Fullerenes Interaction with Hemagglutinin

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Abstract. Fullerenes are a unique class of nanostructures. Hemagglutinin is a versatile viral surface protein. In this work nanostructure interaction with this surface marker is studied computationally. A series of fullerenes was considered and their interaction with hemagglutinin is observed in order to develop new antiviral nanostructure-based drugs.

Keywords: *hemagglutinin*, *influenza virus*, *fullerene*, *antiviral*.

1. Introduction

Antiviral drug development is a key component in nowadays research. Molecular recognition based on surface proteins and its inhibition is well explored and exploited in drug development strategy. Introducing nanostructures which will presumably interact with viral surface proteins attracted researchers since 1985 [1]. Fullerenes were proved to have biological activity [2]. Only few classes of nanostructure have bioactivity similar to fullerenes. From stability point of view, fullerenes are the most stable and easy to obtain [3]. Also, anti- HIV nanotherapeutics explored the fullerenes, with good results [4]. Shape and geometry together with solvent accessible area are essential components of every nano-drug structure.

Methods: In order to explore fullerene space, a series of 40 congeneric fullerenes (the isomers of C_{40} fullerene – see Figure 1) were considered. Compounds were minimized using MMFF94 force field in order to compile with PDB structure for hemagglutinin (PDB ID 6n41) [5]. Hemagglutinin structure was prepared using the same force field, with all ligands being removed. A binding site algorithm, based on van der Waals charges, was used in order to detect proper binding pockets. Hemagglutinin-fullerene complexes were obtained using a docking procedure using as binding site the cavities revealed by the search algorithm. For each fullerene, only best pose was retained. Complexes were classified according to complex total energy (kcal/mol). Lowest and highest energy complex were collected.

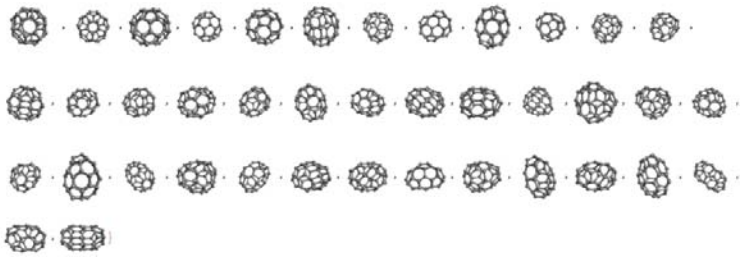
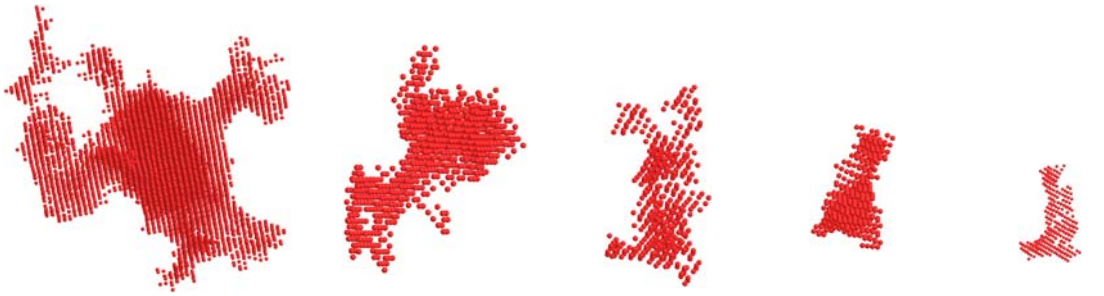


Figure 1. Fullerenes of the C_{40} series.

2. Results

Binding pockets of hemagglutinin are represented in Figure 2, as water clusters. In the docking study, the cavity 1 was used.

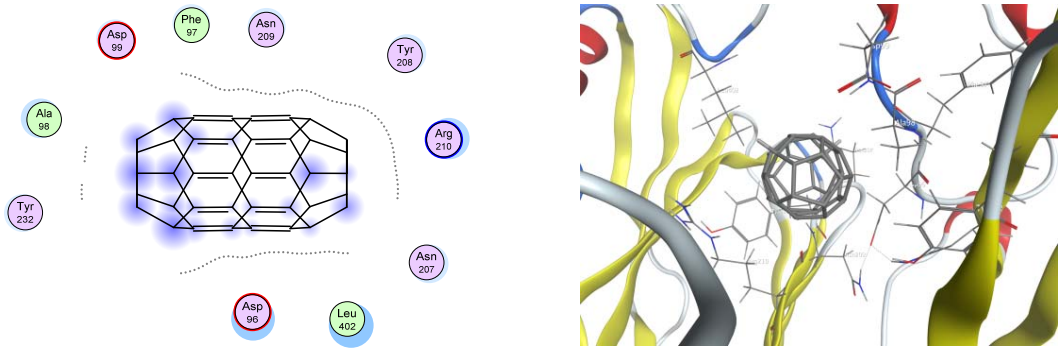


Cavity 1	Cavity 2	Cavity 3	Cavity 4	Cavity 5
4057.6 Å^3	1686.53 Å^3	189.952 Å^3	107.088 Å^3	77.312 Å^3

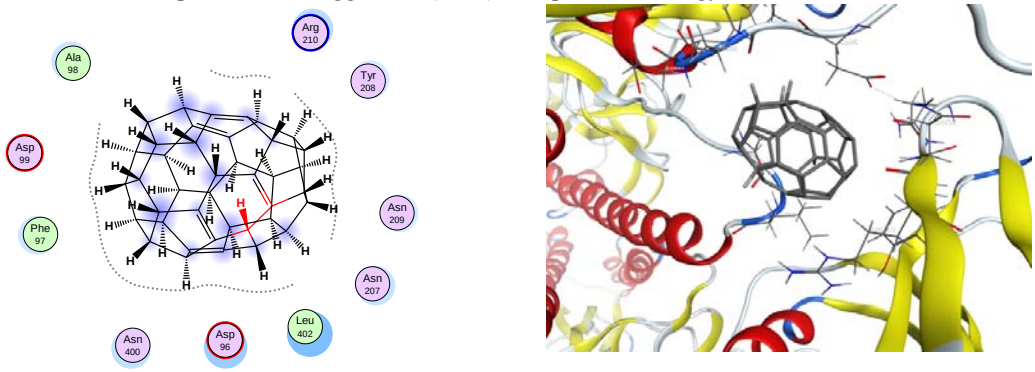
Figure 2. Hemagglutinin binding pockets

Figure 3 shows the highest energy complex formed by #1 and the lowest energy conformation with #32. Fullerene-hemagglutinin conformations are represented in detail. Only steric interactions with surrounding aminoacids are observed.

Molecular weight vs total complex energies (kcal/mol) were considered (Figure 4). No correlation is observed between these two variables (t-test), thus the mass effect was ruled out.



#1 in complex with hemagglutinin (6n41); complex total energy: -151.997 kcal/mol



#32 in complex with hemagglutinin (6n41); complex total energy: -176.025 kcal/mol

Figure 3. Hemagglutinin–fullerene complexes.

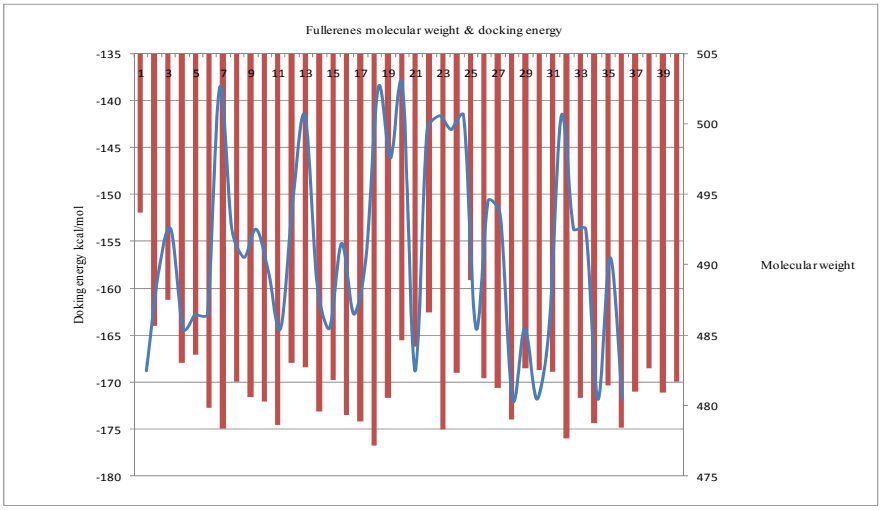


Figure 4. Docking energy as function of the molecular weight.

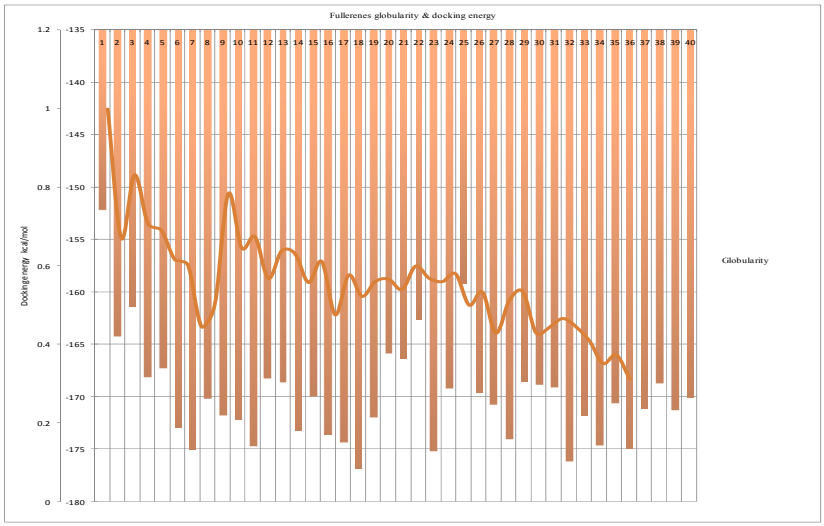


Figure 5. Globularity test.

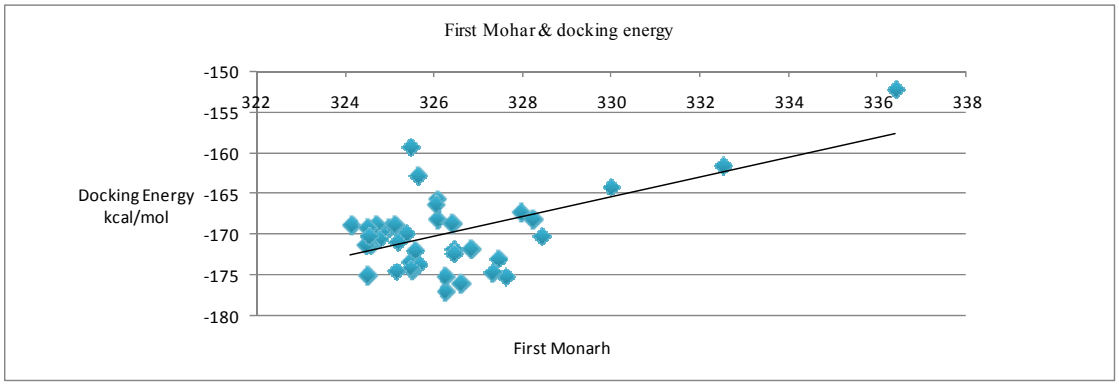


Figure 6. The First Mohar correlated with the docking energy.

Globularity [6] of fullerenes is represented in Figure 5; the shown tendency of energy is to be larger for larger globularity and that globularity and energy are positively correlated (t test: $r^2 = 0.24$). However, this low value of correlation suggests that only few conformations fit intimately with the receptor. Among other descriptors, in respect to possible docking energy, the First Mohar descriptor presented a correlation of $r^2 = 0.327$ (Figure 6).

3. Discussion

Shape and docking energy have a low correlation: a perfect sphere does not have best docking energy and an asymmetrical structure has not a poor docking energy. Results show that rather intermediate shapes form more stable strong bound complexes with hemagglutinin. By implying the hydrogen bonding algorithm, it was observed that the hydrogenated form of fullerenes are more bioactive than the ''normal'' fullerenes. The ability of forming hydrogen bonds is important in any ligand-receptor complex. These results suggest that a potential fullerene bionano-structure likes to be at some point protonated. Correlation of docking energy with the first Mohar index suggests the equilibrium behavior of the fullerene – hemagglutinin complexes, obtained by the docking procedure. First Mohar descriptor is computed using Laplacian matrix [7]. Model correlation suggests that the equilibrium was not yet been reached and probably further functionalization of fullerenes are needed in order to attain a feasible stable complex.

Conclusions

Computationally, fullerenes show bioactive properties. In silico hydrogenation of fullerenes increases their bioactivity i.e., the capacity of forming stronger, stable complexes with a certain target. Hemagglutinin forms with fullerenes (in silico) energetically favorable complexes.

References

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