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## Nucleosides, Nucleotides and Nucleic Acids

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### Conformation of 3'-Substituted 2',3'-Dideoxyribonucleosides in Aqueous Solution; Nucleoside Analogues with Potential Antiviral Activity

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CONFORMATION OF 3'-SUBSTITUTED 2',3'-DIDEOXYRIBONUCLEOSIDES  
IN AQUEOUS SOLUTION;  
NUCLEOSIDE ANALOGUES WITH POTENTIAL ANTIVIRAL ACTIVITY

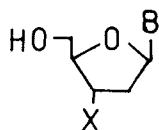
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**Abstract.** Conformation of several 3'-substituted 2',3'-di-  
deoxyribonucleosides has been studied by <sup>1</sup>H and <sup>13</sup>C NMR  
spectroscopy in <sup>2</sup>H<sub>2</sub>O.

Besides the well known anti-HIV drug, 3'-azido-3'-deoxy-  
thymidine, several 3'-substituted derivatives of 2',3'-di-  
deoxyribonucleosides exhibit activity against human immuno-  
deficiency virus type 1.<sup>1</sup> For this reason the conform-  
ations that this kind of nucleosides may adopt in aqueous  
solution are also of considerable interest. In the present  
work vicinal <sup>1</sup>H,<sup>1</sup>H (sugar protons) and <sup>13</sup>C,<sup>1</sup>H1' coupling  
constants determined in <sup>2</sup>H<sub>2</sub>O have been employed to elucidate  
the conformational properties of nucleosides 1-4.

Analysis of the sugar ring-puckering by the two-state,  
N = S, model<sup>2</sup> showed that the 3'-substituent has only a



1a: B = T, X = OCH<sub>2</sub>SCH<sub>3</sub>  
1b: B = T, X = OCH<sub>2</sub>OCH<sub>3</sub>  
1c: B = T, X = OCH<sub>2</sub>N<sub>3</sub>  
1d: B = T, X = OCH<sub>2</sub>CN

2a: B = C, X = OCH<sub>3</sub>  
2b: B = C, X = OCH<sub>2</sub>SCH<sub>3</sub>  
2c: B = C, X = OCH<sub>2</sub>OCH<sub>3</sub>  
2d: B = C, X = OCH<sub>2</sub>N<sub>3</sub>

3a: B = A, X = OCH<sub>2</sub>SCH<sub>3</sub>  
3b: B = A, X = N<sub>3</sub>  
4: B = G, X = OCH<sub>2</sub>SCH<sub>3</sub>

minor influence on the relative stability of the C2'exo and C2'endo conformers. As with unmodified 2'-deoxyribonucleosides, the latter type of puckering is slightly favoured, the mole fraction,  $x_S$ , ranging from 0.7 to 0.8. Only with 3b the C2'endo conformer is slightly less predominant ( $x_S = 0.6$ ). The spread in the optimized pseudorotation parameters obtained for this form, keeping those of the C2'exo form constrained ( $P_N = 9.5^\circ$ ,  $\Phi_N = 35.3^\circ$ ), is also small:  $153^\circ < P_S < 168^\circ$ ,  $31^\circ < \Phi_S < 34^\circ$ .

Variations in the conformation about the C4'-C5' bond are hardly detectable. The gg populations, calculated on the basis of the coupling constants of conventional gg, gt and tg forms,<sup>3</sup> range from 46 to 59 %, the gt form being slightly more stable than the tg form ( $0.28 < x_{gt} < 0.37$ ;  $0.13 < x_{tg} < 0.20$ ).

$^3J(C2, H1')$  and  $^3J(C6, H1')$  values obtained with 1a (2.2; 3.8 Hz) and 2b (1.6; 3.2 Hz) were almost identical with those reported earlier for thymidine and 2'-deoxycytidine,<sup>4</sup> suggesting that the 3'-substituent has no effect on the conformation about the N-glycosidic bond.

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