# Theoretical Study of 9-β-D-Erythrofuranosyladenine and Corresponding Carbocyclic Analogues. Evidence for a Base-Activated Conformational Lock

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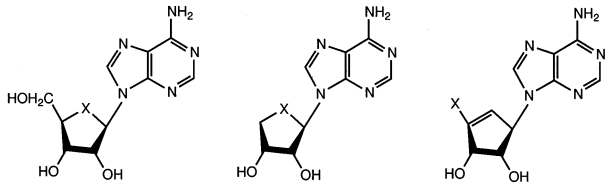
The conformational surfaces of three nucleoside analogues have been investigated computationally, where an adenine is attached to a diol of tetrahydrofuran, a diol of cyclopentane, and a diol of cyclopentene. In each system, the lowest-energy conformer displays a conformational lock into the south position by an internal hydrogen bond between O2′H of the five-membered ring and the N3 nitrogen of adenine. When aqueous solvation is accounted for by the PCM method, the preference for the locked conformer is diminished. A pseudorotation angle of 9-(*trans*-2′,*trans*-3′dihydroxycyclopentyl)adenine has been determined to be 176.8° by fitting the measured $^3J_{HH}$ values using PSEUROT which is in good agreement with the calculated value of 169.3°.

## Introduction

Nucleosides are the monomeric building blocks of nucleic acids and are composed of a heterocyclic base and ribofuranose unit. When the ring oxygen of the furanose group is replaced by a methylene, the class of compounds that results is referred to as carbocyclic nucleosides (CN).[1] Aristeromycin (**1**) is the carbocyclic nucleoside analog[2] of the naturally occurring adenosine (**2**) and has been found to display antiviral properties.[3] The clinical potential of **1** is, however, limited by its cytotoxicity, which has been attributed to metabolism to its 5′-phosphates (that is, nucleotides).[4]

Several years ago, efforts were undertaken to seek aristeromycin- based compounds with greater therapeutic possibilities via derivatives incapable of phosphorylation to the undesirable nucleotides.[5] With this in mind, several labs[6,7] prepared and assayed **3**, a compound lacking the C-4′ hydroxymethylene of **1**. This proved very successful, as **3** was found to retain the significant antiviral properties of **1** but without cyctotoxicity.[8,9] This result led to **4**, a more natural-like furanose form of **3** (an erythrofuranose derivative). Surprisingly, **4** was found to be inactive.[9] If the C4′−C5′ bond of aristeromycin is unsaturated, Neplanocin A is obtained (**5**), another well-known antiviral agent.[10] Very recently, the X-ray structure of the target enzyme *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase[11] has been solved with **6** (replacing the $CH_2OH$ group of **5** with hydrogen) bound into the active site.[12]




**1**, X=$CH_2$
**2**, X=O

**3**, X=$CH_2$ (**B**)
**4**, X=O (**A**)

**5**, X=$CH_2OH$
**6**, X=H (**C**)

The analysis of conformations within biologically relevant five-membered rings, such as nucleosides and nucleotides, has attracted much attention.[13,14] Altona has proposed the pseudorotation phase angle ($P$) and maximum torsion angle ($\nu_{max}$) as two useful parameters for describing ring conformations.[15] The conformation of sugars as well as CNs can be described by the same parameters.[16] The variation of these parameters can be used to understand why certain compounds are more active than others. If a model compound has the same ring conformation as a parent natural compound, then it is more likely to bind to the natural receptor site in vivo. Of course, substituents play a very important role in determining the most stable conformer in bioactive compounds. For example, conformers can be locked into a certain position by the appropriate choice and location of substituent.[17]

The tetrahydrofuran and cyclopentane rings are known to adopt two conformers: twisted and envelope. The passage from one envelope form to another can occur without going through the planar form by a process called pseudorotation.[18] This concept was first applied to five-membered sugar-containing nucleosides by Altona,[15] who also defined the pseudorotational phase angle ($P$) and maximum puckering ($\nu_{max}$).

It was found[16] that nucleosides are mainly in the southern (C2′-endo) or in the northern (C3′-endo) hemispheres in the pseudorotation cycle (see below). In addition to the many

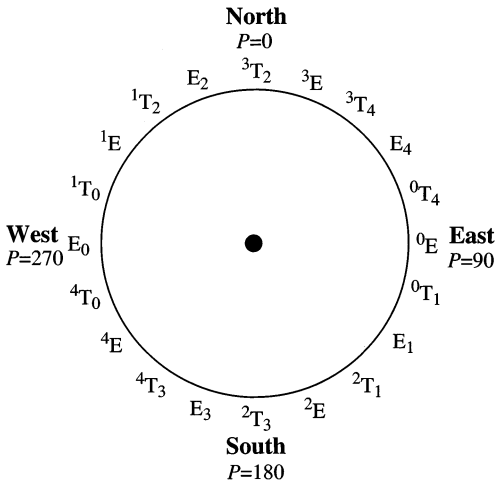



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**TABLE 1: Relative Energies (kcal/mol) of A, B, and C Conformers at MMFF and DFT Levels of Theory**

| conformer | MMFF94 | B3LYP/6-31G(d,p)// MMFF94 | B3LYP/3-21G// B3LYP/3-21G | B3LYP/6-31G(d,p)// B3LYP/3-21G | B3LYP/6-31+G(d,p)// B3LYP/6-31+G(d,p) |
|---|---|---|---|---|---|
| **A1** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **A2** | 3.68 | 6.25 | 10.06 | 6.37 | **→A1** |
| **A3** | 4.22 | 6.79 | 11.63 | 6.12 | |
| **A4** | 4.43 | 7.90 | 11.21 | 6.91 | 4.76 |
| **A5** | 4.55 | 9.45 | 12.09 | 8.81 | |
| **A6** | 5.19 | 6.87 | 12.90 | 6.79 | |
| **A7** | 5.21 | 9.46 | 15.20 | 8.07 | |
| **A8** | 5.33 | 6.05 | 8.04 | 5.64 | 4.68 |
| **A9** | 5.97 | 7.07 | 12.41 | 6.27 | |
| **A10** | 6.29 | 8.48 | 9.25 | 7.38 | |
| **A11** | 6.32 | 7.62 | 10.91 | 6.23 | |
| **A12** | 6.35 | 7.91 | 12.78 | 7.04 | |
| **A13** | 6.55 | 9.44 | 13.09 | 8.76 | |
| **A14** | 6.71 | 9.12 | **→A12** | **→A12** | |
| **B1** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **B2** | 0.08 | −0.29 | 0.46 | 0.43 | −0.40 |
| **B3** | 0.49 | −4.99 | −9.43 | −5.40 | −4.51 |
| **B4** | 0.66 | −0.99 | 1.88 | 0.64 | |
| **B5** | 0.88 | −4.33 | **→B3** | **→B3** | |
| **B6** | 1.19 | −1.30 | 1.16 | 0.58 | |
| **B7** | 1.22 | −1.42 | −0.76 | −0.77 | |
| **B8** | 2.03 | 0.13 | **→B1** | **→B1** | |
| **B9** | 2.38 | 2.61 | −0.40 | 1.81 | |
| **B10** | 2.97 | 1.39 | 2.27 | 0.96 | |
| **B11** | 3.41 | 2.13 | −0.20 | 0.87 | |
| **B12** | 4.07 | 2.07 | 4.49 | 2.96 | |
| **B13** | 4.46 | 3.24 | 3.28 | 4.99 | |
| **B14** | 4.60 | 2.07 | 4.06 | 2.11 | |
| **B15** | 4.67 | 1.76 | 3.49 | 1.00 | |
| **B16** | 4.84 | 2.65 | 2.82 | 3.25 | |
| **B17** | 5.33 | 1.00 | 4.28 | 3.11 | |
| **B18** | 5.77 | 3.96 | **→B16** | **→B16** | |
| **B19** | 5.80 | 1.93 | 1.75 | 2.37 | |
| **B20** | 5.87 | 2.27 | **→B15** | **→B15** | |
| **B21** | 6.12 | 1.27 | 3.95 | 2.03 | |
| **B22** | 6.18 | 4.31 | 8.45 | 3.82 | |
| **C1** | 0.00 | 0.00 | 0.00 | 0.00 | |
| **C2** | 0.64 | −1.78 | −1.21 | −0.92 | 0.00 |
| **C3** | 0.80 | −6.42 | −7.38 | −4.75 | −4.03 |
| **C4** | 0.88 | −1.51 | **→C1** | **→C1** | |
| **C5** | 1.67 | −1.35 | **→C3** | **→C3** | |
| **C6** | 2.63 | 1.29 | 0.80 | −0.80 | 0.08 |
| **C7** | 2.70 | 0.03 | 1.32 | 0.28 | |
| **C8** | 2.80 | 1.19 | **→C1** | **→C1** | |
| **C9** | 2.81 | −0.21 | 0.69 | −0.90 | |
| **C10** | 3.79 | 0.61 | 3.46 | 1.35 | |

experimental studies on conformers of nucleosides and modified nucleosides, several theoretical studies have also been reported.[19]

A theoretical investigation of **4**, **3**, and **6** (**A**, **B**, and **C**) was undertaken to determine the nature of the lowest-energy conformers. It is of considerable interest to know whether differences in the conformation of the cyclopentyl and furanose rings of **3** and **4**, a feature that has been the source of variable activity in other nucleoside derivatives,[1h] might be responsible for the difference in activity between **3** and **4**.

## Methods

**Experimental.** NMR spectra of **B** were recorded (Bruker DRX 500) in DMSO-$d_6$ with DCl added to simplify the spectra through deuterium exchange. The coupling constants were found by irradiating corresponding peaks and the assignments made by using COSY, HETCOR, and NOESY spectra.

**Computational.** A search of low-energy conformers was made for **A**, **B**, and **C** by using the MMFF molecular mechanics force field (MMFF94)[20] and the Monte Carlo method (with default options) as implemented in the Spartan 5.1 program.[21] Within an energy range of 7 kcal/mol, 14 conformers were returned for **A**, 23 for **B**, and 10 for **C**. One conformer returned for **B** required breaking and reforming the five-membered ring and was, therefore, removed from consideration.

Each of the MMFF94-minimized conformers was subjected to a single-point calculation at the B3LYP/6-31G(d,p)//MMFF94 level using Gaussian 98.[22] These structures were then fully optimized at the B3LYP/3-21G level, and single-point energies were obtained at the B3LYP/6-31G(d,p)//B3LYP/3-21G level.[23] Four conformers of **A** and three of **B** and **C** were selected for further optimization at the B3LYP/6-31+G(d,p) level. The energy ordering given by MMFF94 was used to designate the conformers of **A** (**A1**−**14**), **B** (**B1**−**B22**), and **C** (**C1**−**C10**). The conformational parameters for each conformer were found by using ConforMole.[24] Relative energies (kcal/mol) at different levels of theory are given for **A**, **B**, and **C** in Table 1, whereas structural data [pseudorotation phase angle ($P$), maximum torsion angle ($\nu_{max}$), and base torsion angle ($\chi$)] for the same conformers are given in Table 2. Molecular plots of the conformers optimized at the B3LYP/6-31+G(d,p) level are given in Figures 1 (**A** conformers), 2 (**B** conformers), and 3 (**C** conformers)). Cartesian coordinates of conformers optimized

**TABLE 2: Pseudorotation Phase Angle ($P$), Maximum Torsion Angle ($\nu_{max}$) and Torsion Angle ($\chi$ = C5′−C1′−N9−C4)[a] for Conformers of A, B, and C**

| | MMFF94 | | | B3LYP/3-21G | | | B3LYP/ 6-31+G(d,p) | | |
|---|---|---|---|---|---|---|---|---|---|
| confor. | $P$ | $\nu_{max}$ | $\chi$ | $P$ | $\nu_{max}$ | $\chi$ | $P$ | $\nu_{max}$ | $\chi$ |
| **A1** | 176.8 | 37.2 | 174.1 | 154.8 | 41.8 | 168.2 | 169.3 | 36.2 | 169.9 |
| **A2** | 20.3 | 37.0 | 189.0 | 0.0 | 36.0 | 167.9 | | →**A1** | |
| **A3** | 199.2 | 36.3 | 62.8 | 222.6 | 38.4 | 64.8 | | | |
| **A4** | 31.6 | 35.7 | 82.4 | 25.0 | 38.3 | 65.1 | 30.9 | 33.9 | 72.9 |
| **A5** | 15.3 | 38.3 | 187.1 | 2.3 | 39.0 | 164.7 | | | |
| **A6** | 181.2 | 37.2 | 66.8 | 161.1 | 41.7 | 73.2 | | | |
| **A7** | 181.4 | 38.3 | 212.1 | 159.0 | 40.7 | 217.4 | | | |
| **A8** | 207.8 | 38.3 | 65.3 | 233.2 | 48.0 | 73.3 | 223.5 | 40.7 | 68.6 |
| **A9** | 188.3 | 36.3 | 63.9 | 220.9 | 37.7 | 69.9 | | | |
| **A10** | 354.0 | 37.0 | 186.4 | 305.0 | 44.8 | 150.5 | | | |
| **A11** | 181.3 | 40.9 | 176.9 | 178.4 | 44.4 | 164.6 | | | |
| **A12** | 30.2 | 33.2 | 84.7 | 29.6 | 36.5 | 74.9 | | | |
| **A13** | 195.6 | 39.5 | 212.5 | 238.5 | 48.7 | 263.0 | | | |
| **A14** | 16.4 | 35.4 | 104.0 | | →**A12** | | | | |
| **B1** | 41.0 | 42.0 | 65.8 | 34.6 | 45.1 | 58.6 | 43.1 | 42.4 | 61.1 |
| **B2** | 205.6 | 41.2 | 56.0 | 225.9 | 44.1 | 63.2 | 189.4 | 40.8 | 57.5 |
| **B3** | 175.5 | 43.4 | 144.8 | 145.9 | 46.3 | 162.4 | 151.9 | 42.0 | 161.1 |
| **B4** | 195.4 | 42.5 | 60.4 | 213.5 | 46.1 | 64.6 | | | |
| **B5** | 208.3 | 42.8 | 190.0 | | →**B3** | | | | |
| **B6** | 200.1 | 42.4 | 58.1 | 219.9 | 45.9 | 67.3 | | | |
| **B7** | 40.4 | 42.6 | 67.7 | 34.7 | 44.1 | 61.1 | | | |
| **B8** | 46.4 | 41.8 | 66.7 | | →**B1** | | | | |
| **B9** | 273.5 | 36.4 | 83.1 | 288.0 | 41.4 | 83.4 | | | |
| **B10** | 46.2 | 42.5 | 69.1 | 41.9 | 44.0 | 61.2 | | | |
| **B11** | 173.8 | 43.1 | 307.6 | 136.7 | 48.2 | 324.1 | | | |
| **B12** | 200.1 | 42.4 | 245.2 | 231.9 | 43.3 | 242.3 | | | |
| **B13** | 333.3 | 41.3 | 196.1 | 301.0 | 46.5 | 158.5 | | | |
| **B14** | 34.2 | 42.5 | 258.9 | 32.0 | 44.4 | 244.8 | | | |
| **B15** | 37.7 | 42.5 | 222.6 | 42.7 | 44.3 | 226.1 | | | |
| **B16** | 339.2 | 39.7 | 200.3 | 301.4 | 43.9 | 166.9 | | | |
| **B17** | 204.5 | 42.6 | 233.9 | 231.1 | 44.0 | 229.4 | | | |
| **B18** | 328.9 | 40.1 | 196.3 | | →**B16** | | | | |
| **B19** | 175.0 | 43.9 | 307.2 | 142.8 | 48.0 | 332.6 | | | |
| **B20** | 38.5 | 42.1 | 247.5 | | →**B15** | | | | |
| **B21** | 31.5 | 42.3 | 241.8 | 32.1 | 43.2 | 239.7 | | | |
| **B22** | 192.2 | 45.2 | 59.3 | 165.7 | 49.6 | 56.1 | | | |
| **C1** | 348.2 | 18.0 | 71.2 | 334.6 | 15.0 | 69.4 | | | |
| **C2** | 347.6 | 18.4 | 74.2 | 345.6 | 20.6 | 69.9 | 349.3 | 17.7 | 66.1 |
| **C3** | 161.1 | 20.5 | 181.8 | 158.7 | 32.4 | 172.3 | 160.8 | 26.7 | 175.3 |
| **C4** | 346.6 | 16.2 | 72.4 | | →**C1** | | | | |
| **C5** | 346.3 | 19.8 | 193.3 | | →**C3** | | | | |
| **C6** | 345.5 | 24.6 | 206.1 | 165.6 | 21.6 | 234.9 | 164.6 | 26.4 | 237.7 |
| **C7** | 344.4 | 22.8 | 208.4 | 342.3 | 28.3 | 214.0 | | | |
| **C8** | 347.8 | 16.8 | 77.9 | | →**C1** | | | | |
| **C9** | 344.2 | 22.6 | 204.3 | 344.8 | 21.0 | 195.8 | | | |
| **C10** | 160.0 | 18.6 | 62.2 | 159.7 | 32.0 | 74.1 | | | |

[a] This torsion angle describes the orientation of the base (90−270° anti, 0−90° and 270−360° syn).

at the B3LYP/3-21G and B3LYP/6-31+G(d,p) levels are available as Supporting Information.

The PSEUROT program[25] calculates $^3J_{HH}$ values from the generalized Karplus equation and compares them with experimental values to determine the endocyclic dihedral angles from exocyclic H−C−C−H dihedral angles. The program assumes the coexistence of two conformations, south and north.[26] The relationship between exocyclic dihedral angles and endocyclic dihedral angles is given as $\varphi_{exo} = A\varphi_{endo} + B$, where the $A$ and $B$ values[15c,15d] are found by fixing $\nu_{max} = 38$ and varying $P$ values in increments of 30° for the entire pseudorotational cycle and optimizing at the B3LYP/3-21G level (Figure 4). The other $\nu$ values were found from the formula, $\nu_i = \nu_{max} \cos(P + 4\pi i/5)$.[15b] For values of P along the pseudorotation circle, the optimization was started with the base in the anti and syn orientation. The plot in Figure 4 was made from the energies of structures in the lower-energy orientation for each value of $P$. For angles of $P$ between 60° and 240°, the energy of the ring was lower with the base in the anti orientation (see Supporting Information for table of energies). From these structures, the $A$ and $B$ values were found (Table 3).

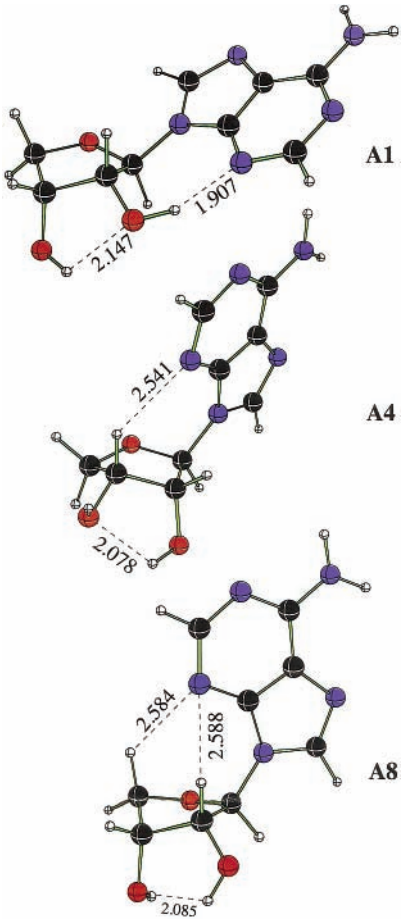



**Figure 1.** B3LYP/6-31+G(d,p) optimized conformers **A1**, **A4**, and **A8**.

## Results and Discussion

**Conformational Analysis of A.** At the B3LYP/6-31G(d,p)//MMFF94 level, the most stable conformer **A1** (south/anti) was calculated to be 6.05 kcal/mol more stable (Table 1) than the next lowest-energy conformer, **A8** (south/syn). At the B3LYP/3-21G//B3LYP/3-21G level, **A1** was 8.04 kcal/mol more stable than **A8**. The DFT optimization moved the ring conformation of **A1** toward the east ($P$ = 176.8° → 154.8°), whereas **A8** moved toward the west ($P$ = 207.8° → 233.2°). Conformer **A14** collapsed to **A12** when optimized at the B3LYP/3-21G level, indicating that the barrier between them disappears at the DFT level. Comparing relative energies at the B3LYP/6-31G(d,p) level when B3LYP/3-21G geometries are used rather than MMFF94 geometries, the largest change in relative energies is about 1.4 kcal/mol (Table 1).

The next step in refinement is to optimize several conformers at the B3LYP/6-31+G(d,p) level. Because of the significant amount of computer time required, only four conformers of **A** were chosen, two south (anti and syn; **A1** and **A8**) and two north (anti and syn; **A2** and **A4**). During the course of geometry optimization, conformer **A2** collapsed to **A1**, indicating that the activation barrier between them disappeared when a larger basis set was applied. The energy difference between **A1** and **A8** decreased to 4.68 kcal/mol. The lower energy of **A1** is due to an "internal conformational lock"[27] created by a hydrogen bond

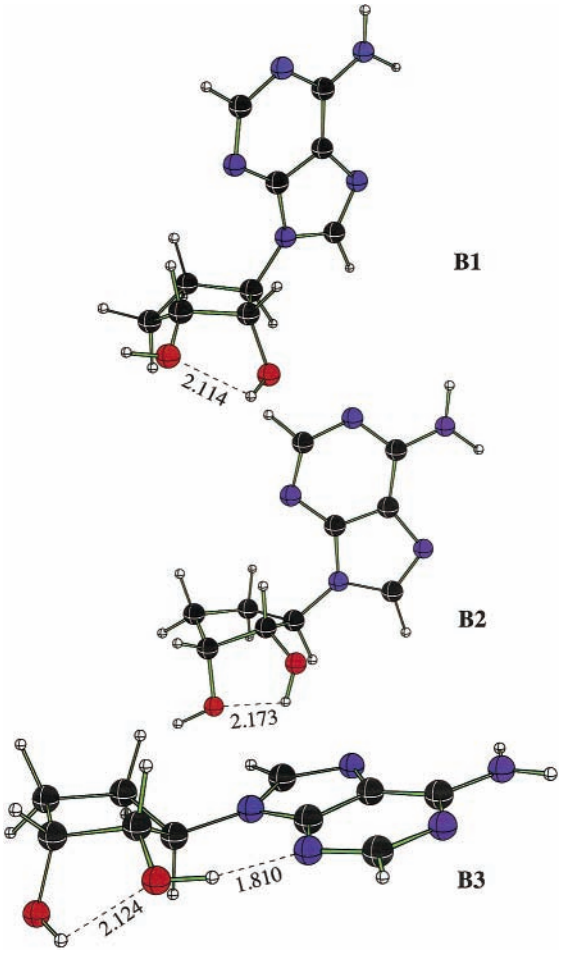
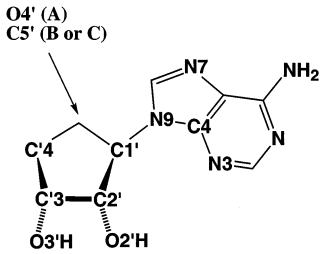



**Figure 2.** B3LYP/6-31+G(d,p) optimized conformers **B1**, **B2**, and **B3**.

between N3 in the adenine base and the hydrogen of O2′ on the 5 ring (see standard atomic labeling below). The base is




syn in both **A4** (north, $P = 30.9°$) and **A8** (south, $P = 223.5°$) and the relative energies are very similar (4.76 and 4.68 kcal/mol, respectively), which indicates that, without the "internal lock", north and south conformers have similar stabilities.

At each level of theory, conformer **A1** remained lowest in energy because of the two consecutive hydrogen bonds (O3′H···O2′ and O2′H···N3; see Figure 1 and Table 1), which also locks **A1** into a south conformer. Although the level of theory used for geometry optimization did not affect the orientation of the base (see dihedral angle $\chi$ in Table 2), the pseudorotation angle changed by up to 49.0° in going from MMFF94 to B3LYP/3-21G. In the case of **A2**, optimization at the B3LYP/6-31+G(d,p) level resulted in the collapsed to **A1**, a 169° change in pseudorotation angle (0.0° → 169.3°).

The second lowest energy conformer, **A8**, is in the southern part of pseudorotational cycle with a syn orientation of the base. There are two relatively short nonbonded CH···N interactions

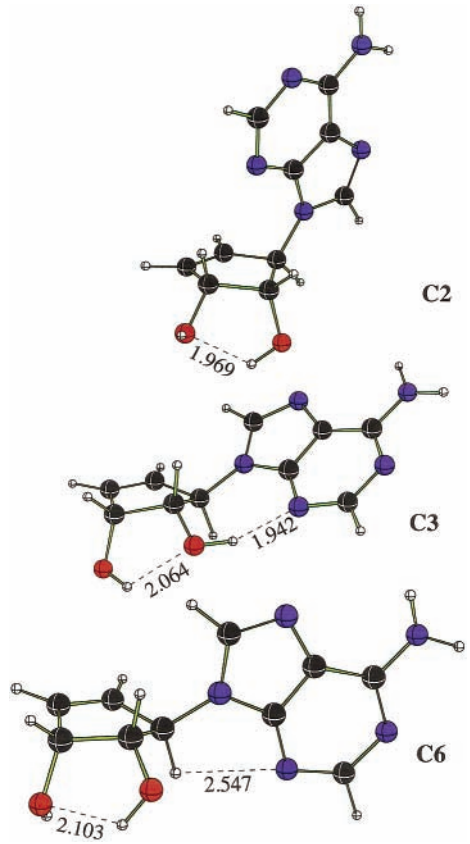



**Figure 3.** B3LYP/6-31+G(d,p) optimized conformers **C2**, **C3**, and **C6**.

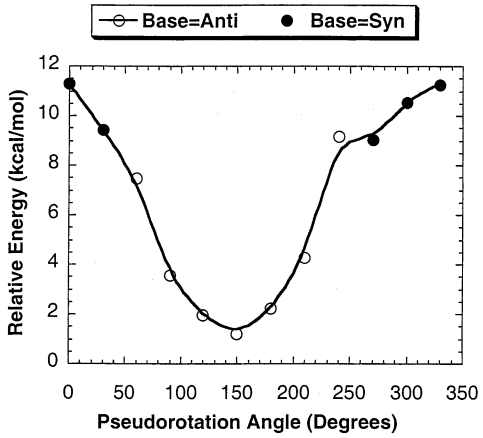



**Figure 4.** Pseudorotation potential energy surface of **B** optimized at the B3LYP/3-21G level. Empty circles indicate an anti orientation of the base, whereas filled circles indicate a syn orientation of the base.

**TABLE 3: *A* and *B* Values (u and d Represents Up and Down Relative to the Adenine)**

| exocylic dihedral angle ($\varphi$) | *A* | *B* | $R^2$ | exocylic dihedral angle ($\varphi$) | *A* | *B* | $R^2$ |
|---|---|---|---|---|---|---|---|
| H1′−H2′ | 1.16 | 123.4 | 0.994 | H1′−H5'u | 1.17 | −125.7 | 0.983 |
| H2′−H3′ | 1.07 | −4.6 | 0.992 | H3′−H4′d | 1.14 | −120.4 | 0.998 |
| H1′−H5′d | 1.17 | −5.4 | 0.998 | H3′−H4′u | 1.05 | 0.1 | 0.998 |

(2.588 and 2.584 Å, Figure 1 and Table 4) in **A8** which are reminiscent of the CH···N type interactions found in the crystal structures of nucleic acids.[28] Two of the short CH···N contacts C3′H···N3 (**A4**) and C2′H···N3 (**A8**) involve a $sp^3$ hybridized carbon with a OH substituents. It is known that electronegative substituents attached to carbon increase the strength of CH···N

**TABLE 4: Length (Å) and the Angle (degrees) of Hydrogen Interactions for Conformers of A, B, and C**

| conformer | bond type | length | angle |
|---|---|---|---|
| **A1** | O2′H···N3 | 1.907 | 113.7 |
| | O2′H···O3′ | 2.147 | 152.1 |
| **A4** | O2′H···O3′ | 2.078 | 118.4 |
| | C3′H···N3 | 2.541 | 123.9 |
| **A8** | O2′H···O3′ | 2.085 | 119.1 |
| | C2′H···N3 | 2.588 | 119.5 |
| | C4′H···N3 | 2.584 | 126.9 |
| **B1** | O2′H···O3′ | 2.114 | 113.3 |
| **B2** | O2′H···O3′ | 2.173 | 113.3 |
| **B3** | O3′H···O2′ | 2.124 | 113.6 |
| | O2′H···N3 | 1.810 | 155.6 |
| **C2** | O2′H···O3′ | 1.969 | 123.3 |
| **C3** | O3′H···O2′ | 2.065 | 117.1 |
| | O2′H···N3 | 1.942 | 152.7 |
| **C6** | O2′H···O3′ | 2.103 | 118.7 |
| | C1′H···N3 | 2.547 | 107.4 |

hydrogen bonding by increasing the hydrogen acidity.[29,30] In a recent analysis of neutron diffraction structures of CH···N hydrogen bonded systems,[31] the mean H···N distance was found to be $\bar{r} = 2.43$ Å (range 2.32−2.50 Å) and the mean CH···N angle was found to be $\bar{\alpha} = 150°$ (range 139−166°). Because the CH···N distances and angles in **A** (Table 4) are out of this observed range, the interactions are likely to be weaker than normal CH···N hydrogen bonds but perhaps sufficient to stabilize conformers **A4** and **A8** with a syn orientation of the base. In this respect, it is interesting to note that an AIM analysis of CH···O hydrogen bonding has recently been carried out on several nucleosides.[32] Such an analysis of the CH···N interaction in **A** might reveal whether it should be considered as a hydrogen bond.

The conformational analysis of **A** has been done experimentally by Kline et al.[14e] From an analysis of the cyclopentyl $^1$H−$^1$H coupling constants determined in water using PSEUROT, they reported a dominant South conformer (95%) with a pseudorotation angle of 180.1°.[33] The pseudorotation angle of **A1** by the B3LYP/6-31+G(d,p) level is in good agreement (169.3°). In the gas phase, only one conformer is expected. However, solution effects will likely diminish the preference for the locked conformer (see discussion of solvation effects below).

**Conformational Analysis of B.** In contrast to **A**, single-point energies at the B3LYP/6-31G(d,p)//MMFF94 level of theory show significant differences in relative energies. Specifically, **B3** and **B5** were stabilized by 5.48 and 5.21 kcal/mol relative to **B1**, respectively. When the conformers **B1**−**B22** were optimized at the B3LYP/3-21G level, **B3** became the lowest-energy conformer (9.43 kcal/mol lower than **B1**) and **B5** collapsed to **B3**. The adenine base is syn in **B1** and anti in **B3**. **B1** is in a north conformation, whereas **B2** and **B3** are in south conformations. At the B3LYP/6-31G(d,p)//B3LYP/3-21G level, the ordering is **B3** < **B7** < **B1** < **B2** at relative energies of −5.40, −0.77, 0.00, and 0.43 kcal/mol, respectively. Because **B7** and **B1** appear to have very similar values of $P$, $\nu_{max}$, and $\chi$, only conformers **B1**, **B2**, and **B3** were optimized at the B3LYP/6-31+G(d,p) level. At this level, **B3** is 4.51 kcal/mol lower in energy than **B1**. The $P$, $\nu_{max}$, and $\chi$ values of **B3** are 151.9°, 42.0°, and 161.1° which are very similar to the lowest conformer **A1** (169.3°, 36.2°, and 169.9°) which indicates that **A** and **B** both have nearly the same conformation which is about 4.5 kcal/mol more stable than the next lowest energy conformer.

The parameters for the hydrogen bonding in **B** are given in Table 4. It can be seen that the O2′H···N3 hydrogen bond is shorter in **B3** than in **A1** (1.810 versus 1.907 Å) which may be due to the greater puckering in cyclopentane ring ($\nu_{max} = 42.4°$) compared to the tetrahydrofuran ring ($\nu_{max}$=36.2°; see Figure 2 and Table 2).

**TABLE 5: Chemical Shifts ($\delta$, ppm) and $^1$H−$^1$H Coupling Constants ($^3J_{HH}$, Hz) for Compound B[a]**

| nuclei | chemical shift ($\delta$, ppm) | coupling constants ($^3J_{HH}$, Hz) H1′ | H2′ | H3′ |
|---|---|---|---|---|
| H1′ | 4.7(6.02) | | | |
| H2′ | 4.3(4.94) | 9.31(6.7) | | |
| H3′ | 4.0(4.54) | | 3.97(4.6) | |
| H4'u | 2.1(4.56) | | | 4.91(3.8) |
| H4′d | 1.6(4.09) | | | 1.82(1.7) |
| H5'u | 2.0 | 9.2 | | |
| H5′d | 2.2 | 9.2 | | |

[a] The experimental values for **A** are in parentheses. Reference 14e.

**TABLE 6: Comparison of Geometric Parameters for X-ray Structure of A and Calculated Values (B3LYP/6-31+G(d,p)) of A1**

| parameters[b] | X-ray[a] (**A**) unit A | unit B | theory (**A1**) |
|---|---|---|---|
| $P$ | 168.9 | 117.0 | 169.3 |
| $\nu_{max}$ | 44.4 | 40.6 | 36.2 |
| $\chi$ | 246.1[c] | 69.4 | 169.9 |
| C1′−C2′ | 1.508 | 1.519 | 1.547 |
| C2′−C3′ | 1.532 | 1.541 | 1.536 |
| C3′−C4′ | 1.514 | 1.536 | 1.526 |
| C4′−O4′ | 1.458 | 1.438 | 1.452 |
| O4′−C1′ | 1.422 | 1.409 | 1.409 |
| C1′−N9 | 1.458 | 1.447 | 1.468 |
| C2′−O2′ | 1.404 | 1.415 | 1.405 |
| C3′−O3′ | 1.415 | 1.420 | 1.420 |

[a] Serianni, A. S. unpublished results. Unit cell ($P2_12_12_1$) contains two molecules of **A**. [b] Pseudorotation angle ($P$), pseudorotation amplitude ($\nu_{max}$), torsion angle ($\chi$ = C5′−C1′−N9−C4′), and bond distances (Å). [c] The corresponding value from X-ray in aristeromycin (**1**) is 246.5 (−113.5). Kishi, T.; Muroi, M.; Kusaka, T.; Nishikawa, M.; Kamiya, K.; Mizuno, K. *Chem. Pharm. Bull.* **1972**, *20*, 940. For the X-ray structure of adenosine (**2**), see: Lai, T. F.; Marsh, R. E. *Acta Crystallogr.* **1972**, *B28*, 1982.

Relative energies at the B3LYP/6-31G(d,p)//B3LYP/3-21G level (Table 1) suggest that **B** has only one dominant conformation (the "locked" conformation). Under the one-state assumption and using the experimental proton coupling constants obtained in DMSO (Table 5), PSEUROT6.3 gives $P = 176.8°$ and $\nu_{max} = 41.9°$ with an RMS error of 0.6 Hz.

Thibaudeau et al.[16] have compared the X-ray and solution phase structures of aristeromycin (**1**). In aqueous solution, **1** has $P = 136.1°$ and $\nu_{max} = 37.4°$ compared to the X-ray value of 89.0° and 40.8°, respectively. The ratio of syn:anti in solution is about 46:56, whereas the base is anti in the X-ray structure (torsion angle, $\chi = 246.1°$). The authors[16] conclude that the "solution- and the solid-state structure of aristeromycin are indeed different".

In the course of their study, Thibaudeau et al.[16] reparametrized the Haasnoot−Altona Karplus equation to obtain a better fit between calculated and experiment coupling constants for aristeromycin (**1**). When these parameters are used in the PSEUROT program for **B** (and assuming one state), the RMS is reduced to 0.5 Hz with very similar values of $P$ and $\nu_{max}$ (176.3° and 41.2°, respectively).

In the X-ray structure of **A**, there are two molecules per unit cell (Table 6) with pseudorotation angles ($P$) of 168.9° and 117.0° which can be compare to $P = 169.3°$ for **A1**. The base torsion angles ($\chi$) are 246.1° (anti) and 69.4° (syn) which can be compared to $\chi = 169.9°$ (syn) in **A1**. Although there is some

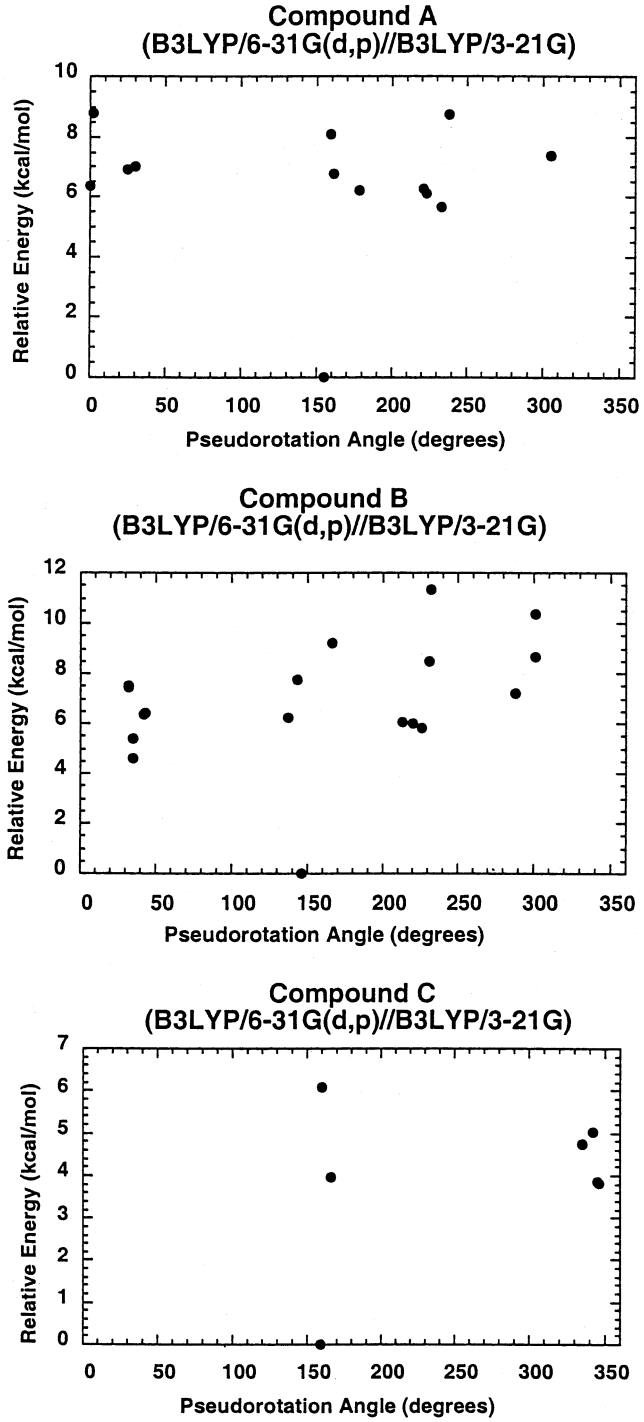



**Figure 5.** (a) *P* versus relative energy (kcal/mol) at B3LYP/3-21G for **A1**−**A14**. (b) *P* versus relative energy (kcal/mol) at B3LYP/3-21G for **B1**−**B22**. (c) *P* versus relative energy (kcal/mol) at B3LYP/3-21G for **C1**−**C10**. The lowest energy conformer has a very similar *P* value for **A1** ($P = 154.8°$), **B3** ($P = 145.9°$), and **C3** ($P = 158.7°$)

similarity between the calculated structure (**A1**) and each of the two molecules in the unit cell (unit A and unit B), neither unit in the X-ray structure displays the hydrogen lock between O2′H of the sugar and N3 of the adenine base. Thus, similar to aristeromycin (**1**), it appears that the conformer of **A** is different in X-ray and gas/solution phases.

**Conformational Analysis of C.** A total of 10 conformers were returned from the MMFF94 search which were reduced to seven by optimizing at the B3LYP/3-21G level of theory. From these structures, conformers **C2**, **C3**, and **C6** were further optimized at the B3LYP/6-31+G(d,p) level (Figure 3). The low

**TABLE 7: Relative Energies (kcal/mol) of Modified Nucleotides in Water by PCM/B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p)[a]**

| | gas phase ($\epsilon = 1.0$) | water ($\epsilon = 78.39$) |
|---|---|---|
| **A1** | 0.00 | 0.00 |
| **A4** | 4.76 | 2.49 |
| **A8** | 4.68 | 1.38 |
| **B1** | 4.51 | 1.80 |
| **B2** | 4.11 | 0.93 |
| **B3** | 0.00 | 0.00 |
| **C2** | 4.03 | 3.75 |
| **C5** | 0.00 | 0.00 |
| **C6** | 3.95 | 0.16 |

[a] Dielectric constant is given in parentheses.

number of conformers can be accounted for by the presence of the double bond in the five-member ring.

The unsaturated five-membered ring in **C** was analyzed in the same manner as the saturated five-membered rings of **A** and **B** which allowed direct comparison of results. The lowest-energy conformer of **C** (**C3**) displayed the same O2′H···N3 lock as found in **A1** and **B3** (Figures 1 and 2). The **C3** conformer, which is in the southern hemisphere ($P = 160.8°$), is 4.03 kcal/mol more stable than the next lowest conformer. The maximum puckering ($\upsilon_{max} = 26.7°$) in **C3** is less than in the corresponding saturated rings of **A1** (36.2°) and **B3** (42.0°), which is due to the stiffening of the ring by the double bond. The second lowest energy conformer (**C2**) is in the northern hemisphere ($P = 349.3°$, $\upsilon_{max} = 17.7°$) with a syn orientation of the base. The third lowest conformer (**C6**) is only 0.12 kcal/mol higher than **C2** and is in the southern hemisphere ($P = 164.6°$, $\upsilon_{max} = 26.4°$) with an anti orientation of the base.

It is interesting to point out that the conformer with the base in an pseudoaxial position (**C2**) has a $\upsilon_{max}$ value about 10° smaller than the conformers with the base in an pseudoequatorial position (**C3** and **C6**). It is possible that the $\pi_{C4'-C5'}$ electrons can conjugate with the $\sigma^*_{C1'-N9}$ orbital in **C2** which may flatten the ring.[34]

**General Considerations.** As discussed above, **A**, **B**, and **C** all have similar structures for the lowest energy conformation. The absence of other conformations close in energy to the locked conformer is emphasized by plotting conformer energies as a function of pseudrotation angle (Figure 5). Houseknecht et al.[24c] report the conformational analysis of 3-O-methyl-α-D-arabino-furanoside and found a significantly different distribution which suggests that the nature of substituents in the five-membered ring has a large effect on the conformational preferences.

**Solvation Effects.** A major limitation of the present calculations is that they refer to the gas phase (dielectric constant, $\epsilon = 1.0$), whereas NMR measurements are usually performed in water ($\epsilon = 78.39$) or DMSO ($\epsilon = 46.70$). In the presence of solvent molecules, the specific hydrogen-bond lock O2′H···N3 will weaken or may completely disappear. To evaluate the effect of solvation, single-point calculations were made with the polarized continuum model (PCM) solvation method[36] at the PCM/B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) for conformers of **A**, **B**, and **C** (Table 7). For **A** and **B**, the locked conformers (**A1** and **B3**) are still the lowest energy by about 1 kcal/mol which suggests that the lowest energy conformers are unchanged in the presence of solvation. For **C**, the locked conformer **C5** is only 0.2 kcal/mol more stable than **C6**. Both conformers are in the south, but there may be nearly free rotation of the base around the C1′−N9 bond. It is interesting to point

out that in aristeromycin (**1**) the ratio of syn to anti in water has been determined to be 44:56 from NOE enhancements.[16]

## Conclusions

The lowest energy conformer of three nucleosides containing an adenine base (**A**, **B**, and **C**) each displays an internal hydrogen bond between O2′H of the five-membered ring and the N3 nitrogen of the adenine base. The very short hydrogen bond O2′H···N3 distances in **A**, **B**, and **C** of 1.907, 1.810, and 1.942 Å, respectively, indicate a conformational lock that could have biological significance. In the gas phase, the locked conformer is over 4 kcal/mol more stable than the next lowest conformer. When aqueous solvation is modeled using PCM, the preference is reduced to about 1 kcal/mol for **A** and **B** and to about 0.2 kcal/mol for **C**. Given the known difference in the antiviral properties of **B** and **C** versus **A** (**B** and **C** are active, **A** is inactive), we conclude that the conformational lock proposed with structures **A1**, **B3**, and **C3** does not account for the observed biological property correlation.

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**Supporting Information Available:** Relative energies (kcal/mol) at the MMFF94 level and total energies (hartrees) at DFT levels (Table S1, 1 page). Relative energies (kcal/mol) and total energies (hartrees) at the B3LYP/3-21G//B3LYP/3-21G level of structures on the pseudorotation potential energy surface of **B** (Table S2, 1 page). Cartesian coordinates for relevant structures optimized for **A**, **B**, and **C** conformers at the B3LYP/3-21G and B3LYP/6-31+G(d,p) levels of theory (Tables S3 and S4, 29 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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