

The Thiohydroxamate System

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ABSTRACT: *The natural occurrence of thiohydroxamates, their methods of preparation, reactivity, properties of their derivatives including Barton's esters and complexes during the last 25 years, as well as a survey of their biological properties are reported in this review.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:169–194, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10017

INTRODUCTION

Thiohydroxamic acids (*N*-hydroxythioamides) are a class of compounds containing a group of four significantly different atoms: C_{sp²}, S, N, and O. Unexpectedly, this unique class of bonds is relatively widespread in nature, and has been known to man as the bitter component in spices for as long as sweetening additives.

The specific system of bonds sulfur–carbon–nitrogen–oxygen results in a higher acidity of the thiohydroxyamide hydrogen atom that creates good conditions for formation of the intermolecular hydrogen bond, while the large van der Waals radius of the sulfur atom limits the conformational freedom. The free activation energy during rotation about the C–N bond is higher by 4.3 kcal/mol than in hydroxamic acids [1]. Simple thiohydroxamic acids have p*K*_a values from 4.2 to 5.6 compared to a p*K*_a of the order of 9 for the corresponding hydrox-

amic acids [1]. Thus, thiohydroxamic acids form metal complexes at lower pH values than the corresponding hydroxamic acids. The specific bond system causes thiohydroxamic acids to be excellent double dentate ligands capable of complexing cations of different metals. These bioligands are being used in nature for transport of many cations. They are also used in analytical chemistry for the quantitative determination of many metals. In the past 25 years, by using the specific reactivity of the thiohydroxamic system, *O*-acyl derivatives of thiohydroxamic acids have found wide application in organic chemistry as a source of efficiently generated carbon, sulfur, nitrogen, or phosphorus radicals.

In the case of thiohydroxamic acids, similarly as in the case of thioamides, we are faced with a tautomeric equilibrium, where the structure of the *N*-hydroxythioamide **1** remains in equilibrium with the structure of the *N*-hydroxythioimide **2**. In other words, thiohydroxamic acid is in equilibrium with thiohydroxamic acid (Scheme 1).

However, results of recent studies indicate that the thiohydroxamic form in the liquid state or in solution is not present in significant concentrations. Only the thiohydroxamic acid form is present in the solid state [2]. On the contrary, *S*-alkyl derivatives of thiohydroxamic acids exist in nature as they form relatively strong bonds and are relatively easy to synthesize.

NATURALLY OCCURRING THIOHYDROXIMATES AND THIOHYDROXAMATES

Sulfated *S*-glucosyl thiohydroximates occurring in plants are a specific group of compounds

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