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Intramolecular Hydrogen Bonding in Primary Hydroxyl of Thymine 1-(1-Deoxy-ß-D-Psicofuranosyl) Nucleoside

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Abstract: A conformational analysis of 1-(1-Deoxy-β-D-Psicofuranosyl) thymine (1) and 1-(β-D-Ribofuranosyl) thymine (2) has been performed by using the semiempirical AM1 methodology. A topological analysis of the total charge density and the Laplacian of both molecules is carried out in order to assess the presence of an intramolecular hydrogen bond. It is concluded that a clear hydrogen bond exists in structure (1) in such a way that the primary alcohol is experimentally found totally unreactive with any reagent in any condition.

INTRODUCTION

As part of a program on the synthesis and the structure determination of C $-1'$-branched nucleosides as potenty antiviral agents, we have recently investigated the study of *1-(1-Deoxy-β-D-Psicofuranosyl) thymine (1)*[1]. The structure of *(1)* differs from the natural ribonucleoside counterpart *1-(β-D-Ribofuranosyl) thymine (2)*[2] in that a methyl group replaces *H-1'*.

From NMR data and molecular mechanics calculations using the MM2 force field, it was concluded that the very predominant furanose conformation in *(1)* is a North-type conformation, whereas *(2)* shows almost an equal population of pseudorotamers in North South conformational equilibrium of the ribose moiety[2]. Another big difference was observed between *(1)* and *(2)* : the primary alcohol of *(1)* was found totally unreactive with any reagent in any condition[3]. In this report we show that this unreactivity could be due to a hydrogen bond between this hydroxyl and the oxygen at 2-position of the thymine base which was found in an unnatural *syn* conformation.

In the recent years Bader and co-workers have developed a methodology[4-11] based on the topological analysis of the charge density that characterizes hydrogen bonds. According to this methodology, the total electronic charge density $\rho(r)$ and its Laplacian $\nabla^2\rho(r)$ are considered. The Laplacian of the charge density is defined as the sum of the three principal curvatures of the $\rho(r)$ function at each point in space. That is:

$$\nabla^2\rho\,(x) = \frac{\partial^2\rho}{\partial x^2} + \frac{\partial^2\rho}{\partial y^2} + \frac{\partial^2\rho}{\partial z^2}$$

When two neighbouring atoms are chemically bonded to one another, a bond critical point (r_c) in the charge density appears between them. At the bond critical point $\nabla\rho(r_c) = 0$, the charge density being a minimum at r_c along the bond path but a maximum along any orthogonal displacement. In turn, the Laplacian of the charge density at a point r in space determines where electronic charge is locally concentrated $(\nabla^2\rho(r) < 0)$ or depleted $(\nabla^2\rho(r) > 0)$. So when $\nabla^2\rho(r_c)$ is negative the electronic charge is locally concentrated in the internuclear region. This occurs due to shared (covalent) interactions. Conversely, for closed-shell interactions $\nabla^2\rho(r_c)$ is positive. These last kind of interactions are dominated by the contraction of charge away from the interaction surface towards each of the nuclei. In a closed-shell interaction the atoms are bonded as a consequence of the charge that is concentrated within the basin of each atom. Talking all this into account, a hydrogen bond[11] is defined as one in which a hydrogen atom is bond to the acid fragment by a shared interaction and to the base by a closed-shell interaction.

CALCULATIONAL DETAILS

Given the size of the systems to be treated (between 32 and 35 atoms), we have taken the semiempirical AM1[12] method to evaluate the energies of the systems. Minimum energy structures have been located by means of the Powell method[13] as implemented in the AMPAC[14] program.

Topological analysis of the AM1 charge density was performed by means of programs developed in our group that make use of the density matrix as obtained from a GAUSSIAN 92[15] run.

RESULTS AND DISCUSSION

First of all, we have performed the conformational analysis of both nucleosides: *1-(1-Deoxy-β-D-Psicofuranosyl) thymine (1)* and *1-(β-D-Ribofuranosyl) thymine (2)*.

For both compounds, two different minima have been located that correspond to the *anti* and *syn* conformations. Figure 1 schematically depicts both conformations for compounds *(1)* and *(2)*.
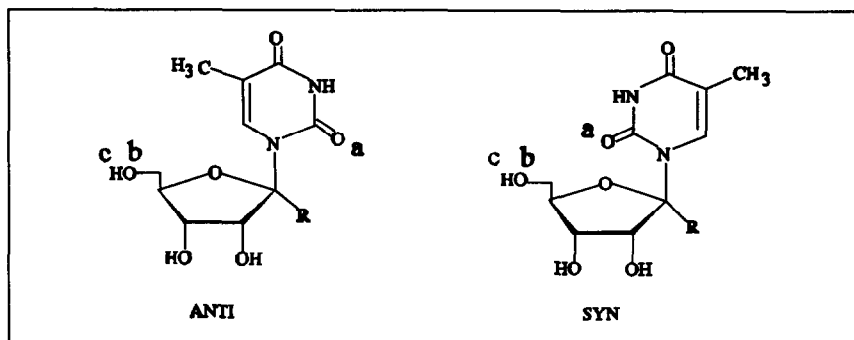
Figure 1. Anti and syn conformations of thymine 1-(1-Deoxy-Psicofuranosyl) (1)
and thymine 1-(β-D-Ribofuranosyl) (2) nucleosides. For compound (1) R=CH₃
and for compound (2) R=H.

In table 1 the heats of formation of the different minima located are presented along with the corresponding distances between the oxygen *(a)* and hydrogen *(c)* which are revelant in order to assess the existence of a hydrogen bond.

Table 1. Heats of Formation of the syn and anti
Structures of both (1) and (2) Compounds.

Conformation	$d(O_a-H_c)$ [(a)]	Heat of Formation[(b)]
syn (1)	2.18	-235.36
anti (1)	6.29	-228.69
syn (2)	2.39	-235.33
anti (2)	6.23	-235.27

(a) in Å.
(b) in kcal/mol.

It is noteworthy that whereas for compound *(2)* both conformations have almost identical stabilization energies, compound *(1)* clearly shows the *syn* structure as energetically preferred. It seems obvious, then, that the introduction of a methyl group in the *1'*position tends to favor the *syn* conformation versus the *anti* one.

From the analysis of oxygen-hydrogen distances, also seen in Table 1, it seems clear the presence of a hydrogen bond for the *syn* conformation of the ribonucleoside analogue *(1)*. This point has been verified by means of a topological analysis of the charge density. Figures 2 and 3 respectively present the isodensity contour plots of $\rho(r)$ and $\nabla^2\rho(r)$ in the $O_{(b)}$-$H_{(c)}$---$O_{(a)}$ plane for the *syn* structure of *(1)*. We note that tails of

charge density corresponding to nuclei other than the ones used to define the plane but no far away are intercepted by this plane.
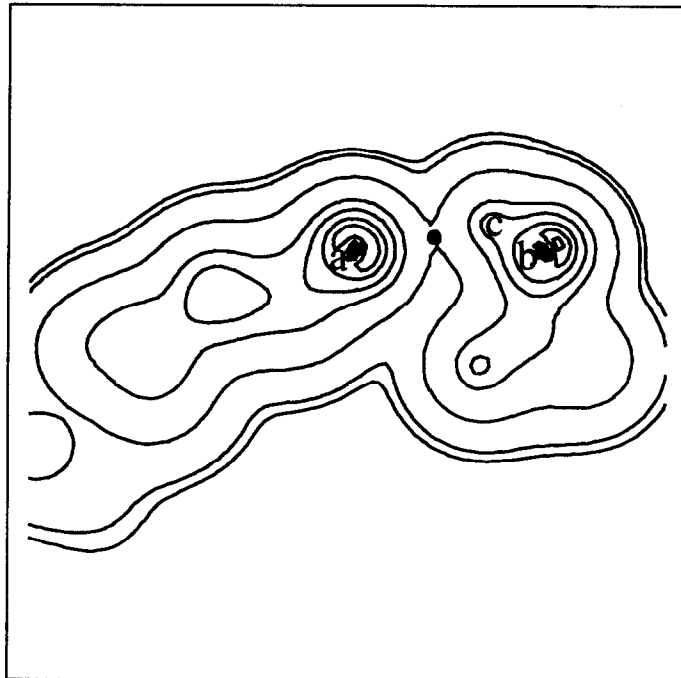

Figure 2. Isodensity contour of $\rho(r)$ *in the* $O_{(b)}$-$H_{(c)}$---$O_{(a)}$ *plane at the minimum energy structure of compound (1).*

A careful look at Figures 2 and 3 clearly reveals the presence of the *O-H* bond for the primary hydroxyl group $O_{(b)}$-$H_{(c)}$ located in the upper right side of Figures 2 and 3. This bond, clearly indicated by a bond critical point between $O_{(b)}$ and $H_{(c)}$ has a negative value of the Laplacian $\nabla^2\rho(r)$ (Figure 3) and so, as expected, it is of a covalent type. On the other hand, Figure 2 also reveals the presence of a bond between the hydrogen and the oxygen $O_{(a)}$. The bond critical point is indicated by a dot in Figures 2 and 3. As the bond critical point is located in the positive zone of the Laplacian, this bond belongs to the closed-shell type so that it can be concluded that a clear hydrogen bond exists in this structure.

Our results then, confirm that an intramolecular hydrogen bond exists in the *1-(1-deoxy-β-D-psicofuranosyl) thymine* structure in such a way that the primary alcohol is experimentally found totally unreactive with any reagent in any condition.
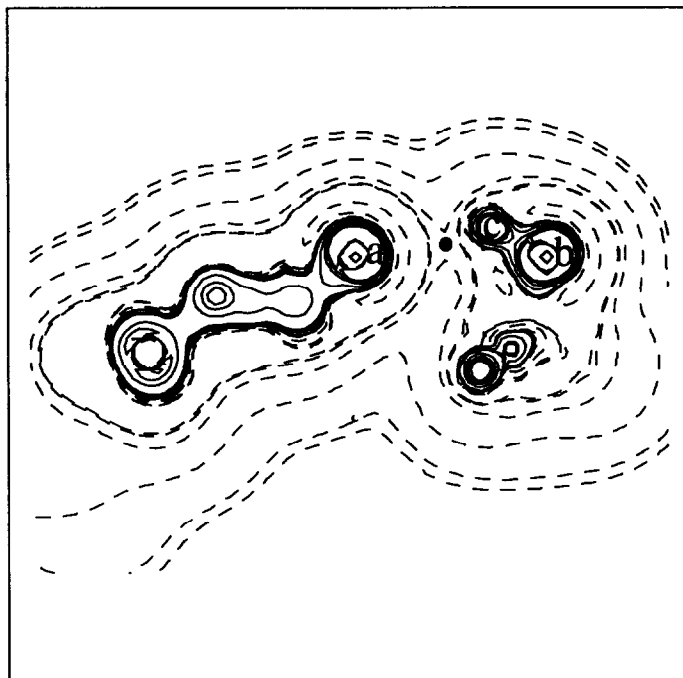
Figure 3. Isodensity countour plots of the Laplacian $\nabla^2\rho(r)$ in the $O_{(b)}$-$H_{(c)}$---$O_{(a)}$ plane at the minimum energy structure of compound (1). Dashed lines correspond to regions in which $\nabla^2\rho(r) > 0$ and solid lines correspond to regions in which $\nabla^2\rho(r) < 0$.

REFERENCES

1. Faivre-Buet V.; Grouiller A.; Descotes G. *Nucleosides & Nucleotides 1992*, 11, 1651.

2. Plavec J.; Buet V.; Grouiller A.; Koole L.; Chattopadhyaya J. *Tetrahedron* **1991**, 47, 5847.

3. Thesis of Faivre-Buet V. (Dissertation N° 130-91, Université Claude-Lyon I, *July 1991*).

4. Bader, R. F. W.; Tal, Y.; Anderson, S. G.; Nguyen-Dan. T. T. *Isr. J. Chem. 1980*, 19, 8.

5. Bader, R. F. W.; Essen, H. *J. Chem. Phys.* **1984**, 80, 1943.

6. Bader, R. F. W.; McDougall, P. J.; Lau, C. D. H. *J. Am. Chem. Soc.* **1984**, 106, 1594.

7. Bader, R. F. W.; McDougall, P. J. *J. Am. Chem. Soc.* **1985**, 107, 6788.

8. Bader, R. F. W.; Carroll, M. T.; Cheeseman, J. R.; Chang, C. *J. Am. Chem. Soc.* **1987**, 109, 7968.

9. Shi, Z.; Boyd, R. J. *J. Chem. Phys.* **1988**, 88, 4375.

10. Sagar, R. P.; Ku, A. C. T.; Smith, V. H. *Jr. J. Chem. Phys.* **1988**, 88, 4367.

11. Bader, R. F. W. *Atoms in Molecules. A Quantum Theory*; Oxford University Press: New York, *1990*.

12. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1984**, 80, 3265.

13.   Powell, M. J. D. *Numerical Methods for Nonlinear Algebraic Equations.*; Rabinowitz, Gordon & Breach: New York, *1970*, Ch. 6 & 7.

14.   Liotard, D. A.; Healy, E. F.; Ruiz, J. M.; Dewar, M. J. S. AMPAC-version 2.1. *Quantum Chemistry Program Exchange, program 506, QCPE Bull.* **1989**, 9, 123.

15.   Gaussian 92, Revision C, Frisch, M. J.; Trucks, G. W.; Head-Gordon M.; Gill, P. M. W.; Wong, M.W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, **1992**.