Using Molecular Dynamics in Modeling Fluorescent Rosette Nanotubes

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Introduction

Rosette nanotubes (RNTs) are soft organic nanomaterials self-assembled from Watson-Crick inspired guanine-cytosine (G∧C) hybrid building blocks with complementary hydrogen bonding sites and stabilizing π-π interactions and hydrophobic effects.[1] These materials have substantial design flexibility and a range of applications, which is partly attributed to their diverse surface functionalization and a chemically/physically tunable channel for guest molecule loading. Several studies have established their biocompatibility and applications in nanomedicine such as in coatings for medical devices and materials for tissue engineering.[2] With novel applications in mind and in an effort to streamline its synthesis, a new tricyclic G∧C motif (Figure 1A) was designed and synthesized to self-assemble into fluorescent RNT in solution. Verification of the self-assembly to tubular structures and fluorescence properties are reported elsewhere.[3] In this work, classical molecular modeling techniques were applied to aid in the characterization of this new RNT, to predict its structure and self-assembly, and to provide better insight in designing similar molecules.

Methods

Molecular dynamics (MD) and the statistical mechanical theory of solvation, also known as the 3 dimensional reference interaction site model (3D-RISM) theory were applied to predict the stable conformations of the motif and RNT. RNT models were built from minimized G∧C motifs and MD simulations were run in different conditions to determine the stability and probable structure of the nanotubes. 3D-RISM integral equations were then solved for the system to determine the energetics and to propose a self-assembly pathway for the RNTs. The self-assembly process was investigated further by randomly placing G∧C motifs on top of a template (a short helical coil RNT), in a simulation cell and running MD simulations in experimental conditions to observe the growth of the RNT *in silico*. In addition, the potential for drug encapsulation using this novel RNT was tested by loading it with Gemcitabine, a small molecule drug that is used to treat various carcinomas, and running MD simulations in physiological conditions to determine the stability the drug-RNT complex. All simulations were done using the Schrödinger Materials Science Suite on high performance computers in the Discovery Cluster of Northeastern University.

Results and Discussion

The results suggest that this tricyclic G∧C motif can either form helical coils (HC) (Figure 1B) or ring stacks (RS) (Figure 1C) depending on the conditions used in the simulation. Based on molecular dynamics, the HC configuration of the RNT is more stable than the RS configuration in all the conditions tested. While the thermodynamics analysis suggests RS is slightly more

stable than HC in water. Moreover, when a RS has stabilized in simulation, the 7-membered rosette conformation seems more favorable than the 6-membered configuration. The self-assembly simulations showed that π-π stacking is the dominant interaction in the formation of aggregates of the motif at high temperatures. And for the first time, the growth of the helical coil RNT from free motifs in the solution was observed *in silico*. The stable helical coil seems to drive the alignment of free G∧C motifs to conform to the rest of the RNT. In addition, the switch from HC to RS was also observed during the self-assembly study when the temperature of the simulation cell was increased to 70 °C. Finally, the MD simulations suggest that the Gemcitabine-RNT complex (Figure 1D) is stable, making a fluorescent RNT-delivered Gemcitabine a highly probable solution for drug display and delivery.

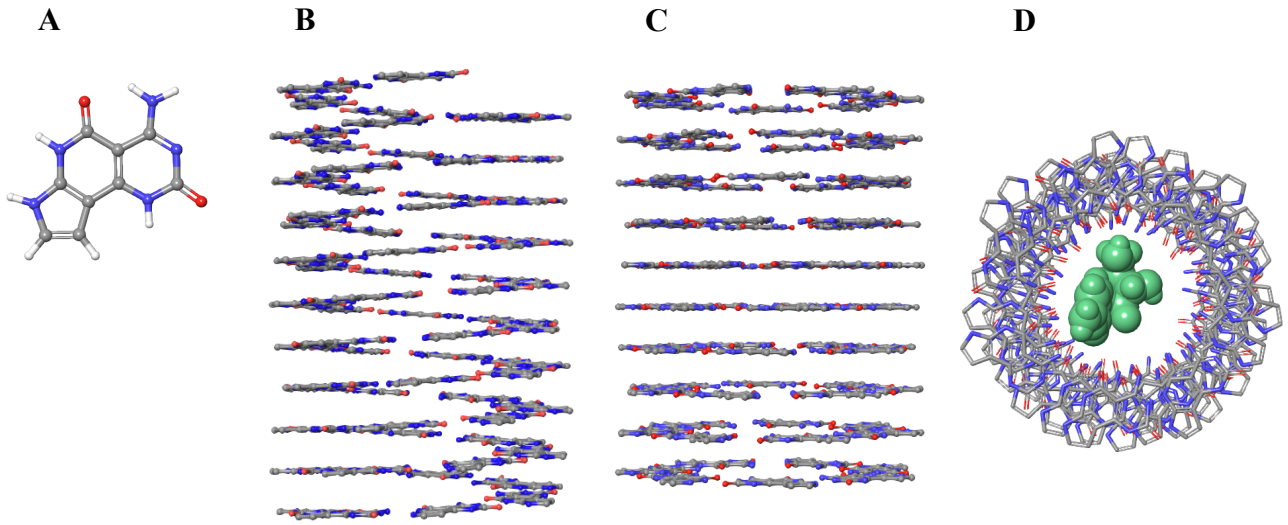

Figure 1: The tricyclic G∧C motif **(A)** with complementary hydrogen bonding sites can form rosette nanotubes as helical coils **(B)** or ring stacks **(C)** with seven motifs depending on simulation conditions. The gemcitabine-RNT complex **(D)** was observed to be stable in simulations at physiological conditions, making this RNT a potential vehicle for drug display and delivery.

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