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# Substrate specificity of peptide adsorption: A model study

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Applying the contact density chain-growth algorithm to lattice heteropolymers, we identify the conformational transitions of a nongrafted hydrophobic-polar heteropolymer with 103 residues in the vicinity of a polar, a hydrophobic, and a uniformly attractive substrate. Introducing only two system parameters, the numbers of surface contacts and intrinsic hydrophobic contacts, respectively, we obtain surprisingly complex temperature and solvent dependent, substrate-specific pseudophase diagrams.

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From recent experiments of the adsorption of short peptides at semiconductor substrates, it is known that different surface properties (materials such as Si or GaAs, crystal orientation, etc.) as well as different amino acid sequences strongly influence the binding properties of these peptides at the substrate [1,2]. This specificity will be of particular importance for future sensory devices and pattern recognition [3] at the nanometer scale. The reasons for this binding specificity are far from being clear, and it is a big challenge from the experimental and theoretical point of view to understand the basic principles of substrate–peptide cooperativity. This problem can be seen as embedded into a class of similar studies, where the adsorption and docking behavior of polymers is essential, e.g., protein-ligand binding [4], prewetting and layering transitions in polymer solutions as well as dewetting of polymer films [5], molecular pattern, electrophoretic polymer deposition and growth [6].

The experimental equipment has reached such a high resolution allowing for precise identification of single molecule shapes at the substrate, and the available computational capacities combined with sophisticated algorithms will make it possible to examine the problem of a hybrid interface between biological and inorganic materials [7] step by step.

In a first step, we have recently analyzed the adsorption of a finite, nongrafted homopolymer at an attractive substrate in a cavity and discussed in detail the phase diagram in the thermodynamic limit, as well as pseudotransitions that depend strongly on the given number of monomers [8]. Similar studies of grafted polymers are reported in Refs. [9–11]. For heteropolymers the thermodynamic limit is unreachable because of the sequence of different types of monomers. This "disorder-inducing" sequence renders the heteropolymer adsorption a distinguishingly different problem to homopolymer substrate-binding. The pseudophase transitions of the heteropolymer system will strongly depend on three main points: the sequence, the monomer-specific interaction with the substrate, and the total number of monomers in the chain. In this work, we particularly focus on the substrate-specificity. In order to reduce the complexity of the problem to a minimum, we study the hydrophobic-polar (HP) model [12], where the heteropolymer consists of a given sequence of only two types of monomers: hydrophobic (H) and polar (P). We use the simplest form of the model, where only the hydrophobic force acts and the number of nearest-neighbor contacts between H monomers being nonadjacent along the chain, $n_{\mathrm{HH}}$, is related to the energy of the heteropolymer. The interaction with the substrate is modeled in a like manner: The energy of the heteropolymer is reduced by the number of nearest-neighbor contacts between the substrate and those monomers that experience the attractive force of the substrate. For all other monomers the influence of the substrate is only entropic.

In order to study the specificity of surface binding, we investigate three attractive substrate models. In the first variant, all monomers, independent of their hydrophobic or polar character, are equally attracted by the substrate and the energy of the system is proportional to the total number of monomer-surface contacts, $n_s^{\mathrm{H+P}}$. In the second and third model, the substrate is either hydrophobic or polar, i.e., in the first case only the hydrophobic monomers in the heteropolymer sequence are attracted, and in the latter the attraction between substrate and heteropolymer dipoles dominates. In these models, the respective hydrophobic substrate contacts, $n_s^{\mathrm{H}}$, and polar surface contacts, $n_s^{\mathrm{P}}$, are energetically favored. Thus, the models can be expressed in the energetic form

$$E_s(n_s,n_{\mathrm{HH}}) = -\varepsilon_s n_s - \varepsilon_{\mathrm{HH}} n_{\mathrm{HH}}, \tag{1}$$

where, depending on the substrate model, $n_s = n_s^{\mathrm{H+P}}$, $n_s^{\mathrm{H}}$, or $n_s^{\mathrm{P}}$. For our qualitative study, it is sufficient to choose for all three models the same energy scales $\varepsilon_s = 1$ and $\varepsilon_{\mathrm{HH}} = s$, where $s$ denotes the solubility which controls the solvent quality (the larger the value of $s$, the worse the solvent). Since we are interested in the fluctuations of the respective contact numbers with respect to temperature $T$ and solubility $s$, we define the contact density as $g(n_s,n_{\mathrm{HH}}) = \delta_{n_s 0} g^{\mathrm{u}}(n_{\mathrm{HH}}) + (1-\delta_{n_s 0}) g^{\mathrm{b}}(n_s,n_{\mathrm{HH}})$, with the contributions of the densities of conformations without ($g^{\mathrm{u}}$) and with ($g^{\mathrm{b}}$) contact to the substrate. In order to regularize the influence of the unbound conformations and for computational efficiency, the heteropolymer is restricted to reside in a cage, i.e., in addition to the physically interesting attractive surface there is a steric, neutral wall parallel to it in a distance $z_w$. The value of $z_w$ is

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chosen sufficiently large to keep the influence on the unbound heteropolymer small (in this work we used $z_w=200$). Introducing the partition sum $Z_{T,s}=\Sigma_{n_s,n_{\mathrm{HH}}} g(n_s,n_{\mathrm{HH}})\exp(-E_s/k_BT)$ and denoting thermodynamic expectation values of a quantity $O(n_s,n_{\mathrm{HH}})$ by $\langle O\rangle$, the contact correlation matrix $M_{xy}(T,s)=\langle xy\rangle_c=\langle xy\rangle-\langle x\rangle\langle y\rangle$ with $x,y=n_{\mathrm{HH}},n_s$ separates the fluctuations of the surface and hydrophobic contacts according to the respective energy scale vector $(\varepsilon_{\mathrm{HH}},\varepsilon_s)=(s,1)$, and therefore the energetic fluctuations are accounted for in the specific heat, defined by (from now on we set $k_B\equiv 1$)

$$C_V(T,s)=\frac{1}{T^2}(s,1)M(T,s)\begin{pmatrix}s\\1\end{pmatrix}. \tag{2}$$

The heteropolymer sequence we chose in our study possesses 103 monomers (37 being hydrophobic, 66 polar) as introduced in Ref. [13] and often used for benchmark tests of new algorithms [13–16]. The advantage is that this heteropolymer forms a nicely compact hydrophobic core in the low-energy conformations (as depicted for $s=1$ and $n_s=0$, e.g., in Ref. [16]), completely screened from the solvent by a shell of polar monomers.

In order to calculate the contact densities for the three systems, we have applied an enhanced version of the multicanonical chain-growth algorithm [17,18]. In contrast to move-set based METROPOLIS Monte Carlo or conventional chain-growth methods which would require many separate simulations to obtain results for different parameter pairs $(T,s)$ and which frequently suffer from slowing down in the low-temperature sector, our method allows the computation of the *complete* contact density for each system within a *single* simulation run. Since the contact density is independent of temperature and solubility, energetic quantities such as the specific heat can easily be calculated for all values of $T$ and $s$ (nonenergetic quantities require accumulated densities to be measured within the simulation, but this is also no problem).

In Figs. 1(a)–1(c), the contour profiles of the specific heats for the different substrates are shown (the brighter the color the larger the value of $C_V$). We interpret the ridges (for accentuation marked by white and gray lines) as the boundaries of the pseudophases. It should be noted, however, that in such a finite system the exact positions of active regions exhibited by fluctuations of other quantities usually deviate, but the qualitative behavior is similar [16]. The gray lines indicate the main transition lines, while the white lines separate pseudophases that strongly depend on specific properties of the heteropolymer, such as its exact number and sequence of hydrophobic and polar monomers. As a first result, we have found that the binding-unbinding transition appears to be first-order-like. Assuming the contact numbers $n_s$ and $n_{\mathrm{HH}}$ to be kind of order parameters adequately describing the state of the heteropolymer, we define the contact free energy as $F_{T,s}(n_s,n_{\mathrm{HH}})=-T\ln[g(n_s,n_{\mathrm{HH}})\exp(-E_s/T)]$ and the probability for a macrostate with $n_s$ substrate and $n_{\mathrm{HH}}$ hydrophobic contacts as $p_{T,s}(n_s,n_{\mathrm{HH}})=g(n_s,n_{\mathrm{HH}})\exp(-E_s/T)/Z_{T,s}$. Close to the binding-unbinding transition, adsorbed and desorbed states coexist. This is exhibited by two clearly separated minima of the contact free energy $F_{T,s}(n_s,n_{\mathrm{HH}})$. In the figures we have marked the coexistence line, where both minima take the same value, by the dashed black lines. At lower temperatures, the most probable conformation is an adsorbed one, while for higher temperatures desorbed conformations dominate.

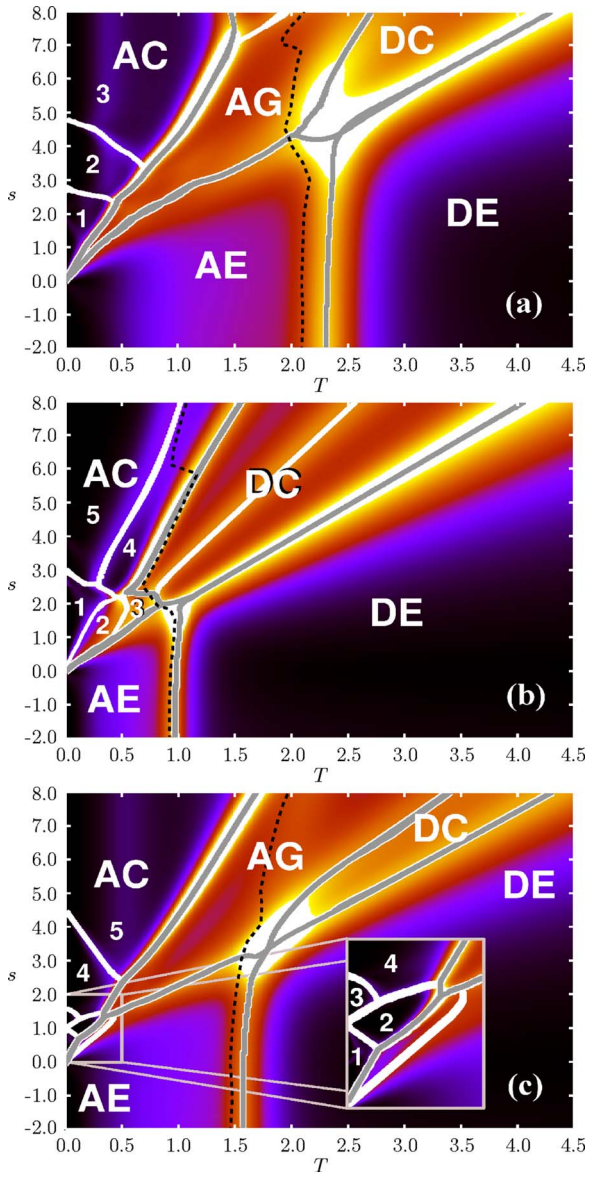


FIG. 1. (Color online) Pseudophase diagrams of the 103mer near three different substrates that are attractive for (a) all, (b) only hydrophobic, and (c) only polar monomers.

Despite the surprisingly rich and complex phase behavior, there are main "phases" that can be distinguished in all three systems. These are separated in Figs. 1(a)–1(c) by gray lines. Comparing the three systems we find that they all possess pseudophases, where adsorbed compact (AC), adsorbed expanded (AE), desorbed compact (DC), and desorbed expanded (DE) conformations dominate, similar to the generic phase diagram of the homopolymer [8–11]. "Compact" here means that the heteropolymer has formed a dense hydrophobic core, while expanded conformations exhibit dissolved,

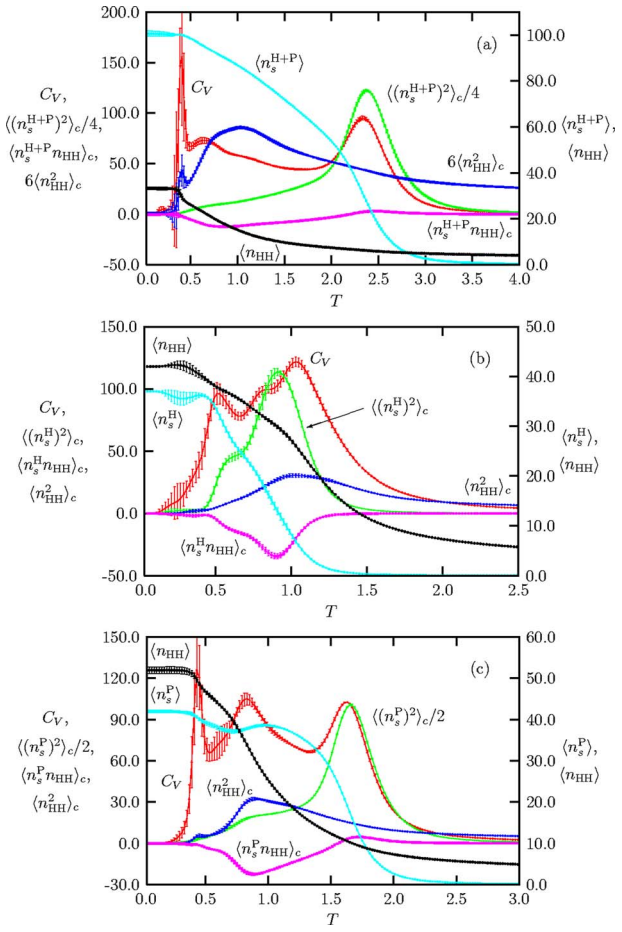


FIG. 2. (Color online) Temperature dependence of specific heat, correlation matrix components, and contact number expectation values of the 103mer for surfaces attractive for (a) all, (b) only hydrophobic, and (c) only polar monomers at $s=2$.

random-coil-like structures. The sequence and substrate specificity of heteropolymers generates, of course, a rich set of new interesting and selective phenomena not available for homopolymers. One example is the pseudophase of adsorbed globules (AG), which is noticeably present only in those systems, where all monomers are equally attractive to the substrate [Fig. 1(a)] and where polar monomers favor contact with the surface [Fig. 1(b)]. In this phase, the conformations are intermediates in the binding-unbinding region. This means that monomers currently desorbed from the substrate have not yet found their position within a compact conformation. Therefore, the hydrophobic core, which is smaller than in the respective adsorbed phase (i.e., at constant solubility $s$), appears as a loose cluster of hydrophobic monomers.

In Figs. 2(a)–2(c), we have plotted, exemplified for $s=2$, the statistical averages of the contact numbers $n_s$ and $n_{\mathrm{HH}}$ as well as their self- and cross-correlations $M$ for the three systems. For comparison we have also included the specific heat, whose peaks correspond to the intersected transition lines of Figs. 1(a)–1(c) at $s=2$. From Figs. 2(a) and 2(c) we read off that the transition from AC to AG near $T\approx 0.4$ is mediated by fluctuations of the intrinsic hydrophobic contacts. The very dense hydrophobic domains in the AC subphases lose their compactness. This transition is absent in the hydrophobic-substrate system [Fig. 2(b)]. The signal seen belongs to a hydrophobic layering AC subphase transition, which influences mainly the number of surface contacts $n_s^{\mathrm{H}}$. The second peak of the specific heats belongs to the transition between adsorbed compact or globular (AC, AG) and expanded (AE) conformations. This behavior is similar in all three systems. Remarkably, it is accompanied by a strong anticorrelation between surface and intrinsic contact numbers, $n_s$ and $n_{\mathrm{HH}}$. Not surprisingly, the hydrophobic contact number $n_{\mathrm{HH}}$ fluctuates stronger than the number of surface contacts, but apparently in a different way. Dense conformations with hydrophobic core (and therefore many hydrophobic contacts) possess a relatively small number of surface contacts. Vice versa, conformations with many surface contacts cannot form compact hydrophobic domains. Finally, the third specific-heat peak marks the binding-unbinding transition, which is, as expected, due to a strong fluctuation of the surface contact number.

The strongest difference between the three systems is their behavior in pseudophase AC, which is roughly parametrized by $s>5\ T$. If hydrophobic and polar monomers are equally attracted by the substrate [Fig. 1(a)], we find three AC subphases in the parameter space plotted. In subphase AC1, filmlike conformations dominate, i.e., all 103 monomers are in contact with the substrate. Due to the good solvent quality in this region, the formation of a hydrophobic core is less attractive than the maximal deposition of all monomers at the surface, the ground state being $(n_s^{\mathrm{H+P}},n_{\mathrm{HH}})_{\min}=(103,32)$. In fact, instead of a single compact hydrophobic core there are nonconnected hydrophobic clusters. At least on the used simple cubic lattice and the chosen sequence, the formation of a single hydrophobic core is necessarily accompanied by an unbinding of certain polar monomers and, in consequence, an extension of the conformation into the third spatial dimension. In fact, this happens when entering AC2 $[(n_s^{\mathrm{H+P}},n_{\mathrm{HH}})_{\min}=(64,47)]$, where a single hydrophobic two-layer domain has formed at the expense of losing surface contacts. In AC3, the heteropolymer has maximized the number of hydrophobic contacts and only local arrangements of monomers on the surface of the very compact structure lead to the still possible maximum number of substrate contacts. $F_{T,s}$ is minimal for $(n_s^{\mathrm{H+P}},n_{\mathrm{HH}})_{\min}=(40,52)$.

The behavior of the heteropolymer adsorbed at a surface that is only attractive to hydrophobic monomers [Fig. 1(b)] is apparently different in the AC phase. Since surface contacts of polar monomers are energetically not favored, the subphase structure is determined by the concurrence of two hydrophobic forces: substrate attraction and formation of intrinsic contacts. In AC1, the number of hydrophobic substrate contacts is maximal for the single hydrophobic layer, $(n_s^{\mathrm{HH}},n_{\mathrm{HH}})_{\min}=(37,42)$. The *single* two-dimensional hydrophobic domain is also maximally compact, at the expense of displacing polar monomers into a second layer. In subphase AC2, intrinsic contacts are entropically broken with minimal free energy for $35\leqslant n_{\mathrm{HH}}\leqslant 40$, while $n_s^{\mathrm{HH}}=37$ remains maximal. Another AC subphase, AC3, exhibits a hydrophobic layering transition at the expense of hydrophobic substrate con-

tacts. Much more interesting is the subphase transition from AC1 to AC5. The number of hydrophobic substrate contacts $n_s^{\mathrm{HH}}$ of the ground-state conformation dramatically decreases (from 37 to 4) and the hydrophobic monomers collapse in a one-step process from the compact two-dimensional domain to the maximally compact three-dimensional hydrophobic core. The conformations are mushroom-like structures grafted at the substrate. AC4 is similar to AC5, with advancing desorption.

Not less exciting is the subphase structure of the heteropolymer interacting with a polar substrate [Fig. 1(c)]. For small values of $s$ and $T$, the behavior of the heteropolymer is dominated by the concurrence between polar monomers contacting the substrate and hydrophobic monomers favoring the formation of a hydrophobic core, which, however, also requires cooperativity of the polar monomers. In AC1, filmlike conformations ($n_s^{\mathrm{P}}=66$, $n_{\mathrm{HH}}=31$) with disconnected hydrophobic clusters dominate. Entering AC2, hydrophobic contacts are energetically favored and a second hydrophobic layer forms at the expense of a reduction of polar substrate contacts $[(n_s^{\mathrm{P}},n_{\mathrm{HH}})_{\mathrm{min}}=(61,37)]$. In AC3, the upper layer is mainly hydrophobic $[(n_s^{\mathrm{P}},n_{\mathrm{HH}})_{\mathrm{min}}=(53,45)]$, while the poor quality of the solvent ($s$ large) and the comparatively strong hydrophobic force let the conformation further collapse [AC4: $(n_s^{\mathrm{P}},n_{\mathrm{HH}})_{\mathrm{min}}=(42,52)$] and the steric cooperativity forces more polar monomers to break the contact to the surface and to form a shell surrounding the hydrophobic core [AC5: $(n_s^{\mathrm{P}},n_{\mathrm{HH}})_{\mathrm{min}}=(33,54)$].

Summarizing, we have performed a detailed analysis of the pseudophase diagrams in the $T$-$s$ plane for a selected heteropolymer with 103 monomers in cavities with an adsorbing substrate being either attractive independently of the monomer type, or selective to hydrophobic or polar monomers, respectively. Beside the expected adsorbed and desorbed phases, we find a rich subphase structure in the adsorbed phases with compact hydrophobic domains, which is specific to heteropolymers. In particular, the formation of layered subphases in the low-temperature region depends mainly on the quality of the solvent.

Here, we have mainly focused on the contact numbers $n_s$ and $n_{\mathrm{HH}}$, but the study of structural quantities, such as the gyration tensor, which exhibits a phase-dependent asymmetry in the components parallel and perpendicular to the substrate, confirms our interpretation of the subphase behavior of the system [19]. Since current experimental equipment is capable to reveal molecular structures at the nanometer scale, it should be possible to investigate the grafted structures dependent on the solvent quality. This is essential for answering the question under what circumstances binding forces are strong enough to refold peptides or proteins. The vision of future biotechnological and medical applications is fascinating as it ranges from protein-specific sensory devices to molecular electronic devices at the nanoscale.

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