CHEMICAL REVIEWS

Review

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Molecularly Imprinted Polymers

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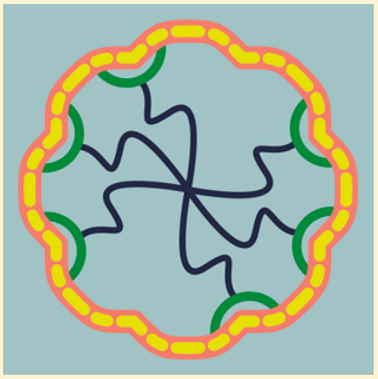
ABSTRACT: Molecularly imprinted polymers are synthetic receptors for a targeted molecule. As such, they are analogues of the natural antibody–antigen systems. In this review, after a recounting of the early history of the general field, we specifically focus on the application of these polymers as sensors. In these applications, the polymers are paired with a reporting system, which may be electrical, electrochemical, optical, or gravimetric. The presence of the targeted molecule effects a change in the reporting agent, and a calibrated quantity of the target is recorded. In this review, we describe the imprinted polymer production processes, the techniques used for reporting, and the applications of the reported sensors. A brief survey of recent applications to gas-phase sensing is included, but the focus is primarily on the development of sensors for targets in solution. Included among the applications are those designed to detect toxic chemicals, toxins in foods, drugs, explosives, and pathogens. The application of computational chemistry to the development of new imprinted polymers is included as is a brief assessment of future developments.



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1. INTRODUCTION TO MIPS

1.1. General Concepts of MIP Sensing

Sensing the ambient environment has become ubiquitous in the modern world. Molecular recognition, perhaps the ultimate form of sensing, is fundamental to biological processes and is currently the focus of much chemical research due to its importance in processes such as catalysis, separations, and sensing. While natural systems can produce antibodies against a range of foreign bodies, the use of such receptors in chemical processes faces a number of impediments, such as cost and sensitivity to environmental conditions. A goal of modern sensor research is the creation of synthetic receptors that mimic the natural antibody–antigen behavior with similar specificity and sensitivity. This molecular recognition, in combination with modern techniques to monitor changes in the recognition elements, offers the promise of selective, sensitive sensors capable of detecting and monitoring targets in a noninvasive manner. This type of sensor is the ultimate focus of this review.

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Figure 1. General process of imprinting. The template interacts with monomers or polymers to form a cavity around the template molecule, and the template is subsequently removed, leaving behind the empty molecularly imprinted cavity for rebinding the target molecule. Reprinted from ref 2. Copyright 2017 American Chemical Society.

Molecularly imprinted polymers, MIPs, are best described as synthetic analogues to the natural, biological antibody−antigen systems. As such, they operate by a "lock and key" mechanism to selectively bind the molecule with which they were templated during production. MIPs potentially offer the specificity and selectivity of the biological receptors with the explicit advantages of durability with respect to environmental conditions and low cost. For example, natural receptors typically require storage and application at temperatures in the range of the human body temperature, while MIPs, based on a polymer host, can usually be stored indefinitely, as a rule do not require special environmental storage conditions, and can be applied over a much wider temperature range. There are multiple production methods[2−5] that will be detailed in a later section of this review, but all of the methods follow the same basic outline: (1) a polymer is produced containing the template or target molecule bound, covalently or noncovalently, to a functional group of the host, (2) the template molecule is removed from the polymer host, leaving a target-specific cavity available for rebinding, and (3) the MIP is exposed to the target-containing sample, and the cavity selectively uptakes the target molecule from a complex sample. The general process is shown schematically in Figure 1.[2] An additional advantage of the synthetic receptors is near-universality, especially with regard to small molecules. MIPs can be produced for almost any target molecule, which contrasts with the biological systems where the target must match an available antibody or an antibody must be specifically produced for that target. Moreover, antibodies are more easily produced for macromolecules rather than smaller, molecular targets. Cost is sometimes an additional factor; MIPs are generally inexpensive in comparison to natural antibody costs. Coupling the MIPs to a sensing "reporter" system provides a device useful for monitoring the environment or screening for abnormalities.

For this review, the standard definition of sensor as contained in the Oxford dictionaries is adopted: "A device which detects or measures a physical property and records, indicates, or otherwise responds to it". For a chemical sensor, the "physical property" is the presence of the target molecule. Important parameters in the application of MIPs in sensors include the imprinting factor (IF), binding capacity (BC), and response time (RT). IF is defined as the ratio of binding of the template in the imprinted polymer to its binding in the nonimprinted polymer (NIP), the control. The binding capacity is calculated as the ratio of the concentration of target molecule adsorbed from the test solution divided by the initial concentration of that solution (multiplied by 100%). The definition of response time is somewhat ambiguous, since it is differently defined by different researchers. The standard description of response is the time required to reach 63.2% of the final signal starting from the time the stimulus is applied. These three definitions are those that are used in the text.

This review is focused on the literature spanning the years from 2013 through late 2017. Much MIP research is directed to separations, the production of a specific chromatography material, for example. While these reports are presented when appropriate, the review focuses on MIPs that are integral parts of sensors, rather than ancillary devices to a standard analytical method. MIP sensors have been developed for gases and liquids. The review will describe some of the gaseous sensing devices but will primarily focus on samples that are in solution.

1.2. Early MIP History

A search of *Chemical Abstracts* indicates the first paper that specifically reported an "imprinted polymer" appeared in 1984 and was written by K. Mosbach and B. Sellergren in Lund.[6] The first paper written by G. Wulff in which the term imprinted polymer was used appeared in 1985,[7] although Wulff had been publishing papers in a series entitled "Enzyme-Analog Built Polymers" since 1973.[8] These early researchers developed different aspects of the science. The Mosbach group focused on the use of noncovalent interactions between the host and target, while Wulff tended to use covalent binding to create the imprint. The difference between the two methods is most obvious in the chemistry needed to remove the templating molecules from the MIP. Importantly, the covalent synthesis is expected to produce a more homogeneous set of rebinding cavities and, potentially, more target-specific MIPs. Mosbach[9−12] and Sellergren described developing separation and sensing materials, Wulff[13−17] extensively employed imprinted polymers in catalytic reactions as is clear from the title of his early series of papers, and K. Shea,[18−21] beginning in 1993, working in a similar vein, reported on rather unique biological applications, such as a plastic antibody inserted into living mice. The first use of the term "molecularly imprinted polymer sensor" appears to have been reported by S. Piletsky, in 1992, although papers describing the production of MIPs, in general, from this author appear in the Russian literature as far back as 1989. Research from these groups spans the time period from the late 1990s into recent years and has led to research focused on various applications of this technology.

1.2.1. Commercialization. Commercialization of MIPs has been a slow process. Most commercial applications involve materials for separation rather than sensors. Perhaps the greatest detriment to the development of MIP-based materials for sensors, or for that matter chromatographic purposes, is the occurrence of nonspecific binding to the templated material. This occurs because the polymer itself is an adsorbent and some, even weak, interaction with the target molecule is unavoidable. Additionally, nonhomogeneous binding sites result in a range of rebinding constants complicating the intended use of the polymers. The application of MIPs as sensors is also made more difficult by the need to extract the

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target molecule from the as-produced polymer. In some sensing applications, the presence of any unextracted target interferes with the ability to sense the rebinding. Given the significant number of MIP sensing reports in the chemical literature, it is reasonable to speculate that commercial applications of MIPs to sensors will appear in the near term.

Several companies were formed by early proponents of the use of MIPs in separation science and have achieved some success. MIP Technologies was formed in Sweden with Sellergren and Mosbach as the principals. It was later acquired by Biotage AB, a purification/separations firm. MIP Diagnostics was founded by Piletsky. K. Haupt, who has published extensively in the MIP field, started Polyintell SAS in France. Finally, Semorex, Ltd. in Israel includes B. Green among its founders, and G. Wulff is a prominent member of its Board. Perhaps the most visible commercial application of MIPs is that Sigma-Aldrich offers a series of MIP-based extraction materials under the SupelMIP line of solid-phase extraction, SPE, columns.

The focus, here, on the use of MIPs as the active elements in chemical sensors as reported in the literature over the past 5 years owes much to the pioneering work of these research groups.

1.3. Production Methods

There are several methods for the preparation of MIPs, resulting in different guest−host polymer properties. These methods include (1) synthesis from monomers in the presence of the template, (2) phase inversion using polymer precipitation by addition of an incompatible solvent or by evaporation of the solvent from a networked solution of polymer plus template, and (3) soft lithography or surface stamping. Table 1 presents several examples of each approach

Table 1. Some Recent Examples of the Various MIP Production Techniques

production method	target molecule
phase inversion	maltose[22]
	kaempferol[23]
	PCBs[24]
	methylene blue/orange[25]
synthesis	folic acid, methotrexate[26]
	cinnamic acid[27]
	salicylic acid[28]
	dibutyl phthalate[29]
soft lithography	dansyl-L-phenylalanine[30]
	caffeine[31]
	theophylline[32]
	2,4-D[33]

to the production of molecularly imprinted polymers. The list is obviously not exhaustive and is merely intended to serve as an introduction to the possible avenues of MIP production. Additional examples are discussed in the text.

1.3.1. Synthesis. Synthesis is the most general production method and involves allowing a functional monomer to interact in solution with the target molecule to develop a network of covalently or noncovalently interacting complexes. The functional monomer provides, for example, hydrogen-bonding functionality or a reactive substituent that will form a covalent bond to the template. Some common functional monomers are acrylamide, methyl methacrylate (MMA), methacrylic acid (MAA), aniline, and pyrrole. After sufficient mixing, a cross-linking agent such as ethylene glycol dimethacrylate (EGDMA) and a polymerization initiator, typically azobis(isobutyronitrile) (AIBN), is added, heating or ultraviolet radiation driven polymerization is initiated, and the reaction proceeds to completion, producing powdered material suitable for separations. Alternatively, to produce films rather than powders, the reaction mixture may be coated onto any number of substrates and polymerization started in place using photoinitiation. Figure 2 shows a typical synthetic

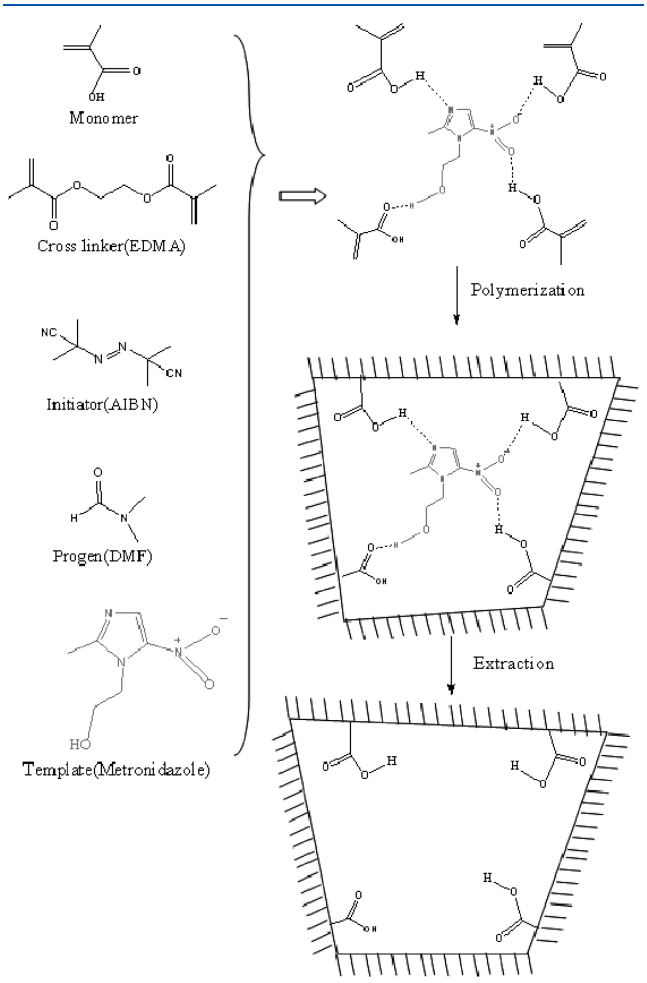

Figure 2. Synthesis production of MIPs. The template is mixed with a functional monomer capable of a hydrogen-bonding interaction and a porogen solvent (top right). A cross-linker and initiator are added to the mixture, and polymerization is completed (middle right). Finally, the template molecule is extracted using a suitable solvent, and the MIP is ready for rebinding. Reprinted from ref 5. Copyright 2009 American Chemical Society.

process schematically, in this case, for the production of an MIP targeted to metronidazole, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, used to treat protozoan infections.[5] In the process, all of the components, including the template, the functional monomer MAA, the EGDMA cross-linker, and the AIBN initiator, are dissolved in the DMF porogen solvent, deoxygenated, and heated for 24 h. After grinding and sieving, Soxhlet extraction is used to remove the template, leaving behind binding cavities.

1.3.2. Phase Inversion. The phase inversion process eliminates the synthetic aspect of MIP production, typically at a cost of less homogeneous binding sites due to the absence of

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significant polymer cross-linking. The major advantage is simplicity and faster production. A solvent that is compatible with both the host polymer and the template is used to dissolve the two components; in this case, one begins with the fully polymerized host. Mixing allows the formation of the guest−host complex in solution, and the MIP is obtained by the addition of a "poor" solvent that causes the polymer (bound to its guest template molecule) to precipitate. In terms of sensing, this produces a solid that is convenient for separation purposes but requires special handling to be included in a sensing device. An alternative to solvent precipitation is allowing the solvent to evaporate either in bulk or after (spin or dip) coating a substrate. This procedure allows the formation of films that are more directly applicable to sensing applications. Figure 3 shows the use of phase

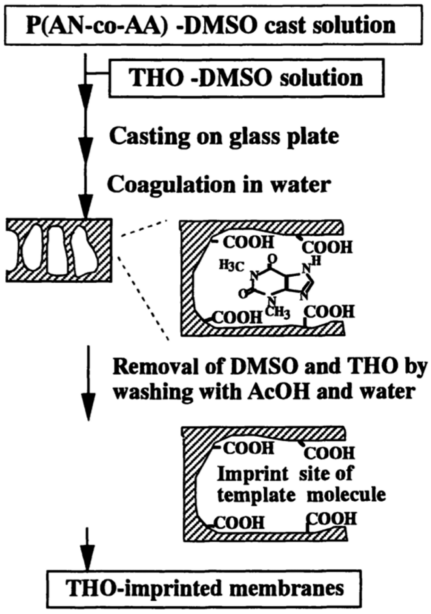

Figure 3. Phase inversion production of MIPs. A scheme for production of a theophylline-templated MIP using phase inversion with H_2O is shown. Reprinted from ref 4. Copyright 1998 American Chemical Society.

inversion to produce an MIP templated to the asthma treatment theophylline.[4] In this specific process, the template is mixed with a poly(acrylonitrile-*co*-acrylic acid) copolymer for 20 h in DMSO. The solution is then cast onto the glass substrate and placed into water which coagulates the networked material into a membrane. The water also removes the DMSO porogen and the bound template, leaving empty cavities for analytical use.

1.3.3. Soft Lithography. "Soft lithography", a process used extensively by the Whitesides research group,[34−38] is intended to produce a surface-imprinted material and is generally applied to the sensing of large molecules that would be hindered from passing into cavities below the surface. The process is simple in concept but requires significant care in preparation. The most direct version involves the creation of a stamp composed of a self-assembled array of the template that is then pressed into a partially polymerized film and kept in place until the film is fully polymerized. Removal of the stamp includes washing out of the template molecule, leaving binding sites on the surface. This is shown schematically in Figure 4 for the imprinting of MIPs to *Escherichia coli*.[3] Specifically, in this

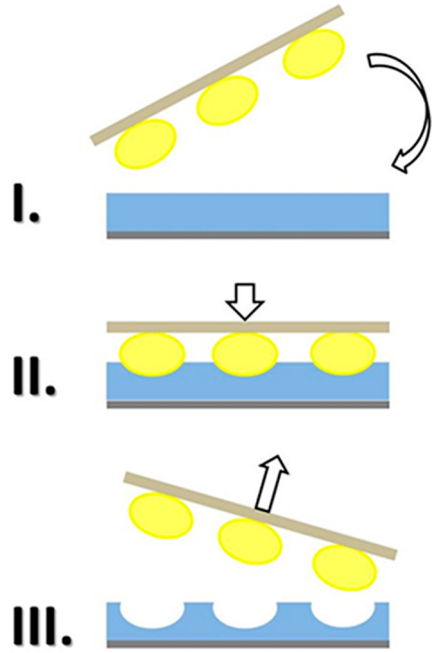

Figure 4. Soft lithography or surface stamping method of MIP preparation. A template stamp is produced on a polymer film usually via self-assembly. The stamp is pressed into a polymerizing film. Finally, the stamp is removed from the polymerized film, and the binding cavities are left behind. Reprinted from ref 3. Copyright 2017 American Chemical Society.

experiment, the MIP host was created by mixing a commercial epoxy resin into cyclopentanone. This solution was spin coated onto a glass substrate, and the stamp was pressed into the film and cured with UV light. The stamp was produced in poly(dimethylsiloxane), which was placed in a bath of the bacterium to self-assemble. Excess material was removed, and glucose was used as a release layer on the stamps. The stamp and the *E. coli* were removed by washing, leaving the surface imprinted and prepared for rebinding.

The choice of MIP production method can be application driven. Phase-inversion-produced MIPs typically lack cross-linking, rendering the rebinding cavities susceptible to collapse during template extraction. However, this technique provides a simple way to produce thin film MIPs. The synthesis method, generally including a cross-linking component, provides more rigid and more homogeneous binding sites, but that rigidity comes at the potential cost of binding site accessibility and a more complex procedure. Regardless of the technique used to prepare the MIPs, electron microscopy or atomic force microscopy images such as those shown in Figure 5 are used to characterize the material morphology. The micrographs indicate that the porogen effect, the use of a solvent that leads to "holes" in the prepared MIP film, is substantial and results in morphological features ranging from regularly spaced and identical diameter pores in the film to a film that takes on the appearance of a membrane. These pores provide access to the interior of the film for the analysis of small molecules using any number of coupled sensing techniques.

2. TYPES OF MIP SENSORS

The relative sensitivities of the different detection techniques are difficult to assign in general terms. Instead, one must examine the values reported for each of the references included

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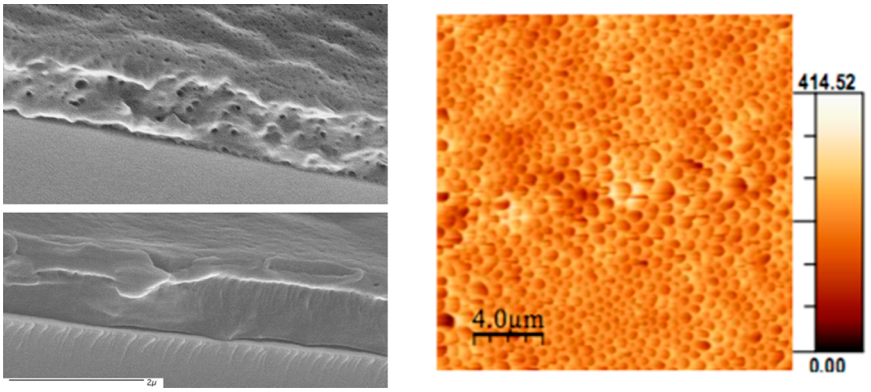

Figure 5. (Left) SEM cross-section micrograph of a 10% L-glutamine imprinted nylon-6 film and (right) AFM image of a 10% fructose imprinted poly(4-vinylphenol) film.

in the review. This approach is necessary because the limits of detection will depend not only on the technique, but also on the specific application. That is, some of the targets may be more amenable to a given technique, or the general detection method may be modified for a particular use case in a manner not generally applicable for other sensors. The values reported here do, however, provide an indication of the range of possible results for a given detection scheme.

2.1. Chemiresistors, Capacitance Sensors, Field Effect Transistors, and Electrochemical Impedance Spectroscopy

These electrical techniques represent the most basic measurement methods for sensor implementation with MIP recognition polymers, although such sensors also require the production of electrodes and/or leads on a dielectric substrate. The techniques are, as a group, known as conductometric methods. The need for a conductive component is typically met by using a conductive "reporting" layer above the set of electrodes or by making a composite MIP that includes a conductive material such as carbon nanotubes, metallic nanoparticles, or a conductive copolymer. Most conductometric applications found in the literature involve gas-phase samples.

Capacitive sensors are simple in concept: one version involves a conductive sandwich consisting of a solid conductive layer on an insulating substrate, a dielectric MIP, and a lattice-like top electrode to allow sampling.[39] Figure 6 shows an image of such a sensor along with its equivalent circuit. The two electrodes are connected to an appropriate electronic monitor, which may be a simple meter or one of the many specialized capacitance/impedance measuring chips available from major suppliers. Adsorption of the template onto the MIP changes both the capacitance and the dissipation factor of the sensor. A brief survey of recent capacitance measurements is shown in Table 2 as an example of the technique.

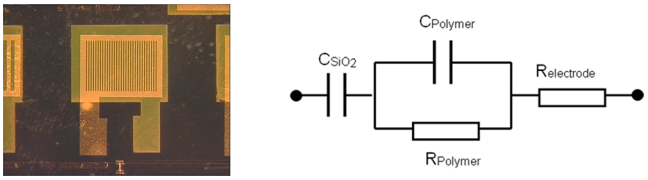

Figure 6. Micrograph of a capacitance sensor designed to detect L-alanine and built on a deposited silicon dioxide layer atop a silicon substrate, along with the equivalent circuit.

Table 2. Select Survey of Some Recent Capacitive, CHEMFET, and Fluorescence Quenching Sensing Reports[a]

method	target	LOD
capacitance	2,4-D[46]	91 pM
	blood type[47]	2×10^{10} cells L^{-1}
	E. coli[48]	7×10^{4} CFU L^{-1}
	amphetamines[49]	10 μM
	morphine[50]	6 μM
	metergoline[51]	1 μM
CHEMFET	D-arabitol[41]	0.12 mM
	inosine[52]	0.62 μM
	dopamine[53]	0.1 pM
fluorescence quenching	cocaine[54]	0.25 μM
	tributyltime[55]	44 nM

[a]Limits of detection (LODs) are included to provide an indication of the range of observed values.

A *chemiresistor* requires less elaborate electrode preparation than the capacitive sensor. Only a single electrode layer is needed, and this may be a simple electrode pair with the polymer filling the space between the electrodes or a more sophisticated interdigitated electrode, IDE, configuration with as many as 160 pairs of electrodes and the MIP coating the entire IDE.[40] A necessary component of the chemiresistor is a conductive film in contact with the MIP. This is attained by using a conductive polymer, typically polyaniline, polypyrrole, or poly[3,4-(ethylenedioxy)thiophene], (PEDOT), as the MIP host, by mixing one of these conductive polymers into a composite with the MIP, by using a composite material composed of the MIP and a conductor such as carbon nanotubes (CNTs) or gold nanoparticles, or by using two layers on the sensor, one conductive and the second an MIP layer coated atop that film. The electronics for recording changes in resistance caused by the adsorption/desorption of the target molecule are readily implemented. One can use a simple ohmmeter or a more flexible Wheatstone bridge or apply a constant current with a voltage measurement to detect the varying resistance. Many gas-phase MIP sensors use the chemiresistor configuration, and a brief survey of applications can be found in Table 3.

A chemical *field effect transistor*, CHEMFET, generally offers more sensitivity than a chemiresistor, albeit with a more complicated production method.[41] In this case, the sensor has three different electrodes: source, drain, and gate, with the MIP coated onto the gate. A potential is applied to the gate, and the

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Table 3. Brief List of Recent Gas-Sensing Publications

method	target	LOD, μM
QCM	acetone, acetaldehyde, methanol, formaldehyde, acetates[245]	86
	alcohols[246]	43
	formaldehyde[230]	16
	aldehydes[247]	0.3
SPR	α-pinene[232]	0.9
	formaldehyde[233]	33
chemiresistor	nitrobenzene[228]	16
	ethanol[229]	11
	formaldehyde[248,249]	1
	toluene[250]	8.7
	hydrogen cyanide[251]	6.5
	acetone, chloroform, isopropyl alcohol, toluene[252]	74
	mango ripeness[227]	

adsorption/desorption of the template onto the gate affects the net gate voltage and, hence, the electrical conduction through the transistor. The polymer must be conductive, with the same available options for creating the conductive material as those described for the chemiresistor. Some examples are shown in Table 2. The chemiresistor and the CHEMFET are shown schematically in Figure 7.[42]

Electrochemical impedance spectroscopy is a sophisticated sensitive sensor technique that measures electrical parameters reflecting changes at the electrode surface in the electrolyte solution.[43] The current through the working electrode, the MIP, is recorded as a function of an oscillating potential over a range of frequencies. The (complex) impedance is modeled by an equivalent circuit that includes the resistance and capacitance of the surface. These parameters are reflective of the amount of target molecule adsorbed into the film, enabling a calibration curve with subsequent analysis of actual samples. As always, the limit of detection depends on the specific experimental system and target molecule, but limits of detection, LODs, as low as 141 pM[44] and even 1 pM[45] may be attained in liquid samples.

2.2. Quartz Crystal Microbalance (QCM) Sensors

These devices are useful for both gas- and liquid-phase samples, although liquid measurements need to account for other, simultaneous changes due to the solvent composition and temperature. The sensors utilize a surface coated with the MIP and offer real time measurements. The QCM consists of a thin, piezoelectric quartz crystal sandwiched between a pair of metal electrodes. Under an applied alternating current field, a stress is created and the crystal vibrates at its resonant frequency. Adsorption of the target molecule onto the MIP surface increases the mass of the crystal and effects a change in the resonant frequency, as shown in the following equation:

$$\Delta m = - C\Delta f \quad (1)$$

where C is the mass sensitivity constant (ng cm^{-2} Hz^{-1}), Δm is the increase in mass, and Δf is the change in the resonant frequency. The microbalance is used in an oscillation circuit with either a frequency counter or a network analyzer to monitor the frequency change, and an intermediate layer is often used to increase the adhesion of the MIP and to change the baseline frequency by increasing the mass. A sensitivity of 1 ng cm^{-2} is typical.

2.3. Electrochemical Sensors

These sensing techniques are primarily applied to liquid samples and involve three electrodes: the MIP is applied to the working electrode that is assembled with counter and reference electrodes in a cell. If the measurement is current based at constant potential, the method is called amperometric; current measurements during varying potentials are known as potentiometric methods. In either case, the peak current, as the voltage is scanned, is proportional to the concentration of the target molecule. The number of variations of these two general methods can be overwhelming, but the basic concepts remain the same.

2.4. Other Sensors/Sensitivity

Some liquid-phase testing uses MIP-coated *surface plasmon resonance (SPR)* crystals to detect adsorption of the target molecule onto the imprinted polymer. Plasmon resonance is the oscillation of conduction electrons existing between materials of two differently signed dielectric constants, in this case the crystal and a metal; the sensor crystals have a thin layer of gold or silver overcoated with the MIP. The resonance frequency is stimulated by incident radiation. Adsorption of the template onto the MIP changes the index of refraction and, therefore, the plasmon resonance frequency. *Optical MIP sensors,* designated as MIOMs by some (molecularly imprinted optosensing materials) have been employed in both gas and liquid phases. These optical sensors generally function by fluorescence quenching and rely on quantum dots as the active element. The quantum dot is activated by a coating that is then used in the reaction that leads to the imprinted polymer layer; adding the specificity of the MIP does not detract from the

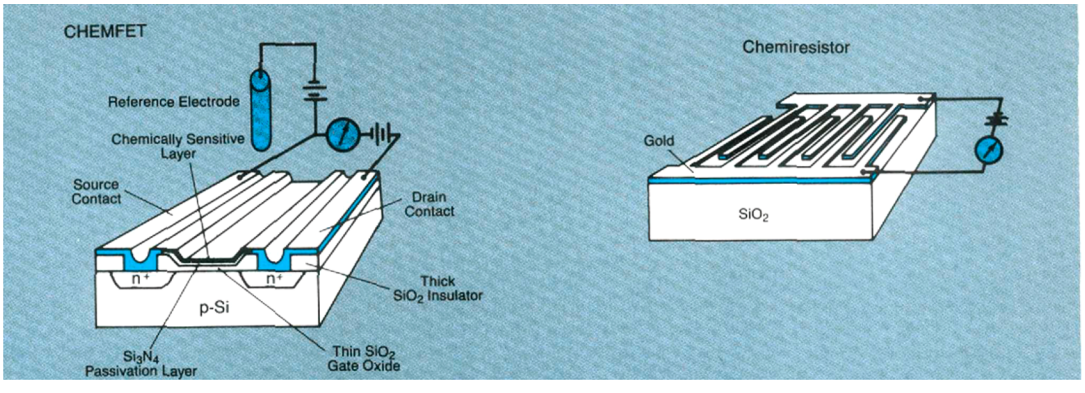

Figure 7. Schematic diagram of a CHEMFET (left) and a chemiresistor (right). Adapted from ref 42. Copyright 1984 American Chemical Society.

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intrinsic fluorescence of the quantum dot. The binding efficiency is monitored by the decrease in signal, and reports of as much as 93% quenching have been reported.[54] The sensitivity of fluorescence measurements is evident in this type of sensor; LODs as low as 44 nM have been reported.[55] Two examples of the use of this technique are included in Table 2.

All of the sensor types described here appear in the literature that is described in subsequent sections of the text. The final choice of format for a given application can be arbitrary but is most often dictated by the target molecule and its source. We note, again, that target-specific limits of detection were included in Tables 2 and 3 and in the preceding text. However, providing a general listing of the relative LODs for the techniques depends on many variables and would be unreliable. The numbers provided should be considered as typical of attainable values for the sensitivity of the various techniques.

3. APPLICATIONS OF MIPS

3.1. Non-sensing Applications

MIPs have been employed in numerous applications apart from sensing. These applications include targeted drug delivery,[56−80] in some ways the opposite of drug sensing, chromatographic separations of related molecules and food adulterants,[81−204] purification of biological and chemical reagents,[161,205,206] industrial safety,[78] and environmental separations/analyses.[55,84,93,97,101,102,117,124,149,151,171,186,207−226] Many of these applications are of sufficient general interest as to be suitable topics for their own reviews. Since this review is focused on sensor applications of MIPs, we simply point the reader to the references related to these topics and proceed to examine the applications of MIPs to sensing.

3.2. Gas Sensing Applications

This brief survey of gas sensing applications also serves to elaborate on the various sensing mechanisms, conductometric, electrochemical, QCM, SPR, and optical, discussed in the previous section of this review. The applications described in this section are intended to simply and quickly demonstrate the capability to detect vapor-phase targets. A brief list of some examples of recent publications is provided in Table 3.

Mangoes exhibit specific volatile organic profiles as a function of the stage of ripeness. As an example of the utility of MIP sensing, mango ripeness was examined by sensing the targets α-pinene, γ-terpinene, and terpinolene as ripening reporting agents.[4,227] These volatile organic carbons, VOCs, were selected after GC−MS studies indicated that they were present only at weeks 8−10, when mangoes were deemed "ripe". The MIP used in this test was based on cross-linked poly(methacrylic acid); the target molecule was mixed with MAA, EGDMA, and AIBN in THF, purged, and allowed to react. The capacitance change (pF) was used to monitor for the presence of the signaling molecules. The authors proposed to add other volatile organics to an array of sensors to use MIP sensing as a field test for the optimum harvesting time. The feasibility of the MIP sensor as a field detection device for ripeness is quite good, but such an application requires additional studies that were not included in the paper. For example, a calibration curve for capacitance change as a function of the terpene concentration and a set of experiments that monitor the VOCs as a function of the fruit growth time are critical to such a future application.

Nitrobenzene and ethanol vapors were separately detected in one laboratory[228,229] using similar MIP-based chemiresistors. Samples of the former were studied using a methacrylic acid−vinylbenzene−divinylbenzene MIP, intended to operate on both acid−base (acrylic acid−nitro group) and $\pi-\pi$ stacking (of the benzene rings) interactions. The sensor was prepared from the initially produced MIP powder, graphene, and poly(methyl methacrylate) (PMMA) as a composite, to which graphite was added, and the composite was drop coated onto an eight-fingered interdigitated electrode. The graphitic "impurities" were required to differentiate between the imprinted and nonimprinted signals, although the reason for this requirement (or the impetus for the inclusion) was not revealed. Swelling of the polymer film was studied as an integral part of the detection process. Swelling is a feature of MIPs that has been somewhat neglected. In this instance, it is reported to be the major influence on the conductance of the sensor by separating the graphene conducting elements. A linear range from 0.5 to 60 ppm with a detection limit of 0.2 ppm was reported. The ethanol chemiresistor used an identical MIP, but in this application, the polymer was synthesized as approximately 10 nm particles. PMMA was used as an adhesive polymer for the nanoparticles by first dissolving it in THF. Once dissolved, the MIP nanoparticles and multiwalled carbon nanotubes (MWCNTs) were added, and the composite was drop coated onto the electrodes. The linear range and LOD were similar to those in the nitrobenzene studies, as expected from the similar approach. The selection of the adhesive PMMA polymer, required because the MIP is a suspended solid, was critical to the success of the two studies. The polymer was required to provide the necessary base for the nanoparticle MIP while avoiding or at least minimizing nonspecific binding. Both of these MIPs operate at the parts per million scale, leaving the need for improvement to detect lower concentrations, especially of the industrially important nitrobenzene.

Formaldehyde is a prototypical target for newly developed MIP sensors. It is an easily manipulated liquid sample when introduced as formalin, a mixture of methanol, water, and formaldehyde. Moreover, formaldehyde is commonly recognized as a major indoor pollutant, especially in new construction, and is a contributor to "sick building syndrome". Recently, two different research laboratories[230,231] used alternative reporting mechanisms to monitor the ambient concentration of formaldehyde. The two experiments also differed in the MIP recognition elements. However, both experiments utilized formalin as the formaldehyde source and in doing so necessitated the examination of sensor response to methanol and water vapor. Tang et al.[231] used an electropolymerized pyrrole MIP synthesized onto a titanium dioxide nanotube array to reversibly detect the target gas by changes in the conductivity of the sensor at a relatively high 1 ppm LOD level. Testing the selectivity of the sensor by exposure to 10% H_2O resulted in a signal that was approximately one-third that of the response to formalin. The results are encouraging and should be further tested with a calibrated mixture of formaldehyde in an inert gas. Hussain and co-workers[230] used a copolymer system consisting of styrene, methacrylic acid, and ethylene glycol dimethacrylate to detect formaldehyde at levels as low as 500 ppb using a suspension of MIP nanoparticles coated onto a QCM. The use of nanoparticles alleviated issues with the sensor response to relative humidity at levels of 50% or greater.

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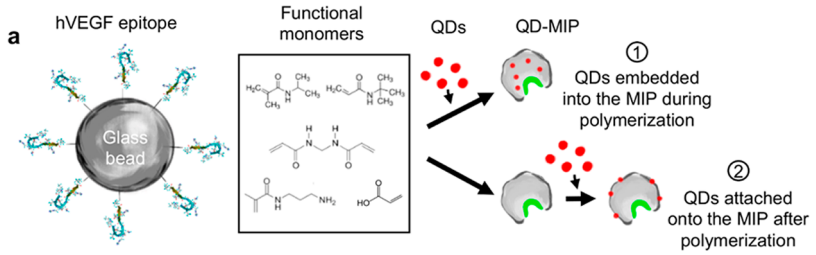

Figure 8. Schematic representation of the synthetic procedure to produce the VEGF-targeted MIP nanoparticles. Reprinted from ref 1. Copyright 2017 American Chemical Society.

Terpenes[232] and, again, formaldehyde[233] were monitored using MIP-driven surface plasmon resonance. SPR detection of the target presence is an interesting variation of an MIP sensor, but is considerably more complicated than the conductance or capacitive devices discussed previously for gases. SPR systems are more suited for laboratory testing than field monitoring studies. The molecule α-pinene was the template in an EGDMA-cross-linked poly(methacrylic acid) MIP deposited onto gold nanoparticles and coated onto a glass substrate with a reported 2 s response time.[232] The response of the sensor was sensitive to the production parameters, including the film thickness. The utility of the sensor is unknown since no LOD was reported. Formaldehyde detection,[233] in this instance using a 15 ppm dilution of the target in nitrogen, was carried out via SPR in a gold-coated optical fiber. The electropolymerized polypyrrole-based MIP was shown to have a linear response and to be sensitive down to the 2 ppm level. As shown above, other formaldehyde sensing mechanisms have produced more sensitive devices. These SPR studies have been included to show the opportunities for alternative sensing mechanisms, but such devices require improvements to routinely reach the effectiveness of the SCM and electrical sensors.

3.3. Liquid/Solution Sensing Applications

Among the many applications of MIP sensors to liquid samples are those directed at amino acids, pesticides, pathogens, food adulterants, explosives, environmental pollutants, drugs (pharmaceuticals and street drugs), and biomedical marker molecules. We will describe a range of specific adaptations for each of these applications to provide an indication of the capabilities of molecularly imprinted polymer sensors and the various methods of detecting the presence of the target molecule in the sensor. The selection of both the general applications and the specific MIP sensors presented in more detail is subjective and biased by the interests of the author. There are many more applications and examples of each than can possibly be contained in any review.

3.3.1. Biomarkers. Many MIP biomarker-targeted sensors[1,45,121,168,234−244] were developed to test for the presence of a carcinoma. Other interesting MIP biomarker-templated systems were targeted to the presence of an active infection or a specific diseased organ. In general, the long-range focus is the development of a synthetic set of diagnostic tools to replace the current natural-receptor-based tests such as enzyme-linked immunosorbent assay, ELISA. Selvolini and Marrazza[239] have reviewed the applications of a range of MIP-based sensors, optical and electrochemical, to biomarker molecules that include prostate-specific antigen (PSA), cancer antigen 125, bilirubin, and neopterin. This provides an excellent introduction to the field.

In a specific example of quantum dot fluorescence quenching based applications, Cecchini et al.[1] used a vascular endothelial growth factor, VEGF, targeted MIP coupled to CdTe quantum dots to fluorescently identify angiogenesis, since malignant tumors often lead to increased blood flow. The solid-phase, nanoparticle synthesis scheme is shown in Figure 8. The template was a short-length, nine amino acid, epitope of the growth factor. The epitope was bound to amine-functionalized glass beads, and 170 nm MIP particles were synthesized onto the beads using a mixed acrylic acid−acrylamide monomer system before removal of the epitope template. Testing using batch rebinding experiments proved that the MIP was binding the entire protein. Further testing used tumor xenografts in zebrafish embryos with two different human melanoma cell lines, and the MIP was found to bind to the target cells in the embryos; the MIP migrated to the tumor mass. Reporting was by means of the near-infrared emission from the quantum dots. Testing demonstrated the absence of heavy metal toxic effects if the exposure time was sufficiently brief, on the order of 48 h or less. The authors speculated that the next set of experiments could include a therapeutic bound to and delivered by the MIP and noted the advantages of the MIP detection: rapid production, long shelf life, biocompatibility, and no immunological response. No detection limit was reported; the research was directed to the feasibility of replacing antibody testing with an MIP detector. The results were clearly encouraging and offered the potential for a new set of diagnostic tools. A related fluorescence imaging protocol was reported by Karfa and co-workers[235] using carbon nanodots (CNDs), Ag/AgCl nanoparticles as the core, and vinyl-functionalized monomers to produce 100 nm imprinted polymer particles for sensing α-fetoprotein, a hepatocellular carcinoma biomarker. The nanodots are attached via linkers to the nanoparticles, and the MIP is coated atop the Ag/AgCl@CND particles. Unlike most quantum dot detections which monitor fluorescence quenching, the fluorescence of this unique system increases in the presence of the target protein with a 10 min response and an imprinting factor of approximately 3. The authors report the limit of detection at 0.61 nM without false positives or false negatives in spiked human blood serum and plasma; recovery in the spiked samples averaged 100%. Currently, α-fetoprotein is monitored by PCR or ELISA, and this MIP provides a direction to make the analysis less expensive and more rapid.

In addition to these fluorescence-based MIP sensors, cancer biomarkers have been targeted using electrochemically based sensors. Sharma et al.[240] used flow injection analysis with open circuit potential measurements to detect neopterin, an indicator of immune activation resulting from a number of possible malignancies or from graft rejection. The electropolymerized MIP was synthesized from two components:

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cysteine-functionalized bisthiophene and boronic acid-functionalized thiophene monomers. In this novel approach, the two components were employed to target the two functionalities on the target molecule, the diol and the pterin, with a covalent and a noncovalent interaction, respectively. The limits of the analysis were tested in synthetic, spiked serum samples, indicating that the method was suitable to 0.22 mM concentrations with an imprinting factor of 6. While interesting as a novel imprinting system, the LOD is relatively high, and any use of this system for real world diagnostics must await improvements in that result. A different electrochemical sensor, involving cyclic voltammetry detection, was developed by Tang et al.[243] to detect interleukin-8, a biomarker molecule for the colon cancer cell line growth factor. This unique sensor was based on superparamagnetic Fe_3O_4/graphene oxide/MIP core−shell particles with a very low detection limit of 0.04 pM. The graphene oxide-modified superparamagnetic nanoparticles self-assembled on the electrodes in the presence of a magnetic field. The MIP was then formulated from aminophenylboronic acid with an acrylamide cross-linker on the assembled nanoparticles; the boronic acid functionality forming hydrogen bonds with the target molecule. The sensor successfully detected interleukin-8 in saliva with an imprinting factor of 5 and discriminated against potential interfering molecules such as cytochrome *c*. The authors speculated on its usefulness as a cost-effective screening method for the target molecule and cancer detection, replacing, for example, ELISA in a rapid screening for IL-8. The LOD and the ease of application provide evidence that such a replacement is feasible. Truta et al.[244] reported a potentiometric sensor, described by the researchers as a "smart polymer antibody material", targeted to carnitine, a biomarker of ovarian cancer. The novel surface-based sensor consisted of cross-linked imprinted styrene material cast onto different substrates as part of a poly(vinyl chloride) membrane, a surface-imprinted sensor. A graphite surface served as the electrode, with the membrane material occupying a 1 mm void between the electrodes. The LOD was support dependent with a best value near 1 μM for glass, and the MIP was selective when challenged with bovine serum albumin (BSA) or creatinine. The production of this MIP involves a number of complicated steps. The resulting LOD renders the use of such an intricate system problematic, at the moment, for practical applications.

Other researchers have reported the development of MIP sensors for biomarkers of cardiac disease[237,241] and oxidative cellular damage[236] using electrochemical sensors. Moreira et al.[237] developed an inexpensive, disposable MIP-based sensor to detect myoglobin using a screen-printed electrode and cyclic voltammetry.[244] The preparation procedure was analogous to that described above by Truta et al. for carnitine. The ability to sense the target protein was confirmed by testing in urine. The MIP sensor was proposed as a point-of-care screening tool for ischemia patients but suffers from the same complexity as the carnitine MIP and, for the moment, remains an excellent laboratory device. Shumyantseva and co-workers[241] reported a square wave voltammetry based sensor also targeted to myoglobin for cardiac disease detection. The electropolymerized imprinted polymer, using an *o*-phenylenediamine functional monomer, was conjugated to multiwalled carbon nanotubes, which not only provided an additional conductive pathway for detecting the presence of the target protein, but also increased the sensitivity of the sensor. With an LOD of 10 pM and an imprinting factor of 10, this MIP offers promise for further development as a diagnostic test. A final example of a biomarker MIP was reported by Martins et al.[236] targeting 8-hydroxy-2′-deoxyguanosine with a detection limit of 3.5pM using electrochemical impedance spectroscopy (EIS). The production of this sensor deviated slightly from traditional methods. 3-Mercapto-1-hexanol was self-assembled on a gold substrate. Subsequently, a mixture of phenol and the target molecule was electropolymerized onto the surface using interaction with the hydroxyl group of the hexanol. The sensor was tested with directly diluted urine samples and proposed as a faster, less expensive alternative to the usual immunoassay procedures to estimate oxidative DNA damage. An imprinting factor of 6.3 was reported, and the sensor selectivity was demonstrated by successful competitive binding against uric acid. The authors speculate that the process could be adapted to other biomolecules, a reasonable assumption based on the positive results reported for this sensor.

3.3.2. Pharmaceutical and Drugs of Abuse Detection.

Molecularly imprinted polymer sensors have been developed for a range of drug targets, both pharmaceuticals[44,253−264] and street drugs.[54,265] Here, we look in more detail at sensors for cocaine, glucose, a range of antibiotics, bronchodilators, and creatinine. The look at antibiotics also provides details on the range of possible methods to detect target molecule presence in the sensor, including electrochemical techniques, surface plasmon resonance, fluorescence, and nanocantilevers.

Recently reported MIP sensors to rapidly detect the presence of cocaine utilized fluorescence[54] and potentiometric[265] methods. The former[54] combined an MIP synthesized by mixing a divinylbenzene functional monomer and EGDMA with PEG-coated, Mn-doped ZnS quantum dots (QDs). The PEG-coated ZnS dots offered significantly lower toxicity than more commonly employed QDs. The fluorescence of the dots was quenched when cocaine or one of its metabolites was present, but not in the presence of other drugs of abuse such as tetrahydrocannabinol (THC), codeine, or morphine. Using a 1:20 ratio of diluted urine directly without any workup and the standard addition method provided a quick measure of the presence of the drug to a detection limit of 250 nM, a level that is below the accepted value for confirming cocaine abuse. The analysis time was estimated as 15 min, and an imprinting factor of 23 was found. The accuracy of the test was confirmed by comparison of the results with HPLC/MS/MS determinations. The authors speculated that this method could replace the radioimmunoassay procedure currently in use after further development, and the successful demonstration of the method offers that possibility. The potentiometric sensor,[262] an ion-selective electrode, using acrylamide monomer-produced MIP nanoparticles of ∼100 nm diameter anchored in a poly(vinyl chloride) (PVC) matrix to produce an imprinted membrane, demonstrated cocaine detection down to 1 nM concentration.[265] The MIP particles were synthesized using a solid support, and histamine was templated into a control polymer which was employed instead of the usual NIP or nonimprinted polymer. Real samples, in human blood serum, were evaluated and found to be accurately analyzed by comparison to the standard technique. A unique feature of this MIP was the successful use of a "dummy template", a substitute for the target of interest for chemical reasons. Benzoylecgonine, a cocaine metabolite, was used for its hydrogen-bonding capability, yet the sensor was capable of rebinding cocaine, proving the success, at least for this instance, of the imprinting technique. The sensor also rebound other cocaine metabolites.

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The high sensitivity of this sensor is encouraging. Although significant work demonstrating the equivalence of this potentiometric technique and the previous fluorescence method to current standards is necessary, detection of abused drugs using MIPs is certainly feasible.

Creatinine levels reflect the health of kidney function, and a rapid, easily administered test is the goal of a wide range of researchers, including several developing MIP sensors with different quantification techniques. Here, we examine and compare three different MIP techniques. One example, electrochemical impedance spectroscopy of a multilayered MIP-based sensor, had an LOD of 141 pM.[44] The development of the MIP surface followed a novel path. The host polymer was constructed by first depositing a carboxylic acid-functionalized PVC layer on a gold electrode. After activation, creatinine was allowed to self-assemble on this initial layer, and subsequently, an acrylamide polymer was cross-linked into the empty space on the surface. Creatinine was removed from the surface, leaving behind the binding cavities. The system was tested on samples from a range of volunteers with clinically measured creatinine levels (using the standard Jaffe test), and the results were in excellent agreement. Potential interfering molecules, such as glucose and urea, were not detected by the sensor. The authors speculated that this could be a general model for a range of disease-identifying sensors and represented a potential suite of point-of-care test devices. Cassandra and Ghemey[253] took a different approach, coating magnetic Fe_3O_4 nanoparticles with a cross-linked acrylic acid-based MIP. The presence of creatinine was noted via ultraviolet spectroscopy of the creatinine solutions after adsorption, and imprinting factors of approximately 5 were reported against such potentially interfering molecules as creatine and L-tyrosine in human serum; however, no LOD measurement was provided. While scientifically intriguing with respect to MIP science, the use of the imprinting or extraction solution as the basis for analysis presents significant real-world difficulties. Additionally, the use of the magnetic particles, while providing a convenient method of separation from any solution, does not in this instance add any improvement to the overall MIP function. A colorimetric test[266] for creatinine with acrylic acid−acrylamide-based MIPs coated onto poly(vinylidene difluoride) (PVDF) microfiltration membranes represents a modernization of the standard Jaffe test. The target molecule adsorbed onto the creatinine-specific membrane was quantified by treatment of the MIP with picrates, the Jaffe test, and a 250 μM detection limit was reported. The MIP increases the sensitivity of the Jaffe test by concentrating the target since the test is carried out on the MIP membrane. The test was described as an improvement in both simplicity and cost over standard methods of analysis and was selective in tests against potential interferents in urine such as creatine, glucose, sarcosine, and urea. The results from the MIP system for patients with known renal disfunction were in excellent agreement with those from HPLC measurements. This represents a clever mechanism for taking a well-known and widely used method into a new, more sensitive realm using MIP technology.

Diabetes is a major health issue and has spawned wide-ranging research to develop sensors to rapidly detect glucose levels and to use as the sensing partner to self-regulating insulin pumps. Up to the present time, MIPs have not played a role in the solution to the commercial aspects of this problem. Two interesting, but different, approaches to the use of MIPs in glucose sensors have recently been reported. Both devices are potentiometric sensors (employing EIS), but one uses a covalent approach[254] and the other a hydrogen-bonding technique[262] to MIP formation. Kim et al.[254] detected glucose in saliva and blood using an acrylamide−boronic acid MIP layer attached to a conductive poly(terthiophene) layer above a screen-printed carbon electrode. MIP preparation revolves around the covalent bond forming *cis*-diol reaction between the boronic acid and the glucose molecules, generating a proton that contributes to the electrochemical cell operation. The MIP exhibits an EIS response in the range of 100 nM even in the presence of other saccharides, including fructose, sucrose, galactose, and some disaccharides and has an IF of approximately 6. The sensor was functional in physiological blood samples and in saliva from volunteers who provided samples prior to and 2 h after a meal. The blood glucose levels agreed with those obtained by a commercial glucose meter, and the results from the two types of physiological samples were in the ranges generally expected for healthy adults. The results offer the possibility of noninvasive monitoring of glucose levels in diabetic patients, but this and any other glucose sensor that is directed to continuous monitoring must undergo substantial testing before securing approval for human use. An alternative MIP glucose sensor[262] was produced from methacrylic acid and EGDMA. The reported LOD was 20 μM with an imprinting factor of 2. Production of this MIP was significantly simpler than that described by Kim et al.;[254] however, the assembly into the working electrode of the EIS experimental system was not included in the report. Assessment of the potential for this sensor to commercial development is not possible due to the missing details, but a speculative analysis renders it much less probable than that of Kim et al.

Clenbuterol is a β-agonist that simultaneously increases the production of epinephrine. It is not approved for use in the United States but is still available for use in livestock in other countries. This drug was the target of two recent sensor development projects using different reporting and production techniques. The first[260] involved an MIP produced from a custom-synthesized methacrylate monomer functionalized with clenbuterol and EGDMA cross-linker onto the surface of a polystyrene multiwell plate. The template was then removed from the resulting polymer by base hydrolysis. The unique feature of this MIP was its synthesis using a covalent technique, while rebinding into the cavities of the MIP was by means of noncovalent, hydrogen bonding. This production−rebinding pair of processes has not been previously reported, hence its inclusion as a novel method here. The investigators claimed to have created a biomimetic version of an ELISA assay with a detection limit of 0.36 pM and an analysis range up to 3.6 μM. The rebinding of clenbuterol was not a "direct" process; the clenbuterol was conjugated to horse radish peroxidase, and the reaction of the enzyme with other components of the sensor was recorded by absorbance in a plate reader. Spiked water and minced pork samples were used to evaluate the effectiveness of the sensor, and the response was validated against HPLC measurements. Less than 1% of potential interfering molecules were detected by this sensor using real sample matrixes. It is difficult to sketch the process by which a device of this sort could reach commercial release, but the basic science is intriguing. The second device[259] was a potentiometric sensor with an MIP combining functionalized carbon nanotubes and functionalized chitosan on either a

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poly(vinyl chloride) membrane or a carbon paste electrode. Detection limits were on the order of 10 pM with response times in the 1 min range and a device lifetime of 24 weeks. The simplicity of this sensor is appealing for further development.

A number of MIP-based sensors have been reported for the quantification of antibiotics in different types of samples. A general strategy for cyclic voltammetry antibiotic sensors was proposed by Lian et al.[255] In it, a pyrolytic graphite substrate was coated with electropolymerized polypyrrole. The target molecule was kanamycin, an antibiotic indicated for serious infections. Amplification of the CV signal was observed using horseradish peroxidase and hydrogen peroxide additives in the electrochemical cell. The presence of the antibiotic in the MIP film results in a decrease in the conductivity compared to that of a kanamycin-free film. Concentrations as low as 20 nM were detected. Potential interfering antibiotics, including streptomycin, did not significantly change the conductivity. The sensor was successfully tested on real samples, in particular honey and milk, spiked with kanamycin. While successful, this sensor is too complex to be used in the field, and such use must necessarily await variations in the methodology. Luo et al.[256] developed a surface plasmon resonance sensor to detect ciprofloxacin at levels as low as 10 pM with an imprinting factor (IF) of 2.6. The MIP was produced from itaconic acid functional monomer and EGDMA cross-linker. The only similar molecule producing any response in the MIP was ofloxacin, a very closely related antibiotic with a surprising IF of 3.8. Impressively, a device with three different sensors (a nonimprinted control, a ciprofloxacin MIP, and an azithromycin MIP) was created and shown to provide different patterned responses to the two individually targeted antibiotics. The MIP sensor functions quite well, and the multisensor device is promising, but using SPR in real time, in a commercial application, is difficult. A different ciprofloxacin sensor directed to detect the antibiotic in water used a micromechanical (atomic force microscopy (AFM) based) cantilever coated with an MIP synthesized from methacrylic acid, 2-hydroxyethyl methacrylate (HEMA), and EGDMA in nanoparticle (160 nm diameter) form.[258] The antibiotic was detected on the cantilever by what was described by the investigators as a "dip and dry" technique; i.e., it was not employed directly in the solution. The sensor exhibited a 7-fold preference for binding the target over the related enrofloxacin antibiotic with concentrations as low as 1.5 μM. The authors cite the advantages of the sensor as "low-cost, fast and sensitive". Given the AFM-based readout, the application of this sensor to field studies is limited, but its basis is certainly unique. Vancomycin was the target of a solid-phase-synthesized acrylamide−acrylic acid nanoparticle MIP-based sensor[267] that used an optical fiber grating as the substrate, defined as a "long-period grating sensor" by the authors. The MIP was produced using a solid support ,and the sensing depends on the change in refractive index due to the nature (target present or absent) of the MIP coating. In laboratory samples, an LOD of 10 nM was determined. Even in a complex sample matrix such as porcine plasma, the sensor was sensitive, detecting concentrations of the antibiotic at 10 μM, and selective against other, related antibiotics such as amoxicillin and gentamicin. The presence of the target molecule was detected by the transmission spectrum of the grating; however, the change in refractive index of the sample solution precluded the determination of a calibration curve. Tetracycline[264] and erythromycin[263] were targeted by two other sensors developed with MIP materials. For the tetracycline sensor, the MIP, which was synthesized from methacrylic acid and the EGDMA cross-linker, was deposited on a platinum nanoparticle-embedded Ti substrate. This cyclic voltammetry based sensor was 10−14 times more sensitive in competitive binding experiments against related antibiotics but offered only a limited analytical range of 0.22−22 μM. Erythromycin was templated in a sol−gel-produced silane polymer coated onto gold nanoparticles around a SiO_2 core (AuNP@SiO_2-MIP) and exhibited an LOD of 12 nM. The decrease of the fluorescence of the gold nanoparticles was used as the reporting mechanism as a function of the erythromycin concentration in solution. The imprinting factor was calculated to be 4. Erythromycin was detected in both spiked human urine and saliva. This simple system, the use of the fluorescence of gold nanoparticles, holds promise as a general approach to drug sensors.

3.3.3. Environmental Sensing and Pesticide Detection. MIP solid-phase extraction materials and sensors can play a significant role in the study of environmental hazards. The MIP materials included here, both sensors (primarily) and preconcentrators for chromatographic analyses, were primarily directed toward the detection of pesticides, including dimethoate,[97] malathion,[124] chlorpyrifos,[214,224] triazines,[101,102,117,218] pyrethroids,[149,225] diazinon,[171,186,214,216] and carbamates.[215] However, a few of the cited reports addressed the detection of other environmental hazards.[55,151,209] MIPs templated by polychlorinated aromatic molecules were the topic of a recent review[209] paper that discussed the difficulty and nonselectivity in templating materials for specific members of this class of molecules due to the structural similarity of potential targets. The report focused on the concept of developing group-selective MIPs using inhomogeneous binding sites for the simultaneous detection of multiple, but related, pollutant molecules, i.e., employing one of the negative aspects of imprinting as an advantage.

Two recent papers report on the use of MIPs as components (preconcentrators) of systems to detect pyrethroid insecticides, one in fish[225] and the other in olive oil.[149] This type of MIP application is common in pesticide analysis, and these two examples are included for completeness. The former, for quantification of cypermethrin, was based on a methacrylic acid functional monomer. The MIP was graft polymerized onto a dense polypropylene membrane, a unique approach to solvent extraction of the target pesticide prior to GC analysis. The graft polymerization method was believed to produce more homogeneous binding sites in the MIP. The membrane was demonstrated to be most selective for the target cypermethrin but extracted all five of the related pyrethroid molecules. In the second MIP, acrylamide copolymerized with methacrylic acid was the functional monomer for the MIP used to analyze the insecticide, deltamethrin, in olive oil. This MIP was produced by means of the "standard" bulk polymerization method and used for SPE prior to HPLC analysis. The selectivity for the targeted pyrethrin was shown to be in the range of 1.5 to 2:1. These stand as excellent examples of the ancillary use of MIPs as preconcentrators in analytical chemistry.

Two recent reports described the use of electrochemical detection methods with MIP-coated electrodes. The detection of the organochlorine pesticide, lindane, an agricultural treatment, was the target of research reported by Anirudan and Alexander.[213] The methacrylic acid, nanoparticle MIP was

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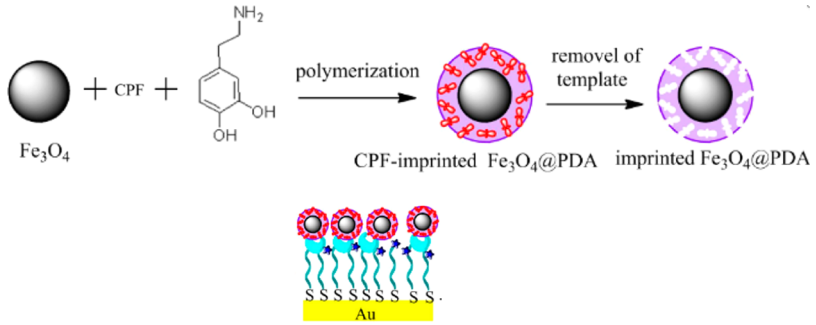

Figure 9. (Top) Schematic formation of the imprinted magnetic nanoparticles. (Bottom) Symbolic representation of the imprinted nanoparticles attached to the thiol ligands on a gold surface for sensing. Reprinted from ref 224. Copyright 2013 American Chemical Society.

grafted onto vinyl-functionalized multiwalled carbon nanotubes and cross-linked in place. The sensor, which could detect the target molecule at levels as low as 100 pM, was tested by evaluating the lindane levels in spiked fruit and vegetable samples (recoveries >98%) using a simple two-electrode potentiometric measurement, essentially a lindane-specific electrode. The sensors were found to be stable over nine consecutive experiments and were selective against other, related organochlorine pesticides. Two different linear ranges were reported, with the signal significantly greater at lower concentrations. The pesticide diazinon, once a residential treatment, but now restricted to agricultural uses, was imprinted[216] in a nanoparticle format using a methacrylic acid functional monomer. Square wave voltammetry was used to detect the presence of the target molecule in a typical electrochemical cell arrangement where the MIP was coated onto a carbon paste working electrode, and increases in the intensity of the reduction potential of the pesticide were recorded as a function of increasing concentration. The sensor was tested with spiked well water and apple samples with no obvious matrix effect, and recoveries were on the order of 92−100%. The reported LOD was 0.79 nM.

Wang et al.[222] developed a complex chemiluminescent sensor for the pesticide 2,4-D on a paper substrate that operated on the competitive binding between the free target molecule and immobilized tobacco peroxidase labeled 2,4-D on the MIP. The free 2,4-D displaced the labeled material, freeing the enzyme and producing a decrease in chemiluminescence from that of the well-known H_2O_2−luminol chemiluminescent reaction system included in the sensor. The decrease in emission was proportional to the 2,4-D concentration in solution. The sensitivity of the sensor was at the femtomolar level. The method appears to be a general platform for the detection of other pesticides and, speculatively, a method for food inspection. Zor et al.[55] used a polypyrrole-imprinted MIP in a composite with silica beads and graphene quantum dots to detect tributyltin in seawater by photoluminescent quenching upon rebinding of the target. The general technique was proposed as a platform for the detection of small molecules and was selective over the closely related mono- and dibutyltin competition in binding studies. The limit of detection was reported to be 0.45 nM. The sensitivity of the fluorescence quenching method is evident from these two applications.

One additional MIP-based method was used to detect a pesticide. Surface plasmon resonance was employed as the reporting method for a surface-imprinted sensor[224] to detect the organophosphate pesticide chlorpyrifos. The chemical sensing component was produced by polymerizing dopamine on Fe_3O_4 magnetic nanoparticles. The nanoparticles were then conjugated to an alkylmercaptan self-assembled on the gold surface for sensing. This is demonstrated in Figure 9.[224] The reported detection limit was 0.76 nM in apples, and selectivity experiments provided promising results (a selectivity of at least 10:1) against three related pesticides even in a complicated matrix such as apples. The time scale for use of the sensor, however, is quite long. Incubation in the analysis cell requires at least 30 min.

3.3.4. Food Analysis. The majority of published reports over the past five years, approximately 130, involving MIP-based analysis of foodstuffs relate to solid-phase extraction materials and will not be discussed here. We focus, instead, on the use of MIPs to rapidly detect toxins, drugs, and industrial chemicals in food using a variety of detection methods.

Quartz crystal microbalances (QCMs) were used to determine the concentrations of histamine[268] and lovastatin[269] in foods. Histamine,[268] at sufficient concentrations, is known to cause allergy-like food poisoning. The histamine-targeted MIP was produced via a sol−gel process with a silane functional monomer, coated onto the QCM using poly(vinyl chloride) as an adhesive polymer, and the concentration of histamine was determined by the frequency change of the crystal. An imprinting factor of 5 was reported. The system was tested on spiked fish products, and the results from these tests were confirmed by HPLC. The detection limit was reported to be approximately 10^{-4} mg kg^{-1}, and the MIP was selective against related molecules, including histidine, tyramine, and phenylethylamine. MIPs were stable for a tested period of six months and also produced results in agreement with the HPLC measurements for randomly selected canned fish samples. Although well-known as a cholesterol-moderating pharmaceutical, lovastatin[269] is also present naturally in some foods, including red yeast rice. The MIP film was produced of poly(2-hydroxyethyl methacrylate−(methacryloylamino)-aspartic acid) and had a reported detection limit of 30 pM in the sampled red yeast rice. Analysis was completed by flow injection into a QCM-containing cell. The measured incubation time for maximum response was a reasonable 10 min, and no response was observed for the structurally related citrinin and lovastatin hydroxy acid molecules. The latter result was interpreted as indicating that the binding sites in the MIP were homogeneous.

Surface-enhanced Raman spectroscopy, SERS, was used in an MIP sensor of the plastic precursor melamine in tap water and milk.[270] Methacrylic acid was the functional monomer for the melamine SERS sensor, which was produced as a

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composite with silver nanoparticles to yield a "one-step" device; the sample after workup from the commercial sources was applied directly to the nanoparticles, and SERS analysis was then undertaken. The composite material, with a poly(methacrylic acid)-based MIP, had a limit of detection of 1.9 μM in skim milk and 16.5 μM in tap water with testing times of 6 and 25 min, respectively. The latter response time was considerably longer than most MIP screening tests require. A second difficulty with bringing this method to more widespread application is the use of a 25 mW near-infrared laser and a monochromator in the detection train. While it is possible to miniaturize such components, it is difficult and expensive.

A silane-hosted molecularly imprinted polymer[271] was grafted onto ZnS quantum dots to yield a phosphorescence quenching sensor to detect the mycotoxin patulin in apple juice. The unique feature of this sensor was templating with what the investigators label a "dummy target", 6-hydroxynicotinic acid. The stated advantages of using the stand-in template include negating the effect of incomplete template removal from the MIP and the elimination of template "bleeding" from the MIP (slow leaching out during the rebinding process of the incompletely removed template). These are the two advantages of using a "stand-in" for the actual template. The resulting sensor had an imprinting factor of approximately 2 and specifically recognized patulin in competitive binding with other mycotoxins. The MIP sensor proved to be accurate by comparison with HPLC analysis of the same samples. The phosphorescent quenching signal was maximized at relatively long 30 min of exposure to the sample.

Electrochemical methods, in particular differential pulse voltammetry (DPV), are commonly employed techniques for detection in MIP sensors. The three-electrode cell, DPV method was applied to the analysis of both food toxins and antibiotics in foodstuffs. Erythromycin and ampicillin were the antibiotic targets. The erythromycin MIP[272] was hosted in a poly(methacrylic acid) polymer deposited onto a carbon paste electrode and exhibited an imprinting factor of 2 with a limit of detection in spiked honey and dairy products of ~10 nM, which is one-third of the federally permitted limit in these products. The MIP functional monomer solution was in the now standard 1:4 ratio, which is speculated to maximize the number of homogeneous binding cavities. Electrodes were shown to be fully functional for 21 tests. Ampicillin was imprinted in a poly(methacrylic acid) host[273] and deposited on the electrode after successive deposition of gold nanoparticles and acid-functionalized multiwalled carbon nanotubes. The performance was similar to that described above for the erythromycin sensor using the same DPV technique; the LOD was 1 nM. The antibiotic was detected in protein precipitated egg and milk samples, indicating that the sample matrix was not an influence on the signal. The ampicillin response was essentially unchanged when analyzed in the presence of a range of other antibiotics. DPV was also the analytical method of choice for MIP sensors used to detect food toxins. The *Penicillium verrucosum* produced mycotoxin, ochratoxin A, was imprinted in a polypyrrole host on carbon nanotubes. The composite was deposited and dried on a polished glassy carbon electrode.[274] Recoveries of between 84% and 104% of the toxin in spiked beer and wine samples were reported with no pretreatment. The reported LOD was 4.1 nM using a 15 min incubation time prior to DPV analysis. The same electrode was used in six consecutive determinations.

3.3.5. Explosives Detection. Recent developments in the MIP detection of explosives, a critical aspect of current sensor research, have focused on the usual 2,4,6-trinitrotoluene, TNT, related materials as well as more modern threats such as triacetone triperoxide, TATP. The field of MIP analysis applied to explosives was reviewed by Lu et al.,[275] where the advantages of these artificial antibodies were well-documented. Unfortunately, all of the recently reported sensors for explosives require the target to be in solution. The most urgent need in explosives detection is for a vapor-phase sensor that can continuously monitor for the presence of concealed material. The sensors described below are applicable to the determination of explosives in polluted water sources and for the testing of extracted soil samples. Vapor-phase sensors are inherently difficult for these compounds due to their low vapor pressures.

TATP is an easily, if dangerously, prepared explosive that can be used either to initiate larger explosive devices or in a standalone improvised explosive device, IED. It is unique in its lack of the nitro groups found in most other explosives. Mamo and Gonzalez-Rodriguez[276] developed a polypyrrole MIP that was electropolymerized onto a glassy carbon electrode. The surface-active sensor was selective for the target TATP in the presence of other common explosives such as pentaerythritol tetranitrate (PETN), hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), octahydro-1,3,5,7-tetranitro- 1,3,5,7-tetrazocine (HMX), and TNT using differential pulse voltammetry detection. The reported range was 554 nM to 299 μM with an LOD of 182 nM when TATP was initially dissolved in acetonitrile. This was the first reported, direct electrochemical determination of the TATP target, which was assumed to interact with the MIP by means of hydrogen bonding.

A TNT molecularly imprinted sensor was developed by Cennamo et al.,[277] who used flow-injected surface plasmon resonance detection in a plastic optical fiber. The fiber was coated with a gold film after removal of the cladding and its replacement with a photoresist material. The acrylic MIP, produced from methacrylic acid and EGDMA, was then added above the gold layer. This particular film was, unfortunately, so thick that it hampered the response time and increased that parameter to 20 min when the concentration of TNT was 260 μM in aqueous solution. The sensor was innovative and relatively low cost due to the use of off-the-shelf, small-size optical components (a critical requirement for MIP-SERS sensing). Two other aqueous TNT sensors coupled DPV to the MIP. Shi et al.[278] used a polyaniline/graphene composite as the conducting element and EGDMA-cross-linked acrylamide as the functional monomer, advocating the use of such a two-layer system for any environmental monitoring. The MIP was said to offer a π-donor−acceptor system along with possible hydrogen-bonding interactions to produce binding and subsequent cavity formation. Although the sensor was directed to the detection of TNT, picric acid was used as the templating molecule. Presumably, the hydrogen bonding of the hydroxyl group in picric acid provided more efficient cavity formation, and the greater solubility of picric acid provided higher templating concentrations than were possible with TNT. TNT was also the target of an MAA/EGDMA-based MIP in the second DPV investigation.[279] This electrode was constructed on a commercially printed electrochemical cell, and the system was successfully evaluated against other, potentially interfering nitroaromatics. The small volume in these experiments, 20 μL, is very promising, as is the 2−3 min

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response time. The authors cite the advantages of their system as "low cost, fast and highly sensitive", assertions that appear to be valid.

The investigators of a reported fluorescence sensor detected 2,4,6-trinitrophenol,[280] picric acid. The functional monomer was a custom-synthesized molecule, bis(2,2′-bithienyl)(4-aminophenyl)methane. The MIP component was embedded in a thiophene cross-linking fluorophore for signal reporting, shown to be selective to the target, and reached a level of 4 pM detection. The MIP was employed as a simple test strip; the liquid sample dropped directly onto the material, which was then analyzed in the fluorimeter. An important aspect of the measurement was that the fluorescence intensity increased with increasing picric acid concentration, as opposed to fluorescence quenching experiments reported using quantum dots. This increase in intensity was attributed to the generation of charge transfer in the presence of the target. A selectivity factor of 5 versus TNT was reported. A series of nitroaromatics, including picric acid, TNT, trinitrobenzene, and dinitrotoluene, were separately targeted to MIPs.[281] The detection scheme was unique, involving simultaneous chronoamperometry and "piezoelectric microgravity" (QCM) measurements. The reported output of this simultaneous detection is shown in Figure 10. The LOD for the

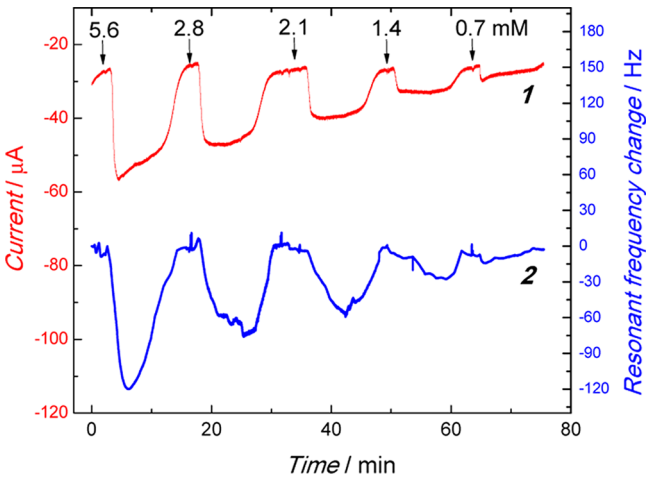

Figure 10. Simultaneous chronoamperometry and QCM determination of flow-injected solutions of TNT. Reprinted from ref 281. Copyright 2013 American Chemical Society.

nitroaromatics was on the order of 10 μM in aqueous solution, with little cross-sensitivity. The MIP was produced using a custom-synthesized functional monomer, bis(2,2′-bithienyl)-(4-aminophenyl)methane, and operated by $\pi-\pi$ stacking. Scanning electron microscopy (SEM) showed that the relatively smooth detection surface had grains in the size range of 20−30 nm. The selectivity factor was between 2 and 5 against other common explosives.

3.3.6. Pathogen Detection. Malik et al.[282] have reviewed the application of MIP sensors to viral pathogens, which represents a major step in the use of the technique. Small-molecule applications abound, but applying the concept to live organisms or epitopes of organism markers takes the method into the realm of very large targets.

Surface plasmon resonance by the Cranfield University research group was used to detect two different viruses, bacteriophage MS2[283] and adenovirus.[284] A novel aspect of this research was the comparison of the MIP sensor to a sensor using the natural adenovirus antibodies. The MIP sensor operated at concentrations over a range of 0.01−20 pM using a composite of functional monomers, acrylamides and acrylic acid, produced by solid-state synthesis as nanoparticles with a diameter of approximately 265 nm. The nanoparticles exhibited a K_d more than 2 orders of magnitude greater than that for the natural receptors. The measured LOD for the MIP was 0.02 pM, which should be compared to that of the natural receptor, 0.008 pM. The MIP clearly offered excellent performance in comparison with the natural antibodies, with the advantages of ease of production and lower cost. The same group targeted the bacteriophage MS2[283] with an MIP built from an identical composite polymer and directly imprinted on an SPR crystal. The nanoparticles were of a similar size, 205−238 nm. SEM images provided direct evidence of the bacteriophage binding to the immobilized nanoparticles. The assay was regenerative, and the investigators speculated that an analogous method may be applied to the detection and removal of any number of waterborne viruses.

Electrochemical methods of detection were applied to a pair of bacterial strains. *E. coli* O157:H7 was surface imprinted on polydopamine.[285] This unique sensor also included polyclonal antibodies to the bacterium conjugated to N-doped graphene quantum dots. The reaction of the bacterium bound to the MIP with QD-bound antibodies generated an electrochemical luminescent signal that was linearly proportional to the bacterial concentration down to 100 colony forming units (CFU) mL^{-1} in water samples with good selectivity. The imprinted polymer, in this device, acted as a concentrator of the target bacterium. The authors speculated that such a device could lead to an increased rate of disease diagnosis and treatment. *Staphylococcus aureus*, a source of gastroenteritis, was detected using electrical impedance spectroscopy by detecting protein A, one of its outer membrane proteins.[286] The electrochemical cell included the working electrode that was composed of the MIP based on the 3-aminophenol functional monomer and deposited on single-walled carbon nanotubes. The detection limit was found to be 0.6 nM, and excellent selectivity in the presence of BSA was reported. In real sample matrixes, for example, tap water, the LOD was 16.8 nM, indicating that inorganic ions in the sample interact with this particular polymer. Such a "simple, disposable" sensor could provide on-site screening for the bacterium in place of the usual culturing that takes days; incubation for this analysis was 20 min.

A quartz crystal microbalance was used to monitor adsorption onto an MIP film described by Poller et al.[3] The sensor used surface imprinting of a commercially available epoxy resin (Epon1002F) with *E. coli* using a self-assembled stamp after testing a number of other "ready-to-use" polymers. The authors note that polymers with a negative charge were more effective in binding the target bacterium because the negative *E. coli* are surrounded by a cationic layer when present in water. The device was sensitive over a range of 0.4 to 7.3 × 10^7 CFU mL^{-1} with a response time of a few minutes. The use of the commercial polymer, in lieu of synthesized specialty polymers, is a distinct advantage in terms of simplicity and speed of production. Finally, Wangchareansak et al.[287] imprinted a number of influenza A subtype viruses on a composite polymer that was produced from a mixture of acrylic acid, acrylamide, and methacrylate with an acrylamide cross-linker. This particular composite was not sufficiently

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selective to allow differentiation among the various influenza subtypes. However, the researchers found that the addition of vinylpyrrolidone to the composite provided selectivity but did not provide a rationale for this effect. The authors demonstrated that quantities as low as 105 particles mL^{-1} could be detected and that targeted MIPs were selective to the template with which they had been prepared, allowing the differentiation of H5N1, H5N3, H1N1, H1N3, and H6N1 subtypes in a rapid screening procedure that offers intriguing possibilities for diagnosis.

3.3.7. Chiral Molecule Detection. An intriguing and very practical feature of molecularly imprinted sensors is the ability to discriminate between a pair of enantiomers. Much of the recent literature focuses on the use of the chirality-based MIPs as separation agents for HPLC analysis.[288−290] However, several direct sensing experiments have been reported and are discussed here.

A quartz crystal microbalance MIP sensor was used to differentiate racemic mixtures of thalidomide from (*R*)-thalidomide.[59] This surface-imprinted sensor utilized bisphenol A as a contributing functional element for hydrogen bonding in a polyurethane host film, which resulted in different frequency shifts for the racemic mixture and the (*R*)-enantiomer in an MIP that was templated to the latter, enabling their analytical distinction. The QCM was developed as a dual system containing an MIP and an NIP, the latter to control for environmental and solvent effects. The two samples also demonstrated that the enantiomers had a 2-fold difference in their binding energies to the coated microbalance, which operated in a linear range of 38−775 μM, with a limit of detection near 0.4 μM. Two reports from the same research group, Pandey and Jhu[45] and Saksena et al.,[291] described impedance spectroscopy sensors that were templated to distinguish between D- or L-ascorbic acid. The working material was polyaniline doped with ferrocenesulfonic acid and deposited onto a carbon dot modified graphite electrode. The L-ascorbic acid-imprinted sensor discriminated against the response of the foreign chiral molecule. The target molecule was detected in serum samples down to a limit of 1 μM and was able to accurately detect L-ascorbic acid levels in a blood serum matrix. The sensor exhibited minimal response to potential interfering substances such as D-ascorbic acid, uric acid, and dopamine in competitive binding studies. A novel thin layer chromatography analytical method was described for the determination of the enantiomeric purity of the non-steroidal anti-inflammatory drug (NSAID) naproxen using an acrylamide functional monomer.[292] The nanoparticular MIP was templated for D-naproxen and coated onto a glass plate using an aqueous mixture of Plaster of Paris as the stationary phase. To avoid cracking of the coating, a small quantity of ethanol was used as a wetting agent. Aqueous solutions of acetic acid were used as the mobile phase, and the D-naproxen was found to be less mobile. Visualization on the chromatography plate demonstrated that the racemates were completely separated with a separation factor of 1.58.

4. COMPUTATIONAL MODELING OF MIPS

Computational science has been applied to a range of chemical problems, and while the number of published reports is relatively small, the field of molecularly imprinted sensors is no exception. Some of the progress up to approximately 2013 has been previously reviewed by Nicholls et al.,[293,294] as well as Cowen, Karin, and Piletsky,[295] who present reports on a range of computational methods applied to the prediction of MIP properties. These reviews demonstrate the computational advances made in selecting functional monomers, cross-linkers, and solvents, as well as the important task of choosing the correct ratio of functional monomer to templating molecule for improved selectivity in the MIP. Here, we present a subjective, more recent collection of intriguing applications of computational methods *to the development of actual sensor MIPs*. These studies encompass a range of computational methods focused on several different aspects of MIP sensor production. Density functional theory (DFT) methods are typically used to calculate the "binding energy" of the host polymer to the target molecule, although some studies employ less accurate (but less computationally expensive) semiempirical calculations to the same end. The application of the polarizable continuum model allowed some of these calculations to be extended to the liquid phase to compare solvents and/or porogens for particular formulations. Finally, some researchers have used molecular dynamics software in place of ab initio or DFT methods for polymer host selection.

4.1. Computational Development of MIP Sensors for Pharmaceuticals

Density functional and ab initio theories were applied to the development of MIPs used in sensors to detect the presence of a number of pharmaceutical targets. Azimi and Javabakht[296] used the ab initio HF/6-31G theoretical model to study hydrogen bonding between the functional monomer methacrylic acid and the antihistamine hydroxyzine. The authors had previously synthesized such an MIP and were, therefore, aware of the suitability of the monomer. The calculations indicated that a ratio of 1:4, template to functional monomer, resulted in the optimal hydrogen-bonding energy, 310 kJ mol^{-1}. The cross-linker, ethylene glycol dimethacrylate, was subsequently added in the calculation, and the resulting imprinted polymer structure was used for selectivity studies. The template molecule was preferentially bound, even in a comparison with the closely related molecule cetirizine. The selectivity was determined by comparing the energy upon computationally rebinding the template or potential interfering molecules. Finally, the chloroform porogen was included in the selectivity calculations using DFT at the B3LYP/6-31G level and shown to leave the relative ordering of the selectivity unchanged. The authors note that this latter test implies that the usual gas-phase calculations are sufficient to predict selectivity, indicating that considerable computational effort may be reduced. In a predominately experimental report, Karimaian et al.[297] utilized DFT, B3LYP/6-31G**, the polarizable continuum model, and water as the solvent to develop the optimal polymer for the production of an MIP to detect minoxidil, a drug to treat male baldness. The authors report examining a range of potential functional monomers, including *O*-phenylenediamine, gallic acid, and *p*-aminobenzoic acid in solo, binary, and ternary combinations, before choosing the best option, the ternary group of monomers, as having the greatest hydrogen-bonding energy. The computational prediction was borne out by the experimental production of all of the calculated sensors. The experimental MIP, using the three functional monomers, was shown to optimally detect minoxidil to an LOD of 0.01 μM. Aswini and co-workers[298] using B3LYP/6-31+G* found the best host material and template:host ratio using the template functional monomer interaction energy as the criterion. This resulted in

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the application of a novel functional monomer, 4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid, to produce a selective, differential pulse voltammetry, electrochemical MIP sensor capable of real world sampling with a dynamic range from 0.4 to 17 μM and a limit of detection of 0.32 μM. Sensing the essential amino acid L-serine was the focus of purely computational research by Singh and Singh.[299] These investigators also employed high-level DFT, B3LYP/6-31++G** with a basis set superposition error correction, to optimize the interaction energy between the template and 10 different commonly used functional monomers. The goal was to determine the optimal hydrogen-bonding host and use the results of these calculations to transfer the vacuum computational results into the aqueous phase using the polarizable continuum model. The net result was that the preferred functional monomers for imprinting in water were 2-vinylpyridine and acrylamide, a prediction of the required target to monomer ratio, 1:3, and quantification of the difficulty of using polar solvents in hydrogen-bonded MIPs; the binding energies of the prepolymerization complexes decreased significantly in such solvents. Other applications of DFT computational methods to MIP sensing of drug molecules were reported by Torkkashvand, Gholivand, and Taherkhani[300] to detect mesalamine, an anti-inflammatory for bowel disease, in a study similar to that of Nezhadali and Mojarrab,[301] who reported development of a sensor for the β-blocker metoprolol using DFT to identify the functional monomer and the optimal porogen. Des-Azevedo et al.[302] took a different computational approach, using the molecular mechanics program SYBYL, typically used for drug studies, in guiding the development of an electrochemical sensor for 17-β-estradiol in environmental water samples.

4.2. Computational Development of Other MIP Materials

Computational methods have been employed in the development of MIP sensors for targets other than pharmaceutical molecules. In these studies, the range of computational software was wider than in the pharmaceutical sensor development described above. For example, Bates and coworkers[303] used the molecular dynamics program GROMACS to determine the optimal ratio of the melamine target molecule to functional monomer to improve the detection of the contaminant in milk. The functional monomer itaconic acid was chosen using compiled binding data known as the "polymer calculator". The experimental material was shown to have an imprinting factor of 2.25 and, unlike the other systems described in this report, was employed in a chromatographic analysis rather than as a sensor. The B3LYP/6-31G* theoretical method was used by Qi et al.[217] to optimize the detection of a series of six carbamate pesticides in environmental water samples. The calculations indicated that methacrylic acid was the best of a set of four potential functional monomers. This was determined by comparing the interaction energies of the monomers with the carbofuran target molecules. The calculations were extended to the solution phase using the polarizable continuum method with a range of dielectric constants representing different porogens. The latter results confirmed the assumption that low dielectric constant solvents are preferable for binding in hydrogen-bonding MIPs to avoid competitive binding between the solvent and the target molecule. The experimental results led to the selection of chloroform, one of the two optimal theoretical porogens, for MIP production with an LOD of approximately 1 ng mL^{-1}. Lastly, Terracina and co-workers[304,305] used a semiempirical quantum mechanical method, PM6, to study the geometry of the binding sites for targets such as histamine and theophylline in chloroform and followed with molecular mechanics (MM) docking to test the selectivity of the predicted MIP systems for binding the two targets. The unique aspect of this wholly computational report was the use of multiple target molecules in the binding calculations. The MM calculation allowed a more realistic polymerization mixture, and as many as 15 target molecules were included in the quantum mechanical calculations, allowing for both polymer and target clustering, as well as partial binding cavity formation. Although the authors did not experimentally test their predictions, this type of calculation shows great promise in reducing the experimental effort in the development of MIP sensors, by leading researchers to the most promising system in a more realistic approach than single target molecule binding to the functional monomer. We expect that computational assistance in the development of MIP sensors will become much more common with the advances in the ease of application of the available software packages.

5. PROSPECTS FOR THE FUTURE

The applications of MIPs span a large range of scientific realms. While we are focused on their use as sensors, this review provides at least a glimpse into the various other uses for these artificial antibodies. The wide range of scientific expertise involved in MIP development bodes well for the future of the science. One expects, with so much intellectual capital applied, that major advances are still to be realized.

One clear advantage of imprinted polymer sensors is specificity, and this feature would be useful in the further development of the "electronic nose". The typical electronic nose device is an array of 9 or 16 sensors, a 3 × 3 or 4 × 4 configuration, which are each sensitive to different stimuli. The identity of the sample is determined by the response of the collection of sensors, typically by their intensities, using principal component analysis.

One interesting, and perhaps obvious, example of the potential for these devices is wine analysis.[306] The number of volatile organic compounds in wine is large, and the industry relies on human perception (and olfactory gas chromatography) to quantify the final flavor profile. A 16 metal oxide semiconductor (MOS) sensor array was compared to a human panel with both trained on the same set of 17 volatile organic flavor components. Both individual flavors and overall wine flavor, adulterated or proof, were analyzed. The array was capable of separating adulterated from proof wine, but less successful in perception, the assignment of wine varietals, for example.

A second field that is ideal for electronic nose devices is diagnostic screening. A nine-sensor array composed of catalytic metal films and MOS sensors was targeted to breath analysis of NO, NH_3, and H_2S at 80% relative humidity.[307] This device was proposed as an example of a simple method of noninvasive diagnostic screening for kidney disease and asthma, both of which modify the normal levels of the three molecules in exhaled breath. As is true of all current electronic nose devices using nonspecific sensors, principal component analysis (PCA) accomplished the assignment of concentrations of the various target molecules.

The various sensors used in these two examples are nonspecific, and it is only through multiple films that an

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assignment to a particular target molecule may be accomplished. Replacement of the MOS and metal films by MIP films eliminates the need for PCA; each target molecule may be directly read from a sensor templated to only that molecule. While we await the first fully MIP electronic nose, it is clear that, for a complex system such as wine or medical diagnosis, the future is definitely imprinted.

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The author declares no competing financial interest.

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