Molecular dynamics simulations of peptide nucleic acids (PNA) based on a flexible asymmetric unit

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Abstract

Peptide nucleic acids[1] are synthetic, non-natural DNA homologues where the phosphate-ribose backbone is replaced by a peptide motif. This replacement enhances the binding properties of the hybrids and endows a higher enzymatic resistance. From their beginnings, PNA's have attracted attention as result of their potential properties at the nanoscale: therapeutics (antisense and antigene), biosensing and information tagging.[2] Despite of the different types of peptide monomers elaborated, the applications are only focused on the original aminoethylglicine PNA (Figure 1A).

Figure 1

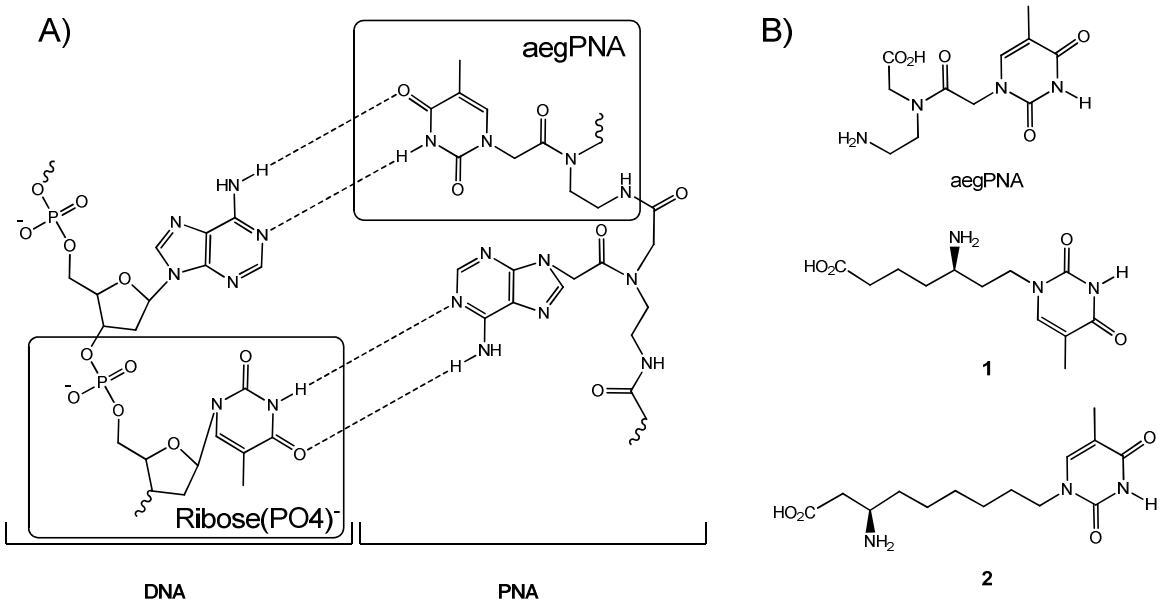

Figure1: A, structural comparison between natural DNA and aminoethylglicine type PNA (aegPNA). B: comparison between aegPNA monomer, Leumann type **1**, and homologue **2**.

A novel thymine-PNA monomer **1**, originally designed by Leumann[3], which possess a flexible backbone is being synthesized in our group in an asymmetric fashion. The methodology used is similar to the previously published[4] synthesis of a homologue **2** of Leumann´s PNA monomer (Figure 1B). Although the properties of the prime aminoethylglicine PNA monomer have been described extensively in literature, novel units require similar studies[5], advancing the knowledge about how interact these systems and the way we could take advantage of them.

We present here one of these studies, a theoretical work about the binding properties of a Leumann type PNA oligomer with a complementary natural DNA strand. We use a molecular dynamics protocol to explore the conformational behavior of the hybrid systems as well as the separated oligomers in water. Binding energies were extracted from the last frames of the simulation by means of MM-PBSA calculations.

Figure 2

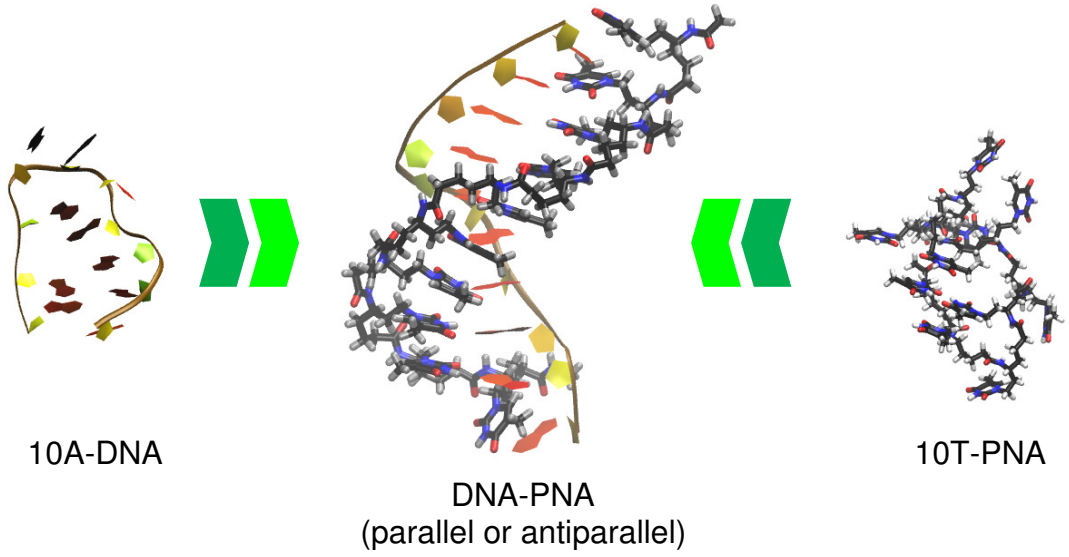

Figure 2: oligomeric systems involved in the present study at their final conformations.

The results show a mimetic behavior of the PNA strands compared with natural DNA (Figure 2), presenting helical folding with two different orientations: parallel or antiparallel. Binding energy decomposition indicates a higher binding enthalpy compared with the combination of two anticomplementary DNA natural strands, but a lower solvation free energy, due to removing the negative charge in the PNA scaffold. Neglecting entropic contributions, DNA-PNA systems have higher binding affinities, being more favorable than the original DNA-DNA duplexes.

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References

[1] Nielsen P.E., Egholm M., Berg R.H., Buchardt O., Science, **254** (1991) 1497.
[2] Nielsen P.E., Chem. Biodivers., **7** (2010) 786.
[3] Saviethri, D.; Leumann, Ch.; Scheffold, R., Helv. Chim. Acta**, 79** (1996) 288.
[4] Garrido, N. M.; Rubia, A., G.; Nieto, C.; Díez, D., Synlett, **4** (2010) 587.
[5] Siriwong, K.; Chuichay, P.; Saen-oon, S.; Chaturong, S.; Vilaivan, T.; Hannongbua, S., Biochem. Bioph. Res. Co., **372** (2008) 765.