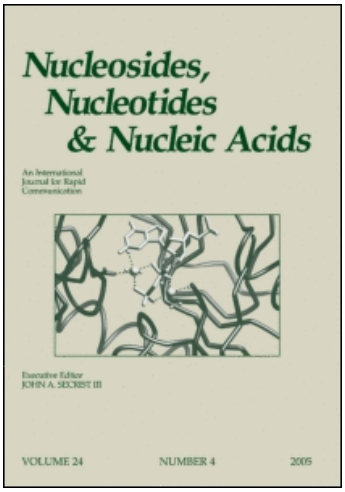

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Configurational and Conformational Analysis of Regular and Modified Nucleosides by 1D-NOE Difference Spectroscopy

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CONFIGURATIONAL AND CONFORMATIONAL ANALYSIS OF REGULAR AND MODIFIED NUCLEOSIDES BY 1D-NOE DIFFERENCE SPECTROSCOPY

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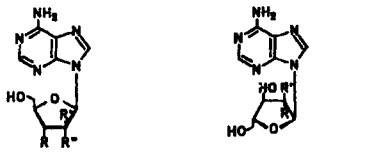
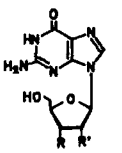
1D-Nuclear Overhauser enhancement (NOE) spectroscopy on regular and modified nucleosides provides qualitative and semiquantitative information about configurational and conformational parameters. The formula scheme shows selected nucleosides which were studied with this technique.

As shown in the table saturation of H-1' of β-D-nucleosides results in characteristic NOE factors of 1.5-2.6 % of the H-4' signal while there is none at H-3'. Exeptions are nucleosides with O-4'-exo conformation of the glyconic moiety. Irradiation of H-1' of α-D-ribo and α-D-arabinonucleosides yields NOE factors on both, H-3' (1.5-3.7 %) and H_β-2' (10-11 %) while that on H-4' is zero. α-D-2'-Deoxyribonucleosides exhibit only weak enhancements at H-3' upon irradiation of H-1' (1 %) which points to a high population of S-type puckered molecules. Nevertheless, the assignment of α-configuration follows from the typical NOE factors (5-7 %) measured at H_β-2' [1].

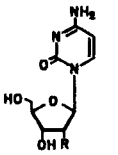


1β: R = R* = OH; R' = H
2β: R = R' = OH; R* = H
3β: R = OH; R' = R* = H
4β: R = R' = R* = H

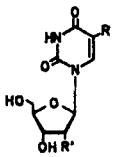
5α: R = H; R' = OH
6α: R = OH; R' = H



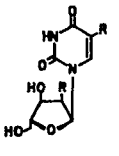
7β: R = R' = OH
8β: R = OH; R' = H
9β: R = R' = H



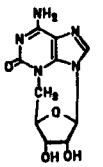
10β: R = OH
11β: R = H



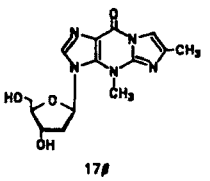
12β: R = H; R' = OH
13β: R = CH_3; R' = H



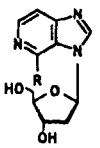
14α: R = H; R' = OH
15α: R = CH_3; R' = H



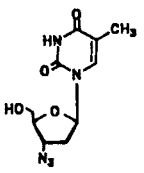
16β



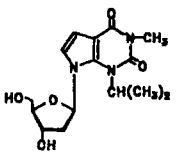
17β



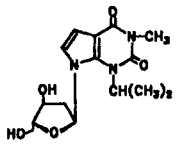
18β: R = Cl
19β: R = NH_2



20β



21β



22α

Table. Results of Proton-Proton 1D NOE Measurements.

	Proton irradiated	NOE (%)		Proton irradiated	NOE (%)
1β	H-1' H-8	H-2' (1.9); H-4' (2.1); H-8 (9.8) H-1' (8.0); H-2' (3.6); H-3' (0.9)	12β	H-1' H-6	H-2' (2.2); H-4' (1.7); H-6 (2.1); H-1' (2.9); H-2' (7.0); H-3' (2.5);
2β	H-1' H-8	H-2' (9.9); H-4' (2.0); H-8 (2.8) H-1' (1.7); H-2' + H-3' (3.1)	13β	H-1' H-6	H_{α}-2' (6.3); H-4' (2.3); H-6 (2.1); H^{2}1' (2.5); H_2-2' (4.6); H-3' (1.5);
3β	H-1' H-8	H_{α}-2' (6.1); H-4' (1.3); H-8 (6.3); H^{2}1' (6.0); H_{β}-2' (2.2); H-3' (0.5);	14α	H-1' H-6	H-2' (10.0); H-3' (3.7); H-6 (1.8); H-1' (1.3); H-4' (5.3);
4β	H-1' H-8	H_{α}-2' (6.6); H-4' (1.8); H-8 (4.8); H^{2}1' (4.3); H_2-2' (1.4); H_{β}-3' (2.1);	15α	H-1' H-6	H_{β}-2' (7.0); H-3' (1); H-6 (2.3); H^{2}1' (2.0); H_{α}-2' (3.4); H-4' (4.3);
5α	H-1' H-8	H-2' (10.9); H-3' (1.5); H-8 (2.7); H-1' (1.7); H-4' (1.8);	16β	H-1' H-8	H-8 (10.1); H-4' (3.0); H-1' (11.3); H-2', H-3' (0);
6α	H-1' H-8	H-2' (8.1); H-3' (3.0); H-8 (6.4); H-1' (5.7); H-2' (4.2); H-4' (1.9);	17β	H-1' H-8	H-8 (0); CH_3 (13.7); H-1' (0); H_{β}-2' (7.8); H-3' (2.9);
7β	H-1' H-8	H-8 (3.0); H-2' (1.6); H-4' (1.8); H-1' (3.6); H-2' (5.7); H-3' (1.1);	18β	H-1' H-8	H-8 (0.8); H_{α}-2' (5.0); H-4' (1.5); H-1' (1); H-3' (1.2); H_{β}-2' (3.7);
8β	H-1' H-8	H-8 (3.1); H_{α}-2' (5.6); H-4' (1.6); H-1' (3.1); H^{α}_{β}-2' (3.7); H-3' (1.1);	19β	H-1' H-8	H_{α}-2' (6.3); H-4' (2.9); H-8 (5.2); H^{2}1' (4.5); H_{β}-2' (4.2);
9β	H-1' H-8	H_2-2' (7.8); H-4' (2.0); H-8 (2.6); H^{2}1' (2.7); H_{β}-2' (3.2); H_{β}-3' (2.8);	20β	H-1' H-6	H_{α}-2' (8.0); H-4' (2.0); H-6 (2.3); H^{2}1' (2.7); H-3' (3.0); H_{β}-2' (4.6);
10β	H-6	H-1' (3.6); H-2' + H-3' (8.5);	21β	H-1' H-8	H-8 (0); H-4' (2.0); H_{α}-2' (4.7); H-1', H-2', H-3' (0);
11β	H-1' H-6	H_{α}-2' (6.9); H-4' (1.7); H-6 (2.1); H^{2}1' (2.2); H_2-2' (2.9); H-3' (1.9);	22α	H-1' H-8	H-8 (0); H_{β}-2' (6.2); H-3' (1.1); H-1' (0); H-4' (2.3); H-2' (6.5).

Purine- or pyrimidine numbering was used throughout.

From computer modeling of nucleosides based on force-field calculations it is known that H-8 (purine numbering) or H-6 (pyrimidine numbering) are the closest protons to H-1' if the conformation is syn [2] while in the anti conformation the closest protons to H-8/H-6 are H_{β}-2' and H_{β}-3'. This results in more or less strong NOE factors of H-1' and H_{β}-2'/H_{β}-3' upon saturation of H-8/H-6 depending on the preferred conformation around the N-glycosylic bond. For a rough semiquantitative estimation of the populations of syn and anti conformers the NOE data of the conformationally fixed nucleosides 16β and 17β were measured and used for calibration. While the H-1' signal of 16β exhibits a maximal intensity enhancement upon saturation of H-8 (11.3 %) irradiation of H-8 of 2'-deoxywyosine (17β) leads to a maximal NOE of H_{β}-2' + H_{β}-3' (10.7 %) [3]. Inspection of the NOE data of the β-D-configurated nucleosides (Table) shows that most compounds exhibit a preferred anti conformation. For α-nucleosides qualitative information about syn/anti populations can be drawn from the NOE data of H-1' and H-4'/H_{α}-2' upon irradiation of H-8/H-6.

β-D-Configurated nucleosides with anti conformation exhibit different spatial proximities between H-8 and H_{β}-2' and/or H_{β}-3' depending on the sugar puckering: for S-type puckered compounds the closest proton to H-8/H-6 is H_{β}-2' while in N-type puckered nucleosides, both H_{β}-2' and H_{β}-3' are close to the base protons. Almost equal minimum distances between these protons should result in similar NOE factors so that the NOE at H_{β}-3' upon irradiation of H-8/H-6 is an indicator of the population of N-type puckered molecules. As can be seen from the table the 2',3'-dideoxyribofuranosides 4β and 9β tend to an equal distribution of N- and S-conformers while the other β-D-configurated compounds prefer S-type sugar puckering.

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