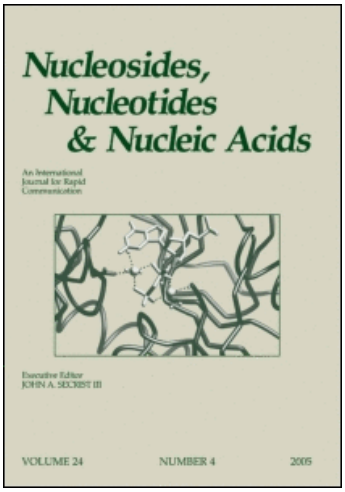

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A High Field NMR Study of 2'-Deoxyribo-C-Nucleosides

P. Francois[a]; E. Sonveaur[a]; R. Touillaux[a]
[a] Departement de Chimie, Universite Catholique de Louvain, Louvain-La-Neuve, Belgium

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A HIGH FIELD NMR STUDY OF 2'-DEOXYRIBO-C-NUCLEOSIDES

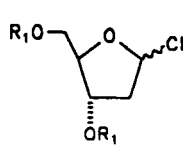
P. François, E. Sonveaux*, and R. Touillaux
Département de Chimie, Université Catholique de Louvain,
1, Place Louis Pasteur, B-1348 Louvain-La-Neuve, Belgium.

Abstract : A rule to establish the structure of alpha and bêta isomers of C-nucleosides, based on ^1H-^1H coupling constants is proposed and checked.

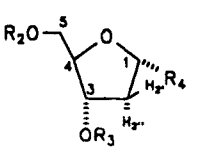
2'-deoxyribo-C-nucleosides are interesting drugs or mimics of natural nucleosides because the C-C bond linking the aglycone residue to the sugar backbone is resistant to chemical and enzymatic cleavage. C-nucleosides derived from **3**[1,2] and **4a**, **4b**[2] were recently incorporated into double stranded DNA to analyze the role of hydrophobicity, stacking, side-chain flexibility and hydrogen bonding on the thermodynamic stability of the double helices. A major concern in the synthesis of these compounds is the obtention of pure alpha and bêta anomers, and the determination of their structure.

The assignment of the alpha or bêta configuration of C-nucleosides is not straightforward. Indeed, the analysis has to take into account both the anomery at C_1 and the conformation of the sugar ring. The ring being rather flexible, there exist no simple rule of thumb[3]. This study shows that it is possible to discriminate between alpha and bêta C-nucleosides on the basis of their ^1H NMR spectra if at least one of the isomers is in a pure S or N conformation.

C-nucleosides **2a** and **2b**, **4a** and **4b** were obtained from **1** as mixtures of diastereoisomers, and were separated chromatographically[4]. Millican et al. previously obtained **3a** and **3b** by another route[1], and the X-ray structure of **3b** has been determined[5]. However, there is no correlation available between NMR spectra and structures in this series. We thus also



1 R_1=pchlorobenzoyl

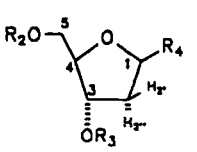


α isomer

2a R_2=R_3=pchlorobenzoyl
R_4=phenyl

3a R_2=R_3=benzoyl
R_4=phenyl

4a R_2=DMTr, R_3=H
R_4=-CH_2-CH_2-CH_2-$CONH_2$
(6 7 8)



β isomer

2b, 3b, 4b: R_2, R_3, R_4, as in the a series

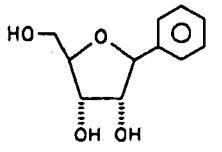


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TABLE 1: Conformational analysis of 2a,b (ϕ_{HH} = dihedral angle between vicinal protons)

	2b							2a					
	J_{exp}	ϕ^N_{HH}	J^N_{calc}	ϕ^S_{HH}	J^S_{calc}	J^{moy}		J_{exp}	ϕ^N_{HH}	J^N_{calc}	ϕ^S_{HH}	J^S_{calc}	J^{moy}
1-2'	10,87	95,9	1,63	157,5	10,96	10,96		7,0	-34,7	5,76	36,8	7,32	6,59
1-2"	5,3	-24,3	8,77	36,7	5,45	5,45		5,5	-155,9	8,94	-82,4	1,54	5,02
2'-3	6,1	39,3	7,24	-31,7	5,98	5,98		6,9	24,9	8,92	-34,0	5,61	7,17
2"-3	1,0	159,8	9,70	88,8	1,20	1,20		3,7	145,0	7,33	86,8	1,26	4,12
3-4	1,5	-158,4	8,10	-105,5	1,67	1,67		3,2	-125,8	3,93	-109,7	2,03	2,92
P		9,5		154,4		RMS			309,3		148,8		RMS
Φ_m		35,3		35,7		0,15			35,3		39,7		0,37
X		0		1					0,47		0,53		
Conformation		$^3T_2$		$^2T_1$					^3E		^2_1T		

TABLE 2A: Vicinal H-H coupling constants calculated for α and β nucleosides when N($^3_2$T) and S($^2_3$T) conformers are in equimolar concentrations

J_{calc}	α	β
1-2'	7,6	5,7
1-2"	4,6	7,5
2'-3	6,5	6,4
2"-3	5,4	5,5
3-4	4,4	4,4

TABLE 2B: Rules to assign an α or β configuration to nucleosides

	J_{trans}	N($^3_2$T)	S($^2_3$T)
α	1-2"	>9,5	<2
	3-2"	>9,5	<2
β	1-2'	<2	>9,5
	3-2"	>9,5	<2

synthesized **2b** from ß-1-(phenyl)-1-deoxy-D-ribofuranose **5** (of known absolute configuration[6]) by a stereospecific route[2,4].

The 1D and 2D COSY 500Mhz ^1H NMR spectra of **2a**, **2b**, **4a** and **4b** were recorded[7].

A conformational analysis was performed according to Altona's method[8]. The relevant nucleoside is supposed to be in equilibrium between two extreme conformations, N and S. The maximum torsion angles, Φ_{mN}, Φ_{mS}, the pseudorotation angles, P_N, P_S, and the molar fractions X_N, X_S of the two conformers are allowed to vary in order to get a fit between calculated and observed coupling constants. The results are reported in Table 1. Compound **2b** is in a single S conformation whose parameters are similar to those observed in the solid state (P=172°, Φ_m= 39°)[5]. Compound **2a** is an equilibrium mixture of conformers. The parameters of one of the extreme conformations found (N) are similar to those of cristalline α-1-(3-pyridyl)-1,2-dideoxy-D-ribofuranose (P=324,5°, Φ_m= 38,6°)[9].

Using Altona's model, we then systematically varied the proportions of N and S forms[10] to get an insight into the effect of the conformational equilibrium on the alpha/bêta assignment based on coupling constants. For an equimolar concentration of conformers, alpha and bêta anomers are practically undistinguishable, as shown in Table 2A. However, we calculated that, if either a N or a S conformation emerges as the dominant species, the set of H_1-H_2-H_3 trans coupling constants ($J_{H1\text{-}H2''}$ and $J_{H3\text{-}H2''}$ for the alpha anomer, and $J_{H1\text{-}H2'}$, $J_{H3\text{-}H2''}$ for the bêta anomer) are of definite diagnostic value (Table 2B.: a small coupling constant corresponds to a dihedral angle of approximately 90°, and a large one to a roughly trans diaxial relationship of the coupled protons).

These rules were then used to assign the bêta configuration to the slow eluting isomer **4b**. The **4a** isomer appears to be a mixture of conformers, as **2a**.

The diagnostic tool we propose is not ambiguous, contrary to the usual one (routinely used for N-nucleosides) based on the multiplicity of the signal corresponding to the proton on C_1[11,12]. According to this last rule, an alpha isomer should feature a pseudo-quadruplet for H_1 ($J_{H1\text{-}H2'} \neq J_{H1\text{-}H2''}$), and a bêta isomer a pseudo-triplet ($J_{H1\text{-}H2'} = J_{H1\text{-}H2''}$). This is based on the implicit assumption that, for all nucleosides featuring a N,O-acetal bond, the same

conformations dominate. However, for C-nucleosides, both the alpha/bêta isomery and the actual conformational state of the five-membered ring have to be taken into account.

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2 The details of the synthetic steps and the biophysical studies related to these compounds will be published elsewhere.

3 Among proposed methods are the comparison of the chemical shifts of the diastereotopic protons on C_2[11], the comparison of the ^{13}C chemical shifts of C_4 and C_5[12], and the NOE observed on the protons of the sugar ring[13].

4 Reagents and procedures : **from 1 to 2** : i, diphenylcadmium; ii, preparative TLC on silica, ethyl acetate/petroleum ether (1:15, v/v); Rf, **2a**, 0.23, **2b**, 0,20. **From 1 to 4** : i, excess penten-4-yl-magnesium bromide; ii, ozone,-78°c, HCl in methanol (1M); iii, conc. ammonia; iv, DMTrCl, pyridine; v, preparative TLC on silica, methylene chloride/methanol (95:5, v/v + 1% triethylamine) : 5 successive elutions on the same plate; **4a**, front, **4b**, queue. **From 5 to 2b** : i, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane; ii, phenylchlorothionocarbonate; iii, AIBN/n-Bu_3SnH; iv, $(Bu)_4N^+F^-$; v, p-chlorobenzoylchloride.

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