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The 2nd, CREST Workshop

On the Hybrid MC/MD Reaction Method: Application to 2-Chlorobutane Racemization Process in DMF Solution

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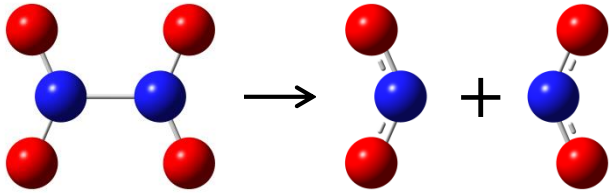
M. Nagaoka, **YS**, T. Okamoto, N. Takenaka, Chem. Phys. Lett. 583 (2013) 80.

Introduction

Chemical Reaction is Rare Event.

- In diffusion in solids and chemical reactions, etc., many systems spend the majority of their time in phase space regions [1].



e.g.

99.9999999% in the initial state of N_2O_4 dissociation reaction at 273 K.

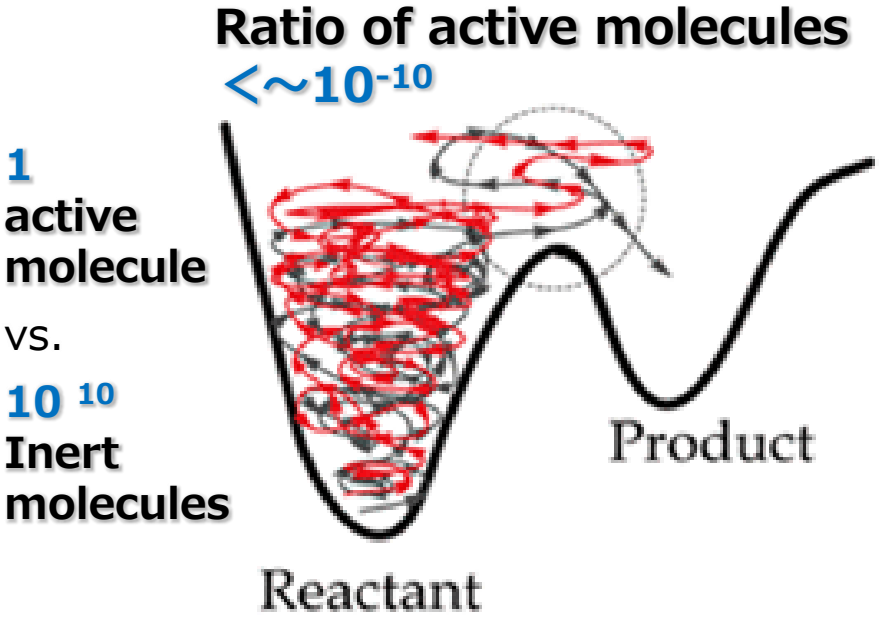
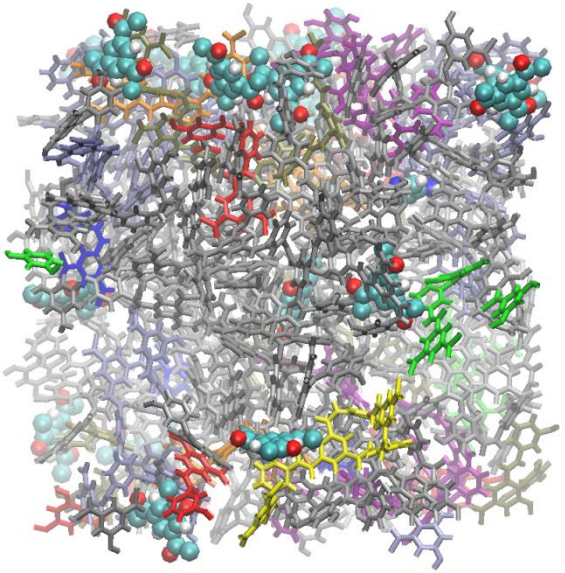


Fig. Schematic representation of N_2O_4 dissociation reaction

[1] e.g., E.A. Carter, G. Ciccotti, J.T.Hynes, R. Kapral, Chem. Phys. Lett. 156 (1989) 472.

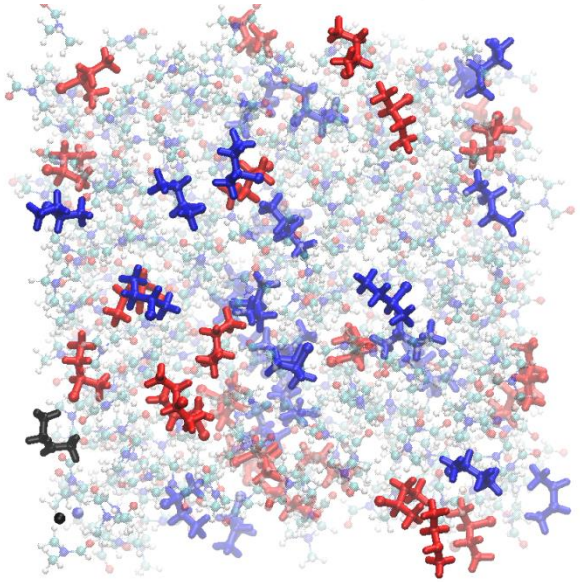
How to Treat Complex Chemical Reaction Systems ?

- With traditional molecular simulations, it is difficult to treat complex chemical reaction systems such as polymer membrane.



We have developed the hybrid Monte Carlo (MC) / molecular dynamics (MD) reaction method [2].

For demonstration, we applied the method to 2-chlorobutane racemization in DMF solution [2].



[2] M. Nagaoka, **YS**, T. Okamoto, N. Takenaka, Chem. Phys. Lett. 583 (2013) 80.

Method

Hybrid MC/MD Reaction Method

①Run MD simulation in the region *R* until some pair of atoms meets the necessary conditions and select configuration state *r*.

②Virtually react it to generate a configuration state *s*, relaxing the whole system through MD simulation.

③Compute ΔU_{rs} (= U_s - U_r) and accept (or reject) the reaction step according to the transition probability

$$W_{r\to s} = \min\left\{1,\ \exp\left[-\beta \Delta U_{rs}\right]\right\}$$

under the Metropolis scheme.

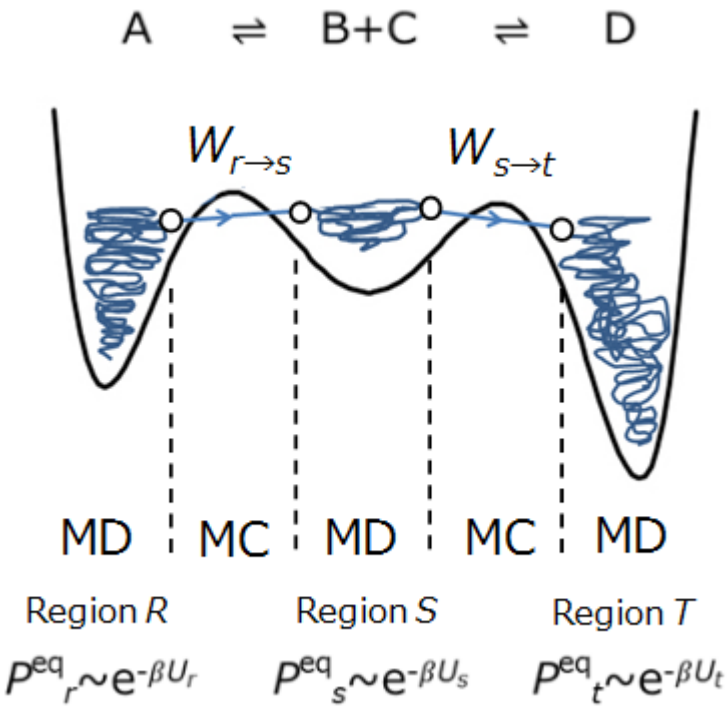


Fig. The concept of the method

➡ The change of state due to chemical reactions is realized by repeating the MC/MD cycle.

Model System & Computational Details

Model System: 2-Chlorobutane in DMF Solution

- Application to 2-chlorobutane racemization in *N*,*N*-dimethylformamide (DMF) solution assuming the S_N1 mechanism.

Realization of a state with ~0% e.e., the expected purity of (*R*)- to (*S*)-enantiomers of the racemic mixture.

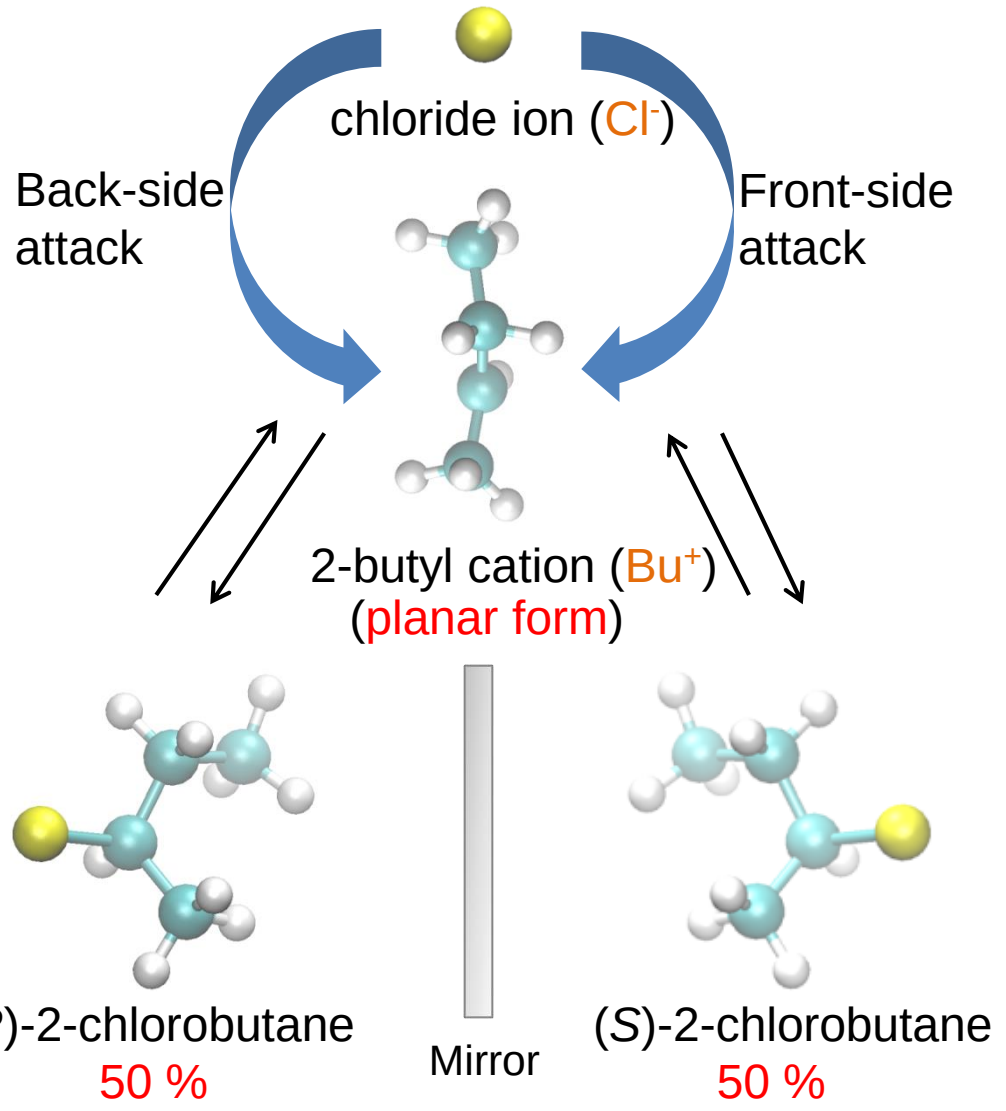


Fig. Racemization (S_N1 mechanism)

Computational Details

- 50 (*R*)-2-chlorobutane (red) and 350 DMF molecules.
- General Amber force field (GAFF),RESP charge.
- Periodic boundary condition.
- NPT-MD for 1 ns (313 K and 1 atm) for a relaxation.
- The concentration of (*R*)-2-chlorobutane molecules was ~1.65 mol/L.
- The NVT-MD (313 K) simulation time in one MC/MD cycle was set to 10 ps.
- For 900 MC/MD cycles.

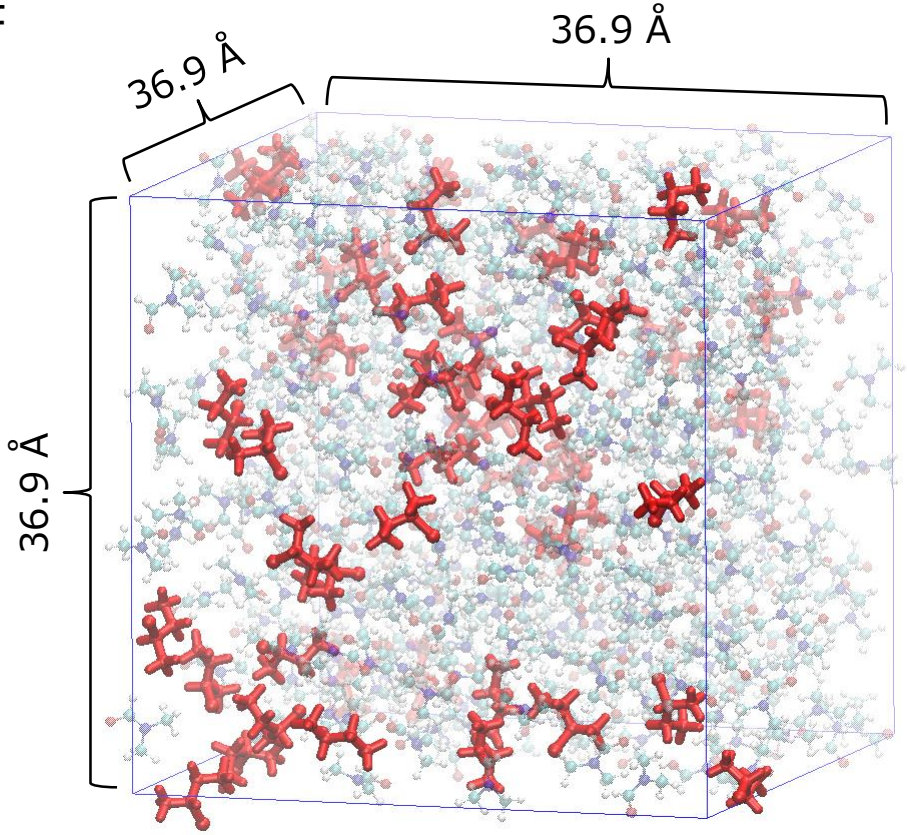


Fig. Initial structure

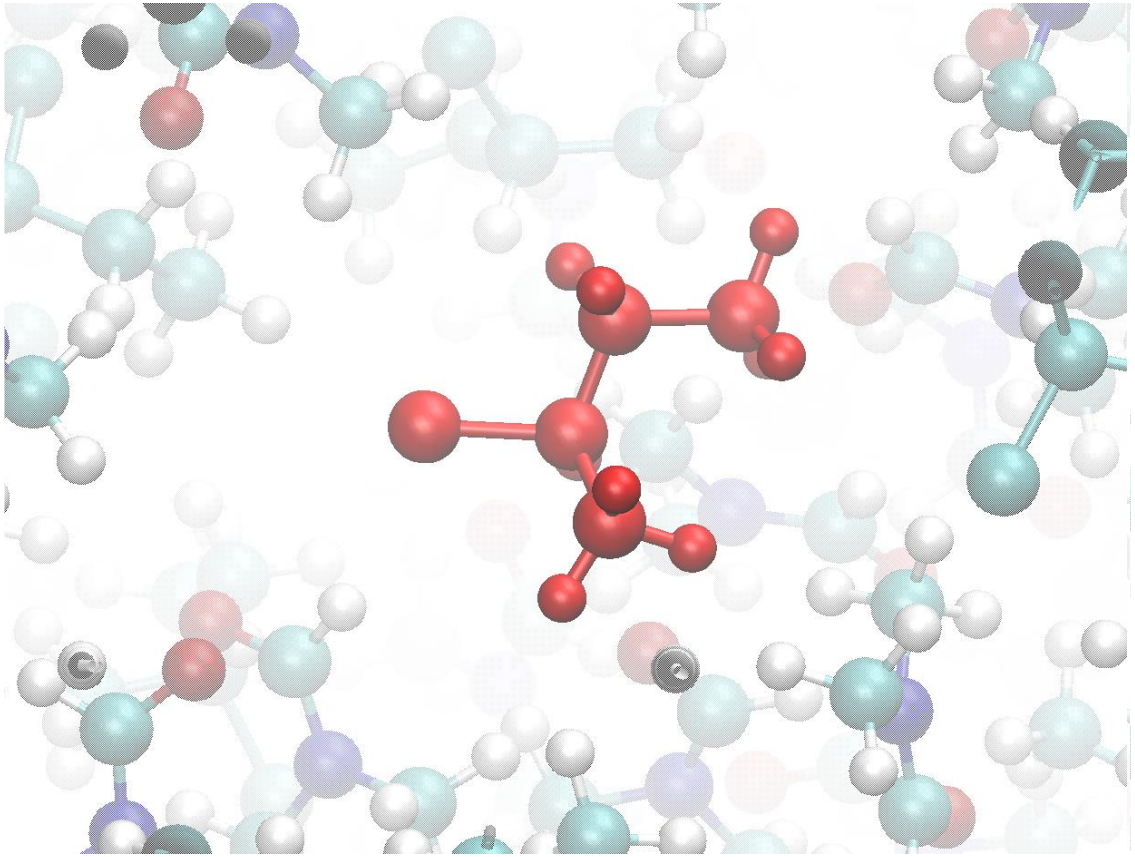
Results & Discussion

Present Hybrid MC/MD Reaction Simulation

①Run MD simulation until some pair of atoms meets the necessary conditions.

②Virtually react it, relaxing the whole system.

③Accept (or reject) the reaction step under the Metro-polis scheme.

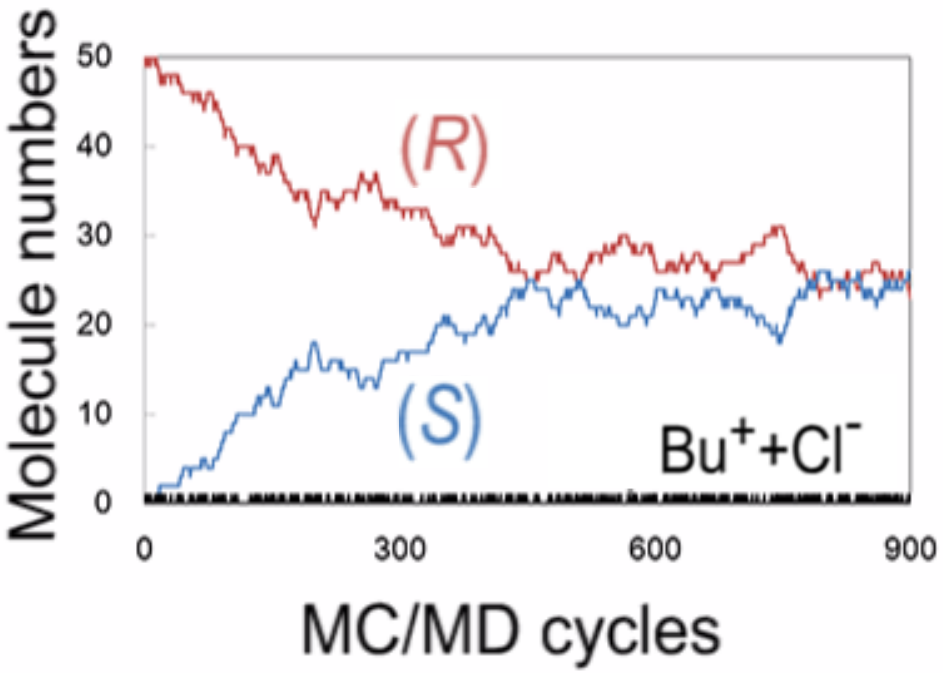


MD trajectory for a chemical bond of Bu^+ and Cl^- to (*R*)-2-chlorobutane

Realization of Racemization – Numbers –

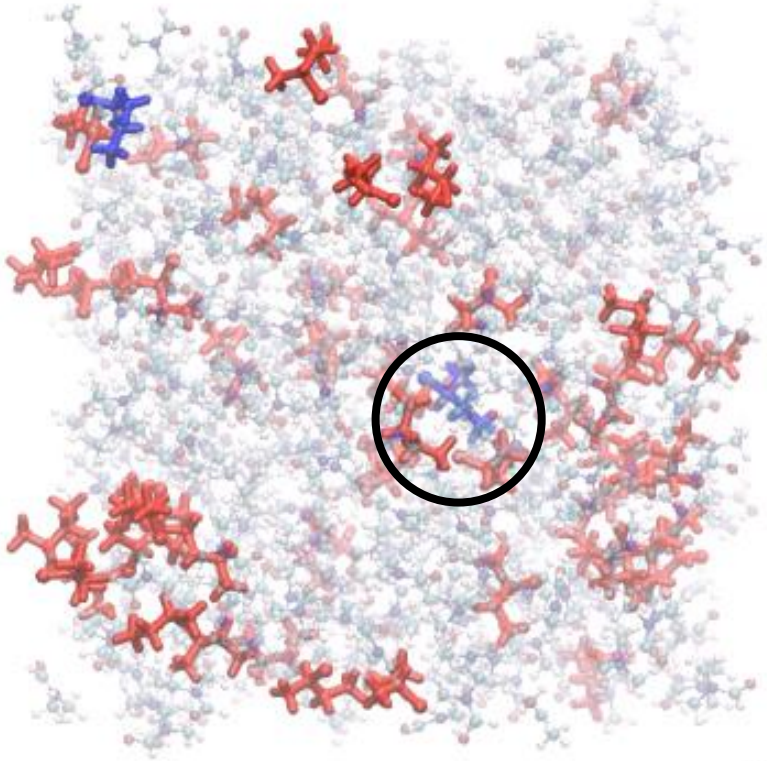
- Decomposition and formation occurred frequently, and the ratio of (*R*)- to (*S*)-enantiomers changed.
- Their equilibrium numbers, estimated as averages over the last 100 MC/MD cycles, were **25.3** and **24.4**, respectively.

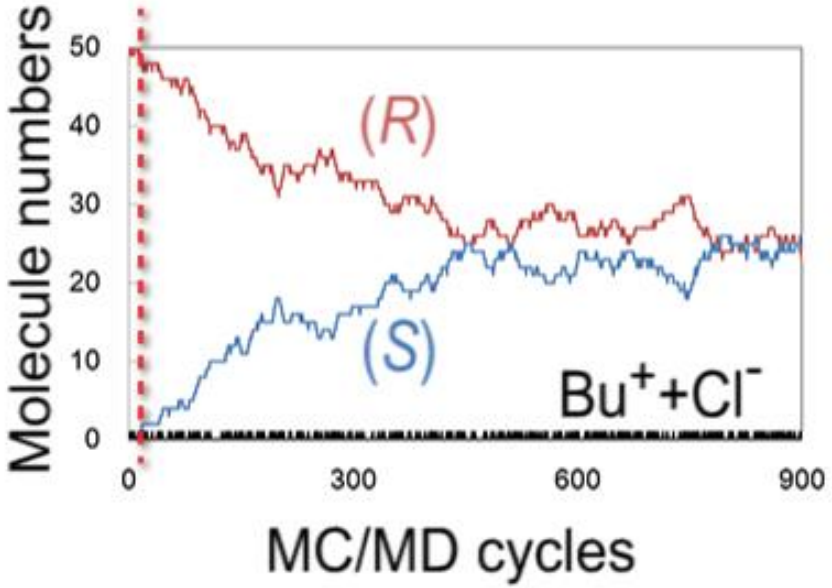
➡ (*R*)- and (*S*)-2-chlorobutane exist in equal numbers of ~25.



Realization of Racemization – Structure –

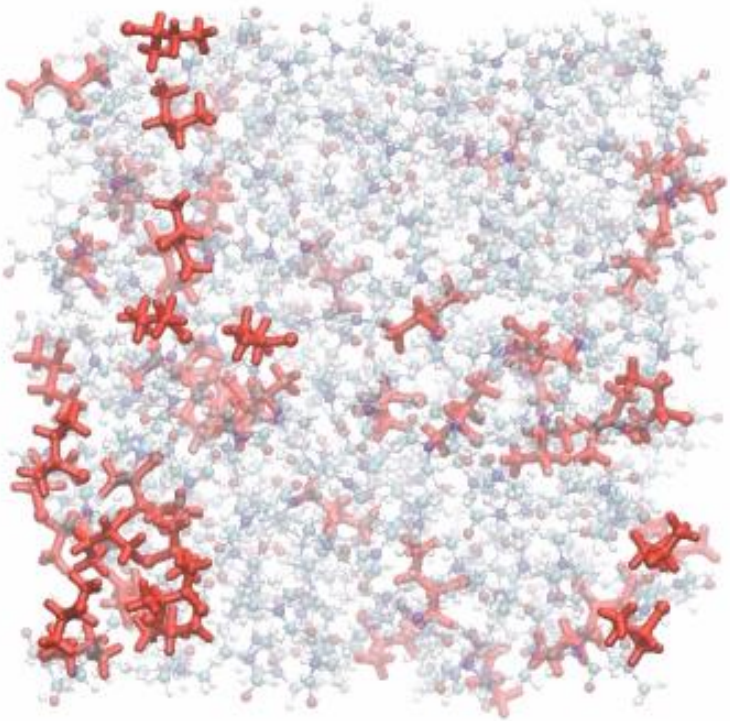
(*R*) → Bu^++Cl^- → (*S*)

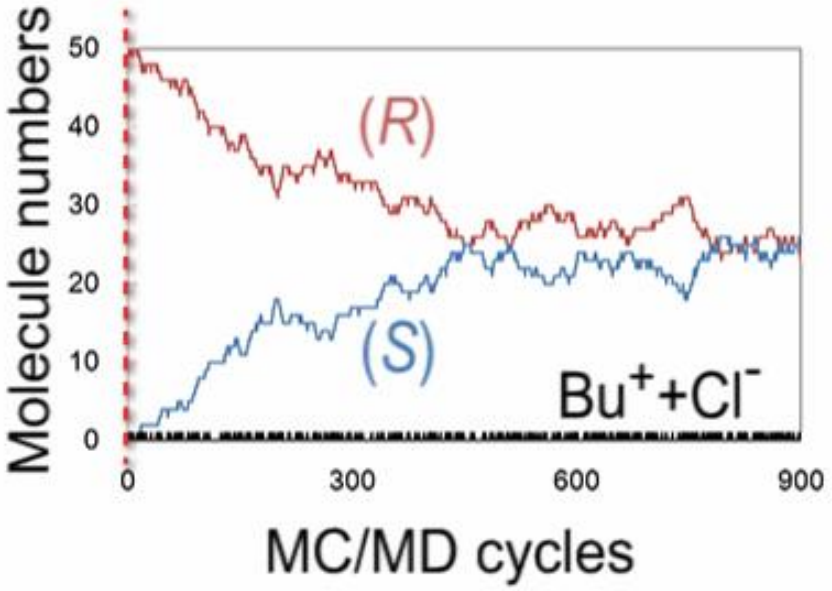




18 cycle

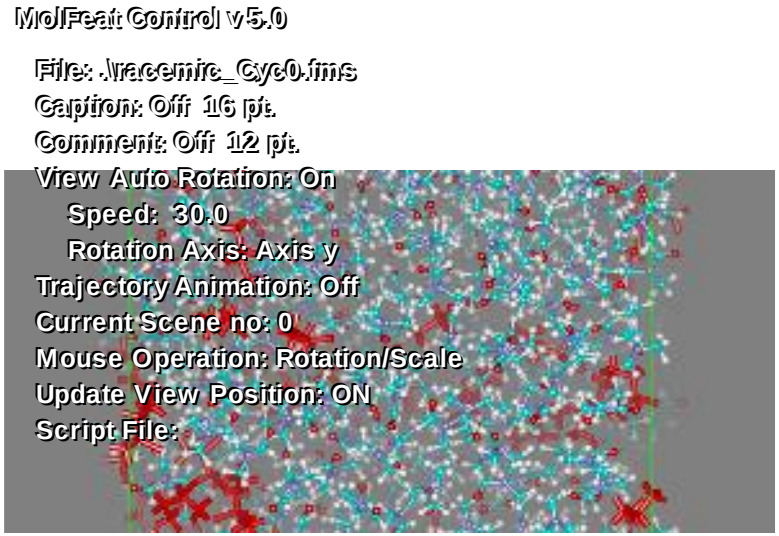
Realization of Racemization – Structure –





0 cycle

Realization of Racemization – Homogeneity –



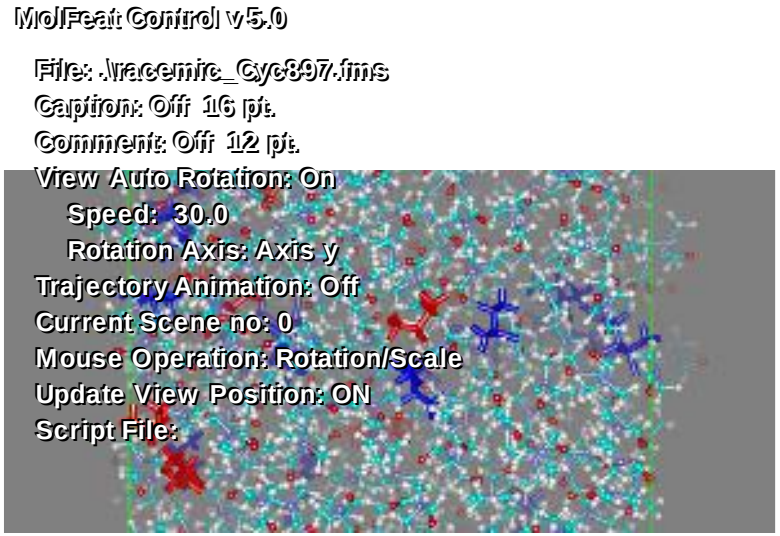


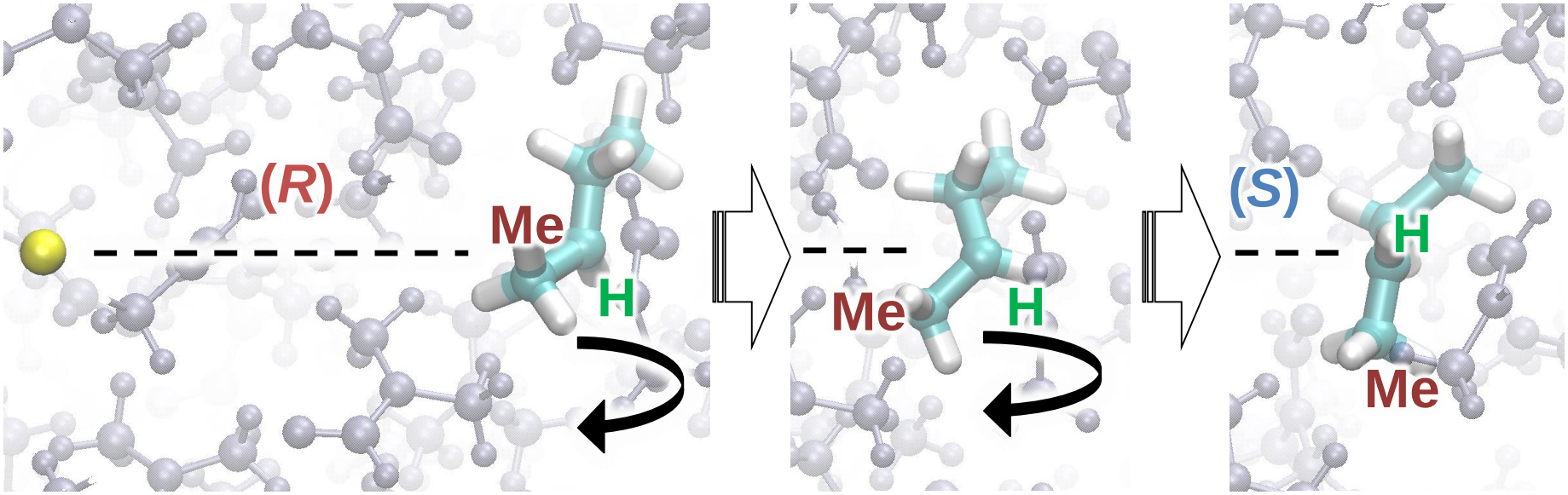
Fig.(a) Initial state (0 MC/MD cycle)

Fig.(b) Equilibrium state (897 MC/MD cycles)

- The whole system became equilibrium state, and (*R*)- and (*S*)-enantiomers distribute homogeneously in the solution.

➡ 2-chlorobutane racemization has been realized, as the molecular structural change was treated in atomic scale.

An observation: Isomerization with Internal Rotation



t =1.6 ps *t* =2.0 ps *t* =3.0 ps

- It was observed that Isomerization of 2-chlorobutane occurs by the internal rotation of both the methyl substituent (Me) and hydrogen (H) of Bu^+, which is different from the usual S_N1 mechanism in the text book [3].

[3] e.g., K.P.C. Vollhardt, N.E. Schore, Organic Chemistry Structure and Function, 6th ed., W. H. Freeman & Co, New York, 2006.

Conclusion

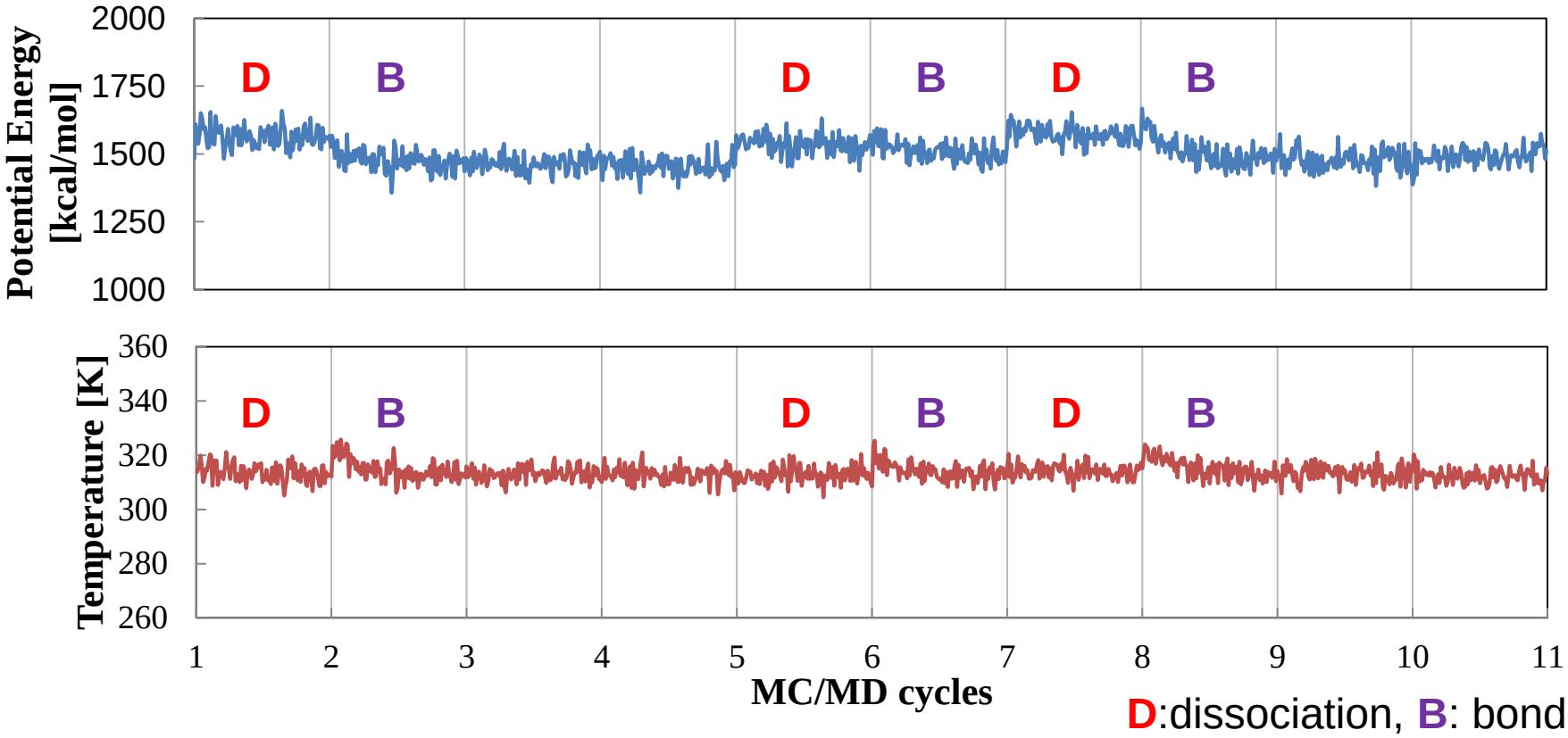
- **We proposed a hybrid MC/MD reaction method** in order to achieve atomistic molecular simulation of complex chemical reaction systems.

- **This method** was applied to (*R*)-2-chlorobutane molecules in DMF solution system, and **worked very well to realize a stereochemical mechanism for the racemization**.

- It was observed that Isomerization of 2-chlorobutane occurs by both the internal rotation of the methyl substituent and hydrogen of Bu^{+}.

Thank you for your attention

Potential Energy and Temperature Change



- A sudden increase in potential energy occurred during chemical reaction and dissipated into the surrounding solvent.

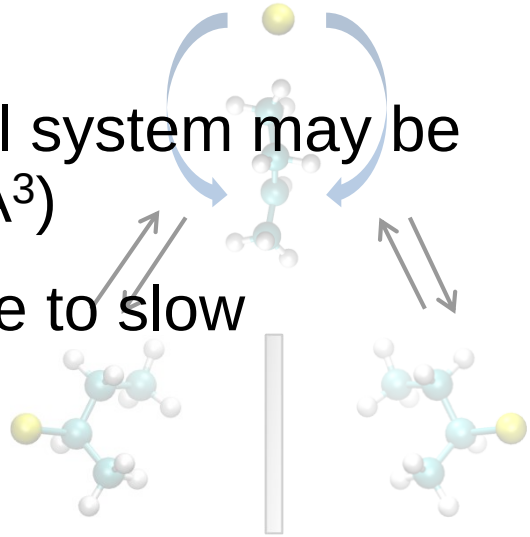
➡ The method worked well to attain thermal equilibrium, searching for a lower potential energy state under the constant temperature scheme.

How to recombine with Cl^- ?

A Bu^+ may be recombined with Cl^- approaching from the front- or back-side in a normal S_N1 mechanism [4].

However…

- The number of Bu^+ or Cl^- molecule in actual system may be only ~1.19×10^7 in 1 L. (~1 in $36.9^3 \times 10^{26}$ Å^3)
- Diffusion coefficient of Cl^- should be low due to slow diffusion of DMF solvent (1.21×10^{-13} m^2/s).



A Bu^+ would be recombined with Cl^- that dissociated a little before, and therefore the racemization would progress slowly.

[4] e.g., K.P.C. Vollhardt, N.E. Schore, Organic Chemistry Structure and Function, 6th ed., W. H. Freeman & Co, New York, 2006.

Realization of Racemization – Homogeneity –

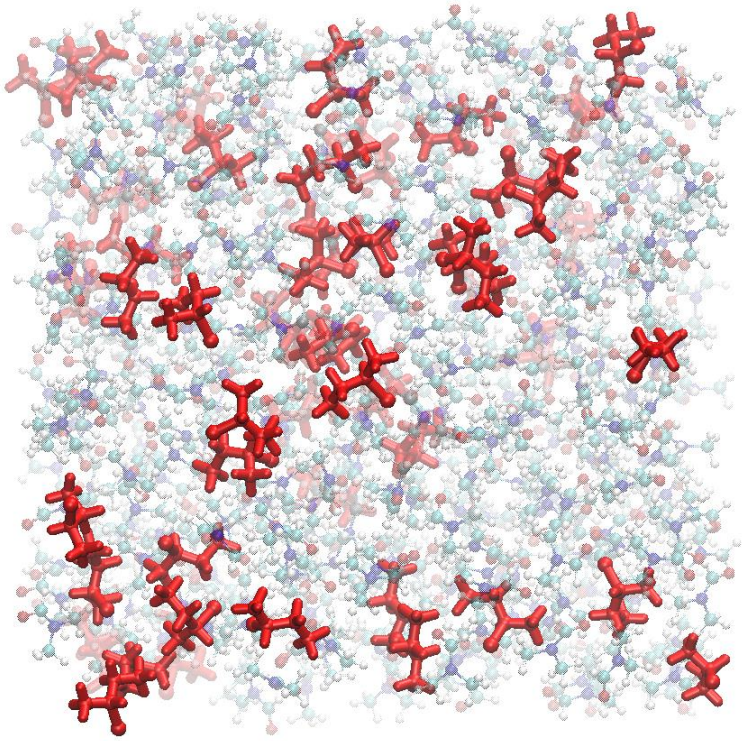


Fig. Initial state (0 MC/MD cycle)

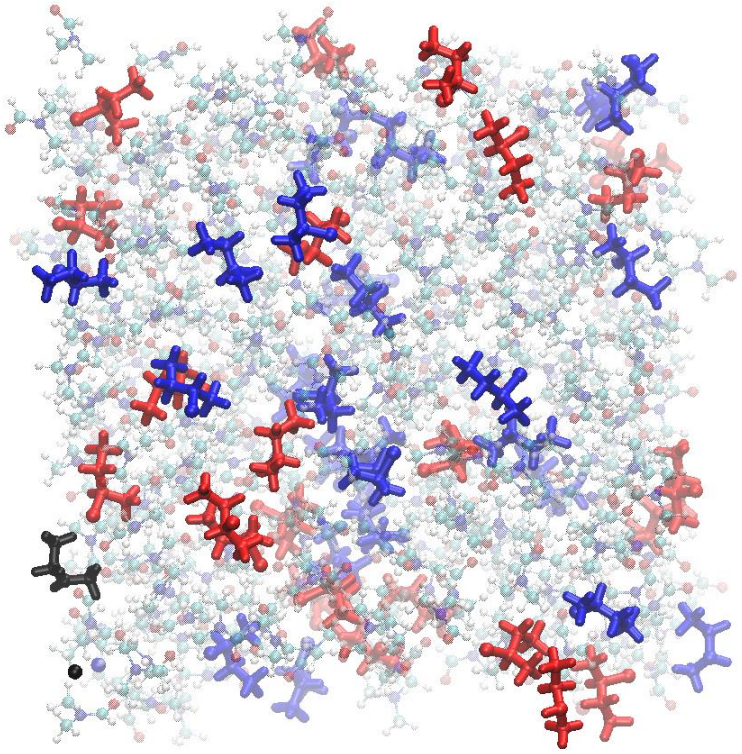


Fig. Equilibrium state (897 MC/MD cycles)

- The whole system became equilibrium state, and (*R*)- and (*S*)-enantiomers distribute homogeneously in the solution.

➡ 2-chlorobutane racemization has been realized, as the molecular structural change was treated in atomic scale.