On the Interaction of Bare and Hydrated Aluminum Ion with Nucleic Acid Bases (U, T, C, A, G) and Monophosphate Nucleotides (UMP, dTMP, dCMP, dAMP, dGMP)

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The B3LYP/6-311+G(2df,2p) density functional approach was used to study the interaction that aluminum trication, in the bare and hydrated forms, establishes with the nucleic acid bases and the corresponding monophosphate nucleotides. In this investigation, we determine equilibrium geometry of all possible complexes resulting from the attachment of the ion on the different binding sites selected on each ligand. The relative energies of complexes and metal ion affinities are also given. The most meaningful aspect was found to lie in the energetics of this interaction that underlines a very high affinity of aluminum ion for the examined biological systems.

1. Introduction

The interaction of metal cations with nucleic acids is topical in the bioinorganic field because of its possible effects on synthesis, replication, and structural integrity of DNA and RNA.[1−4]

The interaction with phosphate group was more frequently observed, although evidence exists also for the direct attack of some ions on purine and pyrimidine bases. Generally, there are not simple rules to use to determine if an ion prefers to bind to these bases rather than to phosphate, but it is known that the binding to the last group, contrarly to what occurs when the metal ions bind to the bases, tends to stabilize the DNA double helix.

In the recent literature, numerous studies in which alkali,[5−16] alkaline earth,[17−22] and some transition mono- and divalent metal ions[20,23−37] interact with DNA and RNA nucleobases or base pairs are reported. Much less work was devoted to trivalent cations, such as Al(III), and their triply charged biological complexes.[38−44]

The toxicity of aluminum (III) was presumed 30 years ago.[45] Since this date, many authors[46,47] suggested that an high concentration of Al^{3+} in the human body, can be responsible for a renal malfunction that causes further pathologies such as anaemia, and encephalopathy. Furthermore, Al^{3+} was hypothesized to have a role in the onset of Alzheimer's disease,[48] amyotrophic lateral sclerosis, and Down's syndrome.[49] Uptake and retention of aluminum in tissues are favored by zinc deficiency[50] that is a possible condition of pregnant women, children, and the elderly.[51] In the studies on the aqueous solution of some metallic ions, Birchall[52] suggested that silicon deficiency also can enhance the uptake and toxicity of aluminum. Al^{3+} is able to compete with other metal ions, such as magnesium and iron, for preferential coordination to biological systems because of its high Lewis acidity and slow exchange of the ligands.[53−55] For instance, previous investigations demonstrated that the replacement of Mg^{2+} with Al^{3+} has an inhibitory effect on the enzyme-induced phosphate transfer reactions.[54] The localization of aluminum ion in cells occurs preferentially in the neuron nuclei, and affects the conformational variations of DNA necessary for genetic expression.[56] Some work, concerning the interaction of aluminum ion with biological systems, suggested its great affinity for phosphate in DNA.[57] Because of its hard acid nature, aluminum ion reacts favorably with hard bases that are generally oxygen-containing ligands.[41] Martin,[58] in contrast to the previous opinions, proposed that, in the cell nucleus, Al^{3+} binds to the ATP rather than to DNA. In the investigation of Zhang et al.,[59] the interaction between Al^{3+} and DNA was studied by UV spectroscopy and cyclic voltammetry (CV) under neutral pH conditions using $[Co(phen)_3]^{3+/2+}$ as indicator. The results of this study showed that the binding site for the aluminum cation is the phosphate group of the DNA backbone and that it binds to the nucleic acid much more strongly than the indicator. The large affinity of Al^{3+} for DNA was confirmed by the UV spectrum. An electrostatic nature of the binding of Al^{3+}−DNA was also supposed.

No theoretical analysis was attempted until now to describe the interaction between Al^{3+} and DNA or RNA nucleobases and monophosphate nucleotides.

In this paper, we report the first computational study in this respect. The aim of this work is the determination of structural, conformational, and energetic properties of the complexes that Al^{3+} ion forms with the ligands reported in the Chart 1. The aluminum ion affinity values for these systems will be useful to deduce which nucleobase is more susceptible to the ion attack and which is the preferred binding site on the ligands. Furthermore, this work will provide a contribution to clarify why aluminum may be toxic for cells.

2. Computational Details

We have performed a density functional (DF) study of all the species involved in the reactions

$$Al^{3+} + L \rightarrow Al^{3+}-L \quad (1)$$

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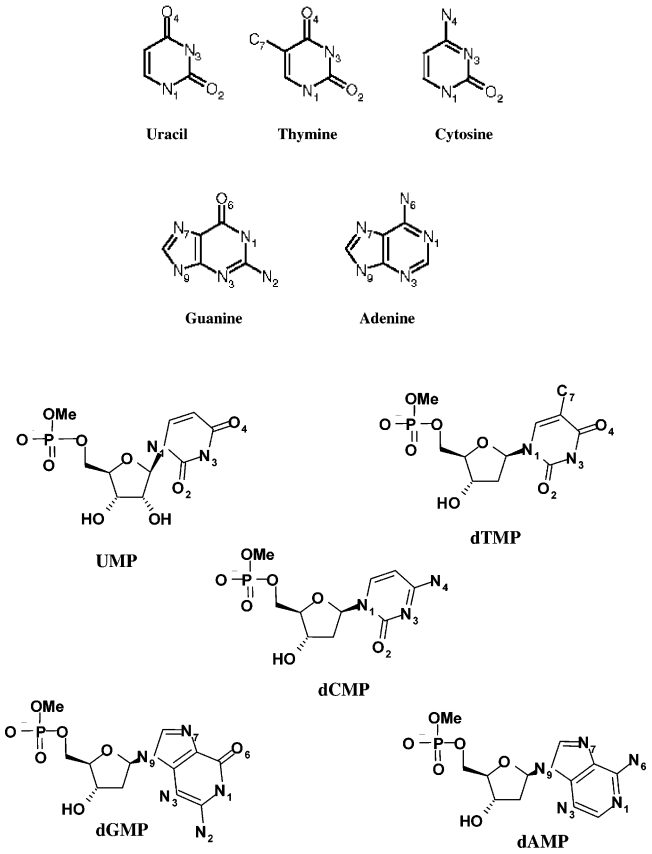
CHART 1



where L = uracil (U), thymine (T), cytosine (C), adenine (A), guanine (G), uridine monophosphate (UMP), deoxythymidine monophosphate (dTMP), deoxycytidine monophosphate (dCMP), deoxyadenosine monophosphate (dAMP), and deoxyguanosine monophosphate (dGMP).

All computations were done using Gaussian 03 code[60] with the hybrid Becke exchange (B3)[61]−Lee, Yang, and Parr correlation (LYP)[62] functionals. Optimizations were performed with the orbital 6-311G** [63] triple-ζ type set. Harmonic vibrational frequencies were computed, at this same level of theory, to verify the nature of minima of obtained complexes. A valence triple-ζ 6-311+G(2df,2p) basis set that contains one set of diffuse and two sets of polarization functions on every atom[63] was used for a better estimate of energies. Zero point energy (ZPE) corrections were enclosed in all energetic data.

Aluminum ion affinity (AlIA) was evaluated as negative variation of ΔH for reaction 1 and reported at 298 K.

The strategy adopted in the calculations with solvated aluminum was suggested by the results obtained in the initial calculations with the bare cation in which we have ascertained the existence of several mono- and bicoordinated Al^{3+}−L adducts for each nucleobase and nucleotide.

In the supposition that hydrated aluminum is also at least monocoordinated to the particular ligand, five water molecules were considered to complete its inner coordination sphere. This approach allowed us to determine the possible variation of the coordination mode on going from bare to hydrated metal ion. In fact, water molecules and binding sites on the ligand have the possibility to compete in the coordination process of aluminum ion, on the basis of the following reaction scheme:

$$[Al(H_2O)_5{-}L]^{3+} \rightarrow [Al(H_2O)_{5-n}{-}L]^{3+} + nH_2O$$

TABLE 1: B3LYP/6-311+G(2df,2p) Absolute (*E* in a.u.) and Relative (ΔE in kcal/mol) Energies for Free Tautomers of Nucleobases and Their Complexes with Al^{3+} Cation at 0 K

	L		Al^{3+}−L			
	E	ΔE		*E*	ΔE	AlIA[a]
U1	−414.884518	0.0	U1Al		11.7	424.5
			U1Al-ap		35.0	
U2		11.7	U2Al		6.0	
U3		18.9	U3Al	−655.982151	0.0	
T1	−454.188940	0.0	T1Al	−695.335482	0.0	466.9
			T1Al-ap		54.5	
T2		12.6	T2Al		15.3	
T3		18.3	T3Al		12.3	
C1	−394.980359	0.0	C1Al	−636.132818	0.0	470.6
			C1Al-ap		71.2	
C2		1.3	C2Al		38.2	
C3		2.1	C3Al		22.0	
C4		2.3	C4Al		32.6	
G1	−542.631348	0.0	G1Al		40.2	
G2		0.7	G2Al	−783.864968	0.0	522.2
G3		1.8			38.0	
G4		2.3	G4Al		76.0	
G5		4.4	G5Al		28.8	
A1	−467.369809	0.0	A1Al		50.3	457.2
A2		8.1	A2Al		23.7	
A3		18.5	A3Al	−708.581175	0.0	

[a] Aluminum ion affinity values (AlIA in kcal/mol) are given at 298 K.

where *n* takes the value of 0 in the presence of monocoordination, and the value of 1 if the hydrated ion is bicoordinated.

NBO analysis[64] was performed for all obtained complexes.

3. Results and Discussion

3.1. Interaction with Bare Cation. *3.1.1. Nucleobases Complexes.* An interesting aspect of nucleobases is their tendency to tautomerize.

In agreement with experimental findings,[65−69] previous theoretical works[70−79] demonstrated, especially for cytosine and guanine nucleobases, that many tautomeric forms have an energy that falls in a narrow range of values. The computations concerning this issue are reported in Table 1 in the first two columns.

The four cytosine tautomers, as well as the five for guanine, and the three for uracil, thymine, and adenine, which we have selected (see Figure 1), are the most stable forms. The literature data concerning the evaluation of energetic barriers for the tautomerization of nucleobases[6] in which proton shifts are usually involved, underline the difficulty of the interconversion between all tautomeric forms. However, it has been proven experimentally[65−69] that C1 and C2 tautomers of cytosine and G1 and G2 of guanine coexist. For uracil, thymine, and adenine, the rare tautomers (enol structures) L2 and L3 lie at energy values much higher with respect to the canonical form (keto structure) L1; consequently, U1, T1, and A1 are substantially prevalent irrespective of conditions. This is not the case of cytosine and guanine, for which the previous experience[5,6,17,23−25] suggests that the tautomeric forms L1 and L2 (for cytosine also L3) could have a crucial role in determining the correct metal ion affinity value.

The coordination sites for the metal ion were chosen on the basis of literature data concerning the interactions of Al^{3+} or other cations with biomolecules.[5,6,17,23−25,80] They involve the oxygen (both on the nucleobases and phosphate group) and nitrogen atoms for the monocoordination, and the −N, O−, −O, O−, and −N, N− pairs of atoms for the bicoordination. The out-of-plane interaction between the cation and the aromatic

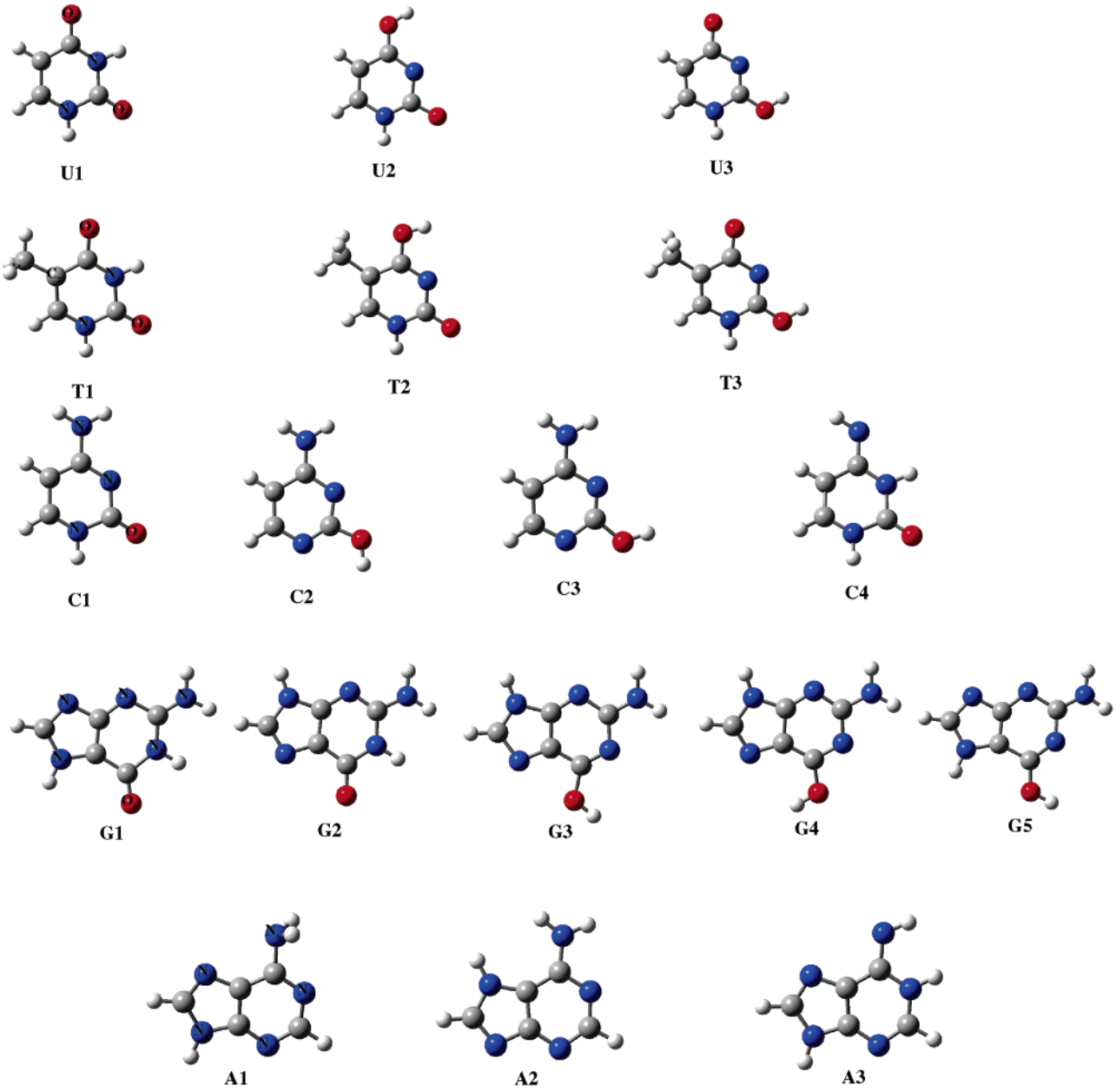


Figure 1. Low-lying tautomeric forms for each nucleobase.

rings was studied for both purines and pyrimidines, but π-complexes were obtained only in the cases of uracil, thymine, and cytosine. On the other hand, this type of interaction was never found for adenine and guanine.

A very large number of systems was examined in this phase of the study. In Figure 2, we have shown only the picture of the most likely complex $Al^{3+}-L$ for each base. The other complexes and their main dimensions can be found in the Supporting Information (see Figure 1S). However, in Table 1, we have reported the energetic data concerning all complexes obtained with each tautomer of Figure 1.

Al^{3+} forms four complexes with uracil tautomers. The rare forms U2 and U3 give rise to the most stable compounds (U2Al, U3Al) in which the cation appears to be bicoordinated to N3 and to the ketonic oxygen on duty.

The attack of Al^{3+} on the π-system of U1 generates a complex (U1Alap) whose rearrangements after the optimization rule out a simple electrostatic interaction. In fact, aluminum cation inserts in the C−N3 bond changing the uracil cycle nature. However, this system lies at very high energy (35 kcal/mol) with respect to the global minimum; thus, its formation is quite out of the question.

Taking into account that U1 is the energetically favored tautomeric form of uracil, we can indicate the U1Al system as the most probable one although it lies at 11.7 kcal/mol above the most stable complex U3Al. In U1Al, the cation is monocoordinated to the O4 atom with a bond length of 1.780 Å. The Al−O4−C valence angle is 157°.

For thymine, the number of complexes was the same as that of uracil. The stability order of these systems is, however, quite different. The global minimum T1Al is a monocoordinated complex in which the Al−O4 distance is 1.741 Å and the Al−O4−C angle of 176° is closer to linearity than the analogous angle in U1Al.

The less favored adduct is again the apical complex T1Alap. It lies at 54.7 kcal/mol above the most stable one, and as in the case examined before, the aluminum cation inserts in the cycle. The formation of this system and that of the bicoordinated

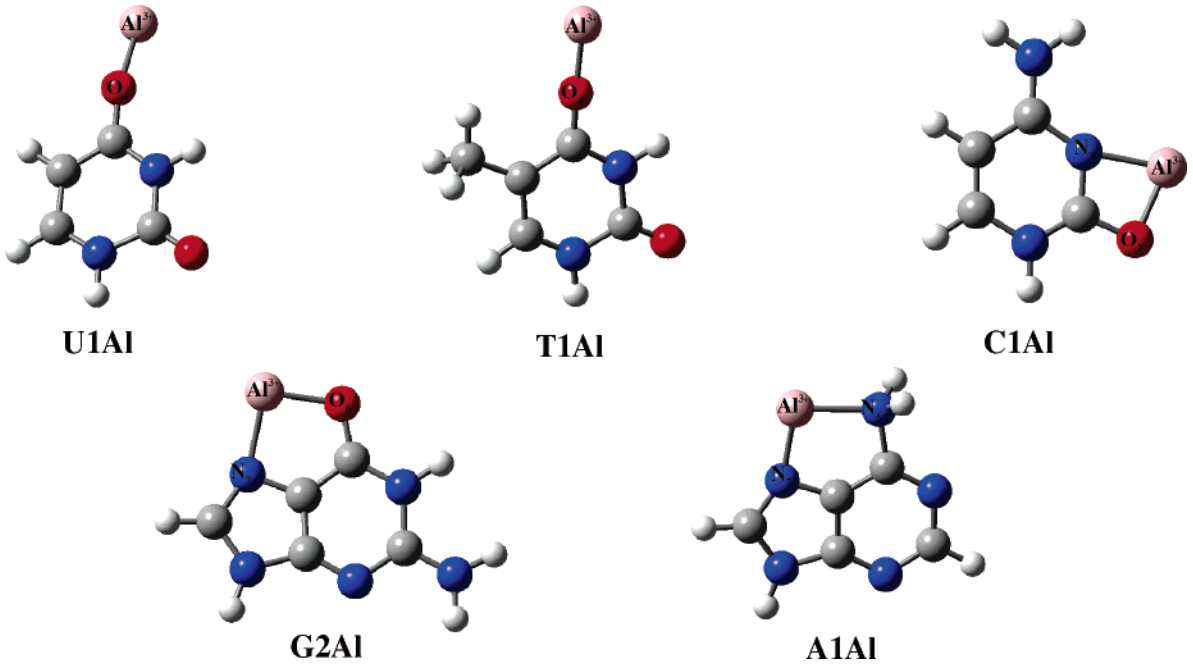


Figure 2. Equilibrium structures of the most likely complex Al^{3+}−L for each nucleobase.

complexes T2Al and T3Al, lying at 15.5 and 12.4 kcal/mol, respectively, is again improbable.

As far as the Al^{3+}−cytosine complexes are concerned, we found the following stability order: C1Al > C3Al > C4Al > C2Al ≫ C1Alap. As is evident from Table 1, the energetic separation between complexes is larger than that between free tautomers. This means that, despite the coexistence of some free tautomers, the aluminum affinity value for this base will depend only on the stability of metalated species.

In the most stable system C1Al, Al^{3+} cation is coordinated to both N3 and O2 atoms with bond lengths of 1.865 and 1.743 Å, respectively. This same result was previously obtained in a combined experimental−theoretical study on the interaction between aluminum atom and cytosine.[81]

The Al^{3+} in apical position on the C1 canonical tautomer destroys the cytosine ring planarity forming two σ-bonds with the N3 and C5 atoms (see Figure 1S). This rearrangement requires high energy (71.2 kcal/mol); thus, we can discard with certainty the real existence of this species.

The interactions of Al^{3+} with the π-system of pyrimidine bases are therefore purely fictitious, and the data obtained in this work do not confirm some literature findings that suggested this type of interaction for other metal ions.[82−84]

The aluminum−guanine complexes appear to be separated by large energy gaps.

The G2 tautomer forms the most stable complex G2Al. This species shows the cation coordinated to N7 and O6 with bond lengths of 1.939 and 1.819 Å, respectively.

The other canonical tautomer (G1) gives rise to an adduct that is located at 40 kcal/mol above the global minimum.

A previous experimental/theoretical work devoted to the determination of the neutral aluminum effect on the photochemistry of guanine[85] cannot be considered useful for a comparison because the neutral atom and ion behave differently.

The three tautomers of adenine interact with Al^{3+} cation, giving as many complexes.

As for other metal ions,[5,17,23−25] the most stable system is formed with A3 owing to the presence of imino nitrogen that is highly reactive toward positively charged species. However, A3, and likewise the A2 tautomer, is decidedly less stable than A1; thus, considering also the noticeable height of the interconversion barriers (45.86 and 38.78 kcal/mol are required for the A1→A3 and A1Al→A3Al transformation processes, respectively), the most likely complex should be A1Al. In this last system, the aluminum is practically bicoordinated to N7 and N6 atoms with distances of 1.833 and 2.013 Å, respectively. Although the distance between Al^{3+} and N6 gives an indication of a weak interaction, the absence of this bond leads to a structure that, like with other metal ions,[17] lies at very high energy.

Some theoretical work[18,20] has suggested that the interaction of adenine with cations should generate the N7-monocoordinated species. We think that the disagreement with our findings is because, in all these investigations, the authors never consider that the $-NH_2$ group on the base can be pyramidal. This is of fundamental importance for determining the most stable structure of the cation−adenine complex since an amino group lying in the molecular plane introduces a strong repulsion toward the incoming ion preventing the bicoordination.

The NBO analysis and the net charge values on Al^{3+} in all the studied systems provide some indication about the nature of the bond with the considered ligands. In the cases of monocoordination on oxygen atom, the bond appears to be covalent with a consistent ionic contribution. The oxygen participates in the covalent bond with a 2p orbital (100%) and aluminum ion with the 3s (96%) and a 3d (4%). In the N,O bicoordination, the N−Al^{3+} bond is characterized by a slight ionic contribution but is essentially covalent, while the O− Al^{3+} bond is basically ionic. In the N−Al^{3+} interaction, a nitrogen p orbital (100%) and the 3s (88.5%) and 3d (11.5%) orbitals of the aluminum ion are involved. The charge transfer occurs always from ligand to metal ion. The net charge value on Al^{3+} after the complex formation is on the order of $1.2|e|$.

3.1.2. Nucleotide Complexes. The subject of this part of the study is the interaction of aluminum ion with monophosphate nucleotides. To our knowledge, no literature information about the sugar involvement in the interaction exists.

The monophosphate nucleotides considered here are reported in Chart 1.

TABLE 2: B3LYP/6-311+G(2df,2p) Absolute (*E* in a.u.) and Relative (Δ*E* in kcal/mol) Energies for Free Nucleotides and Their Complexes with Al^{3+} Cation at 0 K

L		Al^{3+}−L			
	E		*E*	Δ*E*	AlIA[a]
UMP	−1517.774964	UMP-al		88.4	
		UMP-phos		68.4	813.0
		UMP-ap	−1759.582069	0.0	
dTMP	−1481.832937	dTMP-al		55.7	
		dTMP-phos		27.4	852.4
		dTMP-ap	−1723.637498	0.0	
dCMP	−1422.621170	dCMP-al		124.2	
		dCMP-phos		88.1	830.0
		dCMP-ap	−1664.486384	0.0	
dGMP	−1570.271800	dGMP-al	−1812.175941	0.0	
		dGMP-phos		85.9	856.3
dAMP	−1495.009712	dAMP-al	−1736.874311	0.0	
		dAMP-phos		73.3	844.1

[a] Aluminum ion affinity values (AlIA in kcal/mol) are given at 298 K.

The presence of the sugar−phosphate group in N1/N9 position (in the case of uracil, thymine, and cytosine/guanine, and adenine) makes the number of the tautomeric forms of nucleotides lower than that of nucleobases. Furthermore, the steric hindrance due to the dimension of this group makes some attachment sites inaccessible by metal ion. These arguments, together with previous results indicating that the most stable/likely Al^{3+}−L complexes derive from L1 tautomers, suggest that only calculations concerning the most usual canonical forms of nucleotides are meaningful. For each of them, we have explored all suitable attachment sites. Data were reported in Table 2, whereas structures of the most stable complexes are in Figure 3. For the other complexes, we refer the reader to both Supporting Information (Figure 2S) and Figure 4.

In the case of uridine monophosphate, three different positions were considered for the attack of cation. These involve the O4 atom and the π-system on uracil, and the oxygen atoms of the phosphate group. The O2 atom results in being sterically inaccessible because of the sugar proximity.

From Table 2, it can be observed that the optimization produces three minima. Among them, the most stable structure seems to derive from the interaction of Al^{3+} in apical position on the π-system of uracil ring. Really, the final complex UMP-ap does not conserve any original characteristics after the geometry optimization. The cation appears to be coordinated simultaneously to phosphate group and O4 atom because of a folding that involves both the first and second structural units of nucleotide (see Figure 4). Since such a type of folding should not actually occur in RNA, this finding must be considered valid only for an isolated UMP nucleotide.

The interaction with O4 atom on uracil was found to be the less favored one. The complex obtained in this case lies at 88.4 kcal/mol above the mentioned fictitious minimum. Thus, the most probable adduct in RNA should be that in which Al^{3+} is coordinated to the oxygen atoms of phosphate with an average distance of 1.849 Å.

This same situation arises again in the cases of thymidine and cytidine monophosphates.

The different magnitude of the energetic gaps (Δ*E*) between the various dTMP and dCMP complexes, obtained by selecting the same attachment sites as in UMP, can be ascribed to the degree of stabilization of the apical system that in turn depends on the number and strength of bonds that the cation forms with the different structural units in each nucleotide (see Figure 4).

For dGMP and dAMP, the apical complexes do not exist, so we have selected only two suitable attachment sites for the cation: the phosphate group for both nucleotides, and the N7−O6 and N7−N6 positions for guanosine and adenosine, respectively.

As far as these two nucleotides are concerned, we again found results that must be explained critically.

In fact, as can be observed in Figure 4, the complexes in which we should expect the simultaneous interaction of cation

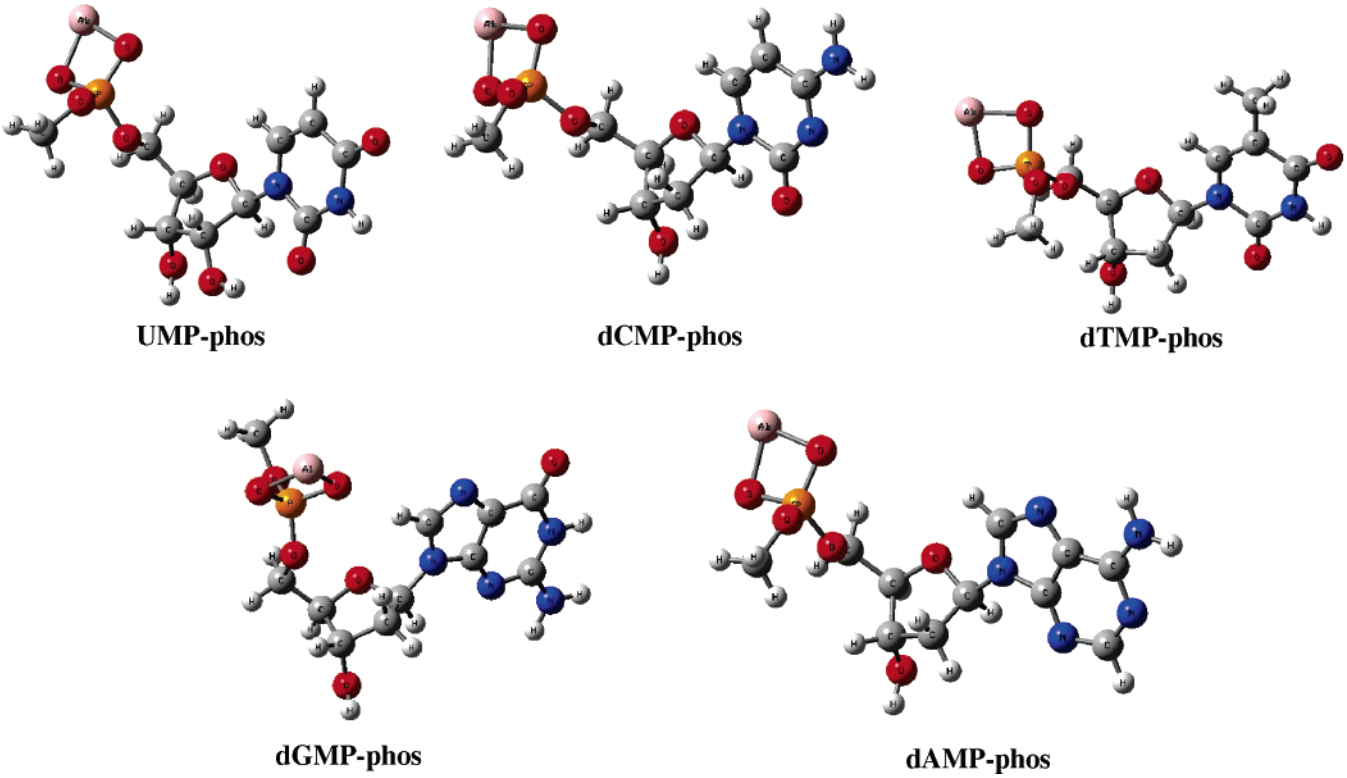


Figure 3. Equilibrium structures showing the interaction of Al^{3+} on phosphate group of nucleotides.

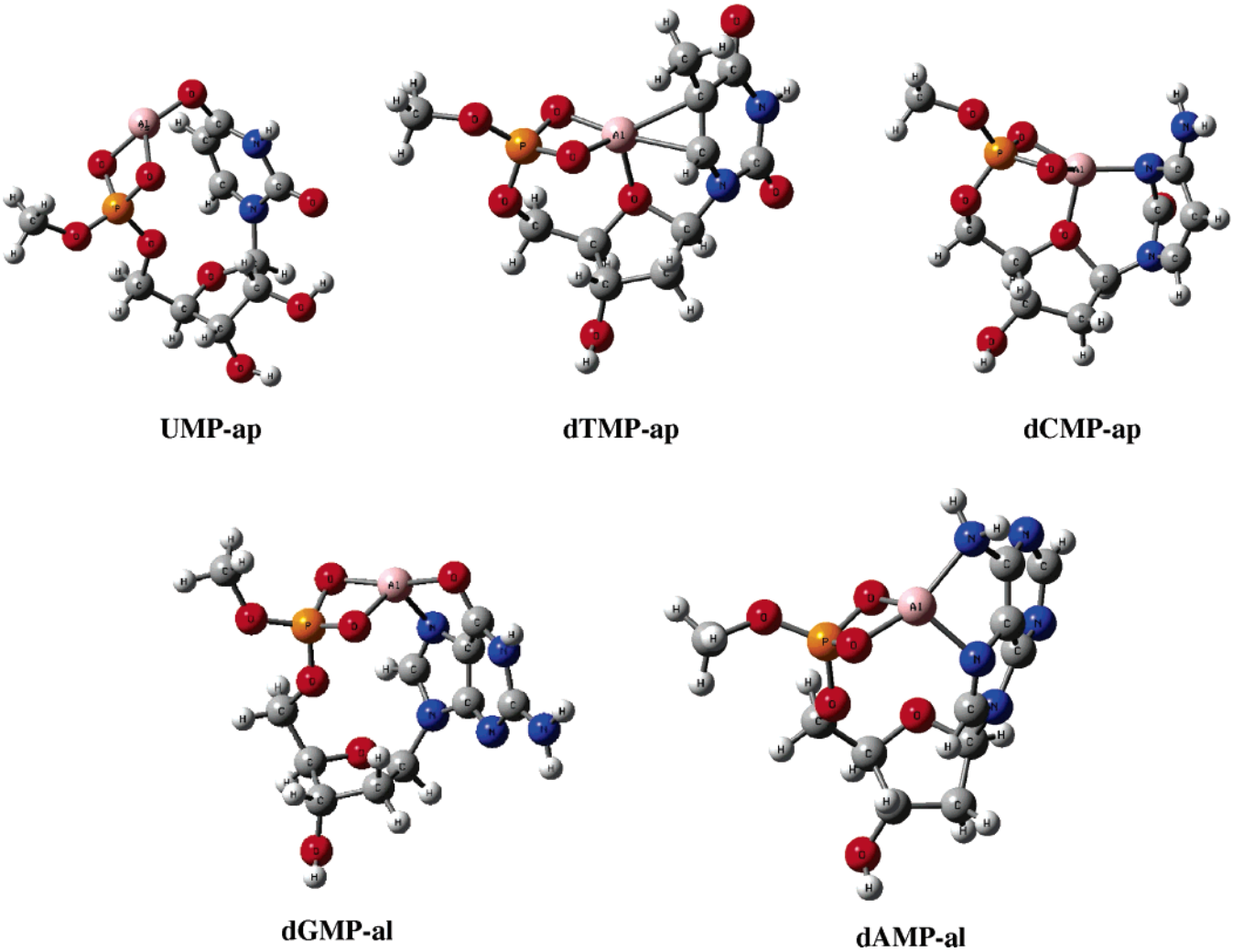


Figure 4. Folding in some Al^{3+}−monophosphate nucleotide complexes.

with guanosine N7−O6 and adenosine N7−N6 atoms, show also an involvement of the phosphate group. This additional interaction stabilizes the systems by 85.2 and 73.3 kcal/mol, respectively, with respect to those in which Al^{3+} is coordinated just to the phosphate.

Although these foldings involving the phosphate until the capture of the ion are not plausible in RNA and DNA, they nevertheless contribute to give some indication about the affinity of aluminum ion toward the various structural units of the nucleotides. In agreement with experimental suggestions, the largest affinity is found for the phosphate group.

For this reason, NBO analysis was performed only for the complexes of Figure 3.

Natural net charge on the complexed aluminum indicates that, in all cases, an average of $0.6|e|$ is transferred from the ligand to the cation. The slight covalent contribution to the bond arises from the molecular orbital formed by the overlap between the sp (p character 86.11%) and spd (s character 49.3, p character 48.3) hybrid orbitals of oxygen and aluminum ion, respectively

As suggested by Puškar et al.,[86] the interactions of aluminum ion with σ-bonding ligands in the gas phase are not always well described using the electrostatic model alone. They have demonstrated that the ligands that act as good σ-electron donors having the capacity to accept the back-donation of electron density from Al^{3+} into antibonding orbitals give generally very stable complexes.

In our case, owing to the complexity of the ligands, it is not easy to do a more detailed analysis of the orbital situation to determine the possible back-donation degree.

However, the ligand−cation charge transfer and the molecular orbitals that we found can be considered as a further confirmation of the mixed covalent−ionic nature of the bond that aluminum forms with some ligands.

3.2. Interaction with Hydrated Cation. The aqueous chemistry of aluminum ions is complicated by the presence of various mono- ($[Al(OH)]^{2+}$, $[Al(OH)_2]^{+}$, soluble $[Al(OH)_3]$, etc.) and polynuclear species depending on pH values and concentrations of Al^{3+}.[80] At a pH more acidic than ∼5, the ion remains unhydrolyzed, and the main mononuclear species is $[Al(H_2O)_6]^{3+}$. At a physiological pH, the soluble hydroxo complexes of Al^{3+} should be taken into account to describe the solution state of this ion. However, for a hydrated Al^{3+} coordinated to the negative phosphate group of nucleotides or to the donor atoms of nucleobases, the high positive charge of this small ion, responsible for the more acidic character of water molecules, is partially neutralized and the hydroxo complexes are less likely. Thus, we have chosen the model $[Al(H_2O)_5{-}L]^{3+}$ to study the effect of the metal microhydration on the coordination type and on the bond nature. On the other hand, this model was already used in some previous works[87,88] concerning the interaction of hydrated aluminum ion with biological molecules.

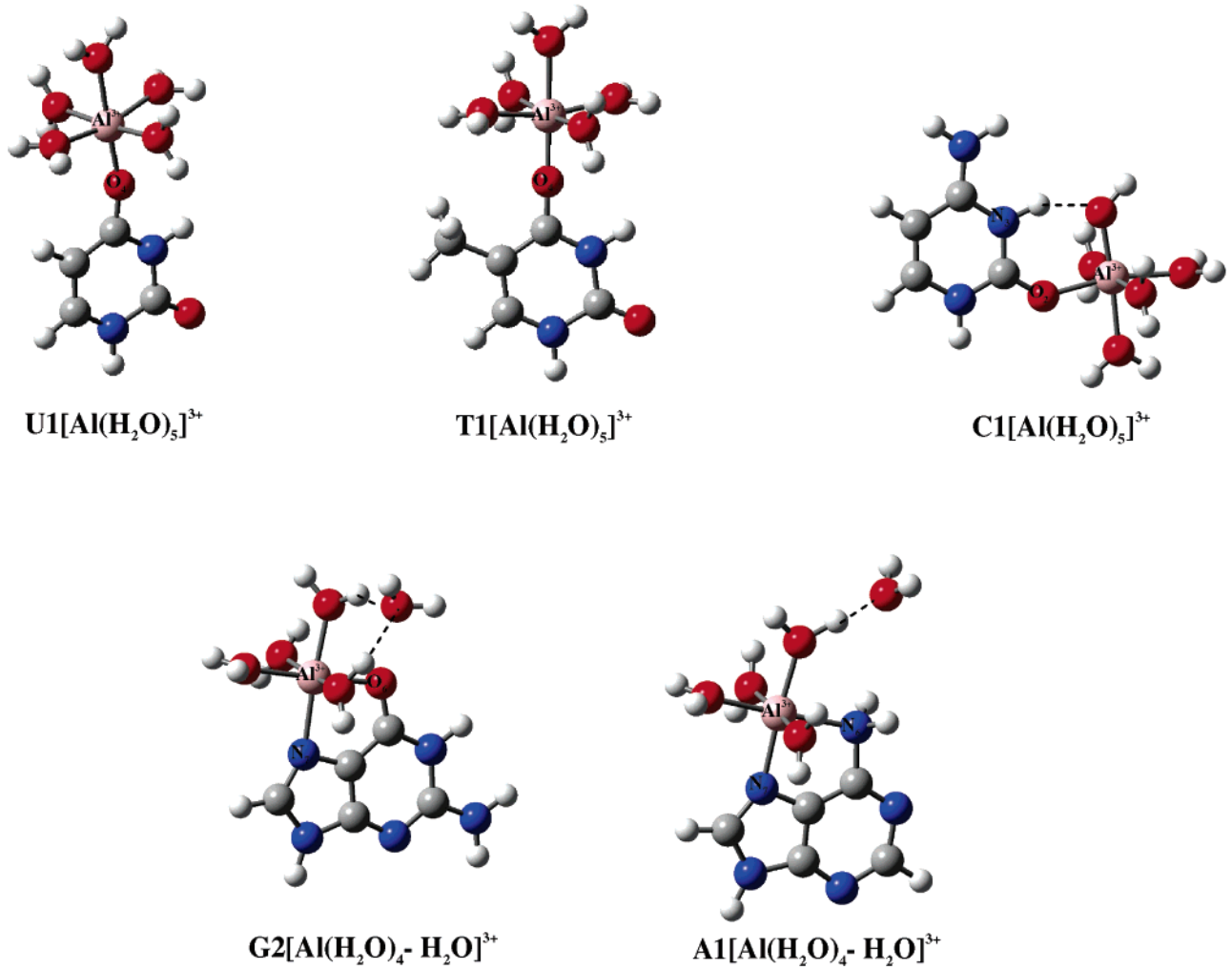


Figure 5. Equilibrium structures of the five $[Al(H_2O)_5]^{3+}$−nucleobase complexes.

TABLE 3: B3LYP/6-311+G(2df,2p) Absolute (*E* in a.u.) Energies for Nucleobases Complexes with the Al$[(H_2O)_5]^{3+}$ Cation at 0 K

$[Al(H_2O)_5]^{3+}$−L	*E*	AlAI[a]
U1$[Al(H_2O)_5]^{3+}$	−1038.674211	103.6
T1$[Al(H_2O)_5]^{3+}$	−1077.979872	104.4
C1$[Al(H_2O)_5]^{3+}$	−1018.852272	155.2
G2$[Al(H_2O)_5]^{3+}$	−1166.496908	151.9
A1$[Al(H_2O)_5]^{3+}$	−1091.161075	104.6

[a] Aluminum ion affinity values (AlIA in kcal/mol) are given at 298 K.

Al^{3+} hexa- and penta-aqua complexes were found to have a Th and an irregular triangular bipyramidal symmetry, respectively. The water affinity for the $[Al(H_2O)_5]^{3+}$ species was computed to be 48.6 kcal/mol. To take into account the loss of a further water molecule, which is the case for a cation bicoordinated to a nucleobase, we have evaluated also the affinity of the water molecule for the tetrahydrated $[Al(H_2O)_4]^{3+}$ system. The obtained value was 50.7 kcal/mol.

3.2.1. Nucleobase Complexes. Complexes resulting from hydrated cation−nucleobase interactions were reported in Figure 5. Energetic parameters were collected in Table 3.

All attempts to find a stable complex in the case of the interaction of aluminum ion with the π-system of the nucleobase rings failed. Only for uracil did we obtain a mimimum that is, however, identical to that arising from the interaction of the cation with the O4 atom of nucleobase (see Figure 5).

Uracil and thymine gave rise to two monocoordinated adducts whose structures are not so different from those found in the previous computations for the bare ion. Hydrated Al^{3+} establishes with the O4 atom of the considered nucleic acid bases a bond of 1.756 and 1.757 Å, respectively. The cation assumes a nearly octahedral geometry.

For cytosine, the final product presents interesting features. Contrary to what happens for bare cation, hydrated aluminum is monocoordinated to the O2 atom of the base with a distance of 1.913 Å. The hydrogen of one water molecule is transferred to N1 although it remains anchored to the −OH group with a hydrogen bond of 1.730 Å. This can be due to the residual polarizing effect of the aluminum ion on the water molecules of the first sphere.[89] The analogous complex in which this solvent molecule conserves its hydrogen atom lies at 8.1 kcal/mol.

The solvation sphere does not modify the coordination type of aluminum cation to purine bases.

The results for guanine and adenine show that the $[Al(H_2O)_5]^{3+}$ species expels one water molecule in order to establish two simultaneous bonds with N7 and O6 and N7 and N6 atoms, respectively. In both cases, the ejected solvent molecule remains in the proximity of the complexes thanks to some hydrogen bonding with the inner sphere (see Figure 5).

In the guanine−Al$[(H_2O)_4H_2O]^{3+}$ system, the bond that aluminum forms with oxygen is shorter than that with nitrogen (1.914 versus 2.040 Å). This is normal for aluminum because of its large affinity for oxygen containing species. Instead, the

TABLE 4: B3LYP/6-311+G(2df,2p) Absolute (E in a.u.) Energies for Nucleotides Complexes with Al[$(H_2O)_5$]$^{3+}$ Cation on Phosphate Group, at 0 K.

	E	AlAI
UMPphos[$Al(H_2O)_5$]$^{3+}$	−2141.988293	369.4
dTMPphos[$Al(H_2O)_5$]$^{3+}$	−2106.084851	393.6
dCMPphos[$Al(H_2O)_5$]$^{3+}$	−2046.909101	416.2
dGMPphos[$Al(H_2O)_5$]$^{3+}$	−2194.575419	426.1
dAMPphos[$Al(H_2O)_5$]$^{3+}$	−2119.300890	418.3

[a] Aluminum ion affinity values (AlIA in kcal/mol) are given at 298 K.

larger basicity of N7 with respect to N6 explains the different strength and length of N7−Al^{3+} (1.987 Å) and N6−Al^{3+} (2.124 Å) bonds in the adenine complex.

NBO analysis indicates that hydrated aluminum establishes an ionic bond with nucleobases. This can be deduced comparing the total charge on the cation before and after the interaction (2.1 vs 1.9|*e*|, respectively).

3.2.2. Nucleotide Complexes. Since in the interaction with nucleotides the naked aluminum ion is always mainly attracted by the phosphate group, in the case of hydrated cation we considered only this attachment site. Really, since the computations are performed in the gas phase, where nucleotides enjoy a wide conformational freedom, the potential involvement of the other structural units is however possible during the optimization process.

The energetic data and the equilibrium geometries of the stable adducts Al[$(H_2O)_n$]$^{3+}$−nucleotides were collected in Table 4 and Figure 6, respectively.

Contrary to what was found in the complexes of the bare ion in which we had the bicoordination of the metal center, now all five structures show the pentahydrated aluminum linked to a single oxygen atom of the phosphate. This means that the cation prefers to keep a water molecule rather than to bind another oxygen atom. All the structures are characterized by a number of hydrogen shifts or hydrogen bond interactions, between the oxygen atoms of water molecules and those of phosphate group, that introduce stabilizing effects. In the dTMPphos−Al[$(H_2O)_5$]$^{3+}$ complex also the sugar moiety appears to be involved in the hydrogen bond network.

The bond between the hydrated ion and the oxygen atom of the phosphate is again completely ionic as revealed by the comparison between total net charge on free and coordinated hydrated cation (2.1 vs 1.9|*e*|, respectively).

3.3. Aluminum Ion Affinity. The aluminum ion affinity (AlIA) values reported in Table 1 indicate that the nucleobases interact very favorably with the naked cation in the order G > C > T > A > U.

The highest values of AlIA are obtained in correspondence with bicoordinated complexes. The reason that adenine does not follow this trend strictly can lie, as mentioned before, in the weak interaction between Al^{3+} and N6 atom.

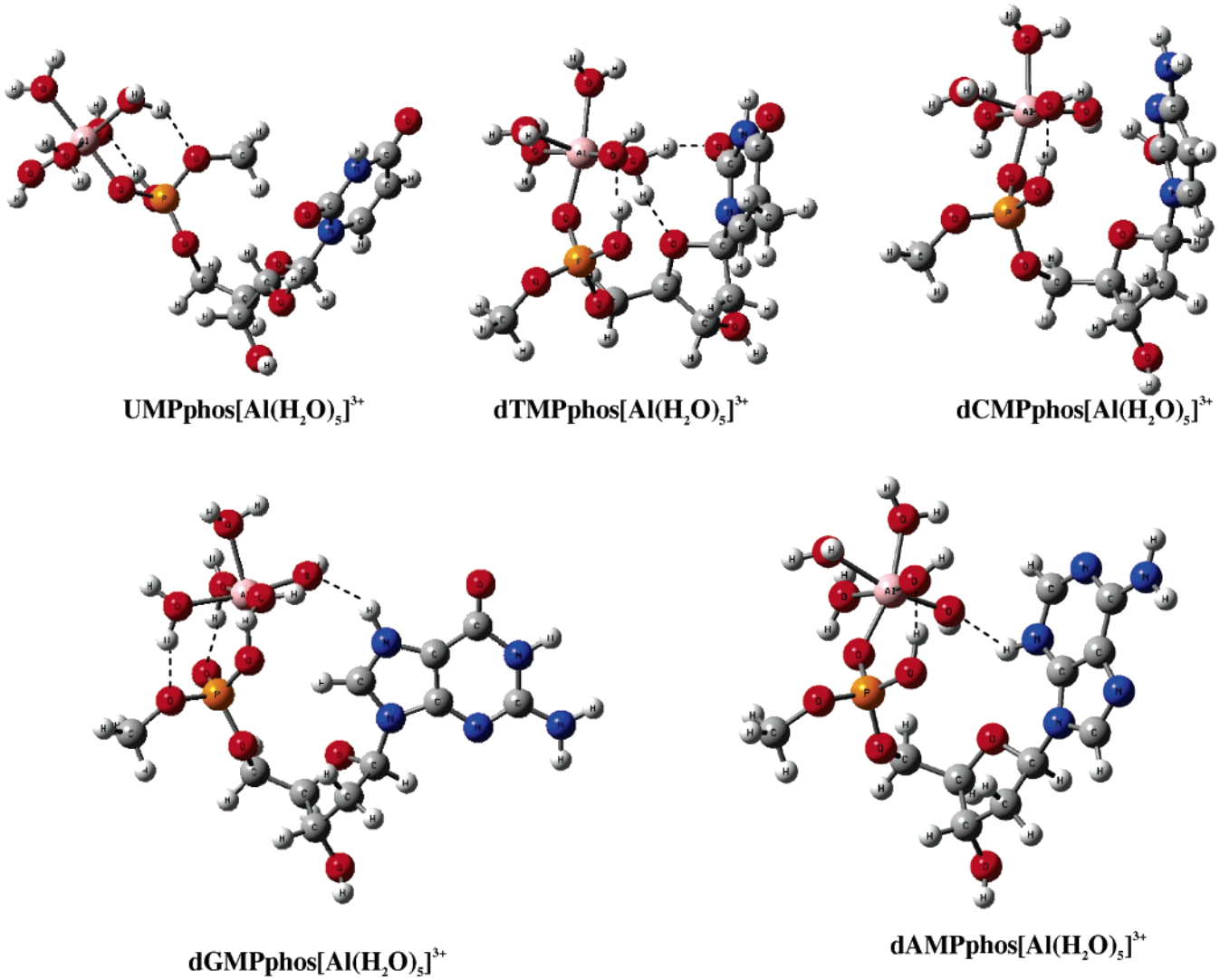


Figure 6. Equilibrium structures of the five [$Al(H_2O)_5$]$^{3+}$−nucleotide complexes.

The addition of a solvation shell to the metal center reduces drastically (see Table 3) the AlIA values. This is not surprising if we take into account that hydrated aluminum has an orbital availability very different from that of bare cation and that the strength with which it can bind additional ligands decreases gradually.

Actually, the loss of the second water molecule from the $Al[(H_2O)_6]^{3+}$ species, requires an energetic cost that is larger than that required for the loss of the first solvent molecule (101.4 vs 48.6 kcal/mol).

The new trend of AlIA values is: C > G > A ≥ T ≥ U.

At a first glance, this sequence seems to be totally different from that obtained in the previous case, but the AlIA values of A, T, and U are not sufficient to establish a rigorous trend because of their similarity. The inversion of the AlIA values of guanine and cytosine can be attributed to the change of the coordination type and to the protonation of N3 on cytosine. AlIA values for nucleotides were computed taking as references the complexes in which the metal cation is linked to the phosphate group. In fact, we think that although these are not the most stable species because of the high flexibility of nucleotides in gas phase, they probably become the most significant ones when the nucleotides are kept "strained" in DNA and RNA helices.

In the case of naked aluminum ion, AlIA values are very high thanks to the bond that the metal ion forms with the two oxygen atoms on which the negative charge of phosphate group is delocalized.

The Al^{3+}affinity follows the order dGMP ≥ dTMP > dAMP > dCMP > UMP.

No comparison is possible with values obtained for nucleobases since another structural unit is involved in the interaction.

Nucleotides interact with hydrated cation less strongly than with the naked one. The AlIA values, as expected, have a magnitude completely different from that obtained in the absence of water molecules. This can be explained not only by the fact that the solvated cation has a minor capacity of coordination but also by the different nature of the bond and by the different metal coordination type. Thus, a new order of AlIA values is obtained: dGMP > dAMP ≥ dCMP > dTMP > UMP.

4. Conclusions

This paper collects the results of the first computational study concerning the interaction of the bare and hydrated aluminum cation with nucleobases and monophosphate nucleotides.

The most significant aspects of the investigation are reported here.

Aluminum ion forms stable complexes with all the considered ligands.

The coordination type on nucleobases remains essentially the same when the hydration shell is added to the naked cation, but binding energy values decrease significantly in accordance with the different orbital availability of the metal cation and with the change of bond nature.

Except for the sugar moiety, all other selected sites can be suitable for the cation attack on nucleotides. The phosphate group is practically always involved in the interaction.

Naked ion appears to be coordinated to both oxygen atoms of phosphate, while hydrated aluminum ion binds only one of these two atoms since the other is often involved in some hydrogen bonding with water molecules of the metal solvation shell.

Also in this case and for the same previous reasons, binding energies decrease on going from bare to hydrated cation.

Very high binding energies involved in this interaction demonstrate the elevated affinity of aluminum trication for both nucleobases and nucleotides.

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Supporting Information Available: Figure containing equilibrium geometries for all relative minima for each nucleobase. Figure containing the high lying Al^{3+}−monophosphate nucleotide complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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