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Hierarchical polymeric architectures through molecular imprinting in liquid crystalline environments

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ABSTRACT

The use of liquid crystalline (LC) media as sacrificial templates during the polymer synthesis has been explored. The LC-media introduce morphological features into resultant polymers which when used together with molecular imprinting can produce materials with hierarchical architectures. Bupivacaine (**1**) imprinted co-polymers of 2-hydroxyethylmethacrylate (HEMA) (**2a**) and 1,4-divinylbenzene (DVB) (**3a**) were synthesized using photochemical initiation in lyotrophic liquid crystalline phases of AOT (**5**) in water/p-xylene and Triton X-100 (**6**) /water systems. SEM studies revealed the impact of the LC-media on polymer morphology, with polymer brush-like structures, with bristles of ≈ 30 nm diameter. The polymer morphology reflects that of the hexagonal phase of the LC medium. The rebinding characteristics of polymer films were evaluated quartz crystal microbalance (QCM, under FIA conditions). The influence of the presence of imprinting-derived recognition sites in AOT (**5**) in water/*p*-xylene polymer film induced brush-like features which provided a 25-fold enhancement of sensor sensitivity. This chemosensor was shown to be selective for the local anesthetic template, bupivacaine, through studies using the structural analogues ropivacaine and mepivacaine.

1. Introduction

Materials facilitating Ångström- or nano-scale events such as in chemical catalysis or molecular recognition, *e.g.* in biosensors and biomaterials, require architectures that present appropriate chemical functionalities for interaction while possessing structural (morphological) features for regulating access to the material surface [1]. Surface-based sensing technologies are a particular challenge due to two factors, the need for recognition events to take place close to the transducer surface, and the impact of this limited volume. Accordingly, the development of strategies for maximizing the number of recognition sites in close proximity to transducer surfaces has the potential to impact upon sensor technologies based upon quartz crystal microbalance (QCM), surface plasmon resonance (SPR), total internal reflectance fluorescence spectroscopy (TIRF) and electrochemical sensing [2–7]. In these contexts, sensor surfaces based upon thin polymer film coating-based sensor surfaces have risen in prominence due to their mechanical and chemical stabilities, range of polymer functionalities available and the capacity to regulate film thickness by using electrochemical or INIFERTER-based synthesis strategies [8–11].

One strategy for introducing recognition sites into thin polymer films is the use of the molecularly imprint technique (MIP) [11–14]. This has attracting significant attention due to the relative ease with which the ligand-recognition characteristics of the material can be the templating process, in conjunction with the general advantages of thin polymer films referred to above. In spite of these developments, there is an ever-growing need for more sensitive methods for the detection of toxins, biomarkers, chemical warfare agents and illicit drugs [15–18]. This is driving the development of molecularly imprinted thin film materials with morphological characteristics that can facilitate the access of analyte to recognition sites in close proximity to the transducer surface. To date these have included the use of ultra-thin films [19–21] and the creation of hierarchical thin-film polymer architectures where nanostructuring is combined with molecular imprinting. Common to those examples using the latter approach is the use of sacrificial materials, either organic or inorganic, to guide the formation of structural features, voids, on the nanometer-micrometer scales that allow efficient mass-transfer to the Ångström–nanometer scale recognition sites [22–26].

In efforts to develop molecularly imprinted materials with even higher solvent accessible surface areas, we have examined the use of a liquid crystalline (LC) medium (Triton X-100/water) for the synthesis of bupivacaine-selective molecularly imprinted 3-aminophenylboronic acid-*p*-phenylenediamine co-polymer (MIP) films [27]. This

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electrochemical synthesis was performed under cyclic voltammetric conditions on gold-coated quartz (Au/quartz) resonators. It was apparent from SEM studies that the polymerization had taken place in the hexagonal phase, as witnessed by the presence of brush-like bundles of polymer fibrils on the 30–100 nm scale. QCM studies demonstrated the presence of template-selective binding sites, and a ≈250% enhancement in sensitivity relative to thin films of the same polymer. These results have prompted a more detailed study of scope of this method for preparing fibrous polymers in general, and to examine its use in molecular imprinting for generating a broader range of hierarchical material architectures.

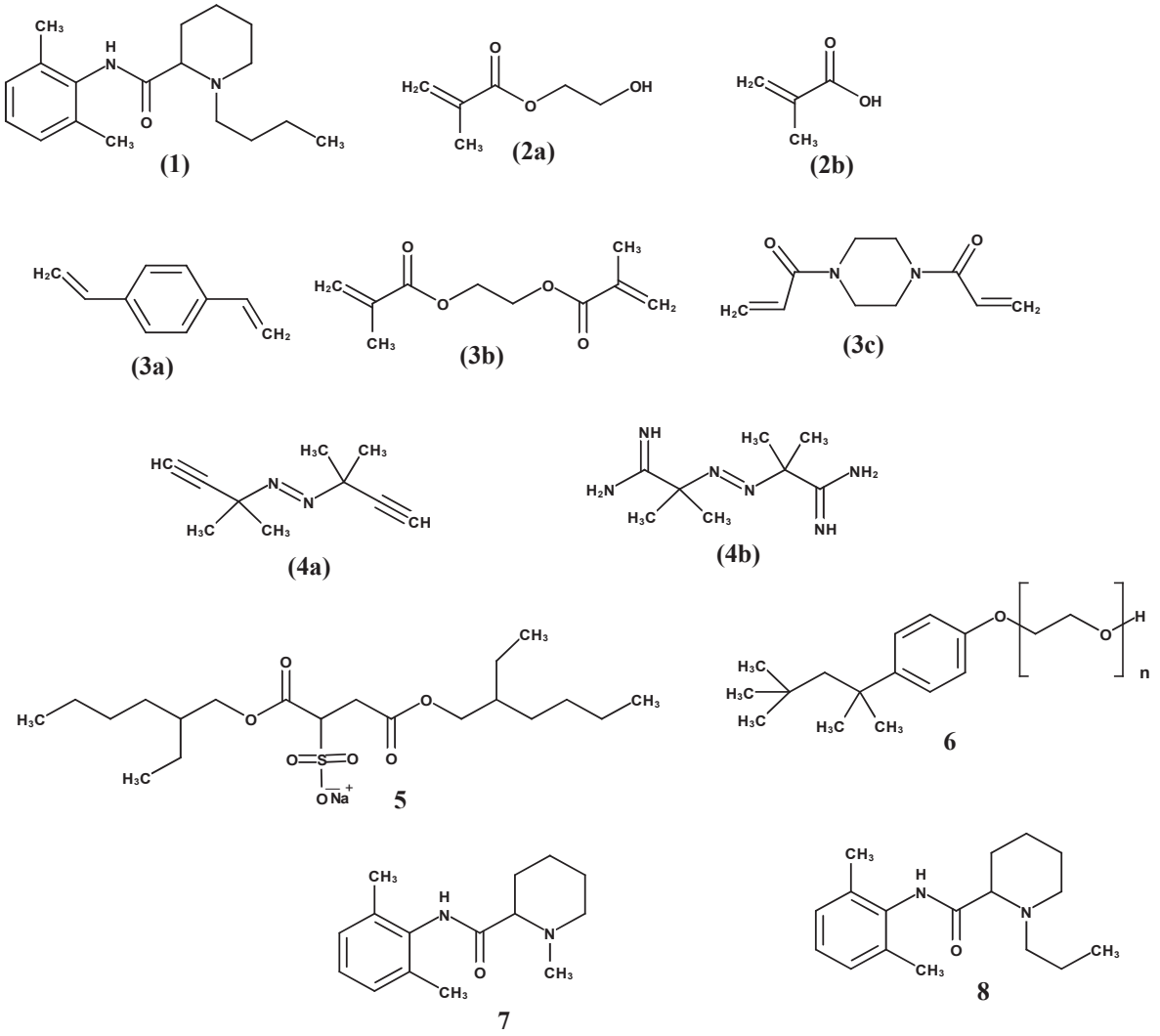
In the present study, we have commenced a broader exploration of the scope of polymerization in LC-media through a study using a series of polymer systems commonly used in molecular imprinting protocols: HEMA-DVB, HEMA-EGDMA and MAA-BAP. Preparation of these polymers in thin films in the presence and absence of surfactant, has been undertaken and the materials characterized by SEM, zeta-potential and QCM studies under flow injection analysis conditions.

2. Materials and methods

2.1. Chemicals

Bupivacaine hydrochloride (1), 2-hydroxyethyl methacrylate (HEMA, 2a), methacrylic acid (MAA, 2b), 1,4-divinylbenzene (DVB, 3a), ethylene glycol dimethylmethacrylate (EGDMA, 3b), 1,4-bis(acryloyl)piperazine (BAP, 3c), 2,2′-azobis(2-methylpropionitrile) (AIBN, 4a), 2,2′-azobis(2-methylpropionamidine) dihydrochloride (ABAH, 4b), dioctyl sulfosuccinate sodium salt (AOT, 5), Triton X-100 (TX-100, 6), and toluene were purchased from Sigma-Aldrich Inc., Sweden (see Scheme 1). The water used was a Milli-Q gradient water filtration system (Millipore, MA, USA) was used to purify distilled water to ultrapure grade with resistance values of ≤18.2 MΩ Ultrapure water-Milli Q water. Mepivacaine (7) and ropivacaine (8) were from AstraZeneca R&D, Sweden. [^{3}H]-bupivacaine hydrochloride (1 Ci/mmol) was from Moravek Biochemicals Inc., USA.

Bupivacaine free-base was prepared from bupivacaine hydrochloride (1 g) by partitioning between dichloromethane (75 mL) and NaOH (aq) (2 M, 75 mL). The organic phase was washed three times with 20 mL of NaCl (aq) (1M, pH 8.0, 20 mL). The organic phase was



Scheme 1. Structural formulas of template functional monomer, crosslinker and initiator employed for synthesis of molecularly imprinted polymers: Bupivacaine (1), 2-hydroxyethyl methacrylate (HEMA, 2a) methacrylic acid (MAA, 2b), 1,4-divinylbenzene (DVB, 3a), ethylene glycol dimethacrylate (EGDMA, 3b), 1,4 bis (acryloyl)piperazine (BAP, 3c) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 4a) and 2,2′-azobis(2-methylpropionamidine) dihydrochloride (ABAH, 4b). Chemical structure of surfactant molecules used for the preparation of liquid crystalline medium: dioctyl sulfosuccinate sodium salt (AOT) (5) and TX-100 (6). Chemical structures of bupivacaine analogues: mepivacaine (7) and ropivacaine (8).