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Size matters: Challenges in imprinting macromolecules

Songjun Li[a,*], Shunsheng Cao[a], Michael J. Whitcombe[b], Sergey A. Piletsky[b]

[a] School of Materials Science & Engineering, Jiangsu University, Zhenjiang 212013, China
[b] Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK

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ABSTRACT

A large number of molecularly imprinted polymers (MIPs) have been investigated and reported over the last decade. Various templates have been successfully exploited and used, leading to significant advances in separation, adsorption, catalysis, sensing, and drug delivery. Among all the templates, small molecules have dominated in the synthesis of MIPs. In contrast, progress made in imprinting macromolecules has been slow, mainly due to the challenges presented by the size, structure and conformational fragility of biological macromolecules. In this review, we focus on discussing some key issues involved in the imprinting of macromolecules from recent publications. The similarity and difference between imprinting small molecules and macromolecules are highlighted. Other aspects relating to polymer design and function are also discussed.

Contents

Abbreviations: Boc, *t*-butyloxycarbonyl; BSA, bovine serum albumin; DMF, *N*,*N*-dimethyl formamide; DNA, deoxyribose nucleic acid; dsDNA, double-stranded DNA; EPR, electron paramagnetic resonance; ESR, electron spin resonance; FT-IR, Fourier transform infra-red; HbA1c, glycated haemoglobin; HRP, horseradish peroxidase; K_D, dissociation constant; MIP, molecularly imprinted polymer; MPC, 2-methacryloyloxyethyl phosphorylcholine; NMR, nuclear magnetic resonance; QCM, quartz crystal microbalance; SAM, self-assembled monolayer; SBR, sulphate-reducing bacteria; SDS, sodium dodecyl sulphate; SPR, surface plasmon resonance; ssDNA, single-stranded DNA; dsDNA, double-stranded DNA; Troc, 2,2,2-trichloroethyloxycarbonyl; UV, ultra-violet; VDAT, 2-vinyl-4,6-diamino-1,3,5-triazine.

* Corresponding author. Tel.: +86 15052990380.
E-mail address: Lsjchem@ujs.edu.cn (S. Li).

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1. Introduction

The focus of the present paper is on the design of MIPs and particularly macromolecules-imprinted polymers with biorecognition properties. This choice is motivated by the fact that the most exciting features of the design and function of biological and biomimetic materials rely on the phenomenon of molecular recognition. The functional aspects of these materials characteristically involve two steps: the recognition process itself and the generation of a signal leading to a response of the system. Examples of biorecognition systems include: enzymes, which can be viewed as molecular machines that catalyze reactions in a highly specific manner; receptors, which perform recognition and transport operations; antibodies, involved in the generation of an immune response; and DNA, involved in the encoding and translation of genetic information. Polymer chemists working in molecular imprinting can learn from these systems about how to develop materials with superior recognition, catalytic and signalling functions. MIPs with biorecognition function have enormous potential to be used in the development of a new generation of stable biomimetic sensors, in affinity separation matrices, for drug development and delivery and in biomedical imaging. The potential for MIPs to impact on these technological areas has stimulated intense activities in hundreds of research centres and companies across the world in order to capitalize on the attributes of these "smart" materials. Substantial progress has been achieved in recent years in the design and application of MIPs, and in particular for small molecular targets [1–11]. Progress in the preparation and use of materials imprinted with specific recognition properties for biological macromolecules such as proteins, polysaccharides and nucleic acids has so far been relatively modest [12–17]. This paper reviews major developments in the area, highlighting technical difficulties related to the imprinting of macromolecules in contrast to small organic substances and offers potential solutions to existing problems.

The term "molecular imprinting" has been in use for some time (at least since the late 1960s) to describe the concept of inducing molecular recognition by "stamping" the impression of molecules into a polymeric network, recording a chemical and stereochemical "negative image" of the template molecule in the process [18–25]. A broader and more complete definition of molecular imprinting can be stated as: the process of template-induced formation of specific recognition sites (binding or catalytic) in a material where the template directs the positioning and orientation of the material's structural components by a self-assembly mechanism. The material itself could be oligomeric (a typical example is the DNA replication process), polymeric (organic MIPs and imprinted inorganic matrices such as silica gel) or 2-dimensional surface assembly (grafted monolayer). To be useful in a technological sense, the imprints should be "fixed" by a polymerization, cross-linking, precipitation or condensation process which cements the relative positions of the structural components before separation or removal of the template species. The imprinting process is therefore seen as a way to produce a range of materials with biomimetic recognition properties, with applications in separation [26–31] adsorption [32,33] sensing [34–42], catalysis [9,43–50], drug delivery [51–56], *etc.*

The history of molecular imprinting can be dated back to the induction of specific adsorption properties in silica-gel performed by Polyakov [57] and Dickey [58] in the 1930s and 1940s respectively. Dickey's work was concerned in the development of silica with specific molecular recognition ability for methyl- and ethyl orange dyes [58]. Although the earlier reports did not straight refer to the term "molecular imprinting" (describing instead as the synthesis of "selective adsorbents"), the concept described corresponds to what we now recognize as molecular imprinting. The first example of molecular imprinting in synthetic polymers is often attributed to Wulff in 1972, with the development of an enantioselective polymer imprinted with D-glyceric acid [59,60]. This initial report coincided with a publication from Takagishi and Klotz [61], which described the introduction of template-imprinted binding sites (for methyl orange) in a pre-formed polymer (polyethyleneimine) modified with thiobutyrolactone and cross-linked through the formation of disulphide linkages. The group of Wulff extended their initial success with glyceric acid by imprinting a series of saccharide derivatives, such as phenyl-α-D-mannopyranoside [62,63]. Interactions between the template phenyl-α-D-mannopyranoside and the functional monomers (two molecules of 4-vinylbenzeneboronic acid) were covalent in nature (cyclic boronate esters). Polymerization in the presence of ethyleneglycol dimethacrylate allowed this covalent complex to be fixed within the cross-linked polymeric network. Boronate esters are thermodynamically stable but hydrolytically labile linkages, enabling removal of the template under relatively mild conditions, leaving behind an "imprint" capable of specifically recognizing the template phenyl-α-D-mannopyranoside, through reforming boronate ester bonds in the imprint site. After optimization of the polymer preparation, the capability of the polymers to resolve a racemic mixture was demonstrated in both batch and chromatographic modes, with separation factors (α), describing racemic resolution of D- and L-configurations of the template, as high as 6.0. The imprinting of saccharides with boronic acid esters is now recognized as a typical approach of "covalent imprinting". Other examples include the use of Schiff's bases [64,65] and ketals [66] to form reversible covalent imprints in synthetic polymers are in a similar fashion.

A simpler protocol, referred to as "non-covalent imprinting", was introduced by Mosbach and colleagues using the same highly cross-linked polymers as Wulff, by employing only non-covalent interactions between the template and functional monomers [67–69]. The switch in emphasis from the covalent to the non-covalent imprinting has led to impressive advances in the field and uptake of the methodology by research groups in many different disciplines, since it effectively removes the need of synthetic chemistry. Although most of the following discussions relate to the non-covalent imprinting in (meth)acrylate-based polymers (essentially based on the method first presented by Mosbach and co-workers), it is worth reminding readers that other materials and methods are also