Prediction of the structural change of the amyloid β protein at the fibril end: DFT-RISM study

Yasuhiro Oishi

Graduate schoool of science, Univesity of Hyogo

RIKEN Symposium
Second Workshop on Fundamentals in Density Functional Theory
(2024/2/21)

Acknowledgement

・Discussion on experiments

【Prof. H. Ogi and Prof. K. Nakajima (U. Osaka)】

・Comment on RISM calculation

【Prof. M. Otani and Prof. S. Hagiwara (U. Tsukuba)】

・Discussion on calculation model and DFT calculation

【Prof. K. Kusakabe and Prof. M. Kitatani (U. Hyogo)】

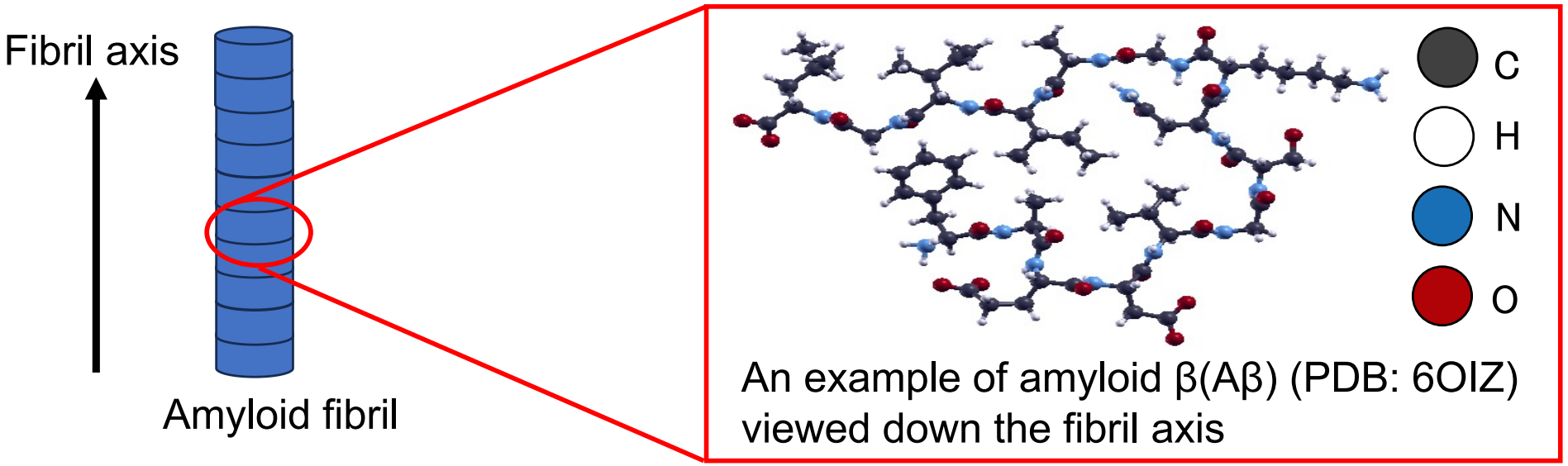
Reference

・Y. Oishi, H. Ogi, S. Hagiwara, M. Otani, K. Kusakabe. *ACS omega*, 7, 35, 31120-31125 (2022).

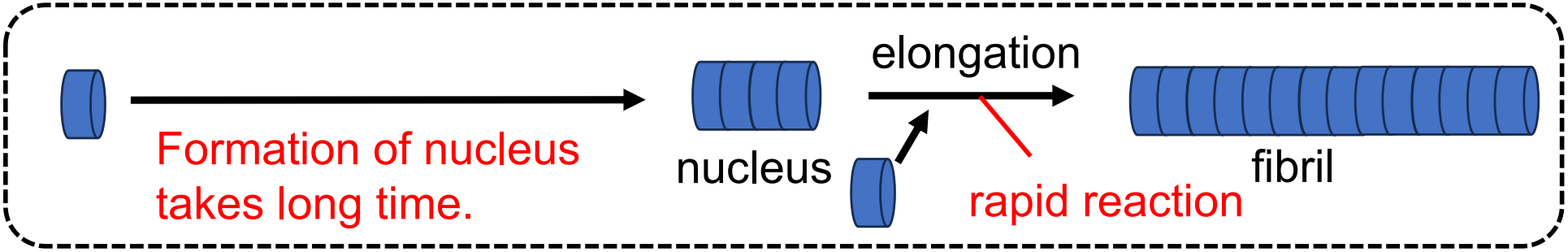
・Y. Oishi, M. Kitatani, and K. Kusakabe. *Beilstein Archives,* 2023, 1, 59 (2023)

Amyloid β aggregates to form fibril.

Amyloid fibril is an aggregate of proteins.



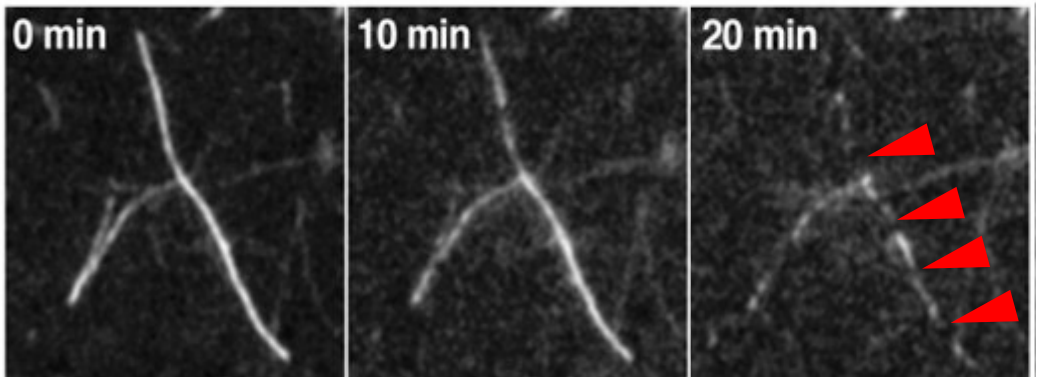
Formation of fibril causes Altzheimer disease.



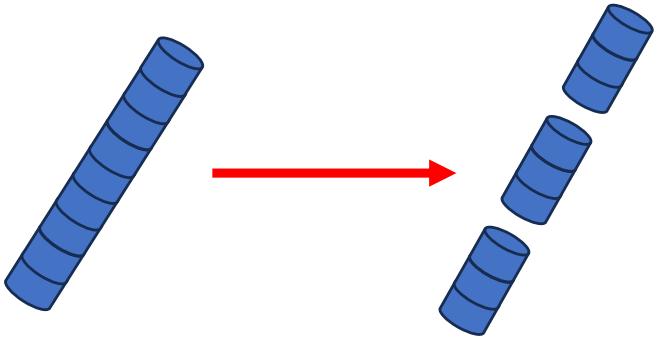
To prevent the onset of disease, the fibril should be disaggregated into monomers.

Disaggregation by fragmentation

Disaggregation behavior observed by fluorescence microscope

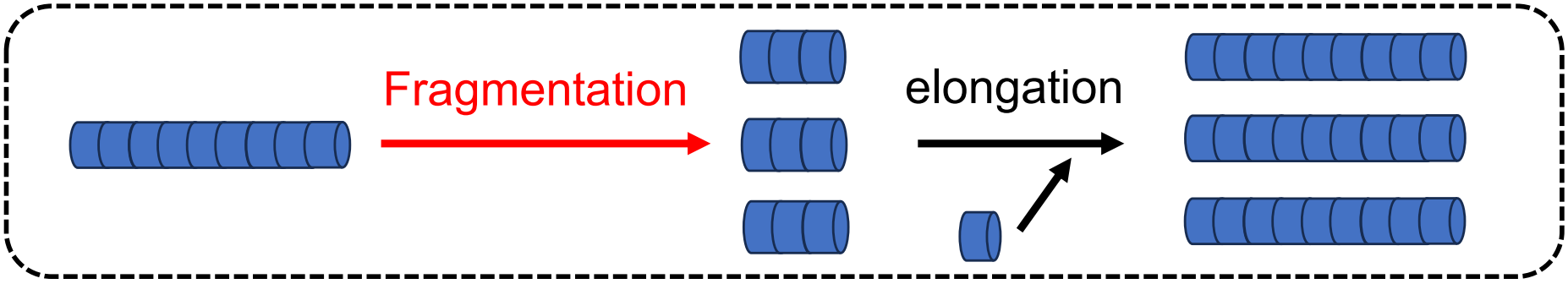


K, Noi., et al., *Anal. Chem.* (2021)

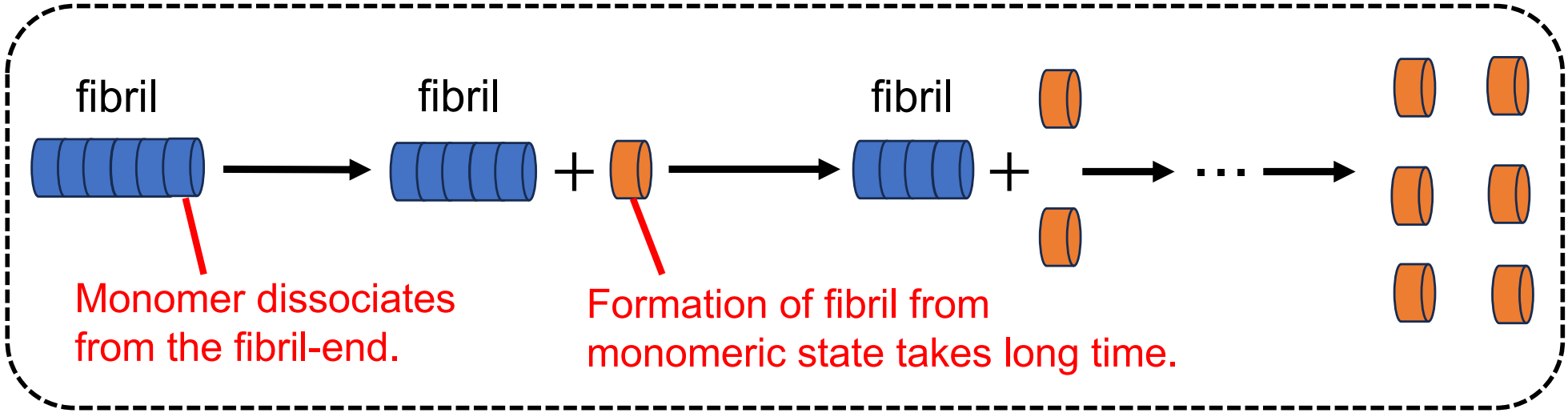


This is not a desirable disaggregation, because fragmentation increases elongated fibrils.

Xue, W. F., et al., *J. Biol. Chem.* (2009)



Disaggregation by dissociation of monomer



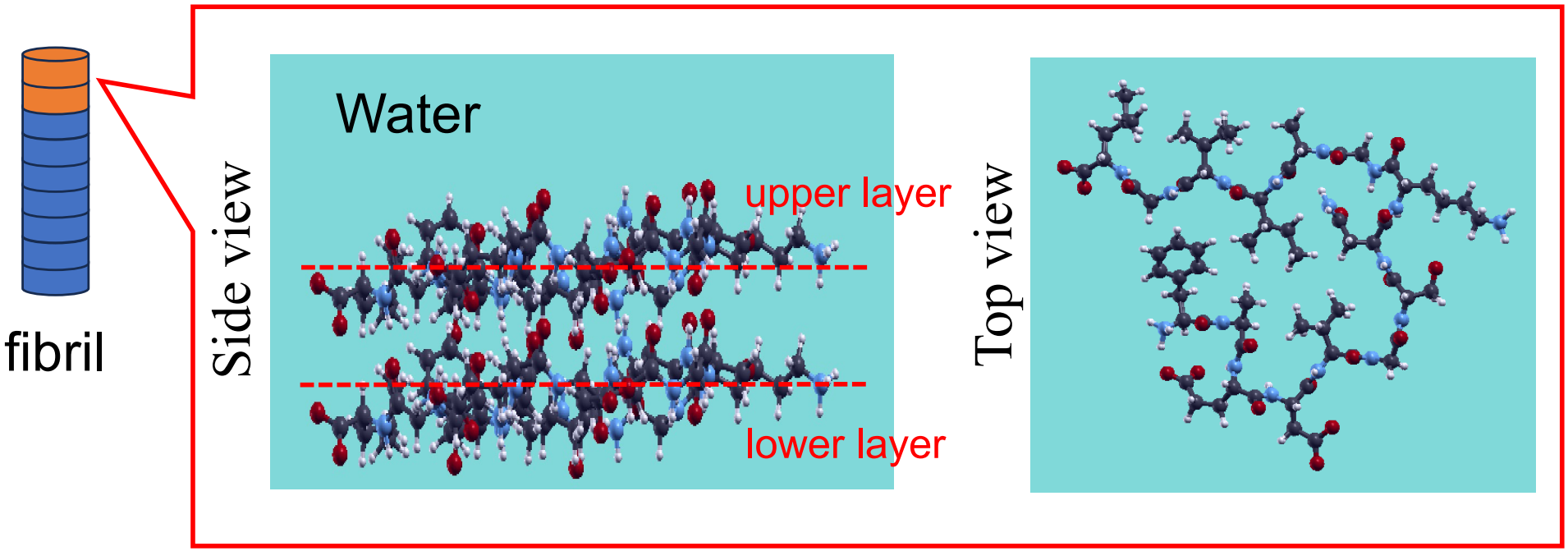
The number of fibrils unchanges. ➡ Desireble !

Purpose of this study

Understanding motion of Aβ at the fibril end leading to the disaggregation based on DFT approach.

Calculation model for Aβ at the fibril-end

Aβ dimer was used as a model for fibril-end strucure.



Water molecules were expressed as an ensemble-averaged distribution function, determined by RISM (※).

(※) Reference interaction site model (RISM)

J. P. Hansen and I. R. McDonald, (Academic, London, 1976).

Scheme of DFT-RISM method

Kovalenko, A; Hirata, F.
J. Chem. Phys. (1999).

RISM equation determines the total and direct correlation function $h_\gamma(\boldsymbol{r})(=g_\gamma(\boldsymbol{r})-1)$ and $c_\gamma(\boldsymbol{r})$.

$$h_\gamma(\boldsymbol{r}) = \sum_\alpha \int d\boldsymbol{r}' c_\alpha(\boldsymbol{r}')\,\chi_{\alpha\gamma}(\boldsymbol{r}'-\boldsymbol{r})$$

$$g_\gamma(\boldsymbol{r}) = \begin{cases} \exp\left[-\beta u_\gamma(\boldsymbol{r}) + h_\gamma(\boldsymbol{r}) - c_\gamma(\boldsymbol{r})\right] & (h_\gamma(\boldsymbol{r}) \le 0) \\ 1 - \beta u_\gamma(\boldsymbol{r}) + h_\gamma(\boldsymbol{r}) - c_\gamma(\boldsymbol{r}) & (h_\gamma(\boldsymbol{r}) > 0) \end{cases}$$

$u(\boldsymbol{r})$ is the two-body interaction potential.

$$u_\gamma(\boldsymbol{r}) = \sum_A 4\sqrt{\epsilon_\gamma \epsilon_A}\left[\left\{\frac{(\sigma_\gamma+\sigma_A)/2}{|\boldsymbol{r}-\boldsymbol{R}_A|}\right\}^{12} - \left\{\frac{(\sigma_\gamma+\sigma_A)/2}{|\boldsymbol{r}-\boldsymbol{R}_A|}\right\}^{6}\right] - q_\gamma\left(\int \frac{n(\boldsymbol{r}')}{|\boldsymbol{r}-\boldsymbol{r}'|}d\boldsymbol{r}' + v_{\mathrm{local}}(\boldsymbol{r})\right)$$

$g_\gamma(\boldsymbol{r})$ →

← $n(\boldsymbol{r})$

Kohn-Sham equation with solvation potential $v_{solv}(\boldsymbol{r})$ determines electron density $n(\boldsymbol{r})$.

$$v_{\mathrm{solv}}(\boldsymbol{r}) = \int d\boldsymbol{r}' \frac{\sum_\gamma q_\gamma \rho_\gamma g_\gamma(\boldsymbol{r}')}{|\boldsymbol{r}-\boldsymbol{r}'|}$$

$$\left(-\frac{1}{2}\nabla_i^2 + v_{\mathrm{H}}(\boldsymbol{r}) + v_{\mathrm{xc}}(\boldsymbol{r}) + v_{\mathrm{ext}}(\boldsymbol{r}) + v_{\mathrm{solv}}(\boldsymbol{r})\right)\psi_i = \epsilon_i\psi_i$$

$$n(\boldsymbol{r}) = \sum_i |\psi_i(\boldsymbol{r})|^2$$

$h_\gamma(\boldsymbol{r})$ $c_\gamma(\boldsymbol{r})$ $n(\boldsymbol{r})$

Free energy as a sum of DFT energy and solvation energy

$$A = E_{\mathrm{DFT}} + \Delta\mu_{\mathrm{solv}} \qquad \Delta\mu_{\mathrm{solv}} = k_{\mathrm{B}}T\sum_\gamma \rho_\gamma \int d\boldsymbol{r}\left[\frac{1}{2}\{h_\gamma(\boldsymbol{r})\}^2\Theta(-h_\gamma(\boldsymbol{r})) - c_\gamma(\boldsymbol{r}) - \frac{1}{2}h_\gamma(\boldsymbol{r})c_\gamma(\boldsymbol{r})\right]$$

Computational details

Structural optimization by conventional DFT

Structural optimization by DFT-RISM

Computational details for DFT

- Energy functional : PBEsol+D3
- Energy cutoff for wavefunction: 25 Ry
- Energy cutoff for charge: 250 Ry
- $\boldsymbol{k}$-mesh : Gamma point

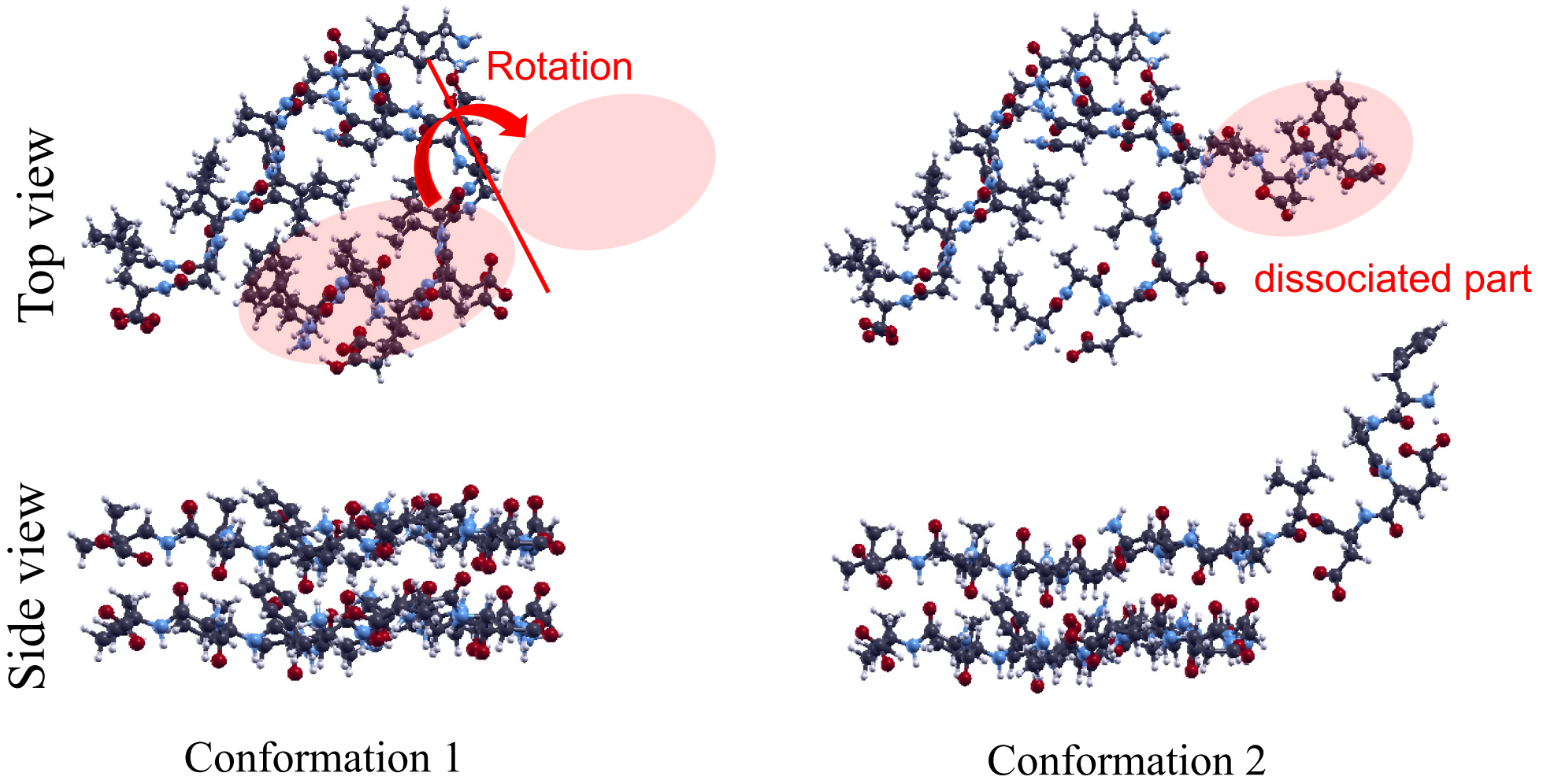
Computational details for RISM

- Solvent : water (SPC model)
- Temperature and density : 300 K, 1 g/cm^3
- Lenard-Jones parameter for DFT particle : Universal force field

All calculations were carried out using Quantum ESPRESSO.

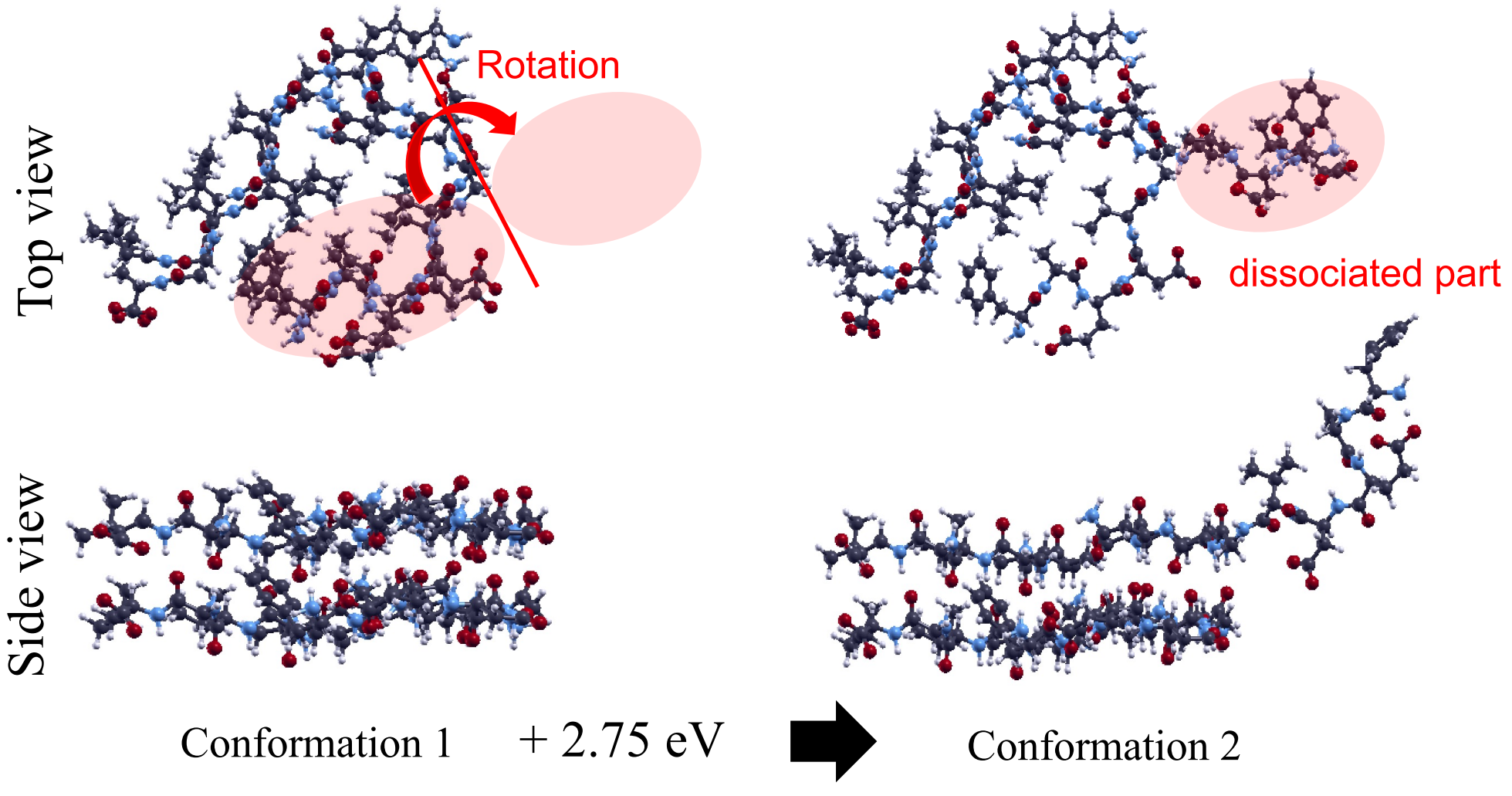
Result of the structural optimization by DFT

Structural optimization by DFT without water



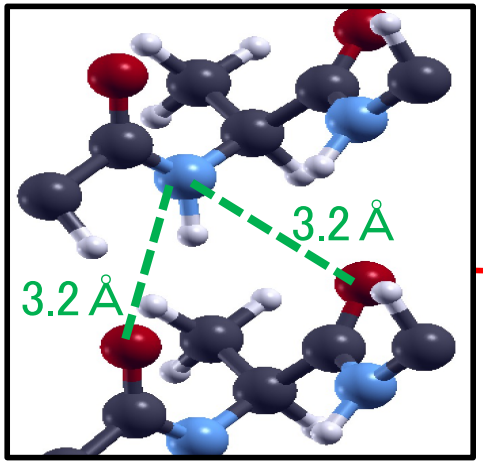
Result of the structural optimization by DFT

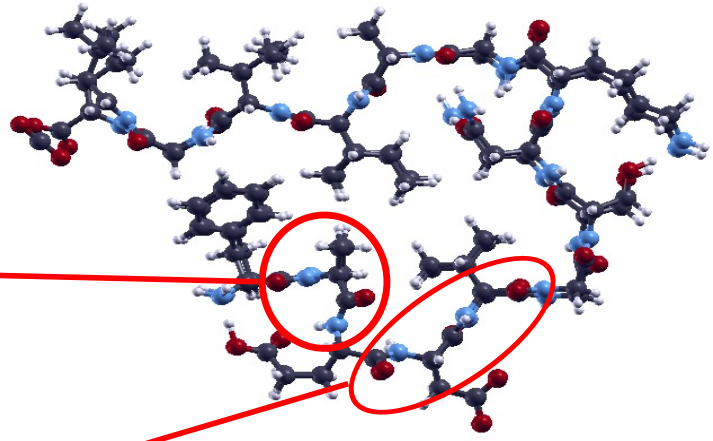
Structural optimization by DFT without water



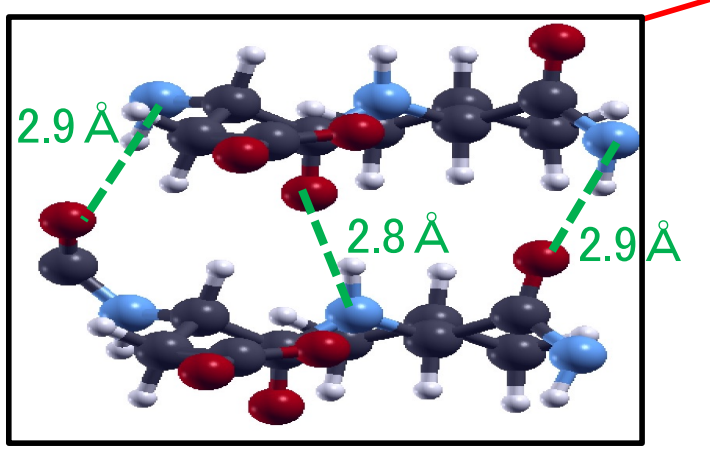
Dissociation of upper layer requires huge energy loss.

Result of the structural optimization by DFT

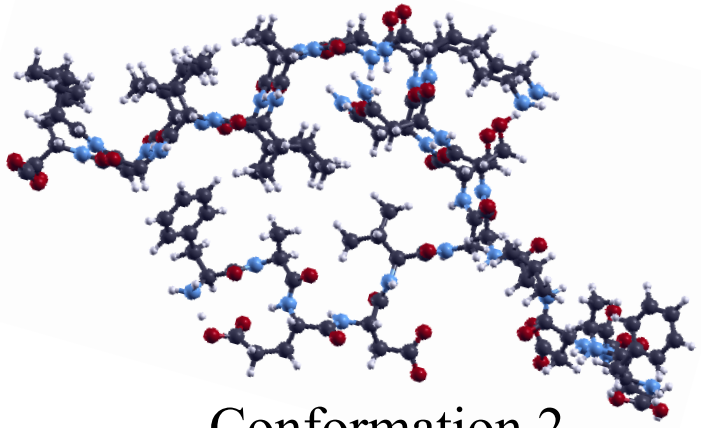




Conformation 1



Side view of Conformation 1

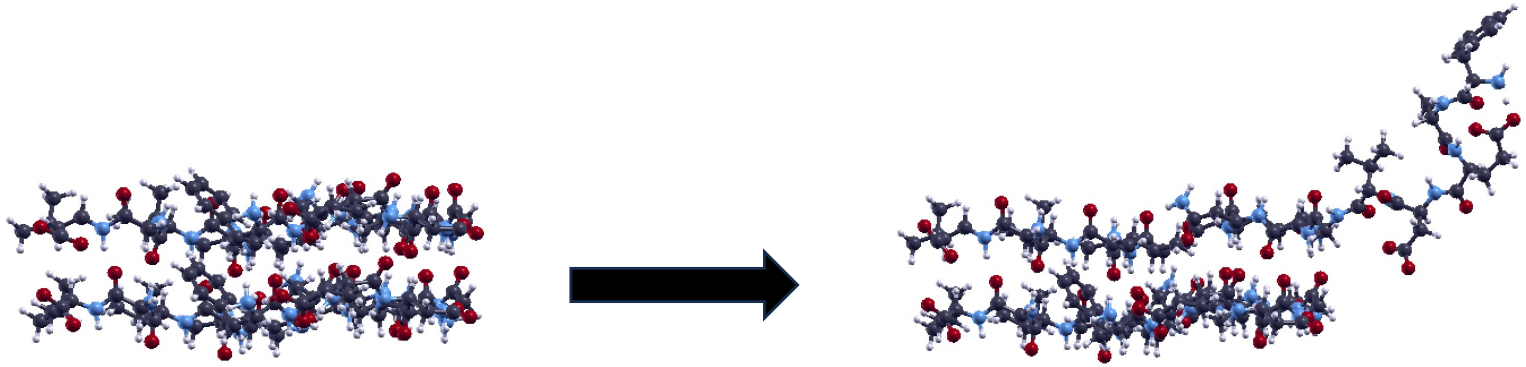


Conformation 2

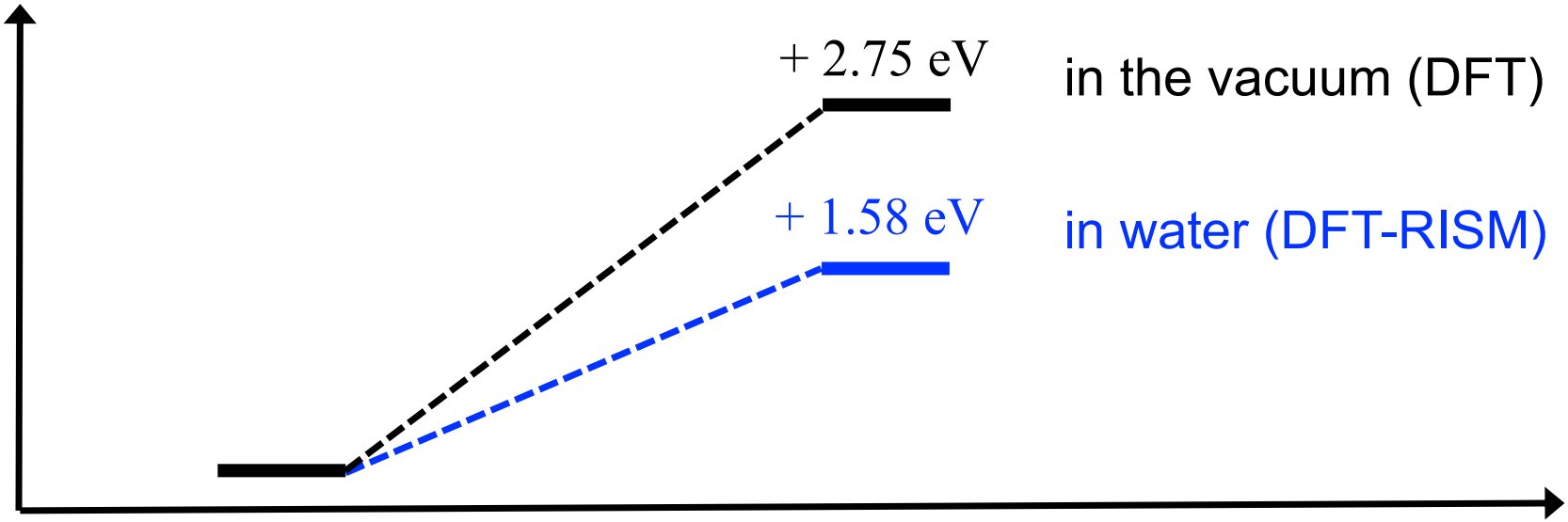
The energy loss partly comes from the cleavage of hydrogen bonds connecting two layers.

Result of the structural optimization by DFT-RISM

Relative energy of conformation 2 to conformation 1

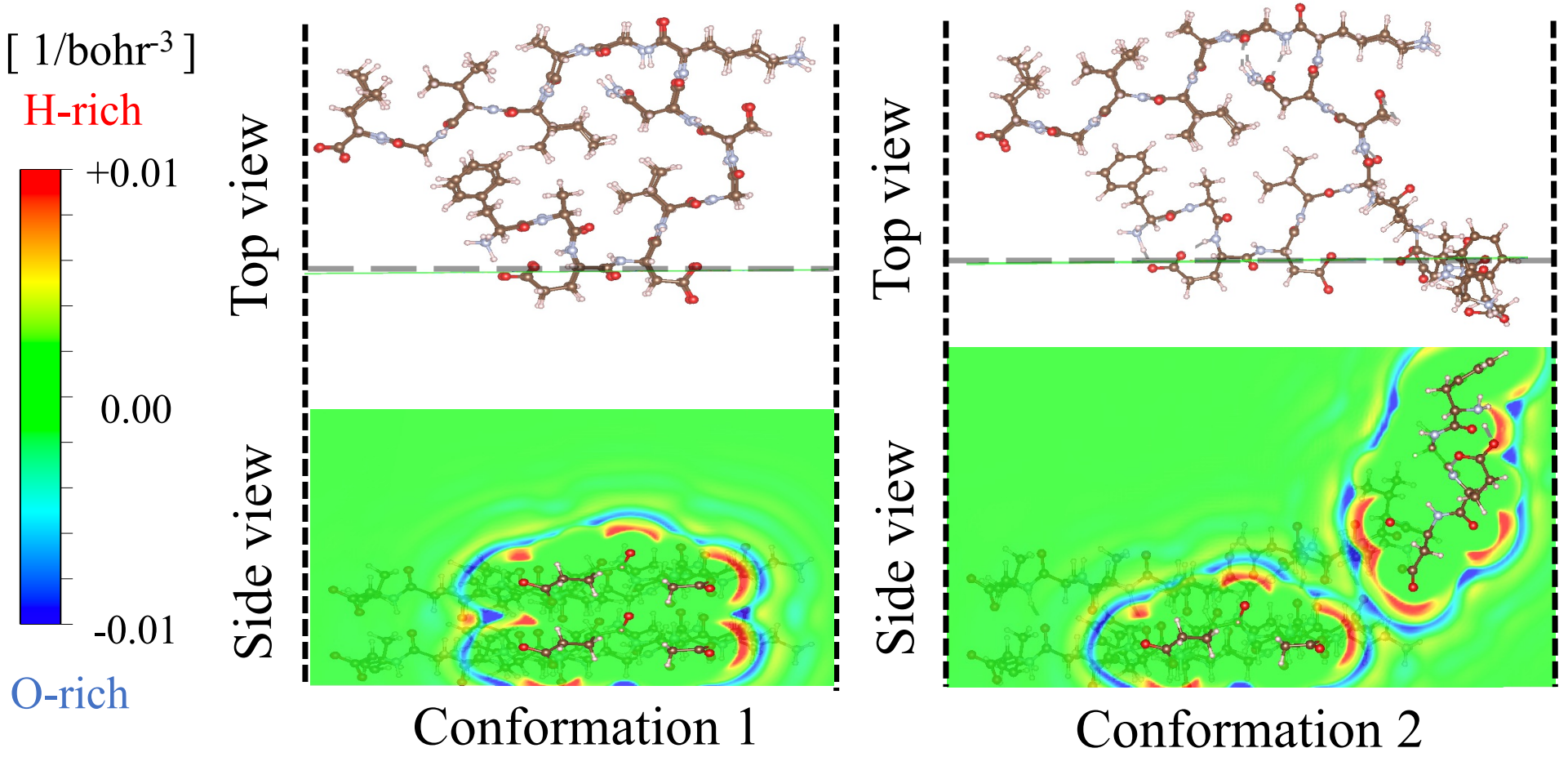


Conformation 1 Conformation 2



The dissociation of upper layer tends to happen more easily in water than in the vacuum.

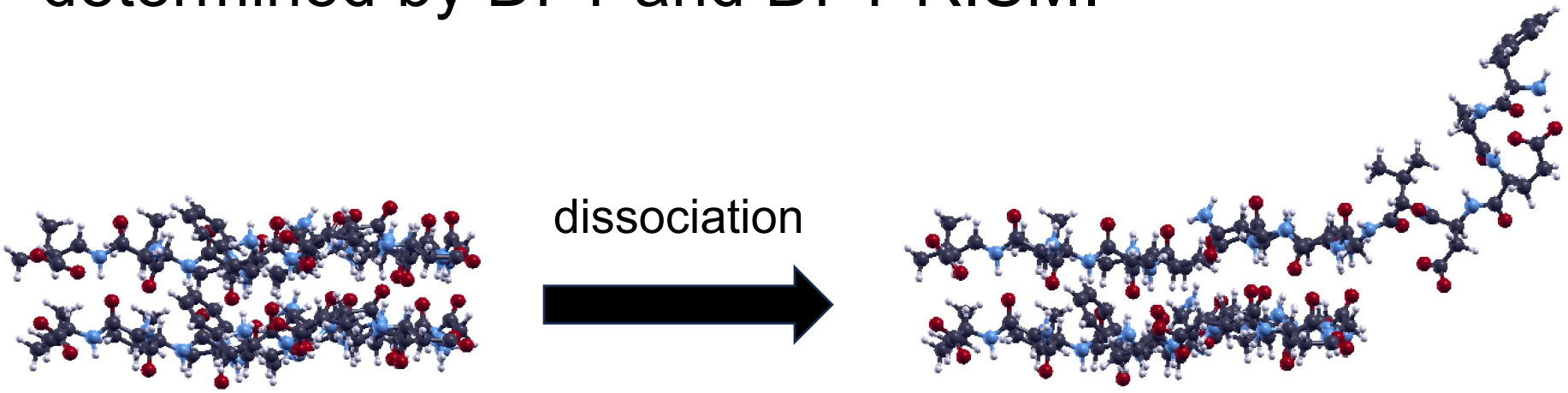
Charge density distribution of water



Hydration of the polar portion exposed upon dissociation improves the stability of conformation 2.

Summary

Stable dimer structure of amyloid β protein was determined by DFT and DFT-RISM.



- Dissociation requires huge energy loss.
- Hydration lowers energy loss upon dissociation.