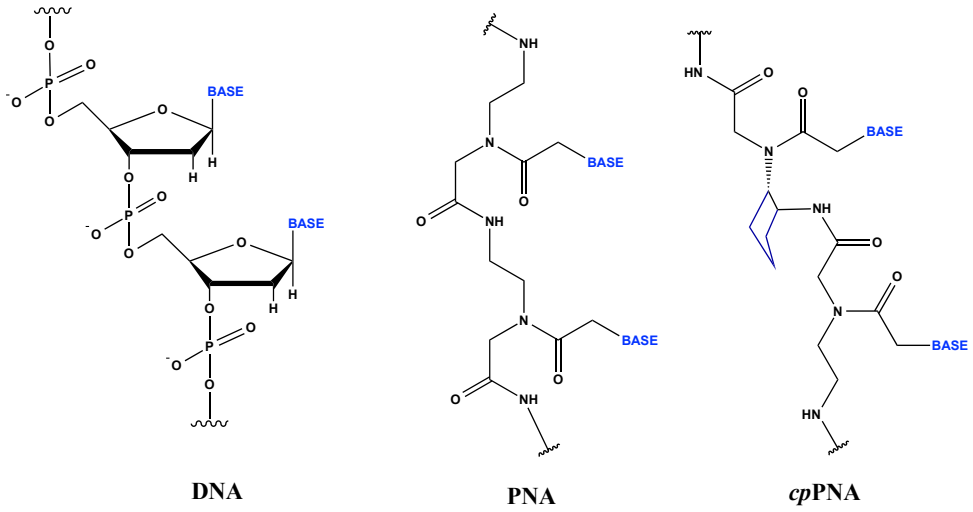
Title: Molecular dynamics study of cyclopentane-modified peptide nucleic acids

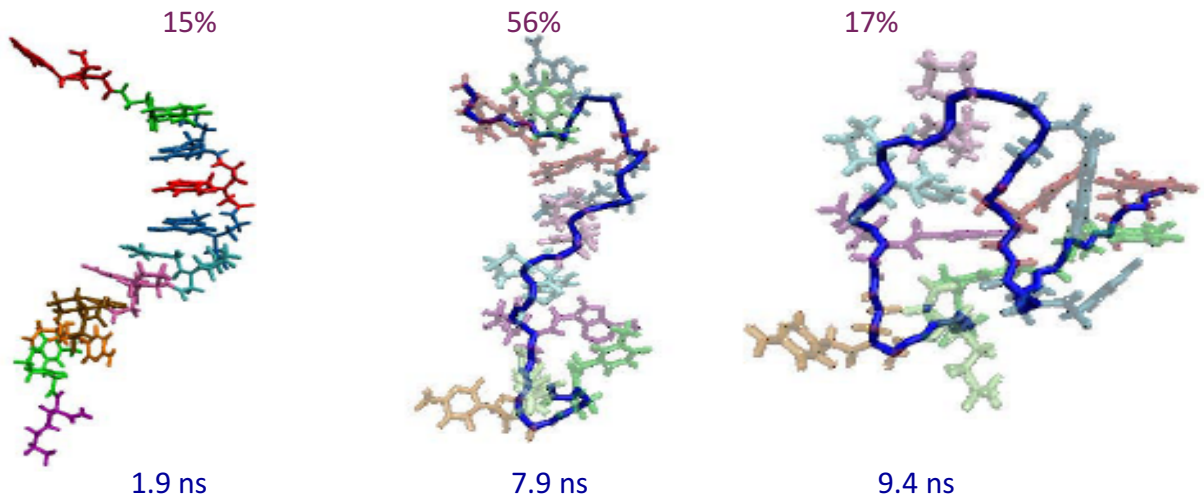
Abstract

A PNA molecule is a DNA strand where the sugar-phosphate backbone has been replaced by a structurally homomorphous pseudopeptide chain consisting of N (2-amino-ethyl)-glycine units. PNA binds strongly to both DNA and RNA. However, an analysis of the X-ray and NMR data show that the dihedral angles of PNA/DNA or PNA/RNA complexes are very different from those of DNA:DNA or RNA:RNA complexes. In addition, the PNA strand is very flexible. One way to improve the binding affinity of PNA for DNA/RNA is to design a more pre-organized PNA structure. An effective way to rigidify the PNA strand is to introduce ring structures into the backbone. In several experimental studies, the ethylenediamine portion of aminoethylglycine peptide nucleic acids (*aeg*PNA) has been replaced with one or more (S,S)-trans cyclopentyl (*cp*PNA) units. This substitution has met with varied success in terms of DNA/RNA recognition.

In the present work, molecular modeling studies were performed to investigate PNA and modified PNA analogs. Detailed investigations on the conformational and dynamical properties of single stranded *aeg*PNA and *cp*PNA were undertaken to determine how the cyclopentane ring will improve binding and to determine the contributions of both entropy and dihedral angle preference to the observed stronger binding. The effects of single and multiple modifications of the PNA backbone were also analyzed to understand changes in conformational and dynamical properties.



Comparison of DNA, PNA and *cp*PNA structures



Representative structures of the most populated clusters from MD simulations of *cp*PNA