TRIPEPTIDE STABILIZED NANOEMULSIONS FOR CANCER THERAPY.

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Introduction

Carboplatin is a known chemotherapy medication that is used to treat various types of cancer. One of the challenges of this class of anticancerous drugs is its high level of toxicity to the human body, which results in low clinical dosings of the drug and ultimately ineffective therapy. A carboplatin derivative consisting of two oleic acids attached to a platinum head, also used to kill cancer cells, is investigated in this project through chemical simulation software. For drug delivery to the human body, the carboplatin derivative requires an emulsifier to stabilize it and shield its toxic agents. It has been observed that the carboplatin derivative molecules aggregate together and precipitate in the absence of an emulsifier, making them ineffective for cancer therapy. There are several types of emulsifiers such as lipids, and forms of polypeptides or copolymers. In this project, peptide emulsifiers are used as stabilizing agents for the carboplatin derivative. It has been studied that peptides are promising self assembly candidates. Along with the peptide's biodegradable properties, peptide self-assembly is a viable approach for the formation of nanoscale objects, and can thus be used as emulsifiers (Scott 2016).

In the first phase of this project, general features of oleic acid aggregates in water solution are investigated. In the second, tripeptides, specifically KYF (Lysine- Tyrosine - Phenylalanine) and DFF (Aspartic Acid- Diphenylalanine), are added to these aggregates in order to study the tripeptide stabilized nanoemulsions. The simulations gave insight about the interactions present in the nanoemulsions.

Discussion of Results

PHASE I:

The project began with 3 simulations consisting of 50 oleic acid molecules in water solution that were run for 30 nanoseconds each. All simulations in this project are at 300 K and 1 bar conditions. The molecules are arranged arbitrarily and the entire system when solvated in water was a total of approximately 15,000 molecules each. The first simulation had 35 protonated and 15 unprotonated oleic acids. It was observed that the aggregate remained intact and nearly all the carboxyl groups, regardless of charge, were on the surface while the hydrophobic carbon chains remained in the center of the aggregate. In order to investigate how charge density affects the stability of the aggregate, the second and third simulations contained more negatively charged oleic acids. The second simulation contained 40 unprotonated and 10 protonated oleic acids and all the acids were unprotonated in the last simulation. It was observed that the last two aggregates were not as compact and several molecules were outside the aggregate. This was explained by the charge repulsion present between the acids, since a majority of them were negatively charged.

Since the first simulation with 35 protonated and 15 deprotonated acids was the most stable aggregate, this charge ratio was used for the remainder of the project. The number of oleic acids in was increased to 100 and the system was run for 100 nanoseconds. When these acids were solvated, there was a total of 30,000 molecules. It was suspected that bidentic hydrogen bonds would form in the center of the larger aggregate due to the volume expanding at a higher rate than the surface area once its radius increases, however, the center of the aggregate did not contain any of these bonds. Despite this finding, it is important to note that the size may have to be increased to several hundred or thousand molecules to observe this kind of bonding in the center of the aggregate, since there would not be enough space on the surface of the aggregate and molecules would be forced into the interior of it.

PHASE II:

In this phase, each type of tripeptide was added to the oleic acid systems. One hundred tripeptides were placed uniformly surrounding the 100 oleic acid aggregate after its 100 ns trajectory. The compound system amounted to 50,000 molecules when it was solvated in water and was run for 100 ns. The first tripeptide studied was KYF(Lysine-Tyrosine-Phenylalanine). It was immediately apparent that the tripeptides remained on the surface of the aggregate. A reoccuring finding upon investigation of the emulsion is the ionic interactions between the positive amine group in KYF and the negative charge of an deprotonated carboxyl group in oleic acid. in many instances, intramolecular ionic interactions were observed among the negatively charged carboxyl group and the positively charged amine group of KYF (Figure 1). Additionally, the polar groups of surface peptides, the two amine groups and hydroxyl of the phenol faced the surrounding water. KYF's phenyl group is found in the pockets of the oleic acid aggregate where the chains of carbon from oleic acid are, indicating a hydrophobic interaction(Figure 2).

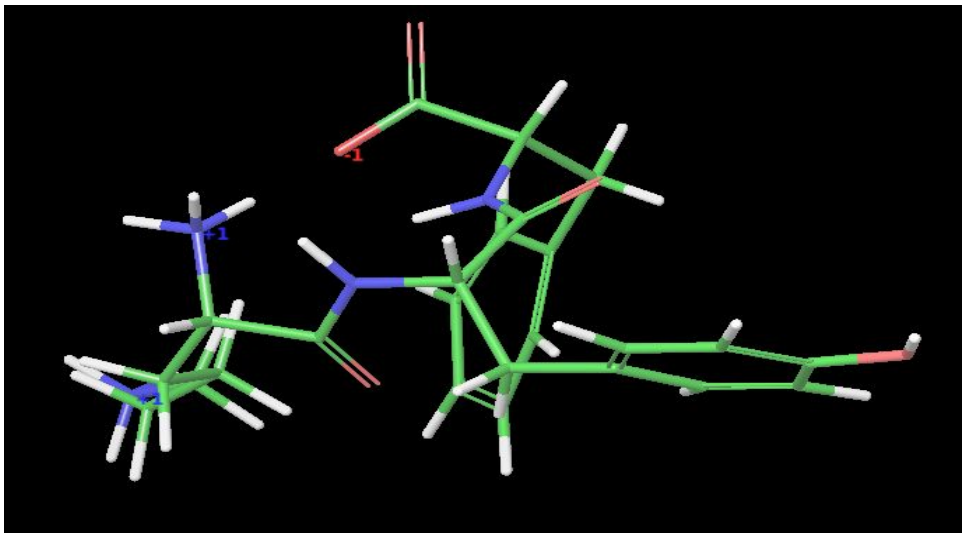

Figure 1- representative image of KYF folded for an ionic intramolecular interaction(amine group in blue with +1 formal charge and carboxylate group with -1 formal charge in red)

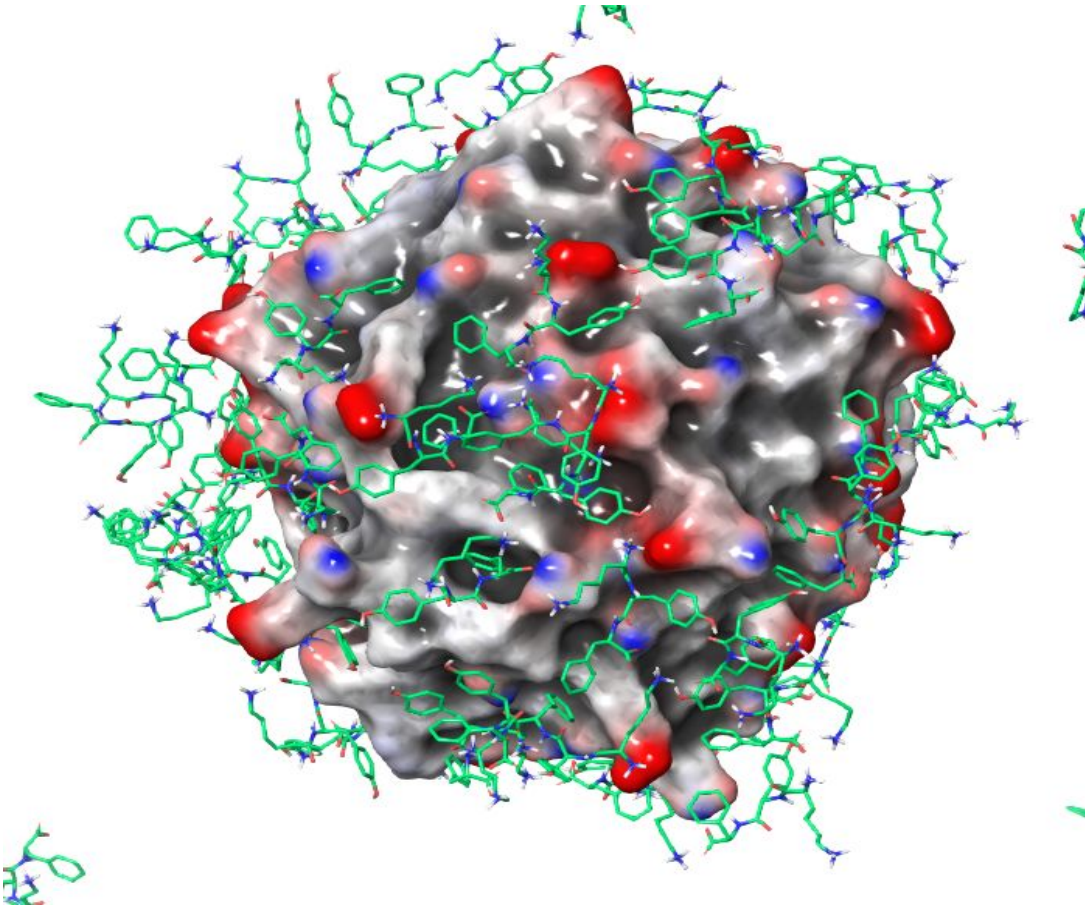

Figure 2- structure of tripeptides(green) interacting with the oleic acid aggregate(carbons are gray, carboxyl groups are in red, amine groups are in blue)

The second tripeptide studied along with the oleic acids is DFF. After its 100 ns trajectory, the aggregate was no longer intact as it was with KFF. Nearly half of the peptides were not interacting with the aggregate, but instead remained in solution or formed peptide aggregates (Figure 3&4). In fact, the aggregate itself did not remain intact at the end of the trajectory and oleic acids formed smaller aggregates with DFF. However, the oleic acids along with DFF would continuously compact and scatter apart in solution throughout the trajectory. This was not the case in the KYF trajectory since it generally remained one compact aggregate throughout its trajectory. In all of the scattered aggregates, negatively charged carboxyl groups on oleic acid formed interactions with positively charged amine groups on DFF (Figure 5).Additionally, ionic intermolecular interactions between peptides were often observed in this system between the positively charged amine group and negatively charged carboxylate.

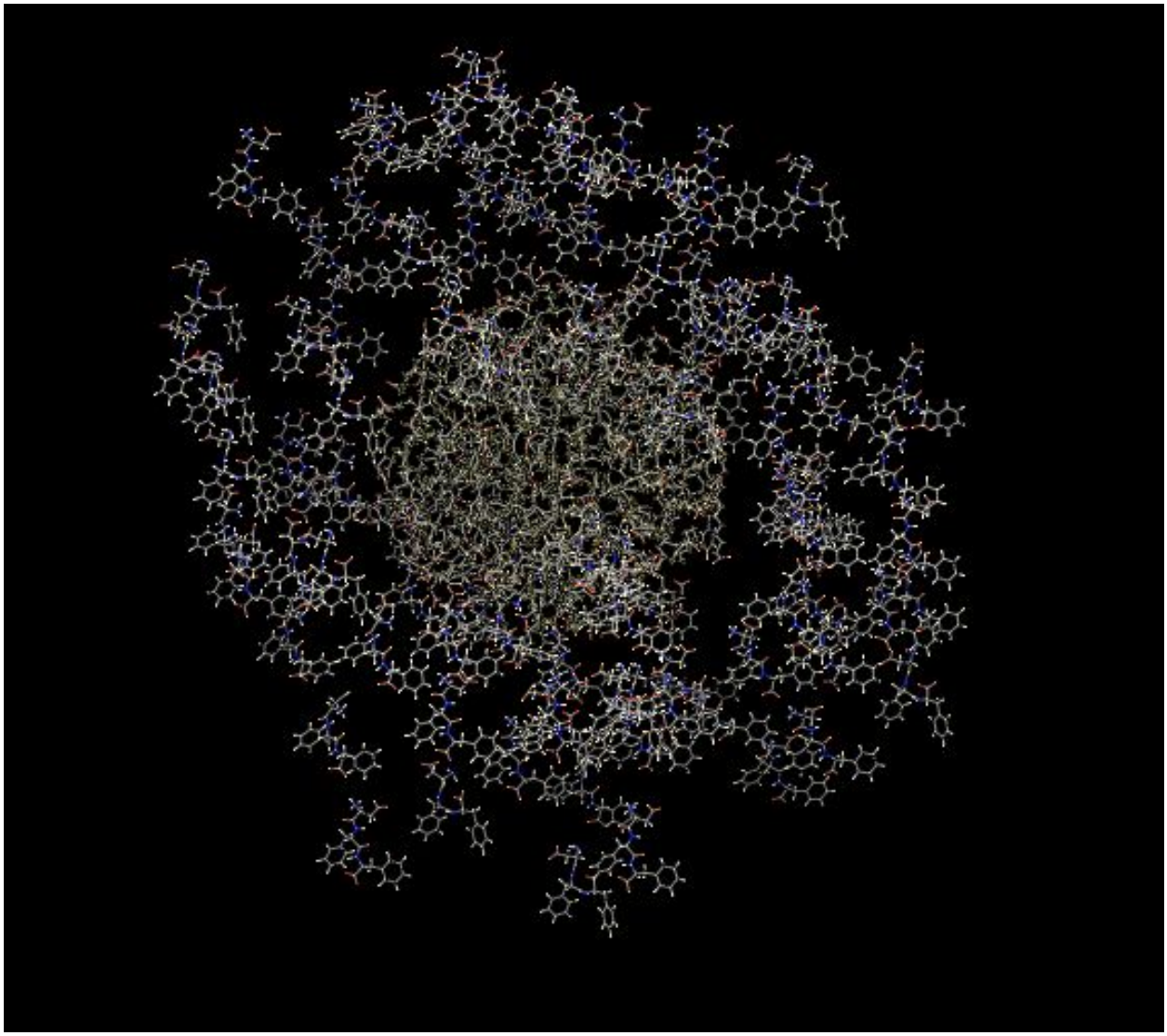

Figure 3- DFF and oleic acid system at 0 ns

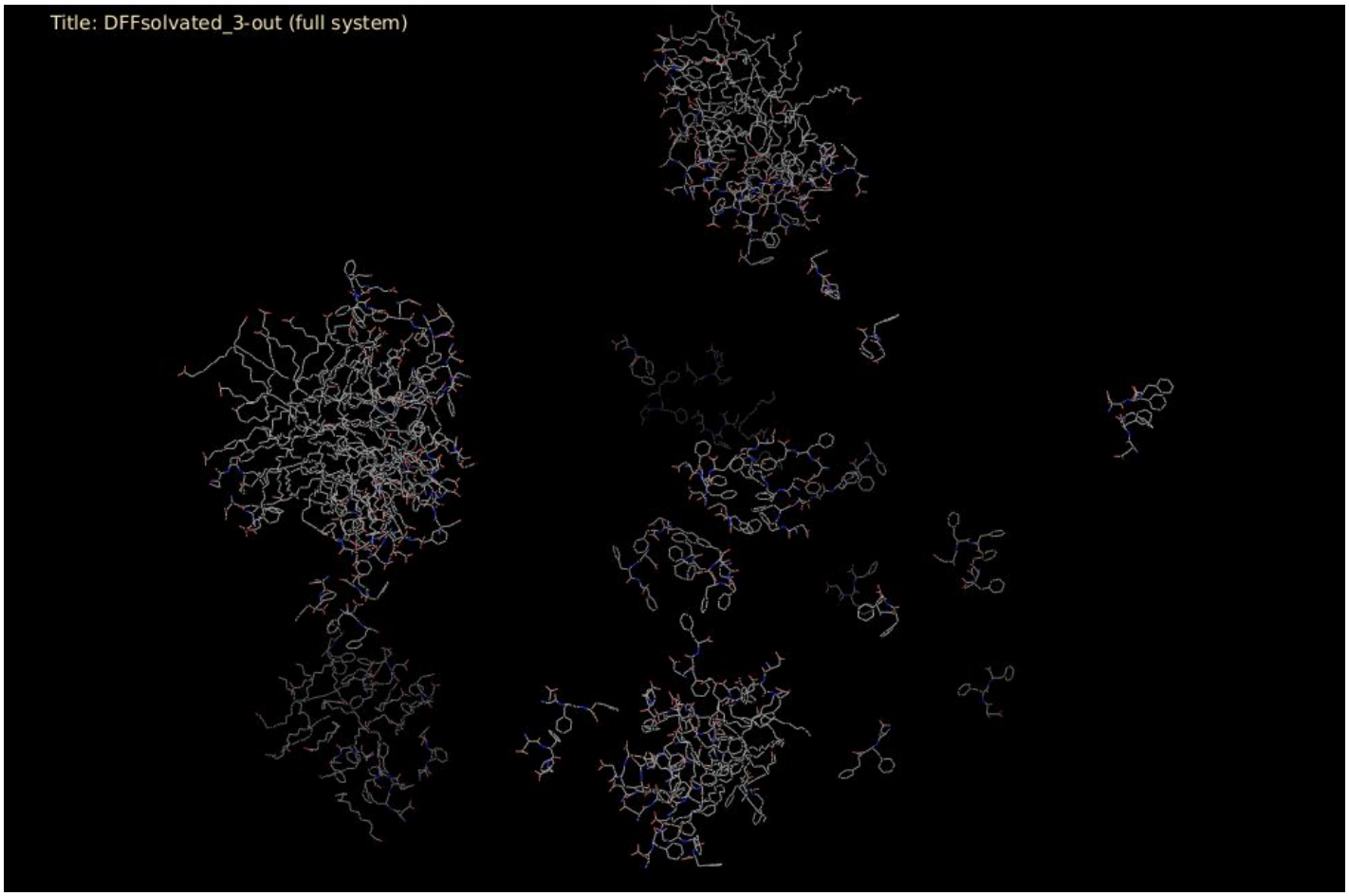

Figure 4- DFF and oleic acid system at 100 ns

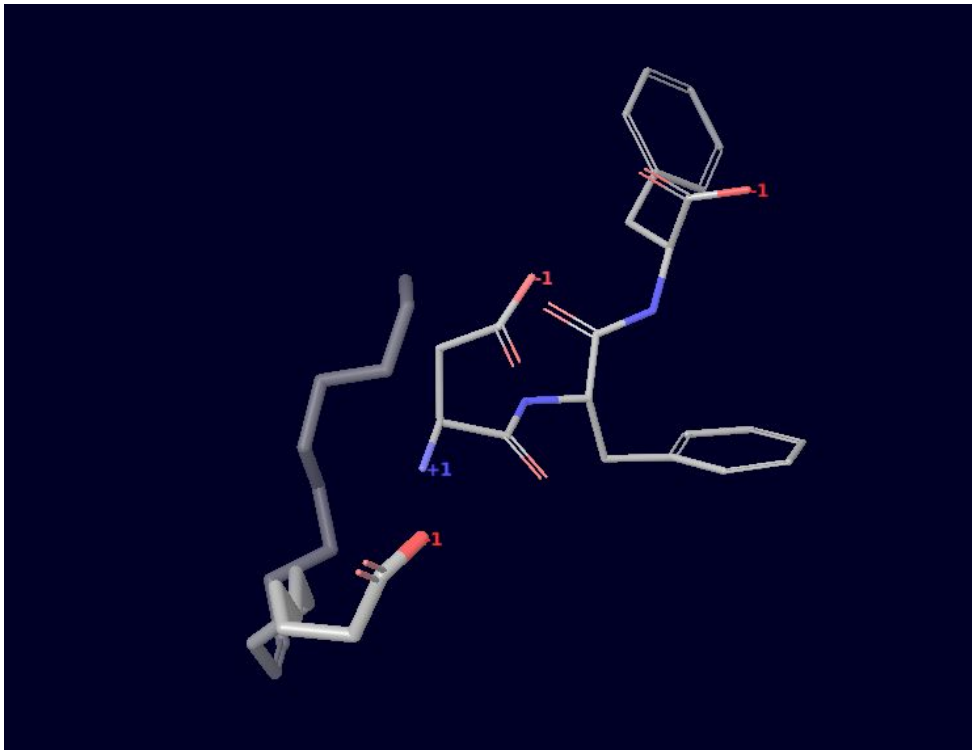

Figure 5- example of ionic interaction between oleic acid and DFF that was often observed

Conclusion

This project gave insight to general features of oleic acid aggregates with and without tripeptides. A very extreme and unexpected difference of the two system's overall structure between KYF and DFF requires further research into why this occurred. Additionally, more molecular modeling is required utilizing the carboplatin derivative along with different kinds of peptides in order to accurately investigate the interactions of the nanoemulsion.

Resources

Scott, Gary.,et al. "Emulsifiers: Tripeptide Emulsifiers: Tripeptide Emulsifiers (Adv. Mater. 7/2016). " Advanced Materials, vol. 28, no.7 , 2016.