

Conformational Study of New AZT Derivatives

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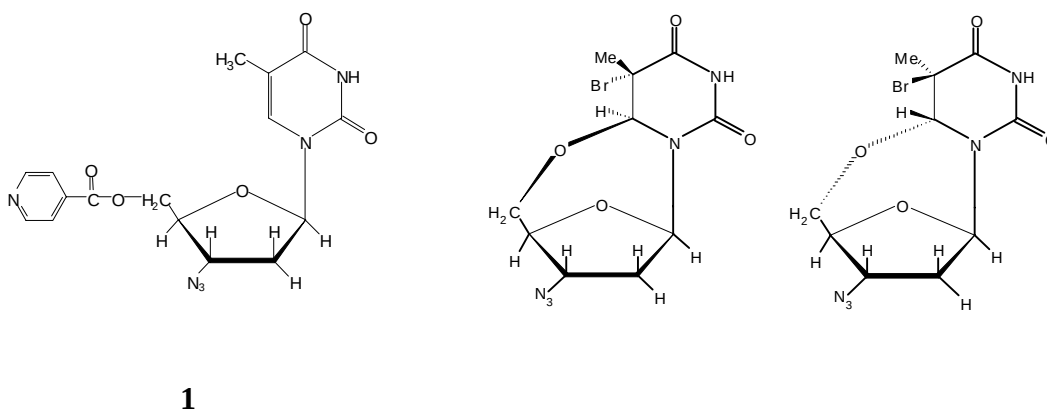
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Abstract: A conformational study of three new AZT derivatives was made by semiempirical methods in order to find a structural correlation between these derivatives and AZT.

Introduction

Background information of the conformational properties of 3'-azido-3'-deoxythymidine (AZT) and its derivatives in aqueous solution may contribute to the understanding of the relationship between chemical structure and biological activity of 2',3'-deoxynucleosides and consequently to help in the design of more active drugs. Besides, it has been suggested that the inhibitory action of these compounds may be related to the preferred conformation of modified furanose sugar. Our aim was to find out the conformational structure of three new AZT derivatives **1**, **2** and **3** [1] as well as their differences with AZT.



Experimental

Study of the different potential surfaces of the three AZT derivatives using AM1 [2] was performed. The stationary points were characterized by force constant calculation. Results were correlated with spectroscopic data.

Results and Discussion

The study of **1**, **2** and **3** with semiempirical methods have enable to find different conformers. Based on these results, the following correlation may be established:

- AZT and **1** exhibit similar conformers confirming the analogous behavior with other pyrimidinic nucleosides which display a dynamic equilibrium in solution where the two conformers (North and South) experience constant transformation [3].
- Studies of (-)-*trans*-(5S,6S)-**2** and (+)-*trans*-(5R,6R)-**3** compounds show an abnormally distinct conformation from AZT.¹ The estimate of the pseudorotation phase angle reveals the rigid structures of these drugs, which do not evidence conformational equilibrium in solution, the azide being the only free rotation group.
- Diastereomers **2** and **3** exhibit an extra conformational parameter compared with other pyrimidinic nucleosides: the *chair* or *boat* conformation in the third ring formed between the sugar and the base.

In all cases, a reasonable correlation was noticed between theoretical and spectroscopic data.

Acknowledgements: CONICET, CONICOR, SECyT-UNC.

References and Notes

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