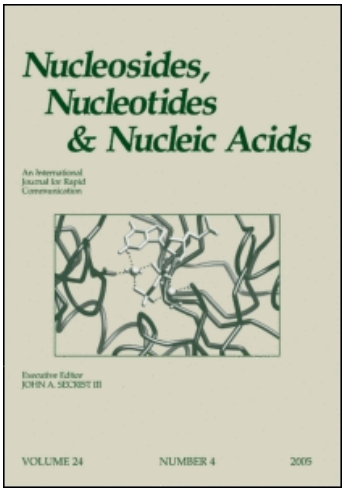

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Helmut Rosemeyer[a]; Natalya Ramzaeva[a]; Matthias Zulauf[a]; Horst Thomas[a]; Yaoming Chen[a]; Cathrin Mittelbach[a]; Frank Seela[a]
[a] Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Osnabrück, Germany

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STERIC AND STEREOELECTRONIC EFFECTS OF 7-DEAZAPURINE BASES ON THE SUGAR CONFORMATION OF 2'-DEOXYNUCLEOSIDES

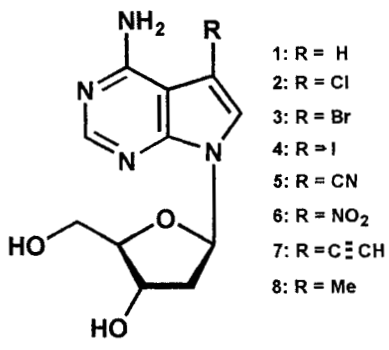
Helmut Rosemeyer, Natalya Ramzaeva, Matthias Zulauf, Horst Thomas, Yaoming Chen, Cathrin Mittelbach, and Frank Seela*

Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastr. 7, D-49069 Osnabrück, Germany.

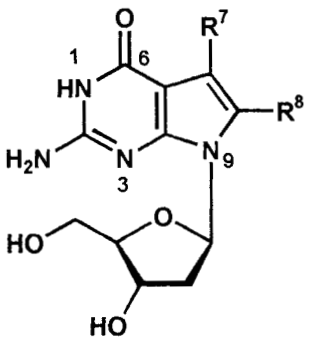
ABSTRACT.- Conformational analyses of the sugar moieties of a series of 7-(8)-substituted 7-deazapurine-2'-deoxynucleosides on the basis of vicinal [^{1}H,^{1}H] coupling constants is presented using the *PSEUROT 6.0* program.

An antisense construct of an oligo(2'-deoxyribonucleotide) has to adopt A-conformation if it is bound to the RNA target. One of the characteristics of an A-DNA is the $C_{3'}$-endo pucker (north sugar); the B-DNA exhibits a $C_{2'}$-endo pucker (south sugar). Therefore, the synthesis of 2'-deoxyribonucleosides which show the maximal N-conformer populations of the sugar moiety is of interest.

In 7-deazapurine 2'-deoxyribonucleosides it is found that the substituents of the pyrrole ring can influence the sugar puckering. Such conformational changes on a series of 7-(8)-substituted 7-deazapurine-2'-deoxynucleosides (formula scheme, **1** - **17**)[1-3] have been studied on the basis of vicinal [^{1}H,^{1}H] coupling constants using the *PSEUROT 6.0* program[4,5].



1: R = H
2: R = Cl
3: R = Br
4: R = I
5: R = CN
6: R = NO_2
7: R = C≡CH
8: R = Me



9: $R^7 = R^8 = H$
10: R^7 = Cl; R^8 = H
11: R^7 = H; R^8 = Cl
12: R^7 = Br; R^8 = H
13: R^7 = I; R^8 = H
14: R^7 = Me; R^8 = H
15: R^7 = H; R^8 = Me
16: $R^7 = R^8$ = Cl
17: R^7 = Hexin(1)-yl
R^8 = H

TABLE. ^{3}J(H,H) Coupling constants of the sugar moieties and N/S-conformer populations of compounds **1-17** at 303K.

Compound	^{3}J(H,H) [Hz] 1',2'	1',2''	2',3'	2'',3'	3',4'	Conformation % N	%S
dA	7.20	6.50	6.50	3.30	3.20	28	72
1	6.60	7.60	7.00	3.00	3.00	24	76
2	7.50	6.35	6.25	3.25	3.50	30	70
3	7.05	6.55	6.60	3.15	3.40	29	71
4	6.90	6.50	6.50	3.10	3.30	29	71
5	6.80	6.55	6.25	3.65	3.45	34	66
6	6.80	6.75	6.00	4.15	3.85	38	62
7	7.50	6.40	6.20	3.20	3.40	29	71
8	8.00	6.25	6.15	3.05	3.00	26	74
dG[6]	7.30	6.50	6.30	3.60	3.20,	29	71
9	7.25	6.50	6.25	3.00	3.35	28	72
10	6.95	6.60	6.65	3.70	3.80	34	66
11	7.45	7.20	6.80	2.85	3.30	22	78
12	6.50	6.90	6.40	3.00	3.00	28	72
13	6.60	7.00	6.40	3.20	3.60	31	69
14	7.20	6.45	6.20	3.05	3.25	28	72
15	8.00	6.70	6.75	2.25	3.20	18	82
16	7.30	7.30	7.10	3.50	3.65	27	73
17	7.55	6.45	6.10	3.20	3.10	28	72

Solvent, D_2O; RMS, $\leq$ 0.4 Hz; $|\Delta J_{max}| \leq$ 0.5 Hz

Calculations were performed using pseudorotational starting parameters recommended in the user's manual of the program [Φ_{max} = 36° (both N and S); P_N = 19°; P_S = 156°]. The input contained the following coupling constants: J(H1',H2'), J(H1',H2''), J(H2',H3'), J(H2'',H3'), and J(H3',H4'). During the iterations either the puckering parameters (P, Φ_{max}) of the minor conformer (N) or the puckering amplitudes of both conformers were constrained. In all cases the RMS values were $\leq$ 0.4 Hz and the $|\Delta J_{max}| \leq$ 0.5 Hz.

From the data given in the table some general trends can be deduced: Enhancement of the bulkyness of a substituent in position 8 drives the N $\Leftrightarrow$ S equilibrium of a 7-deaza-2'-deoxyguanosine (**9**, **11**, **15**) towards S sugar puckering. This conformation generally correlates with the syn-conformation at the N-glycosylic bond. The nature of this effect seems to be mainly steric as a linear correlation exists

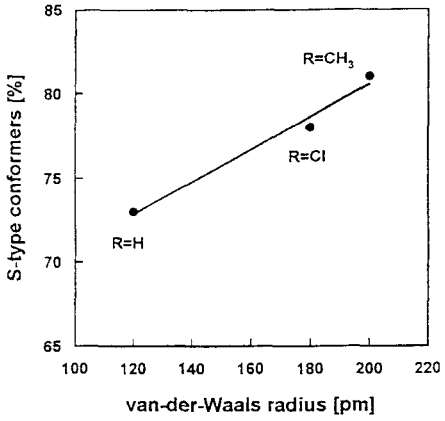


FIGURE 1. S-type conformer population of 8-substituted 7-deaza-2'-deoxyguanosines as function of the van der Waals radii of substituents.

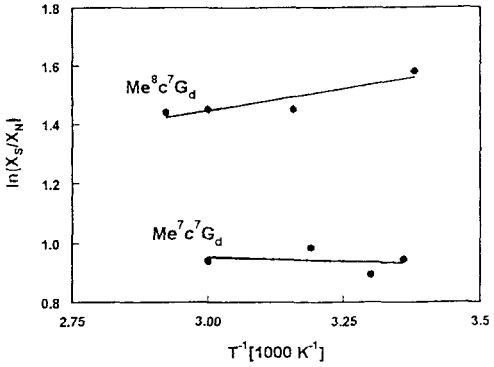


FIGURE 2. van't Hoff plots of $\ln(X_S/X_N)$ vs. 1000/T for $Me^8c^7G_d$ and $Me^7c^7G_d$.

between the S-type conformer population and the van der Waals radii of the 8-substituents (*Figure 1*).

Only the sterically demanding 7-deaza-8-methyl-2'-deoxyguanosine (**15**) exhibits a noticable temperature dependence. From a van't Hoff plot (*Figure* 2) the thermodynamics of the N ⇔ S interconversion could be estimated ($Me^8c^7G_d$: ΔH = -0.8 kcal/mol, ΔS = 0.4 cal/K mol; $Me^7c^7G_d$: ΔH = 0.2 kcal/mol, ΔS = -2.5 cal/K mol).

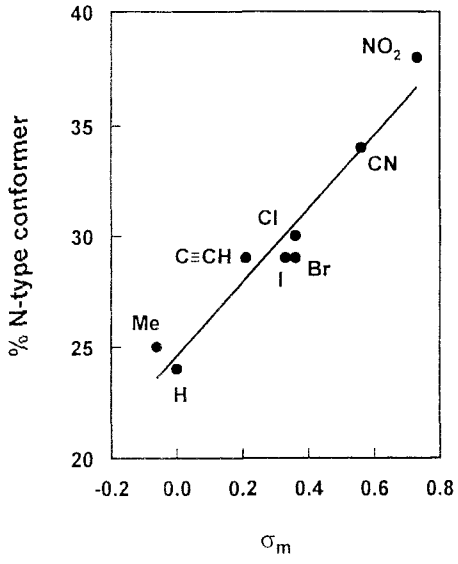


FIGURE 3. N-type conformer population of 7-substituted 7-deaza-2'-deoxyadenosines (**1** - **8**) vs. the σ_m values of substituents.

Figure 3 demonstrates the stereoelectronic influence of 7-substituents on the N ⇔ S equilibrium of a series of 7-deaza-2'-deoxyadenosines (**1** - **8**).

The figure clearly demonstrates that the higher the electron-withdrawing effect of the 7-substituent is, the more the N ⇔ S equilibrium of the sugar moieties is biased towards N-conformation[7]. In case of the 7,8-dichloro-substituted 7-deaza-2'-deoxyguanosine (**16**) the steric effect of the 8- and the electronic effect of the 7-substituent compensate each other, so that for this compound the distribution of N- and S-conformers is almost the same as for the unsubstituted 7-deaza-2'-deoxyguanosine (**9**). Electron-withdrawing substituents in position 7 of 7-deazapurine 2'-deoxynucleosides preform the sugar moiety towards a conformation (N-type) which they also adopt in an A-DNA.

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