Developing the Statistical Mechanics Theory of Liquids in Chemistry and Biophysics

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We have been exploring the chemical and biological processes in solutions, based on the statistical mechanics of liquids, especially, on the integral equation theory of molecular liquids or the "RISM" and "3D-RISM" theories.[1–3] Such exploration can be realized by combining the statistical mechanics theories with the other theoretical methods in the molecular science, which describes the different aspects of the physics such as the quantum processes and the liquid dynamics.

Our recent attention is focused on the "molecular recognition" and "fluctuation" of bio-molecules, which are the two key-processes in the living system. For examples, for an enzymatic reaction to take place, substrate molecules should be accommodated by the enzyme. The process is nothing but the molecular recognition which is regulated by the solvation free energy of the enzyme-substrate (ES) complex, and by the structural fluctuation of the protein.

1. A Water Molecules Identified as a Substrate of Enzymatic Hydrolysis of Cellulose: A Statistical-Mechanics Study[4]

Among the technologies to utilize the solar energy, the cellulose decomposition due to the enzymatic hydrolysis is getting the highest expectation, because the available resource on the earth is essentially inexhaustible, and the reaction proceeds in natural conditions without using precious metals as a catalyst. However, there is a high barrier to be cleared for the technology to be established as the ultimate substitute for the fossil fuel, that is, how to improve the efficiency of the enzyme. In order to improve the efficiency, one has to clarify the mechanism of the enzymatic hydrolysis reaction. We have started to investigate the problem last year based on the 3D-RISM theory, taking a cellulase-cellohexaose complex as an example.

There are two models proposed by experimentalists for the mechanism of the enzymatic hydrolysis reaction of cellulose, the inverting and retention processes, which can be distinguished by the distance between the two catalytic residues, and by the position of a water molecule as the substrate of the reaction. In our particular example of the Cel44A-cellohexaose complex, the distance is ~5.5 Å for the retention process, whereas that for the inverting process is ~10.0 Å. The water molecule in the inverting process can make hydrogen bonds only with one of the catalytic residues due to the large separation between the residues, while the molecule can make hydrogen-bonds with the both catalytic residues in the retention process (Figure 1).

Shown in Figure 2 is our result for the distribution of water molecules (yellow and green spots) around the active site of the ES-complex. We have identified the water molecule (colored green) as the substrate of the reaction, since the peak of which is distinctly high among other spots. The water molecule is apparently making hydrogen-bonds with the two catalytic residues, Glu186 and Glu359. This is a clear support to the retention mechanism explained above.

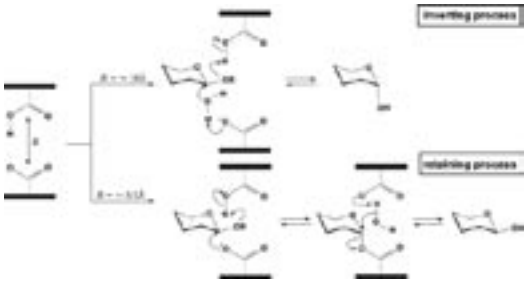

Figure 1. Schematic description of enzymatic hydrolysis of cellulose.

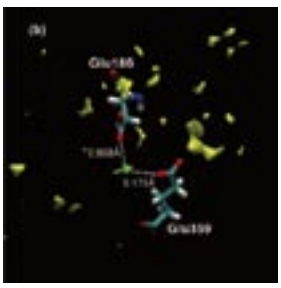

Figure 2. Distribution of water around the active site of the ES-complex.

2. RISM-SCF Study of Temperature and Solvent Dependence of the Free-Energy Surface of the Intramolecular Electron-Transfer[5)]

The free energy surfaces along the intramolecular electron transfer reaction of 1,3-dinitrobenzene radical anion in acetonitrile and methanol are investigated with the reference interaction site model self-consistent field theory. The scheme of the intramolecular electron transfer reaction of 1,3-dinitrobenzene radical anion is shown in figure 3. Although acetonitrile and methanol have similar values of the dielectric constant, the free energy profiles are quite different. In the methanol solution, the charge is strongly localized on one of the nitrile substituents due to a strong hydrogen bond between 1,3-dinitrobenzene and the solvent, while the polarization is not so large in the case of acetonitrile. The temperature dependence of the reorganization energy, the coupling strength and the activation barrier are evaluated in both acetonitrile and methanol. The reorganization energy and the activation barrier decrease with increasing temperature for both cases. The electronic coupling strength also shows similar tendency in the temperature dependence: it increases with increasing temperature in the both solvents, but with different rates. The behavior is explained in terms of the strong polarization induced by the hydrogen bond between solute and solvent in the methanol solution.

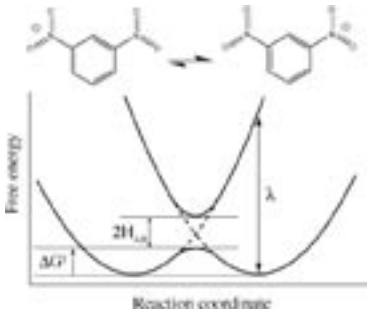

Figure 3. The scheme of the intramolecular electron transfer reaction of 1,3-dinitrobenzene radical anion.

3. On the Proton Exclusion of Aquaporins: A Statistical Mechanics Study[6,7)]

The proton exclusion from aquaporins (AQPs) is one of the most important questions to be solved in the fields of biochemistry, medicine and pharmacology. Although the channels are extremely permeable for water, approximately a billion molecules per second pass through the channel, protons are strictly excluded from the permeation. The mechanism should be readily examined if one can calculate the distribution of the hydronium ion in the channel. The information of the hydronium-ion distribution in the channel may also be useful for examining the possibility of the proton-jump mechanism, because a proton should be existing most likely in the form of the hydronium ion except for the moment of barrier crossing. In this study, we apply the 3D-RISM theory to AQP1 and GlpF for elucidating the proton exclusion from those channels.

In Figure 4, the contour map of the electrostatic potential due to the channel atoms, the 3D-distribution of the water and of hydronium ions, and the one-dimensional profile of the distribution of the solution components are depicted along the channel axis. In both channels, water distributes continuously throughout the channel, while the distribution of hydronium ions is intermitted by gaps due to the electrostatic repulsion originated from the positive charges in the channels. The gap is very large in the case of AQP1, extending from R197 to the NPA region. From the results, we can readily conclude in the case of AQP1 that protons are excluded from permeation primarily due to the electrostatic repulsion inside channel. On the other hand, in the case of GlpF, the results leave slight possibility for proton to permeate through the gap around R206 by the proton jump mechanism. However, the mechanism does not work entirely through out the channel due to the formation of the bipolar orientation at the NPA region. So, a proton has small but discernable conductivity in GlpF through the combined mechanism of the proton jump and the diffusion of hydronium ions in accord with the experiment.

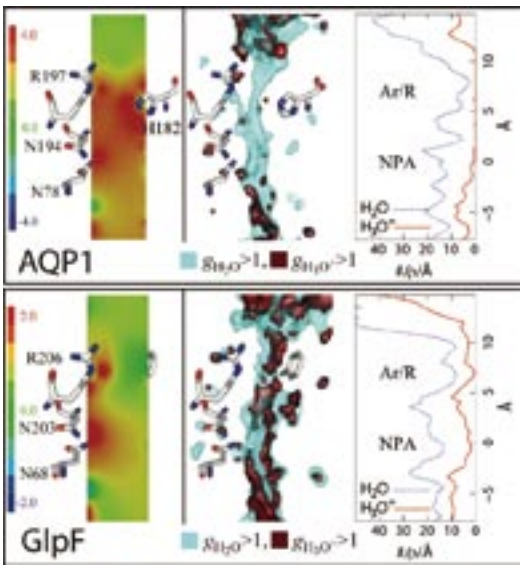

Figure 4. The distribution functions of water and hydronium ion in aquaporin channels. The contour colors show the electrostatic potential of protein in esu unit.

References

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