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Synthesis of a Cyclopentane Amide DNA Analogue and Its Base Pairing Properties

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Synthesis of a Cyclopentane Amide DNA Analogue and Its Base Pairing Properties

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ABSTRACT

cpa-DNA monomers containing the bases adenine and thymine have been synthesized starting from the known compound **1** in 12 steps. Partially and fully modified cpa-thymidine and cpa-adenosine containing oligodeoxynucleotides were synthesized by standard oligonucleotide chemistry. Fully modified homo-cpa-A sequences lead to duplex destabilization by $-1.4^{\circ}\text{C}/\text{mod.}$ relative to DNA. As its congener bca-DNA, cpa-DNA prefers left-handed duplex formation where possible.

We have recently reported on the synthesis and pairing properties of the new DNA analogue bicyclo[3.2.1]-amide (bca) DNA.^[1] In this DNA analogue the bases are attached via a linear amide linker, as in PNA, to a conformationally constrained DNA-backbone unit. This structural difference results in lengthening of the distance between the backbone and the base relative to DNA. In order to establish the importance of the structural rigidity of the bca backbone on the pairing properties, we

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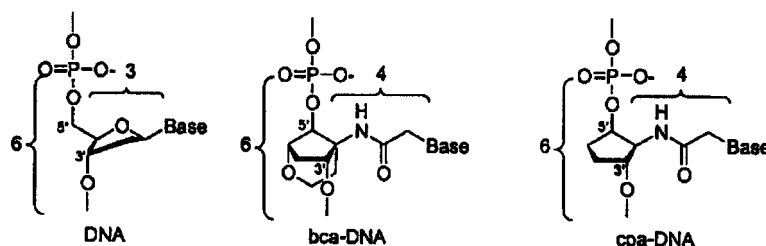
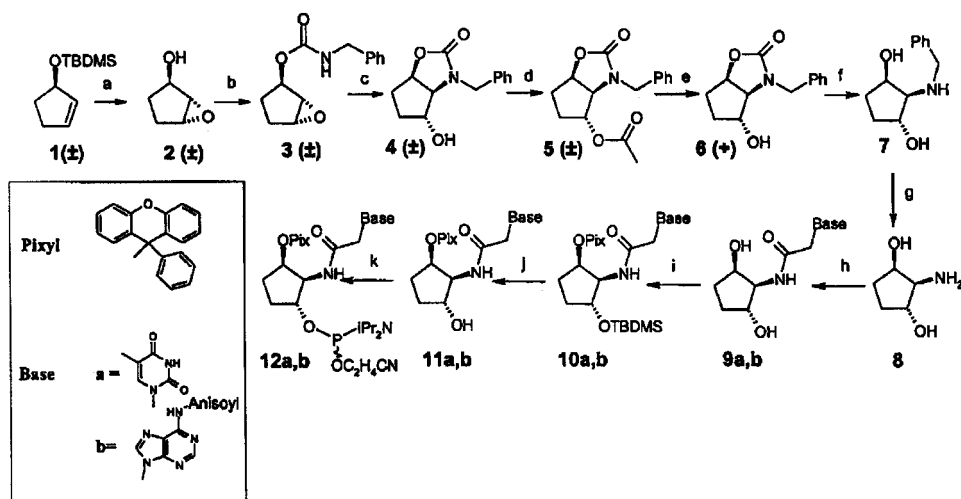


Figure 1. Representation of the chemical structures of DNA, bca-DNA and cpa-DNA, highlighting the number of bonds between base and backbone.

designed a structurally simpler variant cpa-DNA, in which the six-membered ring is absent (Fig. 1).

Starting from the known compound **1**,^[2] we synthesized the enantiopure phosphoramidite building blocks with the bases A and T in 12 steps according to Sch. 1. A series of oligonucleotides with single substitution of t^{cpa} , as well as completely modified oligonucleotides with a^{cpa} and t^{cpa} were prepared by standard phosphoramidite chemistry. Complex formation of the thus prepared sequences was then analyzed with natural and modified complements by means of UV-melting curves (T_m) and CD-spectroscopy. According to the T_m data (Table 1),



Scheme 1. a. i) mCPBA, CH_2Cl_2 , rt, 42%; ii) TBAF, THF, rt, 93%; b. BnNCO, toluene, 90°C, 79%; c. NaH, DMF, rt, 76%; d. Ac₂O, DMAP, pyridine, rt, 97%; e. PLE, phosphate buffer, pH = 7, 30°C, 31%; f. 8N KOH, 80°C EtOH, 82%; g. 10% Pd/C, H₂, MeOH, rt, 98%. h. EDC, base acid (A or T), DMF, rt, 65% for 9a, 66% for 9b; i. i) 9-chloro-(9-phenyl)-xanthene, pyridine DMSO, rt, ii) TBDMS-Cl, imidazole, DMF, rt; 33% from 9a, 31% from 9b; j. TBAF, THF, rt, 92% from 10a, 98% from 10b; k. (iPr₂N)PCl(OC₂H₄CN), DIPEA, THF, rt, 59% from 11a, 63% from 11b.

Table 1. T_m values of duplexes ($^{\circ}\text{C}$) total oligonucleotide conc.: $5\text{ }\mu\text{M}$ in 10 mM Na-cacodylate, 1 M NaCl, $\text{pH} = 7.0$.

	$d(t^{\text{cpa}})_{10}$	$dTd(t^{\text{bca}})_{10}$	$d(T)_9$	$d(T)_5dt^{\text{cpa}}d(T)_4$	$d(T)_{10}$
$d(a^{\text{cpa}})_9$	15.5	$< 1^a$	4.2	n.m	4.0
$d(A)_{10}$	n.m ^b	n.m	28.3	17.5	32.1
$r(A)_{10}$	n.m	n.m	20.1	9.7	24.5
$dTd(a^{\text{bca}})_{10}$	n.m	21.6	19.1	8.1	23.6

^aconc. = $4\text{ }\mu\text{M}$.

^bn.m = no T_m observed.

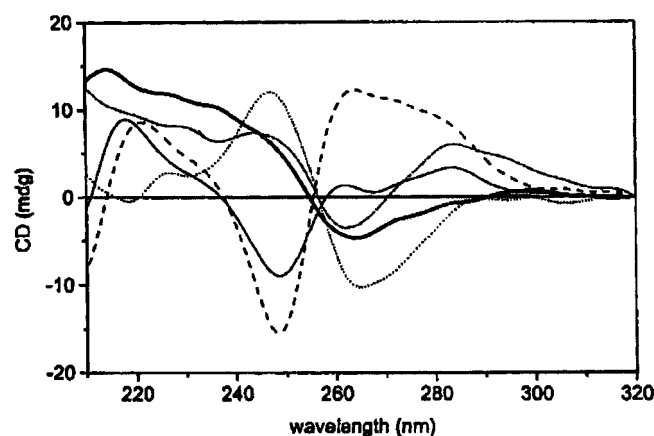


Figure 2. CD spectra of duplexes (exper. conditions as indicated in Table 1). Solid: $d(A)_{10}/d(T)_{10}$; dash: $r(A)_{10}/d(T)_{10}$; dot: $d(a^{\text{cpa}})_9$; dash dot: $d(a^{\text{cpa}})_9/d(T)_9$; thick solid: $d(a^{\text{cpa}})_9/d(t^{\text{cpa}})_{10}$.

monomodification (not unexpectedly) lead to strong duplex destabilization relative to complementary natural duplexes ($-14.6^{\circ}\text{C}/\text{mod.}$ for DNA, $-14.8^{\circ}\text{C}/\text{mod.}$ for RNA).

The modified thymidine oligomer $d(t^{\text{cpa}})_{10}$ was not able to form duplexes with a corresponding homoadenosine oligomer of any backbone type investigated except with $d(a^{\text{cpa}})_9$. However, the homoadenosine oligomer $d(a^{\text{cpa}})_9$ was able to form duplexes with homothymidine oligomers of any backbone investigated although with considerable loss in affinity relative to DNA ($< -1.4^{\circ}\text{C}/\text{mod.}$).

Interestingly the CD traces of duplexes containing $d(a^{\text{cpa}})_9$ were enantiomorphic to that of natural DNA, indicative for left-handed duplex structures (Fig. 2). The single strand $d(a^{\text{cpa}})_9$ itself seems to be preorganized as a left-handed helix contrary to that of $dTd(a^{\text{bca}})_{10}$ that is preorganized as right handed helix (data not shown). It seems therefore that removing the six-membered ring of the bicyclic backbone promotes the left-handed helix formation.



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