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Bicyclo[3.2.1]-DNA: A DNA Analog Containing a Rigid Backbone and a Flexible Base-Pairing Region

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BICYCLO[3.2.1]-DNA: A DNA ANALOG CONTAINING A RIGID BACKBONE AND A FLEXIBLE BASE-PAIRING REGION.

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ABSTRACT: Bicyclo-[3.2.1]-pyrimidine nucleoside phosphoramidites were synthesized from a common bicyclo-[3.2.1] "sugar" intermediate. Oligomers up to 20 nucleotides in length were synthesized successfully. UV melting curve and thermodynamic analysis of these oligomers reveal stable, antiparallel duplexes

We designed the nucleoside analog bicyclo-[3.2.1] system to lock the γ and δ torsion angles to that observed in a B-DNA helix while allowing torsion angles ν^0 and ν^4 to be conformationally flexible, to which a base may be attached. With the goal in mind of incorporating this analog into nucleic acid oligomers, the appropriate pyrimidine phosphoramidite monomers **1** and **2** were synthesized.¹

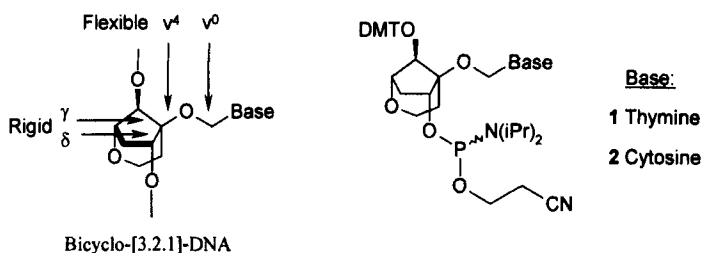


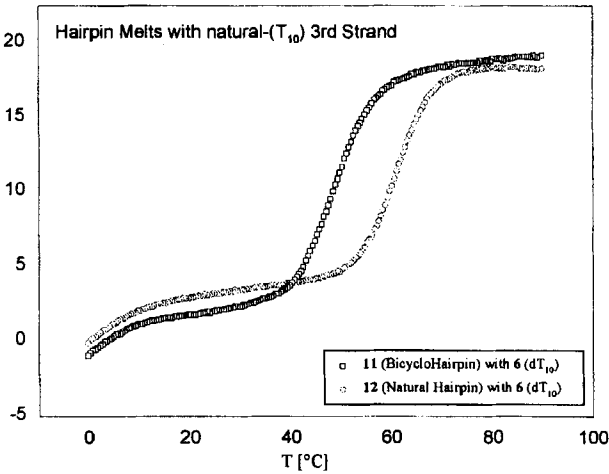
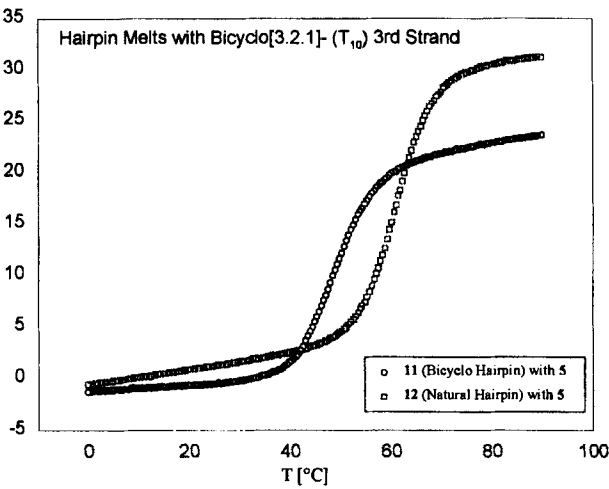
FIG. 1

Fully modified oligonucleotides up to 20 bases in length were successfully synthesized using standard automated solid-phase methodology.

- | | |
|--|---|
| 3 5'-T ₅ - <u>T</u> -T ₄ -3' | 9 5'- <u>TCT</u> ₂ C ₃ <u>TCTCT</u> ₅ <u>CT</u> ₂ T-3' |
| 4 5'-T ₃ - <u>T</u> ₄ -T ₃ -3' | 10 5'-TCT ₂ C ₃ TCTCT ₅ CT ₃ -3' |
| 5 5'- <u>T</u> ₉ T-3' | 11 5'-A ₁₀ C ₃ <u>T</u> ₉ T-3' |
| 6 5'-T ₁₀ -3' | 12 5'-A ₁₀ C ₃ T ₁₀ -3' |
| 7 5'- <u>T</u> ₅ -(<u>CT</u>) ₄ <u>CT</u> -3' | 13 5'-A ₁₀ -3' |
| 8 5'-T ₅ -(CT) ₅ -3' | 14 5'-(AG) ₅ A ₅ -3' |
| | 15 5'-A ₃ GA ₅ GAGAG ₃ AAGA-3' |
| | 16 5'-AGAAG ₃ AGAGA ₅ GA ₃ -3' |
- C = Bicyclo-[3.2.1]-cytosine, T = Bicyclo-[3.2.1]-thymine, all others are natural nucleotides.

Entry	Duplex	T _m (° C)	ΔT _m / mod.	ΔH (kcal/mol ⁻¹)	ΔS (cal K ⁻¹ mol ⁻¹)	ΔG ^{25° C} (kcal/mol ⁻¹)
A	3•13	25.5	-7.5	nd	nd	nd
B	4•13	13.3	-4.9	nd	nd	nd
C	5•13	5.0	-3.1	nd	nd	nd
D	6•13	33.0	0	nd	nd	nd
E	7•14	37.6	-1.3	-54.2 ± 0.4	-149.4 ± 1.3	-9.7 ± 0.8
F	8•14	54.9	0	-101.1 ± 0.4	-281.6 ± 1.3	-17.1 ± 0.7
G	9•15	48.1	-0.7	-94.5 ± 0.8	-268.0 ± 2.4	-14.7 ± 1.6
H	10•15	61.9	0	-150.7 ± 1.2	-420.9 ± 3.5	-25.2 ± 1.8
I	9•16	~15	n/a	n/a	n/a	n/a
J	10•16	24.6	n/a	n/a	n/a	n/a
K	11	42.6	-1.4	-47.6 ± 0.3	-150.2 ± 0.9	-3.3 ± 0.6
L	12	56.9	0	-61.7 ± 0.1	-187.2 ± 0.4	-6.4 ± 0.3

All UV melts were obtained in 10 mM Na-Cacodylate, pH 7.0, 1 M NaCl. Oligonucleotide concentration: A-D 4 μM, E-L 2 μM.



Synthesized oligonucleotides were analyzed by UV melting curves to determine the effects of bicyclo-[3.2.1]-nucleosides on duplex stability and binding orientation, and thermodynamics were determined from curve-fitting analysis.

To assess the propensity of bicyclo-[3.2.1]-DNA to bind to either natural or hybrid duplexes in the pyrimidine triplex motif, modified decamer **5** and natural decamer **6** were targetted to hairpins **11** and **12**. In each case no denaturation of third strand is visible. However, natural decamer **14** was able to bind both the natural and hybrid hairpins, demonstrating that while bicyclo-[3.2.1]-DNA is unable to bind as a third strand, its presence in a duplex does not preclude triplex formation by a natural third strand.

REFERENCE

- 1 for synthetic conditions see: Egger, A., *et al.*, *Helv. Chim. Acta*, **1998**, *81*, 734.
Epple, C., Leumann, C. *Chem. Biol.*, **1998**, *5*, 209.