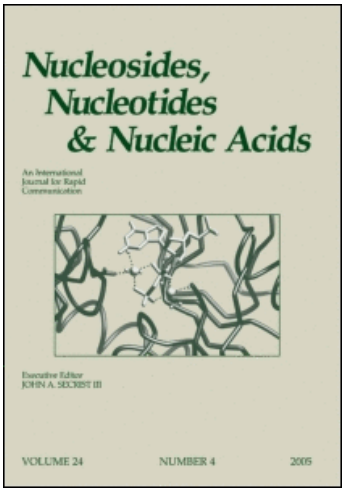

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Conformationally Restrained Chiral PNA Conjugates: Synthesis and DNA Complementation Studies

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To cite this Article Gangamani, B. P. , Decosta, M. , Kumar, V. A. and Ganesh, K. N.(1999) 'Conformationally Restrained Chiral PNA Conjugates: Synthesis and DNA Complementation Studies', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1409 — 1411
To link to this Article: DOI: 10.1080/07328319908044735
URL: http://dx.doi.org/10.1080/07328319908044735

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1409–1411 (1999)

CONFORMATIONALLY RESTRAINED CHIRAL PNA CONJUGATES: SYNTHESIS AND DNA COMPLEMENTATION STUDIES

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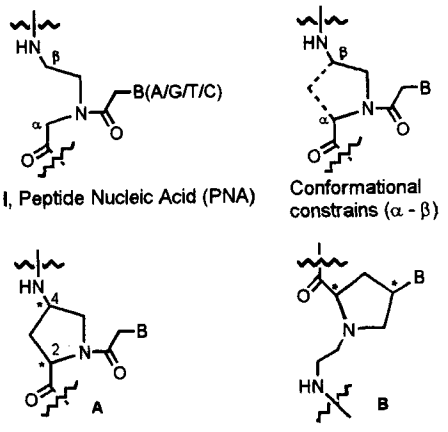
In recent times, PNA (**I**), a structural mimic of DNA in which the sugar-phosphate backbone is replaced by N-(2-aminoethyl)glycine (*aeg*) linkage has emerged as a potential antisense therapeutic agent.[1] A major limitation of PNAs from an application perspective is their poor solubility in aqueous medium and being achiral, they bind to cDNA in both parallel (N-PNA/5'-DNA) and antiparallel (N-PNA/3'-DNA) modes. In this connection, we have designed spermine conjugated and conformationally constrained PNA analogues to generate the 4-aminoprolyl backbone (**II**).[2] These were synthesised and evaluated for their DNA binding abilities by using UV and CD spectroscopic studies. It is seen that incorporation of one 4-aminoprolyl unit at the N-terminus of a PNA chain not only enhances the inherent binding of PNA to DNA, but also imparts significant bias in parallel and antiparallel binding with cDNA. Conjugation of spermine at C-terminus enhanced the PNA solubility .

The PNAs (**5,6**), prolyl PNA analogues (**1-4,7,8**) and DNA (**10-13**) (Table 1) were obtained by solid phase synthesis using appropriate monomers as described before.[2] The data on UV-T_m (Table 2) indicate that (i) conjugation of L-/D-*trans* prolylamino unit at N-terminus or within the sequence of a PNA increases the T_m of hybrids with DNA, (ii) N-terminus D-*trans* stabilizes the antiparallel binding while L-*trans* promotes parallel binding, (iii) chiral units within the sequence reverse this orientational selectivity of binding, (iv) conjugation of spermine stabilizes duplexes retaining the orientation selectivity.

Table 1. PNA and DNA sequences
NH_2-**PNA**- $CONHCH_2CH_2COOH$,
where **PNA** =

1 (Dt.T*)-$AT_2AT_2AT_2$
2 (Lt.T*)-$AT_2AT_2AT_2$
3 CTC(Lt.T*)-$AT_2AT_2AT_2$
4 CTC(Dt.T*)-$AT_2AT_2AT_2$
5 $TAT_2AT_2AT_2$
6 $CTCTAT_2AT_2AT_2$
7 6-CONH-spermine
8 4-CONH-spermine
9 3-CONH-spermine
10 5'*d* AAT AAT AAT A 3'
11 5'*d* ATA ATA ATA A 3'
12 5'*d* AAT AAT AAT AGA G 3'
13 5'*d* G AGA TAA TAA TAA 3'



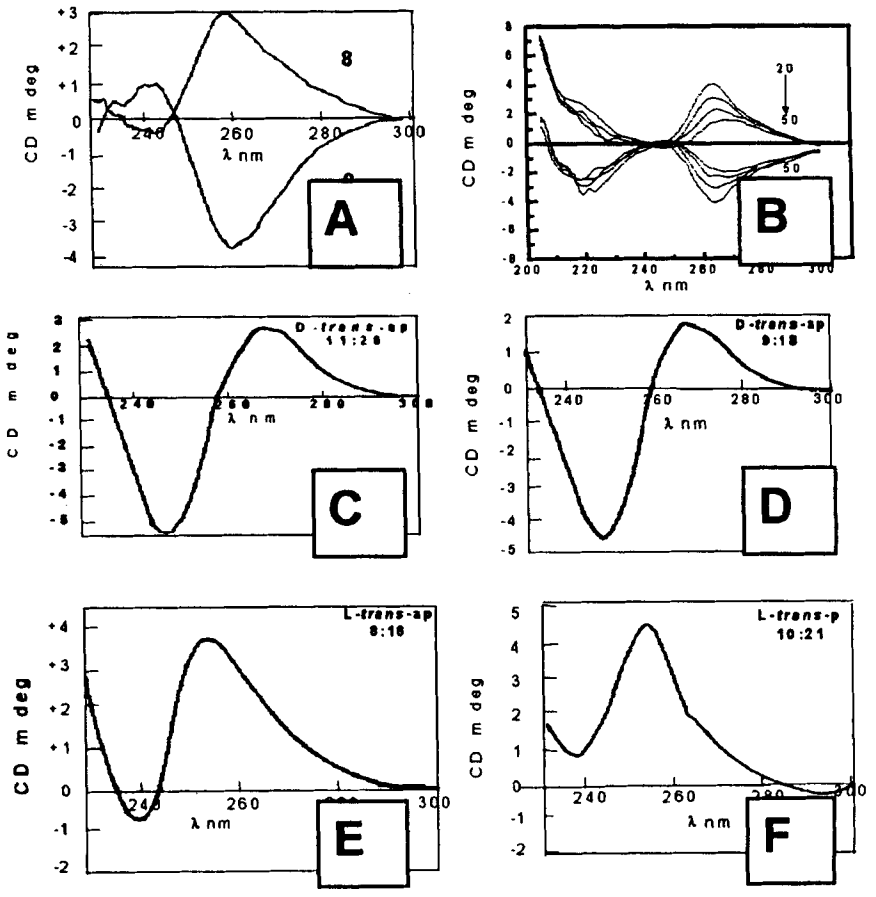


Figure 1. CD spectra of PNA:DNA hybrids

Table 2. UV-T_m of PNA:DNA hybrids

PNA	DNA	Orientation	T_m
5	**10**	*ap*	28.5
5	**11**	*p*	28.0
1 (Dt-10)	**10**	*ap*	38.5
1 (Dt-10)	**11**	*p*	31.5
2 (Lt-10)	**10**	*ap*	35.5
2 (Lt-10)	**11**	*p*	*nd*
6	**12**	*ap*	28
6	**13**	*p*	27.5
4 (Dt-13)	**12**	*ap*	33.5
4 (Dt-13)	**13**	*p*	*nd*
3 (Dt-13)	**12**	*ap*	*nd*
3 (Dt-13)	**13**	*p*	33.5
7 (*sp*-PNA)	**12**	*ap*	38.5
7 (*sp*-PNA)	**13**	*p*	*nd*
15 (Dt-13 *sp*-PNA)	**12**	*ap*	38.0
15 (Dt-13 *sp*-PNA)	**13**	*p*	34.5
16 (Dt-13 *sp*-PNA)	**12**	*ap*	42.0
16 (Dt-13 *sp*-PNA)	**13**	*p*	40.0

Circular dichroic spectra of single stranded prolyl PNAs indicate a mirror image relationship for D-*trans* and L-*trans* prolyl PNAs (Figure 1A and B). In the corresponding duplexes with cDNA , D-*trans* antiparallel duplexes show B-DNA conformation (Figure 1C and D), while L-*trans* PNA displays A-conformation (Figure 1E and F). These results suggest that considerable scope exists for chiral manipulation of PNA structures to tune them for optimal and selective interaction with cDNA.

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