Low-dimensional projection approach for efficient sampling of molecular recognition and polymer aggregation†

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The one-dimensional projection (ODP) approach is extended to two-dimensional umbrella sampling (TDUS) and is applied to three different complex systems in combination with a reactive force field (ReaxFF). TDUS is capable of showing detailed features of the free-energy surface (FES) of the double-proton transfer of the acetic acid dimer. It also revealed the direct relationship between the types of hydrogen bonding and binding strengths in the case of adrenaline molecular recognition by SIVSF (Serine, Isoleucine, Valine, Cysteine, and Phenylalanine). The study of polymer aggregation using TDUS shows that aggregation is preferred with a less-polar solvent, which is also consistent with the experimental observation of a tape-casting process. Therefore, TDUS can be generally useful in FES explorations from simple chemical reactions to complex processes of molecular recognition and polymer aggregation.

Simulations with the ReaxFF approach are typically significantly faster than the QM/MM approach. Its recent advances of sophisticated parameter fitting approaches21–26 appear to be promising, allowing its application to complex systems from biology to solid-state materials.

Even with these much more economical methods, to perform simulations within a reasonable amount of time, one still has to consider the efficiencies of samplings. A simple sampling strategy assumes that the evolution of a trajectory will sufficiently sample the configurational space of interest if the simulation time is long enough. However, such an approach is computationally inefficient and undesirable because transitions between local states typically are rare. In particular, the bond making/breaking chemical reactions occur on time scales that are significantly longer than those accessible using standard AIMD, QM/MM, and even ReaxFF methodologies.

Much effort has been devoted to developing efficient conformational sampling methods such as the transition path sampling,27 targeted molecular dynamics,28 constrained dynamics,29 parallel tempering or replica exchange,30–34 metadynamics,35–38 the Wang–Landau (WL) method39–41 essential molecular dynamics,42 the adaptive biasing force method,43 configurational bias sampling,44–46 expanded ensemble methods,47 umbrella sampling,48 and others.49–51 Many of these enhanced sampling methods is largely dependent on the appropriate definition of a reaction coordinate or a set of collective variables (CV). The CV approach has been extremely successful due to its ability to sample large regions of the configurational space. However, it is usually difficult to define a CV set that can consider the entire relevant configurational space, in particular, in the case of large biological systems.

1 Introduction

Molecular dynamics (MD) simulations can provide a free-energy surface (FES), which allows a better understanding of complex chemical processes by explicitly including the important aspect of entropic efforts. Because of the computational overhead, however, MD simulations have been mostly performed with classical force fields, which limits their applications to the conformational FES. Thus, most of the simulations were performed with standard classical MD software such as LAMMPS,1 Amber,2,3 Charm,4 Gromacs,5 and Genesis.6 With the advances in computer algorithms and performance, however, numerous studies have been devoted to the description of bond making/breaking dynamics of chemical reactions using ab initio MD (AIMD).7–11 However, its application to large-scale systems is still not practical. A hybrid approach of quantum mechanics and molecular mechanics (QM/MM)12–14 has been a practical compromise between cost and accuracy. Therefore, it has been applied to many chemical reactions in solution and biological molecules.15–19 An alternative to the QM/MM approach is the reactive force field (ReaxFF),20 which can describe bond making/breaking as well as conformational dynamics within the same simulations.

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Recently, we proposed a one-dimensional (1D) projection (ODP) technique\textsuperscript{16} to expedite this process. With the help of a projected “advancement of reaction” control parameter, it was demonstrated that multidimensional samplings could be performed with a single parameter, thus drastically reducing computational overhead. The ODP technique successfully yielded the FES of the double-proton-transfer reaction of the acetic acid dimer and the hydrolysis of the methylidiazonium ion.

In this study, the combinations of ODP with ReaxFF were explored. Because ReaxFF is much more economical than QM/MM, a two-dimensional (2D) extension of ODP was considered for extracting more information from the simulations. For this purpose, the original ODP was implemented into LAMMPS.\textsuperscript{1}

As for test examples, ODP with ReaxFF was initially applied to the evaluation of the proton transfer reaction of the acetic acid dimer. After that, protein–peptide docking was investigated, which is a molecular recognition process that plays a crucial role in the field of drug discovery. For this purpose, the molecular recognition of adrenaline by methyl-capped serine, isoleucine, valine, cysteine, and phenylalanine (SIVSF) was investigated, and the results were compared with the experimental infrared (IR) spectra.\textsuperscript{52} Finally, a polymer aggregation of polyvinyl butyral (PVB) was also studied to demonstrate the feasibility of our approach. Because polymer aggregations are industrially important subjects, understanding them at a molecular level can accelerate new material discoveries. Polymer aggregation strongly depends on the solvent environment,\textsuperscript{53} and therefore the MD simulations were performed with three different types of solvent (toluene, ethanol, and their mixture).

2 Theoretical background

2.1 ODP umbrella sampling

In the standard umbrella sampling approach, the geometries of each umbrella window are restricted by the harmonic potential of

$$U_{umb}^{j} = \frac{1}{2} \sum_{i}^{N} w_{i} (r_{i} - u_{j}^{i})^{2},$$

where $U_{umb}$ is the bias potential energy at the $j$th window, $r_{i}$ is the $i$th collective variable to simulate the reaction path or the structure conformation search, $w_{i}$ is the $i$th bias force at geometry $u_{j}^{i}$ for the $j$th sampling window. In the standard umbrella sampling, the preferred coordinate is a set of $N$ bond distances, bond angles, torsion angles, etc. However, such restrictions with many bias forces not only result in a high computational cost but also disturb the free-energy sampling space, making the evaluation of the FES along the chemical reaction or structural conformation search difficult.

To simplify it, we defined a transition vector $T$, and “the advancement of reaction ($\xi$)” as (see Fig. 1)

$$T = P - R,$$

$$\xi = (X - R) \frac{T}{|| T ||},$$

where $P$, $R$, and $X$ are the final, initial, and any arbitrary geometries of the target molecule, respectively. With the transition vector $T$, one can define “the advancement of reaction ($\xi$)” for an arbitrary coordinate $X$. These vectors can be represented by either Cartesian, internal, or by distance matrix coordinates, describing the system geometries.

Then, the multidimensional bias potential in eqn (1) can be simplified into an ODP along the $\xi$ for the $j$th sampling window as

$$U_{umb}^{j} = \frac{1}{2} w_{\xi} (\xi - u_{j}^{\xi})^{2},$$

where $w_{\xi}$ and $u_{j}^{\xi}$ are harmonic force constant and its center position along the reaction coordinate $\xi$, respectively.

2.2 The perpendicular direction

The perpendicular direction ($X^{\perp}$) to eqn (2) can be defined as

$$X^{\perp} = (X - R) \frac{T}{|| T ||},$$

$$x_{p} = |X^{\perp}|,$$

which can take another bias potential as

$$U_{umb}^{j} = \frac{1}{2} w_{xp} (x_{p} - u_{j}^{xp})^{2}.$$

In our previous study,\textsuperscript{16} a constant harmonic potential was applied along this perpendicular direction to keep the overall configurational space near the reaction coordinates, thereby, reducing sampling overhead. For the case of AIMD, like for QM/MM, reducing the number of umbrella windows is an important issue. However, adding more windows is not a major problem in the case of the economical ReaxFF. Therefore, one can also perform an umbrella sampling along this perpendicular direction in addition to the reaction coordinate, which is still much more efficient than multidimensional sampling. This particular procedure of 2D sampling along both $\xi$ and $x_{p}$ is termed “Two-Dimensional Umbrella Sampling” (TDUS) in this paper. TDUS might not be attractive in MD simulations with expensive \textit{ab initio} methods, however, it should generally provide more details than ODP. Therefore, TDUS should be the preferred choice in the case of ReaxFF.
2.3 Practical implementation of LAMMPS software

For practical simulation, the reaction coordinate $\zeta$ and the tangent vector $X^\perp$ are normalized by the transition vector $T$:

$$\zeta^x = \frac{\zeta}{|T|}, \quad (8)$$

$$X^x_p = \frac{x_p}{|T|}. \quad (9)$$

Inserting eqn (8) and (9) into eqn (4) and (7), one obtains the final formulation as follows:

$$U_{umb}^f = \frac{1}{2}w_\zeta |T|^2 \left( \zeta - u_\zeta \right)^2, \quad (10)$$

$$U_{umb}^{l,f} = \frac{1}{2}w_{X_p} |T|^2 \left( x_p - u_{X_p} \right)^2. \quad (11)$$

Taking the derivative of $U_{umb}^f$ in eqn (10) with respect to the nuclear coordinate $a$, one can obtain the bias force for the reaction coordinate $\zeta$ as follows:

$$\frac{\partial U_{umb}^f}{\partial a} = w_\zeta |T|^2 \left( \zeta - u_\zeta \right) \left( \frac{\partial X}{\partial a} \right)^T_T T \quad (12)$$

Likewise, the derivative of $U_{umb}^{l,f}$ with respect to the nuclear coordinate $a$ is

$$\frac{\partial U_{umb}^{l,f}}{\partial a} = w_{X_p} |T|^2 \left( x_p - u_{X_p} \right) \sum_{i=1}^{N} \frac{X_i}{|T|^2} \left( \frac{\partial X}{\partial a} \right)^T_T T \quad (13)$$

With these equations, the gradient contributions of $\frac{\partial U_{umb}^f}{\partial a}$ and $\frac{\partial U_{umb}^{l,f}}{\partial a}$ were calculated along the normalized reaction coordinate $\zeta^x$ and the tangent vector distance $x_p^x$, respectively.

3 Computational details

The above equations were implemented into the LAMMPS software. Three different chemical systems were adopted in the current study (Fig. 2).

First, the double-proton-transfer reaction between the acetic acid dimer (Fig. 2(a)) was studied using ReaxFF. For the ReaxFF parameter, we followed the work of Vashisth et al.\textsuperscript{54} TDUS along the $\zeta^x$ and tangent vector distance $x_p^x$ were performed with the corresponding 21 and 23 windows, respectively. As a result, NVT simulations of 525 independent trajectories were performed for 10 ps. See Table 1 and the Results and discussion section for the definitions of detailed reaction coordinates.

Second, the conformational samplings of molecular recognition between peptide and organic molecules embedded in a water solvent were investigated. For this purpose, a simple protein docking between a small SIVSF polypeptide and adrenaline was used (Fig. 2(b)). The experimental IR study by Sekiguchi et al. reported two distinctive peaks, indicating two different conformational isomers of SIVSF–adrenaline peptide docking.

![Fig. 2](https://example.com/f2.png)

**Fig. 2** Schematic illustration of the chemical structures used in this study. The labels $(r_1, r_2, r_3, r_4, \text{etc.})$ are indices for making internal coordinates (see detail in main manuscript) (a) acetic acid dimer (b) SIVSF–adrenaline complex (c) PVB.

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<td>$r_1$</td>
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<tr>
<td>$r_4$</td>
<td>2.08</td>
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**Table 1** Internal coordinates for the initial reactants and products for acetic acid proton transfer, where $r_1, r_2, r_3$ and $r_4$ are the distance between the oxygen and hydrogen atoms, and the positions depicted in Fig. 2(a), respectively
To search for these two structures, TDUS was performed along the docking reactions with 21 evenly divided windows along $\zeta^2 = 0.0–1.0$ and 15 windows along $x_p' = 0.0–0.42$. As a result, NVT simulations of 315 trajectories were performed for 1 ns. See Table 2 and the Results and Discussion section for initial and final structures. After the FES was obtained for the SIVSF–adrenaline complex, normal mode vibration analysis was performed using the MD trajectory around the lowest and metastable free-energy area (see Results and discussion for details), and the result was compared with the experimental IR spectra. In the experiment, the SIVSF–adrenaline complex was isolated using electrospray ionization, and then the conformational fluctuation of the complex was suppressed using a cold ion trap (the temperature was 10 K). To fit the simulation to the experimental condition as much as possible, the geometry of the SIVSF–adrenaline complex was extracted from the MD trajectory, and geometry optimization was performed for the respective structures, then normal vibration analysis was performed for each optimized structure. The Amber force field was used for peptide docking, and the geometry optimization and vibration analysis were performed using FMO implemented in GAMESS parallelized with GDDI. The FMO HF-D/6-31G(d) Hessian was used to evaluate the vibration spectra for the SIVSF–adrenaline peptide docking. The obtained vibration frequencies were scaled by 0.8953 to compare with the experimental IR spectra.

Finally, polymer aggregations of PVB (Fig. 2(c)) solvated by toluene, ethanol, and a mixture of them were investigated. Again, TDUS was performed with 21 windows evenly divided along $\zeta^2 = 0.0–1.0$ and 10 windows along $x_p' = 0.0–0.27$, yielding NVT simulations of 210 trajectories for 1 ns. A detailed description of the initial and final structures can be found in the Results and Discussion section and Table 3.

All the initial geometries were equilibrated with NVT for 200 ps, then an additional NPT simulation was performed for 1 ns to relax the periodic box size. The final geometry and box size were used for the following NVT production runs. The MD simulation was performed with a Nose–Hoover thermostat. The velocity Verlet integrator was used for time integration with the time step of 0.1 fs for acetic acid, and 0.5 fs for the other systems.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Internal coordinate for initial geometry and final geometry for molecular recognition of the adrenaline–SIVSF complex, where $r_{14}$, $r_{25}$, $r_{36}$, and $r_{26}$ are the distances between oxygen and hydrogen atoms, and the positions depicted in Fig. 2(a)</th>
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<tr>
<td>R</td>
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<td>$r_{26}$</td>
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4 Results and discussion

4.1 Proton transfer in the acetic acid system

In our previous study, ODP was initially tested with the simple double-protonation reaction of the acetic acid dimer in combination with the QM/MM setup, which requires two asymmetric coordinates for the entire reaction. The same reaction between acetic acid dimer was also adopted here with a different computational setup. In this paper, the acetic acid dimer is surrounded by 2134 water molecules with the periodic boundary condition. The entire system is described using ReaxFF only. In addition, the two asymmetric coordinates were replaced with four simple bond length coordinates ($r_1$, $r_2$, $r_3$, and $r_4$) (Fig. 2). The initial reactant $R$ and final product $P$ coordinates are described by these coordinates as shown in Table 1.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Internal coordinate for PVB, and the distance between atoms is shown. The respective positions of atoms are labeled from 1 to 8, and the distance between pairs of atoms is used for making a transition vector. The label for each atom corresponds to Fig. 9</th>
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<td>For reactant</td>
<td>Intra distance of left polymer</td>
</tr>
<tr>
<td>atm1 atm2 atm3 atm4</td>
<td></td>
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<tr>
<td>atm4 32.82</td>
<td>—</td>
</tr>
<tr>
<td>atm3 77.49</td>
<td>46.47</td>
</tr>
<tr>
<td>atm4 97.10</td>
<td>66.01</td>
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</tbody>
</table>

For reactant | Intra distance of right polymer |
| atm1 atm2 atm3 atm4 |
| atm6 31.01 | — | — | — |
| atm7 66.02 | 36.19 | — | — |
| atm8 106.51 | 78.07 | 42.75 | 46.36 |

For reactant | Inter distance between polymers |
| atm1 atm2 atm3 atm4 |
| atm8 71.31 | 68.45 | 76.67 | 84.97 |
| atm6 59.20 | 55.82 | 64.32 | 77.03 |
| atm4 83.88 | 69.38 | 62.74 | 77.26 |

For product | Intra distance of left polymer |
| atm1 atm2 atm3 atm4 |
| atm2 19.54 | — | — | — |
| atm4 21.27 | 33.18 | — | — |
| atm8 19.07 | 16.81 | 19.90 | — |

For product | Intra distance of right polymer |
| atm1 atm2 atm3 atm4 |
| atm6 9.82 | — | — | — |
| atm7 18.03 | 19.56 | — | — |
| atm8 17.05 | 16.46 | 10.98 | — |

For product | Inter distance between polymers |
| atm1 atm2 atm3 atm4 |
| atm8 14.97 | 18.73 | 18.45 | 13.89 |
| atm6 10.17 | 17.13 | 24.24 | 19.84 |
| atm7 12.10 | 26.20 | 12.57 | 16.78 |
| atm8 9.87 | 16.46 | 21.51 | 12.81 |
As described in the computational details, a 2D FES along the \( x_0 \) (x-axis) and \( x_p \) (y-axis) was obtained (Fig. 3(a)). The symmetrical nature of the FES due to the identical structure of the initial reactant and product was well reproduced. The two stable regions (b and c) are clearly seen in Fig. 3(a). The corresponding structures are also shown below the figure. The representative structures of (b and c) are marked by orange and sky-blue colors, respectively. As compared with (b), two exchanged protons are clearly shown in (c) with the exchanged colors. A metastable structure was found around \( x_0 ' = 0.4 \) and \( x_p ' = 0.35 \) with the current ReaxFF simulations, and its schematic structure is shown in (d). Both protons are attached to the same acetic acid molecule, forming a pair of MeC(OH)\(_2\)\(^+\) and MeC(O)\(_2\) ions. Its mirror image structure (f) is also seen at \( x_0 ' = 0.6 \) and \( x_p ' = 0.35 \), which is the opposite arrangement of the two protons (the two protons are attached to the sky-blue side). Although the free energy of this pair is 8 kcal mol\(^{-1}\) higher than the initial neutral acetic acid molecules, it is clear that the overall reaction path is lowered by its existence. A barrier (e) dividing the reactant and the metastable species (d) is seen at \( x_0 ' = 0.3 \) and \( x_p ' = 0.29 \).
A weak barrier (g) dividing the two metastable structures exists at $\xi' = 0.5$ and $x_p' = 0.33$. The mirror image metastable structure ($\xi' = 0.6$ and $x_p' = 0.35$) is connected with the product through a weak barrier (h) at $\xi' = 0.7$ and $x_p' = 0.29$. The geometric structure of this weak barrier corresponds to a simultaneous double-proton transfer. In short, the overall reaction occurs in a fairly complex sequence of (b) → (e) → (d) → (g) → (f) → (h) → (c), which was not observed in our previous study.\textsuperscript{16} To compare with the previous 1D FES by QM/MM, the minimum free energy along the above sequence was traced (Fig. 4). The QM/MM calculation also located the metastable state with a reaction barrier of 11.71 kcal mol$^{-1}$. The corresponding ReaxFF barrier is 9.51 kcal mol$^{-1}$, which is somewhat lower. Nevertheless, both ReaxFF and QM/MM locate a similar metastable structure.

If the reaction occurs in the region of $x_p' < 0.2$, the two hydrogen atoms should exchange places simultaneously without the ion pair intermediate, which accompanies a larger reaction barrier of

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**Fig. 6** (a)–(c) are geometry-optimized structures related to group A in Fig. 4, and (e)–(g) are geometry-optimized structures related to group B in Fig. 4. The initial structures are picked-up from trajectory during the TDUS MD simulations (see Computational details for more detail).
around 12 kcal mol\(^{-1}\). As shown in the above proton transfer, the 2D extension of ODP can better visualize the FES details.

### 4.2 Adrenaline molecular recognition by SIVSF polypeptide

The TDUS method was applied to peptide docking as described in the Computational details section, to assess its applicability to more complex situations. For this purpose, the adrenaline recognition by the SIVSF polypeptide was adopted. The experimental IR study suggested two distinctive binding conformations of the adrenaline–SIVSF complex structure,\(^5\) which have different types of hydrogen bonding configuration. The adrenaline can interact with SIVSF through either the OH groups of the phenyl part (5 and 6 in Fig. 2(b)) or the \(\text{NH}_2^+/\text{OH}\) pair (3 and 4 in Fig. 2(b)). Thus, we define the reactant and product geometric vectors so as to represent the two limiting binding configurations with the help of distance matrix coordinates. The corresponding interatomic distance coordinates for each reactant and product are shown in Table 2, and the atomic positions for the respective distance matrix coordinates are labeled in Fig. 2(b).

The result of TDUS analysis is shown in Fig. 5, where the most stable conformation is found around \(\xi_0 = 0.25\) and \(\chi_0 = 0.30\), which corresponds to the hydrogen bond configurations between the OH of the benzene side and the OH of the SIVSF polypeptide (group A in Fig. 5). The bindings through OH and \(\text{NH}_2^+\) on the other side of adrenaline with a slightly higher energy (1.5 kcal mol\(^{-1}\)), corresponds to Group B (\(\xi_0 = 0.85\) and \(\chi_0 = 0.33\)), where no clear minimum is seen. The preferred binding configuration of group A was consistent with the propositions of previous experiments. Although the experimental IR study suggested two structural binding configurations, the detailed structures could not be obtained. In the MD trajectory of group A, we found three types of conformational isomers (Fig. 6(a–c)). They are classified by the hydrogen bonding types. In Fig. 6(a) there are three hydrogen bonds between adrenaline and SIVSF, in which all of the OH in adrenaline are utilized for forming hydrogen bonding (–OH···OH\(_{\alpha}\), –OH···O–C and –HO···HO···)

![Fig. 7](image)

**Fig. 7** Vibrational IR of the respective structural isomers shown in Fig. 5. The vibrational spectra (a–f) correspond to the structural isomers (a)–(f). The left (A) and right (B) are related to group A and B in Fig. 4, respectively. (g and h) are the experimental vibrational spectra taken from ref. S2.
with SIVSF. In Fig. 6(b) there are also three hydrogen bonds but of different types (–OH···OH–, –OH···O–C and –HO···O=C). The third structure of Fig. 6(c), also has three hydrogen bonds of different types (–OH···OH–, –OH···O–C and –NH···O=C). Although they differ in the specific bonding types, the three hydrogen bonds in each binding configurations can make a strong adrenaline–SIVSF interaction.

In contrast, the binding complexes from Group B have 1–2 hydrogen bonds (Fig. 6(d–f)). The most frequently found structure is the hydrogen bonding between the serine in peptide and NH in adrenaline. The hydrogen bond between the OH of serine and adrenaline is also found in Fig. 6(d), and the OH in adrenaline is also bonded to the oxygen atom of C=O in Fig. 6(e). In the case of Fig. 6(f), there is no hydrogen bond utilizing the OH of adrenaline. Therefore, it is clear that Group B has fewer hydrogen bonds than group A. According to our simulations, these differences in terms of hydrogen bonding configurations are directly correlated with the FES. Therefore, the interpretation of molecular recognition strength by hydrogen bonds was well validated by our study.

For better comparisons with experiments, normal mode vibration analysis was performed on the conformers in Fig. 6, and the results were compared with the experimental IR spectra. The corresponding vibration spectra for each conformer are shown in Fig. 7. It would be informative to analyze the OH stretching regions because they are most affected by hydrogen bond formation. A significant difference between the respective vibration peaks was observed for frequencies over 3600 cm\(^{-1}\). Free OH stretches that do not form a hydrogen bond in the structure were found to produce several intense peaks around 3650 cm\(^{-1}\) (Fig. 6(f)). Similar vibration frequencies around 3650 cm\(^{-1}\) can be found with slight redshifts (Fig. 7(d) and (e)). In contrast, the structure of Fig. 6(a) produces much more redshifted frequencies around 3650 cm\(^{-1}\). Similar trends were also found in Fig. 6(b) or (c), but with a smaller degree of redshift. Overall, the frequencies near 3650 cm\(^{-1}\) correlate well with the number of hydrogen bonds and also with their strength. The observed frequency shift by Sekiguchi et al.\(^{52}\) from 3650 cm\(^{-1}\) to 3600 cm\(^{-1}\) was also interpreted as binding configurational differences. Our theoretical study supports this interpretation and further suggests the corresponding structures.

Among the three hydrogen bonds in Fig. 6(a), two of them utilize the OH of the benzene ring and the other OH is from the stereocenter of carbon. In this particular case, it is \(\beta\)-adrenaline. Structurally, its enantiomer (\(\alpha\)-adrenaline) is expected to have difficulty in forming the same type of hydrogen bond. Therefore, our simulation also suggests that the chirality of the stereocenter would play an important role in molecular recognition between adrenaline and the SIVSF complex. This interpretation is consistent with recent experimental research by Tamura et al.\(^{61}\)

### 4.3 Polymer aggregation process

Finally, the complex polymer aggregation in the solvent was investigated to demonstrate the feasibility of the TDUS approach. For this purpose, the free-energy landscapes with three different solvent systems (toluene, toluene: ethanol 50:50, and ethanol) were analyzed, as noted in the Computational details section. PVB is an industrially important material for tape casting of ceramics. In general, the combination of polymer and solvent molecules plays a very important role in tape casting. The dispersibility and stability of their mixture are key parameters for controlling the quality of ceramic materials.

For the reaction coordinate of the polymer aggregation, the typical internal coordinates are not useful because there are no internal coordinates between the two polymer counterparts to be aggregated. Instead, a coarse-grain approach of aggregation is introduced here. We first selected eight representative atoms, that were evenly spaced (Fig. 8). After that, all the combinations of inter- and intratatomic distance matrix coordinates are generated. The values of the initial and final distances are listed in Table 3. The calculations resulting in 28 interatomic distances served as a collective variable for the TDUS method.
The free-energy landscape of PVB aggregation with pure toluene solvent and the corresponding most stable geometry are shown in Fig. 9(a). A shallow minimum is seen near $\zeta' = 250$ and $x_p' = 30$, indicating that the two PVB chains aggregate well with each other by inter- and intra-hydrogen bonding. The toluene solvent has no polarity, and therefore it is reasonable for the two PVBs to aggregate mutually. The environment of the 50:50 mixture of the toluene and ethanol solvent moves the minimum position to $\zeta' = 170$ and $x_p' = 40-70$ in Fig. 9(b), indicating that the two chains are less aggregated, which is also seen in the more loosely bound geometry of the two PVB chains.

By contrast, the free-energy landscape of PVB in pure ethanol is quite different from the other simulation results. The minimum appears at $\zeta' = 70$ and $x_p' = 60$, which corresponds to the nearly dissociated PVB configuration (Fig. 9(c)). With this geometry, the PVB chains mostly interact with the surrounding ethanol molecules without hydrogen bonding between the PVB chains.

Overall, it is generally observed that the minimum position faithfully correlates with the polarity of the solvent, which is consistent with the experimental observation of the tape-casting process. When the binder is dissociated with each other, the ceramic material can be uniformly distributed, preventing the formation of a void region, which results in dielectric breakdown. Many experiments suggested that the ethanol solvent is the best diffusability for PVB polymer used in this study, which is consistent with our simulations. It proves the applicability of our TDUS method in such a complex situation. In short, the introduction of our coarse-grain approach to aggregation yielded physically meaningful and experimentally consistent results. It provides a simple and practical protocol in the study of such a complex process.

Fig. 9 Free-energy landscape of PVB aggregation (left), and the most stable geometries (right). The orange and sky-blue colors denote the polymer chains. (a) Simulation result with toluene solvent, (b) simulation result with mixture of toluene and ethanol, and (c) simulation result with ethanol solvent.
5 Conclusion

In this study, the previous ODP approach was extended to TDUS. The method was implemented with LAMMPS and was used with ReaxFF for three different applications. The samplings along the additional direction revealed much more detailed features of the FES and its corresponding dynamics. In the application to double-proton transfer of the acetic acid dimer, the TDUS yielded a complex reaction sequence of (b) → (e) → (d) → (g) → (f) → (h) → (c) reaction path, which was not clear in the 1D research.

In the case of molecular recognition of adrenaline by SIVSF, TDUS clearly shows the corresponding atomistic structures of the experimentally suggested two different binding configurations. It also revealed the direct relationship between the types of hydrogen bonding and their molecular recognition strength. For example, the stable conformers have three hydrogen bonds, concluding that the number of hydrogen bonds is the major factor in molecular recognition. Furthermore, the theoretical vibrational studies clearly correlated between the hydrogen bonding configurations and the OH stretching frequency shift, supporting the experimental interpretations. Detailed structural analysis also revealed the importance of chiral selectivity for molecular recognition.

The study of polymer aggregation using the TDUS method also shows a clear relationship between the preference of aggregation and solvent polarity. Our simulation showed that with a less-polar solvent, aggregation is preferred, which is consistent with the experimental observation of the tape-casting process.

All of the above results suggest that the TDUS approach is generally useful in the FES explorations from simple chemical reactions to complex processes of molecular recognition and polymer aggregation.

Conflicts of interest

There are no conflicts to declare.

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References