorimetric analysis of metal ions (8, 14-32) or hydroxamic acids (33).
**BIOLOGICAL APPLICATIONS**

The discovery of the involvement of siderophores, an iron(III) hydroxamic acid complex, in microbial iron transport, was one of the striking progress in hydroxamic acid chemistry. 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 anemia (10). Hydroxamic acids found as naturally occurring compounds, mainly in fungi which are active as antibiotics and antitumor agents (34-36). Many synthetic hydroxamic acids also show fungicidal, antimalarial and antibacterial activity thus, employed as therapeutic reagents (37). These are also used for the treatment of disease related to connective tissue degradation (38) as inhibitors of matrix metalloproteinase and TNF α secretion (39, 40) and as anti-inflammatory agents (41, 42). Some hydroxamic acids show DNA cleavage properties (43) and some inhibit DNA biosynthesis (44), on the other hand many of them are powerful carcinogens (45), and inhibit influenza virus polymerase (46).

**AGRICULTURAL APPLICATIONS**

Hydroxamic acids have established their vitality in agriculture field, three to four decades ago. These reagents are also used in alternating benzohydroxazinone levels in plants, which helps in plant defense mechanism for insects and disease resistance and for increasing herbicide tolerance in plants (47, 48). These are also used as cultivators in corn seedling to reduce water potentials on germination period (49) and in breeding for aphid resistance in wheat (50). These are found to present in the roots of maize (48).

**TECHNICAL APPLICATIONS**

Among the many applications, the noteworthy are in the floatation techniques (51), where the extraction of metals from the ores are performed efficiently. Hydroxamic acids containing polymer paints are used as corrosion inhibitors (52). These reagents play remarkable role in the field of photography as potential compound for producing films, as photographic sensitive materials and also for improved shelf life and latent image stability (53-59). Some of the hydroxamic acids are used for the treatment of transition
metals containing pigments particles (60) and some are used as laundry detergents and as surfactants (61). Oxalohydroxamic acid is used in combustible compounds as primers for gun ammunition and other priming powders (62). Some hydroxamic acids show laser action and fluorescent properties (63). Polystyrene – based hydroxamic acid esters are used as acyl transfer reagents (64), some other substituted benzohydroxamic acids have an unexpected role of enhancement in the intramolecular carboxylic acid–catalysed cleavage (65).

N–Aryl substituted hydroxamic acids are versatile metal extractants. The solvent extraction is largely concerned with the equilibrium distribution of solute species between aqueous solutions and an immiscible solvent, and the application of a variety of physicochemical techniques has produced a good understanding of the overall principles that govern such extraction equilibria.

Keeping the above points in mind, attention has been focussed on the determination of physico-chemical properties of these reagents in order to study the nature of an interaction between solute and solvent molecules and their protonation behaviour in mineral acid solutions.

THE SCOPE AND SUMMARY OF THE PRESENT INVESTIGATION

The proposed investigation describes the synthesis of ten N–aryl hydroxamic acids containing various groups in CHAPTER II. These were synthesised by reacting acid chlorides with freshly prepared hydroxylamines, in presence of a base, at low temperature. The compounds were analysed for the elements present and the values agreed with the theoretical ones. The melting points of these reagents tally with the values recorded in the literature. The UV and IR spectral data are tabulated and discussed.

In CHAPTER III a method is investigated for the spectrophotometric determination of N–aryl hydroxamic acids, which form water-insoluble deep violet or reddish-violet complexes with vanadium(V), in acidic solutions. The intensities of the coloured extracts are determined at the respective wavelength of maximum absorption. The effect of several
variables on quantitative colour development are examined. The method gives precise
and accurate results. It is practically specific in its reaction for N-arylsubstituted hydroxamic
acids.

The results of the determination of some physical parameters of N-arylhydroxamic
acids have been recorded in CHAPTER IV. The parameters investigated are partition
coefficients (K_D) in various organic solvent-aqueous systems, density (ρ), molar volumes
(V_1), solubility parameter (δ_c), primary medium activity coefficient (γ_1), free energy of transfer
(ΔG^0_t) of a solute in solvent and values of 1000ρ/M, of these chelating reagents, which are
of interest in analytical solvent extraction. The partition data are discussed successfully
on the basis of Regular Solution Theory, an attempt is made to correlate the values of K_D,
for a number of common organic solvents, with some physical parameter characteristics
of the solvents. Such parameters include dielectric constant (ε), solvent polarity
(E_r and π^*) and the solubility parameter values (δ).

Protonation behaviour of N-arylhydroxamic acids is described in CHAPTER V. These
reagents act as weak organic bases in presence of strong acidic solutions.

$$\text{B} + \text{H}^+ \quad \xrightarrow{\text{p}K_{\text{B}H^+}} \quad \text{BH}^+$$

The dissociation constants, pK_{B\text{H}^+} of conjugate acids of these weak bases are determined
spectrophotometrically by measuring in concentrated aqueous perchloric acid solutions,
the ionisation ratio, I. The protonation data are analysed following the three classical
procedures, Hammett Acidity Function Method (HAFM)(66), Bunnett-Olsen Method
(BOM)(67) and Excess Acidity Method (EAM)(68,69), which is a modified version of
Margiano-Cimino-Passerini Method(70). HAFM and BOM involve acidity function whereas,
EAM uses overlapping indicator and does not involve an acidity function. The percentage
of protonated species as a function of perchloric acid concentration and slope
parameters (m, φ and m*) of dissociation of conjugate acid of N-arylhydroxamic acids have
been obtained and compared. Effect of various substituents on protonation behaviour of
these reagents is also discussed.