A model $S_{N2}$ reaction of 2-chlorobutane with $OH^-$ is examined from the dynamical point of view by means of the molecular dynamics (MD) methods. The reactions are simulated in both the gas phase and the water solvent by the QM- and the ONIOM-MD methods, respectively. The MD simulations show that a migration of the kinetic energy between the atoms generated by the fluctuation of the kinetic energy of the atoms triggers the reaction. When some requirements of the velocity vector with a certain direction of the specific atoms participating in the reaction are satisfied by the migration of the kinetic energy, the substrate is led to the transition state and then to the product in turn. The time required to pass the transition state becomes shorter in the water solvent compared to the case of the gas phase, which shows that the reaction proceeds more quickly in the water solvent. Another pattern of the requirement of the velocity vector with a certain direction of the specific atoms for the reaction, which makes the reaction rate faster, is also found at a higher temperature in the water solvent.

Keywords: Molecular dynamics simulation, $S_{N2}$ reaction, Requirement for the reaction, Solvent effect

1 INTRODUCTION

The chemical reaction of the molecule involving the breaking and the formation of the chemical bonds is usually treated by the quantum mechanical method \cite{1, 2}. We can estimate the reactivity of a newly designed chemical compound on the basis of the heat of reaction and the energy barrier obtained from the energy profile of a plausible reaction path determined by the quantum mechanical method as we know. Although the quantum mechanical calculation provides the static information of the stationary points of the energy profile, i.e., the equilibrium structure and the transition state, and also the energy curve of the intrinsic reaction coordinate (IRC) that connects these points, it never gives all of the dynamical information during the chemical reaction itself as a matter of course. However, we have been increasingly interested in the dynamical event that happens during the reaction, since the recent development of both hardware and software of the computation has made the molecular dynamics (MD) simulation of the chemical reaction possible. For example, we want to know how does the reaction start, how does the reaction go over the energy barrier and so on. Although the various examinations concerning the dynamics of the chemical reaction have recently provided the new findings \cite{3–8}, the problem how does the rare event of the chemical reaction take place remains unsolved. It is still a challenging subject to understand the process of the chemical reaction from the dynamical point of view.

The molecular dynamics (MD) method would be a powerful tool to obtain dynamical information concerning the thermal vibration of the substrate, the driving force of the chemical reaction and so on. We have developed the QM- and the ONIOM-molecular dynamics (MD) methods \cite{9} to conduct the MD simulation of the chemical reaction, where the energy and its gradient are calculated by the quantum mechanical method on the fly, and applied them to the enzymatic reaction of cytidine and cytosine deaminase \cite{10, 11}, the organometallic reaction of the Pt complexes \cite{12, 13}, the nucleophilic substitution at the Si atom \cite{14}, the elementary reaction of germanone \cite{15} and so on. We have given an insight into these chemical reactions from the dynamical aspects and proposed a dynamical effect of the environment such as the substituent and the solvent on the chemical reaction so far. In the recent reports of the nucleophilic substitution at the Si atom and the reaction of germanone, we suggested that the distribution of the kinetic energy in the substrate is an important factor to cause the reaction, which is related to the present study.

In this study, we conducted the QM- and the ONIOM-MD simulations for one of the typical organic reaction, the $S_{N2}$ reaction, in order to shed a light on the dynamics of the chemical reaction. The $S_{N2}$ reaction is of significant importance in chemistry and biochemistry \cite{16–20}, because it is essentially concerned with the important reaction processes. Therefore, it has always become a target of both experimental and computational studies. We selected the reaction of 2-chlorobutane with $OH^-$ to follow a $S_{N2}$ reaction and performed the MD simulations in the gas phase and the water solvent at a certain temperature starting from the cluster of 2-chlo-
robust with OH\textsuperscript{−}. We followed the reaction of the substrate with the thermal energy 4 to 7 times larger than the energy barrier of the reaction. When a part of the thermal energy is utilized for the formation and the breaking of the chemical bond, the S\textsubscript{N}2 reaction proceeds. As a result of our analyses, we have found that the migration of the kinetic energy inside the substrate caused by the fluctuation of the kinetic energy of the atoms triggers the reaction and the velocity vectors of the specific atoms really control the reaction. We have also revealed the dynamical effects of the surrounding solvent molecules, which are the crucial factors that affect the reaction rate. Following the explanation of the computational details, we first discuss the QM-MD simulations in the gas phase and next the ONIOM-MD simulations in the water solvent. Conclusions are summarized in the final section.

2 COMPUTATIONAL DETAILS

2.1 Quantum Mechanical (QM) Calculations

Before performing the molecular dynamics (MD) simulations, we optimized the structures and calculated the energy profile for the S\textsubscript{N}2 reaction of 2-chlorobutane with OH\textsuperscript{−} we adopted as a model. The geometry optimizations and energy calculations were carried out at the Hartree-Fock (HF) level with the 6-31G(d) basis set we used for the calculations of the energy and its gradient of the MD simulations. We also performed the same calculations by the density functional theory (DFT) at the M06-2X [21] level using the 6-311++G (d,p) basis set in order to confirm that the HF level well reproduces the tendencies in the geometry and the energetics of the S\textsubscript{N}2 reaction. The equilibrium and transition state structures were identified by the number of imaginary frequencies calculated from the analytical Hessian matrix. The reaction coordinates were followed from the transition state to the reactant and the product by the intrinsic reaction coordinate (IRC) technique [22]. All of the quantum mechanical (QM) calculations were performed using the GAUSSIAN09 program package [23].

The optimized geometries and the relative energies at both M06-2X/6-311++G(d,p) and HF/6-31G(d) levels are presented in Figure S1. Both levels give the same tendency in the change in the important distances, d(C\textsubscript{1}-Cl\textsubscript{5}) and d(C\textsubscript{1}-O\textsubscript{15}), during the reaction and the same energy profile that is highly exothermic and has a small energy barrier, indicating that the MD simulation even with the energy and its gradient at the HF/6-31G(d) level is reliable. According to our experience, the MD simulation of the reaction with such small energy barrier of 2.9 kcal/mol at the HF level is possible only by the control of the temperature of the system [14, 15].

2.2 QM- and ONIOM-Molecular Dynamics (MD) Simulations

For the molecular dynamics (MD) simulations, we used the QM- and ONIOM-molecular dynamics (MD) methods [9]. The direct MD simulations were performed for the cluster of 2-chlorobutane with OH\textsuperscript{−} with and without the water solvent calculating the energy and its gradient by the QM or the ONIOM method on the fly. The time evolution of the nuclei was performed using the Beeman algorithm [24] with a time step of 1 fs under the constant temperature through the use of Berendsen’s velocity scaling algorithm [25]. In the QM-MD simulations without the water solvent, the energy was calculated at the HF level of theory with the basis set 6-31G (d) for the cluster of 2-chlorobutane with OH\textsuperscript{−}. On the other hand, in the ONIOM-MD simulations with the water solvent, the cluster of 2-chlorobutane with OH\textsuperscript{−} was included in the inner part and treated by the QM method at the HF/6-31G (d) level. To mimic the water solvent, 2109 water molecules are placed inside the spherical space with the radius of 25 Å, where the substrate is centered. No periodic or constrained spherical boundary conditions were used during the MD simulations. All the water molecules were involved in the outer part of the ONIOM method and treated by the molecular mechanics (MM) method with the TIP3P [26] force field parameters. The van der Waals parameters of the general Amber force field (GAFF) [27] were used for the C, Cl, O and H atoms of the substrate of 2-chlorobutane with OH\textsuperscript{−}, while the percentage of the torsional contributions for 2-chlorobutane with OH\textsuperscript{−} are set to zero.

The optimized structures of the cluster of 2-chlorobutane with OH\textsuperscript{−} with and without the water solvent were used as the initial geometry of the QM- or the ONIOM-MD simulation. The potential energies relative to that of the optimized structure are presented throughout the manuscript. The geometry optimizations for the system with and without the water solvent were performed by the QM- or the ONIOM-MD method by solving the Newton’s equation of motion at zero Kelvin. The nuclei with initial velocities of zero start to move on the potential energy surface downward. The nuclei slowly come close to the minimum of the potential energy surface with the velocities always maintained small by the scaling of the Berendsen thermostat and finally stop at the minimum with the velocities of zero.

The QM-MD simulations in the gas phase were performed at 300 K, 400 K and 500 K and the ONIOM-MD simulations with the water solvent were conducted at 300 K and 350 K. The data collected every 10 fs from 5 ps to 100 ps were used to calculate the average and the standard deviation of the geometric parameters and the potential and the kinetic energies, because the energies of the entire system as well as the temperature become almost constant after 5 ps.

Of the QM- and the ONIOM-MD simulations without the reaction, the QM-MD simulation at 500 K and the ONIOM-MD simulation at 350 K include the isomerization of the 2-chlorobutane from the trans to the gauche form. However, this isomerization of the 2-chlorobutane does not affect so much the analyses performed in this study. As shown in Table S1, there was no notable trend in the average and the standard deviation of the distances of the cluster of 2-chlorobutane with OH\textsuperscript{−} among the QM- and the ONIOM-MD simulations without the reaction at the various temperature. However, those of the distance d(C\textsuperscript{1}-C\textsuperscript{3}) in addition to the distances between the C\textsuperscript{1} and the atoms connected to the C\textsuperscript{1} except for the distance d(C\textsuperscript{1}-Cl\textsuperscript{5}) increase when the temperature is raised, which shows that this part of the cluster is sensitive to the increase in the kinetic energy.

2.3 Ratio of the kinetic energy of the atoms

We used the ratio of the kinetic energy of each atom in order to show the distribution of the kinetic energy of the system, since we
confirmed the good correlation between the kinetic energy and its ratio of the atom in each MD simulation by the plots of its ratio vs. the kinetic energy. The frequency of the increase and decrease of the kinetic energy presented in this study is the frequency that the ratio of the kinetic energy smaller than the average became larger than the average for the atoms and is the frequency that the kinetic energy smaller than the average became larger than the average for the water molecules.

2.4 Color of the atoms to show the magnitude of the ratio of their kinetic energies

In the case that the two colors, blue and red, are used, blue shows that the ratio of the kinetic energy of the atom is smaller than the average of that, and red shows that it is larger than the average of that. For the water molecule of the solvent, the blue of the oxygen shows that the kinetic energy of the water molecule is smaller than that corresponds to the temperature set in the MD simulation and the red of the oxygen shows that it is larger than that corresponds to the temperature set in the MD simulation. In the case that four colors, blue, green, yellow, and pink and red, are used, blue shows that the ratio of the kinetic energy of the atom is less than 5%, green shows that it is 5% to 10%, yellow shows that it is 10% to 15%, pink shows that it is 15% to 20% and red shows that it is more than 20%.

3 RESULTS AND DISCUSSION

3.1 QM-Molecular Dynamics (MD) Simulations in the Gas Phase

We first examined the distribution of the kinetic energy and its time evolution of the reactant, 2-chlorobutane with OH$^-$, because the fluctuation of the kinetic energy assigned to each atom is thought to generate a migration of the kinetic energy and a driving force to overcome the energy barrier of the reaction. Although the magnitude of the kinetic energy of the three atoms, C1, Cl5 and O15, will be especially important for the S_N2 reaction of the present system, the average of the kinetic energies of these three atoms is relatively small compared to that of other atoms in the gas phase as presented in *Figure 1*. Therefore, some kinetic energies should be provided to these three atoms, C1, Cl5 and O15, in order to cause the S_N2 reaction. In fact, a migration of the kinetic energy is always generated within the system by the fluctuation of the kinetic energy of each atom. Here, we focused on the migration of the kinetic energy to the C1, Cl5 and the O15 atoms from the surrounding other atoms. When the increase in the kinetic energy of one atom and the decrease in that of another atom occur at the same time, we recognized as a migration of the kinetic energy to one atom from another atom. The increase and decrease of the kinetic energy in the migration between two atoms is displayed in *Figure S2-1* to *S2-30* and the frequency of the migration to the C1, Cl5 and the O15 atoms is summarized in *Figure 2*. The number of times is obviously much larger for the migration to the C1 atom than the migration to the Cl5 and the O15 atoms. Also, a large amount of the kinetic energy is frequently transferred into the C1 atom from the Cl4, C2 and the C3 atoms, for example, as shown by the number of the dots in the area more than ±10% of the horizontal and the vertical axes of the graph of *Figure S2-1* to *S2-30*. In fact, the migration of the kinetic energy mainly occurs in the main chain Cl4-C2-C1-C3 of 2-chlorobutane as mentioned later, which is the same as the case in the water solvent where the kinetic energy is uniformly distributed in the system. Thus, the migration of the kinetic energy from the Cl4, Cl2 and the Cl3 atoms to the C1 atom should be thought to make an occasion to cause the S_N2 reaction.

*Figure 3* shows the time evolution of the kinetic energy of each atom from 91.60 ps to 91.67 ps in the QM-MD simulation of the cluster of 2-chlorobutane with OH$^-$ in the gas phase at 300 K without the S_N2 reaction. As shown by the blue and the red colors of the first row, which are frequently switched each other, the kinetic energy of each atom fluctuates and becomes larger and smaller than the average repeatedly. Such changes in the kinetic energy produces a flow of the kinetic energy inside the molecular system. The flow of the kinetic energy mostly appears in the main chain Cl4-C2-C1-C3, and the large kinetic energies localized on the C3 and

**Figure 1.** Average (A1, B1) and the standard deviation (A2, B2) of the kinetic energy (kcal/mol) (A1, A2) and its ratio (%) (B1, B2) of each atom of the reactant during the QM- and the ONIOM-MD simulations without the reaction in the gas phase and in the water solvent at the various temperature.

**Figure 2.** Frequencies of the movement of the kinetic energy to the Cl(A), Cl5(B) and the O15(C) atoms in the reactant during the QM- and the ONIOM-MD simulations without the reaction in the gas phase and in the water solvent at the various temperature.

**Figure 3.** Frequencies of the movement of the kinetic energy to the Cl(A), Cl5(B) and the O15(C) atoms in the reactant during the QM- and the ONIOM-MD simulations without the reaction in the gas phase and in the water solvent at the various temperature.
the C4 atoms are provided to the C1 and the C2 atoms throughout the simulation. On the other hand, not so large kinetic energy is provided to the Cl5 and the O15 atoms. However, the kinetic energy provided to the Cl5 and the O15 atoms tends to stay for a while. This is shown by the small frequency of the increase and decrease of the kinetic energy of the Cl5 and the O15 atoms, which is similar to the case of the inner atoms, H6, H7 and H8 (Figure 4). The largest amount of the kinetic energy is transferred to the C1 atom at 91.64 ps mainly from the C3 and the C4 atoms as presented in Figure 3. As a result, the kinetic energy of the C1 atom increases to 2.6 kcal/mol and its ratio becomes 28.6%.

Although the kinetic energy of the C1 atom becomes maximum at 91.64 ps, the SN2 reaction does not occur, because the vector of the velocity of the C1 atom is not directed to the O15 atom, as shown by the fourth row in Figure 3. The direction of the velocity vectors of the C1, Cl5 and the O15 atoms is thought to be important to cause the SN2 reaction. We therefore calculated the velocity vectors, \( \mathbf{v}_1' \), \( \mathbf{v}_2' \) and \( \mathbf{v}_3' \), of the C1, Cl5 and the O15 atoms (Figure 5). The changes in the magnitude of the velocity vectors, \( \mathbf{v}_1' \), \( \mathbf{v}_2' \) and \( \mathbf{v}_3' \), are displayed in Figure 6B. Figure 6B shows that the S\(_{22}\) reaction
which would be crucial factors controlling the SN2 reaction.

The migration of the kinetic energy mainly occurs in the main chain C4-C2-C1-C3 and the kinetic energy sometimes stays at the CP and/or the O15 atoms throughout the simulation also at 500 K, as mentioned for the simulation at 300 K. The time evolution of the magnitude of the kinetic energy of each atom of the substrate at 500 K before and after the S$_{n2}$ reaction is displayed in Figure 8. Figure 8 shows that the C$^i$ atom obtains a kinetic energy from the C$^4$ atom during 0.02 ps from 60.92 ps and the kinetic energy of the C$^1$ atom increases to 2.68 kcal/mol at 60.94 ps. The large kinetic energy of the C$^1$ atom is held until 60.96 ps, although some amount of it once dissipates at 60.95 ps.

The change in the magnitude of the velocity vector v$_1$ of the C$^1$ is displayed in Figure 9. Figure 9B2 obviously shows a double peak of the v$_1$ at 60.94 ps and 60.96 ps. Although there are many single peaks of the v$_1$ as shown by Figure 9B1, the double peak of the v$_1$ is indispensable to commence the S$_{n2}$ reaction. Also, it should be noted that not only v$_1$ of the C$^1$ but also the v$_2'$ of the Cl$^5$ and the v$_3'$ of the O15 have a certain magnitude at 60.94 ps and 60.96 ps. In the first peak at 60.94 ps, the v$_1$ is 0.26 Å/ps, and in the second peak at 60.96 ps, v$_1$ is 0.19 Å/ps. Both peaks of the v$_1$ and the v$_2'$ tend to be broad. As a result of our search, we found two cases of the double peak of the v$_1$ having a certain magnitude in the QM-MD simulation at 400 K (Figure S4). However, the reactant does not reach the transition state in these two cases due to the too small magnitude of the v$_2'$ and the v$_3'$. There were no other double peak of the v$_1$ with a certain magnitude in the QM-MD simulation at 500 K. Thus, it is thought that the S$_{n2}$ reaction never starts without the v$_1$, and the v$_2'$ with a certain magnitude, even if the v$_1$ has a large magnitude. In most cases in the gas phase, the velocity vector v$_1$ would play an important role to climb the energy barrier, because the Cl$^5$ and the O15 originally have a small kinetic energy and the kinetic energy of other atoms is mainly transferred not to the Cl$^5$ and the O15 but to the C$^1$. Furthermore, we never found the double peak of the v$_1$ having a certain magnitude in the QM-MD simulation at 500 K.

The reactant would be successfully activated to the transition state by the consecutive generation of the velocity vectors, i.e., (i) first, the generation of the v$_1$ of the C$^1$ and the v$_3'$ of the O15 to shrink the C$^1$-O15 bond and (ii) secondly, the generation of the v$_2'$ of the C$^1$ and the v$_4'$ of the Cl$^5$ to stretch the Cl$^5$-Cl$^5$ bond, as shown by Figure 10A. An enough thermal energy would be efficiently afforded to a vibrational mode of the reaction by (i) and (ii). It should be noted here that the substrate remains the transition state for 0.09 ps from 60.97 ps to 61.06 ps, which is obviously shown by a broad energy barrier (Figure 7A1) and no change in the distances of both the shortened C$^1$-O15 and the elongated Cl$^5$-Cl$^5$ bonds (Figure 7A2) in this period. Although the v$_3'$ of the O15 is very small from 60.97 ps to 61.03 ps, it increases to a certain magnitude at 61.04 ps and is held for 0.06 ps. Thereby, the substrate gradually descends the energy barrier. The v$_1$ of the O15 would push the transition state toward the product as shown by Figure 10A. Although the kinetic energy distributed to the O15 atom tends to be held for a while as mentioned above, its magnitude is small in the gas phase so that the probability that a v$_1$ with an enough magnitude to complete the reaction appears is also small. Therefore, the time required to pass the transition state tends to be long, which makes the reaction slow. Thus, the fluctuation of the distribution of the kinetic energy of the atoms of the substrate triggers the reaction and the reaction is completed when a requirement of the v$_1$, v$_2'$, and the v$_3'$ of the

Figure 7. Changes in the potential energy and the distances, d (Cl$^5$-Cl$^1$) and d (O15-C1'), of the substrate during the MD simulations with the S$_{n2}$ reaction. In parts A1 and A2, the QM-MD simulation was performed in the gas phase at 500 K. In parts B1 and B2, the ONIOM-MD simulation was performed in the water solvent at 300 K. In parts C1 and C2, the ONIOM-MD simulation was performed in the water solvent at 350 K.
3.2 ONIOM-Molecular Dynamics (MD) Simulations in the Water Solvent

The distribution of the kinetic energy of the reactant, 2-chlorobutane with OH\textsuperscript{-}, in the water solvent is different from that in the gas phase, as shown in Figure 1. Although the magnitude of the kinetic energy of the three atoms, C\textsubscript{1}, Cl\textsubscript{5} and O\textsubscript{15}, which would be important for the present S\textsubscript{N}2 reaction, is small in the gas phase, it becomes large in the water solvent, because the ratio of the kinetic energy of the C\textsubscript{3} and the C\textsubscript{4} atoms decreases and instead that of these three atoms increases. Therefore, the average of the kinetic energy of these three atoms at 300 K in the water solvent is nearly the same as that at 500 K in the gas phase and it becomes larger at a higher temperature 350 K in the water solvent. This would be one of the reasons why the fluctuation of the potential energy of 2-chlorobutane with OH\textsuperscript{-} becomes larger in the water solvent (Table 1). As for the migration of the kinetic energy, the frequency of the migration from the terminal carbon, the C\textsubscript{3} and the C\textsubscript{4}, to the C\textsubscript{1}, Cl\textsubscript{5}, and the O\textsubscript{15} atoms is especially reduced (Figure 2) due to the interaction of the C\textsubscript{1} and the C\textsubscript{4} atoms with the surrounding water solvent. Although the frequency of the migration of the kinetic energy decreases in the water solvent, the probability to obtain the kinetic energy required for the reaction would increase because the C\textsubscript{1}, Cl\textsubscript{5}, and the O\textsubscript{15} atoms originally have a large kinetic energy and its fluctuation is also large. The frequency of the increase and decrease of the kinetic energy of the atoms is also affected by the surrounding water solvent. It is notable that the frequency is highly reduced for the Cl\textsubscript{5} and the O\textsubscript{15} atoms (Figure 4). This indicates that the kinetic energy provided to the Cl\textsubscript{5} and the O\textsubscript{15} is more strongly held in the water solvent. The holding of the large kinetic energy of the Cl\textsubscript{5} and the O\textsubscript{15} atoms is an important factor to make the reaction rate faster as mentioned later.

The molecule of the water solvent very often switch their position each other, as we previously reported [14]. This is evident, for example, when we focus on the water molecules in the area within the radius of 5 Å from the C\textsubscript{1} atom (Figure S5A1 and S5B1). As shown by Figure S5A2 and S5B2, the number of the water molecules in this area largely fluctuates between 3 and 18 at 300 K and the magnitude of this fluctuation becomes larger at 350 K. The total amount of the kinetic energy of the water molecules in this area also synchronously fluctuates with the change in the density of the water molecule, as we have found in the case of the nucleophilic substitution at the Si atom [14]. Figure S6 shows a good correlation between the number of water molecules and the total kinetic energy of the water molecules existing in the area within the radius of 5 Å from the C\textsubscript{1} atom at both 300 K and 350 K. It is thought that
The fluctuation of the kinetic energy of the surrounding water molecules affects the kinetic energy of the outer atoms of the substrate, Cl, H10, H11, H12, H13, O15, and H16, because the kinetic energies of the outer atoms of the substrate and the surrounding water molecules synchronously fluctuate, as shown by Figure S7. The frequency of the increase and decrease of the kinetic energy of the outer atoms of the substrate would be reduced in phase with that of water molecules in the area within the radius of 5 Å from the C1 atom that is smaller compared to that of each water molecule (Table S2) and each atom of the substrate except for the O15 (Figure 4).

Here, we again focused on the migration of the kinetic energy to the C1, Cl5, and O15 atoms, because a migration of the kinetic energy is always generated within the system by the fluctuation of the kinetic energy of each atom and the kinetic energies provided to these three atoms, C1, Cl5, and O15, can trigger the SN2 reaction. In the water solvent, the SN2 reaction occurred even at 300 K, because the average and fluctuation of the potential energy of the reactant became larger by the solvent effect [14]. We therefore examined the SN2 reaction at 300 K and 350 K in the water solvent.

Also at 300 K and 350 K in the water solvent, the migration of the kinetic energy mainly occurs in the main chain C4-C2-C1-C3 of 2-chlorobutane and the kinetic energy provided to the Cl5 and O15 atoms is held for a while. In addition, the migration of the kinetic energy occurs in the H2O—C4-C2-C1-C3—H2O chain in some cases, as shown by Figure S8 and S9 and a large kinetic energy tends to be stored at the terminal H atoms in the water solvent. The time evolution of the magnitude of the kinetic energy of the substrate in the water solvent at 300 K before and after the SN2 reaction are displayed in Figure 11. A same pattern of the v1', v2', and v3' (Figure 10B) as that at 500 K in the gas phase is required in order to complete the reaction. However, the time needed to pass the transition state is only 0.05 ps, which is 0.04 ps shorter compared to the case in the gas phase at 500 K. If the requirement of the magnitude of the v1', v2', and v3' in pattern B in Figure 10 is not precisely satisfied, the SN2 reaction does not occur. At 57.87 ps, 15% to 20% of the entire kinetic energy of the substrate is localized on the H7. This kinetic energy of the H7 migrates to the C1 together with the kinetic energy of the C4 at 57.88 ps. Thereby, the kinetic energy of the C1 increases to 3.14 kcal/mol at this moment. Although some amount of this kinetic energy dissipates once at 57.89 ps, it returns again to the C1 at 57.90 ps. Moreover, the velocity vector v3' of the O15 atom is already large at 57.93 ps and the O15 atom keeps attacking the C1 atom from 57.93 ps to descend the energy barrier. During the descending the energy barrier, the heat of the reaction is gradually transmitted to the Cl5 promoting the Cl5 dissociation, as shown by the increase in the kinetic energy of the Cl5 after 57.96 ps (see Figure 11 and 12),

Figure 9. Changes in the kinetic energies of the atoms (A1, A2) and the magnitude of the velocity vectors, v1', v2', and v3', of the C1, Cl5, and the O15 atoms (B1, B2) during the QM-MD simulation of the substrate in the gas phase with the SN2 reaction at 500 K. In parts A1 and A2, the following colors apply: black, C1; brown, C2; pale blue, C3; orange, C4; blue, Cl5; green, H6; red, O15; dotted black, total kinetic energy of the substrate. In parts B1 and B2, the following colors apply: black, v1' of C1; blue, v2' of Cl5; red, v3' of O15. (A1 and B1) and (A2 and B2) have different time scales.

Figure 10. Required velocity vectors, v1', v2', and v3', and time for the SN2 reaction. A, at 500 K in the gas phase; B, at 300 K in the water solvent; C, at 350 K in the water solvent.
Table 1. Average and the standard deviation of the potential and the kinetic energies of the substrate, the energy barrier of the reaction and the heat of reaction.

|                      | Potential energy of the substrate (kcal/mol) | Kinetic energy of the substrate (kcal/mol) | Energy barrier of the reaction\(^a\) (kcal/mol) | Heat of reaction\(^b\) (kcal/mol) |
|----------------------|---------------------------------------------|-------------------------------------------|-----------------------------------------------|---------------------------------|
|                      | Average | Standard deviation | Average | Standard deviation |                              |                              |
| In the gas phase\(^c\) | 300 K    | 7.9 | 1.3 | 12.8 | 2.7 |
|                      | 400 K    | 10.6 | 1.7 | 17.1 | 3.6 |
|                      | 500 K    | 13.2 | 2.2 | 21.5 | 4.7 |
| In the water solvent\(^d\) | 300 K    | 10.0 | 2.0 | 12.3 | 2.2 |
|                      | 350 K    | 18.2 | 3.1 | 20.5 | 3.3 |
|                      | 500 K    | 20.9 | 4.6 | 20.9 | 4.6 |
| Equation\(^e\) | 300 K    | 12.5 | 2.7 | 12.5 | 2.7 |
|                      | 350 K    | 14.6 | 3.2 | 14.6 | 3.2 |
|                      | 400 K    | 16.7 | 3.6 | 16.7 | 3.6 |
|                      | 500 K    | 20.9 | 4.6 | 20.9 | 4.6 |

Quantum mechanical calculation

|                      | Potential energy of the substrate (kcal/mol) | Kinetic energy of the substrate (kcal/mol) | Energy barrier of the reaction\(^a\) (kcal/mol) | Heat of reaction\(^b\) (kcal/mol) |
|----------------------|---------------------------------------------|-------------------------------------------|-----------------------------------------------|---------------------------------|
|                      | Average | Standard deviation | Average | Standard deviation |                              |                              |
| HF/6-31G (d)         | 2.9     | -71.3 |

\(^a\) In the molecular dynamics simulation, the energy barrier of the reaction is the difference between the average of the potential energy of the reactant and the maximum of the potential energy during the reaction (see Figure S3 and Figure 7). In the molecular dynamics simulation, the heat of reaction is the difference between the average of the potential energy of the reactant and that of the product (see Figure S3). The data comes from the QM-MD simulation with the SN2 reaction at 500 K while without the SN2 reaction at 300 K and 400 K, because the SN2 reaction does not occur at 300 K and 400 K. The data comes from the ONIOM-MD simulation with the SN2 reaction at both 300 K and 350 K. The average \(<E>\) and the standard deviation \(\sigma_E\) of the potential and the kinetic energies of the substrate are calculated as follows, \(<E>=(1/2)kRT\) and \(\sigma_E=RT/(2f)^{1/2}\). Here, \(f\) is number of degree of freedom, \(R\) is the gas constant and \(T\) is the temperature. See Ref. 12 for detail.

which is similar to the case in the gas phase at 500 K.

When the temperature is raised up to 350 K, a different pattern of the requirement of the \(v_1\), \(v_2\) and \(v_3\) for the SN2 reaction was found as shown by Figure 10C. This is because the larger kinetic energy tends to be localized on the O15 and the Cl5 atoms at the higher temperature in the water solvent. Figure 13 shows that the O15 and the Cl5 atoms always have large kinetic energies and the \(v_2\) with a large magnitude are very often generated. The time evolution of the magnitude of the kinetic energy of the substrate and the \(v_1\), \(v_2\) and \(v_3\) of the O15, Cl5 and the O15 atoms before and after the SN2 reaction are displayed in Figure 14. As shown by Figure 14, a large kinetic energy is localized on the O15 atom from 30.10 ps to 30.15 ps, while a large kinetic energy is also localized on the C1 atom from 30.14 ps to 30.17 ps. In each period, the \(v_2\) and \(v_3\) have a large magnitude, and both the \(v_2\) and \(v_3\) have a large magnitude at the same time from 30.14 ps to 30.15 ps. In addition, a large \(v_1\) appears at 30.14 ps. This is clearly shown by Figure 13B2. In that situation, the reactant would be led to the transition state instantaneously. The transition state is also immediately directed to the product, because a large \(v_1\) is held even after the transition state is generated. This is obviously shown by the changes in the distances, d (O15-C1) and d (C1-Cl5), shown in Figure 7C2. Thus, the reaction would be fast in the water solvent event at 350 K, because the substrate immediately passes the transition without staying.

3.3 Importance of the Solvent Effects and the Distribution of the Kinetic Energy

The potential energy of the substrate constantly fluctuates due to its thermal vibration by the kinetic energy afforded at a temperature, as shown by Figure S3. When a kinetic energy is sufficiently transmitted to a vibrational mode of the reaction coordinate in the thermal fluctuation, the substrate is activated to the transition state and the SN2 reaction takes place. Therefore, if the fluctuation of the potential energy of the substrate becomes larger, the probability of the occurrence of the SN2 reaction would increase [12, 13]. In fact, although the SN2 reaction does not occur in the gas phase at 300 K and 400 K, in which the fluctuation of the potential energy is less than 2 kcal/mol, it occurs in the gas phase at 500 K, in which its fluctuation becomes more than 2 kcal/mol (Table 1). It should be noted that the energy barrier of 9.0 kcal/mol for the SN2 reaction calculated by the molecular dynamics method in the gas phase at 500 K is about three times larger than that of 2.9 kcal/mol calculated by the quantum mechanical method. Although the substrate energetically becomes higher by 13.2 kcal/mol due to the kinetic energy, the reaction part of O15—C1-Cl5 would not be efficiently
activated, because the kinetic energy is largely localized in the outer part in the gas phase (Figure 1).

The energy barrier is reduced to 6.0 kcal/mol in the water solvent at 300 K, because the kinetic energy is distributed uniformly all over the substrate in the water solvent. The fluctuation of the potential energy of 2.0 kcal/mol is also large compared to the case of the gas phase at 300 K by the solvent effects [14]. Therefore, the S\textsubscript{N}2 reaction occurs even at 300 K in the water solvent. When the temperature is raised up to 350 K, the energy barrier is further reduced to 1.5 kcal/mol, because the substrate is efficiently activated by the large thermal energy of 18.2 kcal/mol. The fluctuation of the potential energy also increases to 3.1 kcal/mol. Both the smaller energy barrier and the larger energy fluctuation would make the reaction easier. As mentioned above, the distribution of the kinetic energy also affects the generation of the velocity vectors required for the SN\textsubscript{2} reaction and the time required to pass the transition state. The distribution and its time evolution of the kinetic energy in the water solvent generate a different pattern of the velocity vectors to cause the SN\textsubscript{2} reaction and make the time required to pass the transition state shorter, which makes the reaction faster.

3.4 An Insight into the Isomerization and the Side Reaction

We also have given an insight into the isomerization between the trans and the gauche forms of 2-chlorobutane making the cluster with OH\textsuperscript{−} in both the gas phase and the water solvent and the side reaction of the carbene formation in the water solvent on the basis of the time evolution of the kinetic energy of the atoms. See, the Supporting Information for the discussion.
We examined a model SN2 reaction of 2-chlorobutane with OH\textsuperscript{−} from the dynamical point of view by means of the QM- and the ONIOM-MD methods. The MD simulations of the SN2 reaction were conducted starting from the cluster of 2-chlorobutane with OH\textsuperscript{−}. In order to initiate the reaction, the migration of the kinetic energy within the reactant, which is caused by the fluctuation of the distribution of the kinetic energy, is indispensable. The migration of the kinetic energy mainly occurs in the main chain of 2-chlorobutane and the kinetic energy provided to the terminal chlorine and the OH\textsuperscript{−} oxygen atoms tends to be held for a while. When the kinetic energy is localized on the atoms participating in the reaction, the SN2 reaction starts. However, some requirements of the velocity vectors of the specific atoms participating in the reaction must be satisfied to reach the transition state and then go to the product. The reaction is completed by a combination of those velocity vectors with a certain magnitude. We found that the time required to pass the transition state, which seriously affects the reaction rate, is significantly dependent on the distribution of the kinetic energy of the substrate. The MD simulations showed that the time required to pass of the transition state is shorter in the water solvent than in the gas phase, which suggests that the reaction proceeds more quickly in the water solvent, because the distribution of the kinetic energy of the substrate is considerably different between two cases in the gas phase and the water solvent. Another pattern of the requirement of the velocity vectors of the specific atoms for the SN2 reaction, which makes the reaction rate faster, was also found at a higher temperature in the water solvent. We also gave an insight into the isomerization of 2-chlorobutane and the side reaction of the carbene formation. Although the energy barrier becomes larger in the sequence, carbene formation > SN2 reaction > isomerization, the reaction that actually occurs is determined by the distribution of the kinetic energy of the substrate at that moment.

**5 SUPPORTING INFORMATION**

The detail of the discussion for ‘An Insight into the Isomerization and the Side Reaction’, Figure S1-S14 and Table S1-S2 (PDF).

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