The DNA-stabilising nucleoside 7-iodo-2′-deoxytubercidin: its structure in the solid state and in solution

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The crystal structure of 7-iodo-2′-deoxytubercidin 2 has been determined and was compared with those of 2′-deoxytubercidin 3 and 2′-deoxyadenosine 4. The bulky 7-iodo substituent lies 13.2 pm below and the nitrogen of the 6-amino group 5.5 pm above the 7-deazapurine plane. The puckering of compound 2 is $_{3'}E$ while compound 3 shows a $^{2'}T_{3'}$ sugar pucker. The conformation in aqueous solution, determined by ^{1}H NMR spectroscopy, is only slightly different, showing a $^{2'}E$ conformation. The glycosylic bond torsion angle is *anti* in all cases.

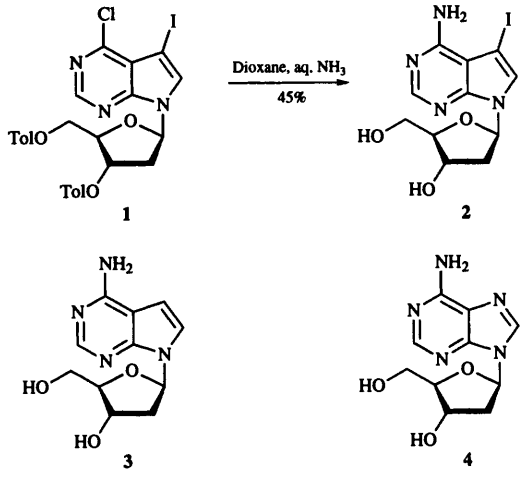
Introduction

The major groove of B-DNA is the main binding site for metal ions, antibiotics and proteins. The 5-methyl group of the thymine base being located within this groove. From model building it can be seen that the 5-substituents of pyrimidine bases have steric freedom in the B-DNA structure and in this context it is of interest to note that the 7-position of purine bases is sterically similar to the 5-position of pyrimidines. Nevertheless, the introduction of substituents into the 7-position of purines (purine numbering is used throughout the general section) is problematic, as 7-alkylation generates a positive charge on the base. This causes structural changes; *e.g.* a transition from a B- to a left-handed Z-DNA structure. The replacement of a purine moiety by a 7-deazapurine base circumvents the charge problem and allows the introduction of a great variety of substituents into this position.

The synthesis of a number of 7-substituted 7-deazapurine 2′-deoxyribonucleosides and their incorporation into DNA fragments has been reported by our laboratory.[1] These residues stabilise the B-DNA structure, especially when introduced in alternating oligonucleotides.[1,2] This effect is different from that of 8-substituted purine nucleosides showing *syn*-conformation at the N-glycosylic bond, which destabilises the B-DNA and forces the molecule into a Z-DNA structure.[3-5] It was therefore of interest to study the structure of a 7-substituted 7-deazapurine 2′-deoxyribonucleoside both in the crystal and in the solution phase. 7-Iodo-2′-deoxytubercidin **2** was selected for this investigation. It carries a bulky 7-substituent and is a central intermediate for DNA-labelling using Pd-catalysed cross-couplings.[6,7] Moreover, it shows an exceptionally high stability of the glycosylic bond to acid-catalysed hydrolysis.

Results and discussion

Compound **2** was prepared previously by glycosylation of 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine[8] with 2-deoxy-3,5-di-*O*-(4-toluoyl)-β-D-*erythro*-pentofuranosyl chloride[9] using a three-step reaction route (see Scheme 1).[10] In the present work the deprotection of compound **1** was combined with displacement of chlorine, which gave the same total yield (28%)[10] of compound **2** on the basis of 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine. Compound **2** crystallises from either water or MeOH solutions. It shows a UV maximum at 283 nm (ε = 8500 dm^3 mol^{-1} cm^{-1}) which is bathochromically shifted compared with the value for 2′-deoxytubercidin **3** (λ_{max} = 270 nm, ε = 12 300[11]). The iodo nucleoside **2** is more difficult to protonate (pK_a = 4.5) than the parent 2′-deoxytubercidin **3** (pK_a = 5.3[12]) but easier than 2′-deoxyadenosine **4** (pK_a = 3.8[12]). For the single-crystal X-ray analysis compound **2** was crystallised from Pr^{i}OH.



Scheme 1

Conformation in solid state

The structure of the iodo nucleoside **2**, as observed in the crystal structure by single-crystal X-ray diffraction, is shown in Fig. 1. The crystal parameters are summarised in the Experimental section. The space group ($P2_1$) is identical with that of 2′-deoxyadenosine crystals but different from that of the non-substituted 2′-deoxytubercidin ($P2_12_12_1$).[13,14]

The 7-deazapurine base of **2** is planar. The deviations of its carbon and nitrogen atoms from the least-squares planes are in the range of ±1.3 pm [N(1) = 1.0(9) pm; C(2) = −0.3(10) pm; N(3) = 2.2(7) pm; C(4) = −2.1(8) pm; C(5) = −0.5(11) pm; C(6) = −1.3(10) pm; C(7) = 1.2(10) pm; C(8) = 1.3(11) pm; N(9) = −1.5(8) pm]. In compound **2** there is a strong interaction between the iodo and amino ligands in positions 6 and 7, implying the presence of hydrogen bonding. The difference Fourier analysis shows that the hydrogen atoms of the amino ligand are nearly coplanar with the carbon–nitrogen skeleton. However, the iodo ligand lies 13.5(14) pm below and the nitrogen atom of the amino ligand 5.2(18) pm above the 7-

Table 1 Selected bond lengths (pm) and bond angles (°) of 7-iodo-2′-deoxytubercidin **2** in comparison with data of 2′-deoxytubercidin **3**[13] and 2′-deoxyadenosine **4**[14]

	2 ($1^7c^7A_d$)	**3** (c^7A_d)	**4** (dA)
N(1)–C(2)	134.1(6)	133.3(3)	134.2
N(1)–C(6)	133.6(6)	134.9(3)	135.4
C(2)–N(3)	132.9(6)	133.5(3)	133.3
N(3)–C(4)	133.9(5)	134.8(2)	134.7
C(4)–C(5)	140.6(6)	138.8(3)	139.3
C(5)–C(6)	141.3(5)	141.0(3)	141.3
C(6)–N(6)	135.3(6)	133.8(3)	133.9
C(5)–C(7)	142.5(5)	143.2(3)	138.7[a]
C(7)–C(8)	136.4(5)	135.5(3)	131.5[a]
C(8)–N(9)	139.2(5)	138.9(3)	137.1
N(9)–C(4)	136.5(5)	137.2(2)	137.1
N(9)–C(1′)	145.3(5)	144.9(2)	147.4
C(1′)–C(2′)	153.2(9)	151.5(3)	152.4
C(2′)–C(3′)	153.1(7)	152.3(3)	152.4
C(3′)–C(4′)	150.3(11)	152.3(3)	153.2
C(4′)–O(4′)	146.8(9)	144.2(2)	144 4
C(1′)–O(4′)	141.6(6)	143.3(2)	141.2
C(3′)–O(3′)	143.4(6)	142.0(3)	141.3
C(4′)–C(5′)	152.9(8)	150.3(3)	150.2
C(5′)–O(5′)	142.5(8)	141.6(3)	142.4
C(6)–N(1)–C(2)	117.9(4)	117.1[b]	119.5
N(1)–C(2)–N(3)	128.9(5)	129.4[b]	128.4
C(2)–N(3)–C(4)	111.9(4)	112.0[b]	111.0
N(3)–C(4)–C(5)	126.1(4)	125.4[b]	127.2
N(3)–C(4)–N(9)	125.1(4)	126.3[b]	127.1
N(9)–C(4)–C(5)	108.8(3)	108.4[b]	105.8
C(4)–C(5)–C(6)	115.3(4)	116.5[b]	116.4
C(4)–C(5)–C(7)	106.0(3)	107.3[b]	110.7[a]
C(6)–C(5)–C(7)	138.7(4)	136.3[b]	132.9[a]
C(5)–C(6)–N(1)	119.7(4)	119.6[b]	117.5
C(5)–C(6)–N(6)	122.2(4)	122.5[b]	124.0
N(1)–C(6)–N(6)	117.9(4)	117.9[b]	117.5
C(5)–C(7)–C(8)	108.1(4)	106.6[b]	103.6[a]
C(5)–C(7)–I(7)	127.8(3)		
C(8)–C(7)–I(7)	123.9(3)		
C(7)–C(8)–N(9)	108.7(4)	110.0[b]	114.2[a]
C(8)–N(9)–C(1′)	126.4(4)	125.5[b]	129.2
C(4)–N(9)–C(1′)	125.0(4)	125.7[b]	124.5

[a] C(7) is replaced by N(7). [b] Calculated with the data of ref. 13 and the program of ref. 24.

deazapurine plane. Bond lengths and angles within the base are comparable to those of similar compounds, in particular with those of compounds **3** and **4** (Table 1).[13,14] Only the angle C(6)–C(5)–C(7) is somewhat larger in compound **2** [138.7(4)°] than in compound **3** [136.3°]; we propose that this may be due to steric repulsion of the iodine substituent and the amino group. The glycosylic bond length of compound **2** (145.3 pm) is almost identical with that of 2′-deoxytubercidin (144.9 pm). Both are slightly shorter than the corresponding bond length of 2′-deoxyadenosine (147.4 pm).

The orientation of the base relative to the sugar (*syn*/*anti*) is defined by the torsion angle χ^1 [O(4′)–C(1′)–N(9)–C(4)]; the preferred conformation around the N-glycosylic bond of a natural 2′-deoxynucleoside is usually in the *anti* range. As can be seen from Table 2 and Fig. 1, this angle changes in the solid state from 7-iodo-2′-deoxytubercidin **2** (−147.1°) to 2′-deoxytubercidin **3** (−104.4°) by more than 40°. Thus, compound **2** adopts an almost perfect *anti* orientation similar to that of 2′-deoxyadenosine **4** (−165.1°).

The most frequently observed ring conformations of nucleosides are C-2′-*endo* and C-3′-*endo*.[16] Some 2′-deoxyribonucleosides, such as 2′-deoxyadenosine monohydrate, exhibit a C-3′-*exo* ($_3$·*E*) conformation.[17] This envelope conformation is also found for 7-iodo-2′-deoxytubercidin (see Fig. 2) but not for 2′-deoxytubercidin **3** ($^2T_{3'}$) and 2′-deoxyadenosine **4** (C-3′-*endo*). In the crystal lattice the molecules of compound **2** are interconnected with each other by hydrogen bonds. This system of crystal-structure-stabilising bonds is shown in Fig. 3. The

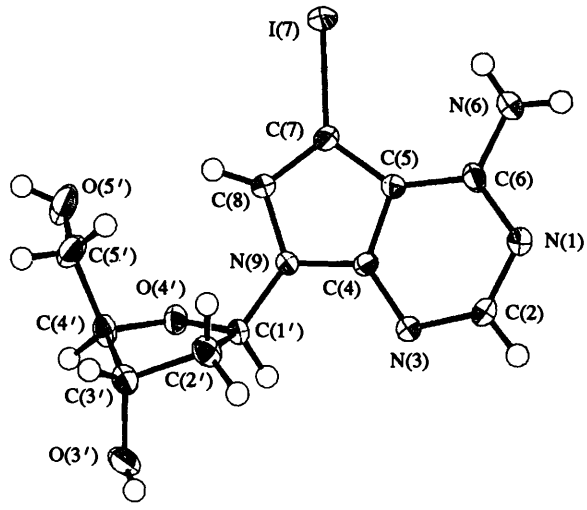


Fig. 1 Molecular structure of 7-iodo-2′-deoxytubercidin **2** in the solid state and atomic numbering. Anisotropic displacement ellipsoids representing the 50% probability density of the corresponding atoms are shown; hydrogen atoms are drawn as spheres with arbitrary radius.

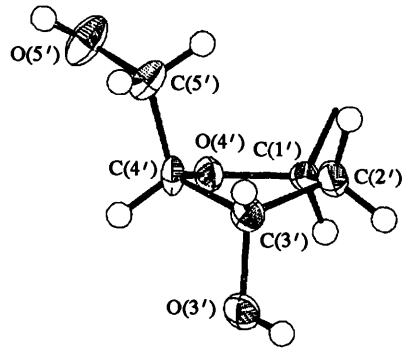


Fig. 2 Perspective view of the 2′-deoxyribose conformation of 7-iodo-2′-deoxytubercidin **2**

O···O and O···N distances within these hydrogen bonds range from 282.1 to 301.8 pm. The angles X–H···Y vary around 165°.

Conformation in solution

In contrast to their behaviour in the solid state, nucleosides can exist in various conformations in solution (*syn* ⇔ *anti*; *N* ⇔ *S*) which are usually described by two-state models; the energy barrier between the states is low (6 kcal mol^{-1}).†[18,19] ^{1}H Nuclear Overhauser enhancement spectroscopy (NOE) has been found to give reliable information about the preferred populations of the *syn*/*anti* conformers. A calibration method for a semi-quantitative estimation of conformer populations has been developed on the basis of NOE measurements.[20] Applying this method, we found that compound **2** exhibits a larger *anti*-conformer population than do the nucleosides **3** and **4** (Table 3). However, exact torsion angles cannot be determined.

The combination of the concept of pseudorotation with vicinal ^{1}H,^{1}H-coupling constants has led to a generalised Karplus equation.[21] This was applied to the 2′-deoxyribose moiety of 7-iodo-2′-deoxytubercidin **2** and of the parent compounds **3** and **4**. For this purpose vicinal ^3J(H,H) coupling constants (Table 4) were taken from well resolved ^{1}H NMR spectra measured in D_2O. The conformation in solution (*N* ⇔ *S*) of the 2′-deoxyribose moiety can be deduced from the pseudorotational parameters *P* and Φ_m by application of the PSEUROT

† 1 cal = 4.184 J.

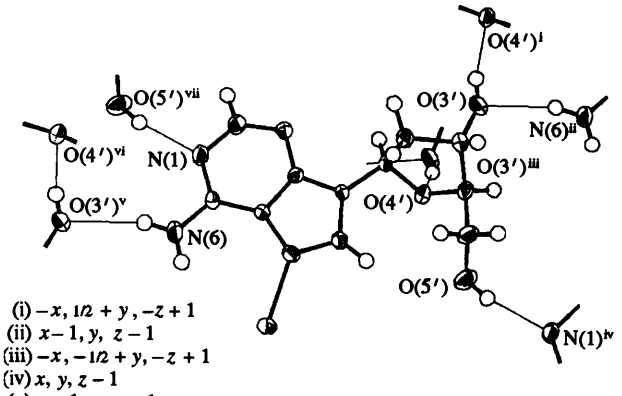
Table 2 Torsion angle (°) of the 2′-deoxyribonucleosides **2**–**4**

	2 ($I^7c^7A_d$)	**3** (c^7A_d)[13]	**4** (dA)[15]
C(1′)–C(2′)–C(3′)–C(4′), ν_2	−32.8(6)	−38.9(2)	35.4
C(2′)–C(3′)–C(4′)–O(4′), ν_3	33.3(7)	29.7(2)	−34.2
C(3′)–C(4′)–O(4′)–C(1′), ν_4	−21.2(7)	−8.2(2)	19.7
C(4′)–O(4′)–C(1′)–(C2′), ν_0	−0.4(5)	−16.9(2)	3.3
O(4′)–C(1′)–C(2′)–C(3′), ν_1	21.1(5)	34.8(2)	−24.9
O(4′)–C(4′)–C(5′)–O(5′)	55.3(8)	61.9(2)	58.5[a]
C(3′)–C(4′)–C(5′)–O(5′), γ	171.5(4)	179.6(2)	175.5
O(3′)–C(3′)–C(4′)–C(5′), δ	156.0(4)	152.7(2)	81.7
O(4′)–C(1′)–N(9)–C(8), χ^2	38.1(13)	62.5(2)	23.4
O(4′)–C(1′)–N(9)–C(4); χ^1	−147.1(8)	−104.4(2)	−165.1

[a] Calculated with the data of ref. 14 and the program of ref. 24.

Table 3 NOE Data of 7-iodo-2′-deoxytubercidin **2**, 2′-deoxytubercidin **3**[20] and 2′-deoxyadenosine **4**[20] measured in $(CD_3)_2SO$

	Proton irradiated	NOE observed [%] (±0.2%)	%*anti* (±3%)
2	8-H	1′-H(3.3), 3′-H (1.1)	71
3	8-H	1′-H(4.1), 2′-H$^{\beta}$ (3.8), 3′-H (0.8), 7-H (6.7)	64
4	8-H	1′-H (6.0), 2′-H$^{\beta}$ (2.2), 3′-H (0.5)	47



(i) $-x, 1/2 + y, -z + 1$
(ii) $x-1, y, z-1$
(iii) $-x, -1/2 + y, -z + 1$
(iv) $x, y, z-1$
(v) $x + 1, y, z + 1$
(vi) $-x + 1, 1/2 + y, -z + 2$
(vii) $x, y, z + 1$

Fig. 3 Hydrogen-bonding scheme within the solid-state structure of 7-iodo-2′-deoxytubercidin **2**; bond lengths: N(4)···O(2) = 301.8; O(3)···N(2) = 282.1; O(2)···O(1) = 283.4 pm; angles: N(4)–H(4)··· O(2) = 160.89°; O(2)–H(2)···O(1) = 163.78° O(3)–H(3)···N(2) = 167.71°.

program (version 6.2; licensor: Professor Dr C. Altona, Gorlaeus Laboratories, Leiden, The Netherlands). The data are listed in Table 4.

As can be seen from Table 4, 7-iodo-2′-deoxytubercidin **2** exhibits a similar sugar conformation to 2′-deoxyadenosine **4** while the $N \Leftrightarrow S$ equilibrium of 2′-deoxytubercidin is slightly biased towards the *S*-conformation. The pseudorotational angle P_s of compound **2** (159°) corresponds to a ^2E conformation of the sugar ring which is similar to the $_3E$ conformation observed in the solid state. Neither the glycosylic bond length nor the conformation around this bond is affected significantly by the bulky 7-iodo substituent. In the case of 8-substituted purine nucleosides, however, bulky substituents turn the base into the *syn*-conformation.[5] With bulky 7-substituents the DNA can retain the B-type structure. As the 7-iodo substituent causes the major groove of B-DNA to become hydrophobic an increased duplex stability is expected. Indeed, the alternating oligonucleotide d(I^7c^7A-T)$_6$[22] shows a T_m-value of 60 °C, which is 24 °C higher than of the non-substituted d(c^7A-T)$_6$.[23]

Experimental

General

All compounds were characterised by UV, ^{1}H and ^{13}C NMR spectra and were shown to be pure by TLC. NMR Spectra: ACV-250-Bruker spectrometer (Bruker, Germany); *J*-values in Hz. UV Spectra: U-2000 spectrometer (Hitachi, Japan). Mp: Büchi SMP-20 apparatus (Büchi, Switzerland); uncorrected. Column flash chromatography (FC): silica gel 60 (Merck, Germany) at 0.5 bar (5×10^4 Pa).

4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine 2

A mixture of 4-chloro-7[2-deoxy-3,5-di-*O*-(4-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine **1**[10] (2.0 g, 3.2 mmol) in 25% aq. NH_3–1,4-dioxane (1 : 1) (160 ml) was stirred for 48 h at 110 °C in an autoclave. The solvent was evaporated off and the residue was purified by FC (CH_2Cl_2–MeOH 9 : 1) to give needles from Pr^{i}OH (1.20 g, 45%), mp 194 °C [lit.,[10] 194 °C]; TLC (silica gel; CH_2Cl_2–MeOH 9 : 1) 0.40; λ_{max}(MeOH/nm) 283 (ε/dm^3 mol^{-1} cm^{-1} 8500); δ_H[250 MHz; $(CD_3)_2SO$] 2.16 (1 H, m, 2′-H$_a$), 2.46 (1 H, m, 2′-H$_b$, superimposed by Me_2SO), 3.53 (2 H, m, 5′-H$_2$), 3.80 (1 H, m, 4′-H), 4.31 (1 H, m, 3′-H), 5.02 (1 H, t, *J* 5.4, 5′-OH), 5.23 (1 H, d, *J* 3.9, 3′-OH), 6.48 (1 H, t, *J*7, 1′-H), 6.65 (2 H, br, NH_2), 7.64 (1 H, s, 6-H) and 8.09 (1 H, s, 2-H); δ_C[125 MHz; $(CD_3)_2SO$] 51.9 (C-5), 62.0 (C-5′), 71.0 (C-3′), 83.0 (C-1′), 87.5 (C-4′), 103.2 (C-4a), 126.9 (C-6), 149.8 (C-7a), 152.0 (C-2) and 157.3 (C-4); C-2′ is superimposed by Me_2SO.

X-Ray crystal structure 7-iodo-2′-deoxytubercidin

Crystals (size 0.20 × 0.12 × 0.045 mm) were prepared as described above and fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data. $C_{11}H_{13}IN_4O_3$. M = 376.15, monoclinic; space group $P2_1$, a = 8.436(1), b = 7.285(1), c = 10.832(1) Å, β = 106.08(1)°, V = 639.65 Å^3, Z = 2, D_x = 1.953 Mg m^{-3}, Mo-Kα radiation (λ = 0.710 73 Å^3), μ = 2.514 mm^{-1}, F(000) = 368, T = 293(2) K.

Data collection and processing. Data were collected on a Siemens P4 four-cycle diffractometer with Mo-Kα radiation and graphite monochromator. A total of 2280 reflections were collected in a range $1.96° \leq \theta \leq 28.00°$, giving 2274 independent reflections [R(int) = 0.0296]. The data were not corrrected for absorption effects.

Solution and refinement. The structure was solved by standard Direct methods. Full-matrix least-squares refinements based on F_0^2 were performed with non-hydrogen atoms assigned anisotropic thermal parameters. Hydrogen atoms were assigned isotropic parameters. The final R_1- and wR_2-values for data with $I > 2\sigma(I)$ were 0.0300 and 0.0709, respectively. Corresponding values for all data were 0.0364 and 0.0740, respectively. The goodness-of-fit based on F_0^2 was 1.073. The absolute structure parameter was defined to 0.00(4).

The final difference Fourier map had peak maxima and minima at 0.588 and −0.553 e Å^{-3}, without any stereochemical

Table 4 Coupling constants (Hz) and pseudorotational parameters of 2'-deoxyribonucleosides.[a]

	$J(1',2')$	$J(1',2'')$	$J(2',3')$	$J(2'',3')$	$J(3',4')$	%S	P_N	P_S	Φ_m	RMS
2	6.9	6.5	6.5	3.1	3.3	72	18	159	38	0.07
3	6.6	7.6	7.0	3.0	3.0	77	18	166	38	0.25
4	7,2	6.5	6.5	3.3	3.2	72	18	157	38	0.19

[a] Temp., 303 K; solvent, D_2O.

relevance. Literature programs were used for the solution, refinement and graphical presentation of the structure.[24-27] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/26.

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