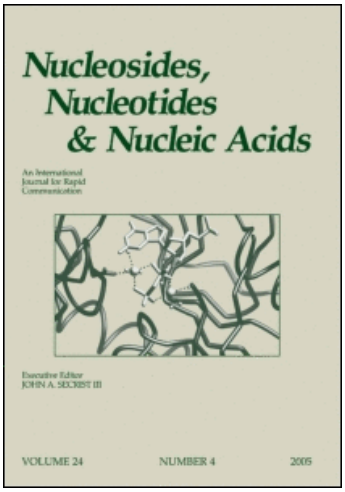

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CONFORMATION OF 3'-SUBSTITUTED 2',3'-DIDEOXYRIBONUCLEOSIDES IN AQUEOUS SOLUTION; NUCLEOSIDE ANALOGUES WITH POTENTIAL ANTIVIRAL ACTIVITY

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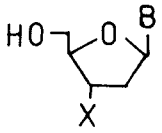
Abstract. Conformation of several 3'-substituted 2',3'-dideoxyribonucleosides has been studied by ^{1}H and ^{13}C NMR spectroscopy in $^{2}H_2O$.

Besides the well known anti-HIV drug, 3'-azido-3'-deoxythymidine, several 3'-substituted derivatives of 2',3'-dideoxyribonucleosides exhibit activity against human immunodeficiency virus type 1.[1] For this reason the conformations that this kind of nucleosides may adopt in aqueous solution are also of considerable interest. In the present work vicinal $^{1}H,^{1}H$ (sugar protons) and $^{13}C,^{1}H1'$ coupling constants determined in $^{2}H_2O$ 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[2] showed that the 3'-substituent has only a



1a: B = T, X = OCH_2SCH_3
1b: B = T, X = OCH_2OCH_3
1c: B = T, X = OCH_2N_3
1d: B = T, X = OCH_2CN

2a: B = C, X = OCH_3
2b: B = C, X = OCH_2SCH_3
2c: B = C, X = OCH_2OCH_3
2d: B = C, X = OCH_2N_3

3a: B = A, X = OCH_2SCH_3
3b: B = A, X = N_3
4: B = G, X = OCH_2SCH_3

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 ($P_N = 9.5^o$, $\Phi_N = 35.3^o$), is also small: $153^o < P_S < 168^o$, $31^o < \Phi_S < 34^o$.

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,[3] 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,[4] suggesting that the 3'-substituent has no effect on the conformation about the N-glycosidic bond.

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