Ab initio QM/MM-Monte Carlo studies on hydration of uracil

(Center for Quantum Life Sciences and Graduate School of Science, Hiroshima University)
Dong-Xia Zhao(趙東霞), 岩田末廣, 相田美砂子

Introduction

Hydration of nucleic acid bases plays an important role in structural and biological processes [1]. Many efforts have been devoted to investigating the interactions of water molecules with nucleic acid bases and the base pairs as well. Uracil, as the structurally most simple nucleic acid base, has received a great deal of attention. Uracil contains a set of alternating C=O and N-H groups, which are hydrophilic sites that are most energetically favourable for hydrogen bonding to the water molecules.

Computational Methods

Using geometry optimization method with B3LYP/6-31++G*, our study showed that up to seven water molecules can be hydrogen bonded to the main hydrophilic sites of uracil. In the case of the complex of uracil (Ura), the water molecules are located near the mean plane of the pyrimidine ring. The total binding energies of the complexes $Ura(H_2O)_n$ (n=1-7) were calculated at the optimized structures for all these clusters. The most stable conformations of these complexes were obtained.

By using the hybrid representations of QM/MM-vib model [2], the structures and binding energies for the most stable conformations for $Ura(H_2O)_n$ (n=1-7) have also been obtained. The theoretical level of B3LYP/6-31++G* was used for the QM subsystem (the uracil molecule), the Gao-parameters [3] were for the QM and MM junction, and TIP3P-parameters [4] were employed for the MM subsystems (the remaining water molecules). Furthermore, the system that contains a uracil molecule and surrounding 100 water molecules has been studied with the QM/MM-vib/CAV [2] method using the HONDO package. The uracil molecule is selected as a QM subsystem, and all the water molecules (solvent molecules) are treated as MM subsystems.

Results and discussion

The size dependence of the total binding energies of the most stable structures of $Ura(H_2O)n$ (n=1 – 7) is depicted in Figure 1. The total binding energies obtained with the B3LYP/6-31++G* and QM/MM-vib nearly linearly increase with the number n. As shown in Figure 1, the binding energies of these complexes obtained with QM/MM-vib are in accord with *ab initio* binding energies. The difference of the two curves is accounted for by the larger water-water interaction in TIP3P than in B3LYP. The structures obtained using QM/MM-vib are similar to the corresponding structures optimized with B3LYP/6-31++G* for the most stable conformations of $Ura(H_2O)_n$ (n=1-7), which implies the appropriateness of QM-MM junction.

To look for the stable configurations of a uracil molecule and surrounding 100 water molecules, we first search a lower energy configuration of solvent molecules (MM parts) for the uracil molecule (QM) using the MC simulated annealing procedure, which is repeated many times. The local minimum configuration obtained is only one of numerous configurations, but it represents the characteristics of the solvent distribution around a uracil molecule. The optimization of the geometry is performed, including both the QM part and MM part. The structure of the first hydration shell (shown in Figure 2) was obtained and analyzed, which is considered as the structural part of a nucleic acid base. As listed in the

table 1, the surrounding water molecules obviously affect the structure of the uracil molecule, especially on the C=O and N-H groups which are hydrophilic sites. From the variations of the bond lengths of these groups, the C=O and N-H groups are strongly influenced by interaction with water molecules, especially for C4=O4 group. The radial distribution functions are used to express the structure and understand the property of solvent (water molecules) and solute (the uracil molecule). The average distribution of solvent molecules is obtained around a uracil molecule with Monte Carlo (MC) method.
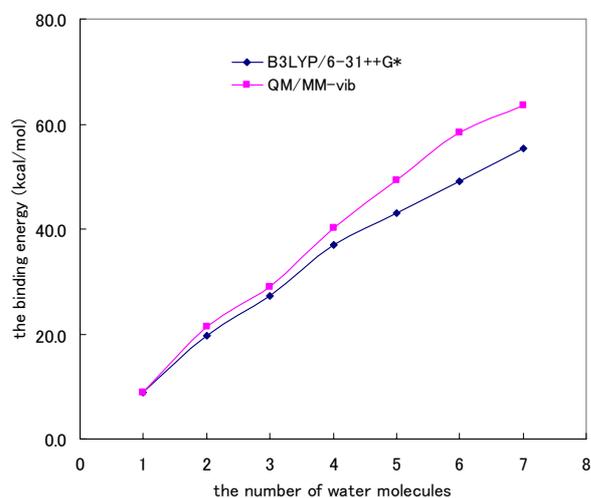

Figure 1. Size dependence of the total binding energies of the most stable structures of Ura(H$_2$O)$_n$ (*n*=1-7) obtained by B3LYP/631++G* and QM/MM-vib methods, where n denotes the number of water molecules
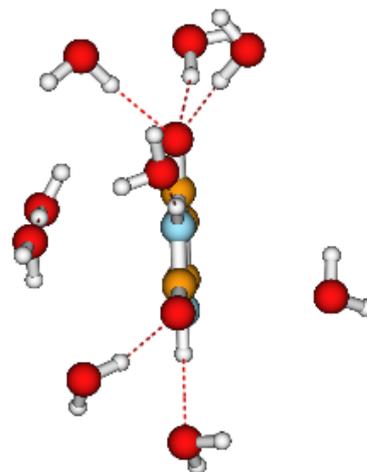

Figure 2. The configuration of the first hydration shell of uracil, including the H-bonding to the hydrophilic sites composed of six and three water molecules in out-of-plane coordinate. (view from the side)

Table 1. The variations of some special bond lengths about the uracil molecule for the Ura(H$_2$O)$_7$ and uracil surrounded by 100 water molecules, respectively.

Bond length (Å)	N1-H1	C2=O2	N3-H3	C4=O4	C5-H5	C6-H6
Isolated uracil	1.012	1.220	1.015	1.223	1.082	1.085
Ura(H$_2$O)$_7$	1.020	1.228	1.026	1.241	1.078	1.081
variation	**0.008**	**0.008**	**0.011**	**0.018**	**-0.004**	**-0.004**
Uracil surrounded by 100 water molecules	1.021	1.225	1.022	1.246	1.081	1.084
variation	**0.010**	**0.005**	**0.006**	**0.024**	**-0.001**	**-0.001**

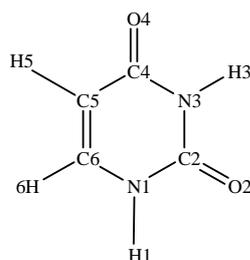**Note that: The labeling of the atoms involved is shown in Figure 3**

Figure 3. Schematic picture of uracil with labeling of atoms used in the table 1.

Reference
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[3]. M. Freindorf and J. Gao, J. Comput. Chem. 1996, 17, 386.
[4]. W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. 1983, 79, 926.