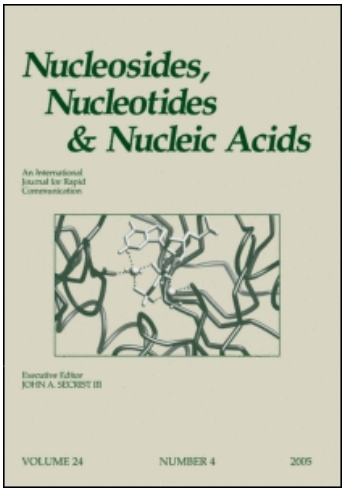

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Evaluation of Thymidine, Dideoxythymidine and Fluorine Substituted Deoxyribonucleoside Geometry by the MIND0/3 Technique The Effect of Fluorine Substitution on Nucleoside Geometry and Biological Activity

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To cite this Article Bergstrom, D. E. , Swartling, D. J. , Wisar, A. and Hoffmann, M. R.(1991) 'Evaluation of Thymidine, Dideoxythymidine and Fluorine Substituted Deoxyribonucleoside Geometry by the MIND0/3 Technique The Effect of Fluorine Substitution on Nucleoside Geometry and Biological Activity', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 693 — 697
To link to this Article: DOI: 10.1080/07328319108046575
URL: http://dx.doi.org/10.1080/07328319108046575

NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 693-697 (1991)

Evaluation of Thymidine, Dideoxythymidine and Fluorine Substituted Deoxyribonucleoside Geometry by the MINDO / 3 Technique: The Effect of Fluorine Substitution on Nucleoside Geometry and Biological Activity

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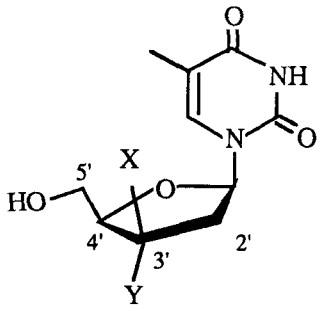
Abstract

The MINDO/3 technique was used to evaluate the geometry of thymidine and four structural analogs, 3'-fluoro-3'-deoxythymidine (**2**), 3'-fluoro-2',3'-dideoxy-β-D-lyxofuranosylthymine (**3**), 3'-deoxythymidine (**4**), and 3',3'-difluoro-3'-deoxythymidine (**5**). The relative proportion of N (3'-endo, 2'-exo, P = 0°) and S (2'-endo, 3'-exo, P = 180°) conformers was determined for each of the analogs. Whereas the energy difference between the N and S forms of most deoxyribonucleoside derivatives differ by at most 1 to 2 kcal/mol, the N conformation for nucleosides **4** and **5** are respectively 2.9 and 4.0 kcal/mol more stable than the S form. The optimal value of χ for each of the analogs in the N conformation was -102° (**4**) and -97° (**5**). The fluorine in the up position at C3' of deoxyribose appears to be a strong attractor for the H-6 proton on the thymine when the the sugar is in the N conformation.



1 X = H, Y = OH

2 X = H, Y = F

3 X = F, Y = H

4 X, Y = H

5 X, Y = F

6 X = H, Y = N_3

Results and Discussion

3'-Fluoro-3'-deoxythymidine shows nearly an identical energy profile to thymidine (not shown) in the S form for rotation about the glycosidic bond. The energy minima for χ falls at approximately -135°(anti conformation) (figure 1) which is 7.5 kcal/mol below the energy minimum for the syn form at 68°. The N form is less stable and shows two energy minima for χ in the anti region at -140° and -85° which are respectively 1.4 and 1.3

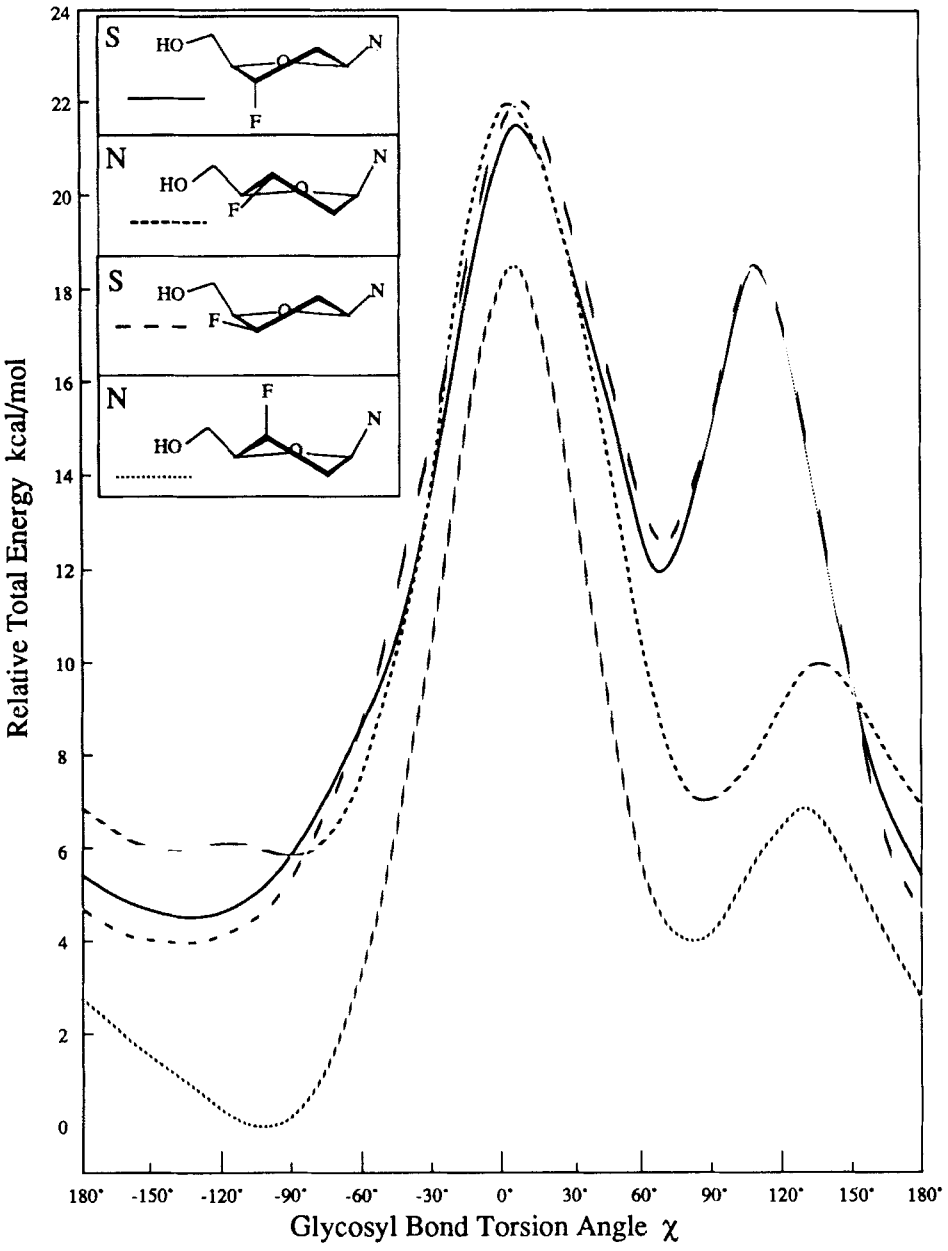


Figure 1

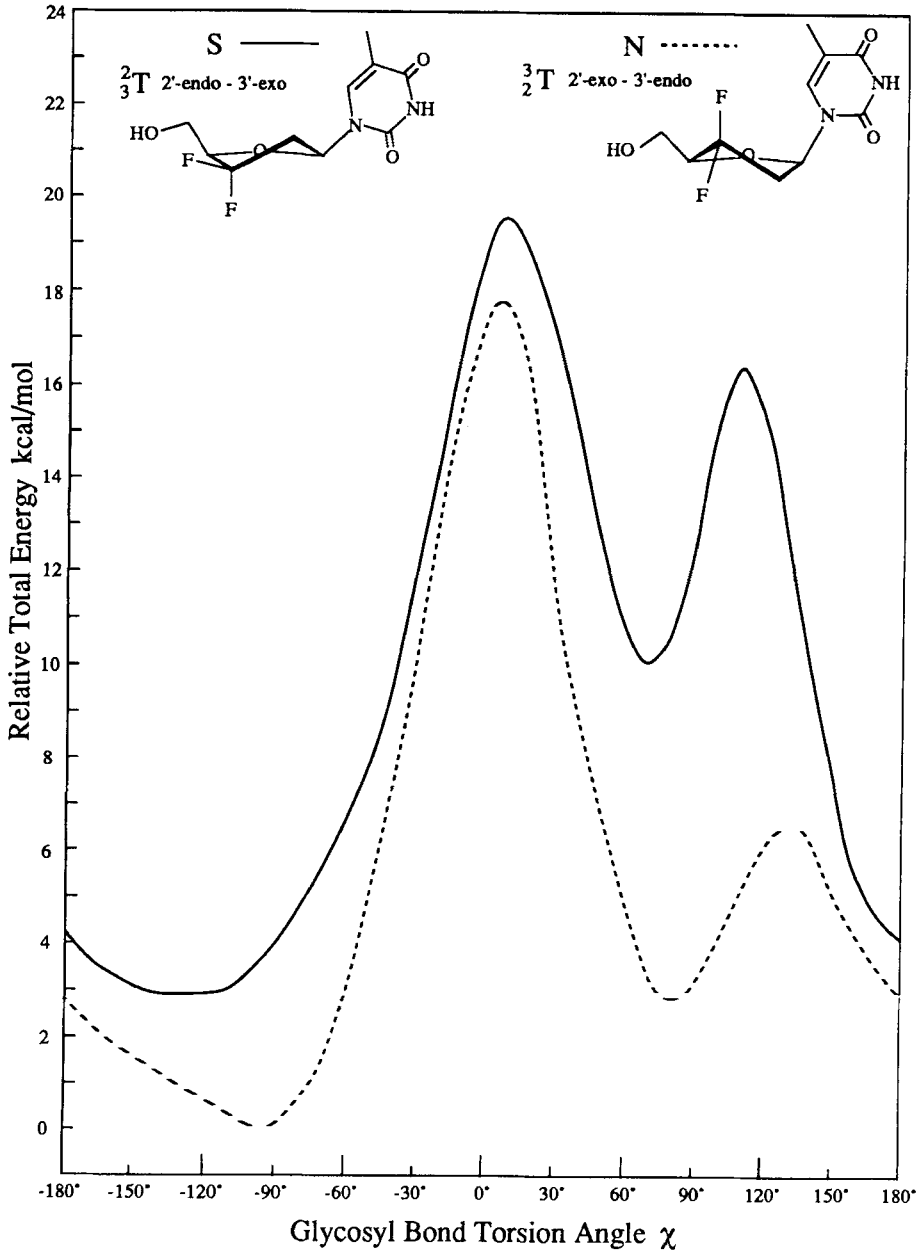


Figure 2

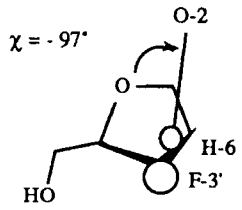


Figure 3

kcal/mol higher energy than the minima for the S form at -135°. The relative populations of the two sugar conformations would therefore be about 90% S and 10% N. When the position of the fluorine is inverted at C3', the conformational preferences of the compound is dramatically altered. The N form becomes far more stable than the S form (the energy difference is 4.0 kcal/mol giving an N to S ration of 99.9% to 0.1%). The same observation was made for 3',3'-difluoro-3'-deoxythymidine (figure 2). The energy profile for χ when the sugar is locked into the S conformation closely matches the thymidine profile but there is a significantly lower energy minimum for χ = -97° in the N form. This minimum is 2.88 kcal/mol lower energy giving an N to S ratio of 99.2% to 0.8%. This preference for the N conformer is far greater than what one would predict solely on the basis of the gauche effect.[1] However, the basis for this result becomes apparent on noting that the glycosidic bond lies at the bottom of a steep energy well with χ at -97 and -102 for compounds **4** and **5** respectively. . As shown in the diagram (Figure 3) this corresponds to H-6 on the pyrimidine lining up directly with the CF-3' bond. The distances H6-F3´ and C6-F3´ in this stable conformation are 2.16Å and 3.02Å, respectively. These distances are typical for hydrogen bonds. In this case, when atoms H6 and F3´ approach each other forming the C6-H6...F3´ hydrogen bond, our calculations show that the electron density decreases on hydrogen and increases on fluorine giving occasion to extended attraction.

The substantial difference in the value of χ between thymidine (**1**) and 3',3'-difluoro-3'-deoxythymidine (**5**) (-140 versus -97°) and the low population of molecules in the S conformation could be the structural effect which results in the inability of **5** to act as an effective anti-HIV agent. Molecular mechanics calculations on the potent antiviral agent 3'-azido-3'-deoxythymidine (**6**) provide an interesting contrast to our results for compounds **3** and **5**. Using a molecular mechanics force-field approach Herzyk et al arrived at an optimal geometry for this molecule that was very close to that of thymidine.[2] There was a slight overall preference for the C2' endo sugar pucker (S) for which χ fell at -153°. In the 3'-endo conformation (N) χ fell at -155°. This is much closer to the value of -145° that we found for thymidine, hence it appears that AZT should encounter no geometry restrictions as it encounters the enzymes leading to 5'-triphosphate and in eventual binding to HIV reverse transcriptase. A recent study which correlated ribosyl ring conformations in the solid state and anti-HIV activity for a series of eight 2',3'-dideoxy nucleoside analogs concluded that analogs which preferred C3' exo (S) conformations were significantly more active than those which preferred a C3' endo conformation(N).[3] Our results are in qualitative agreement since among the three active anti-HIV compounds examined in our study, the S domain conformation is easily achieved although not necessarily the most populated.

Acknowledgement

The National Institutes of Health is gratefully acknowledged for support of this research through NIH Grant AI 20480. The University of North Dakota is thanked for computer time on the IBM 3091E-120 (VP), on which all calculations reported in this manuscript were carried out.

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