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Physicochemical Characteristics Polyphenols as Antioxidants

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Abstract

The aim of this study was to assess the physicochemical characteristics and antioxidant activity phenolic compounds. Phytoncide extracts such as terpene, essential oils and flavonoid from trees have shown antioxidant effects. Polyphenols are a large family of naturally occurring organic compounds characterized by multiples of phenol units.

Many of them have been found in plant-based foods and some are structurally and functionally related to flavonoids phenolic compounds. In this project, thermodynamic and stereochemical properties of several types of biochemical molecules that can be used as a biological antioxidant were studied. Computational and biomedical simulations were used, and have been proven useful in assessing the physicochemical stability of molecules. Molecular editing programs were used to model, optimize, and compare the resulting molecular optimization energies of the phenolic compounds.

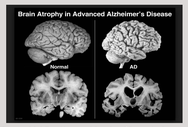
Introduction

Alzheimer's disease (AD) is characterized by its step by step deterioration with periods of stability, punctuated with rapid decline in cognitive function. Such deterioration involves the loss of neurons and synapses in the cerebral cortex and certain subcortical regions of the brain.

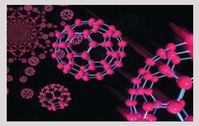
This loss causes gross atrophy of the affected regions; which includes degeneration of the temporal and parietal lobe, parts of the frontal cortex and cingulate gyrus, and eventually a reduction in the respective regions of the brain.

Computational biomedical simulation technology provides an alternative method for future solution of AD. In recent years, potential solutions in applications-related nanotechnology use nanofullerene complexes, due to their ability to virtually attach large quantity of proton H. Multiple pathways through oxidative stress can produce cell injury in the human brain.

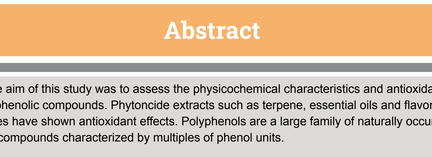
Oxidative stress is the earliest symptom of AD. Excessive accumulation of Reactive Oxygen Species (ROS) in brain caused by simultaneous dys-functioning of a number of mechanisms results in AD. ROS also results in major damage to proteins and lipids by increasing lipid peroxidation and causing unwanted oxidation of proteins as well as nucleic acids.



Normal/ AD affected brains*(Google image)*



Fullerenes*(Google image)*



Gd-Fullerene complex*(Google image)*

Problem

Uncontrolled radical reactions from ROS and beta-amyloid cause AD. However, new medical nano-molecules are not actively able to replace traditional drugs as their stability and safety are not proved.

Objective

The optimization energy, stability of fullerenes, polyhedral boron compounds, and other complexes were measured when combined with carboxylic and hydroxyl groups to analyze their aptitude for medical usage in the treatment of AD.

Hypothesis

The hypothesis of our research is that there are better and safer chemical compounds and fullerene derivatives with less optimization energy.

The analysis of thermodynamic stability, electron properties of fluorescent functionalized fullerenes, PC61BA-(Gd-DO3A), and other nanoparticles will result in establishing the exohedral molecule as an effective contrast agent.

Materials and Method

- Chemcraft and Avogadro are molecular editing programs with an auto-optimization feature that determines the theoretical values of the structure's atomic properties.
- They allow users to build virtually any molecule with the optimized geometry according to various force field options.
- The first factor is thermodynamic stability. This factor can be measured by the optimized energy of the molecule. The smaller the optimized energy, the better its thermodynamic stability.
- The second factor is reactivity, activity, or conductivity. This factor can be measured by the dipole moment. The higher the dipole moment is, the better reactivity the molecule has.
- The third factor is electrostatic potential map. A colorful electrostatic potential map means that the molecule has a higher electrostatic potential, which leads to the conclusion of high reactivity.

Chemiluminescence

Solutions 0.2 g luminol added	Table Vinegar+ Water (5%)	Water (control)	Water + Baking Soda($NaHCO_3$)	Water + Aqueous Fullerene Derivative	Water + Hydrogen Peroxide
LRT(min)	1.22	3.25	4.25	2.05	4.21

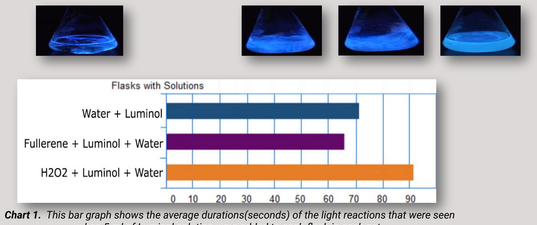
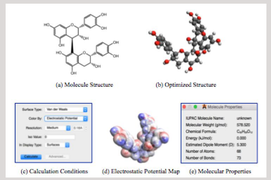


Chart 1. *This bar graph shows the average durations(seconds) of the light reactions that were seen when 5 ml of Luminol solution were added to each flask in each set.*

This proves the original hypothesis that objects that are treated with oxidizing solutions (in this case, hydrogen peroxide), which have the highest number of reactive oxygen species, will have the highest amount of chemiluminescence emitted from them.

Polyphenol and Polyhedral Boron Compounds as Potential Diagnostic and Therapeutic AD Agents

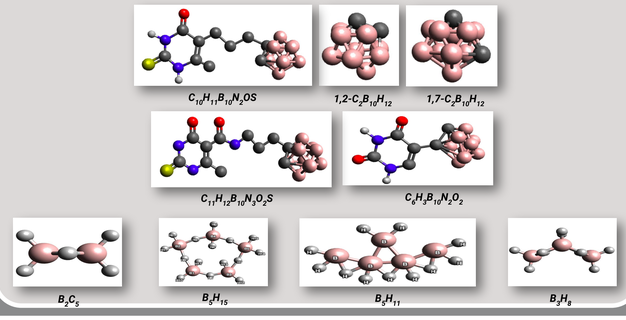


Compound	Energy
cis-resveratrol	165.843
trans-resveratrol	111.385
cis-piceid	243.138
trans-piceid	190.498

Molecules	Measured Enthalpy (kJ/mol)
$C_{10}H_{11}B_{10}N_2OS$	7022
$1,2\text{-}C_2B_{10}H_{12}$	4930
$1,7\text{-}C_2B_{10}H_{12}$	4930
$C_{11}H_{12}B_{10}N_3O_2S$	8732
$C_6H_3B_{10}N_2O_2$	8011
B_5H_{11}	423

In studying the use of boron in human systems, there are debates supported by conflicting evidence of whether the use of boron is safe and effective. While there are only small numbers of studies on the human-use in safety and effectiveness of boron, the majority of which are optimistic, hormone regulation, improving cognitive function, and osteoarthritis have proven to be the consequences of using boron in human systems.

Table 6. *Optimized energy of boron complexes*



Stability and Optimization Energy of Fullerenes and the Use of Functionalized Fullerenes as Contrast Agents

- Fullerenes react with ROS to give off hydrogen atoms that helping stabilize ROS as fullerenes have OH bonds.
- As the fullerene's energy (enthalpy) increases, the hydrogen atom in OH bonds easily fall out and bond with ROS.
  - The more OH bonds there are, the more hydrogen it can give off under certain solvents, and the fullerene needs more and more energy to stabilize the ROS compound.

Various clusters of compound were created in Avogadro. Their structures obtained from optimization in Avogadro are given in figures. As complexity increases, the optimized energy increases as well, albeit with increased variation within cluster. Unlike stereo and quantum studies , which found that clusters with less optimized energy are energetically preferred, in our study, the isomers or clusters with bigger optimized energy are preferred.

Figure 1. *C40 Fullerene*

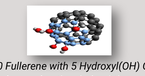


Figure 2. *C40 Fullerene with 5 Hydroxyl(OH) Groups*

While there is a general trend of increase in optimized energy with increasing the chain of the molecules, variation of the energy increases as well.

ID	kcal/mol
1OH	25861.9
2OH	25723.5
3OH	25686.8
4OH	25638.6
5OH	25591.8

Table 1. *Optimized Energy of C40 - Hydroxyl group (OH)*

The configuration of C40 Fullerene with 5 Carboxylic (COOH) Groups is considered to be unstable due to its angle strain as it is shown below.

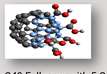


Figure 3. *C40 Fullerene with 5 Carboxylic (COOH) Groups*

ID	kcal/mol
1COOH	26039.3
2COOH	25309.3
3COOH	24974.6
4COOH	24707.9
5COOH	24215.2

Table 2. *Optimized Energy of C40-(COOH) group*

Also, although a general trend of increase in optimized energy with increasing the chain of the molecules exists, variation of the energy was observed.

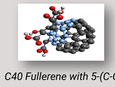


Figure 4. *C40 Fullerene with 5-(C-COOH) Group*

ID	kcal/mol
1C-COOH	27117.6
2C-COOH	27437.1
3C-COOH	28526.2
4C-COOH	28966.3
5C-COOH	29748.9

Table 3. *Optimized Energy of C40 - C-COOH (C3 tris malonic acid)*

Figure 4 shows that the increase in optimized energy with increasing the chain of the molecules was observed for the C40 Fullerene with OH groups.

ID	1	2	3	4	5
C40 OH	25861.9	25723.5	25686.8	25638.6	25591.8
C40 COOH	26039.3	25309.3	24974.6	24707.9	24215.2
C40 C-COOH	27117.6	27437.1	28526.2	28966.3	29748.9

Table 4. *Summary-Optimization Energy of the 3 Groups(C40 - OH, COOH, C-COOH) (kJ/mol)*

When comparing the derivatives on C40 and C82 fullerene models, it was observed that C82 derivatives had much lower optimization energy levels (kJ/mol) than those of C40. Although the C82 derivatives may have a larger number of carbon atoms than the C40 derivatives – C82 derivatives possess a more spherical shape - allowing them to have a lower enthalpy.

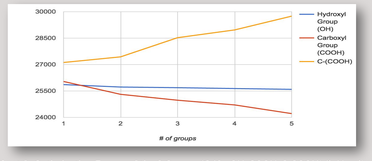


Chart 2. *Optimization Energy of the 3 Groups (C40 - OH, COOH, C-COOH) (kJ/mol)*

Magnetic resonance imaging (MRI) contrast agents are used in the diagnosis of Alzheimer's Disease. The contrast agent identifies amyloid beta peptide, an indicator for Alzheimer's Disease.

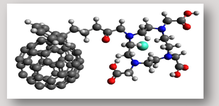


Figure 5. *Model of $PC_{61}BA$-(Gd-DO3A)*

$PC_{61}BA$-(Gd-DO3A) is synthesized by conjugating 6,6-phenyl-C_{61} butyric acid ($PC_{61}BA$) with gadolinium 1,4,6,10-tetraazacyclododecane-1,4, 7-tetraacetic acid complex (Gd-DO3A). $PC_{61}BA$-(Gd-DO3A) is highly stable.

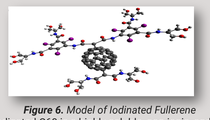


Figure 6. *Model of Iodinated Fullerene*

This iodinated C60 is a highly soluble, non-ionic, and highly-iodinated fullerene. Iodinated molecules, like Iohexol and iodinated C60, are effective X-ray contrast agents.

Compound	Energy (kJ/mol)
$PC_{61}BA$-(Gd-DO3A)	13894.8
Iodinated C60	64440.3
C60-(Gd-DOTA)	34988.7

Table 7. *Optimized Energy of Functionalized Fullerenes*

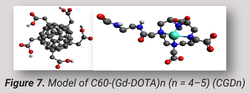
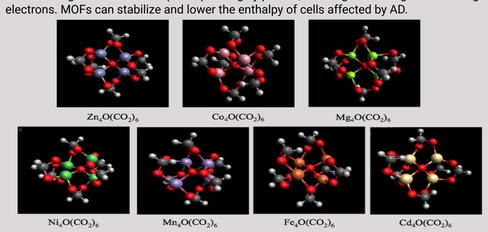


Figure 7. *Model of C60-(Gd-DOTA)n (n = 4–5) (CGDn)*

Table 7 shows optimized energy of the functionalized fullerenes. $PC_{61}BA$-(Gd-DO3A), which has lower energy than iodinated C60, is more thermodynamically stable.

Metal-organic frameworks (MOFs)

Metal-organic frameworks (MOFs) are highly porous, allowing absorbing and donating electrons. MOFs can stabilize and lower the enthalpy of cells affected by AD.



Molecular Formula	Molecular Weights	Opt. E(kJ/mol)
$Zn_4O(CO_2)_6$	553.672	324.858
$Co_4O(CO_2)_6$	527.884	1,325.666
$Mg_4O(CO_2)_6$	389.372	372.661
$Ni_4O(CO_2)_6$	526.925	1,512.325
$Mn_4O(CO_2)_6$	511.904	1,143.882
$Fe_4O(CO_2)_6$	515.532	1,175.643

Table 8. *Enthalpy of Joints in the MOFs*

Enthalpy Analysis

- With the help of maleic anhydride, we found that the N-methylpyrrolidinofullerene produces fullerene and azomethine ylide.
- Anhydride, dipolarophile maleic anhydride can improve the process of retro cycloaddition by either reducing the activation barrier of the reaction, or by stabilizing the final generated 1,3-dipole.
- The dipolarophile maleic anhydride, present in a reaction, allows total reaction energy changes from highly exothermic to substantially exothermic.

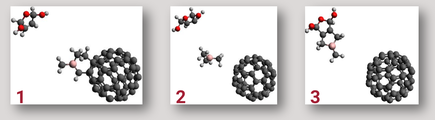


Chart 3. *Enthalpy of Fullerene measured in kJ/mol*

Conclusion

- The theoretical structure of each feasible nano-scaled fullerene compounds has been studied in this project.
- Based on the predicted stability of each molecule, it can be predicted which compound can be used more efficiently to assess the thermodynamic stability.
- Using the quantum chemical calculations, we hypothesized that presented analysis of thermodynamic stability and electron properties of fluorescent functionalized fullerenes, boron compounds and MOFs will be used as effective contrast agents.
- Optimization configuration energy was collected in order to compare each chemical compound's stability.
  - It is known that the less energy needed to stabilize the compound, the more stable the compound is.
  - Calculations show some compounds converge easily, which makes them suitable to use in biochemical compound or drugs.
- When fullerene reacts with ROS it easily gives off hydrogen, and helps to stabilize ROS as fullerene has OH bond.
- As the fullerene's energy (enthalpy) increases, the hydrogen part of OH bond easily falls out and bonds with ROS.
- The more OH bond there is, the more hydrogen it can give off under certain solvent, meaning that it needs more and more energy to stabilize the ROS compound.
- We not only want fullerene to give out lots of Hydrogen, but also be very stable and can be effectively used in terms of its volumes, as there is always a trade-off between stability and reactivity.

Future Work

There is much more work necessary to validate that fullerenes and other nanomolecule derivatives are safe to use in AD treatment by stopping uncontrolled radical reactions. Therefore, before testing derivatives on animals and measuring their oxidative stress, other types of fullerene derivatives must be investigated to find the fine-tuned balance between stability and reactivity. Analyzing their changes in enthalpy and optimization energy when combined with other chemical groups for medical usage will be a goal that gives us much more information to predict the safety and stability of the chemicals.

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