The *High-Anti* Conformation of 7-Halogenated 8-Aza-7-deaza-2′-deoxyguanosines: A Study of the Influence of Modified Bases on the Sugar Structure of Nucleosides

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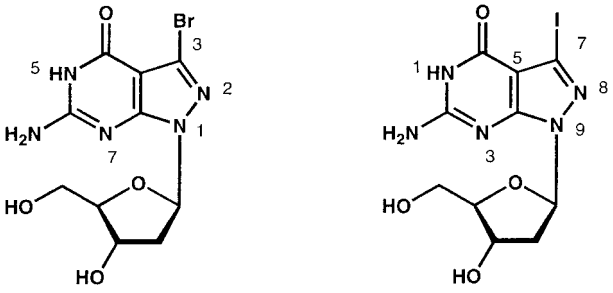
The conformation of the 7-bromo- and 7-iodo-substituted 8-aza-7-deazapurine nucleosides **1** and **2** in the solid state and in aqueous solution was studied by single-crystal X-ray analyses and by ^{1}H-NMR spectroscopy. In the solid state, both compounds display a *high-anti* conformation around the glycosylic bond, and their 2′-deoxy-β-D-ribofuranose moieties adopt an *N*-type sugar puckering. The orientation of the exocyclic C(4′)–C(5′) bond was found to be *ap* in both cases. In D_2O solution, both compounds display *i*) an 8–10% higher *N*-conformer population than 2′-deoxyguanosine and *ii*) a preference of the *–sc* conformation about the C(4′)–C(5′) bond. A comparative study on the influence of modified bases on the sugar structure of nucleosides is made.

Introduction. – The conformational flexibility of nucleic acids can be more complex than that of peptides because the sugar-phosphate backbone conformation is descibed by five single-bond rotations in addition to five sugar torsions [1a]. It is expected that in many cases, the conformational changes among nucleoside or nucleotide structures obey a certain conformational pathway. This means that the movement of one torsion is linearly coupled with another one [2][3]. In general, the molecular structures of nucleosides and nucleotides have been regarded as conformationally 'rigid' [4] probably due to the small variances of torsion angles. Besides *gauche* and anomeric effects [5], important determinants of the overall structure of a nucleoside are the steric and stereoelectronic effects of the nucleobases [6]. In a series of influential reports, at first *Gassen* and coworkers [7], and later *Chattopadhyaya* and coworkers [8] have demonstrated the importance of such effects on both the structure of a nucleoside as well as on the secondary structure of a DNA molecule. Recently, our interest was focussed on the stereoelectronic influence of modified nucleobases – and here in particular of aza- and deazapurines – on the structure and stability of oligonucleotides containing such compounds [9–13]. We have observed that the incorporation of 8-aza-7-deazapurine 2′-deoxynucleotides into oligodeoxynucleotides exerts an extraordinary influence on their duplex stability which is significantly enhanced over that of the parent unmodified oligomers [14–16]. This may be traced to an altered secondary structure of the base-modified oligomers with probably enhanced stacking interactions

and/or stronger H-bonds which might be similar to a 'vertical' DNA with the nucleobases being nearly parallel to the helix axis [1b][17][18].

In this communication, we report on the three-dimensional structures of two 7-halogeno-substituted 8-aza-7-deaza-2′-deoxyguanosines **1** and **2**, both in the solid state and in aqueous solution. The unusual conformation of these nucleosides as well as striking pecularities of their sugar-moiety structure prompted us to undertake a detailed comparative study on more than 60 nucleosides with respect to the interdependence of different structural parameters. The conformational control of the biomolecular function of oligonucleotides by nucleoside building blocks such as **1** and **2** is discussed.

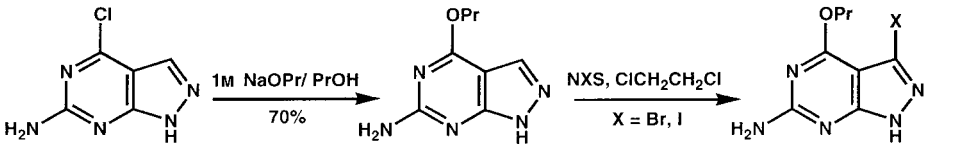


1 systematic numbering

2 purine numbering

Results and Discussion. – *Syntheses.* The synthesis of the nucleosides **1** and **2** recently described by us [19] was now improved by using different starting materials. Thus, we undertook the preparation of the 7-bromo- and the 7-iodo-substituted 8-aza-7-deaza-6-propoxypurines **5a**,**b** (purine numbering is used throughout the *General Part*) starting with compound **4** (obtained from **3**; see *Scheme 1*). The halogenation reaction was performed with either *N*-bromo- or *N*-iodosuccinimide (NXS, X = Br and I, resp.) in 1,2-dichloroethane and gave the desired compounds **5a**,**b** in 64–65% yield [20].

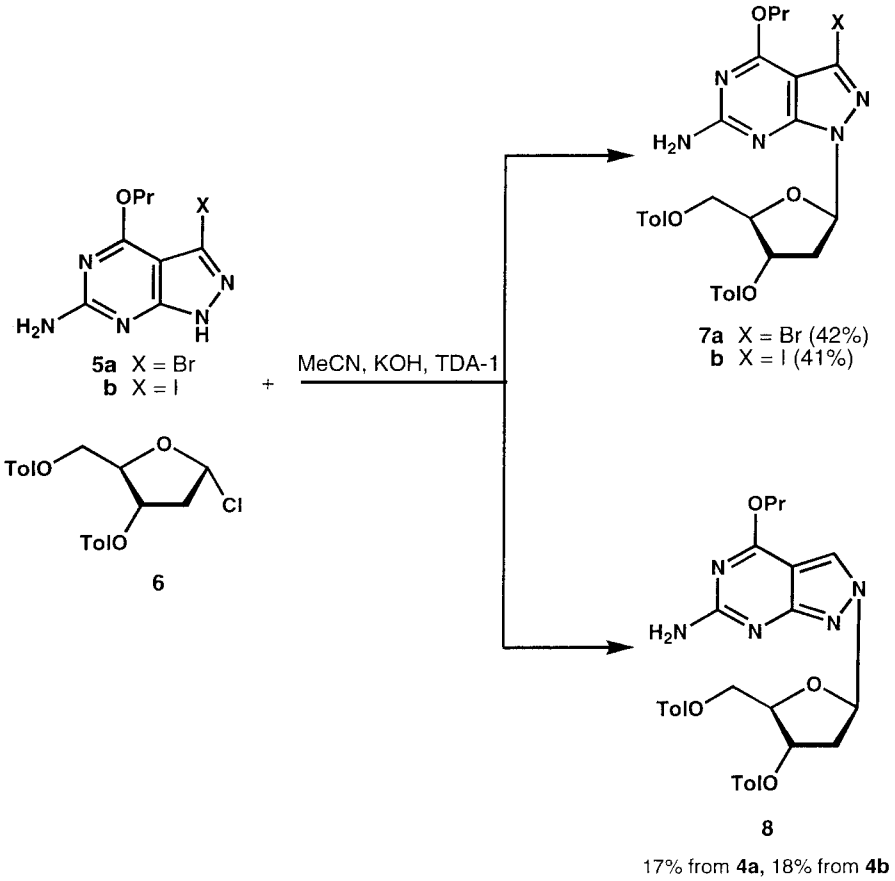
Scheme 1

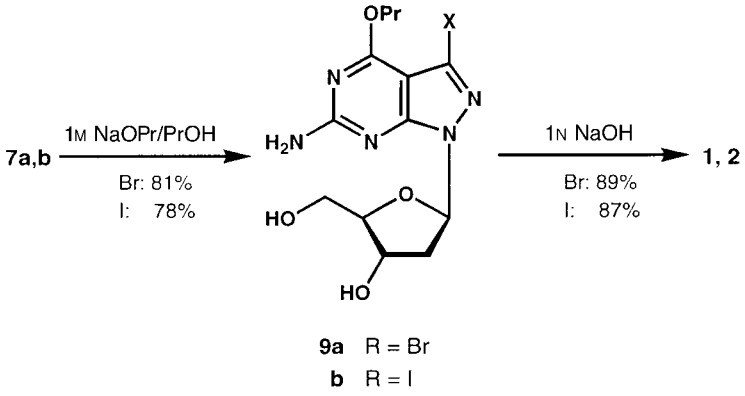


3 **4** **5a** X = Br (64%) **b** X = I (65%)

Subsequent glycosylation of **5a**,**b** with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**6**) [21] resulted in the desired 7-halogenated nucleosides **7a**,**b** in 42 and 41% yield, respectively, together with the dehalogenated N^8-nucleoside **8** (*Scheme 2*).

Scheme 2


OPr
X
N
N
H2N
N
N
H
5a X = Br
b X = I
+
MeCN, KOH, TDA-1
TolO
O
Cl
TolO
6
OPr
X
N
N
H2N
N
N
TolO
O
TolO
7a X = Br (42%)
b X = I (41%)
OPr
N
N
H2N
N
N
TolO
O
TolO
8
17% from 4a, 18% from 4b


7a,b
1M NaOPr/PrOH
Br: 81%
I: 78%
OPr
X
N
N
H2N
N
N
HO
O
HO
1N NaOH
Br: 89%
I: 87%
1, 2
9a R = Br
b R = I

Such a dehalogenation reaction has already been observed during the preparation of corresponding alkoxy compounds [22]. Deblocking of **7a**,**b** with 0.1M NaOPr/PrOH furnished the unprotected nucleosides **9a,b**. Hydrolysis of the propoxy groups of **9a**,**b** was performed in 1N NaOH (*ca.* 30 min at 60°) yielding compounds **1** and **2**. All new compounds were characterized by ^{1}H- and ^{13}C-NMR spectroscopy (*Table 1* and *Exper. Part*) as well as by elemental analyses.

Table 1. *^{13}C-NMR Chemical Shifts of 8-Aza-7-deazapurine Nucleobases and Related 2′-Deoxy-ribofuranosides*[a])

	C(7)[b]) C(3)[d])	C(5)[b]) C(3a)[d])	C(6)[b])[c]) C(4)[d])[c])	C(2)[b])[c]) C(6)[d])[c])	C(4)[b])[c]) C(7a)[d])[c])	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	OCH_2
1	122.0	98.4	158.1	156.3	156.5	83.1	37.6	70.8	87.4	62.4	–
2	101.9	93.7	157.5	155.1	155.8	83.2	37.7	70.9	87.4	62.4	–
4	131.7	95.6	163.5	162.1	158.9	–	–	–	–	–	67.3
5a	118.3	95.4	163.0	162.5	159.4	–	–	–	–	–	67.4
b	99.2	89.2	162.9	161.9	159.0	–	–	–	–	–	67.1
7a	119.9	96.2	163.0	162.6	158.7	83.4	34.8	74.9	81.3	64.0	67.6
b	100.2	91.7	163.1	162.2	159.3	83.4	34.8	75.0	81.3	64.1	67.5
8	124.8	98.1	164.9	163.5	162.3	90.1	36.8	74.9	82.0	64.3	67.4
9a	119.2	96.0	162.9	162.4	158.5	83.2	37.5	70.1	87.4	62.3	67.5
b	100.1	90.1	163.0	162.0	158.1	83.2	37.4	70.9	87.4	62.4	67.4

[a]) Measured in (D_6)DMSO at 303K. [b]) Purine numbering. [c]) Tentative. [d]) Systematic numbering.

Conformation in the Solid State. The glycosylation site of the 8-aza-7-deazapurine ring system (N(9)) and the β-D-anomeric configuration of nucleosides **1** and **2** were confirmed by single-crystal X-ray analysis (*Figs. 1* and *2*).

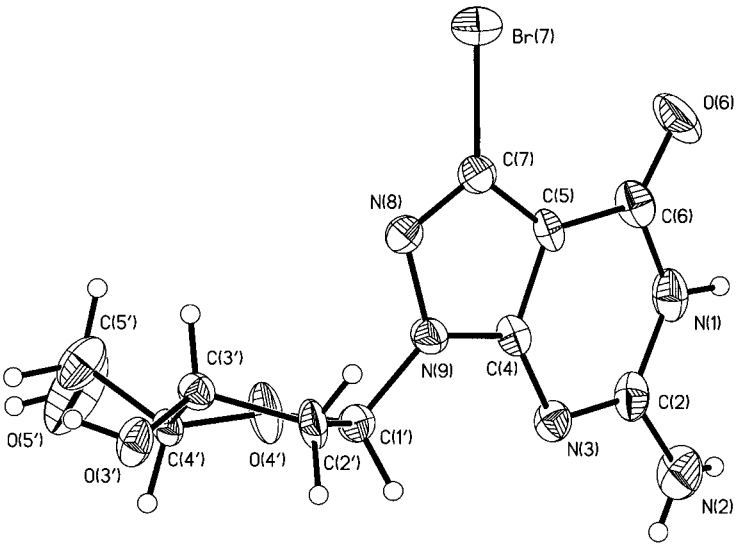


Fig. 1. *Molecular structure of 8-aza-7-bromo-7-deaza-2′-deoxyguanosine* (**1**) *in the solid state and atomic numbering.* Anisotropic displacement ellipsoids representing the 50% probability density of the corresponding atoms are shown; H-atoms are shown as spheres with arbitrary radius.

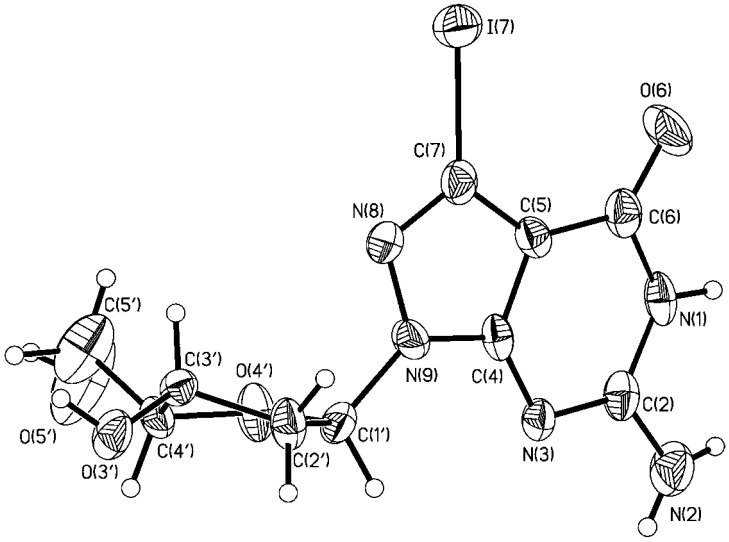


Fig. 2. *Molecular structure of 8-aza-7-deaza-2′-deoxy-7-iodoguanosine* (**2**). For details in the solid state and atom numbering, see legend to *Fig. 1.*

Both compounds show the *high-anti* conformation (space group $P2_12_12_1$ (No. 19)) (*Fig. 3*) with very similar glycosylic torsion angles χ(O(4′)–C(1′)–N(9)–C(4): – 92.9 and – 93.2, resp.) [1c]. The sugar moieties of **1** and **2** exhibit both an *N*-type puckered pentofuranose ring [1d] (*Fig. 4*) and the *ap* (g^-) conformation about the C(4′)–C(5′) bond [1e]. This means that – compared, *e.g.*, to 2′-deoxyadenosine [9] – in both cases, the nucleobase and the CH_2OH group undergo a disrotatory motion so that the *Coulomb* repulsion between N(8) and O(5′) as well as O(4′) is minimized.

The crystal parameters are summarized in the *Exper. Part*. Bond lengths for both compounds are listed in *Table 2*, bond angles in *Table 3*, and torsion angles in *Table 4*.

The nucleobases of both compounds **1** and **2** are planar, with their C- and N-atoms showing a deviation of max. ±0.052/0.043 Å[1])[2]) from the least-squares plane of the ring system. The bromo and iodo substituents show greater deviations from this plane. The NH_2 group atom N(2) lies 0.005(8)/0.013(7) Å[1]), the bromo/iodo substituents X(7) 0.067(7)/0.094(6) Å[1]), and C(1′) of the sugar unit 0.215(7)/0.182(6) Å[1]) below the plane and the oxo group O(6) 0.033(8)/0.066(7) Å[1]) above this plane.

Both crystal structures are stabilized by the same H-bonding pattern (*Fig. 5*). Because the iodo substitutent is larger than the bromo substituent, there are some differences in the construction of the H-bond system and the *van der Waals* contacts.

Two strong H-bonds are observed in the solid state. The first of those strong bonds is between H(3′O) and O(6) of a neighboring molecule bond ①: d(H ··· O) = 1.916(6)/1.929(4) Å[1]), angle (O–H ··· O) = 160.6(2)°/165.8(2)°[1]). The second strong H-bond

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[1]) Values given first refer to compound **1**, values given second refer to **2**.

[2]) N(1) = – 0.047(4)/0.041(3) Å, C(2) = – 0.027(5)/ – 0.014(4) Å, N(3) = 0.025(4)/0.010(4) Å, C(4) = 0.030(5)/0.023(4) Å, C(5) = 0.052(5)/0.043(5) Å, C(6) = 0.024(4)/0.020(4) Å, C(7) = – 0.008(5)/ – 0.008(4) Å, N(8) = – 0.049(4)/ – 0.042(3) Å, N(9) = 0.002(4)/0.009(3) Å.

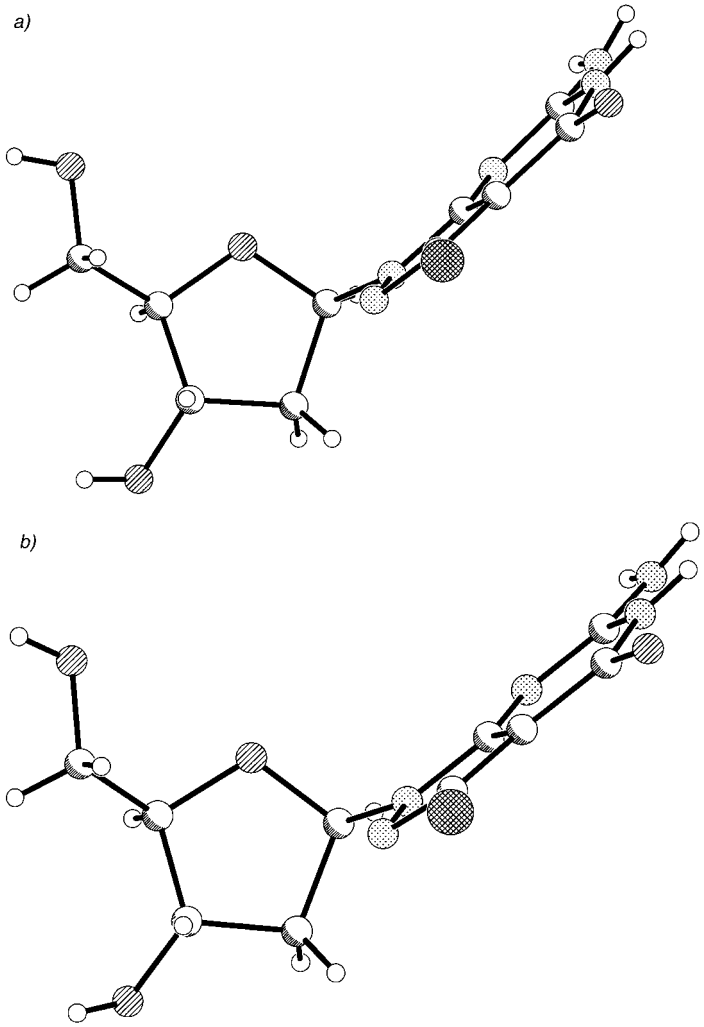

Fig. 3. *Perspective view of* a) *8-aza-7-bromo-7-deaza-2′-deoxyguanosine* (**1**) *and* b) *8-aza-7-deaza-2′-deoxy-7-iodoguanosine* (**2**) *displaying the* high-anti *orientation of the base*

links the H-atoms of the NH_2 function, H(22), to Br(7)/I(7) in another neighboring molecule bond ②: $d(H\cdots X) = 3.029(6)/3.045(4)$ Å[1]), angle $(N-H\cdots X) = 133.8(1)^\circ/141.9(1)^\circ$[1]). In addition to these strong bonds, a number of weaker contacts exist which are shown in *Fig. 5*. The main differences between **1** and **2** are summarized in *Table 5*.

To the best of our knowledge, these crystallographic analyses are the first which describe the solid state structure of a β-D-2′-*deoxy*ribonucleoside bearing an 8-aza-7-deazapurine base. However, X-ray data of several corresponding β-D-*ribo*nucleosides as well as of other '*ortho*-azapurine' or '*ortho*-azapyrimidine' β-D-*ribo*nucleosides (*e.g.*, formycin or 6-azauridine) appeared in the literature [23–25]. Like compounds **1** and **2**,

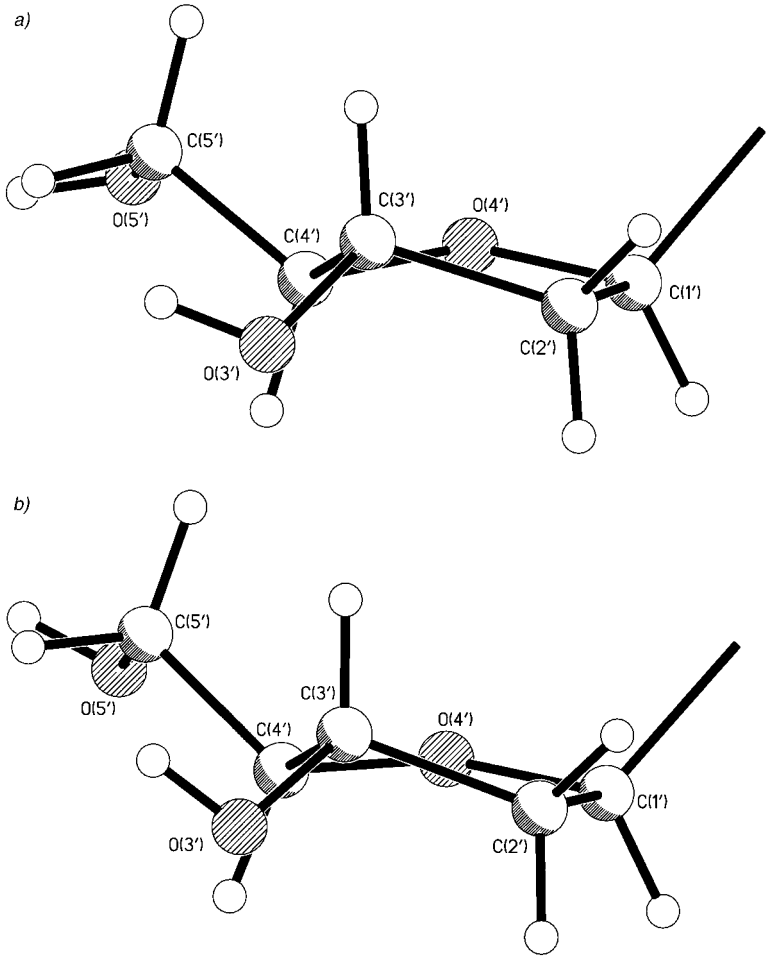

Fig. 4. *Perspective view of the 2′-deoxyribose conformation of* a) *8-aza-8-bromo-7-deaza-2′-deoxyguanosine* (**1**) *and* b) *8-aza-7-deaza-2′-deoxy-7-iodo-guanosine* (**2**)

all these nucleosides exhibit the unusual *high-anti* (−*sc*) conformation about the glycosylic bond with a torsion angle χ of *ca.* −90° which was assumed to be responsible for their anomalous biophysical and biochemical behavior, both, on the monomeric as well as on the polymeric level [26–28].

Comparative Study on the Influence of Modified Bases on the Sugar Structure of Nucleosides on the Basis of X-Ray Data. Inspection of the crystallographic data of compounds **1** and **2** revealed some striking pecularities which prompted us to make a comparative conformational study on a series of purine and pyrimidine β-D-ribo- and 2′-deoxy-β-D-ribonucleosides. This study uses X-ray data published earlier [29] and correlates bond length differences with the torsion angle χ around the glycosylic bond.

Steric and stereoelectronic effects of modified nucleobases exert a strong influence on the conformation of the ribose moiety [30] as well as on the different bond lengths

Table 2. *Bond Lengths* [A] *for* **1** ($C_{10}H_{12}BrN_5O_4$) *and* **2** ($C_{10}H_{12}IN_5O_4$)

Bond	**1**	**2**	Bond	**1**	**2**
N(1)–C(2)	1.373(9)	1.367(6)	C(7)–Br7	1.876(5)	–
N(1)–C(6)	1.414(9)	1.383(6)	C(7)–I(7)	–	2.060(4)
C(2)–N(3)	1.326(8)	1.321(6)	N(8)–N(9)	1.393(6)	1.387(5)
C(2)–N(2)	1.315(9)	1.334(6)	N(9)–C(1′)	1.443(7)	1.441(5)
N(3)–C(4)	1.344(7)	1.349(6)	C(1′)–O(4′)	1.432(6)	1.428(6)
C(4)–N(9)	1.356(7)	1.358(5)	C(1′)–C(2′)	1.529(7)	1.517(6)
C(4)–C(5)	1.400(8)	1.386(6)	C(2′)–C(3′)	1.516(7)	1.504(6)
C(5)–C(7)	1.404(8)	1.425(6)	C(3′)–O(3′)	1.426(6)	1.421(5)
C(5)–C(6)	1.428(9)	1.431(6)	C(3′)–C(4′)	1.519(7)	1.507(6)
C(6)–O(6)	1.215(8)	1.225(6)	C(4′)–O(4′)	1.442(6)	1.436(5)
C(7)–N(8)	1.309(8)	1.316(6)	C(5′)–O(5′)	1.400(8)	1.426(7)

Table 3. *Bond Angles* [°] *for* **1** ($C_{10}H_{12}BrN_5O_4$) *and* **2** ($C_{10}H_{12}IN_5O_4$)

Angle	**1**	**2**	Angle	**1**	**2**
N(3)–C(2)–N(1)	123.5(6)	123.4(4)	C(4)–N(9)–N(8)	112.6(5)	111.5(3)
N(2)–C(2)–N(1)	116.8(6)	116.6(4)	C(4)–N(9)–C(1′)	126.5(5)	127.7(4)
C(2)–N(3)–C(4)	112.6(5)	112.4(4)	N(8)–N(9)–C(1′)	119.9(4)	119.9(3)
N(3)–C(4)–N(9)	125.7(5)	124.8(4)	O(4′)–C(1′)–N(9)	108.4(4)	109.1(4)
N(3)–C(4)–C(5)	128.5(4)	128.3(3)	O(4′)–C(1′)–C(2′)	106.6(4)	106.5(3)
N(9)–C(4)–C(5)	105.8(5)	106.9(4)	N(9)–C(1′)–C(2′)	113.0(5)	112.9(4)
C(4)–C(5)–C(7)	104.4(5)	104.8(3)	C(3′)–C(2′)–C(1′)	104.8(4)	105.1(3)
C(4)–C(5)–C(6)	118.8(5)	118.5(4)	O(3′)–C(3′)–C(2′)	109.1(4)	108.9(3)
C(7)–C(5)–C(6)	136.6(5)	136.6(4)	O(3′)–C(3′)–C(4′)	114.2(4)	114.6(3)
N(1)–C(6)–C(5)	110.7(5)	111.0(4)	C(2′)–C(3′)–C(4′)	102.9(4)	103.4(3)
N(8)–C(7)–C(5)	113.8(5)	111.7(4)	O(4′)–C(4′)–C(5′)	107.6(4)	107.9(4)
N(8)–C(7)–Br(7)	119.9(4)	–	O(4′)–C(4′)–C(3′)	104.6(4)	105.4(3)
C(5)–C(7)–Br(7)	126.2(5)	–	C(5′)–C(4′)–C(3′)	114.6(4)	115.0(4)
C(5)–C(7)–I(7)	–	126.9(3)	C(1′)–O(4′)–C(4′)	109.7(4)	110.2(3)
C(7)–N(8)–N(9)	103.4(4)	105.1(3)			

Table 4. *Torsion Angles for the Sugar Units of* **1** ($C_{10}H_{12}BrN_5O_4$) *and* **2** ($C_{10}H_{12}IN_5O_4$)

Torsion angle	**1**	**2**	Torsion angle	**1**	**2**
C(4)–N(9)–C(1′)–O(4′)	– 93.2(6)	– 92.9(5)	C(2′)–C(1′)–O(4′)–C(4′)	– 10.8(6)	– 5.7(4)
N(8)–N(9))–C(1′)–O(4′)	74.3(6)	75.0(5)	C(1′)–O(4′)–C(4′)–C(5′)	150.6(5)	146.4(4)
C(4)–N(9)–C(1′)–C(2′)	148.8(5)	148.9(4)	C(1′)–O(4′)–C(4′)–C(3′)	28.3(6)	23.0(4)
N(8)–N(9)–C(1′)–C(2′)	– 43.7(7)	– 43.2(6)	O(3′)–C(3′)–C(4′)–O(4′)	– 151.9(5)	– 149.2(4)
O(4′)–C(1′)–C(2′)–C(3′)	– 11.0(7)	– 13.9(5)	C(2′)–C(3′)–C(4′)–O(4′)	– 33.9(6)	– 30.6(4)
N(9)–C(1′)–C(2′)–C(3′)	108.0(5)	105.9(4)	O(3′)–C(3′)–C(4′)–C(5′)	90.4(6)	92.2(5)
C(1′)–C(2′)–C(3′)–O(3′)	148.8(5)	149.2(4)	C(2′)–C(3′)–C(4′)–C(5′)	– 151.5(5)	– 149.3(4)
C(1′)–C(2′)–C(3′)–C(4′)	27.1(6)	26.9(5)	O(4′)–C(4′)–C(5′)–O(5′)	53.3(8)	54.1(6)
N(9)–C(1′)–O(4′)–C(4′)	– 132.8(5)	127.9(4)	C(3′)–C(4′)–C(5′)–O(5′)	169.2(6)	171.5(5)

such as N(9 or 1)–C(1′), C(1′)–O(4′), and O(4′)–C(4′) [31]. The *N*-glycosylic bond is usually significantly longer than the adjacent C(1′)–O(4′) bond. Recently, a linear dependence of the torsion angle χ from the bond-length difference of the bonds C(4′)–O(4′) and O(4′)–C(1′) was reported which was looked upon as a manifestation of the anomeric effect [32][33]. An extended version of the graph [C(4′)–O(4′)] – [O(4′)–C(1′)] *vs.* χ is now given in *Fig. 6*. It is based on the X-ray data of 64 purine and

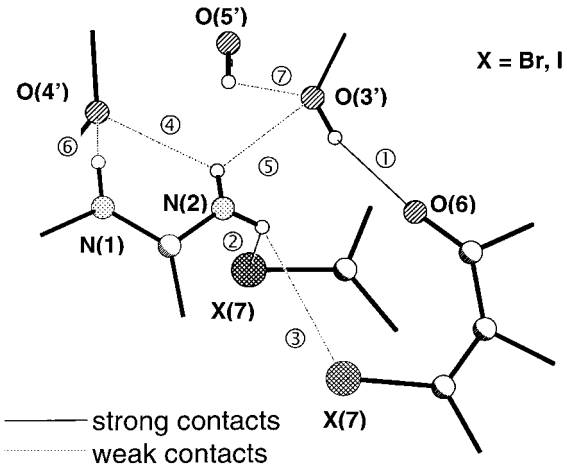

Fig. 5. *Hydrogen bonding system of compounds* **1** *and* **2** *in the solid state*

Table 5. *Hydrogen Bond Lengths* d($H\cdots X$) [Å] *in the Solid State of* **1** ($C_{10}H_{12}BrN_5O_4$) *and* **2** ($C_{10}H_{12}IN_5O_4$)

Bond	**1**	**2**	Bond	**1**	**2**
①	1.916(6)	1.929(4)	⑤	2.522(7)	2.764(5)
②	3.029(6)	3.045(4)		2.314(6)	2.379(5)
③	3.358(6)	3.447(5)	⑥	2.439(6)	2.337(5)
④	2.535(8)	2.423(6)			

pyrimidine ribo- and 2′-deoxyribonucleosides [29] including compounds **1** and **2** described above (see *Table 6*).

Fig. 7 shows the dependence of χ from the bond-length difference of the bonds (N(9 or 1)–C(1′) and C(1′)–O(4′) taken from the X-ray analyses (*Table 6*). Also here, a linear correlation can be observed. Obviously, the difference in bond length between C(4′)–O(4′) and O(4′)–C(1′) (0–7 pm) and N(9 or 1)–C(1′) and C(1′)–O(4′) (0–12 pm) regulates the sugar puckering and therewith the torsion angle about the *N*-glycosylic bond (χ). From the graphs it can be seen that compounds **1** and **2** as well as other '*ortho*-azapurine' and '*ortho*-azapyrimidine' nucleosides, adopting the *high-anti* conformation, exhibit almost equal bond-length values.

The bond-length differences discussed above are obviously influenced by the π-electron system of the base. Unusually high or low χ values which deviate strongly from the graph are the result of intramolecular H-bonds or steric interactions (repulsion or attraction). Examples are guanosine, 2′-deoxyguanosine, or 1-deazaguanosine [34][35]. Here, a H-bond between the 5′-OH group in the $+sc\,(g^+)$ conformation and either N(3) (1-deazapurines) or the 2-NH_2 group of guanine causes the relatively unusual *syn* conformation of the base (*Figs. 6* and *7*).

It is well-established that the π-electron density in the heterocyclic systems of the bases is conducted through the adjacent furanose atoms C(1′), O(4′) and C(4′), explaining – in part – the shortening of the C(1′)–O(4′) bond relative to C(4′)–O(4′). This is due to a σ-resonance of the lone electron pairs at O(4′) with the electronic system of the heterocycle by through-bond and through-space interactions [30]. Apart

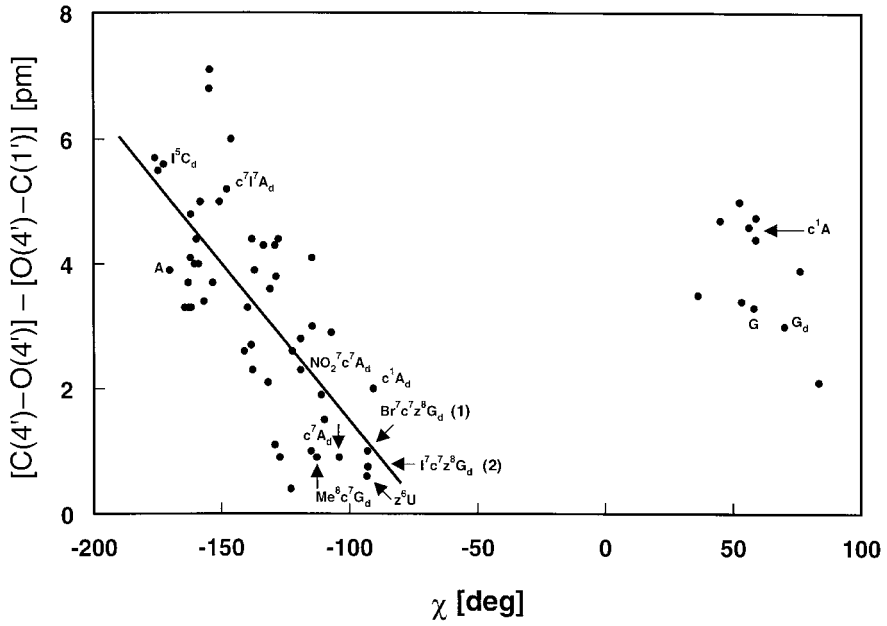

Fig. 6. *Bond-length difference of the bonds C(4′)–O(4′) and O(4′)–C(1′)* vs. *the torsion angle* χ *(O(4′)–C(1′)–N(9 or 1)–C(4 or 2)) of 64 ribo- and 2′-deoxyribonucleosides according to the* Entries 1–64 *of* Table 6 (see [29])

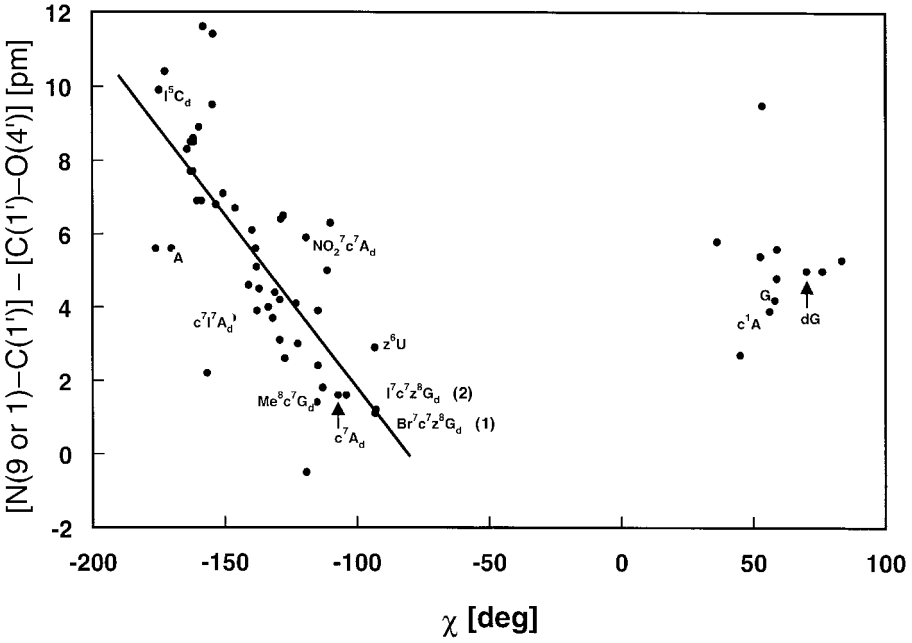

Fig. 7. *Bond-length difference of the bonds N(9 or 1)–C(1′) and C(1′)–O(4′)* vs. χ *of 64 ribo- and 2′-deoxyribonucleosides according to the* Entries 1–64 *of* Table 6 (see [29])

Table 6. *Torsion Angle χ and Bond-Length Differences of Purine and Pyrimidine Nucleosides*[a]).

Entry (see [29])	χ [°]	Bond N(9 or 1)–C(1′) [pm]	Bond C(1′)–O(4′) [pm]	Bond C(4′)–O(4′) [pm]	*Entry* (see [29])	χ [°]	Bond N(9 or 1)–C(1′) [pm]	Bond C(1′)–O(4′) [pm]	Bond C(4′)–O(4′) [pm]
1	45.0	143.6	140.9	145.6	*33*	58.9	147.3	141.7	146.1
2	– 107.0	143.8	142.2	145.1	*34*	– 176.0	149.2	143.6	149.3
3	– 114.6	144.4	142.0	146.1	*35*	53.3	150.2	140.8	144.1
4	– 122.2	144.5	141.5	144.1	*36*	58.8	145.8	141.0	145.8
5	– 133.4	145.2	141.2	145.5	*37*	52.6	145.8	140.4	145.4
6	– 127.2	145.2	142.6	143.5	*38*	70.5	144.6	146.8	145.7
7	– 122.9	145.4	141.3	141.7	*39*	58.1	145.3	141.2	145.6
8	– 114.5	145.9	142.0	145.0	*40*	– 139.6	147.8	141.7	145.0
9	– 130.9	146.0	141.6	145.2	*41*	– 112.8	145.1	143.3	144.2
10	– 127.7	146.7	140.2	144.6	*42*	– 158.1	152.4	140.8	145.8
11	– 137.9	146.7	141.6	146.0	*43*	– 156.7	146.7	144.5	147.9
12	83.4	146.6	141.3	143.4	*44*	– 162.9	148.8	141.1	144.8
13	36.3	146.8	141.0	144.5	*45*	– 162.8	149.7	141.2	144.5
14	76.0	146.6	141.6	145.5	*46*	– 172.5	150.8	140.4	146.0
15	– 136.9	146.0	141.5	145.4	*47*	– 137.7	147.1	143.2	145.5
16	– 170.1	146.7	141.1	145.0	*48*	– 158.8	148.9	142.0	146.0
17	– 146.0	147.0	140.3	146.3	*49*	– 131.7	146.1	142.4	144.5
18	– 128.6	147.4	141.0	144.8	*50*	– 164.2	149.4	141.1	144.4
19	– 153.3	147.5	140.7	144.4	*51*	– 174.7	150.9	141.0	146.5
20	– 138.2	147.6	142.0	144.7	*52*	– 129.1	147.1	144.0	145.1
21	– 140.9	148.0	143.4	146.0	*53*	– 93.2	144.3	143.2	144.2
22	– 160.4	149.2	142.3	146.3	*54*	– 92.9	144.0	142.8	143.6
23	– 159.7	149.4	140.5	144.9	*55*	70.0	147.1	142.1	145.1
24	– 161.9	149.6	141.0	145.8	*56*	– 104.0	144.9	143.3	144.2
25	– 161.7	149.7	141.2	144.5	*57*	– 147.0	145.3	141.6	146.8
26	– 154.4	150.4	139.0	146.1	*58*	– 111.0	146.6	141.6	143.5
27	– 162.0	149.0	141.3	145.4	*59*	– 119.0	147.5	141.6	143.9
28	– 150.6	148.1	141.0	146.0	*60*	– 115.0	144.8	143.4	144.4
29	– 154.6	149.0	139.5	146.3	*61*	– 93.3	146.2	143.3	143.9
30	– 137.9	146.7	141.6	146.0	*62*	– 109.8	150.2	143.9	145.4
31	– 129.0	146.4	142.2	146.5	*63*	– 90.7	144.1	142.7	143.7
32	– 119.0	142.7	143.2	146.0	*64*	56.1	145.3	141.4	146.0

[a]) For compound names (*Entries 1–64*) and references for crystallographic data; see [29].

from these stereoelectronic effects, another factor has to be taken into account: the O(4′) atom carries a net charge of – 0.16 e, suggesting that it is a weak H-bridge acceptor, and, in fact, H-bonds to this atom have been observed in a few nucleoside crystal structures. Especially in the case of favorable configurational juxtaposition of O(4′) and OH groups, such H-bonds appear feasible [1f,g].

As the π-electron excess of the imidazole moiety of a purine is strongly reduced by the π-deficient pyrimidine system, the C(8) atom becomes the most electron-deficient site in the non-ionized molecule, and, thus, H–C(8) is the most acidic proton bound to a purine-ring C-atom [36]. This is promoted by electron-withdrawing substituents. The same is true for H–C(6) of a pyrimidine ring. As a consequence, one can assume an attractive interaction between H–C(8) of a purine or H–C(6) of a pyrimidine and O(4′) of an attached sugar ring, especially when χ ranges around – 180° [37a]. Such an

attractive interaction should lead to a deformation of the furanose ring with bond stretching and bond shortening as depicted in *Fig. 8*.

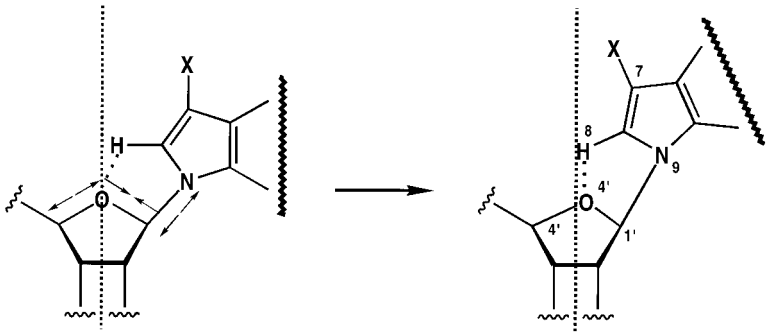

Fig. 8. *Bond stretching* (← →) *and shortening* (→ ←) *within the sugar moiety of a nucleoside due to stereoelectronic effects and hydrogen bonding*. Stretchings and shortenings are exaggerated for a better visualization.

Both effects, the stereoelectronic effect of the heterocycle *via* through-bond as well as through-space interactions and an attractive interaction between an acidified H–C(8) or H–C(6), respectively, and O(4′), would act in the same direction, namely a highly negative χ value (*anti* conformation) as well as the particular bond-length alterations which are indeed observed. On the other hand, the reduced acidity of H–C(8) (purines) or H–C(6) (pyrimidines) or the introduction of an N-atom into position 8 of a purine or position 6 of a pyrimidine moiety leads to a distorsion of χ towards the *high-anti* range. This induces a change of the sugar puckering from *S* to *N* as in the latter conformation, the steric repulsion between H_β–C(2′) and N(8) (or N(6)) is minimized. Indeed *N*-type puckering has been found for '*ortho*-azanucleosides' in the crystal and also in the case of the 8-aza-7-deaza-2′-deoxyguanosines **1** and **2**.

Conformation of Compounds **1** *and* **2** *in Solution.* As in the solid state, nucleosides exist in various conformations in solution. The topology of a nucleoside in solution is decided mainly by two dynamic two-state and one three-state equilibria: *i*) the *syn-anti* equilibrium of the base about the glycosylic bond, *ii*) the sugar puckering ($N \rightleftarrows S$, ${}^{3'}T_{2'} \rightleftarrows {}_{3'}T^{2'}$), and *iii*) the rotational equilibrium about the C(4′)–C(5′) bond ($\gamma^{g^+} \rightleftarrows \gamma^{t} \rightleftarrows \gamma^{g^-}$). These equilibria are interdependent, and the energy barrier between the most preferred conformational states is usually low [1d].

The conformational analysis of the furanose puckering of compounds **1** and **2** was performed by the PSEUROT program (version 6.2) [37b] which calculates best fits of experimental ${}^3J(H,H)$ values (${}^3J(1',2')$, ${}^3J(1',2'')$, ${}^3J(2',3')$, ${}^3J(2'',3')$, and ${}^3J(3',4')$) to the five conformational parameters (P and ψ_m for both *N*- and *S*-type conformers and corresponding mole fractions). The populations of the staggered rotamers across the C(4′)–C(5′) bond were calculated from ${}^3J(4',5')$ and ${}^3J(4',5'')$ according to *Westhof et al.* [38]. The data are presented in *Table 7*.

For comparison, the data of 2′-deoxyguanosine (G_d) [10], 7-deaza-2′-deoxyguanosine (c^7G_d) [10], 8-aza-7-deaza-2′-deoxyguanosine ($c^7z^8G_d$) [10], as well as of 8-aza-7-cyano-7-deaza-2′-deoxyguanosine ($CN^7c^7z^8G_d$) are included [39]. Scrutiny of the conformational data reveals that the 8-aza-7-deazapurine 2′-deoxynucleosides exhibit

all a significantly more pronounced *N*-conformer population compared to G_d as well as to c^7G_d. Within the series of 8-aza-7-deaza-2′-deoxynucleosides, the 7-cyano derivative shows the highest *N*-conformer population (46%), while the 7-halogeno derivatives **1** and **2** exhibit almost the same values as the unsubstituted parent compound $c^7z^8G_d$. These findings are due to the stereoelectronic effect of the 7-cyano substituent and are in line with results observed for corresponding 7-deazapurine nucleosides. Interestingly, the 7-halogeno derivatives of $c^7z^8G_d$ crystallize in the pure *N*-form as the sole crystalline state. This has already been observed for 7-deaza-2′-deoxyadenosine and its 7-nitro derivative [40].

Table 7. *^{3}J(H,H) Coupling Constants of the Sugar Moieties and Conformer Populations of 2′-Deoxynucleosides at 303 K*[a])

	^3J(H,H) [Hz][b])							Conformation					Pseudorotational Parameters			
	1′,2′	1′,2″	2′,3′	2″,3′	3′,4′	4′,5′	4′,5″	%*N*	%*S*	%γ^{g^+}	%γ^t	%γ^{g^-}	P_N	P_S	$\psi_{m(N)}$	$\psi_{m(S)}$
1	6.55	6.65	6.20	3.85	4.30	4.60	6.00	39	61	27	44	29	19	152.1	36	31.5
2	6.55	6.65	6.50	4.10	3.70	4.30	6.00	37	63	30	44	25	19	160.7	36	30.3
$CN^7c^7z^8G_d$	6.10	6.45	6.00	4.65	4.40	4.60	6.20	46	54	25	47	28	19	159.9	36	35.6
$c^7z^8G_d$	6.65	6.65	6.25	3.65	3.90	4.30	5.90	36	64	31	43	26	19	157.8	36	30.4
c^7G_d	7.25	6.50	6.25	3.00	3.35	4.20	5.00	28	72	43	33	24	19	157.2	36	30.1
G_d	7.30	6.50	6.30	3.60	3.20	3.60	4.70	29	71	53	30	17	19	160.5	36	32.1

[a]) Solvent, D_2O; r.m.s. $\leq$ 0.4 Hz; $|\Delta J_{max}| \leq$ 0.4 Hz. [b]) Primed and doubly primed locants are used to distinguish between the two protons at C(2′) or C(5′).

Concerning the conformation about the C(4′)–C(5′) bond, also an interesting relationship can be seen from *Table 7*. While G_d exhibits a $+sc$ rotamer population of 53% (γ^{g^+}), it is diminished to 31% in the case of $c^7z^8G_d$, while the populations of the other two staggered conformers are enhanced by an almost equal amount. Introduction of 7-substituents decreases the $+sc$ population further, whereby the compound with the most electron-withdrawing substituent (CN) exhibits the lowest value ($CN^7c^7z^8G_d$, 25% γ^{g^+}). This trend is opposite to that found for 7-substituted 7-deazapurine nucleosides [9].

Temperature-Dependent CD and UV Measurements on Oligonucleotides Containing Compounds **1** *or* **2**. To shed more light on the conformational control of the structure and stability of oligodeoxynucleotides by the conformation of compounds **1** or **2**, temperature-dependent CD spectra of $Br^7c^7z^8G_d$ (**1**), $I^7c^7z^8G_d$ (**2**), and the parent $c^7z^8G_d$ as well as of the homooligomer 5′-$(I^7c^7z^8G_d)_6$ were measured (10 mM Na-cacodylate buffer, 10 mM $MgCl_2$, 100 mM NaCl (pH 7.0); 10–90°) (*Fig. 9*). As can be seen from *Fig. 9,b*, the homooligomer exhibits an unusual CD spectrum at room temperature, the *Cotton* effects of which are changed at high temperature: at 90° the CD spectrum displays a similar shape as those reported for homooligonucleotides built-up from (8-2′)-bridged nucleotides [41][42] in which the *high-anti* conformation of the bases is chemically locked.

The temperature dependence of the CD spectrum of the homooligomer implies strong stacking interactions between the bases. This could be verified by measuring the temperature-dependent UV spectra of 5′-$(I^7c^7z^8G_d)_6$ as well as of 5′-$(Br^7c^7z^8G_d)_6$ [43]. *Fig. 10* displays cooperative melting curves of these homomers in a 1:1 mixture of

10 mM Na-cacodylate buffer (10 mM $MgCl_2$, 100 mM NaCl, pH 7) and formamide from which T_m values of ca. 52° and 54°, respectively, could be estimated. In pure buffer, the T_m values range above 85°. This cooperative melting represents either single-strand destacking or a dissociation of a duplex.

Relevance of a Conformational Preorganization of a Nucleoside Structure for the Biomolecular Function of an Oligonucleotide. Evidence that the conformational properties of base-modified nucleosides are maintained in short nucleic-acid fragments exerting influence on the structure and stability of corresponding oligonucleotides was first described between 1978–1983 by *Gassen* and coworkers [7] who demonstrated the influence of 5-substituted uridine derivatives on the conformation and base/base stacking interactions within di-, tri-, and tetraribonucleotides of the (A-U) type. They were able to prove that electron-attracting substituents such as NO_2 or halogeno enhance the base/base interaction while electron donating groups (NH_2) diminish the

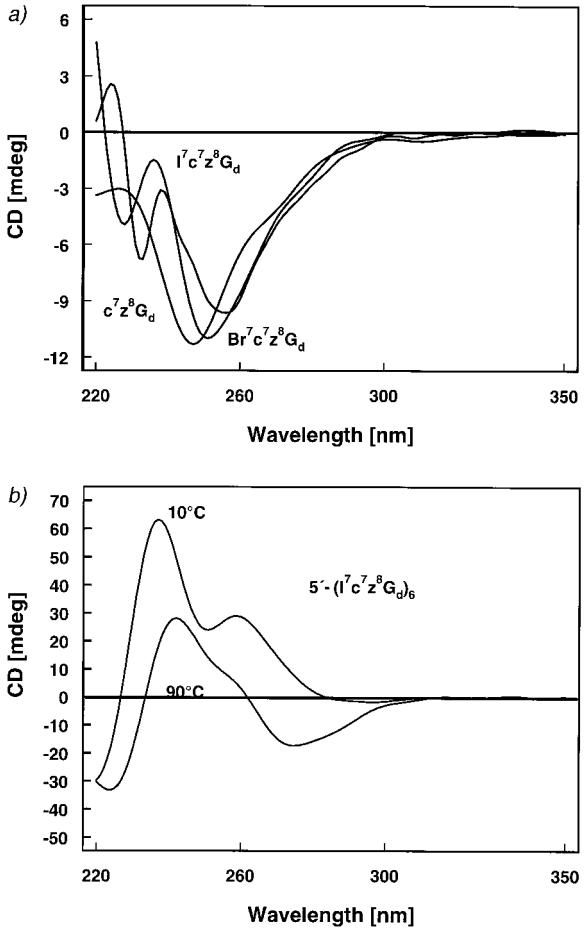

Fig. 9. *CD Spectra of* a) *$I^7c^7z^8G_d$, $Br^7c^7z^8G_d$, and $c^7z^8G_d$ at 10° and* b) *5′-d($I^7c^7z^8G)_6$ at 10 and 90°.* In 10 mM Na-cacodylate, 10 mM $MgCl_2$, 100 mM NaCl (pH 7).

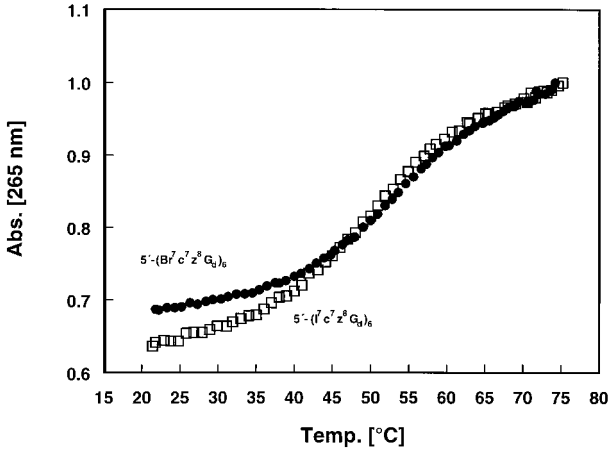

Fig. 10. *Melting curves of 5′-(I⁷c⁷z⁸G_d)₆ and 5′-(Br⁷c⁷z⁸G_d)₆.* In 10 mM Na-cacodylate, 10 mM $MgCl_2$, 100 mM NaCl (pH 7)/formamide 1:1 (*v/v*).

stacking. Also *Chattopadhyaya* and coworkers demonstrated in a convincing manner the decisive importance of intramolecular stereoelectronic effects within a nucleoside on the secondary structure of an oligonucleotide [44]: they demonstrated by NMR spectroscopy that the unmodified oligomer 5′-d(CGCGAATTCGCG) exists entirely in a B-DNA form, whereas a corresponding analogue containing the carbocyclic nucleoside 2′-deoxyaristeromycin instead of A_d, which does not show the stabilizing stereoelectronic effect in the cyclopentane moiety, exists in a dynamic equilibrium as hairpin and duplex (1:1, $c_t = 2$ mM).

The more pronounced *N*-type sugar pucker of compounds **1** and **2** should merge an oligonucleotide towards an A-type secondary structure. If this is the case, hybridization with a complementary oligoribonucleotide should be increased. However, this is not the case due to the *high-anti* conformation of these base-modified nucleosides [45]. This unusual conformation might be the reason why 5′-triphosphates of 8-aza-7-deazapurine 2′-deoxyribonucleosides are not as efficient substrates for various DNA polymerases [46] as the corresponding triphosphates of 7-deazapurine β-D-2′-deoxyribonucleosides.

Homooligonucleotides built-up exclusively from such 8-aza-7-deazapurine 2′-deoxyribonucleoside building blocks should adopt a secondary structure which is neither a B- nor an A-DNA but probably a *vertical* DNA with strongly stacked bases in an almost parallel orientation to the helix axis. This assumption is cherished by results reported by *Olson* and *Dasika* who predicted, on the basis of a theoretical analysis, the preferred conformational parameters of such an unusual DNA structure [17][18]. These are *i*) a *high-anti* conformation of the bases, *ii*) an *N*-type sugar pucker, and *iii*) an *ap* conformation about the C(4′)–C(5′) bond – all conformations which have been established for compounds **1** and **2**. Such a secondary nucleic-acid structure has been realized for polynucleotides built-up from modified purine nucleotides with a covalent bridge between C(8) and C(2′) locking the base in the *high-anti* conformation [41][42].

Nevertheless, oligodeoxyribonucleotides containing only a few 8-aza-7-deaza- or 8-azapurine 2′-deoxynucleotides adapt to the general B-DNA structure forming stabilized duplexes due to enhanced stacking interactions.

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Experimental Part

1. *General*. Flash chromatography (FC): at 0.4 bar on silica gel *60 H* (*Merck*, Darmstadt, Germany). Thin-layer chromatography (TLC): Aluminium sheets silica gel *60 F_{254}* (0.2 mm; *Merck*, Darmstadt, Germany). TLC Scanning: *CS-930-TLC* scanner (*Shimadzu*, Japan). Solvent systems for FC and TLC: CH_2Cl_2/MeOH 98:2 (*A*), CH_2Cl_2/MeOH 95:5 (*B*), CH_2Cl_2/MeOH 9:1 (*C*), CH_2Cl_2/acetone 98:2 (*D*), CH_2Cl_2/acetone 95:5 (*E*). M.p.: *Büchi-SMP-20* apparatus (*Büchi*, Switzerland); not corrected. UV Spectra: a *150-20* spectrometer (*Hitachi*, Japan). NMR Spectra: *AC-250* and *AMX-500* spectrometer (*Bruker*, Germany); δ values in ppm downfield from internal $SiMe_4$ (^{1}H, ^{13}C). Microanalyses were performed by *Mikroanalytisches Labor Beller* (Göttingen, Germany).

2. *X-Ray Crystal Structure of 6-Amino-3-bromo-1-(2-deoxy-β-*D-erythro-*pentofuranosyl)-1,5-dihydro-4*H-*pyrazole[3,4-*d*]pyrimidin-4-one* (**1**) *and 6-Amino-1-(2-deoxy-β-*D-erythro-*pentofuranosyl-1,5-dihydro-3-iodo-4*H-*pyrazolo[3,4-*d*]pyrimidin-4-one* (**2**). *Crystal Data*[3]). Single crystals (size $0.45 \times 0.15 \times 0.15$ mn for **1** and $0.45 \times 0.15 \times 0.09$ mn for **2**) were prepared as described and fixed at the top of a Lindemann capillary with epoxy resin.

$C_{10}H_{12}BrN_5O_4$ (**1**) and $C_{10}H_{12}IN_5O$ (**2**); both orthorhombic and space group $P2_12_12_1$ (No. 19), $a = 20.429(3)$/20.371(2)[1]), $b = 7.275(1)$/7.339(1)[1]), $c = 8.216(1)$/8.4881(1) Å[1]), $V = 1221.0(2)$/1269.0(3) Å^3[1]); $Z = 4$/4[1]), $D_x =$ 1.883/2.058 Mg m^{-3}[1]), $\mu = 3.391$/2.547 mm^{-1}[1]), $F(000) = 696$/798[1]), T 293(2) K for both.

Data Collection and Processing. Data for both compounds were collected on a *Siemens-P4-four*-cycle diffractometer with MoK_α radiation (–) 0.71073 Å and a graphite monochromator [47]. A total of 2829/3329[1]) reflections were collected in a range of $2.48° \leq \theta \leq 25.00°$/2.00°[1]) $\leq \theta \leq 22.99°$, giving 2055/1720[1]) independent reflections (R(int) 0.0488/0.0208[1])). An absorption correction was carried out using ψ-scans (T_{min} 0.4975/0.6637[1]), T_{max} 0.9002/0.9974[1])).

Solution and Refinement. Both structures were solved by standard direct methods. Full-matrix least-squares refinements based on F_0^2 were performed with non-H-atoms assigned anisotropic thermal parameters. All H-atoms were found in difference *Fourier* syntheses but were constructed in geometrically reasonable positions (bond lengths, bond angles). Especially the planar geometry of the NH_2 group and its orientation relative to the ring atoms was confirmed from difference *Fourier* synthesis. For all H-atoms, a common isotropic thermal parameter was refined.

Programs from the *Siemens* SHELXTL program package were used for the solution, refinement, and graphical representation of the structures [47]. A total of 182/184[1]) parameters were refined, so that a data-to-parameter ratio of 11.2/9.3[1]) resulted. The final R_1 and wR_2 values for data with $I > 2\sigma(I)$ were 0.0435/0.0226[1]) and 0.903/0.0598[1]). Corresponding values for all data were 0.0538/0.0235[1]) and 0.0950/0.0610[1]). The goodness-of-fit based on F_0^2 was 1.030/1.109[1]). The absolute structure parameter was refined to 0.03(2)/ – 0.04(3). The final difference *Fourier* map had peak maxima and minima at 0.457/0.285[1]) and – 0.401/ – 0.271 e Å^{-3}[1]), without any configurational relevance.

3. *Syntheses. 4-Propoxy-1*H-*pyrazolo[3,4-d]pyrimidin-6-amine* (**4**). A soln. of 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine [48] (6.8 g, 0.04 mmol) in 1M NaOPr/PrOH (100 ml) was refluxed for 1 h. Upon cooling, NaCl was precipitated with Et_2O (100 ml) and was filtered off. The filtrate was neutralized with 96% AcOH and evaporated. The residue was dissolved in MeOH and precipitated as pale-yellow needles by addition of ice-cold H_2O. Recrystallization from aq. MeOH yielded **4** (3.3 g, 70%) Colorless needles. M.p. 211°. TLC (silica gel, *C*): R_f 0.6. UV (MeOH): 244(5100), 276(6600). ^{1}H-NMR ((D$_6$)DMSO): 0.92 (t, $J = 5.9$, Me); 1.7 (m, CH_2); 4.31 (t, $J = 6.4$, CH_2O); 6.52 (s, NH_2); 7.75 (s, H–C(3)); 12.8 (s, NH). Anal. calc. for $C_8H_{11}N_5O$ (193.2): C 49.73, H 5.74, N 36.25; found: C 49.53, H 5.74, N 36.10.

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[3]) Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-106122 and CCDC-106123 for **1** and **2**, respectively. Copies of the data can be obtained, free of change, on application to the *CCDC*, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44(0)1223-336033 or e-mail: deposit@ccdc. com.oc.uk).

*3-Bromo-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidin-6-amine* (**5a**). To a soln. of **4** (1.0 g, 5.2 mmol) in 1,2-dichloroethane (50 ml), *N*-bromosuccinimide (1.0 g, 5.6 mmol) was added. After heating under reflux for 1 h, the solvent was evaporated to yield an orange solid which was washed with H_2O (2 × 100 ml), filtered off, and dissolved in MeOH. Decolorization with charcoal, filtration, and addition of ice-cold water to the filtrate gave a yellowish precipitate. Recrystallization from aq. MeOH yielded **5a** (0.91 g, 64%) colorless needles. M.p. 221° (dec.). TLC (silica gel, *C*): R_f 0.7. UV (MeOH): 248 (6100), 274 (7100). ^{1}H-NMR ((D$_6$)DMSO): 0.99 (*t*, *J* = 5.6, Me); 1.74 (*m*, CH_2); 4.33 (*t*, *J* = 6.4, CH_2O); 6.79 (*s*, NH_2); 13.05 (*s*, NH). Anal. calc. for $C_8H_{10}BrN_5O$ (272.1): C 35.31, H 3.7, N 25.74; found: C 35.47, H 3.77, N 25.67.

*3-Iodo-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidin-6-amine* (**5b**). As described for **5a**, with **4** (1.0 g, 5.2 mmol) and *N*-iodosuccinimide (1.3 g, 5.7 mmol, 2 h); **5b** (1.1 g, 65%). Colorless needles M.p. 223°. TLC (silica gel, *C*): R_f 0.7. UV (MeOH): 248 (6000), 274 (7000). ^{1}H-NMR ((D$_6$)DMSO): 1.07 (*t*, *J* = 5.8, Me); 1.77 (*m*, CH_2); 4.35 (*t*, *J* = 6.4, CH_2O); 6.7 (*s*, NH_2); 13.08 (*s*, NH). Anal. calc. for $C_8H_{10}IN_5O$ (319.1): C 30.11, H 3.16, N 21.95; found: C 30.26, H 3.17, N 21.89.

*3-Bromo-1-[2-deoxy-3,5-di-*O-*(*p-*toluoyl)-β-*D*-*erythro*-*pentofuranosyl]-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidine-6-amine* (**7a**) *and 2-[2-Deoxy-3,5-di-*O-*(*p-*toluoyl)-β-*D*-*erythro*-*pentofuranosyl]-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**8**). A suspension of powdered KOH (1.24 g, 22 mmol) and **5a** (5.5 mmol) in anh. MeCN (100 ml) was stirred for 10 min at r.t. Then, TDA-1 (= tris[2-(2-methoxyethoxy)ethyl]amine; 200 µl, 0.6 mmol) was added, and stirring was continued for another 10 min. Then, 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**6**) [3] (2.56 g, 6.6 mmol) was added in portions. After 20 min, insoluble material was filtered off, and the filtrate was evaporated. The resulting foam was applied to FC (silica gel, column 15 × 6 cm, *D*, then *E*): **7a** (from the faster-migrating zone) and **8** from the slower-migrating zone).

Data of **7a**: 1.3 g, 42% of colorless foam. TLC (silica gel, *D*): R_f 0.43. UV (MeOH): 243 (38500), 276 (10900). ^{1}H-NMR ((D$_6$)DMSO): 1.02 (*t*, *J* = 7.0, Me); 1.78 (*m*, CH_2); 2.36, 2.40 (2*s*, 2 *Me*C$_6$H$_4$); 2.66 (*m*, H$_\alpha$–C(2′)); 3.17 (*m*, H$_\beta$–C(2′)); 4.37–4.46 (*m*, CH_2O, 2 H–C(5′), H–C(4′)); 5.73 (*m*, H–C(3′)); 6.55 (‘*t*’, *J* = 5.7, H–C(1′)); 7.07 (*s*, NH_2); 7.28–7.92 (4*d*, *J* = 8.1, 2 MeC$_6$*H*$_4$). Anal. calc. for $C_{29}H_{30}BrN_5O_6$ (624.5): C 55.78, H 4.84, N 11.20, found: C 55.86, H 4.86, N 11.05.

Data of **8**: 620 mg (17%) of colorless foam. TLC (silica gel, *B*): R_f 0.53. UV (MeOH): 240 (35100), 283 (9500), 296 (8700). ^{1}H-NMR ((D$_6$)DMSO): 0.94 (*t*, *J* = 7.3, Me); 1.75 (*m*, CH_2); 2.34, 2.38 (2*s*, 2 *Me*C$_6$H$_4$); 2.74 (*m*, H$_\alpha$–C(2′)); 3.10 (*m*, H$_\beta$–C(2′)); 4.26–4.57 (*m*, CH_2O, 2 H–C(5′), H–C(4′)); 5.82 (*m*, H–C(3′)); 6.40 (‘*t*’, *J* = 5.6, H–C(1′)); 6.46 (*s*, NH_2); 7.24–7.92 (4*d*, *J* = 8.1, 2, MeC$_6$*H*$_4$); 8.45 (*s*, H–C(3)). Anal. calc. for $C_{29}H_{31}N_5O_6$ (545.6): C 63.84, H 5.73, N 12.84; found: C 63.73, H 5.70, N 12.84.

*1-[2-Deoxy-3,5-di-*O-*(*p-*toluoyl)-β-*D*-erythro-*pentofuranosyl]-3-iodo-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidin-6-amine* (**7b**) *and* **8**. As described for **7a**, with **5b** (5.5 mmol): **7b** (1.4 g, 41%). White foam of TLC (silica gel, *D*): R_f 0.44. UV (MeOH): 243 (38000), 276 (10500).^{1}H-NMR ((D$_6$)DMSO): 1.02 (*t*, *J* = 7.2, Me); 1.79 (*m*, CH_2); 2.38, 2.40 (2*s*, 2*Me*C$_6$H$_4$), 2.66 (*m*, H$_\alpha$–C(2′)), 3.19 (*m*, H$_\beta$–C(2′)), 4.37–4.49 (*m*, CH_2O, 2 H–C(5′), H–C(4′)), 5.72 (*m*, H–C(3′)), 6.55 (‘*t*’, *J* = 6.2, H–C(1)), 7.00 (*s*, NH_2); 7.34–7.93 (4*d*, *J* = 8.1, MeC$_6$H$_4$). Anal. calc. for $C_{29}H_{30}IN_5O_6$ (671.5): C 51.87, H 4.50, N 10.43; found: C 52.07, H 4.51, N 10.36.

From the slower-migrating zone (*cf.* **7a**/**8**), **8** was isolated as a colorless foam (640 mg, 18%).

*3-Bromo-1-[2-deoxy-β-*D*-erythro-pentofuranosyl]-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidine-6-amine* (**9a**). A soln. of **7a** (2.5 g, 4 mmol) in 0.1M NaOPr/PrOH (100 ml) was stirred for 1.5 h at 40°. Then, the soln. was adsorbed on silica gel and chromatographed (silica gel, column 12 × 4 cm), *A*, then *B*): **9a** (1.25 g, 81%). Colorless needles . M.p.180°. TLC (silica gel, *B*): R_f 0.3. UV (MeOH): 256 (7500), 278 (9100). ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*t*, *J* = 7.4, Me); 1.77 (*m*, CH_2); 2.18 (*m*, H$_\alpha$–C(2′)); 2.68 (‘*q*’, *J* = 6.4, H$_\beta$–C(2′)); 3.35, 3.47 (*m*, 2 H–C(5′)); 3.77 (*m*, H–C(4′)); 4.34 (*m*, CH_2O, H–C(3′)); 4.67 (*t*, *J* = 5.5, OH–C(5′)); 5.22 (*d*, *J* = 4.2; OH–C(3′)); 6.36 (‘*t*’, *J* = 6.2, H–C(1′)), 6.99 (*s*, NH_2). Anal calc. for $C_{13}H_{18}BrN_5O_4$ (388.2): C 40.22, H 4.67, N 18.04; found: C 40.15, H 4.73, N 18.10.

*1-[2-Deoxy-β-*D*-erythro-pentofuranosyl]-3-iodo-4-propoxy-1*H-*pyrazolo[3,4-*d*]pyrimidin-6-amine* (**9b**). As described for **9a**, with **7b** (2.5 g, 3.7 mmol) in 0.1M NaOPr/PrOH (100 ml, 2 h, 40°): **9b** (1.27 g, 78%). Colorless needles. M.p. 191°. TLC (silica gel, *B*): R_f 0.3. UV (MeOH): 256 (7500), 278 (9100). ^{1}H-NMR ((D$_6$)DMSO): 1.1 (*t*, *J* = 7.0, Me); 1.82 (*m*, CH_2); 2.22 (*m*, H$_\alpha$–C(2′)); 2.76 (‘*q*’, *J* = 6.4, H$_\beta$–C(2′)); 3.40, 3.52 (*m*, 2 H–C(5′)); 3.82 (*m*, H–C(4′)); 4.41 (*m*, CH_2O, H–C(3′)); 4.73 (*t*, *J* = 4.9, OH–C(5′)); 5.24 (*d*, *J* = 3.7, OH–C(3′)); 6.37 (‘*t*’, *J* = 5.9, H–C(1′)), 6.96 (*s*, NH_2). Anal. calc. for $C_{13}H_{18}IN_5O_4$ (435.2): C 35.88, H 4.17, N 16.09; found: C 36.02, H 4.26, N 15.93.

*4*H-*Pyrazolo[3,4-*d*]pyrimidin-4-ones* **1** *and* **2**. All anal. data were identical with those published earlier [19].

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