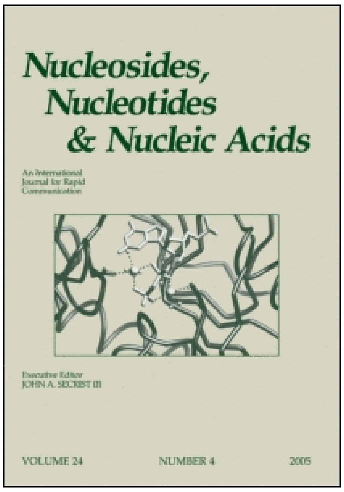

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SYNTHESIS AND BASE PAIRING PROPERTIES OF 9-DEAZAPURINE N^7-NUCLEOSIDES IN OLIGONUCLEOTIDE DUPLEXES AND TRIPLEXES

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ABSTRACT

The 9-deazaguanine N^7-2′-deoxyribofuranoside (**3**) as well as the bromo and iodo derivatives **4a**,**b** were synthesized and incorporated in oligonculeotide duplexes and triplexes. Their base pairing properties were investigated and compared with those of the parent purine N^7-2′-deoxyribofuanosides.

INTRODUCTION

Several reports have communicated on the base pairing properties of nucleosides linked via nitrogen-7 or position-8 to the nucleobase (1–3). The nucleosides **1** and **2** with the unusual N^7-glycosylation site form stable base pairs in duplex and triplex DNA (1,2,4). Now, we report on the synthesis and base pairing properties of the 9-deazaguanine N^7-nucleosides **3** and **4a**,**b** which are remarkably stable analogs of the purine nucleosides. The pyrrolo[3,2-d]pyrimidine nucleosides were incorporated in oligonucleotide duplexes as well as in triplex-DNA. Their base pairing properties were compared with compound **2**.

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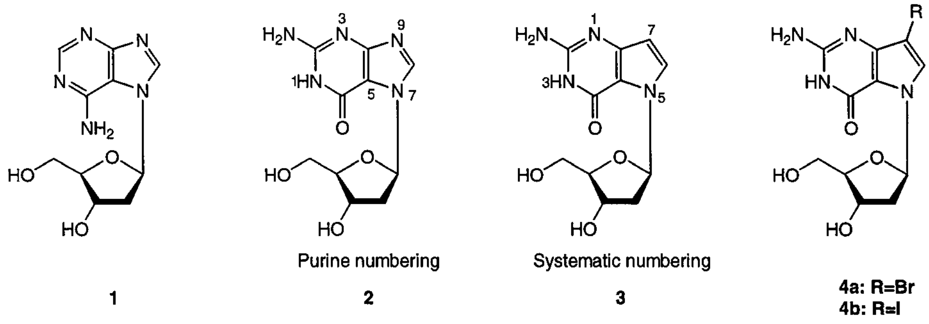
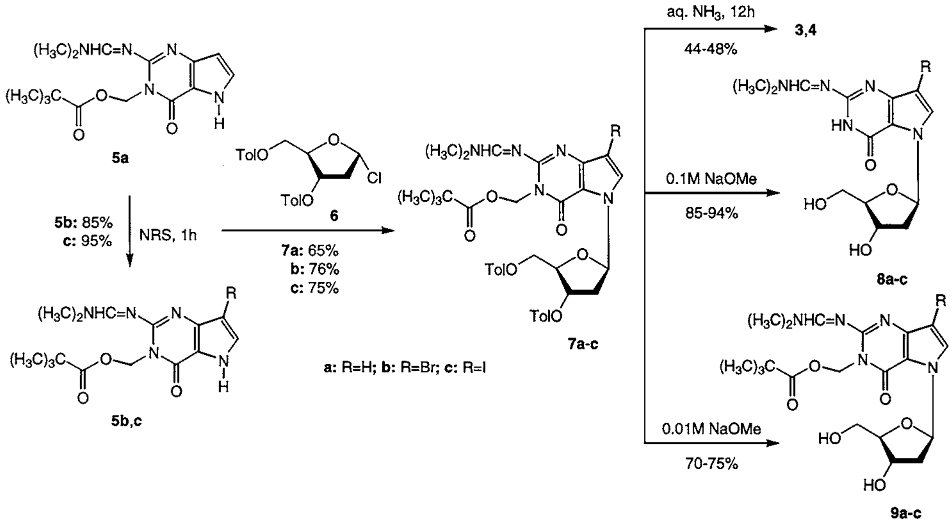
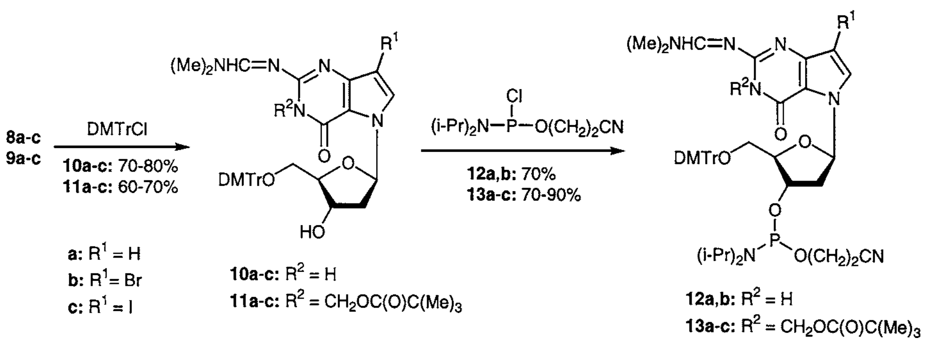
*Corresponding author.



Scheme 1.



Scheme 2.



Scheme 3.

Table 1. Antiparallel Duplexes with N^{7}G$_d$-iC$_d$ and c^{9}N^{7}G$_d$-iC$_d$ Base Pairs[a)]

aps-Duplexes		Tm [°C]	aps-Duplexes		Tm [°C]
5′-d(TAGGTCAATACT)	**14**	47	5′-d(TA**4a4a**T CAATA CT)	**16**	40
3′-d(ATCCAGTTATGA)	**15**		3′-d(AT**iCiC** A GTTATGA)	**17**	
5′-d(TA**iCiC**TCAATA CT)	**18**	40	5′-d(TA**4b4b**TCAATA CT)	**20**	40
3′-d(AT **2 2** AGTTATGA)	**19**		3′-d(AT**iCiC** A GTTATGA)	**17**	
5′-d(TA **3 3** T CAATACT)	**21**	38			
3′-d(AT**iCiC** A GTTATGA)	**17**				

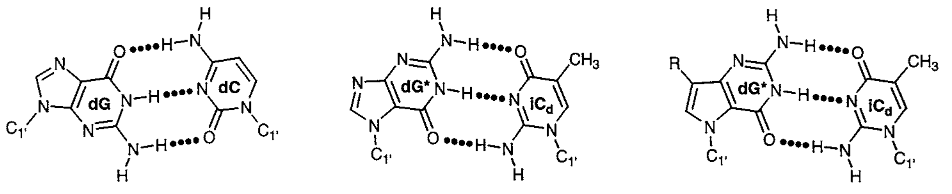
[a)] Measured at 260 nm in 0.1M NaCl, 10 mM MgCl$_2$, and 10 mM Na-cacodylate (pH 7.0) at 5 μM of single strand concentration. iC$_d$ = 5-methyldeoxyisocytidine.

RESULTS AND DISCUSSION

The synthesis of the nucleosides **3** (5) and **4a**,**b** utilized the nucleobases **5a** (6) and **5b**–**c** as precursors. Compounds **5b**,**c** were obtained from **5a** by regioselective halogenation. The stereoselective nucleobase-anion glycosylation of **5a**–**c** with the halogenose **6** furnished the N^7-β-D-nucleosides **7a**–**c**. Deblocking of **7a**–**c** (0.01M NaOMe) resulted in a selective detoluoylation (→**9a**–**c**), while treatment of **7a**–**c** with 0.1M NaOMe cleaved the pivaloyloxymethyl group (→**8a**–**c**). Treatment of **7a**–**c** with conc. aq. NH$_3$ furnished the nucleosides **3** and **4**.

Next, formamidine protecting groups were introduced. The half-life values of depotection were 8 min for **8a**, 12 min (**8b**) and 17 min (**8c**) (25% aq. NH$_3$, 40°C). The protected nucleosides **8a**,**b** as well as **9a**–**c** were tritylated (→ **10a**–**c** and **11a**–**c**) and were converted in building blocks for solid-phase synthesis (**12a**,**b** and **13a**–**c**).

The base-pairing properties of the nucleosides **3** and **4a**,**b** were investigated on duplexes with antiparallel chain orientation. According to Table 1 compounds **3** and **4a**,**b** form base pairs with 5-methyl-2′-deoxyisocytidine (iC$_d$) in aps-duplexes (**16·17**, **20·17** and **21·17**). This is in line with observations made on the base pairing properties of the purine N^7-nucleoside **2** (2) (see duplex **18·19**). In this case a strong base pair with iC$_d$ was formed. Furthermore, the bulky bromo and iodo substituents



WC-Base Pair I

Reverse WC-Base Pair II
dG* = **2**

Reverse WC-Base Pair III
dG* = **3, 4a,b**

Scheme 4.

Table 2. Oligonucleotides Forming the Base Triplets **3**:dG-dC and dC:dG-dC[a]

5′-d(TTT**X**TTTT**X**T**X**T**X**TT
5′-d(GCGCGAAA**G**AAAA**G**A**G**A**G**AACCCGG)
3′-d(CGCGCTTT**C**TTTT**C**T**C**T**C**TTGGCC)

5′-d(TTT**X**TTTT**XXXXX**TT
5′-d(GCGCGAAA**G**AAAA**GGGGG**AACCCGG)
3′-d(CGCGCTTT**C**TTTT**CCCCC**TTGGCC)

X	T_m [°C] pH 6.5	T_m [°C] pH 8.0	**X**	T_m [°C] pH 6.5	T_m [°C] pH 8.0
3	45/72	44/72	**3**	53/74	52/74
C	45/72	16/72	**C**	24/74	n.t./74

[a] Measured at 260 nm in 10 mM HEPES, 50 mM NaCl, 10 mM $MgCl_2$ and 0.5 mM spermine at 1 μM of single strand concentration. N.t.: no transition.

introduced in position-9 of the heterocycle (**4a**,**b**) are well accommodated in the duplex structure.

The results of Table 1 raise the question about the structure of the base pairs. Several base pair motives were considered. Due to the almost identical T_m-values of the duplexes containing **2**,**3** and **4a**,**b** and the fact that the tridentate base pairs (II and III) are similar to the tridentate WC-base pair of I, the motifs II and III are the most likely ones.

Earlier, the triplex formation of oligomers containing N^7G_d(**2**) as well as of an acyclic derivative of **2** recognizing a dG-dC pair of a duplex DNA was described (4,7). Now, compound **3** was introduced into the third strand of a triplex (Table 2). Sigmoidal melting curves with a biphasic profile were obtained in all cases. The higher T_m-values are assigned to the duplex melting while the lower ones describe the triplex dissociation.

Table 2 shows that triplex melting is independent from the pH-value, when compound **3** is a constituent of the base triplet. The triplexes containing dC-residues at that position require protonation before triplex formation. As the sugar phosphate backbone of the pyrimidine-rich third strand becomes distorted by the incorporation of **3**, the stability of the triplex is higher when the **3**-residues are in a consecutive order instead of being dispersed. The advantage of compound **3** compared to **2** is its remarkable glycosylic bond stability and the possibility to introduce reporter groups at the 9-position (**4a**,**b**).

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