Nature of the stacking interactions of nucleotide bases in water

A Monte Carlo study of the hydration of thymine molecule associates

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The results of a Monte Carlo study of the hydration of a thymine molecule, its stacked and H-bonded dimers are presented. It is shown that the stacking interactions of thymine molecules in water arise mainly due to the increase in the water–water interaction during the transition from monomers to dimer. It has been found out that stacked base associates are more preferable than H-bonded dimers in water. This preference is mainly due to the energetically more favourable structure of water around the stack.

Monte Carlo study *Nucleotide base stacking* *Stacked associate* *Water structure* *Base pair*

1. INTRODUCTION

Despite numerous investigations, the nature of the stacking interactions of nucleotide bases is as yet unrealized. Besides, it remains unelucidated why stacked dimers are more preferable than in-plane hydrogen-bonded (H-bonded) base pairs.

2. METHODS

The results of the hydration simulation of a thymine molecule, its stacked and H-bonded dimers in a cluster approximation at 298 K by the Monte Carlo-Metropolis method [1] are presented here (cluster consisting of 200 water molecules).

The computation method is given in [2,3]. Like our previous work [2,3], one of the bases in the stacked thymine dimer was moved randomly according to the Metropolis algorithm.

3. RESULTS AND DISCUSSION

The computation results of the average magnitudes of the potential energy (U) for the system, the water–water interaction energy (U_{ww}), water–base interaction energy (U_{wb}) and base–base interaction energy (U_{bb}) are listed in table 1. The results of the computation [3] for the cluster of 200 water molecules are also given in table 1.

The data of table 1 allow calculation of the energetic characteristics of thymine molecules' association reaction in water, the stacked dimer being formed. The calculated magnitudes of the changes for the potential energy and water–water, water–base and base–base interaction energies, the expressions for which are given in [2], amount to -5, -22, 22.3 and -5.1 kcal/mol, respectively.

The results obtained show that it is the change of the water–water interaction energy associated with the structural rearrangement of water around monomers during their association that is the main factor promoting stacked dimer stabilization in water. The stacked associate is considerably less stabilized by the base–base interaction. At the same time, the stack is substantially destabilized by the water–base interaction as compared to isolated monomers.

Table 1 also lists the changes of the potential

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Table 1

Energetic characteristics of the hydration of stacked and hydrogen-bonded thymine dimers

Systems	N	U	U_{ww}	U_{wb}	U_{bb}
Stacked thymine	200	−8.24 ± 0.02	−7.76 ± 0.02	−90.9 ± 0.2	−5.13 ± 0.01
dimer + water	39	−10.06 ± 0.02	−8.16 ± 0.02	−69.0 ± 0.1	−5.13 ± 0.01
	82	−9.23 ± 0.02	−8.13 ± 0.02	−85.3 ± 0.2	−5.13 ± 0.01
Coplanar thymine	200	−8.11 ± 0.02	−7.64 ± 0.02	−85.5 ± 0.2	−9.38
base pair + water	39	−9.83 ± 0.02	−8.01 ± 0.02	−61.6 ± 0.1	−9.38
	82	−9.11 ± 0.02	−8.02 ± 0.02	−79.9 ± 0.1	−9.38
Thymine + water	200	−8.05 ± 0.02	−7.77 ± 0.02	−56.6 ± 0.1	–
Water	200	−7.89 ± 0.02	−7.89 ± 0.02	–	–
Changes of energies	200	−26	−24	−5.4	4.25
during the transition	39	−9.0	−5.9	−7.4	4.25
from base pair to stack	82	−9.8	−9.0	−5.4	4.25

N, number of water molecules considered in the system; U, total potential energy (kcal/mol water); U_{ww}, water–water interaction energy (kcal/mol water); U_{wb}, water–base pair interaction energy (kcal/mol system); U_{bb}, base–base interaction energy (kcal/mol system). $U = U_{ww} + (1/N)(U_{wb} + U_{bb})$. Three lowest rows: changes of potential energy and water–water, water–base, base–base interaction energies during the transition from base pair to stack in water (kcal/mol system)

energy (ΔU) and water–water (ΔU_{ww}), water–base ΔU_{wb}), base–base (ΔU_{bb}) interaction energies in the process of the transition from the H-bonded dimer to the stacked one. It follows from these data that in water the stacked thymine associate is energetically more preferable than the H-bonded dimer. This preference is mainly determined by the ΔU_{ww} value and is due to the energetically more favourable structure of water around the stack. The water–base interaction also stabilizes the stack as compared to the base pair, at the same time the stack being destabilized by the base–base interaction.

For a more detailed understanding of the nature of the preference of stacked dimer as compared to H-bonded dimer, the energetic characteristics for the subsystems of thymine dimer–nearest water molecules (39 and 82) obtained from the water cluster considered above are also given in table 1. Furthermore, the values ΔU, ΔU_{ww}, ΔU_{wb} and ΔU_{bb} for these subsystems are also listed.

These data show that the greater energetic favourability of the thymine stack as compared to the base pair is also observed for the nearest water molecules (39 and 82) around dimers. However, for the subsystem considered the magnitude of ΔU makes only a small contribution to this value for the system including 200 water molecules. This testifies to the fact that the energetic preference of the thymine stack as compared to the base pair is due to the layers of water molecules more distant from the dimer. Since the magnitudes of ΔU_{ww} for subsystems are small in comparison with the value of ΔU_{ww} for the whole cluster (see table 1), the dominant contribution of the latter to ΔU is also determined by more distant layers of water molecules. This fact distinguishes the hydration of thymine associates from those of uracil [2,3] considered by us, their values of ΔU and ΔU_{ww} in the case of the whole cluster being only determined by the nearest 39 water molecules.

In fig.1, 2 stereo-drawings of one of the Monte Carlo configurations are presented during the simulation of stacked and H-bonded thymine dimers in water. It is seen that the distribution of water molecules around the stack and base pair is different. The water molecules nearest to the base pair are mostly localized in the region above and below the H-bonds between the bases, whereas water is distributed more uniformly around the stack. This leads to a higher structuring of water molecules and to a lower water–water interaction energy for the system of stacked dimer–water.

Attention should be drawn to the fact that the dihedral angle between the base planes of the stacked thymine dimer amounts to 39°. This is

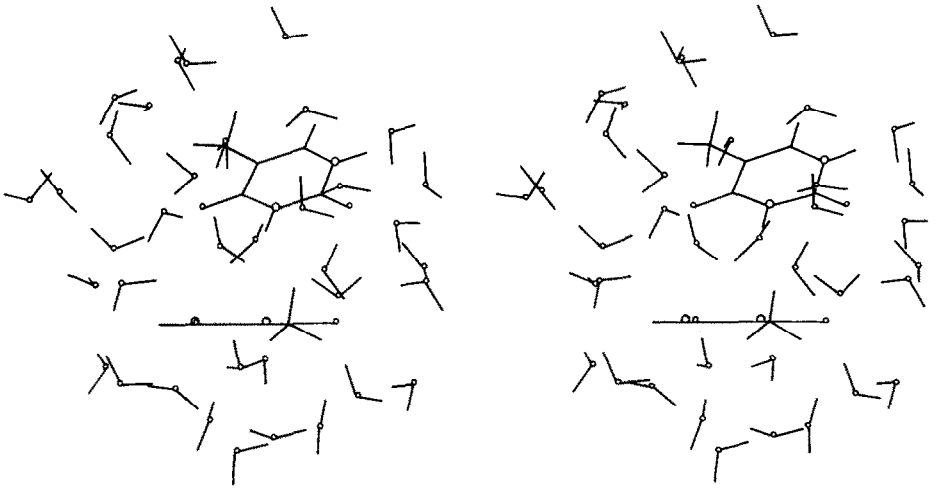

Fig.1. Stereo-drawing of one of the Monte Carlo configurations during the simulation of the stacked thymine dimer in water. Only water molecules within 7 Å from the centre of the dimer are displayed.

much greater than the dihedral angle (17°) for the stacked uracil dimer [2]. The analysis performed for other Monte Carlo configurations has given similar magnitudes.

Thus, the results of our study show that the stacking interactions of thymine molecules in water are mainly due to the change of the water–water interaction around monomers during base association. This confirms an assumption [4–7] about a decisive role of water in base stacking.

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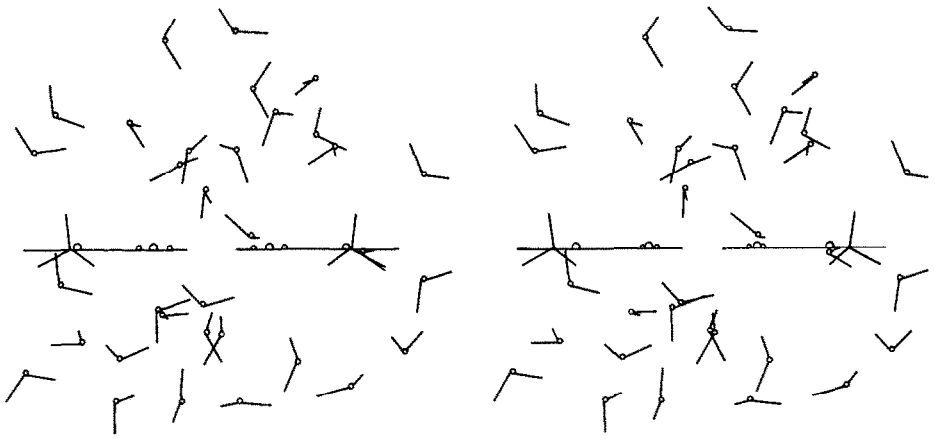

Fig.2. Stereo-drawing of one of the Monte Carlo configurations during the simulation of the H-bonded thymine dimer in water. Only water molecules within 7 Å from the centre of the dimer are displayed.

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