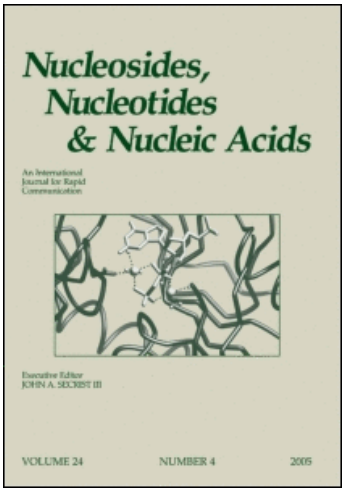

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PARALLEL-STRANDED DNA FORMED BY NEW BASE PAIRS RELATED TO THE ISOGUANINE-CYTOSINE OR ISOCYTOSINE-GUANINE MOTIFS

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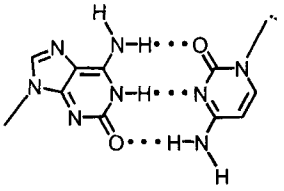
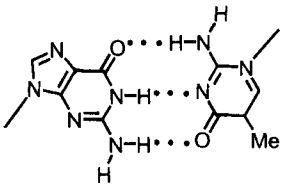
ABSTRACT: Parallel-stranded (ps) oligonucleotide duplexes containing several new base pairs formed between 7-deazaisoguanine and cytosine, 8-aza-7-deaza-isoguanine and cytosine, and 5-aza-7-deaza guanine and guanine are described. The stability of the ps-hybrids increased if the duplex contains 8-aza-7-deazaisoguanine instead of isoguanine and is decreased by 7-deazaisoguanine incorporation. The purine-purine base pair between 5-aza-7-deazaguanine and guanine was found to be more stable than that of 5-methylisocytosine with guanine.

Parallel-stranded (ps) DNA is formed when isoguanine pairs with cytosine (**I**) or isocytosine with guanine (**II**).[1-3] The $isoG_d$-dC base pair in ps-hybrids is more stable than the dG-dC pair in antiparallel-stranded (aps) duplexes. The higher stability of the $isoG_d$-dC base pair dictates the chain orientation when additional dA-dT base pairs are present.[4]

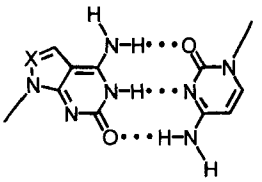


$isoG_d$ - dC (I)



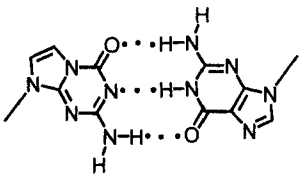
dG - me^5iC_d (II)

This report describes ps-oligonucleotide duplexes containing base pairs which are related to those of **I** or **II**. The new base pair motifs are shown below and are formed by the following nucleobases: 7-deazaisoguanine-cytosine (**IIIa**), 8-aza-7-deazaisoguanine-cytosine (**IIIb**), 5-aza-7-deazaguanine-guanine (**IV**).



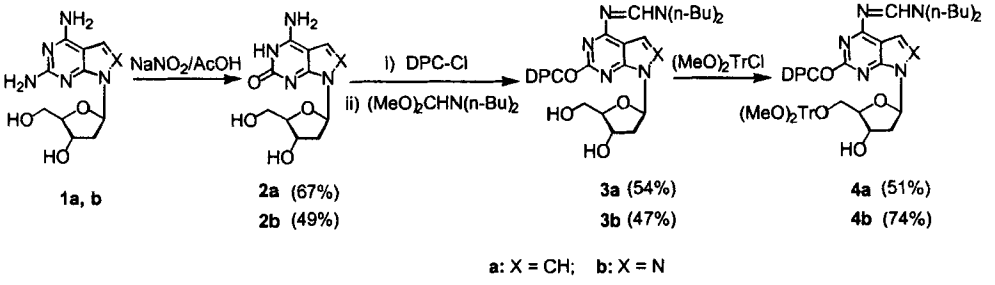
c^7iG_d - dC (IIIa, X = CH)

$c^7z^8iG_d$ - dC (IIIb, X = N)



$c^7z^5G_d$ - dG (IV)

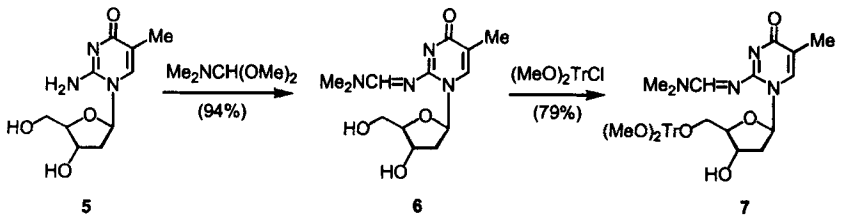
The nucleosides 7-deaza-2'-deoxyisoguanosine (**2a**) and 8-aza-7-deaza-2'-deoxyisoguanosine (**2b**) were prepared by selective deamination of compounds **1a**[5] or **1b**[6] with sodium nitrite (67% of **2a** and 49% yield of **2b**). Compounds **2a** and **2b** were protected on the oxo groups with diphenylcarbamoyl chloride (DPC-Cl) and on the amino groups with the di(n-butyl)aminomethylidene residues to give compounds **3a** and **3b**. The tritylation (**3a,b** → **4a,b**) was performed under standard conditions (Scheme 1).[7]



Scheme 1

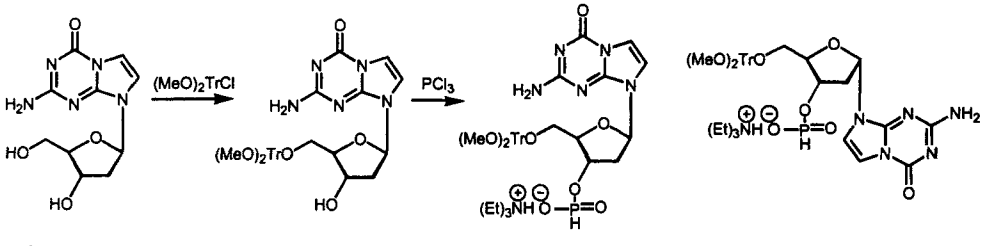
In a similar way compound **5** was converted into the DMT-derivative **7** (Scheme 2). For protection of compound **5** the *N,N*-dimethylaminomethylidene residue was chosen to give **6**. Protection with DMT-Cl furnished the derivative **7**.[8] Similar building blocks of compound **5** have already been described.[9,10] For the synthesis of the oligonucleotides containing 5-aza-7-deazaguanine the nucleoside **8a** and its α-D anomer **8b** served as starting materials. As phosphonate chemistry was employed in this case and the nucleophilicity of the amino groups of **8a,b** was low, their protection was unnecessary. The DMT-derivatives **9a** and **9b** were directly prepared from the nucleosides and then converted into the phosphonates **10a** and **10b** (Scheme 3).

During hybridization studies with ps-oligonucleotides containing $isoG_d$-dC as well as dA-dT base pairs it became apparent that the dA-dT base pairs destabilize ps-duplexes with regard to their aps-counterparts while $isoG_d$-dC base pairs increase their stability. In



5 6 7

Scheme 2



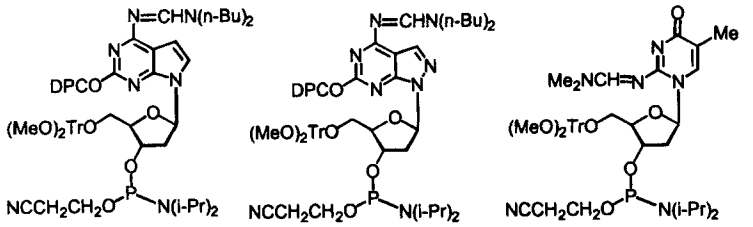
8a **9a** **10a** **10b**

8b: α-D instead of ß-D **9b:** α-D instead of ß-D

Scheme 3

order to increase the stability of duplexes with random composition further derivatives such as 7-deaza-2'-deoxyisoguanosine (**2a**) or 8-aza-7-deaza-2'-deoxyisoguanosine (**2b**) were incorporated instead of $isoG_d$ and 5-aza-7-deaza-2'-deoxyguanosine (**8a**) instead of $isoC_d$. For this purpose the phosphoramidites **11-13** were prepared. These compounds as well as **10a** and also the α-D-anomer **10b** were employed in solid-phase oligonucleotides synthesis. Although bulky DPC-groups were used in the case of compounds **11** or **12** a steric hindrance was not observed during the coupling step of solid-phase synthesis.

Table 1 shows the T_m-values as well as thermodynamic data of alternating self-complementary hexanucleotides. The replacement of $isoG_d$ by $c^7z^8iG_d$ (**16•16**) results in duplex stabilization with regard to the parent oligonucleotide (**14•14**). When compound c^7iG_d was introduced (**15•15**) the duplex became destabilized. It was also observed that the ps-duplex **17•17** showed about the same stability as that of **15•15**.



11 12 13

TABLE 1. T_m-Values of the ps-duplexes formed by alternating oligonucleotides [a]

parallel duplexes	T_m (°C)	ΔH° (kcal/mol)	ΔS° (cal/mol·K)	$\Delta G°_{298}$ (kcal/mol)
5'-d(iG-C-iG-C-iG-C) **(14)** • • • • • • 5'-d(iG-C-iG-C-iG-C) **(14)**	33	-34	-88	-6.2
5'-d(**2a**-C-**2a**-C-**2a**-C)[b] **(15)** • • • • • • 5'-d(**2a**-C-**2a**-C-**2a**-C) **(15)**	22	-40	-112	-5.3
5'-d(**2b**-C-**2b**-C-**2b**-C) **(16)** • • • • • • 5'-d(**2b**-C-**2b**-C-**2b**-C)**(16)**	41	-47	-128	-7.8
5'-d(iC-G-iC-G-iC-G) **(17)** • • • • • • 5'-d(iC-G-iC-G- iC-G) **(17)**	21	-39	-109	-5.0

a) Measured in 1 M NaCl, 0.1 M $MgCl_2$, 60 mM Na-cacodylate buffer, pH 7.0; the oligonucleotide concentration is 10 μM. b) **2a** = 7-deaza-2'-deoxyisoguanosine; **2b** = 8-aza-7-deaza-2'-deoxyisoguanosine; iC_d = 2'-deoxy-5-methylisocytidine.

Also non self-complementary duplexes were investigated (Table 2). In this case the ps-duplex with $isoG_d$-dC base pairs (**18•19**) was more stable than that containing me^5iC_d-dG (**22•23**). However, when duplexes contain the 5-aza-7-deazaguanine-guanine base pairs (**IV**) as in **20•21** an even higher stability was observed than that containing the 5-methylisocytosine-guanine pairs (**I**). This indicates that purine-purine base pairs are well accommodated in ps-DNA.

In the cases discussed above the parallel chain orientation was generated by an interchange of the substituents thereby altering the donor-acceptor pattern of one nucleobase residue. Other examples have been described which use a configurational change of the anomeric center (from ß-D to α-D) in one nucleoside residue participating in a base pair.[11] Consequently, the use of 5-aza-7-deazaguanine α-D-2'-deoxyribonucleoside (**8b**) instead of the ß-D-compound **8a** should change the orientation of the hybrid **20•21** from parallel back to antiparallel. The ß-D-oligonucleotides **20•21** formed

TABLE 2. T_m-Values and thermodynamic data of oligonucleotides [a]

duplexes	T_m (°C)	ΔH° (kcal/mol)	ΔS° (cal/mol·K)	$\Delta G°_{298}$ (kcal/mol)
5'-d(iG-iG-iG-C- C- C) (**18**) • • • • • • 5'-d(C- C- C-iG-iG-iG) (**19**)	46	-63.8	-174.2	-9.8
5'-d(**8a-8a-8a**-G -G -G)[b] (**20**) • • • • • • 5'-d(G- G -G-**8a-8a-8a**) (**21**)	50	-50.0	-128.0	-9.7
5'-d(iC-iC-iC-G- G- G) (**22**) • • • • • • 5'-d(G- G- G-iC-iC-iC) (**23**)	35	-48.8	-132.2	-7.8
5'-d(**8b-8b-8b**-G -G -G) (**24**) • • • • • • 3'-d(G- G -G-**8b-8b-8b**) (**24**)	54	-49	-127	-9.5

a) see Table 1. b) **8a** = 5-aza-7-deaza-2'-deoxyguanosine; **8b** = α-D-anomer of 5-aza-7-deaza-2'-deoxyguanosine; iC_d = 2'-deoxy-5-methylisocytidine.

only a stable duplex in a mixture when the chains could be aligned under parallel orientation. The oligonucleotide **24** formed a self-complementary aps-duplex with a rather high T_m-value of 54°C (Table 2). The chain orientation of this duplex (**24•24**) is antiparallel which is the result of the configurational change at the anomeric center (**8a** → **8b**). It is interesting that such a stable purine-purine duplex is formed although the configurational change from ß-D to α-D occurs within the same strand of the oligonucleotide duplex.

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7. Selected data for **4b**: ^{1}H NMR ($(CD_3)_2SO$) δ 0.94(6H, m, 2 x CH_3), 1.28 and 1.99(8H, 2m, 2 x CH_2CH_2), 2.31 and 2.77(2H, 2m, H-2'), 3.01 and 3.53(4H, 2m, 2 x NCH_2), 3.65-3.67(8H, m, H-5' and 2 x CH_3O), 3.94(1H, m, H-4'), 4.55(1H, m, H-3'), 5.32(1H, d, HO-3'), 6.56(1H, m, H-1'), 6.68-7.44(23H, m, DMT and DPC), 8.05(1H, s, H-3), 8.85(1H, s, HC=N).
8. Selected data for **7**: ^{1}H NMR ($(CD_3)_2SO$) δ 1.46(3H, s, CH_3), 2.21(2H, m, H-2'), 3.04(3H, s, CH_3N), 3.16(3H, s, CH_3N), 3.21(2H, m, H-5'), 3.73(6H, s, 2 x CH_3O), 3.92(1H, m, H-4'), 4.33(1H, m, H-3'), 5.30(1H, d, HO-3'), 6.70(1H, t, J = 7.2 Hz, H-1'), 6.84-7.31(13H, m, DMT), 7.69(1H, s, H-6), 8.59(1H, s, HC=N).
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