

Analysis of Synthesis of Heavy Metal Chelating Agent with Four Chelating Groups

Hariom Meena

Research Scholar

University of Technology, Jaipur

Dr. Renu Saxena

Supervisor

University of Technology, Jaipur

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Abstract

Although heavy metals are necessary for many biological activities, such as cell growth and reproduction, biomolecule synthesis, several enzymatic reactions, and the body's immune system, an excessive amount of them can be hazardous. On the basis of theoretical assessments of ligand design, the elements involved in the creation of therapeutic chelating agents are described. Hydroxamate-based arrangement stage chelating chemicals have been created to precisely connect trivalent elements like iron and aluminium within the sight of divalent metals like calcium. These arrangement stage chelating synthetic compounds' iron complexation behaviour has been investigated using UV-Vis spectrophotometric techniques. By acting as chelating agents, these hydroxamate chelators could be used to remediate iron and aluminium overburden. A group of the extremely restrictive chelators have been immobilised on powerful assistance by diverse connections. These chelators have been used to remove aluminium from contaminated TPN components like a calcium gluconate arrangement because of their sturdy backings. Our tars may be able to remove over 90% of the aluminium from commercial calcium gluconate combinations. Emergency rooms will soon adopt this innovation, which removes aluminium from calcium gluconate arrangements by using hydroxamate functionalized gums. Preterm infants and people who are critically ill and need TPN solutions would benefit greatly from this invention.

Keywords: Heavy metal, Chelating agent, Synthesis, Hydroxamate ligands, Chelating groups.

1. INTRODUCTION

The main form of treatment for metal toxicity and overload has been chelation therapy. Chelation therapy removes excess metals from biological systems quickly by using a chelating chemical that combines with metals. The chelating agent removes metal ions from naturally occurring ligands like proteins and transforms them into less dangerous structures that can be quickly eliminated without coming into further contact with the body.

A chelating agent or chelator is a multi-dentate ligand that binds to various coordination sites on a metal particle. The number of coordination sites that a ligand engages is measured by its denticity. Chelating synthetic chemicals bind metal particles even more irreversibly than monodentate ligands. When a metal particle and something like two practical groups of a chelator come together, chelates—heterocyclic rings—are created. An outline of catechol 1.1 (Figure 1) shows that it is a bidentate chelator that joins with metals to form a chelate ring with five members.



Figure: 1. Catechol and its chelation with metals

1.1. Common Chelating Agents: Pharmacology and Toxicology

High solubility in water, resistance to biotransformation, the capacity to access metal storage sites, the ability to maintain chelating activity at bodily fluid pH levels, and the ability to create less toxic metal complexes than the free metal ion are all desirable properties of an ideal chelator.

During World War II, the arsenic-based poison gas Lewisite was the subject of a trial countermeasure known as dimercaprol, a naturally occurring dithiol particle also known as English Enemy of Lewisite or BAL. Numerous naval force members developed severe lead poisoning after the Second World War, which was ultimately linked to their employment painting transport frames. This discussed the use of EDTA as a lead chelating agent for medical applications. BAL has been deemed a doctor's medicine for general metal

intoxication due to its extraordinary potential for treating human arsenic and mercury damage. In the 1960s, meso 2,3-dimercaptosuccinic acid (DMSA), a comparable dithiol with unquestionably less harmful effects, was created from BAL. As a mercury-chelating agent, sodium 2,3-dimercaptopropane 1-sulfonate (DMPS) was developed by experts in the former Soviet Union. Chelation therapy has typically been used to try and reduce a person's body weight of dangerous metals in those with substantial adverse effects and elevated natural markers. Chelating agents can affect the poisonousness of a metal by releasing the dangerous metal generally into urine. A chelating agent that forms a stable complex with a dangerous metal, reducing the nearby danger, can shield organic targets from the metal particle. During complex formation, the iron chelator desferrioxamine (DFOA) completely covers Fe³⁺ surface, preventing free extreme responses that iron may otherwise interfere with. However, a chelator may occasionally expose the metal to the outside air, increasing the metal's toxicity. Instead of protecting the Fe³⁺ particle's outer shell, ethylenediamine-tetraacetic acid (EDTA) shapes an open complex (crate complex) to increase the reactant Fe³⁺ capacity for producing oxidative pressure. The designs of certain chelating agents are depicted in Figure 2.

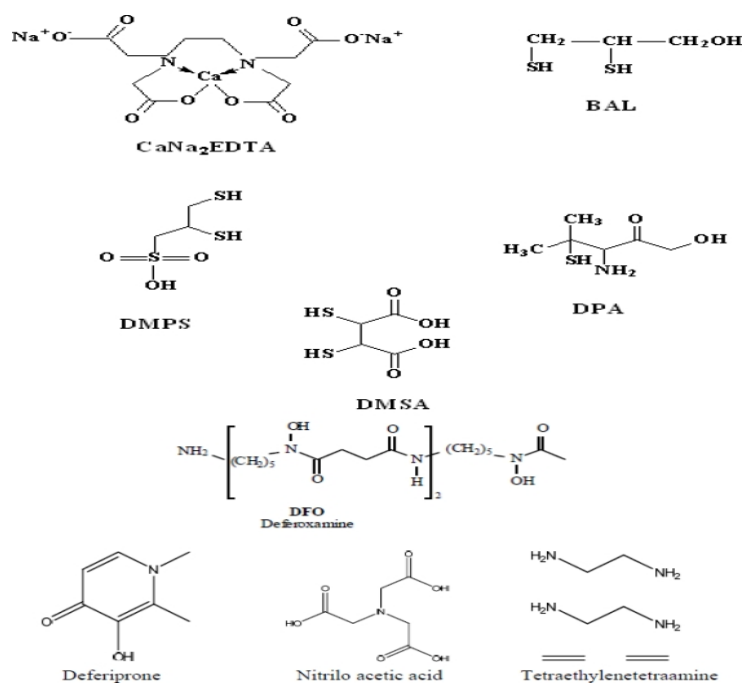


Figure: 2. the compositions of different chelating agents used to treat heavy metal toxicity.

2. LITERATURE REVIEW

Maher Almaqtari and Kh. Al-Azab (2018) Using infrared, mass spectrometry, electronic, mellowing point, and conductivity gauges, we have combined and created new structures of Co(II), Ni(II), and Cu(II) with paracetamol and 1,10-phenanthroline. The ability of the two ligands to function as bidentate chelating agents has been demonstrated. 1,10-phenanthroline coordinates through its two nitrogen particles, whereas paracetamol arranges through the amide bunch's carbonyl cluster and nitrogen molecule. In light of the second electronic ghostly assessments, the buildings have been given an octahedral math. The buildings' capacity to prevent the development of a few gramme positive and gramme negative tiny living forms was evaluated.

Haşim Fatma (2018) The accumulation of maleic anhydride and p-chloroaniline allowed for the delivery of a remarkable p-chlorophenyl maleanilic acid ligand (L). By reacting to metal hexacarbonyl accumulation with bidentate maleanilic acid ligand, new mixed organometallic chelates of the proposed general equation $[M(CO)_4L]$, where M = Cr, Mo, or W, were provided in an idle nitrogen atmosphere. Key tests, FT-IR, mass spectra, 1H -NMR, and warm assessments were used to conceptualise the newly developed unique ligand and its organometallic chelates. The findings suggest that the produced organometallic chelates have an octahedral structure. Human hepatocellular carcinoma cell line hepG-2, human colon disease cell line HCT-116, and human breast cancer cell line MCF-7 were tested in vitro using the free ligand and its chromium chelate (human chest carcinoma). The findings suggested that both the primary ligand and its chelate of chromium had significant anticancer action.

Steam improved ethanol, according to Alejandra Villagran, Gómez, et al. (2018) who over-strengthened Ni impetuses. Wet impregnation and chelating solutions were used to create the impetuses (citrus extract, CA, nitrilotriacetic acid, NTA, and ethylenediaminetetraacetic acid, EDTA). The solids were described using X-ray diffraction, BET explicit surface area, temperature tailored reduction, X-ray photoelectron spectroscopy, and thermogravimetry analysis. After 7 hours of reaction, the catalyst created from EDTA solution was the most effective and distinctive, with a minor quantity of carbon still present. This behaviour was attributed to a more favourable Ni-CeO₂ interaction caused by the tiny NiO molecule size

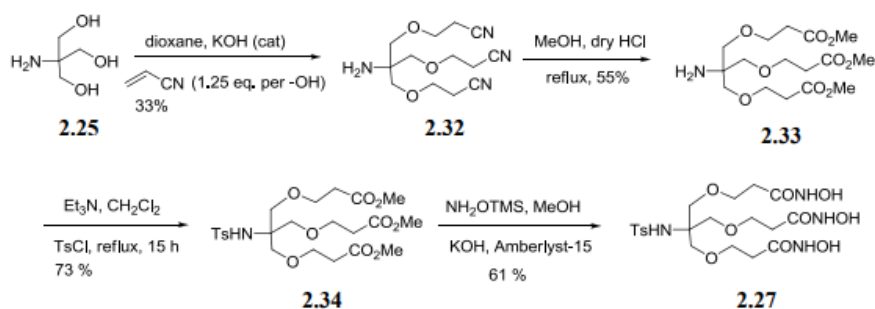
attained with the employment of a chelating agent. Additionally, this specimen displayed the smallest metallic nickel molecule size and a high Ce³⁺/Ce⁴⁺ ratio.

Among others, Memon, Saima, and Memon (2014) Different diketones, salicylaldehydes, or 2-hydroxyacetophenes are combined with various amines to create the Schiff bases. These bases result in stable metal chelates that hold or shine in the UV or conspicuous spectrum of light when mixed with metal and oxo-metal cations. The Schiff bases have been used in spectrophotometry, spectrofluorimetry, gas chromatography, liquid chromatography, and thin electrophoresis to identify metal particles. Schiff's bases are increasingly being used in particle explicit terminals that do research on metal particles. This evaluation covers the chelation characteristics, quick synthesis, and analytical uses of Schiff bases.

3. SYNTHESIS OF NOVEL TRIPODAL TRIHYDROXAMATE LIGANDS

3.1. Synthesis of 222-THA

Spilling and coworkers earlier synthesised the trihydroxamate 222-THA 2.27. (Scheme 1). To create the tris-nitrile 2.32, the tris 2.25 was combined with acrylonitrile in the presence of catalytic amounts of KOH. The triol's poor solubility in dioxane is probably to blame for the low yield of 33%. Recent research has shown that using additional solvents, including acetonitrile, can increase yield. The tris-methyl ester 2.33 was produced by the reaction of 2.32 with refluxing methanolic HCl, and it was then combined with Et₃N and tosyl chloride (TsCl) in CH₂Cl₂ to create the sulfonamide tris-ester 2.34. The ester was reacted with O-trimethylsilyl hydroxylamine (NH₂OTMS) in MeOH to produce hydroxamic acid 2.27. Recrystallization solidified and purified the ligand 2.27, and X-ray crystallography was used to confirm its structure (Figure 3).



Scheme: 1. Synthesis of 222-THA

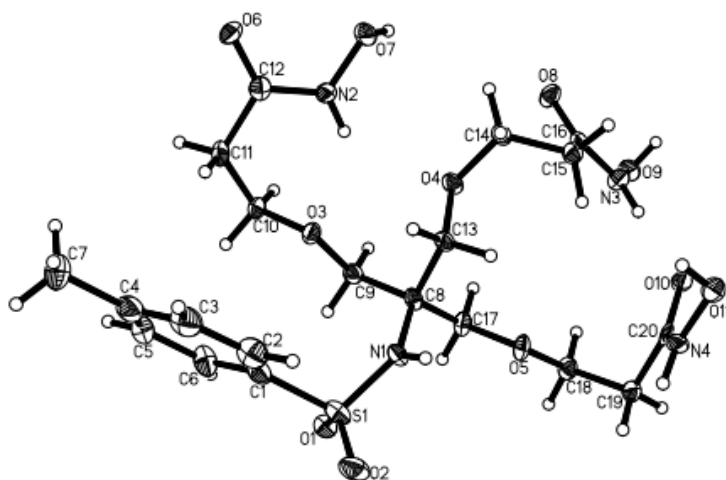
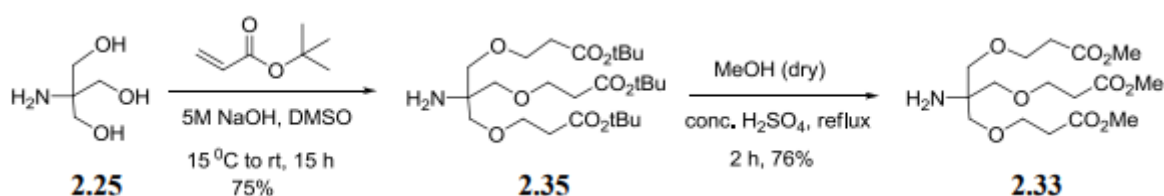


Figure: 3. Crystal structure of 222-THA

A more useful and compelling manufactured pathway from 2.25 to 2.33 has been made (Plan 2). As well as increasing the synthesis, the response conditions were gotten to the next level. The compound tris-tert-butyl ester 2.35 was created in 75% yield by treating the tris 2.25 with tert-butyl acrylate within the sight of 5M NaOH in DMSO. By handling 27 tert-butyl esters with gathered sulfuric acid in dry MeOH, the substance 2.33 was delivered with a 76% yield. This course's general yield of 57% from 2.25 to 2.33 (Plan 2) is fundamentally higher than the first course's yield of 18%. (Plot 1). Following this better manufactured approach, compound 2.33 was made in amounts more noteworthy than 20 g.

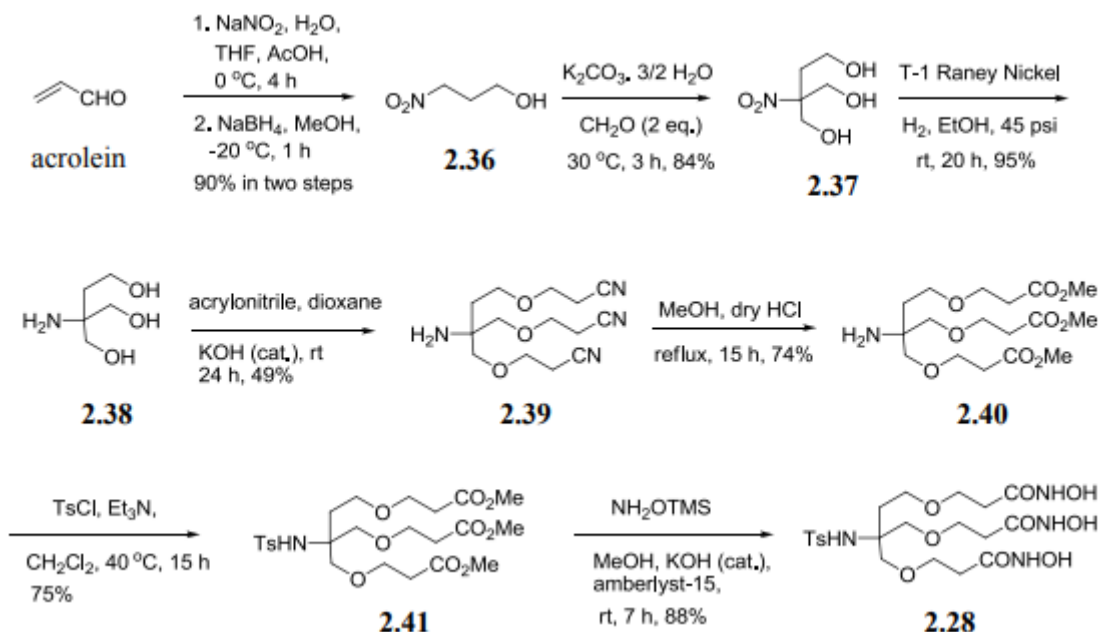


Scheme: 2. a more efficient synthetic route to compound 2.33

3.2. Synthesis Of 223-THA

The unsymmetric tripodal ligand 223-THA 2.28 was mixed with acrolein first (Plan 3). Acrolein was converted into 3-Nitropropanol 2.36 in accordance with the detailed recipe. 3-nitropropanal was created when sodium nitrite was added to acrolein in the presence of acidic acid. As a result, this molecule was reduced with sodium borohydride to give 3-nitro

propanol 2.36 throughout the course of the two cycles, with an overall yield of 90%. By expanding 2.36 to two formaldehyde reciprocals under base catalysis, nitrotriol 2.37 was produced in an 84% yield. The nitro gathering of 2.37 was reduced to an amine by hydrogenation using specifically produced T-1 Raney nickel as an incentive to produce aminotriol 2.38 in virtually measurable yield (see the exploratory segment for the strategy of assembling T-1 Raney Nickel). T-1 Raney Nickel has a very strong pyrophoric character because hydrogen gas delivered during the communication of aluminium and base is constrained on the profoundly permeable nickel surface. Under various hydrogenation circumstances, such as 10% palladium on charcoal with H₂, move hydrogenation with 10% palladium on charcoal, or using ammonium formate and initiated zinc, this reduction proved ineffective. Compound 2.38 was treated with acrylonitrile in the presence of KOH pellets dissolved in dioxane at a synergistic focus to produce tris nitrile 2.39. Again, the unimpressive 49% yield was attributed to the triol's unsatisfactory dioxane solvency. In 74% of the responses to 2.39 in refluxing methanolic HCl, the tris-methyl ester 2.40 was produced. It was then converted into the sulfonamide tris-ester 2.41 in 75% of the responses to 2.40 using tosyl chloride and Et₃N in CH₂Cl₂. Compound 2.41 was converted to the hydroxamate ligand 2.28 in 88% yield by reacting with O-trimethylsilyl hydroxylamine and KOH in methanol and then protonating the product with solid acidic pitch (amberlyst-15). The natural compound was sticky strong and, according to a ¹H-NMR analysis, it was 5% carboxylic acid polluted. This contamination was most likely caused by the hydrolysis of hydroxamic acid groups. The result was improved by passing the compound through a small area of silica covered in quaternary amines. PE-Hatchet IMPUTABLE 2.42 The counter anion in the quaternary amine was derived from acetic acid. Because it has a more pronounced acidity than hydroxamic acid, carboxylic acid requires longer to maintain on such a section. It should be noted that hydroxamic acids cannot be removed using standard stage silica gel chromatography due to a partnership with silica that causes disintegration.

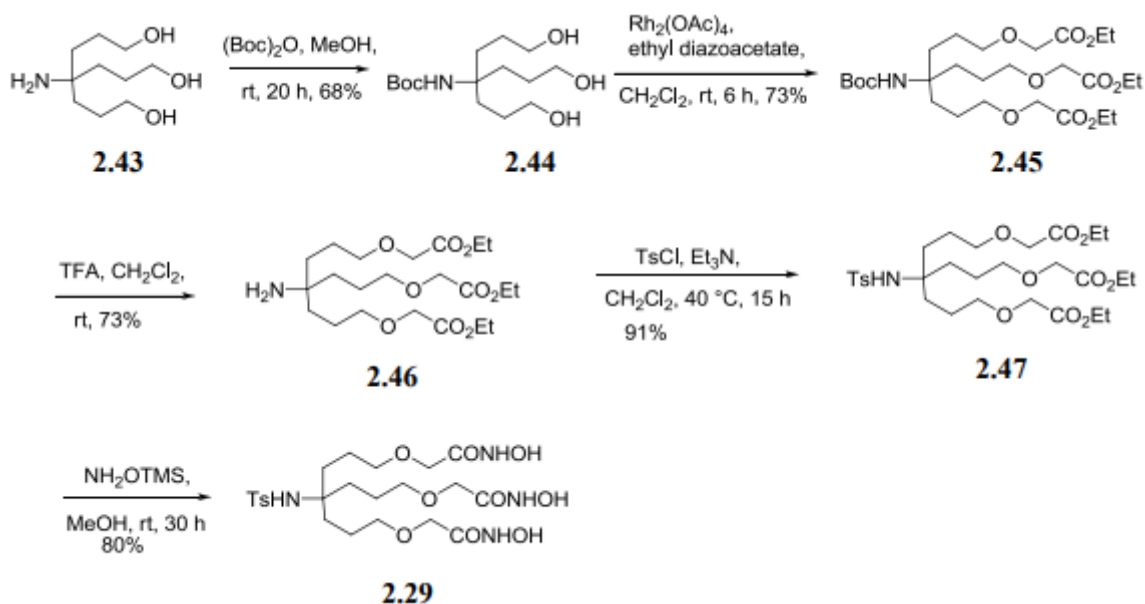


Scheme: 3. Synthesis of 223-THA

3.3. Synthesis of 333-THA

The even tripodal ligand 333-THA was synthesised from commercially available 4-amino-4-(3-hydroxypropyl)heptane-1,7-diol 2.43. (Plan 4). With three hydroxyl groups present, the amino grouping of compound 2.43 was specifically Boc-secured, resulting in compound 2.44 being produced with a yield of 68%. By alkylating hydroxyl groups with ethyl diazoacetate under the influence of rhodium acetic acid derivation, tryster 2.45 was produced in 73% yield. The release of nitrogen gas from ethyl diazoacetate leads to the production of rhodium carbenoid animal types, which embed into the oxygen hydrogen obligation of the liquor. Mono- and di-alkylated compounds were also discovered. The trialkylated item 2.45 was then made by blending these mixes and subjecting them to additional alkylating chemicals. Although this reaction was carried out at 40 °C, other catalysts, such as Cu(acac)₂, were also utilised, however the yield was lower (30%). After Boc-deprotection with TFA, the free amine 2.46 was generated in 73% yield. In 91% of the cases, the amine's re-protection with the tosyl bunch produced the sulfonamidetriester 2.47. Frame 2.29, the 333-THA ligand, reacted with tri-ester and O-trimethylsilyl hydroxylamine with an 80% yield. In contrast to earlier instances of converting esters to hydroxamates, this most recent reaction was carried

out without the catalytic quantity of KOH. Only 2.47 is different from the examples before it, which were methyl esters instead of ethyl esters.



Scheme: 4. Synthesis of 333-THA

Recrystallization from an ethanol/isopropanol mixture (1:1) was used to clean the uninteresting trihydroxamate ligand 2.29, and X-beam crystallography was also used to lay out its design.(Figure 4).

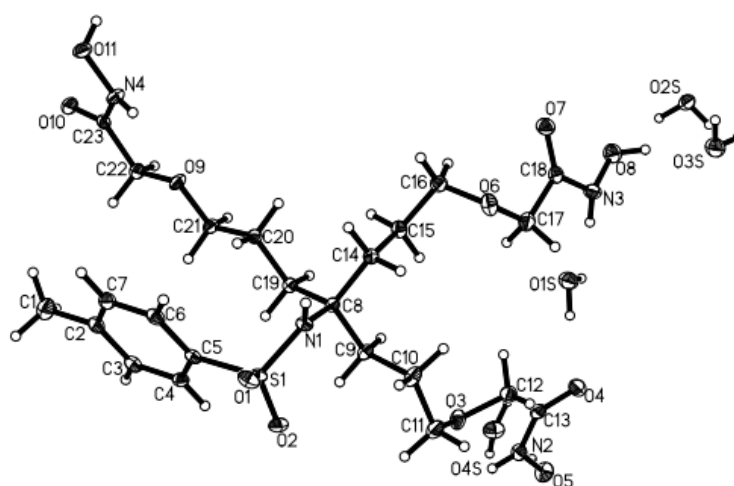


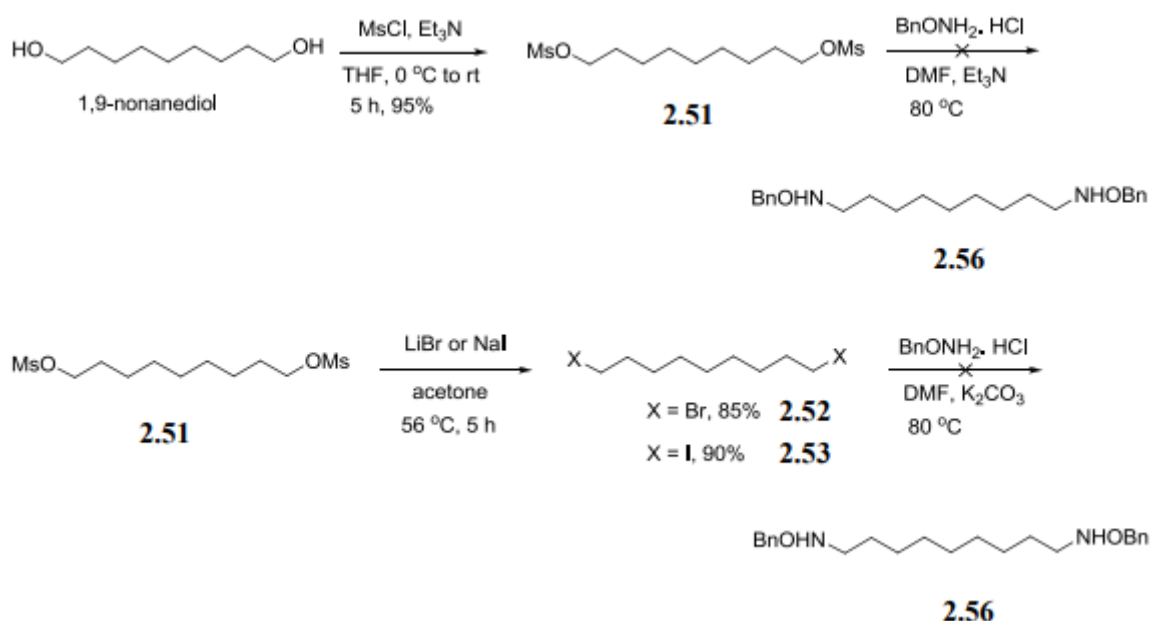
Figure: 4. Crystal structure of 333-THA

4. SYNTHESIS OF NOVEL TETRAHYDROXAMATE LIGANDS

4.1. Synthesis of tetrahydroxamate-A

Tetrahydroxamate-A 2.49 was made through the convergent synthesis of two coupling partners: dicarboxylic acid 2.61 and benzyl protected hydroxylamine 2.57 (scheme 6). (Scheme 7).

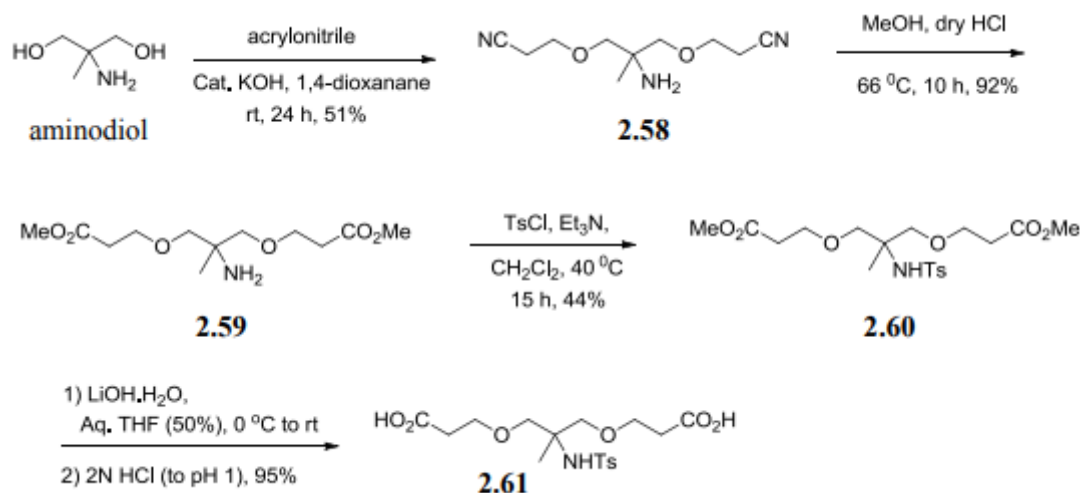
1,9-nonanediol was changed to dimesylate³² 2.51 in the underlying work to combine bis-hydroxylamine 2.56, which can be switched over completely to the coupling accomplice 2.57, by responding with methanesulfonyl chloride within the sight of triethylamine (Plan 5). We couldn't deliver the benzyl safeguarded dihydroxylamine 2.56 in the wake of attempting to nucleophilically break down mesyl groups with O-benzyl hydroxylamine. One more effort to change over dimesylate into 1,9-diiodononane and 1,9-dibromononane by the Finkelstein response was fruitful. When joined with O-benzyl hydroxylamine, diiodo and dibromo nonane didn't create the ideal item.



Scheme: 5. Attempted synthesis of O-benzylhydroxylamine

The ester 2.60 was alkaline hydrolyzed to produce the di-carboxylic acid 2.61 (Scheme 6), which was then protonated with a mineral acid. The Spilling et al. technique, previously disclosed, was used to make ester 2.60. ²⁴ To create the bis-nitrile 2.58, the aminodiol was

combined with acrylonitrile in the presence of KOH in a catalytic quantity. The sulfonamide bis-ester 2.60 was produced by reacting 2.58 with tosyl chloride and Et₃N in refluxing methanolic HCl to produce the bis-methyl ester 2.59.



Scheme: 6. Synthesis of dicarboxylic acid 2.61

4.2. Synthesis of tetrahydroxamate-A with free amine

It was discovered that tetrahydroxamate-A 2.49 has little water solubility, making it difficult to determine this ligand's metal-restraining affinities in fluid arrangement. As a result, we chose to create the ligand 2.63 (Figure 5), which, aside from the presence of an unprotected essential amine bunch, is fundamentally identical to tetrahydroxamate-A. The tosyl cluster in tetrahydroxamate-A protects the amine. The idea is that by having free amine nearby, the ligand and associated trivalent metal complex will be easier to dissolve in water.

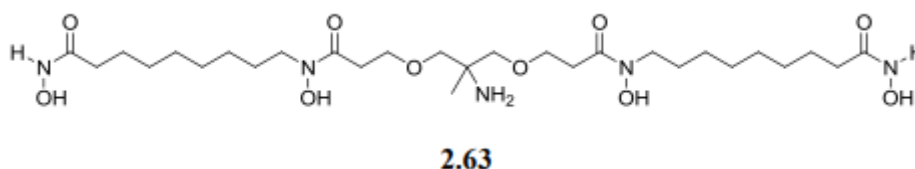


Figure: 5. Tetrahydroxamate-A (free amine)

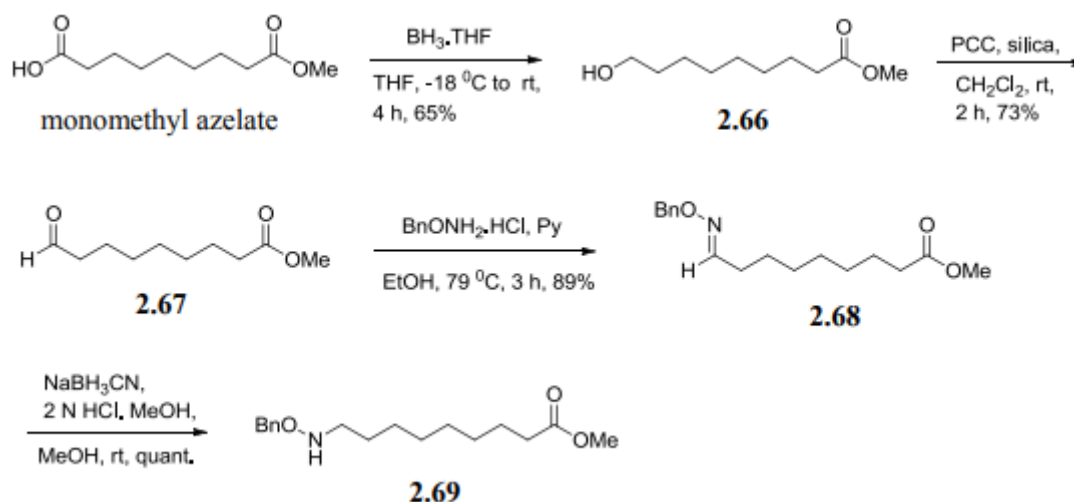
Sodium amalgam and dibasic sodium phosphate in MeOH were used to try and deprotect the tosyl group from the ligand 2.49, but only breakdown products were produced. The majority of tosyl deprotection techniques described in the literature use difficult reaction

circumstances. Compound 2.49 might not endure such reaction conditions. Therefore, we made the decision to add a protective collection to the amine that can be easily removed at the end of the synthesis. Cbz-seemed to be a respectable rival because it could be successfully deprotected with benzyl groups by direct hydrogenolysis at the final stage of production.

Synthesis of tetrahydroxamate-B

Di-carboxylic acid 2.61, which was utilized in the synthesis of tetrahydroxamate-A, was joined with hydroxylamine 2.69 to make tetrahydroxamate-B.

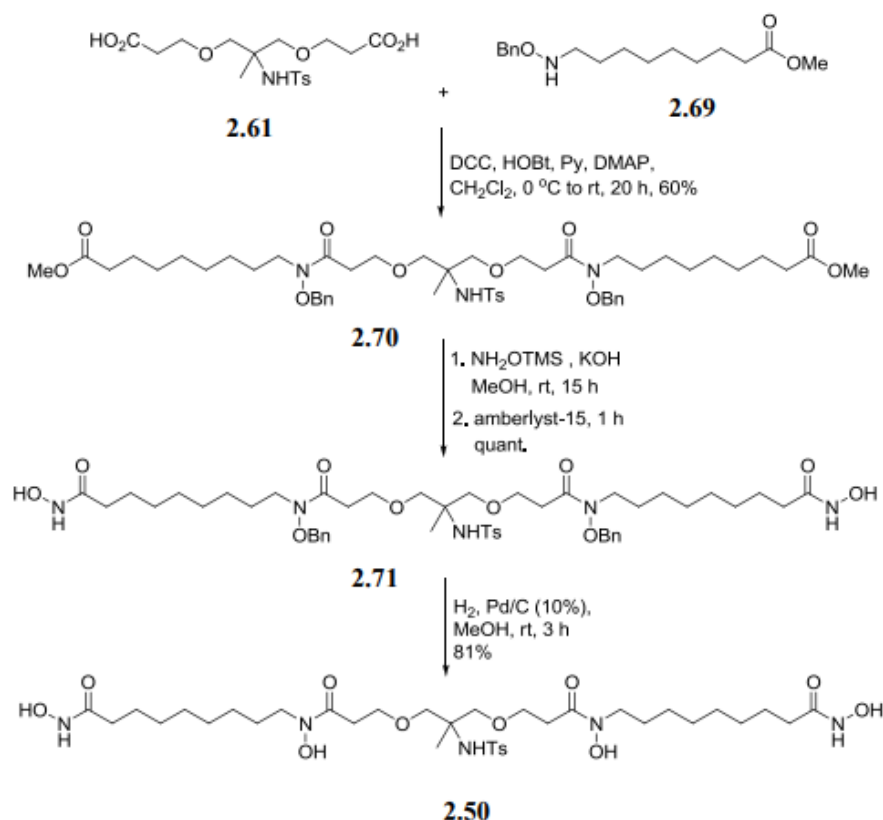
Beginning material for the hydroxylamine 2.69 synthesis was monomethyl azelate (Plan 9). Following a recorded procedure, monomethyl azelate was oxidized to deliver the aldehyde 2.67. Monomethyl azelate's carboxylic acid gathering was specifically changed over utilizing borane in THF to a liquor within the sight of an ester bunch, yielding liquor 2.66. To make the oxime 2.68 in 89% yield, the liquor gathering of compound 2.66 was oxidized back to aldehyde 2.67, which was then responded with pyridine and O-benzylhydroxylamine hydrochloride in refluxing ethanol. Sodium cyanoborohydride decrease of the oxime came about in quantitatively 2.69 of benzyl-safeguarded hydroxylamine.



Scheme: 9. Synthesis of O-benzylhydroxylamine

The resulting DCC (Plan 10) response between hydroxylamine 2.69 and di-carboxylic acid 2.61 created benzyl safeguarded hydroxamic acid dimethyl ester 2.70 in 60% yield, which was in this manner sanitized by chromatography. The synthetic 2.71 was then delivered in a

quantifiable yield by responding the ester groups of compound 2.70 with O-trimethylsilyl hydroxylamine. Tetrahydroxamate-B 2.50 was created by hydrogenolyzing the benzyl- safeguarded hydroxamic acid groups of 2.71. Tetrahydroxamate-B is more dissolvable in water than tetrahydroxamate-A, most probable since it has terminal hydroxamic acid groups.



Scheme: 10.O-benzylhydroxylamine and dicarboxylic acid combine to create tetrahydroxamate-B in the end.

5. CONCLUSION

The agents utilised for this purpose have the capacity to chelate metals, which can be particularly helpful for their antioxidant characteristics. Antioxidants are essential for reducing ROS's harmful effects and oxidative damage. One of the most used techniques in food, biological, and pharmaceutical applications is metal chelating activity. Five high affinity trivalent metal chelators are designed and synthesised after detailed structural analysis of literature examples of natural and synthetic siderophores. Two of these were dipodal tetrahydroxamates, tetrahydroxamate-A 2.49, while the other two were tripodal

trihydroxamates, 222-THA 2.27, 223-THA 2.28, and 333-THA 2.29. To improve its solubility in water, compound 2.63, which has a terminal primary amine group, slightly modified the structure of tetrahydroxamate-A 2.49.

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