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Polymer Brush-Modified Microring Resonators for Partition-Enhanced Small Molecule Chemical Detection

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Silicon photonic microring resonators have emerged as a promising technology for the sensitive detection of biological macromolecules, including proteins and nucleic acids. However, not all species of interest are large biologics that can be targeted by highly specific capture agents. For smaller organic chemicals, including many toxic and regulated species, a general approach to improving sensitivity would be desirable. By functionalizing the surface of silicon photonic microring resonators with polymer brushes, small molecules can selectively partition into the surface-confined sensing region of the optical resonators. This in turn leads to response enhancements in excess of 1000% percent, relative to non-functionalized sensors, for representative targets including 4-methylumbelliferyl phosphate, a simulant for highly toxic organophosphates, Bisphenol A, an industrial pollutant, as well as other small organic analytes of interest. There are many polymer brush chemistries compatible with silicon resonators, making this a general strategy towards tuning sensor selectivity and specificity by optimizing interactions between the agent(s) of interest and the polymer construct.

The sensitive, selective, and quantitative real-time measurement of non-chromophoric, non-fluorogenic species remains a challenge for a range of analytical applications, including environmental analysis, and chemical warfare agent detection. For example, the detection of small molecules such as bisphenol A, diethyl phthalate, melamine, triclosan, and organophosphates is crucial for applications ranging from consumer safety to chemical warfare defense. However, these analyses are complicated by the fact that these targets do not contain convenient spectroscopic signatures amenable to simple measures, thus often requiring more sophisticated (and complicated) spectroscopic approaches. Physical property detectors are an attractive solution to these detection problems as they do not rely on analyte chromophoric properties, lending them high versatility but at a cost of reduced specificity and sensitivity. Refractive index-based optical sensors, such as photonic crystals, surface plasmon resonance detectors, microcavity resonators, and interferometric techniques, have shown particular promise for chemical detection, yet suffer from temperature-induced drift, insufficient sensitivity, poor selectivity, and often a low dynamic range, excluding their use in detection of many analytes. Silicon photonic microcavity-based sensors, owing in particular to their high sensitivity and large dynamic range, are therefore attractive for these detection applications. Furthermore, the intrinsic scalability of silicon microfabrication might allow for widely deployed sensor array networks.

Silicon photonic microring sensor array technology has previously been utilized for the surface-sensitive, refractive index-based detection of biomolecular targets, including proteins,[1] miRNA,[2] and DNA.[3] This technology has also been applied to monitor layer-by-layer assembly[4] and chemical reactions occurring at the sensor surface.[5] Unfortunately, when there are no specific binding motif/recognition elements (i.e. antibodies or DNA compliments), detection capabilities significantly decrease, as there is no interaction to localize the analyte within the surface-confined sensing region. Previously microring resonator arrays were modified using surface-initiated atom-transfer radical polymerization (ATRP) to grow polymer brushes directly from the ring surface (Figure 1), and brush

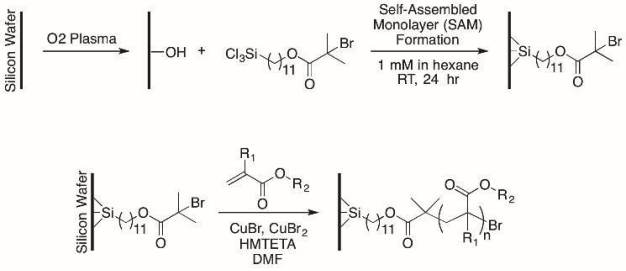

Figure 1. Sensor functionalization process. Bare chips are activated with oxygen plasma followed by chemical grafting of the initiator monolayer. Surface-bound polymer brushes are then grown from the sensor surface by ATRP.

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growth could be tracked in real time directly from the resulting shift in resonance wavelength.[6] ATRP is a living radical polymerization technique which effectively grows relatively monodisperse and structurally controlled polymers.[7] Polymer brushes grown using surface-initiated (SI) ATRP can possess low polydispersity, and there is generally control over composition, grafting density, and chain length.[8]

This led to consideration of using ATRP-based organic modifications to change the sensor surface chemistry in hopes of enhancing the sensitivity and molecular selectivity through non-covalent molecular interactions. Light is confined within the microring waveguide via total internal reflection and the evanescent field that extends from the sensor surface has an exponential decay length (1/e) of 63 nm,[4] putting the majority of the active sensing volume within 100 nm of the ring surface. ATRP-grown polymer brushes are particularly attractive as a general approach to organic surface modification, as they can conveniently be grown to thicknesses of ~100 nm with amenability to a diverse set of functional group chemistries. Notably, thicker polymer layers deposited via drop casting or spin coating would be limited by slow response times and relatively poorer sensitivity. The polymer brushes serve to localize molecular species within the evanescent field of the sensors, significantly increasing the sensor response by 1-2 orders of magnitude for given concentrations of analyte, and providing a pathway towards greater sensor selectivity.

This concept was first investigated using the common pharmaceutical standards caffeine and acetaminophen. Hydrophilic PNIPAM (43 nm dry thickness), and hydrophobic PMMA, (24 nm dry thickness) polymer brushes were grown off the microring resonator arrays using literature SI-ATRP procedures. Brush thicknesses were determined by ellipsometry, using bulk wafers derivatized in the same reaction flask. The resulting modified arrays were then exposed to water-based solutions of each standard using integrated microfluidics as described previously.[9]

Initial observations reveal enhanced response of the analytes on the modified rings compared to bare, unmodified rings, due to localization of the organic molecules within the organic brush on microring surface. In order to just focus on the amount of analyte partitioned into the polymer brush, and not bulk refractive index changes in solution, the response from unmodified sensors was subtracted from the polymer brush-modified microrings, as shown in Figure 2. (Non-subtracted resonance shift data, as well as percentage enhancement compare to unmodified sensors, can be found in Figure S1.) Analyte enhancement is observed within both polymer brushes; however, acetaminophen shows a significantly greater response when interacting with the PNIPAM brush, with a 10-fold larger resonance shift compared to the response of PMMA-modified microrings, and 400% enhancement over unmodified sensors.

The enhancement is almost certainly due to partitioning of the small molecule analyte into the organic layer. While there are many factors which can drive partitioning, the effect of solvent and brush swelling is likely important. PMMA is hydrophobic, and swells only 2% in water,[10] in contrast to the much more hydrophilic PNIPAM brush, which likely extends further into solution, providing a more accessible construct for chemically-selective analyte partitioning.

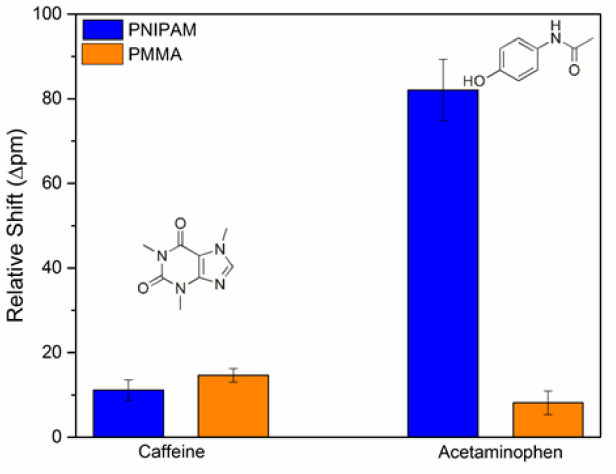

Figure 2. Resonance wavelength shifts measured for PNIPAM- and PMMA-modified microring resonators upon exposure to 10 mM aqueous solutions of caffeine and acetaminophen. The responses from bare microrings (20 pm for caffeine and 27 pm for acetaminophen) was subtracted to remove bulk refractive index effects. Partition-based signal enhancement was observed for both polymer brushes; however, the greatest selective enhancement was observed for acetaminophen interacting with PNIPAM-modified microrings. Error bars represent the standard deviations from four individual microring responses from a single detection experiment. Non-subtracted resonance shifts and percent enhancement values can be found in Figure S1.

Further exploring the role of brush extension and response, the partitioning of bisphenol A (BPA), a toxic industrial chemical, into PNIPAM (230 nm thick) and PMMA (250 nm thick) polymer brushes was probed in both aqueous and 90:10 water:acetonitrile solutions. For both brushes, the response to a 10 mM solution of BPA was increased in the acetonitrile-containing solvent, as shown in Figure 3. Again, the more hydrophilic PNIPAM brush showed a larger response, but the addition of a small amount of organic solvent, which presumably swelled both polymer brushes, led to a substantial increase in observed resonance wavelength shift for both brushes. Interestingly, the relative percent enhancement between PNIPAM and PMMA remained constant (~9-fold larger for PNIPAM) in both solvent systems (see Figure S2).

To further investigate the nature of the resonance wavelength shift, PMMA- and PDMAEMA-modified microrings were exposed to aqueous solutions of methanol, ethanol, and octanol (see SI). These experiments revealed that sensors showed large responses only when the solubilities of the alcohol and polymer brush were well matched, supporting the proposed partition-driven sensing mechanism. PMMA sensors only responded to octanol and hydrophilic PDMAEMA brushes showed large responses when exposed to methanol and ethanol, which are known to be good solvents for the polymer.

These initial experiments indicate the possibility of using polymer brush-modified microring resonators for small molecule, organic compound detection, and the potential to tune

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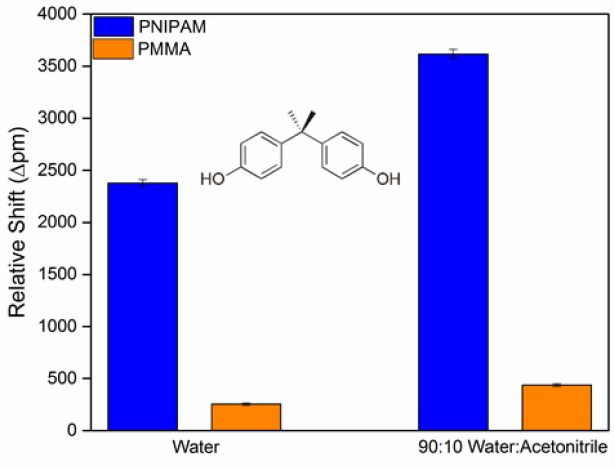

Figure 3. Resonance wavelength shifts measured for PNIPAM- and PMMA-modified microring resonators upon exposure to 10 mM solutions of bisphenol A prepared in both water and a 90:10 water:acetonitrile mixture. The responses from bare microrings (25 pm and 152 pm for water and water:acetonitrile,respectively) was subtracted to remove bulk refractive index effects. Greater overall response was observed for the relatively more hydrophilic PNIPAM brush in both solvent systems, but both brushes showed signal enhancement as the addition of the organic solvent likely increased brush swelling and partitioning of BPA within both polymer brushes. Error bars represent the standard deviations from four individual microring responses from a single detection experiment. Non-subtracted resonance shifts and percent enhancement values can be found in Figure S2.

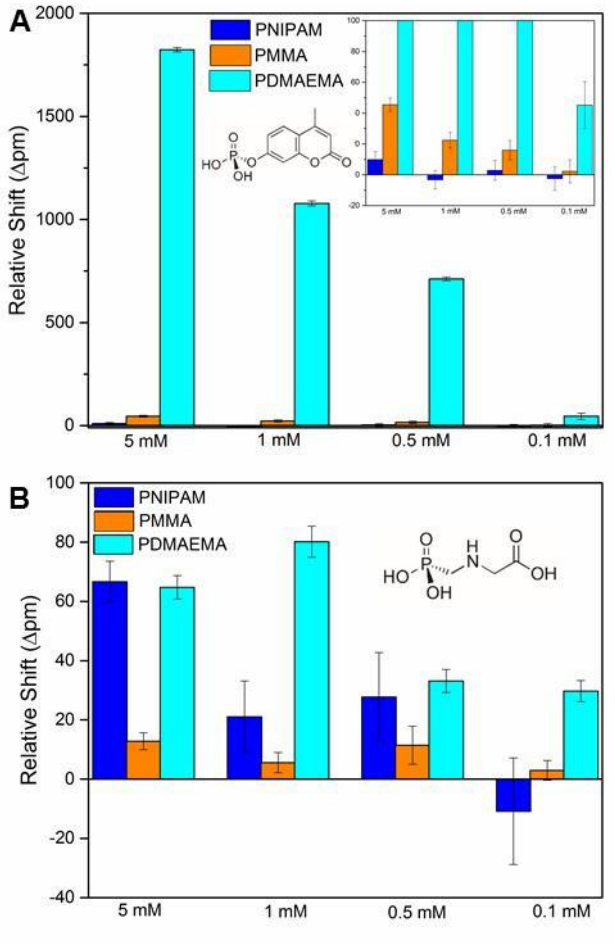

Figure 4. Resonance wavelength shifts measured for PNIPAM-, PMMA-, and PDMAEMA-modified microring resonators upon exposure to various concentrations of aqueous solutions of phosph(on)ate analytes. In all cases, responses from bare microrings were subtracted to remove bulk refractive index effects, and error bars represent the standard deviations from four individual microring responses from a single detection experiment. **A)** Solutions of 4-methylumbelliferyl phosphate showed largest enhancements for PDAEMA brushes, but also significant enahncements for PMMA-modified sensors (see inset). **B)** Glyphoshate solutions elicited enhanced responses from the hydrophilic PDAEMA- and PNIPAM-modified sensors, compared to PMMA. Interestingly, the differential responses between the three different brush modifications suggests that arrays of uniquely brush-modified sensors might be able to provide an analyte-specific response that would have utility in target identification. Non-subtracted resonance shifts and percent enhancement values can be found in Figures S3 and S4, respectively.

analyte sensitivity and selectivity by altering brush:analyte:solvent interactions. One particularly interesting application for which rapid, highly sensitive analyses of non-chromophoric species would be important is the detection of chemical warfare agents and chemically similar pesticides. Nerve-based chemical warfare agents (CWAs) are a particular concern, given that many organophosphate CWAs have IC_{50} values on the order of parts per billion,[11,12] yet lack chromophoric or fluorogenic signatures. This excludes their detection using standard instrumentation such as UV-Vis and fluorescence spectroscopy. More advanced trace analytical techniques, such as mass spectrometric methods, are difficult to deploy into the field, thus limiting real time monitoring, as would be important for detection of CWAs. By contrast, robust silicon microfabrication could allow for wide-scale deployment of microring resonators when appropriately-modified to meet these analytical detection challenges.

As a preliminary test of the applicability of polymer brush-modified microring resonators, the detection of 4-methylumbelliferyl phosphate, a CWA simulant, was investigated. Three different types of polymer brushes were grown on microring resonator array substrates: PNIPAM (43 nm thick), PMMA (24 nm thick), and PDMAEMA (26 nm thick). First, four different concentrations of 4-methylumbelliferyl phosphate were separately flowed across the differentially-modified sensors, with the resonance wavelength shifts (with bare microring response subtracted) shown in Figure 4a. In all cases, a concentration-dependent response is observed, with the PDMAEMA brush showing the largest degree of enhancement—at least 20-fold for greater signals compared to other brush chemistries, and 5000+% response enhancement compared to non-functionalized sensors (see Figure S3).

We also investigated the detection of glyphosate, and found that enhanced responses are also observed for this herbicide (Figure 4b). Notably, the overall resonance wavelength shifts are much smaller for this analyte, as the refractive index of glyphosphate is lower than the aromatic 4-methylumbelliferyl phosphate analyte; however, the effects of bulk refractive index change have been corrected by again subtracting the bare resonator signal. This reinforces the observation

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that molecular partitioning plays a substantial role in dictating sensor response as higher refractive index analytes partitioned within polymer brush-modified microrings show enhanced sensor response.

Importantly, the differential signal measured by the different brush-modified microrings suggests the potential for array-based target identification. Specifically, arrays of differentially-functionalized microrings could potentially, in a single detection experiment, provide both quantitative concentration determination, as well as a target-specific signature that would facilitate agent identification. This could be analogous to the highly successful optoelectronic "nose" arrays, which respond to the subtly different chemical reactivities of volatile organic compounds.[13] The origin of specific intermolecular forces that lead to this differential response are beyond the scope of this manuscript; however, we speculate that a combination of brush and analyte solubilities in the solvent system play an important role in sensor response that could be optimized for particular target agents of interest.

In conclusion, polymerbrush-modified silicon photonic microring resonators were found to exhibit differential chemical interactions with small molecule analytes, enhancing the sensor response in excess of 1000% for some brush-analyte combination, compared to unmodified sensors. Presumably, this enhancement is due to intermolecular interactions that could be optimized to be highly specific and sensitive for particular classes of target analytes. At this early stage, the results are encouraging as the brushes and small molecules selected represent several different, generally-relevant classes of analytes. Future work will focus on optimizing polymeric constructs for specific analytical targets and applications. For example, one could presumably select a polymer brush, such as poly(methacryoyloxyethyl trimethylammonium fluoride) (poly-METAF) that would have optimized partitioning or even specific reactions with a CWA such as malathion. These types of highly specific interactions would lead to even lower LODs, making this chip-integrated measurement approach useful in detecting low-abundant analytes such as CWAs.

Supporting Information Summary

The supporting information contains both uncorrected resonance shift data and percent enhancements for Figures 2-4, as well as a detailed description of alcohol paritioning experiments. Real-time resonance shift data, a detailed explanation of the microring resonator technology, and a full experimental section are also provided.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: chemical sensor · optical detection · microcavity resonator · polymer brush · sensor array

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