

Exploring the Mechanisms of Reactions in Solution from Transition Path Sampling Molecular Dynamics Simulations

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Abstract: Recent advances in molecular dynamics simulations of rare reaction events and aggregation processes are reviewed. Therein the central focus is dedicated to employing the transition path sampling method to study reactions in solution. We describe systematic approaches for generating initial transition pathways and efficient strategies for computationally feasible exploration of further transition routes. The unprejudiced study of reaction mechanisms is illustrated for reactions in aqueous solution and other complex systems. Transition path sampling allows very detailed investigation of solvent effects. Apart from stabilization of reactant, transition, or product state ensembles, this also includes the role of the solvent as a heat bath and as a putative reaction partner. The latter issue is of particular importance for reactions in aqueous solutions, which involve proton-transfer steps that may be assisted by water molecules via the Grotthuss mechanism.

1. Introduction

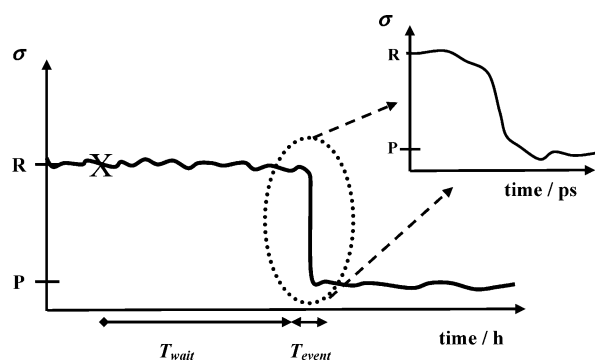
Many processes in solution chemistry pose two fundamental problems to the computational chemist: the need to study complex simulation models and to overcome large energy barriers, which separate reactants from product states. Apart from these limitations, molecular dynamics simulations in principle appear perfectly suited for the investigation of reaction mechanisms at the atomistic level of detail.

In large model systems, the computational demand not only is caused by the evaluation of a specific atomic arrangement but also is related to the immense configurational manifold arising from the large number of atoms. This particularly applies to processes, which involve the crossing of rare intermediate states. Their investigation is complicated by the need to scan a large number of possible arrangements in order to find the transition state(s). In molecular dynamics simulations this implies long ‘waiting’ times, before the event of interest actually occurs. These waiting periods may easily exceed the scope even of sophisticated hardware by several

orders of magnitude, hence rendering the observation of many processes from direct simulation practically impossible.

In an attempt to circumvent this problem, two major approaches have emerged over the past decades. The most straightforward ansatz is to enhance the kinetics of rare events by applying elevated temperature, pressure, or strong super-concentration of a particular molecular species. While in principle this strategy helps crossing any reaction barrier, the stronger the artificial process acceleration is chosen the more careful the results have to be considered. Excessive driving may easily lead to the skipping of important intermediates or even cause the system to follow completely different mechanistic routes. Similar limitations are related to the widely used approach of applying external driving forces. This method is based on the choice of a presumed reaction coordinate. The desired process is then induced by artificial potentials or constraints, which are functions of this coordinate. As a consequence, the mechanistic analysis may only be given in terms of predefined models of the reaction coordinate. In principle this limitation may be overcome by performing several independent investigations based on various mechanistic models. However in complex systems

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Scheme 1. Illustration of an Order Parameter Plot as a Function of Time^a

^a While the system remains for relatively long times in the metastable reactant (R) and product (P) state regimes, the transition occurs on a much faster time scale.

the number of putative mechanistic routes typically is too large to account for all possibilities.

Recently, Chandler et al. introduced the transition path sampling (TPS) method for the molecular dynamics simulation of rare events.^{1,2} This approach concentrates on a relatively short time interval in which the process of interest takes place and completely ignores the waiting period required for its observation from unconstrained simulation. As a consequence, TPS allows the study of rare events without artificial driving of the process. Moreover, no prejudicing of the reaction coordinate is needed, and the reaction mechanisms may instead be obtained as a result from the simulations. This makes TPS a very powerful tool for unbiased mechanistic investigations.

In the past few years, the TPS approach was successfully applied to a broad spectrum of processes, ranging from reactions^{3–17} to conformational rearrangements^{18–20} and phase transitions.^{21–29} In each of these fields TPS allowed to expand the scope of molecular dynamics simulations. The present microreview describes how this method can be used for mechanistic studies of reactions in solution chemistry and identification of the role of the solvent molecules. This work was inspired by a series of recent studies, which revealed new mechanistic insights into reactions and aggregation processes in solution and demonstrated the ability of TPS to provide a very detailed picture of the solvent effect.^{3–16}

2. Theory

2.1. Rare Events. Many bond breaking and formation processes are related to the crossing of large energy barriers, which separate the meta stable reactant and product states. For reactions in solution this may apply to both the reactants and the solvent molecules. The latter issue may be illustrated at the example of the association of a pair of Na⁺ and Cl[−] ions. In the gas phase the reaction Na⁺ + Cl[−] (separate ions) → Na⁺⋯Cl[−] (contact ion pair) is governed by the Coulomb attraction and does not exhibit an energy barrier. However, in aqueous solution the formation of a Na⁺⋯Cl[−] contact ion pair requires the penetration of solvent spheres. This process implies breaking and rearrangement of hydrogen bonds, which is related to an activation energy of about 14 kJ/mol.³

At room temperature this barrier is only around 3 $k_B T$, and one has reasonable chances to observe the reaction to

occur spontaneously within the picosecond to nanosecond time scale accessible to molecular dynamics simulations. However, for larger activation energies the ‘waiting times’ needed before the reactive events happen are considerably larger. A typical scenario of this kind is illustrated in Scheme 1. The plot shows a general order parameter σ , which reflects a quantitative measure of the reaction progress as a function of time. (For the association of Na⁺⋯Cl[−] σ may be simply defined as the interionic distance). When starting a molecular dynamics simulation from an arbitrarily chosen configuration of the reaction state (indicated by the X in Scheme 1), the total time needed to observe the formation of the reaction products is given as the sum of the waiting period before the reactive event occurs and the duration of the reactive event itself.

$$T_{\text{simulation}} = T_{\text{wait}} + T_{\text{event}}$$

The larger the reaction barrier, the longer are the observed waiting times. Like this the simulation time needed for the reaction to occur may exceed the duration of the reactive event by several orders of magnitude. The key idea of the TPS approach is to only focus on the relatively short time sketch T_{event} and to largely ignore the waiting time. This concept is particularly useful for processes, which involve large energy barriers and imply long waiting times. Though T_{wait} may be very large, many of such reactions occur on a femtosecond to picosecond scale, i.e., T_{event} is sufficiently small to be covered by a molecular dynamics simulation.

While the crossing of high energy barriers accounts for a large number of rare events, slow processes may also originate to a diffusive character of the system under consideration. In an entirely diffusion controlled reaction T_{event} is large, while T_{wait} is zero. TPS then becomes quite inefficient, and other methods such as steered molecular dynamics or free energy sampling approaches are more suitable.

2.2. Transition Path Sampling in Complex Systems.

While a detailed description of the TPS approach is given in refs 1, 2, 28, and 29, in this subsection we summarize the method only briefly and instead focus on more technical tricks of the trade for applying TPS to complex systems. The latter are collected from a series of studies dedicated to reactions in solution and phase transitions.^{11–13,17,22–24,26}

The TPS approach represents an iterative simulation scheme, for which at least one dynamical pathway of the rare event is needed as a prerequisite. Systematic ways to generate such initial trajectories are discussed in section 2.4. Provided a first trajectory of the rare event is given, we need to define a quantitative descriptor of the reaction progress σ , as illustrated in the previous section 2.1. While the optimal reaction descriptor is of course the reaction coordinate, the latter is a priori not known. However, it is sufficient to use just one component of the reaction coordinate for describing the reaction progress. In contrast to the complete reaction coordinate, one of its components is typically very easy to find. In many cases σ is simply chosen as the distance of two atoms which undergo a bond formation or breaking in the course of the reaction.

Starting from an initial reaction pathway further trajectories are generated in an iterative procedure. For this a snapshot is taken from the preceding transition pathway, and slight changes are incorporated. This configuration variation (shooting) should be considered as a Monte Carlo step and therefore must be implemented in a manner that the simulation ensemble is conserved. This may be illustrated at the example of the microcanonical ensemble, which implies constant total energy. An easy way to realize such shooting moves is to keep the atomic positions constant and apply only momentum changes. Like this the potential energy is constant, and the conservation of the kinetic energy may be achieved from velocity rescaling. It should be noted that the momentum changes must also conserve the total momentum and angular momentum of the simulation system.

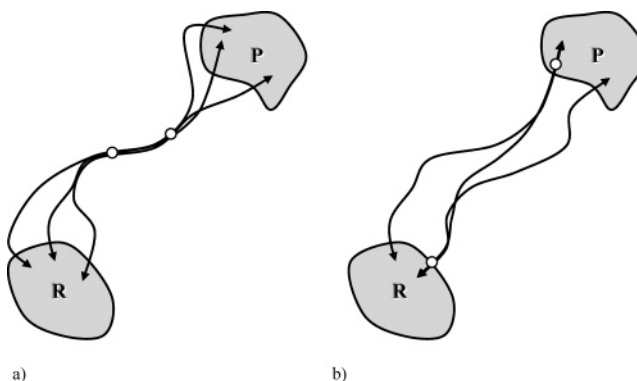
The modified configuration is then propagated in both directions of time, and the resulting trajectory is checked for the process of interest. For this purpose the reaction descriptor σ is used as a quantitative measure for the identification of pathways which go from the reactant state regime to a product state or vice versa. In case the desired event takes place, the new trajectory is chosen for generating further ones. Harvesting in an iterative manner leads to a manifold of dynamical pathways, each reflecting a possible transition route. The sampling of reaction pathways is not biased from prejudicing the reaction coordinate but instead relies on a reasonable choice of the reaction descriptor. Since σ is typically much more safe to guess than all of the components of the reaction coordinate, TPS may be considered as an unbiased method for studying reaction mechanisms.

2.3. Ergodicity and Efficient Ways of Sampling Transition Pathways. One of the most powerful features of TPS is related to its Monte Carlo type of sampling reactive trajectories. Once ergodicity is reached, the relevance of a transition route may be directly concluded from the occurrence of corresponding trajectories. For this reason the first transition pathway does not need to be a favorable one. In the course of TPS iterations the starting pathway will converge towards the preferred regions in trajectory space of reactive events.

As in all Monte Carlo simulations ergodicity of TPS, i.e., the knowledge of all reaction routes is often hard to reach. However, in solution chemistry the primary interest is related to the identification of the most preferred mechanism, while unlikely reaction pathways play a much less important role. Rather than full transition trajectory ergodicity it is therefore usually sufficient to ensure that TPS has visited the region of trajectory space corresponding to the most favored reaction mechanism.

When starting TPS from an initial trajectory which reflects an unfavorable mechanistic route, it is therefore necessary to continue the sampling iterations until the Monte Carlo moves have evolved to the most preferred class of pathways through the transition state ensemble. In a series of recent studies we elaborated some tricks of the trade how this process can be speeded up considerably.^{17,24,26} To demonstrate the underlying principles, it is educative to compare two different ways of sampling transition trajectories as

Scheme 2. Different Types of Sampling Trajectories Connecting the Reactant (R) and Product (P) State Regimes^a



^a a) Shooting moves (o) at close distance imply poor trajectory decorrelation, though the sampling of R and P appears good. b) Trajectory modifications are applied in R and P only, resulting in good sampling of all patches of the reaction pathways.

shown in Scheme 2a,b. The illustration 2a reflects a sampling run in which the shooting moves were chosen within a short time interval compared to the total length of the transition trajectories. The shooting moves typically represent only small configuration changes. Only in the course of sufficiently long time propagation such small modifications may result in large trajectory deviations. This may be seen from the quite broad sampling of the reactant and product state regime in illustration 2a. The problematic issue indicated in Scheme 2a is related to the sampling of intermediate configurations close to the small time window in which the shooting is applied. In this region trajectory decorrelation is rather poor, and the sampling is usually far from ergodicity. This phenomenon becomes particularly inconvenient if all shooting moves are incorporated close to the transition state surface. In this case the trajectory evolution toward the most favored region of the transition state regime, i.e., the convergence of pathways to the preferred reaction mechanism requires a very large number of sampling iterations.

To avoid this limitation, subsequent shooting moves should be chosen as far as possible from each other. A very efficient approach of this kind is described in ref 26. In this work, the shooting moves are only applied at the ends of the reactive trajectories, i.e. in alternating order in the reactant and in the product state regime. Sampling in this manner proved to be very successful for fast trajectory convergence to the favored mechanistic route. This feature is illustrated in Scheme 2b. Note that the sampling of the reactant and product states is quite good, even if the shooting is applied close to these regions in trajectory space. Indeed, the shooting moves from the reactant states are used for broad sampling of the product state regime and vice versa. Like this the ends of the reaction pathways are changed in alternating order, while the intermediate sketches are rectified in each of the TPS iterations.

The use of only two states for shooting furthermore facilitates the implementation of an automated adjustment of the shooting parameters, which govern the extent of the configurational changes in each Monte Carlo move. This issue may become of considerable importance if reactant and

product state are separated by a rough free energy landscape including several barriers and local minima. In such cases the conventional TPS approach typically yields very low acceptance probabilities in both stable states. Applying only small changes during the shooting moves helps increasing the acceptance ratio, however, at the price of only small trajectory variation. To find a compromise between low acceptance ratios and large trajectory modification, we implemented an automatic procedure for adapting the shooting moves on-the-fly.²⁶ Therein the shooting parameters are multiplied by a factor larger than 1 in case of a successful reactive event and divided by the same number in the opposite case. After convergence of this procedure this leads to an average acceptance rate of 50%, which we suggest as a suitable compromise for computationally efficient exploration of the trajectory space of reactive events.²⁶

While this two-state shooting approach is very suitable for the investigation of reaction mechanisms, the computation of rate constants requires a different sampling strategy. The original TPS scheme as developed by Chandler and co-workers^{1,2} provides knowledge of the acceptance ratio as a function of an order parameter describing the reaction progress. From this one can calculate the reactive flux and the net rate constant. A particularly elegant procedure of this kind is represented by the transition interface sampling variation of TPS, which was recently introduced by Bolhuis and co-workers.^{30,31}

Regardless of how the shooting moves are implemented, the checking of trajectory decorrelation and pathway convergence to the favored reaction route(s) is of vital importance for a proper mechanistic analysis. For this purpose, the Lyapunov coefficient represents a quantitative measure for the investigation of trajectory decorrelation.²⁸ Another approach is to start TPS from an unfavorable reaction route and count the number of sampling iterations needed for trajectory evolution to the most favored reaction mechanism. A particularly robust convergence check may be achieved by starting several independent sets of TPS simulations, each starting from different initial pathways which correspond to different mechanistic routes.^{22,24} Evolution of all sets of TPS iterations to the same class of trajectories offers a quite evident proof of convergence.

Apart from running straightforward TPS iterations, one may also take use of special sampling techniques established for enhancing ergodicity in standard Monte Carlo simulations. Examples for such approaches are parallel tempering,^{28,29} Wang-Landau sampling,³² and biased TPS.¹⁷

2.4. Preparation of the Initial Trajectory of a Reactive Event. In some cases the initial trajectory needed as a prerequisite for TPS iterations can be prepared by modeling a putative intermediate from intuition and propagation in both directions of time. However, for complex processes more systematic approaches may be much more efficient. We developed such a strategy, which appears quite flexible and was successfully applied in a large variety of simulation studies.^{13,22–27} As a starting point, a geometric model $G_{R\leftrightarrow P}$ in real space connecting an arbitrarily chosen reactant to a product state must be prepared. If sufficient knowledge of a possible reactant and product state is available, $G_{R\leftrightarrow P}$ could

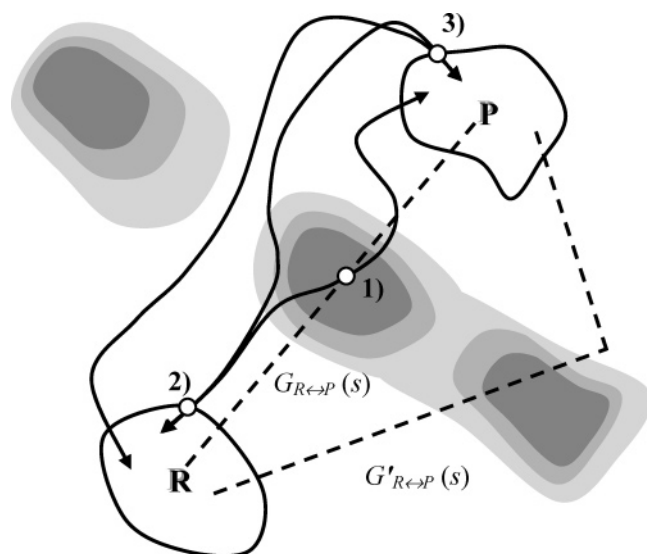
be chosen as simple as a linear interpolation of the related coordinates. The geometric model should be continuous, such that each configuration of $G_{R\leftrightarrow P}$ may be specified by a single interpolation variable s .

The search for a trajectory which connects the reactant and the product state regimes is based on selecting putative intermediates $G_{R\leftrightarrow P}(s)$ and assigning random velocities. The velocities should be generated in a way that the resulting trajectory belongs to the desired simulation ensemble. This may be critical in the microcanonical ensemble, which implies $E_{\text{kin}} = E_{\text{tot}} - E_{\text{pot}}$. If $G_{R\leftrightarrow P}(s)$ represents a very unfavorable configuration, the potential energy might be larger than the desired total energy. For starting from such classically forbidden points in phase space, one may however choose $E_{\text{kin}} = 0$ and start TPS at a somewhat larger total energy. In the course of TPS iterations one may then gradually decrease E_{tot} to the desired value.

Let us assume $s = 0$ in the reactant state regime and $s = 1$ for the product state region and first investigate the time propagation of the two configurations $G_{R\leftrightarrow P}(s=0)$ and $G_{R\leftrightarrow P}(s=1)$. When starting a molecular dynamics simulation from a configuration close to the stable reactant or product regime, the resulting trajectory typically evolves to the nearest minimum of the free energy landscape. As this applies to both directions of time propagation, the related pathways lead from reactant to reactant states or from product to product states, respectively. However, by starting from a putative intermediate with $0 < s < 1$ a reactive event, i.e., a trajectory going from reactants to products or vice versa may be found. For this s needs to be chosen sufficiently close to the intersection of $G_{R\leftrightarrow P}(s)$ and the transition state ensemble. By means of an interval bisection procedure such a value for s is usually found within a few iterations.^{13,22–27} It is useful to prepare several initial trajectories from various geometric models $G_{R\leftrightarrow P}(s)$, $G'_{R\leftrightarrow P}(s)$, etc., which should differ considerably from each other (Scheme 3). This allows starting TPS in different regimes of trajectory space—ideally at different mechanistic routes—to check pathway convergence as discussed in section 2.3. Examples for this approach are described in detail in refs 17 and 22–25.

It should be stated that a linear interpolation of *all* atomic positions of the reactant and product state configurations may lead to unphysical intersections. To avoid this problem one might reduce the interpolation to a few degrees of freedom like one or two characteristic bond lengths. However, in many cases the system under consideration is too complex to formulate a geometric model from intuition. For example this applies to crystal nucleation from solution, in which only limited knowledge of the explicit arrangement of the reaction products is available. The geometric model may then be prepared from a molecular dynamics run, in which artificial driving forces are applied to enhance the reaction process. This may be incorporated by elevated temperature, pressure, or other thermodynamic driving such as manipulated chemical potentials. The latter approach was used in our recent study of NaCl aggregation from aqueous solution.¹³ Therein the van der Waals parameters for the ion–water interactions were changed to lower the solubility of the ions. From this artificial crystallization trajectory configurations were cut and

Scheme 3. Sampling of Transition Pathways Starting from an Intermediate Generated from Geometric Modeling (Dashed Curves)^a



^a While trajectory 1) might cross the transition state ensemble via a rather unfavorable configuration, subsequent shooting moves 2), 3), etc. cause pathway evolution towards more preferred reaction routes.

considered as putative intermediates $G_{R \leftrightarrow P}(s)$, where s reflects the time at which the snapshot was taken.

3. TPS in Solution Chemistry

3.1. System Complexity. The most commonly used picture of a reaction relies on the existence of a single, well-defined reactant state. The latter is assumed to be connected to a single product state via 'the' transition state. Processes in solution however take place in complex systems of high dimensionality. The reduction of an ensemble of states to a single point in phase space therefore needs to be considered with caution. Indeed, even for one of the most simple reactions in solution, the dissociation of a $\text{Na}^+\cdots\text{Cl}^-$ ion pair in aqueous solution, Chandler and co-workers identified a manifold of transition states.^{3,9} On the basis of TPS simulations they generated around 1000 trajectories of this reaction. The analysis revealed the complexity of the underlying mechanism and the importance of solvent degrees of freedom for the understanding of the reaction coordinate.^{3,9}

In a recent work, we investigated the formation of NaCl aggregates of around 20 ions from an aqueous solution.¹³ From the study of this complex process a variety of different ion aggregates was found. In other words, the product state regime reflects a large area in phase space and may clearly not be reduced to a single ionic arrangement. This phenomenon is related to the interplay of the water molecules and the ions. In aqueous solution the polar water molecules may stabilize the ion aggregates by forming $\text{H}_2\text{O}\cdots\text{Na}^+$ and $\text{HOH}\cdots\text{Cl}^-$ bridges (Figure 1), while in the gas phase the configurational manifold of NaCl clusters of comparable size is significantly lower.³³

3.2. Investigating Reaction Mechanisms and the Transition State Ensemble. The complexity of the simulation systems encountered in solution chemistry makes the investigation of reaction mechanisms difficult yet not entirely

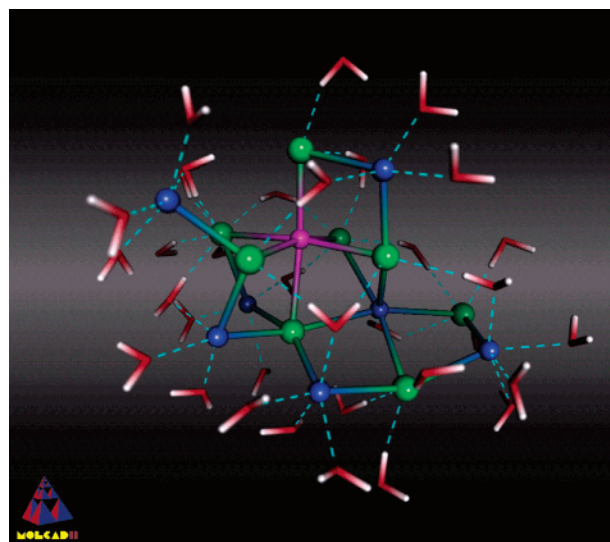


Figure 1. Na_8Cl_8 aggregate in aqueous solution as obtained from TPS molecular dynamics simulations 8. Sodium and chloride ions are colored in blue and green, respectively. The sodium ion of the Na^+Cl^-_6 octahedra is highlighted in purple.

impossible. For reactions in solution the solvent usually plays an important role and solvent degrees of freedom hence are part of the reaction coordinate. While the various types of solvent effects are specified in the next section, we shall first focus on more technical aspects for identifying reaction mechanisms and transition states of processes in complex systems in general.

When analyzing the NaCl aggregates discussed in ref 13, we identified common features in each of the reaction pathways. For one of the aggregates this is illustrated in Figure 1. Roughly in the center of the aggregate a sodium ion is observed, which exhibits no water molecule in its first coordination sphere. Instead, it is octahedrally coordinated by six chloride ions. While the arrangement of the remaining ions varies considerably, the Na^+Cl^-_6 octahedron forms a stable core in the aggregates. This motif of the NaCl crystal structure was found to be a common feature and was therefore proposed as characteristic for the formation of stable aggregates of around 20 Na^+ and Cl^- ions. In more general terms, we investigated the reactive pathways for common features and interpreted them as aspects of the reaction mechanism. This strategy proved quite effective in a series of studies related to reactions in complex systems.^{11–13,17}

For the identification of common features in reactive pathways we recommend to also investigate the trajectories of failed attempts generated in the course of TPS iterations. Each of these trajectories was derived from small variations of a successful reaction pathway. The failed attempts therefore often represent pathways, in which the reaction almost took place, but at least one important contribution to the reaction mechanism was missing. Comparing such pathways with the trajectories of successful reaction attempts may help a lot in finding detailed information of the reaction mechanism. While the main characteristics of the reaction mechanism are usually easy to observe from the ensemble

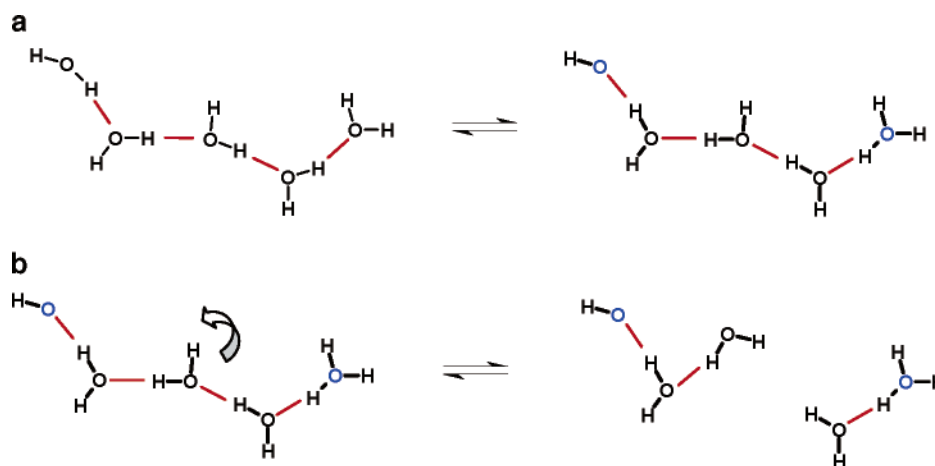


Figure 2. a. First step of the water autodissociation as observed from TPS Car-Parrinello molecular dynamics simulations.⁴ The formation of an $\text{H}_3\text{O}^+\cdots\text{OH}^-$ contact ion pair is avoided by multiple proton-transfer steps resulting in charge separation over several water molecules. b. The hydrogen bonded chain of water molecules, which allowed fast OH^- and H^+ transport, is broken. This prevents the fast recombination of the separated charges.

of successful trajectories, contrasting true reaction pathways to failed attempts is particularly suitable for identifying the fine details.

The approaches described above should help understanding reaction mechanisms at least from a qualitative point of view. Some of the ‘common features’ characterizing the reaction mechanism may actually be variables that can be clearly defined and hence used to construct the reaction coordinate. For examples, this holds for bond distances and angles. However, for more complex features of the reaction mechanism the determination of explicit variables is typically much more complicated. A very elegant way of performing a reaction coordinate analysis within an automated scheme was recently presented by Ma and Dinner.¹⁶ In this work a large set of variables is related to the committer analysis of the reaction by means of artificial intelligence. Performing neural network calculations Ma and Dinner succeeded to isolate a small number of relevant variables which were demonstrated to be sufficient for describing the $\text{C}_{7\text{eq}} \rightarrow \alpha_{\text{R}}$ isomerization of the alanine dipeptide in aqueous solution.¹⁶

An important contribution to a deeper understanding of reaction mechanisms may be provided from exploring the ensemble of transition states. The underlying committer analysis is described in detail in refs 1, 2, 28, and 29 and shall be summarized only briefly here. Following the definition of Du et al. the transition states represent configurations in real space, which—after assigning random velocities—will evolve to either the reactant or product state regime at equal probability.³⁴ The transition state analysis may hence be accomplished by the following scheme: for each reaction pathway a series of snapshots is chosen. For each of these snapshots $\{r_i\}_{i=1..N_{\text{atoms}}}$ a number of may be 100 phase points $\{r_i, v_i\}_{i=1..N_{\text{atoms}}}$ is prepared by combining the atomic positions r_i with different sets j of random velocities $v_i(j)$ generated in accordance to the desired simulation ensemble. Then the time propagation of each configuration $\{r_i, v_i(j)\}$ is investigated from molecular dynamics simulations. The different velocity sets j provide a statistical estimate of the probability p_R of $\{r_i\}$ to evolve to the reactant state regime. The manifold of transition states

comprises all configurations $\{r_i\}$ with $p_R(\{r_i\}) = 0.5$. It should be noted that a single reaction pathway may cross the transition state ensemble several times before connecting the reactant and the product state regimes.

3.3. The Solvent Effect. Depending on the simulation system the solvent may be involved in different ways in the reaction process. The most direct role the solvent can play is that of a *possible reactant*. A prominent example for this issue is given by proton transfer reactions in aqueous solution. Therein the water molecules may act as proton donors and acceptors. Moreover, protons may be transported along the hydrogen-bonded network of water molecules via a Grotthuss type mechanism. The importance of this phenomenon for the autodissociation of water was recently demonstrated from TPS Car-Parrinello molecular dynamics simulations.⁶ The direct formation of an $\text{H}_3\text{O}^+\cdots\text{HO}^-$ contact ion pair is disfavored by the strong tendency of recombining the separated charges.³⁵ Instead, the dissociation involves multiple proton-transfer steps resulting in oxonium and hydroxide ions, which are separated by several coordination spheres. The overall reaction hence reads $\text{H}_2\text{O} + n\cdot\text{H}_2\text{O} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + n\cdot\text{H}_2\text{O} + \text{OH}^-$ (with $n \geq 3$ and $n=3$ in Figure 2a). To stabilize the right-hand side of Figure 2a the hydrogen bonded chain connecting the separated charges must be broken (Figure 2b). As a consequence, water dissociation not only implies the formation of a specific solvent arrangement to favor the forward reaction but also requires the dissociation of the assisting chain of hydrogen bridged water molecules to avoid back-reaction. An analogous picture was recently observed for the rate-determining step in acid-catalyzed amide hydrolysis in aqueous solution.¹¹ Therein a water molecule performs a nucleophilic attack on the amide bond by adding an OH^- group to the amide and transferring a proton to the solvent. Contrasting reactive trajectories and failed attempts, we found that the formation of stable reaction products requires further proton-transfer steps leading to H^+ migration to the aqueous solvent. This process occurs in the same way as observed in the water dissociation reaction: The proton migration is assisted by a hydrogen-bonded chain of several water molecules, which must be disconnected after

the reaction took place in order to avoid immediate back-reaction. This phenomenon might play an important role in acid/base reactions in aqueous solutions in general and clearly should be considered in mechanistic studies of such processes.

A less obvious yet important solvent effect observed for reactions in solution is related to *different energetic and/or entropic favoring* of the reactant, transition, or product state ensemble. For polar solvents, this phenomenon mainly accounts for the Coulomb interaction of the reacting molecules and the embedding media. This type of solvent effect is often modeled by an electrostatic continuum approach. However, for charge transfer reactions such as the autodissociation of water described above, the fluctuations of the electric field induced by the solvent are of key importance. Spontaneously formed solvent arrangements may trigger the reaction by lowering the reaction barrier or even fully biasing the reacting system in favor of a product state.

While simulation studies based on static approaches can only identify correlations of specific solvent arrangements and the reaction process, TPS molecular dynamics simulations allow the investigation of a time-resolved picture. Impressive examples for such studies were presented by Chandler and co-workers, who investigated the flux of water molecules during the dissociation of NaCl ion pairs^{3,9} and the role of solvent fluctuations in the water autoionization process.⁶

A purely kinetic aspect of the solvent effect is reflected by its role as a *heat bath*. Reactions, which require the crossing of energetically disfavored intermediates, imply the accumulation of sufficient kinetic energy to allow the system to overcome the energy barrier. Before the reaction takes place, the system must therefore ‘focus’ kinetic energy to the reaction coordinate degree of freedom. This usually occurs at the cost of perpendicular modes. This effect may be illustrated from our recent study of helium insertion into a C₆₀ buckyball.¹² Instead of a polar solvent, which would predominantly interact via Coulomb forces, this simulation model comprised of a box of 1000 helium atoms mimicking an autoclave scenario. Prior to the penetration of the C₆₀ by a helium atom, we observed a series of collisions in the gas atmosphere. These collisions occur in such a way that the momentum of one of the helium atoms increases at the cost of the kinetic energy of the other. In the successful reaction attempts, this process accumulated sufficient kinetic energy on a single helium atom and directed its momentum toward the buckyball molecule, such that the helium crossed the insertion barrier.

The helium atom, which penetrates the C₆₀, was observed to use almost all of its kinetic energy for overcoming the potential energy barrier. However, after crossing the transition state, the helium atom regains kinetic energy when approaching the product state. This kinetic energy is sufficiently high to allow recrossing of the potential energy barrier and must therefore be dissipated to other degrees of freedom to avoid immediate back-reaction. Indeed, some of the failed reaction attempts exhibited a helium insertion,

followed by reflection at the inner wall of the buckyball molecule and expulsion in opposite direction of the insertion route.

4. Conclusions

We reviewed a series of molecular dynamics studies of reactions in solution using the TPS approach. Typically, reactions in solution are complex, and their investigation may particularly benefit from the advantages of the TPS simulation scheme. Therein the mechanistic study can be based on a manifold of reaction pathways and a series of trajectories related to failed attempts. Contrasting both classes of pathways offers very profound insights into the reaction dynamics including the role of the solvent molecules. The solvent effect may be rated to several phenomena including catalytic functions, energetic, and/or entropic favoring and the role of a heat bath.

TPS may be combined to all variations of molecular dynamics simulations, including classical,^{3–5,7,9,13,15,16} mixed quantum/classical,^{10,12,17} and ab initio^{6,8,11,14} approaches. The study of reactions in solution typically requires including a large number of solvent molecules to the simulation model and therefore implies considerable computational efforts. A series of tricks of the trade collected from several recent studies of rare events in complex systems is summarized and discussed in detail.

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