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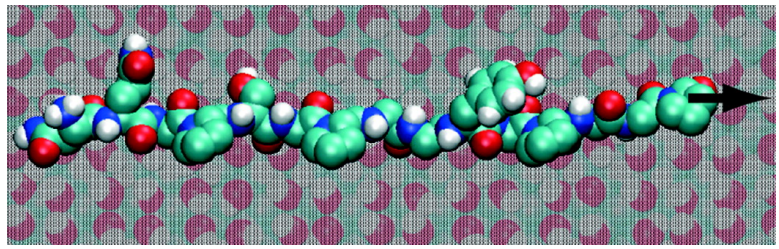

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Polypeptide Friction and Adhesion on Hydrophobic and Hydrophilic Surfaces: A Molecular Dynamics Case Study

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Abstract: Using all-atomistic MD simulations including explicit water, the mobility and adhesion of a mildly hydrophobic single polypeptide chain adsorbed on hydrophobic and hydrophilic diamond surfaces is investigated by application of lateral and vertical pulling forces. Forced motion on the hydrophilic surface exhibits stick-slip due to breaking and reformation of hydrogen bonds; in contrast, on the hydrophobic surface, the motion is smooth. By carefully tuning the driving force magnitude, the linear-response regime is reached on a hydrophobic surface and equilibrium values for mobility and adhesive strength are obtained. On the hydrophilic surface, on the other hand, slow hydrogen-bond kinetics prevents equilibration and only upper bounds for adhesion force and mobility can be estimated. Whereas the desorption force is rather comparable on the two surfaces and differs at most by a factor of 2, the mobility on the hydrophilic surface is at least 30-fold reduced compared to the hydrophobic one. A simple model based on a single particle diffusing in a corrugated potential landscape suggests that cooperativity is rather limited and that the small mobility on a hydrophilic surface can be rationalized in terms of incoherently moving monomers. The experimentally well-known peptide mobility in bulk water is quantitatively reproduced in our simulations, which serves as a sensitive test on our methodology employed.

1. Introduction

The surface diffusivity of adsorbed polymers is key to the kinetics of polymer adsorption and desorption and the response of adsorbed polymer films to external mechanical stress or shear flow. Applications that depend on controlling the interplay between polymer adhesion statics and kinetics are abundant, examples include polymeric lubrication, surface modification, surface adhesion, and colloidal stabilization.[1] One underlying parameter in all these situations is the bare mobility of a single polymer in adhesive contact with a surface. Surprisingly, studies addressing the friction of a single surface-adsorbed polymer are rare. The situation is more complicated than for solid-body friction[2] since the normal force for an adsorbed polymer is not externally controlled but rather self-adjusts according to the surface-polymer adhesive strength. Experimentally, the diffusion of single polymers adsorbed on surfaces from dilute solution is interesting in its own right and has been followed by optical or scanning probe techniques and diffusion constants have been determined.[3−6] In a complimentary approach, single polymers have been pulled or peeled off from solid surfaces with an AFM using different rates and angles.[7] For polymer melts at surfaces, single polymer diffusion times have been determined and are coupled to the reptation dynamics in the melt.[8,9] On the theoretical side, different coarse-grained models have been proposed for the dynamics of adsorbed polymer chains and used to work out scaling laws for polymer friction as a function of chain length and surface structure.[10−14] In this work, we study the forced motion of a spider silk peptide 15-mer (i) in bulk water, (ii) at a hydrophobic diamond surface, and (iii) at a hydrophilic diamond surface using all-atomistic MD simulations including explicit water. Our studied peptide is mildly hydrophobic and strongly adsorbs on both hydrophilic/phobic diamond substrates,[15] as is quite typical for a wide class of proteins.[16] MD simulations have been shown to correctly describe the electrophoretic mobility of single-stranded RNA in bulk water.[17] They provide a powerful tool for studying single-molecule force experiments.[18] From another perspective, a hydrophobic polymer adsorbed onto a hydrophobic flat surface can serve as a model

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with simplified geometry for polymer collapse driven by hydrophobic attraction and in particular for the so-called molten-globule state of globular proteins.

Our simulated peptide mobility in bulk water quantitatively compares with experimental diffusion measurements, which serves as a sensitive test on our employed simulation methodology and in particular proves that the experimentally relevant linear-response regime can be reached in all-atomistic MD simulations. The mobility on the hydrophobic substrate is only slightly reduced compared to the bulk value. This is related to the water depletion layer on hydrophobic substrates[19,20] and the loose coupling between water and the substrates, leading to a finite slip length.[21] In contrast, on the hydrophilic surface the peptide mobility is greatly reduced, which is remarkable as the adsorption free energy is not much higher compared to the hydrophobic surface. Using a simple scaling argument based on a single particle diffusing in a corrugated potential landscape, this behavior is traced back to the coordinated breaking and reforming of hydrogen bonds. Within this model, the cooperativity is found to be quite small, i.e. the peptide monomers can be envisioned to move rather independently from each other over the surface. The main result is that while peptide adhesion strengths on hydrophilic and hydrophobic substrates are quite comparable, the friction forces and thus kinetics are wildly different: the mobility on hydrophobic surfaces is comparable to the bulk water mobility, whereas on a hydrophilic surface the kinetics is dramatically slowed down. This means that peptide adsorption on hydrophobic surfaces should exhibit fast equilibration, while on polar surfaces adsorption relaxation will be slowed down even on the level of single polymers when entanglement effects are not taken into account. Similar behavior is expected for synthetic chains and also DNA or RNA. Likewise, relaxational dynamics during the hydrophobic collapse of peptides or polymers should be fast compared to the dynamics of polymeric globules formed by hydrogen bonds.

2. Methods

MD simulations with a duration of up to 40 ns are carried out with the Gromacs package[22] using periodic boundary conditions in the isobaric−isothermal ensemble with $P = 1$ bar and $T = 300$ K and total momentum set to zero. If not stated otherwise, we use an $N = 15$ amino acid long polypeptide, NQGPSGPGGYGPGGP, which is the terminal part of an actual spider silk protein sequence.[15] It contains nonpolar glycine (G) and proline (P) as well as polar asparagine (N), glutamine (Q), serine (S), and tyrosine (Y) residues and thus shows both hydrophilic as well as hydrophobic character, which is essential for the present study. For mobility studies in bulk water, the polypeptide is placed in a 10 nm × 4 nm × 4 nm box filled with about 5400 SPC water molecules[23] and pulled along the long box side. Parameters for the diamond surfaces and the polypeptide are taken from the Gromos96 force field[24] which is a robust parameter set and has been thoroughly tested to give the correct peptide solvation thermodynamics.[25] A diamond slab of approximate dimensions $d_x \times d_y \times d_z = 6$ nm × 3 nm × 1.8 nm, with the (100) surface fully terminated with hydrogen atoms and all partial charges set to zero serves as a hydrophobic model surface. Its contact angle with water is 106°.[15] To render a hydrophilic surface, half of the surface hydrogen atoms are replaced by hydroxyl groups, using the Gromos96 bond and partial charge parametrization of the COH group as defined in a serine residue. We have also performed simulations with different hydroxyl surface densities which yield comparable results and thus demonstrate that 50% OH termination is a typical representation of a hydrophilic surface.[26] About 3000 water molecules are added above the diamond slab filling the simulation box of approximate size $b_x \times b_y \times b_z = 6$ nm × 3 nm × 6 nm. A one-dimensional harmonic spring is attached to the terminal N residue with a force constant between 20 and 1200 k_BT nm^{-2} and is moved with a velocity V between 0.1 and 250 m/s either in the lateral $\hat{x}$ direction or in the normal $\hat{z}$ direction, with the force acting only in the moving direction. When the pulling force acts in the lateral direction, one probes the frictional response of the chain and no equilibrium work is performed. If the force acts perpendicular to the surface, the work has an equilibrium component, which reflects the free energy needed to desorb the chain, and in addition a nonequilibrium dissipative contribution, which results from a combination of solvent and surface friction. Monomer mobilities μ are calculated in the lateral-pulling scenario from the average force measured by the spring extension, $\bar{F}_x$, according to

$$\mu = NV/\bar{F}_x \tag{1}$$

where N is the number of amino acids in the peptide chain. The experimentally more relevant diffusion constants D are obtained from the Einstein relation, $D = \mu k_BT$. Errors are estimated by block averaging after reaching a steady state. We have also performed simulations where a constant lateral force is applied on each peptide atom and the resulting mean velocity is determined;[26] the surface-mobilities in such constant-force simulations are within error bars the same as for a peptide connected to a spring moving at constant velocity (the ensemble used for all results discussed in this paper), which demonstrates the equivalence of the different ensembles.

3. Results and Discussion

The laterally driven polypeptide shows dramatically different behavior on the hydrophilic and hydrophobic diamond. For the data in Figure 1 we chose the lateral pulling velocity on the hydrophobic surface (gray, $V_x = 10$ m/s) 20 times larger than on the hydrophilic one (black, $V_x = 0.5$ m/s) in order to obtain friction force responses of the same order of magnitude. Still, the mean friction force on the hydrophobic substrate of about $\bar{F}_x = 170$ pN is smaller than on the hydrophilic substrate which averages to about $\bar{F}_x = 600$ pN. Even more strikingly, the friction force on the hydrophobic substrate is rather constant while on the hydrophilic surface loading-release cycles with force spikes of up to $F_x = 1.5$ nN are observed. This is mirrored by the displacement of the pulled amino acid ΔX in Figure 1b, which for the hydrophilic surface displays pronounced stick-slip behavior. Note that the force acting on monomers decays quite quickly along the polymer contour and vanishes at the trailing peptide end, while stick-slip cascades propagate along the chain. The scaling dependence of the mobility of a whole polymer $\mu^{poly} = \mu/N$ with length N has been intensely discussed.[5,3,13,14] For smooth no-slip surfaces Rouse scaling $\mu^{poly} \propto 1/N$ is expected and confirmed in Figure 2 for chains of

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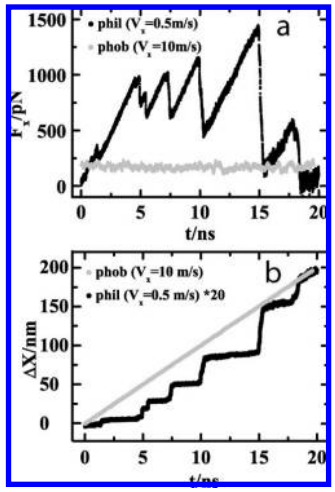

Figure 1. Time evolution of (a) lateral friction force F_x and (b) lateral displacement ΔX of a polypeptide ($N = 15$) pulled laterally over a hydrophobic (gray, $V_x = 10$ m/s) and a hydrophilic diamond surface (black, $V_x = 0.5$ m/s). Note that the displacement on the hydrophilic surface is multiplied by a factor 20 in order to make up for the 20-times smaller puling velocity. The forced motion is qualitatively different on both surfaces: smooth gliding is observed on a hydrophobic substrate, whereas on the polar surface stick-slip motion occurs.

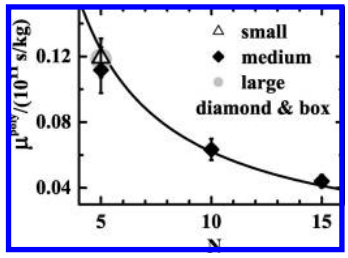

Figure 2. Polypeptide mobility on hydrophobic surface under lateral pulling ($V_x = 5$ m/s) as a function of the number of amino acids N in the chain. Rouse scaling ($\mu^{poly} \propto 1/N$) shown as solid line. For the 5mer, simulations on diamond slabs of different size give converged results: *small* with $d_x \times d_y = 3$ nm $\times$ 3 nm and 1500 water molecules (empty triangle), *medium* with 6 nm $\times$ 3 nm and 3000 water molecules (black diamonds), and *large* with 12 nm $\times$ 3 nm and 6150 water molecules (gray circle). The slab thickness is always $d_z = 1.8$ nm, the box height $b_z \approx 6$ nm.

length $N = 5$, 10, and 15 on a hydrophobic surface at fixed pulling velocity $V_x = 5$ m/s, which is sufficiently close to the linear-response limit. In the same figure, we present simulations with three different box sizes (and different number of water molecules) for fixed peptide length $N = 5$ and check that finite box-size and hydrodynamic cutoff effects are negligible. In Figure 3a we show variations of the friction force F_x with the pulling speed V_x for the whole peptide while in (b) the mobility μ per monomer is shown. The rather small variation of μ with V_x in Figure 3b for bulk water (crosses) and on the hydrophobic surface (gray diamonds) demonstrates that nonequilibrium effects are present, but at the same time that the experimentally relevant linear response can be estimated by extrapolation of the data to the limit $V_x \rightarrow 0$. We obtain for the bulk case (crosses) $\mu_{bulk} = (90 \pm 30) \times 10^{10}$ s/kg which is fully compatible with experimental diffusion measurements of peptides (see Table 1). At low pulling rates, we obtain a 3-fold increase in friction, $\mu_{phob} = (30 \pm 10) \times 10^{10}$ s/kg, on the hydrophobic surface (gray diamonds) compared to bulk water. On the hydrophilic surface (filled black circles) simulations are difficult to perform since the large frictional forces lead to frequent desorption events. Based on the limited data for which

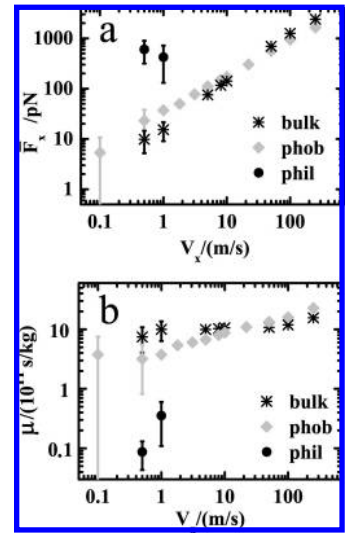

Figure 3. (a) Average lateral friction force $\bar{F}_x$ and (b) average monomer mobility μ according to eq 1 of a polypeptide consisting of 15 amino-acids as a function of the lateral pulling speed V_x. Simulations are performed in bulk water (crosses), on a hydrophobic diamond surface (gray diamonds), and on a hydrophilic diamond surface (black circles).

Table 1. Linear Response ($V_x \rightarrow 0$) Monomer Mobilities of Polymers in Bulk Water and Adsorbed onto Hydrophobic and Hydrophilic Substrates

polymer	bulk water or surface type	μ/(10^{10} s/kg)[a]	ref.
peptide[b]	bulk water	94	27
peptide	bulk water	90 ± 30	this work
peptide	on hydrophobic diamond	30 ± 10	this work
PEG*c*	on hydrophobized silica (SAM)	8.0	5
ds-DNA	on cationic lipid bilayer	1.2	3
peptide	on hydrophilic diamond	<1	this work
ds-DNA	on mica	0.17	6

[a] Monomer mobility via $\mu = N\mu^{poly}$ except noted otherwise. [b] 15mer mobility from scaling law in ref 27 with $M_r = 1298$ g/mol. [c] $\mu = N^{3/2}\mu^{poly}$.

reliable mobilities could be determined, we can only establish an upper bound of about $\mu_{phil} = 1 \times 10^{10}$ s/kg, assuming that μ monotonically decreases as $V_x \rightarrow 0$. Hence, the mobility is drastically reduced on the hydrophilic surface. For surface adsorbed polymers, peptide data is not available. For PEG polymers on hydrophobized silica the experimental mobility (Table 1) is of the same order as our value for the peptide on the hydrophobic surface. For DNA on two different hydrophilic substrates, the experimental mobilities are much lower and again close to our simulations estimate for a peptide chain on a hydrophilic surface (see Table 1). Considering the spread in the experimental data, the different polymers used and problems with converting experimental data to mobilities per monomer, the agreement seems satisfactory. As an additional source of complication, we mention that surface heterogeneities, impurities, and roughness modify surface mobilities.[11−14]

Scaling predicts a chain of unperturbed radius R_0 under tension to be stretched when the pulling force F becomes of the order $F \approx k_BT/R_0$. Reaching the linear-response limit in the simulations thus requires the friction force to satisfy $F_x < k_BT/R_0$. Our simulation results in Figure 3a yield for the entire polypeptide ($N = 15$) at the slowest speed $V_x = 0.1$ m/s a friction

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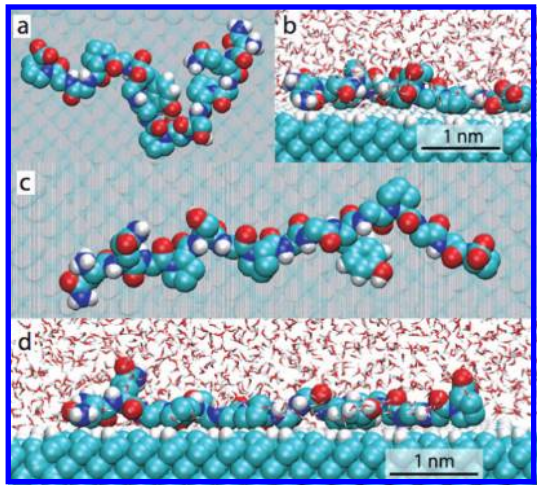

Figure 4. Snapshots of a polypeptide chain with $N = 15$ pulled laterally over a hydrophobic diamond surface; (a) top and (b) side view at $V_x = 1$ m/s, (c) top, and (d) side view at $V_x = 10$ m/s. The peptide assumes a more stretched conformation with increasing pulling rate, at low pulling rates the peptide is partly coiled.

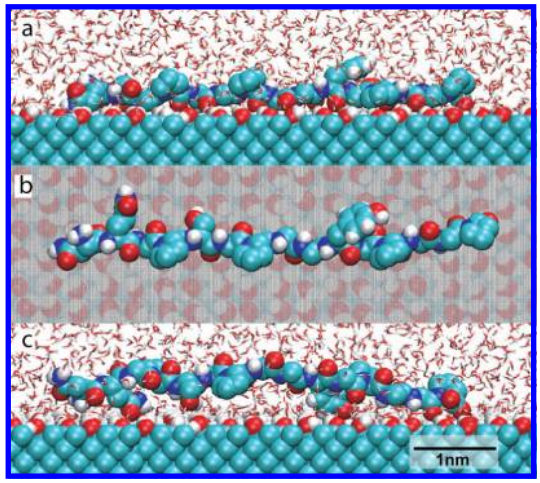

Figure 5. Representative conformations of a polypeptide chain with $N = 15$ amino acids adsorbed onto a hydrophilic diamond surface and laterally pulled at a speed of $V_x = 0.5$ m/s. Snapshots are taken from the simulation run shown in Figures 1 and 6b at simulation time $t = 7.0$ ns ((a) side and (b) top view), and (c) $t = 17.7$ ns (side view). The peptide stays in a stretched conformation during the whole simulation.

force of $F_x \approx 5$ pN on the hydrophobic and of the order of $F_x = 100$ pN on the hydrophilic surface. Using $k_BT = 4.14$ pN nm we see that with our relatively small simulated chains with $R_0 \approx 1$ nm conformations on the hydrophobic substrate should be unperturbed at the slowest pulling speeds. This is demonstrated by chain snapshots in Figure 4a,b for $V_x = 1$ m/s, and Figure 4c,d for $V_x = 10$ m/s, that exhibit a crossover from stretched at high speeds to coiled at low speeds. Note that irrespective of the pulling speed, the polymer is strongly adsorbed on the surface with no intervening water molecules, as seen in the side views. The average distance between C_α atoms and diamond C atoms is $\bar{Z}_{phob} = (0.45 \pm 0.02)$ nm independent of the pulling speed. For the hydrophilic surface, in contrast, linear response is not reached and chains are strongly stretched even at the slowest pulling speeds, as demonstrated in Figure 5, where we show snapshots for a simulation with $V_x = 0.5$ m/s.

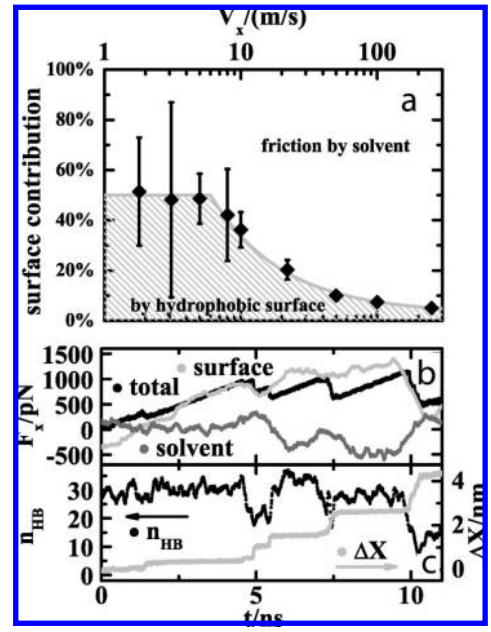

Figure 6. (a) Relative surface contribution to the total frictional force for a polypeptide ($N = 15$) pulled laterally over a *hydrophobic* surface as a function of pulling speed V_x. For small velocities, in the linear-response regime, the surface contributes directly roughly half of the total friction force. (b+c) Polypeptide ($N = 15$) on a *hydrophilic* surface laterally driven with $V_x = 0.5$ m/s. (b) Time evolution of total frictional force F_x (black) and the surface F_x^{surf} (light gray) and solvent $F_x^{H_2O}$ (dark gray) contributions. Force data are smoothed over 1 ns. Note that the water contribution to friction force is negative over large durations, corresponding to forward thrust of the peptide due to direct peptide-water interactions. (c) Number of hydrogen bonds between peptide and substrate n_{HB} (black, smoothed over 100 fs), and displacement ΔX (gray). Note that the breakage of H-bonds coincides with slippage events and with negative water friction.

To find out about the nature of friction on the hydrophobic surface, the *relative* surface friction contribution, that is, the fraction of friction due to direct forces between the peptide and the surface, is shown in Figure 6a. With increasing pulling velocity the surface contribution decreases from about 50% below $V_x = 10$ m/s down to 5% at $V_x = 250$ m/s. Based on the saturation for small pulling velocities, we conclude that friction in the linear response regime on a hydrophobic surface originates about half-from direct interactions with the surface, and half-from peptide-solvent interactions, which reflects the absence of strong localized peptide-surface bonds. Together with the high water mobility on the surface, which is caused by the pronounced depletion layer between water and any hydrophobic substrate,[20] this explains the remarkably high surface mobility of a peptide at the hydrophobic surface.

At the hydrophilic surface, the situation is very different, as shown in Figure 6b. The friction force acting on the peptide (black line) is dominated by surface forces (light gray); in fact, the force coming from solvent directly (dark gray) is small but predominantly negative and thus pushing the peptide along the direction of motion. We interpret the negative force contribution as coming from water molecules that rush into cavities formed by freshly broken peptide-surface bonds, which clearly shows that the response is far from the linear regime. To gain more insight into the microscopics of friction on the hydrophilic surface, we show in Figure 6c the time evolution of the number of all hydrogen bonds, n_{HB}, between surface groups and peptide groups (shown in black, defined by a distance between all possible donor and acceptor atoms of 0.35 nm or less) together with the displacement of the pulled amino acid (gray curve).

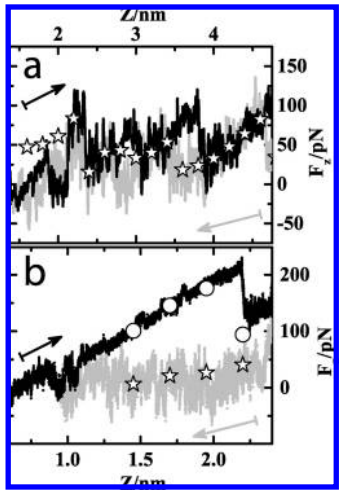

Figure 7. Vertical force F_z as a function of the peptide height Z for a peptide chain vertically driven at velocity $V_z = 0.1$ m/s away and toward the surface (black and gray). Static data are obtained at constant height (averaged over 4 ns after equilibrating for 4 ns) and are denoted by symbols. (a) On the hydrophobic surface hysteresis between force traces is small and static data (stars) converge when starting from configurations of either dynamic trace. The mean force averaged over the whole trace length amounts to $F_z = 44$ pN. (b) On the hydrophilic surface large hysteresis is present and static data with different initial configurations do not coincide (circles and stars). An upper estimate for the mean force is obtained by averaging over the pulling force and amounts to roughly $F_z = 98$ pN.

The average n_{HB} is about 30, meaning that each amino acid participates in about two hydrogen bonds to the surface. Slippage events are shown to coincide with the breaking of surface-peptide hydrogen bonds and negative water friction.

It is particularly interesting to contrast the observed difference in friction on hydrophobic/philic substrates with the corresponding adhesion strengths. In Figure 7, we show vertical forces obtained while moving the peptide end away (black) and toward (gray curves) the (a) hydrophobic and (b) hydrophilic substrate at $V_z = 0.1$ m/s. In (a), the hysteresis is quite small and forces are comparable to static simulations (stars) where the terminal group is kept fixed for 8 ns. The average adhesion force in the static simulations turns out to be 44 pN. In (b), the large hysteresis shows that equilibrium is not reached on hydrophilic substrates and even long-time static simulations with initial configurations taken from different moving directions (stars and circles) show strong hysteresis. The average desorption force obtained from the black force trace in Figure 7b amounts to 98 pN and constitutes an upper bound on the equilibrium desorption force. The equilibration problems on the hydrophilic surface are consistent with the mobilities estimated in the lateral-pulling geometry: there, we estimated for the entire polypeptide ($N = 15$) at the slowest speed $V_x = 0.1$ m/s friction forces of $F_x \approx 5$ pN and $F_x \approx 100$ pN on the hydrophobic/philic surfaces. Thus, friction is small compared to equilibrium desorption forces on hydrophobic surface, but dominating on hydrophilic surfaces at velocities reachable in simulations. The situation is much more favorable in AFM experiments where pulling speeds are typically smaller by 5 orders of magnitude. The estimated friction forces in a typical AFM experiment with $V_x = 1$ μm/s for a complete C16 polypeptide comprised of 560 amino acids would be 2 fN on the hydrophobic diamond and 60 fN on the hydrophilic surface. Compared to the desorption force or to the typical AFM force resolution of about 1 pN, the friction forces are thus irrelevant.[28,29] With longer chains however, or with modified surface morphologies, single-molecule friction forces might also be measurable with the AFM.

The low mobility on the hydrophilic substrate can be rationalized by a comparison with the scenario of a diffusing single particle in a sinusoidal potential of the form $U(x) = (\varepsilon/2)\sin(2\pi x/a)$ with periodicity a and depth ε. In the linear-response regime, the particle mobility μ_ε relative to its bare mobility μ_0 turns out to be $\mu_\varepsilon/\mu_0 = I_0^{-2}(\varepsilon/2k_BT)$ where I_0 is the modified Bessel function.[30] Let us now connect to the problem of diffusion of a peptide and ask how large the potential depth ε must be in order to lead to a 100-fold decrease of the mobility μ_ε (which we associated with the mobility on the hydrophilic substrate) compared to the bare mobility μ_0 (which we associate with the mobility on the hydrophobic substrate). Note that we associate the quasi particle in the effective model with a peptide substrand of an at this point undetermined length which moves independently from the peptide rest. By inverting the expression $\mu_\varepsilon/\mu_0 = 100$, we obtain a quasi-particle binding energy of $\varepsilon = 8.5\ k_BT$. This energy corresponds roughly to the binding free energy per amino acid of contour length $a = 0.37$ nm from the hydrophilic substrate: Noting that the desorption force is nothing but the binding free energy per length, we write $F_z = \varepsilon/a = 8.5\ k_BT/0.37\ \text{nm} \approx 95$ pN (using $k_BT = 4.14$ pN $\cdot$ nm), which is quite consistent with our rough simulation estimate for the desorption force from the vertical pulling scenario in Figure 7b). We see that the activation energy ε that we infer from the mobility matches the adsorption energy per amino acid. This suggests that the length of the independently diffusing subunit amounts to a single amino acid. Supporting this conclusion, the energy $\varepsilon = 8.5\ k_BT$ corresponds roughly to the free energy of two hydrogen bonds,[31] while at the same time the mean number of hydrogen bonds per amino acid is two (see Figure 6c). The mobility per amino acid can thus be rationalized in terms of the simultaneous breaking and reforming of the hydrogen bonds belonging to a single amino acid. We conclude that the cooperativity is small and amino acids move rather independently over the hydrophilic surface. Although this conclusion seems at first sight surprising, it reflects the pronounced backbone flexibility of a peptide chain, which effectively decouples neighboring amino acids from each other since there are two flexible torsional degrees of freedom per amino acid in the backbone. Note that this is very different from solid-state friction, where cooperativity effects are pronounced on flat surfaces.[2] Likewise, for polymers with stiff backbones such as double-stranded DNA, the friction forces should be much higher than for the peptide chains studied here.

For the peptide adsorption force on the hydrophobic substrate a similar argument can be made: in this case the adsorption is not due to some specific binding between peptide and substrate, but rather due to eliminating unfavorable hydration of the hydrophobic peptide chain as it is pushed toward the water surface. Assuming a peptide cross-section of about $d \approx 1$ nm and using the water surface tension $\gamma \approx 70$ mN/m, the adsorption force (which is the free energy per unit length) follows as $F_z \approx \gamma/d \approx 70$ pN, of the same order as the desorption

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force measured in the simulations on the hydrophobic substrate. Since almost no bonds are broken as the peptide moves laterally along the water-hydrophobe interface, the friction is to a large extent caused by dragging water along and thus similar to the bulk friction.

4. Conclusions

Summarizing, polypeptide friction forces on hydrophobic and hydrophilic surfaces are vastly different, even though the adhesion strength on both surfaces is rather similar. On hydrophobic surfaces we find good lubrication with peptide mobilities close to bulk water. In contrast, for a hydrophilic surface hydrogen bonds transiently lock the peptide, leading to a stick-slip type of motion and to mobility coefficients orders of magnitude lower. This has numerous consequences for the dynamics of polymer adsorption, but also for the interior dynamics of peptides. Specifically, the initial kinetics of protein collapse, which is driven by hydrophobic attraction, should be fast because of the small friction forces involved.

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