Epoxyaconitic Acid as Prospective Capping Ligand for Magnetite Nanoparticles: Synthesis and Complexation with Magnetite

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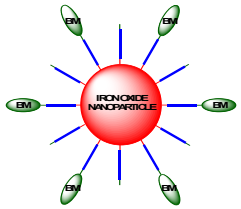
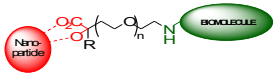
Abstract

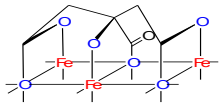
The purpose of this research is the synthesis of a novel organic ligand based on *trans*-aconitic acid. After the successful synthesis of epoxyaconitic acid, a complex with the ligand and the magnetite nanoparticles was created. At each step of the process, the structure of the intermediates was analyzed in a variety of manners. ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and dynamic light scattering have been used to confirm the structure of the intermediates and the final product. The final complexation of epoxyaconitic acid with magnetite has been discussed.

Background

The overall purpose of this project is the development and synthesis of novel MRI-contrast and delivery agents based on iron oxide nanoparticles. Gadolinium-based MRI contrast agents have a high T1 relaxivity value and are currently in use. However, they have toxic side effects, and it would be useful to replace them with new, iron oxide-based MRI contrast agents. It was found by NMR relaxivity measurements that iron oxide might have a comparable relaxivity, so research now focuses on functionalizing the nanoparticles and making them biocompatible. As shown on the scheme below, an organic ligand forms a complex with the iron oxide nanoparticle. The structure of complex between iron oxide and citric acid has been proposed in our earlier work. Several carboxylic acids have been proposed as potential ligands, and future work involves the synthesis of organic ligands based on modified poly α-hydroxycarboxylic acids. Then, various biomolecules can be attached to the ligand, which functionalize the complex.







BINDING OF CITRIC ACID ON IRON OXIDES SURFACE

Selection of the precursors

Two important aspects in ligand design for the MRI contrast and delivery agents in this research are:

the formation of a bond between iron oxide and ligand that is strong enough to survive in the application environment;

the designed material should be biocompatible.

Poly α-hydroxycarboxylic acids, such as citric acid, were proposed as ligands due to formation of strong bonds with iron oxide and natural origin of them.
Trans-aconitic acid was chosen as a prospective precursor for the synthesis of a ligand based on modified citric acid.

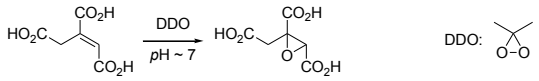
Synthetic Approach via Triethyl *trans*-Aconitate

The first step in this synthesis was protection of carboxylates via esterification with ethanol. The acid-catalyzed esterification of *trans*-aconitic acid was completed using an azeotropic distillation of formed water. Triethyl aconitate was produced with a yield of 32%.

Two methods were used to attempt to epoxidize the triethyl aconitate. The first method utilized silver (I) oxide and iodine. However, the epoxidized product was not detected. The other method attempted was epoxidation by dimethyldioxirane (DDO). However, the epoxidized product was not detected by mass spectrometry.

Had the epoxidation of triethyl aconitate been successful, the next step would have been hydrolysis using potassium hydroxide. Then, this product would be used for coating the iron-oxide nanoparticle.

Synthetic Approach via *trans*-Aconitic Acid

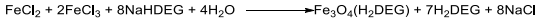


Dimethyldioxyrane (DDO) is reported to be inefficient reagent for the epoxidation of electronically poor double bonds such as in case of conjugated carboxylates. However, during this study it was found that in case of *trans*-aconitic acid epoxydation with DDO leads to epoxyaconitic acid. The procedure includes generating DDO *in situ* in the presence of *trans*-aconitic acid and a buffer solution (*p*H ~ 8). After recrystallization, epoxyaconitic acid was obtained with a yield of 60%. Using NMR spectrometry, the purity of epoxyaconitic acid was determined to be greater than 95%.

Reasonable explanation: Epoxidation by DDO was successful because deprotonation of the carboxylic acid groups takes place in the buffer solution. This can lead to decreasing of the *–C* -effect of the carboxyl groups that are not strong acceptors anymore, as opposed to the ester groups.

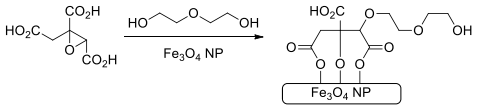
Complexation of Epoxyaconitic Acid with Magnetite

Magnetite colloid was prepared according to the scheme below:



This colloid was oxidized using oxygen gas to produce an air-stable form according to reaction:

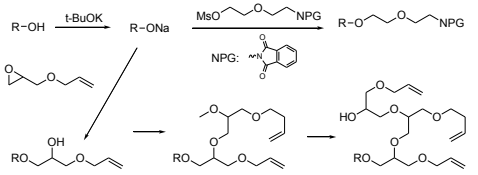
A 0.1 M solution of epoxyaconitic acid in anhydrous diethylene glycol (H_2DEG) was mixed with colloid of magnetite in a ratio of 2 moles of ligand per 5 moles of iron:



The obtained complex was isolated in the form of brownish powder, which was strongly magnetic. This complex was washed multiple times and accumulated on a magnet with the mother liquor being discarded each time to ensure that unbound organic compounds have been removed. The solid was then treated with basic aqueous solution in order to separate the organic ligand from iron oxide for further analysis. ESMS and NMR analysis proved that diethylene glycol was present in the mother liquor. There were certain peaks in both spectra that could belong to hydroxycitric acid; however integral intensity ratio in proton NMR spectrum was too high for the diethylene glycol peaks. With respect to ESMS, there was no molecular ion peak for the adduct of diethylene glycol and hydroxycitric acid, but there was a peak of (M+1)-28 in positive mode. This peak would correspond to the molecular ion that has lost a carbon monoxide molecule. The fragmentation pattern for this peak resembles the fragmentation for peaks of epoxyaconitic acid, which might be indirect evidence for the hydroxycitric acid-diethylene glycol adduct formation on the surface of the iron oxide nanoparticles.

Future Work

If the synthesis of the magnetite complex with epoxyaconitic acid is successful, the next step would be the incorporation of a different type of bridge such as polyetheleneglycol fragments with amino group on the end or branching with AGE. This would serve as the site where biomolecules could be attached.



Acknowledgements

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