

Chapter One

Introduction

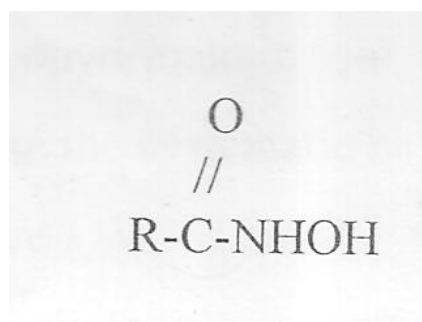
1.1: Introduction:

1.1.1: Definition and structure of hydroxamic acid:

hydroxamic acid are organic weak acids , and their strength is similar that of a carboxylic acid , also can be considered is n-acyl derivatives of hydroxylamine .

hydroxamic acid were known as compounds which having the bidentate functional grouping .according to their chelating properties ,they are used as excellent complexing agent for avast number of metal ions . and hence they have been used as analytical reagents in both organic and inorganic chemistry (vogel ,1978)

1.1.2: hydroxamic acid general formula:



They are classified by mikes and turkova into three main group:

- 1) Primary hydroxamic acid.
- 2) Secondary hydroxamic acid.
- 3) Cyclic hydroxamic acid.

In the solution hydroxamic acid existing the two tautomeric



Keto form contains one easily replaceable proton (monobasic acid). While the enolic form may dissociate two protons (dibasic acid).

Those two tautomeric forms provide a number of sites, which are available for metal ion co-ordination.

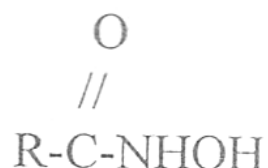
The keto form predominates in acidic medium while the enol form predominates in alkaline medium. Complexation of metal ions by hydroxamic acid is the basis of a number of analytical determinations. The best known complex is that with Fe(III) whose beautiful purple color is the basis for the sensitive qualitative and quantitative determination of carboxylic acids and their derivatives.

1.2 Nomenclature:

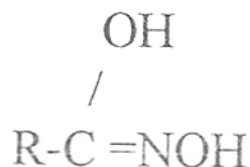
Hydroxamic acids belong to a group of organic compounds which are derived from hydroxylamine, these derivatives having as their principle functional group.

The hydroxylamine residue $>\text{N-OH}$ are described in literature under the general name of oxime these oximes show ever are usually classified according to parent organic substance from which they are derived, thus we have the aldoximes derived from aldehyde, ketoxime from ketone, and also hydroxyl aromatic

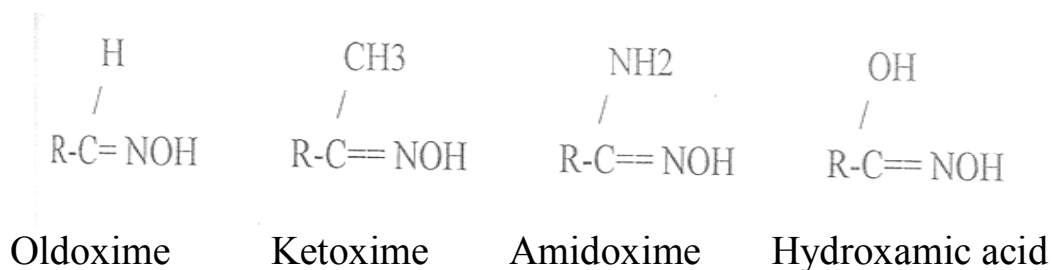
aldehyde , keton or – diketone respectively . according to the classification compound having the N-hydroxyamide grouping



Or the tautomeric oximino alcohol grouping



Which are obviously the derivatives of carboxylic acid are termed as hydroxamic acid . these are related to the other members of the class namely the aldoximes , the ketoximes and the as shown below :-



Hydroxamic acid occure into two tautomeric froms , the enol and keto forms



Since hydroxamic acid are derivative of carboxylic acid their nomenclature must be based on them , thus in naming specific compound , the practice is to drop the ice of the related carboxylic acid and substitute the letter O for it, followed hydroxmic acid in the last . this for benzoic acid we derived benzohydroxamic acid (Exner and simon ,1965).

This system of nomenclature leads to some problems according to these rules for carpohydroxamix and for carpicacid .

the hydroxamic acid would also be carpohydroxamic acid , there fore in these and similar cases an attempt was made to use systematic name as basis of nomenclature , thus carpoic acid derivative is named hexane hydroxamic acid while decanohydroxamix acid is given to carpic acid derivatives.

1.3 properties of hydroxamic acid:

1.3.1 physical properties:

All the hydroxamic acids are white crystalline solids except the nitro and the iodo substituted acid which are yellow and violet respectively (Mohamed,1999) . the solid reagent are very stable to the action of heat light & air .

Chloroform solution if stored in amber-colored bottles ,are stable for several days (Agrwal,1980)

They are sparingly soluble In water , but soluble in organic solvent like benzene ,diethylether ethylalcohol , carbon tetrachloride and chloroform .

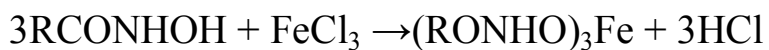
1.3.2: Characterization:

Hydroxamic acids have been characterized in the term of their elemental analysis , melting point, color test and spectral data which in many cases obtained basically for their characterization such as infrared uv-vis and in some cases proton nuclear magnetic resonance ,mass spectra and thin layer chromatography (Das and Shome ,1960)

1.3.2.1: Color test:

All hydroxamic acids gave characteristic violet extracts with the vanadium (V) from strong hydrochloric acid (2-120M) solutions

and characteristic red or purple coloration in aqueous media with ferric chloride according to the equation .



In this color test, chloroform must be free from ethanol. Otherwise the extract were unstable and containing ethanol gradually acquired reddish brown color and recorded shift in spectral characteristic , other alcohols when added to the chloroform Extracts exhibits similar behavior , with cupric ions characteristic green blue insoluble salt are formed this reaction is frequently utilized in the isolation and purification of the mono hydroxamic acid as well as ammonia .

The acidity of the OH grouped its superession to intra molecular hydrogen bonding more identification of hydroxamic acid was done by X-ray diffraction , which is very useful for identification and bond length and bond angels (Sandell ,1960).

1.3.2.2: Infrared:

In the infrared spectra , only those band which are associated with hydroxamic acid functional groups have been assigned , in these acid the (OH) stretching vibration have been assigned in the region $3200\text{-}3230\text{cm}^{-1}$ it is known that the O-H stretching when free appears around 3600 cm^{-1} , hydrogen bonding shifts those bands to lower frequencies are mainly due to the ability of acidic hydrogen of the O-H group to form H-bond with electron

rich atom in the hydroxamic acids the lower shift of the (OH) group is due to the intra molecular hydrogen bonding of the type – OH-COO. The (C=O) and (N-O) bands are assigned at about 1620-920 cm^{-1} , respectively.

1.3.3: Chemical properties:

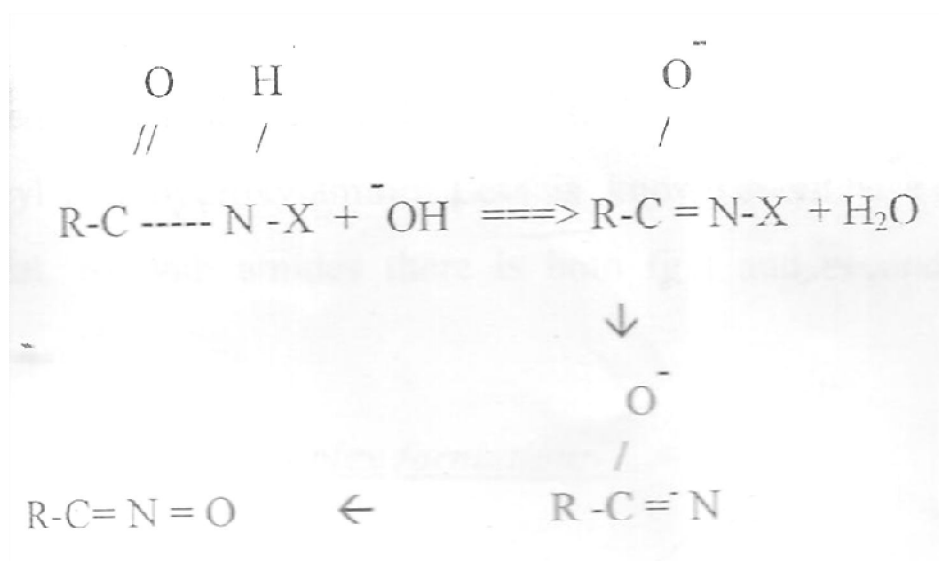
The reaction of hydroxamic acid resemble those of the acid amides in many respects. However the presence of second oxygen atom in O=C-N-O chain of hydroxamic acid alter both the nucleophilic reactivity and the pattern of substitution compared to amide thus hydroxamic acid are stronger nucleophiles than amide, number of pka value are reported in the literature and those are in the order 9 pka units approximately 6 units more acidic than amide and similar to those of carbonate and therefore can be titrated with a base using phenolphthaline as indicator the acidity of hydroxamic acid may be attributed essentially to the – OH group. They are stronger than phenol, but they are weak acids, their lower acidity is attributed to intra molecular hydrogen bond.

1.3.3.1: Oxidation:

Hydroxamic acids when oxidized by several oxidizing agent in aqueous and non aqueous media yield, a variety of products, apparently by a free radical mechanism nitrites, amides and nitroso condensation products are found.

1.3.3.2: Rearrangement:

Hydroxamic acids react with a base to form a salt, the anion of the salt then releases a negative carboxylate ion and rearranges to an iso cyanate.



Triphenylaceto Hydroxamic acids was first to show this rearrangement by Jones and Co-workers.

1.3.3.3: Nucleophilic reaction:

There are three possible sites of substitution reaction N, N-O, and C=O, O- sulphonylated. N alkyl hydroxamic acids are readily converted to 2- substituted N- alkylamides upon treatment with tri ethylamine and a nucleophile. The formation of 2-Chloroamides was first observed during attempts to prepare O-sulphonylated hydroxamic acid. Hydroxamic acid upon

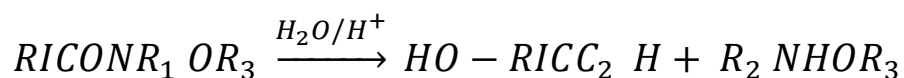
treatment with methane sulphonylchloride and triethylamine, a good yield of 2. Chloromides were obtained after purification.

Also the hydroxamate anion is a particularly effective nucleophile for attack on a phosphorous atom of phosphine phosphoric anhydride, halides, and phosphoro flourodates.

1.3.3.4: Hydrolysis:

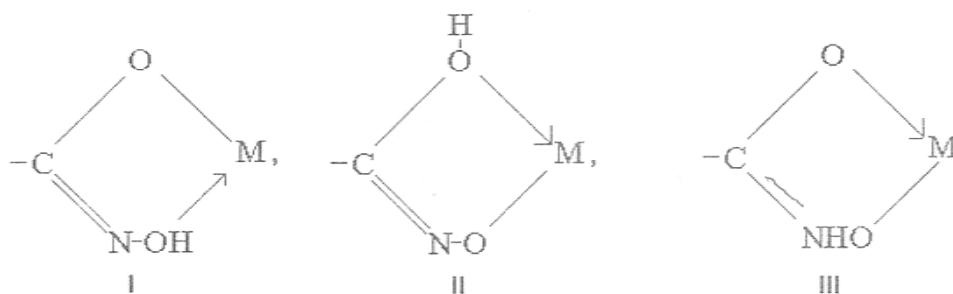
A recent kinetic studies showed that the hydrolytic decomposition of N-aryl hydroxamic acid catalyzed both hydronium and hydroxylions.

Period at react with the synthetic hydroxamic acid to split the molecule into the aryl and hydroxylamine less is known base catalyzed hydrolysis except that as with amides there is both first and second order dependence on the (OH). (Sndeler, 1972).



1.3.3.5 Metal complex formation:

Hydroxamic acid usually act as bidentate ligands and since there exist two tautomeric forms of the acids, the structure of their metal complexes may be represented in three different ways as shown below:



The other possible structures are excluded as they would lead to the formation of unstable four-membered rings involving the metal-nitrogen linkage depending on the pH. Hydroxamic acid reacts with metal ions with different stoichiometric ratios. For the violet complex of Iron (III) with benzo hydroxamic acid at low pH the ratio is 1:1 while it is 1:2 (Red) at higher pH values especially in the presence of excess reagent. Many transition metals such as Cobalt (II), Nickel (II), Copper (II), Zinc (II), Iron (II) form stable complexes with hydroxamic acids.

Hydroxamic acids from both natural occurring or synthetic sources have a strong affinity for iron (III) and a large variety of synthetic hydroxamic acids have been used for extractive spectrophotometric determination.

The simplest member of this class is acetohydroxamic acid which undergoes a series of rapid stepwise reactions with iron (III) to yield a strong 1:3 complex at neutral pH- (Miller, 1989).

1.4: Preparation of Hydroxamic acids:

There is more than one method for the preparation of hydroxamic acid, which were described by Yale the most common methods are:

1. The reaction between hydroxylamine and an ester proceeds rapidly at room temperature, particularly in the presence of an equimolar quantity of sodium alkoxide. (Salah, 1997). In the absence of alkaline reagent longer period of time is required. The reaction may be carried out in the water, sodium carbonate replacing sodium alkoxide.
2. The reaction between an acid anhydride or acidhalid and hydroxylamine, yielded acetohydroxamic acid. Acidhalid and hydroxylamine in the presence of alkali, in addition to the mono hydroxamic acid, further acylated products. In some instance this method was to be preferred other methods.

Other methods of preparation, although they are sates factory but they have limited application they can be summarized as:

3. Oxidation of aldoxime, amine, aldehydes, amides and nitries the reaction between caros reagent (per sulphuric acid $H_2S_2O_8$) and benzaldoxime give benzohydroxamic acid. The oxidation of primary amine by persulphuric acid yielded hydroxamic acid.

4. The rearrangements of nitro-paraffin by mineral acids, Victor Mayer found that heating nitro-paraffin with hydrochloric acid in sealed tube gave hydroxamic acid as an intermediate product.
5. The reaction between an aldehydes and a compound capable of yielding free nitrosyl sodium nitrohydroxamic was prepared by which react with certain aldehydes to yield sodium salt of mono hydroxamic acid.
6. The reaction between an amide and hydroxamine Aliphatic and aromatic amides reacted with hydroxyl ammonium chloride at moderate temperature (20-100)C° yield monohydroxamic acid.

1.5: Application of hydroxamic acid:

1.5.1 Analytical application of hydroxamic acid:

Hydroxamic acids have been used an analytical reagent in organic and inorganic analytical applications, specifically in gravimetry, titremetry, spectrophotometry and solvent extraction, they are considered to be a good complexing behavior with abroad range of metal ions.

1.5.1.1: Gravimetric application:

Hydroxamic acid have been used as precipitant for many metal ions in the presence of other elements, it is important to know the precipitate formation, it is sensitive to pH change.

We can use hydroxamic acid to precipitate metal ion like copper, nickel, cadmium, uranium, niobium and tantalum this due to their insolubility in aqueous phase.

In 1963 Maiumber and Pal used phenyl acetylhydroxamic acid to separate, titanium and zirconium from niobium in anoxalate medium at pH (6.5-7.5) in the presence of ammonium chloride at room temperature.

N-benzoyl phenyl hydroxamic acid (NBPHA) is the most widely used reagent in gravimetric analysis for many reasons:

- 1- Its stable in acids except concentrated nitric acid.
- 2- Slightly soluble in water and readily soluble in organic solvent such as chloroform.
- 3- It is precipitated with metal ion have a granular form facilitating
- 4- Stable in air and moderate temperature and also not active for light.
- 5- The precipitated is not contaminated can be weighed directly (NBPHA) can be used for aluminum, titanium and copper.

Agrawal and Co-worker studied the quantitative and determination and separation of rare earth element and some other metal ions by N-m-toly-m-nitro-benzohydroxamic acid.

Thio-benzophenylhydroxamic acid has been used in the gravimetric determination of copper. This reagent is insoluble in water but soluble in strong acid or weakly basic solution.

N-benzophenylhydroxamic acid has been used for the determination of mercury in the presence of other ions. The yellow products form on extraction of mercury (II) with the chloroformic benzoylhydroxamine solution give maximum absorption at 340 nm.

The optimum pH range is (6.1 – 7.4) mercury is also determined by weighing of the complex (Musser, 1990).

1.5.1.2: Spectrophotometric application:

Hydroxamic acid are among the most selective and sensitive reagent for the spectrophotometric determination of several metal ions.

The intense coloration given by many metal ions with hydroxamic acid makes the latter often useful as colorimetric reagent.

The most characteristic reaction of the hydroxamic acid is red-violet coloration developed with ferric (III) in acid medium below pH2 and the organic complex which develops gradually above (pH3).

Ultra violet spectra for aryl hydroxamic acid their N- and O-substituted derivatives show large wave length absorption (220-260) associated with the aryl rings.

Other spectral analysis are used to elucidate the structure of hydroxamic acids in example X-ray diffraction, infrared spectroscopy, nuclear magnetic reasons (N.M.R), electron spin and mass spectra.

1.5.2 Biological activity of hydroxamic acid:

Hydroxamic acid known as constituent of growth factor food additives, antibiotic antagonists, tumour inhibitors, antifungal agent and cell-division factors. Several of them have used as drugs.

Hydroxamic acid also potent and specific inhibitor of urease activity.

Themrolysin elastase and aminopeptidases, these enzyme are metal oporotinases and the mechanism of inhibition appears to involve chelation of metals at their active sides.

Hydroxamic acid are important bio ligands constituting part of the naturally accruing siderophres and behaving as antibiotics. Chelating therapy agent and inhibitors of enzymes including urease, matrix metal oproteinases and prostaglandin H syntheses.

Hydroxamic acid are biologically and medically important.

The fact that the synthesis of the hydroxamic acid analogue of spirin (II), as a choice prompted e.g. in microbial iron transport, in the inhibition of nickel, dependent urease and the Zinc, dependent matrix metallo proteinase enzyme.

This activity is largely due to the ability of hydroxamic acid to form very stable metal chelates. (Mamion, 2004).

Chapter Two

Experimental and Results

2.1: Apparatus and instrument:

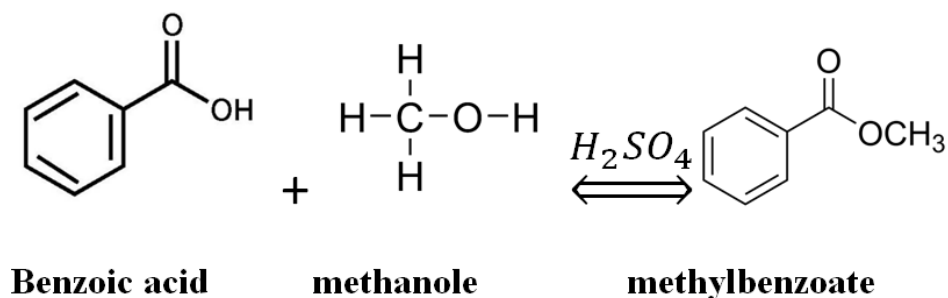
- Round bottomed flask
- Conical flask
- Reflux condenser
- Separatory funnel
- Simple distillation
- Water bath
- Infra red spectrometry
- Determination melting point

2.2: Materials:

- Benzoic acid
- Methanol
- Ether
- Saturated sodium chloride
- Sodium bicarbonate 0.05M
- Magnesium sulfate
- Hydroxyl amine hydrochloride 10%
- Ferric chloride

2.3: Preparation of Methyl Benzoate:

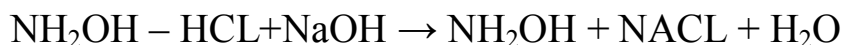
By fisher esterification



10 g of benzoic acid and 25 ml Methanol were placed in 125 ml round bottomed flask, cooled the mixture rise then 3 ml of concentrated sulfuric acid was added slowly and carefully down the walls of the flask, then the mixture was mixing and attach reflex condenser, then the mixture was refluxing condenser, then the mixture was refluxing for one hour in water bath, then the mixture was cooling and decant into separatory funnel containing 50 ml of water and 35 ml of ether was added to separatory funnel, shake thoroughly and drain off the water layer, then ether layer in seperatory funnel was washed with 256 ml of water, followed by 25 ml of 0.5 M sodium bicarbonate to remove unreacted Benzoic acid, then shake and drain off the bicarbonate layer, then the ether layer in separatory funnel was washed by saturated sodium chloride solution and then drain off the ether layer in the flask, and remove the either by simple distillation, then 2-3 g of magnesium sulfate was added, then decant the methyl benzoic.

2.4: Preparation of hydroxyl amine:

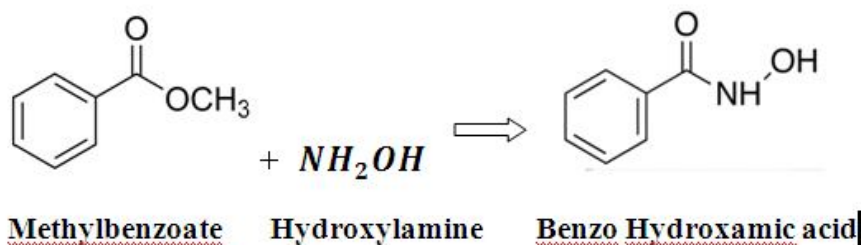
(0.06 mole) 4.2 g of hydroxyl amine hydrochloride was weighted in beaker then 50 ml of sodium hydroxide solution 10% was added with constant stirring by glass rod, then obtained yield of free hydroxyl amine solution.



2.5: Preparation of benzo hydroxamic acid:

By coupling reaction between free hydroxyl amine and methyl benzoate:

0.06 mole of free hydroxyl amine was added to 100 ml beaker containing 0.055 mole of methyl benzoate solution, then stirred by glass rod then the white precipitate was filtrated and washed by cold water, dried throw air.



2.6: Recrystallization:

The product of benzohydroxamic acid was dissolved in methanol then heated in water bath and filter the impurities, then evaporated the methanole and obtain. The white crystalline of benzohydroxamic acid.

2.7: Characterization of hydroxamic acid:

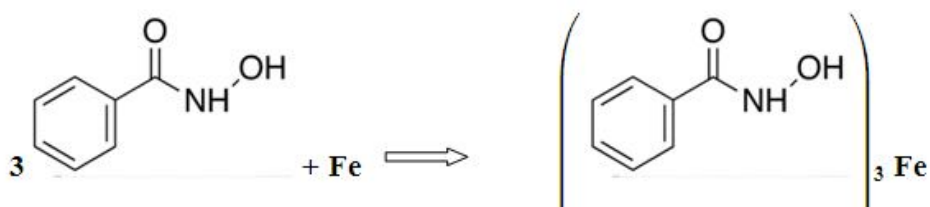
2.7.1: Melting point :

Small amount of solid benzohydroxamic acid was placed in small capillary tube then putted in the device then reading the melting point results:

Hydroxamic acid	Melting point	Literature melting point
Benzohydroxamic acid	128C ^o	126-130 C ^o

2.7.2: Color reaction:

Ferric chloride solution was added to test tube containing benzo hydroxamic acid in aqueous media then gives blood red color.



2.7.3: Infrared spectroscopy for benzo hydrxamic acid:

Make: SHIMADZUE. Model NO. (FT-IR-8400)

Hydroxamic acid	Functional groups in cm ⁻¹			
	o-H	C=O	C-N	N-o
Benzohydroxamic acid	3298.05	1614.31	1323.08	900.70

Chapter Three

Discussion

Discussion:

In this study were prepared Methylbenzote by esterification of benzoic acid in acid media and prepared free hydroxyl amine hydrochloride with sodium hydroxide 10%, and prepared benzohydroxamic acid by coupling reaction between free hydroxyl amine with methyl benzoate and identified by physical properties (melting point 128°C) and characterization by react with Fe (III) give blood red color and by infrared spectroscopy OH (3298.05 cm^{-1}), C=O (1614.31 cm^{-1}), N-O (900.70 cm^{-1}), C-N (1323.08 cm^{-1}).

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