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Modeling the dynamic folding and surface-activity of a helical peptide adsorbing to a pendant bubble interface

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ABSTRACT

We have designed a peptide with switchable surface activity, where the folded (α-helical) form of the peptide is amphiphilic and the unfolded form is not. To understand the factors influencing the dynamics of the switchability, a model is developed for the transport of the surface active form of the peptide from the solution onto air–water interface. As is the case with the low molecular weight head–tail surfactants, the transport involves the bulk diffusion of the folded form to the surface and the kinetic adsorption onto the interface. Unlike the head–tail surfactants, the diffusion can be augmented by the kinetics of the folding of the peptide from the unfolded form. The model is formulated within the context of the transport of the peptide from a uniform bulk solution onto an initially clean air–water interface in a pendant bubble system, where the transport rate can be measured by recording the reduction in surface tension using the shape analysis of the bubble. Experiments are undertaken and compared to the predictions of the model simulations of the tension reduction for a range of values of the kinetic adsorption constant and the folding kinetic constant. The results indicate that the kinetic adsorption rate of the folded peptide onto air–water interface dominates the dynamic process, which contrasts many head–tail surfactants where diffusion typically dominates over kinetics adsorption. Moreover, our 'best-fits' suggest that there is a phase transition at high surface concentrations that slows the long-time adsorption of the peptides to the interface. Finally, the numerical solution is compared with an asymptotic solution, showing agreement with our findings that the fundamental dynamics of the tunable surface-active peptide are indeed controlled by the adsorption step.

1. Introduction

Switchable surface activity, the process by which the amphiphilicity of the molecule can be controlled by a external stimuli, can be used in a variety of applications, from separations to drug delivery [1–3]. We apply novel dynamically folding peptides to yield switchable surface activity, where the folded helical state is amphiphilic, but the random coil state is not amphiphilic. The focus of this work is to elucidate the fundamental behavior of amphiphilic helical peptides by modeling the dynamic surface tension measured by the pendant bubble technique, Fig. 1.

Various other groups have achieved switchable surface activity with 'traditional' surfactant architectures. The Abbot group has studied redox-based dynamics to control the hydrophobicity of ferrocenyl surfactant systems [4]. Switching the oxidation state of the ferrocene group in the surfactant actively controls surface activity. These studies have also examined the dynamic surface tension relaxation as a function of redox state using pendant bubble tensiometry. Moreover, a successful model of the dynamic surface tension as a function oxidation state has been developed to quantify the parameters involved in the transfer of this surfactant from the bulk to the air–water interface [5,6]. Another tunable system involving photoresponsive surfactants applies UV light to control the *cis*- and *trans*-conformations of an azobenzene group [7–9]. Cicciarelli et al. have used the pendant bubble technique to measure the dynamic surface tension due to adsorption of the surfactant and modeled this process to study the transport of several molecular variations in the azobenzene system [10,11]. Here, instead of redox reaction or light as a switch, we use the 'reaction' between folded and unfolded peptide to tune the surface activity of the amphiphilic peptide.

The primary structure of a peptide can be designed in such a way that upon folding the hydrophobic and hydrophilic domains become spatially disjoint, leading to amphiphilic behavior. The folding can be induced by an external stimulus. This design is in contrast to the typical mode of protein adsorption, where adsorption of a natural protein is coupled to unfolding and exposure of the hydrophobic core to the interface. Miller et al. review this process for proteins, describing the dynamic and equilibrium adsorption of protein–surfactant systems [12]. In contrast, our adsorbing

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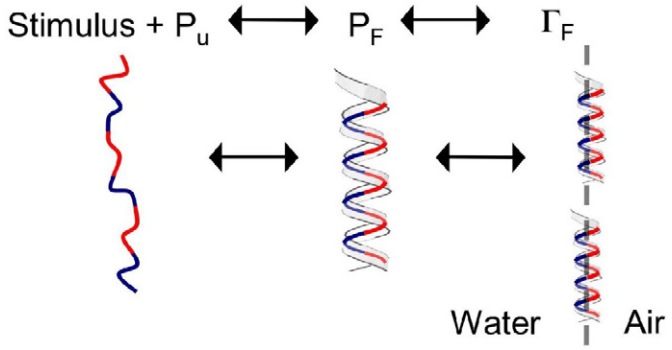

Fig. 1. Schematic diagram for the random coil and helical states of the peptide, where the folded helical state adsorbs onto air–water interface.

peptide system mimics nature's ability to stabilize secondary structure on binding. Many proteins found in nature are natively disordered, but when they bind to the protein's specific target, the disordered structure folds into a more ordered state [13]. From this, we know that folding and binding are often cooperative processes leading to enhanced kinetics of binding to macromolecular targets [14]. Applying these dynamics to peptide design, one can create novel peptide sequences that have dynamic surface activity by folding in response to environmental cues. Such a peptide with tunable surface activity can be designed to bind to a wide range of targets, coupling dynamic surface activity to selective binding.

The transport model described here examines a peptide (HEAKELLKEWAKLLKKLLKEAKE) that is described in Jain et al. [15]. Our peptide design follows from work in DeGrado's lab, where the role of hydrophobic periodicity in the amino acid sequence defines the secondary structure and the amphiphilicity. Their work with leucine–lysine (LK) peptides shows that the correct periodicity can stabilize amphiphilic secondary structure at hydrophobic interfaces [16]. These designs are also analogous to antibacterial [17] and hemagglutinin peptides [18] found in nature. Others have applied periodic sequences to mimic these naturally occurring amphiphilic peptides. Notably, the Szoka group has designed synthetic GALA peptides composed of 30-amino acids (the sequence contains primarily glutamic acids, leucines and alanines). These peptides mimic the activity of viral hemagglutinin, and several papers explore the peptide behavior, including the mechanism of pore formation, rates of membrane permeabilization, the effect of environmental cues such as pH, and the role of sequence [19–24]. Similarly, our model peptide exhibits dynamic surface activity that is coupled to the folding of the peptide into an amphiphilic α-helix.

The aim of this paper is to develop to develop a model for transport of the surface active form of the peptide to an interface to understand the factors controlling the dynamics of switchability. Adsorption of the folded peptide at the air–water interface involves three steps: (1) the folding 'reaction,' (2) the diffusion of the folded peptide from the bulk solution to the sublayer surface, and (3) the adsorption from the sublayer onto the air–water interface. The diffusion and adsorption equation in the model are based on existing models for surfactants, and adding the dynamic folding and unfolding of the peptide. Unknown parameters involved in the modeling are the folding kinetic constant (k_1), adsorption rate constant (β), desorption rate constant (α) and maximum surface packing concentration (Γ_∞). We determine folding/unfolding rates and adsorption constants by measuring the reduction in surface tension as the folded peptide diffuses toward the sublayer and, subsequently, adsorbs onto the fresh air–water interface ($\Gamma = 0$ at time $= 0$). By modeling this folded peptide exchange with diffusion–adsorption equations, surface concentration (Γ) can be predicted as a function of the folding rate and adsorption constants. We derive an equation of state by relating surface tension (γ) to surface concentration (Γ). From this equation of state, our model can predict the dynamic reduction in surface tension. Thus, fundamental aspects of the folding rate and adsorption/desorption rates are elucidated by comparing model behavior with experimental results.

In the following section we describe three components of this work. First, we describe the application of the pendant bubble apparatus to characterize the surface tension of a folding peptide. Second, we describe the modeling of the helical peptide folding, diffusing and adsorbing to an air–water interface. And third, we describe our selection and application of the equation of state, allowing us to compare the experimental results with our transport model.

2. Material and methods

The peptide sequence is synthesized by The Rockefeller University Proteomics Resource Center and stored in the fridge (at $-20\,^\circ$C). The peptide is used without any modification. All aqueous solutions are prepared using clean water from a Milli-Q water purification system. Sodium chloride ($\geqslant$990 ppm and $\leqslant$1010 ppm Na) obtained from Fisher Scientific (NJ) is used for preparing peptide solution in salt. All peptide solutions are prepared freshly for each experiment. All experiments were conducted at $23 \pm 2\,^\circ$C.

2.1. Measurement of the dynamic and equilibrium surface tension

Pendant bubble tensiometry is used to measure the surface tension relaxation and equilibrium tensions. The apparatus used for the measurement is described by Pan et al. [25] and Subramanyam and Maldarelli [26]. Experimental protocol is described in Jain et al. [15]. Briefly, a pendant bubble is created at the tip of the inverted needle in an aqueous solution with a known peptide concentration, and the image of the bubble is captured by a CCD camera and analyzed. Using this technique, the peptide is characterized as a function of its concentration in 1 M NaCl solution. Surface tension relaxation due to adsorption of folded peptide onto the nascent air–water interface is measured. Equilibrium surface tensions for different concentrations of peptide are determined from the long-time asymptotes of the dynamic surface tension profiles. We observe (Fig. 2) that over four orders of magnitude in peptide concentration (0.1 g/l to 10^{-5} g/l) the equilibrium surface tensions remain constant. This supports an assumption that the adsorption of the fully folded helical state is irreversible.

2.2. Model formulation

The following discussion describes our model for the adsorption of the peptide onto the interface. The interface is peptide free initially, i.e. surface concentration $\Gamma = 0$ at time $= 0$. Diffusivity of the folded and unfolded peptide is assumed to be same, and convection in the cuvette is taken to be negligible. The unfolded peptide is initially in equilibrium with the folded peptide.

$$C_r \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_\alpha\,, \tag{1}$$

$$\sigma = \frac{C_{\alpha\infty}}{C_{r\infty}} = \frac{k_1}{k_{-1}}. \tag{2}$$

The dynamic behavior can be described by coupling a diffusion and kinetic model, which characterizes folding as a function of peptide concentration.

$$\frac{\partial C_\alpha}{\partial t} = D_\alpha \frac{\partial^2 C_\alpha}{\partial x^2} + k_1 C_r - k_{-1} C_\alpha, \tag{3}$$

$$\frac{\partial C_r}{\partial t} = D_r \frac{\partial^2 C_r}{\partial x^2} - k_1 C_r + k_{-1} C_\alpha. \tag{4}$$