Self-assembly via anisotropic interactions
Modeling association kinetics of patchy particle systems and self-assembly induced by critical Casimir forces
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4 Rotational diffusion affects the self-assembly pathways of patchy particles

Predicting the kinetics of the self-assembly of particles with anisotropic interactions, for instance, colloidal patchy particles or proteins with multiple binding sites, is important for the design of novel high-tech materials as well as for understanding biological systems such as viruses or regulatory networks. Often stochastic in nature, such self-assembly processes are fundamentally governed by rotational and translational diffusion. Whereas the rotational diffusion constant of particles is usually considered to be coupled to the translational diffusion via the Stokes-Einstein relation, in the past decade it has become clear that they can be independently altered by e.g. molecular crowding agents or via external fields. Because virus capsids naturally assemble in crowded environments such as the cell cytoplasm but also in aqueous solution in vitro, it is important to investigate how varying the rotational diffusion with respect to translational diffusion alters the kinetic pathways of self-assembly. Using recently developed path-sampling techniques, we can sample and analyze the entire self-assembly kinetic network of simple patchy particle systems. For assembly of a designed cluster of patchy particles we find that changing the rotational diffusion does not change the equilibrium constants, but significantly affects the dynamical pathways, and enhanced (suppresses) the overall relaxation process and the yield of the target structure, by avoiding (encountering) frustrated states. Besides insight, this finding provides a design principle for improved control of nanoparticle self-assembly.
4.1 Introduction

In nature, self-assembled complex structures and networks often provide function. Prime examples are virus capsides, where capsomer proteins with specific interaction sites self-assemble into various structures, such as icosahedrons and decahedrons. Protein complexes can also spontaneously form in the living cell, e.g. in signal transduction networks. Self-assembly of small designed building blocks also can provide novel (bio)materials with desired properties. Such building blocks can consist of proteins, synthetic polypeptides, but also of colloidal particles. Particularly, the advent of novel synthesis routes for colloidal particles with a valence, so called “patchy particles” opened up avenues for designing colloidal superstructures. Numerous experimental, theoretical and numerical studies have enabled understanding the phase behaviour of these particles, predicting not only interesting building blocks for new functional materials, but also demonstrating new physics [4, 13, 55, 65].

Design principles for colloidal superstructures can predict which structure is the most thermodynamically favorable state [59]. However, the fact that kinetics often trumps thermodynamics can hamper such design of colloidal superstructures. Strong directional binding and slow dissociation can kinetically trap patchy particle systems in a malformed state, rendering it unable to reach the designed equilibrium (ground) state [5]. Controlling the self-assembly of colloidal particles thus requires understanding how the system evolves towards equilibrium, which is dictated by the kinetic network between all the states the system can occur in. Several studies have demonstrated that the assembly towards the final ground state is affected by changing the interaction between patchy particles [70, 130], which affects both the thermodynamics and kinetics of the system. In contrast, here we study how the pathways change upon changing the dynamics only. Colloidal dynamics is often stochastic, and well described by over-damped Langevin (Brownian) dynamics. The rotational and translational diffusion constant of anisotropic particles is under standard conditions coupled via the Stokes-Einstein relation. However, in environments with high molecular crowding or in external fields the Stokes-Einstein relation is not necessarily valid anymore [131, 133]. Depending on the molecular crowder, the ratio between the rotational and translation diffusion constant can go up or down. In this work we investigate how varying this ratio influences the equilibrium kinetic network for small self-assembled clusters of colloidal patchy particles. Such particles provide a simple model for self-assembly protein complexes such as in viruses or signal-transduction networks. Understanding and prediction of the colloidal self-assembly mechanisms requires the rate constants and pathways for all possible dissociation and association events in the kinetic network. However, on the time-scale of the dynamics of the microscopic particles, binding and certainly dissociation processes are usually rare events due to high free energy barriers caused by strong directional binding. As straightforward dynamical simulation is extremely inefficient, we employed the Single Replica Transition Interface Sampling (SRTIS) algorithm to collect all possible (un)binding trajectory ensembles relevant to the patchy colloid assembly [104]. Surprisingly, even for
the dimerization of a 1-patch particle we already find an effect of the rotation on
the formation dynamics. Next, we investigate a dimerization of 2-patch particles,
which exhibits an intermediate state and multiple pathways of formation. How-
ever, the effect of the rotation becomes truly important if metastable intermediates
are possible, such as in tetrahedron formation of a 3-patch particle. Here we find
that varying rotational diffusion favors one pathway over the other, without chang-
ing the equilibrium constants. Finally, we investigate the entire nine-state kinetic
network of a tetrahedron cluster, and show that a change in the rotational diffusion
shifts the preferred self-assembly pathways significantly. While for low rotational
diffusion the overall rate constant of tetrahedron formation decreased, frustrated
states are avoided, leading to significantly less kinetic trapping. Controlling the
kinetic network would offer an extra control in the design of new self-assembled
functional materials. Including the interplay between rotational and translational
diffusion in the self-assembly design of new supra-colloidal structures could open
up new opportunities for controlling the bottom-top synthesis of functional mate-
rials. Moreover, this work help to understand how rotational diffusion influences
self-assembly processes in naturally occurring crowded environments such as the
biological cell. As it has been established that the crowded environment in a cyto-
plasm decreases the ratio of rotational diffusion over the translation diffusion [133],
our simulations provide an additional explanation why protein complex assembly
does not suffer more from kinetic trapping as one would naively expect.

4.2 Methods and Simulation details

Model Patchy Particles

We model the particles as patchy hard spheres with diameter $\sigma$. For a center-to-
center distance, $\sigma < R_{ij} < 2\sigma$, the patch potential is:

$$u_{ij}(R_{ij}, \Omega) = -\epsilon \sum_{p_{ij}} e^{-kr_{ij}} e^{-(\theta_i^2 + \theta_j^2)/w^2}$$  \hspace{1cm} (4.1)$$

where $\Omega$ denotes the orientations of the particles, $\sum_{p_{ij}}$ is the sum over all patch
pairs, $k$ controls the range of the interaction, $r_{ij}$ is the distance between patch
centres, $\theta_\alpha$ is the angle between patch vector of particle $\alpha$ and the vector connecting
the centre of $\alpha$ and the centre of the patch on the other particle and $w$ is a
parameter that controls the patch width (see Fig. 4.2). Note that the arccosine is
needed for the angle calculation. As the patch widths in this work are all small,
we used an approximation for the arccosine in order to speed up the simulation
significantly. The model in this chapter is different than in chapter 5 and 6. This is
to accommodate the need for multiple bonds between particle pairs in section 4.4.

In our simulations we used Dynamic Monte Carlo (DMC) to evolve the system in
time via translational and rotational MC moves, as described in chapter 2.
Simulation and SRTIS settings

One-patch dimer. Two hard spheres of radius $\sigma$ are each decorated with one patch of range $k^{-1} = 4.0\sigma$ and width $w = 0.7$. Note that for this value of $w$, the potential depth $\epsilon = 20k_B T$ has to be sufficiently high for a stable dimer. The dimer is put in a periodic cubic box of size $5\sigma$, which sufficiently stabilizes the unbound state. Only two different states are defined, the bound state ($B$), when the energy of the system, $E_{sys} = \sum_{i<j} u_{ij}$, is lower than $-12k_B T$, and the unbound state ($U$), when the particles are separated more than $2\sigma$, which is also where we truncate the potential to zero. For the bound state we choose the first interface at the stable state definition and the rest of the interfaces are separated by $3k_B T$ until maximum energy is reached. For the unbound state it is necessary to define many interfaces close to the zero point energy: \{0, 0, 10^{-14}, 10^{-12}, 10^{-10}, 10^{-8}, 10^{-6}, 10^{-4}, 10^{-2}\}, to bias the system towards $B$ also when the particles are not properly aligned.

Two-patch dimer. The potential parameters are identical to one patch case, except that the patch width is decreased ($w = 0.1$) to ensure the two patches do not overlap. The state and interface definition are identical to the one-path system, except more interfaces surround the bound state, since the bound state is lower in energy. Tetramer. Model parameters for this system are $\epsilon = 12k_B T$, $w = 0.1$ and $k = 4.0\sigma^{-1}$. To decrease the diffusive pathway for the four particles, we altered the box size for this system to $4.0\sigma$. The bound state is defined as $E_{sys} < -20k_B T$, with three correct bonds formed, and the intermediate state as $E_{sys} < -10k_B T$, with two bonds formed in a frustrated state. Again, we use the system energy as the order parameter for the interfaces. The interfaces for each state are separated by $3k_B T$ starting from their minimum energy. The same interfaces and state definition for the unbound state as before are used. Each state state is recognized according to their appropriate topology defined by their bonds.

4.3 Dimer of one patch particles

Two hard spheres of radius $\sigma$ with a single, relatively narrow, attractive patch, analogous to a binding site on a globular protein, can form a dimer. Although, due to the simplicity of the system, no energetically frustrated trap can exist, it is insightful to understand whether and how rotational diffusion can change the dynamical pathway taken during dissociation or association. We sample the path ensemble for this two-state binding process with SRTIS. The interfaces around stable states are defined by the energy of the system. We construct the free energy landscape, as well as the (un)binding rate constants, see Eqs. 2.50 and 2.40. Fig. 4.2 shows the free energy as a function of the distance between the particles, $R_{12}$, and the sum of the angles $\phi = \phi_1 + \phi_2$, with $\phi_{1,2}$ the angle between the patch vectors and the inter particle vector $\vec{R}_{12}$. The bound state is the free energy minimum at $\phi = 0$ and $R_{12} = \sigma$. At larger distances, the orientational part of the free energy becomes symmetric with respect to $\phi$, indicating particles can freely rotate in the unbound state where the interaction vanishes. Between these minima
Figure 4.1: Cartoon of the patchy dimer with parameters used in the potential, and order parameters used for the free energy and reactive path density plots.

Table 4.1: Flux, crossing probabilities and rate constants TIS one patch dimer assembly in MC cycle units

<table>
<thead>
<tr>
<th>State</th>
<th>$f_{SE} = 0.1$</th>
<th>$f_{SE} = 1.0$</th>
<th>$f_{SE} = 10.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\langle \phi_{0I} \rangle$</td>
<td>$P(\lambda_{mI}</td>
<td>\lambda_{1I})$</td>
</tr>
<tr>
<td>B</td>
<td>$3.58_4 \times 10^{-3}$</td>
<td>$4.03 \times 10^{-5}$</td>
<td>$0.223_9$</td>
</tr>
<tr>
<td>U</td>
<td>$1.29_1 \times 10^{-3}$</td>
<td>$3.58 \times 10^{-2}$</td>
<td>$0.0059_1$</td>
</tr>
<tr>
<td></td>
<td>$5.22_4 \times 10^{-3}$</td>
<td>$8.862 \times 10^{-5}$</td>
<td>$0.216_1$</td>
</tr>
<tr>
<td></td>
<td>$1.312_9 \times 10^{-3}$</td>
<td>$4.516 \times 10^{-2}$</td>
<td>$0.015_3$</td>
</tr>
<tr>
<td></td>
<td>$1.669_1 \times 10^{-2}$</td>
<td>$1.508 \times 10^{-4}$</td>
<td>$0.043_3$</td>
</tr>
<tr>
<td></td>
<td>$1.472 \times 10^{-3}$</td>
<td>$5.100 \times 10^{-2}$</td>
<td>$0.039_3$</td>
</tr>
</tbody>
</table>

an (entropic) binding free energy barrier is visible. Naturally, the free energy landscape does not change with the rotational diffusion as it solely depends on the interactions between the particles. In contrast, varying the rotation diffusion ratio $f_{SE}^2 = \frac{D_0^0 \sigma^2}{3D_t^0}$ significantly alters the dynamical pathways between B to U. Fig. 4.2 visualizes the projection of these dynamical paths, i.e. the reactive path density $n_r(q)$, see Eq. 2.51 in the $R_{12}$, $\phi$ plane. The path density broadens for higher rotational diffusion, and significantly changes shape, as indicated by the red curve of maximum path density connecting U to B. The reactive path density also yields the orientational escape distribution as a function of $\phi$ at the boundary of the unbound state (see Fig. 4.2). This distribution indicates the probability of orientation at dissociation, and is skewed to lower values of $\phi$ for low rotational diffusion, while becoming symmetric for high rotational diffusion. The enhancement at $\phi = \pi$ is due to the projection. The change in reactive pathways is also visible in the reactive current (see Fig. 4.2) which gives the average velocity
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Figure 4.2: The free energy (top left), reactive path densities (top right), escape distribution (bottom left) and reactive currents (bottom right) for the one patch particle system for different values of $f_{SE}$ as a function of the distance between particles, $R_{12}$, and the angle $\phi = \phi_1 + \phi_2$, with $\phi_{1,2}$ the angles between the patch vectors and the inter-particle vector. The binding pathway clearly changes with rotational diffusion constant, from more reactive pathways via translation for slow rotational diffusion toward reactive pathways more via rotation for fast rotational diffusion, without changing the free-energy landscape.

at which the particles move along the reactive pathways, and hence does not contain off-pathway excursions. Both the reactive path density and the reactive current reveal that for low $f_{SE}$, i.e. slow rotational diffusion, the particles follow a straight pathway along the radial coordinate. For higher $f_{SE}$, and faster rotational diffusion, they follow a more curved association route from the unbound state into the attractive well. Note that due to microscopic reversibility, dissociation pathways are the reverse of the association trajectories. The difference in behavior can be understood by realizing that particles need to be aligned for binding. In the case of slow rotational diffusion, particles that are not aligned when close together will diffuse away transitionally before binding can occur.

The rate constants are given by $k_{IJ} = \phi_I P(\lambda_{0|I} | \lambda_{11}) = \phi_I P(\lambda_{mI} | \lambda_{11}) P(\lambda_{0|I} | \lambda_{mI})$, where $\phi_I$ is the flux out of state $I$, and $P(\lambda_{mI} | \lambda_{11})$ and $P(\lambda_{0|I} | \lambda_{mI})$ are crossing probabilities defined in section 2.5. The measured fluxes out of the stable states, the crossing probabilities and the rate constants are given in table 4.1. Increasing rotational diffusion by two orders of magnitude, enhances the absolute rate constants by a factor ten. Nevertheless, the ratio between the rate constants does not change, as this is determined by thermodynamics. Note that while the bond energy is $20k_B T$, the ratio $k_{BU}/k_{UB} \approx 0.1$ indicating that $U$ is still relatively
stable with respect to $B$. Of course, this is also dependent on the width of the attractive patch and the simulation volume (concentration of the colloids).

### 4.4 Dimer of two patch particles

We subsequently performed SRTIS of dimer formation for particles with two patches, where association occurs via a multiple step mechanism. Figure 4.3 shows

![Diagram of two patch particles](image)

**Figure 4.3:** The free energy and reactive path densities for the two patch particle system for different values of $f_{SE}$ as a function of the distance $r_{i,j}$ between the formed bonds in the bound state. The concertedness of assembly is changed by changing the rotational diffusion. For fast rotational diffusion misalignment will still lead to binding, whereas less so for slow rotational diffusion.

The free energy and the reactive path density as a function of the bond distances, $r_{1,2}$ (the bonds are identified in the bound state). This projection yields a more detailed assembly picture. Again, the free energy is independent of $f_{SE}$ and shows a minimum at $r_1 = r_2 = 0$. Here the two particles do not concertedly assemble into the dimer state, but first form one bond, followed by a rotation around this bond into the dimer state. The two peaks near the dimer state around $r_{12} = 0.25$ in the reactive path density indicate both dimer permutations have been sampled. Note
that the low path density at the origin is caused by the truncation of the paths as they reach the bound state. Increasing the rotational diffusion slight changes the reactive path density toward a broader single-bond peak, as the requirement for alignment is relaxed, and hence 'concertedness’ decreases. To summarize, for fast rotational diffusion misalignment will still lead to binding, whereas less so for slow rotational diffusion.

4.5 Tetrahedron assembly

To understand the effect of rotational diffusion on a more complex kinetic network, we study the formation of a tetrahedron consisting of particles with three patches. The patch vectors are set at an angle of 60° w.r.t each other, so that the patches form an equilateral triangle on the surface of the particle. The ground state of this system is a tetrahedron. As a first step, we study the final transition in the self-assembling process, namely the addition of the fourth particle to a preformed trimer cluster, while keeping the trimer constrained.

Besides the bound state $B$ and unbound state $U$, there is now also an intermediate state $I$ where the fourth particle ‘wrongly’ binds with two bonds to the trimer. To escape from this frustrated intermediate state, a bond has to be broken before the complete tetrahedron can form. We study how the kinetic network between these three states changes when the rotational diffusion is changed. The rate constant calculation is more intricate than the simple dimer system, see Eq.

![Figure 4.4: Population ratio for the intermediate state over the unbound state, as the system relaxes starting from a fully populated bound state, for different rotational diffusion constants. It is clear that for fast rotational diffusion, the intermediate state is populated relatively more than for slow rotational diffusion. For all rotational diffusion constants the system equilibrates towards the same thermodynamic state.](image-url)
The inset in Figure 4.4 shows the kinetic network. We per-

Figure 4.5: Top: Net flux graph for the tetrahedron assembly. The arrow size indicates the relative magnitude of the flux. For faster rotational diffusion, the system avoids the trimer state $Tr$ more than for slow diffusion, and follows a more frustrated pathway via states $T_{f1}$, $T_{f2}$ and $T_{f3}$, an extension of the principle shown for the constrained tetrahedron system. Middle: cartoon images of all states defined except for the unbound state. Bottom left: Population ratio for the trimer state, $Tr$, over the frustrated tetramer state, $T_{f2}$, as the system relaxes starting from a fully unbound state for different rotational diffusion constants, demonstrating how the system equilibrates during assembly. For fast rotational diffusion the trimer state is more populated during the equilibration. For all rotational diffusion constants the system equilibrates towards the same thermodynamic state. Bottom right: Committors to $T_d$, $q_i^+$, for all intermediate states as a function of the rotational diffusion factor, $f_{SE}$. The committor for the frustrated tetramers decreases with decreasing $f_{SE}$. In contrast, the committor of $Tr$ increases.
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formed SRTIS and computed the rate matrix $K$ for different values of $f_{SE}$, and computed the time evolution of the population by $p(t) = p(0)e^{-Kt}$. To show how $f_{SE}$ influences the assembly pathway we consider the ratio $P_I/P_U$ of the intermediate state population over the unbound state. Figure 4.4 shows this ratio as a function of time, for a system initially in the bound state. While all curves decay eventually to the same equilibrium population, at short times the population ratio $P_I/P_U$ scales roughly linearly with the rotational diffusion ratio $f_{SE}$. Rotational diffusion thus significantly influences the pathways for self-assembly, or in this case disassembly.

Next, we examine the self-assembly of four free particles into a tetrahedron. We define a set of 9 states: {Unbound state ($U$), one dimer ($D_1$), two dimers ($D_2$), trimer ($Tr$), frustrated trimer ($Tr_f$), frustrated tetramer states ($T_{f1}$, $T_{f2}$, $T_{f3}$) and the fully assembled tetrahedron state ($T_d$)} (see Figure 4.5 for graphical representations). Again we do not define states that can transit to one of the nine defined states by barrier-less rotation around bonds. Performing a SRTIS simulation results in a complete rate matrix $K$. Applying transition path theory to the computed rate matrices results in flux matrices, as well as committors for each state for the transition from $U$ to $T_d$, see Eq. 2.55 [110]. Fig. 4.5 shows a graphical summary of this information for different values of $f_{SE}$. While the net flux generally decreases with decreasing rotational diffusion, the thickness of arrows correspond to the normalized net flux, in order to emphasize the differences in self-assembly pathways taken. For slow rotational diffusion $f_{SE} = 0.1$, the $U-D-Tr-Tr_f-T_d$ pathway carries most of the flux. For higher $f_{SE}$, the $Tr$ state is avoided, as was the case in the constrained tetrahedron system. Therefore, at high rotational diffusion, the transition between $U$ and $T_d$ occurs preferably via frustrated states, $T_{f1}$, $T_{f2}$ and $T_{f3}$, which are then more accessible. Transitions along $Tr_f$ are favourable, even for low $f_{SE}$, probably due to combinatorial entropy since there are more ways to (dis)assemble into $Tr_f$ than into $Tr$. Another way to demonstrate the influence of rotational diffusion on the assembly is to show the population dynamics of the trimer state, $Tr$, over the frustrated tetramer state, $T_{f2}$ (see Fig. 4.5). The population of the trapped intermediate state $T_{f2}$ is initially significantly less populated for slow than fast rotational diffusion, indicating that indeed for assembly with fast rotational diffusion particles aggregate more easily towards frustrated states. Indeed, this also implies that for larger systems beyond the tetramer the frustrated states will lead to an even stronger trapping effect. We show that the correctly formed tetrahedron pathway dominates for slow rotational diffusion by analyzing the rate matrices using such strong traps.

In Fig. 4.5 the committor $q_i^+$, defined as the probability that from state $i$ state $T_d$ will be reached before reaching $U$, is shown as function of $f_{SE}$. The committor for the frustrated tetramers decreases with decreasing $f_{SE}$. In contrast, the probability for $Tr$ increases, indicating again that for slow rotational diffusion a less frustrated pathway is followed.
Population dynamics of a trapped system

In principle, the gain in relative flux towards correctly formed structures should result in a better yield of the designed ground state, and in less kinetic trapping. While in our examples the intermediate states are not truly kinetic traps, we envision that for more complex target structures, which compete against completely disordered aggregates, the price paid for slowing down the dynamics is outweighed by taking the correct self-assembly route and could lead to higher relative yields. We tried to simulate this situation with our measured rate matrices to clarify this line of reasoning. To model kinetic trapping we have changed the rate matrix such that every tetramer state is a sink, where no population can escape from. This simulates the situation in which reaching a malformed tetramer state will catastrophically end up in a disordered aggregate, or adversely that a properly formed tetrahedron will not disassemble again. Additionally, we set that the only correct binding pathway is via $T_\text{r}$, so that there is only one good assembly pathway. We can clearly see in Fig. 4.6 that indeed the relative population of the correctly formed tetrahedron versus all other tetramer states increases with decreasing rotational diffusion. Note that now the populations will not end up at the same value, because population gets lost in the trapped/frustrated Tetramer states.

![Figure 4.6: An effort to replicate kinetic trapping due to frustrated states](image)

Figure 4.6: An effort to replicate kinetic trapping due to frustrated states by performing population dynamics with the computed rate matrices, however, with all tetramer states as sinks. Here we show the relative population of the fully formed tetrahedron versus the sum of populations of the frustrated states $T_f$. The yield of $T_d$ increases for slower rotational diffusion.
4.6 Analysis of simple master equation model

To illustrate how our main finding extends to large systems we have analyzed a simple abstract model using a master equation population analysis. This abstract model consists of a number of states, shown in Fig. 4.7 in which the first digit in the index of the states denotes the stability index, e.g. in terms of bonds between particles, while the second digit denotes the frustration index, e.g. the number misaligned bonds. We assume that the initial state 11 can jump to state 21, which can then become frustrated, or misaligned, by jumping to state 22. The rate constants \( k_t^+ \) and \( k_t^- \) denote, respectively, the associating and dissociation rate constants, for making such particle bonds. The \( k_r^+ \) and \( k_r^- \) denote the rotational move that causes misalignment of bonds. We set \( k_r^- = 0.1 k_r^+ \), to mimic that the number of possible frustrated states is increasing with the number of misaligned bonds. We choose \( k_t^- = 0.01 k_t^+ \), such that the assembly into the ground-state 51 is favorable with respect to the trapped state. Figure 4.7 shows a maximum of five bonded particles, but of course this model can handle any number of bonds in the system, by simply extending this figure. We solve the corresponding master equation of this model for two settings: \( k_t^+ = k_t^- = 10^{-5} \) corresponding of fast rotation dynamics, and \( k_t^+ = 10^{-6} \) and \( k_t^- = 10^{-5} \), corresponding to slow rotation dynamics. We monitor the ratio of population of the final state with respect to all other states \( p_{final}/(1 - p_{final}) \). This ratio is shown in Fig. 4.8 for the slow and fast diffusion case for a model with 15 bonded states, i.e.. 15 particles
in the assembly. Clearly, the slow diffusion case rises much more quickly than the fast. This is because the direct route, without frustration is preferred to the trapped state, since the moves into the frustrated states are less likely. We can also look at the relative increase of the slow rotational diffusion ratio versus the fast rotational diffusion ratio. This is shown in the right panel of the Fig. 4.8. The yield of the final state for slow $k_r^+$ is more than a 100 times larger than for the fast rotational diffusion. This ratio only becomes larger for assembly of a larger number of particles. The increased yield eventually decreases again, because the system with fast rotational diffusion will eventually relax to the equilibrium state, where the yields should be equal. This simple analysis shows that our finding is generic and can be extended to larger systems.

### 4.7 Conclusion

Our path-sampling simulations demonstrate the proof-of-concept that altering the rotational diffusion can affect the kinetic network and hence the mechanism of self-assembly for simple patchy particle systems. For the dimer system of one-patch and two-patch particles the mechanism of reactive pathways changes significantly with rotational diffusion, from a translational reactive pathway for slow rotational diffusion, to a rotational reactive pathway for fast rotational diffusion. The pathways do not need to follow the free energy landscape, and avoid the saddle point when the dynamics are changed. In the assembly of a constrained tetrahedron of four particles decorated with three patches, faster rotational diffusion increases the likelihood of a route via the intermediate state. This effect is even stronger for the full tetrahedron assembly, where the frustrated states and kinetic traps are avoided when rotational diffusion is suppressed. We argue that these results hold beyond the tetramer, and can be seen as a generic effect. We support this argument by analyzing the population dynamics of a simple Markov model that
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mimics a much larger assembly process. This analysis clearly shows that slower rotational diffusion results in less frustration and in orders of magnitude higher yields. This generalization makes our finding into a genuine novel principle for controlling and understanding complex self-assembly kinetics.

Appendix

Crossing probability one patch system

In Fig. 4.9 we show the crossing probability as a function of the order parameter used in the TIS simulations, the energy of the system, for both the bound and unbound state for the one patch system described in the main text. Clearly, the crossing probability of B and U for low rotational diffusion is always lower than for fast rotational diffusion. The points are the Wang-Landau density of paths, $\log g(\lambda_i)$, which have become equal to the crossing probability. There is a steep drop at low energies for the crossing probability of $U$ after which $P(\lambda)$ only slowly decays with decreasing energy, which makes it necessary to set interfaces at low values of the energy.

![Crossing probability](image)

Figure 4.9: Left: the logarithm of the crossing probability as a function of the energy of the system for both $B$ (solid line) and $U$ (dashed line) for the one patch system described in the main text for $f_{SE} = 0.1$ (red), 1.0 (green) and 10 (blue) after a converged TIS simulation. Right: the same crossing probability for $U$ now versus $\log \lambda = \log(-E)$. The points are the Wang-Landau density of paths, $\log g(\lambda_i)$, which are equal to the crossing probability.

Typical diffusive paths for the one-patch dimer

In Fig. 4.10 we depict typical diffusive paths from the path ensemble on top of their respective reactive path density for $f_{SE} = 0.1, 1.0$ and 10. Note that for low rotational diffusion the path is mostly sampling horizontal (translational axis), while for the high rotational diffusion the paths are exploring much more in a vertically (rotation axis), as expected. For these high values of $f_{SE}$ many rotations of the particle pair can be made in one path before binding.
Figure 4.10: The reactive path densities for the one patch particle system for \( f_{SE} = 0.1, 1.0 \) and 10 (left to right) as a function of the distance between the particles, \( R_{12} \), and the vector inner product between the patch vectors of both particles, \( \phi \). A typical diffusive path is shown on top of the density plots.

**Overall rate constants for the full tetrahedron assembly**

The overall forward and backward rate constants for the transition between the bound tetrahedron \( T_d \) and the fully unbound state \( U \) as computed from TPT according to Eq. 2.57 are shown in Fig. 4.11. Note that both forward and backward rate constants scale roughly linearly with \( f_{SE} \), such that the ratio of the two stays constant.

Figure 4.11: The overall rate constants from the fully assembled tetrahedron to the unbound state (top) and from the unbound state to the fully assembled tetrahedron (bottom) as a function of rotational diffusion factor \( f_{SE} \).

**Scaling with the unbound state dwell time**

Decreasing the rotational diffusion via \( f_{SE} \) does increase the timescale of all relaxation processes (see Fig. 4.12). Also the unbound state dwell time increases. We can therefore investigate whether the overall assembly relaxation times trivially depends on this unbound state dwell time. In Fig. 4.12 we show the population of the tetrahedron state with the time axis rescaled by the time spent in the unbound
state. When all relaxation processes in the assembly scale in the same way, all curves should collapse on top of each other. This is clearly not the case. In fact, the ordering of the curves remains the same. We can understand this by realizing that the timescale in the unbound state is dominated by the translational diffusion, and less so by rotation. Changing the rotational diffusion thus has some effect on the unbound timescale, but not dramatically so.

**Time step set by rotational diffusion constant**

When the rotational diffusion is lowered by decreasing \( f_{SE} \), the overall dynamics naturally also slows down (see Fig. 4.12). However, as we could also have changed the translational diffusion instead of the rotational diffusion, we can take the same data and scale the rate constants such that the time-step is now set by the rotational diffusion constant. As Fig. 4.13 clearly shows, the tetrahedron population grows fastest when the translational is faster than the rotation.

Figure 4.12: Left: population of the fully formed tetrahedron with respect to the equilibrium population. Right: Relative population of the fully formed tetrahedron when the time-step is rescaled with the time spent in the unbound state.

Figure 4.13: Population of the fully formed tetrahedron when the time-step is set by the rotational diffusion constant. The tetrahedron population grows fastest when the translation is faster than the rotation.