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Molecular Dynamics Study of Sorafenib Anti-Cancer Drug: Inclusion Complex in Amphiphilic Cyclodextrin

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Cyclodextrins (CDs) are cyclic oligosaccharides able to solubilize hydrophobic drugs in water enhancing their bioavailability. Sorafenib (SOR) is a lipophilic oral multikinase inhibitor that impedes proliferation, angiogenesis, and invasion of cancer cells with low water-solubility. Recently, amphiphilic cyclodextrins (aCDs) have been investigated as possible nanocarrier for systemic administration of SOR increasing its bio-availability. A theoretical study about inclusion complexes of SOR drug and a model of aCD system using molecular mechanics (MM) and molecular dynamics (MD) methods is here reported. At first, the single molecule aCD (SC6OH, heptakis(2-O-oligo(ethylene oxide)-6-hexylthio)-β-CD bearing 14 units of ethylene-oxide at the CD secondary rim) and SOR drug are studied. Then, the interaction between aCD and SOR is investigated. The theoretical results display different types of interaction geometries. The most stable geometry of the *host-guest* complex showed the lowest potential and favorable interaction energy and the fluorine atoms of SOR drug molecule are directed toward the hydrophobic primary rim of the aCD, while the part of the SOR rich in oxygen atoms is directed toward the hydrophilic secondary rim. This theoretical result is in a good agreement with NMR data in literature about same aCD as host of Sorafenib anti-cancer drug.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides recognized as pharmaceutical adjuvants for the past 20 years.[1–3] CDs with approximatively truncated-cone shape have a hydrophilic outer surface and a hydrophobic central cavity. They can form noncovalent host-guest complexes hosting lipophilic drugs. Sorafenib (SOR) is an oral hydrophobic multikinase inhibitor important in the cancer-therapy to prevent proliferation, angiogenesis and invasion of cancer cells. Up to present days its application is limited at oral administration because of its low water-solubility. Recently, chemically modified β-CDs derivatives have been synthesized [4–6] in order to improve CD interactions with hydrophobic drugs in order to enhance drug release through cell membrane. One of the possible modifications is to chemically bind aliphatic chains of different lengths on the primary or secondary β-CD rim in order to obtain amphiphilic β-cyclodextrins (aCD),[6] see **Scheme 1**.

In the past 20 years, molecular mechanics (MM) and molecular dynamics (MD) simulations are demonstrated to be a very useful tool to atomistically investigate noncovalent interactions in particular in host-guest complexes formation process and possible self-aggregation.[7–9]

In this work, the interaction between SC6OH amphiphilic cyclodextrins (aCD) as a possible nanocarrier and SOR drug has been investigated adopting MM and MD methods using a simulation protocol proposed in previous work.[10–13] The theoretical results are comparable with NMR experiments data in literature.[6] In particular, in this work, after the study of the single model aCD (SC6OH, heptakis(2-O-oligo(ethylene oxide)-6-hexylthio)-β-CD bearing 14 units of ethylene-oxide at the CD secondary rim, see Scheme 1) and SOR molecule, the complex formation process in implicit water [10–13] was investigated. These theoretical studies are in general helpful to better understand noncovalent interactions important for functional composite materials in different fields from nanomedicine, materials engineering, life science.[13–16] Simulations in explicit water are work in progress. The most stable *host-guest* geometry found explains signals in NMR data in literature in good agreement. The results will be presented and discussed in the next Section.

2. Molecular Mechanics (MM) and Molecular Dynamics (MD) Simulations

The study of the interactions between aCD SC6OH and SOR anticancer drug was carried out through molecular modeling using InsightII/Discover programs (Accelrys Inc.) with the CVFF force field [17] in implicit water using the dielectric constant of water distance dependent. The simulation protocol adopted is reported in previous work.[10–13] All energy minimizations in

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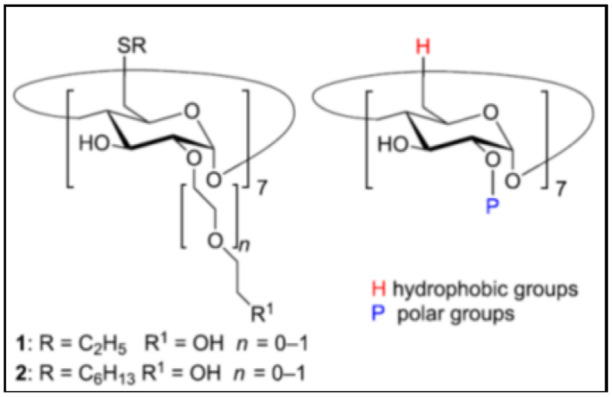

Scheme 1. Structure of aCD SC6OH with $n = 1$ studied in this work, having hydrophobic thioalkyl C6 ($R = C_6H_{13}$) at the primary rim, and polar oligoethylene glycol $(\text{-}OCH_2CH_2\text{-})_n$ with $n = 1$ at the primary rim.

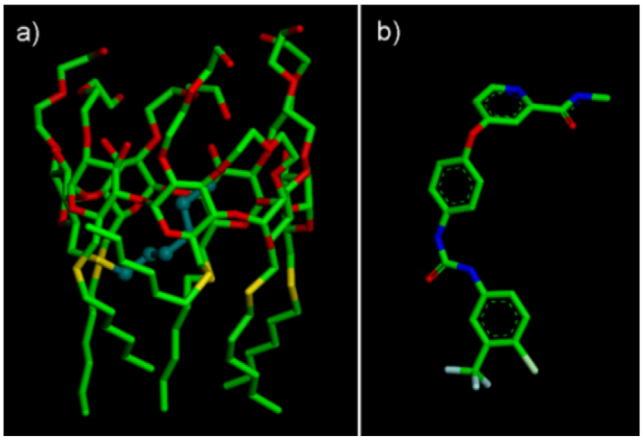

Figure 1. The figure shows the isolated aCD SC6OH molecule and the Sorafenib drug molecule in the most stable optimized geometries calculated after MD run respectively in the panel a) and b). The carbon atoms are in green, oxygen in red, nitrogen in blue, fluorine in light blue. Only the alkyl chain included in the aCD cavity is in dark green ball and stick; the hydrogen atoms omitted for clarity.

MM study were carried out up to an energy gradient lower than $4 \cdot 10^{-3}$ kJ mol^{-1} Å^{-1}. The most stable optimized geometries calculated after MD run at constant temperature (300K) lasting 1 ns and energy minimizations of different conformations assumed by isolated aCD and SOR drug is reported in **Figure 1**.

Interestingly, the isolated aCD molecule displays self-inclusion phenomena. This kind of phenomenon was just study by Raffaini in previous work [12] and it is common in modified CDs. It will be interesting to observe that after inclusion of drug in the hydrophobic aCD, this alkyl chain self-included in the isolated molecule comes out of the cavity in order to maximize the interaction with hydrophobic drug by solubilizing it. Then, the interaction between aCD and SOR in a 1:1 stoichiometry without assuming any a priori inclusion complexes was studied starting from four trial geometries having SOR drug near the primary or the secondary aCD rim with fluorine atoms near or far from the specific rim. The simulation protocol adopted consist in three steps: I) Energy minimizations of initial trial aCD/SOR geometries, II) MD run at room T, and then III) Optimization

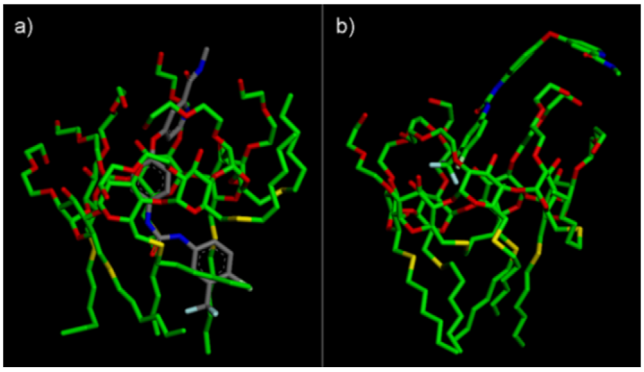

Figure 2. The figure shows the most stable and the metastable optimized geometries calculated after MD run of the inclusion complex and of the metastable system formed respectively in the panel a) and in the panel b). The aCD carbon atoms are in green, the SOR carbon atoms are in grey, oxygen in red, nitrogen in blue, fluorine in light blue. The hydrogen atoms omitted for clarity.

of the system when the equilibrium state was achieved and also of many configurations saved during the MD runs in search of the most stable host-guest inclusion complex and the possible different metastable geometries.[10–13] The most stable inclusion complex and metastable geometries without inclusion in the aCD cavity were found (see **Figure 2**).

Interestingly, SOR interact with aCD in the metastable geometry without inclusion; in the most stable geometry, SOR is completely included in the hydrophobic aCD cavity with the fluorine atoms directed towards the apolar chains, as found after NMR experiments reported in literature.[8] In **Figure 3**, the potential energy and the centers of mass distance between SOR and aCD calculated during MD run, which leads to the formation of inclusion complex are reported.

After the inclusion process, the host-guest complex is very stable. The similarity maps of the Root-Mean-Square Distances (RMSD, see ref. [10] for information on using RMSD for the data analysis) calculated between instantaneous configurations assumed by the system during MD run allows to detect the formation of the inclusion compound and to recognize different families of conformers, both for stable and for metastable geometries. In **Figure 4** at left, the inclusion complex formed is stable and populated at room temperature in particular from 1.8 to 3 ns. In Figure 4 at right, the same information about the metastable complex displayed in Figure 2 is shown.

3. Conclusions

CDs are cyclic oligosaccharides able to solubilize hydrophobic drugs in water enhancing their bioavailability. Using MM and MD methods the interaction between an amphiphilic CD and Sorafenib, a hydrophobic anti-cancer drug, was studied. The most stable *host-guest* geometry found shows that the fluorine atoms of SOR drug are directed toward the hydrophobic primary rim of the aCD, while the part of the SOR rich in oxygen atoms is directed towards the hydrophilic secondary rim, in good agreement with data obtained from NMR experiments. Also, metastable geometries with the anticancer drug adsorbed on the more hydrophilic secondary rim are observed. The incorporation of SOR within the

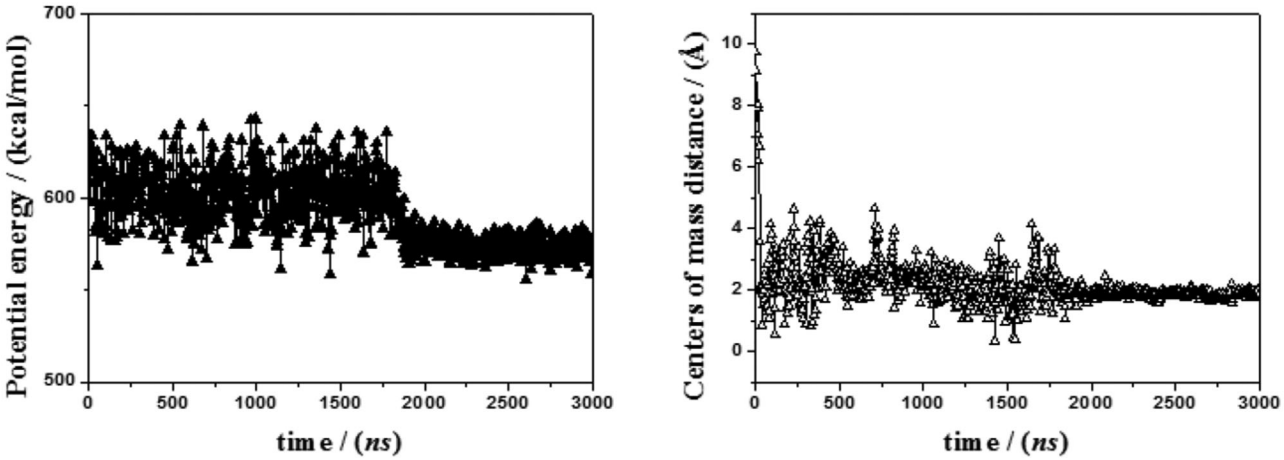

Figure 3. The potential energy and the centers of mass distance between SOR and aCD calculated during the MD run in which the inclusion process takes place respectively at left and at right.

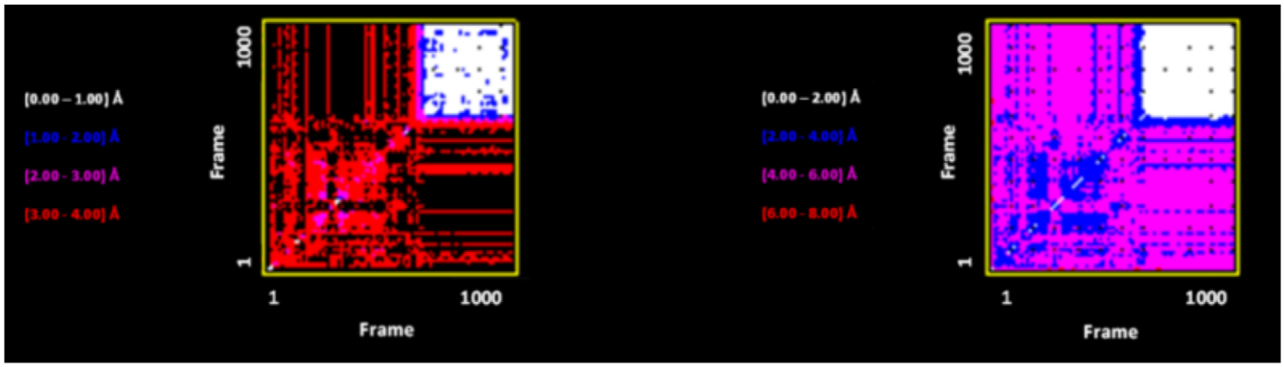

Figure 4. The similarity maps of the Root-Mean-Square Distances between instantaneous configurations assumed by the system during MD where most inclusion complex are formed and at right during MD run there SOR interacts with primary rim without inclusion in the cavity.

hydrophobic cavity induces new arrangements of aCD, with the expulsion of the self-included apolar chain in the cavity present in the isolated system. The complex is stabilized by hydrophobic interactions among the aromatic rings of the SOR, the hydrophobic aCD cavity, and the apolar chains at primary rim, together with some H-bonds between the SOR molecule and the polar chains at the secondary rim. The complex formed is stable and populated during MD run. Possible self-aggregation enhancing the drug concentration will be studied in order to better understand possible stable aggregates formation.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

β-cyclodextrin, amphiphilic cyclodextrin, anti-cancer drug, drug delivery, *host-guest* complexes, molecular dynamics, solubilization, sorafenib

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