On the role of hydrophobic groups in nucleotide base stacking

A Monte Carlo study of hydration of thymine dimers

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The results of a Monte Carlo study of the hydration of two stacked thymine dimers are presented. In water the stack in which the methyl groups are separated from each other is energetically less favourable than that in which these groups are close to each other. This difference is already found when considering the nearest water molecules only. The nature of approaching of thymine methyl groups in the case of base stacking is discussed.

Monte Carlo study *Nucleotide base stacking* *Stacked associate* *Water structure* *Hydrophobic group*

1. INTRODUCTION

The study of the effect of methyl groups on the formation of stacked associates of nucleotide bases in water is of great interest because of the role of hydrophobic interactions in the stabilization of molecular aggregates and biopolymers. Though Monte Carlo studies of the nature of base stacking interactions have been carried out recently [1–5], the question as to the role of methyl groups has not been considered. Meanwhile, study of the hydration of stacked complexes of thymine molecules allows one to begin investigation of this problem. The respective stacked dimers in water are the simplest model systems for studying the role of hydrophobic groups in base stacking.

2. METHODS

The results of the hydration simulation of stacked thymine dimers by the Monte Carlo-Metropolis method in a cluster approximation (200 water molecules) at 298 K are presented.

Similarly to our previous work [1–4], one of the bases in each stack was moved randomly according to the Metropolis algorithm. As the starting configurations for thymine dimers the most favourable structures resulting from theoretical calculations for a vacuum were used: an antiparallel structure and an antiparallel one with the additional rotation around the glycosidic bond by 180°. Those configurations lead to different types of stacks in water denoted A-stack and O-stack, respectively.

To equilibrate each system we have used 600000 configurations. The calculation of average properties has been performed on 500000 subsequent configurations. A more detailed description of the calculation is given in [1,2].

3. RESULTS AND DISCUSSION

The average values of the potential energy (U) of the system, water–water interaction energy (U_{ww}), water–base interaction energy (U_{wb}), base–base interaction energy (U_{bb}) and the number of water–water H-bonds in which a water molecule participates (n_{Hb}) are listed in table 1. The respective differences (ΔU, ΔU_{ww}, ΔU_{wb}, ΔU_{bb} and Δn_{Hb}) are also presented.

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Table 1

Energetic and structural characteristics of stacked thymine dimers

System	N	Type	U	U_{ww}	U_{wb}	U_{bb}	n_{Hb}	ΔU	ΔU_{ww}	ΔU_{wb}	ΔU_{bb}	Δn_{Hb}
Stacked thymine dimer + water	200	O	−8.24	−7.76	−90.9	−5.1	1.81	−34	−38	5.4	−0.5	6
		A	−8.07	−7.57	−96.3	−4.6	1.75					
	39	O	−10.06	−8.16	−69.0	−5.1	1.94	−12.1	−21.1	9.7	−0.5	2
		A	−9.75	−7.62	−78.7	−4.6	1.83					
	82	O	−9.23	−8.13	−85.3	−5.1	1.92	−8.2	−15.6	7.6	−0.5	2
		A	−9.13	−7.94	−92.9	−4.6	1.88					

N, number of the 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 interaction energy (kcal/mol system); U_{bb}, base–base interaction energy (kcal/mol system); n_{Hb}, number of water–water H-bonds in which one water molecule participates; ΔU, ΔU_{ww}, ΔU_{wb} and ΔU_{bb}, differences for corresponding energies of the system during the transition from A- to O-stack (kcal/mol system); Δn_{Hb}, difference in number of water–water H-bonds in the systems

From the data of table 1, it is seen that the energetic preference of a more stable dimer (O-stack) as compared to a less stable one (A-stack) is in fact completely determined by the water–water interaction. Water is more ordered around the more stable dimer, as can be seen from a greater number of water–water H-bonds (see Δn_{Hb} in table 1). Base–base interactions do not contribute to the difference between stacking energies of both types of stacks. The water–base interaction stabilizes a less favourable dimer to a greater extent. Similar conclusions are also valid for clusters formed by base and 39 or 82 nearest water molecules.

Stereo drawings of one Monte Carlo configuration of the thymine O-stack with nearest water molecules and the thymine A-stack with nearest water molecules are given in fig.1,2. From analysis of the figures and the data in table 1 we can make an important observation. The methyl groups of both thymine molecules in a more favourable O-stack are located close to each other. On the other hand, in the case of a less favourable A-stack those

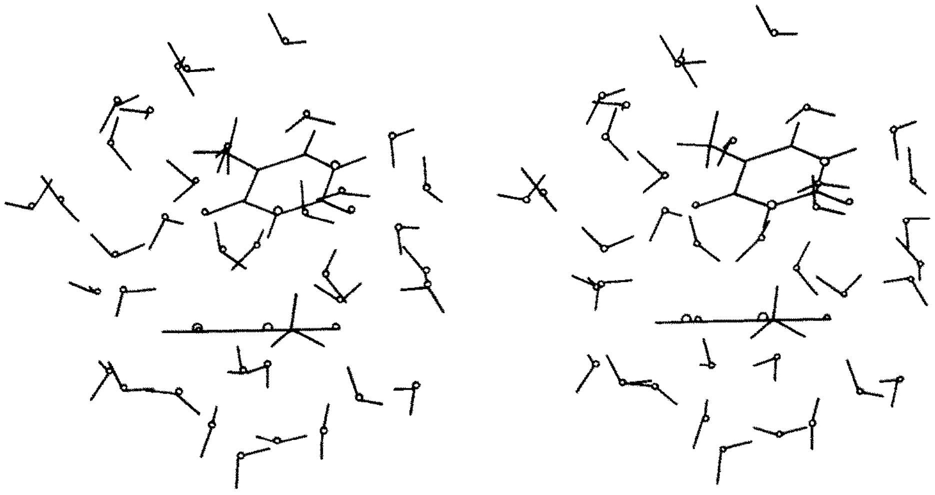

Fig.1. Stereo drawing of one Monte Carlo configuration of the thymine O-stack in water. Only those water molecules which are located within 7 Å from the centre of the stack are displayed.

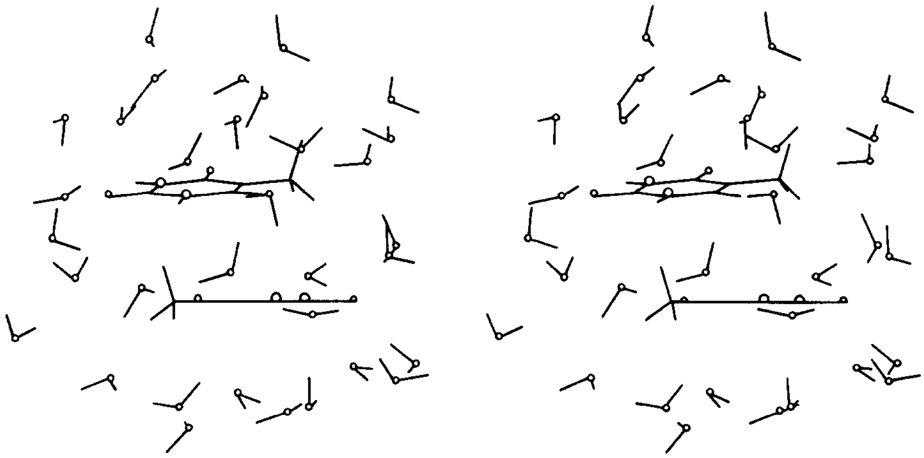

Fig.2. Stereo drawing of one Monte Carlo configuration of the thymine A-stack in water. Only those water molecules which are located within 7 Å from the centre of the stack are displayed.

groups are separated from each other. This phenomenon is analogous to the known hydrophobic effect for two non-polar molecules or groups.

The phenomenon observed is most likely due to the action of methyl groups and not to the rotation of one of the base rings around the glycosidic bond. It seems that the preference of A-stack over O-stack in the case of uracil [6] testifies to the latter supposition.

The nature of methyl groups approaching in the O-stack can be qualitatively understood from the radial distribution of the number of water molecules, number of H-bonds and water–water interaction energy even for clusters of 39 water molecules. Analysis of these functions for thymine A- and O-stacks shows that water ordering is low around the methyl groups in the A-stack. This is due to a smaller number of water molecules in the vicinity of methyl groups for the A-stack. The transition from the A- to O-stack leads to an increase in the number of water molecules in the following layers: 3.3–3.8, 4.8–5.3 and 6.3–6.8 Å. As a result, a greater number of water–water H-bonds is found in those layers. The decrease in the number of water–methyl group contacts during this transition leads to the formation of additional water–water H-bonds in the 6.3–6.8 Å layer; this increases the water ordering in the layer.

This obviously leads to a noticeable increase in the energy of the system. The energetic contribution to the preference of the O-stack made by the 6.3–6.8 Å layer (−22.5 kcal/mol) is really very close to the value of ΔU_{ww} for the cluster including 39 nearest water molecules (see table 1). An additional decrease in the energy of the whole system is due to the cooperative effect of neighbouring methyl groups in the thymine O-stack on the structure of more distant layers of water molecules (see table 1).

The approaching of the methyl groups of thymine molecules during the formation of the O-stack is typical of a hydrophobic effect. However, unlike the classical case the enthalpy term contributes substantially to the stabilization of the thymine O-stack. A similar effect is observed for all the studied cases of nucleotide base association in water [7,8].

Thus, hydration simulation of stacked thymine dimers has shown that the configurations obtained differ strongly from those for a vacuum (cf. fig.1,2 with the corresponding figures in [9]). As a result, a noticeable decrease of the absolute value of U_{bb} was found during the transition from vacuum to water. Comparison of our data for uracil stacked dimer (unpublished) with the variable and fixed (vacuum) geometry indicates the change of not only U_{bb} but also U_{ww} and U_{wb}. Therefore, the results of studies of base stacking in water based on the use of fixed geometry should be treated with great caution (cf. [5]).

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