Organic Acids

Chelating Agents
Chelation Therapy

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1 - Introduction
Chelation therapy is the administration of chelating agents to remove heavy metals from the body. Chelation therapy has a long history of use in clinical toxicology. For the most common forms of heavy metal intoxication — those involving lead, arsenic or mercury — a number of chelating agents are available. Ethylene Diamine Tetra Acetate (EDTA) is used intravenously and is the treatment of choice for lead poisoning. Dimercapto succinic acid (DMSA) has been recommended for the treatment of lead poisoning in children by Poison Centers around the world. Other chelating agents, such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and alpha lipoic acid (ALA), are used in conventional and alternative medicine.

No approved medical research has found any benefits to chelation therapy for any use other than removal of heavy metals from the body, as well as essential first row transition metals and the U.S. Food and Drug Administration (FDA) considers over-the-counter (OTC) chelation products to be "unapproved drugs and devices and that it is a violation of federal law to make unproven claims about these products. There are no FDA - approved OTC chelation products."
2 – History

Chelating agents were introduced into medicine as a result of the use of poison gas in World War I. The first widely used chelating agent, the organic dithiol compound di mercaprol (also named British anti-lewisite or BAL), was used as an antidote to the arsenic-based poison gas, lewisite. The sulphur atoms in BAL's mercaptan groups strongly bond to the arsenic in lewisite, forming a water-soluble compound that entered the bloodstream, allowing it to be removed from the body by the kidneys and liver. BAL had severe side-effects.

After World War II, a large number of navy personnel suffered from lead poisoning as a result of their jobs repainting the hulls of ships. The medical use of ethylene diamine tetra acetic acid (EDTA) as a lead chelating agent was introduced. Unlike BAL, it is a synthetic amino acid and contains no mercaptans. EDTA side effects were not considered as severe as BAL.

In the 1960s, BAL was modified into DMSA, a related dithiol with far fewer side effects. DMSA quickly replaced both BAL and EDTA, becoming the US standard of care for the treatment of lead, arsenic, and mercury poisoning, which it remains today. More recently, esters of DMSA have been developed which are reportedly more effective; for example, the mono iso amyl ester (MiADMSA) is reportedly more effective than DMSA at clearing mercury and cadmium.

Research in the former Soviet Union led to the introduction of DMPS, another dithiol, as a mercury-chelating agent. The Soviets also introduced ALA, which is transformed by the body into the dithiol dihydrolipoic acid, a mercury- and arsenic-chelating agent. DMPS has experimental status in the US FDA, while ALA is a common nutritional supplement.

Since the 1970s, iron chelation therapy has been used as an alternative to regular phlebotomy to treat excess iron stores in people with haemochromatosis.
Other chelating agents have been discovered. They all function by making several chemical bonds with metal ions, thus rendering them much less chemically reactive. The resulting complex is water-soluble, allowing it to enter the bloodstream and be excreted harmlessly.

Calcium-disodium EDTA chelation is approved by the U.S. Food and Drug Administration (FDA) for treating lead poisoning and heavy metal toxicity. In 1998, the U.S. Federal Trade Commission (FTC) pursued the American College for Advancement in Medicine (ACAM), an organization that promotes "complementary, alternative and integrative medicine" over the claims made regarding the treatment of atherosclerosis in advertisements for EDTA chelation therapy. The FTC concluded that there was a lack of scientific studies to support these claims and that the statements by the ACAM were false.[8] In 1999, the ACAM agreed to stop presenting chelation therapy as effective in treating heart disease, avoiding legal proceedings. In 2010 the U.S. Food and Drug Administration (FDA) warned companies who sold over-the-counter (OTC) chelation products and stated that such "products are unapproved drugs and devices and that it is a violation of federal law to make unproven claims about these products. There are no FDA-approved OTC chelation products."

3 - Approved medical use

Chelation therapy is used as a treatment for acute mercury, iron (including in cases of thalassemia), arsenic, lead, uranium, plutonium and other forms of toxic metal poisoning. The chelating agent may be administered intravenously, intramuscularly, or orally, depending on the agent and the type of poisoning.

Several chelating agents are available, having different affinities for different metals. Common chelating agents follow:

**Chelator**

Di mercaprol (British anti-Lewisite; BAL)

**Used in**

- acute arsenic poisoning
- acute mercury poisoning
- lead poisoning (in addition to EDTA)
Lewisite poisoning (for which it was developed as an antidote)

Di mercapto succinic acid (DMSA)
- lead poisoning
- arsenic poisoning
- mercury poisoning

Di mercapto-propane sulfonate (DMPS)
- severe acute arsenic poisoning
- severe acute mercury poisoning

*Mainly in:*
- copper toxicity

*Occasionally adjunctive therapy in:*

Penicillamine
- gold toxicity
- arsenic poisoning
- lead poisoning
- rheumatoid arthritis

Ethylene diamine tetra acetic acid (calcium disodium versante) (CaNa₂-EDTA)
- lead poisoning

Deferoxamine and Deferasirox
- acute iron poisoning
- iron overload

### 2 –1 - Medically diagnosed heavy metal poisoning

Some common chelating agents are EDTA (ethylene diamine tetra acetic acid), DMPS (2,3-di mercapto propane sulfonic acid), TTFD (thiamine tetra hydro furfuryl disulfide), and DMSA (2,3-dimercaptosuccinic acid). Calcium-disodium EDTA and DMSA are only approved for the removal of lead by the Food and Drug Administration while DMPS and TTFD are not approved by the FDA. These drugs bind to heavy metals in the body and prevent them from binding to other agents. They are then excreted from the body. The chelating process also removes vital nutrients such as vitamins C and E, therefore these must be supplemented.

### 4 – Unapproved use in alternative medicine

Alternative medicine uses chelation therapy as a non-standard treatment for some ailments, including heart disease and autism.

In 2010 the U.S. Food and Drug Administration (FDA) warned companies who sold over-the-counter (OTC) chelation products and
stated that such "products are unapproved drugs and devices and that it is a violation of federal law to make unproven claims about these products. There are no FDA-approved OTC chelation products."

Attempts have been made to use it in treating kidney dysfunction, calcific band keratopathy (an eye disorder), and ovarian cancer. Currently there is a US National Center for Complementary and Alternative Medicine (NCCAM) trial being conducted on the chelation therapy's safety and efficacy for patients with coronary artery disease. NCCAM Director Stephen E. Straus cited the "widespread use of chelation therapy in lieu of established therapies, the lack of adequate prior research to verify its safety and effectiveness, and the overall impact of coronary artery disease" as factors motivating the trial. The proposed study has been criticized as unethical, unnecessary and dangerous, with multiple studies conducted in the past demonstrating that it provides no benefits.

4 - 1 - Heart disease

The use of EDTA chelation therapy as a treatment for coronary artery disease has not been shown to be effective and is not approved by the U.S. Food and Drug Administration (FDA). Several possible mechanisms have been proposed, though none have been scientifically validated. The US National Center for Complementary and Alternative Medicine began conducting the Trial to Assess Chelation Therapy (TACT) in 2003. Patient enrollment was to be completed around July 2009 with final completion around July 2010, but enrollment in the trial was suspended on September 26, 2008 for an investigation by OHRP after complaints about ethical concerns such as inadequate informed consent. The trial has been criticized for lacking prior Phase I and II studies, and particularly because previous controlled trials have not indicated benefits. The American College for Advancement in Medicine, a controversial organization created to promote chelation therapy, has played a part in the adoption of the TACT clinical trial, which has led to further criticism of the trial. Atwood et al. have argued that methodological flaws and lack of prior probability make this trial "unethical, dangerous, pointless, and wasteful."
The final results of TACT, published in November 2012, showed no support for the use of chelation therapy in coronary heart disease, particularly the claims to reduce the need for coronary artery bypass grafting.

The American Heart Association states that there is "no scientific evidence to demonstrate any benefit from this form of therapy" and that the "United States Food and Drug Administration (FDA), the National Institutes of Health (NIH) and the American College of Cardiology all agree with the American Heart Association" that "there have been no adequate, controlled, published scientific studies using currently approved scientific methodology to support this therapy for cardiovascular disease."[3] Like other scientific commentators, they note that any improvement among heart patients undergoing chelation therapy can be attributed to the placebo effect and lifestyle changes discovered in conventional medicine but recommended by chelationists; "quitting smoking, losing weight, eating more fruits and vegetables, avoiding foods high in saturated fats and exercising regularly". They note their concern that patients could put off proven treatments for heart disease like drugs or surgery. A 2005 systematic review found that controlled scientific studies did not support chelation therapy for heart disease. It found that very small trials and uncontrolled descriptive studies have reported benefits while larger controlled studies have found results no better than placebo. The Mayo Clinic states that "chelation studies have found that chelation didn't work as a heart disease treatment."

In 2009, the Montana Board of Medical Examiners issued a position paper concluding that "chelation therapy has no proven efficacy in the treatment of cardiovascular disease, and in some patients could be injurious."

4 – 2 - Autism

Based on the discredited hypothesis that mercury poisoning may trigger the symptoms of autism, chelation therapy is widely used by alternative therapists to treat autism, with some surveys suggesting 2–8% of children with autism have had the therapy. Parents either have a doctor use a treatment for lead poisoning, or buy unregulated
supplements. Aspies For Freedom, an autistic rights organization, considers this use of chelation therapy unethical and potentially dangerous.\textsuperscript{[29]} There is strong epidemiological evidence that refutes links between environmental triggers, in particular thiomersal-containing vaccines, and the onset of autistic symptoms. There is no scientific support for chelation therapy as a treatment for autism.

4 – 3 - Controversy
The efficacy, safety, and much of the theory behind these alternative practices are disputed by the medical community. In 2001, researchers at the University of Calgary reported that cardiac patients receiving chelation therapy fared no better than those who received placebo treatment.

In 1998, the U.S. Federal Trade Commission (FTC) charged that the web site of the American College for Advancement in Medicine (ACAM) and a brochure they published had made false or unsubstantiated claims. In December 1998, the FTC announced that it had secured a consent agreement barring ACAM from making unsubstantiated advertising claims that chelation therapy is effective against atherosclerosis or any other disease of the circulatory system.

The use of chelation therapy by alternative medicine practitioners for behavioural and other disorders is considered pseudoscientific as there is no proof that it is effective.

Chelation therapy has inherent risks associated with due to the non-specificity of chelating agents for metals. Many essential metals such as: iron (found in cytochromes and hemes, cobalt (found in vitamin b12, zinc (found in carbonic anhydrase), copper (found in bilirubin oxidase, and molybdenum (found in xanthine oxidase), can also be removed by chelating agents. All of these first row transition metals will form square planar or octahedral chelates. The chelate effect in inorganic chemistry, predicts that these metals will preferably bind to poly dentate ligands such as chelating agents in preference to mono or bi dentate ligands found in proteins and enzymes. Chelating agents not only remove heavier metals but also essential metals and this risk is often overlooked in those seeking to use chelation therapy.
4 – Prevalence

The American College for Advancement in Medicine estimates that 800,000 patient visits for chelation therapy were made in the United States in 1997.

5 - Side effects and safety concerns

As approved pharmaceuticals, the various chelating agents may cause specific side effects if used improperly. When protocols are followed, there is a low occurrence of side effects. DMPS injections may cause skin reactions at the injection site. Other side effects reported include fever, headache, nausea. No death has been linked to DMPS. The EDTAs when used according to protocol are equally safe. Most important is the correct use and a slow infusion time (1gr/hr or less of NaEDTA or CaEDTA). Side effects are largely avoided if general medical caution is exercised. Most importantly, renal function has to be checked before any chelation substance is used.[41] 2007 research with lab rats indicates giving chelating agent DMSA to rats without high levels of lead may cause lasting cognitive damage. The German Environmental Agency (Umweltbundesamt) listed DMSA along with DMPS as the two most useful and safe chelating agents available at this time. 'Chelation treatment is the preferred medical treatment for reducing toxic effects of metals.'

Chelation therapy can be hazardous when used inappropriately. In August 2005, chelation therapy conducted by an ACAM member killed a 5-year-old boy with autism; a 3-year-old non autistic girl died in February 2005, and a non autistic adult died in August 2003. These deaths were due to cardiac arrest caused by hypocalcemia during chelation therapy. In two of the cases hypocalcemia appears to have been caused by the administration of Na$_2$EDTA (Disodium EDTA) and in the third case the type of EDTA was unknown.[45] Only the 3-year-old girl had been medically assessed and found to have an elevated blood lead level and resulting low iron levels and anemia, a proper medical cause for chelation therapy to be conducted.[46] According to protocol, EDTA should not be used in the treatment of children.[47] More than 30 deaths have been recorded in association with IV-administered disodium EDTA since the 1970s.
Chelation

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1 - Introduction
Chelation describes a particular way that ions and molecules bind metal ions.\textsuperscript{[1]} According to the International Union of Pure and Applied Chemistry (IUPAC), chelation involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central atom. Usually these ligands are organic compounds, and are called chelants, chelators, chelating agents, or sequestering agents.

2 - Chelate effect[edit source]

<table>
<thead>
<tr>
<th>Cu(^{2+}) complexes with methyl amine (left) and ethylene diamine (right)</th>
<th>Ethylene diamine ligand, binding to a central atom with two bonds</th>
</tr>
</thead>
</table>

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The chelate effect describes the enhanced affinity of chelating ligands for a metal ion compared to the affinity of a collection of similar non-chelating (mono-dentate) ligands for the same metal.

Consider the two equilibria, in aqueous solution, between the copper(II) ion, \( \text{Cu}^{2+} \) and ethylene diamine (en) on the one hand and methylamine, MeNH\(_2\) on the other.

\[
\begin{align*}
\text{Cu}^{2+} + \text{en} & \rightleftharpoons [\text{Cu(en)}]^{2+} \quad (1) \\
\text{Cu}^{2+} + 2 \text{MeNH}_{2} & \rightleftharpoons [\text{Cu(MeNH}_{2})_{2}]^{2+} \quad (2)
\end{align*}
\]

In (1) the bidentate ligand ethylene diamine forms a chelate complex with the copper ion. Chelation results in the formation of a five-membered ring. In (2) the bi-dentate ligand is replaced by two mono-dentate methylamine ligands of approximately the same donor power, meaning that the enthalpy of formation of Cu—N bonds is approximately the same in the two reactions. Under conditions of equal copper concentrations and when the concentration of methylamine is twice the concentration of ethylene diamine, the concentration of the complex (1) will be greater than the concentration of the complex (2). The effect increases with the number of chelate rings so the concentration of the EDTA complex, which has six chelate rings, is much higher than a corresponding complex with two mono-dentate nitrogen donor ligands and four mono-dentate carboxylate ligands. Thus, the phenomenon of the chelate effect is a firmly established empirical fact.

The thermodynamic approach to explaining the chelate effect considers the equilibrium constant for the reaction: the larger the equilibrium constant, the higher the concentration of the complex.

\[
[\text{Cu (en)}] = \beta_{11} [\text{Cu}][\text{en}] \\
[\text{Cu (Me NH}_{2})_{2}] = \beta_{12} [\text{Cu}][\text{Me NH}_{2}]^{2}
\]

Electrical charges have been omitted for simplicity of notation. The square brackets indicate concentration, and the subscripts to the stability constants, \( \beta \), indicate the stoichiometry of the complex. When the analytical concentration of methylamine is twice that of ethylene
diamine and the concentration of copper is the same in both reactions, the concentration [Cu(en)] is much higher than the concentration [Cu(MeNH₂)_2] because β₁₁ >> β₁₂.

An equilibrium constant, K, is related to the standard Gibbs free energy, ΔG ⊲ by

\[
\Delta G \Leftrightarrow = -RT \ln K = \Delta H \Leftrightarrow - T\Delta S \Leftrightarrow
\]

where \( R \) is the gas constant and \( T \) is the temperature in kelvins. \( \Delta H \Leftrightarrow \) is the standard enthalpy change of the reaction and \( \Delta S \Leftrightarrow \) is the standard entropy change.

It has already been posited that the enthalpy term should be approximately the same for the two reactions. Therefore the difference between the two stability constants is due to the entropy term. In equation (1) there are two particles on the left and one on the right, whereas in equation (2) there are three particles on the left and one on the right. This means that less entropy of disorder is lost when the chelate complex is formed than when the complex with monodentate ligands is formed. This is one of the factors contributing to the entropy difference. Other factors include solvation changes and ring formation. Some experimental data to illustrate the effect are shown in the following table.

<table>
<thead>
<tr>
<th>Equilibrium</th>
<th>log β</th>
<th>ΔG ⊲</th>
<th>ΔH ⊲ / kJ mol⁻¹</th>
<th>kJ -TΔS ⊲ / kJ mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd²⁺ + 4 Me NH₂ ⇋ Cd(MeNH₂)₄²⁺</td>
<td></td>
<td></td>
<td>-37.4</td>
<td>19.9</td>
</tr>
<tr>
<td>Cd²⁺ + 2 en ⇋ Cd(en)₂⁺</td>
<td>6.55</td>
<td>-57.3</td>
<td>-57.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.62</td>
<td>-56.48</td>
<td>-56.48</td>
<td>-4.19</td>
</tr>
</tbody>
</table>

These data show that the standard enthalpy changes are indeed approximately equal for the two reactions and that the main reason for the greater stability of the chelate complex is the entropy term, which is much less unfavorable. In general it is difficult to account precisely
for thermodynamic values in terms of changes in solution at the molecular level, but it is clear that the chelate effect is predominantly an effect of entropy.

Other explanations, including that of Schwarzenbach, are discussed in Greenwood and Earnshaw (loc. cit).

3 - In nature

Virtually all bio chemicals exhibit the ability to dissolve certain metal cations. Thus, proteins, polysaccharides, and poly nucleic 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).

3 – 1 - In biochemistry and microbiology

Virtually all metalloenzymes feature metals that are chelated, usually to peptides or cofactors and prosthetic groups. Such chelating agents 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 pyocyanin and pyoverdin that bind iron. Enterobactin, produced by E. coli, is the strongest chelating agent known.

3 – 2 - 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. 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 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 bio remediation, e.g. removal of $^{137}$Cs from radioactive waste.
4 – Applications
Chelators are used in producing nutritional supplements, fertilizers, chemical analysis, as water softeners, commercial products such as shampoos and food preservatives, medicine, heavy metal detox, and industrial applications.

In 2010, the Asia-Pacific region was the largest outlet, generating about 45% of worldwide demand for chelating agents. The region was followed by Western Europe and North America. The global chelating agents market is expected to reach more than 5 million tones in 2018.

4 – 1 - Nutritional supplements
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.

During this period, synthetic chelates were also being developed. An example of such synthetics is ethylene diamine tetra acetic acid (EDTA). These synthetics applied the same concept of chelation and did create chelated compounds; however, 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 will randomly chelate and strip another mineral from the body.

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 a metal ion from a soluble metal salt with a mole ratio of one to three (preferably two) moles of amino acids. 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.

4 – 2 - Fertilizers

Metal chelate compounds are common components of fertilizers to provide micronutrients. These micronutrients (manganese, iron, zinc, copper) are required for the overall 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 for this purpose.

4 – 3 - Heavy metal detoxification

Chelation therapy is the use of chelating agents to detoxify poisonous metal agents such as mercury, arsenic, and lead by converting them to a chemically inert form that can be excreted without further interaction with the body, and was approved by the U.S. Food and Drug Administration in 1991. In alternative medicine, chelation is used as a treatment for autism, although this practice is controversial due to the absence of scientific plausibility, lack of FDA approval, and its potentially deadly side-effects.

Although they can be beneficial in cases of heavy metal poisoning, chelating agents can also be dangerous. Use of disodium EDTA instead of calcium EDTA has resulted in fatalities due to hypocalcemia.

4 – 4 - Other medical applications

Chelation 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 is also used in root canal treatment as an intracanal irrigant. EDTA softens the dentin which may improve access to the entire canal length and is utilized as an irrigant to assist in the removal of the smear layer.

Chelate complexes of gadolinium are often used as contrast agents in MRI scans.

4 – 5 - Chemical applications
Homogeneous catalysts are often chelated complexes. A typical example is the ruthenium(II) chloride chelated with BINAP (a bidentate phosphine) used in e.g. Noyori asymmetric hydrogenation and asymmetric isomerization. The latter has the practical use of manufacture of synthetic (−) - menthol.

Citric acid is used to soften water in soaps and laundry detergents. A common synthetic chelator 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.

Products such as Bio-Rust and Evapo-Rust are chelating agents sold for the removal of rust from iron and steel.

5 – Etymology
The ligand forms a chelate complex with the substrate. Chelate complexes are contrasted with coordination complexes composed of mono dentate ligands, which form only one bond with the central atom. The word chelation is derived from Greek meaning "claw"; the ligands lie around the central atom like the claws of a lobster.
Clathro Chelate

Structure of a clathro chelate complex, \([Co\text{ (sepulchrate)}]^3+\).

In coordination chemistry, clathro chelates are ligands that encapsulate metal ions. Chelating ligands bind to metals more strongly than related mono dentate ligands, and macro cyclic ligands bind more strongly than typical chelating ligands. It follows, that bi- or poly macro cyclic ligands would bind to metals particularly strongly. Clathro chelates are usually derived from bi macro cyclic ligands.

The first examples were derived from the tris(dioximate)s of cobalt(II) and iron(II). The synthesis entails replacement of the hydrogen-bonded proton center with BF\(^2^+\) or BOR\(^2^+\) group:

\[
Fe(HON = CMeCMe=NOH)(ON = CMeCMe=NO)_2]^{2^-} + 2 BF_3 \rightarrow Fe(ON = CMeCMe=NO)_3(BF)_2 + 2 HF_2^-
\]

Also well known are the clathro chelates called sepulchrates derived from tris(ethylene di amine ) cobalt (III):

\[
[Co(H_2NCH_2CH_2NH_2)_3]^3+ + 6 CH_2O + 2 NH_3 \rightarrow [Co[N(CH_2HNCH_2CH_2NHCH_2)_3N]^3+ + 6 H_2O
\]

The insertion and removal of metals from the binding pocket of clathro chelates can be very slow. For this reason, many clathro chelates are prepared by the reactions of pre-coordinated ligands. These reactions often do not directly break any metal-ligand bonds,
but occur in the second coordination sphere. The slowness of the metal ion exchange enables certain experiments that would otherwise be difficult or impossible. For example, it is possible to optically resolve the equivalent of \([\text{Co}(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2)_3]^{2+}\). In the absence of the special geometry imposed by the clathro chelate, the lifetime of Co(II)-amine complexes is typically very short. In this way, this family of complexes enables studies on self-exchange redox reactions between Co (II) and Co (III) partners that would be impossible with simpler ligand systems.
Acetyl Acetone

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1 - Introduction
Acetyl acetone is an organic compound that famously exists in two tautomeric forms that rapidly interconvert. The more stable tautomer is a diketone formally named pentane-2,4-dione. The less common tautomer is the enol form. The pair of tautomers rapidly interconvert and are treated as a single compound in most applications. It is a colourless liquid that is a precursor to acetyl acetonate (ac-ac), a common bi dentate ligand. It is also a building block for the synthesis of heterocyclic compounds.

<table>
<thead>
<tr>
<th>IUPAC name : Pentane-2,4-dione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names : Hacac</td>
</tr>
<tr>
<td>Molecular formula</td>
</tr>
<tr>
<td>Molar mass</td>
</tr>
<tr>
<td>Density</td>
</tr>
<tr>
<td>Melting point</td>
</tr>
<tr>
<td>Boiling point</td>
</tr>
<tr>
<td>Solubility in water</td>
</tr>
</tbody>
</table>
2 – Properties
The keto and enol forms of acetyl acetone coexist in solution; these forms are tautomers. The $C_{2v}$ symmetry for the enol form displayed on the left in Scheme I has been verified by many methods, most prominently being NMR spectroscopy and IR spectroscopy.\cite{3} In the gas phase, the equilibrium constant, $K_{\text{keto-enol}}$ is 11.7, favoring the enol form. The equilibrium constant tends to remain high in nonpolar solvents; the keto form becomes more favorable in polar, hydrogen-bonding solvents, such as water. The enol form is a vinylogous analogue of a carboxylic acid.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$K_{\text{keto-enol}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas Phase</td>
<td>11.7</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>42</td>
</tr>
<tr>
<td>Toluene</td>
<td>10</td>
</tr>
<tr>
<td>THF</td>
<td>7.2</td>
</tr>
<tr>
<td>DMSO</td>
<td>2</td>
</tr>
<tr>
<td>Water</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Scheme 1. Tautomerism of 2,4-pentanodione

2 – 1 - Acid - base properties
Acetyl acetone is a weak acid:

$$C_{5}H_{8}O_{2} \rightleftharpoons C_{5}H_{7}O_{2}^- + H^+$$
IUPAC recommended pK\textsubscript{a} values for this equilibrium in aqueous solution at 25 °C are 8.99±0.04 (I = 0), 8.83 ± 0.02 (I = 0.1 M NaClO\textsubscript{4}) and 9.00±0.03 (I=1.0 M NaClO\textsubscript{4}) (I=Ionic strength).\textsuperscript{[6]} Values for mixed solvents are available. Very strong bases, such as organolithium compounds, will deprotonate acetyl acetone twice. The resulting dilithio species can then be alkylated at C-1.

<table>
<thead>
<tr>
<th>solvent</th>
<th>T / °C</th>
<th>pK\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 % ethanol / water</td>
<td>30</td>
<td>9.8</td>
</tr>
<tr>
<td>70 % dioxane / water</td>
<td>28</td>
<td>12.5</td>
</tr>
<tr>
<td>80 % DMSO / water</td>
<td>25</td>
<td>10.16</td>
</tr>
<tr>
<td>DMSO</td>
<td>25</td>
<td>13.41</td>
</tr>
</tbody>
</table>

3 – Preparation
Acetyl acetone is prepared industrially by the thermal rearrangement of iso propenyl acetate.

\[
\text{CH}_2(\text{CH}_3)\text{COC(O) Me} \rightarrow \text{Me C(O)CH}_2\text{C(O)Me}
\]

Laboratory routes to acetyl acetone begin also with acetone. Acetone and acetic anhydride upon the addition of BF\textsubscript{3} catalyst:

\[
(\text{CH}_3\text{CO})_2\text{O} + \text{CH}_3\text{C(O)CH}_3 \rightarrow \text{CH}_3\text{C(O)CH}_2\text{C(O)CH}_3
\]

A second synthesis involves the base-catalyzed condensation of acetone and ethyl acetate, followed by acidification:

\[
\text{NaOEt} + \text{EtO}_2\text{CCH}_3 + \text{CH}_3\text{C(O)CH}_3 \rightarrow \text{NaCH}_3\text{C(O)CHC(O)CH}_3 + 2 \text{EtOH}
\]

\[
\text{NaCH}_3\text{C(O)CHC(O)CH}_3 + \text{HCl} \rightarrow \text{CH}_3\text{C(O)CH}_2\text{C(O)CH}_3 + \text{NaCl}
\]

Because of the ease of these syntheses, many analogues of acetyl acetonates are known. Some examples include

\[
\text{C}_6\text{H}_5\text{C(O)CH}_2\text{C(O)C}_6\text{H}_5 \quad \text{(dbaH)}
\]
and $(\text{CH}_3)_3\text{CC(O)CH}_2\text{C(O)CC(CH}_3)_3$.

Hexa fluoro acetyl acetonate is also widely used to generate volatile metal complexes.

### 4 – Reactions

#### 4 – 1 – Condensations

Acetyl acetone is a versatile bi-functional precursor to heterocycles because both keto groups undergo condensation. Hydrazine reacts to produce pyrazoles. Urea gives pyrimidines. Condensation with aryl- and alkyl amines to gives the mono- and then the diketimines wherein the O atoms in acetyl acetone are replaced by NR ($R = \text{aryl, alkyl}$).

#### 4 – 1 - Coordination chemistry

The acetyl acetone anion, acac⁻, forms complexes with many transition metal ions. A general method of synthesis is to react the metal ion with acetyl acetone in the presence of a base (B):

$$M^{2+} + z \text{(acacH)} \rightleftharpoons M(\text{acac})_z + z \text{BH}^+$$

which assists the removal of a proton from acetylacetone and shifts the equilibrium in favour of the complex. Both oxygen atoms bind to the metal to form a six-membered chelate ring. In some cases the chelate effect is so strong that no added base is needed to form the complex. Since the metal complex carries no electrical charge, it is soluble in non-polar organic solvents.

### 5 – Biodegradation

Enzymatic breakdown: The enzyme acetyl acetone dioxygenase cleaves the carbon-carbon bond of acetyl acetone, producing acetate and 2-oxopropanal. The enzyme is Fe (II)-dependent, but it has been proven to bind to zinc as well. Acetyl acetone degradation has been characterized in the bacterium *Acinetobacter johnsonii*.

$$\text{C}_5\text{H}_8\text{O}_2 + \text{O}_2 \rightarrow \text{C}_2\text{H}_4\text{O}_2 + \text{C}_3\text{H}_4\text{O}_2$$
Amino Poly Carboxylic Acid

The glycinate ion can form a chelate complex with a metal ion with the EDTA anion. Aspartic acid is an amino di carboxylic acid and precursor to other ligands.

Contents
1 Introduction
2 Structure
3 Applications

1 - Introduction
An amino poly carboxylic acid (complexone) is a compound containing one or more nitrogen atoms connected through carbon atoms to two or more carboxyl groups. Amino poly carboxylates that have lost acidic protons (ionized), form strong complexes with metal ions. This property makes amino poly carboxylic acids useful in a wide variety of chemical, medical, and environmental applications.

2 - Structure
The parent of this family of ligands is the amino acid glycine, H₂NCH₂CO₂H, in which the amino group, NH₂, is separated from the carboxyl group, CO₂H by a single methylene group, CH₂. When the carboxyl group is deprotonated the glycinate ion can function as a bi
dentate ligand, binding the metal centre through the nitrogen and one of two carboxylate oxygen atoms, to form chelate complexes of metal ions.

Replacement of a hydrogen atom on the nitrogen of glycine by another acetate residue, $\text{CH}_2\text{CO}_2\text{H}$ gives imino di acetate acid, IDA, which is a tridentate ligand. Further substitution gives nitrilo tri acetate acid, NTA, which is a tetra dentate ligand. These compounds can be described as amino poly carboxylates. Related ligands can be derived from other amino acids other than glycine, notably aspartic acid.

Higher denticity is achieved by linking two or more glycinate or IDA units together. EDTA contains two IDA units with the nitrogen atoms linked by two methylene groups and is hexa dentate. DTPA has two CH$_2$CH$_2$ bridges linking three nitrogen atoms and is octa dentate. TTHA has ten potential donor atoms.

3 - Applications

The chelating properties of aminopolycarboxylates can be engineered by varying the groups linking the nitrogen atoms so as to increase selectivity for a particular metal ion. The number of carbon atoms between the nitrogen and carboxyl group can also be varied and substituents can be placed on these carbon atoms. Altogether this allows for a vast range of possibilities. Fura-2 is noteworthy as it combines two functionalities: it has high selectivity for calcium over magnesium and it has a substituent which makes the complex fluorescent when it binds calcium. This provides a means of determining the calcium content in intra-cellular fluid. Details concerning applications of the following examples can be found in the individual articles and / or reference.
Fura-2

IDA

NTA

EDTA

DTPA

EGTA

BAPTA

NOTA

DOTA
ATMP

ATMP or amino tris (methylene phosphonic acid) is a phosphonic acid. It has chelating properties. It can be synthesized from the Mannich-type reaction of ammonia, formaldehyde, and phosphorous acid.

IUPAC name;
[Bis(phosphono methyl) amino] methyl phosphonic acid

Other names:
Tris(phosphono methyl) amine;
Nitrilo tri methyl phosphonic acid;
Amino tris(methyl phosphonic acid);
ATMP;
NTMP

Molecular formula \( \text{C}_3\text{H}_{12}\text{N}\text{O}_9\text{P}_3 \)

Molar mass 299 g mol\(^{-1}\)

Appearance White solid

Density 1.33 g / cm\(^3\) (20 °C)

Melting point 200 °C decomp.

Solubility in water 61 g / 100 mL
2 - Properties
ATMP has better anti scale performance than that of polyphosphate through its excellent chelating ability, low threshold inhibition and lattice distortion process. It can prevent scale formation in water systems. ATMP is the phosphonate analog of nitrilo tri acetic acid. Payah

3 - Applications
Detergents and cleaning agents
Water treatment
Scaling inhibition
Chelation
**BAPTA**

![BAPTA molecule](image)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC name</td>
<td>1,2-bis (o-amino phenoxy) ethane-N,N,N',N'-tetra acetic acid</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{22}H_{24}N_{2}O_{10}</td>
</tr>
<tr>
<td>Molar mass</td>
<td>476.433 g/mol</td>
</tr>
<tr>
<td>Density</td>
<td>1.494 g/cm³</td>
</tr>
<tr>
<td>Melting point</td>
<td>177–179 °C</td>
</tr>
</tbody>
</table>

BAPTA (1,2-bis(o-amino phenoxy) ethane-N,N,N',N'-tetra acetic acid) is a calcium-specific amino poly carboxylic acid. The presence of four carboxylic acid functional groups makes possible the binding of two calcium ions. The extensive flexibility of the carboxylate ligands is critical to the coordination of calcium and other metal ions.

There is a range of reported values for the dissociation constant of BAPTA, though 0.2 µM appears consistently.[1] The rate constant for calcium binding is 500 µM⁻¹ s⁻¹.
BDTH$_2$

Content
1 Introduction
2 Preparation
3 Potential applications
3.1 Dietary supplement and controversy

1 - Introduction
BDTH$_2$ (also called BDET and BDETH$_2$; trade names B9, MetX and OSR#1) is an organo sulfur compound that is used as a chelation agent. It is a colourless solid. The molecule consists of two thiol groups and linked via a pair of amide groups. The compound is banned in the US as a treatment of autism, despite a marketing campaign aimed at parents of children with this disorder.

2 – Preparation
This compound is prepared by treating cysteamine with isophthaloyl dichloride to give the desired amide:

3 - Potential applications
Like most thiols, BDTH$_2$ binds to mercury salts to form thiolate complexes. In principle, it could be used to remove mercury from water for industrial applications under a wide range of conditions, including the high pH and cyanide of the effluent from gold mining. In industrial use, BDTH$_2$ is easy to make, does not form disulfides, and can be used either as-is or in the form of sodium or potassium salts that are more soluble in water.

BDTH$_2$ binds to mercury with a strong, nonpolar covalent bond within a water-insoluble organic framework. The resulting BDT–Hg
precipitate is stable, and leaches mercury only under highly acidic or basic conditions. BDTH$_2$ also binds to other elements, including arsenic, cadmium, copper, lead, and selenium. It is effective and economical for removing small traces of mercury from polluted soil, as the precipitate is inert and can be left in the soil after treatment.

4 - Dietary supplement and controversy

Despite the fact that chelation therapy has not been shown to have a beneficial effect, BDTH$_2$ had been marketed under the name OSR#1 as a dietary supplement for treatment of autism. The U.S. Food and Drug Administration determined that BDTH$_2$ is a drug rather than a supplement and issued a warning, resulting in its removal from the market. The main proponent of the compound, Dr. Boyd Haley, was chairman of the department of chemistry where research is also conducted on the utility of this compound for remediation of heavy metal pollution.
1 - Introduction

Citric acid is a weak organic acid with the formula C₆H₈O₇. It is a natural preservative/conservative and is also used to add an acidic or sour taste to foods and soft drinks. In biochemistry, the conjugate base of citric acid, citrate, is important as an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms.

Citric acid is a commodity chemical, and more than a million tonnes are produced every year by fermentation. It is used mainly as an acidifier, as a flavoring, and as a chelating agent.
IUPAC name: 2-hydroxy propane -1,2,3- tri carboxylic acid  
Other names: 3-carboxy-3-hydroxy penta nedioic acid  
2-hydroxy-1,2,3-propane tri carboxylic acid

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Molecular formula</td>
<td>$\text{C}_6\text{H}_8\text{O}_7$</td>
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<tr>
<td>Molar mass (anhydrous)</td>
<td>192 g / mol</td>
</tr>
<tr>
<td>Molar mass (monohydrate)</td>
<td>210.14 g / mol</td>
</tr>
<tr>
<td>Appearance</td>
<td>crystalline white solid</td>
</tr>
<tr>
<td>Odor</td>
<td>odorless</td>
</tr>
<tr>
<td>Density (anhydrous)</td>
<td>1.665 g / cm$^3$</td>
</tr>
<tr>
<td>Density (monohydrate)</td>
<td>1.5 g / cm$^3$</td>
</tr>
<tr>
<td>Melting point</td>
<td>156 $^\circ$C, 429 K, 313 °F</td>
</tr>
<tr>
<td>Boiling point</td>
<td>310 $^\circ$C, 583 K, 590 °F (decomposes)</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>73 g / 100 ml (20 °C)</td>
</tr>
<tr>
<td>Solubility</td>
<td>very soluble in ethanol</td>
</tr>
<tr>
<td></td>
<td>soluble in ether, ethyl acetate</td>
</tr>
<tr>
<td></td>
<td>insoluble in benzene, chloroform</td>
</tr>
<tr>
<td>Main hazards</td>
<td>skin and eye irritant</td>
</tr>
<tr>
<td>Flash point</td>
<td>155 $^\circ$C</td>
</tr>
<tr>
<td>Auto ignition temperature</td>
<td>345 $^\circ$C</td>
</tr>
<tr>
<td>Explosive limits</td>
<td>1.8 - 4.8 %</td>
</tr>
<tr>
<td>LD$_{50}$</td>
<td>3000 mg / kg (rat, oral)</td>
</tr>
</tbody>
</table>

2 – Properties

At room temperature, citric acid is a white crystalline powder. It can exist either in an anhydrous (water-free) form or as a monohydrate. The anhydrous form crystallizes from hot water, while the monohydrate forms when citric acid is crystallized from cold water. The monohydrate can be converted to the anhydrous form by heating above 78 °C. Citric acid also dissolves in absolute (anhydrous) ethanol (76 parts of citric acid per 100 parts of ethanol) at 15 °C.
In chemical structure, citric acid shares the properties of other carboxylic acids. When heated above 175 °C, it decomposes through the loss of carbon dioxide and water.

Citric acid is a slightly stronger acid than typical carboxylic acids because the anion can be stabilized by intra molecular hydrogen-bonding from other protic groups on citric acid.

3 - Discovery and production

The discovery of citric acid has been credited to the 8th century alchemist Jābir ibn Hayyān (Geber). Medieval scholars in Europe were aware of the acidic nature of lemon and lime juices; such knowledge is recorded in the 13th century encyclopedia Speculum Maius (The Great Mirror), compiled by Vincent of Beauvais. Citric acid was first isolated in 1784 by the chemist Carl Wilhelm Scheele, who crystallized it from lemon juice. Industrial-scale citric acid production began in 1890 based on the Italian citrus fruit industry.

In 1893, C. Wehmer discovered Penicillium mold could produce citric acid from sugar. However, microbial production of citric acid did not become industrially important until World War I disrupted Italian citrus exports. In 1917, the American food chemist James Currie discovered certain strains of the mold Aspergillus niger could be efficient citric acid producers, and the pharmaceutical company Pfizer began industrial-level production using this technique two years later, followed by Citrique Belge in 1929.

In this production technique, which is still the major industrial route to citric acid used today, cultures of A. niger are fed on a sucrose or glucose-containing medium to produce citric acid. The source of sugar is corn steep liquor, molasses, hydrolyzed corn starch or other inexpensive sugary solutions. After the mold is filtered out of the resulting solution, citric acid is isolated by precipitating it with lime (calcium hydroxide) to yield calcium citrate salt, from which citric acid is regenerated by treatment with sulfuric acid.
3 – 1 - Other methods

Prior to the fermentative process, citric acid was isolated from citrus fruits. The juice was treated with lime (Ca(OH)₂) to precipitate calcium citrate, which was isolated and converted back to the acid.

In 2007, worldwide annual production stood at approximately 1,600,000 tones. More than 50% of this volume was produced in China. More than 50% was used as acidulent in beverages, some 20% in other food applications, 20% for detergent applications and 10% for related applications other than food, such as cosmetics, pharmaceutics and in the chemical industry.

4 – Occurrence

Citric acid exists in greater than trace amounts in a variety of fruits and vegetables, most notably citrus fruits. Lemons and limes have particularly high concentrations of the acid; it can constitute as much as 8% of the dry weight of these fruits (about 47 g/L in the juices[10]). The concentrations of citric acid in citrus fruits range from 0.005 mol/L for oranges and grapefruits to 0.30 mol/L in lemons and limes. Within species, these values vary depending on the cultivar and the circumstances in which the fruit was grown.

5 – Biochemistry
5 – 1 - Citric acid cycle

Citrate, the conjugate base of citric acid is one of a series of compounds involved in the physiological oxidation of fats, proteins, and carbohydrates to carbon dioxide and water.

This series of chemical reactions is central to nearly all metabolic reactions, and is the source of two-thirds of the food-derived energy in higher organisms. Hans Adolf Krebs received the 1953 Nobel Prize in Physiology or Medicine for the discovery. The series of reactions is known by various names, including the "citric acid cycle", the "Krebs cycle" or "Szent - Györgyi — Krebs cycle", and the "tri carboxylic acid (TCA) cycle".
5 – 2 - Other biological roles
Citrate is a vital component of bone, helping to regulate the size of calcium crystals.

6 – Applications
The dominant use of citric acid is as a flavoring and preservative in food and beverages, especially soft drinks. Within the European Union it is denoted by E number E330. Citrate salts of various metals are used to deliver those minerals in a biologically available form in many dietary supplements. The buffering properties of citrates are used to control pH in household cleaners and pharmaceuticals. In the United States the purity requirements for citric acid as a food additive are defined by the Food Chemicals Codex, which is published by the United States Pharmacopoeia (USP).

6 – 1 - Foods, other
Citric acid can be added to ice cream as an emulsifying agent to keep fats from separating, to caramel to prevent sucrose crystallization, or to recipes in place of fresh lemon juice. Citric acid is used with sodium bicarbonate in a wide range of effervescent formulae, both for ingestion (e.g., powders and tablets) and for personal care (e.g., bath salts, bath bombs, and cleaning of grease). Citric acid is also often used in cleaning products and sodas or fizzy drinks.

Citric acid sold in a dry powdered form is commonly sold in markets and groceries as "sour salt", due to its physical resemblance to table salt. It has use in culinary applications where an acid is needed for either its chemical properties or for its sour flavor, but a dry ingredient is needed and additional flavors are unwanted (e.g., instead of vinegar or lemon juice).

6 – 2 - Cleaning and chelating agent
Citric acid is an excellent chelating agent, binding metals. It is used to remove lime scale from boilers and evaporators. It can be used to soften water, which makes it useful in soaps and laundry detergents. By chelating the metals in hard water, it lets these cleaners produce foam and work better without need for water softening. Citric
acid is the active ingredient in some bathroom and kitchen cleaning solutions. A solution with a 6% concentration of citric acid will remove hard water stains from glass without scrubbing. In industry, it is used to dissolve rust from steel. Citric acid can be used in shampoo to wash out wax and coloring from the hair.

Illustrative of its chelating abilities, citric acid was the first successful eluant used for total ion-exchange separation of the lanthanides, during the Manhattan Project in the 1940s. In the 1950s, it was replaced by the far more efficient EDTA. It can be used to substantially slow setting of Portland cement.

6 – 3 - Cosmetics and pharmaceuticals
Citric acid is widely used as a pH adjusting agent in creams and gels of all kinds. In this role, it is classified in most jurisdictions as a processing aid and so does not need to be listed on ingredient lists.

Citric acid is an alpha hydroxy acid and used as an active ingredient in chemical peels.

Citric acid is commonly used as a buffer to increase the solubility of brown heroin. Single-use citric acid sachets have been used as an inducement to get heroin users to exchange their dirty needles for clean needles in an attempt to decrease the spread of AIDS and hepatitis.\[^{12}\] Other acidifiers used for brown heroin are ascorbic acid, acetic acid, and lactic acid; in their absence, a drug user will often substitute lemon juice or vinegar.

Citric acid is used as one of the active ingredients in the production of antiviral tissues.

6 – 4 – Dyeing
Citric acid can be used in food coloring to balance the pH level of a normally basic dye. It is used as an odorless alternative to white vinegar for home dyeing with acid dyes.
6 – 5 - Industrial and construction
Citric acid can be used as a successful alternative to nitric acid in passivation of stainless steel.

6 – 6 – Photography
Citric acid can be used as a lower-odor stop bath as part of the process for developing photographic film. Photographic developers are alkaline, so a mild acid is used to neutralize and stop their action quickly, but commonly used acetic acid leaves a strong vinegar odor in the dark room.
Cryptand

Contents
1 introduction
2 Structure
3 Properties
4 Uses

1 - introduction
Cryptands are a family of synthetic bi- and poly cyclic multi
dentate ligands for a variety of cations. The Nobel Prize for
Chemistry in 1987 was given to Donald J. Cram, Jean-Marie Lehn,
and Charles J. Pedersen for their efforts in discovering and
determining uses of cryptands and crown ethers, thus launching the
now flourishing field of supra molecular chemistry. The term cryptand
implies that this ligand binds substrates in a crypt, interring the guest
as in a burial. These molecules are three dimensional analogues of
crown ethers but are more selective and complex the guest ions more
strongly. The resulting complexes are lipophilic.

2 – Structure
The most common and most important cryptand is
N[CH₂CH₂OCH₂CH₂OCH₂CH₂]₃N; the formal IUPAC (International
Union of Pure and Applied Chemistry) name for this compound is
1,10-diaza-4,7,13,16,21,24- hexaoxabicyclo [ 8.8.8 ] hexacosane.
This compound is termed [2.2.2] cryptand where the numbers indicate
the number of ether oxygen atoms (and hence binding sites) in each of
the three bridges between the amine nitrogen "caps". Many cryptands
are commercially available under the trade name "Kryptofix". All-
amine cryptands exhibit particularly high affinity for alkali metal
cations, which has allowed the isolation of salts of K⁺.

3 – Properties
The 3-dimensional interior cavity of a cryptand provides a
binding site - or nook - for "guest" ions. The complex between the
cationic guest and the cryptand is called a cryptate. Cryptands form
complexes with many "hard cations" including NH₄⁺, lanthanoids,
alkali metals, and alkaline earth metals. In contrast to crown ethers, cryptands bind the guest ions using both nitrogen and oxygen donors. This three-dimensional encapsulation mode confers some size-selectivity, enabling discrimination among alkali metal cations (e.g. Na\(^+\) vs. K\(^+\)).

4 – Uses

Cryptands are more expensive and difficult to prepare, but offer much better selectivity and strength of binding than other complexants for alkali metals, such as crown ethers. They are able to bind otherwise insoluble salts into organic solvents. They can also be used as phase transfer catalysts by transferring ions from one phase to another. Cryptands enabled the synthesis of the alkalides and electrides. They have also been used in the crystallization of Zintl ions such as Sn\(_9\)\(^{4-}\).
Deferasirox

Contents
1 introduction
2 Properties of deferasirox
3 Synthesis
4 Risks

1 - introduction
Deferasirox (marketed as Exjade) is a rationally-designed oral iron chelator. Its main use is to reduce chronic iron overload in patients who are receiving long-term blood transfusions for conditions such as beta-thalassemia and other chronic anemias. It is the first oral medication approved in the USA for this purpose.

It was approved by the United States Food and Drug Administration (FDA) in November 2005. According to FDA (May 2007), renal failure and cytopenias have been reported in patients receiving deferasirox oral suspension tablets. It is approved in the European Union by the European Medicines Agency (EMA) for children 6 years and older for chronic iron overload from repeated blood transfusions.

Systematic (IUPAC):
[4-[(3Z,5E)-3,5-bis(6-oxo-1-cyclohexa-2,4-dienylidene) -1,2,4-tri azolidin-1-yl] benzoic acid

Bioavailability 70%
Protein binding 99%
Metabolism Hepatic glucuronidation

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2 - Properties of deferasirox

The half-life of deferasirox is between 8 and 16 hours allowing once a day dosing. Two molecules of deferasirox are capable of binding to 1 atom of iron which are subsequently eliminated by fecal excretion. Its low molecular weight and high lipophilicity allows the drug to be taken orally unlike desferoxamine which has to be administered by IV route (intravenous infusion). Together with deferiprone, deferasirox seems to be capable of removing iron from cells (cardiac myocytes and hepatocytes) as well as removing iron from the blood.

3 – Synthesis

Deferasirox can be prepared from simple commercially available starting materials (salicylic acid, salicyl amide and 4- hydrazino benzoic acid) in the following two-step synthetic sequence:

The condensation of salicyloyl chloride (formed in situ from salicylic acid and thionyl chloride) with salicyl amide under
dehydrating reaction conditions results in formation of 2-(2-hydroxy phenyl)-1,3(4H)-benzoxazin-4-one. This intermediate is isolated and reacted with 4-hydrazino benzoic acid in the presence of base to give 4- ( 3,5 - bis ( 2 - hydroxy phenyl ) -1,2,4 - tri azol -1- yl ) benzoic acid (Deferasirox).

4 – Risks

Deferasirox was the # 2 drug on the list of 'Most frequent suspected drugs in reported patient deaths' compiled by the Institute for Safe Medical Practices in 2009. There were 1320 deaths reported, perhaps explained by an update to the ADE data of Novartis, and a new boxed warning about gastrointestinal haemorrhage as well as kidney and liver failure.
2,3–Di Hydroxy Benzoic Acid

IUPAC name: 2,3-Di hydroxy benzoic acid
Other names:
Hypo gallic acid;
2 - Pyro catechuic acid;
O - Pyro catechuic acid
Molecular formula C\textsubscript{7}H\textsubscript{6}O\textsubscript{4}
Molar mass 154 g mol\textsuperscript{-1}
Appearance Colorless solid
Melting point 204-206 °C
Solubility in water Low

1 - Introduction

2,3-Dihydroxy benzoic acid is a natural phenol found in *Phyllanthus acidus* and in the aquatic fern *Salvinia molesta*.

It is a dihydroxy benzoic acid, a type of organic compound. The colorless solid occurs naturally, being formed via the shikimate pathway. It is incorporated into various siderophores, which are molecules that strongly complex iron ions for absorption into bacteria. 2,3-DHB consists of a catechol group, which upon de protonation binds iron centers very strongly, and the carboxylic acid group by which the ring attaches to various scaffolds via amide linkages. A famous high affinity siderophore is enterochelin, which contains three di hydroxy benzoyl substituents linked to the de psi peptide of serine. It is a potentially useful iron-chelating drug.
2, 3-Di Mercapto-1-Propane Sulfonic Acid

\[
\text{SH} \quad \text{HS} \quad \text{SO}_3\text{H}
\]

IUPAC name: 2,3-Di mercapto-1-propane sulfonic acid
Molecular formula: \( \text{C}_3\text{H}_8\text{O}_3\text{S}_3 \)
Molar mass: 188 g / mol

1 - Introduction

2,3- Di mercapto-1-propane sulfonic acid (abbreviated DMPS) and its sodium salt (known as Unithiol) are chelating agents that form complexes with various heavy metals. They are related to di mercaprol, which is another chelating agent.

The synthesis of DMPS was first reported in 1956 by V. E. Petrunkin. The effects of DMPS on heavy metal poisoning, including with polonium-210, were investigated in the following years. DMPS was found to have some protective effect, prolonging the survival time.

A study was undertaken of DMPS use by workers involved in the production of a calomel skin bleaching lotion and in direct contact with mercurous chloride and that already showed elevated urine mercury levels. The sodium salt of DMPS was found to be effective in lowering the body burden of mercury and in decreasing the urinary mercury concentration to normal levels.

DMPS administrated to a mercury poisoned animal model failed to remove the mercury from tissues and reduce the inorganic mercury burden in the brain. A 2008 study reported a case of Stevens–Johnson syndrome (SJS), a potentially serious disease, in a child undergoing chelation therapy with DMPS; the SJS resolved gradually after the chelation therapy was stopped.
Di Mercapto Succinic Acid

Contents
1 Introduction
2 History
3 Stereochemistry
4 Preparation and reactivity
5 Medical use

1 - Introduction
Di mercapto succinic acid (DMSA), is the organo sulfur compound with the formula \( \text{HO}_2\text{CCH(SH)CH(SH)CO}_2\text{H} \). This colorless solid contains two carboxylic acid and two thiol groups, the latter being responsible for its mildly unpleasant odour. It occurs in two diastereomers, meso and the chiral \( dl \) forms. The meso isomer is used as a chelating agent.

<table>
<thead>
<tr>
<th>IUPAC name</th>
<th>( \text{meso-2,3- di mercapto succinic acid} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>succimer, APRD01236 (Drugbank), Chemet</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>( \text{C}_4\text{H}_6\text{O}_4\text{S}_2 )</td>
</tr>
<tr>
<td>Molar mass</td>
<td>182.22 g / mol</td>
</tr>
<tr>
<td>Melting point</td>
<td>125 °C</td>
</tr>
</tbody>
</table>

2 – History
DMSA was first synthesized by V. Nirenburg in the Urals Polytechnic Institute, commissioned by one of the electrical enterprises of Sverdlovsk, which consumed many tons of mercury
and was looking for a medicine to prevent poisoning of personnel. In 1957, it was found by Chinese scientists that DMSA can effectively treat antimony poisoning due to overdose of tartar emetic.\[^2\] Pronounced protective effect in animal poisoning with arsenic and mercury was first shown by I. Okonishnikova in 1962.

### 3 – Stereo chemistry

The 2,3- di mercapto succinic acid molecule has two stereo centers (two asymmetric carbons), and can exist as three different stereoisomers. The $2S,3S$ and $2R,3R$ isomers are a pair of enantiomers, whereas the $2R,3S$ isomer is a meso compound and thus optically inactive.

\[
\begin{align*}
(2R,3R)-2,3\text{-dimercapto succinic acid} \\
(2R,3S)-2,3\text{-dimercapto succinic acid} \\
(2S,3S)-2,3\text{-dimercapto succinic acid} \\
\end{align*}
\]

### 4 - Preparation and reactivity

DMSA may be prepared by reacting acetylene di carboxylic acid with sodium thio sulfate or thio acetic acid followed by hydrolysis. The dimethyl ester is also known.

Meso 2,3-dimercapto succinic acid binds to "soft" heavy metals such as $\text{Hg}^{2+}$ and $\text{Pb}^{2+}$, mobilizing these ions for excretion. It binds to metal cations through the thiol groups, which ionize upon complexation.

### 5 - Medical use

Di mercapto succinic acid (CHEMET) is indicated for the treatment of lead poisoning in children with blood level measured
above 45 µg / dL. The use of DMSA is not approved for prophylactic / prevention of lead poisoning in anticipation of exposure in known lead contaminated environments. Its elimination half-life is 2.5-3.5 h. DMSA can cross the blood–brain barrier of mice,[5] but not that of humans, limiting its use to extracting heavy metals from parts of the body other than the central nervous system.

Another application for DMSA is for provocation of tissue heavy metals in anticipation of a urine test. This is sometimes called a "challenge" or "provoked" heavy metals test. DMSA is used to help mobilize heavy metals stored in body tissues (and therefore not typically present in the circulation) and increase the excretion of heavy metals in the urine. In a study by Howard Frumkin et al., this sort of test was shown to not reliably provide an indication of past chronic mercury exposure, something it was often used for.[8] A 2004 study by GP Archbold, et al. called the results of a DMSA challenge test "misleading" for the purposes of diagnosing mercury toxicity.[9] Moreover, DMSA share the limitation of extracellular distribution, which makes it unable to cross the cell membrane and chelate heavy metals from intracellular sites.

The relative activities of a series of novel monoalkyl esters of meso-2,3- dimercapto succinic acid (MiADMSA) have been examined as agents for the mobilization of cadmium, lead and arsenic owing to the ability of these monoesters to cross cell membranes. The monoesters were found to be more effective than the parent compound DMSA. The complexes (monoesters of DMSA) seem to penetrate cells (not possible in the case of DMSA), which helps in targeting intracellular sites in the body and aids in the removal of toxic metal ions in the cytosol and organelles inside the cell.
1 - Introduction

1,4,7,10-tetra aza cyclo dodecane-1,4,7,10 - tetra acetic acid (also known as DOTA) is an organic compound with the formula (CH₂CH₂NCH₂CO₂H)₄. The molecule consists of a central 12-membered tetraaza (i.e., containing four nitrogen atoms) ring. DOTA is used as a complexing agent, especially for lanthanide ions. Its complexes have medical applications as contrast agents and cancer treatments.

<table>
<thead>
<tr>
<th>IUPAC name</th>
<th>1,4,7,10-tetra aza cyclo dodecane-1,4,7,10- tetra acetic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>DOTA, DotA, tetraxetan</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C₁₆H₂₈N₄O₈</td>
</tr>
<tr>
<td>Molar mass</td>
<td>404 g mol⁻¹</td>
</tr>
<tr>
<td>Appearance</td>
<td>White crystalline solid</td>
</tr>
</tbody>
</table>
2 – Terminology

The acronym DOTA is jargon for both the tetra carboxylic acid and its various conjugate bases. In the area of coordination chemistry, the tetra acid is called H$_4$DOTA and its fully deprotonated derivative is DOTA$^{4-}$. Many related ligands are referred to using the DOTA acronym, although these derivatives are generally not tetra carboxylic acids or the conjugate bases.

3 – Structure

DOTA is derived from the macro cycle known as cyclen. The four secondary amine groups are modified by replacement of the N-H centers with N-CH$_2$CO$_2$H groups. The resulting amino poly carboxylic acid, upon ionization of the carboxylic acid groups, is a high affinity chelating agent for di- and trivalent cations. The tetra carboxylic acid was first reported in 1976. At the time of its discovery DOTA exhibited the largest known formation constant for the complexation (chelating) of Ca$^{2+}$ and Gd$^{3+}$ ions. Modified versions of DOTA were first reported in 1988 and this area has proliferated since.

As a poly dentate ligand, DOTA envelops metal cations, but the denticity of the ligand depends on the geometric tendencies of the metal cation. The main applications involve the lanthanides and in such complexes DOTA functions as an octa dentate ligand, binding the metal through four amine and four carboxylate groups. Most such complexes feature an additional water ligand, giving an overall coordination number of nine.

For most transition metals, DOTA functions as a hexadentate ligand, binding through the four nitrogen and two carboxylate centres. The complexes have octahedral coordination geometry, with two pendent carboxylate groups. In the case of [Fe(DOTA)]$, the ligand is hepta dentate.

4 – Uses

4 – 1 - Cancer treatment and diagnosis

DOTA is used as part of some cancer therapies, where it functions as a chelating agent for the radioisotope $^{90}$Y$^{3+}$. DOTA can be conjugated to monoclonal antibodies by attachment of one of the four
carboxyl groups as an amide. The remaining three carboxylate anions are available for binding to the yttrium ion. The modified antibody accumulates in the tumour cells, concentrating the effects of the radioactivity of $^{90}$Y. Drugs containing this module receive an International Nonproprietary Name ending in *tetraxetan*:

- Yttrium ($^{90}$Y) clivatuzumab tetraxetan
- Yttrium ($^{90}$Y) tacatuzumab tetraxetan

DOTA can also be linked to molecules that have affinity for various structures. The resulting compounds are used with a number of radioisotopes in cancer therapy and diagnosis (for example in positron emission tomography).

Affinity for somatostatin receptors, which are found on neuroendocrine tumours:

- DOTATOC, DOTA-(Tyr$^3$)-octreotide or edotreotide
- DOTA-TATE or DOTA-(Tyr$^3$)-octreotate

Affinity for the proteins streptavidin and avidin, which can be targeted at tumours by aid of monoclonal antibodies:

- DOTA - biotin

**4 – 2 - Contrast agent**

The complex of Gd$^{3+}$ and DOTA is used as a gadolinium-based MRI contrast agent under the name gadoteric acid.

**5 – Synthesis**

DOTA was first synthesized in 1976 from cyclen and bromoacetic acid. This method is simple and still in use.
DTPMP or diethylene triamine penta(methylene phosphonic acid) is a phosphonic acid. It has chelating and anti corrosion properties.

IUPAC name:
[[((Phosphono methyl ) imino)]bis[[2,1-ethanediyl nitrilo bis (methylene)]]tetra kis-phosphonic acid

Other names:
DTPMPA, Di ethylene tri amine penta (methylene-phosphonic acid)

Molecular formula: \( C_9 H_{28} N_3 O_{15} P_5 \)
Molar mass: 573
Appearance: solid

2 - Properties
DTPMP is normally delivered as salts, because the acid form has very limited solubility in water and tends to crystallize in concentrated aqueous solutions. It is a nitrogenous organic poly phosphonic acid. It shows very good inhibition of the precipitation of barium sulfate (\( BaSO_4 \)). At high alkali and high temperature (above 210 °C) environments DTPMPA has better scale and corrosion inhibition effect than other phosphonates.
3 - Applications
Detergents and cleaning agents
Water treatment
Scaling inhibitor
Chelating agent
De flocculation agent / settling retarder
Anti corrosion agent
EDDHA or ethylene di amine-N,N'-bis (2-hydroxy phenyl acetic acid) is an iron - chelating chemical used in bacterial siderophore studies.

### IUPAC name
2-[2-[2-Hydroxy-1-(2-hydroxy phenyl)-2-oxo ethyl] amino] ethyl amino]-2-(2-hydroxy phenyl) acetic acid

### Other names:
Ethylene di amine-N,N'-bis (2-hydroxy phenyl acetic acid)

### Molecular formula
\( \text{C}_{18}\text{H}_{20}\text{N}_{2}\text{O}_{6} \)

### Molar mass
360

## 2 - History

The Fe-EDDHA story starts on December 11, 1953 in Berkeley, California, at a meeting sponsored by Geigy Chemical Corporation. It was at this meeting that Arthur Wallace of UCLA and Harry Kroll of Geigy met on a brain - storming session aimed at dreaming up the structure of a stable iron chelate.

The first attempts to make fe -EDDHA commercially and agriculturally viable were made by Dr. Ramesh Patel of Agricon Chemicals, a leading plant nutritionist and industrialist from India.
He was awarded Padma Bhushan for this service to the agricultural world. In India the development, and use of EDDHA, EDTA and other such chelate fertilizers today is largely successful due to the pioneering efforts of such private players in India.
EDDS

**Contents**
1 Introduction
2 Structure and properties
3 Synthesis
   3.1 From aspartic acid
4 Coordination chemistry
5 Uses

1 - Introduction
Ethylene di amine-\(N,N'\)-di succinic acid (EDDS) is an amino poly carboxylic acid. It is a colourless solid that is used as chelating agent that may offer a biodegradable alternative to EDTA, which is currently used on a large scale in numerous applications.

<table>
<thead>
<tr>
<th>IUPAC name</th>
<th>Ethylene di amine -(N,N')- di succinic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>(C_{10}H_{16}N_{2}O_{8})</td>
</tr>
<tr>
<td>Molar mass</td>
<td>292 g mol(^{-1})</td>
</tr>
<tr>
<td>Density</td>
<td>1.44 g mL(^{-1})</td>
</tr>
<tr>
<td>Melting point</td>
<td>220 - 222 °C</td>
</tr>
</tbody>
</table>

2 - Structure and properties
EDDS has two chiral centers, and as such three stereo isomers. These are the enantiomeric (R,R) and (S,S) isomers and the achiral meso (R,S) isomer. As a biodegradable replacement for EDTA, only the (S,S) stereoisomer is of interest. The (R,S) and (R,R) stereoisomers are less biodegradable, whereas the (S,S) stereoisomer
has been shown to be very effectively biodegraded even in highly polluted soils.

3 – Synthesis
EDDS was first synthesized from maleic acid and ethylene diamine. Some microorganisms have been manipulated for industrial-scale synthesis of (S,S)-EDDS from ethylene diamine and fumaric acid or maleic acid, which proceeds as follows:

3 – 1 - From aspartic acid
(S,S)-EDDS is produced stereospecifically by the alkylation of an ethylene dibromide with L-aspartic acid. Racemic EDDS is produced by the reaction of ethylene diamine with fumaric acid or maleic acid.

4 - Coordination chemistry

In its octahedral complexes, edds poses the six-membered chelate rings in the equatorial positions.

In comparing the effectiveness of (S,S)-EDDS versus EDTA as chelating agents for iron (III):

<table>
<thead>
<tr>
<th>Formation Reaction</th>
<th>Formation Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{Fe} (\text{H}_2\text{O})_6]^{3+} + (\text{S,S})\text{-EDDS}^{4-} \rightarrow \text{Fe} [(\text{S,S})\text{-EDDS}]^- + 6 \text{H}_2\text{O})</td>
<td>(K_{\text{EDDS}} = 10^{20.6})</td>
</tr>
<tr>
<td>([\text{Fe} (\text{H}_2\text{O})_6]^{3+} + \text{EDTA}^{4+} \rightarrow \text{Fe} (\text{EDTA})^- + 6 \text{H}_2\text{O})</td>
<td>(K_{\text{EDTA}} = 10^{25.1})</td>
</tr>
</tbody>
</table>
Because of the lower stability for $[\text{Fe}(S,S)-\text{EDDS}]^-$, the useful range being roughly $3 < \text{pH}_{(S,S)-\text{EDDS}} < 9$ and $2 < \text{pH}_{\text{EDTA}} < 11$. However, this range is sufficient for most applications.

Another comparison that can be made between $(S,S)$-EDDS and EDTA is the structure of the chelated complex. EDTA’s six donor sites form five five-membered chelate rings around the metal ion, four $\text{NC}_2\text{OFe}$ rings and one $\text{C}_2\text{N}_2\text{Fe}$ ring. The $\text{C}_2\text{N}_2\text{Fe}$ ring and two of the $\text{NC}_2\text{OFe}$ rings define a plane, and two $\text{NC}_2\text{OFe}$ rings are perpendicular to the plane that contains the $\text{C}_2$-symmetry axis. The five-membered rings are slightly strained. EDDS’s six donor sites form both five- and six-membered chelate rings around the metal ion: two $\text{NC}_2\text{OFe}$ rings, two $\text{NC}_3\text{OFe}$ rings, and one $\text{C}_2\text{N}_2\text{Fe}$ ring. Studies of the crystal structure of the $\text{Fe}[(S,S)-\text{EDDS}]^-$ complex show that the two five-membered $\text{NC}_3\text{OFe}$ rings project out of the plane of the complex, reducing the equatorial ring strain that exists in the $\text{Fe}[\text{EDTA}]^-$ complex. The complex also has $\text{C}_2$ symmetry.

5 – Uses

$(S,S)$-EDDS is a biodegradable chelating agent that offers an alternative to EDTA, of which 80 million kilograms are produced annually. Under natural conditions, EDTA has been found to convert to ethylene di amine tri acetic acid and then cyclize to the diketo piperizide, which accumulates in the environment as a persistent organic pollutant. When EDDS is applied in chemical-enhanced soil remediation in excessive case (e.g., when applied for ex-situ soil washing), higher extraction efficiency for heavy metals can be achieved and the amount of extraction is less independent with the EDDS dosage;\cite{10} On the other hand, during soil remediation which involves continuous flushing, metal extraction is often limited by the amount of EDDS. Under EDDS deficiency, initial unselective extraction of heavy metals was observed, followed by heavy metal exchange and re-adsorption of heavy metals that have lower stability constant with EDDS.
EDTMP

Contents
1 Introduction
2 Properties and applications

1 – Introduction
EDTMP or ethylene di amine tetra (methylene phosphonic acid) is a phosphonic acid. It has chelating and anti corrosion properties. EDTMP is the phosphonate analog of EDTA. It is classified as a nitrogenous organic poly phosphonic acid.

IUPAC name :
[ bis ( phosphono methyl) amino ] methyl phosphonic acid

Other names :
Ethylene di amine tetra ( methylene phosphonic acid),
EDTMP

Molecular formula : \( \text{C}_6\text{H}_{20}\text{N}_2\text{O}_{12}\text{P}_4 \)
Molar mass : 436
Appearance : solid
Solubility in water : limited

2 - Properties and applications
EDTMP is normally delivered as its sodium salt, which exhibits good solubility in water.

Used in Water treatment as an anti scaling and anti corrosion agent, the corrosion inhibition of EDTMP is 3–5 times better than that
of inorganic polyphosphate. It has good chemical stability and thermal tolerance. It shows excellent scale inhibition ability under temperature 200 °C. It functions by chelating with many metal ions.

The anti-cancer drug Samarium ($^{153}$Sm) lexicronam is also derived from EDTMP.
EGTA (Chemical)

IUPAC name: ethylene glycol-bis(2-amino ethyl ether) -N,N,N',N'-tetra acetic acid
Molecular formula: C_{14}H_{24}N_{2}O_{10}
Molar mass: 380 g mol⁻¹
Melting point: 241 °C

EGTA (ethylene glycol tetra acetic acid) is an amino poly carboxylic acid, a chelating agent. It is a colourless solid that is related to the better known EDTA. Compared to EDTA, it has a lower affinity for magnesium, making it more selective for calcium ions. It is useful in buffer solutions that resemble the environment in living cells[1] where calcium ions are usually at least a thousand fold less concentrated than magnesium.

The pKa for binding of calcium ions by tetrabasic EGTA is 11.00, but the protonated forms do not significantly contribute to binding, so at pH 7, the apparent pKa becomes 6.91. See Qin et al. for an example of a pKa calculation.

EGTA has also been used experimentally for the treatment of animals with cerium poisoning and for the separation of thorium from the mineral monazite. EGTA is used as a compound in elution buffer in the protein purification technique known as tandem affinity purification, in which recombinant fusion proteins are bound to calmodulin beads and eluted out by adding EGTA.

EGTA is often employed in dentistry and endodontics for the removal of smear layer.
Ethylene Diamine Tetra Acetic Acid  
(EDTA)

Contents
1 Introduction
2 Synthesis
3 Nomenclature
4 Coordination chemistry principles
5 Uses
   5.1 Industry
   5.2 Medicine
   5.3 Cosmetics
   5.4 Laboratory applications
5 Toxicity and environmental considerations
6 Methods of detection and analysis

1 - Introduction
Ethylene di amine tetra acetic acid, widely abbreviated as EDTA (for other names ), is an amino poly carboxylic acid and a colourless, water-soluble solid. Its conjugate base is named ethylene di amine tetra acetate. It is widely used to dissolve lime scale. Its usefulness arises because of its role as a hexa dentate ("six-toothed") ligand and chelating agent, i.e. its ability to "sequester" metal ions such as Ca$^{2+}$ and Fe$^{3+}$. After being bound by EDTA, metal ions remain in solution but exhibit diminished reactivity. EDTA is produced as several salts, notably disodium EDTA and calcium disodium EDTA.
2 – Synthesis

The compound was first described in 1935 by Ferdinand Munz, who prepared the compound from ethylene di amine and chloro acetic acid. Today, EDTA is mainly synthesized from ethylene di amine (1,2-di amino ethane), formaldehyde, and sodium cyanide. This route yields the sodium salt, which can be converted in a subsequent step into the acid forms:

\[
\begin{align*}
H_2NCH_2CH_2NH_2 + 4 CH_2O + 4 NaCN + 4 H_2O & \rightarrow (NaO_2CCH_2)_{2}NCH_2CH_2N(CH_2CO_2Na)_{2} + 4 NH_3 \\
NaO_2CCH_2)_{2}NCH_2CH_2N(CH_2CO_2Na)_{2} + 4 HCl & \rightarrow (HO_2CCH_2)_{2}NCH_2CH_2N(CH_2CO_2H)_{2} + 4 NaCl
\end{align*}
\]

In this way, about 80M kilograms are produced each year. Impurities cogenerated by this route include glycine and nitrilo tri acetic acid; they arise from reactions of the ammonia coproduct.
3 – Nomenclature
To describe EDTA and its various protonated forms, chemists distinguish between EDTA$^{4-}$, the conjugate base that is the ligand, and $H_4$EDTA, the precursor to that ligand. At very low pH (very acidic conditions) the fully protonated $H_6$ EDTA $^{2+}$ form predominates, whereas at very high pH or very basic condition, the fully deprotonated $Y^{4-}$ form is prevalent. In this article, the term EDTA is used to mean $H_{4-x}$ EDTA$^{x-}$, whereas in its complexes EDTA$^{4+}$ stands for the tetra-deprotonated ligand.

4 - Coordination chemistry principles

In coordination chemistry, EDTA$^{4-}$ is a member of the amino poly carboxylic acid family of ligands. EDTA$^{4+}$ usually binds to a metal cation through its two amines and four carboxylates. Many of the resulting coordination compounds adopt octahedral geometry. Although of little consequence for its applications, these octahedral complexes are chiral. The anion $[Co(EDTA)]^-$ has been resolved into enantiomers. Many complexes of EDTA$^{4+}$ adopt more complex structures due to (i) the formation of an additional bond to water, i.e. seven-coordinate complexes, or (ii) the displacement of one carboxylate arm by water. Ferric complex of EDTA is seven-coordinate. Early work on the development of EDTA was undertaken by Gerold Schwarzenbach in the 1940s. EDTA forms especially strong complexes with Mn (II), Cu (II), Fe (III), Pb (II) and Co (III).
Several features of EDTA's complexes are relevant to its applications. First, because of its high denticity, this ligand has a high affinity for metal cations:

\[
[\text{Fe(H}_2\text{O)}_6]^{3+} + \text{H}_4\text{EDTA} \rightleftharpoons [\text{Fe(EDTA)}]^− + 6 \text{H}_2\text{O} + 4 \text{H}^+ \quad (K_{eq} = 10^{25.1})
\]

Written in this way, the equilibrium quotient shows that metal ions compete with protons for binding to EDTA. Because metal ions are extensively enveloped by EDTA, their catalytic properties are often suppressed. Finally, since complexes of EDTA\(^4−\) are anionic, they tend to be highly soluble in water. For this reason, EDTA is able to dissolve deposits of metal oxides and carbonates.

5 – Uses
5 – 1 – Industry

In industry, EDTA is mainly used to sequester metal ions in aqueous solution. In the textile industry, it prevents metal ion impurities from modifying colours of dyed products. In the pulp and paper industry, EDTA inhibits the ability of metal ions, especially Mn\(^{2+}\), from catalyzing the disproportionation of hydrogen peroxide, which is used in "chlorine-free bleaching." In a similar manner, EDTA is added to some food as a preservative or stabilizer to prevent catalytic oxidative de coloration, which is catalyzed by metal ions.\(^8\) In soft drinks containing ascorbic acid and sodium benzoate, EDTA mitigates formation of benzene (a carcinogen).

The reduction of water hardness in laundry applications and the dissolution of scale in boilers both rely on EDTA and related complexants to bind Ca\(^{2+}\), Mg\(^{2+}\), as well as other metal ions. Once bound to EDTA, these metal centers tend not to form precipitates or to interfere with the action of the soaps and detergents. For similar reasons, cleaning solutions often contain EDTA.

The solubilization of ferric ions, at or below near neutral pH can be accomplished using EDTA. This property is useful in agriculture including hydroponics. However, given the pH dependence of ligand formation, EDTA is not helpful for improving Fe solubility in above
neutral soils. Otherwise, at near-neutral pH and above, iron(III) forms insoluble salts, which are less bioavailable to susceptible plant species. Aqueous \([\text{Fe (edta)}]\) is used for removing ("scrubbing") hydrogen sulfide from gas streams. This conversion is achieved by oxidizing the hydrogen sulfur to elemental sulfur, which is non-volatile:

\[
2 \text{[Fe (edta)]}^+ + \text{H}_2\text{S} \rightarrow 2 \text{[Fe (edta)]}^{2-} + \text{S} + 2 \text{H}^+
\]

In this application, the ferric center is reduced to its ferrous derivative, which can then be reoxidized by air. In similar manner, nitrogen oxides are removed from gas streams using \([\text{Fe(edta)}]^2\). The oxidizing properties of \([\text{Fe (edta)}]\) are also exploited in photography, where it is used to solubilize silver particles.

EDTA was used in the separation of the lanthanide metals by ion-exchange chromatography. Perfected by F.H. Spedding et al. in 1954, the method relies on the steady increase in stability constant of the lanthanide EDTA complexes with atomic number. Using sulfonated polystyrene beads and copper(II) as a retaining ion, EDTA causes the lanthanides to migrate down the column of resin while separating into bands of pure lanthanide. The lanthanides elute in order of decreasing atomic number. Due to the expense of this method, relative to counter-current solvent extraction, ion-exchange is now used only to obtain the highest purities of lanthanide (typically greater than 4N, 99.99 %).

5 – 2 – Medicine

EDTA is used to bind metal ions in the practice of chelation therapy, e.g., for treating mercury and lead poisoning.\(^{[11]}\) It is used in a similar manner to remove excess iron from the body. This therapy is used to treat the complication of repeated blood transfusions, as would be applied to treat thalassaemia. The U.S. FDA approved the use of EDTA for lead poisoning on July 16, 1953, under the brand name of Versenate, which was licensed to the pharmaceutical company Riker. Alternative medical practitioners believe EDTA acts as a powerful antioxidant to prevent free radicals from injuring blood vessel walls,
therefore reducing atherosclerosis. The U.S. FDA has not approved it for the treatment of atherosclerosis.

Dentists and endodontists use EDTA solutions to remove inorganic debris (smear layer) and lubricate the canals in endodontics. This procedure helps prepare root canals for obturation. Furthermore, EDTA solutions with the addition of a surfactant loosen up calcifications inside a root canal and allow instrumentation (canals shaping) and facilitate apical advancement of a file in a tight/calcified root canal towards the apex. It serves as a preservative (usually to enhance the action of another preservative such as benzalkonium chloride or thiomersal) in ocular preparations and eyedrops. In evaluating kidney function, the complex \([\text{Cr(edta)\textsuperscript{}}\text{]^-}}\) is administered intravenously and its filtration into the urine is monitored. This method is useful for evaluating glomerular filtration rate.

EDTA is used extensively in the analysis of blood. It is an anticoagulant for blood samples for CBC/FBEs.

Laboratory studies also suggest that EDTA chelation may prevent collection of platelets on the lining of the vessel [such as arteries] (which can otherwise lead to formation of blood clots, which itself is associated with atheromatous plaque formation or rupture, and thereby ultimately disrupts blood flow). These ideas have so far been proven ineffective,\textsuperscript{[18]} however, a major clinical study of the effects of EDTA on coronary arteries is currently (2008) proceeding.\textsuperscript{[19]} EDTA played a role in the O.J. Simpson trial when the defense alleged that one of the blood samples collected from Simpson's estate was found to contain traces of the compound.

EDTA is a slime dispersant, and has been found to be highly effective in reducing bacterial growth during implantation of intraocular lenses (IOLs).

5 – 3 – Cosmetics

In shampoos, cleaners and other personal care products EDTA salts are added as a sequestering agent to improve their stability in air.
5 – 4 - Laboratory applications
In the laboratory, EDTA is widely used for scavenging metal ions: In biochemistry and molecular biology, ion depletion is commonly used to deactivate metal-dependent enzymes, either as an assay for their reactivity or to suppress damage to DNA or proteins. In analytical chemistry, EDTA is used in complexometric titrations and analysis of water hardness or as a masking agent to sequester metal ions that would interfere with the analyses. EDTA finds many specialized uses in the biomedical laboratories, such as in veterinary ophthalmology as an anti-collagenase to prevent the worsening of corneal ulcers in animals. In tissue culture EDTA is used as a chelating agent that binds to calcium and prevents joining of cadherins between cells, preventing clumping of cells grown in liquid suspension, or detaching adherent cells for passaging. In histopathology, EDTA can be used as a decalcifying agent making it possible to cut sections using a microtome once the tissue sample is demineralized. EDTA is also known to inhibit a range of metallo-peptidases, the method of inhibition occurs via the chelation of the metal ion required for catalytic activity. EDTA can also be used to test for bioavailability of heavy metals in sediments.

6 - Toxicity and environmental considerations
EDTA is in such widespread use that questions have been raised whether it is a persistent organic pollutant. Research indicates that under many conditions, EDTA is fully bio-degradable. However, when simulating certain non-optimal degradation conditions (high pH), less than 1% of the EDTA was degraded instead to ethylene diamine tri-acetic acid, which can then cyclize to 3-ketopiperazine-N,N-diacetate, a cumulative, persistent, organic chemical with unknown effects on the environment. An alternative chelating agent with fewer environmental pollution implications is EDDS.

EDTA exhibits low acute toxicity with LD$_{50}$ (rat) of 2.0 – 2.2 g/kg. It has been found to be both cytotoxic and weakly genotoxic in laboratory animals. Oral exposures have been noted to cause reproductive and developmental effects. The same study by Lanigan also found that both dermal exposure to EDTA in most cosmetic formulations and inhalation exposure to EDTA in aerosolized
cosmetic formulations would produce exposure levels below those seen to be toxic in oral dosing studies.

7 - Methods of detection and analysis

The most sensitive method of detecting and measuring EDTA in biological samples is selected-reaction-monitoring capillary-electrophoresis mass-spectrometry (abbreviation SRM-CE/MS), which has a detection limit of 7.3 ng/mL in human plasma and a quantitation limit of 15 ng/mL. This method works with sample volumes as small as ~7-8 nL.

EDTA has also been measured in non-alcoholic beverages using high performance liquid chromatography (HPLC) at a level of 2.0 μg/mL.
Etidronic Acid (HEDP)

Contents
1 Introduction
2 Chelating Agent and Anti-oxidant
3 Use
   3.1 Pharmaceutical
   3.2 Chemical

1 - Introduction
Etidronic acid (INN) or 1-hydroxy ethane 1,1-di phosphonic acid (HEDP) is a bisphosphonate used in detergents, water treatment, cosmetics and pharmaceutical treatment.

An etidronate is a salt of etidronic acid, abbreviated MₙHEDP (M: is a cation, n: number of M maximum 4).

<table>
<thead>
<tr>
<th>Systematic (IUPAC) name :</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1-hydroxy ethan-1,1-diy) bis ( phosphonic acid)</td>
</tr>
<tr>
<td>Formula</td>
</tr>
<tr>
<td>Mol. mass</td>
</tr>
</tbody>
</table>

2 - Chelating Agent and Anti-oxidant
Etidronic acid is a chelating agent and may be added to bind or, to some extent, counter the effects of substances, such as calcium, iron or other metal ions, which may be discharged as a component of grey wastewater and could conceivably contaminate groundwater supplies. As a phosphonate it has corrosion inhibiting properties on unalloyed steel. Etidronic acid also acts to retard rancidification and oxidation of fatty acids.
HEDP and its salts are added to detergents and other cleaning agents to prevent the effects of hard water. It is also used in peroxide bleaching to prevent degradation of peroxides by transition metals.

Etidronic acid is listed as an ingredient of several cosmetic formulations where it is used for suppressing radical formation, emulsion stabiliser and viscosity control. While etidronic acid has not been limited from inclusion in cosmetics and does have legitimate uses, it is recommended that, as with most cosmetic products (particularly soaps), the product should be thoroughly rinsed from the skin after use.

Etidronic acid is also included among swimming pool chemicals. It is used as a stain inhibitor to prevent metal ions coming out of solution and staining the sides of swimming pools.

3 - Use
3 – 1 – Pharmaceutical
Etidronic acid (trade name Didronel) is a bisphosphonate used to strengthen bone, treat osteoporosis, and treat Paget's disease of bone.

Bisphosphonates primarily reduce osteoclastic activity, which prevents bone resorption, and thus moves the bone resorption / formation equilibrium toward the formation side and hence makes bone stronger on the long run. Etidronate, unlike other bisphosphonates, also prevents bone calcification. For this reason, other bisphosphonates, like alendronate, are preferred when fighting osteoporosis. To prevent bone resorption without affecting too much bone calcification, etidronate must be administered only for a short time once in a while, for example for two weeks every 3 months. When given on a continuous basis, say every day, etidronate will altogether prevent bone calcification. This effect may be useful and etidronate is in fact used this way to fight heterotopic ossification. But in the long run, if used on a continuous basis, it will cause osteomalacia.

3 – 1 – Chemical
HEDP is used as scale and corrosion inhibition in circulating cool water system, oil field and low-pressure boilers in fields such as
electric power, chemical industry, metallurgy, fertilizer, etc. In light woven industry, HEDP is used as detergent for metal and nonmetal. In dyeing industry, HEDP is used as peroxide stabilizer and dye-fixing agent; In non-cyanide electroplating, HEDP is used as chelating agent. The dosage of 1–10 mg / L is preferred as scale inhibitor, 10 – 50 mg / L as corrosion inhibitor, and 1000 – 2000 mg / L as detergent. Usually, HEDP is used together with poly carboxylic acid.
Fura – 2

Fura-2, an amino poly carboxylic acid, is a ratio metric fluorescent dye which binds to free intracellular calcium. It was the first widely-used dye for calcium imaging, and remains very popular. Fura-2 is excited at 340 nm and 380 nm of light, and the ratio of the emissions at those wavelengths is directly correlated to the amount of intracellular calcium. Regardless of the presence of calcium, Fura-2 emits at 510 nm of light. The use of the ratio automatically cancels out confounding variables, such as variable dye concentration and cell thickness, making Fura-2 one of the most appreciated tools to quantify calcium levels. More recently, genetically-encoded calcium indicators based on spectral variants of the green fluorescent protein, such as Cameleons,\textsuperscript{[2]} have supplemented the use of Fura-2 and other small molecule dyes for calcium imaging.
Gluconic Acid

Contents
1 Introduction
2 Chemical structure
3 Occurrence and uses

1 - Introduction
Gluconic acid is an organic compound with molecular formula C_6H_{12}O_7 and condensed structural formula HOCH_2(CHOH)_4COOH. It is one of the 16 stereo isomers of 2,3,4,5,6 - penta hydroxy hexanoic acid.

In aqueous solution at neutral pH, gluconic acid forms the gluconate ion. The salts of gluconic acid are known as "gluconates". Gluconic acid, gluconate salts, and gluconate esters occur widely in nature because such species arise from the oxidation of glucose. Some drugs are injected in the form of gluconates.

<table>
<thead>
<tr>
<th>IUPAC name</th>
<th>D - Gluconic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>Dextronic acid</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_6H_{12}O_7</td>
</tr>
<tr>
<td>Molar mass</td>
<td>196 g / mol</td>
</tr>
<tr>
<td>Appearance</td>
<td>Colorless crystals</td>
</tr>
<tr>
<td>Melting point</td>
<td>131 °C</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>Good</td>
</tr>
</tbody>
</table>

2 - Chemical structure
The chemical structure of gluconic acid consists of a six-carbon chain with five hydroxyl groups terminating in a carboxylic acid group. In aqueous solution, gluconic acid exists in equilibrium with the cyclic ester glucono delta - lactone.
3 - Occurrence and uses

Gluconic acid occurs naturally in fruit, honey, kombucha tea, and wine. As a food additive (E574), it is an acidity regulator. It is also used in cleaning products where it dissolves mineral deposits especially in alkaline solution. The gluconate anion chelates Ca$^{2+}$, Fe$^{2+}$, Al$^{3+}$, and other metals. In 1929 Horace Terhune Herrick developed a process for producing the salt by fermentation.

Calcium gluconate, in the form of a gel, is used to treat burns from hydrofluoric acid; calcium gluconate injections may be used for more severe cases to avoid necrosis of deep tissues. Quinine gluconate is a salt between gluconic acid and quinine, which is used for intramuscular injection in the treatment of malaria. Zinc gluconate injections are used to neuter male dogs. Iron gluconate injections have been proposed in the past to treat anemia.
Homo Citric Acid

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC name</td>
<td>2-Hydroxy butane-1,2,4-tri carboxylic acid</td>
</tr>
<tr>
<td>Other names</td>
<td>Homo citric acid, Homo citrate</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C$<em>7$H$</em>{10}$O$_7$</td>
</tr>
<tr>
<td>Molar mass</td>
<td>206 g mol$^{-1}$</td>
</tr>
<tr>
<td>Appearance</td>
<td>Colorless solid</td>
</tr>
</tbody>
</table>

Homo citric acid is an organic compound with the formula HOC(CO$_2$H)(CH$_2$CO$_2$H)(C$_2$H$_4$CO$_2$H). This tri carboxylic acid occurs naturally as a component of the iron-molybdenum cofactor of certain nitrogenase proteins. Biochemists often refer to this cofactor as homo citrate, which is the conjugate bases that predominate in neutral aqueous solutions of this species.

The molecule is related to citric acid by the addition of one methylene unit, hence the prefix "homo." Unlike citric acid, homo citric acid is chiral. The acid exists in equilibrium with the lactone.
Imino Di Acetic Acid

![Chemical structure of Imino Di Acetic Acid]

IUPAC name:
2 - (Carboxy methyl amino) acetic acid

Other names:
Di glycol amidic acid

Molecular formula: $\text{C}_4\text{H}_7\text{N}\text{O}_4$

Molar mass: 133 g mol$^{-1}$

Appearance: Colourless crystals

Density: 1.436 g mL$^{-1}$

EU classification: Xi

Imino di acetic acid, HN(CH$_2$CO$_2$H)$_2$, often abbreviated to IDA, is a di carboxylic acid amine (note that the nitrogen atom forms a secondary amino group, not an imino group as the name suggests). The imino di acetate anion can act as a tridentate ligand to form a metal complex with two, fused, five membered chelate rings. The proton on the nitrogen atom can be replaced by a carbon atom of a polymer to create an ion-exchange resin, such as chelex 100.

IDA forms stronger complexes than the bi dentate ligand glycine and weaker complexes than the tetra dentate ligand nitrilo tri acetic acid.

![Metal complex with the imino di acetate anion]

A metal complex with the imino di acetate anion

By capillary electrophoresis IDA is typically used for modulating peptide mobility.

76
Indo-1 is a popular calcium indicator similar to Fura-2. In contrast to Fura-2, Indo-1 has a dual emissions peak. The main emission peak in calcium-free solution is 475 nm while in the presence of calcium the emission is shifted to 400 nm. It is widely used in flow cytometry. The penta potassium salt is commercially available and preferred to the free acid because of its higher solubility in water. While Indo-1 is not cell permeable the penta acetoxy methyl ester Indo-1 AM enters the cell where it is cleaved by intracellular esterases to Indo-1. The synthesis and properties of Indo-1 were presented in 1985 by the group of Roger Y Tsien.
Nitrilo Tri Acetic Acid

Contents
1 Introduction
2 Production and use
3 Coordination chemistry and applications

Nitrilo tri acetic acid (NTA) is the amino poly carboxylic acid with the formula N(CH₂CO₂H)₃. It is a colourless solid that is used as a chelating agent, it which forms coordination compounds with metal ions (chelates) such as Ca²⁺, Cu²⁺, and Fe³⁺.

Preferred IUPAC name;
2,2′,2″-Nitrilo tri acetic acid

Systematic name:
2-[Bis (carboxy methyl) amino] acetic acid

Other names:
Tri glycine

Molecular formula: C₆H₉NO₆
Molar mass: 191 g mol⁻¹
Appearance: White crystals
GHS signal word: WARNING
EU classification: Xn
Flash point: 100 °C
LD₅₀: 1.1 g kg⁻¹ (oral, rat)
2 - Production and use

This compound is commercially available as the free acid and as the sodium salt. It is produced from ammonia, formaldehyde, and sodium cyanide or hydrogen cyanide. World wide capacity is estimated at 100 thousand tones per year.

3 - Coordination chemistry and applications

The uses of NTA are similar to that of EDTA, both being chelating agents. In contrast to EDTA, NTA is easily biodegradable and is almost completely removed during wastewater treatment. It is used for water softening and as a replacement to sodium and potassium triphosphate in detergents, and cleansers.\[^4\] NTA is a tri podal tetra dentate tri anionic ligand.

\[
\begin{array}{c}
\text{Structure of the complex of NTA}^{3-} \text{ and Ca}^{2+}.
\end{array}
\]

In the laboratory, this compound is used in complex metric titrations. A variant of NTA is used for protein isolation and purification in the His - tag method. The modified NTA is used to immobilize nickel to a solid support. This allows separation of proteins containing "tag" containing six histidine residues at either terminus.
Pentetic Acid (DTPA)

Contents
1 Introduction
2 Coordination properties
3 Applications
4 Related compounds

1 - Introduction
Pentetic acid or di ethylene tri amine penta acetic acid (DTPA) is an amino poly carboxylic acid consisting of a di ethylene tri amine back bone with five carboxy methyl groups. The molecule can be viewed as an expanded version of EDTA and is used similarly. It is a white, water - soluble solid.

<table>
<thead>
<tr>
<th>IUPAC name : Pentetic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names :</td>
</tr>
<tr>
<td>DTPA;</td>
</tr>
<tr>
<td>H_5dtpa;</td>
</tr>
<tr>
<td>Di ethylene tri amine penta acetic acid;</td>
</tr>
<tr>
<td>Penta (carboxy methyl) di ethylene tri amine</td>
</tr>
<tr>
<td>Molecular formula: C_{14}H_{23}N_{3}O_{10}</td>
</tr>
<tr>
<td>Molar mass: 393 g mol^{-1}</td>
</tr>
<tr>
<td>Appearance: White crystalline solid</td>
</tr>
<tr>
<td>Melting point: 220 °C</td>
</tr>
<tr>
<td>Boiling point: decomposes at a higher temp.</td>
</tr>
<tr>
<td>Solubility in water: &lt; 0.5 g / 100 mL</td>
</tr>
<tr>
<td>Flash point: Does not burn</td>
</tr>
</tbody>
</table>
2 - Coordination properties

The conjugate base of DTPA has a high affinity for metal cations. Thus, the penta-anion $\text{DTPA}^{5-}$ is potentially an octa dentate ligand assuming that each nitrogen center counts as a and each COO$^-$ group counts as a center for coordination. The formation constants for its complexes are about 100 greater than those for EDTA.\(^3\) As a chelating agent, DTPA wraps around a metal ion by forming up to eight bonds. Transition metals, however, usually form less than eight coordination bonds. So, after forming a complex with a metal, DTPA still has the ability to bind to other reagents, as is shown by its derivative pendetide. For example, in its complex with copper(II), DTPA binds in a hexa dentate manner utilizing the three amine centers and three of the five carboxylates.

3 – Applications

Like the more common EDTA, DTPA is mainly used for sequestering metal ions that otherwise decompose hydrogen peroxide, which is used to bleach pulp in paper making. Several million kilograms are produced for this purpose annually.

Its chelating properties are useful in deactivating calcium and magnesium ions in hair products. DTPA is used in over 150 cosmetic products.\(^5\) Additionally, DTPA is used in MRI contrasting agents. DTPA improves MRI images by forming a complex with a gadolinium ion, which alters the properties of nearby water molecules.

DTPA has been considered for treatment of radioactive materials such as plutonium, americium, and other actinides. In theory, these complexes are more apt to be eliminated in urine. It is normally administered as the calcium or zinc salt, since these ions are readily displaced by more highly charged cations. DTPA forms complexes with thorium (IV), uranium (IV), neptunium (IV), and cerium (III/IV).

4 - Related compounds

Compounds that are structurally related to DTPA are used in medicine, taking advantage of the high affinity of the tri amino penta carboxylate scaffold for metal ions.
In ibritumomab tiuxetan, the chelator tiuxetan is a modified version of DTPA whose carbon backbone contains an iso thio cyanato benzyl and a methyl group.

In capromab pendetide and satumomab pendetide, the chelator pendetide (GYK-DTPA) is a modified DTPA containing a peptide linker used to connect the chelate to an antibody.

Pentetreotide is a modified DTPA attached to a peptide segment.

DTPA and derivatives are used to chelate gadolinium to form a MRI contrast agent, such as Magnevist.

Technetium is chelated with DTPA for ventilation perfusion scan (V/Q scan) and renal scan.
Phosphonate

\[
\text{General ester of phosphonic acid.}
\]

Contents
1 Introduction
2 Basic properties
3 Production
   3.1 Bisphosphonates
4 Occurrence in nature
5 Uses
   5.1 Metal chelants
   5.2 Niche uses
6 Toxicology
7 Biodegradation
8 Phosphonate compounds

1 - Introduction
Phosphonates or phosphonic acids are organo phosphorus compounds containing C- \( \text{PO} \) (OH)\(_2\) or C- \( \text{PO} \) (OR)\(_2\) groups ( where \( R = \) alkyl, aryl). Phosphonic acids and phosphonate salts are typically white, nonvolatile solids that are poorly soluble in organic solvents, but soluble in water and common alcohols. Many commercially important compounds are phosphonates, including Glyphosate, the herbicide "Roundup", and Ethephon, a widely used plant growth regulator. Bisphosphonates are popular drugs for treatment of osteoporosis.

\[
\text{Clodronic acid is bisphosphonate used as a drug to treat osteoporosis.}
\]

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2 - Basic properties
Phophonates feature tetrahedral phosphorus centers. They are structurally closely related to (and often prepared from) phosphorous acid.

\[ \text{Phosphonic acids and derivatives are chemically and structurally related to phosphorous acid.} \]

Phosphonate salts are the result of deprotonation of phosphonic acids, which are diprotic acids:

\[
\begin{align*}
\text{RPO(OH)}_2 + \text{NaOH} & \to \\
\text{H}_2\text{O} + \text{R PO (OH)(ONa)} & \text{ (mono sodium phophonate)} \\
\text{RPO(OH)(ONa) + NaOH} & \to \\
\text{H}_2\text{O} + \text{RPO(ONa)}_2 & \text{ (mono sodium phophonate)}
\end{align*}
\]

Phosphonate esters are the result of condensation of phosphonic acids with alcohols.

3 – Production
Several methods exist for the preparation of phosphonic acids and its salts. Most processes begin with phosphorous acid (aka phosphorous acid, \( \text{H}_3\text{PO}_3 \)), exploiting its reactive \( \text{P-H} \) bond.

Phosphonic acid can be alkylated under Mannich conditions to give amino methylated phosphonates, which are useful as complexants. One example is the industrial preparation of nitrilo tris (methylene phosphonic acid):

\[
\begin{align*}
\text{NH}_3 + 3 \text{H}_3\text{PO}_3 + 3 \text{CH}_2\text{O} & \to \\
\text{N (CH}_2\text{PO}_3\text{H}_2)_3 + 3 \text{H}_2\text{O}
\end{align*}
\]
Phosphonic acid also can be alkylated with acrylic acid derivatives to afford carboxyl functionalized phosphonic acids. This reaction is a variant of the Michael addition:

$$\text{CH}_2=\text{CHCO}_2\text{R} + 3 \text{H}_3\text{PO}_3 \rightarrow (\text{HO})_2\text{P(O)CH}_2\text{CH}_2\text{CO}_2\text{R}$$

Phosphonic esters are prepared using the Michaelis – Arbuzov reaction. For example, methyl iodide catalyzes the conversion of trimethyl phosphite to the phosphonate ester di methyl methyl phosphonate:

$$\text{P} (\text{OMe})_3 \rightarrow \text{Me PO} (\text{OMe})_2$$

These esters can be hydrolyzed to the acid ($\text{Me} = \text{methyl}$):

$$\text{Me PO} (\text{OMe})_2 + \text{H}_2\text{O} \rightarrow \text{Me PO} (\text{OH})_2 + 2 \text{Me OH}$$

In the Michaelis – Becker reaction, a hydrogen phosphonate diester is first deprotonated and the resulting anion is alkylated.

### 3 – 1 – Bisphosphonates

Bisphosphonates were first synthesized in 1897 by Von Baeyer and Hofmann. An example of such a bisphosphonate is HEDP (Etidronic acid or Didronel). One example is 1-hydroxy ethane-1,1-diphosphonic acid, which is prepared from phosphorous acid and acetic anhydride:

$$2 \text{H}_3\text{PO}_3 + (\text{CH}_3\text{CO})_2\text{O} \rightarrow \text{CH}_3\text{C(OH)(PO}_3\text{H}_2)_2 + \text{CH}_3\text{CO}_2\text{H}$$

### 4 - Occurrence in nature

- **2-amino ethyl phosphonic acid:** the first identified natural phosphonate.
- **Glyphosate, the herbicide** "Roundup", is a phosphonate.
Phosphonates are one of the three sources of phosphate intake in biological cells. The other two are inorganic phosphate and organo phosphates.

The naturally-occurring phosphonate 2-amino ethyl phosphonic acid was first identified in 1959 in plants and many animals, where it is localized in membranes. Phosphonates are quite common among different organisms, from prokaryotes to eubacteria and fungi, mollusks, insects and others. They were first reported in natural soils by Newman and Tate (1980). The biological role of the natural phosphonates is still poorly understood. Bis- or poly phosphonates have not been found to occur naturally.

5 – Uses
In 1998 the consumption of phosphonates was 56,000 tons worldwide - 40,000 tons in the US, 15,000 tons in Europe and less than 800 tons in Japan. The demand of phosphonates grows steadily at 3 % annually.

5 – 1 - Metal chelants
Since the work of Schwarzenbach in 1949, phosphonic acids are known as effective chelating agents. The introduction of an amine group into the molecule to obtain - \( \text{NH}_2 - \text{C-PO(OH)}_2 \) increases the metal binding abilities of the phosphonate. Examples for such compounds are NTMP, EDTMP and DTPMP. These phosphonates are the structural analogues to the well-known amino poly carboxylate such as EDTA. The stability of the metal complexes increases with increasing number of phosphonic acid groups. Phosphonates are highly water-soluble while the phosphonic acids are only sparingly so.

Phosphonates are effective chelating agents. That is, they bind tightly to di- and trivalent metal ions, which is useful in water softening. In this way, they prevent formation of insoluble precipitates (scale). The binding of these ligands also suppresses the catalytic properties of metal ions. They are stable under harsh conditions. For these reasons, an important industrial use of phosphonates is in cooling waters, desalination systems, and in oil fields to inhibit scale formation. Phosphonates are also regularly used in reverse osmosis.
systems as anti-scalants. Phosphonates in cooling water systems also serve to control corrosion of iron and steel. In pulp and paper manufacturing and in textile industry they serve as "peroxide bleach stabilizers," by chelating metals that could inactivate the peroxide. In detergents they are used as a combination of chelating agent, scale inhibitor, and bleach stabilizer. Phosphonates are also increasingly used in medicine to treat disorders associated with bone formation and calcium metabolism. Furthermore they serve as carriers for radionuclides in bone cancer treatments.

5 – 2 - Niche uses

In organic synthesis, phosphonates are used in the Horner-Wadsworth-Emmons reaction. In conjunction with organo silicates, phosphonates are also used to treat "sudden oak death", which is caused by the fungus-like eukaryote Phytophthora ramorum.

6 – Toxicology

The toxicity of phosphonates to aquatic organisms is low. Reported values for 48 h LC50 values for fish are between 0.1 and 1.1 mM. Also the bio concentration factor for fish is very low.

7 – Biodegradation

In nature bacteria play a major role in the degradation of phosphonates. Due to the presence of natural phosphonates in the environment, bacteria have evolved the ability to metabolize phosphonates as nutrient sources. Some bacteria use phosphonates as a phosphorus source for growth. Amino phosphonates can also be used as sole nitrogen source by some bacteria. The poly phosphonates used in industry differ greatly from natural phosphonates such as 2-aminoethylphosphonic acid, because they are much larger, carry a high negative charge and are complexed with metals. Biodegradation tests with sludge from municipal sewage treatment plants with HEDP and NTMP showed no indication for any degradation. An investigation of HEDP, NTMP, EDTMP and DTPMP in standard biodegradation tests also failed to identify any biodegradation. It was noted, however, that in some tests due to the high sludge to phosphonate ratio, removal of the test substance from solution observed as loss of DOC was observed. This factor was attributed to
adsorption rather than biodegradation. However, bacterial strains capable of degrading amino poly phosphonates and HEDP under P-limited conditions have been isolated from soils, lakes, wastewater, activated sludge and compost.

"No biodegradation of phosphonates during water treatment is observed but photo degradation of the Fe (III) - complexes is rapid. Amino poly phosphonates are also rapidly oxidized in the presence of Mn(II) and oxygen and stable breakdown products are formed that have been detected in wastewater. The lack of information about phosphonates in the environment is linked to analytical problems of their determination at trace concentrations in natural waters. Phosphonates are present mainly as Ca and Mg-complexes in natural waters and therefore do not affect metal speciation or transport."[4] Phosphonates interact strongly with some surfaces, which results in a significant removal in technical and natural systems.

8 - Phosphonate compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEPn</td>
<td>2-Amino ethyl phosphonic acid</td>
</tr>
<tr>
<td>AMP</td>
<td>Amino-tris-(methylene-phosphonic acid)</td>
</tr>
<tr>
<td>ATMP</td>
<td>Amino tris (methylene phosphonic acid)</td>
</tr>
<tr>
<td>BPMG</td>
<td>N,N-Bis (phosphono methyl)glycine</td>
</tr>
<tr>
<td>CEPA</td>
<td>2-carboxy ethyl phosphonic acid</td>
</tr>
<tr>
<td>DMMP</td>
<td>Di methyl phosphonate</td>
</tr>
<tr>
<td>DTPMP</td>
<td>Di ethylene tri amine penta (methylene phosphonic acid)</td>
</tr>
<tr>
<td>EDTMP</td>
<td>Ethylene di amine tetra (methylene phosphonic acid)</td>
</tr>
<tr>
<td>HDTMP</td>
<td>Hexa methylene di amine tetra (methylene phosphonic acid)</td>
</tr>
<tr>
<td>HEDP</td>
<td>1-Hydroxy ethyl idene-1,1-di phosphonic acid</td>
</tr>
<tr>
<td>HPAA</td>
<td>2-Hydroxy phosphono carboxylic acid</td>
</tr>
<tr>
<td>PBTC</td>
<td>Phosphono butane-tri carboxylic acid</td>
</tr>
<tr>
<td>PMIDA</td>
<td>N- (phosphono methyl) Imino di acetic acid</td>
</tr>
<tr>
<td>TDTMP</td>
<td>Tetra methylene di amine tetra (methylene phosphonic acid)</td>
</tr>
</tbody>
</table>
Phytochelatin

Chemical structure of phytochelatin. \( n = 2-11 \).

Contents
1 Introduction
2 Related peptides
3 History

1 - Introduction
Phytochelatins are oligomers of glutathione, produced by the enzyme phytochelatin synthase. They are found in plants, fungi, nematodes and all groups of algae including cyanobacteria. Phytochelatins act as chelators, and are important for heavy metal detoxification. They are abbreviated PC2 through PC11.

A mutant *Arabidopsis thaliana* lacking phytochelatin synthase is very sensitive to cadmium, but it grows just as well as the wild-type plant at normal concentrations of zinc and copper, two essential metal ions, indicating that phytochelatin is only involved in resistance to metal poisoning.

Because phytochelatin synthase uses glutathione with a blocked thiol group in the synthesis of phytochelatin, the presence of heavy metal ions that bind to glutathione causes the enzyme to work faster. Therefore the amount of phytochelatin increases when the cell needs more phytochelatin to survive in an environment with high concentrations of metal ions.

Phytochelatin seems to be transported into the vacuole of plants, so that the metal ions it carries are stored safely away from the proteins of the cytosol.
2 - Related peptides
There are groups of other peptides with a similar structure to phytochelatin, but where the last amino acid is not glycine:

<table>
<thead>
<tr>
<th>Type</th>
<th>Structure</th>
<th>Has been found in</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytochelatin</td>
<td>(γGlu-Cys)_n-Gly</td>
<td>many organisms</td>
<td>Glutathione</td>
</tr>
<tr>
<td>Homo phytochelatin</td>
<td>(γGlu-Cys)_n-Ala</td>
<td>legumes</td>
<td>Homo glutathione</td>
</tr>
<tr>
<td>Desglycine phytochelatin</td>
<td>(γGlu-Cys)_n</td>
<td>maize, yeasts</td>
<td></td>
</tr>
<tr>
<td>Hydroxy methyl -phytochelatin</td>
<td>(γGlu-Cys)_n-Ser</td>
<td>grasses</td>
<td>Hydroxy methyl glutathione</td>
</tr>
<tr>
<td>Iso - Phytochelatin (Glu)</td>
<td>(γGlu-Cys)_n-Glu</td>
<td>maize</td>
<td>Glutamyl cysteinyl glutamate</td>
</tr>
<tr>
<td>Iso - Phytochelatin (Gln)</td>
<td>(γGlu-Cys)_n-Gln</td>
<td>horseradish</td>
<td></td>
</tr>
</tbody>
</table>

3 – History
Phytochelatin was first discovered in 1981 in fission yeast,[7][8] and was named cadystin. It was then found in higher plants in 1985 and was named phytochelatin. In 1989 its enzyme, phytochelatin synthase, was discovered.
Poly Aspartic Acid

Contents
1 Introduction
2 Properties and structure
3 Synthesis
4 Applications

1 - Introduction
Poly aspartic acid (PASA) is a bio degradable, water-soluble poly amino acid with potential to replace many non-biodegradable polymers. It is used as a pure homo polymer and in various copolymers. In nature PASA exists as fragments of larger proteins with length up to 50 amino acids, so far it was not isolated as a pure homo polymeric material from any natural sources. First isolation of synthetic oligomeric sodium poly aspartate, obtained by thermal poly condensation of aspartic acid, was done by Hugo Schiff in late 19th century. Later it was proposed that thermal polymerization process leads through poly succinimide intermediate. Poly aspartic acid is currently produced on the industrial scale and is available as commercial product in forms of acid and sodium poly aspartate.

Poly aspartic acid
Other names : PASP
Molecular formula \((\text{C}_4\text{H}_5\text{NO}_3)_n\)
Molar mass variable

2 - Properties and structure
PASA is a yellow liquid miscible with water. Due to presence of carboxylic groups it is polyelectrolyte with anionic character.
Naturally occurring PASA fragments consists of α, -linked L-aspartatic acid.\textsuperscript{[2]} In contrast, the repeating unit of synthetic poly aspartic acid may exist in four different isomeric forms depending on the stereochemistry of starting material ( D - and L- aspartic acid) and synthetic procedure leading to α and β links.

3 – Synthesis

There are currently many different synthetic protocols available leading to PASA. In the simplest and the oldest approach aspartic acid is heated to high temperature resulting in water release and the formation of poly succinimide. In the subsequent step this polymer is reacted with sodium hydroxide in water which yields partial cleavage of the succinimide ring. In this process sodium-DL-(α,β)-poly (aspartate) with 30 % α - linkages and 70 % β-linkages randomly distributed along the polymer chain , and racemized chiral center of aspartic acid is produced . There were many catalysts reported for
improving thermal polymerization method. Main benefits from their application is increasing of the conversion rate and higher molecular weight of the product. Poly aspartic acid can also be synthesized by polymerization of maleic anhydride in presence of ammonium hydroxide. High control over repeating unit isomers can be achieved by polymerization of N-carboxy anhydrides (NCA) derivatives, by polymerization of aspartic acid esters or by application of enzyme catalyzed reaction. Pure homo polymers, D- or L- PASA with α- or β-links only, can be synthesized using those methods.

4 – Applications

Poly aspartic acid and its derivatives are environmentally friendly, biodegradable alternative to traditional poly anionic materials, in particular as replacement for poly acrylic acid. PASA has ability to inhibit deposition of calcium carbonate, calcium sulfate, barium sulfate and calcium phosphate salts and can be used as an anti-scalinig agent in cooling water systems, water desalination processes, and waste water treatment operations.\textsuperscript{[18]} In addition and due to its ability to chelate metal ions it provides corrosion inhibition.\textsuperscript{[8]} It can act as a super-swelling material in diaper / feminine-hygiene products and food packaging. It can also be used as biodegradable detergent and dispersant for various applications. There is a broad interest in this material from biomedical and material research community.
Sodium Poly Aspartate

Contents
1 Introduction
2 Polymerization
3 Uses

1 - introduction

Sodium poly aspartate is a sodium salt of poly aspartic acid. It is biodegradable condensation polymer based on the amino acid aspartic acid.

<table>
<thead>
<tr>
<th>Sodium poly aspartate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC name : Poly aspartic acid sodium salt</td>
</tr>
<tr>
<td>Molecular formula : (C₄H₄NNaO₃)ₙ</td>
</tr>
<tr>
<td>Molar mass : variable</td>
</tr>
</tbody>
</table>

2 - Polymerization

The polymerization reaction is an example of a step-growth polymerization to a polyamide and in one practical procedure¹ aspartic acid is simply heated to 180 °C resulting in water release and the formation of a poly(succinimide) with succinimide repeating units. In the subsequent step this polymer is reacted with sodium hydroxide in water which results in partial cleavage of the amide bonds. Two different bonds (α and β) are hydrolyzed resulting in a sodium poly(aspartate) copolymer with 30 % α-linkages and 70 % β-linkages.

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3 - Uses[edit source]

This material can be synthesized in an environmentally friendly way and is biodegradable, thus it is a green alternative to several materials such as sodium polyacrylate used in disposable diapers and agriculture.

In addition and due to its water-solubility and ability to chelate metal ions, poly aspartate is used as a biodegradable anti-scaling agent and a corrosion inhibitor.
Tri Sodium Citrate

Contents
1 Introduction
2 Applications
   2.1 Food
   2.2 Buffer
   2.3 Medical uses

1 - Introduction
Tri sodium citrate has the chemical formula of Na₃C₆H₅O₇. It is sometimes referred to simply as sodium citrate, though sodium citrate can refer to any of the three sodium salts of citric acid. It possesses a saline, mildly tart flavor. For this reason, citrates of certain alkaline and alkaline earth metals (e.g. sodium and calcium citrates) are commonly known as "sour salt" (occasionally citric acid is erroneously termed sour salt).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium citrate</td>
<td></td>
</tr>
<tr>
<td>IUPAC name :</td>
<td>Tri sodium citrate</td>
</tr>
<tr>
<td></td>
<td>Tri sodium 2- hydroxy propane-1,2,3- tri carboxylate</td>
</tr>
<tr>
<td>Other names :</td>
<td>Citrosodine</td>
</tr>
<tr>
<td></td>
<td>Citric acid , tri sodium salt</td>
</tr>
<tr>
<td></td>
<td>Sodium citrate</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>Na₃C₆H₅O₇</td>
</tr>
<tr>
<td>Molar mass</td>
<td>258  g / mol ( water free ),</td>
</tr>
<tr>
<td></td>
<td>294  g / mol ( dehydrate )</td>
</tr>
<tr>
<td>Appearance</td>
<td>White crystalline powder</td>
</tr>
<tr>
<td>Density</td>
<td>1.7 g / cm³</td>
</tr>
<tr>
<td>Property</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Melting point</td>
<td>&gt; 300 °C</td>
</tr>
<tr>
<td></td>
<td>hydrates lose water ca. 150 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>Decomposes</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>42.5 g / 100 ml (25 °C)</td>
</tr>
<tr>
<td>Main hazards</td>
<td>Irritant</td>
</tr>
</tbody>
</table>

2 – Applications

2 – 1 – Food

Sodium citrate is chiefly used as a food additive E331, usually for flavor or as a preservative. Sodium citrate is employed as a flavoring agent in certain varieties of club soda. Sodium citrate is common as an ingredient in Bratwurst, and is also used in commercial ready to drink beverages and drink mixes, contributing a tart flavour.

2 – 2 – Buffer

As a conjugate base of a weak acid, citrate can perform as a buffering agent or acidity regulator, resisting changes in pH. Sodium citrate is used to control acidity in some substances, such as gelatin desserts. It can be found in the mini milk containers used with coffee machines. The compound is the product of antacids, such as Alka-Seltzer, when they are dissolved in water.

2 – 3 - Medical uses

In 1914, the Belgian doctor Albert Hustin and the Argentine physician and researcher Luis Agote successfully used sodium citrate as an anticoagulant in blood transfusions. It continues to be used today in blood collection tubes and for the preservation of blood in blood banks. The citrate ion chelates calcium ions in the blood by forming calcium citrate complexes, disrupting the blood clotting mechanism.

In 2003, Oöpik, et al., showed the use of sodium citrate (0.5 grams per kg of body weight) improved running performance over 5 km by 30 seconds.

Sodium citrate is used to relieve discomfort in urinary tract infections, such as cystitis, to reduce the acidosis seen in distal renal
tubular acidosis, and can also be used as an osmotic laxative. It is a major component of the WHO Oral Rehydration Solution.

It is used as an antacid, especially prior to an anesthesia, for caesarian section procedures to reduce the risks associated with the aspiration of gastric contents.
<table>
<thead>
<tr>
<th>List : Organic Acids Chelating Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelation Therapy</td>
</tr>
<tr>
<td>Chelation</td>
</tr>
<tr>
<td>Clathro Chelate</td>
</tr>
<tr>
<td>Acetyl Acetone</td>
</tr>
<tr>
<td>Amino Poly Carboxylic Acid</td>
</tr>
<tr>
<td>ATMP</td>
</tr>
<tr>
<td>BAPTA</td>
</tr>
<tr>
<td>BDTH2</td>
</tr>
<tr>
<td>Citric Acid</td>
</tr>
<tr>
<td>Cryptand</td>
</tr>
<tr>
<td>Deferasirox</td>
</tr>
<tr>
<td>2,3-Di Hydroxy Benzoic Acid</td>
</tr>
<tr>
<td>2,3-Di Mercapto-1-Propane Sulfonic Acid</td>
</tr>
<tr>
<td>Di Mercapto Succinic Acid</td>
</tr>
<tr>
<td>DOTA (Chelator)</td>
</tr>
<tr>
<td>DTPMP</td>
</tr>
<tr>
<td>EDDHA</td>
</tr>
<tr>
<td>EDDS</td>
</tr>
<tr>
<td>EDTMP</td>
</tr>
<tr>
<td>EGTA (chemical)</td>
</tr>
<tr>
<td>Ethylene Diamine Tetra Acetic Acid (EDTA)</td>
</tr>
<tr>
<td>Etidronic Acid (HEDP)</td>
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<tr>
<td>Fura - 2</td>
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<td>Homo Citric Acid</td>
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<td>Imino di Acetic Acid</td>
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<td>Indo -1</td>
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<tr>
<td>Nitrilo Tri Acetic Acid</td>
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<tr>
<td>Pentetic Acid (DTPA)</td>
</tr>
<tr>
<td>Phosphonate</td>
</tr>
<tr>
<td>Phytochelati</td>
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<tr>
<td>Poly Aspartic Acid</td>
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<tr>
<td>Sodium Poly Aspartate</td>
</tr>
<tr>
<td>Tri Sodium Citrate</td>
</tr>
<tr>
<td>List : Organic Acids Chelating Agents</td>
</tr>
</tbody>
</table>