International Journal of Applied Research 2018; 4(2): 35-39

ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2018; 4(2): 35-39
www.allresearchjournal.com
Received: 27-09-2017
Accepted: 29-01-2018

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Studies on the synthesis and structures of hydroxamic acids and their activities in chemistry and biology

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Abstract
A hydroxamic acid is a class of organic compounds bearing the functional group RC(O)N(OH)R', with R and R' as organic residues and CO as a carbonyl group. They are amides (RC(O)NHR') wherein the NH center has an OH substitution. Hydroxamic acids are hydrophilic organic compounds that can exhibit keto-iminol tautomerism, and both tautomers may exist as Z (zusammen) or E (Entgegen) diastereomers. They are much weaker acids than the structurally related carboxylic acids RC(=O)OH, and produce hydroxamate ions. The deprotonation could be either from the nitrogen or the oxygen, making them *N*-acids or *O*-acids. Hydroxamic acids, having the bidentate functional grouping (I), fulfil the basic requirement of complex formation with metal ions and, therefore, form an important family of chelating agents. Structurally, hydroxamic acids can be represented in their two tautomeric form of type (II) and (III). By substituting the hydrogen atom attached to the nitrogen atom in (II) by alkyl or aryl groups, numerous N-substituted hydroxamic acids of type (IV) can be obtained. The complex formation of hydroxamic acids of type (IV) usually takes place with the replacement of the hydroxylamine hydrogen by the metal ion and ring closure through the carbon oxygen. The most important enzymes that are inhibited by hydroxamic acids are matrix metalloproteinases, TNF-α converting enzyme, angiotensin converting enzyme, lipoxygenase, urease, peptide deformylase, histone deacetylase, procollagen C-proteinase, aggrecanase, and carbonic anhydrase. Thus the hydroxamic acid moiety plays an important role as a pharmacophore to develop drugs against a variety of diseases, such as cancer, cardiovascular diseases, HIV, Alzheimer's, malaria, allergic diseases, tuberculosis, metal poisoning, iron overload, etc. Besides, hydroxamic acid moiety has also been exploited to develop potential insecticides, antimicrobials, antioxidants, anti-corrosive agents, siderophores, and as a means of flotations of minerals. It is also discussed that hydroxamic acids are also effective nitric oxide (NO) donors, because of which they produce hypotensive effects. Hydroxamic acids find many applications in chemistry and biology and have been the subject of many experimental investigations. Theoretical studies are not as frequent.

Keywords: hydroxamic acid, aldehyde, carboxylic acid, amide, alcohol, synthesis

1. Introduction
Hydroxamic acids have been known since 1869 with the discovery of oxalohydroxamic acid by Lossen [1]. Hydroxamic acids, that can be represented by a general formula RCONR0OH, where R, R′ may be an aryl or substituted aryl moiety, refer to a class of organic acids, which are much weaker than structurally related carboxylic acids [2] (Marmion *et al*. 2004). However, the real momentum on studies on the synthesis and structures of hydroxamic acids and their biological activities was gained after 1980. According to the IUPAC Gold Book [3] (McNaught and Wilkinson 1997), hydroxamic acids are ''Compounds, RC (=O) NHOH, derived from oxoacids R_kE $(=O)_l(OH)m$ (l=0) by replacing –OH by –NHOH, and hydrocarbyl derivatives thereof. Specific examples are preferably named as N-hydroxy amides''. They contain the oxime (–N–OH) and the carbonyl (C=O) groups (Fig. 1).
Hydroxamic acids are hydrophilic organic compounds that can exhibit keto-iminol tautomerism, and both tautomers may exist as Z (zusammen) or E (entgegen) diastereomers [4]. They are much weaker acids than the structurally related carboxylic acids RC (=O) OH, and produce hydroxamate ions. The deprotonation could be either from the nitrogen or the oxygen, making them *N*-acids or *O*-acids. The hydroxamic acid grouping imparts chelating properties [5] to these acids and their N-substituted derivatives, which serve as bidentate di-oxygen ligands toward many metal ions such as Fe (III) and Cu (II). The complexes are highly colored and are useful for the

spectrophotometric and gravimetric analysis of the metal ions [6] (Agrawal and Roshania 1980). Hydroxamate ions are best known as iron chelators [7] (Miller 1989). Some hydroxamates are siderophores, which are compounds produced by microorganisms for the abstraction of iron from iron-deficient environments [8] (Kehl 1982; Raymond *et al*. 1984; Weinberg 1989). Hydroxamic acids have particular affinities for 'hard' cations such as Fe(III), Np(IV), and Pu(IV) [9] (Baroncelli and Grossi 1965; Barocas *et al*. 1966; Desaraju and Winston 1986; Taylor *et al*. 1998) with which they form five-membered chelate rings [10]. The use of hydroxamate coordination polymers as molecular magnets (Kahn 2000) has also been explored [11] (Milios *et al*. 2002). Due to all these applications, the coordination chemistry of hydroxamates has evoked much interest [12] (Brown *et al*. 2001; Gaynor *et al*. 2001).

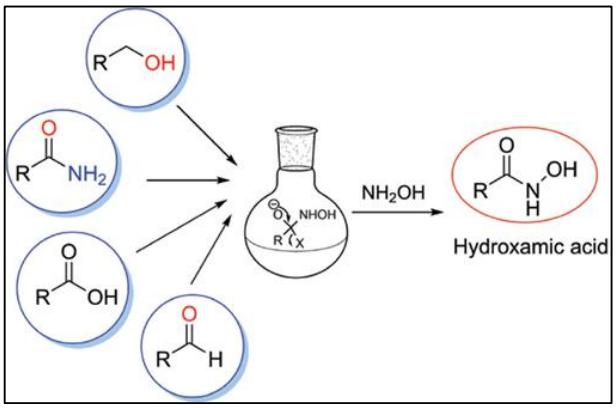

Fig 1: structure of hydroxamic acids

A recent theoretical study has been carried out on a new application of hydroxamic acids, as collectors for selective flotation of diaspore over aluminosilicates [13] (Marmion *et al*. 2004). Jiang *et al*. (2012) [14] carried out a Density Functional Theory (DFT) study of the effect of carboxyl hydroxamic acids on the flotation behavior of diaspore and aluminosilicate minerals. Gece and Bilgiç (2010) [15] studied the corrosion inhibition characteristics of two hydroxamic acids, i.e. oxalyldihydroxamic acid and pimeloyl-1,5-di-hydroxamic acid, on carbon steel using DFT. However, in spite of their various applications, very little was known about their structures for more than even 100 years after they were first reported by Lossen (1869) [1]. A variety of hydroxamic acid derivatives have recently been touted for their potential use as inhibitors of hypertension, tumor growth, inflammation, infectious agents, asthma, arthritis, and more [16] ((Chittari *et al*. 1998). It is no surprise, therefore, that a number of experimental and theoretical studies directed toward the elucidation of the structures and properties of hydroxamic acids have appeared in the literature. This article reviews the present-day knowledge of simple hydroxamic acids and their properties obtained from theoretical studies.

2. Structure of hydroxamic ACID

Hydroxamic acids are solids and oily liquids, soluble in water upto a size of about six carbons and nearly insoluble in ether. These are weak acids comparable to phenol in strength. These are also weakly basic and form salts with strong acids in non-aqueous media [17]. Complexation of metal ions by hydroxamic acids is the basis of a number of analytical determinations. The best known of these complexes is that with Fe^{3+} whose beautiful purple colour forms the basis for the sensitive qualitative and quantitative determination of carboxylic acids and their derivatives [17]. Hydroxamic acids are usually prepared from either esters or acid chlorides by a reaction with hydroxylamine salts. Hydroxamic acids can also be synthesized from aldehydes via the Angeli-Rimini reaction [18]. A well-known hydroxamic acid reaction is the Lossen rearrangement. Hydroxamic acids are generally the products of hydroxylamine (NH_2OH) and carboxylic acids (RCOOH). When an acyl group replaces one of the nitrogen bound hydrogens in the hydroxylamine molecule, a monohydroxamic acid, RCONHOH, is formed. This occurs when an O/N-protected hydroxylamine molecule is allowed to react with an activated acyl group as shown below:

$RCOX+NH_2OH=RCONHOH+HX$

In their capacity to undergo alkylation as well as in their ability to form colored metallic chelates, the monohydroxamic acids strongly resemble compounds known to exist in tautomeric equilibria. A considerable amount of evidence is at hand to substantiate the existence of the tautomeric form of the monohy- droxamic acid, RC (OH)=NOH. In the very early work an uncertainty existed as to which hydrogens in the hydroxylamine molecule were substituted by the first and second acylating groups. It is now generally accepted that the first acyl group is bound to the nitrogen atom, while the second acyl group is held by the oxygen. Devocelle *et al*. (2003) [19], however, reported a convenient two-step procedure for the parallel synthesis of low molecular weight hydroxamic acids from carboxylic acids and hydroxylamine with the use of polymer supported 1-hydroxybenzotriazole.

3. Monohydroxamic ACIDS

The monohydroxamic acids have been prepared by many methods. The most general is the reaction between an ester and hydroxylamine. Other methods, although satisfactory in certain instances, have limited application. In aqueous solution the monohydroxamic acids behave as weak acids: aceto- hydroxamic acid, for example, has an ionization constant of $0.28X10^{-1}$. The monohydroxamic acids can be titrated with alkali, using phenolphthalein as the indicator. They reduce Fehling's solution. Their most characteristic reaction is the intense dark violet color produced with ferric chloride. With cupric acetate, characteristic green-blue insoluble copper salts are formed. This reaction is frequently utilized in the isolation and purification of the mono-hydroxamic acids. Monohydroxamic acids have been proposed recently as flotation agents for certain copper ores [20] (104). The methods which have been utilized for the preparation of monohydroxamic acids are:

A. The reaction between an ester and hydroxylamine

The reaction between an ester and hydroxylamine in absolute alcohol proceeds rapidly at room tempera- ture, particularly in the presence of an equimolecular quantity of sodium alkoxide. In the absence of the alkaline reagent longer periods of time are required. The reaction may be carried out in water, sodium carbonate replacing the sodium alkoxide [21].

B. The oxidation of aldoximes, amines, amides, and nitriles

The reaction between Caro's reagent (persulfuric acid, $H_2S_2O_8$) and benzaldoxime gave, amongst other products,

benzohydroxamic acid [22]. The reaction appeared to be of general application with oxides [23]. The presence of hydroxamic acids was determined by the color test with ferric chloride. Benzamine and toluidine were oxidized to the corresponding monohydroxamic acids; the reaction failed with acetamide, propionamide, and oxamide. Nitriles, when oxidized with hydrogen peroxide, yielded hydroxamic acids [24].

C. The rearrangement of nitroparafins by mineral acids

Senthilnithy *et al* [25] found that heating nitroparaffins with hydrochloric acid in sealed tubes gave hydroxylamine as one of the products. He correctly surmised that theinter-mediate product was a hydroxamic acid. The mechanism of the rearrangement of acinitroparaffins into the tautomeric forms of the monohydroxamic acids is not well understood. One mechanism assumes the addition of hydrochloric acid or sulfuric acid to the aci-nitroalkane, followed by loss of water and rearrangement [26]. Muri *et al*. [27] studied the kinetics of the reaction and found it to be monomolecular.

D. Miscellaneous preparations of monohydroxamic acids

Ponzio (230) [28] found that $(O_2N)_3\,CNC_6H_5$ reacted in moist ether to yield phenylazoformo- hydroxamic acid, C_6H_5=NCONHOH. A mixture of methyl alcohol and potassium nitrite when irradiated with ultraviolet light gave formohydroxamic acid [29]. Acetohydroxamic acid was obtained by the reaction between acetyl chloride and aromatic isonitroso ketones [30], and by the hydrolysis of ace-tonitrolic acid, $CH_3C\,(NO_2)$=NOH [31].

4. Biological activities of hydroxamic ACIDS

Hydroxamic acids exhibit a wide variety of biological activities [32] (Kehl 1982). This has resulted in investigations on their role in biology, besides urease inhibition. Most of these studies have been directed at AHA. For instance, its interaction with the vanadate ion has been studied both experimentally and theoretically [33] (Duarte *et al*. 1998; Santos *et al*. 2003). Vanadate is a phosphate analog and can act as both an inhibitor of phosphate-metabolizing enzymes as well as an activator. Hydroxamic acids have also been investigated as siderophores [34] (Santos *et al*. 1998; Edwards *et al*. 2005; Domagal-Goldman *et al*. 2009). In this connection, experimental and DFT studies have been performed [35] (Edwards *et al*. 2005; Domagal-Goldman *et al*. 2009) on complexes of Fe(III) with desferrioxamine B (DFO-B), the most extensively studied siderophore with respect to mineral dissolution. DFO-B is a linear trihydroxamic acid composed of 1,5-diaminopentane and succinic acid residues. Besides inhibition of urease, hydroxamic acids also inhibit a large number of other enzymes. Quantitative Structure Activity Relationship (QSAR) studies, MD, quantum mechanical, and docking studies directed toward the development of hydroxamic acid inhibitors for histone deacetylases (HDACs) [36] (Dallavalle *et al*. 2009; Guo *et al*. 2005; Ragno *et al*. 2008), lipoxygenase [37] (Hadjipavlou-Litina and Pontiki 2002), peptide deformylase (PDF) [38] (Wang *et al*. 2006, 2008), MMPs [39] (Hu and Shelver 2003; Kumar and Gupta 2003; Tuccinardi *et al*. 2006), and collagenase [40] (Kumar and Gupta 2003) have been reported.

Hydroxamic acids have been shown to inhibit urease enzymes both *in vitro* and *in vivo*. This activity has therapeutic implications for the prevention and treatment of urinary stones associated with urinary tract infections caused by urea-splitting bacteria. Recent progress in hydroxamic acid chemistry has been stimulated by the isolation of several naturally occurring and the synthesis of a number of medicinally active hydroxylamine derivatives. Notable among these are the antibiotic cycloserine [41] (45) [611], the antitumor antibiotic hadacidin [42] (46)[621], and the heteroaromatic antibiotic aspergilla acid [43] (47). A wide spectrum of biological activities has been reported as a full recent review.

A series of o-, m-, and p-alkoxybenzo- hydroxamic acids was found to be highly effective against pathogenic fungi [44] [h4], while salicohydroxamic acids and derivatives are effective antibacterial and antifungal agents. A series of terephthalate- hydroxamic and other dicarbohydroxamic acids have been investigated as potential antimalariaIs [45] [69]. One of the metabolites of the carcinogenic N-(2-fluorenyl) acetamide is N-(2-fluorenyl) acetohydroxamic This points to the potentially important biological oxidation of amides by N-hydroxylation and it is conceivable that other com- pounds containing monosubstituted amide groups can form similar metabolites.

5. Conclusions

Hydroxamic acids find a number of applications in chemistry and biology due to their roles as chelating agents, inhibitors of various enzymes, nitric oxide donors, siderophores, and many others. A large number of experimental and theoretical studies have been directed at understanding their unique chemistry. Theoretical studies have mostly focused on elucidation of the ground state structures and acidities. It is now well established that this acid prefers the Z keto structure, in which there is strong intramolecular hydrogen bonding, and proton dissociation takes place from the nitrogen. It is also established that protonation of FHA occurs at the carbonyl oxygen. In solution, hydroxamic acids form intermolecular hydrogen bonds with the solvent, but the solvent is not able to dislodge the strong intramolecular hydrogen bonds. Hence, deprotonation from –OH is difficult, and this is reflected in the slower rate of complexion with metal ions. It is heartening to note that the theoretical calculations complement experimental determinations. In fact, much of the literature concerns combined experimental and theoretical studies, and both are in accord with each other. This goes a long way in affirming belief in state-of-the-art theoretical calculations, which have now become possible, for small to medium-sized molecules, at least.

Although the structures of hydroxamic and hydroximic acids and derivatives are fairly well established, the fine structure of the anion of hydroxamic acid, as well as its hydrolysis and behavior on nucleophilic substitution, remain to be clarified. Perhaps, the greatest endeavor in the next decade will be in the area of the biological evaluation of hydroxamic acid derivatives. In the meantime the study of hydroxamic acids will remain a viable part of chemistry. While tremendous progress has been made over the past 30 years in understanding and applying the chemistry of hydroxamic acids and N-hydroxyimides, a number of problems remain to be solved.

6. Acknowledgements

The author is grateful to Prof. Ramesh Chandra, Head of Chemistry, and University of Delhi for providing overall

support during my work. The author is also grateful to the management committee of Pentagon College for their valuable guidance time to time.

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