Intramolecular Hydrogen Bonds in Canonical 2′-Deoxyribonucleotides: An Atoms in Molecules Study

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The molecular structure and relative stability of different conformers of isolated canonical 2′-deoxyribonucleotides thymidine-5′-phosphate (pdT), 2-deoxycytidine-5′-phosphate (pdC), 2-deoxyadenosine-5′-phosphate (pdA), and 2′-deoxyguanosine-5′-phosphate (pdG) were calculated using the B3LYP/6-31++G(d,p) level of theory. The results of the calculations reveal that, for all nucleotides except pdG, conformers with a syn orientation of the base do not correspond to a minimum on the potential energy surface. In the case of pdA and pdC, conformers with an orthogonal orientation of the nucleobase are located instead, north/syn conformers. These conformers as well as syn conformers of pdG are stabilized by intramolecular N–H···O hydrogen bonds. Analysis of the electron density distribution within the atoms in molecules theory reveals the presence of numerous C–H···O hydrogen bonds in the nucleotides. However, a more detailed consideration of the properties of these bonds demonstrates that many of them should be considered as strong attractive electrostatic interactions rather than true hydrogen bonds. True hydrogen bonds are represented mainly by C6/C8–H···O5′/O–P in anti conformers and the N–H···O–P bonds in syn conformers. It is demonstrated that the values of ellipticity of the electron density at the bond critical point (BCP) and the distance between BCP and ring critical point are the most reliable indicators for determining the true intramolecular hydrogen bonds.

Introduction

Hydrogen bonding plays a pivotal role in DNA structure and function.[1,2] In particular hydrogen bonds are responsible for the formation of Watson–Crick pairs of nucleic acid bases. Therefore, the ability of nucleic acid constituents, especially nucleobases, to form hydrogen bonds has been the subject of numerous experimental and theoretical studies (refs 3 and 4 and references therein). However, these studies are mainly focused on the intermolecular hydrogen bonds between nucleobases[3,5] or between DNA constituents and water (refs 6 and 7 and references therein), peptides,[8–10] or other organic molecules.[11–13] The possibility of the formation of intramolecular hydrogen bonds was not considered. This is quite reasonable in the case of nucleobases where the formation of intramolecular hydrogen bonds is almost impossible. However, an analysis of the molecular structure of canonical 2′-deoxyribonucleosides[14–16] revealed the existence of intramolecular O–H···O and C–H···O bonds, which may significantly influence the equilibrium conformation and relative stability of conformers. In particular, the formation of the O–H···O hydrogen bond results in significant stabilization of conformers with a syn orientation

of the nucleobase with respect to a sugar fragment.[15] Hocquet suggested[17] that differences in the properties of the intramolecular C–H···O bond are responsible for the different value of the χ torsion angle in 2′-deoxycytidine and the steepest potential energy profile for the rotation around a glycosidic linkage characterized by this torsion angle.

The situation is even more complex in the case of nucleotides. Theoretical studies[18,19] of the molecular structure of canonical 2′-deoxyribonucleotides (DNTs), namely, 2′-deoxythymidine-5′-phosphate (pdT), 2′-deoxycytidine-5′-phosphate (pdC), 2-deoxyadenosine-5′-phosphate (pdA), and 2′-deoxyguanosine-5′-phosphate (pdG), have revealed the presence of numerous intramolecular N–H···O and C–H···X (X = O, N) hydrogen bonds. It was found that every conformation of each DNT contains up to four intramolecular hydrogen bonds. Formation of these hydrogen bonds significantly influences the equilibrium conformation of the nucleotides. In particular this concerns the orientation of the nucleobase and phosphate group with respect to a sugar fragment. An especially strong influence of intramolecular hydrogen bonds is observed for dianions of DNTs where the presence of very strong C–H···O bonds results in significant deformation in the conformation of the furanose ring. Formation of N–H···O intramolecular bonds is also responsible for the stabilization of conformers with a syn orientation of nucleobases[19,20] in the case of pdG.

On the basis of the appearance of different intramolecular hydrogen bonds in DNTs, it was suggested[18] that all hydrogen bonds be divided into two categories: reference hydrogen bonds and specific hydrogen bonds. The first type of hydrogen bonds

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exists in many conformers of every DNT. Therefore, they should be considered as one of the driving forces determining the molecular structure of DNTs. Specific hydrogen bonds are observed in some conformers and may be responsible for some deformation of the geometrical parameters of DNTs in these conformers.

It should be noted that the C−H···O hydrogen bonds are rather weak.[21] Canonical hydrogen bonds (for example, O−H···O) have a well-defined range of geometrical parameters, in particular the OH···O distance is within 1.5−2.1 Å. However, despite the approximately same size of O−H and C−H fragments, the C−H···O bonds have considerably larger C−H···O distances.[22] Namely, the CH···O distance in these bonds may be significantly longer, up to 2.5 Å. Therefore, the existence of C−H···O bonds is always a subject of careful consideration. Experimental confirmation of the existence of such intramolecular hydrogen bonds is often ambiguous because it requires comparison with model compounds. This is an opportunity for theoretical methods to supply reliable information and to characterize intramolecular C−H···O bonds.

One of the most powerful approaches for describing chemical bonds is provided by topological analysis of the electron density distribution within Bader's atoms in molecules (AIM) theory.[23] In accord with the AIM theory any chemical bond including the hydrogen bond is characterized by the presence of the so-called bond critical point (BCP). This means that in this point electron density has a minimal value along the line of the bond and a maximal value in two orthogonal directions. The properties of electron density at this point are closely related with the energy of the bond and its nature.

However, recent studies of the electron density distribution in various molecular complexes[16,24,25] demonstrates that the presence of the BCP is a necessary but not sufficient condition for the existence of a chemical bond, especially in the case of weak hydrogen bonds. For example, it was demonstrated that BCPs are observed between the carbon atoms belonging to different rings in the benzene dimer[25] despite the absence of chemical bonds between these pairs of atoms. Thus, it was concluded that the presence of BCP reflects the existence of an interaction between two atoms, but classification of this interaction should be the subject of a more detailed investigation.

Therefore, Popelier et al.[26,27] have derived a set of extended requirements for the existence of hydrogen bonds based on AIM analysis of hydrogen-bonded systems. These criteria include a range of suitable values of electron density and the Laplacian of electron density at BCP (BCP criteria) and requirements of the corresponding changes of atomic charge, energy, volume, polarization momentum, and radius due to the formation of a hydrogen bond compared to noninteracting monomers ("two molecules" criteria). The application of these criteria allows weak hydrogen bonds and nonbonded electrostatic interactions between atoms with opposite charges to be distinguished. Such an approach was successfully applied for investigations of various hydrogen-bonded systems[28,29] including nucleic acid base pairs[30,31] and systems containing C−H···X bonds.[30,32,33]

Using Popelier's criteria, Hocquet analyzed intramolecular C−H···O hydrogen bonds in ribonucleosides[17] and 2′-deoxyribonucleosides.[16] It was demonstrated that the hydrogen bonds between the O5′ atom of the hydroxyl group and the H6 or H8 atom of the nucleobase meet all of the requirements and should be considered a true intramolecular hydrogen bond that influences the structure and properties of these DNA constituents. Other C−H···O bonds in 2′-deoxyribonucleosides should be

considered to be electrostatic interactions rather than hydrogen bonds despite the presence of the BCP.

In the present paper we have extended Popelier's analysis for the case of 2′-deoxyribonucleotides. We have analyzed intramolecular hydrogen bonds in canonical 2′-deoxyribonucleotides using the AIM theory. Taking into account that nucleotides in nucleic acids exist in a monoanionic state only, monoanions of DNTs have been calculated. Only conformers relevant to the DNA structure have been considered. There are conformers with syn and anti orientations of the base with respect to sugar, the C2′-endo and C3′-endo conformations of the furanose ring, and the +sc and ap orientation of the phosphate group around the C4′−C5′ and C5′−O5′ bonds (α and β torsion angles). It is demonstrated that only several of the intramolecular C−H···X interactions may be considered as real hydrogen bonds. Other interactions should be treated as strong electrostatic interactions. In addition, it is revealed that the application of a more diffuse basis set in the calculations results in the disappearance of minima on the potential energy surface corresponding to the syn orientation of the base in pdT, pdA, and pdC.
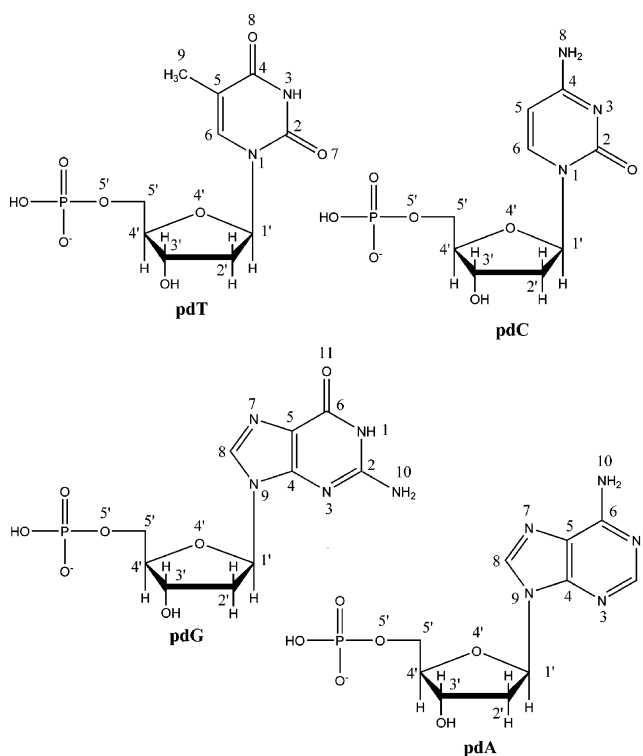
Method of Calculation

The molecular structures of nucleotides were calculated using the density functional theory with the Becke's three-parameter exchange functional and the gradient-corrected functional of Lee, Yang, and Parr.[34−38] To provide a sufficient description of the hydrogen bonds, the standard 6-31++G(d,p) basis set[39,40] containing diffuse functions was applied in all calculations. Local minima were verified by establishing that the matrix of energy second derivatives (Hessian) has only positive eigenvalues. The energy of the zero-point vibrations was calculated at the same level of theory (B3LYP/6-31++G(d,p)) within harmonic approximation. All calculations were performed using the Gaussian 03 program.[41]

The total energy of all conformers was also calculated at the MP2/aug-cc-pvdz level of theory using a geometry optimized

Intramolecular Hydrogen Bonds in 2′-DNTs

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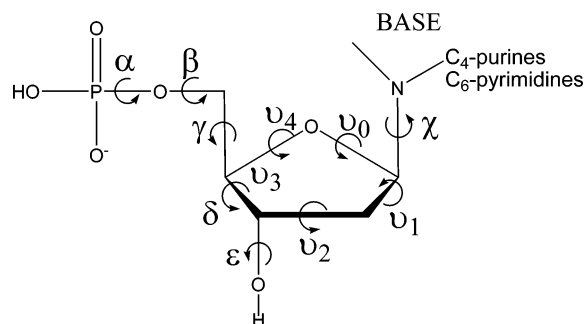
Figure 1. Notation of selected torsion angles in 2′-deoxyribonucleotides.

by DFT calculations (single-point calculations). These calculations have been performed by the NWChem package.[42]

An analysis of the electron density distribution was carried out within Bader's AIM approach[23] using the B3LYP/6-31++G(d,p) wave function. The existence of intramolecular hydrogen bonds was established based on the presence of bond $(3,-1)$ critical points between two nonbonded atoms. An AIM analysis has been performed using the AIM2000 program[43] with all default options. An integration of atomic properties over atomic basins has been carried out in natural coordinates with a tolerance of 0.001 per integration step. In the case of the hydrogen atoms of amino groups the β sphere radius was shortened to 0.3 au to be smaller than the distance between the integrated hydrogen atoms and the nearest critical point.

The most important torsion angles for our consideration were denoted (Figure 1) in accord with ref 1. The puckering of the furanose ring was described by a pseudorotation angle (P) and the degree of puckering (ν_{max}). These values were calculated using standard equations in accord with ref 44.

The exact conformation of the furanose ring was denoted in accord with ref 1. For example, notation ^2E describes the C(2′)-endo envelope conformation; the $^2T_3$ notation corresponds to the C(2′)-endo-C(3′)-exo twist conformation; etc. It should be noted that the south and north regions of the pseudorotation angle include several exact conformations of a five-membered ring. There are ^2E, $^2T_1$, $^2T_3$, and $_3E$ conformations for the south region ($P = 144-190°$) and $^3T_2$, ^3E, and $^3T_4$ for the north region ($P = 0-36°$).

All conformers are denoted in accord with the orientation of the base and the conformation of the furanose ring. For example, a south/anti conformer is one where the conformation of the sugar belongs to the south region and the base has an anti orientation with respect to the furanose ring.

Results and Discussion

Molecular Structure and Relative Stability of Conformers of 2′-Deoxyribonucleotides. A comparison of the molecular structure of DNTs calculated using the 6-31(d) basis set as reported earlier[18,19] and the 6-31++G(d,p) basis in this work (Table 1) indicates that an increase in the size of the basis set results in only slight changes in the geometrical parameters of the considered molecules. A decrease of differences between the O4′−C bond lengths and the degree of pyramidality of the amino groups are among variations of molecular parameters observed when going from the 6-31G(d,p) to the 6-31++G-(d,p) basis set.

The application of an extended basis set allows the clear dependence of lengths of the C3′−O3′ bonds on the conformation of the furanose ring (Table 1) to be detected. This bond in the south conformer is systematically longer compared to the north conformer. The biggest differences are found for pdG ($\Delta l = 0.031$ Å for anti and 0.018 Å for syn conformers), while this value for other DNTs is considerably smaller ($\Delta l = 0.012-0.014$ Å). The existence of such a dependence clearly indicates that the C3′−O3′ bond is involved in some stereoelectronic interactions such as the anomeric effect despite the absence of a second heteroatom bound to the C3′ atom.
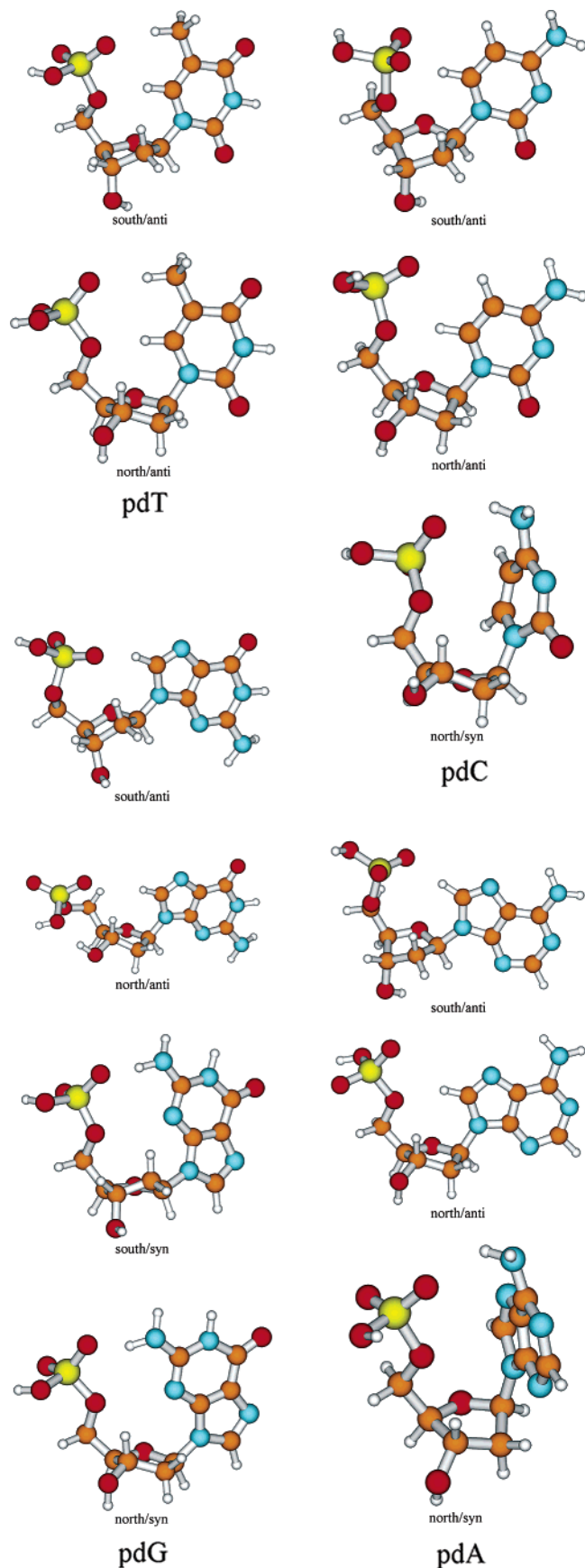
The most striking differences in the molecular structure of DNTs due to the application of an extended basis set are found for conformers with a south/syn orientation of the nucleobase. The results of our calculations reveal that pure south/syn conformers correspond to local minima on the potential energy surface only in the case of pdG (Figure 2). Earlier it was demonstrated[19,20] that only south/syn conformers of pdG are stabilized by the formation of a strong intramolecular N−H⋯O hydrogen bond between the amino and the phosphate groups. All other south/syn conformers were stabilized by the C−H⋯O hydrogen bond or by other intramolecular interactions. Therefore, a more rigorous treatment of the anionic states of DNTs due to the application of diffuse functions results in the disappearance of these conformers also for pdT and pdA. Previously similar results were obtained for dianions of DNTs.[18,19] In the case of monoanions the absence of syn conformers was observed only for pdC.[18]

In addition, the pdC and pdA conformers with an almost orthogonal orientation of the nucleobase with respect to the C1′−H bonds are found instead of the north/syn conformers (Figure 2). Such an orientation of the cytosine and adenine moiety is stabilized by the intramolecular N−H⋯O hydrogen bond between the amino and the phosphate groups following

TABLE 1: Selected Geometrical Parameters of 2′-Deoxyribonucleotides

parameter	pdT south/anti	pdT north/anti	pdC south/anti	pdC north/anti	pdC north/syn	pdA south/anti	pdA north/anti	pdA north/syn	pdG south/anti	pdG north/anti	pdG south/syn	pdG north/syn
C2(C4)−N10(N8)H$_2$			1.377	1.376	1.373	1.367	1.365	1.367	1.393	1.389	1.353	1.355
N9(N1)−C1′ (Å)	1.468	1.488	1.473	1.487	1.493	1.456	1.470	1.473	1.451	1.477	1.451	1.454
C1′−O4′ (Å)	1.429	1.412	1.423	1.416	1.418	1.423	1.414	1.420	1.425	1.414	1.425	1.421
C4′−O4′ (Å)	1.449	1.443	1.450	1.444	1.457	1.452	1.446	1.454	1.445	1.457	1.447	1.437
C3′−O3′ (Å)	1.438	1.425	1.438	1.426	1.437	1.439	1.425	1.429	1.446	1.415	1.445	1.427
O5′−P (Å)	1.687	1.689	1.680	1.694	1.676	1.684	1.692	1.691	1.689	1.679	1.661	1.657
Σ(NH$_2$) (deg)			349.4	350.8	335.8	354.0	353.8	335.1	338.7	340.7	349.4	346.1
OH−P−O5′−C5′ (deg)	83.5	76.6	61.2	93.2	69.0	68.4	−72.7	73.4	150.3	−106.5	66.4	65.1
β (deg)	180.0	178.4	142.6	155.3	159.3	132.9	−163.2	174.2	101.0	96.7	174.0	−166.8
γ (deg)	10.6	55.3	40.1	53.0	42.2	30.6	53.2	51.2	30.6	−66.9	42.7	47.4
δ (deg)	143.5	86.6	142.3	85.9	98.2	142.9	90.1	100.2	134.3	99.7	139.1	86.5
χ (deg)	−115.7	−148.5	−144.1	−155.8	162.1	−130.2	−139.6	122.4	−110.7	−117.3	70.9	62.0
P (deg)	181.4	12.9	184.9	5.1	330.7	171.9	3.3	320.9	146.5	358.7	158.2	44.0
ν_{max} (deg)	33.3	28.9	34.3	30.9	34.5	36.5	27.3	35.1	40.2	28.6	36.4	26.8
conformation	$_3T^2$	$^3T_2$	$_3T^2$	$^3T_2$	$_2T^1$	$^2T_3$	$^3T_2$	$^1T_2$	$_2T^1$	$_2T^3$	$_2T^1$	$^4T_3$

Figure 2. Molecular structure of stable conformers of 2′-deoxyribo-nucleotides.

TABLE 2: Relative Energy of Conformers of 2′-Deoxyribonucleotides

		B3LYP/6-31++G(d,p)			MP2/aug-cc-pvdz//B3LYP/6-31++G(d,p)		
molecule	conformer	ΔE_{DFT}	ΔG^{0K}	ΔG^{298K}	ΔE_{MP2}	$\Delta G^{0K\,a}$	$\Delta G^{298K\,a}$
pdT	south/anti	0	0	0	0	0	0
pdT	north/anti	3.35	3.15	3.19	4.58	4.37	4.41
pdC	south/anti	0	0	0	2.55	2.02	2.31
pdC	north/anti	0.44	0.48	0.44	2.55	2.07	2.31
pdC	north/syn	3.14	3.67	3.38	0	0	0
pdA	south/anti	0	0	0	0	0	0
pdA	north/anti	4.15	4.00	4.14	5.61	5.46	5.59
pdA	north/syn	7.56	8.08	7.76	1.96	1.92	2.16
pdG	south/anti	9.64	9.82	10.02	9.45	9.64	9.84
pdG	north/anti	4.74	5.66	5.60	5.62	6.54	6.48
pdG	south/syn	0	0	0	0	0	0
pdG	north/syn	4.58	4.40	4.51	5.57	5.40	5.51

^{a} Values of ZPE and G_t were obtained from the B3LYP/6-31++G(d,p) calculations.

of the phosphate group. The absence of an amino group makes impossible the presence of any syn conformers of pdT, unlike the previously reported case.[18]

Among south and north conformers of DNTs the south/anti conformer is significantly more stable for pdT and pdA (Table 2). In the case of pdC the difference in energy between south/anti and north/anti conformers is considerably smaller. Nevertheless, the south/anti conformer remains the most stable one. North/syn conformers of pdC and pdA possess significantly higher relative energy. An unexpected inversion of stability of conformers is observed for pdG. Conformers with a syn orientation of guanine are more stable compared to anti conformers, in agreement with the previous study[45] with the south/syn conformer being the most favorable one. However, among anti conformers, the north/anti conformer possesses significantly lower energy compared to the south/anti conformer (Table 2). Similar results were obtained earlier only for dianions of pdG.[19,45] Probably, a more rigorous treatment of the anionic state and the intramolecular hydrogen bond with an extended 6-31++G(d,p) basis set is responsible for the inversion of the relative stability of conformers of pdG.

A different explanation of the unusual stability of the north/anti conformer of pdG may be derived from an analysis of intramolecular hydrogen bonds. This conformer contains the O—H⋯O bond between the phosphate and the O3′—H hydroxy groups, leading to a significant decrease in the energy of the molecule. However, such a hydrogen bond is impossible in DNA where the O3′ atom is involved in a phosphodiester linkage with a neighboring nucleotide. Therefore, high stability of the north/anti conformer of pdG may be observed only in an isolated nucleotide.

To verify the obtained results, a more rigorous account of electron correlation using the MP2/aug-cc-pvdz method has been performed. As follows from the data presented in Table 2, the application of the MP2 level does not change the order of stability of anti conformers of DNTs. Only some increase of differences in energy between south/anti and north/anti conformers is observed. However, the MP2 method significantly decreases the relative energy of orthogonal (north/syn) conformers of pdC and pdA (Table 2). In the case of pdC this conformer becomes the most stable, and the energy of this conformer in pdA is lower compared to the north/anti conformer. Such stabilization may be caused by differences in energy of deformation of the fragments of these DNTs calculated at the DFT and MP2 levels of theory. In particular, it was recently demonstrated[46] that the MP2 method slightly underestimates the

significant out-of-plane deformation of the pyrimidine ring. The formation of this type of hydrogen bond is impossible in south conformers of pdC and pdA because of the equatorial orientation

conformational flexibility of the pyrimidine ring in uracil compared to the CCSD(T) data. The value of ring deformation energy calculated within the density functional theory is sligthly higher compared to the MP2 data. Similar effects may be expected for other fragments of DNTs. Therefore, the contribution of these differences in deformation energy may be considerable.

Thus, an analysis of the geometrical parameters and relative stability of conformers indicates that the application of diffuse functions is required for a correct description of the molecular structure and energetics of DNTs. An absence of diffuse functions may lead to the appearance of artificial local minima on the potential energy surface.

Criteria for the Existence of Hydrogen Bonds within the AIM Theory. The AIM theory provides a significant amount of information about the properties of any chemical bonds including hydrogen bonds. However, as already mentioned, the most important difference between covalent chemical bonds and hydrogen bonds is the strength and range of variations of the geometrical parameters of the bonds. For example, the lengths of the C−C bond can vary within 0.4−0.5 Å (from 1.14 Å in acetylene up to 1.6 Å in strained polycyclic hydrocarbons), while a change in the length of the hydrogen bond expressed as the H···X distance can be up to 1 Å. Therefore, before analyzing this information, we shall describe the properties that are crucial to stating unequivocally that these hydrogen bonds exist.

According to the AIM theory,[23] the presence of a hydrogen bond like any chemical bond must correspond to the existence of a bond path between the hydrogen atom and the acceptor containing the BCP, in topological analysis of the electron density distribution. This is the requirement and first criteria for the existence of any chemical bond. In the case of hydrogen bonds several additional criteria were developed.[26,27] Two of them concern properties of the BCP, namely, the value of electron density ρ at the BCP should be between 0.002 and 0.035 au and the value of the Laplacian of electron density $\nabla^2(\rho)$ should be within 0.024−0.139 au. Besides that, some useful information about the stability of hydrogen bonds may be retrieved from the values of bond ellipticity at the BCP[47] and the distance between the BCP and the ring critical point (RCP).[16] RCP is defined as a (3,+1) critical point and exists whenever a succession of bond paths closes into a ring. An abnormally high value of ellipticity and the short distance between BCP and RCP usually indicate locally unstable topology of electron density, a so-called bifurcation point,[23] which is not observed for normal hydrogen bonds. Taking into account that all criteria mentioned above deal with the properties of the BCP, they can be referred to as BCP criteria.

Other criteria of hydrogen bonds relate to the changes in the atomic properties of interacting atoms. According to the AIM theory, the atom is characterized by its atomic charge q, atomic polarization moment M, atomic volume ν, atomic energy E and atomic radius r. The calculation of changes of these properties is based on a rigorous definition of atom in molecules within the AIM theory as a region of space bound by its interatomic surfaces (zero flux surfaces).

The application of these criteria requires reference molecules representing "monomers" noninteracting with each other where the atoms involved in the hydrogen bonding are unbound. Therefore these criteria may be referred to according to Hocquet[16] as "two molecules" criteria. The choice of a reference molecule is the most difficult problem in the case of intramolecular hydrogen bonds. The presence of multiple hydrogen bonds between the phosphate, the sugar, and the nucleobase
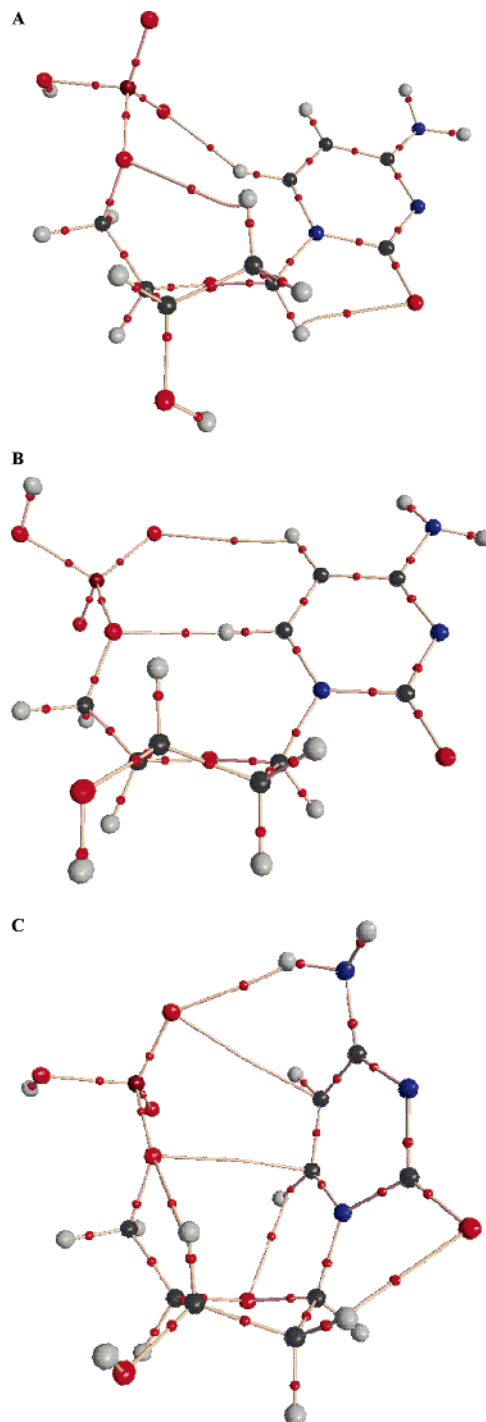
Figure 3. Molecular graph of all conformers of pdC according to AIM theory: (A) south/anti conformer, (B) north/anti conformer, (C) north/syn (orthogonal) conformer.

makes it impossible to use the method applied by Hocquet for 2′-deoxyribonucleosides,[16] based on the absence of intramolecular C−H···O hydrogen bonds in some conformations of molecules. Therefore we use isolated bases, sugar, and the methyl-substituted phosphate anion as "monomers" for calculating the properties of unbound atoms. Certainly, such a choice provides some systematic errors in determining the changes in the atomic properties due to the formation of intramolecular hydrogen bonds, because of the considerable influence of the negatively charged phosphate group on the geometrical parameters and the electron density distribution within the sugar and nucleobase mentioned earlier.[18,19,45] However, we believe that

TABLE 3: Geometrical Parameters, Characteristics of (3,−1) BCPs, and Distances Between BCP and RCP for All Potential Intramolecular Hydrogen Bonds[a]

molecule	conformer	D−H···A	H···A (Å)	D−H···A (deg)	ρ (Å/au³)	$\nabla\rho$ (e/au⁵)	e	L_{RCP} (au)
pdT	south/anti	**C9−H···O−P**	**2.331**	**166.3**	**0.0125**	**0.0376**	**0.0437**	**1.89**
		C1′−H···O7	2.211	110.7	0.0198	0.0785	0.8871	0.46
		C2′−H···O5	2.495	109.4	0.0112	0.0413	0.2387	1.03
		C6−H···O5′	**2.161**	**160.5**	**0.0182**	**0.0512**	**0.0670**	**1.73**
pdT	north/anti	**C9−H···O−P**	**2.253**	**178.6**	**0.0143**	**0.0424**	**0.0317**	**2.26**
		C6−H···O5′	**2.128**	**171.2**	**0.0188**	**0.0529**	**0.0773**	**1.52**
pdC	south/anti	**C6−H···O−P**	**2.195**	**149.4**	**0.0174**	**0.0477**	**0.0294**	**2.69**
		C1′−H···O7	2.238	104.0	0.0197	0.0804	0.9646	0.44
		C2′−H···O5′	2.513	111.0	0.0109	0.0393	0.3163	0.93
pdC	north/anti	C5−H···O−P	2.785	121.2	0.0052	0.0201	0.1969	1.06
		C6−H···O5′	**2.069**	**161.5**	**0.0220**	**0.0611**	**0.0650**	**1.56**
pdC	north/syn	**N8−H···O−P**	**2.150**	**141.2**	**0.0169**	**0.0523**	**0.0861**	**1.75**
		C6−H···O4′	2.255	99.7	0.0196	0.0855	1.6105	0.39
		C3′−H···O5′	2.332	107.6	0.0144	0.0609	1.6211	0.30
		C2′−H···O7	**2.290**	**118.1**	**0.0159**	**0.0561**	**0.2114**	**1.17**
pdA	south/anti	**C8−H···O−P**	**2.028**	**177.6**	**0.0228**	**0.0610**	**0.0366**	**2.57**
		C2′−H···O5′	2.519	111.0	0.0110	0.0398	0.4462	0.82
pdA	north/anti	**C8−H···O5′**	**2.200**	**154.8**	**0.0160**	**0.0472**	**0.0800**	**1.78**
pdA	north/syn	N6−H···O−P	2.215	129.3	0.0148	0.0510	0.1760	3.92
		C2′−H···N3	2.322	120.9	0.0157	0.0518	0.1158	1.46
pdG	south/anti	C2′−H···O−P	2.262	153.7	0.0154	0.0441	0.0574	1.93
		C8−H···O−P	**2.030**	**162.1**	**0.0223**	**0.0640**	**0.0396**	**2.14**
pdG	north/anti	C3′−H···O−P	2.490	135.1	0.0108	0.0085	0.0795	1.40
		O3′−H···O(H)−P	**1.792**	**166.2**	**0.0357**	**0.0263**	**0.0620**	**2.37**
pdG	south/syn	**N10−H···O−P**	**1.681**	**174.6**	**0.0457**	**0.1335**	**0.0262**	**2.82**
		C2′−H···N3	**2.359**	**127.2**	**0.0138**	**0.0456**	**0.0489**	**1.32**
		C2′−H···O5′	2.638	108.7	0.0081	0.0325	2.0929	0.31
PdG	north/syn	**N10−H···O−P**	**1.714**	**161.5**	**0.0426**	**0.1248**	**0.0427**	**2.61**
		C3′−H···N3	2.893	111.7	0.0055	0.0192	0.4419	0.92

[a] True hydrogen bonds are listed in bold.

such vagueness cannot affect significantly the qualitative conclusions concerning general trends in changes of atomic properties.

Bond Critical Point Criteria. The most immediate evidence of bonding within the AIM theory is the existence of a bond path containing BCP between two atoms. The collection of bond paths within a molecule represents a molecular graph showing all intramolecular bonding interactions including also hydrogen bonds. An example of a molecular graph for all located conformers of pdC is visualized in Figure 3.

The molecular graph from AIM analysis demonstrates the presence of a network of bond paths corresponding to all chemical bonds in agreement with the Lewis model of molecules. The results of the calculations reveal also the existence of bond paths corresponding to potential intramolecular hydrogen bonds in DNTs. The main part of these hydrogen bonds represents the interaction of nucleobases with phosphate and sugar. Only a few examples of interactions between phosphate and sugar or between different atoms of sugar are observed. Geometrical parameters, characteristics of BCP, and the distance between BCP and RCP of these potential hydrogen bonds are listed in Table 3. Thus, all these interactions meet the first criteria for hydrogen bonds.

All revealed interactions could be divided into three groups based on geometrical parameters and values of electron density and Laplacian of the electron density. The first group, which may be called "well-defined" hydrogen bonds, includes first of all classical N−H···O and O−H···O hydrogen bonds in pdG characterized by the shortest H···O distances and the highest values of ρ and $\nabla^2(\rho)$. On the basis of the sum of van der Waals radii of the hydrogen and oxygen (2.45 Å, for reliability we used the shortest radii by Zefirov and Zorkii[48]) and geometrical criteria[22] of classic hydrogen bonds (H···A < 2.3 Å, D−H···A > 130°), the N−H···O bond in the north/syn conformer of pdC

and some C−H···O bonds in all DNTs should be also considered as belonging to this group.

Among well-defined C−H···O bonds the main part includes interactions with participation of the C6−H atom of pyrimidine and the C8−H atom of purine fragments for conformers with an anti orientation of the base. This agrees well with the conclusion by Hocquet about the ability of these hydrogen atoms to form stable intramolecular hydrogen bonds in 2′-deoxyribonucleosides.[16,17] However, in DNTs, a clear difference is revealed between purine and pyrimidine nucleotides. In the case of pdT and pdC, the C6−H···O5′ hydrogen bond is observed in all conformers except the south/anti conformer of pdC where the C6−H atom interacts with the oxygen of the phosphate group. An opposite situation is found for purine nucleotides. The C8−H···O−P hydrogen bond is located in south/anti conformers of pdA and pdG, while the C8−H···O5′ bond is formed in the north/anti conformer of pdA. Unlike these conformers, interactions with the participation of the C8′−H atom were not found in the north/anti conformer of pdG (Table 3).

The values of electron density and Laplacian of electron density at the BCP for all of these hydrogen bonds meet Popelier's criteria mentioned above (Table 3). The range of variation of the properties of the BCP for well-defined hydrogen bonds (ρ > 0.015 au, $\nabla^2(\rho)$ > 0.044 au) may be used for further classification of other intramolecular interactions in DNTs. An analysis of the ellipticity of these hydrogen bonds (ϵ < 0.09) and the distance between BCP and RCP (L_{RCP} > 1.5 au) does not indicate any instability of these interactions, and these values also may be used as reference for further consideration.

The second group of hydrogen bonds includes interactions that do not meet BCP criteria. The value of the Laplacian of the electron density at the BCP is smaller than 0.024 au for the C5−H···O−P bond in the north/anti conformer of pdC and the

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C3′−H···N3 bond in the north/syn conformer of pdG (Table 3). Therefore these interactions should be considered to be electrostatic interactions rather than real hydrogen bonds. They are characterized by the longest H···O distances (more than 2.7 Å), small values of the C−H···O angles (less than 122°), and the electron density at BCP (ρ < 0.006). In addition, these interactions have relatively high ellipticity at the BCP (ϵ > 0.19) and a shorter distance to the RCP (L_{RCP} < 1.1 au).

The remaining interactions belong to the third group, and they require additional careful consideration. Using characteristics of the two groups of interactions mentioned above, we can classify these potential intramolecular hydrogen bonds in DNTs. First of all we should consider the N−H···O interaction in the north/syn conformer of pdA (Table 3). This interaction demonstrates all properties of the inherent hydrogen bond, namely, clear directionality and influence on the conformation of the molecule. The formation of this hydrogen bond results in out-of-plane deformation of the pyrimidine ring of adenine and stabilization of an unusual conformer with orthogonal orientation of the base with respect to sugar. All BCP properties of this hydrogen bond (Table 3) are within the ranges typical for well-defined hydrogen bonds mentioned above except the N−H···O angle that is only 129.3° and the value of ellipticity at BCP that is too high for normal hydrogen bonds (Table 3). Therefore, this interaction undoubtedly should be classified as a real hydrogen bond. The high value of ellipticity probably reflects the weak character of this bond, which is in agreement with the relatively long H···O distance and the small value of the N−H···O angle.

Consideration of the N−H···O interaction as a true hydrogen bond allows the criteria for the existence of hydrogen bonds to be refined. In particular, this concerns the value of ellipticity at the BCP that should be less than 0.18.

An analysis of the BCP properties of the remaining potential intramolecular hydrogen bonds demonstrates that all values of ρ and $\nabla^2(\rho)$ meet Popelier's criteria (Table 3). Therefore, these magnitudes cannot be used for the classification of the interactions under consideration. The values of bond ellipticity and the distance between the BCP and the RCP are much more informative for this purpose. The C1′−H···O7 interaction in the south/anti conformer of pdT and pdC, the C6−H···O4′ and the C3′−H···O5′ interactions in the north/syn conformer of pdC, and the C2′−H···O5′ interaction in the south/syn conformer of pdG are characterized by extremely large values of ellipticity (ϵ > 0.8) and very short distances between the BCP and the RCP (L_{RCP} < 0.5 au). This indicates that the topology of the electron density distribution at these BCPs is very unusual and lies out of range for normal hydrogen bonds. Therefore, these interactions cannot be considered as hydrogen bonds and should be treated as strong electrostatic interactions. It should be noted that the H···O distances for some of these interactions are relatively short (2.21−2.33 Å), but the values of the C−H···O angle are considerably smaller than 120° (99.7−110.7°). This demonstrates that the H···O distance cannot be a good indicator for the existence of hydrogen bonds. It should be combined with the value of the C−H···O angle that is normally larger than 120°.

At least the characteristics of two interactions (C3′−H···O−P in the north/anti conformer and C2′−H···N3 in the south/syn conformer of pdG) are very similar to the characteristics of well-defined hydrogen bonds. Only the H···O distance in the C3′−H···O−P bond (2.490 Å) is considerably longer compared to other hydrogen bonds (Table 3). However, this probably is compensated by a higher value of the C−H···O angle (135.1°).

TABLE 4: Atomic Properties of Selected Atoms in Reference Molecules

molecule	atom	q	M	n	$-E$	r
thymine	H(C6)	0.008	0.145	50.4	0.619	2.55
	H(C9)	0.064	0.135	46.5	0.600	2.55
cytosine	H(N8)	0.424	0.177	29.0	0.451	2.55
	H(C5)	0.021	0.134	48.9	0.616	2.55
	H(C6)	0.050	0.124	46.7	0.611	2.55
	O7	−1.214	0.420	141.1	75.255	3.40
adenine	H(N6)	0.448	0.169	27.9	0.430	2.55
	H(C8)	0.076	0.132	45.9	0.589	2.55
	N3	−1.166	0.190	125.2	54.835	3.60
guanine	H(N10)	0.443	0.173	28.0	0.439	2.55
	H(C8)	0.063	0.127	46.6	0.600	2.55
	N3	−1.164	0.204	123.2	54.837	3.60
ABS	H(C1′)	0.010	0.148	50.4	0.630	2.55
	H(C2′)	0.014	0.143	50.4	0.626	2.55
	H(C3′)	0.015	0.146	50.0	0.637	2.55
	H(O3′)	0.569	0.176	23.0	0.376	2.55
	O4′	−1.035	0.008	105.7	75.093	3.40
methyl phosphate	O5′	−1.276	0.322	109.9	75.210	3.40
	O−P	−1.536	0.570	156.7	75.185	3.40

Therefore, these interactions undoubtedly should be considered as true hydrogen bonds.

The most interesting situation is observed for the C2′−H···O7 interaction in the north/syn conformer of pdC. The geometrical parameters of this potential hydrogen bond are almost suitable for hydrogen bonding. The C−H···O angle is slightly smaller than 120° (Table 3). The values of ellipticity and L_{RCP} are also close to suitable ranges but are slightly outside the normal values. Therefore, it is possible to consider this interaction as a hydrogen bond, but it represents a borderline case for the classification of such interactions.

The remaining interactions (C2′−H···O5′ in the south/anti conformer of pdT, pdC, and pdA) are characterized by unsuitable geometrical parameters, a shorter distance between the BCP and RCP, and considerably higher ellipticity at the BCP (Table 3). Therefore these interactions also should be considered as electrostatic interactions rather than the hydrogen bonds.

"Two Molecules" Criteria. As is mentioned above, the calculation of the changes of the atomic properties due to the formation of intramolecular hydrogen bonds requires an estimation of these properties for some model reference molecules containing unbound atoms. Taking into account the character of hydrogen bonds in DNT molecules, modeled isolated fragments of DNTs can be used as reference molecules. Therefore, for the reference molecules, we have chosen unsubstituted thymine, cytosine, adenine, and guanine, 2′-deoxyfuranose (ABS), and methyl phosphate anion. This choice of reference molecules allows a proper analysis of interfragment

Methylphosphate anion

ABS

Guanine

Adenine

Thymine

Cytosine
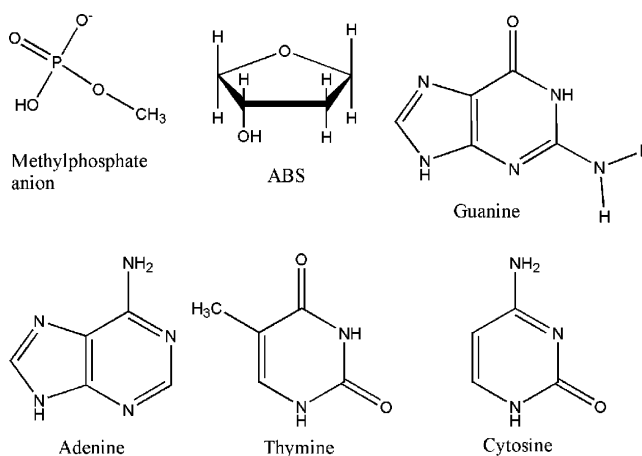
TABLE 5: Changes in Atomic Charges (Δq), Polarization Moment (ΔM), Volume (Δv), and Radii (Δr) of Atoms Involved in Potential Intramolecular Hydrogen Bonds in DNTs

molecule	conformer	D−H···A	atom	Δq	ΔM	Δv	ΔE	Δr
pdT	south/anti	**C6−H···O5'**	**H(C6)**	**0.092**	**−0.043**	**−14.8**	**0.025**	**1.00**
			O5'	**−0.02**	**0.002**	**−15.2**	**−0.330**	**0.86**
		C2'−H···O5'	H(C2')	0.057	−0.024	−9.0	0.010	0.52
			O5'	−0.02	0.002	−15.2	−0.330	0.66
		C1'−H···O7	H(C1')	0.057	−0.023	−9.7	−0.003	0.73
			O7	−0.02	−0.053	−3.4	−0.600	0.93
		C9−H···O−P	**H(C9)**	**0.095**	**−0.046**	**−10.0**	**0.029**	**0.78**
			O−P	**0.021**	**0.087**	**−5.3**	**−0.630**	**0.72**
pdT	north/anti	**C6−H···O5'**	**H(C6)**	**0.101**	**−0.047**	**−14.8**	**0.029**	**0.99**
			O5'	**−0.012**	**0.002**	**−13.0**	**−0.316**	**0.90**
		C9−H···O−P	**H(C9)**	**0.107**	**−0.051**	**−11.0**	**0.034**	**0.85**
			O−P	**0.022**	**0.095**	**−5.0**	**−0.633**	**0.80**
pdC	south/anti	**C6−H···O−P**	**H(C6)**	**−0.411**	**−0.168**	**−6.3**	**−0.201**	**0.93**
			O−P	**0.003**	**0.026**	**−7.7**	**−0.619**	**0.83**
		C1'−H···O7	H(C1')	0.050	−0.015	−8.7	−0.004	0.63
			O7	−0.025	−0.077	−2.2	−0.593	0.92
		C2'−H···O5'	H(C2')	0.062	−0.023	−7.5	0.015	0.55
			O5'	−0.014	0.007	−9.7	−0.320	0.62
pdC	north/anti	**C6−H···O5'**	**H(C6)**	**−0.408**	**−0.176**	**−8.5**	**−0.206**	**1.05**
			O5'	**−0.016**	**−0.011**	**−17.1**	**−0.316**	**0.95**
		C5−H···O−P	**H(C5)**	**−0.317**	**−0.649**	**−49.4**	**−0.237**	**0.3**
			O−P	**0.003**	**0.044**	**−0.9**	**−0.616**	**0.29**
pdC	north/syn	C6−H···O4'	H(C6)	−0.498	−0.142	3.4	−0.242	0.67
			O4'	−0.009	0.038	−9.1	−0.636	0.93
		C3'−H···O5'	H(C3')	0.053	−0.022	−7.8	0.007	0.51
			O5'	−0.015	0.020	−12.4	−0.316	0.85
		C2'−H···O7	**H(C2')**	**0.057**	**−0.021**	**−8.3**	**0.011**	**0.69**
			O7	**−0.247**	**−0.390**	**−21.7**	**−1.052**	**0.83**
		N8−H···O−P	**H(N8)**	**−0.361**	**0.080**	**9.9**	**−0.175**	**0.93**
			O−P	**−0.006**	**0.008**	**−12.0**	**−0.619**	**0.89**
pdA	south/anti	C2'−H···O5'	H(C2')	0.077	−0.019	−7.0	0.030	0.55
			O5'	−0.011	0.003	−9.1	0.290	0.61
		C8−H···O−P	**H(C8)**	**0.146**	**−0.043**	**−13.9**	**0.064**	**1.09**
			O−P	**0.005**	**0.010**	**−13.6**	**−0.020**	**0.98**
pdA	north/anti	**C8−H···O5'**	**H(C8)**	**0.106**	**−0.043**	**−10.8**	**0.037**	**0.91**
			O5'	**−0.010**	**−0.004**	**−12.1**	**−0.312**	**0.83**
pdA	north/syn	C2'−H···N3	H(C2')	0.070	−0.021	−9.08	0.018	0.75
			N3	−0.057	0.002	−6.0	−0.481	1.06
		N6−H···O−P	H(N6)	0.038	−0.015	−4.76	0.019	0.81
			O−P	−0.016	0.001	−9.9	0.621	0.86
pdG	south/anti	**C2'−H···O−P**	**H(C2')**	**0.109**	**−0.042**	**−13.6**	**0.036**	**0.85**
			O−P	**−0.003**	**0.014**	**−16.6**	**−0.635**	**0.78**
		C8−H···O−P	**H(C8)**	**0.141**	**−0.040**	**−14.5**	**0.055**	**1.07**
			O−P	**−0.003**	**0.014**	**−16.6**	**−0.635**	**0.99**
pdG	north/anti	**C3'−H···O−P**	**H(C3')**	**0.048**	**−0.028**	**−9.5**	**0.010**	**0.62**
			O−P	**0.001**	**0.005**	**−10.8**	**−0.020**	**0.57**
		O3'−H···O−P	**H(O3')**	**0.065**	**−0.054**	**−10.4**	**0.041**	**1.33**
			O(H)−P	**0.008**	**0.026**	**−12.2**	**−0.018**	**1.17**
pdG	south/syn	C2'−H···O5'	H(C2')	0.101	−0.036	−13.0	0.029	0.36
			O5'	−0.019	0.044	−10.1	−0.337	0.52
		C2'−H···N3	**H(C2')**	**0.101**	**−0.036**	**−13.0**	**0.029**	**0.36**
			N3	**0.003**	**−0.120**	**−12.2**	**−0.496**	**1.48**
		N10−H···O−P	**H(N10)**	**0.125**	**−0.066**	**−13.8**	**0.079**	**1.44**
			O−P	**0.010**	**0.001**	**−15.7**	**−0.637**	**1.28**
pdG	north/syn	C3'−H···N3	H(C3')	0.101	−0.031	−11.2	0.029	0.27
			N3	0.028	−0.086	−11.1	0.019	0.38
		N10−H···O−P	**H(N10)**	**0.119**	**−0.062**	**−13.0**	**0.075**	**1.40**
			O−P	**0.009**	**−0.005**	**−15.2**	**−0.026**	**1.25**

[a] True hydrogen bonds are listed in bold.

hydrogen bonds between the bases, the phosphate group, and the sugar to be provided. In the case of the C−H···O interactions within the sugar, such an analysis may be performed because of the absence of these bonds in ABS due to changes in the conformation of the furanose ring in abasic sugar.

The atomic properties of the hydrogen atoms in reference molecules reflect the general ability of these atoms to form hydrogen bonds (Table 4). In particular the atomic charges increase in the group C−H (ABS) < C−H (bases) < N−H <

O−H. The hydrogen atoms of the C−H bonds also possess significantly higher atomic polarizability and lower atomic energy.

An analysis of the changes of the atomic properties of the atoms forming hydrogen bonds (Table 5) demonstrates an agreement with the hydrogen bond criteria. Interactions between atoms result in an increase in the positive charge and atomic energy and a decrease in the polarization moment and volume of the hydrogen atoms. Also mutual penetrations of interacting

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atoms are observed; that is, the atomic radii of both bonded atoms in DNTs are shorter compared to reference molecules containing unbound atoms (Table 5). Thus, all interactions under consideration fulfill all conditions to be considered hydrogen bonds from the viewpoint of the "two molecules" criteria.

A comparison of the changes in the atomic properties for different interactions in DNTs demonstrates that, in general, a strengthening of hydrogen bonds results in an increase in the changes of atomic properties (Table 5). However, this is only a general trend, not clear dependence. For example, changes in atomic charge, polarization momentum, and volume for the N−H···O bond in the north/syn conformer of pdA are smaller compared to the C1′−H···O7 interaction in the south/anti conformer of pdT, which cannot be considered a true hydrogen bond according to the BCP criteria (Table 3). It should be noted that the mutual penetration of atoms in these two interactions is almost the same. Therefore the conclusion about the close relation between the concepts of mutual penetration developed within the AIM theory[26] and local softness seems ambiguous because two different hydrogen atoms obviously have different softness but almost the same mutual penetration.

Thus, it is possible to conclude that changes in atomic properties of interacting atoms cannot provide clear criteria to distinguish true hydrogen bonds and strong electrostatic interactions. Hocquet made a similar conclusion for nucleosides,[14,16] which is in agreement with the prediction by Platts[32,33] in the case of Δq and ΔE.

Conclusion

The results of the calculations using the extended 6-31++G-(d,p) basis set reveal that minima on the potential energy surface of DNTs corresponding to the conformers with a south/syn orientation of the nucleobase exist only in pdG where they are stabilized by the formation of intramolecular N−H···O hydrogen bonds between the amino and phosphate groups. Two conformers of pdC and pdA are revealed with an almost orthogonal orientation of the base with respect to sugar, instead of north/syn conformers of these nucleotides. This indicates that application of diffuse functions is a requirement for a correct description of the geometry of 2′-deoxyribonucleotides. An application of basis sets without diffuse functions may lead to the appearance of an artificial additional minima on the potential energy surface.

South/anti conformers are the most stable for all DNTs, except pdG where the south/syn conformer has the lowest energy. Among conformers of pdG with an anti orientation of the guanine moiety, the north/anti conformer is more stable, probably because of the formation of an additional intramolecular O−H···O hydrogen bond.

A topological analysis of the electron density distribution in DNTs reveals numerous intramolecular D−H···A interactions that may be considered as potential hydrogen bonds. However, a more detailed analysis of the properties of bond critical points for these interactions allows a clear enough distinction between true hydrogen bonds and strong electrostatic interactions of atoms with opposite charges to be made. On the basis of these data it is demonstrated that geometrical parameters and values of the electron density and the Laplacian of electron density cannot be used for classification of such interactions. Only the values of the bond ellipticity (ϵ) and distance between BCP and RCP allow a distinction between true hydrogen bonds and strong electrostatic interactions to be made. According to this analysis true hydrogen bonds should be characterized by the following values of BCP properties: $\epsilon < 0.1$ and $L_{RCP} > 1.4$ au for well-

defined hydrogen bonds and $\epsilon < 0.22$ and $L_{RCP} > 1.1$ au for all hydrogen bonds including very weak hydrogen bonds.

On the basis of these results it is possible to refine the classification of intramolecular hydrogen bonds in DNTs proposed earlier.[18,19] All hydrogen bonds may be divided into two groups: reference hydrogen bonds encountered in many conformations of all DNTs and specific hydrogen bonds that occur only in separate conformers of some nucleotides. The results of the calculations demonstrate that conformers with an anti orientations of the base are characterized by the C6/C8−H···O5′ or the C6/C8−H···O−P hydrogen bond. The former bond is more common for pyrimidine DNTs and the latter for purine nucleotides. Syn conformers contain two reference hydrogen bonds: N−H···O−P between the amino and the phosphate groups and C2′−H···O7/N3. These hydrogen bonds should significantly influence the orientation of the nucleobase with respect to the sugar and the phosphate fragments. Reference hydrogen bonds are also responsible for stabilization of the syn conformers of pdC, pdA, and pdG.

There are only three specific hydrogen bonds. There are C−H···O−P bonds between the methyl and the phosphate groups in both conformers of pdT, C2′−H···O−P bonds in the south/anti conformer of pdG, and O3′−H···O−P bonds in the north/anti conformer of pdG. The formation of the latter hydrogen bond is possible only in isolated nucleotides. Therefore in real DNA only two specific hydrogen bonds may occur. However, it should be noted that these hydrogen bonds are rather weak and probably do not influence significantly the properties of DNTs.

The other intramolecular interactions such as C1′−H···O7 in south/anti conformers of pdT and pdC should be considered as strong electrostatic interactions rather than true hydrogen bonds. In this case, probably, the presence of BCP in the electron density distribution reflects the existence of strong nonbonded interactions.

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