

Polymer Brushes: Routes toward Mechanosensitive Surfaces

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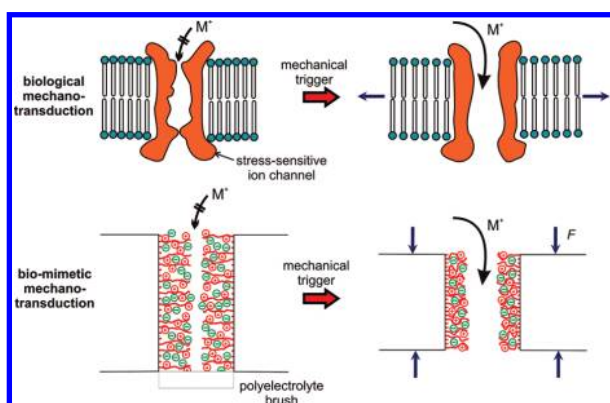
CON SPECTUS

Soft nanotechnology involves both understanding the behavior of soft matter and using these components to build useful nanoscale structures and devices. However, molecular scale properties such as Brownian motion, diffusion, surface forces, and conformational flexibility dominate the chemistry and physics in soft nanotechnology, and therefore the design rules for generating functional structures from soft, self-assembled materials are still developing.

Biological motors illustrate how wet nanoscale machines differ from their macroscopic counterparts. These molecular machines convert chemical energy into mechanical motion through an isothermal process: chemical reactions generate chemical potential and diffusion of ions, leading to conformational changes in proteins and the production of mechanical force. Because the actuation steps form a thermodynamic cycle that is reversible, the application of mechanical forces can also generate a chemical potential. This reverse process of mechanotransduction is the underlying sensing and signaling mechanism for a wide range of physiological phenomena such as hearing, touch, and growth of bone. Many of the biological systems that respond to mechanical stimuli do this via complex stress-activated ion channels or remodeling of the actin cytoskeleton. These biological actuation and mechanosensing processes are rather different from nano- and microelectromechanical systems (NEMS and MEMS) produced via semiconductor fabrication technologies.

In our group, we are working to emulate biological mechanotransduction by systematically developing building blocks based on polymer brushes. In this soft nanotechnology approach to mechanotransduction, the chemical building blocks are polymer chains whose conformational changes and actuation can be investigated at a very basic level in polymer brushes, particularly polyelectrolyte brushes. Because these polymer brushes are easily accessible synthetically with control over parameters such as composition, chain length, and chain density, brushes provide a robust platform to study the coupling of mechanical forces with conformational changes of the chains.

This Account provides an overview of our recent research in the design of mechanosensitive polymer brushes starting with the demonstration of nanoactuators and leading to our first attempts toward the creation of artificial mechanotransduction elements. As the brushes collapse in response to external triggers such as pH and ion concentration, polyelectrolyte brushes provide stimuli-responsive films. These collapse transitions lead to the generation of mechanical forces, and by reversing the chain of events, we designed a mechanically responsive film with a chemical output. Having reported an initial proof-of-principle experiment, we think that the stage is set for the preparation of more elaborate mechanosensitive surfaces.



Introduction

Mechanotransduction, the transformation of a mechanical stimulus into a chemical response, is a vital process in many biological systems. In

humans, mechanosensitive cells provide feedback for many important processes, including hearing and touch sensitivity, urine and blood flow, and fetal development.^{1,2} The mechanisms by which

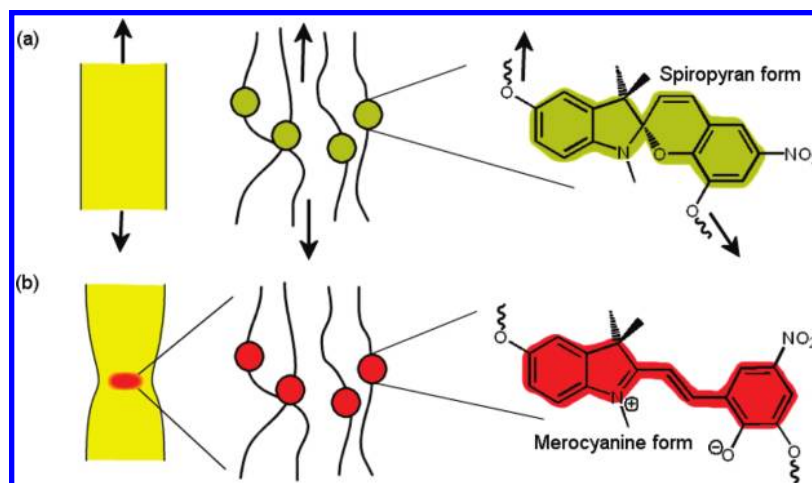


FIGURE 1. Stress-indicating mechanochromic polymer: (a) under stress and (b) after undergoing critical stress, showing the mechanochromic isomerization of the spiropyran mechanophore.¹⁹

living cells transduce mechanical forces into chemical responses are complex and often involve the coupling of individual cells to other cells or to the extracellular matrix³ in order to transfer the force from the bulk tissue to the individual cell.

When cells respond to a generalized deformation, the mechanosensitive component is often a stretch-sensitive ion channel, a protein in the cell membrane that opens into a permeable channel when a force is applied to the membrane.^{4,5} This permits permeation of some chemical species (often ions, especially calcium), which initiates a chemical signaling process within the cell.

The unfolding of proteins under tension has also been implicated in cellular mechanotransduction.^{6,7} Mechanical forces can cause cryptic receptor sites, sequestered in the native folded state, to be revealed; they can alter the distance between receptor sites, resulting in altered binding constants and either preventing or promoting the binding of a particular substrate; they can also alter the shape of the binding site.⁸ Coupling of these mechanoreceptor proteins to the cell's cytoskeleton, to the extracellular matrix, or to neighboring cells allows a macroscopic force to be focused onto specific molecules.

Research in soft nanotechnology has long been aimed at imitating biological processes, including mechanochromic transduction.^{9,10} Nano- and microelectromechanical devices for many applications will need methods of sensing mechanical forces and turning them into specific signals, and nature provides many examples of robust nanoscale mechanotransduction systems.^{1–3} Biomimetic mechanotransduction falls under the general heading of mechanochemistry, which, in its broadest definition, includes any process in which the application of mechanical force leads to the activation of a chem-

ical reaction.¹¹ The focus of this Account, however, is on the narrower area of mechanotransduction, in which a mechanochromic process produces a specific signal such as a change in light absorption or the concentration of a chemical species.

The majority of synthetic mechanosensitive systems are polymer-based, as polymer chains can efficiently transfer the applied force to the mechanosensitive group.¹² One non-polymer-based system was demonstrated by Sheth et al., who showed that piroxicam crystals under mechanical stress exhibit a color shift due to intermolecular proton transfer.¹³

Mechanochromic polymers, that is, polymers that exhibit a color change on the application of mechanical stress, have been investigated due to their possible use in materials applications. For example, materials could be developed that would change color where the stress was greatest, highlighting possible failure locations. The mechanochromism in many of these polymers cannot be strictly defined as mechanochromic but results from physical processes such as order–disorder transitions in semicrystalline polymers^{14,15} or the alteration of intercolloidal distances in polymer/colloid composites.¹⁶ Another physical output is encountered in piezoelectric polymers where mechanical deformation generates an electric field over the material.^{17,18} There are fewer truly mechanochromic polymer systems, although recent work by Davis et al.¹⁹ has demonstrated the transmission of mechanical stress from polymer backbones to mechanoresponsive spiropyran groups embedded within the chains (see Figure 1). The same group showed by modeling and by experiment that force acting on mechanophores embedded in polymer chains can bias reaction pathways, resulting in different products from thermally activated processes,²⁰ a conclusion supported by molecular modeling studies by Ribas-Arino et al.²¹ and Konôpka et al.²²

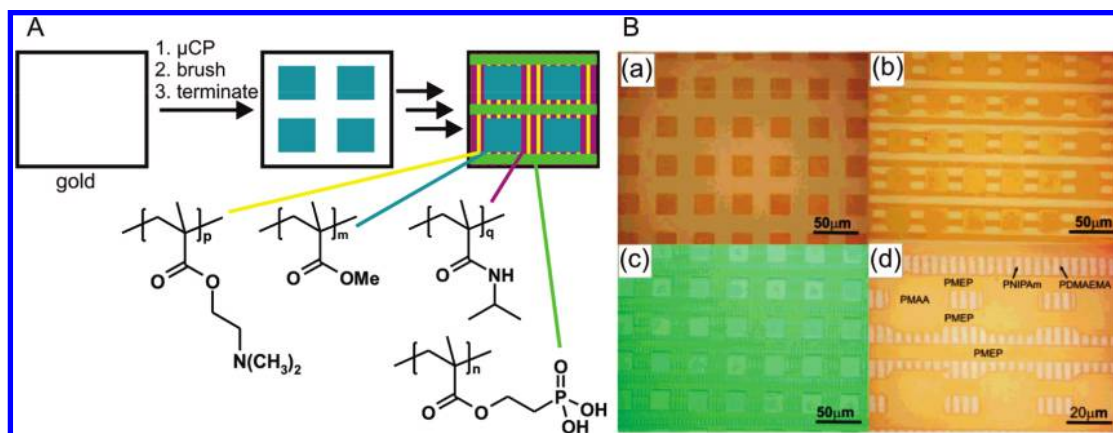


FIGURE 2. (A) Scheme of the preparation of patterned multicomponent polymer brushes. (B) Optical images of patterned polymer brushes: (a) poly(methacrylic acid) (PMAA) squares, (b) after subsequent growth of poly(methacryloyloxyethyl phosphate) (PMEP) lines, (c) after subsequent growth of poly(*N*-isopropylacrylamide) (PNIPAm) lines, and (d) backfilling with poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA).³⁵

Mechanosensitive polymers have also been synthesized that contain coordination centers.^{23,24} These polymers contained catalytically relevant metals such as palladium and silver, and ultrasonication was found to induce mechanochemical ligand dissociation. Polymers with metal complexes are one particular example of chemomechanical polymers that are based on supramolecular chemistry, where coordinative interactions drive the assembly of macromolecular building blocks.²⁵

However, despite these recent advances, little work has been done on closely mimicking cellular mechanotransduction, which occurs on the micro- or nano-, rather than the macro-, scale, which produces pH shifts or molecular signals, and which is localized primarily at the cell surface. Synthetic systems with these characteristics would be useful components in soft nanotechnological devices. In this Account, we will outline a long-term research program to design polymer-based building blocks that can be assembled into mechanotransduction devices that mimic some of these key characteristics found in biological systems.

Choice of Building Blocks: Polymer Brushes

Polymer brushes are attractive building blocks for mechanosensitive systems because their conformation and chemical state are highly sensitive to the environment and their synthesis is very flexible with respect to their molecular design.

Polymers readily respond to changes in solvent quality as determined by temperature,^{26–28} pH,²⁹ salt concentration, and cosolvents by conformational changes resulting from stretching or collapse of random coils. In order to couple these conformational changes with the generation of mechanical forces,

polymers can be attached to a surface, leading to polymer brushes. The attachment can be achieved by inducing a controlled polymerization from a surface-confined initiator layer ("grafting-from").^{30–32} In this way, the thickness, composition, grafting density,^{33,34} and architecture of polymer brushes can be precisely adjusted. Figure 2 demonstrates how microcontact printing of initiator self-assembled monolayers (SAMs) and subsequent surface-initiated polymerization lead to very complex surface coatings by accurately controlling the lateral dimensions and composition of polymer brushes.³⁵ In terms of mechanotransduction, the synthesis also may need to allow for incorporating mechanically sensitive building blocks into the brush, which can be realized by copolymerization with vinyl-functionalized mechanophores or by polymer-analogous reactions.

At sufficiently high grafting densities, the polymer chains in a brush stretch away from the surface due to excluded volume interactions or, in the case of polyelectrolyte brushes, due to the osmotic pressure of the mobile counterions in the brush.^{36,37} We are particularly interested in polyelectrolyte brushes where the magnitude of the conformational changes is greatly amplified compared with neutral polymer brushes. The thicknesses of polyelectrolyte brushes are very sensitive to changes in the salt concentration and to the nature of the salt.^{38–41} The reversible collapse transition in monovalent salt solutions is related to reduced chain stretching as a result of charge screening in the brush. In some cases, (multivalent) ions can show strong ion pairing with the charges on the brushes, leading to "hydrophobic" collapse where dehydration occurs in addition to pure charge screening.^{38,39} Investigations on the conformational changes occurring in polyelectrolyte brushes are straightforward because the brush

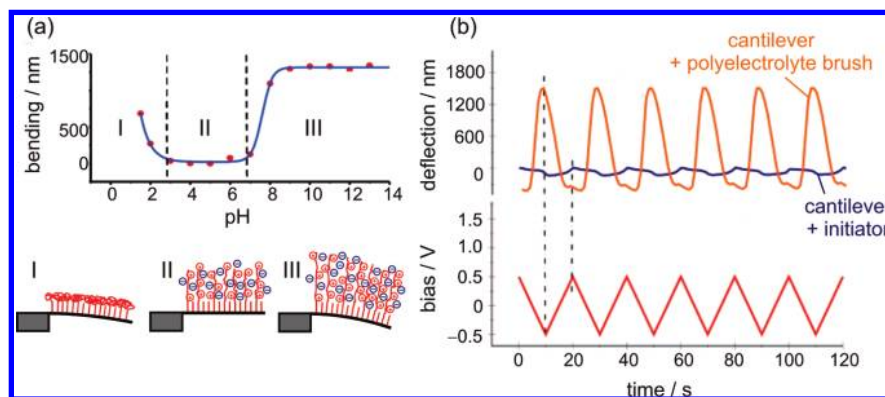


FIGURE 3. (a) Bending of a cantilever coated on one side with a pH-responsive PMEP brush and cartoon depiction of the conformational changes of the brush.⁵⁰ (b) Electroactuation of PMETAC coated cantilevers where bending is driven by an electrical bias.⁵⁴

thickness in different environments can be easily determined.^{38,42,43} Also, the collapse event per se can be visualized by probing the quenching of the fluorescence of dyes bound to the polymer backbone⁴⁴ or by electrochemically detecting the diffusion of ions through the brush.⁴⁵

The crucial step now remaining in the realization of building blocks for mechanotransduction systems is the reversal of the brush collapse cycle: as we will show below, the output of a conformational change in response to a chemical trigger is mechanical work. We need to design a system that yields a chemical output in response to a mechanical disturbance. We think that we can realize such a system based on polyelectrolyte brushes, as we will explore below, after a more detailed description of the generation of mechanical forces using brushes.

Mechanical Forces

The stretching or collapse of the chains in a polymer brush leads to stress in the plane of the film. These surface stresses are readily detected in brushes grown on cantilevers, because they lead to considerable bending of the cantilevers, providing a straightforward route to “soft” nanoactuators.⁴⁶

We and others have demonstrated that polymer brushes attached to one side of a cantilever, can reversibly bend the cantilever due to conformational changes of the brush in response to changes in environmental conditions.^{50–53} Figure 3a shows how conformational changes in a pH-sensitive polymer brush induce cantilever bending. More recently, we demonstrated how electroactuation is achieved by changes in the structure of the brush phase directly near an electrified interface (within a few nanometers).⁵⁴ The relation between cantilever deflection and the applied voltage is shown in Figure 3b. At both negative and positive applied voltages, the total ion concentration near the interface increases, leading to an ion osmotic pressure contribution to the surface stress. In

addition, electrostatic energy results in an expansive stress when the field strength is high near the cantilever, while at negative bias, the polycation brush segments form a dense layer at the surface, which also exerts an expansive osmotic pressure, mainly due to volume constraints. Stoney's equation⁴⁷ provides a quantitative theory of cantilever bending resulting from a stressed active layer. However, it does not specify the origin of the surface stress. In coupling Stoney's theory with a thermodynamic treatment of the active layer, Sushko⁴⁸ has related cantilever bending to the physical and chemical processes occurring within the polymer brush. Also, surface stresses arising from grafted neutral polymer brushes have been treated theoretically using simple scaling arguments based on the Alexander–de Gennes blob model.⁴⁹ It should be noted that although these cantilever experiments provide direct routes to the conversion of chemical energy into mechanical motion, in the majority of experimental studies the response times of the brushes have been rather slow, with a notable recent exception of subsecond response times reported by Parnell and co-workers.⁵⁵

Mechanotransduction in Brushes

For mechanotransduction, the actuation process needs to be inverted: The chemical potential inside the brush must be changed by a mechanical stimulus.⁴⁶ We recently demonstrated such a mechano-chemical system based on strong polyelectrolyte brushes where a compressive force shifted the ionic strength inside the brush.⁵⁶

Normally, when two polyelectrolyte brushes are compressed against each other, a repulsive force emerges between them.^{57–60} Theory⁵⁷ and simulation⁵⁸ of compressed brushes show that the origin of this force can be threefold: The electrostatic repulsion between the monomer units and the osmotic pressure of the counterions increase when the available free volume is reduced by compression,

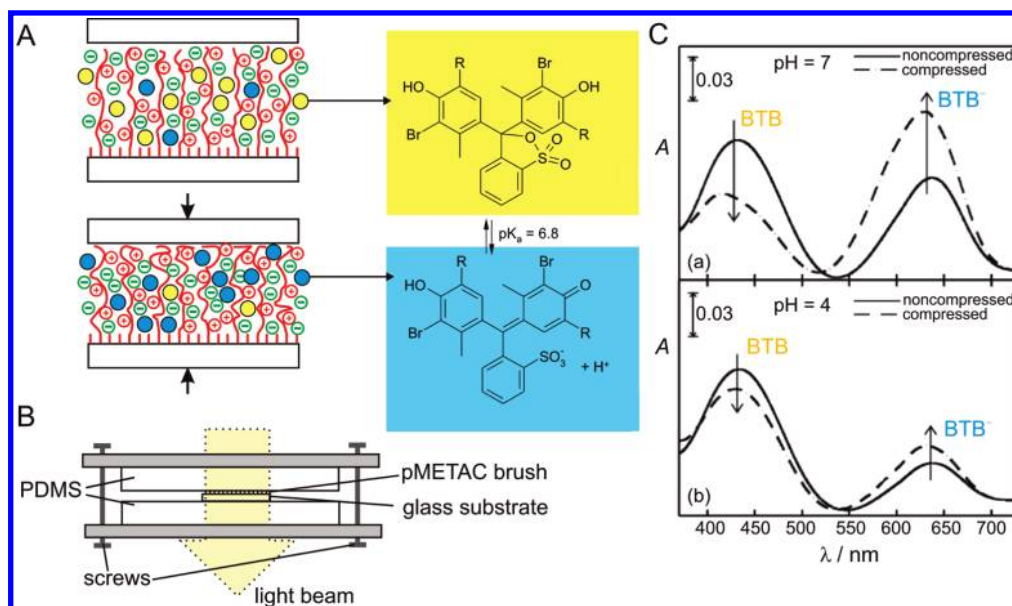


FIGURE 4. (A) Sketch of the impact of compression on the dissociation equilibrium of BTB immobilized in a PMETAC brush. (B) Cell used for compression experiments. (C) UV-vis spectra of BTB immobilized in undeformed (straight lines) and compressed (dashed lines) PMETAC brushes at pH 7 (a) and pH 4 (b).⁵⁶

and excluded volume effects can act between the polymer strands. In case of a weak polyelectrolyte brush, the degree of charging is variable and charge-related repulsive interactions can be balanced by a shift of the polyelectrolyte's dissociation equilibrium toward the neutral state.⁵⁹ Consequently, the deformation of weak polyelectrolyte brushes leads to a shift of the material's pK_a .⁶⁰ Although few studies have focused on the chemical response of weak polyelectrolyte brushes to compression, these systems clearly form useful mechanotransduction elements where one may mechanically trigger the pH inside the brush.

In elegant work, Klein and co-workers demonstrated that *strong* polyelectrolyte brushes in water provide a very efficient lubrication layer as evidenced in surface force measurements.⁶¹ Effectively, the brushes are resistant both to collapse (as this would involve the compression of a highly charged layer) and to entanglement, due to the dense nature of the brushes. Indeed, surface-initiated polymer brushes grown on mica exhibited similar properties: measured normal forces in water showed a long-range repulsion arising from an electrical double layer that extended beyond the polyelectrolyte layers and a stronger, shorter-range repulsion when the polyelectrolyte brushes were in contact.^{62,63}

Our basic premise on how to use strong polyelectrolyte brushes as mechanotransduction elements is based on the realization that resistance to collapse under mechanical pressure and the ready collapse in the presence of salts could be exploited when one designs a system that is highly charged but contains a hidden source of salt that emerges when the

brushes are subjected to mechanical forces, leading to charge screening and collapse of the brushes.

As sketched in Figure 4A, we have reduced this concept to practice by adsorbing a pH-sensitive dye, namely, bromothymol blue (BTB), into polyelectrolyte brushes.⁵⁶ BTB dissociates from a neutral into an anionic form above its pK_a of 6.8. The dissociation is accompanied by a color change from yellow (neutral) to blue (anionic). In our studies, we produced strong cationic poly([2-methacryloyloxy]ethyl)trimethylammonium chloride (PMETAC) brushes on glass substrates. The immobilization of BTB was realized by soaking the brushes in a solution of the dye. Subsequently, the PMETAC brushes were sandwiched between polydimethylsiloxane (PDMS) slides in a modified IR liquid cell, and the assembly was compressed (see Figure 4B). According to Klein and co-workers, pure PMETAC brushes are very resistant to compression. However, in the presence of BTB, the repulsive force arising upon compression could be balanced by dissociation of BTB. The dissociation locally produces ions, which induce charge screening inside the brush. Charge screening compensates for both the increase of the osmotic pressure upon compression and the electrostatic repulsion between approaching segments of the polymer chains. Figure 4C shows how the resulting color change of BTB could be readily detected by UV-vis spectroscopy where under compression, the absorption band of the anionic dye grew at the expense of the absorption band of the neutral form. The change in absorption was irreversible since compression induced strong ion-pairing interactions between the positively charged quaternary

ammonia groups of PMETAC and the anionic BTB. However, the results unambiguously demonstrate the formation of a mechanotransduction element based on strong polyelectrolyte brushes, where a mechanical input was converted into a change of the ionic strength inside the brush.

Electroactive polymer brushes may provide another interesting mechanotransduction system. Instead of actuating brushes by an electrochemical stimulus, one may detect the change of the brushes' electrochemical properties (e.g., the redox potential of attached probes) when a mechanical force is exerted onto it. If the chemical state of the brush (e.g., charge density) is changed by a mechanical trigger, the redox behavior of the attached probe could change, due to altered electrostatic interactions with the brush. Such changes of the brushes' redox properties could be characterized by cyclic voltammetry and electrochemical impedance spectroscopy.⁴⁵

Output

So far, we have demonstrated that polyelectrolyte brushes can act as mechanotransduction elements in a sense that a mechanical force triggers a change of the chemical potential inside the brush. In most mechanosensitive systems, a mechanical input changes the light absorption of the polymeric material, which is interesting for stress sensors and damage-reporting polymers. For instance, when spiropyran moieties were incorporated into elastomers, the material responded to an elongational strain by a color change from yellow to red (see Figure 1).¹⁹ Bruns et al. demonstrated how a protein complex that exhibits fluorescence resonance energy transfer (FRET) can be used to detect cracks in polymers by an increased FRET signal around damaged regions.⁶⁴ Essentially, BTB-modified PMETAC brushes yield an optical output as well. Here, the change of the ionic strength inside the brush upon compression is directly connected to a change of the absorption wavelength of the dye and may be useful to quantify strain distributions along a surface. However, an optical output is a physical response, while mimicking biological mechanotransduction requires a mechanism that couples the change of the chemical potential to a *chemical* reaction cascade. This step, which is the crucial link between a system with mechanoresponsive properties and a real biomimetic device, is missing so far. However, one may envision various routes that allow for connecting mechanically induced signaling in a brush to chemical reactions.

In living cells, one task of mechanosensitive proteins is the control over ion transport through membranes. Recently, Azzaroni and co-workers reported on polymer films with conical nanopores onto which pH-responsive polymer brushes

were grafted.^{65,66} By changing the pH of the bulk liquid, the charge on the pore walls was adjusted, which gave control over the ion transport through the pores. In terms of mechanotransduction, a reversal of the mechanism could be imagined in a way that a force applied to the membrane changes the degree of charging of a mechanoresponsive brush inside the pores. Due to the resulting change of the electrostatic repulsion between penetrating ions and the brush, the ion transport across the membrane could then be controlled by deformation. Simultaneously occurring conformational changes of the brush may even enhance the effect. Clearly, this would lead to an artificial system that closely mimics the functional principle of biological stress-activated ion channels.

An example where a mechanical stimulus induced bond scission was reported by Sheiko, Matyjaszewski, and co-workers who discovered how the adsorption of brush-like macromolecules to a surface can lead to mechanochemical degradation of the polymers.^{67,68} Due to spreading of long side chains on the substrate, a mechanical tension was exerted on the polymer backbone and eventually cleaved carbon–carbon bonds. Generally speaking, the mechanical trigger for breaking these bonds does not necessarily need to involve an adsorption event but may also be applied to highly branched brushes that are grafted to solid supports.

An alternative route for mechanically inducing chemical reactions relies on the stress-activated exposure of catalysts. This concept was introduced by Sijbesma and co-workers who showed how transesterification and olefin metathesis reactions could be triggered by ultrasound.²³ On a molecular level, sonication split a metal complex with polymeric ligands, thus exposing the active center of the catalyst. Tentatively, this approach may apply to all supramolecular systems where the interactions between macromolecular ligands and an active species can be overcome by mechanical stimuli.

Mertz et al. reported on mechanically switching an enzymatic reaction by stretching polyelectrolyte multilayers that contained alkaline phosphatase.⁶⁹ Stretching caused pore formation in the top polyelectrolyte layer and thus exposed the enzyme, which then catalyzed the hydrolysis of fluorescein diphosphate. A similar concept would be to couple deformation-induced conformational changes of a polyelectrolyte brush to the activity of an immobilized catalyst. For this purpose, a catalyst must be deeply buried inside a collapsed brush but become exposed when deformation of the substrate induces swelling, thus starting the chemical conversion of the respective reactant. The embedded catalyst does not necessarily need to be an enzyme but could also consist of platinum nanocrystals. According to a recent study of Schrinner et

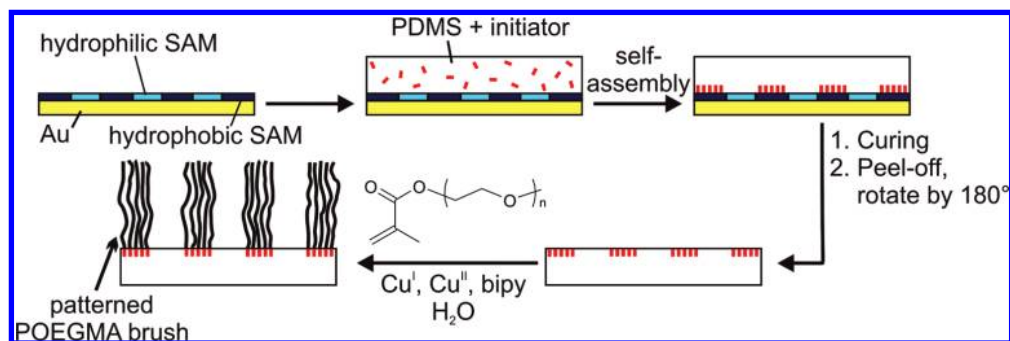


FIGURE 5. Sketch of the preparation of patterned poly(oligo(ethylene glycol) methacrylate) (POEGMA) brushes on PDMS.⁷¹

al., such nanocrystals can be generated inside polyelectrolyte brushes by partial dissolution of a nanoalloy of gold and platinum.⁷⁰ The resulting nanocrystals are strongly retained in the brush and act as very efficient catalysts in the reduction of *p*-nitrophenol to *p*-aminophenol.

Further Work: Flexible Substrates

When we recapitulate possible attempts toward mechanotransduction elements, it appears that compression of a brush on a rigid substrate is not the mechanical trigger of choice. For instance, nanoporous membranes are flexible and deform when a normal compressive force is applied to the brush. Thus, it would be much more attractive to apply the mechanical stimulus to a substrate, which then transfers the signal to the brush. This requires a flexible, deformable support material where stretching, bending, or wrinkling of the substrate can alter the degree of lateral forces in the brushes and the associated degree of ion pairing.

A major challenge has been how to grow brushes on flexible substrates. A first attempt comprised the functionalization of PDMS with an initiator and subsequent growth of polymers from PDMS.⁷¹ As depicted in Figure 5, a small weight percentage of allyl 2-bromo-2-methylpropionate (the initiator) was added to the PDMS mixture prior to curing. This initiator was selectively brought to the surface by curing the PDMS against a master with an octadecanethiol (ODT) SAM on top. Polymerization of oligo(ethylene glycol) methacrylate yielded hydrophilic poly(oligo(ethylene glycol) methacrylate) (POEGMA) on the surface. Unfortunately, the brush growth is less well-controlled than on silica or gold, and although we have been able to grow polyelectrolyte brushes from patterned PDMS substrates, the synthesis needs further optimization.

Alternatively, instead of a stretchable surface, we considered flexible substrates suitable for bending. Following the preparation scheme illustrated in Figure 6A, we recently produced free-standing gold microstructures coated with poly-

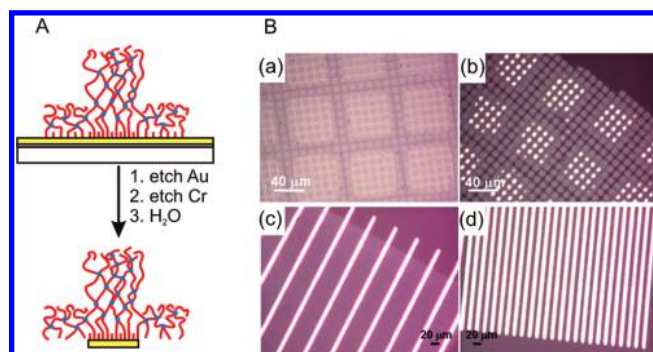


FIGURE 6. (A) Schematic representation of the preparation of free-standing structured poly(glycidyl methacrylate) (PGMA) films by microcontact printing, brush growth, cross-linking, and subsequent chemical etching of gold and chromium. (B) Optical micrographs of free-standing squares (a, b) and strips with squares (c, d) of PGMA after complete etching of the gold substrate.⁷²

mer brushes.^{72,73} By taking advantage of the etch-resistant properties of polymer brushes, we were able to produce free-standing ultrathin polymer films with well-defined overall dimensions, patterned with microscopic Au films. Free-floating films were obtained by etching the Cr adhesion layer, after which the films easily floated onto water. Figure 6B demonstrates how flexible the method is with respect to the geometry of the entities. The mechanical properties of hierarchical films with and without Au were investigated by wrinkling analysis. The angle between the direction of the applied forces and features in the films was very important to the formation and orientation of wrinkles. These gold structures effectively form a free floating cantilever system that bends due to the surface stresses generated by the thin polymer brush layer.

Conclusions and Outlook

The synthetic flexibility of surface-initiated polymer brush growth makes it a versatile platform for functional polymer films. The ability to grow polyelectrolyte brushes provides stimuli-responsive films as the brushes collapse in response to external triggers such as pH and ion concentrations. We have discussed how these collapse transitions lead to the genera-

tion of mechanical forces and how, by reversing the chain of events, a mechanically responsive film with a chemical output can be designed. Although we have reported an initial proof-of-principle experiment, the challenges in the wider experimental realization of such systems are considerable. First of all, a suitable chemical output must be identified (whether this is change in ion mobility through a membrane or switching of catalytic activity within the films) and second, the polymer brush layer must be able to be stimulated mechanically. This can be done by compressing the brushes vertically (which is easy experimentally, but makes the coupling to and measurement of a chemical output more challenging) or by bending, compressing or stretching brushes laterally. The latter requires further breakthroughs in the controlled brush growth from flexible substrates. However, we believe that the major building blocks are now in place and the stage is set for preparation of more elaborate mechanosensitive surfaces.

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FOOTNOTES

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