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Solvent Dependence of Conformational Distribution, Molecular Geometry, and Electronic Structure in Adenosine

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Solvation dynamics of adenosine in water and chloroform solvents under ambient conditions has been investigated using both force-field molecular dynamics (MD) and first-principles Car−Parrinello molecular dynamics (CPMD) calculations. First, the solvent dependence of the equilibria between anti−syn forms, C(3′)-*endo*−C(2′)−*endo* conformations, and carbinol group rotamers has been discussed from MD calculations. We find that in both the solvents the adenosine molecule can remain either in anti or syn conformations. But, the anti−syn interconversion occurs relatively faster in water solvent than in chloroform solvent. Because of the relatively larger time scale for the interconversion, anti and syn conformational states of adenosine are studied separately in water and chloroform solvents using CPMD calculations. The dipole moments calculated from CPMD and MD calculations for adenosine in water are significantly larger than in chloroform solvent. On the basis of the CPMD calculations, the syn form of adenosine in water has a larger dipole moment than the anti form. Moreover, the molecular geometry of anti and syn forms of adenosine in these two solvents is reported. We report a remarkable solvent effect on the geometry of the anti form of the adenosine, which is attributed to differences in the intermolecular and intramolecular hydrogen-bonding stabilization. We also report the solvent effect on the frontier Kohn−Sham orbitals and energy gaps for anti−syn conformational states. Finally, we report the solvation shell structure of adenosine in both the solvents, and we find that the solvent−solute interaction is site-specific in the case of water while in chloroform solvent the interaction is globular isotropic in nature.

1. Introduction

The connection between the structure of a biological molecule and its chemical reactivity is well documented in the literature and is known as the principle of structure−activity relationship.[1,2] The structure of a biological molecule is determined by many factors, such as the sequence of the building blocks, solvents,[3,4] pH,[5] ligands, temperature,[6] and pressure.[7] Hence, the function of a biological molecule can be altered or tuned by change in any of these parameters. Investigations into the structure of the biological molecules due to change in these parameters are very important to understand the working mechanism of these molecules as biocatalysts. Both experimental and theoretical techniques have been used extensively to understand these structural variation in the biological molecules.[8−12] Here, we study the solvent effect on the conformational equilibrium and molecular geometry in the case of a small biologically important molecule, namely, adenosine. Adenosine plays an important role in the biochemical processes such as energy transfer and signal transduction. Adenosine has been studied in different solvents (such as water,[13] DMSO,[13,14] and ammonia[15]) as well as in its condensed solid form. X-ray diffraction studies at different temperatures are reported for solid adenosine.[16,17] Adenosine crystallizes in a monoclinic space group with two molecules per unit cell. In the crystal, the packing is such that the adenine units are arranged in stacking with an interplanar distance of 3.57 Å. Another important structural aspect is the conformation of the furanose ring which is C(3′)-*endo* in nature. In the crystal, each adenosine molecule is hydrogen bonded to six neighboring molecules. Further studies of adenosine include photophysical dynamics of adenosine in solution, reported by Pancur et al.,[18] and the fluorescence behavior of adenosine in neutral solution, studied using synchrotron excited time-resolved fluorescence spectroscopy.[19] The excited-state deactivation processes and relaxation dynamics for adenosine in water have been reported from femtosecond time and wavelength resolved fluorescence and absorption spectroscopic studies.[20] Magnetic circular dichroism studies are also reported for adenosine in water for the range 200−300 nm.[21] The conformational equilibrium of adenosine in aqueous solution has been discussed in detail in the literature.[22,23] Adenosine and other such nucleosides can exist either in syn (closed) or anti (open) form, and the interconversion between these two conformations is achieved by the pivot move along the C−N glycosidic bond.[22] It has been reported that in the crystalline phase the nucleosides have a conformational preference toward the anti conformation. On the basis of the NOE measurements and MCD[23] studies, it has been reported that the syn conformation is not excluded for the purine nucleosides in solution. In fact, the anti−syn equilibrium can be shifted[14] toward syn conformation by placing bulky substituent in C_{11}[24] (see Figure 1) or by changing to nonaqueous solvent. Ultrasonic relaxation studies[25] on adenosine in aqueous solution report three different relaxation processes which are listed as (1) the relaxation process due to the solvation of the adenosine, (2) the relaxation process due to the anti−syn conformational equilibrium, and (3) the relaxation process due to the ribose ring puckering equilibria. Interestingly, the second relaxation process due to anti−syn conformational equilibrium is missing in the pyrimidine nucleosides. The activation energy

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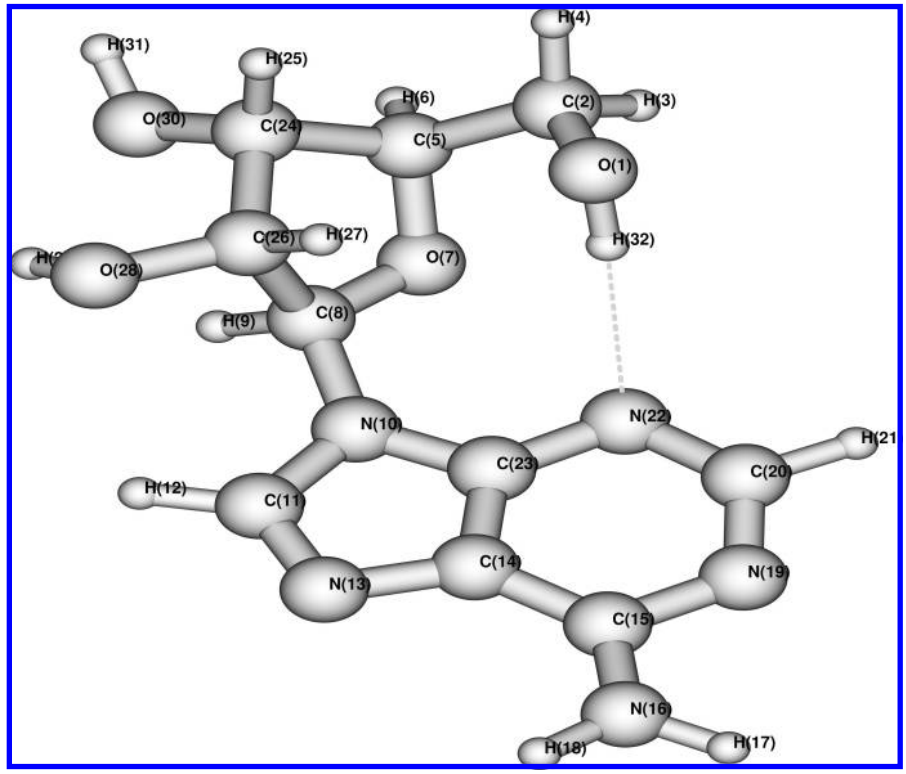

Figure 1. Molecular structure and labeling for adenosine.

for the anti−syn interconversion is 6.2 kcal/mol, which is calculated from the temperature dependence of adenosine relaxation time.[25] We are not aware of any experimental study on the solvation dynamics of adenosine in chloroform which is a nonpolar solvent. Also, there are not much reports in the literature on the solvent dependence of geometry of the furanose ring and hydroxy methyl (carbinol) group which are the other flexible fragments in the adenosine molecule.

There are a very few theoretical calculations on adenosine molecule. Extended Huckel theory based calculations[26] were carried out on adenosine-like nuceleotides in the gaseous phase which report the molecular geometry of anti and syn conformational states in the gaseous phase. The calculations based on the classical potential method[13] report various minimum-energy structures along the glycosidic torsion angle rotation and among the furanose ring conformational states and carbinol group rotamers. Recently, theoretical studies by Santoro et al.[27] using a polarizable continuum model and time-dependent density functional theory report the electronic spectra of adenosine in water solvent.

From the above it follows that a detailed theoretical study on the anti−syn conformational equilibrium for adenosine in aqueous and nonaqueous solvents complements and aids the understanding of the reported experimental studies. Here, we have studied adenosine in water and chloroform solvents. Our interest is to study the solvent effect on different conformational equilibria and to study the solvent-induced changes in the molecular geometry and electronic structure. We have used force field molecular dynamics (MD)[28] and first-principles Car−Parrinello molecular dynamics (CPMD)[29,30] to study the molecular motions in both a detailed short and a longer time scale. The effect of solvents on the molecular geometry and electronic structure is investigated from the CPMD calculations. Because of the computational expenses of the CPMD calculations, this technique has been used to study relatively smaller systems.[31−34] We cannot currently afford this method to understand the molecular processes such as conformational transitions occurring on a relatively longer time scale without the aid of enhanced sampling techniques[35] which are yet to be implemented within the Car−Parrinello mixed quantum mechanics/molecular mechanics setup. But an averaging of properties over different conformational states is very important to exactly predict and compare with the experimental spectra and NMR results. Therefore, this study also illustrates the strength of combined and judicious use of less accurate but computationally less demanding molecular dynamics calculations and first-principles CPMD calculations that are more accurate but very expensive tools. To clearly indicate when these two different computational techniques have been used, the study is divided into two sections in the discussions below.

2. Computational Details

2.1. Molecular Dynamics Calculations. Earlier reported molecular orbital calculations[26] on a single molecule of adenosine finds that the anti form of adenosine is more stable than the syn form. Also, in the crystal phase except guanosine, all the nucleosides exist in the anti form.[36] So in the present study the initial structure for adenosine is prepared in the anti conformation. Then adenosine was solvated both in TIP3P water and in chloroform solvents separately. We have used the parm99[37] force field to describe the interaction of adenosine. For water solvent TIP3P water model and for chloroform GAFF[38] force field have been used. A total of 6685 water molecules were included for adenosine−water solute solvent system (now onward referred as the ADO−water system). The simulation was carried out in an orthorhombic box with dimensions 56.9, 61.4, and 58.2 Å. And in the case of adenosine−chloroform solute solvent system (which is referred as the ADO−chloroform system), 1438 chloroform solvents were included in a orthorhombic box of dimensions 56.6, 60.5, and 57.1 Å. The simulations were carried out using the periodic boundary condition. Both the systems were studied at room

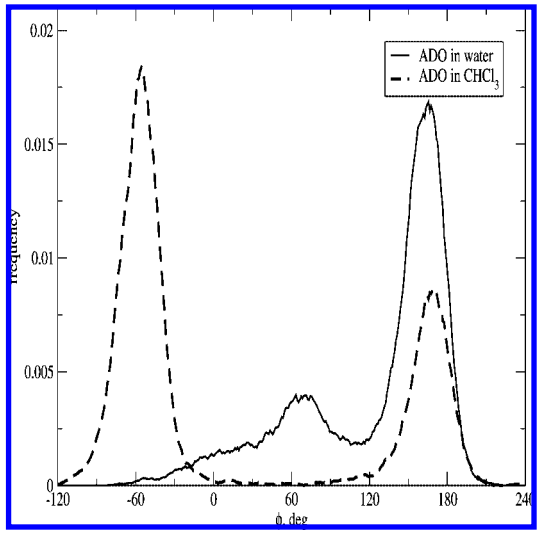

Figure 2. Anti−syn conformational distribution for adenosine (referred to as ADO) in water and chloroform solvents.

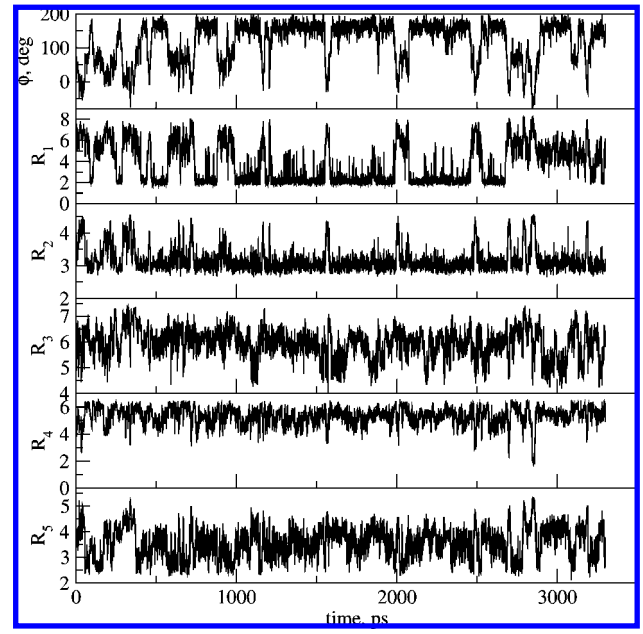

Figure 3. Time evolution of various molecular structural parameters defining the conformational state of adenosine in water.

temperature and at 1 atm pressure in an isothermal−isobaric ensemble. In these calculations, the temperature and the pressure of the system are maintained to the required values using the weak-coupling algorithm[39] which couples the system to external baths. First, the MD calculations were carried out using amber8[40] software by keeping adenosine fixed in space, and the total time scale for this run was 100 ps. This calculation allows the solvent structure around adenosine molecule to relax and equilibrate and avoid the stabilization of adenosine by intramolecular hydrogen bonding before fully solvated. The time step for the integration of equation of motion was 1 fs. Following this a long MD calculation was performed without the spatial constraint on adenosine. The total time scale for this run was 3.3 ns for the ADO−water system and 4.85 ns for the ADO−chloroform case. The particle mesh Ewald[41] method was used for treating electrostatic interactions.

2.2. Solvent Dependence of Different Conformational Equilibria. ***2.2.1. Anti−Syn Conformational Equilibrium.*** Here, we discuss the conformational equilibrium between the anti−syn forms of adenosine in water and chloroform solvents. Since this interconversion process occurs in a relatively larger time scale (which will be discussed in the later part of the text), only the MD results are presented. The anti−syn conformations are defined on the basis of relative positioning of the ribose ring to the adenine base through the glycosidic bond. We have considered the atoms $H_9-C_8-N_{10}-C_{23}$ (see Figure 1) for the definition of the dihedral angle, ϕ. The conformation is refined to be anti when ϕ is around $\pm 60°$, and the conformation is defined to be syn when the ϕ is around 180°. We have calculated the dihedral angle distribution from the trajectories (obtained from MD calculations) for the ADO−water and ADO−chloroform systems which is shown in Figure 2. On the basis of the two major peaks observed, we report that adenosine can exist in both anti and syn forms in water. This is in complete agreement with relaxation spectra reported by Rhodes and Schimmel,[25] which suggests that the adenosine in aqueous solution is in anti−syn equilibrium. Even in chloroform solvent, the adenosine can adopt the anti and syn conformational states. The distribution curve shows that adenosine in chloroform strictly exists in any one of these two conformational states. But in the case of water it exists in almost all conformational states with higher preference to anti−syn states. We find that the population of syn form is larger (the percentage population is 67.3%) in water solvent while the population of anti form is more (the percentage population is 68.5%) in chloroform solvent. The distribution curve (see Figure 2) with ϕ value beyond 120° has been assigned for the syn form. Moreover, in the case of water solvent the interconversion occurs frequently with a rate of 25.8 jumps/ns, while the rate in chloroform solvent is 1.9 jumps/ns. Figure 3 shows the time evolution of ϕ and various intramolecular bond lengths, R_1, R_2, R_3, R_4, and R_5 in water solvents. These are the bond lengths between the pairs of atoms 32−22, 7−22, 31−22, 29−22, and 28−12, respectively (for the numbering see Figure 1). It is clearly seen from Figure 3 that when the molecule is in syn form, the value of R_1 falls close to 2 Å, which suggests an intramolecular hydrogen bonding between the hydroxyl group connected to C_2 and N_{22}. It is also noticeable that the bond lengths R_2 and R_5 are closer to 3 and 2.5 Å, respectively, in this conformation. But when the molecule is in anti form, all of these bond lengths are larger in magnitude. It is important to notice that only R_4 becomes shorter with a value close to 2 Å for a fraction of time, which means the formation of intramolecular hydrogen bonding between the hydroxyl group connected to C_{26} and N_{22}. Other than this, it appears that the anti form is mostly stabilized by intermolecular hydrogen bonding with solvent water molecules.

Figure 4 displays the time evolution of ϕ, R_1, R_2, R_3, R_4, and R_5 for adenosine in chloroform solvent. In the chloroform solvent, the conformational jumps are not very frequent as in water. In chloroform solvent, the syn form has a similar geometry like the syn form in water. Similar to the case in water solvent, the bond lengths R_1 and R_2 are relatively lower with magnitudes closer to 2 and 3 Å, respectively. In chloroform solvent, when the molecule is in anti form, the molecule is stabilized only by intramolecular hydrogen bonding, which is seen from the time evolution of the bond length R_4. The value of R_4 is closer to 2 Å when the molecule is in anti form. This brings considerable difference in the molecular geometry of the anti form of adenosine in water and chloroform solvents. In the case of water solvent, the anti form of adenosine is mostly stabilized by intermolecular hydrogen bonding while in the case of chloroform solvent the stabilization is completely due to intramolecular hydrogen bonding. The anti form in chloroform

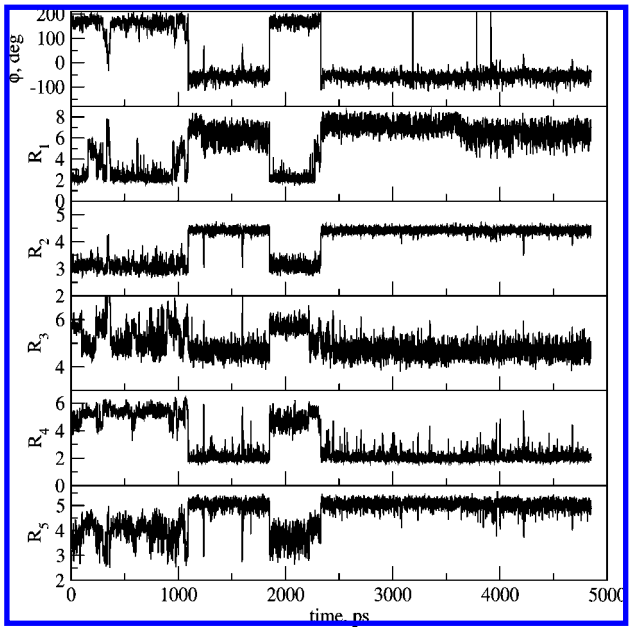

Figure 4. Time evolution of various structural parameters defining the conformational state of adenosine in chloroform.

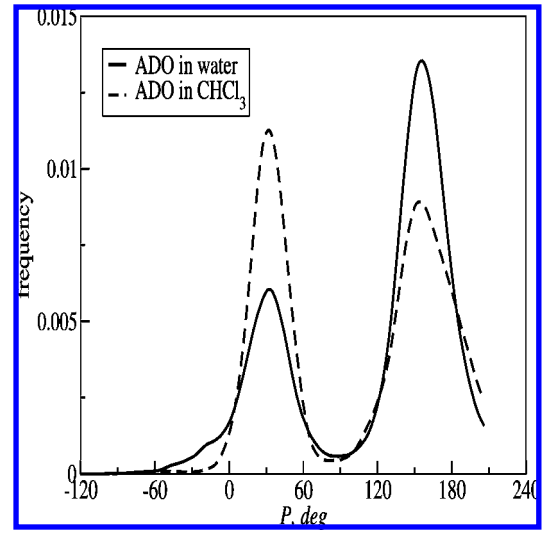

Figure 5. C(3′)-*endo*−C(2′)-*endo* conformational distribution for adenosine in water and chloroform solvents.

prefers $\phi = -60°$ since this conformation can be stabilized by intramolecular hydrogen bonding between the atoms 29−22. But in the case of water this is not the case as the molecule can also be stabilized by intermolecular hydrogen bonding. Because of this reason, the anti−syn conversion in water seems to be connected through many stable intermediate conformational states. In other words, the adenosine in chloroform remains in a conformation where there can be at least one intramolecular hydrogen bonding, and hence the allowed conformational states for adenosine are very limited, probably two. But adenosine in water can exist even in intermediate conformational states where the stabilization of the solute molecule occurs through intermolecular hydrogen bonding with solvent water molecules. This also reduces the cost of the anti−syn interconversion process which can be seen from the frequency of jumps.

2.2.2. C(3′)-endo−C(2′)-endo Conformational Equilibrium. The furanose ring has been reported to be one of the most flexible degrees of freedom in the nucleic acid chain, and the barrier for the interconversion between puckered states has been reported to be less than 5 kcal/mol from proton magnetic resonance measurements.[42] X-ray studies[43] and measurements in solution[44] for the nucleosides report that the furanose ring exists either in C(3′)-*endo* or in C(2′)-*endo* conformational form.[44] In this subsection, we have analyzed the molecular geometry of the furanose ring of adenosine in water and in chloroform solvents. Following the convention set up by Altona and Sundaralingam,[44] we have calculated the dihedral angles, θ_0, θ_1, θ_2, θ_3, and θ_4 to characterize the conformational state of furanose ring. We find that the adenosine exists in either C(3′)-*endo* or in C(2′)-*endo* forms in both water and chloroform solvents. Figure 5 shows the conformational distribution of the furanose ring. The conformational distribution of furanose ring is defined by the pseudo-rotation angle. The pseudo-rotation angle, *P*, is calculated as it is described from eq 2 in the work by Altona and Sundaralingam.[43] When the *P* is close to 0°, the furanose ring is in C(3′)-*endo* state, and when *P* is close to 180°, the furanose ring is said to be in C(2′)-*endo* state. We find that there is more preference for the C(2′)-*endo* for furanose ring of adenosine in water solvent. This is in complete agreement with the proton NMR reported for adenosine in aqueous solution and in ammonia solution which reports a larger population for C(2′)-*endo*.[15] The reported mole fraction of C(2′)-*endo* is 0.6. The calculated percentage population of C(2′)-*endo* form in water solvent is 68%, which is in closer agreement with the experimental results. In the case of adenosine in chloroform solvent, C(3′)-*endo* state is preferred, and the percentage population of this form is 55%.

2.2.3. Carbinol Group Rotamers Equilibrium. The carbinol group connected to the ribose ring is another important flexible degrees of freedom in adenosine. The rotation along C_2-C_5 bond of the carbinol group results in many possible rotamers. But due to the steric repulsion, not all the rotamers are allowed to exist but a very few. In the literature, the carbinol group connected to the ribose ring is reported to exist in three major rotamers, namely, *gg*, *gt*, and *tg*.[15] On the basis of the spin−spin couping constants, relative population of different rotamers of carbinol group is reported[45] in aqueous solution. The population of *gg* and *gt* are closer to 70% and 20%, respectively, in aqueous solution when compared to a larger preference of the latter rotamer in solid state. We have investigated the possible rotamer states of the carbinol group for adenosine in water and chloroform solvents. Figure 6 shows the dihedral angle, ϕ_{MEOH}, distribution in water and chloroform solvents. The $\phi_{MEOH} = -60°$ represents a *gg* rotamer. $\phi_{MEOH} = 60°$ and $\pm 180°$ represent *gt* and *tg* conformers, respectively. In both the solvents the population of *tg* rotamer is negligible while those of *gg* and *gt* rotamers are dominant. Interestingly, there is a considerable effect on the population of the rotamers due to solvents. The populations of *gg* and *tg* conformers in water are 82% and 19%, respectively, which are in agreement with experimental results based on proton NMR.[45] In the chloroform solvent, the populations of *gg* and *gt* rotamers are 65% and 35%, respectively.

2.3. Car−Parrinello Molecular Dynamics Calculations. We have used the CPMD3.11[46] software to perform the CPMD calculations on the ADO−water and ADO−chloroform systems. As seen in Figure 2, the time scale being more than few hundred picoseconds for the anti−syn conformational interconversion, which is too long to study using nonenhanced first-principles MD calculations.[35] For studying the two main conformational forms of adenosine, we have prepared different solute−solvent systems where the solute can be in anti and syn forms. In our present calculations, we have used Becke, Lee, Yang, and Parr (BLYP) gradient corrected functional[47,48] and Troullier−Martins

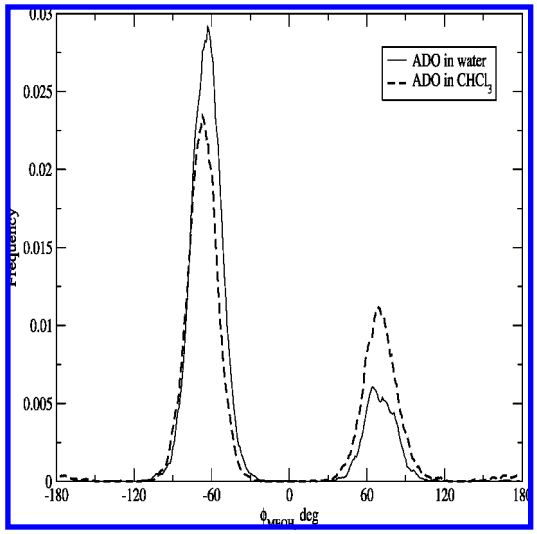

Figure 6. Carbinol group conformational distribution for adenosine in water and chloroform solvents from MD calculations.

norm conserving pseudopotentials.[49] The electronic wave functions were expanded in a plane wave basis set, and the cutoff used was 80 Ry. We have used 5 au as the time step for the integration of equation of motion, and we have used 600 amu as the fictitious electronic mass. The calculations were carried out in a QM/MM setup,[50] where the solute molecule (here it is anti or syn form of adenosine) is treated in an accurate density functional theory level while the solvents (water and chloroform) are treated with a less accurate molecular mechanics force field. The interaction between QM and MM systems involves electrostatic, short-range repulsion and long-range dispersion interaction terms. The CPMD calculations involve following three procedures: (1) Quenching run: the electronic and ionic temperature of initial structure is quenched to remove any hot spot in the system due to inaccurate molecular starting geometry. (2) Scaled temperature run: a short run using temperature scaled dynamics done to bring the system to the required temperature and pressure. (3) Nose run: in this run, the system is kept to interact with the Nose thermostat at the required temperature. Nose thermostat mimics the real system connected to a heat bath to maintain the system temperature. The total time scales for the Nose production runs are between 4 and 6 ps.

2.4. Results and Discussion. ***2.4.1. Molecular Geometry of Adenosine.*** The molecular geometry of adenosine can be discussed easily in terms of the following structural units: (1) adenine ring, (2) furanose ring, (3) the glycosidic bond connecting these two units, and (4) the carbinol group. The adenine ring has been reported to be in a planar shape, and it has been reported to undergo less deformation or conformational change when compared to furanose ring and other flexible segments of adenosine.[17] So, we do not analyze the geometry of adenine ring in detail. In crystalline phase, adenosine has been reported to exist in anti conformation[16,17] with the calculated dihedral angle between C−N−C−O as −172.1°.[17] On the basis of the X-ray studies, it has been reported that the furanose ring remains in either C($_{2'}$)-*endo* or C($_{3'}$)-*endo* forms. Here, we discuss the geometry of the anti and syn conformational states of adenosine in water and chloroform solvents separately. The molecular geometry is discussed in terms of the dihedral angle of glycosidic bond and the conformation of furanose ring and carbinol group. Table 1 reports a few average structural quantities for adenosine in the antisyn conformational states in two different solvents. Table 1 displays the dihedral angle

TABLE 1: Geometrical Parameters (Along with the Standard Deviations in Parentheses) for Adenosine from CPMD Calculations

solvent	form	ϕ	θ_0 (τ_2)	θ_1 (τ_3)	θ_2 (τ_4)	θ_3 (τ_0)	θ_4 (τ_1)
water	anti	22 (30)	−24 (9)	7 (10)	17 (12)	−32 (10)	36 (7)
water	syn	166 (32)	20 (10)	−33 (9)	36 (11)	−22 (12)	2 (7)
$CHCl_3$	anti	−86 (33)	−25 (9)	6 (11)	18 (15)	−34 (13)	37 (8)
$CHCl_3$	syn	175 (28)	−30 (7)	21 (8)	−2 (9)	−17 (8)	30 (7)

(referred as ϕ) of the glycosidic bond connecting adenine and furanose rings. For the syn form, the average ϕ appears as 166° and 174° in water and chloroform solvents, respectively. The values for ϕ calculated from MD calculations are 162° and 167°, which are closer in agreement with the CPMD calculated values. But a larger deviation is seen for the ϕ values obtained for anti conformation. The average values obtained from CPMD calculations are 22° and −86° respectively in water and chloroform solvents while the MD calculated values appear at 53° and −54°, respectively. As it has been already seen from the MD simulations, the geometries of the anti form in water and chloroform solvents differ considerably. The ϕ value for anti form in water is 22°, while the value of ϕ in chloroform solvent is −86°. Interestingly, the adenine and furanose rings are almost in the same plane in the case of anti form in chloroform solvent, while in the case of water solvent these two rings are aligned perpendicular to each other. Figure 7a,b displays the geometry of the anti form in water and chloroform solvents. But there is not much difference in the geometry of the syn form in these solvents which can be seen from the similar ϕ values. Also, Table 1 reports different dihedral angles (referred as θ_0, θ_1, θ_2, θ_3, and θ_4) to describe the conformational state of furanose ring. θ_0, θ_1, θ_2, θ_3, and θ_4 are the dihedral angles about the bonds $C_{26}-C_{24}$, $C_{24}-C_5$, C_5-C_7, C_7-C_8, and C_8-C_{26}, respectively (see Figure 1). These are the average values obtained from entire CPMD trajectory and have to be taken carefully due to larger flexibility of the furanose ring. On the basis of the magnitude and sign of these dihedral angles, we find that in both solvents the anti form of adenosine lies in a conformation between C($_{2'}$)-*endo* and C($_{1'}$)-*exo*.[43] The syn form in chloroform solvent

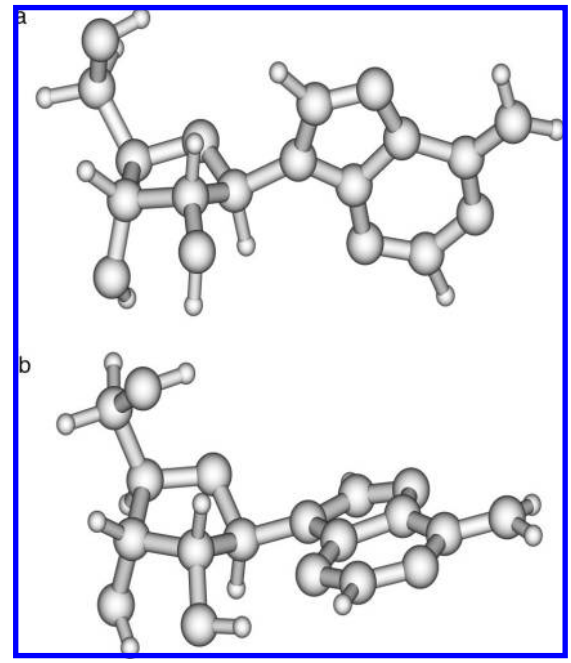

Figure 7. Molecular structure of anti form of adenosine (a) in water and in (b) chloroform solvents.

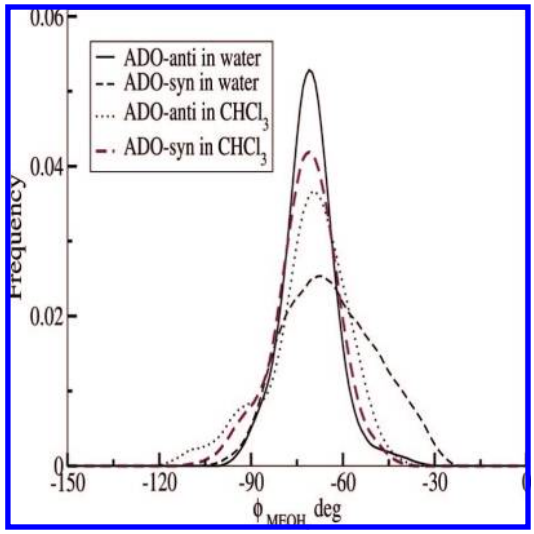

Figure 8. Hydroxy methyl group conformational distribution for adenosine in water and chloroform solvents from CPMD calculations.

remains in C(2′)-*endo*. On the other hand, the syn form of adenosine in water remains in a conformation far away from the reported stable conformations that are C(3′)-*endo* or C(2′)-*endo*. From the average values of different θ_{0-5}, we find that the conformation is between O(1′)-*endo* and C(4′)-*exo*.[43] This has to be attributed to the selection of the initial structure for syn form of adenosine where the furanose ring conformation was (energetically) far away from the reported minimum-energy conformations, and if the simulation is carried out long enough, the furanose ring conformation will eventually evolve into any one of the stable conformations. As it has been reported from experiments,[44] we also find that furanose ring has either C(2′)-*endo* or a conformation closer to this. We have an exception in the case of syn form in water which is far away from the reported minimum-energy conformations. Table 1 also includes the standard deviation (σ) calculated for all the six dihedral angles using the equation

$$\sigma = \sqrt{(\bar{X}^2 - (\bar{X})^2)} \quad (1)$$

It is a measure of how much these dihedral angles can vary due to thermal energy. The relatively larger values of standard deviation reported for ϕ show that the glycosidic bond undergoes large-amplitude torsional motion than the furanose ring bonds. This has to be related to closed molecular geometry of furanose ring. Also, the magnitude for the standard deviation suggests that both the furanose ring and glycosidic bond do not undergo major conformational changes during the time scale for the Nose run. Figure 8 displays the distribution of ϕ_{MEOH} obtained from the CPMD trajectory for anti and syn forms in water and chloroform solvents. In all the four cases, the conformation of carbinol group appears to be *gg*. We do not see any interconversion to *gt* form within our simulation time scale. So, we are unable to comment on the population distribution and relative stability of the *gg*, *gt*, and *tg* forms in different solvents.

2.4.2. Electronic Structure of Adenosine. The position of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) plays a major role in the chemical reactivity and electronic absorption spectra of a molecule.[51] Even though the physical significance of Kohn−Sham orbitals of density functional theory is questionable, many calculations show that the Kohn−Sham orbitals can be used to discuss the molecular properties and reactivity.[52] Here, we are discussing the energies of the frontier orbitals and energy gap of adenosine molecule in different solvent environments. Also, we discuss the effect of conformational flexibility in the energies of frontier orbitals. Table 2 reports the orbital energies for HOMO-2, HOMO-1, HOMO, LUMO, LUMO+1, and LUMO+2 orbitals for the anti−syn conformational forms in water and chloroform solvents. Table 3 reports the LUMO−HOMO energy gap. The orbital energies are obtained from the average of 10 evenly spaced snapshots obtained from the trajectory with the interval of 12.1 fs. In other words, Kohn−Sham orbitals calculations were carried out for only a small window of time scale (which is 121 fs) of the entire trajectory (of length 4−6 ps). Individual energies of the frontier orbitals of these snapshots and the averages for anti and syn states are plotted in Figure 9. The deviation in the orbital energy calculated for the instantaneous configurations is more for the adenosine in water solvent which has to be attributed to the flexibility of the molecule in this solvent, allowing it to continuously span different conformational states. In the case of adenosine in chloroform solvent, the deviation in the orbital energies is very small due to the rigidity of the molecule that is stabilized by intramolecular hydrogen bonding. The actual energies of HOMO and LUMO are higher (in magnitude) by at least 0.03 eV for the syn form than the anti form in the water solvent. The trend is the same in the case of chloroform solvent, too; but now the energy difference is on the order of 0.02 eV. The HOMO−LUMO gap for anti form is slightly larger when compared to the syn form in both the solvents.

2.5. Comparison between CPMD and MD Results. ***2.5.1. Structure of the Solvation Shell of Adenosine.*** In this section, we discuss the solute−solvent structure using radial distribution functions (rdfs) obtained from the MD and CPMD calculations. It has been already discussed in the literature[53] that the center-of-mass (c.o.m.) rdf could not be much useful to analyze the solvation structure of molecules with complex geometry such as adenosine. For the molecules with geometry other than the globular shape, it is important to define a more convenient distribution function such as minimum-distance distribution function as discussed by Canuto et al.[54] So, we have looked into the $g_{\mathrm{X-S(COM)}}(r)$, which is the solute-all-atoms and solvent-center-of-mass rdf. Here, r is the distance between any of the solute atoms and the solvent c.o.m. This rdf is similar to the minimum-distance distribution function as discussed in the work by Georg et al.[53] In the present case, coordinates of the center of mass of the solvent molecules are used for the distance calculation, while Georg et al.[54] uses the solvent atom distance which is closer to the solute. Parts a and b of Figure 10 show the $g_{\mathrm{X-S(COM)}}(r)$ for adenosine in water and chloroform solvents, respectively. The first peak appearing in rdf for water is due to the water molecules bonded (through intermolecular hydrogen bonding) to adenosine. From a careful analysis of the trajectory, we find that there are a maximum of five water molecules that can be bonded to adenosine in its anti form, which becomes four in the syn form. All three hydroxyl groups of the furanose ring form hydrogen bonding with water molecules, and both hydrogen atoms of NH_2 groups are involved in bonding with water molecules (refer to Figure 11). The small lowering of the first peak height for the syn form of adenosine is due to the unavailability of carbinol hydroxyl group for intermolecular hydrogen bonding. When compared to the rdf of anti and syn forms of adenosine from CPMD, the rdf from MD simulations report the lowest first peak height which we find due to the

TABLE 2: Kohn−Sham Orbital Energies in eV (Along with the Standard Deviations in Parentheses) for Adenosine

solvent	form	HOMO-2	HOMO-1	HOMO	LUMO	LUMO+1	LUMO+2
water	anti	−6.34 (0.27)	−6.13 (0.24)	−5.80 (0.22)	−2.13 (0.21)	−1.58 (0.25)	−1.42 (0.22)
water	syn	−6.25 (0.19)	−5.98 (0.15)	−5.57 (0.16)	−1.93 (0.20)	−1.45 (0.16)	−1.21 (0.13)
$CHCl_3$	anti	−6.45 (0.02)	−6.14 (0.04)	−6.04 (0.04)	−2.36 (0.03)	−1.72 (0.02)	−1.16 (0.01)
$CHCl_3$	syn	−6.45 (0.12)	−6.22 (0.08)	−5.96 (0.07)	−2.30 (0.08)	−1.68 (0.07)	−1.40 (0.10)

TABLE 3: Energy Gaps for Adenosine

solvent	form	ΔE, eV
water	anti	3.67
water	syn	3.64
$CHCl_3$	anti	3.68
$CHCl_3$	syn	3.66

dynamical bond breaking and forming. In other words, the water molecules that are bonded to adenosine are involved in dynamical exchange between the first and second solvation shell which result in the lowering of the average number of water molecules in the first solvation shell and hence the first peak height. Unless the time scales for the CPMD and MD calculations are comparable, it is difficult to make any comment on the relative stability of intermolecular hydrogen bonding in these two cases. We have also plotted the spatial density diagram (Figure 11b and Figure 11c are provided in the Supporting Information) of water solvents around adenosine in its anti and syn form. The anti form of adenosine displays five major lobes that are attributed to the five water molecules that are bonded to adenosine through intermolecular hydrogen bonding. In the case of syn form there are only four lobes of water density which describes that there are four regions to find the water molecules around adenosine. In the case of adenosine in water, the first and second solvation shells appear between 1.5−2.2 and 2.2−4.1 Å, respectively. In the case of adenosine in chloroform, the first and second solvation shells appear between 2−6.9 and 6.9−10.5 Å, respectively. The rdfs obtained from CPMD calculations for anti−syn conformational forms in chloroform solvent appear to be similar to the rdfs obtained from MD simulations (which is the weighted average over these conformational states). From the plots, it seems that the anti and syn conformational states do not have a significant effect on the solvation structure of adenosine in chloroform solvent. Overall, the solvation of adenosine in water is site-specific where the solvent molecules interact with specific sites of solute molecule. As we have seen above, the water molecules are bonded to hydroxyl groups of the furanose ring and to the hydrogen atoms of the NH_2 group. In the case of the chloroform solvent, the solvation does not appear to be site-specific, but it is globular isotropic in nature.

2.5.2. Atomic Charges and Dipole Moments of Adenosine. Molecular dipole moments are affected significantly when the molecule goes from a gas phase to a condensed phase.[55] There exist many experimental reports for the solvent-induced changes in solute dipole moments and charge distribution.[55] The change in the dipole moment of the solutes is not

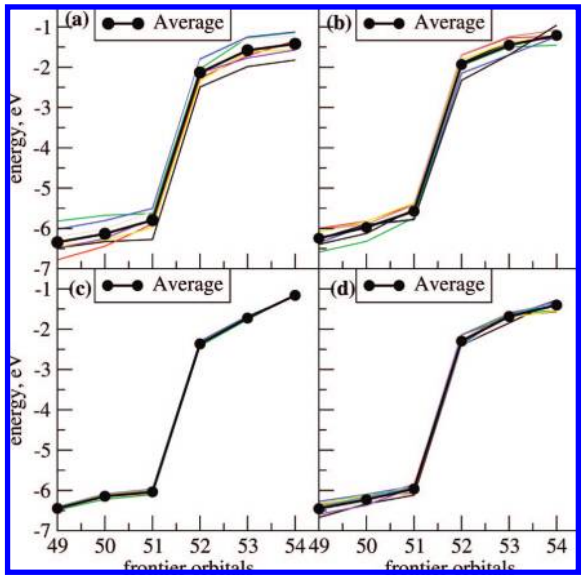

Figure 9. Energies of frontier orbitals for different snapshots and the averages: (a) anti form in water, (b) syn form in water, (c) anti form in chloroform, and (d) syn form in chloroform.

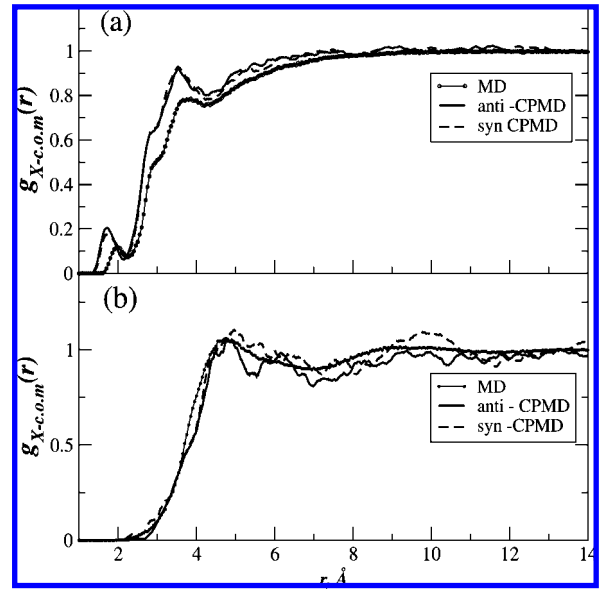

Figure 10. Solute-all-atoms and solvent-center-of-mass rdf for adenosine anti and syn forms in water (a) and chloroform (b).

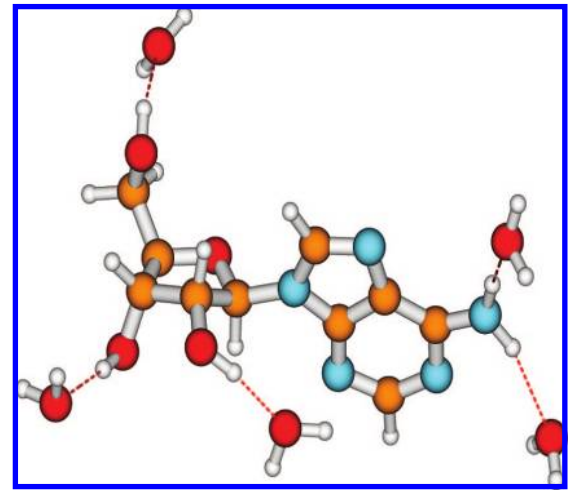

Figure 11. (a) Molecular structure of anti form of adenosine and the water molecules bonded through intermolecular hydrogen bonding.

TABLE 4: RESP and Average DRESP Charges (Along with the Standard Deviations) for Heavier Atoms in Adenosine

		DRESP charges			
atom	RESP (Amber)	anti−water	syn−water	anti−$CHCl_3$	syn−$CHCl_3$
O_1	−0.6223	−0.2906 (0.06)	−0.2535 (0.08)	−0.1067 (0.03)	−0.1184 (0.02)
C_2	0.0558	−0.0132 (0.00)	0.0012 (0.00)	0.0030 (0.00)	−0.0053 (0.00)
C_5	0.1065	0.0425 (0.00)	−0.0129 (0.00)	0.0298 (0.00)	0.0295 (0.00)
O_7	−0.3548	−0.1526 (0.08)	−0.1799 (0.07)	−0.0064 (0.00)	−0.0609 (0.03)
C_8	0.0394	0.0473 (0.00)	0.0697 (0.01)	0.0612 (0.01)	0.0319 (0.01)
N_{10}	−0.0251	0.1165 (0.03)	0.1201 (0.03)	0.0920 (0.01)	0.0634 (0.01)
C_{11}	0.2006	0.0478 (0.00)	0.0370 (0.00)	0.0135 (0.00)	0.0070 (0.00)
N_{13}	−0.6073	−0.3227 (0.06)	−0.3414 (0.07)	−0.1611 (0.02)	−0.1680 (0.03)
C_{14}	0.0515	0.0018 (0.00)	−0.0408 (0.00)	−0.0543 (0.00)	−0.0591 (0.01)
C_{15}	0.7009	0.0862 (0.01)	0.0436 (0.00)	0.0580 (0.01)	0.0687 (0.01)
N_{16}	−0.9019	−0.0666 (0.00)	−0.0888 (0.01)	−0.0448 (0.01)	−0.0481 (0.01)
N_{19}	−0.7615	−0.2464 (0.08)	−0.3186 (0.06)	−0.1608 (0.02)	−0.1280 (0.01)
C_{20}	0.5875	0.0334 (0.00)	0.0609 (0.00)	0.0332 (0.00)	0.0389 (0.00)
N_{22}	−0.6997	−0.3066 (0.06)	−0.0147 (0.00)	−0.0561 (0.01)	−0.0611 (0.01)
C_{23}	0.3053	0.0681 (0.01)	0.0819 (0.01)	0.0404 (0.01)	0.0201 (0.00)
C_{24}	0.2022	−0.0371 (0.00)	−0.0299 (0.00)	0.0041 (0.00)	0.0401 (0.00)
C_{26}	0.0670	0.0087 (0.00)	−0.0079 (0.00)	0.0110 (0.00)	−0.0059 (0.00)
O_{28}	−0.6139	−0.2954 (0.08)	−0.3930 (0.07)	−0.0675 (0.01)	−0.1392 (0.03)
O_{30}	−0.6541	−0.3487 (0.06)	−0.3829 (0.06)	−0.1279 (0.01)	−0.0279 (0.00)

TABLE 5: RESP and Average DRESP Charges (Along with the Standard Deviations) for Hydrogen Atoms in Adenosine

		DRESP charges			
atom	RESP (Amber)	anti−water	syn−water	anti−$CHCl_3$	syn−$CHCl_3$
H_3	0.0679	0.0618 (0.01)	0.0495 (0.01)	0.0450 (0.01)	0.0185 (0.00)
H_4	0.0679	0.0577 (0.01)	0.1406 (0.04)	0.0265 (0.00)	0.0306 (0.00)
H_6	0.1174	0.1147 (0.02)	−0.0301 (0.00)	0.0103 (0.00)	0.0145 (0.00)
H_9	0.2007	0.0269 (0.01)	0.1263 (0.04)	0.0240 (0.00)	0.0235 (0.00)
H_{12}	0.1553	0.1201 (0.02)	0.1317 (0.02)	0.0210 (0.00)	0.0621 (0.01)
H_{17}	0.4115	0.1520 (0.02)	0.1803 (0.04)	0.0938 (0.01)	0.0992 (0.01)
H_{18}	0.4115	0.1431 (0.02)	0.1584 (0.04)	0.0973 (0.01)	0.0877 (0.01)
H_{21}	0.0473	0.0715 (0.01)	0.0548 (0.00)	0.0269 (0.00)	0.0180 (0.00)
H_{25}	0.0615	−0.0500 (0.01)	0.1670 (0.06)	−0.0223 (0.00)	0.0396 (0.01)
H_{27}	0.0972	0.0925 (0.01)	0.1429 (0.04)	−0.0040 (0.00)	−0.0202 (0.00)
H_{29}	0.4186	0.2615 (0.08)	0.3254 (0.05)	0.0255 (0.00)	0.0266 (0.00)
H_{31}	0.4376	0.3169 (0.06)	0.2882 (0.05)	0.0194 (0.00)	0.1467 (0.01)
H_{32}	0.4295	0.2598 (0.05)	−0.0853 (0.01)	0.0789 (0.01)	−0.0213 (0.00)

significant when the solvent is nonpolar and has very less dielectric constant. Reichardt has reported that the solute dipole moments remain closer to gas-phase values when the solvent is nonpolar in nature such as *n*-hexane, benzene, and 1,4-dioxane.[56] Here, we investigate such solvent-induced changes in atomic charges and dipole moments for adenosine in its anti and syn forms in water and chloroform solvents. At moderate temperatures, the dielectric constant values for water and chloroform are 80−88 and 3.5−5.8, respectively.[57] We have looked into the dynamic restrained ESP (DRESP)[58] charges obtained from CPMD calculations for all the atoms in the anti and syn forms in water and chloroform solvents. Table 4 reports the atomic charges for relatively heavier atoms such as C, O, and N while Table 5 reports the atomic charges for H atoms. Tables 4 and 5 also report the RESP charges used in MD calculations along with the average DRESP charges. The tables also display the standard deviation (in parentheses) calculated for the DRESP charges, which is a measure of how much the charges can vary in magnitude with respect to the average values. The deviation is considerably larger for some atoms, which is even up to 30% of the average value. The RESP charges appear to be larger in magnitude when compared to the charges from CPMD calculations. In the case of syn form of adenosine in water solvent, the DRESP charges on many heavier atoms appear to be larger in magnitude than in the case of anti form. This has to be attributed to the larger dipole moment of the syn form. In contrast to this, the DRESP charges on different atoms appear to be of the same order in the case of anti and syn forms of adenosine in chloroform solvent. It is also important to notice that the magnitude of furanose ring oxygen is smaller when compared to the charges of hydroxyl group oxygen atoms.

TABLE 6: Dipole Moment for Anti and Syn Forms of Adenosine in Gas Phase and in Solvents[a]

solvent	form	μ from Amber	μ from CPMD
	anti		3.19
	syn		2.87
$CHCl_3$	anti	3.07	3.33 (0.8)
$CHCl_3$	syn	3.02	2.88 (0.8)
water	anti	5.68	3.86 (1.2)
water	syn	4.29	5.87 (1.7)

[a] The values in parentheses are the standard deviation values.

Table 6 displays the dipole moments calculated from MD and CPMD calculations for anti and syn forms in different solvents. Also, Table 6 displays the gaseous phase dipole moments calculated for the optimized structure of anti and syn form of adenosine using CPMD. As has been discussed by Reichardt,[56] we do not see any significant changes in the dipole moments when the solute goes into a chloroform solvent from the gas phase. The dipole moment of anti form of adenosine remains as 3.19 and 3.33 D in gas phase and chloroform solvent, respectively, while the dipole moment of syn form of adenosine

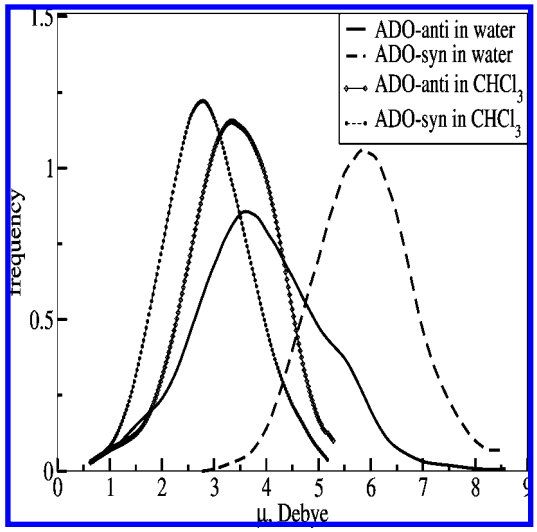

Figure 12. Dipole moment distribution for different conformational states of adenosine in water and chloroform solvents.

remains as 2.87 and 2.88 D in gas phase and chloroform solvent, respectively. The dipole moment for each MD configuration was calculated from RESP charges and the atomic coordinates using the equation

$$\bar{\mu} = \sum_{i=1}^{n} q_i \bar{r}_i \qquad (2)$$

where the summation is over all the atoms in adenosine molecule. Here, q_i is the RESP charge on the ith atom with the atomic coordinate, $\bar{r}_i$. The averaging has been done for the anti and syn forms separately, and the values are displayed in Table 6. Both MD and CPMD calculations report a larger dipole moment for adenosine in water solvent than in the case of chloroform solvent. This is in complete agreement with the earlier reports[55,56] where the solute dipole moments are larger in a polar solvent than in a nonpolar solvent. From the CPMD calculations, the syn form in water solvent of adenosine appears to have a larger dipole moment (by 2 D) when compared to the anti form. In contrast to this, the dipole moments calculated from MD trajectory report a larger dipole moment for the anti form. In the literature, the practical problems rising due to the conformation dependence of charges and the dipoles have been discussed in detail.[59] There are a few reports of successful molecular simulations using the high-quality charges that are derived from multiple conformation molecular electrostatic potential.[60] Here, we find a case where the magnitude of dipole moments calculated from MD is very different for different conformational states of adenosine when compared to the CPMD calculated values. This clearly illustrates the need to use polarizable charges for the molecules that are considerably flexible with respect to their internal degrees of freedom. The dipole moments calculated from MD remain similar for both the anti and syn forms of adenosine in chloroform. But the CPMD estimates a larger dipole moment (by 0.5 D) for adenosine in chloroform. Figure 12 shows the dipole moment distributions (using the dipole moments obtained from CPMD calculations) for anti and syn forms of adenosine in water and chloroform solvents. It is important to notice a larger deviation for the dipole moments of adenosine in water when compared to chloroform which has to be attributed to a larger conformational flexibility of adenosine molecule in water solvent.

2.6. Conclusions. The effect of solvents on the anti−syn conformational equilibrium for adenosine has been investigated. The interconversion seems to be a faster process in water solvent which is due to the stabilization of intermediate states by intermolecular hydrogen bonding. In contrary, in chloroform solvents the intermediate states cannot be stabilized due to the inability to form intermolecular hydrogen bonding, and hence the interconversion process seems to be infrequent. So, in other words, the interconversion process seems to have a larger barrier in the case of chloroform solvent while the barrier height is brought down significantly in the case of water solvent due to the stabilization of intermediate conformational states. As has been reported experimentally, the furanose ring remains in either C(2′)-*endo* conformation or a conformation structurally close to this. MD results predict the correct trend for dipole moment for adenosine in different solvents, but it seems to fail in producing the dipole moment for different conformational state of adenosine in water.

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Supporting Information Available: Figures 3, 4, 11b, and 11c. This material is available free of charge via the Internet at http://pubs.acs.org.

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