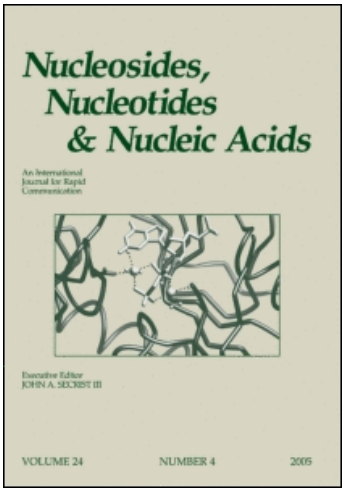

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Towards a DNA-Like Duplex Without Hydrogen Bonds

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Towards a DNA-Like Duplex Without Hydrogen Bonds

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ABSTRACT

The inverse quadrupolar moments of the phenyl and pentafluorophenyl residues in the base pair P-F^5 promotes strong intramolecular stacking interactions in DNA duplexes. The more natural base pairs are replaced by this novel pair the higher the thermodynamic stability of the resulting duplex if they are arranged in an alternating fashion.

Based on the recent observation that hydrophobic effects can be exploited in addition to complementary hydrogen bonding to create novel base pairs,[1,2], we have incorporated the pentafluorophenyl-(F^5) and phenyl-C-deoxyribosides (P) shown below (Fig. 1) into synthetic oligonucleotides. The inverse quadrupolar moments of the phenyl and pentafluorophenyl residues are expected to lead to edge-to-edge attractive intermolecular forces.[3,4]

The synthesis of phenyl-2-deoxyriboside phosphoramidite has been described before.[5] The novel pentafluorophenyl congener $\mathbf{F^5}$ was prepared starting from 2-deoxyribonolactone (Sch. 1).[6] Silyl-protected 2-deoxyribonolactone **2** was added

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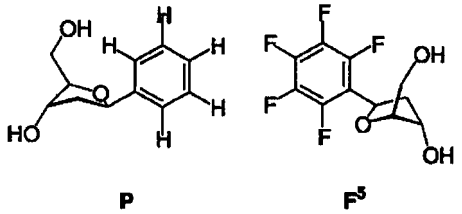
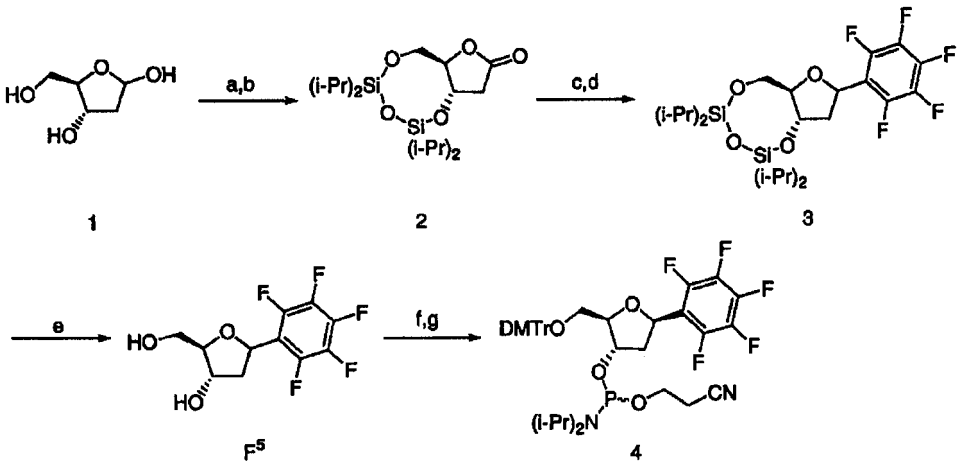


Figure 1. Structures of the monomers used to investigate the stability of F^5-P base pairs in oligodeoxynucleotide.

to lithiopenta-fluorobenzene. The intermediate hemiacetal was reduced in situ with Et_3SiH to give an inseparable 9:1-mixture (β/α) of the two anomers **3**. These could be separated by chromatography after deprotection of the deoxyribose moiety and reprotection as 5′-dimethoxytrityl ethers. Pentafluorophenyl-β-D-riboside phosphoramidite building block **4** was then obtained by standard phosphitylation. Oligonucleotides containing **P** and $\mathbf{F^5}$ (Table 1) were prepared using a regular solid-phase DNA synthesis protocol.

When incorporated in the middle of a 10-mer DNA duplex, one or two F^5-P pairs lead to destabilization as judged from thermal melting profiles. However, if four consecutive pairs of alternating sequence are present, duplex stability exceeds that of the corresponding reference duplex with four A-T base pairs in the same positions.

Experiments towards the enzymatic replication of P-F^5 base pairs have not been successful so far. The F^5 triphosphate could not be incorporated opposite P by DNA polymerase I (Klenow fragment) under running start or primer extension conditions.



Scheme 1. (a) Br_2, H_2O, r.t., 4d, dark. (b) $(^iPr_2SiCl)_2O$, imidazole DMF, r.t., 24 h, 83% (from 1). (c) BuLi, C_6F_5Br, Et_2O, −78°C, 3.5 h. (d) BF_3-Et_2O, Et_3SiH, CH_2Cl_2, −78°C to 0°C, overnight, 22% (from 2). (e) TBAF, THF, r.t., 2.5 h, 87%. (f) DMTCl, DMAP, py., r.t., 3.5 h, 70%. (g) $^iPr_2NP(Cl)OCH_2CH_2CN$, $^iPr_2EtN$, THF, r.t., 1 h, 92%.

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Table 1. T_m value [°C] determined from UV melting experiment (Duplex concentration: 4 μM. Buffer: 10 mM Na_2PO_4, 150 mM NaCl, pH 7.0. Detection at 260 nm, T_m = mean value of three melting curve, heating rate = 0.5°C/min) and thermodynamic data (Duplex concentration: 1–32 μM. Buffer: 10 mM NaH_2PO_4, 150 mM NaCl, pH 7.0).

Oligonucleotide	T_m [°C]	ΔT_m/mod [°C]	$\Delta H°$ [kcal/mol]	$\Delta S°$ [cal/mol.K]	$\Delta G°$ (25°C) [kcal/mol]
d(CTGAATCGAC)• d(GTCGATTCAG)	45.0	–	−77.6	−213	−13.8
d(CTGAPTCGAC)• d(GTCGAF^{5}TCAG)	30.6	−14.4	−61.5	−175	−9.1
$d(CTGATATCAG)_2$	38.0	–	−67.5	−192	−10.1
$d(CTGAGCTCAG)_2$	48.5	+10.5	−82.3	−231	−13.3
$d(CTGAF^5PTCAG)_2$	30.0[a]	−4.0	–	–	–
$d(CTGF^5PF^5PCAG)_2$	44.0	+1.5	−94.3	−273	−13.0

[a]Monomolecular hairpin at 4 μM.

In conclusion, complementary charge distribution as in the phenyl/pentafluorophenyl C-nucleosides $\mathbf{F^5}$ and **P** comprises a novel design principle for artificial base pairs. The results from this study highlight the importance of favorable intrastrand stacking interactions in the thermodynamic stabilization of oligonucleotide duplexes.

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