Stereoelectronic effects of modified purine bases on the sugar conformation of nucleosides: pyrrolo[2,3-*d*]pyrimidines

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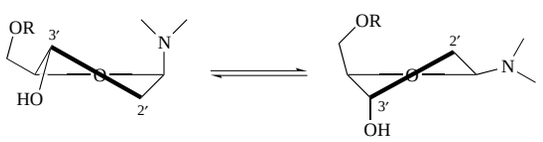
Steric and stereoelectronic effects of 7- and 8-substituents of 7-deaza-2′-deoxy-adenosine and -guanosine on the dynamic sugar puckering as well as on the conformation about the C(4′)–C(5′) bond have been studied. (*i*) The higher the electron-attracting effect of the substituents, the more the N⇌S (North⇌South) equilibrium of the pentofuranose moiety is biased towards the N-conformation. (*ii*) The higher the electron-withdrawing effect of the 7-substituents, the higher the $\gamma^{(+)g}$ (+sc) rotamer population around the C(4′)–C(5′) bond. The interdependencies of the conformational equilibria of 7-deazapurine nucleosides and their influence on oligonucleotide secondary structures are discussed.

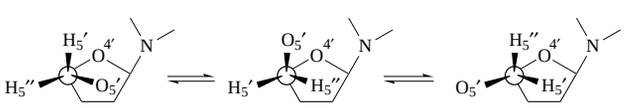
Introduction

The base moiety of a nucleoside residue is directly involved in carrying genetic information and its propagation in the replication process of nucleic acids by Watson–Crick or Hoogsteen hydrogen bonded base pairing. Comparatively little is known about how the aglycone and the constituent pentofuranose moiety form the steric and stereoelectronic partnership that gives the nucleic acids their unique role in storing genetic information, however.

Two dynamic two-state and one three-state equilibrium decide the topology of a nucleoside in solution. These are (*i*) the *syn*⇌*anti* equilibrium of the base about the N-glycosylic bond, (*ii*) the puckering of the pentofuranosyl moiety (N⇌S; $^{3'}T_{2'}\rightleftharpoons{}_{3'}T^{2'}$) and (*iii*) the rotational equilibrium about the C(4′)–C(5′) bond ($\gamma^{+(g)}\rightleftharpoons\gamma^{t}\rightleftharpoons\gamma^{-(g)}$). These equilibria are interdependent, and the energy barrier between the preferred conformational states is usually low.[1]



North (N) sugar ($^{3'}T_{2'}$) South (S) sugar ($_{3'}T^{2'}$)



+sc [(+)g] ap [(-)g] -sc [t]

The effect of nucleobases at C(1′) in driving the two-state N⇌S pseudorotational equilibrium in *N*-(β-D-ribofuranosyl) nucleosides consists of two counteracting contributions from (*i*) the anomeric effect [= stereoelectronic interactions between O(4′) and the nucleobase nitrogen at C(1′)], which places the aglycone in the pseudoaxial orientation and (*ii*) the inherent steric effect of the nucleobase, which opposes the anomeric effect by its tendency to take up the pseudoequatorial position. The latter is sterically possible only in the S-type conformations.[2]

The N⇌S equilibrium of the sugar moiety of *N*-(β-D-ribofuranosyl) nucleosides in solution is energetically controlled by various *gauche* effects: the *gauche* effects of the O(4′)–C(4′)–C(3′)–O(3′) and O(2′)–C(2′)–C(1′)–N fragments bias the pseudorotational equilibrium towards S, whereas it is driven to N by the *gauche* effect of O(4′)–C(1′)–C(2′)–O(2′). In the case of 2′-deoxy-β-D-ribofuranosyl-*N*-nucleosides this latter effect is of course absent—one of the reasons for the generally preferred S-type sugar puckering of 2′-deoxy-β-D-ribofuranosyl nucleosides.[2]

In an extensive and detailed study Chattopadhyaya and coworkers were able to differentiate for the first time between the *gauche* and anomeric effects by comparison of the thermodynamics of the pseudorotational equilibrium of the pentofuranose moiety in various regular and modified *N*- and *C*-nucleosides.[3–14]

In this manuscript we investigate this phenomenon on 7-deazapurine nucleosides. In particular, the tuning of the sugar puckering and also indirectly the conformation about the C(4′)–C(5′) bond of corresponding 2′-deoxynucleosides is studied and the influence of various substituents on the steric and stereoelectronic (anomeric) effects is investigated. The interdependence of the different conformational equilibria as well as their importance for the secondary structure and stability of the corresponding oligodeoxynucleotides is discussed.

Results and discussion

The pseudorotation concept[15] was introduced to describe the continuous interconversions of the pentofuranose puckering of nucleosides. The geometry of the sugar ring is conveniently described using the Altona–Sundaralingam parameters, namely the phase angle of pseudorotation (*P*) and the puckering amplitude (ϕ_m).[16,17] A survey of nearly 200 X-ray crystal structures of nucleosides and nucleotides found nucleosides in both the north (N) and south (S) conformations, the first of which is centred around $P = 18°$ [C(3′)-*endo*], whereas the second is around $P = 162°$ [C(2′)-*endo*].[18] For most β-D-ribonucleosides the ratio between N- and S-states is approximately 1:1, and for 2′-deoxy-β-D-ribonucleosides 1:3.

Rotation about the C(4′)–C(5′) bond plays a crucial role in positioning the 5′-phosphate group of a nucleotide relative to the sugar and the base. The exocyclic CH_2OR group may exist in three staggered conformations designated +sc [(+)*g*], −sc (*t*) and ap [(−)*g*]. These three ranges are not uniformly populated because their distribution is dependent on the sugar puckering and on the base.

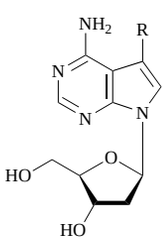
The preferred puckering conformations of furanose moieties in nucleosides and the relative proportions of N- and S-conformers are controlled by steric and stereoelectronic effects of substituents. Thus, a systematic survey of conformational pre-

Table 1 $^3J_{H,H}$ Coupling constants of the sugar moieties and conformer populations of 2′-deoxynucleosides at 303 K[a]

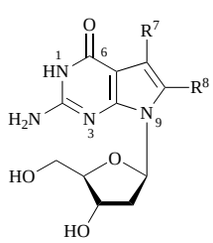
	$^3J_{H,H}$/Hz							Conformation				
Compound	1′,2′	1′,2″	2′,3′	2″,3′	3′,4′	4′,5′	4′,5″	% N	% S	% $\gamma^{(+)g}$	% γ^{t}	$\gamma^{(-)g}$
dA	7.20	6.50	6.50	3.30	3.20	3.45	4.30	28	72	59	25	16
1	6.60	7.60	7.00	3.00	3.00	3.80	4.80	24	76	49	31	20
2	8.00	6.25	6.15	3.05	3.00	4.05	4.85	26	74	46	31	23
3	7.50	6.35	6.25	3.25	3.50	3.90	4.80	30	70	48	31	21
4	7.05	6.55	6.60	3.15	3.40	3.90	4.70	29	71	49	30	21
5	6.90	6.50	6.50	3.10	3.30	3.90	4.70	29	71	49	30	21
6	6.80	6.55	6.25	3.65	3.45	3.60	4.70	34	66	53	30	17
7	6.80	6.75	6.00	4.15	3.85	3.50	4.60	38	62	55	29	16
8	7.50	6.40	6.20	3.20	3.40	3.80	4.60	29	71	52	29	20
9	6.70	6.45	5.90	2.95	3.45	3.95	4.40	31	69	52	26	21
dG[3]	7.30	6.50	6.30	3.60	3.20	3.60	4.70	29	71	53	30	17
10	7.25	6.50	6.25	3.00	3.35	4.20	5.00	28	72	43	33	24
11	6.95	6.60	6.65	3.70	3.80	4.20	5.30	34	66	39	37	24
12	7.45	7.20	6.80	2.85	3.30	3.25	4.75	22	78	56	30	14
13	6.50	6.90	6.40	3.00	3.00	4.10	5.00	28	72	44	33	23
14	6.60	7.00	6.40	3.20	3.60	4.20	5.00	31	69	43	33	24
15	7.20	6.45	6.20	3.05	3.25	4.25	5.10	28	72	41	34	25
16	8.00	6.70	6.75	2.25	3.20	3.15	4.10	18	82	65	23	12
17	7.30	7.30	7.10	3.50	3.65	3.75	5.30	27	73	44	37	19
18	7.55	6.45	6.10	3.20	3.10	4.10	4.90	28	72	45	32	23
19	6.85	6.55	6.55	3.55	3.75	3.80	5.00	33	67	47	20	33

[a] Solvent, D_2O; RMS, ⩽ 0.4 Hz; $|\Delta J_{max}|$ ⩽0.5 Hz.

ferences of 2′-substituted adenosine and uridine derivatives in solution has shown that the amount of N-conformers increases linearly with the electronegativity of the 2′-substituents.[19] The sugar conformation is, moreover, influenced by modification of the base. Structures **1**–**19** show 7-deaza-2′-deoxynucleosides



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



10 $R^7 = R^8 = H$
11 R^7 = Cl; R^8 = H
12 R^7 = H; R^8 = Cl
13 R^7 = Br; R^8 = H
14 R^7 = I; R^8 = H
15 R^7 = Me; R^8 = H
16 R^7 = H; R^8 = Me
17 $R^7 = R^8$ =Cl
18 R^7 = Hexyn-1-yl; R^8 = H
19 R^7 = CN; R^8 = H

(purine but not systematic pyrrolo[2,3-*d*]pyrimidine numbering is used throughout this manuscript) of which the sugar puckering as well as the conformation about the C(4′)–C(5′) bond has been evaluated.

Sugar puckering has been studied on the basis of five vicinal ^{1}H–^{1}H coupling constants (Table 1) using the PSEUROT 6.2 program.[20,21] The populations of the staggered conformations about the C(4′)–C(5′) bond were calculated according to Westhof *et al.*[22] using the vicinal ^{1}H–^{1}H couplings between H(4′) and H(5′) as well as H(5″), respectively, and applied to eqns. (1)–(3).

$$\% \gamma^{(+)g} = \{1.46 - [^3J_{4',5'} + {}^3J_{4',5''}]/8.9\} \times 100 \quad (1)$$

$$\% \gamma^{t} = \{^3J_{4',5''}/8.9 - 0.23\} \times 100 \quad (2)$$

$$\% \gamma^{(-)g} = \{^3J_{4',5'}/8.9 - 0.23\} \times 100 \quad (3)$$

All vicinal ^{1}H–^{1}H couplings of the sugar protons as well as the evaluated populations of conformers are given in Table 1.

From these data some general trends can be deduced. Enhancement of the bulkiness of a substituent in position 8 drives the N⇌S equilibrium of a 7-deaza-2′-deoxyguanosine (**10**, **12**, **16**) towards S-type sugar pucker. The conformation generally correlates with the *syn* conformation about the *N*-glycosylic bond. The nature of this effect seems to be mainly steric because a linear correlation exists between the S-conformer population and the van der Waals radii of the 8-substituents (data not shown).

An interdependence exists between the sugar puckering of the 8-substituted 7-deaza-2′-deoxyguanosines and their conformation about the C(4′)–C(5′) bond: the higher the S-conformer population, the higher the $\gamma^{(+)g}$ rotamer population. Regarding the temperature dependence of sugar conformation only the sterically demanding 7-deaza-8-methyl-2′-deoxyguanosine (**16**) exhibits a noticeable change between 296 and 343 K.

From van't Hoff plots (data not shown) the thermodynamics of the N⇌S interconversions could be estimated ($Me^8c^7G_d$, **16**: $\Delta H = -3.3 \pm 0.4$ kJ mol^{-1}, $\Delta S^{298} = -1.7 \pm 0.8$ J K^{-1} mol^{-1} $Me^7c^7G_d$, **15**: $\Delta H = -0.8 \pm 0.4$ kJ mol^{-1}, $\Delta S^{298} = -10.5 \pm 1.0$ J K^{-1} mol^{-1}). The thermodynamic data of N⇌S interconversion of the 8-methylated compound **16** are similar to those of 2′-deoxyguanosine ($\Delta H = -2.5 \pm 0.3$ kJ mol^{-1}, $\Delta S^{298} = -0.8 \pm 0.8$ J K^{-1} mol^{-1}).[3]

Fig. 1 demonstrates the stereoelectronic influence of 7-substituents on the N⇌S equilibrium of a series of 7-deaza-2′-deoxyadenosines (**1**–**9**). The graph shows that the higher the electron-attracting effect of the 7-substituents (expressed by their Hammett constants σ_m[23]), the more the N⇌S equilibrium of the sugar moieties is biased towards N conformation.

The 7-nitro compound **7** exhibits the highest N-conformer population. Indeed, an X-ray analysis of this nucleoside also shows N-type sugar puckering.[24] X-Ray crystal structures of N-nucleosides generally show a shortening of the O(4′)–C(1′) bond relative to C(4′)–O(4′) by about 3 pm[13] (d*A* 3.2 pm[25]) which has been considered to be a manifestation of the anomeric effect. In the case of 7-deaza-2′-deoxyadenosine (2′-deoxytubercidin) this relative shortening amounts to only 0.9 pm.[26] This value increases to 2.3 pm in the case of the nitro compound **6** indicating the enhanced stereoelectronic effect of

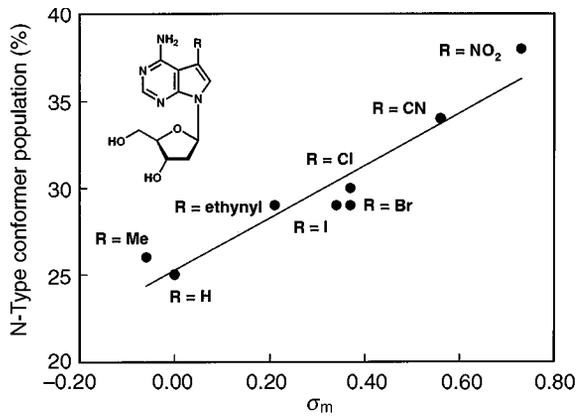


Fig. 1 N-Type conformer population of 7-substituted 7-deaza-2′-deoxyadenosines as a function of the Hammett constants σ_m of the 7-substituents

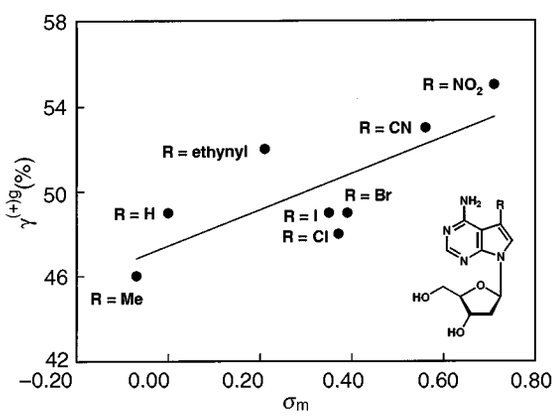


Fig. 2 $\gamma^{(+)g}$ Rotamer population of 7-substituted 7-deaza-2′-deoxyadenosines as a function of the Hammett constants σ_m of the 7-substituents

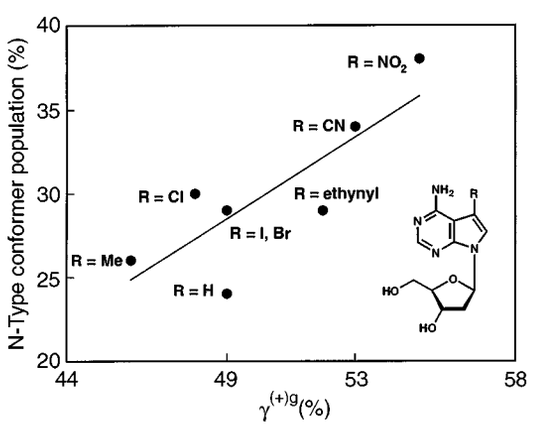


Fig. 3 N-Type conformer population *versus* $\gamma^{(+)g}$ rotamer population of 7-substituted 7-deaza-2′-deoxyadenosines

the nucleobase on the sugar compared to the unsubstituted parent nucleoside.[24]

In case of the 7,8-dichloro-substituted 7-deaza-2′-deoxyguanosine (**17**) the steric effect of the 8- and the stereoelectronic 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 (**10**). An analogous result is obtained if the $\gamma^{(+)g}$ population of compound **17** is compared with that of **10**; also the conformation at the C(4′)–C(5′) bond of both compounds is almost identical.

A plot of the $\gamma^{(+)g}$ rotamer population of the 7-substituted 7-deaza-2′-deoxyadenosine **1**–**9** *vs.* the corresponding σ_m constants (Fig. 2) shows a correlation: the more electron-attracting

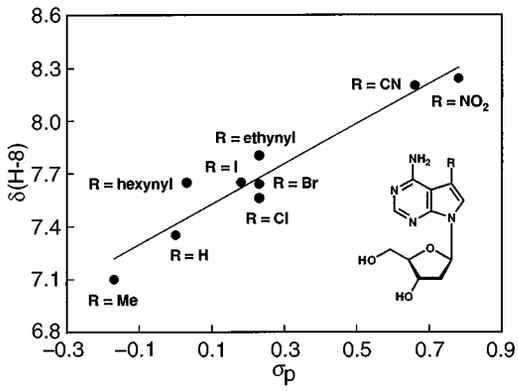


Fig. 4 ^{1}H NMR chemical shifts of the H-8 signals of 7-substituted 7-deaza-2′-deoxyadenosines *versus* the Hammett constants σ_p of the 7-substituents

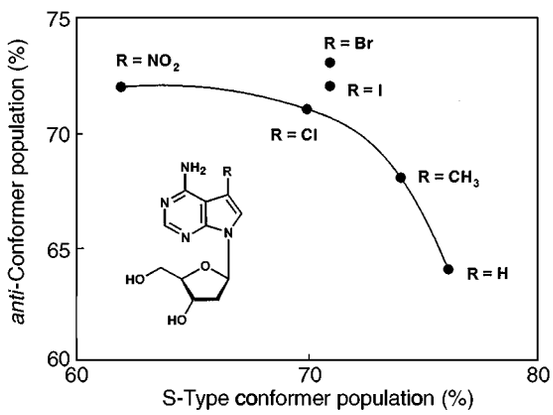


Fig. 5 *Anti*-conformer population *versus* S-type conformer population of 7-substituted 7-deaza-2′-deoxyadenosines

the 7-substituent, the higher the $\gamma^{(+)g}$ population. Combining the correlations of Figs. 1 and 2 demonstrates the interdependence of both conformational equilibria, the sugar puckering (N-conformer population) and the rotation about the C(4′)–C(5′) bond (Fig. 3): electron-withdrawing substituents drive the equilibria towards N as well as to $\gamma^{(+)g}$.

The electronic influence of the different 7-substituents of 7-deaza-2′-deoxyadenosine derivatives on the electron distribution is sensitively monitored by the ^{1}H NMR chemical shifts of the corresponding H(8) signals, as the δ values parallel the Hammett σ_p constants of the substituents (Fig. 4).

The deviation of the downfield shift (0.2–0.3 ppm) measured for the terminal alkynyl-substituted compounds **8** and **9** is striking. This may be due to a strong diamagnetic anisotropy of the C≡C triple bond leading to a significant deshielding of the *ortho*-located H(8) atoms.

The fact that such an extraordinary deshielding cannot be observed for the 7-cyano- or 7-nitro-substituted derivatives **6** and **7** is noteworthy. These differences in the electronic effects of the 7-substituents between compounds **8** and **9** on the one hand and compounds **6** and **7** on the other hand are in line with the finding that only the 7-alkynyl-substituted derivatives exhibit strong fluorescence while **6** and **7** do not.[27]

In a previous paper a graphical method for a quantitative determination of *syn* and *anti* conformer populations of regular and modified nucleosides based on one-dimensional ^{1}H NOE measurements was reported.[28] Applying this method to the 7-substituted 7-deaza-2′-deoxyadenosines **1**–**5** and **7**, their conformation about the *N*-glycosylic bond was calculated, and the *anti*-conformer population was plotted *vs.* their S-conformer population (Fig. 5).

From this graph another trend in conformational interdependence can be observed. Enhancement of S-type sugar puckering coincides with a decrease in *anti* conformers.

The data reported above and their interdependencies fall qualitatively into line with results which have been evaluated for other ribo- and 2′-deoxyribo-nucleosides, in particular for 5-substituted uridine derivatives. Due to the different electron affinities of the donor and acceptor groups in position 7 of the pyrrolo[2,3]pyrimidine bases, the electron distribution within the π system of the heterocycle is altered. Since electron-attracting groups strengthen the bonding interaction between a lone pair at O(4′) and the π* orbital of the C(7)–C(8) double bond, they should favour small dihedral angles χ and an increased N-conformer population. Electron-donating groups are expected to exert an opposing influence.[29]

Substituent influence of 7-deazapurine bases on the oligonucleotide structures

The formation of an oligonucleotide single or double strand from nucleotide units follows a restriction of the conformational flexibilities discussed above. This increment of ΔG for the extension of an oligonucleotide chain counterbalances the formation of extra base stacks and two or three hydrogen bonds.[30] The growth of the double helix is spontaneous (cooperative zipper mechanism[31,32]), due mainly to the demanding geometrical constraints of the sugar–phosphate backbone which are implied by the stereochemistry of the nucleotide unit. This, in its preferred conformation, is preformed to suit this purpose. These geometrical restraints imply that the preferred conformation of a nucleoside or nucleotide is of importance with respect to a preorganization of single- and double-stranded helices.

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 described between 1978–1983 in the influential manuscripts of Gassen and co-workers[33–35] who demonstrated the influence of 5-substituted uridine derivatives ($R^5 = NH_2$, Cl, Br, NO_2) 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 nitro or halogeno (Cl, Br) enhance the base–base interaction while electron-donating groups (NH_2) diminish the stacking; these effects were measured in terms of hypochromicity values (λ, 260 nm). A similar trend can be observed when the thermal hypochromicity data of alternating oligodeoxyribonucleotides of the type $d(A^*–T)_6$ containing 7-substituted 7-deaza-2′-deoxyribonucleosides such as compounds **1**–**5** (= A*) are compared: the 7-halogeno-substituted oligonucleotides exhibit a 5–7% higher hypochromicity (H = 20–22%) than $d(c^7A–T)_6$ of $d(Me^7c^7A–T)_6$ (H = 15%).[36] The significantly higher duplex stability of the first compared to the latter may be, therefore, at least partly traced to enhanced stacking interactions.

Because the N-type conformations of 7-deaza-2′-deoxynucleosides bearing electron-withdrawing 7-substituents favour the stacking interactions they are good candidates to merge an oligonucleotide towards an A-type secondary structure. This has recently been shown in the finding that a short homomeric oligonucleotide, namely 5′-$d(I^7c^7G_5–G)$, hybridizes strongly with poly(C) under formation of an A-type DNA–RNA hybrid.[37,38] As A-DNA and A-RNA double helices are isomorphous it can be anticipated that an oligodeoxynucleotide consisting of compounds such as 7-nitro- or 7-cyano-7-deaza-2′-deoxy-adenosine or -guanosine can be easily and effectively hybridized with a complementary RNA target which would improve their applicability as antisense oligonucleotides.

Experimental

All compounds used (**1**–**19**) were prepared in our laboratory and details are published elsewhere.[39–42] 7-Cyano-7-deaza-2′-deoxyguanosine was prepared very recently by cyanilation of protected **14** and subsequent deprotection.[43] 7-Deaza-7-nitro-2′-deoxyadenosine **7** was prepared according to Verdine and co-workers[44] as well as by another route according to ref. 24. The compounds were dissolved in D_2O at a concentration of approximately 20 mM.

N/S Conformer calculations were performed using pseudorotational starting parameters recommended in the user's manual of the program [$\Phi_m = 36°$ (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_m) of the minor conformer (N) or the puckering amplitudes of both conformers were constrained. In all cases the RMS values were ≤0.4 Hz and the $|\Delta J_{max}| \leq 0.5$ Hz. The rotamer populations about the C(4′)–C(5′) bond were calculated according to eqns. (1)–(3) using $J_{H4',H5'}$ and $J_{H4',H5''}$. All measurements were performed twice on a Bruker AMX-500 NMR spectrometer at 303 K unless otherwise stated with a delay time of 1 h to allow temperature stabilisation.

Acknowledgements

Financial support from the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (BMBF) is gratefully acknowledged.

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Paper 7/02501G
Received 11*th April* 1997
Accepted 20*th June* 1997