Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4901–4906

TETRAHEDRON

An electron density study on *cis*-1-(2-hydroxymethyl-cyclopentenyl)uracils

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Received 6 January 2003; revised 27 March 2003; accepted 24 April 2003

Abstract—A topological charge electron density analysis using the Atoms in Molecules (AIM) theory on B3LYP/6-31++G**//B3LYP/6-31G* charge densities was performed for the series of the five *cis*-1-(2-hydroxymethyl-Δ^n-cyclopentenyl))uraciles (n=1–5). These compounds are carbocyclic analogues of nucleosides that belong to an important class of antiviral or antitumoral compounds where the hydroxymethyl group and the heterocyclic base are bonded to adjacent carbons of a cyclopentene ring. The change of position of the double bond within the cyclopentene ring does not significantly affect the electron distribution of the base (that always carries a substantial negative charge), but alters the orientation of the base and the hydroxymethyl group (3-, and 4-cyclopentenyl derivarives being the exception as they present very similar conformations).

1. Introduction

The application of diverse 2′,3′-dideoxynucleosides as antiviral or antitumoral drugs has promoted the interest on the synthesis and structural study of new analogues of these compounds in recent years.[1,2] These compounds work by blocking viral reproduction, inhibiting reverse transcriptase.[3,4] Many modifications of 2′,3′-dideoxynucleosides have been tested. One of them, the replacement of the endocyclic oxygen atom of the pentose ring with a methylene group[5] has been very successful in reducing phosphorylase and hydrolase catalyzed reactivity, increasing the in vivo half life. One of these compounds, the potent HIV-1 inhibitor carbovir,[6] combines this modification with the inclusion of a double bond in the five-membered ring. Thus, the sugar ring is replaced by a cyclopentene with a hydroxymethyl group bonded to the 3′ position. Looking for new active analogues, our group has prepared several carbocyclic nucleoside analogues of pyrimidine or purine with the hydroxymethyl group and the heterocyclic base bonded to contiguous carbons of the carbocycle.[7–9] The modification of the position of the double bond within the cyclopentene ring has also attracted our attention, as it has been reported that this kind of structural change on carbovir analogues have produced compounds with antiviral activity.[10] In this work we report the results obtained in a theoretical structural study of the five *cis*-1-(2-hydroxymethyl-Δ^n-cyclopentenyl) uracils that we have carried out to predict the structural differences within previously synthesized compounds.[11]

Because of the importance of structural features in activity and function, nucleoside analogues have been the subject of numerous structural investigations. Nevertheless, most of the studies hitherto performed on these kind of compounds are conformational analyses, normally carried out with semiempirical or molecular mechanics calculations. Thus, the conformation of nucleoside analogues has been extensively reviewed.[12–15] Recently, we have performed a comparative study of the HF/6-31++G**//HF/6-31G* charge densities of *cis*-1-(2-hydroxymethyl-4-cyclopentenyl)uracil and their 5/6-fluoro- and 5/6-chloro-derivatives,[16] some of them synthetized in our laboratory.[11] That study, performed with the Atoms in Molecules (AIM) theory[17,18] concluded that 5/6 halogenation on the base does not introduce any significant modification on the atomic and bond properties of the cyclopentene ring.[16] This fact points to a certain independence between the electronic properties of base and carbocycle. To test this hypothesis we have performed another AIM topological charge density study considering the five different cyclopentene rings (Fig. 1). One of the main objectives of this work is to describe how the position of the double bond modifies the charge electron distribution of the base.

2. Computational technique

The main conformational characteristics of carbonucleosides can be described by using three dihedral angles:

Keywords: 1,2-disubstituted-carbonucleosides; AIM theory; electronic structure; conformation.

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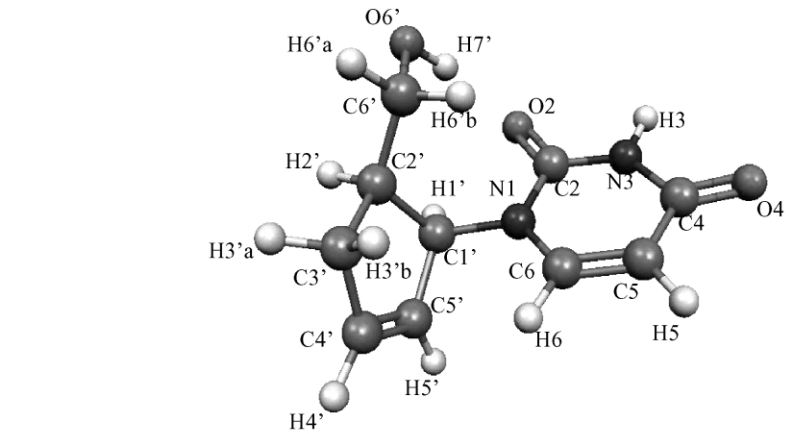
doi:10.1016/S0040-4020(03)00707-5



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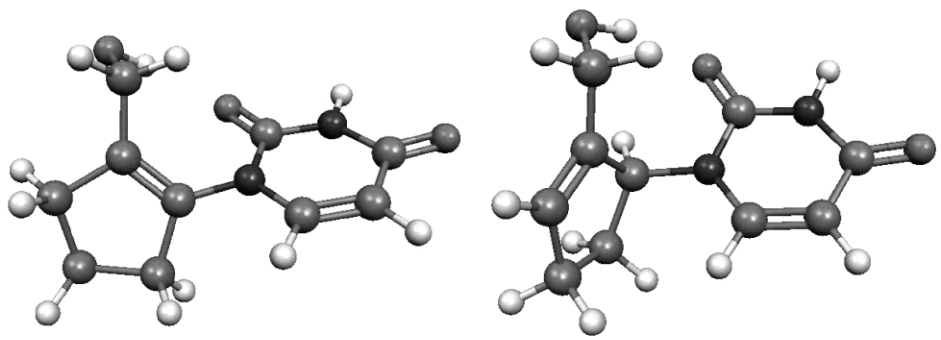

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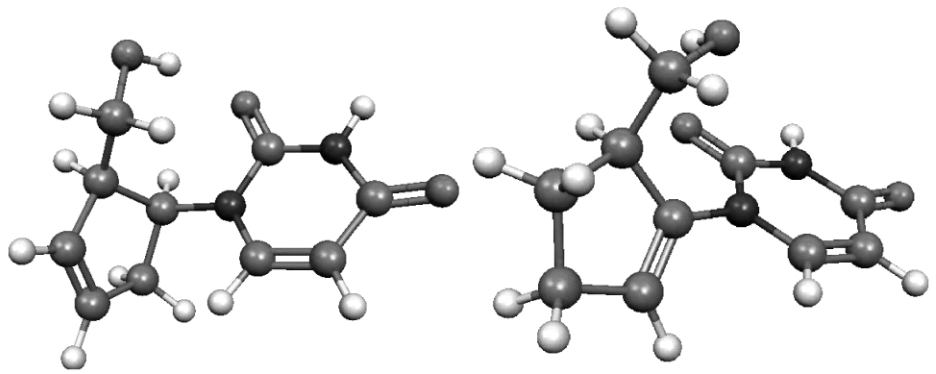

3 **5**

Figure 1. Nomenclature, structure numbering, and conformation for the compounds here studied. Molecular structures drawn with program Molekel[31,32] using the Gaussian optimized geometries.

C2′–C1′–N1–C2, ω_1, O6′–C6′–C2′–C3′, ω_2, and H7–O6′–C6′–C2′, ω_3, that respectively indicate the disposition around the glycosyl bond, and the orientation of the oxygen and hydrogen of the hydroxymethyl group.[19] Thus, the conformations can be named with an acronym obtained by joining capital letters denoting the approximate values of $\omega_1\omega_2\omega_3$ dihedral angles (G≈60°, M≈-60°, T≈180°, S≈90°, R≈-90°). Structure–activity studies on carbonucleosides have also paid important attention to the angle formed by the planes of the heterocylic base and 5-membered rings, ξ. Another important geometrical feature for a carbonucleoside is the conformation displayed by the cyclopentene ring, which is accounted by the Cremer–Pople parameters:[20] puckering amplitude, Q, and phase angle ϕ.

B3LYP/6-31++G**//B3LYP/6-31G* calculations were carried out by using the Gaussian98 package.[21] All the optimizations were performed on an initial RTM conformation of the *cis*-1-(2-hydroxymethyl-Δ^n-cyclopentenyl)-uracil (in what follows, the molecules are designated by a boldface number corresponding to the *n* locant of the double bond). This conformation was found as the most stable in the conformational analysis previously carried out for

molecule **4** at the HF level[16] and in another study that combined AM1 calculations and X ray diffraction.[7] It was also found as the most stable conformer in other pyrimidyl carbocyclic analogues of nucleosides.[22,23] The AIM atomic and bond properties were calculated by using the AIMPAC[24] and MORPHY[25,26] programs on the previously Gaussian-98 computed charge densities.

The AIM theory allows the calculation of atomic properties by integration of the proper density function within regions, Ω, bounded by a zero flux surface for the gradient of the charge vector field. Ω regions can be identified with molecular atoms. The discussion performed in this work is based on the values of: the electron atomic population of an atom, $N(\Omega)$, its energy $E(\Omega)$, the first moment of the charge density, $\mu(\Omega)$, volume, $v(\Omega)$, and the unitary Shannon entropy in the space of positions, $Sh(\Omega)$.

The AIM theory also defines major elements of molecular structure in terms of the properties of critical points in the electron density ρ. Along the path defined by the maximum electron density line (bondpath) connecting two bonded atoms there exists a critical point for the charge density, termed a bond critical point (BCP). Whenever a set of bonded atoms form a cycle, a ring critical point (RCP) appears as a topological consequence. Properties of interest at the BCPs are: the electronic charge density, ρ; the total energy density, H, and the laplacian of the charge density, $\nabla^2\rho$, the bond ellipticity, defined as $\varepsilon=(\lambda_1/\lambda_2-1)$, where λ_1 and λ_2 are, respectively, the largest and the smallest of the two curvatures of the charge density perpendicular to the bond path.

The virial ratio (defined as $\gamma=-V/T$, where V and T respectively refer to the potential energy and the electron kinetic molecular energy) always differs from 2 by less than 9.5×10^{-3}. The additivity errors obtained as the difference between a molecular property and the summation of their atomic counterparts [$N-\sum N(\Omega)$ or $E-\sum E(\omega)$] were always smaller (in absolute value) than 9.0×10^{-3} a.u. and 5.5 kJ mol^{-1}, respectively (Table 1). Also, all the atomic properties were obtained with absolute integrated values of the kinetic energy error,[17] $|L(\Omega)|$, lower than 2.6×10^{-3} a.u. All these data indicate that $N(\Omega)$ values can be considered reliable up to three figures and $E(\Omega)$ ones up to four.

3. Results and discussion

3.1. Molecular geometry and hydrogen bonds

Geometry optimizations of the same RTM initial conformation yielded very different geometries for the five molecules. In particular, molecules **1** and **5** present ξ values that are very different from those of the remaining compounds (Table 1). The cycle displays an envelope conformation in all the molecules, the largest distortion from this conformation corresponding to molecules **1**, where ϕ deviates 3.4° from a perfect envelope conformation, and **3** (with a ϕ distortion of 2.6°). Some meaningful distortions can also be observed for Q. Thus, **3** and **4** present the most puckered cycle, whereas the flattest ring corresponds to **2**.

Table 1 also contains the dihedral angles employed to describe main conformational features (ω_1, ω_2, and ω_3) and also the dihedral angle C4′–C2′–C1′–N1, Ω_4, that indicates the relative disposition of the cyclopentene substituents. The dihedral angle controlling the base disposition (Ω_1) displays important variations in **1** and **5**. That is, in those molecules where the double bond contains C1′. The orientation of O6′ is significantly affected in **2** and even more in **1**, whose conformer has to be named RMM according to the aforementioned nomenclature convention. This fact can be explained taking into account that the carbon bonded to the hydroxymethyl group is part of the double bond in **2** and **1**. The internal arrangement of the hydroxyl group only experiences important variations in **5**. In this case, the explanation is based on the specific hydrogen bond (HB) in which this hydrogen is involved (see below). ω_4 displays the variations that could be expected bearing in mind the diverse positions of the double bond. Thus, molecules **4** and **3** (where the double bond is placed far from both substituents) are the only ones with similar ω_4 values (Table 1).

There is a bondpath connecting H7′ and O2 in the five conformers. It corresponds to the HB between these atoms. The largest variations displayed by the properties of its BCP are found in **5**, where both the interatomic distance and the O6′–H7′···O2 angle point to a weaker strength (Table 2). Both the conformational distortion (especially noticeable

Table 1. Total molecular electronic energies, E, (in au), virial ratios, γ, errors obtained for the additivity of integrated atomic energies (in kJ mol^{-1}) and electron populations (in au), and main geometrical features: Q (in au), ϕ,[a] ξ, and dihedral angles, co$_i$ (in degrees)

	1	2	3	4	5
E	−723.5265	−723.5260	−723.5198	−723.5222	−723.5214
γ	2.00934	2.00932	2.00931	2.00931	2.00933
$E-\sum E(\Omega)$	−0.1	−4.8	−2.4	−2.6	−5.5
$N-\sum N(\Omega)$	0.002	0.006	0.005	0.005	0.009
ξ	58.7	104.6	96.7	97.5	46.3
Q	0.378	0.286	0.499	0.474	0.384
ϕ	104.6	−109.0	−146.6	−179.1	145.4
ω_1	−60	−95.7	−94.2	−91.4	−48.3
ω_2	−74.3	−130.6	−165.1	−162.9	−179.4
ω_3	−64.1	−73.2	−63.4	−63.2	37.7
ω_4	1.2	65.1	32.1	32.0	−44.6

ϕ (ϕ=0° corresponds to an envelope conformation where C2′ and the base are on the same side of the plane containing the other four atoms of the cycle. ϕ=−36° describes an envelope conformation where C3′ and the hydroxymethyl group are at opposite sides of the plane defined by the other atoms of the five member ring.), ξ, and dihedral angles, ω_i (in degrees).

Table 2. Geometrical, atomic, and BCP properties (in au, but R in Å and θ in degrees) for the hydrogen bonds found in the molecules here studied

Bond	X–H7′···O2, X=O6′					X–H2′···O2, X=C2′
	1	**2**	**3**	**4**	**5**	**5**
$10^3\rho(\mathbf{r})_{BCP}$	22.3	23.3	24.8	26.3	18.9	12.0
$10^3\nabla^2\rho(\mathbf{r})_{BCP}$	69.3	66.9	71.5	76.7	63.3	45.3
R (XH···O2)	1.992	1.980	1.950	1.921	2.111	2.517
10^3H($\mathbf{r}_c$)	−0.15	−0.51	−0.50	−0.41	0.28	1.52
θ (X–H···O2)	148.2	159.6	162.2	162.6	131.3	103.3
N(X)	9.118	9.132	9.144	9.146	9.136	5.916
N(H7′)	0.389	0.390	0.392	0.390	0.402	0.990
Sh(H7′)	1.949	1.922	1.926	1.910	2.020	2.908
N(O2)	9.228	9.224	9.222	9.222	9.227	9.227
$10^3\rho(\mathbf{r})_{RCP}$	8.9	7.8	6.5	6.5	8.4	11.7
$10^3[\rho(\mathbf{r})_{BCP}-\rho(\mathbf{r})_{RCP}]$	13.4	15.4	18.3	19.8	10.5	0.3
R (BCP−RCP)	0.986	0.980	1.059	1.070	1.501	0.326

for Ω_3) and the weakness of this bond can be related to the formation of a second HB between H2′ and O2, that is even weaker according to its C–H···O nature. Also worth remarking is the proximity between the BCP and RCP associated to this hydrogen bond, and the similarity of their charge densities, what again points to its feeble nature. This bond is also substantially weaker than other C–H···O bonds previously found in other conformers of **4**.[16]

3.2. Electronic properties

The analysis of the effects due to the position of the cyclopentene double bond on the electronic properties is done in three steps. First, we review the variations experienced by the most significant electron properties of the three main regions that can be considered in the carbonucleoside: cyclopentene ring, A, heterocyclic base, B, and hydroxymethyl group, C. Secondly, we describe the modifications displayed by the properties of every atom. Finally, we consider the variations shown by several bond properties.

The global charges of the three above detailed regions (Table 3) present very similar values in all the molecules, with significant opposite charges for the cyclopentene ring (positive) and the base (−0.50±0.02 a.u.). The negative charge on B explains why the iodonium cation formed with the double bond of the cyclopentene ring during the iodination of **4** with N-iodosuccinimide places exclusively the iodine atom and the base on the same face of the ring A.[27] The global charge of the C group only overpasses 0.03 a.u. in **1** and **2**, when it is bound to an sp^2 carbon atom of A.

Table 3. Net charge, q; energy, E; and unitary Shannon entropy, Sh, for the three zones in the molecule (see text). All the properties in au

	1	**2**	**3**	**4**	**5**
q(A)	0.463	0.435	0.476	0.474	0.515
q(B)	−0.528	−0.488	−0.491	−0.486	−0.509
q(C)	0.067	0.059	0.021	0.017	0.003
E(A)	−193.8377	−193.0780	−193.8377	−193.8489	−193.7982
E(B)	−414.5762	−414.5455	−414.5532	−414.5407	−414.5723
E(C)	−115.1127	−115.1043	−115.1298	−115.1335	−115.1530
Sh(A)	30.13	29.96	29.95	29.97	30.03
Sh(B)	27.42	27.38	27.35	27.38	27.41
Sh(C)	12.79	12.79	12.79	12.78	12.92

It can be observed that A, B, and C global charges in **3** and **4** are almost equal, and the same can be said about the remaining properties presented in Table 3. If we use **4** as reference compound, we see that: (a) ring A transfers charge to B and C in **5**; (b) C group transfers electron charge to A in **2**; and (c) The majority of the electron charge taken from C in **1** is transferred to B.

It can be observed that the variations experienced by the fragment energies along the series can be related with the corresponding variations shown by the electron population, if molecule 1 is excluded (Fig. 2). In 1, the spatial proximity between B and C groups enforced by the double bond gives rise to a specific behaviour.

Two of the Sh values shown in Table 3 are especially high. These are that of the C group in 5 and that of cycle A in 1. The first value can be explained because of the formation of an additional HB. In fact, Sh(H7′) value in 5 is 0.110 higher than in 4. The second value can be related to the position of the double bond in ring A. Thus, a big part (0.160) of the observed variation is due to C1′ and C2′ atoms.

The analysis of the atomic properties of the pyrimidyl ring indicates an extraordinary constancy along the series that is specially remarkable for $N(\Omega)$, $\mu(\Omega)$, $\nu(\Omega)$, and Sh(Ω). In

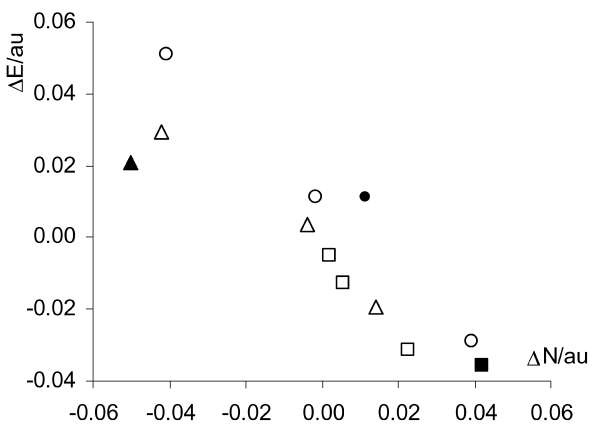

Figure 2. Plot of the relative energy, ΔE, vs the relative electron population, ΔN, (all values in au and referred to molecule **4**) for the diverse zones [(○) cyclopentene ring A, (□) pyrimidyl base B, (△) hydroxymethyl group C] of molecules here studied. The bold type symbols correspond to molecule **1** and open face ones to **2**–**4**.

fact the largest variations observed for atoms N3, C4, C5, H3, O4, and H5 do not overpass 0.006 a.u. for $N(\Omega)$, 0.01 a.u. for $\mu(\Omega)$, 0.7 a.u. for $\nu(\Omega)$, and 0.01 for Sh(Ω). $E(\Omega)$ display larger variations, mainly due to geometrical differences, but they never reach 12 kJ mol^{-1}. Small, but significant variations can be observed for H6 (limited by 0.01 a.u. for N(H6), 14.6 kJ mol^{-1} for E(H6), 1.1 a.u. for ν(H6) and 0.039 for Sh(H6)). They can be related to the different steric repulsions established between H6 and the cyclopentene ring along the series of molecules here studied. The atomic properties of O2 also display noticeable variations (up to 0.006 a.u. in N(O2), 42.5 kJ mol^{-1} in E(O2), 0.02 a.u. in μ(O2), and 1.4 a.u. in ν(O2)) in those molecules where the O2···H7′–O6′ HB experience the biggest distortions (2 and 5). Thus, the effect directly due to the position of the double bond only (and slightly) affects those atoms of the base that are α (N1) or β (C2 and C6) to the cyclopentene (Table 4). The only remarkable variation takes place at N1 when the double bond involves C1′ (molecules 1, and 5), whose electron population, contrary to what could be expected, is enlarged (almost 0.04 a.u.) when N1 is bonded to an sp^2 carbon.

The variations experienced by the atomic properties of the group C are generally negligible. The exception is Sh(H7′), whose variation exceeds 0.11 in the series, proving itself as a good HB estimator. For the remaining quantities, the largest variations take place in molecule **2** and do not overpass 0.02 a.u. for $N(\Omega)$ and $\mu(\Omega)$.

The atomic properties of the cyclopentene ring depend on the hibridization and on wether each atom is bonded (or not) to the B and C substituents. Thus, the 25 cyclopentenyl carbon atoms here studied can be divided into seven groups as is shown in the Sh(Ω)/$N(\Omega)$ diagram (Fig. 3). These kind of diagram was also successfully employed to achieve a detailed classification of carbon and hydrogen atoms in

Table 4. Main atomic properties with significant variations in zones B and C of molecules **1**–**5**. Absolute values for **4** in au. The remaining values (all in au but E in kJ mol^{-1}) are relatives to those in **4**

Atom	Quantity	**4**	**1**	**2**	**3**	**5**
C6′	$N(\Omega)$	5.414	0.001	0.001	0.002	0.013
	$E(\Omega)$	−37.6899	−23.0	0.8	−0.8	−30.9
	$\mu(\Omega)$	0.56	−0.019	−0.015	0.003	−0.001
	$\nu(\Omega)$	45.674	0.5	1.1	0.3	0.5
	Sh(Ω)	2.235	0.000	0.003	0.002	0.007
N1	$N(\Omega)$	8.191	0.039	0.006	0.006	0.038
	$E(\Omega)$	−55.4745	−74.4	−40.1	−19.4	−101.0
	$\mu(\Omega)$	0.17	−0.070	−0.011	−0.013	−0.078
	$\nu(\Omega)$	72.083	1.7	0.4	−1.3	0.7
	Sh(Ω)	2.778	0.010	0.001	−0.002	0.006
C2	$N(\Omega)$	4.136	0.003	0.001	0.000	−0.017
	$E(\Omega)$	−36.9120	23.8	8.1	−0.3	45.5
	$\mu(\Omega)$	0.254	0.020	0.003	0.000	0.003
	$\nu(\Omega)$	29.28	0.2	0.2	−0.1	−0.6
	Sh(Ω)	1.472	0.005	0.001	−0.001	−0.013
C6	$N(\Omega)$	5.566	0.004	−0.009	0.000	0.005
	$E(\Omega)$	−37.8275	−9.0	15.0	−3.8	−12.4
	$\mu(\Omega)$	0.694	−0.020	−0.008	−0.009	−0.015
	$\nu(\Omega)$	61.975	−0.2	−0.6	−0.1	−0.3
	Sh(Ω)	2.365	0.003	−0.004	−0.002	0.003

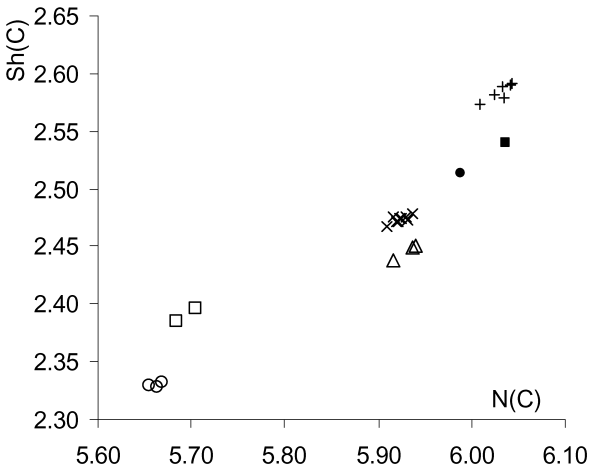

Figure 3. Sh(C) vs N(C) (in au) representation for the carbon atoms of the 5-membered ring of molecules **1**–**5**. (○) C3 sp^3, (□) C3 sp^2, (△) C1 sp^3, (●) C1 sp^2 in **1**, (■) C1 sp^2 in **2**, (×) C sp^3 not bonded to any substituent, (+) C sp^2 not bonded to any substituent.

n-alkanes.[28] The same classification is supported by the remaining atomic properties here considered.

It has to be stressed that $\rho(\mathbf{r})$ variations are the BCPs linearly correlated with those of H($\mathbf{r}$) and the bond length, R, (r^2 coefficients are respectively: 0.97 and 0.94) for every zone of the molecule. The same is true for $\nabla^2\rho(\mathbf{r})$ when the C═O bonds are excluded because of their previously reported specific character.[1,29,30] Thus, the study of BCP properties can be reduced to that of $\rho(\mathbf{r})$ and ε.

Confirming the trends that were observed for atomic properties, the largest modifications displayed by the BCP properties of the heterocycle correspond to the C1′–N1 bond. They take place in molecules **1** and **5**, where the strength of this bond is reinforced (Table 5). Smaller modifications (with regard to **4**) are also observed in molecule **3**. There is also a remarkable constancy in the BCP properties of the cyclopentene double bond, ε being the exception for **1** and **5** (Table 6).

4. Conclusions

The reported study allows us to conclude that changes in the position of the double bond within the cyclopentene ring only affect the electron distribution of the heterocycle in N1. In fact the electron population of this atom is enlarged when it is bonded to the cyclopentene ring by an sp^2 carbon. Nevertheless, only molecules **3** and **4** display similar geometries. Thus, both the base and the hydroxylic H are

Table 5. Main bond properties for the C1′–N1 bond. Absolute values for **1** and relative to them for the remaining molecules. All values in au, but R in Å

C1′–N1	$\rho(\mathbf{r}_c)$	$\nabla^2\rho(\mathbf{r}_c)$	R, (Å)	ε	$H(\mathbf{r}_c)$
4	0.2358	−0.5723	1.499	0.038	−0.2691
1	0.0327	−0.1595	−0.063	0.005	−0.1030
2	0.0025	−0.0154	−0.005	0.005	−0.0098
3	0.0063	−0.0434	−0.011	0.001	−0.0201
5	0.0372	−0.2034	−0.067	0.014	−0.1087

Table 6. Main bond properties for the double bond. Absolute values for **1** and relative to them for the remaining molecules. All values in au, but R in Å

	$\rho(\mathbf{r}_c)$	$\nabla^2\rho(\mathbf{r}_c)$	R' (Å)	ε	$H(\mathbf{r}_c)$
4 (C4′=C5′)	0.3467	−1.0026	1.337	0.3687	−0.3884
1 (C1′=C2′)	−0.0019	0.0196	0.003	0.0508	0.0027
2 (C2′=C3′)	−0.0013	0.0165	0.001	0.0038	0.0028
3 (C3′=C4′)	0.0001	0.0012	−0.001	−0.0031	−0.0004
5 (C5′=C1′)	−0.0006	0.0065	0.002	0.0504	−0.0007

rotated in **5** with regard to **4** and the angle between the planes varies to 46.3°. In **2** the hydroxymethyl group is rotated and the cyclopentene ring becomes flatter than in **4**. Finally, the orientation of the base and the hydroxymethyl group is changed and the angle between planes is then reduced to 58.7° in **1**. The cyclopentene ring keeps an almost perfect envelope conformation in all the molecules.

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