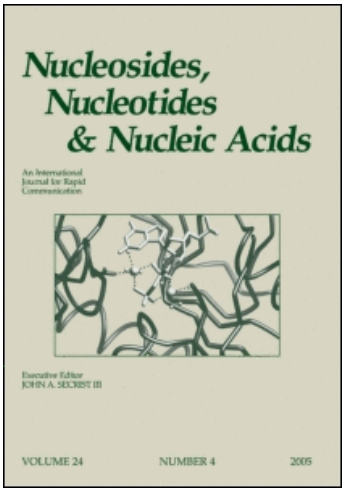

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DNA Containing Non-Nucleosidic Phenanthrene Building Blocks with Asymmetrical Linkers

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DNA CONTAINING NON-NUCLEOSIDIC PHENANTHRENE BUILDING BLOCKS WITH ASYMMETRICAL LINKERS

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□ *The synthesis and hybridization properties of oligonucleotides containing phenanthrene building blocks with non-nucleosidic linkers of different length are described. It was found that the length of the linkers, as well as the combination of unequal linkers can have a substantial influence on the thermal stability of the modified DNA.*

Keywords phenanthrene building blocks; non-nucleosidic linkers; thermal stability

Modified oligonucleotides have found widespread application as diagnostic and research tools. Furthermore, due to the repetitive, well-defined arrangement of their building blocks, nucleic acids, and related types of oligomers are ideal objects for the designed construction of larger assemblies and architectures.[1−7] In previous work we showed that non-nucleosidic phenanthrene building blocks with identical linkers on both sides can be used as base surrogates leading to stable hybrids.[8,9] We have now extended our studies to the investigation of hybrids containing non-identical linkers. These data are described herein.

The synthesis of the phenanthrene-derived phosphoramidite building blocks containing linkers of different lengths is shown in Scheme 1. The preparation of the phenanthrene derivatives started from phenanthrene-3,6-dicarboxylic acid (**1**), which had been prepared according to the method described previously.[8,10] Derivatization with the corresponding α,ω-aminoalcohols gave the amides **2a–d**. Subsequent phosphitylation provided the phosphoramidites **3a–d**. The phenanthrene-derived phosphoramidite building blocks **3a–d** were subsequently incorporated into oligonucleotides by standard oligonucleotide synthesis. Coupling yields with the modified phosphoramidites were equal to the ones obtained with automated nucleoside building blocks. After deprotection (conc. ammonia,

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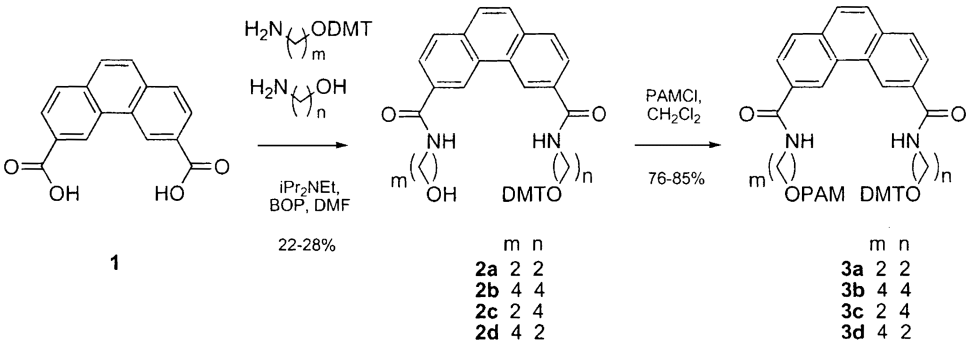
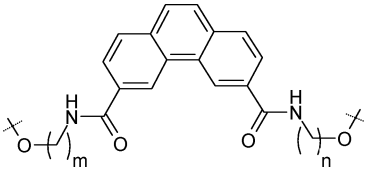


SCHEME 1 Synthesis of the phenanthrence-derived phosphoramidite building blocks.

55°C), all oligomers were purified by reversed-phase HPLC and characterized by high-resolution mass spectrometry.

Thermal denaturation experiments revealed that all phenanthrene containing oligonucleotides form a stable duplex. The data indicate that the linker length is an important factor for the overlap of the phenanthrene residues. A remarkable destabilisation results if the linker is too short for

TABLE 1 Influence of the replacement of natural base pairs by phenanthrene building blocks containing different types of non-nucleosidic linkers on the thermal stability of duplex DNA (Conditions: 100 mM NaCl, pH 7.4, 10 mM TrisHCl, 1 μM DNA duplex).

Entry	Duplex	Tm(°C)	ΔT(°C)
1	5′ AGC TCG GTC ATC GAG AGT GCA 3′ TCG AGC CAG TAG CTC TCA CGT	68.0	
2	5′ AGC TCG GTC A**2P2**C GAG AGT GCA 3′ TCG AGC CAG T**2P2**G CTC TCA CGT	62.3	**−6.7**
3	5′ AGC TCG GTC A**4P4**C GAG AGT GCA 3′ TCG AGC CAG T**4P4**G CTC TCA CGT	67.3	**−0.7**
4	5′ AGC TCG GTC A**2P2**C GAG AGT GCA 3′ TCG AGC CAG T**4P4**G CTC TCA CGT	66.3	**−1.7**
5	5′ AGC TCG GTC A**4P4**C GAG AGT GCA 3′ TCG AGC CAG T**2P2**G CTC TCA CGT	60.0	**−8.0**
6	5′ AGC TCG GTC A**2P4**C GAG AGT GCA 3′ TCG AGC CAG T**2P4**G CTC TCA CGT	66.2	**−1.8**
7	5′ AGC TCG GTC A**4P2**C GAG AGT GCA 3′ TCG AGC CAG T**4P2**G CTC TCA CGT	68.0	**0.0**
8	5′ AGC TCG GTC A**2P4**C GAG AGT GCA 3′ TCG AGC CAG T**4P2**G CTC TCA CGT	68.0	**0.0**
9	5′ AGC TCG GTC A**4P2**C GAG AGT GCA 3′ TCG AGC CAG T**2P4**G CTC TCA CGT	69.3	**1.3**
mPn			

sufficient overlap of the phenanthrenes, (see Table 1, entries 2 and 3). If phenanthrene building blocks with linkers of different length are placed in opposite positions, a difference of 6.3°C in the Tm (melting temperature) is observed between the two different possibilities (see Table 1, entries 4 and 5). Thus, it seems that the interaction of the phenanthrene units with the adjacent base pairs has a significant influence on the thermal stability of the duplex.

Hybrids with asymmetrical phenanthrene building blocks (i.e., when the two linkers on a particular phenanthrene are of different length) are generally well tolerated (Table 1, entries 6–9). The highest Tm value was observed with the hybrid containing the building block **3c** (see Scheme 1) in each oligomer (Table 1, entry 9).

In conclusion, oligodeoxynucleotides containing 3,6-disubstituted phenanthrenes with various combinations of non-nucleosidic linkers were prepared and investigated. The thermal stability of the hybrids was found to be influenced by the length of the linkers, as well as by the relative arrangement of the different linkers. In addition, also the oligonucleotide sequence is important for the stability of the respective hybrids.

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