Nature of the stacking interaction of nucleotide bases in water: a Monte Carlo study of the hydration of uracil molecule associates

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The results of a Monte Carlo study of the hydration of a uracil molecule, its stacked and H-bonded dimers are presented. It is shown that the formation of the stacked dimer is mainly governed by the energetically favourable change of water structure during the transition of monomers to dimer. The formation of the coplanar base pair is less favourable than that of the stack.

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

1. INTRODUCTION

Experimental data show that nucleic acid bases form stacked associates in water. Coplanar base pairs in water have not been successfully detected [1]. At the same time it follows from theoretical investigations [2,3] that coplanar base pairs in vacuum have a lower energy as compared to stacked ones of the same composition. Analysis of the whole complex of experimental and theoretical data has allowed us [3,4] to conclude that water plays an important role in the formation of stacked associates. In spite of numerous efforts, the energetic preference of stack formation in water and the factors stabilizing stacks have been insufficiently studied. It is not clear why stacks are more favoured in water than coplanar base pairs.

2. METHODS

The results of Monte Carlo simulation of a pure cluster of 200 water molecules as well as of this cluster containing uracil, stacked and coplanar uracil dimers are presented here. Simulations were performed at 298 K. All the clusters were placed into a sphere 22 Å in radius, its volume being greater than the volume of 200 water molecules. The atom–atom potential functions were used with the parameters from [5-7]. In the process of computation one of the molecules of the stacked uracil dimer was moved randomly according to the Metropolis algorithm. A more detailed description of the computation method is given in [8].

3. RESULTS AND DISCUSSION

The computation results of the average values of potential energy $\bar{U}$ for the system, the water–water interaction energy $\bar{U}_{\mathrm{WW}}$, the water–base interaction energy $\bar{U}_{\mathrm{WB}}$, the base–base interaction energy $\bar{U}_{\mathrm{BB}}$ and the number of water–water H-bonds in which a water molecule participates $n^{\mathrm{P}}_{\mathrm{Hb}}$ (index of structurization in the system) are given in table 1.

The energy change in the reaction of the association of two uracil molecules in water with the formation of stacked dimer i.e., uracil + uracil + N water molecules → uracil dimer + N water molecules can be written as follows:

$$\Delta U = \Delta U_{\mathrm{WW}} + \Delta U_{\mathrm{WB}} + \Delta U_{\mathrm{BB}}$$

$$\Delta U_{\mathrm{WW}} = N \cdot [(\bar{U}_{\mathrm{WW}}\,(\mathrm{d}) - \bar{U}\,(\mathrm{w})) - 2(\bar{U}_{\mathrm{WW}}\,(\mathrm{m}) - \bar{U}\,(\mathrm{w}))]$$

$$\Delta U_{\mathrm{WB}} = \bar{U}_{\mathrm{WB}}\,(\mathrm{d}) - 2\bar{U}_{\mathrm{WB}}\,(\mathrm{m}),\ \Delta U_{\mathrm{BB}} = \bar{U}_{\mathrm{BB}}$$

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Table 1

Energetic and structural characteristics of water and hydrated uracil monomers and dimers

Systems	$\bar{U}$	$\bar{U}_{WW}$	$\bar{U}_{WB}$	$\bar{U}_{BB}$	n^{P}_{Hb}
Stacked uracil dimer + 200 water molecules	−8.18 ± 0.02 (−10.18)	−7.67 ± 0.02 (−8.32)	−98.7 ± 0.2 (−68.3)	−4.20 ± 0.01	1.78 (1.93)
Coplanar base pair of uracil + 200 water molecules	−8.10 ± 0.02 (−9.62)	−7.60 ± 0.02 (−7.88)	−91.6 ± 0.2 (−58.7)	−9.3	1.73 (1.72)
Uracil + 200 water molecules	−7.92 ± 0.02	−7.65 ± 0.02	−54.1 ± 0.1	-	1.75
200 water molecules	−7.89 ± 0.02	−7.89 ± 0.02	-	-	1.95
Changes at transition from base pair to stack	−16.0 (−21.7)	−14 (−17.2)	−7.1 (−9.6)	5.1	5 (4)

$\bar{U}$, average value of total potential energy (in kcal/mol water); $\bar{U}_{WW}$, water–water interaction energy (in kcal/mol water); $\bar{U}_{WB}$, water-base interaction energy (in kcal/mol system); $\bar{U}_{BB}$, the base-base interaction energy (in kcal/mol system); n^{P}_{Hb}, number of water–water H-bonds in which a water molecule paticipates. $\bar{U} = \bar{U}_{WW} + (1/N)(\bar{U}_{WB} + \bar{U}_{BB})$, where N is the number of water molecules in the system. $N = 200$ (or 39 for the values in brackets). Bottom row: energy changes (in kcal/mol system) and the change of the total number of water–water H-bonds in the system

where: N is the number of water molecules in the system (N = 200), d refers to dimers, m to a monomer, and w to water. These values can be calculated from the data presented in table 1: $\Delta U = -46.7$ kcal/mol, $\Delta U_{WW} = -52$ kcal/mol, $\Delta U_{WB} = 9.5$ kcal/mol, $\Delta U_{BB} = -4.2$ kcal/mol. As seen from these data, the change of the water–water interaction (ΔU_{WW}) due to the structural reorganization of water solvating the uracil molecules during their association is the main factor of stack stabilization. The values $\bar{U}_{WW}$ given in table 1 show that the stacked uracil dimer introduced into the water disturbs its structure less than two monomers do. The values of n^{P}_{Hb} also testify to this.

Table 1 gives the value changes of the potential energy, water–water interaction energy, water-base interaction energy, base-base interaction energy and number of H-bond changes in the system at the transition from the base pair to the stack. The changes in values indicate that the formation of the stacked uracil associate in water is more favourable than that of the coplanar base pair mainly due to the change of the term $\bar{U}_{WW}$. The computed n^{P}_{Hb} values indicate directly that the decrease of the water–water interaction energy in the system with a stacked dimer is caused by the increase of water structurization. The uracil dimer–water interaction also promotes the stabilization of the stack as compared to the base pair. The data obtained can explain the difficulty of experimental detection of coplanar base pairs in water.

For a more detailed understanding of the nature of the stability of the stack as compared to the base pair, the energetic and structural characteristics of the uracil dimers for the nearest 39 water molecules obtained from the computation of the water cluster considered above are presented in brackets in table 1. For the cluster chosen, the stacked dimer is also energetically more favourable than the coplanar base pair, the water–water interaction change contributing mainly to the total value. This is caused by the formation of a greater number of H-bonds between water molecules around the stack than around the base pair (see change of number of H-bonds in table 1). The value n^{P}_{Hb} shows quite clearly that the structurization of water around the stack is also higher than around the base pair.

It is worth mentioning that for the nearest 39 water molecules considered the water–base interaction makes a noticeable contribution to a greater stability of the stack in comparison with the base pair. An analysis of the radial distribution of the uracil dimer–water interaction energy for both systems shows that there is a layer of water molecules only 1.5 Å thick around the stack whose interaction with the bases makes a contribution to

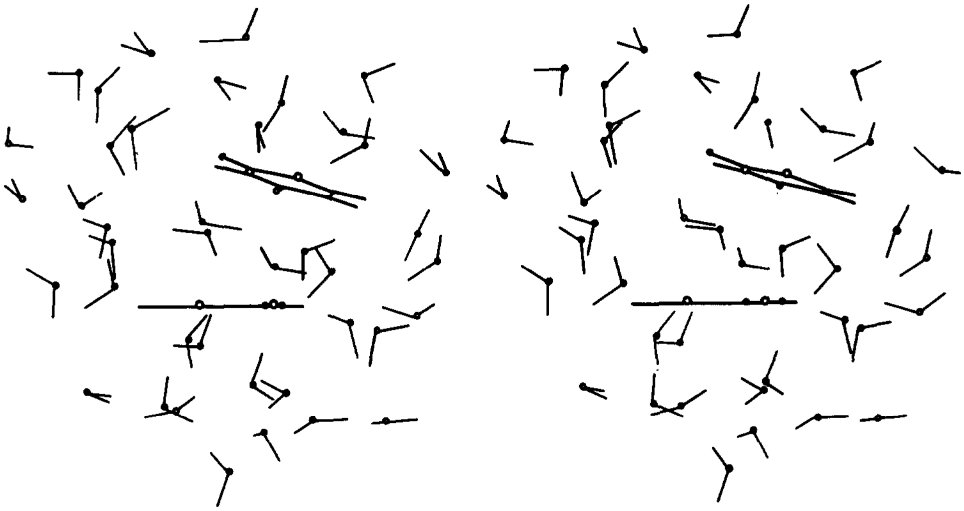

Fig. 1. Stereo-drawing of an instantaneous configuration of the stacked uracil dimer in the surrounding of the nearest water molecules.

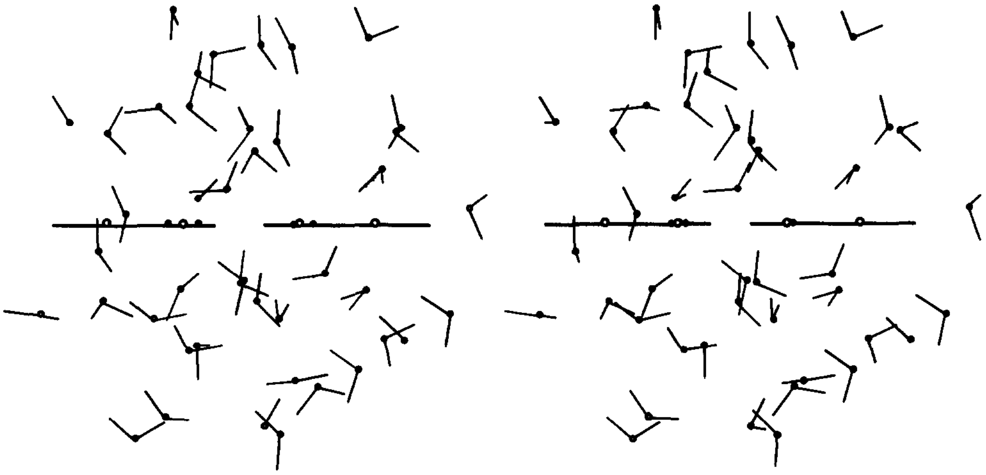

Fig. 2. Stereo-drawing of an instantaneous configuration of the coplanar uracil base pair in the surrounding of the nearest water molecules.

$\bar{U}_{WB}$ as great as −46 kcal/mol. The existence of such a layer in the stack and its absence in the base pair is caused primarily by the different character in the distribution of hydrophilic groups for stacked and coplanar dimers. The presence of such a layer explains the energetic advantage of the stack as compared to the base pair for $\bar{U}_{WW}$, as well that for $\bar{U}_{WB}$.

The stereo-drawings of one of the instantaneous configurations of the nearest water molecules around the stacked and coplanar uracil dimers are given in fig. 1, 2. The figures show clearly that there is really a substantially different distribution of water molecules around the dimers: water is concentrated in the form of a spherical layer around the stacked associate, while the nearest water molecules are mainly located around the coplanar base pair in the region above and below the H-bonds between the bases.

The fact that the nearest 39 water molecules give much the same energetic advantage to the stack in comparison with the base pair, as does the whole water cluster, is of special interest. This indicates directly that the preference in the formation of the stack is caused by the nearest water molecules.

Thus, the results of the Monte Carlo study of the hydration of monomer and dimer uracil forms have shown that the nucleic acid base stacking interaction in water is mainly caused by the increase in water–water interaction around the dimer, as compared with the analogous interaction around monomers.

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