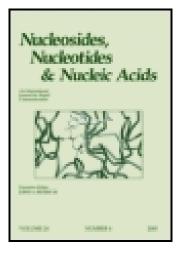
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Duplex Stability of Oligonucleotides Containing 7-Substituted 7-Deaza- and 8-Aza-7-Deazapurine Nucleosides

F. Seela^a, N. Ramzaeva^a & M. Zulauf^a ^a Laboratoriurn für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastr. 7, D-49076, Osnabrück, Germany Published online: 16 Aug 2006.

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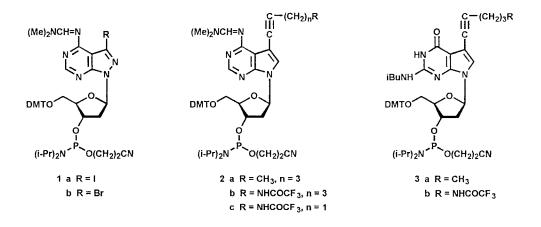
DUPLEX STABILITY OF OLIGONUCLEOTIDES CONTAINING 7-SUBSTITUTED 7-DEAZA- AND 8-AZA-7-DEAZAPURINE NUCLEOSIDES

F. Seela*, N. Ramzaeva, and M. Zulauf

Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastr. 7, D-49076 Osnabrück, Germany.

ABSTRACT.- The synthesis of 7-substituted 7-deaza- and 8-aza-7-deazapurine 2'deoxyribonucleosides, their incorporation into oligonucleotides, and the stability of corresponding duplexes is described.

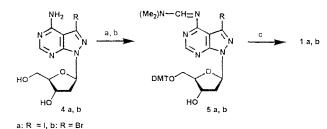
The presence of methyl, as well as halogeno substituents in position 7 of a series of 7-deazapurine-containing oligonucleotides leads to duplex stabilization with retention of the B-DNA structure.^{1,2} In continuation of our investigations on the properties of base-modified oligodeoxynucleotides we now report on the synthesis of the phosphoramidites **1-3** of 7-substituted 8-aza-7-deaza-2'-deoxyadenosine, as well as 7-deazapurine 2'-deoxyribonucleosides. They are employed in solid-phase synthesis of oligonucleotides which are then investigated with regard to duplex stability.



Compounds **4a**,**b**³, **6**⁴, and **9**⁵ served as precursors for the synthesis of the protected nucleosides **5a**,**b**, **8a**-**c** and **11a**,**b** (Scheme 1), which were then converted into

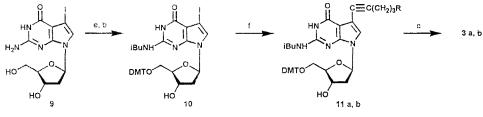
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(Me₂)N-CH-N NH2 Ç≣C-CH₂R Ç≣C-CH₂R d a, b 2 a-c но HO DMTO нό нσ́ нο 6 7 a-c 8 a-c

a: $R = (CH_2)_2CH_3$, b: $R = (CH_2)_2NHCOCF_3$, c: $R = NHCOCF_3$



a: $R = CH_3$, b: $R = NHCOCF_3$

(a): HC(OMe)_2NMe_2, MeOH; (b): DMT-Cl / pyr.; (c): NC(CH_2)_2OP(Cl)N(i-Pr)_2, EtN(i-Pr)_2, CH_2Cl_2; (d): Pd(PPh_3)_4, Cul, DMF, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , pyr.; (f): Pd(PPh_3)_4, Cul, CH_3CN, Et_3N; (e): TMS-Cl, iBu_2O , iBu_2O , iB

Scheme 1

phosphoramidites. The ω -(trifluoroacetyl)aminoalkynyl- and hexynyl nucleosides **7a-c**, and **11a,b** were prepared using the palladium-catalyzed cross-coupling reaction⁶. All compounds were characterized by ¹H-⁷, ¹³C-, and ³¹P-NMR spectra as well as by elemental analyses.

The oligonucleotides containing 7-bromo or 7-iodo-7-deazapurine 2'deoxyribonucleosides exhibit significantly higher T_m -values than those containing 2'deoxyadenosine or -guanosine (Table 1).

Oligonucleotide	⊤ _m [°C] ^a	Oligonucleotide	T _m [°C] ^b
d(A -T) ₆	33	d(G -C)₄	60
d(c ⁷ A - T) ₆	36	d(c ⁷ G - C) ₄	53
d(c ⁷ l ⁷ A - T) ₆	60	d(c ⁷ ⁷ G - C) ₄	70
d(c ⁷ Br ⁷ A - T) ₆	55	d(c ⁷ Br ⁷ G - C)₄	67
d(c ⁷ Me ⁷ A - T) ₆	41	d(c ⁷ Me ⁷ G - C)₄	58
d(c ⁷ Hex ⁷ A - T) ₆	50	d(c ⁷ Hex ⁷ G - C)₄	58
d(c ⁷ X ⁷ A - T) ₆ ^c	50		
d(c ⁷ z ⁸ Br ⁷ A - T) ₆	52		
d(c ⁷ z ⁸ l ⁷ A - T) ₆	56		
d(c ⁷ z ⁸ A - T) ₆	36		

TABLE 1. T_m-Values of 7-deazapurine-containing oligonucleotides.

^a 8 μM Oligomer conc., 60 mM Na-cacodylate, pH 7.1, 100 mM MgCl₂, 1 M NaCl; ^b 10 μM oligomer conc., 10 mM Na-cacodylate, pH 7, 10 mM MgCl₂, 100 mM NaCl; ^c X = $C \equiv CCH_2NH_3^{\oplus}$.

Although, 7-deaza-2'-deoxyguanosine destabilizes the duplex structure $[d(c^{7}G-C)_{4}]$ compared to the parent oligonucleotide containing 2'-deoxyguanosine $[d(G-C)_{4}]$, the replacement of the 7-hydrogen by a methyl $[d(c^{7}Me^{7}G-C)_{4}]$ or a hexynyl group $[d(c^{7}Hex^{7}G-C)_{4}]$ increases the stability of the duplex strongly.

On the other hand, the duplex $d(c^7A-T)_6$ is slightly more stable than $d(A-T)_6$. The replacement of the 7-hydrogen by a methyl $[d(c^7Me^7A-T)_6]$, a hexynyl $[d(c^7Hex^7A-T)_6]$, as well as a 7-(3-aminopropynyl) group $[d(c^7X^7A-T)_6]$ leads to further stabilization of the duplexes (Table 1). In the case of 8-aza-7-deaza-2'-deoxyadenosines the introduction of bromo or iodo substituents in position 7 (1a,1b) shows the same tendency of duplex stabilization as 7-deaza-2'-deoxyadenosines.

Table 1 indicates that substituents in the 7-position of 7- deazapurines have considerable steric freedom within the major groove of DNA and may carry bulky substituents without significantly interfering overall binding. Therefore, the 7-position of 7-deazapurines is an ideal position for the functionalization of DNA with reporter groups.

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- 5a: ¹H-NMR (d₆-DMSO): δ, 2.30 (1H, m, H-2'), 2.84 (1H, m, H-2'), 3.06 (2H, m, 2H-5'), 3.76, 3.78 (6H,2s, NMe₂), 3.71, 3.72 (6H, 2s, 2 OMe), 3.95 (1H, m, H-4'), 4.51 (1H, m, H-3'), 5.30 (1H, d, 3'-OH), 6.58 (1H, t, H-1'), 6.76-7.37 (13H, m, arom. H), 8.47 (1H, s, H-6), 8.98 (1H, s, CH).

8b: ¹H-NMR (d₆-DMSO): δ, 1.74 (2H, m, CH₂), 2.23 (1H, m, H-2'), 2.46 - 2.48 (3H, m, CH₂, H-2'), 3.11, 3.15 (6H, 2s, NMe₂), 3.13 (2H, m, 2H-5'), 3.33 (2H, m, CH₂), 3.74 (6H, s, OCH₃), 3.91 (1H, m, H-4'), 4.34 (1H, m, H-3'), 5.29 (1H, d, 3'-OH), 6.54 (1H, t, H-1'), 6.82-7.36 (13H, m, arom. H), 7.56 (1H, s, H-6), 8.29 (1H, s, H-2), 8.73 (1H, s, CH), 9.43 (1H, s, NH).

11b: ¹H-NMR (d₆-DMSO): δ, 1.12 (6H, m, 2 Me), 1.74 (2H, m, CH₂), 2.23 (1H, m, H-2'), 2.41 (2H, m, CH₂), 2.76 (1H, m, CH), 3.11 (2H, m, 2H-5'), 3.30 (2H, m, CH₂), 3.72 (6H, s, 2 OCH₃), 3.90 (1H, m, H-4'), 4.32 (1H, m, H-3'), 5.27 (1H, d, 3'-OH), 6.39 (1H, t, H-1'), 6.85-7.37 (14H, m, arom.H, H-6), 9.47 (1H, t, NHCOCF₃), 11,53 (1H, s, NH), 11.81 (1H, s, NH).