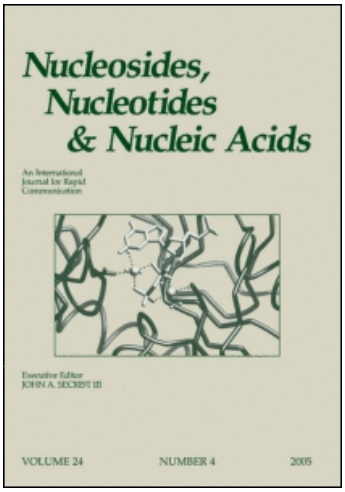

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BICYCLO[3.2.1]-DNA: A DNA ANALOG CONTAINING A RIGID BACKBONE AND A FLEXIBLE BASE-PAIRING REGION.

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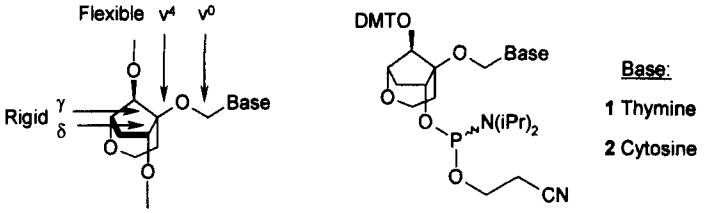
ABSTRACT: Bicyclo-[3.2.1]-pyrimidine nucleoside phosphoramidites were synthesized from a common bicyclo-[3.2.1] "sugar" intermediate. Oligomers up to 20 nucleotides in length were synthesized successfully. UV melting curve and thermodynamic analysis of these oligomers reveal stable, antiparallel duplexes

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 v^0 and v^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]



Bicyclo-[3.2.1]-DNA

FIG. 1

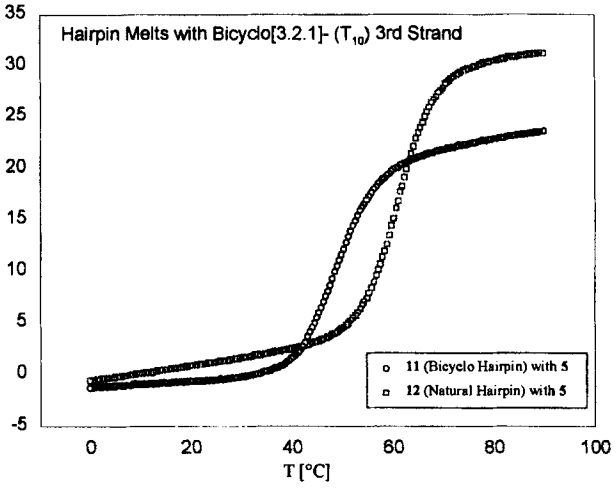
Fully modified oligonucleotides up to 20 bases in length were successfully synthesized using standard automated solid-phase methodology.

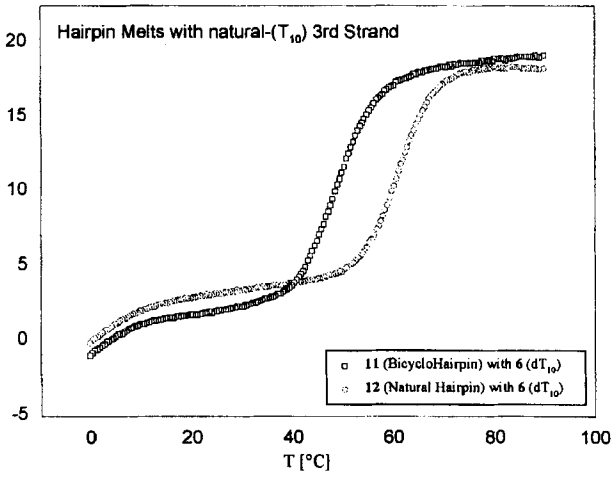
3 5'-T_5-**T**-T_4-3'
4 5'-T_3-**T**$_4$-T_3-3'
5 5'-**T**$_9$T-3'
6 5'-T_{10}-3'
7 5'-**T**$_5$-(**CT**)$_4$**C**T -3'
8 5'-T_5-$(CT)_5$ -3'
9 5'-**TCT**$_2$**C**$_3$**TCTCT**$_5$**CT**$_2$T-3'
10 5'-$TCT_2C_3TCTCT_5CT_3$-3'
11 5'-$A_{10}C_3$**T**$_9$T-3'
12 5'-$A_{10}C_3T_{10}$-3'
13 5'-A_{10}-3'
14 5'-$(AG)_5A_5$-3'
15 5'-$A_3GA_5GAGAG_3AAGA$-3'
16 5'-$AGAAG_3AGAGA_5GA_3$-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})	$\Delta G^{25°C}$ (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** 2μM.





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, modifed 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.