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# Coordination Modes of Hydroxamic Acids in Tin - An Overview

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## Abstract

This review focuses on the synthesis, structural study and application of hydroxamic acid (HAs) and its complexes with organotin (IV) to produce organotin (IV) hdroxamate. Organotin (IV) compounds have received great attention in research field as a photostabilizer in PVC and its application in different aspect, such as marine (in anti-fouling paints and coatings for the protection of ship hulls) and as precursors for $SnO_2$-coatings on glass and in biological field.

Different studies done by researchers highlighted on the organotin (IV) complexes and its applications, and in our study we summarise some of these studies. All information collected by these studies have received great interest and have a vital role in many applications.

**Keywords:** Hydroxamic Acids

## Hydroxamic Acid

Hydroxamic acids are known as one of the key classes of naturally occurring compounds that play a part in many biological systems [1-3] hydroxamic acids also act as metal complexing agents [4-9]. Much of the activity of these compounds is traceable to the presence of the hydroxamic acid group that allows them to chelate to metal ions and mostly with iron [10] which is the most abundant transition metal ion in humans. The biological activity and the chemistry of these compounds make it essential for different applications such as, medical, bio and analytical chemistry [11-13].

Hydroxamic acid is an oxygen donor ligand possessing an affinity for a variety of metal ions [14]. Numerous papers showed that mono hydroxamic acids adopt a typical binding mode and X-ray diffraction study of the benzohydroxamic acids complex of iron(III) [15] has disclosed that the chelation of hydroxamic acid involves the oxygen atoms belonging to the carbonyl and hydroxylamine groups. Hydroxamic acid have become much popular for their biochemical applications in recent years due to the display of a wide range of biological activities, which may be ascribed to their chelating properties with metal ion [6].

The chemistry of HA and their derivatives have received significant interest because of their pharmacological, toxicological and pathological properties since 1959 which is the year of discovery of hydroxamic acids by Wahtroos and Virtanen [16]. Hydroxamic acids play a vital role in many biologically related interactions and its derivatives have a variety of pharmaceutical properties. Recently, the use of peptide and pseudo peptide HA as inhibitors of the matrix metalloproteinase (MMPs) has gained a significant interest especially for cell proliferation [17].

Hydroxamic acids considered low toxic and exhibit a widespread range of applications different field of biological systems such as, tumor inhibitors, antimicrobial agents, anti-tuberculous agents as well as anti-leukemic agents and are a key pharmacophore in a different chemotherapeutic agents, cell-division factors and pigments. Hydroxamic acids have been reported in human medical, for examples pharmaceutical drugs for the treatment of variety of illnesses.

Hydroxamic acids (HAs) are possess chelating mediators for mono-, di- and trivalent metal ions. [18], and also reported as potentially effective corrosion inhibitors for copper [19]. Hydroxamic acids are also known as reducing agents, but they also react as a ligand of di-oxygen chelating agent [20]. Hard-acid cations, and their reactions with iron and other metals have giant a high attention in several scientific areas.

HAs may form complexes with different metal ions, mainly iron (III) and the polymers having hydroxamic acid groups are utilized in metal-ion preconcentration and separation [21]. Furthermore, there is renewed and growing biochemical interest in hydroxamic acids because they have been found to accumulate in natural products [22].

The use of polyhydroxamic acid ion exchange resins for the removal and separation of metal ions has been established. Commercially, chelating ion exchanger is still not available. The ion exchanger resin has been synthesized by either polymerization of monomers containing hydroxamic acid group or by converting the functional groups of ester, amide, carboxylic acid, nitrile, or maleic acid in a polymer into the hydroxamic acid. Treatment of ester with hydroxylamine is a universal method to prepare HAs [23]. The presence of the HAs groups in the polymer solution can be confirmed by the formation of a dark violete colour according to the presence of vanadium ions in the reaction solution. These groups come into existence as the product of decomposition of the HAs and hydrolysis of the ester functional groups in concentrated basic solution under preparative conditions [24].

## Organotin Hydroxamates

Interest in the coordination chemistry of organotin (IV) derivatives towards hydroxamic acids has become important mainly because of its reactivity, the unique structural features and antitumour/antitumour applications. In recent years organotin hydroxamates were studies with attention on the synthesis, investigation of physicochemical properties as well as their structures.

Coordination chemistry of organotin (IV) derivatives towards hydroxamic acids has attained significant cosideration mainly due to the reactivity, the remarkable structural features and their activity against cancer. A wealth of studies on organotin hydroxamates pertaining to synthesis, analysis of physicochemical properties as well as structures have been the matter of great interest. In general, the hydroxamate anion exhibits bidentate chelating ability due to the carbonyl coordination to tin. However, the reports available in literature on X-ray structure determinations of organotin *N- meta* substituted hydroxamates are very few [25-28]. It is thus imperative that structural investigation on such complexes are carried out.

## Synthetic Methods

### Synthesis of Hydroxamic Acids

Hydroxamic acids are used in the preparation of a wide range of heterocyclic compounds [29] Hydrxamic acids are usually found as white solids with the exception of the nitro-and iodo-substituted derivatives exhibiting pale yellow and light pink colours, respectively. Several techniques are reported for synthesizing hydroxamic acids.

Among the common techniques are the conversion of methyl or ethyl esters of carboxylic acids to hydroxamic acids *via* the formation of potassium hydroxamate salt [30-32] (Figure 1). The production of hydroxamic acids from is depicted in Figure 2 acid chlorides using hydroxylamine in the presence of sodium hydrogen [33]. The hydroxamic acids can also be synthesised by intramolecular photorearrangement of alkane nitronate anions [34], and *para*-substituted benzoic acid by using hydroxylamine hydrochloride in the presence of triphenyl phosphine and N-bromosuccinimide under mild basic conditions [35] (Figure 3). Lastly Figure 2.4 is a one-step conversion of carboxylic acid to hydroxamic acid, under neutral pH condition [36].

Some type of biosynthesis production of hydroxamic acids is

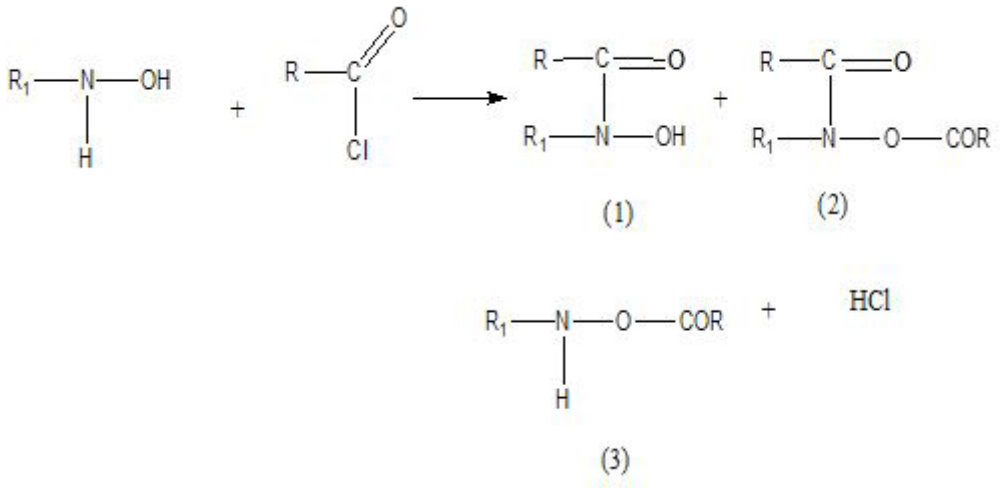


**Figure 1:** Conversion of Acid Chloride to Hydroxamic Acid

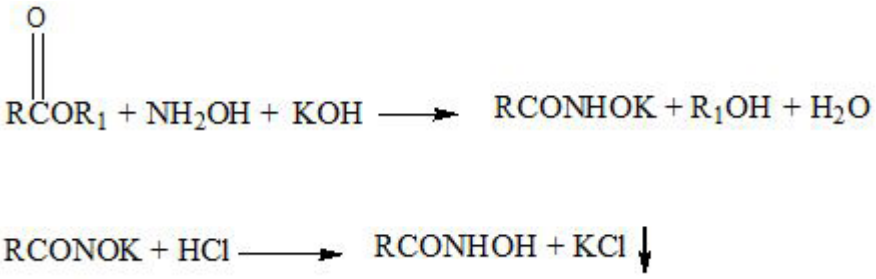


**Figure 2:** Conversion of Esters to Hydroxamic Acid

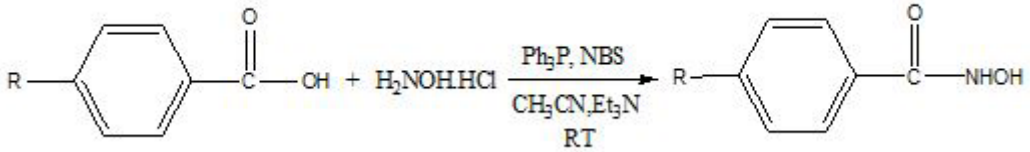


**Figure 3:** Conversion of para-Carboxylic Acid to Hydroxamic Acid using Triphenyl Phosphine and *N* bromosuccinimide in Presence of A mild Base Like Triethyl Amine

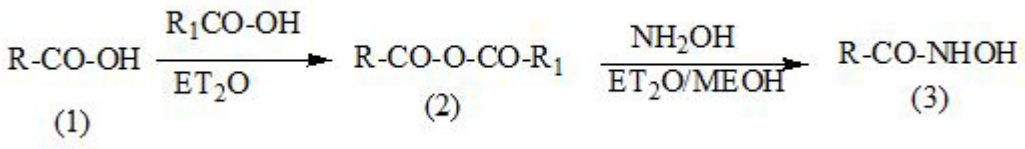


**Figure 4:** Conversion of Carboxylic Acid under Natural Conditions

also reported [37]. A range of enzymes can be used to synthesize different types of hydroxamic acids under mild reaction conditions (pH 7-8, temperature below 50 °C, aqueous media and biological catalysts). Acylation of hydroxaylamine is a common practice for the preparation of primary monohydroxamic acids. The usual acylating agent may be used successfully in the preparation of monohydroxamic acids e.g. anhydrides, acid chlorides and esters etc. However, the use of esters are more common in practice. As a result of the reaction of N-aryl hydroxylamine with an acid chloride, both of its hydrogen atoms are targeted concurrently producing mono (1) and di-(2) substituted derivatives as shown in Figure 4. However such techniques require tedious methods of purifications, including extraction with ammonia [38,39]. Esters react particularly in a strong alkaline medium to form the salt of the required acid in the synthesis of hydroxamic acid and the hydroxamic acid is produced by acidification by passing the formation of diacyl derivatives which may be significant of even dominant when acid chloride or anhydrides are used.

Preparation of the acid chloride is often tiresome when some labile functional groups of other acids are present along with the substrate and further acylation is unavoidable during the reaction with hydroxylamine. From the literature, the neutral condition are not favourable for the reaction of hydroxylamine with esters as shown in Figure 5 and always needs an alkaline condition (pH<10). Hence, this method is not suitable for ester derivatives containing halides, esters and other base-sensitive groups.

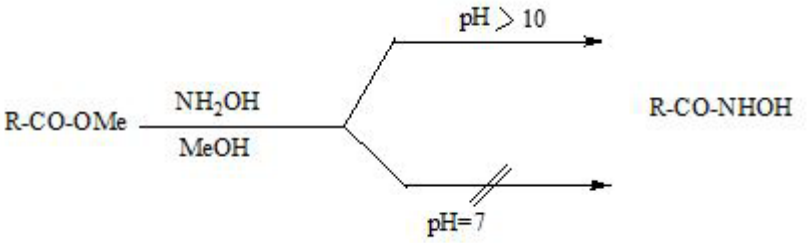


**Figure 5:** Reaction of Ester in an Alkaline Condition

## Synthesis of Organotin (IV) Hydroxamtes

Different methods are enlisted for the syntheses of organotin(IV) hydroxamates e.g. From the condensation reaction of the appropriate diorganotin(IV) oxides or tri-organotin(IV) hydroxides with the free hydroxamic acids in molar ratios of 1:2 and 1:1 for di-and tri- organotin(IV) complexes respectively as; Equations

$R_2SnO + 2R'CONR''OH\ R_2Sn\ (R'CONR''O)_2 + 2H_2O$

$R_3SnOH + R'CONR'OH\ R_3SnR'CONR'O + H_2O$

A replacement reaction of diorganotin(IV) dichloride and trioganotin(IV) chloride using appropriate free ligand with the same molar ratio mentioned above in the presence of triethylamine. However, the liberated HCl can be removed by using triethylamine, as the amine hydrochloride from the reaction mixture, which also serves as the driving force for the reaction [40];

$R_2SnCl_2 + 2R'CONR''OH + 2(C_2H_5)3N\ R_2Sn\ (R'CONR''O)_2 + 2(C_2H_5)_2\text{-}HCl$

$R_3SnCl + R'CONR''OH + (C_2H_5)3N\ R_3SnR'CONR''O + (C_2H_5)_2\text{-}HCl$

Use of diorganotins(IV) oxides and the free ligand with molar ratio 1:2 in the presence of excess 2,2 dimethoxypropane in chloroform at room temperature for 3-4 h has also been reported. The function of 2,2- dimethoxypropane is to absorb the water liberated from the reaction [41].

## Structural Studies

### Structure of Hydroxamic Acids

There are two key structures which have been put forward for hydroxamic acid are: (I) the keto form and (II) the enolic form as shown below in Figure 6:

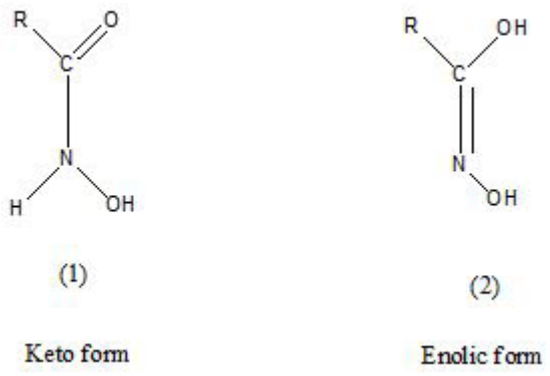


**Figure 6:** Structures of Hydroxamic Acids

Structure (I) contains one easily substitutable proton (monobasic). Structure (II) act as a dibasic acid being in position of the ability to lose two protons. This keto-enol tautomerism is responsible to create a number of sites, which are available for metal ion coordination. The structure (I) predominates in low pH or acidic solutions whereas; structure (II) is dominant in high pH or alkaline medium [42].

Hydroxamic acids being a bidentate ligand are able to meet all the requirements necessary for creation of metal complexes. In the metal chelates formed by hydroxamic acids, coordination is possible by the deprotonation of the OH group and the subsequent (O, O) coordination of carbonyl oxygen and deprotonated OH as confirmed by IR, UV and NMR. It is thus assumed that usually hydroxamic acid metal complexes may have the following structure as shown in Figure 7 in which the metal atom coordinate through the oxygen atoms [43].

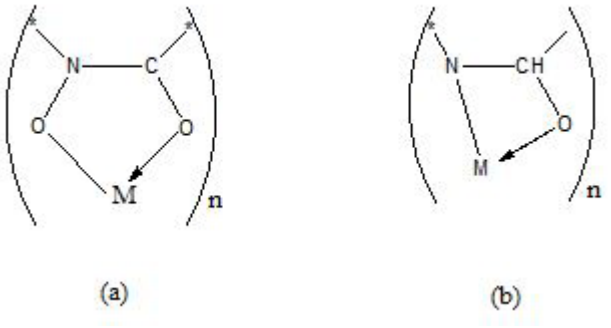


**Figure 7:** Two coordination mode of hydroxamic acid

The mode of bonding described above via the oxygen atoms has been confirmed by X-ray crystallography in a variety of metal complexes [44-46]. No examples of (N, O) coordination have yet been noticed showing the involvement of deprotonation of the NH group as shown in Figure 2.6. However, recently reported experimental and theoretical studies [47-49] for RCONHOH (R=H, $CH_3$), are in support of the idea that these monohydroxamic acids are N acids in the gas phase. Presence of amino group in the hydroxamic acid could involve this group in the coordination and the nitrogen or oxygen atom of the - CONHOH group. Either five or six membered ring may produce aminohydroxamic acids, such as glycinhydroxamic acid (2-aminoacetohydroxamic acid) $NH_2CH_2CONHOH$ which provided the first example of (N, N) coordination in $[Ni(NH_2CH_2CONHOH)_2]$ [50]. Other examples include the glycinhydroxamic acid complexes of CoII and CuII [51] as shown in Figure 8.

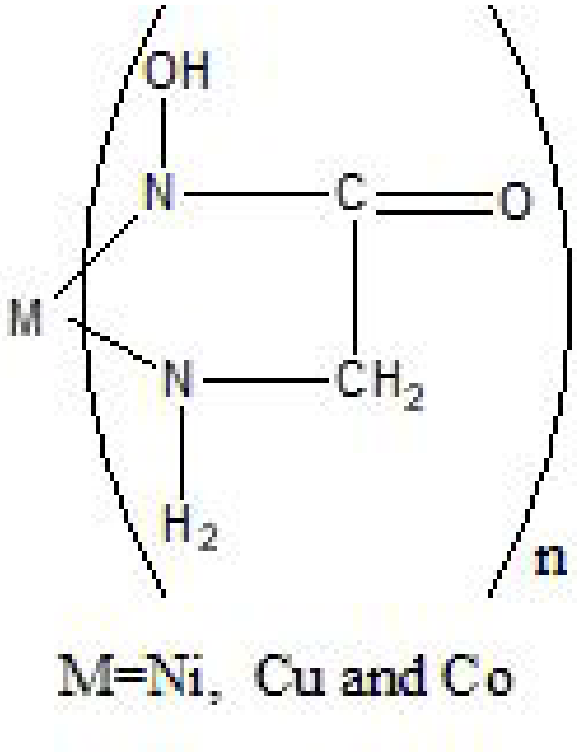


**Figure 8:** Structure of Transition Metal of Glycinhydroxamic Acid

A number of aminohydroxamic acids are reported showing different coordination behaviour, that is (O, O) and (N, N) depending on the type of metal being chelated and on the pH of the solution [52] Mode of coordination of the ligand depends on the type of the ligand owing to electronic and steric effects and the addition of glycine will also contribute to different functionality.

Finally, many studies have been conducted on the structures of HAs in both solution and solid state. Factors such as polymorphism, tautomerism, geometrical isomerism, intra- and intermolecular H-bonding and proton exchange processes must be considered while understanding the mechanism [53].

## Conclusion

The aim of this paper was to review the most important studies of organotin (IV) with hydroxamic acids and its applications, many studies have been done on organotin(IV) compound but still need more time to be work on this compounds to evaluate and found the specific applications in chemical and biological field.

It can be concluded from this review that, hydroxamic acids are very important chelating agents with versatile biological activity, in addition organotin (IV) compounds play vital role as a biocidal activities as well as agricultural and industrial applications.

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