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I am submitting herewith a thesis written by Camille Marie Kite entitled "Synthesis, Characterization, and Functionalization of 2-Vinyl-4,4-Dimethylazlactone Brushes to Create Bio-Inspired Materials." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

S. Michael Kilbey, Major Professor

We have read this thesis and recommend its acceptance:

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Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

Synthesis, Characterization, and Functionalization of 2-Vinyl-4,4-Dimethylazlactone Brushes to Create Bio-Inspired Materials

A Thesis Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Camille Marie Kite
December 2012

DEDICATION

I dedicate this work to my family; they've gotten me through graduate school. From the beginning of my work, they have kept me laughing and smiling and have helped remind me of the good things in life. I thank my parents, Mark and Diane, for raising me to believe in my capabilities and in the dreams that I could achieve. Their encouragement was immensely important in my studies, and without it, I would be lost. I thank my brother, Conrad, for reminding me not to take myself too seriously and to laugh at myself (continuously). Most of all I thank my husband, Jerry, for humoring me when I got a little crazy, for comforting me when I thought things were too much, for reminding me of who I am when I got lost, and most of all, for loving me.

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I thank Tom Malmgren in the Polymer Characterization Laboratory for his expertise in GPC and AFM, and for his help with troubleshooting when things didn't look right.

I thank my fellow group members, Chaitra Deodhar, Anna Zetterberg, Mike Kochemba, Kamlesh Bornani, Jesse Davis, Zach Seibers, and Xu Wang. I thank them for their input and expertise when I needed help, and I thank them for giving me a place to take my compulsively baked sweets. I thank Chaitra for her help in learning the ropes of the lab, including spin coating, ellipsometry, and, of course, fitting neutron data. I especially thank Anna for her contributions made through her undergraduate research. Her work with creation and modification of PVDMA surfaces was key to my research.

ABSTRACT

Functional materials built from polymer scaffolds inspire many potential uses, including as biomaterial surfaces or sensors. In situ functionalization using well-defined polymer "brushes" made by tethering polymer chains to a surface by one of their ends is explored. Specifically, poly(2-vinyl-4,4-dimethylazlactone) (PVDMA) chains, which contain a reactive azlactone ring at each repeat unit, are tethered to a surface to create brushes and these films are functionalized using a variety of small molecules, primarily amines or peptides. Relationships between polymer brush thickness, size of the functionalizing molecule, solution concentration, reaction time, and extent of functionalization were determined through measurements of brush thickness and PVDMA characterizations. These synthesis-structure-property relationships help inform decisions about how to create functional polymer scaffolds with desired properties.

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CHAPTER I
INTRODUCTION

Research with poly(2-vinyl-4,4,dimethylazlactone) (PVDMA) and its monomer VDMA was pioneered largely by Heilmann and coworkers at 3M, beginning in the late 1970s. It is through their studies of VDMA and PVDMA that we know about the reactivity of thiols, alcohols, and primary amines with the carbonyl group within azlactone rings.[1] The addition of these nucleophiles at the carbonyl causes the azlactone ring to open, creating the corresponding methacrylamido-thiol ester, ester, or amide linkages.[1] A major consideration for choosing PVDMA for reactive modification is the ease of its reaction with primary amines and hydroxyls.[2] The lack of side products in reactive modifications of PVDMA is especially attractive.[3]

Polymer brushes are created when polymer chains that are tethered by one end to a surface. In a good solvent or theta solvent, the chains stretch away from the surface as a result of repulsive intermolecular interactions between chains. Polymer brushes can be grafted from a surface (polymerization is initiated at surface) or grafted to a surface (polymerization is complete before attachment to surface), as seen in Figure 1. Both grafting techniques carry advantages and disadvantages. Grafting from allows for a very high grafting density (small distance between chains) to be achieved, but the molecular weight and polydispersity of the brushes cannot be characterized easily because they are tethered to a surface. To address this, a sacrificial initiator can be added to the polymerization solution, creating free chains in solution.

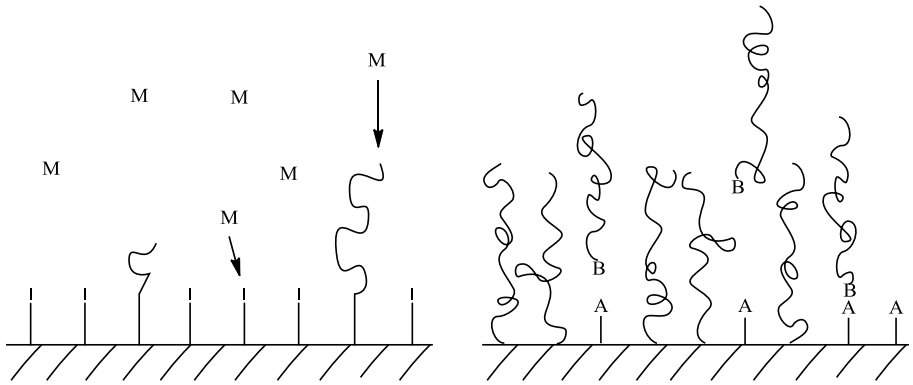

Figure 1. The mechanisms of grafting from (left) and grafting to (right) processes of polymer attachment.

The sacrificial initiator must be chosen carefully in order to ensure that its efficiency is not greater or less than the efficiency of the surface initiator, as this would lead to differences in the molecular weights of free and tethered chains. In the grafting to method, more polymerization methods are available because the polymerization is conducted prior to surface attachment. This allows the molecular weight and polydispersity of the chosen polymer to be measured and known prior to surface attachment. Because the polymerization is complete at the time of grafting, the polymer takes up a large volume when it approaches the surface where it will react, resulting in a steric barrier that excludes subsequent chains from approaching and attaching, thus decreasing the grafting density of the brush system.[4]

Luzinov and coworkers developed a novel method of attaching of polymer brushes to surfaces by reacting end-functional polymers with surface grafted PGMA films.[5] PGMA is

created using conventional free radical polymerization, and after isolation and purification, the PGMA can be grafted to a polished, cleaned silicon substrate by spin coating and annealing.[6] The spin-coated PGMA creates uniform, smooth films consisting of loops and tails, and because not all of the epoxy groups are used when PGMA attaches, residual epoxy groups can be used to attach polymer chains to the PGMA layer, creating brushes. Grafting brushes to a surface has become especially important in recent years, as will be seen later.

Functional polymer brushes with desirable reactive groups located within the brush layer have numerous benefits in the development of "smart" materials and systems.[7] Because of their reactivity, and frequently their steric bulk, functional polymers are difficult to end-graft to a surface. As a result, functional polymer brushes are frequently created by reactive modification of precursor (or protected) polymers using various post-polymerization modification strategies.[7-14] The properties of this modification are not well understood and many questions remain, including the following: (i) Where in the brush layer do the molecules attach? (ii) How is attachment affected by the size of the incoming molecule? (iii) How does the thickness and grafting density of the polymer brush affect the functionalization? and (iv) to what extent is the brush functionalized?

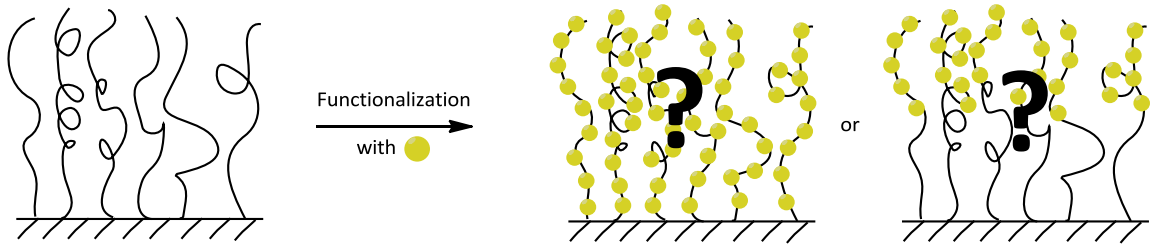

Figure 2. Illustration of uncertainty in extent of functionalization of polymer brushes.

Murata, Prucker, and Rühe offer insight regarding binding of various small molecule primary amines in poly (N-methacryloyl-β-alanine N'-oxysuccinimide ester) (MAC_2AE) brushes formed by surface-initiated polymerization.[12] In their assessment of binding within the brushes, they evaluated the changes in the brush layer using Fourier transform-infrared spectroscopy (FT-IR) and surface plasmon spectroscopy (SPS). FT-IR allows researchers to observe and identify the characteristic bond vibrations between atoms within molecules. When using this method with reactive modification processes, researchers look for changes in the spectrum. SPS allows changes in brush thickness to be determined, and these thickness changes are related to the change in the molecular weight of the brush due to functionalization of the repeat units. Murata and coworkers concluded, based on the disappearance of C=O stretching bands at 1815, 1785, and 1737 cm^{-1} and thickness changes observed via SPS measurements, that the small molecules attached to the brushes. The SPS measurements show that there is a decrease in thickness when the molecules introduced are of lower molecular weight than the N-oxysuccinimide ester leaving group, and an increase in thickness when the

functionalizing molecules introduced are of higher molecular weight than the N-oxysuccinimide ester leaving group.[12] In making these conclusions, two assumptions are made: First, they assume that the grafting density of the brushes does not limit the penetration of small molecules, and second, that all of the N-oxysuccinimide groups are removed and replaced by the small molecule primary amines. I disagree with Murata and coworkers, I believe that the diffusion of the small molecules may be hindered by how close the brushes are in relation to one another, and as a result, the molecules would then be unable to penetrate to the base of the brushes to react with all of the N-oxysuccinimide groups in the brush layer.

In order to address the depth of penetration of small molecules introduced as reactive modifiers, one can use neutron reflectometry (NR) measurements, as shown by Klok *et al*.[10] Neutron scattering is sensitive to scattering length differences between deuterium-labeled molecules. In the research by Klok *et al.*, poly(2-hydroxyethylmethacrylate) (PHEMA) brushes were created by a grafting from process by surface-initiated atom transfer radical polymerization (SI-ATRP). These polymer brushes contained hydrogen atoms, which provided contrast from the deuterated molecules introduced in reactive modification. The hydroxyl groups along the brushes were then activated using *p*-nitrophenyl chloroformate (NPC) and then reactively modified using deuterated amino acids, allowing penetration of small molecules into the PHEMA brushes studied using NR. Klok and coworkers determined whether the NPC activation was complete

throughout the brushes, and whether NPC activation was limited by the grafting density of chains or brush thickness. They also studied the depth of penetration of the deuterated amino acids, including deuterated leucine and deuterated serine, into the activated PHEMA brush layer as a function of both brush thickness and grafting density. It was determined that NPC activation was dependent on both the grafting density and the thickness of the PHEMA brushes.[10] As both grafting density and brush thickness decreased, the extent of the post-polymerization modification increased because NPC activation increased uniformly throughout the PHEMA brush. While this research is extremely relevant to my proposed research, it is important to point out that the findings depend critically on the penetration of the NPC activation. For example, if the amino acids were able to penetrate further into the PHEMA layer than the NPC molecules that are needed for activation, it would be impossible for there to be evidence of this because there would be no reactive "handles" (for attachment of the deuterated amino acids) at those depths in the brushes.

Lokitz, *et al.* used reversible addition-fragmentation chain transfer (RAFT) polymerization to make their PVDMA chains. RAFT polymerization was first reported by Chiefari *et al*. in 1998.[15] Of the major controlled (free) radical polymerization methods, which include atom transfer radical polymerization, nitroxide mediated polymerization, and photoiniferter-based methods, RAFT polymerization is perhaps the most robust because it can be implemented for a wide range of monomers and solvents.[16] This

polymerization method allows researchers to target particular molecular weights and produce polymers having very narrow molecular weight distributions under a variety of conditions.[15,17] Polymers created via RAFT polymerization are especially well-suited for making polymer brushes because of their narrow polydispersities. Polymers having larger polydispersities possess wide variations in chain length, which may lead to variations in grafting density and, eventually affect post-polymerization modification. In RAFT polymerization, free radicals are created and initiate monomers, and then chain growth is controlled by a cycle of reversible addition and fragmentation with either dithioester or trithiocarbonate chain transfer agents (CTAs) mediating the equilibrium between active and dormant species.[18] Different CTAs allow for customization of the terminating functional groups of a polymer chain. As demonstrated by Lokitz *et al*., when PVDMA is synthesized using RAFT polymerization and 2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionoic acid (DMP) is used as CTA, the chains have a carboxylic acid group at one end, as seen in Figure 3.[11] As shown by Lokitz *et al.*, the terminal carboxylic acid end group of the CTA can be used to graft the PVDMA chains to a PGMA film made Luzinov's technique for grafting brushes to a surface.[6,11]

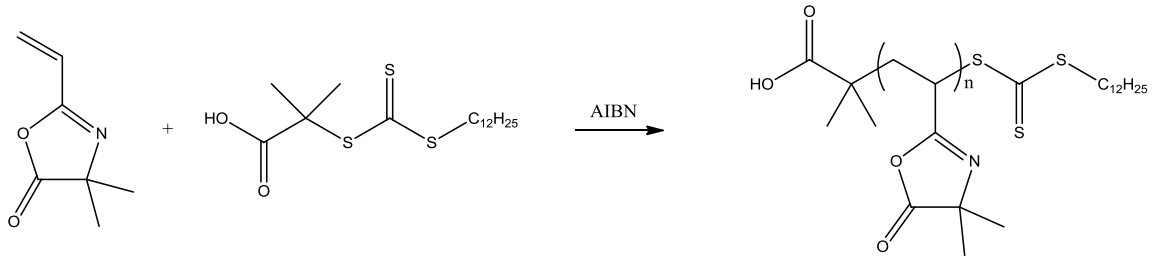

Figure 3. RAFT polymerization of VDMA using DMP with AIBN in benzene at 65 °C.

The modification of PVDMA brushes with primary amines takes advantage of the susceptibility of the azlactone rings to modification by nucleophilic attack of primary amines.[1] In order to make generalizations about the distribution of molecules within polymer brushes, the effect of molecular size on penetration through the PVDMA layer and its role in the extent of functionalization of the brushes is studied. If one knows the thickness of the PVDMA brush layer prior to modification with a primary amine, there should be an appreciable difference in the thickness after modification. This thickness difference is related to the extent of functionalization (the number of groups that have been added through nucleophilic addition to the azlactone ring).

CHAPTER II
FUNCTIONALIZATION AND CHARACTERIZATION OF POLY(2-VINYL-4,4-DIMETHYL AZLACTONE) (PVDMA) BRUSHES WITH PRIMARY AMINES OR GLY-VAL-GLY-VAL-PRO

Introduction

In recent years, interest in functional polymeric materials for use in purification processes, as well as in protein binding and "smart" devices that respond to external chemical or physical cues has grown significantly.[7] Because they can be immobilized on support surfaces, functionalized polymer brushes present a useful way to bind proteins or other molecules. In order to create functionalized polymer brushes, post-polymerization modification is frequently used to overcome issues with high reactivity of monomers and increased steric bulk of brushes.[2,9,19] While a number of approaches used to create functionalized polymer brushes were described in Chapter 1, poly(2-vinyl-4,4-dimethyl azlactone) (PVDMA) is a particularly interesting monomer to begin with because of its ease of polymerization through its vinyl group, its facile reactivity with primary amines and alcohols through its azlactone ring, and the lack of a small molecule leaving group.[1]

Polymer brushes are polymer chains that have been tethered to a surface from one end, which, in a good or theta solvent, stretch away from the surface to alleviate lateral crowding of the chains. Polymer brushes can be grafted from a surface (i.e., polymerization is initiated at the surface) or grafted to a surface (i.e., polymerization is completed before the chains are attached to the surface). The "grafting to" technique is useful in order to ensure uniform characteristics of individual polymer brushes such as molecular weight. By polymerizing monomers prior to surface attachment, there are

more polymerization methods available and the molecular weight and polydispersity of the chosen polymer are known through prior characterizations.[4]

One method of controlled (free) radical polymerization that is especially useful is radical addition-fragmentation chain transfer (RAFT) polymerization. Not only does RAFT polymerization allow polymers having narrow molar mass distributions and target molecular weights to be made, it allows for the end groups to be selected based upon the chain transfer agent (CTA) used.[17] There are a wide array of CTAs to select from, including ones that incorporate carboxylic acid or alkenyl end groups. In the polymerization of VDMA, judicious selection of the CTA 2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionoic acid (DMP) allows chains with carboxylic acid and alkyl end groups to be made.[11] The ability to make end-functional PVDMAs is important because of the attractive properties of the reactive monomer, VDMA, discussed previously. More generally, issues with cross-reactivity and steric constraints of certain functional groups makes it difficult to create particular functionalities, especially in brush form, and this has led many groups to reactively modify polymer brushes.[3,9,10,12,13,19]

Reactive modification of polymer brushes is currently not well understood and it presents many questions to be answered, such as where in the brushes the molecules attach, the percent conversion of the functional groups within the brush, and the size of

molecules that can be added within the brushes as a function of brush thickness and grafting density. Many groups have functionalized polymer brushes,[2,7-14] however little research has been conducted regarding the distribution of small molecules and extent of functionalization in reactively modified brushes.[10,13] In almost all cases where an extent of functionalization has been assessed, only "average" descriptions of how many functional groups has resulted. Using PVDMA brushes and primary, *N*-alkyl amines as a model system, this research begins to address this knowledge gap.

Experimental

Materials

Silicon wafers of size 1 cm x 1.2 cm were purchased from Silicon Quest International. Two-inch diameter, 5000-µm thickness single-side polished silicon wafers for neutron reflectometry studies were purchased from the Institute of Electronic Materials Technology (ITME). Glycidyl methacrylate (GMA, 97%, Aldrich) was distilled under reduced pressure and the middle fraction (~70%) was used. 2-Vinyl-4,4-dimethyl azlactone (VDMA), which was made available through a User project at the Center for Nanophase Materials Sciences at Oak Ridge National Laboratory, was distilled under reduced pressure and the middle fraction (~70%) collected for use. Azobisisobutyronitrile (AIBN, 98%, Aldrich) was recrystallized from methanol and dried under vacuum. 2-Dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionoic acid (DMP) was also provided by the Center for Nanophase Materials Sciences and used as received. Benzene (99.9%, Aldrich), tetrahydrofuran (THF, 99.9%, Aldrich), chloroform (99.8%,

Fisher), n-hexane (95%, Fisher), *N,N*-dimethylformamide (DMF, 99%, Fisher), 1-hexylamine (99%, Aldrich), 1-tetradecylamine (95%, Fisher), 1-octadecylamine (97%, Aldrich), *n*-tetradecyl-d_{29}-amine (98%, C/D/N Isotopes), and the acetate salt- forms of glycine-valine-glycine-valine-proline (GVGVP) pentapeptide (98%, Biomatik) and glycine-valine-glycine (GVG) tripeptide (98%, Biomatik) were used as received.

Instrumentation

PGMA and PVDMA molecular weights were measured using gel permeation chromatography (GPC) on a Tosoh EcoSEC GPC fitted with two Tosoh TSKgel SuperMultiporeHZ-M columns 4µ (4.6 x 150 mm) and a TSKgel SuperMultiporeHZ-M guard column. Measurements were made at 40 °C in THF. Molecular weights were calculated using the EcoSEC Data Analysis package (version 1.04) using poly(methyl methacrylate) standards. Spin coating of silicon wafers was performed using a Headway Research, Inc. spin coater (model PWM32) or a Laurell Technologies spin coater (model WS-650Mz-23NPP) at 2500 rpm for 15 seconds at ambient conditions. Polymer film thicknesses (dry and swollen) were measured using a Beaglehole Instruments phase-modulated Picometer ellipsometer, which uses a 632.8 nm wavelength incident light beam. Measurement of swollen brush thicknesses were performed in a THF-filled cylindrical fluid cell at ambient temperature. Measurements were performed at angles of incidence between 80° and 60° in 1° increments for both dry and solvent-swollen films. A refractive indices of η = 1.50 and 1.46 were used for dried layers of PGMA and

PVDMA, respectively. When fitting dry layer thicknesses, model "slabs" are used to represent PGMA and PVDMA, and thickness is used as a parameter to help guide the fit. Swollen brush thicknesses were determined by fitting the ellipsometric data (at all angles) with both thickness and refractive indices of polymers as parameters used to guide fitting. Preliminary neutron reflectivity measurements were carried out at the Spallation Neutron Source at Oak Ridge National Laboratory on the Liquids Relectometer. Protocols similar to those described by Soto-Cantu *et al.* were followed.[13]

Synthetic Procedures

(i) Wafer cleaning: Silicon wafers were cleaned prior to use in a piranha acid solution (3/1 v/v H_2SO_4/30% H_2O_2) at 80 °C for 45-60 minutes. After cleaning, the wafers were rinsed with deionized water and dried using a stream of nitrogen. Cleaned wafers were used immediately.

(ii) Synthesis of PGMA by conventional free radical polymerization: GMA was combined with AIBN and benzene in a 50 ml round bottom flask and sparged with dry nitrogen for 30 minutes before reacting for 60 minutes at 65 °C while stirring. A typical polymerization uses AIBN and GMA in a ratio of 1:33 and a GMA concentration of 2.3 *M*. PGMA was precipitated into cold hexanes, isolated by decanting, and then dried under vacuum.

(iii) Synthesis of PVDMA by RAFT polymerization: VDMA was combined with DMP, AIBN, and benzene in a 50 ml round bottom flask and sparged with dry nitrogen for 30

minutes. A typical polymerization uses ratios of 1:1078 of AIBN:VDMA and 2:431 of DMP:VDMA. These conditions correspond to [VDMA] = 0.99 *M* and set the theoretical molecular weight to be 30,000 g/mol. The solution containing the monomer, CTA, and initiator was stirred at 65 °C for 18 hours while the polymerization took place. The reaction was quenched by submerging the flask in liquid nitrogen until frozen. After warming to room temperature PVDMA was precipitated into cold hexanes, isolated by decanting, and then dried overnight under vacuum.

(iv) Formation of PGMA-modified silicon surfaces: A solution of 0.25 wt% PGMA in chloroform was used to spin coat clean silicon wafers. After spin coating, the PGMA-modified substrates were annealed under vacuum in an oven preheated to 80 °C for 30 minutes to promote reaction between the epoxy groups of PGMA and hydroxyl groups on the substrate. Wafers were then sonicated for 15 minutes to remove non-covalently bonded PGMA chains. After sonication, the wafers were rinsed with chloroform and dried with a stream of nitrogen.

(v) Formation of PVDMA brushes: A solution of 0.25 wt% carboxylic acid-terminated PVDMA in chloroform was used to spin coat PVDMA onto PGMA-modified silicon wafers. After spin coating, the PVDMA-modified films were annealed under vacuum in an oven preheated to 95 °C to promote reaction between the epoxy groups of PGMA and the carboxylic acid end-group of PVDMA chains. Wafers were then sonicated for 15 minutes to remove non-covalently bonded PVDMA chains, then rinsed with chloroform and dried with a stream of nitrogen.

(vi) Post-polymerization modification of PVDMA brushes with 1-hexylamine, 1-tetradecylamine, or 1-octadecylamine: PVDMA-modified wafers were submerged in amine solutions in chloroform. Amine concentrations of 0.25, 0.50, or 0.75 wt% were employed for 2 or 4 hours to explore the penetration of the amine into the PVDMA brush layer and reaction with the azlactone rings. After reacting, the wafers were sonicated for 15 minutes, rinsed with chloroform, and then dried with a stream of nitrogen.

(vii) Post-polymerization modification of PVDMA brushes with GVGVP or GVG: PVDMA modified wafers were submerged in solutions of 0.25 wt% GVGVP in DMF for 2 hours. After reacting, the wafers were sonicated for 15 minutes, rinsed with DMF, and then dried with a stream of nitrogen. Solutions of 0.25 wt% GVG were attempted; however, a suitable cosolvent for GVG and PVDMA was not identified.

Results and Discussion

Physical Characterization of Functionalized PVDMA-Modified PGMA Surfaces

Tethering polymer chains to a surface using grafting-to polymerization is a desirable method of attaching polymers to a surface because it allows for characterization of the polymer prior to attachment. As will be discussed later, this is important because the molecular weight is needed to determine the grafting density of polymer chains. Grafting density is important because it can affect penetration of molecules into the brush layer.[12] PVDMA brushes were created by tethering chains to a PGMA layer by optimizing a previously demonstrated method, as represented in Figure 4.[11] The

process described generally yielded PGMA films of about 4.5 nm thickness. PGMA films grafted to a surface are attached by opening of the epoxide ring and reaction of surface hydroxyls, but not all of the epoxide rings attach to the surface leaving many epoxide rings available for reaction with PVDMA in a subsequent step.[11]

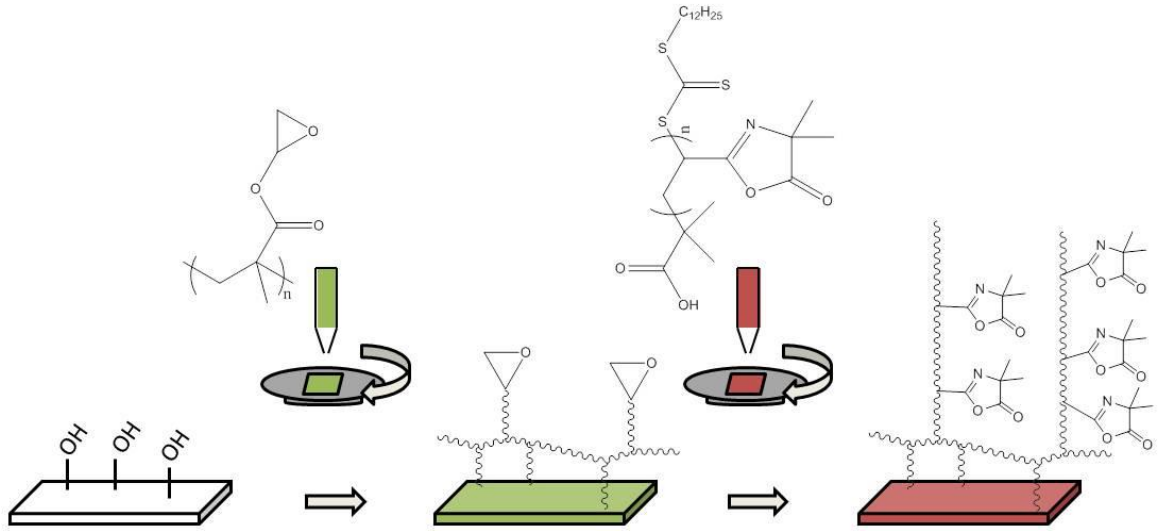

Figure 4. Scheme of PGMA and PVDMA spin coating and creation of PVDMA brushes.

The PGMA thickness did not significantly increase when annealing time increased, nor was it significantly decreased if sonication time was increased. The concentration of PGMA in solutions used for spin coating heavily impacts the thickness of the PGMA layer. PVDMA chains of various molecular weights were used, and these are listed in Table 1. The molecular weights and polydispersities of the PVDMA chains confirm that the polymerization of VDMA is well-controlled.

Table 1. PVDMA Molecular Weights.

PVDMA Target Weight (g/mol)	M_w (g/mol)	M_n (g/mol)	PDI
10k	10,200	9,300	1.10
20k	19,000	17,300	1.09
30k	33,800	29,400	1.15

The PGMA films were then spin coated with PVDMA to create PVDMA brushes. The carboxylic acid end group of the PVDMA chains react with the epoxide rings remaining along the PGMA backbone (because not all of the epoxides react to anchor the PGMA to the silicon substrate[5]) to decorate the PGMA-modified surface with PVDMA, creating PVDMA brushes, as seen in Figure 4. The solutions contained a single molecular weight of PVDMA, allowing for simple calculation of grafting density. The ellipsometric thickness of PVDMA and chain molecular weight are used to calculate grafting density (σ):[5,20]

$$\sigma = \frac{H\rho N_a}{M_n} \tag{1}$$

In this equation, H is the thickness of the dry layer (measured using ellipsometry), ρ is the density of the polymer brush layer (taken to be 1.05 g/cm^3 for PVDMA), N_a is Avogadro's number, and M_n is the number-average molecular weight of the polymer (seen in Table 1). After determining the grafting density of chains, the distance between chains, D, can be calculated using the following equation, which assumes that each chain occupies a circular area on the surface:

$$D = 2(\pi\sigma)^{-1/2} \tag{2}$$

The distance between chains is then compared to the radius of gyration, R_g ($R_g = bN^{3/5}$ for PVDMA b = 0.15 nm, and N = degree of polymerization) to assess the degree of crowding of chains in the brush layer. If $D/2R_g < 1$, then the tethered polymer chains are closer than the size they would adopt in free solution (here, a good solvent is implied because the exponent scaling in the Flory expression for R_g is 3/5), and thus are crowded and in the brush regime. Characteristic values of H, R_g, σ, and D are shown in Table 2. These findings confirm that grafting of the end-functional PVDMA chain results in layers that are in the brush regime. The results also suggest that as the molecular weight of the grafted PVDMA chains increases, the thickness of the brushes increases and the grafting density decreases. This is an expected behavior because as the molecular weight of the chains increases, the volume of the chain increases. An increased chain volume decreases the ability of chains to pack closely, decreasing the grafting density.

Table 2. Summary of PVDMA Brush Thicknesses, Radii of Gyration, Grafting Density, and Distance Between Tethering Points With Varying Molecular Weight.

Sample	M_n (g/mol)	H (nm)	R_g (nm)	σ (chains/nm^2)	D (nm)	$D/2R_g$
AZ.1.035	9,300	3.9	1.9	0.28	2.1	0.58
AZ.1.033	17,300	6.0	2.7	0.20	2.5	0.46
CK.1.079	29,400	6.5	3.7	0.14	3.0	0.41

Summary of Functionalization of PVDMA Brushes with Primary Amines

After characterization of the PVDMA brushes by ellipsometry, 9,300, 17,300, and 29,400 g/mol PVDMA chains were reacted using post-polymerization modification. I began with 30k PVDMA chains. The PVDMA brushes were immersed in solutions of 0.25, 0.50, or 0.75 wt% 1-hexylamine (HA), 1-tetradecylamine (TDA), or 1-octadecylamine (ODA) in chloroform for either 2 or 4 hours, and during this time the azlactone rings can be opened by nucleophilic attack as shown in Figure 5(a). The wafers were then sonicated in chloroform for 15 minutes to remove unreacted amine before ellipsometric measurement. The results of the post-polymerization modification of 30k PVDMA with HA, TDA, ODA, are shown in Table 3. After reaction with primary amines, the brush layers show a marked increase in thickness. When the surfaces are submerged in the amine-containing solution, we theorize that the most accessible azlactone rings at the top of the brushes are functionalized first. As the functionalization of the brush layer progresses, the ring-opened, amine-modified VDMA rings have more steric bulk, which increases the thickness of the brush. This likely changes the packing of the PVDMA chains, and increases intramolecular interactions.

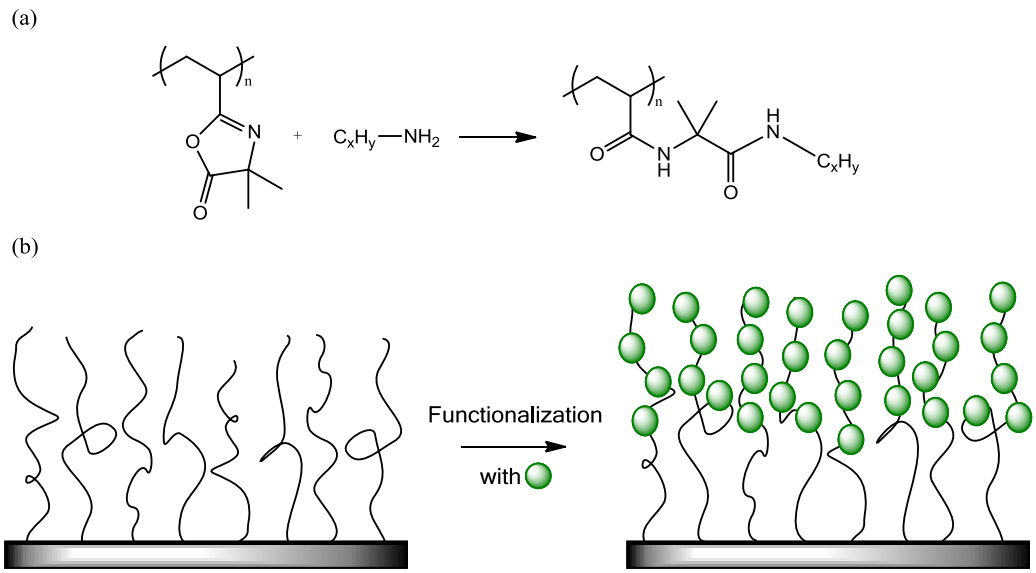

Figure 5. (a) Nucleophilic attack of a primary amine with PVDMA. (b) Drawing of a reactively modified polymer brush, with a thickness increase as a result of post-polymerization modification.

The increased size of the repeating units along the chain may also deter the penetration of functionalizing molecules into the brush layer, thereby decreasing the extent of functionalization, particularly when larger molecules are used to reactively modify the brush. To assess whether the azlactone groups are exhaustively reacted, the extent of functionalization, *f*, which describes the fraction of azlactone rings that are functionalized during the reaction, is determined by the following equation which is adapted from Soto-Cantu *et al.*:[13]

$$f = \frac{[(H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * m_{0_{PVDMA}}) - (H_{PVDMA} * \rho_{PVDMA} * m_{0_{PVDMA\cdot Amine}})]}{[H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * (m_{0_{PVDMA\cdot Amine}} - m_{0_{PVDMA}})]} \quad (3)$$

In this expression, the subscripts on brush thickness *H* denote the "parent" PVDMA brush and the modified PVDMA/amine conjugate, ρ is the density of the polymer, again referring to either the pre-functionalized PVDMA or PVDMA/amine conjugate, and m_0 is

the molar mass of the monomer (139.15 g/mol for PVDMA, 240.44 g/mol for PVDMA+HA, 352.55 g/mol for PVDMA+TDA, and 408.66 for PVDMA+ODA).

The extent of functionalization is calculated based on the dry thickness of the polymer layer as determined by ellipsometry, the bulk density of the unfunctionalized and functionalized polymer, and the molecular weight of the VDMA monomer as well as the molecular weight of the functionalizing agent. Because the molecular weight of the monomer and functionalizing agent are known, this leaves uncertainty in the measurements of brush thickness as well as in the densities of unfunctionalized and functionalized polymers. The dry thickness measurements determined by ellipsometry are expected to be accurate within ±1 nm. A value of ρ = 1.05 g/cm^3 for the density of PVDMA is used, which corresponds to the bulk mass density. However, mass density of a functionalized or unfunctionalized polymer brush may not necessarily be equal to the bulk value because of confinement to the surface, which distorts chain conformation. Also, the value of $\rho_{\text{PVDMA·Amine}}$ is especially complicated when considering modified PVMDA brushes, as the change in monomer mass affects the volume occupied by the reactively modified repeat unit. This expected change in mass density of the reactively modified brushes is not easily characterized because the chains are attached to the PGMA film and, in turn, the silicon surface. Because of the unknown effect of the change, it is assumed that the density of the brushes is not affected meaningfully by

functionalization. This assumption of constant mass density was also invoked by Murata *et al.* and Soto-Cantu *et al*.[12,13]

The results of the post-polymerization modification of 30k g/mol PVDMA brushes with HA, TDA, and ODA suggest that the penetration of the amines is affected by the size of the amine, as is also confirmed by experiments described below. As noted in Table 3, the extent of functionalization of the PVDMA brushes modified with 1-hexylamine appears to be over 100%, suggesting complete functionalization of all azlactone rings within the PVDMA brush layer. This is explained by uncertainties in the values used to calculated *f*, and the correcting calculations are discussed in the Appendix.

Table 3. Summary of Thickness Change and Extent of Functionalization of 1-Hexylamine, 1-Tetradecylamine, or 1-Octadecylamine modified 29,400 g/mol PVDMA Brushes as a Function of Reaction Time and Concentration.

Sample	H_{PVDMA} (nm)	σ (chains/ nm^2)	Functionalizing Agent	Reaction Time (hours)	Amine Solution Concentration (wt%)	$H_{PVDMA/Amine}$ (nm)	Thickness Change (nm)	*f*	*f* Uncertainty
AZ.1.015(a)	6.8	0.15	HA	2	0.25	11.9	5.1	104%	±33%
AZ.1.015(b)	6.1	0.13	HA	2	0.50	11.3	5.2	118%	±33%
AZ.1.027(h)	3.6	0.08	HA	2	0.50	6.7	3.1	120%	±46%
AZ.1.013(b)	6.1	0.13	HA	5	0.25	11.4	5.3	120%	±33%
AZ.1.013(c)	6.5	0.14	HA	5	0.50	12.0	5.5	117%	±32%
AZ.1.013(d)	5.9	0.13	HA	5	0.75	10.8	4.9	115%	±34%
AZ.1.021(a)	6.7	0.14	TDA	2	0.25	15.8	9.1	89%	±11%
AZ.1.021(b)	7.6	0.16	TDA	2	0.50	17.1	9.5	82%	±11%
CK.1.079(a)	6.5	0.14	TDA	4	0.25	10.3	3.8	38%	±18%
CK.1.079(e)	6.4	0.14	TDA	4	0.50	14.0	7.6	78%	±13%
CK.1.079(f)	5.7	0.12	TDA	4	0.50	11.9	6.2	72%	±14%
CK.1.079(b)	6.5	0.14	TDA	4	0.75	13.1	6.6	67%	±14%
AZ.1.017(c)	6.7	0.14	ODA	2	0.75	16.0	9.3	72%	±9%
AZ.1.015(d)	6.8	0.15	ODA	2	0.75	17.0	10.2	78%	±8%
AZ.1.007(c)	5.7	0.12	ODA	5	0.50	14.5	8.8	80%	±9%
AZ.1.011(d)	5.6	0.12	ODA	5	0.50	16.5	10.9	101%	±8%

Additional experiments with PVDMA having smaller molecular weights were completed using 2 hours for the reaction time and a concentration of 0.5 wt% amine (in chloroform) because my prior experiments showed that there were no clear advantages when longer times or higher concentrations were used. Table 4 presents the results of functionalization studies using 17,300 g/mol PVDMA brushes. I propose that the decreased extent of functionalization of the 17,300 g/mol PVDMA brushes is a result of the higher grafting density of these brushes. Because the distance between chains, which is calculated based on the grafting density and listed in Table 2, is smaller in the case of the 17,300 g/mol PVDMA brushes as compared to 29,400 g/mol PVDMA brushes, I hypothesize that the penetration of functionalizing N-alkyl amine molecules is more hindered earlier in the post-polymerization modification.

This trend is also followed for the functionalization of 9,300 g/mol PVDMA brushes, for which results are presented in Table 5. Again, as the grafting density of the brushes increases the extent of functionalization decreases because the shrinking distance between polymer chains makes it more difficult for molecules to penetrate into the brushes and react with the azlactone rings. The entropy of the brushes might also limit reactive modification as a result of stretching the backbone of the chain; as the azlactone rings are reacted the polymer chain is stretched and further reaction becomes thermodynamically unfavored as the entropy decreases.

Table 4. Summary of Thickness Change and Extent of Functionalization of 1-Hexylamine, 1-Tetradecylamine, or 1-Octadecylamine modified 17,300 g/mol PVDMA Brushes.

Sample	H_{PVDMA} (nm)	σ (chains/ nm^2)	Functionalizing Agent	Reaction Time (hours)	Amine Solution Concentration (wt%)	$H_{PVDMA/Amine}$ (nm)	Thickness Change (nm)	*f*	*f* Uncertainty
AZ.1.033(e)	6.0	0.20	HA	2	0.50	9.9	3.9	91%	±38%
AZ.1.033(g)	7.4	0.24	HA	2	0.50	11.2	3.8	72%	±38%
AZ.1.033(h)	7.0	0.23	HA	2	0.50	10.8	3.8	76%	±38%
AZ.1.041(a)	7.0	0.23	HA	2	0.50	10.7	3.7	73%	±39%
AZ.1.033(c)	7.3	0.24	TDA	2	0.50	12.1	4.8	43%	±16%
AZ.1.033(i)	8.0	0.26	TDA	2	0.50	13.1	5.1	42%	±16%
AZ.1.033(j)	7.2	0.24	TDA	2	0.50	13.9	6.6	60%	±14%
AZ.1.037(e)	5.2	0.17	TDA	2	0.50	7.7	2.4	31%	±23%
AZ.1.033(b)	6.3	0.21	ODA	2	0.50	11.0	4.8	39%	±13%
AZ.1.033(d)	6.5	0.22	ODA	2	0.50	15.1	8.6	68%	±9%
AZ.1.033(f)	7.4	0.25	ODA	2	0.50	14.2	6.9	48%	±11%
AZ.1.039(h)	7.8	0.26	ODA	2	0.50	10.2	2.4	16%	±16%

Table 5. Summary of Thickness Change and Extent of Functionalization of 1- Hexylamine, 1-Tetradecylamine, and 1-Octadecylamine Modified 9,300 g/mol PVDMA Brushes.

Sample	H_{PVDMA} (nm)	σ (chains/ nm^2)	Functionalizing Agent	Reaction Time (hours)	Amine Solution Concentration (wt%)	$H_{PVDMA/Amine}$ (nm)	Thickness Change (nm)	*f*	*f Uncertainty*
AZ.1.031(b)	3.7	0.27	HA	2	0.50	5.9	2.2	80%	±55%
AZ.1.035(c)	4.1	0.29	HA	2	0.50	6.0	1.9	65%	±57%
AZ.1.031(e)	4.2	0.30	TDA	2	0.50	8.1	3.9	60%	±19%
AZ.1.031(f)	4.3	0.31	TDA	2	0.50	9.5	5.2	79%	±16%
AZ.1.031(g)	4.8	0.34	ODA	2	0.50	11.2	6.4	69%	±11%
AZ.1.031(j)	4.8	0.34	ODA	2	0.50	9.9	5.1	55%	±13%

The primary amine-functionalization of PVDMA brushes demonstrated several interesting points: there was a definite increase in functionalization as the grafting density of PVDMA chains was increased, an increase in reaction time for functionalization did not lead to significant increases in functionalization of chains, and an increase in amine solution concentrations did not lead to significant increases in functionalization of PVDMA brushes. The extent of functionalization, *f*, also decreased as the size of the functionalizing agent increased. Swelling measurements were also performed on these amine-modified brushes, and those experiments will be described later. The lessons learned with modification of PVDMA brushes with primary alkyl amines were next transferred to experiments involving functionalization of PVDMA brushes with GVGVP pentapeptide.

Attachment of GVGVP to PVDMA-Modified Surfaces

The attachment of peptide sequences is an interesting area of research because it has many potential medical applications, including tailoring protein separation,[7] detecting particular biomarkers, or analyzing complex mixtures. Although biological systems are exceedingly complex, there are a variety of short oligopeptides that provide important functionality, for example, the sequence val-ala-pro-gly (VAPG)[21] promotes smooth muscle cell adhesion, many elastin-like polypeptide sequences target drug delivery to solid tumors,[22] and other elastin-like polypeptide sequences are used in tissue engineering.[23] A sequence of particular interest, gly-val-gly-val-pro (GVGVP), is an elastin-like peptide that promotes liver tissue growth.[23] The study of PVDMA brush

functionalization with primary amines guided the selection of parameters for functionalization with the pentapeptide sequence GVGVP. 0.25 wt% GVGVP/DMF solutions were selected because no clear benefit in terms of extent of functionalization was demonstrated when using higher solution concentrations. Also, the GVGVP peptide is relatively expensive, so it is beneficial to work with lower concentrations. In these studies, a reaction time of 2 hours was used, which is consistent with the functionalization times used to modify the 17,300 g/mol and 9,300 g/mol PVDMA brushes with N-alkyl amines. The results of in-situ functionalization of 29,400 g/mol, 17,300 g/mol, and 9,300 g/mol PVDMA brushes with GVGVP are summarized in Table 6.

The trend of decreased extent of functionalization with increasing grafting density that was established with N-alkyl amine functionalizations is continued with GVGVP-modified surfaces. Also apparent is an overall decrease in the extent of functionalization, presumably as a result of increased steric volume of the functionalizing molecule. Although DMF was chosen because both PVDMA and GVGVP were soluble in it, it is unknown whether the GVGVP-modified, ring-opened PVDMA is also well solubilized by DMF. If the modified PVDMA was less soluble, perhaps due to hydrogen bonding between peptides grafted along the backbone, which are in close proximity due to confinement to the surface, it would further limit penetration and diffusion of GVGVP in the brush.

Table 6. Summary of Thickness Change and Extent of Functionalization of GVGVP-Modified PVDMA Brushes.

Sample	PVDMA Mn (g/mol)	H_{PVDMA} (nm)	GVGVP Solution Concentration (wt%)	$H_{PVDMA/GVGVP}$ (nm)	Thickness Change (nm)	f	f Uncertainty
AZ.1.019(a)	29,400	7.0	0.29	15.0	8.1	32%	±5%
AZ.1.019(b)	29,400	6.0	0.29	10.9	4.9	23%	±7%
AZ.1.025(c)	29,400	7.2	0.25	11.9	4.7	18%	±7%
AZ.1.027(e)	29,400	6.6	0.29	10.8	4.2	18%	±8%
AZ.1.037(a)	17,300	5.6	0.25	7.2	1.6	7%	±11%
AZ.1.037(f)	17,300	5.8	0.25	8.2	2.4	11%	±10%
AZ.1.037(g)	17,300	4.7	0.25	6.8	2.1	12%	±11%
AZ.1.037(i)	17,300	5.7	0.25	7.5	1.8	9%	±11%
AZ.1.035(b)	9,300	3.9	0.29	4.6	0.7	4%	±16%
AZ.1.039(e)	9,300	2.9	0.25	4.0	1.2	11%	±16%

Ellipsometric Swelling Studies of PVDMA Brushes

PVDMA brushes having M_n = 29,400 g/mol were prepared through the spin coating and annealing methods previously described, and measured In the dry and swollen states using multi-angle phase modulated ellipsometry. As before, the brushes were then functionalized with primary amine solutions (in chloroform) or GVGVP solutions (in DMF) for 2 hours. The dry thickness of the modified brush was recorded and then the surface was immersed in THF within an ellipsometric fluid cell. The differences in refractive index of the polymer (η = 1.46) and THF (η = 1.40) create contrast that is discernible using ellipsometry. The results of these studies are shown in Table 7. The swelling factor given is calculated from the ratio of the swollen brush thickness to the dry brush thickness.

Table 7. Ellipsometric Swelling Results of Amine-Modified PVDMA Brushes.

Functionalizing Agent	H_{PVDMA} (nm)	Functionalized H_{PVDMA} (nm)	$H_{Swollen}$ in THF (nm)	$H_{Swollen}$ Change (nm)	f	Swelling Factor ($H_{swollen}/H_{dry}$)
Control	7.4	----	14.1	6.7	----	1.9
HA	6.0	9.9	28.3	18.4	91%	4.7
TDA	6.7	15.8	63.8	48.0	87%	4.0
ODA	5.6	16.5	61.9	45.4	98%	3.8
GVGVP	5.7	14.5	55.3	40.8	44%	3.7

The unmodified PVDMA brushes are characterized by a swollen thickness that is nearly double that of the dry thickness. The swollen thickness changes observed in the modified brushes suggest that their functionalization enhances their swelling either because of increased interchain interactions resulting from bulky side groups attached to the ring-opened PVDMA chains or because the functionalizing agent improves solubility in THF, enhancing the swelling of the chains. The swelling factor decreases as the molecular weight of the functionalizing agent increases, perhaps suggesting that the chain experiences inhibited packing as the repulsion between chains increases due to steric bulk increase.

Neutron Reflectometry Studies with 1-Tetradecylamine-Modified PVDMA Brushes

PVDMA brushes with M_n = 29,400 g/mol were functionalized with 0.25 wt% n-tetradecyl-d_{29}-amine for 4 hours using the procedure described for non-deuterated amines and the sample was then examined using neutron reflectometry. Preliminary fitting of data obtained suggests that a three-layer model with a total thickness of 15.8 nm is appropriate. A three-layer model implies that the n-tetradecyl-d_{29}-amine does not diffuse to the base of the PVDMA brush, creating 3 layers that include a PGMA base layer, an unmodified PVDMA layer, and a PVDMA layer with n-tetradecyl-d_{29}-amine functionalization. As interpreted from the model fit, seen in Figure the thickness of the PGMA base layer is 3.7 nm, the thickness of the unmodified PVDMA layer is 3.4 nm, and the thickness of the n-tetradecyl-d_{29}-amine-modified PVDMA layer is 8.7 nm. These results confirm that the diffusion of molecules within the PVDMA brush layer is limited,

but do not suggest the source of the limitation. Future studies along these lines will be especially important for developing a detailed understanding of the interplay between brush parameters, size of the functionalizing agents, and modification of the brush layer.

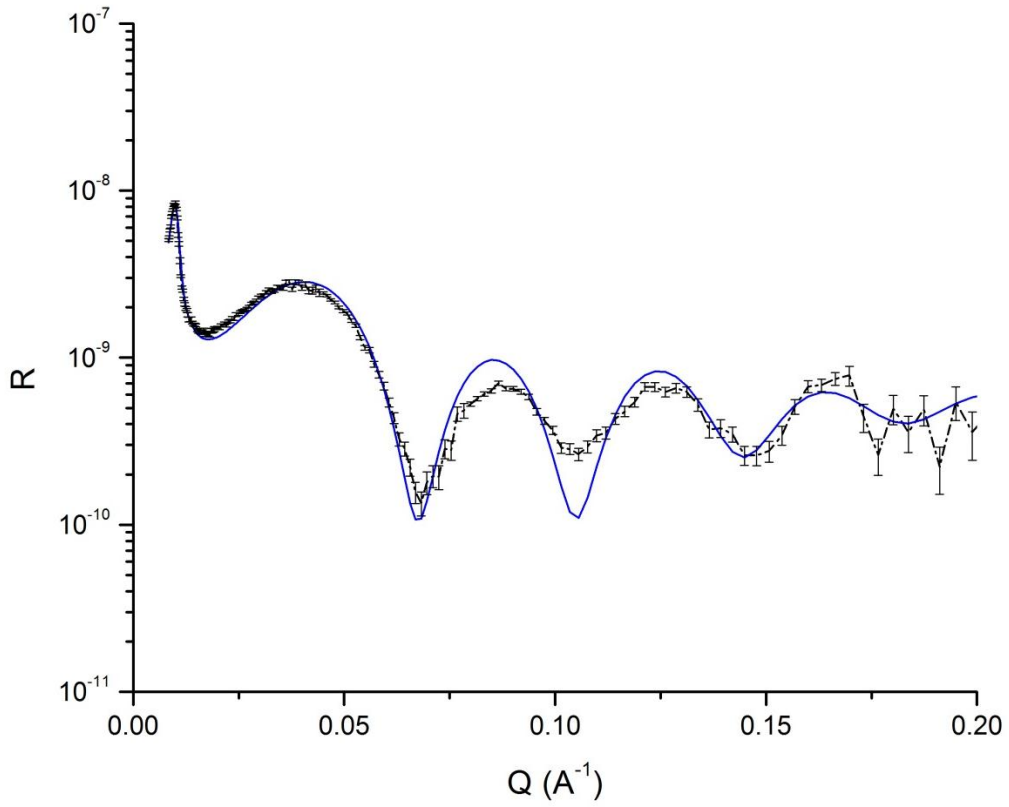

Figure 6. Reflectivity as a function of wave-vector transfer, *Q* for n-tetradecyl-d29-amine-modified PVDMA brushes on a PGMA-modified silicon surface. The data is shown as a dotted black line, and the best fit three layer model is shown as a solid blue line.

Conclusions and Future Work

This body of work describes the effect of functionalization of PVDMA brushes with primary amines and with the pentapeptide GVGVP. In the course of conducting this research a variety of challenges were confronted and solved: namely identifying common solvents between PVDMA and GVGVP, the calculation of uncertainty in *f*, finding a solvent for modified PVDMAs that afforded a significant difference in η for ellipsometric swelling experiments, and the application of neutron reflectometry studies and preliminary fits to gain insight into brush structure and functionalization. Solutions to these challenges enabled new scientific insights to be revealed through the systematic studies described in detail. The unfunctionalized and functionalized thicknesses of the PVDMA brushes were used to determine the extent of functionalization of azlactone rings within the brush layer. These results suggest that as the thickness of the brush increases (and grafting density decreases) the extent of functionalization increases, and that as the size of the functionalizing agent increases the extent of functionalization decreases. The functionalized brushes were also swollen in THF to determine how the behavior of these scaffolds changes after reactive modification. Swelling studies suggest that increasing the size of the functionalizing agent hinders the ability of the chain to swell and the packing of the chain, likely a result of increased repulsion between brushes within the chain.

This work provides footing for follow-up studies, especially *in-vitro* studies regarding the effect of tailoring the chemistry of PVDMA brushes through chemical functionalization on the growth of liver cells. This work has begun through collaboration, using some of the GVGVP-modified brushes produced and characterized in this work. Other interesting avenues to explore might include reactive modification of PVDMA brushes with different peptide sequences. Additional neutron reflectometry studies with deuterated amines or peptides at different PVDMA grafting densities might help answer fundamental questions regarding the extent of functionalization and the distribution of functional groups in brush layers.

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APPENDIX

The uncertainty in the extent of functionalization can be calculated by finding δf.

$$f = \frac{[(H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * m_{0_{PVDMA}}) - (H_{PVDMA} * \rho_{PVDMA} * m_{0_{PVDMA\cdot Amine}})]}{[H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * (m_{0_{PVDMA\cdot Amine}} - m_{0_{PVDMA}})]}$$

$$f = \frac{H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * m_{0_{PVDMA}}}{H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * (m_{0_{PVDMA\cdot Amine}} - m_{0_{PVDMA}})}$$

$$- \frac{H_{PVDMA} * \rho_{PVDMA} * m_{0_{PVDMA\cdot Amine}}}{H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine} * (m_{0_{PVDMA\cdot Amine}} - m_{0_{PVDMA}})}$$

$$\partial f = 0 + \frac{m_{0_{PVDMA}}}{m_{0_{PVDMA\cdot Amine}} - m_{0_{PVDMA}}} * \left[\left(\frac{\rho_{PVDMA}}{H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine}} \partial H_{PVDMA} \right) \right.$$

$$+ \left(\frac{H_{PVDMA}}{H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine}} \partial \rho_{PVDMA} \right)$$

$$+ \left(\frac{H_{PVDMA} * \rho_{PVDMA}}{H_{PVDMA\cdot Amine}{}^{2} * \rho_{PVDMA\cdot Amine}} \partial H_{PVDMA\cdot Amine} \right)$$

$$\left. + \left(\frac{H_{PVDMA} * \rho_{PVDMA}}{H_{PVDMA\cdot Amine} * \rho_{PVDMA\cdot Amine}{}^{2}} \partial \rho_{PVDMA\cdot Amine} \right) \right]$$

The m_0 values are constants assumed to have not uncertainty in measurement. The uncertainty of H values is ±1 nm due to the limitations of ellipsometric measurement. The uncertainty of ρ is assumed to be within ±10% of the ρ value, or ±0.105 g/cm^3.

VITA

Camille Kite is the daughter of Mark and Diane Kite of Stevensville, Michigan. She attended schools in the Lakeshore Public Schools system and graduated from Lakeshore High School in June 2006. She attended Ball State University in Muncie, Indiana, where she planned to study pre-pharmacy. During her coursework and while doing research in the laboratory of Dr. Robert Sammelson, she discovered a love of science, and pursued Chemistry as a major. She graduated in May 2010 with a Bachelor of Science in Chemistry. She received a Graduate Teaching/Research Assistantship to study at the University of Tennessee – Knoxville where she began in August 2010 and joined the research group of Dr. Michael Kilbey, where she studied the functionalization of polymeric materials to create bio-inspired surfaces. Camille graduated from the University of Tennessee – Knoxville in December 2012. She plans to begin a career in industry.