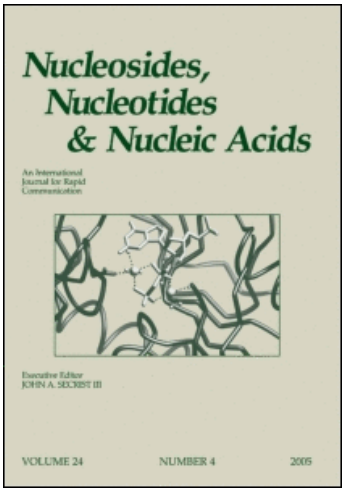

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Structural Pre-organization of Peptide Nucleic Acids

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Structural Pre-organization of Peptide Nucleic Acids

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ABSTRACT

Introduction of constraint via chemical bridging in the *aeg*PNA leads to the five or six membered cyclic structures that may contribute towards maintaining the balance between rigidity and flexibility of the PNA backbone. The significant promise of our approach to use the naturally occurring *trans*-4-hydroxy-L-proline to arrive at different chirally pure cyclic PNA analogs and their DNA binding properties will be presented.

INTRODUCTION

The advent of aminoethylglycyl peptide nucleic acids,[1] *aeg*PNAs as strong and specific DNA/RNA binding agents has triggered lot of research activity towards the development of PNA based antisense/antigene therapeutics. The efforts are mainly directed towards further refining the *aeg*PNA properties such as water solubility, cellular uptake and discrimination between parallel and antiparallel binding modes with target DNA/RNA sequences.[2] Introduction of chirality as well as positive/negative charges in the backbone have met with some success in this direction.[3]

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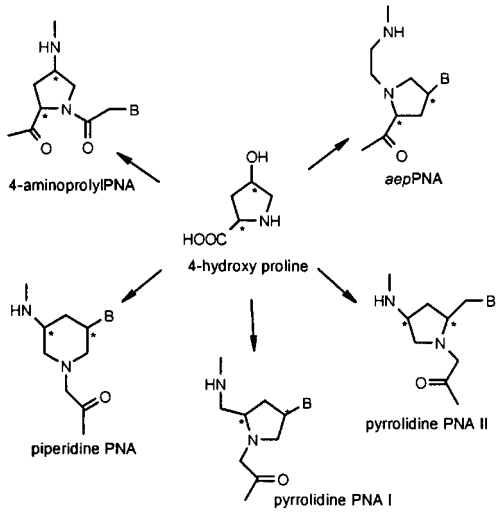
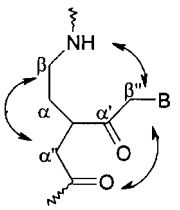
Introduction of constraint via chemical bridging in the *aeg*PNA leads to the five or six membered cyclic structures that may contribute towards maintaining the balance between rigidity and flexibility of the PNA backbone. Sufficient clamping in the *aeg*PNA backbone may reduce entropic loss and help attain a conformation for maximum enthalpic benefits from nucleobase recognition.

RESULTS AND DISCUSSION

Naturally occuring *trans*-4-hydroxy proline is an easily available starting material and is amenable for stereochemical manipulations by known synthetic methods.



The functional groups on the pyrrolidine ring can be used to introduce the required functionalities in order to synthesize the conformationally constrained PNA monomers. The constraints can be in the form of a methylene bridge that joins either the aminoethyl, glycyl or the acetyl linkers in the *aeg*PNA backbone. These efforts are recently been reviewed.[4] The 4-aminoprolylPNA is a result of a methylene bridge introduced between the β carbon atom of aminoethyl segment and the glycyl segment. Homooligomers prepared from this monomer do not bind to the target sequences and show poor water solubility. Introduction of single D-trans and L-trans units at N-terminus imparts structural preorganization as studied by CD spectroscopy and these oligomers exhibit directional selectivity of binding.



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Aminoethylprolyl PNA, *aep*PNA is another PNA modification that can be easily synthesized from hydroxy proline. A methylene bridge is inserted between β carbon atom of ethyl linker to the nucleobase and the glycyl unit. Flexibility in the aminoethyl segment of the backbone remains unaffected. The ring nitrogen is protonated at physiological pH and pyrimidine oligomers are highly water soluble and exhibit high sequence specific binding to the target oligomers with better cellular uptake. Nucleobase dependent binding selectivity is observed in the case of oligomer with mixed PNA-*aep*PNA bacbone and mixed purine-pyrimidine nucleobases.

Pyrrolidine PNA I is another PNA backbone that constrains the flexibility between aminoethyl backbone and the acetyl linker to the nucleobase. The acetamide linker is replaced by ethyl group and the pyrrolidine ring nitrogen is protonated at physiological pH. Synthesis of all four diastereoisomers arising from two chiral centers is completed. D-trans and L-trans oligothymine unit at C-terminus exhibit sequence specific binding towards natural DNA/RNA sequences. One additional atom in the backbone improves the binding efficiency. The ring nitrogen is protonated at physiological pH and oligomers are highly water soluble.

In pyrrolidine PNA II a methylene bridge is introduced between the β carbon atom of aminoethyl segment and α carbon atom of ethyl linker to the nucleobase. Oligothymines show sequence specific binding to the target DNA and discrimination is observed by change in chirality of PNA. The ring nitrogen is protonated at physiological pH and oligomers are highly water soluble.

Piperidine PNA is synthesized by a high yielding stereospecific ring expansion reaction of protected hydroxyprolinol that gives suitably substituted piperidine ring. The methylene bridge is between β carbon atoms in aminoethyl and nucleobase linker arms. The ring nitrogen is protonated at physiological pH and oligomers are highly water soluble. The homothymine mixmer PNA-piperidine PNA show interesting DNA binding properties.

CONCLUSIONS

Here we summarize our efforts to synthesize positively charged DNA mimics with constrained flexibility for applications in antisense/antigene therapeutics and other biological usages. These efforts aim towards evolving a structure having optimum structural preorganization for maximum enthalpic advantage with minimum entropic loss during the recognition process.

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