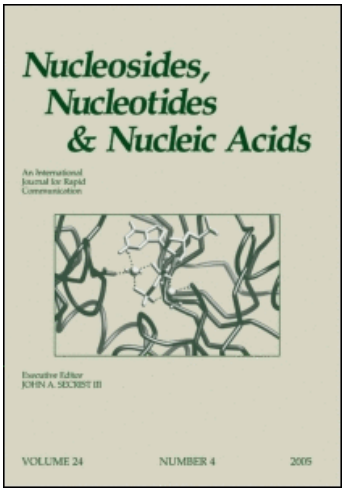

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CONFORMATIONAL ANALYSIS OF NUCLEOSIDES CONSTRUCTED ON A BICYCLO[3.1.0]HEXANE TEMPLATE. STRUCTURE-ANTIVIRAL ACTIVITY ANALYSIS FOR THE NORTHERN AND SOUTHERN HEMISPHERES OF THE PSEUDOROTATIONAL CYCLE

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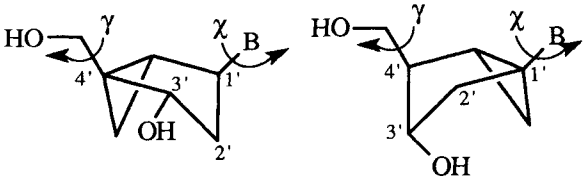
Abstract. A conformational analysis of carbocyclic nucleosides built on a rigid bicyclo[3.1.0]hexane template (**1-4,** Northern and **5-8** Southern) showed that the Northern conformation prefers an *anti* glycosyl torsion angle whereas the Southern conformation favors the *syn* range. Antiviral activity was mostly associated with the Northern conformers.

Introduction.

The complete definition of the conformation of a nucleoside involves the determination of four structural parameters: (a) the orientation about the glycosyl bond (torsion angle χ) as *syn* or *anti* , (b) the orientation of the hydroxymethyl group determined by the torsion angle γ, (c) the puckering of the sugar ring measured by the angle of pseudorotation P, and (d) the maximum out-of -plane pucker given by ν_{max}. For a conventional nucleoside, these parameters are subject to changes that are dependent on the nature of the substituents present on the base and on the sugar moiety. However, when a nucleoside is constructed



$_2$E (North) $_3$E (South)

1,B = Thy; **2**, B = Cyt; **3**, B = Ade; **4**, B = Gua (North)
5,B = Thy; **6**, B = Cyt; **7**, B = Ade; **8**, B = Gua (South)

Figure 1

Table 1. Conformational parameters for bicyclo[3.1.0]hexane nucleosides

Compound	P ± s.d (# conformers) ΔE > Glob. Min.	ν_{max} ± s.d (# conformers)	Glob. Min. Conformation* P, χ, γ	anti/syn	$E_{syn/anti}$ (Kcal/mol)	E_{γ} (Kcal/mol)	P and ν_{max} for Highest Energy conformer
1	343.35 ± 3.53 (n = 14) 5 Kcal/mol	29.95 ± 5.29 (n = 14)	344.37* *anti* γ^+	8/6	8.0	2.8-3.5	P = 337.87 ν_{max} = 38.98
2	344.16 ± 3.70 (n = 12) 5 Kcal/mol	29.33 ± 5.17 (n = 12)	344.23* *anti* γ^+	6/6	7.7	2.8-3.5	P = 338.05 ν_{max} = 38.89
3	342.97 ± 2.50 (n = 12) 1 Kcal/mol	32.17 ± 2.51 (n = 12)	343.46 *anti* γ^+	8/4	2.5	1.5-2.0	P = 338.89 ν_{max} = 35.69
4	344.20 ± 2.65 (n = 12) 2 Kcal/mol	31.42 ± 2.75 (n = 12)	343.45** *anti* γ^+	6/6	2.6	1.5-2.0	P = 338.89 ν_{max} = 35.89
5	192.51 ± 4.22 (n = 9) 5 Kcal/mol	28.09 ± 1.49 (n = 9)	191.28* *syn* γ^-	4/5	9.0	4.4-4.9	P = 198.07 ν_{max} = 31.51
6	194.51 ± 5.91 (n = 10) 5 Kcal/mol	28.20 ± 2.02 (n = 10)	191.62* *syn* γ^-	4/6	7.9	4.4-4.9	P = 200.17 ν_{max} = 32.10
7	190.49 ± 1.85 (n = 9) 1 Kcal/mol	28.00 ± 0.62 (n =9)	190.65 *syn* γ^-	5/4	2.8	3.4-4.4	P = 198.07 ν_{max} = 29.20
8	191.65 ± 1.98 (n = 12) 2 Kcal/mol	27.93 ± 0.69 (n = 12)	190.93 *syn* γ^+	8/4	3.0	3.4-4.4	P = 197.20 ν_{max} = 31.53

(*) Conformation without CH_2OH...O=C(3) H-bond. (**) Conformation without CH_2OH...NH_2-C(2) H-bond.

Table 2. Selected antiviral activity of some 2'-deoxy-*methano-carbocyclic* nucleosides.

	Virus[a] (host cell)	EC_{50}[b] (μg/ml)	CC_{50}[c] (μg/ml)	SI[d]	Control[e] EC_{50} (μg/ml)
1	HSV-1	0.01[f]	>20	>2000	0.30
"	HSV-2	0.12[f]	>20	>167	0.80
"	HCMV	>20	63.7	<3.2	0.30
2	HSV-1	0.14	68.0	486	0.70
"	HSV-2	>20	96.0	<4.8	6.20
"	HCMV	>4.0	8.8	<2.2	0.02
3	HSV-1	72.0	>100	>1.4	0.80
"	HSV-2	13.9	>100	>7.2	4.0
"	HCMV	5.6[f]	>100	>17.9	0.30
7	HSV-1	>100	>100	1	0.20
"	HSV-2	>100	>100	1	0.20
"	HCMV	2.4[f]	>100	>41.7	0.20
4	HSV-1	4.0	>100	>25	0.60
"	HSV-2	9.9	>100	>10.1	1.50
"	HCMV	>20	64.3	<3.2	0.40

[a]HSV-1 = herpes simplex type 1; HSV-2 = herpes simplex type 2; HCMV = human cytomegalovirus. [b]EC_{50} = inhibitory concentration required to reduce virus-induced cytopathogenicity or virus plaques by 50%. [c]CC_{50} = cytotoxic concentration that produces 50% of cell death. [d]SI = selectivity index (CC_{50}/EC_{50}). [e]ACV = acyclovir control (for HSV-1 and HSV-2), GCV = gancyclovir control (for HCMV). [f]These values correspond to a plaque reduction assay.

with a rigid pseudosugar moiety, the third and fourth parameters can be constrained to values typical of strictly Northern (**N**) or Southern (**S**) conformations (Figure 1). We were interested in studying the effect that a constrained pseudosugar moiety would have on the *syn* and *anti* orientation of the glycosyl link since it is known that this equilibrium is finely tuned by the sugar pucker.[1]

Conformational Analysis

A conformational analysis of compounds **1-4** (**N**) and **5-8** (**S**) using MM2 force field parameters was performed by simultaneously changing the values of χ and γ. The potential

energy maps generated revealed the effects that the rigid pseudosugar moiety had on the torsion angles χ and γ, and the energy barriers for the *syn/anti* equilibrium without the stiff pseudosugar moiety compensating for any repulsive interactions (Table 1). If the strong intramolecular H-bond between the primary alcohol and the C-3 pyrimidine carbonyl (favored by the calculations *in vacuo*) is neglected, pyrimidine conformers **1** and **2** favor the *anti* conformation. Similarly for the guanosine analogue **4**, exclusion of the H-bond between the primary alcohol and the C-2 amino group favors the *anti* conformation. Available crystallographic data for **1**[2] and **3**[3] showed that these **N** compounds appear *anti*. For the **S** pyrimidine conformers (**5** and **6**) H-bond favors the expected *syn* conformation. This conformation remais favored even in the absence of H-bonding. The **S** purines also seem to prefer the *syn* conformation where no H-bond contribution was evidenced. The *anti/syn* preference is obviously determined by the energy barrier between these conformations. This energy barrier changes little in each hemisphere and it is lower for purines than for pyrimidines (Table 1). Crystallographic analysis of **5**[4] revealed exclusively the *syn* conformer, whereas in the X-ray structure of **7**[5] the unit cell contained both *syn* and *anti* conformers, thus reflecting a much lower energy barrier. Rotation about γ changed not only for each hemisphere, but it depended on the nature of the base. The trend is that hindrance to rotation of γ is greater for pyrimidines, and that it also increases in the **N** $\rightarrow$ **S** direction. In summary, the energy barriers calculated for χ and γ seem to indicate that the conformational space (number of low energy conformers in Table 1) for pyrimidines is more restricted, particularly for those constrained to the **S** hemisphere.

Antiviral activity.

The compounds were evaluated primarily against herpes (HSV-1 and 2) and HCMV (Table 2). Antiviral activity was mostly associated with the **N** conformers with the exception of the **S** adenosine analogue **7** which showed significant anti-HCMV activity.

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