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Stereochemical Analysis of Porphyrins and Chelators to Control Free Radical

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Abstract

Photodynamic Therapy, or PDT, is a method of cancer treatment which uses a photosynthesizer, oxygen, and a light of a determined frequency. Normally, reactive oxygen species are damaging to normal cells around them and therefore should be eliminated, but their destructive properties also allow them to eliminate cells harmful to the body, such as cancer cells. In photodynamic therapy, the high reactive oxygen species interact with biomolecules and produce oxidative radicals, which is cytotoxic in action. The free radicals then destroy the tumor cell through inducing apoptosis or necrosis.

In this study, various molecules that can help remove reactive oxygen species from normal cells and the different isomers of porphyrin and cyclodextrin, photosynthesizers, were analyzed and compared to reveal which compound would work best. Also, to eliminate the toxic levels of redox metals in nerve cells, especially copper and iron, through selective chelation, this research investigated various iron chelators (EDTA, DTPA among others) from multiple dimensions, including optimization energy, electrostatic potential map, and dipole moment.

Introduction

Due to limitless combinations of metals and linkers in the chelators, pharmaceutical properties of chelators can be tuned for specific applications. Because the molecules exhibit exceptionally high surface areas with large pore sizes, the main application that is used in this project is loading and controlling release of several drug molecules for cancer treatment. In this case, the molecules can be used as drug delivery vehicles as cell-targeting molecules.

Photodynamic therapy has been proved to be helpful in the treatment of diseases such as cancer and many other nonmalignant diseases. When a light between a certain frequency hits the ground state photosynthesizer that is accumulated inside a tumor cell, the molecules enter an excited triplet state and go through photochemical reactions to form highly reactive oxygen species. Reactive oxygen species are unstable molecules containing oxygen and unpaired electrons that can easily react with other molecules. Some examples of them include peroxides, superoxides, hydroxyl radicals, or singlet oxygen. Reactive oxygen species are unstable molecules containing oxygen and unpaired electrons that can easily react with other molecules. Some examples of them include peroxides, superoxides, hydroxyl radicals, or singlet oxyge

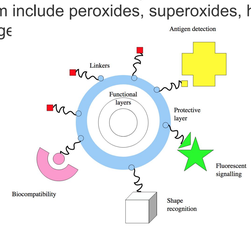


Figure 1.
Attachments on nanoparticles make them more biocompatible

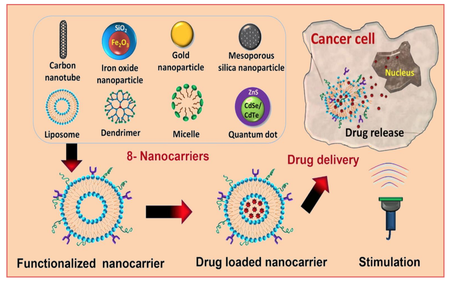
First, the free radicals and Photodynamic therapy and nanoparticles for the potential treatment of diseases such as cancer and many other nonmalignant diseases will be studied. In this project, molecules for reducing heavy metals (that cause Reactive Oxygen Species) using EDTA/DTPA, porphyrin in removing ROS affected cells, and Cyclodextrin in removing ROS affected cells will be studied and modeled using molecular editing programs. 3D structures of the molecule will be built using the Avogadro software and 3 properties will be analyzed: the optimization energy, dipole moment, and electrostatic potential map. Lower optimization energy corresponds to a higher thermodynamic stability of that molecule. The dipole moment helps in predicting the reactivity of conductivity of each molecule, and the electrostatic potential map will help predict the behaviors of complex organic molecules. Through studying these three properties with Avogadro, the molecule's effectiveness in removing reactive oxygen species(ROS) affected cells will be accessed, and potentially determine the best compound to be used for such roles.

Materials and Method

In this paper, open-source molecular editing programs such as Avogadro and Gaussian with an auto-optimization feature that is able to calculate the theoretical values of a molecule's physicochemical properties are used to model the nano-scaled compounds.

The program enables us to build virtually any biochemical compounds. The thermodynamic stability or safety of the nanoparticles can be assessed by optimal Enthalpy(kJ/mol) and the activity of the compounds are determined by the values of Dipole Moment(DM, Debye) and Electrostatic potential maps(EPMs).

Background and Theories



Backgrounds and Theories - Computational Biochemistry

A. Optimization Energy
The Auto Optimize tool in the Avogadro software continuously optimizes the molecular geometry of constructed molecules with the use of Universal Force Field in reproducing the structural features of each element. An interactive interface allows users to manipulate a molecule as the Auto Optimize tool continues to optimize the molecular geometry until dE equals 0. The Opt. E is the minimum potential energy that the molecule can reach in its most optimized, stable form. Generally speaking, lower optimization energy corresponds to higher thermodynamic stability.

B. Dipole Moment
The dipole moment value can be obtained from the molecular properties of each molecule in debye. Dipole moments occur when electrons are shared unequally between or among molecules, and the value represents the size or magnitude of this dipole occurring in the molecule. The dipole moment helps in predicting the reactivity or conductivity of the molecule as well.

C. Electrostatic Potential Map
The electrostatic potential map provides a visual representation of relative electron concentrations in different areas of the molecule, demonstrating the overall distribution of electron charges over the entire molecule. In Avogadro, red represents areas of the greatest electron densities while blue represents areas of the least electron densities. Electrostatic potential maps also show other charge related properties of molecules, as well as visualizing the approximate size and 3D shape of molecules. They can also help predict the behaviors of complex organic molecules. With electrostatic potential maps, electron charge distribution over a molecule depends on the electronegativity of each atom and bond characteristics

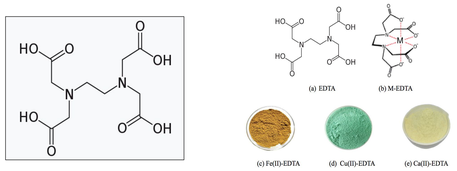
Materials and Methods
The computer software Avogadro was used to model various chelators that were potential candidates for iron chelation therapy in the brain. The molecules were assessed for thermodynamic stability, reactivity/conductivity, and polarization. Thermodynamic stability could be measured through optimized energy. Generally, as optimized energy decreased, thermodynamic stability increased. Reactivity/conductivity was measured through the dipole moments and may act as a good indicator of how the molecule may interact with surrounding particles in vivo. Lastly, electrostatic potential maps were used to visualize the polarization and assess the reactivity level of each molecule.

Photodynamic therapy
Porphyrins have been evaluated in the context of photodynamic therapy (PDT) since they strongly absorb light, which is then converted to energy and heat in the illuminated areas.[1] This technique has been applied in macular degeneration using verteporfin. PDT is considered a noninvasive cancer treatment, involving the interaction between light of a determined frequency, a photo-sensitizer, and oxygen. This interaction produces the formation of a highly reactive oxygen species (ROS), usually singlet oxygen, as well as superoxide anion, free hydroxyl radical, or hydrogen peroxide.[2] These high reactive oxygen species react with susceptible cellular organic molecules such as; lipids, aromatic amino acids, and nucleic acid heterocyclic bases, to produce oxidative radicals that damage the cell, possibly inducing apoptosis or even necrosis.[3]

Data / Results

EDTA Derivatives

EDTA can be produced in a variety of different grades and compositions based upon the requirement of the uses. Metal-EDTAs are extensively used as a chelating agent due to its ability to sequester metal ions. Within biofluid, the carboxylic acid functional groups lose hydrogen to their surroundings, forming a highly electronegative COO^-. Due to redox-active metals' positive electrostatic potential, they are attracted to these functional groups, rendering EDTA as an effective chelator.



(a) EDTA in its natural form. (b) A metal particle inside a chelate. (c), (d), and (e): metal-EDTAs are extensively used as a chelating agent due to its ability to "sequester" metal ions.

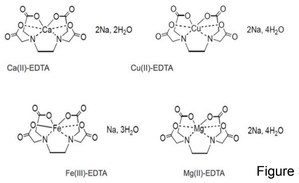
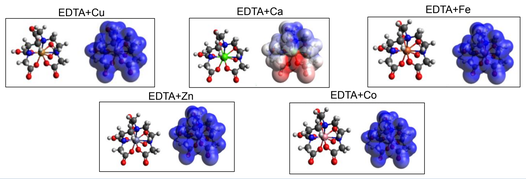


Figure 3. Various types of EDTA chelators

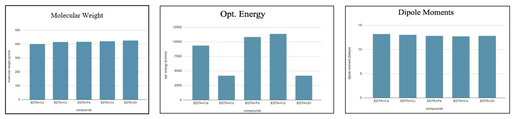
Optimized Images

To define the efficiencies of the nanoparticles, thermodynamic stability can be measured by the optimized energy of the molecule. The smaller the optimized energy, the better its thermodynamic stability.



Compounds (Chelators)	Opt. Energy (kJ/mol)	Dipole Moments (Debye)	Chemical Formula	Molecular Weight (g/mol)
EDTA+Ca	9364.84	13.188	$C_{10}H_{12}CaN_2O_{10}$+	401.340
EDTA+Cu	4165.27	13.021	$C_{10}H_{12}CuN_2O_{10}$+	414.808
EDTA+Fe	10838.5	12.851	$C_{10}H_{12}FeN_2O_{10}$+	417.107
EDTA+Co	11345.3	12.744	$C_{10}H_{12}CoN_2O_{10}$+	420.195
EDTA+Zn	4195.48	12.816	$C_{10}H_{12}N_2O_{10}Zn$+	426.642

Table 1. Optimized energy, dipole moment, chemical formula, and molecular weight of different EDTA metal chelators.

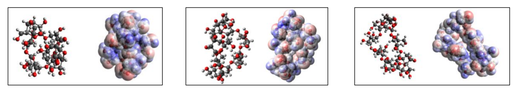


The graph shows that the dipole moments tend to decrease as molecular weight increases.

Figure 9. Graphs displaying the molecular weights, optimized energies, and dipole moments of various metal chelators.

Cyclodextrin

Cyclodextrins have a hydrophobic interior and hydrophilic interior, which allows it to form complexes with other hydrophobic compounds. The cyclodextrins combined with another hydrophobic compound are able to enter body tissues and release biologically active compounds in specific conditions. The release of biologically active compounds depend on the pH change of water solutions(breaks the hydrogen/ionic bonds between host and guest molecules), heating(to disrupt complex structure), or enzymes(cleaving the alpha-1,4 linkages between glucose monomers). Of cyclodextrins, the alpha, beta, and gamma cyclodextrins are being widely used to deliver various drugs such as hydrocortisone or prostaglandin. It helps the drug to be soluble to bodily fluids and be more stable.



alpha-Cyclodextrin

1. Optimization Energy = 15526.8 kJ/mol
2. Dipole moment = 5.439

beta-Cyclodextrin

1. Optimization Energy = 10007.6 kJ/mol
2. Dipole moment = 10.386

gamma-Cyclodextrin

1. Optimization Energy = 11932 kJ/mol
2. Dipole moment = 6.269

Data / Results

Porphyrin

Photodynamic therapy

Porphyrins have been evaluated in the context of photodynamic therapy (PDT) since they strongly absorb light, which is then converted to energy and heat in the illuminated areas. This technique has been applied in macular degeneration using verteporfin. PDT is considered a noninvasive treatment, involving the interaction between light of a determined frequency, a photo-sensitizer, and oxygen. This interaction produces the formation of a highly reactive oxygen species (ROS), usually singlet oxygen, as well as superoxide anion, free hydroxyl radical, or hydrogen peroxide. These high reactive oxygen species react with susceptible cellular organic molecules such as; lipids, aromatic amino acids, and nucleic acid heterocyclic bases, to produce oxidative radicals that damage the cell, possibly inducing apoptosis or even necrosis.

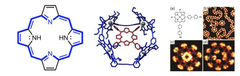
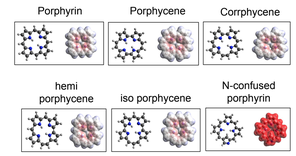


Figure 13. The 18-electron cycle of porphyrin
(https://en.wikipedia.org/wiki/Porphyrin)

Figure 14. Various reported Isomers of porphyrin
(https://en.wikipedia.org/wiki/Porphyrin)

The 18-electron cycle of porphyrin, the parent structure of porphyrin, highlighted. (Several other choices of atoms, through the pyrrole nitrogens, for example, also give 18-electron cycles.)

Compounds (porphyrins)	Opt. Energy (kJ/mol)	Dipole Moments (Debye)	Chemical Formula	Molecular Weight (g/mol)
Porphyrin	652.142	0.048	$C_{20}H_{14}N_4$	310.352
N-confused porphyrin	752.275	18.602	$C_{20}H_{14}N_4$	310.352
Hemiporphycene	772.52	0.256	$C_{20}H_{14}N_4$	310.352
Porphycene	832.034	0.198	$C_{20}H_{14}N_4$	310.352
Corphycene	835.439	0.394	$C_{20}H_{14}N_4$	310.352
Isoporphycene	981.56	0.288	$C_{20}H_{14}N_4$	310.352



Compounds	Opt. Energy (kJ/mol)	Dipole Moments (Debye)	Chemical Formula	Molecular Weight (g/mol)
alpha-Cyclodextrin	15526.8	5.439	$C_{36}H_{60}O_{30}$	972.8
beta-Cyclodextrin	10007.6	10.386	$C_{42}H_{70}O_{35}$	1135
gamma-Cyclodextrin	11932	6.269	$C_{48}H_{80}O_{40}$	1297.1
Porphyrin	1831.35	1.187	$C_{20}H_{14}N_4$	310.4
Porphycene	310.352	0.737	$C_{20}H_{14}N_4$	310.4
Corrphycene	601.8	1.374	$C_{32}H_{34}N_4O_4$	538.6
Hemi Porphycene	600.361	2.333	$C_{20}H_{14}N_4$	310.4
Iso Porphycene	623.947	1.355	$C_{20}H_{14}N_4$	310.4

Table 3. Optimized energy, dipole moment, chemical formula, and molecular weight of the molecules

Discussion and Conclusion

The effective delivery of chemotherapeutics to the tumor site remains a significant challenge for many difficult to treat cancers. Nanotherapeutics offer considerable promise in this area as they show higher tumor uptake, increased efficacy and reduced toxicity compared to their small molecule counterparts. As stability and safety are proved for these new medical nano-molecules, they can actively replace traditional drugs. In general, these highly mixed metal compounds perform better than single metal compounds. However, optimization energy increases. In order to find the optimal molecules, one must take into consideration both stability and complexity. Chelation therapy is a potentially highly effective form of treatment for cancers, and the proper molecule is needed to perform this task of reducing metal ion levels that can be harmful by producing ROS and damaging cells.

In this paper, analogues of porphyrin and cyclodextrin were modeled, analyzed and compared to reveal which compound would work best. To reduce the toxic levels of redox metals, selective chelation was studied through iron chelators to check thermodynamic factors including optimization energy, electrostatic potential map and dipole moment. Also, potential iron chelators were examined through the lens of thermodynamic stability and reactivity. This took the form of optimization energy for stability and dipole moment as well as electrostatic potential map (EPM) for reactivity. Generally, lower optimization energy corresponds to higher stability; however, comparisons across different classes of molecules should be done with caution. Higher dipole moments and colorful EPM corresponds to higher reactivity.