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A study of nucleic acid base-stacking by the Monte Carlo method: Extended cluster approach

Research Article

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Abstract: The adenine-thymine (AT), adenine-uracil (AU) and guanine-cytosine (GC) base associates in clusters containing 400 water molecules were studied using a newly implemented Metropolis Monte Carlo algorithm based on the extended cluster approach. Starting from the hydrogen-bonded Watson-Crick geometries, all three base pairs are transformed into more favorable stacked configurations during the simulation. The obtained results show, for the first time, the transition from planar base pairs to stacked base associates in the Monte Carlo framework. Analysis of the interaction energies shows that, in the water cluster, the stacked dimers are energetically preferable compared to the corresponding Watson-Crick base pairs. This is due to the larger base-water interaction in the stacked structures. The water–water interaction is one of the main factors promoting the formation of stacked dimers, and the obtained data confirm the crucial role of the water-water interactions in base stacking.

Keywords: *Monte Carlo • Cluster • Base stacking • Hydrophobic interaction*

1. Introduction

Noncovalent interactions (hydrogen bonds, ionic bonds, van der Waals forces and hydrophobic interactions) play a fundamental role in many fields, in particular, in molecular biology and nanotechnology. The stacking of aromatic molecules caused by relatively weak noncovalent interactions is an interesting and fundamental phenomenon observed in fields as diverse as organic and medical chemistry, biochemistry, molecular biology, molecular recognition, supramolecular chemistry, material science, separation science and nanotechnology (in particular, DNA nanotechnologies).

One of the most famous examples of stacking is the system of successive base pairs in DNA. In recent years, liquid-phase computer simulations allowed more realistic studies of the stacking phenomenon. Thermodynamic and spectroscopic studies of interacting bases, their derivatives, nucleosides and nucleotides showed that, in aqueous solution, these entities form exclusively stacked associates (see, for example, [1]). Coplanar hydrogen-bonded (H-bonded) base pairs have not been observed in liquid water.

The first computational investigations of stacked nucleic acid bases and their methyl derivatives in water clusters have been conducted more than a quarter century ago [2-10]. These model systems have the advantage that factors such as the presence of the backbone and geometrical constraints of the DNA double helix are eliminated, with the result that the influence of solvent on the molecular associations can be determined directly. The goal of these investigations was to quantitatively understand the physical basis of the formation of stacked associates of nucleic acid bases in water within the framework of solute-solute, solute-solvent and solvent-solvent interactions. Such understanding can only be

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obtained if the method employed is able to provide direct information about ensemble averages of thermodynamic and structural properties. For this reason these studies employed the Monte Carlo (MC) and molecular dynamics (MD) methods to study the base association. The internal energies calculated in the previous MC studies showed that the stacked complexes are more stable than the H-bonded complexes in water [2-10]. Likewise, the resulting free energies for the association of the base pairs in water solution obtained by the MD method showed that H-bonded adenine-thymine (AT) and guanine-cytosine (GC) configurations are preferred in the gas phase but that, in aqueous solution, stacked configurations are preferred [11]. Moreover, the H-bonded complexes are mostly stabilized by electrostatic contributions, whereas the stacked ones are stabilized mainly by van der Waals type interactions [2-11]. It was also found that the stacked complexes are much better solvated by the water solution than the H-bonded pairs [2-12]. This can be explained by the fact that, in the stacked complexes, the solute atoms that can form H-bonds are exposed to water, whereas in the H-bonded associates, these atoms form H-bonds with the other base. Due to the larger number of exposed polar groups, the overall energy gain from H-bonds is greater for stacked structures than for H-bonded associates. This therefore results in additional stabilization of the stacked structures. By comparison of the van der Waals and electrostatic contributions for the different associates, Cieplak and Kollman showed that it is the difference in the net van der Waals interactions that is the main factor contributing to the greater stabilization of the stacked over the H-bonded complexes in aqueous solution [11]. Results obtained in other model studies are consistent with these conclusions.

Although the early MC and MD studies correctly predicted the relative tendency that stacked configurations are favored over H-bonded configurations in water, the solvation models used are not as accurate as would be desirable. For example, theoretical studies by Pohorille *et al*. [6,7] found a destabilizing water contribution to the enthalpy of association, contrary to what is usually assumed [13]. Negative enthalpies were only obtained when the gas-phase solute–solute energy was added to the total energy. This surprising result may be a consequence of using gas-phase geometries for the stacked dimers. The bases were not allowed to move relative to one another, and the position of the base pair in the box was kept fixed throughout the simulation. The interaction energies were calculated by comparing the differences in the total energies for the static complex in solution and for the individual bases. This involves computing a small difference between large fluctuating numbers which may lead to difficulties with precision. In addition, it is possible that the model used in [6,7] is not very suitable for the description of biomolecular solvation, in particular because it is not able to deal with specific solute-solvent interactions.

In an investigation of the stacking between the 9-methyladenine and 1-methylthymine bases the authors of [11] started each simulation of the base associates from their standard B-DNA geometries and only sampled configurational space near these minima. This is a greater approximation for stacked complexes, where the lowest energy configurations would likely involve antiparallel rather than nearly parallel alignment of the base dipole moments. Thus, a more extensive sample of the possible configurations of the stacked base complexes would be needed. In addition, most early MD computer simulations of biomolecular systems starting from a crystal structure can now be considered as rather meaningless [14], simply because the time covered in simulations that were considered “state-of-the-art” during the late 1980s (typically a few hundred picoseconds), was far too short to observe anything of value.

In later work by Dang and Kollman [12] a potential of mean force approach was employed, allowing the estimation of the free energy of association as a function of a reaction coordinate (H-bonded complexes: the distance between the N3 atom and the N1 atom in adenine; stacked complexes: the distance between the centers of mass of the bases). For this, one needs to employ a “coordinate coupling” approach in conjunction with statistical perturbation theory. The obtained results clearly indicate that in solution the stacked configuration is more favorable than the H-bonded configuration. In agreement with earlier conclusions (see above), Dang and Kollman explain this result with the picture that water molecules in solution have better access to the H-bonding groups of the stacked base pair as compared to the corresponding H-bonded configuration. Since the water molecules can interact more favorably with these groups of the stacks, the bases retain most of their H-bonding with water upon formation of the stacked structure. In contrast, upon formation of the H-bonded base pair, water-base H-bonds must be broken as the base-base H-bonds form. Dang and Kollman concluded that the van der Waals stabilization of the bases (through both dispersion and exchange repulsion/hydrophobic effects) stabilizes the stacked configurations over the H-bonded structures in water. However, as pointed out by the authors, the bases were not allowed to have different angular orientations in the stacked configuration and, thus, a more complete sampling of configuration space could reveal more stable configurations.

Using continuum solvation methods, an attempt was carried out to identify the physical origin of base stacking of different dinucleotides [15]. The key result of this study is that Coulombic interactions disfavor base stacking, whereas nonpolar interactions favor base stacking. This is due to the loss of favorable base-solvent electrostatic interactions resulting from the decreased access of the solvent to the polar atoms in the stacked conformation. The reaction field contribution, which is the free energy of moving a molecule from a medium with permittivity ε_i to one with ε_0, tends to be unfavorable. This is because stacking involves the partial replacement of water at the surface of a polar molecule (the base) by a less polarizable medium (the other base). A partition of the free energy implies that both hydrophobicity and the enhancement of Lennard-Jones interactions as a result of close packing are responsible for base stacking. Their relative contributions are, however, parameter dependent and therefore difficult to separate. Though the results agree qualitatively with experimental evidence on the dependence of the stacking energy on the composition of the base pairs, continuum solvation models may not give sufficiently reliable results to obtain quantitative estimates of relative stacking energies. Though solutes are treated explicitly in continuum solvation models, the solvent is represented as a dielectric continuum. As a result, the molecular nature of water as an associated liquid is not correctly described and its particular capacity for hydration, bonding, and solvation in different modes (hydrophilic, hydrophobic, and ionic) is not properly described.

An MP2 study of the most stable configurations of adenine and naphthalene dimers [16] supports the view that stacking is driven primarily by nonelectrostatic interactions. In another study the stacking abilities of ribo- and deoxyribodinucleoside monophosphates in aqueous and organic solutions were investigated using nanosecond unrestrained MD simulations and potential of mean force calculations [17]. The obtained results show that base stacking is favored in aqueous solution. Direct experimental data on the nature of stacking interactions in water at the molecular level is difficult to obtain, if at all possible. Nevertheless, some experimental information on the nature of stacking has appeared in the literature in recent years. Guckian *et al*. [18] used 'dangling end' studies to study stacking in natural nucleosides as well as non-natural analogues in a hexamer DNA duplex. Analysis of the obtained data showed that hydrophobic effects are more important than electrostatic and dispersion effects in stabilizing stacking. An entirely new approach for the characterization of stacking interactions in the DNA double helix was introduced more recently [19,20]. Stacking free-energy parameters were obtained by studying the equilibrium between the stacked and unstacked form of a DNA nick. The two contributions to the thermal stability of the DNA double helix were separated by polyacrylamide gel electrophoresis of DNA molecules with solitary nicks and gaps. It was shown that the base pairing term is destabilizing in the AT pair and somewhat stabilizing in GC pairs. At the same time the base-stacking interactions are always stabilizing for both AT- and GC-containing contacts in the DNA double helix. It was found that the DNA double helix is mainly stabilized by stacking interactions rather than base pairing. Base-stacking interactions do not only dominate the overall stability of the duplex, but also significantly contribute to the dependence of the stability on its base-pair sequence [19]. Therefore, base stacking is the main driving force responsible for the stabilization of the three-dimensional structure of DNA and RNA, a conclusion that is qualitatively in accord with earlier theoretical predictions [2,11,12,21].

A comparison of the results of MC and MD studies on nucleic acid bases in water with similar data from quantum-chemical calculations is of interest. The main difference between quantum-chemical calculations and MC simulations on clusters is the following: Quantum-chemical calculations aim to describe the interactions between the different cluster fragments as accurately as possible, but are limited in the statistical description of the cluster. In contrast, MC simulations can provide a very accurate description of the statistical contribution to the nucleation barrier height by studying the full configurational space of the cluster, but they are restricted to using very simplified interaction potential models. Hence the main difference between these approaches is the configuration space. The first quantum-mechanical study on base pairs that included as much as 200 explicit water molecules investigated the planar H-bonded and four stacked AT associates by the semi-empirical PM6 method [22]. Unlike MC and MD studies, the PM6 calculations fully optimized the geometry of the water molecules and individual bases and therefore took into account distortion of the isolated, paired and stacked bases during the base association reaction. It was found that the formation of the planar AT base pair in a water cluster is energetically unfavorable, due to the destabilizing contribution of the base-water interactions, whereas the base-stacking reaction in water is favorable. The average interaction energy in all studied stacked dimers varies between -11.2 and -20.2 kcal mol^{-1}. The main contribution stabilizing the stacks was found to be the change in the water-water interaction, associated with structural rearrangements of the water molecules around the bases during base association. The favorable change in the water structure as well as the distortion of the isolated bases and base pairs during the base association reaction are factors favoring the formation of the stacks. Full geometry optimization of the planar AT base pair converts it into a nonplanar propeller-twisted and buckled structure. [22] also shows that all stacked associates are energetically preferred over the planar H-bonded base pair. The determining factor in favoring the stacked associates over the planar base pair in an aqueous cluster is the water-base interaction. The larger value (in absolute value) of the water-base interaction energy for the stacked associates compared to the H-bonded base pair suggests that the stacked dimers are much better hydrated, in agreement with previous MC [2-10] and MD [11] studies. The calculated internal energy of hydration of the planar and stacked dimers supports this conclusion. The water-water interaction destabilizes the stacks compared with the planar base pairs due to the less favorable arrangement of the water molecules around the stacks. The distortion factor, defined as the internal energy difference between the paired and isolated bases due to the presence of the water cluster and to geometric changes during the association reaction, also destabilizes the stacks. The greater stability of the stacked over the H-bonded base pairs is therefore entirely due to the differences in the water–base interactions in these associates.

Despite extensive experimental efforts and numerous theoretical calculations, the hydration of relatively apolar molecules, such as the nucleic acid base pairs, and the nature of the noncovalent interactions between such molecules in water are still poorly understood. First of all, simulation of the base hydration was performed for stacked associates experimentally observed in aqueous solutions. These stacked structures have been found in vacuum using quantum-chemical methods. The previous MC studies on base pairs in water clusters [2-5,8-10] kept the center-of-mass of one of the bases fixed in the center of the sphere, whereas the other base was allowed to move according to the Metropolis algorithm. Possibly as a result of this restriction, these simulations did not obtain the correct configuration of the stacked dimer immersed in a water cluster. As a result, to date no one has shown theoretically that the stacked configuration is unambiguously the most favorable structure in water. The nature of the stacking mechanism has been the subject of considerable debate to this day. Theoretical studies have failed to identify clearly the physical origins of stacking interactions. The factors that stabilize the stacking of bases and hence the detailed nature of the stacking stabilization remain not well understood. An additional point of interest is the role of water as a solvent. While the significance of the base stacking phenomenon is well documented, relatively little is known *at the molecular level* about the structural details of the water organization around the base associates. In addition, the preferential formation in water of stacked associates over H-bonded base pairs, as well as the role of hydrophobic groups in base stacking, remains poorly understood. The mechanism underlying the energetic preference of the association reaction of bases in water also requires further study. Finally, the hydration of the monomers (bases, nucleosides, nucleotides), required to allow direct clarification of the role of hydrophobic interactions as a significant factor in the stacking interactions, has generally not been studied. In the current study we attempt to eliminate some of these shortcomings. We introduce a new MC algorithm, based on the extended cluster approach. In contrast to the older MC studies, the simulations with the improved MC method do obtain the correct configuration of the hydrated stacked clusters. Simulations starting from the Watson-Crick base pairs show the conversion from the planar base pairs into stacked associates. The results confirm the suitability of this new MC algorithm for the study of hydrated base associates.

2. Methodological Procedure

The AT, AU and GC base pairs in clusters comprising 400 water molecules were simulated in the canonical (NVT) ensemble, in the standard state (298 K and 1 atm pressure), using the Metropolis MC method [23]. The potential energy surface was modeled using the refined semi-empirical potential functions of Poltev and co-workers [24-26]. The availability of a functional form of the potential energy of the intermolecular water-water, water-base and base-base interactions allows the calculation of various thermodynamic and structural properties of interest and therefore enables a deeper understanding of the hydration mechanism of the dimer at the molecular level. In addition, it has been shown that currently available force fields provide a much better description of the interaction between nucleic acid bases than all but the most recent semi-empirical or low-level ab initio methods [27]. Entropy was not considered in the simulations. This is justified, as it has been shown, both experimentally [1] and theoretically [11], that the association of the bases and their derivatives in water is primarily driven by enthalpy.

We used the MC method based on the physical cluster theory of Abraham [28]. The molecular system is placed in a sphere with impermeable walls so that the center-of-mass of the solute coincides with the center of the sphere. The water molecules are restricted to remain within this sphere. This cluster definition prevents the solute from drifting towards the surface of the water cluster. Following [28], 400 water molecules was placed in a sphere of radius Rc = 24.3 Å, which corresponds to the five volumes of liquid water under standard conditions. The initial uniform density of the water cluster containing 400 molecules initially equals the experimental density of water at room temperature. When this cluster is placed in the spherical volume described above, the density is reduced in the simulation process. This reduced density allows the bases in the stacks to rotate more freely and therefore to occupy any position.

An AT, AU or GC Watson-Crick base pair, optimized at the MP2/6-311G(2df,pd) level of theory, was placed in this water cluster. The 3×10^6 configurations in total (where one configuration consists of one move of all water molecules as well as individual bases in the cluster) were generated, of which the last 1×10^6 configurations were used to calculate the average properties of the stacked structures. Similar simulations were performed for the Watson-Crick base pair with fixed base pair geometry, using 2×10^6 configurations. In this case, the last 0.5×10^6 configurations were used to calculate the averaged properties. The rigid rotor approximation was applied to the movement of the base and water molecules.

The statistical error, which occurs because only a finite number of moves can be considered (*i.e.*, the length of Markov chain), was estimated using a control function method. The complete series of moves is divided into a finite number of intervals. Mean square fluctuations are calculated from the values of the functions determined at each interval. The intervals need to be long enough to avoid correlation between subsequent energy values. The standard deviations of the thermodynamic quantities were then obtained from a series of mean values, each representing the average of an interval containing 10^4 configurations. In these calculations, the statistical error (dispersion value) was calculated with a precision of ±0.5%.

The average potential energy U was decomposed into base-base (U_{bb}), water-base (U_{wb}) and water-water (U_{ww}) contributions. In previous work we found this decomposition essential to analyze the nature of the interaction in both microhydrated clusters as well as nanodroplets of nucleic acid bases [29-32].

3. Results and Discussion

Figs. 1-3 show the variation of the angle α_{bb} between the normals to the planes of the individual bases in the AT, AU, and GC associates as well as the distance R_{bb} between the centers of mass of the bases, as a function of the MC configuration number.

At the start of the simulations on AT, AU, and GC α_{bb} is 0°, which corresponds to the planar Watson-Crick configuration of the base pairs. During the MC simulation, this angle undergoes significant changes. The graph for the AT base pair (Fig. 1) clearly shows that the system reaches an equilibrium state from configuration number 1.5×10^6 onwards, with α_{bb} close to 10°. Also the AU and GC base pairs reach equilibrium states with nearly parallel bases and α_{bb} around 10° (see Figs. 2 and 3).

This value of α_{bb} would be consistent with either a planar or stacked base pair. The distance between the centers of mass of the bases in the base pair (R_{bb}) is more demonstrative to distinguish between planar and stacked structures. This distance is also shown in Figs. 1-3. The R_{bb} values for the Watson-Crick starting configurations are between 5.2 and 7.0 Å. This distance then decreases and becomes close to 3.5 Å, which is typical for stacked configurations. The transition

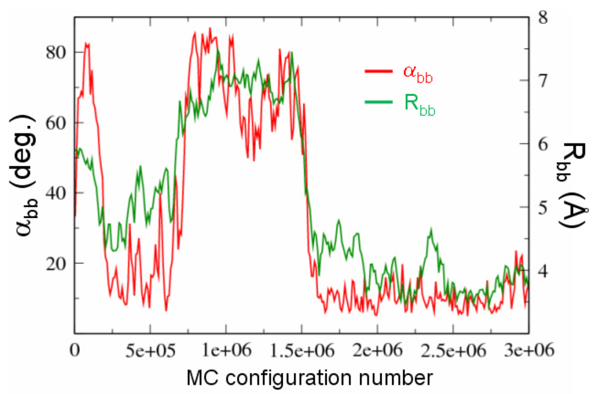

Figure 1. The angle between the normals to the planes of the individual bases (α_{bb}) and the distance between the centers of mass of the bases (R_{bb}) in the AT associate as a function of the MC configuration.

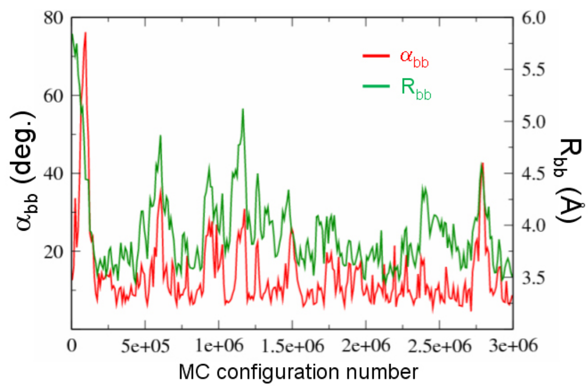

Figure 2. The angle between the normals to the planes of the individual bases (α_{bb}) and the distance between the centers of mass of the bases (R_{bb}) in the AU associate as a function of the MC configuration.

happens rather quickly for AU, whereas it takes more MC configurations to reach the parallel structure for AT and GC. The MC simulations therefore show the transformation of the Watson-Crick base pairs into more favorable stacked configurations for all three base pairs. The α_{bb} angle of ~10° indicates that the adenine and thymine bases in the stacks are not exactly parallel.

We would like to point out that the MC method does not generate a trajectory (*i.e.,* the evolution of a physical system in time), but rather a Markov chain of spatial configurations that are generated according to the rules of the Metropolis algorithm. However, due to their ability to cross energy barriers, MC simulations are more likely to find the most stable energy minima. By continuing the simulations for many configurations after the establishment of the stacked configuration, the MC simulations presented in the current work appear to indicate that the equilibrium state of the stacked configuration is maintained indefinitely. This shows that the formation of the stacked base-base complexes in aqueous solution is favorable from an energetic point of view.

The reduced density of the water cluster due to the large constraining volume used in the simulations allows the bases in the stacks to rotate more freely and therefore to occupy any position. As a result, one of the bases in the base pair can turn by 180 degrees. This did indeed happen in the simulation of the AT base pair.

The results of the calculations of the average values of the systems' potential energy (U), water-water interaction energy (U_{ww}), water-dimer interaction energy (U_{wb}) and base-base interaction energy (U_{bb}) are listed in Table 1. The U values in Table 1 show that the stacked dimers in the water cluster are energetically preferred over the corresponding Watson-Crick base pairs. This is mainly due to the larger base-water interaction.

Although the H-bonded base pairs are not observed experimentally in water, the energy changes in going from the H-bonded to the different stacked dimers are of interest. To elucidate the stability and understand the nature of the formation of the stacks in water it is necessary to calculate the change in the potential energy, ΔU, the change in the water-water interaction energy, ΔU_{ww}, the change in the water-dimer interaction energy, ΔU_{wb} (hydration effect) and the change in the interaction energy between the bases, ΔU_{bb}. ΔU_{ww} corresponds to the energy change due to the formation of a cavity for the dimer bases and the reorganization of the water when these bases are placed in the cavity (hydrophobic effect). These quantities are computed from the data in Table 1 and are presented in Table 2. The data presented in Table 2 show that all stacked associates are energetically preferred over the planar H-bonded base pairs. The large negative ΔU_{wb} values confirm our previous conclusion [22] that it is the water–base interaction that determines the preference of stacked associates over H-bonded base pairs in an aqueous cluster. This is probably due to the smaller hydrophobic surface available in the stacks.

Table 1. Total average interaction energy and its components for the isolated bases and Watson-Crick (WC) and stacked base pairs in water clusters consisting of 400 water molecules (in kcal mol^{-1})

Compound	U	U_{ww}	U_{wb}	U_{bb}
Adenine	-3452.5	-3365.1	-87.4	---
Thymine	-3454.2	-3396.9	-57.3	---
Uracil	-3452.0	-3393.9	-58.1	---
Guanine	-3474.6	-3359.5	-115.1	---
Cytosine	-3468.2	-3377.7	-90.5	---
AT WC	-3487.2	-3351.1	-125.5	-10.6
A/T stack	-3503.1	-3354.5	-144.3	-4.3
AU WC	-3492.3	-3354.4	-126.5	-11.4
A/U stack	-3493.7	-3341.8	-148.3	-3.6
GC WC	-3502.4	-3343.8	-158.6	-22.0
G/C stack	-3534.8	-3323.5	-209.0	-2.3

Table 2. Energy changes for transition from the H-bonded Watson-Crick (WC) base pairs to the stacked associates (in kcal mol^{-1}) in water clusters consisting of 400 water molecules

Process	ΔU	ΔU_{ww}	ΔU_{wb}	ΔU_{bb}
AT WC → A/T stack	-16.0	-3.4	-18.8	6.2
AU WC → A/U stack	-1.4	12.6	-21.8	7.8
GC WC → G/C stack	-10.4	20.3	-50.4	19.7

Table 3. Energetic characteristics of the base stacking reaction in water clusters consisting of 400 water molecules (in kcal mol^{-1})

Process	ΔU	ΔU_{ww}	ΔU_{wb}	ΔU_{bb}
A + T → A/T stack	-15.8	-13.0	1.5	-4.3
A + U → A/U stack	-8.7	-3.2	-1.9	-3.6
G + C → G/C stack	-12.5	-6.7	-3.5	-2.3

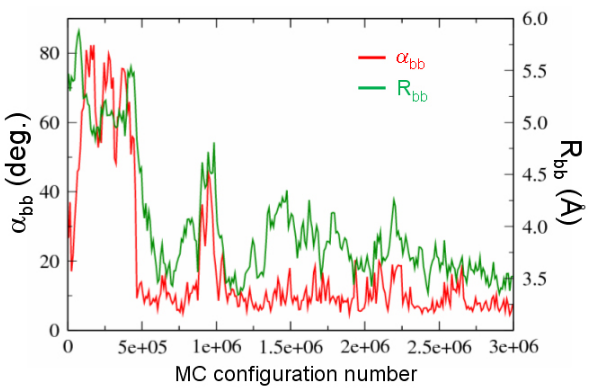

Figure 3. The angle between the normals to the planes of the individual bases (α_{bb}) and the distance between the centers of mass of the bases (R_{bb}) in the GC associate as a function of the MC configuration.

Analysis of the change in the water cluster energy does not give a clear answer on the role of the water-water interactions. Depending on the nature of the solute, these interactions have either a stabilizing (for AT) or destabilizing (AU and GC) effect on the stacks compared with the planar base pairs. The GC stacked associate is particularly destabilized by the water-water interactions but this destabilization is more than compensated by the large stabilization due to the water-base interactions. Thus, the greater stability of the stacked dimers is mainly due to the different water-base interactions in the stacked and H-bonded dimers. As also found in our previous PM6 study, the water-base interaction energies are larger for the stacked than for the H-bonded associates, which confirms that the stacked dimers hydrate better than the H-bonded base pairs. As explained in the Introduction, the reason for this is that the atoms that are H-bonded in the Watson-Crick base pairs are not available for H-bonding with water, whereas in the stacked structures they are. The same conclusion was also reached in an MD study of the association of the nucleotide bases in water [19].

The data presented in Table 1 allow us to calculate the formation energy and its contributions for the three studied stacked associates in the water cluster. The largest stabilizing contribution comes from ΔU_{ww} (except for AU, where ΔU_{ww} and ΔU_{bb} are of similar magnitude) and is associated with the structural rearrangement of the water molecules around the bases during the formation of the stacks. This confirms the previous conclusions in [9,22] on the crucial role of the water-water interaction in base stacking.

We are currently extending this research to include other base pairs (such as the Hoogsteen AT base pair). Results on this work will be published elsewhere.

4. Conclusion

We implemented a new Monte Carlo algorithm based on a spherical boundary and coinciding centers-of-mass of the solute and solvent and applied it to calculate the thermodynamic and structural properties of nucleic acid base pairs in water. For all base pairs considered (AT, AU and GC), the simulations starting from the Watson-Crick structure evolved to stacked associates. The preference of stacked associates over H-bonded base pairs is found to be mainly due to the larger water–base interaction in the stacks. The results show the importance of explicitly allowing the individual bases in the dimer to move. The formation of all stacked associates from their individual bases is favorable, with the water-water interaction playing a crucial role in the process.

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