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Research Article

THEORETICAL AND COMPUTATIONAL STRATEGIES FOR THE FABRICATION OF ENANTIOSELECTIVE RECOGNITION SITE ON MOLECULARLY IMPRINTED POLYMERS

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A B S T R A C T

Molecular imprinting is a promising technique (MIP) for the preparation of polymers with predetermined selectivity, specificity and high affinity which involves arrangement of polymerizable functional monomers around a template molecule. In the present review we focussed on the computational strategies applied for enantiomeric recognition in molecular imprinting technology.

INTRODUCTION

Chirality is an important universal phenomenon in nature. For the in-depth study of pharmacology and biology, efficient enantioselective technologies are essential [1]. Research on enantiomeric recognition of chiral compounds can provide us important information to understand the recognition process in biological systems [2]. Although some progress in chiral discrimination has been achieved during the past decades, the selective detection of individual enantiomer is still the most difficult analytical task owing to the similar physical and chemical properties and the similar molecular configurations of enantiomer [3]. Hence it is important to fabricate practical and rapid available methods for the chiral recognition and separation of enantiomers.

Molecular imprinting is a promising technique for the preparation of polymers with predetermined selectivity, specificity and high affinity which involves arrangement of polymerizable functional monomers around a print molecule [4-7]. The combinations of quantum mechanics and molecular dynamics have produced considerable advancement in the designing and implementation of MIP's. Here in this article we describe a brief account of advancement in molecular imprinting technology for enantioselective sensing system (MIT) in accordance with the theoretical and computational aspects.

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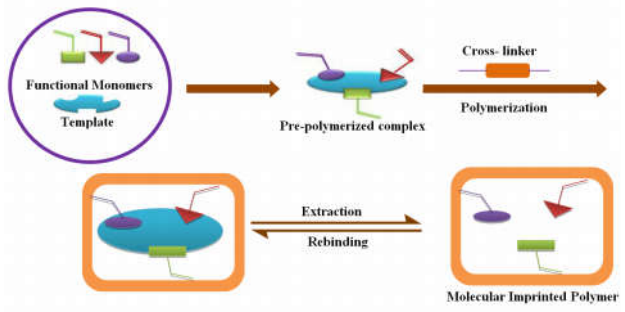
Enantiomeric Sensing System Tailored by Molecular Imprinting Technology

Many naturally occurring and synthetic chemicals exist in an optically active form. They therefore have pairs of enantiomers. Enantiomers of the same compound, indistinguishable on the basis of physical and chemical properties, differ, sometimes significantly so, in physiological effects. The differences may be subtle, but sometimes they have a tremendous importance. They cannot be separated by commonly used methods such as fractional distillation or fractional crystallization, except when the solvent used is optically active. Currently used methods for analysis of optically active compounds are mainly high-performance separation methods such as gas chromatography (GC) and high-performance liquid chromatography (HPLC) using chiral stationary phases, chiral selectors in the mobile phase, or flow reactors for derivatization. Also, efficient electromigration techniques such as capillary electrophoresis (CE) employing chiral selectors are widely used for determination of enantiomers. Other methods are mass spectroscopy, NMR (Nuclear Magnetic Resonance) to the study of molecular recognition, as well as some spectroscopic techniques such as circular dichroism. Those techniques require expensive equipment, and the analysis is often time consuming.

Molecular recognition phenomena have been extensively studied due to the widespread importance of non-covalent interactions in complex formation, catalysis, biochemistry, and chemical sensors. These principles are realized by the

application of host-guest chemistry and are based on intermolecular non-covalent forces. Molecular imprinting is a promising technique for the preparation of polymers with predetermined selectivity, specificity and high affinity which involves arrangement of polymerizable functional monomers around a print or template molecule.Molecularly imprinted polymers (MIPs) have the ability to specifically distinguish and separate a particular molecule from other molecules of similar structures [8]. This property makes MIPs applicable in various fields such as in separation and purification of structurally related compounds, catalysis, biosensors, drug delivery, and in biotechnology. A schematic representation of the molecular imprinting process is shown in Scheme 1.

Compared to other recognition systems, MIPs, which possess three major unique features of structure predictability, recognition specificity and application universality, have received widespread attention and have become attractive in many fields, such as purification and separation, chemo/biosensing, artificial antibodies, drug delivery, and catalysis and degradation, owing to their high physical stability, straightforward preparation, remarkable robustness and low cost [9]. Among the various approaches used during synthesis of MIPs non-covalent interaction can be considered the best one due to easy removal of template, applicable for a variety of molecules, economical and easy method [10].



Scheme 1 Schematic representation of molecular imprinting

Theoretical & Computational strategies

Computational techniques are growing as a promising tool for the design of molecularly imprinted materials. By the knowledge of the structures of the template and the monomer, it is possible to clearly evaluate the interaction between the two and hence to develop a fruitful combination depending on one's need. Attempts have been made to formulate a library of monomers which can plausibly interact with a given template. By the availability of shared workstations and high performance software's, the 'in silico' approaches are gaining predominant importance in this regard.

Quantum computation was the first method to be effectively used in this direction. In simple words, the approaches involve the optimization of the structures of the template and the monomers individually, followed by finding out their interaction, using energy calculations. It is now possible to determine accurately the nature of interaction existing between the two [11]. Various possibilities of the factors like positioning of the template and the monomer, the stoichiometric ratio between the two etc. are generated and the system with the best energy gain is evaluated. Methodologies like ab initio, semi empirical and DFT methods are commonly employed. It is to be remembered that the method and the basis sets involved are selected on the basis of the nature of the material under investigation. Solvent selection being a major factor in MIP interactions, computational approaches have been standardized to incorporate solvent explicit models in to the above strategies.

Another effective computational method is using Molecular mechanics/dynamics simulation techniques. The method gains its significance in the pre-polymerisation stage, where the arrangement of the various monomers (as in the polymer) around the template is evaluated. The solvent explicit models are incorporated along with the monomer molecules to produce an exact replica of the experiment. Techniques like molecular mechanics (involving conformational analysis with time), simulated annealing process (cooling the entire system from a high to low temperature) etc. are employed to obtain the low energy configuration of the system of the interacting molecules. The cross linker influence can also be evaluated in this step. The interaction energy is calculated for the best solvent-template-prepolymer system. CHARMM or AMBER force fields are widely used for the dynamics method.

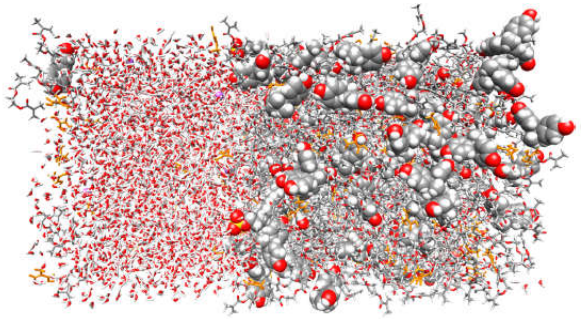


Figure 1 Snapshot from Performed 2-Phase MD Simulation of a Bisphenol A MIP Prepolymerization Mixture, Applied in the Production of MIP Nanoparticles Using the Miniemulsion Polymerization Approach (The Template Is Presented Using a van der Waal Volume Representation and All Other Prepolymerization Components Are Presented Using a Licorice Representation). Ref [12]

An example of the use of quantum-chemical calculations in molecular imprinting is the design of an ester hydrolysis catalyzing polymer based on PM3 calculations. These calculations provided support for the hypothesis that the template used in the MIP synthesis is a mimic of the transition state of the reaction to be catalyzed [13]. Finally, using a quite different approach, Voshell and Gagné [14] used HF/6–31G* and AM1 computational studies to determine the conformational rigidity of a dendritic system used in the imprinting of BINOL. Based on the results, a more rigid dendrimer structure was chosen to lower the binding-site heterogeneity and the enantioselectivity of the resulting MIPs was improved.

One of the first successes in using an MD-based approach for the screening of the best functional monomer for a given template was presented by Piletsky and his coworkers in 2001 [15]. In their approach, they created and utilized a virtual library consisting of a total number of 20 different functional monomers, which were screened against one enantiomer of their template molecule ephedrine. After initially running 30,000 MD steps via the Leapfrog algorithm and generating empirical binding scores, the top four functional monomer–template complexes were then selected and the corresponding MIPs were prepared and evaluated. Here through a

comparison on final MIP performance using these top-ranked monomers and monomers displaying lower binding scores, they demonstrated the potential of their screening approach as a supporting tool in the development of MIPs.

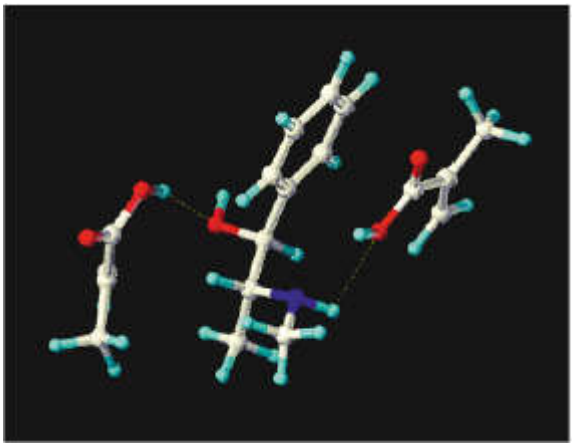


Figure 2 Represents the interaction between the template and the monomer in 1:2 ratio. Ref [15]

CONCLUSIONS

Efforts to employ computational strategies for describing, predicting, and analyzing molecular imprinting systems are a rapidly expanding research area. Experimental work supported by proper theoretical calculation can surely be expected to extend the scope of application of MIP's including in challenging areas sensing where high specificity is the need of the hour. We can expect that the computational tools becomes effective enough to generate molecular imprinting polymers for serving as personalised drug carriers, in near future.

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