CHAPTER I

INTRODUCTION
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1.0 HYDROXAMIC ACIDS: Hydroxamic acids I are the \( N \)-acyl derivatives of hydroxylamine (1,2).

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

HYDROXAMIC ACID (KETO FORM) I

These simple hydroxamic acids can exist in the enol form also,

\[
\begin{align*}
N &\quad OH \\
| \\
R &\quad C \quad OH
\end{align*}
\]

HYDROXAMIC ACID (ENOL FORM) II

Substitution of hydrogen atom bound to nitrogen atom in I by alkyl or aryl group produces \( N \)-substituted hydroxamic acid III.
1.1 SYNTHESIS OF HYDROXAMIC ACIDS: A brief account of a few representative methods for preparing N-substituted hydroxamic acids is given here.

(1) By controlled N-acylation of N-substituted hydroxylamines: Generally, hydroxamic acids are prepared by the acylation of hydroxylamines and N-substituted hydroxylamines:

\[
\begin{align*}
R^' \cdot N \cdot OH \\
R \cdot C = O
\end{align*}
\]

N-SUBSTITUTED HYDROXAMIC ACID

III

\[
\begin{align*}
R_1 \cdot N \cdot OH + R_2 COCl \\
\downarrow \\
R_1 \cdot N \cdot O \cdot C \cdot R_2 \\
\downarrow \\
R_1 \cdot N \cdot OH \\
R_2 \cdot C = O \\
\downarrow \\
R_2 \cdot C = O
\end{align*}
\]

V IV VI
Acylation obviously takes place preferentially at N atom and the desired N-acylated derivative, IV, is the main product. However, simultaneously both mono-O-acylated derivative, V, and di O- and N-acylated derivative, VI, are also produced in relatively small quantities as impurities.

In Bamberger's (3) original method acylation was carried out in aqueous medium. The crude product was thoroughly shaken successively with cold liquor ammonia or 6 M NaOH solution in which the desired N-acylated derivative was soluble. This solution was then acidified with 6 M H$_2$SO$_4$ or HCl to get the desired solid product. This product was further purified by crystallization from suitable solvent mixtures such as ethanol and water or benzene and petroleum ether (60 - 80°C range).

This method was modified by Priyadarshini and Tandon (4) to prepare over two hundred N-substituted hydroxamic acids. In the modified procedure diethyl ether or diethyl ether mixed with petroleum ether (40 - 60°C range) medium was used. Acylation was carried out with acid chloride using an aqueous slurry of NaHCO$_3$ to neutralize the liberated HCl. Equimolar amounts of N-substituted hydroxylamine and acid chloride were taken and the reaction was carried out at
0°C (or lower). Under these conditions the undesirable derivatives V and VI were formed in negligible amounts and could be removed by one or two crystallizations from suitable solvents.

Recently, BRINK and CRUMBLISS (5) prepared N-arylhydroxamic acids by acylation of ethereal solution of appropriate N-substituted hydroxylamine and acid chloride in presence of NaHCO₃ at very low temperature (-78°C), stirring the solution continuously for 8 - 12 hours. The product obtained was shaken with 5M NH₄OH keeping the temperature below 0°C. To the solution thus obtained 6M H₂SO₄ was added dropwise till the pH became ~ 2. Complete precipitation was assured by cooling to -78°C. The product thus obtained was purified by crystallization from ethyl acetate.

(2) Acylation of N-substituted hydroxylamine followed by subsequent hydrolysis of N,O-diacyl substituted product:

\[
\begin{align*}
R_1 \quad & N \quad OH \\
& H \\
+ \\
& Cl \\
\rightarrow \\
R_2 \quad & C = O
\end{align*}
\]

N-Substituted hydroxylamine Acid chloride

\[
\begin{align*}
R_1 \quad & N \quad O \quad C \quad R_2 \\
R_2 \quad & C = O \\
\rightarrow \\
N,O-Di substituted hydroxamic Acid Hydrolysis
\end{align*}
\]
N-Arylsubstituted hydroxamic Acid + Carboxylic Acid

This method results in wastage of at least 50% acid chloride and gives the desired product in poor yield (6-8).

(3) N-Acylation of N-arylhydroxylamines by carboxylic acids in presence of dicyclohexylcarbodiimide (DCC):

Preparation of hydroxamic acids by this method (9-11) involves rigid reaction conditions.

\[
\begin{align*}
\text{H} & \quad \text{Cl-} - \text{N} - \text{OH} \quad \text{HOCH}_2\text{COOH} \quad \text{DCC} \quad \text{Cl-} - \text{N} - \text{OH} \\
& \quad \text{HO} - \text{CH}_2\text{OCOCH}_2^- - \text{C} = \text{O} \\
& \quad \text{VII} \\
& \quad \text{Cl-} - \text{N} - \text{OH} \\
& \quad \text{HO} - \text{CH}_2 - \text{C} = \text{O} \\
& \quad \text{VIII}
\end{align*}
\]

The product VII has to be converted to the final product VIII by saponification of crude product.
Certain nitroso compounds and aldehydes are disproportionated under the influence of aluminium alcoholate to give N-substituted hydroxamic acids (12).

\[ \begin{align*}
R_1 - N = O + R_2 - C = O & \xrightarrow{\text{Aluminium alcoholate}} R_1 - N - OH \\
H & R_2 - C = O
\end{align*} \]

This method is lengthy and tedious. Full experimental details and wide applicability are lacking.

Incubation of nitroso aromatic compounds by yeast trans-ketolase enzymes and D-xylulose-5-phosphate: CORBETT (13) prepared N-aryl-N-glycohydroxamic acid by this method.

Hydrogenation of nitroso compounds: Hindered aromatic nitroso compounds in ethyl acetate medium using triethyl amine or sodium acetate for buffering are concurrently acylated and hydrogenated with acetyl chloride or acetic anhydride and with 10% palladium on charcoal. This is a difficult method of preparation but has wide poten-
In situ reductive acylation of nitro compounds:

In this method (15, 16) the nitro compound is simultaneously reduced and acylated in situ using zinc dust and acetyl chloride or acetic anhydride.

1.2 Analytical Applications: Hydroxamic acids possessing the functional grouping IX are ideally suited to form

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

stable 5-membered chelates (or inner complex compounds) with metal ions.

\[ M^{n+} + n \left( \begin{array}{c}
\text{R} \\
\text{R}
\end{array} \right) \left( \begin{array}{c}
\text{N} \\
\text{C} = \text{O}
\end{array} \right) \rightarrow \left( \begin{array}{c}
\text{R} \\
\text{R}
\end{array} \right) \left( \begin{array}{c}
\text{N} \\
\text{C} = \text{O}
\end{array} \right) n \quad M^{n+} \]

The water-insolubility, deep colour and preferential solubility in water-immiscible solvents of the metal-chelates of hydroxamic acids have been widely employed for developing gravimetric, colorimetric and solvent extraction methods. Hydroxamic acids have, therefore, found numerous analytical applications.

Hydroxamic acids of structures I and II were the first to be experimented for analytical applications.
Early work reviewed in 1940 by DAVIDSON (17) was mainly concerned with their use in organic analysis. A wide variety of organic functional groups such as carboxylic acids, anhydrides, acid chlorides, esters, lactones, amides, aldehydes, nitro compounds, phenols and alcohols are detected and determined, directly or indirectly, by the iron(III)-hydroxamic acid colour reaction (18, 19, 20).

The chemical basis of these analytical applications is illustrated by the following representative reactions in which a purple iron(III)-hydroxamic acid complex is produced.

\[
\text{NH}_2\text{OH} + \text{R - C = O} \quad \text{Cl} \quad \longrightarrow \quad \text{H - N - OH} \quad \text{R - C = O} \quad \text{HCl}
\]

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

\[
+ \text{Fe}^{++} \quad \longrightarrow \quad \text{H - N - C} \quad \text{Fe}^{+++} \quad \text{H}^+
\]

The above referred colour reaction is very popular and is widely used in biochemical, environmental, and industrial analysis (21-27).

Both hydroxamic acids of structures I/II and III have been widely used for gravimetry, colorimetry, solvent
extraction, complexometry, amperometry, spot tests, chromatography, polarography, atomic absorption spectrometry and Mössbauer spectroscopy etc. These applications are given in several reviews and research monographs (28-30) and so no attempt is made here to catalogue these. The hydroxamic acids have distinguished themselves by two major applications.

(i) **In Colorimetry**: Vanadium(V), Cerium(IV), titanium(IV) and molybdenum(VI) give deeply coloured systems in concentrated acid media. The reaction with vanadium(V) has been widely exploited and there are numerous research papers dealing with a wide variety of analytical applications (31-35). Other coloured systems viz., with iron(III), uranium(VI), Copper(II), gold(III), neodymium(V) and protoactinium(V) etc. are formed in weakly acidic solutions. These have found limited analytical applicability.

(ii) **Solvent separation of metal ions**: Metals such as thorium, uranium, plutonium, americium, beryllium, titanium, zirconium and hafnium etc., used in nuclear energy programmes, have been separated from commonly associated metals by solvent extraction using hydroxamic acids (36-40).

1.3 **APPLICATION IN ENVIRONMENTAL ANALYSIS OF METALLIC POLLUTANTS**: Hydroxamic acids do not form coloured systems with major metallic pollutants like beryllium,
Cadmium, lead, arsenic and mercury. Hence, there are no direct applications in environmental analysis of hydroxamic acids for these metals. Other metallic pollutants copper(II), chromium(III), cobalt(II) and nickel(II) form coloured complexes with hydroxamic acids but the coloured systems lack the desired sensitivity and selectivity. Hence, obviously these systems also do not find any practical applications in environmental analysis. Vanadium is the only metallic pollutant which can be analysed by hydroxamic acids. The vanadium(V)-hydroxamic acid coloured systems, which are generally formed in concentrated acid media, and have the desired selectivity and sensitivity of reactions have been exploited for environmental analysis. Some of the applications of hydroxamic acids for determining vanadium in environmental matrices are given in Table 1.01.

1.4 THE PRESENT INVESTIGATION: The present investigation is prompted by two practical requirements.

(i) Preparation of hydroxamic acids in good yield and high purity: To prepare the hydroxamic acids in good yield and high purity the method proposed by RYADARSHINI and TANDON (4), described in section 1.1 of this Chapter, was used.
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Hydroxamic Acid</th>
<th>Environmental Samples Analysed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Benzo-</td>
<td>Animal tissues and blood</td>
<td>(41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plant materials</td>
<td>(42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crude and residual oil</td>
<td>(43)</td>
</tr>
<tr>
<td>2.</td>
<td>N-Phenylbenzo-</td>
<td>Air borne particulates</td>
<td>(44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fuel oil</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Synthetic, tap, river, sea water</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soil</td>
<td>(46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spinacia, cauliflower, riccia, Puccinia, Spirogyra</td>
<td>(47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Animal materials, potato leaves</td>
<td>(48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dental enamel, bone, biological material</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crude Petroleum</td>
<td>(49)</td>
</tr>
<tr>
<td>3.</td>
<td>N-Benzylbenzo-</td>
<td>Blood and urine</td>
<td>(50)</td>
</tr>
<tr>
<td>4.</td>
<td>N-o-Tolylbenzo-</td>
<td>Sea water</td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Natural water</td>
<td>(51)</td>
</tr>
</tbody>
</table>

Contd.
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Hydroxamic Acid</th>
<th>Environmental Samples Analysed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>o-Methoxy-N-m-tolylbenzo-</td>
<td>Fresh and saline water, rice, tobacco, vegetables, fruits, rat tissues and flesh</td>
<td>(52)</td>
</tr>
<tr>
<td>6.</td>
<td>N-m-Tolylbenzo-</td>
<td>Coal and fly ash</td>
<td>(33)</td>
</tr>
<tr>
<td>7.</td>
<td>N-m-Tolyl-p-methoxybenzo-</td>
<td>Blood and urine</td>
<td>(53)</td>
</tr>
<tr>
<td>8.</td>
<td>N-Phenyl-2-furo-</td>
<td>Brine</td>
<td>(54)</td>
</tr>
<tr>
<td>10.</td>
<td>N-Phenyl-2-naptho-</td>
<td>Blood</td>
<td>(56)</td>
</tr>
<tr>
<td>11.</td>
<td>Salicylo-</td>
<td>Soil</td>
<td>(57)</td>
</tr>
<tr>
<td>12.</td>
<td>N-Phenyl-trans-cinnamo-</td>
<td>Natural water</td>
<td>(51)</td>
</tr>
<tr>
<td>13.</td>
<td>N-Phenyl-N-(2,3-xyllyl)cinnamo-</td>
<td>Petroleum, Vicera, flesh, blood, human hair, pig liver, kidney, apple, potato</td>
<td>(58)</td>
</tr>
</tbody>
</table>
(ii) Development of reliable method for colorimetric determination of vanadium(V) with hydroxamic acids:

Hydroxamic acids form a violet coloured complex with vanadium(V) in hydrochloric acid medium. Stability of this coloured complex is an essential condition for a good analytical reagent. But hydroxamic acids hydrolyse to form hydroxylamine and carboxylic acid which results in instability of the vanadium(V)-hydroxamic acid coloured system. The rate at which a hydroxamic acid hydrolyses depends on the substituents attached to it. A knowledge of kinetics of hydrolysis is thus essential to establish the stability of the compound as an analytical reagent.

In Chapter II, the method for the preparation of hydroxamic acids has been discussed extensively. The properties of hydroxamic acids such as melting points, U.V. and I.R. spectral characteristics besides kinetic data are also reported. The rate-acidity profiles of seven N-substituted hydroxamic acids given in Table 1.02 have been reported in HCl at 45° and 55°. PCMA was found to be the most stable and hence is suitable for analytical work. So the rate acidity profile of this compound was studied using HClO₄ (at 55°) and H₂SO₄ (between 45° and 75°). Also, its stability has been compared with the rates of hydrolysis of hydroxamic acids reported from this laboratory.
<table>
<thead>
<tr>
<th>HYDROXAMIC ACID</th>
<th>TRIVIAL NAME</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-2-TOLYL BENZO-</td>
<td>o-TBHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
<tr>
<td>N-4-TOLYL BENZO-</td>
<td>p-TBHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
<tr>
<td>N-PHENYL n-VALERO-</td>
<td>p(n)VHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
<tr>
<td>N-CH-PHENYL n-VALERO-</td>
<td>p-Cl-P(n)VHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
<tr>
<td>N-Cl-PHENYL PIVALO</td>
<td>p-Cl-PPHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
<tr>
<td>N-Cl-PHENYL n-HEXANO-</td>
<td>p-Cl-P(n)HHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
<tr>
<td>N-PHENYL trans-CINNAMO-</td>
<td>PCHA</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
</tr>
</tbody>
</table>
To establish RCHA as an analytical reagent a method for extraction of vanadium (V) with the cited reagent has been proposed in Chapter III. Its sensitivity and selectivity in different reaction conditions such as acid concentration, reagent concentration and adherence to Beer's law and effect of various foreign ions are investigated. The reagent, found to be highly stable, sensitive and selective was applied for the determination of vanadium in environmental matrices.

In Chapter IV, the mechanism of hydrolysis of RCHA was investigated using all kinetic tools, such as Arrhenius parameters, ionic strength effect, kinetic solvent isotope effect, Bunnett's $\omega$ and $\omega^*$ parameter, Bunnett's $\omega^*$ parameter and Yates-McClieand hydration $r$ parameter. Based on these studies the most probable mechanism for the hydrolysis reaction has been proposed.
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