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Conformational study and electron density analysis of 9-[tetrahydropyran-3-yl]purine derivatives

Laura Estévez,[a,b] María J. González Moa,[b] Carmen Terán[a] and Ricardo A. Mosquera[b,*]

[a]*Department of Organic Chemistry, Universidade de Vigo, Lagoas-Marcosende s/n, 36310-Vigo, Galicia, Spain*
[b]*Department of Physical Chemistry, Universidade de Vigo, Lagoas-Marcosende s/n, 36310-Vigo, Galicia, Spain*

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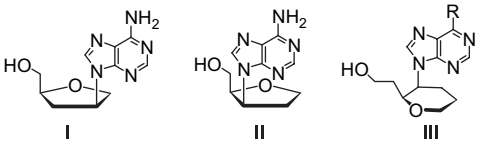
Abstract—A conformational analysis was carried out on *cis*-6-chloro-9-[2-(2-hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]purine and several related model compounds at the HF/6-31++G(d,p) and B3LYP/6-311++G(2d,2p) levels, and also using the semiempirical methods AM1 and PM3. The result of this analysis shows that the molecule prefers an axial disposition of the purine ring, with an approximate cis orientation of C4–N9–C1′–H1′ dihedral angle. The stability of this conformation comes mainly from the formation of a C–H···O···H–O intramolecular three-center hydrogen bond. In this structure, the tetrahydropyran oxygen acts as an acceptor, while both H8 of the purine ring and the hydroxylic hydrogen of the hydroxyethyl group act as donors. Also, the equatorial disposition of the hydroxyethyl group in this conformer reduces its repulsions with the purine ring and the tetrahydropyran hydrogens. The quantum theory of atoms in molecules was applied to study the electronic effects produced by the conformational changes, bonding between tetrahydropyran and purine rings, chlorine substitution, and intramolecular hydrogen bonding.

1. Introduction

A number of nucleoside analogs containing significantly altered carbohydrate moieties posses antiviral or anticancer properties.[1] Modification of the sugar part of nucleosides has led to the development of several derivatives including dideoxynucleosides, carbocyclic nucleosides, acyclic nucleosides, and isonucleosides. These modifications are often associated with increased stability,[1] decreased toxicity,[2] together with target specificity.[1] In isonucleosides the heterocyclic base is linked to C2′ or C3′ of the sugar moiety. The change in the position in the sugar-base bond keeps the spatial arrangement between the base and the 5′-hydroxyl group, while the glycosidic bond is more stable toward enzymatic hydrolysis.[1] A number of isonucleosides showed interesting biological activities.[3] For example, 2′-isodideoxynucleosides like isoddA (**I**) (Scheme 1) are potent anti-HIV agents that act by inhibiting the enzyme reverse transcriptase.[4] Nevertheless, the 3′-isodideoxynucleoside analog 3′-isoddA (**II**) (Scheme 1) has a low level of activity.[5] Thus, some of the structural factors that modify the activity are the distance between the base and the 5′ hydroxyl group, the electronic effects of the oxygen of the ring, and the lack of a hydroxyl group at 3′.[6]



Scheme 1.

Some modified nucleosides with the hydroxymethyl group and the heterocyclic base bonded to contiguous positions of a carbocycle were described in the last years.[7–10] Several of these carbocyclic analogs have exhibited significant and selective antitumoral[9] or antiviral activity, in particular against HIV.[10] Looking for new active compounds, the isodideoxynucleosides of structure **III** (Scheme 1) have also attracted the attention.[11] These derivatives are analogs of 3′-isoddA where tetrahydropyran (THP) replaces tetrahydrofuran and a methylene group enlarges the side chain transforming it into a hydroxyethyl group. This keeps the base and hydroxyl separated by four carbons like in natural nucleosides.

The importance of conformational and electronic factors in activity and function of nucleoside analogs has promoted the interest on their structural studies. Thus, their conformation has been reviewed with some detail.[12–15] Nevertheless, the size of these systems has motivated that the most of the structural studies carried out on them have used semiempirical or molecular mechanics methods exclusively.

Keywords: Purine; Nucleosides; Intramolecular hydrogen bond; Atoms in molecular theory.
* Corresponding author. E-mail: mosquera@uvigo.es

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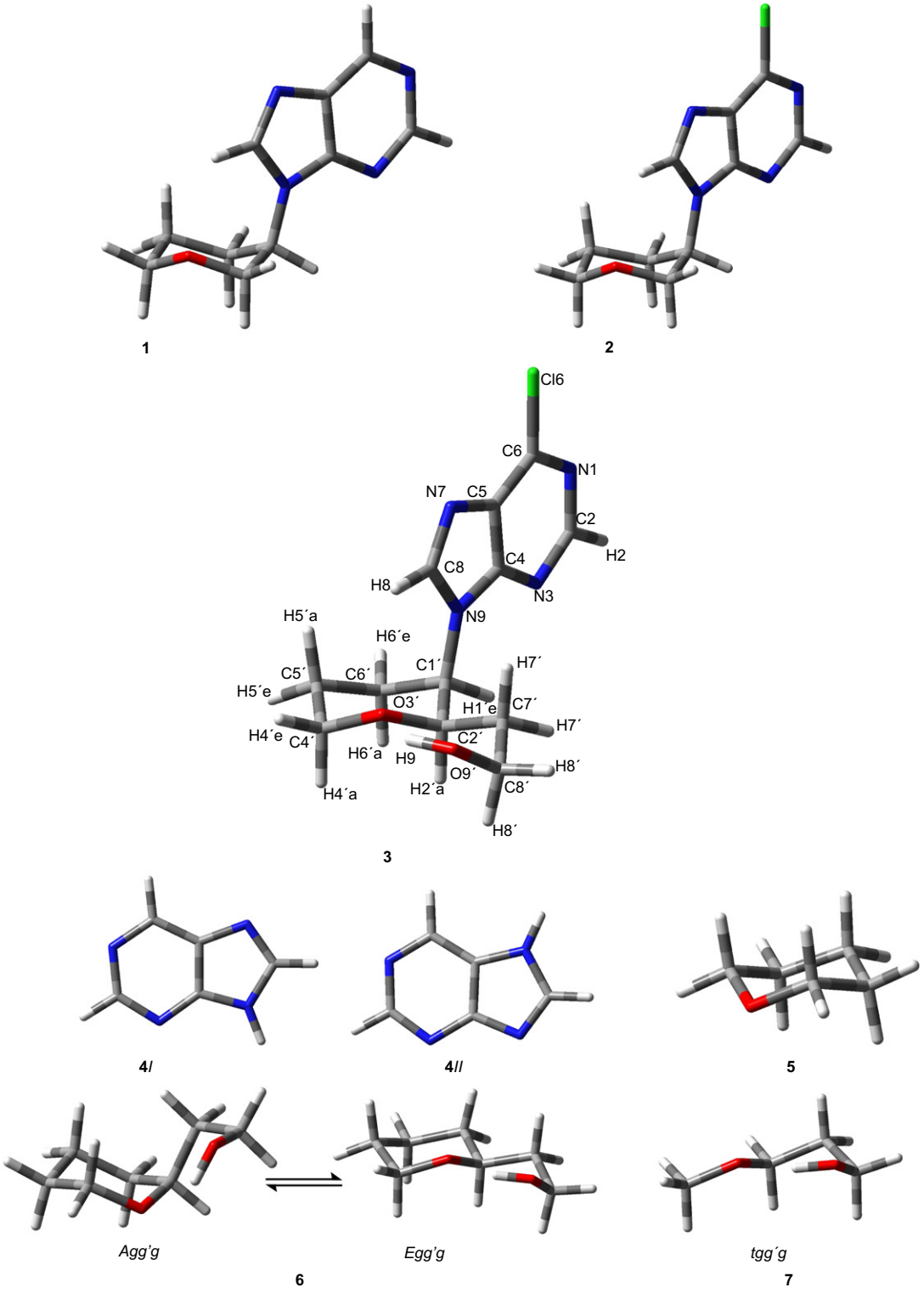

Figure 1. Molecules studied in this work, **1**–**7**.

In this work, we present a detailed conformational analysis for one of these analogs, *cis*-6-chloro-9-[2-(2-hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]purine, complemented by a topological electron density study oriented to detect both the electronic effects due to conformational change and those arising from the introduction of chlorine and hydroxyethyl groups and joining purine and THP rings. To evaluate all these facts we have made use of several model compounds that are structurally related to the nucleoside analog.

In previous papers,[16,17] we have presented the results of HF/6-31++G(d)//HF/6-31G(d) and B3LYP/6-31++G(d,p)//B3LYP/6-31G(d) studies on pyrimidyl carbocyclic analogs of nucleosides based on cyclopentenes. Those results pointed

to certain independence between the electronic properties of the base and the carbocycle. Thus, halogenations of the base[16] and modifications of the carbocycle structure[17] were found to introduce significant conformational effects, although the effects on the electron density were confined to a small part of the corresponding cycle. This paper also aims to test whether the relative independence of the electron distributions of both rings also holds between purine and oxygenated rings.

2. Computational details

Molecules **1** and **2** (Fig. 1) were studied at the HF/6-31++G(d,p) and B3LYP/6-311++G(2d,2p) 6d levels. Due to the size of the system and the high coincidence in the results for both molecules at the two levels of calculation, molecules **3**, **6**, and **7** only were calculated using the HF level. Finally, for model molecules **4** and **5** only B3LYP was used.

Internal rotation around the bond connecting tetrahydropyran (THP) and purine rings in molecules **1** and **2**, N9–C1′, was studied. Therefore, AM1 and PM3 restricted optimizations were performed fixing the C4–N9–C1′–H1′ dihedral angle from 0 to 360° in increments of 10° (Fig. 2) for axial (*A*) and equatorial (*E*) dispositions of the purine ring. Three main conformers were found for both compounds: *AC*, *EC*, and *ET*, where the second letter refers to the approximate cis (*C*) or trans (*T*) geometry of the C4–N9–C1′–H1′ dihedral angle (Fig. 3). Subsequent HF and B3LYP complete optimizations were performed using these minima as starting geometries.

Analogously, rotation around the N9–C1′ bond in molecule **3** was studied using the AM1 method, considering both axial (*AC*) and equatorial (*EC* and *ET*) conformations for the purine ring. In this case, the hydroxyethyl chain was placed in the unique initial conformation that allows the formation of an intramolecular hydrogen bond (IHB) between H9′ and O3′. The O3′–C2′–C7′–C8′, C2′–C7′–C8′–O9′ and C7′–C8′–O9′–H9′ dihedral angles of this conformation display values that are close to 60, −60, and 60°, respectively. The stationary points localized in this semiempirical study were optimized at the HF level. Also, initial conformations with no possibility of IHB between H9′ and O3′ were optimized as references. The nomenclature of the conformers include the dihedral angles listed above using *g*, *g*′, and *t* letters to represent the values of these dihedral angles close to 60, −60, and 180°, respectively.

A quantum theory of atoms in molecules (QTAIM)[18,19] analysis was carried out on the HF and B3LYP electron densities obtained with Gaussian 98 program,[20] using the AIMPAC package of programs.[21,22] To establish the conclusions of this work the following properties were analyzed for each atom, Ω: electron population, $N(\Omega)$, atomic energy, $E(\Omega)$, dipolar moment, $\mu(\Omega)$, and Shannon entropy of the

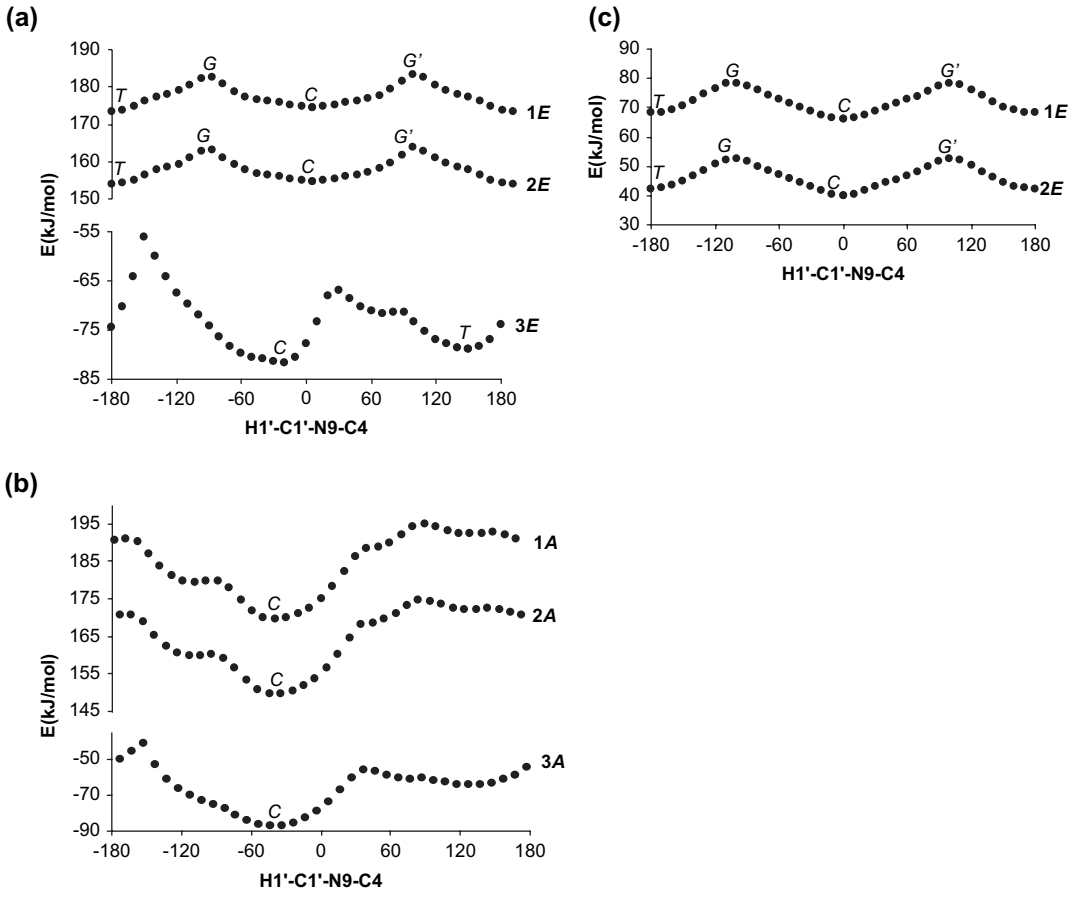

Figure 2. Representation of the AM1 molecular potential energy for molecules **1**–**3** in equatorial (a) and axial (b) dispositions of the purine ring and representation of the PM3 molecular potential for **1** and **2** (c).

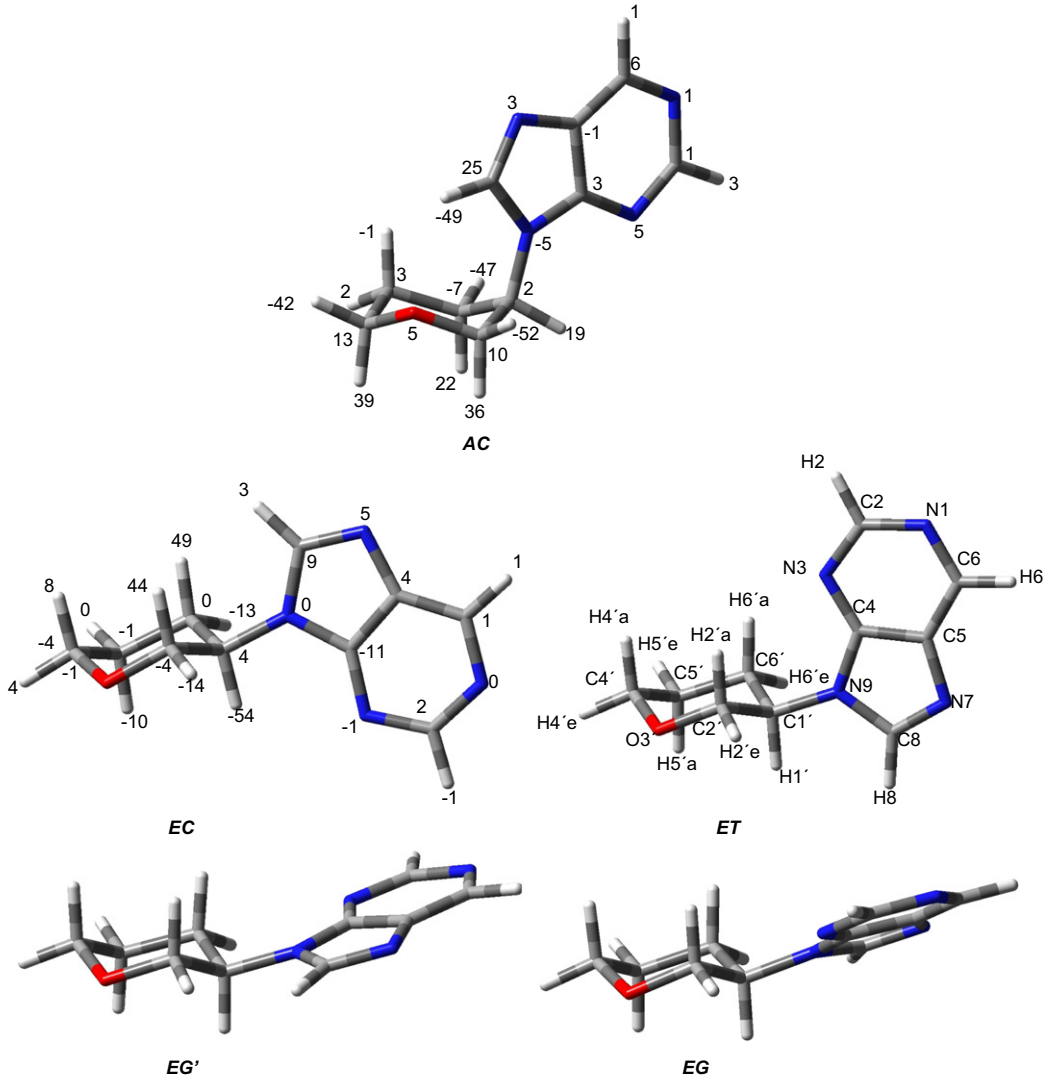

Figure 3. Structure and numbering of the conformers (*AC*, *EC*, and *ET*) and TS (*EG′* and *EG*) of molecule **1**. In *AC* $N(\Omega)$ variations are shown (in a.u. and multiplied by 10^3) with respect to *EC*. In *EC* those variations with respect to *ET* are shown.

electron distribution, Sh(Ω).[23–25] For each bond we looked at the internuclear distance, R, as well as the following bond critical point properties (BCP): ellipticity, ε, electron density, ρ_c, its Laplacian, $\nabla^2\rho_c$, and the value of the total energy density function, H_c.[26]

No atom was integrated with absolute values of $L(\Omega)$ higher than 2.6×10^{-3} a.u. The absolute value of the difference between the total electron population and the summation of $N(\Omega)$ was never higher than 1.2×10^{-2} a.u. The corresponding quantity for the energy was never higher than 8 kJ mol^{-1}.

3. Results and discussion

3.1. Conformational analysis of 1 and 2

Two main conformational equilibriums must be considered for these compounds: (i) the one due to the rotation around the N9–C1′ bond (equilibrium $ET \leftrightarrow EC$); and (ii) the one associated with the THP ring inversion (equilibrium $EC \leftrightarrow AC$).

AM1 and PM3 restricted optimizations along the N9–C1′ internal rotation of molecule **1** with equatorial purine (Fig. 2) indicate the presence of two conformers that differ in the cis (*EC* conformer) or trans (*ET* conformer) disposition of the C4–N9–C1′–H1′ unity. According to HF and B3LYP calculations, both conformers are practically isoenergetic (Table 1). They interconvert through two transition states (TS) (*EG* and *EG′* in Fig. 3) with internal rotational barriers, $\Delta E^{\#}$, lower than 6 kcal mol^{-1} (Table 1), which suggests a free rotation around the N9–C1′ bond. ΔE and $\Delta E^{\#}$ values almost do not change with the calculation level if we exclude that PM3 favors the *EC* over the *ET* conformer, preferred at the other computational levels (Fig. 2 and Table 1).

Rotation around the same bond, N9–C1′, with the purine in axial disposition indicates that there is a main minimum with distorted cis conformation (*AC*), which allows the formation of an IHB between H8 and O3′. Also, this study indicates the presence of other higher energy minima (from 10 to 25 kJ mol^{-1}) with no IHB. In this case, the rotational barrier is slightly higher (25 kJ mol^{-1}) because of H8···O3′ IHB breaking. Although the AM1 study shows a preference for

Table 1. Relative energies (in kJ mol^{-1}) of the conformers and TS of molecules[a–f] **1–7**

		ΔE^{AM1}	ΔE^{PM3}	ΔE^{HF}	ΔE^{B3LYP}
1	*AC*	0.0	0.0	0.0	0.0
1	*EC*	4.8	−0.4	1.0	0.4
1	*ET*	3.9	2.0	−0.2	0.0
1	*EG*	13.4	12.2	19.0	16.3
1	*EG′*	14.0	12.3	20.5	17.3
2	*AC*	0.0	0.0	0.0	0.0
2	*EC*	4.9	−0.3	1.4	0.7
2	*ET*	4.0	2.1	0.6	0.5
2	*EG*	13.5	12.3	19.6	
2	*EM*	14.1	12.4	21.4	17.9
3	*ACgg′g*	0.0	0.0	0.0	
3	*ACttt*	13.5	9.2	9.2	
3	*ECgg′g*	5.7	−1.6	14.2	
3	*ETgg′g*	8.4	4.2	18.3	
3	*ECgtg*	12.7	0.6	22.8	
3	*ECgg′t*	18.6	−1.0	24.6	
3	*ETgg′t*	22.3	4.2	28.9	
3	*ECgg′g′*	10.8	0.1	31.4	
4	*I*				0.0
4	*II*				15.3
6	*Egg′g*			0.0	
6	*Agg′g*			15.9	
7	*tgg′g*			0.0	0.0
7	*ggg′g*			7.6	4.9
7	*tttt*			10.6	10.2
7	*ggg′t*			22.8	20.5
7	*ggg′g′*			28.5	24.4

Absolute electron energy of **5** is −271.86381 a.u. (B3LYP/6-311++G(2d,2p)).

[a] Absolute electron energies of conformer *AC* of **1** is −678.36583 a.u. (HF/6-31++G(d,p)) and −682.72820 a.u. (B3LYP/6-311++G(2d,2p)).

[b] Absolute electron energies of conformer *AC* of **2** is −1137.26302 a.u. (HF/6-31++G(d,p)) and −1142.35547 a.u. (B3LYP/6-311++G(2d,2p)).

[c] Absolute electron energies of conformer *ACgg′g* of **3** is −1290.20036 a.u. (HF/6-31++G(d,p)).

[d] Absolute electron energies of **4***I* is −412.07395 a.u. (B3LYP/6-311++G(2d,2p)).

[e] Absolute electron energies of **6***Egg′g* is −422.97931 a.u. (HF/6-31++G(d,p)).

[f] Absolute electron energies of the conformer *tgg′g* of **7** is −307.01977 a.u. (HF/6-31++G(d,p)) and −308.98749 a.u. (B3LYP/6-311++G(2d,2p)).

the axial conformer (*AC*) over the equatorial ones, HF and B3LYP calculations indicate that the three main conformers (*AC*, *EC*, and *ET*) display energies that do not differ by more than 1 kJ mol^{-1} (Table 1).

The conformational behavior detailed for **1** remains unchanged when a chlorine atom replaces the hydrogen attached to position 6 of the purine ring (molecule **2**). Thus, the same conformers and TS are obtained with no significant changes in the main dihedral angles (variations are smaller than 0.2°). Also, no important variations are observed in the values of ΔE and $\Delta E^{\#}$ (Table 1 and Fig. 2).

3.2. Electronic effects of conformational changes

The QTAIM study of **1** indicates that the *ET*↔*EC* conformational equilibrium does not modify the bond properties, finding that 0.019 is the highest difference for ε, 0.0061 a.u. for ρ_c, 0.0558 a.u. for $\nabla^2\rho_c$, 0.0112 a.u. for H_c, and 0.009 a.u. for *R*. However, the *ET* conformer displays two BCPs between atoms that are not connected in the Lewis structure and that are not present in *EC*. The corresponding 'bond paths' to these BCPs connect N3 with the H2′a and H6′a axial hydrogens (Fig. 4), and their bond properties correspond to weak interactions between closed shells. Thus, ρ_c values are between 6.7×10^{-3} and 7.9×10^{-3} a.u. for the two bond paths at HF and B3LYP levels and the values obtained for H_c in the same conditions go from 9.7×10^{-4} to 10.9×10^{-4} a.u.

In general, atomic properties do not suffer important variations with the conformational change. However, there are significant changes in the H2′a and H6′a THP hydrogens, connected to N3 through the described critical points. These atoms experience the highest reduction in the repulsions when the *ET* conformer (with distances of 2.76 and 2.69 Å, respectively, from H2′ and H6′ to N3) transforms into *EC* (where the comparable distances are, respectively, 2.67 and 2.46 Å, but to H8). The QTAIM populations reflect this situation showing variations of 0.044 and 0.049 a.u. in $N(\Omega)$ (Fig. 3). Another exception corresponds to H1′, whose electron population is 0.054 a.u. smaller in *EC* than in *ET*, as a consequence of the higher repulsions with the 'nonbonded charge concentration' (NBCC) that represents the lone pair of N3 (whose maximum for $-\nabla^2\rho(\mathbf{r})$ is located at 2.36 Å of H1′) compared to the H1′–H8 repulsions in *ET* (with the same interatomic distance of 2.36 Å). It can be signaled that during the internal rotation, the total electron population of each ring is nearly constant (0.002 a.u.).

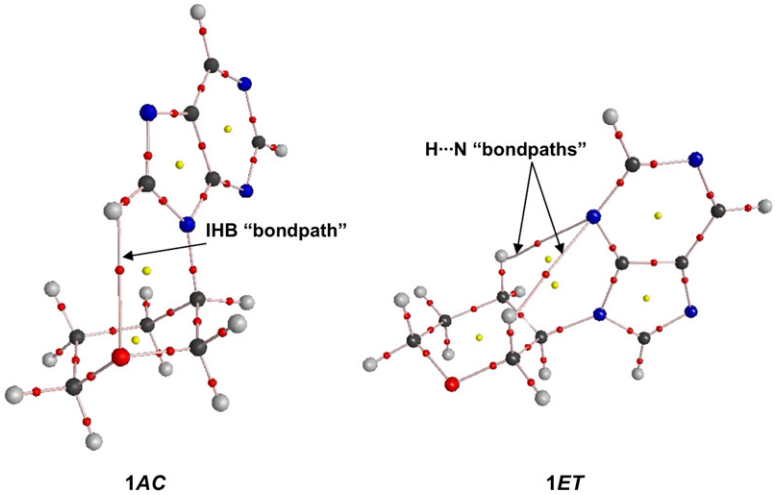

Figure 4. Bond (red) and ring (yellow) critical points in *AC* and *ET* conformers in molecule **1**.[42]

The comparison of the bond properties of *EC* and *AC* shows that the THP ring inversion gives rise to a higher number of modifications than the rotation around N9–C1′. However, they are never higher than 0.057 for ε, 0.0087 a.u. for ρ_c, 0.0836 a.u. for $\nabla^2\rho_c$, 0.0173 a.u. for H_c, and 0.018 a.u. for R. The most noticeable variations are located in N9–C1′ bond and C1′–C bonds of the THP ring. The *AC* conformer presents a BCP and a 'bond path' that can be associated with the H8···O3′ IHB (Fig. 4). In fact, the properties of this BCP display the typical characteristics of hydrogen bonds[27] (ρ_c=0.0117 a.u., $\nabla^2\rho_c$,=0.0453 a.u., H_c=0.0011 a.u., and R=2.342 Å using the HF density of molecule **1** and ρ_c= 0.0115 a.u., $\nabla^2\rho_c$=0.0398 a.u., H_c=0.0013 a.u., R=2.446 Å using the corresponding B3LYP density).

The largest variations experienced by $N(\Omega)$ in the $EC \leftrightarrow AC$ interconversion correspond to hydrogens bonded to C2′, C4′, and C6′ (Fig. 3). It has to be remarked that these hydrogens gain electron density during axial disposition and lose it when they are in equatorial. This fact can be explained by considering the anomeric interactions[28] with O3′ (for hydrogens at C2′ and C4′) and the repulsions with the purine base experienced by the equatorial H6′ in *EC*.

In addition, it is noticeable that the reduction in the population is experienced by H8 when forming the IHB in *AC* (−0.049 a.u.). It can be considered that this population is shared by the purine ring (that receives 0.042 a.u., 0.025 a.u. corresponding to C8) and the THP ring, where the population of O3′ is increased in 0.005 a.u.

The QTAIM analysis of molecule **2** reveals 'bond paths' between N3 and the H2′a and H6′a THP axial hydrogens in the *ET* conformer, and the H8···O3′ IHB 'bond path' in *AC*. As an example of the local character of the effects due to the 6-chlorine substitution, it can be said that the BCP properties of this IHB are the same as the ones in the *AC* conformer of molecule **1**. Again, the only noticeable variations of $N(\Omega)$ between *EC* and *ET* correspond to the hydrogens, that suffer the highest variation of repulsions with the purine ring on going from one conformer to another (−0.053, 0.042, and 0.047 a.u. for H1′, H2′a, and H6′a, respectively). Similarly, the variations of $N(\Omega)$ from *EC* to *AC* follow the trend already indicated for molecule **1**. This behavior continues when B3LYP electron density is used, as it also happens in **1**. In fact, Figure 5 shows the good correlation that exists between the HF and B3LYP descriptions for the variations of the electron population. The straight line in Figure 5 represents $\Delta N^{HF}(\Omega)=\Delta N^{B3LYP}(\Omega)$ case. It can be observed that the main discrepancies from this ideal line are found in the hydrogen atoms involved in the 'bond paths' previously indicated and in H1′.

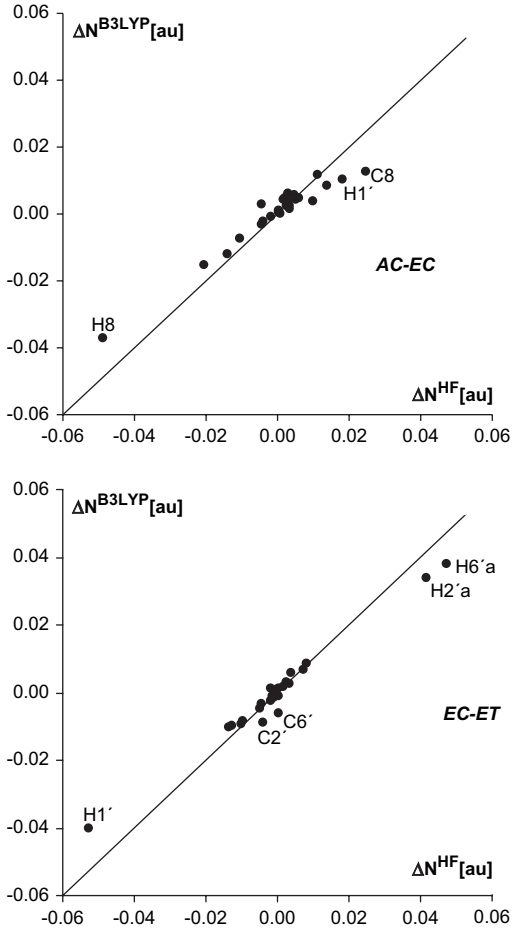

Figure 5. HF versus B3LYP electron population variations due to the conformational changes *AC*–*EC* and *EC*–*ET* in molecule **2**. Plotted line represents the $\Delta N^{B3LYP}=\Delta N^{HF}$ ideal case.

3.3. Purine-9*H*/7*H* tautomery

Purine, **4**, presents a tautomeric equilibrium between N9H and N7H forms (named in this work, respectively, as **4***I* and **4***II*) (Fig. 1). This equilibrium is displaced toward the former, in purine[29–34] as well as in several purine derivatives.[35,36] B3LYP calculations done in this work assign higher stability to form *I* (15.3 kJ mol^{-1}), which agrees with the result obtained at HF/6-31++G(d,p) level (15.9 kJ mol^{-1}).[29] In the case of 6-chloropurine it was observed that the reactions mainly give rise to N9-substitution.[11] In agreement with the B3LYP study, *I* form of the 6-chloropurine is also more stable than *II*, in 8.3 kJ mol^{-1}.

The tautomeric hydrogen presents a high positive charge on *I* and *II* (atomic electron population does not reach 0.6 a.u.). The atoms that suffer the highest variation in their atomic properties between tautomers are those bonded to the tautomeric hydrogen and N3, C4, C5, and C6 (Supplementary data). This behavior is practically kept in 6-chloropurine. Bond properties (Supplementary data) indicate the change in the position of the five-membered ring double bond, when forms *I* and *II* are compared. However, N(N7) is higher for a formally single N7–C8 bond than for the formally double one.

3.4. Effect of the base on the oxacycle

This effect was studied by comparing the properties of compound **1** with those of isolated THP (**5**) (Table 2). In all the conformers, the main variations in the atomic properties (Table 2) occur in the carbon bonded to the purine (C1′). Also, there are significant changes in the properties of H2′a and H6′a axial hydrogens when purine is equatorial, and in the properties of H1′ when purine is axial. In general, the THP cycle gives 0.435 a.u. of electron population to the

Table 2. Electron population variations (in a.u. and multiplied by 10^3) experienced by the atoms of the tetrahydropyran and purine rings with the formation of molecule **1**

THP	ΔN^{1ET}	ΔN^{1AC}	Purine	ΔN^{1ET}	ΔN^{1AC}
C1′	−278	−265	N1	2	2
C2′	−6	−4	C2	1	4
O3′	−1	2	N3	8	12
C4′	9	13	C4	29	21
C5′	1	3	C5	−5	−2
C6′	12	5	C6	3	10
H1′	−27	−60	N7	11	19
H2′a	−42	−22	C8	16	52
H2′e	−11	−19	N9	−28	−33
H4′a	−14	−9	H2	4	6
H4′e	−8	−11	H6	2	4
H5′a	−3	−9	H8	8	−38
H5′e	−13	−19			
H6′a	−45	−17			
H6′e	−12	−30			

Variations calculated, respectively, as **1**–**5** and **1**–**4***I*.

Table 3. Atomic electron population variations due to the chlorine substitution

Atom	*AC*	*EC*	*ET*	*ET*[a]
N1	−5	−4	−4	−6
C2	−20	−21	−20	−8
N3	−4	−2	−1	−1
C4	−4	−3	−4	−14
C5	−39	−40	−39	−69
C6	−87	−88	−87	−79
N7	−16	−17	−17	−19
C8	−1	−4	−4	0
N9	−1	−1	−1	−1
H2	−9	−9	−9	−12
H8	−4	−4	−4	−6
$\Sigma_{purine}\ \Omega$[b]	−189	−194	−192	−216
C1′	3	3	4	7
$\Sigma_{THP}\ \Omega$[c]	2	−8	−11	−9

All the values in a.u., multiplied by 10^3 and calculated from the B3LYP/6-311++G(2d,2p) electron density. Variations calculated as **2**–**1** for *AC*, *EC*, and *ET* conformers.
[a] HF/6-31++G(d,p).
[b] Total variation in the purine ring (excluded Cl6 and H6).
[c] Total variation in the tetrahydropyran ring (C1′ included).

purine according to B3LYP electron densities, which is less than the electron density transferred from cyclopentene to uracil in diverse carbonucleosides (0.50±0.02 a.u.).[17] This electron transference destabilizes the THP ring more than 640 kJ mol^{-1}. The oxacycle also increases its polarization, almost exclusively due to the atomic dipole moment of C1′ (+0.38 a.u.). Bond properties (Supplementary data) indicate that the only noticeable variations happen in the C–H axial bonds that are closer to the purine (C1′–H1′a, C2′–H2′a and C6′–H6′a), which are very slightly reinforced.

3.5. Effect of the oxacycle on the base

Bonding to THP increases the electron population of the purine residue, which already presented a partial negative charge due to the reduced electron population of the tautomeric hydrogen (Section 3.3). So, the summation of the electron populations is increased around 0.05 a.u. in all the conformers with respect to the isolated base, **4***I*, according to B3LYP electron densities. This quantity increases to 0.12 a.u. if we use HF electron densities. Stabilizations of 340 and 345 kJ mol^{-1} in **1***ET* and **1***AC*, respectively, were also found using B3LYP densities. These changes occur by decreasing *N*(N9) and increasing *N*(C4) and *N*(C8) in both equatorial and axial conformers of **1**. In *AC* there is also a notable decrease in the electron population of H8, since it is involved in an IHB (Table 2).

Bond properties of the base are almost not modified. In fact, the maximum variation of ρ in the BCPs of **4** and their equivalents in **1***ET* is not superior to 3.3×10^{-3} a.u. and to 0.02, 1.8×10^{-2} a.u., 1.3×10^{-2} a.u., and 0.01 a.u. for ε, $\nabla^2\rho_c$, H_c, and R, respectively. These margins of variation are practically not modified when **4** and **1***AC* are compared.

3.6. Effect of chlorination of the base

Globally, substitution of H6 by Cl6 removes 0.20 a.u. of electron density from rest of the compound (0.22 a.u. from the HF/6-31++G** study). The variation in the atomic properties (Table 3) leads to conclude that 6-chlorination of the purine only affects in a significant way the atoms located closer than four bonds from the chlorine atom. Also, the effect is more important on the carbon atoms (Supplementary data). Only the variation of μ(N1) is comparable to the one experienced by those carbons. On the contrary, the electron population variation is always considerably inferior in the nitrogen atoms, what is consistent with its character of better attractors for the electron density and with what it was found in previous studies of heterocycles.[37,38]

The effect on the electron density (both on the population, $\Delta N(\Omega)$, and on the distribution, $\Delta\mathrm{Sh}(\Omega)$) of the THP ring is very slight and it is concentrated on C1′, even more affected than some of the purine ring atoms (N3 and N9). However, this ring is significantly destabilized in 6-chloro compounds (Supplementary data). This effect affects exclusively heavy atoms. Thus, O3′ increases its energy by 189 kJ mol^{-1} (54 kJ mol^{-1} in the HF study) and each carbon atom is destabilized between 91 and 99 kJ mol^{-1} (26–33 kJ mol^{-1} in the HF study).

The evolution of the bond properties agrees with the general rule that the most affected atoms are the ones located closer than four bonds from the chlorine. It can be observed (Supplementary data) that the strengthening of the N1–C6 and C5–N7 bonds, while N1–C2, C5–C6, and C4–C5 are debilitated in the 6-chloropurine compound.

Both the trends in atomic and bond properties are common to the three main conformers (*AC*, *EC*, and *ET*) (Table 3). 6-Chlorination has no effect on the H8···O3′ IHB presented by *AC*.

3.7. Study of molecule 3

As expected, the most stable conformers in **3** (Table 1) present an intramolecular hydrogen bond. It was found (using restricted AM1 optimizations) that the internal rotation around the N9–C1′ bond of the most stable conformer of **3** (*ACgg′g*) presents a conformational behavior similar to the one described previously for **1** and **2** (Fig. 2).

The localization of the BCPs with their corresponding 'bond paths' in the QTAIM study shows that IHBs between

different atom pairs in each conformer are formed. Thus, there are IHB 'bond paths' between: H9′ and O3′ (conformers *ECgg′g*, *ETgg′g*, and *ACgg′g*); H4′a and O9′ (conformers *ECgg′g′*, *ECgg′t*, *ETgg′g′*, and *ETgg′t*); and H8 and O3′ (conformers *ACgg′g* and *ACttt*). In the case of the *ACgg′g* conformer the two IHB 'bond paths' localized give rise to the three-center IHB structure shown in Figure 6, where O3′ accepts simultaneously H8 and H9′.

The properties of the BCP associated to IHBs present the typical characteristics[27,39] of these weak bonds (Table 4). Thus, low values of ρ_c with $\nabla^2\rho$ was slightly positive and bond distances were between 2.1 and 2.6 Å. The highest electron density in the BCP and shorter bond distance and, in consequence, the highest bond strength correspond to IHBs where the hydroxyethylic hydrogen (H9′) acts as donor and the THP oxygen (O3′) acts as acceptor. These bonds are characteristic for the *gg′g* disposition of the hydroxyethyl chain and have negative values of H_c. Next in magnitude of ρ_c are the IHB where H8 of purine is the donor and the THP oxygen is the acceptor. This bond is characteristic of the conformers that have the purine ring in axial disposition and presents positive values of H_c. The electron density at the BCP of the H6′a···N3 interactions, typical to *ET* conformers, is only slightly inferior to those of the previous group, and slightly superior to the C–H···O hydrogen bonds that are established in *gg′t* and *gg′g′* conformers between the axial hydrogen bonded to C4′ in the THP ring and the oxygen of the hydroxyethyl group (O9′). The properties of the BCPs do not allow establishing clear distinctions between the three last types of weak interactions.

The O3′···H9′ IHB is stronger in *AC* than in *EC* and *ET* (Table 4), even though O3′ participates simultaneously in another hydrogen bond, which can alter the geometry and makes more difficult to form the IHB in optimal conditions. In this context, it has to be noticed that the IHB with the equatorial hydroxyethyl group (as it happens in *AC*) is already more intense than the corresponding one with the hydroxyethyl in the axial disposition in 2-(2′-hydroxyethyl)THP, **6**. So, in the first case $\rho_c=19.0\cdot10^{-3}$ a.u., while $\rho_c=17.9\cdot10^{-3}$ a.u. in the second one.

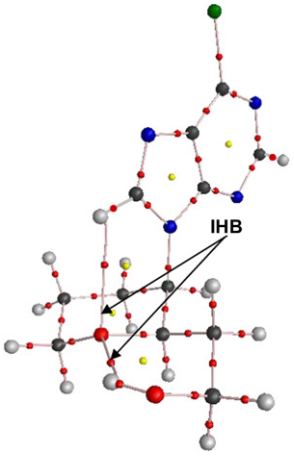

Figure 6. Bond (red) and ring (yellow) critical points of the most stable conformer of molecule **3** *ACgg′g*.[42]

Table 4. Main properties of the critical points associated to the hydrogen bonds in molecule **3**

Conf.	Bond	*R*	$10^3\ \rho$	$10^3\ \Delta\nabla^2\rho$	$10^3\ H$
Acgg′g	O3′···H9′	2.135	17.6	62.4	−0.26
Acgg′g	H8···O3′	2.494	10.5	41.1	1.2
Acttt	H8···O3′	2.474	10.9	42.5	1.1
ECgg′g	O3′···H9′	2.214	16.4	59.2	−0.05
ETgg′g	O3′···H9′	2.205	16.6	59.7	−0.10
ETgg′g	N3···H6′a	2.574	9.9	35.7	1.3
ECgg′t	O9′···H4′a	2.564	8.5	33.4	1.0
ETgg′t	O9′···H4′a	2.566	8.4	33.4	1.0
ETgg′t	N3···H6′a	2.576	9.9	35.4	1.2
ECgg′g′	O9′···H4′a	2.644	7.8	30.2	1.0

All values in a.u., except *R* in Å.

The stability sequence (Table 1) indicates that the preference for the axial purine conformers increases in **3** with regard to **1** and **2**, and they become (from our calculations) the only one present in the conformational mixture. The reason for this preference can be assigned to a balance between the strength of the two IHBs formed and the distortion experienced by the molecule as a consequence of establishing them and because of the presence of a side-chain hydroxyethyl group. In fact, the inclusion of this side chain alters the geometry of *EC* and *ET* conformers, whose C4–N9–C1′–H1′ dihedral angles differ significantly from the corresponding one in molecules **1** and **2** (0 or 180°). Thus, in **3** this dihedral angle presents, respectively, values of −31.8 and 157.4° in *EC* and *ET*. It can be noticed that the *EC* conformer is more stable than the *ET* (4.1 kJ mol^{-1}), inverting the sequence with respect to the molecules without the hydroxyethyl side chain. In the case of *AC* conformers the distortion of the main dihedral angle is already present in molecules **1** and **2** (34.2°) and the inclusion of the side chain reduces it to 22.8°.

Multiple conformers are found when rotating the main dihedral angles of the hydroxylated side chain. The highest stability corresponds to the *gg′g* rotamers in every series of conformers (*AC*, *EC*, and *ET*), since they allow to establish a stronger IHB (O3′···H9′). The variations of the main dihedral angle, C4–N9–C1′–H1′, between rotamers that belong to the same series and without O3′···H9′ IHB never reach 2°.

The QTAIM study indicates that the substitution of one of the hydrogens bonded to C2′ by the hydroxyethyl group produces electron effects that, except for the ones shown by C2′, depend on the axial or equatorial disposition of the purine ring (Table 5). Two reasons for this behavior can be considered: (i) in *AC* conformers the hydroxyethyl group occupies an equatorial position that impede big repulsions with the axial hydrogens of the oxygenated ring, while in *EC* and *ET* conformers the hydroxyethyl group is placed in axial establishing important repulsions with such axial hydrogens; (ii) the formation of the H8···O3′ IHB in the *AC* conformer of **3** is conditioned by the other simultaneous IHB (O3′··· H9′), which does not happen in molecules **1** and **2**.

When we compare the electron populations of the atoms involved in the most intense IHB (O3′···H9′) between the conformers with IHB and that ones where its formation is not possible (*ACgg′g–ACttt*), we observe a very similar

Table 5. Variations of the main atomic properties (all the values in a.u. and multiplied by 10^3 except ΔE in kJ mol^{-1}) due to the effect that produces the hydroxyl chain in molecule **3**

Atom	3*ECgg′g*–2*EC*				3*ACgg′g*–2*AC*			
	Δ*N*	Δ*E*	Δ*μ*	ΔSh	Δ*N*	Δ*E*	Δ*μ*	ΔSh
C2′	111	−154	20	38	109	−167	37	32
O3′	2	27	−23	−4	10	−35	−11	−5
C4′	17	−43	−8	8	13	−26	1	8
C8	1	−13	1	−2	−6	−10	−13	−8
H1′	12	−20	5	11	−8	4	−3	−28
H2′e	8	−34	−3	−42	15	−37	2	−24
H4′a	−19	6	−12	−65	−5	4	−1	−10
H4′e	2	−3	0	0	0	1	0	−1
H8	−5	1	−2	−16	9	−13	0	4

Variations calculated for *EC* and *AC* conformers.

behavior to that one in the model molecule 3-methoxypropanol, **7**, when comparing the rotamers *gg′g* and *ttt* (Fig. 7). Thus, we find that the acceptor oxygen of the IHB does not give electron population to the donor hydrogen when the IHB is formed, but the former gains a little electron population (0.007 a.u. in **3**). On the other hand, as a whole the OH group almost does not lose electron population, even though there are important variations in *N*(O) (+0.024 a.u.) and *N*(H) (−0.025 a.u.). The most important variations of *N*(*Ω*) happen in some of the atoms that bond the OH donor group and the acceptor oxygen (C8′, C7′, C2′, and their hydrogens). This fact was previously found when studying the IHB in 1,3-propanediol[40] and also appears in the model compound **7**. So, when the IHB is established, the electron population of the methylene α to the donor OH is reduced (−0.071 a.u.) and the one of the methylene β is increased (+0.068 a.u.). The reduction in the population of one of the hydrogens, H8′, in *tgg′g* against *tttt* can be related to the double '*gauche*' interaction with the O9′ NBCCs, as it was recently done for several anomeric compounds.[28] The highest variations in *N*(*Ω*) are related to conformational effects and not to the establishment of the IHB. Nevertheless, the formation of that bond explains the reduction in the population of the hydrogens of the CH_2 or CH_3 in α to the acceptor oxygen O9′. This reduction and the increase in the electron density of the α carbon are characteristic of intramolecular and intermolecular hydrogen bonds.[41] This electron redistribution increases the negative charge of the acceptor oxygen. At the same time, the donor hydrogen, H9′, becomes more positive transferring electron density to O9′. This suggests that the formation of the O···H–O IHB is described, according to QTAIM, by an ionic form of type $O^{+\delta}\cdots H^{-\delta}$–O. This form is consequent of the closed shells' interaction character suggested by the small values of ρ_c and positive values of $\nabla^2\rho_c$, which characterize these bonds (Table 4).

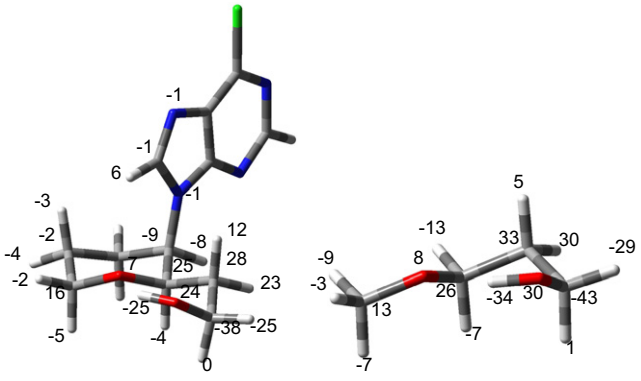

Figure 7. Relative atomic electron populations (in a.u. and multiplied by 10^3) for the most stable conformer of molecule **3**, *ACgg′g* (with respect to its *ACttt* analogs) and for the *tgg′g* conformer of model compound **7** (with regard to *tttt*).

4. Conclusions

According to the calculations carried out in this work, *cis*-6-chloro-9-[2-(2-hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]purine shows a clear conformational preference for the axial disposition of the purine ring with a distorted cis orientation of the C4–N9–C1′–H1′ dihedral angle and a C–H···O···H–O intramolecular three-center hydrogen bond. The presence of the hydroxyethyl side chain is fundamental for this preference, as equatorial and axial conformers of compounds **1** and **2** display very similar molecular energies. In fact, the repulsive interactions of purine and hydrogens of the THP ring with the hydroxyethyl group are larger when purine is equatorial.

Chlorination at position 6 of the purine ring introduces modifications of the electron density that are localized within four bonds of the chlorine atom. However, the THP ring is significantly destabilized in 6-chloro compounds.

The connection between THP and purine rings takes place with a significant electron density transference from the oxacycle to the base ring, which also bears a negative charge in its isolated form because of the scarce electron population within the tautomeric hydrogen basin. This electron transference is somewhat smaller than those previously found between carbocycles and pyrimidine bases. In spite of this electron transference, the QTAIM study reveals that the electron distributions of both rings are significantly independent when the structure or conformation of the other ring is changed. In general, conformational changes take place with slight modifications of the atomic and bond properties.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.084.

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