Structural properties of modified deoxyadenosine structures in solution. Impact of the *gauche* and anomeric effects on the furanose conformation

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Received January 6, 1987

LEO H. KOOLE, HENK M. BUCK, AGNES NYILAS, and JYOTI CHATTOPADHYAYA. Can. J. Chem. **65**, 2089 (1987).

A variable temperature high resolution ^{1}H nuclear magnetic resonance study (at 300 or 500 MHz) of the two modified nucleosides 9-(2′-deoxy-β-D-*threo*-ribofuranosyl)-adenine (**1**) and 9-(3′-deoxy-β-D-*threo*-ribofuranosyl)-adenine (**2**) has been performed. It was found that the furanose conformation in **1** and **2** can be best described as a rapid North (N) ⇄ South (S) equilibrium that is biased toward the N-form. For **1**, a marked temperature dependence of the N ⇄ S equilibrium was found, whereas the furanose conformation in **2** is virtually insensitive to temperature changes. Comparison of these results with the well-known conformational properties of the natural nucleosides 2′-deoxyadenosine (2′-dA) and 3′-deoxyadenosine (3′-dA) revealed that the net result of the *gauche* effect and the anomeric effect is of major importance in determining the furanose conformation. A brief discussion in terms of the thermodynamic parameters that govern the N ⇄ S equilibria in the investigated nucleosides is given.

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On a effectué une étude de résonance magnétique nucléaire à haute résolution (à 300 ou 500 MHz) et à température variable de deux nucléosides modifiés, soit la (déoxy-2 β-D-*thréo*-ribofurannosyl)-9 adénine (**1**) et la (déoxy-3 β-D-*thréo*-ribofurannosyl)-9 adénine (**2**). On a trouvé que la meilleure façon de décrire la conformation du furannose des composés **1** et **2** fait appel à un équilibre rapide nord (N) ⇄ sud (S) dans lequel la forme N est favorisée. Dans le cas du composé **1**, on a observé que l'équilibre (N) ⇄ (S) est soumis à une dépendance marquée sur la température; par ailleurs, la conformation du furannose de la molécule **2** est virtuellement insensible aux changements de température. Une comparaison de ces résultats avec les propriétés conformationnelles bien connues des nucléosides naturels déoxy-2′ adénosine (d-2′ A) et déoxy-3′ adénoside (d-3′ A) révèle que le résultat net de l'effet *gauche* et de l'effet anomérique est important dans la détermination de la conformation du furannose. On présente une brève discussion en fonction des paramètres thermodynamiques qui influencent l'équilibre (N) ⇄ (S) dans les nucléosides étudiés.

[Traduit par la revue]

Introduction[2]

Naturally occurring nucleic acids display a marked structural versatility, which is essential to their function of storing and transmitting genetic information in the living cell (1). In particular, the backbone chain, in which negatively charged phosphate groups alternate with furanose sugar units (ribose in RNAs, 2′-deoxyribose in DNAs), is capable of adopting a variety of distinct conformations. It has been shown that the overall structural flexibility of DNA and RNA is largely determined by the furanose rings in the backbone, and this insight has stimulated extensive experimental (2–4) and theoretical (5–13) research on furanose puckering in nucleosides and nucleotides. We report herein a detailed ^{1}H nmr conformational study on the modified deoxyadenosine systems (14, 15) 9-(2′-deoxy-β-D-*threo*-ribofuranosyl)-adenine (**1**) and 9-(3′-deoxy-β-D-*threo*-ribofuranosyl)-adenine (**2**). Both structures (Fig. 1) have the hydroxyl group on the furanose ring in the unnatural *endo* position.

It should be noted that Mengel and Wiedner (14), as well as Lüdemann *et al.* (16), have previously reported ^{1}H nmr studies on **1** and **2**. However, the work of Mengel and Wiedner does not mention a conformational analysis of the furanose moieties in **1** and **2**. The conformational studies as reported by Lüdemann *et al.* refer exclusively to the solvent ND_3 and a sample temperature of 213 K. In the present work, we determined the conformational properties of **1** and **2** as a function of the sample temperature in the solvents D_2O or dimethyl formamide-d_6. Comparison with the natural nucleosides 2′-deoxyadenosine (2′-dA) and 3′-deoxyadenosine (3′-dA), also called cordycepin, provided new details on the nature of furanose puckering. It is found that the net effect of two stereoelectronic factors (i.e., the *gauche* effect and the anomeric effect) is of major importance in determining the conformational preferences of the sugar unit in solution.

Experimental

Preparation

The preparation of the modified nucleosides **1** and **2** has been described previously (14, 15). The essential step in the synthesis route for both compounds involves the $LiAlH_4$ reduction of a (6*N*,5′) doubly protected 2′,3′-*lyxo*-anhydroadenosine structure. Using $LiAlD_4$ in the reduction step, the synthesis route can be used to introduce deuterium in a stereospecific way (15). After this reaction, one obtains **1** with a deuterium in the *exo* position at $C_{2'}$ ($C_{2'}$(*R*) configuration), and **2** with a deuterium in the *exo* position at $C_{3'}$ ($C_{3'}$(*S*) configuration). The natural nucleosides 2′-dA and 3′-dA were purchased from Sigma.

Nuclear magnetic resonance spectroscopy

The ^{1}H nmr spectra were recorded at different sample temperatures on a Bruker CXP 300 nmr spectrometer[3] (^{1}H frequency: 300.13 MHz),

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[2]Nomenclature in this work follows recent IUPAC–IUB recommendations on nucleotide conformational nomenclature. See D. B. Davies and H. B. E. Dixon, IUPAC–IUB Discussion Draft on abbreviations and symbols for the description of polynucleotide chains. Document J.C.B.N. 14.2 (1980).

[3]NMR facility at the Eindhoven University of Technology.

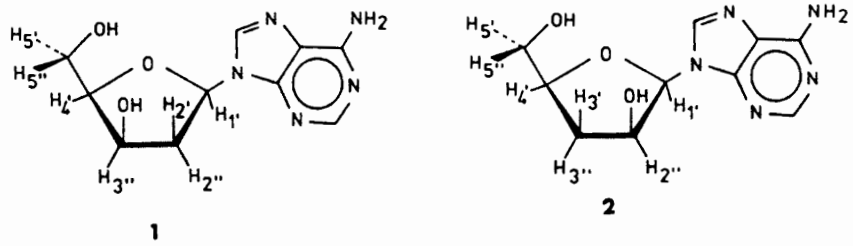


FIG. 1. Structural formulas of the model compounds **1** and **2**. The numbering of the furanose hydrogens is indicated.

or on a Bruker AM 500 nmr spectrometer[4] (^{1}H frequency: 500.1 MHz). In all cases, the field-frequency lock was provided by the solvent (D_2O or dimethyl formamide-d_6). At 300 MHz, we used a spectral window of 3000 Hz; at 500 MHz this was 5000 Hz. Before Fourier transformation, the spectra were zero-filled to 32 or 64 K, and resolution enhanced by an appropriate Gaussian multiplication. In some cases, a standard computer simulation–iteration procedure was employed to obtain accurate values for spin–spin couplings and chemical shifts.

Furanose conformation

The description of the puckered conformation in furanose rings is greatly facilitated by the pseudorotation concept (5, 17), in which the conformations of the five ring torsions are mathematically related to a puckering amplitude (ν_m), and a phase angle of pseudorotation (P). The puckering amplitude identifies the deviation from planarity of the furanose ring. From the large number of X-ray crystallographic studies of nucleosides and nucleotides (18) it is known that ν_m is confined to a narrow range around $\nu_m = 39°$. Potential energy calculations have clearly shown that the stability of the furanose systems decreases sharply when ν_m is varied (2). The phase angle of pseudorotation actually indicates which part of the ring is bent. P lies in the range 0–360°, thus encompassing an entire pseudorotation cycle. Also from crystallographic studies, it is known that P values occur in two distinct and relatively narrow ranges (18). The first range is centered around $P = 18°$ ($C_{3'}$-*endo* ring conformation), and is designated as N (North). The N pucker is characteristic for all RNAs and, for example, the A form of DNA (4). The second range is centered around $P = 162°$ ($C_{2'}$-*endo* ring conformation), and is called S (South). This pucker is found, for example, in B DNA. Conformational studies on nucleosides and nucleotides in solution have shown that the furanose ring is generally involved in a rapid N ⇄ S equilibrium, which is an approximate 1:1 blend for ribose rings, and clearly biased toward the S form for 2′-deoxyribose rings (2, 19–21).

A rationale for this different conformational behavior of ribose vs. 2′-deoxyribose has been given by Olson (2). She stated that the preferred conformation in solution is determined by the so-called *gauche* effect, i.e., the tendency of vicinal oxygen atoms to adopt a *gauche* rotational arrangement (12, 22, 23). For furanose units, this means that the oxygens $O_{2'}$ and $O_{3'}$ are preferentially located in an axial position.

Looking at the N and S forms of ribose, it is seen that the N form corresponds with $O_{2'}$ axial and $O_{3'}$ equatorial, whereas the reverse situation occurs in the S form. Consequently, ribose shows a 1:1 distribution over N and S in solution. 2′-Deoxyribose, on the other hand, has $O_{3'}$ axial in the S form, and $O_{3'}$ equatorial in the N form, which leads to a preference for S in solution. The theory also correctly predicts the experimentally observed preference of 3′-deoxy nucleosides (e.g. cordycepin) for the N pucker (24–26). At first sight, the *gauche* effect theory seems to account for all experimental data that have been obtained on nucleosides and nucleotides in solution. However, a substantial shortcoming is obvious, since the theory does not explain why the N ⇄ S conformational equilibrium in 2′-deoxy nucleosides is virtually temperature independent (25). This experimental fact indicates that the free energy difference between the N and S states is in fact solely determined by entropy factors. Apparently, the entropy is 1–2 eu larger in the S form than in the N form. In contrast, the N ⇄ S equilibrium for 3′-deoxy nucleosides is clearly temperature sensitive (*vide infra*). In this case, raising the temperature leads to increased populations of the S pucker, i.e., the N form is associated with the lowest enthalpy.

In the present work, we have specifically focused on the temperature dependence of the conformational equilibria of **1**, **2**, 2′-dA, and 3′-dA. A brief discussion of the thermodynamic parameters governing the N ⇄ S equilibria is given. It appears to be necessary to account explicitly for the so-called anomeric effect (27), i.e. the preference of the nucleobase to be axially located on the furanose unit.

Results

We have recorded 300- and 500-MHz ^{1}H nmr spectra of **1**, **2**, 2′-dA, and 3′-dA in the temperature range of −40 to 95°C. In the experiments at sample temperatures higher than 0°C, we used D_2O as the medium; all other experiments refer to the solvent dimethyl formamide-d_6. Table 1 summarizes the ^{1}H nmr parameters that were obtained on **1** and **2** at 25°C. The data obtained at other sample temperatures are listed as supplementary material.[5]

*9-(2′-Deoxy-β-D-*threo*-ribofuranosyl)-adenine (1)*

The conformation of the furanose ring in **1** was determined from the relationship between the coupling constants of the vicinal ring protons (i.e., $J_{1'2'}$, $J_{1'2''}$, $J_{2'3'}$, $J_{2''3'}$, and $J_{3'4'}$) and the pseudorotational parameters of the ring. The assignment of the protons $H_{2'}$ and $H_{2''}$ was based on a comparison with the analogue of **1**, in which $H_{2''}$ was substituted by deuterium (15). From this, it follows that $\delta(2'') > \delta(2')$. Using the generalized Karplus equation of Altona and co-workers (28), we calculated the variation of the five ring-coupling constants over the full pseudorotation circuit.[6] A convenient qualitative representation of the conformational equilibrium of the furanose ring in **1** is

[4]Dutch National 500/200 hf NMR facility at Nijmegen, The Netherlands.

[5]Tables of nmr spectral parameters obtained on **1**, **2**, 2′-dA, and 3′-dA may be purchased from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

[6]Analogous calculations have recently been performed for 5-methoxymethyl-1-(2′-deoxy-β-D-*lyxo*-furanosyl uracil). See Fig. 3 in ref. 29.

TABLE 1. Nuclear magnetic resonance spectral data, obtained on 1 and 2 in D_2O, at 25°C

	J			δ^a	
Protons	1	2	Proton	1	2
1'2'	2.6	—	1'	6.27	6.14
1'2"	8.7	5.1	2'	2.44	—
2'3"	1.0	—	2"	2.91	4.60
2"3'	—	6.8	3'	—	1.93
2"3"	5.8	6.8	3"	4.52	2.43
3'4'	—	8.3	4'	4.14	4.25
3"4'	3.5	6.8	5'	3.94	3.80
4'5'	4.2	3.0	5"	3.83	3.70
4'5"	7.3	5.2	2	8.26	8.15
			8	8.14	8.08

[a]Referenced against the HDO residual peak (δ 4.68).

TABLE 2. Calculated population of the N conformer in 1 as a function of the sample temperature (see text)

T	x_N
233	1.00
255	0.98
276	0.97
286	0.96
300	0.94
322	0.91
345	0.89
365	0.86

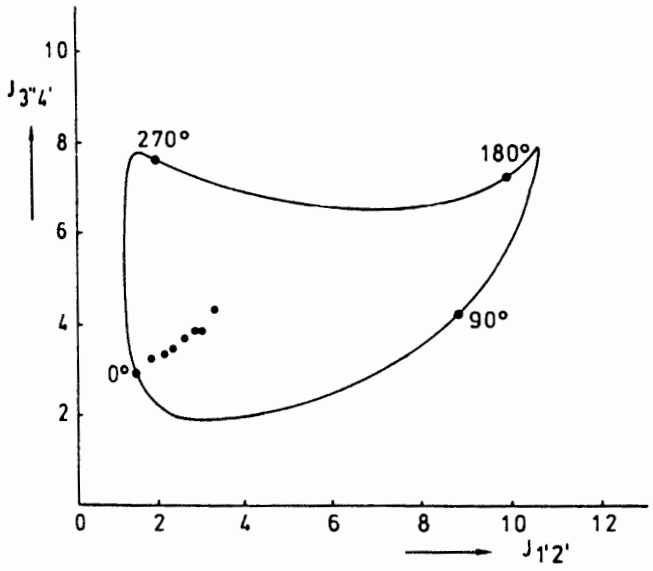


FIG. 2. Calculated variation of the proton–proton coupling constants $J_{1'2'}$ and $J_{3"4'}$ in 1 with the phase angle of pseudorotation (P). The experimental data points are found in the lower left region of the graph.

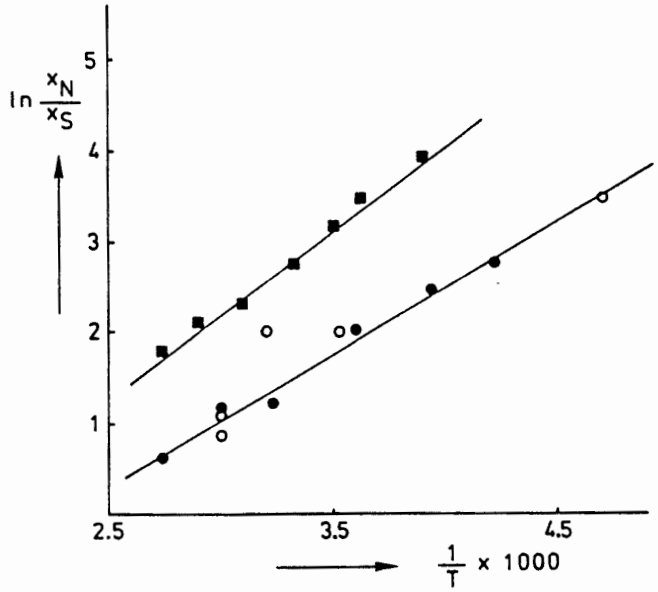


FIG. 3. Van't Hoff plot, based on the experimental data on 1 (black squares) and 3'-dA (black circles). The open circles refer to nmr measurements on 3'-dA, described in ref. 25.

given in Fig. 2, which shows the variation of $J_{1'2'}$ and $J_{3"4'}$ with P. Note that $J_{1'2'}$ is a transoidal coupling, showing a large variation of 9.4 Hz (from 1.2 to 10.6 Hz) over the pseudorotation cycle. The cisoidal coupling $J_{3"4'}$, on the other hand, shows a much smaller variation of 5.9 Hz (from 1.9 to 7.8 Hz). The experimental data points are found in the lower left part of the cycle, close to $P = 0°$. From the plot, it is evident that the conformation of the furanose ring is strongly biased toward the N form. Also, it is seen that the ring conformation varies with the sample temperature in such a way that increasing the temperature results in an enhanced population of an S form, which is found in the upper right region of the graph. A quantitative picture of the furanose conformation could be obtained by application of the PSEUROT method (30), after correct parametrization for the *endo* orientation of the 3'-OH group on the ring.

The PSEUROT algorithm calculates the best fit of P_N, P_S (the phase angles of pseudorotation in the N and S forms), $\nu_{m,N}$, $\nu_{m,S}$ (the puckering amplitudes in the N and S forms), and the mol fraction of the participating conformers, to the experimental spin–spin couplings between the ring protons. The program was run under the reasonable assumption that the N and S forms have the same puckering amplitude. Based on our data, it was found that the furanose conformation in 1 is best described by a dominant N form with $P = 0°$, $\nu_m = 33°$, and a minor S form with $P = 208°$, $\nu_m = 33°$. Table 2 lists the calculated populations of the N form (x_N) as a function of the sample temperature. Interestingly, these data can be used to estimate the thermodynamic parameters of the N ⇄ S conformational equilibrium in 1. In the van't Hoff plot ($\ln x_N/x_S$ vs. $1/T$) of Fig. 3, the data on 1 correspond with the black squares. From the slope of the best-fit line through the data points, it follows that the conversion from N toward S is associated with an increase of the standard enthalpy of 17 kJ/mol. The estimated inaccuracy in this number is ±3 kJ/mol. The intercept with the vertical axis reveals that the standard entropies of the N and S forms differ by approximately 1.5 eu, in favor of S. In addition, the conformation of the exocyclic $C_{4'}$—$C_{5'}$ bond in 1 was analyzed on the basis of the vicinal proton–proton coupling constants $J_{4'5'}$ and $J_{4'5"}$ (28, 31, 32). At a sample temperature of 25°C, it was found that $J_{4'5'}$ = 4.2 Hz, and $J_{4'5"}$ = 7.3 Hz. From this, it was calculated that the populations of γ^+, γ^t, and γ^- are 0.20, 0.60, and 0.20, respectively. Thus, γ^t is the preferred $C_{4'}$—$C_{5'}$ conformation in

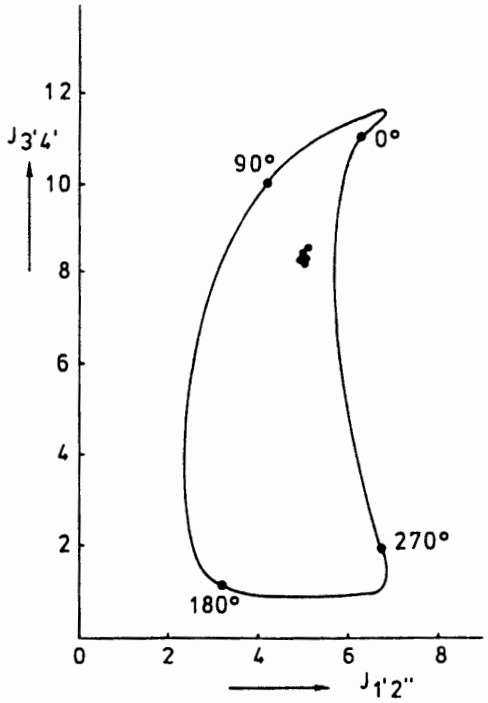


FIG. 4. Calculated variation of $J_{1'2''}$ and $J_{3'4'}$ in **2** with the phase angle of pseudorotation (P). The experimental data obtained on **2** at different sample temperatures are clustered in the midregion of the graph (see text).

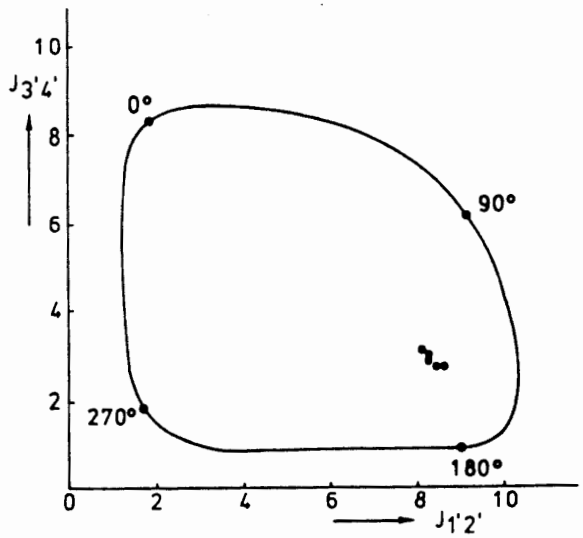


FIG. 5. Calculated variation of $J_{1'2'}$ and $J_{3'4'}$ in 2'-dA with the phase angle of pseudorotation (P).

1, whereas γ^+ always dominates in unmodified nucleosides. Most likely, the cisoidal orientation of the 3'- and 5'-hydroxyl groups in **1** strongly destabilizes γ^+ because of unfavorable electrostatic and (or) steric interactions. Therefore the $C_{4'}$—$C_{5'}$ conformation is strongly biased toward γ^t. We also observed a marked temperature dependency of the $C_{4'}$—$C_{5'}$ conformational equilibrium. Lowering the temperature results in a more pronounced preference for γ^t. Details are given in the supplementary material.

*9-(3'-Deoxy-β-D-*threo*-ribofuranosyl)adenine (2)*

For this compound, the furanose conformation was determined from the vicinal coupling constants $J_{1'2''}$, $J_{2''3'}$, $J_{2''3''}$, $J_{3'4'}$, and $J_{3''4'}$. The assignment of the protons $H_{3'}$ and $H_{3''}$ was based on a comparison with the analogue structure of **2** in which $H_{3''}$ was replaced by deuterium (15). It is found in this way that $\delta(3'') > \delta(3')$. After calculating the dependence of the ring-coupling constants on the phase angle of pseudorotation (28), we could construct Fig. 4, showing the variation of $J_{1'2''}$ and $J_{3'4'}$ with P. Note that $J_{1'2''}$ is a cisoidal coupling with a variation of only 4.5 Hz (from 2.3 to 6.8 Hz) over the entire pseudorotation cycle. A much greater variation of 10.8 Hz (from 0.8 to 11.6 Hz) was calculated for the transoidal coupling $J_{3'4'}$. The experimental data are clustered in the upper region of the graph, close to the line that connects the calculated points for $P = 0°$ and $P = 180°$. Figure 4 immediately shows that the N ⇄ S equilibrium in **2** is virtually temperature independent. Therefore it can be concluded that the enthalpy difference between the N and S forms in **2** is close to zero. Also, it is seen that the distribution over N and S is biased toward N, i.e., the entropy of the N form slightly exceeds that of the S form. In the case of **2**, we confined ourselves to the qualitative description of the furanose conformation as given above. This is due to the fact that the five ring couplings are practically constant over the temperature range of −45 to 95°C. With respect to the $C_{4'}$—$C_{5'}$ conformation it was found that $J_{4'5'} = 3.0$ Hz, and $J_{4'5''} = 5.2$ Hz. From this, we calculated that γ^+, γ^t, and γ^- have the relative populations of 0.53, 0.41, and 0.06, respectively at a sample temperature of 25°C. Lowering the temperature results in a pronounced preference for the γ^+ rotamer. All relevant data are given in the supplementary material.

2'-Deoxyadenosine (2'-dA)

The conformational properties of 2'-dA, an essential building block of DNA, have been studied extensively by means of X-ray crystallography (33) and nmr spectroscopy (25, 34–36). In the crystal structure, 2'-dA shows an N-type furanose ring ($P = 14°$, $\nu_m = 35.5°$). The conformations around the $C_{1'}$—N_9 and $C_{4'}$—$C_{5'}$ bonds are *anti* and γ^+, respectively. From the nmr data, it was concluded that the conformation of the furanose ring in 2'-dA is best described as a rapid N ⇄ S equilibrium. The best-fit pseudorotational parameters for the N form are $P = 10°$, $\nu_m = 35.5°$; for the S form, $P = 167°$, $\nu_m = 35.5°$ (30). In Fig. 5, we have plotted both $J_{1'2'}$ and $J_{3'4'}$ as a function of P (*vide supra*). The calculations were performed for a puckering amplitude of 35.5°. The data points in the graph refer to literature data (25), as well as to our own experiments in D_2O in deuterated dimethyl formamide (see supplementary material). Clearly, the data points are clustered in the lower right region of the plot, indicating that the S form of the furanose ring is slightly preferred in solution. Remarkably, the N ⇄ S equilibrium is virtually insensitive to temperature changes, i.e., the enthalpy difference between the N and S forms is close to zero.

3'-Deoxyadenosine (3'-dA)

The conformation of 3'-dA in the solid state and in solution has also received considerable attention (25, 26). The interest in 3'-dA stems from its pronounced antibiotic properties (37). The X-ray structure shows an N-type furanose ring with $P = 12.7°$, and $\nu_m = 32°$. Westhof *et al.* (25) have recorded nmr spectra of 3'-dA at different temperatures (ranging from −60 to 80°C), and in different solvents (e.g., D_2O, ND_3, and deuterated pyridine). They have shown that the furanose conformation in 3'-dA is heavily biased toward N, and also that the N ⇄ S equilibrium is strongly temperature dependent. Raising the temperature results in an enhanced population of the S form. In

TABLE 3. Calculated population of the N conformer in 3′-dA as a function of the sample temperature (see text)

T	x_N
213[a]	0.97
235	0.94
254	0.92
278	0.88
283[a]	0.75
300	0.77
313[a]	0.88
333[a]	0.75
333[a]	0.70
336	0.76
365	0.62

[a]Abstracted from ref. 25.

this work, we have estimated the thermodynamic parameters governing the N ⇄ S equilibrium in 3′-dA on the basis of our own data (which were obtained in D_2O or in deuterated dimethyl formamide), as well as on Westhof's data. Application of the PSEUROT method revealed that the conformation of the furanose moiety is best described as a rapid equilibrium between a dominant N form with $P = 13°$, $\nu_m = 32°$, and an S form with $P = 169°$, $\nu_m = 32°$. Table 3 summarizes the calculated population of the N form as a function of the temperature. From the van't Hoff plot in Fig. 3 it was calculated that the N ⇄ S transition in 3′-dA is associated with an increase of the standard enthalpy by approximately 14 kJ/mol. The estimated inaccuracy of this number is again 3 kJ/mol. The entropy change of the N → S transition is again approximately +1.5 eu.

Discussion

From the results, it is evident that **1** and 3′-dA have highly similar conformational properties with respect to the furanose rings. In both cases, a pronounced preference for the N form is found. Also, the N ⇄ S equilibria in **1** and 3′-dA show a highly comparable variation with the sample temperature, since the enthalpy differences between N and S (17 ± 3 kJ/mol for **1**; 14 ± 3 kJ/mol for 3′-dA) are essentially similar. A tentative explanation for these findings is derived on the basis of Fig. 6, which shows the N and S forms for both structures. In both cases, the N form is associated with a favorable axial orientation of the adenine base (anomeric effect), as well as a favorable axial orientation of the hydroxyl group on the furanose ring (3′-OH in **1**, or 2′-OH in 3′-dA). The conversion from N toward S results in undesirable equatorial locations of the base and the hydroxyl group in either case. Clearly, the anomeric effect and the *gauche* effect are cooperative, since both effects drive the N ⇄ S equilibrium toward the N form. Logically, the N form has the lower enthalpy, which explains the experimentally observed temperature dependence of the N ⇄ S equilibria in both structures.

For model compound **2** and 2′-dA it holds that the sugar ring is involved in an N ⇄ S equilibrium that is insensitive to temperature changes. Figure 7 offers a tentative explanation for these results. The N conformation for **2** and 2′-dA has a favorable axial location of the base, combined with unfavorable equatorial furanose OH groups, whereas the reverse situation (equatorial base and axial furanose hydroxyl) is found in the

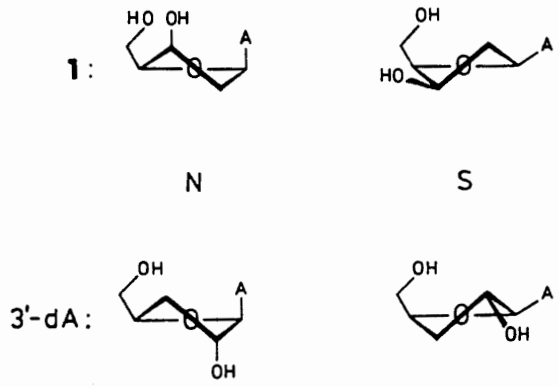


FIG. 6. N and S forms of **1** and 3′-dA. Clearly, the N forms have axial orientation of the adenine base, and axial orientation of the furanose OH. In the corresponding S forms, both the base and the OH group are equatorial.

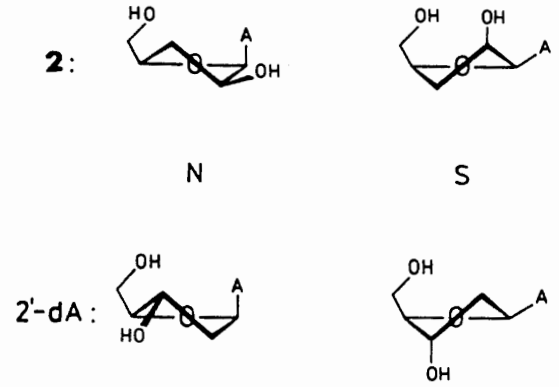
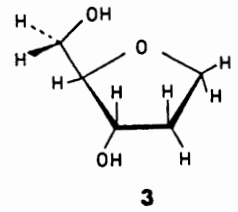


FIG. 7. N and S forms of **2** and 2′-dA. The N forms have axial orientation of the adenine base, combined with an equatorial OH group. The corresponding S forms have an equatorial base, and an axial OH group.



3

FIG. 8. Structural formula of **3**.

corresponding S form. Evidently, the anomeric effect and the *gauche* effect are counteractive in these cases, which apparently results in cancelling of the enthalpy differences between the N and S forms. For 2′-dA, this reasoning is further substantiated by the experimental finding that structure **3**, in which the base is in fact replaced by hydrogen, shows a temperature-dependent N ⇄ S equilibrium with a preference for S.[7] The anomeric effect is eliminated in this case, i.e., the furanose conformation in **3** is solely determined by the *gauche* effect. Variable temperature measurements on **3** have shown that the enthalpy is approximately 8 kJ/mol lower in the S form than in the N form.[7]

The results show that both the *gauche* effect and the anomeric effect should be taken into account for the description of the conformation of the furanose ring in nucleosides and nucleotides. It goes without saying that other factors, such as chemical

[7]L. H. Koole, unpublished results.

modifications of the base or the introduction of bulky groups on the furanose ring, may also have an important impact on the conformation. However, the present theory may offer an explanation for the well-known polymorphism of oligomeric and polymeric DNA structures, since it is clear that the individual 2′-deoxyribose units may occur in N or S without substantially affecting the enthalpy content of the structure. On the other hand, RNA structures are uniform with N-type conformations of the ribose rings. This is consistent with the fact that the anomeric effect actually determines the enthalpy preference for the N form of ribose.

Acknowledgements

H.M.B. thanks the Netherlands Foundation for Chemical Research (SON) and the Netherlands Organization for the Advancement of Pure Research (ZWO) for financial support of this research. J.C. thanks the Swedish Board for Technical Development (STU) and the Swedish Science Research Council (NFR) for financial aid.

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