A combined molecular dynamic and quantum mechanic study of the solvent and guest molecule effect on the stability and length of heterocyclic peptide nanotubes†

Mohammad Izadyar,* Mohammad Khavani and Mohammad Reza Housaindokht

Molecular dynamic simulations were performed to investigate the stability of heterocyclic peptide nanotubes composed of 1,4-disubstituted-1,2,3-triazol ε-amino acid. 45 ns MD simulations were conducted on the cyclic peptide nanotube (CPNT) and cyclic peptide dimer in methanol, chloroform, and water and revealed that these structures are more stable in nonpolar solvents. MM-PBSA and MM-GBSA calculations were employed to analyze the solvent effect on the stability and length of the CPNT. The calculations showed that CPNT in chloroform was more stable and longer as compared to other solvents. In addition, the effect of the guest molecule (ethanol) inside the dimer and CPNT was investigated. The obtained results confirmed that guest molecule(s) stabilized the dimer and CPNT in all solvents. Quantum chemistry calculations on the cyclic peptide dimer were performed at the M06-2X/6-31G(d) level in the gas phase and three solvents. The obtained results from the quantum chemistry study were in good agreement with the MD simulation results. DFT calculations showed that the guest molecule stabilized the dimer structure and electrostatically interacted with the cyclic peptide dimer. Finally, for investigation of the solvent effects on the hydrogen bonds of the cyclic peptide dimer, NBO and AIM analysis were performed.

Introduction

Cyclic peptides (CPs) have been considered in recent years as a suitable material for the formation of organic nanotubes due to their remarkable versatility. These cyclic peptides consist of 6–10 alternating D- and L-ε-amino acid residues, cyclic β-peptides,2,3 and cyclic peptides containing alternating α- and γ- or α- and ε-residues.4–6 Nanotechnology is defined as the preparation and characterization of structures on the nanometer scale and the use of such systems as novel functional materials and devices.7

Nanotubes are particularly interesting structures because of their many applications in different fields such as molecular separation and transport, catalysis, optics, electronics, chemotaxy, and drug delivery. For example, Subramanian and co-workers investigated the ability of some CPNTs to transport the antitumor drug 5-fluorouracil across a lipid bilayer.9 Solvents and amino acid composition are important parameters involved in the stability of CPNT structures. Previous theoretical studies indicate that these structures are more stable in nonpolar solvents.10,11 Materials such as zeolites, graphite, inorganic complexes, lipids, and cyclodextrins can be used to construct nanotubular structures.12 Covalently bonded nanostructures have been thoroughly studied in the past few decades, but research is currently being conducted on non-covalently bonded nanotubes because of their many applications in different fields.13

There are many different routes by which hydrogen bonds can be used to self-assemble nanotubes. Gramicidin A is perhaps the first and most well-known structure involved in the coiling of linear peptides; it has a tubular structure and is found in β-helices,14,15 although there are many others that have since been discovered, including forty-eight residue polytheonamides.16,17 Another example is the assembly of lanreotide peptides into nanotubes, producing tubes with larger internal diameters.18

Nanotubes can also be assembled from sector-like molecules, as in the case of the tobacco mosaic virus (TMV), which consists of a tubular structure of unimeric coat proteins that undergoes self-assembly around a single strand of RNA.19 However, cyclic peptide nanotubes have improved efficiency for transporting molecules and ions as compared to gramicidin A or other structures. The ion transport rates of the self-assembled peptide channels are greater than those of the very efficient and widely-studied gramicidin A channel.20

In this study, we investigated the stability of a heterocyclic peptide nanotube and its dimer consisting of 1,4-disubstituted-1,2,3-triazol ε-amino acid (Scheme 1), in methanol, water,