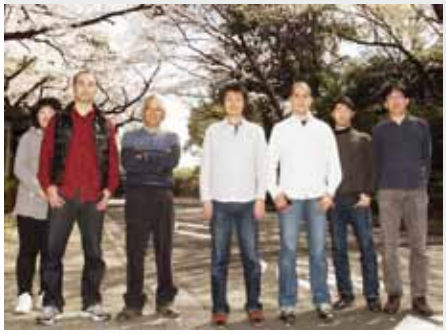
Developing the Statistical Mechanics Theory of Liquids in Chemistry and Biophysics

Department of Theoretical and Computational Molecular Science
Division of Theoretical Molecular Science II



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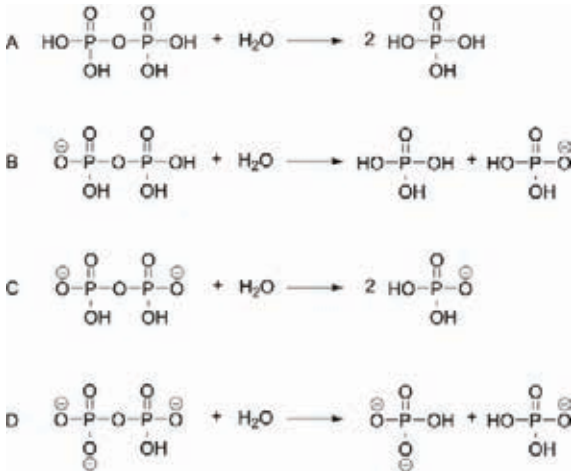
"Molecular recognition" is an essential elementary process for protein to function. The process is a thermodynamic process which is characterized with the free energy difference between two states of a host-guest system, namely, associated and dissociated states. It is readily understood that the structural fluctuation of protein gives a big effect on the free energy barrier. In that respect, the "molecular recognition" is a thermodynamic process which is conjugated with the structural fluctuation of protein.

We have been developing a new theory concerning the molecular recognition, based on the 3D-RISM/RISM theory which is a statistical mechanics of liquids. The theory has successfully "probed" small ligands such as water molecules and ions bound in a small cavity of protein.[1–3)]

1. Elucidating the Molecular Origin of Hydrolysis Energy of Pyrophosphate in Water[4)]

The molecular origin of the energy produced by the ATP hydrolysis has been one of the long-standing fundamental issues. A classical view is that the negative hydrolysis free energy of ATP originates from intra-molecular effects connected with the backbone P–O bond, so called "high-energy bond." On the other hand, it has also been recognized that solvation effects are essential in determining the hydrolysis free energy. Here, using the 3D-RISM-SCF (three-dimensional reference interaction site model self-consistent field) theory that integrates the ab initio quantum chemistry method and the statistical mechanical theory of liquids, we investigate the molecular origin of hydrolysis free energy of pyrophosphate, an ATP analog, in water. We demonstrate that our theory quantitatively reproduces the experimental results without the use of empirical parameters. We clarify the crucial role of water in converting the hydrolysis free energy in the gas phase determined solely by intra-molecular effects, which ranges from endothermic, thermoneutral to highly exothermic depending on the charged state of pyrophosphate, into moderately exothermic in the aqueous phase irrespective of the charged state as observed in experimental data. We elucidate that this is brought about by different natures of solute–water interactions depending on the charged state of solute species: the hydration free energy of low-charged state is mainly subjected to short-range hydrogen-bonds, while that of high-charged state is dominated by long-range electrostatic interactions. We thus provide unambiguous evidence on the critical role of water in determining the ATP hydrolysis free energy.



Scheme 1. Schematic description of the hydrolysis reaction of pyrophosphate for the four possible charged states.

Table 1. The reaction free energies in the gas phase and in the aqueous phase at 298.15 K and 1.0 atm computed by DFT at the B3LYP/6-31+(d) level and the 3D-RISM-SCF theory. Units are in kcal/mol.

Reaction	gas phase (DFT)	aqueous phase (3D-RISM/RISM)	Exp.
A	–1.7	–8.9	–9.5
B	21.3	–6.2	–7.5
C	–56.6	–8.1	–7.7
D	–119.0	–7.7	–7.1

2. Placevent: An Algorithm for Predicting of Explicit Solvent Atom Distribution—Application to HIV-1 Protease and F-ATP Synthase[5)]

Location of water and ions in native structure of protein is of essential importance for its stability and for its functions. However, determination of the position of those species in protein is not an easy task for any experimetal methods currently available, X-ray, NMR, neutron diffraction, and the molecular simulation.

We have created a simple algorithm for automatically predicting the explicit solvent atom distribution of biomolecules. The explicit distribution is coerced from the 3D continuous distribution resulting from a 3D-RISM calculation. This procedure predicts optimal location of solvent molecules and ions given a rigid biomolecular structure and the solvent composition. We show examples of predicting water molecules near the KNI-272 bound form of HIV-1 protease and predicting both sodium ions and water molecules near the rotor ring of F-ATP synthase. Our results give excellent agreement with experimental structure with an average prediction error of 0.45–0.65 Å. Further, unlike experimental methods, this method does not suffer from the partial occupancy limit. Our method can be performed directly on 3D-RISM output within minutes. It is extremely useful for examining multiple specific solvent–solute interactions, as a convenient method for generating initial solvent structures for MD calculations, and may assist in refinement of experimental structures.

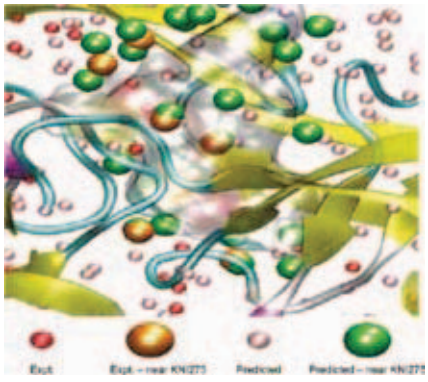


Figure 1. Water molecules near KNI-275. KNI-275 is shown as a translucent surface, HIV-1 protease as a cartoon. Crystal water molecules near KNI-275 are shown in orange, elsewhere in red. Water molecules placed by this method near KNI-275 are shown in green, elsewhere in pink.

3. Modified Andersen Method for Accelerating 3D-RISM Calculations Using Graphics Processing Unit[6)]

Increasing attention has been paid to the 3D-RISM theory due mainly to its capability of treating "solvation" of biomolecules such as protein and DNA without using any adjustable parameters, which is the case in the continuum model. The method was highlighed in several symposiums in the latest ACS meeting held in Philadelphia. Superiority of 3D-RISM to the continuum models, the Poisson-Boltzmann and generalized Born equations, was addressed unambiguously by several talks in the symposiums as far as physical soundness, amount of information produced, applicability to drug design, and so on, are concerned. However, there still remains one point which makes people stick to the continuum models. That is the computation cost. The cost to perform the 3D-RISM calculation is far higher than that of the continuum models. We have proposed a fast algorithm to solve the 3D-RISM equation on a graphics processing unit (GPU). It was the large memory space required for convergence of iteration that banned 3D-RISM from GPU. In order to overcome the difficulty, we replaced the conventional MDIIS algorithm by Anderson's method with some modification. Using this method on a Tesla C2070 GPU, we reduced the total computational time by a factor of eight, 1.4 times by the modified Andersen method and 5.7 times by GPU, compared to calculations on an Intel Xeon machine (8 cores, 3.33 GHz) with the conventional method.

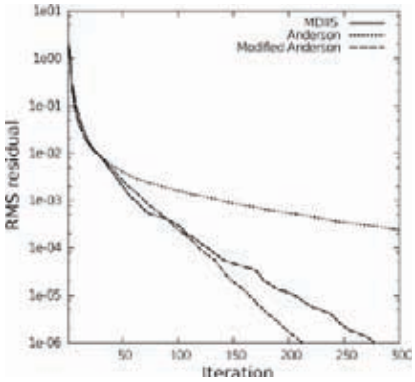


Figure 2. Root mean square residual against the number of iteration steps for the calculation of 3D site distribution profiles of water around a DNA molecule by 3D-RISM. Solid, dotted, and dashed lines are for MDIIS, Anderson, and Modified Anderson algorithms, respectively.

References

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