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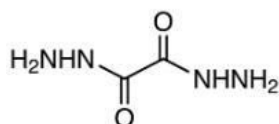


Synthesis and Biocidal Studies of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide and Their Metal Chelates

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ABSTRACT: Synonyms: Oxalic dihydrazide, Ethanedioic acid dihydrazide, Oxalohydrazide, Oxalyl dihydrazide



CAS Number: 996-98-5
MDL Number: MFCD00007608
Molecular Formula: C₂H₆N₄O₂
Molecular Weight: 118.10
Purity/Analysis Method: 96.0% (T)
Form: Crystal
Melting point (• °C): 244

Formula: C₂H₆N₄O₂
MW: 118.1 g/mol
Melting Pt: 244 °C
Density: 1.458 g/cm³ (23 °C)

MDL Number: MFCD00007608
CAS Number: 996-98-5
EINECS: 213-640-2

Malonic acid dihydrazide, 99%

MDL
MFCD00041268
EINECS
000-000-0

Chemical Properties

Formula
C₃H₈N₄O₂
Formula Weight
132.12
Melting point
152-156°
Storage & Sensitivity
Ambient temperatures.

Metal chelates of have turned out to be another group of “general ligands” capable of binding various proteins, cell fragments and cells Chelated metals such as Cu²⁺, Zn²⁺ or Ni²⁺ form coordination compounds with electron-donating N, S, and O atoms in peptides and proteins. The chelating PEG is synthesized by reacting chloromonomethoxy-



PEG with iminodiacetic acid (IDA) under alkaline conditions. Alternatively, IDA-PEG can be prepared from amino monomethoxy-PEG with bromoacetic acid. The chelating PEG when saturated with Cu^{2+} forms a 1:1 complex with the metal ion.

KEYWORDS: Synthesis, Biocidal Studies, Oxalic Acid Dihydrazide, Malonic Acid Dihydrazide, Metal Chelates

I. INTRODUCTION

Metal chelate complexes of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide should be excreted rapidly in the faeces or urine with no redistribution of iron from relatively non-toxic sites such as the liver, to more harmful ones such as the heart. Complexes formed intracellularly should not accumulate within cells, but should leave cells freely. In the case of liver cells this should result in significant excretion of iron in the bile. Clearly this biliary iron-chelator complex should not then be reabsorbed from the gut.^{1,2}

In principle the redistribution of iron can occur if both the chelate and the iron complex freely cross membranes. However, if the free chelate permeates more readily than the complex, a large proportion of liver iron will be excreted via the bile and will thus be unavailable for redistribution to other tissues. Scientists have suggested that an ideal chelator, in addition to forming a lipophilic complex in the tissues where the iron is chelated (in order to facilitate free diffusion out of the cells), should change to a hydrophilic complex once within the plasma so as to maximize urinary iron excretion and minimize redistribution to other tissues. The above concept, although difficult to achieve in practice, highlights an important point relating to modification of the physical properties of chelating agents^{3,4} (both as the free form and as the iron complex) in order to increase the efficacy and safety of therapeutic agents.

Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide has the ability to chelate metals in a similar manner to curcumin as the same diketal structure is present. This has been taken advantage of in binding divalent ions of Cd. Cadmium toxicity can result in hypertension, vascular remodeling, increased arterial stiffness, and oxidative stress. Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide can complex with cadmium and reduce the adverse effects of this divalent ion. The use of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide as an antioxidant activity against Cd intoxication results directly and/or indirectly through free radical scavenging, metal chelation, and other modes of action including regulation of inflammatory enzymes. The use of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide chelation ability to metals has been used beyond its use as a medical means to remove cadmium. Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide has been successfully complexed to metals in a manner similar to curcumin that can be put to additional medical and nutraceutical uses. For example, iridium has been complexed to Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide and been shown to have a lot of potential in cancer treatment.^{5,6} These Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide complexes are readily taken up in human tumor cells and can induce rapid apoptosis in these cells after being irradiated with visible light.

II. DISCUSSION

Chelation by Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide is a type of bonding of ions and molecules to metal ions. It involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central metal atom.^{[1][2]} These ligands are called chelants, chelators, chelating agents, or sequestering agents. They are usually organic compounds, but this is not a necessity, as in the case of zinc and its use as a maintenance therapy to prevent the absorption of copper in people with Wilson's disease.^[3]

Chelation by Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide is useful in applications such as providing nutritional supplements, in chelation therapy to remove toxic metals from the body, as contrast agents in MRI scanning, in manufacturing using homogeneous catalysts, in chemical water treatment to assist in the removal of metals, and in fertilizers.^{7,8}

Numerous biomolecules exhibit the ability to dissolve certain metal cations. Thus, proteins, polysaccharides, and polynucleic acids are excellent polydentate ligands for many metal ions. Organic compounds such as the amino acids glutamic acid and histidine, organic diacids such as malate, and polypeptides such as phytochelatin are also typical chelators. In addition to these adventitious chelators, several biomolecules are specifically produced to bind certain metals (see next section).



In biochemistry and microbiology

Virtually all metalloenzymes feature metals that are chelated, usually to peptides or cofactors and prosthetic groups.^[9] Such chelating agents as Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide include the porphyrin rings in hemoglobin and chlorophyll. Many microbial species produce water-soluble pigments that serve as chelating agents, termed siderophores. For example, species of *Pseudomonas* are known to secrete pyochelin and pyoverdine that bind iron. Enterobactin, produced by *E. coli*, is the strongest chelating agent known. The marine mussels use metal chelation esp. Fe^{3+} chelation with the Dopa residues in mussel foot protein-1 to improve the strength of the threads that they use to secure themselves to surfaces.^{9,10}

In geology

In earth science, chemical weathering is attributed to organic chelating agents (e.g., peptides and sugars) that extract metal ions from minerals and rocks.^[13] Most metal complexes in the environment and in nature are bound in some form of chelate ring (e.g., with a humic acid or a protein). Thus, metal chelates of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide are relevant to the mobilization of metals in the soil, the uptake and the accumulation of metals into plants and microorganisms. Selective chelation of heavy metals is relevant to bioremediation (e.g., removal of ^{137}Cs from radioactive waste).^{11,12}

In the 1960s, scientists developed the concept of chelating a metal ion prior to feeding the element to the animal. They believed that this would create a neutral compound, protecting the mineral from being complexed with insoluble salts within the stomach, which would render the metal unavailable for absorption. Amino acids, being effective metal binders, were chosen as the prospective ligands, and research was conducted on the metal–amino acid combinations. The research supported that the metal–amino acid chelates were able to enhance mineral absorption.^{13,14}

During this period, synthetic chelates such as ethylenediaminetetraacetic acid (EDTA) were being developed. These applied the same concept of chelation and did create chelated compounds; but these synthetics were too stable and not nutritionally viable. If the mineral was taken from the EDTA ligand, the ligand could not be used by the body and would be expelled. During the expulsion process the EDTA ligand randomly chelated and stripped another mineral from the body.^[15]

According to the Association of American Feed Control Officials (AAFCO), a metal–amino acid chelate is defined as the product resulting from the reaction of metal ions from a soluble metal salt with amino acids, with a mole ratio in the range of 1–3 (preferably 2) moles of amino acids for one mole of metal. The average weight of the hydrolyzed amino acids must be approximately 150 and the resulting molecular weight of the chelate must not exceed 800 Da.

Since the early development of these compounds, much more research has been conducted, and has been applied to human nutrition products in a similar manner to the animal nutrition experiments that pioneered the technology. Ferrous bis-glycinate is an example of one of these compounds that has been developed for human nutrition.^[16]

Dental and oral application

Dentin adhesives were first designed and produced in the 1950s based on a co-monomer chelate with calcium on the surface of the tooth and generated very weak water-resistant chemical bonding (2–3 MPa).^[17]

Heavy-metal detoxification

Chelation therapy by Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide is an antidote for poisoning by mercury, arsenic, and lead. Chelating agents convert these metal ions into a chemically and biochemically inert form that can be excreted. Chelation using calcium disodium EDTA has been approved by the U.S. Food and Drug Administration (FDA) for serious cases of lead poisoning. It is not approved for treating "heavy metal toxicity".^[18]

Although beneficial in cases of serious lead poisoning, use of disodium EDTA (edetate disodium) instead of calcium disodium EDTA has resulted in fatalities due to hypocalcemia.^[11] Disodium EDTA is not approved by the FDA for any use,^[18] and all FDA-approved chelation therapy products require a prescription.^[16,17]

Pharmaceuticals

Chelate complexes of gadolinium are often used as contrast agents in MRI scans, although iron particle and manganese chelate complexes of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide have also been explored.^{[21][22]} Bifunctional chelate complexes of zirconium, gallium, fluorine, copper, yttrium, bromine, or iodine are often used for conjugation to monoclonal antibodies for use in antibody-based PET imaging.^[23] These chelate complexes often employ the usage of hexadentate ligands such as desferrioxamine B (DFO), according to Meijs et



al.,^[2] and the gadolinium complexes often employ the usage of octadentate ligands such as DTPA, according to Desreux et al.^[12] Auranofin, a chelate complex of gold, is used in the treatment of rheumatoid arthritis, and penicillamine, which forms chelate complexes of copper, is used in the treatment of Wilson's disease and cystinuria, as well as refractory rheumatoid arthritis.^[10]

Other medical applications[edit]

Chelation by Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide in the intestinal tract is a cause of numerous interactions between drugs and metal ions (also known as "minerals" in nutrition). As examples, antibiotic drugs of the tetracycline and quinolone families are chelators of Fe^{2+} , Ca^{2+} , and Mg^{2+} ions

EDTA, which binds to calcium, is used to alleviate the hypercalcemia that often results from band keratopathy. The calcium may then be removed from the cornea, allowing for some increase in clarity of vision for the patient.

Catalysis

Homogeneous catalysts are often chelated complexes of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide. A representative example is the use of BINAP (a bidentate phosphine) in Noyori asymmetric hydrogenation and asymmetric isomerization. The latter has the practical use of manufacture of synthetic (–)-menthol.

Water softening

Citric acid is used to soften water in soaps and laundry detergents. A common synthetic chelator of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide is EDTA. Phosphonates are also well-known chelating agents. Chelators are used in water treatment programs and specifically in steam engineering, e.g., boiler water treatment system: Chelant Water Treatment system. Although the treatment is often referred to as "softening," chelation has little effect on the water's mineral content, other than to make it soluble and lower the water's pH level.

Fertilizers

Metal chelate compounds of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide are common components of fertilizers to provide micronutrients. These micronutrients (manganese, iron, zinc, copper) are required for the health of the plants. Most fertilizers contain phosphate salts that, in the absence of chelating agents, typically convert these metal ions into insoluble solids that are of no nutritional value to the plants. EDTA is the typical chelating agent that keeps these metal ions in a soluble form.^[15,16]

III. RESULTS

The wide applicability of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide Chelating Agents is due in large measure to their unusual stability. The free acids melt with decomposition at relatively high temperatures: EDTA being stable to 464°F (240°C), and DTPA beginning to decompose at 428°F (220°C). Prolonged heating, however, at temperatures in excess of 212°F (100°C) will cause substantial charring of these acids. The dry alkali metal salts, for example, Na_4EDTA and Na_5DTPA , are unaffected by prolonged heating at temperatures up to 392°F (200°C). Aqueous solutions of the acids and the alkali metal salts are stable indefinitely under any temperature attainable at atmospheric pressure. Temperatures of 400–450°F (204–232°C) may result in decomposition. These solutions are not subject to bacterial or mold breakdown, and are unaffected by high acidity and high alkalinity. They are stable to 10% sulfuric acid and to 20% caustic soda, the limiting factor being solubility in these mediums. Chemically, EDTA, DTPA, HEDTA, and systems of these chelating agents are extremely stable. Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide Chelating Agents actually assist in stabilizing solutions of reducing agents. However, in the presence of strong oxidizing agents such as chromic acid, potassium permanganate, and higher concentrations of peroxides, the materials are degraded as evidenced by the loss of chelating activity.¹⁷ Chelation reaction of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide Chelating Agents are broad-spectrum metal chelating agents. They react with most metals to form stable chelates. These agents do not complex metal atoms in the free metallic state but coordinate only with ionized metals. The most important and useful property of VERSENE™ Chelating Agents is this ability to form stable metal complexes. Chelation of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide is an equilibrium reaction. The generalizations which deserve equilibrium reaction systems apply to chelation as well. One consequence is that small amounts of uncomplexed free metal ion and free chelating agent are present in all systems. These concentrations are so small that they are ordinarily of no practical significance. Also, increasing the relative amount of chelating agent used always serves to decrease the concentration of free metal ions remaining in solution. The system may be described by an equilibrium constant. The stability constant. The equilibrium constant is a mathematical expression that relates the concentrations of the reactants and reaction products involved in any equilibrium reaction.



For chelation reactions this constant is called the “stability constant” and is a measure of the affinity of the complexing agent for a particular metal. It is apparent that a high value for K means a high ratio of chelated to unchelated metal in the system. This is the practical significance of K . Practical significance of $\log K$ Because a high value of the stability constant for a particular metal reflects a high stability for that chelate, the values of the logarithm of the stability constants for a chelating agent with a series of metals may be used to predict behavior of the chelating agent. If a number of different metal ions are present in a system, the chelating agent will react with the metals in order of decreasing $\log K$ values. If, for example, Fe^{+3} , Cu^{+2} , and Ca^{+2} are present in a system, any EDTA added will complex the iron first. When the iron is completely tied up, complexing of copper will begin. The calcium will be complexed only if an excess of EDTA above that required for both iron and copper is added. $\log K$ values $\log K$ values for a displacement series when listed in order of decreasing magnitude. In most instances, any metal will displace from its chelate a metal below it in this series. For example, adding a copper ion to a solution of the calcium chelate of EDTA will result in copper replacing calcium in the chelate of Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide. Since metals vary in their affinity for hydroxide (OH) groups, some deviation from the displacement series occurs. In certain instances, depending on the pH, a metal having a lower $\log K$ value will be chelated in preference to another metal even though the stability constant of the latter is higher.¹⁸

IV. CONCLUSIONS

Most industrial chemical systems that benefit by the addition of chelating agents are not simple systems of water and the metal ions. If they were, the selection of the proper agent and the most efficient use concentration would be clear-cut, based on the stability constants. Factors due to other materials in the system profoundly affect the metal-chelation by Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide reaction. Effect of temperature In general, increased temperatures result in lower stability constants. However, this effect is usually quite negligible, on the order of only one log unit for each 100°F (38°C) of temperature change. Effect of other metal ions Despite the slight effects due to the ionic strength, the only metals that influence the chelation reaction by Oxalic Acid Dihydrazide and Malonic Acid Dihydrazide will be those that form stable chelates. Their effects will be relatively easy to predict from the stability constants. In general, for metals possessing stability constants differing by three log units, the metal forming the most stable chelate will be chelated first, if none of the other environmental factors discussed are operative. If sufficient agent is still present, the lower stability chelate will form next according to the displacement series derived from the stability constants¹⁸

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