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A Review of Computer Simulation-Assisted Molecularly Imprinted Polymers

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Abstract: Molecularly imprinted polymers(MIPs) are synthesized using molecular imprinting technology(MIT) to achieve specific recognition and selective adsorption of template molecules and their analogs. Optimizing the polymerization conditions can significantly enhance their recognition capabilities. However, relying solely on experimental methods for this optimization is resource-intensive and laborious. Computational simulation offers a more convenient, environmentally friendly, and accurate alternative. This paper reviews recent advancements in computational simulation and software used in MIP development, explains the mechanism of molecular bond formation through the analysis of molecular orbital theory and simulation results, and concludes with a prospective look on the need for computational simulation to drive the development of MIT, and the important role of computer simulation in mitigating potential pressures on ecosystems by replacing experiments.

Keywords: MIPs; Computer Simulation; DFT; Quantum Dynamics.

1. Introduction

MIPs are advanced polymer technologies designed to mimic natural recognition mechanisms, such as those seen in enzyme-substrate and antigen-antibody interactions. The synthesised MIPs are macromolecular compounds that match the template molecules perfectly in both spatial structure and binding sites [1], as shown in figure 1. MIPs offer numerous advantages including robust recognition capabilities, stable physicochemical properties, straightforward preparation, minimal solvent use compared with the normal solvent extraction, and reusability. As such, they have found extensive applications in bioseparation and biosensors [2-4]. A critical aspect of MIP construction is the pre-polymerization interaction between the template and the functional monomer. This process involves the binding of functional monomers to template molecules at specific sites, either through polymerization or condensation, forming covalent or non-covalent bonds. Subsequently, the template molecules are eluted, leaving behind a structure that can selectively recognize the original template molecule [5].

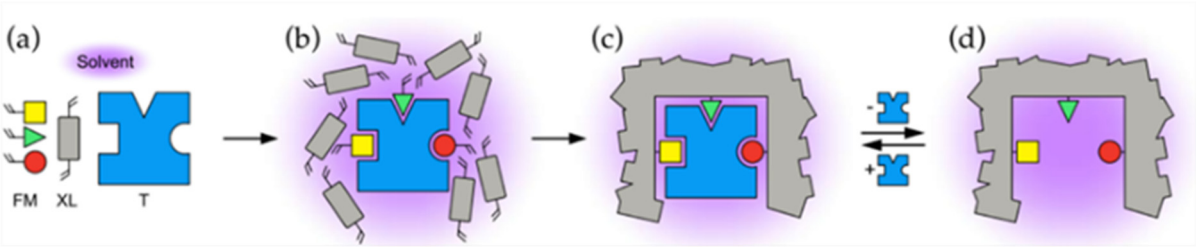

Fig 1. Schematic description of the different stages in the molecular imprinting process. (a) The main polymer components: template (T), functional monomers (FM) and cross-linking monomer(XL) (b) Pre-polymerization mixture, (c) Post-polymerization, (d) Template removal[25].

The molecular structure and physical characteristics of the recognition sites in MIPs are a direct result of the interactions within the pre-polymerization mixture [6,7]. Although the synthesis of MIPs is relatively straightforward, the subsequent optimization process requires a very meticulous and systematic refinement. It begins with selecting functional monomers that exhibit the highest binding energy with the template molecules, ensuring strong recognition capabilities[8]. In addition, different solvents and cross-linking agents have to be selected according to the different properties of the template molecule and the functional monomer, the binding ratio of the functional monomer to the template molecule has to be adjusted, and the polymerization method varies based on analytical requirements[9,10], making traditional MIP synthesis both labor-intensive and resource-demanding. However, the presence of computational simulation mitigates potential pressures on ecosystems by replacing experiments.

In recent years, computational simulation has transformed research across multiple disciplines. Researchers now construct molecular models at the atomic level, using quantum chemical theories to simulate structures, behaviors, physicochemical properties, and reactions[11]. Computer simulations were first used in the field of MIP simulations in 1998. Early studies, however, were fragmented and lacked a systematic approach. Pipeltsky[12] and colleagues later developed a virtual library to screen functional monomers based on molecular modelling, using rational design to optimize MIP preparation. Their findings demonstrated a positive correlation between the binding strength of functional monomers and templates and the effectiveness of recognition in MIPs. Today, computational simulations

including quantum chemical, molecular mechanic and molecular dynamics simulationss, as shown in figure 2, are crucial for understanding interaction mechanisms, detailing pre-polymerized mixtures, and characterizing polymer-ligand interactions at both molecular and electronic levels.

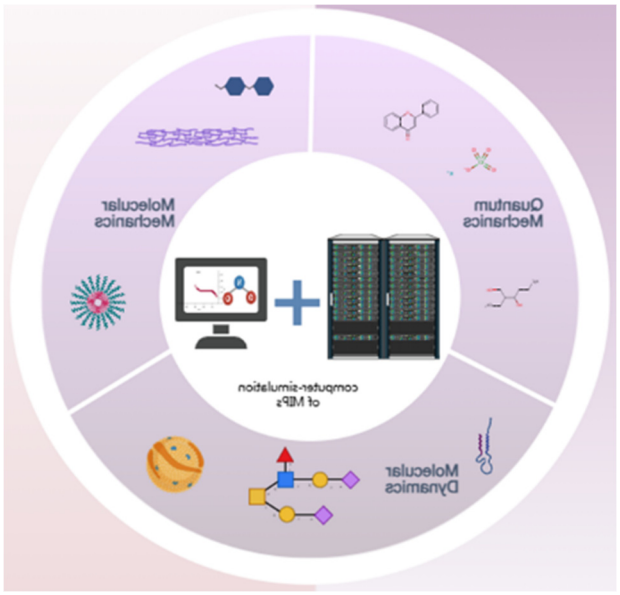

Fig 2. Simplified diagram of computer simulation of MIPs classification. (The inner cycle is a classification of the scope of application of the three simulation methods, for example, QM simulation is suitable for small molecules, such as $KCLO_4$. The outer cycle is a MIPs synthesis process and a simulated process.).

In practical applications, MIPs enhance the efficiency of chemical separation and analysis, addressing challenges in selectivity and separation within complex matrices. They serve as effective adsorbent phases in standard extraction methods, often paired with chromatographic techniques[13]. Additionally, MIPs are integral to sensor technology, where they detect analytes through signals emitted from transducer elements[14,15]. Despite these advances, the design of pre-polymerization systems requires further research to improve selectivity and overall performance. This paper reviews recent advancements in the use of computational simulations for MIPs design, discusses the selection of methods based on molecular properties in the pre-polymerization process, and provides an overview of research and application progress in the field.

2. The Role of Theoretical Calculations in the Field of Molecular Imprinting

In traditional MIP synthesis, methods are generally classified based on the interaction types between the template and the functional monomer. These methods are divided into covalent, non-covalent, and those in between, known as the semicovalent approach or intermediate approach. In non-covalent imprinting, the template and functional monomer undergo non-covalent self-assembly through interactions such as hydrogen bonding, π-π stacking, or electrostatic forces in a suitable solvent. Although this method is widely used, issues such as uneven binding sites and excessive use of functional monomers to stabilize pre-polymerization complexes lead to excessive non-specific binding, which reduces the specific recognition capability of the MIPs.

In the covalent imprinting method, the functional monomer and template molecule are covalently bonded. Under certain conditions, in the presence of a crosslinker and initiator, a polymer is formed. Eventually, the covalent bonds break, releasing the template molecule and producing the imprinted polymer. In this method, the ratio between the template molecule and the functional monomer is relatively fixed, which reduces the generation of non-specific sites. Additionally, the strong covalent interaction aids in the specific recognition of the template molecule by the MIP. However, the process of breaking covalent bonds during the template molecule removal affects the imprinting efficiency.

The semicovalent method involves the template molecule being covalently bonded with the functional monomer, followed by polymer formation under the action of a crosslinker and initiator. The template is then eluted by breaking the covalent bonds. During this process, the polymer generates non-covalent binding sites, allowing the polymer to re-adsorb the template molecule through non-covalent bonds. This method retains the high specificity of covalently prepared polymers for target molecules, while also benefiting from the milder adsorption conditions of non-covalent polymers.

Currently, various synthetic methods have been developed to produce MIPs with evenly distributed binding sites and complete template molecule elution. The synthesis of MIPs involves the formation and breaking of various bonds and interactions between forces. Two key indicators define the success of imprinting: the imprinting factor and the specific recognition ability of MIPs. Computer simulations can assist in optimizing crucial factors, such as the optimal functional monomer, the best imprinting ratio, and the ideal solvent, through theoretical calculations, providing a theoretical foundation for the recognition mechanism of MIPs. Typically, the Density Functional Theory (DFT) method is used to optimize the structure of the template molecule and functional monomer at a specific computational level, and their binding energies are calculated. Furthermore, the Natural Bond Orbital (NBO) theory and electrostatic potential maps can be used to predict molecular binding sites.

Through NBO analysis, it is easy to calculate atomic populations in molecules, the types and compositions of various molecular orbitals, and intra- and intermolecular hyperconjugation interactions. The NBO donor-acceptor electron transfer model can be used to analyze issues such as neutral complexes containing hydrogen bonds, interactions between molecular orbitals, ion-molecule and ion-pair interactions, chemical adsorption phenomena, and interactions between metals and ligands, as well as between metals. This method is applicable not only to general organic and inorganic compounds but also to complex biological macromolecular systems.

For example, Yu[16] used cis-decalin-1-ol as a template, and methacrylic acid (MAA), 4-vinylpyridine (4-VP), methacrylamide (MAD), and acrylamide (AM) as functional monomers. Using the DFT method at the B3LYP/6-31+G (d,p) level, the conformations of the template, functional monomers, and template-monomer complexes were optimized to their lowest energy states. Then, the binding energies between cis-decalin-1-ol and MAA, 4-VP, MAD, and AM were calculated using the M06-2X/def2-TZVP method. Based on the binding energy, MAA exhibited a stronger binding ability to the template, indicating that MAA is the optimal functional monomer.

Subsequently, NBO theory and electrostatic potential maps were used to analyze the interactions between the template

molecule cis-decalin-1-ol and the functional monomer MAA. From the Natural Population Analysis (NPA) charges, it was revealed that the hydroxyl group on the template molecule, particularly O28 as a proton donor and H29 as a proton acceptor, exhibited potential interaction sites. Similarly, the carboxyl group on MAA, especially O3 and O2 as proton acceptors and H4 as a proton donor, also showed potential interaction sites. These analyses suggest that interactions likely occur between the cis-decalin-1-ol template and MAA monomer. Additionally, the electron cloud distribution map confirmed the NPA analysis results, as shown in Fig. 3. In the electrostatic potential map, red regions represent highly electronegative atoms, indicating a tendency to lose electrons, while blue regions indicate strong positivity, suggesting a tendency to accept electrons. This method predicts the interaction sites between template molecules and functional monomers and provides insights into the molecular recognition process. This computational approach offers an intuitive and effective way to analyze electronic structure and chemical bonding characteristics, deepening our understanding of chemical reaction mechanisms and processes. It also provides new perspectives and methods for chemical research and strong theoretical support for fields such as material science and biological sciences.

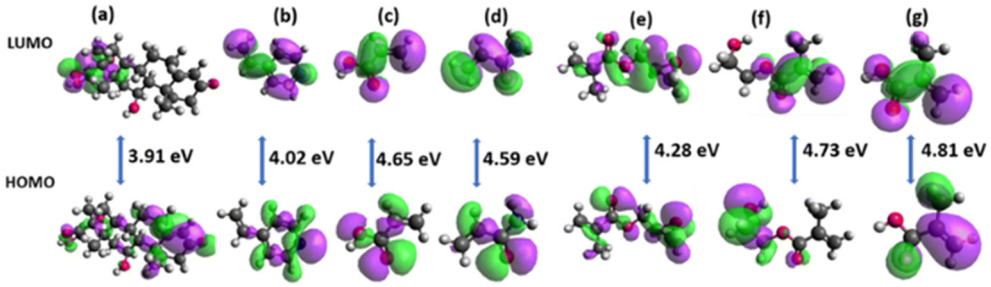

Fig 3. Electrostatic potential map of (a) cis-decahydro-1-naphthol and (b) MAA [16].

Frontier Orbital Theory subdivides the electron cloud distributed around a molecule into different molecular orbitals according to energy levels and posits that the orbitals playing a decisive role in chemical reactions are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Collectively known as frontier orbitals, the energy, charge density distribution, and other information of a molecule's HOMO and LUMO can be used to predict the reactivity order and relative reaction rate in chemical reactions. This theory has widespread applications in theoretical research on chemical reactions and the processes involving biological macromolecules.

Adeleke[17], using epinephrine (EPI) as the template and 4-vinylpyridine (4VP), acrylic acid (AA), aniline (ANI), glycidyl methacrylate (GMA), hydroxyethyl methacrylate (HEMA), and methacrylic acid (MAA) as functional monomers, employed the B3LYP/6-31G method for DFT structure optimization and plotted the HOMO and LUMO molecular orbitals. The HOMO energy of EPI (EHOMO) was -0.298 eV, which was higher than the HOMO energy of all the functional monomers. Additionally, the LUMO energy of EPI (ELUMO) was -0.149 eV, also higher than all the other monomers under study, as shown in Fig. 4.Generally, the lower the LUMO potential, the easier it is for the molecule to gain electrons and undergo a reduction reaction, while the higher the HOMO potential, the easier it is for the molecule to lose electrons and undergo an oxidation reaction. These ELUMO and EHOMO values indicate that EPI exhibits higher reactivity and can be classified as the primary electron donor, while the remaining functional monomers are primarily electron acceptors.By plotting the HOMO and LUMO diagrams, it was shown that EPI's HOMO energy (-0.298 eV) is higher than all the functional monomers, and its LUMO energy (-0.149 eV) is also the highest, indicating that EPI is more likely to lose electrons, making it more reactive and acting mainly as an electron donor. In contrast, the other functional monomers tend to act as electron acceptors. This provides an intuitive and effective explanation for chemical reactions.

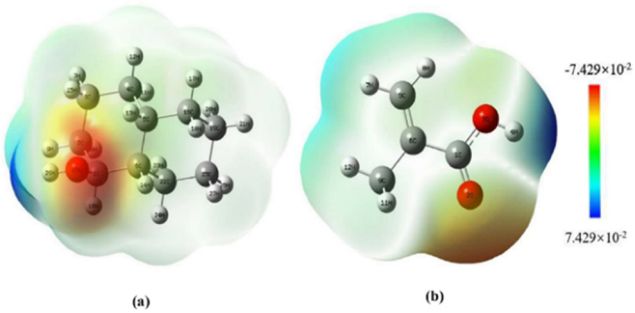

Fig 4. Ground state density surface plots showing frontier molecular orbitals (a) cortisol (b) 4VP (c) AA (d) AM (e) GMA (f) HEMA (g) MAA. The positive phases are purple, and the negative phases are green[17].

To simplify the synthesis process of MIPs and the specific experiments, we will compare three theoretical calculation methods to assist in selecting the appropriate software.

3. Theoretical Methodology

Theoretical methodologies in computational chemistry research encompass a variety of simulation techniques and caculations. These include molecular dynamics(MD) simulations based on the classical molecular mechanics[18], quantum mechanics(QM)[19] and combined quantum mechanics and molecular mechanics (QM/MM)[20-22]. These approaches are instrumental in predicting the binding of intermolecular complexes through molecular docking[23], utilizing polarizable continuum models like Poisson-Boltzmann Models (PBM)[24], and exploring geometric properties of molecular interactions.

3.1. Quantum Mechanics Simulation

QM simulations describe particle motion through wave functions, governed by the Schrödinger equation. This framework helps calculate various molecular parameters-structure, bonding characteristics, total system energy, individual orbital information, and intermolecular interactions, alongside various spectra such as vibrational and electromagnetic spectra, and reactive transition states[25] .

The main methods for solving equations in quantum chemistry include *ab initio* methods[26], density functional theory(DFT) methods, and semi-empirical methods[27]. (1) The *ab initio* method is based on fundamental physical constants like speed of light and Planck's constant, which solves Schrödinger equation without any empirical parameter[28], offering high accuracy at the cost of significant computational resources. (2) The DFT method is based on the Hohenberg-Kohn principle, which uses the electron density instead of the electron wave as the basic quantity of the study. The electron density are decomposed the electron energy into the kinetic energy, the electron-nuclear interaction, the Coulombic repulsion, and the exchange-correlation functionals, which can calculate the molecular bonding energies[29], predicts the structure of the compounds[30] and the reaction mechanism[31]. When a kind of exchange-correlation generalised function called B3LYP [32] was proposed, the DFT algorithm became almost the default method for calculating various problems. All the terms are just functions of the electron density, this method uses a univariate integral instead of the two-electron Coulomb integral as well as an exchange-correlation generalised function VXC instead of the two-electron electron exchange-coupling integral, which is computationally efficient. (3) Semi-empirical calculation method [33-35] uses the empirical parameters fitted by the experimental values to simplify the Schrödinger equation, enhancing computational speed but at the cost of reduced accuracy, particularly when comparing systems with large structural differences.

Common software tools for these simulations, based on *ab initio* or first principle methods, include Gaussian, ORCA, PSI4. And MOPAC, EHMO and HyperChem based on semi-empirical or molecular mechanics methods. Additionally, in quantum chemical simulation calculations, the sites where reactions occur can be judged by frontier orbital theory, and electrostatic potential maps can be drawn to map the electrostatic potential energy of each site of a molecule onto the surface of the molecule's shape, aiding in understanding molecular interactions [36-39].

Our research group utilized density functional theory at the B3LYP/6-31G+(d,p) level using Gaussian 09 software to optimize the molecular structure of the template molecule morphine (MO) and several non-covalent functional monomers: methacrylic acid (MAA), methyl methacrylate (MMA), acrylic acid (AA), acrylamide (AM), 4-vinylbenzoic acid (4-VYL), 4-vinylpyridine (4-VP) and itaconic acid (IA), as shown in figure 5. The electrostatic potential energy was calculated to predict the binding site, and the optimal functional monomer was simulated by comparing the binding energy of different functional monomers with the template molecule.

Based on the analysis of potential binding sites of each monomer and template in figure 3, hydrogen bonding is constructed to form a complex between MO and functional monomers. The bond length and number of hydrogen bonds are analyzed, and the typical range of hydrogen bond length is 1.627-2.169 Å. If the hydrogen bond length is within the typical range, it indicates that it can be connected. Figure 6 shows the 1:1 combination configuration of MO and functional monomers. The hydrogen bond length between MO and functional monomers is within the typical range of hydrogen bond lengths, indicating that they can be connected.

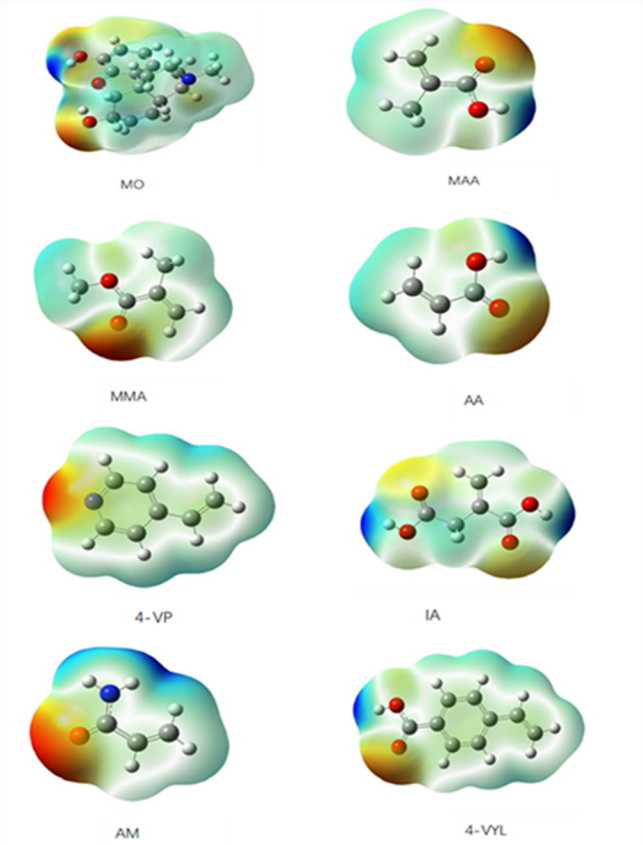

Fig 5. Electrostatic potential diagrams of MO and functional monomers (MAA, MMA, AA, 4-VP, IA, AM, 4-VYL)

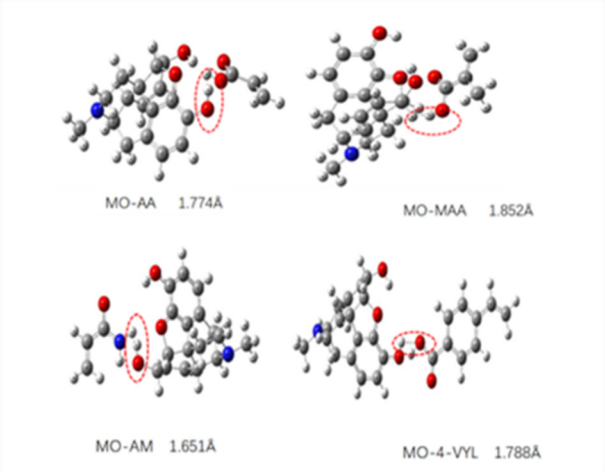

Fig 6. Composite structures of MO recombined with four functional monomers

Finally, we constructed MIPs configurations under different imprinting ratios (the ratio of MO to monomers) to determine the optimal imprinting ratio by calculating the binding energy of possible complexes and comparing the magnitude of the binding energy. The calculation formula is shown in equation (1):

$$E_{interaction}=E_{corrected}-E_{BSSE}-E_{A,bAB}-E_{B,Bab} \quad (1)$$

Where:

$E_{interaction}$ is the binding energy between the template molecules and functional monomers,

$E_{corrected}$ is the energy of the AB complex adjusted for monomer group overlap,

E_{BSSE} is the basis set superposition error correction,

$E_{A, bAB}$ is the energy of A under basis set B,

$E_{B, Bab}$ is the energy of B under basis set B.

This refined methodology section aims to provide a clearer, more detailed explanation of the theoretical approaches and practical applications in the study of molecular imprinting, facilitating a better understanding of the complex interactions and optimizations involved.

3.2. Molecular Mechanics Simulation

Molecular mechanics(MM) simulations are pivotal for studying large systems such as biological macromolecules and polymer systems. QM calculations involve the movement of electrons in the system, the amount of calculations is far beyond the range of the computer for large systems, so it is difficult to simulate by QM methods. Unlike QM methods, MM method simplifies this by calculating the energy based on the positions of atomic nuclei alone. This approach makes it feasible to analyze systems with a vast number of atoms.

In molecular mechanics, each molecule strives to align its geometry—bond lengths and angles[40,41] to closely match their natural values while minimizing non-bonding interactions like van der Waals forces. This process determines the molecule's equilibrium configuration, making MM more cost-effective than QM simulations[42]. With advancements in electronic computers, and particularly through the use of parallel computing and supercomputers, molecular mechanics has been widely used in several research areas, such as organic chemistry, biochemistry, drug design, material design, and so on.

Molecular mechanics describes system energy using potential functions derived from atomic coordinates. Known as the empirical force field method, these functions are developed from empirical data and experimental findings[43]. The accuracy of molecular mechanics critically depends on the correct setup and assumptions underlying the potential functions. Sometimes, these simulations can approach near-quantum mechanical accuracy with significantly reduced computation times, and the simulation time required is only a few tenths or even a few hundredths of that of quantised calculations, which greatly improves the computational efficiency, but does not provide a characteristic of the nature of the electron-dependent distribution in the molecule.

Based on the molecular structure and its properties, molecular force field simulations can describe not only structures but also properties. In the process of MM simulation, the molecular force field is set based on experience, and the molecular force field parameters are generated by fitting the data of a specific molecule. Molecular force fields include all-atomic force fields, combined atomic force field and Coarse-grained force fields. (1) All-atomic force fields, which are the most computationally intensive and most accurate for simulation, take into account each atom in the molecular system and precisely obtain its molecular parameters. (2) The united-atom force field is simplified relative to the all-atomic force field, ignoring the non-polar hydrogen atoms in the system and integrating its parameters to the neighboring atoms with which they are bonded. (3) Coarse-grained force fields further streamline the force field parameters of the molecular structure, often for specific systems, such as treating the amino acid side chain as single particle for force field fitting. So when selecting the molecular force field, it is necessary to study and judge which type of system is more suitable for based on past data[44].

Several well-established force fields used across various simulation platforms are included in the following list outlined in table 1[6,14,25,45-47].

MMX and its derivatives (MM2, MM3, MM4): Molecular mechanics X and its derived force fields are primarily used for non-polar organic molecules, handling tasks from energy calculations to conformational searches.

AMBER and its extensions like ff14SB+GAFF: The assisted model building with energy refinement is suitable for proteins, nucleic acids, and small organic molecules, AMBER is widely employed in commercial software like SYBYL.

OPLS: Optimized potentials for liquid simulations is developed by enhancing the AMBER force field with additional non-bonding interactions, OPLS excels in simulating liquids and is implemented in software like GROMACS.

CHARMM: Chemistry at Harvard macromolecular mechanics force field supports a broad range of molecular simulations and is integrated into tools like Discovery Studio.

GROMOS: Groningen molecular simulation is optimized for macromolecular systems, GROMOS is particularly aligned with thermodynamic data of condensed fluids and is the default force field in GROMACS.

MMFF: Merck molecular force field is an extension of MM3, MMFF supports a comprehensive range of atom types, applicable to both small molecules and macromolecular systems, and is featured in numerous simulation packages.

Table 1. Application of commonly used molecular force fields

Molecular force fields	Applicable to	Software (package)
MM/MM2/MM3/ MM4	non-polar organic small molecules	Gaussian
AMBER	Proteins/nucleic acids/polysaccharides/ small organic molecules	AMBER
FF14SB+GAFF	small organic molecules	SYBYL
OPLS	the physical properties of the molecular system in liquid phase system	GROMACS/ Schrödinger
CHARMM	isolated small molecules/ solvated biomolecular systems	Discovery studio
GROMOS	macromolecular systems	GROMACS
MMFF	organic small molecules/macromolecular systems	Discovery Studio/MOE/ SYBYL/Rdkit

3.3. Molecular Dynamics Simulation

Molecular Dynamics simulations integrate molecular mechanics with Newtonian mechanics to model the behavior of molecules under various conditions. By solving the kinematic equations, MD simulations trace the trajectories of individual particles within a system, thereby identifying energy-minimized molecular structures and characterizing intermolecular interactions. Unlike static single-point energy calculations, MD simulations account for thermal motions, enabling molecules to overcome potential energy barriers. This method is crucial for studying a vast array of molecular properties at virtually any temperature and pressure, making it a valuable tool in understanding molecular structures and dynamics on a granular level. MD simulations are particularly effective in analyzing how conformational fluctuations

influence various binding modes and in estimating binding affinities[48]. Our team successfully completed the docking of nattokinase (PDB ID: 6X3X) with three small molecules: N-isopropylacrylamide (NIPAM), N-hydroxyethyl acrylamide (HEAA), and itaconic acid (IA), utilizing the Surflex-Dock component of the SYBYL-X2.0 software (shown in figure 7).

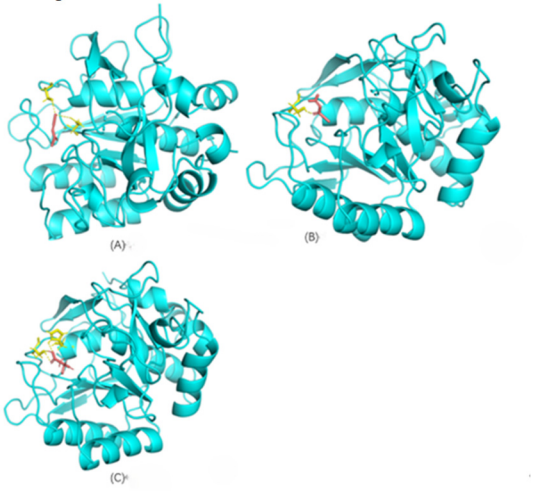

Fig 7. Docking results of (A)NIPAM, (B)HEAA and (C)IA with nattokinase receptor

Following the completion of the docking process, the SYBYL software automatically generates 20 distinct binding conformations based on its scoring function. Two main scoring modules, C_Score and Total_Score, are primarily employed to evaluate the binding affinity of molecules. The C_Score, a comprehensive evaluation tool, integrates multiple scoring functions to provide a more accurate and effective assessment compared to any single function. A C_Score value of 4 or 5 indicates superior binding affinity. Based on the results calculated from both C_Score and Total_Score, itaconic acid (IA) was identified as the most suitable functional monomer.

Table 2. Docking results of NIPAM, HEAA, and IA in nattokinase, respectively

Compound	Total_Score	CSCORE	Hydrogen bond quantity
NIPAM	0.63	5	1
HEAA	0.79	4	2
IA	4.23	5	3

After constructing a molecule accurately, clustering analysis of simulation trajectories helps identify stable molecular configurations under different conditions. The choice of an appropriate molecular force field is critical in this process. Commonly employed force fields include AMBER, OPLS, and CHARMM [49], with specific recommendations based on the molecule type—ff19SB for proteins, OL15/OL3 for DNA/RNA, GLYCAM06j for carbohydrates, and LIPID17 for lipids. The Generalized AMBER Force Field (GAFF) is versatile, applicable to a range of organic molecules, ions, and solvents [50].

Prominent MD simulation software includes AMBER, GROMACS, and NAMD (Nanoscale Molecular Dynamics). NAMD excels in simulating large macromolecular systems on parallel computing architectures, suitable for proteins, nucleic acids, and cellular membranes ranging from 10,000 to 1,000,000 atoms. GROMACS offers robust capabilities for studying biomolecular systems, supporting various molecular dynamics methodologies with an intuitive user interface. It is adept at simulating molecules in solutions or crystals, performing energy minimization and analysis for diverse materials like glass, polymers, and biomolecular solutions. AMBER, known for its suite of empirical force fields, is tailored for biological molecules like proteins and nucleic acids[51,52]. In summary, while molecular simulations typically employ a single force field, combining multiple force fields can enhance simulation accuracy or meet specific experimental needs. The compatibility of force fields must be considered in subsequent analyses, with results often visualized using specialized molecular visualization software[53].

In the context of MIPs, traditional screening methods like *ab initio* computational modeling have been used to refine the selection of template molecules and functional monomers, enhancing MIP selectivity. However, these methods are generally limited to smaller systems due to the computational demand of solving Schrödinger's equation at each energy node. MD simulations, utilizing empirical force fields to estimate interatomic forces and energies over time, enable more comprehensive modeling of larger, multi-component systems in the pre-polymerized mix. This approach provides a deeper understanding of the imprinting process, crucial for optimizing MIP design and functionality[54-56].

MM, MD, and QM are used in theoretical calculations and simulations for various MIP designed. The computational cost of MM optimization is far lower than that of QM, making it faster by several orders of magnitude. However, the accuracy of MM results is limited by the simplifications in its computational model. QM methods can better solve the problem of selecting the appropriate initial orientations of interacting molecules, as they are more accurate than other methods. Therefore, using QM methods to screen functional monomers is a more precise approach. However, the computational complexity of QM increases exponentially with the number of molecules involved in the system. For instance, in mainstream quantum chemistry software like Gaussian, even using an acceptable computational method and basis set such as B3LYP/6-31G(d,p), it becomes very challenging to optimize structures when the system involves 200 atoms. The MD method can effectively address this issue by simulating the dynamic interactions between molecules without considering changes within the molecules themselves, making the simulation method more computationally efficient. Therefore, when designing MIPs involving a large number of molecules, such as optimizing different imprinting ratios between the template and monomers, the MD method is the most widely used. Additionally, the MD method focuses on the motion of atoms in the MIP system and establishes a relationship between temperature and time, allowing for a more realistic simulation of the imprinting system, making the simulation results more representative [57]. Selecting a simulation software that is appropriate for the protocol is necessary to obtain the best simulation results.

4. Selection of Functional Monomers, Solvents and Cross-Linking Agents in the Pre-Polymerization Process by Computer Simulations

4.1. Selection of Functional Monomers

The selection of functional monomers is a critical step in the design of MIPs, increasingly aided by computer simulations and computer-aided design technologies. The effectiveness of MIPs largely depends on the pre-polymerization interactions between the template and functional monomers. This interaction is an equilibrium process, where the stability of the complex determined by the lowest binding energy ΔG_{bind} directly influences the specificity and number of binding sites in the final imprinted polymer. A more stable complex typically results in a polymer with higher selectivity[58].

In the process of designing MIPs through theoretical calculations, the selection of functional monomers is more critical compared to the choice of solvent or the imprinting ratio between the template and the functional monomer, as the functional monomer selection plays a decisive role in the adsorption performance and specificity of the MIP. Structural optimization is the most important step in theoretical calculations for MIP design because the resulting structure determines the subsequent free energy calculations and affects the calculation of binding energy between the template and the functional monomer. Moreover, structural optimization is also the most time-consuming step in the calculation process.

In some previous studies [59,60], the specified molecules were simply placed together as the initial structure before structural optimization, or the reaction sites were predicted by calculating the electrostatic potential of the molecules, and then the regions with negative and positive electrostatic potentials were brought close together to form the pre-polymerization initial structure of the template and functional monomer. After DFT optimization, the optimal cluster structure was obtained. However, this method of optimizing molecular clusters has certain limitations. The structural optimization process in quantum chemistry software is designed to optimize the initial structure to a nearby local minimum point. The goal is to optimize the structure to the global minimum energy on the potential energy surface, but this method often results in only one initial structure, which may only be optimized to one of the many local minima on the potential energy surface. Consequently, the final optimized result may not be the best structure.

However, the best structure obtained through molecular cluster configuration search is more reliable [61]. Molecular dynamics can be used to search for molecular cluster configurations, but this process is quite cumbersome. Another simpler yet effective method is to randomly place a specified number and type of molecules or atoms close together to form spherical clusters. Dozens or even hundreds of such clusters can be generated as initial structures and optimized sequentially, resulting in a batch of molecular cluster configurations at local minima. These configurations can then be ranked by energy to identify the one with the lowest energy. As long as a sufficient number of initial clusters are generated, the global minimum structure will eventually be found. This method can be implemented using the Molclus program [62]. Zhu[63] and colleagues, for example, used the Molclus program to construct cluster structures of different aromatic group deep eutectic solvents (DES) and lignin dimers-DES. Each system had 10 random structures, which were first semi-empirically optimized at the PM6-DH+ level using the MOPAC program, and then further optimized using DFT at the M062X/6–31G(d) level to obtain the lowest energy configuration.

When designing MIPs experiments, the functional monomer used must have the ability to bind to the template molecules, and the cross-linker used must have the ability to maintain the integrity of the imprinted cavities after template extraction. In past designs of MIPs, methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) have been popular choices as the functional monomer and cross-linker, respectively, in non-covalent imprinting systems. The carboxyl groups in MAA can act as hydrogen bond acceptors, donors, and proton donors, facilitating spontaneous polymerization which is crucial for the formation of effective MIPs[64-66]. The Interaction Region Indicator (IRI) is a function that analyzes the wave function information generated after the conventional quantum chemistry calculation to show the weak interaction and chemical bonds between molecules. IRI isosurfaces of the complexes can be visualized using Multiwfn[67] and VMD[68] software, which facilitate the examination of interaction types between the functional monomer and the template molecule. Our group documented the most stable structures of the DES (choline chloride: urea=1: 2), MO, MO-DES complexes (figure 8), and provided IRI isosurface maps for the MO-DES complex (figure 9). Analysis of the MO-DES complex revealed that the tertiary nitrogen atoms of morphine and the alcoholic hydroxyl hydrogen atoms of choline chloride formed hydrogen bonds with a bond length of 1.79939 Å. Similarly, hydrogen bonds were observed between the phenolic hydroxyl hydrogen atoms of morphine and the carbonyl oxygen atoms of urea, also measuring 1.78803 Å. The IRI isosurface maps highlighted a distinct blue region indicating the presence of these hydrogen bonds.

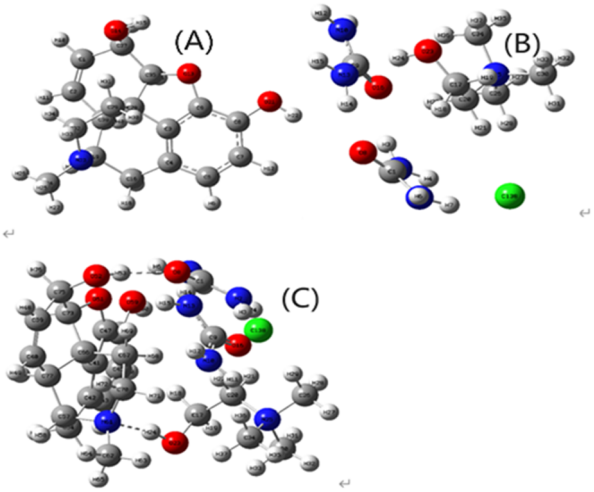

Fig 8. Stabilized conformation diagram of MO (A), DES (B), MO-DES (C)

As the scale of pre-polymerization systems expands, so too does the demand for computational resources and simulation time. Selecting functional monomers based on prior research can substantially reduce computational waste. In the characterization of template-monomer complexes, QM often identifies the optimal functional monomers by evaluating the potential for hydrogen bonding and analyzing the bond

lengths within these bonds. While DFT methods and *ab initio* methods offer high accuracy, they require significant computational power. Alternatively, semi-empirical methods, for example, the favourite AM1[69-71] and PM3[72-74], require fewer resources. For instance, in studies focused on finding the best functional monomers[75], DFT calculations using the B3LYP functional and a 6-31G(d,p) basis set have been common. These studies do not apply symmetry constraints during geometric optimization, allowing for the exploration of various configurations through vibrational frequency calculations to identify the global energy minimum. This approach was exemplified by Pereira TFD et al. [75], who determined the optimal monomer for complexation with the template molecule Carvedilol by calculating the binding energy (ΔE) and Gibbs free energy (ΔG) of the complex.

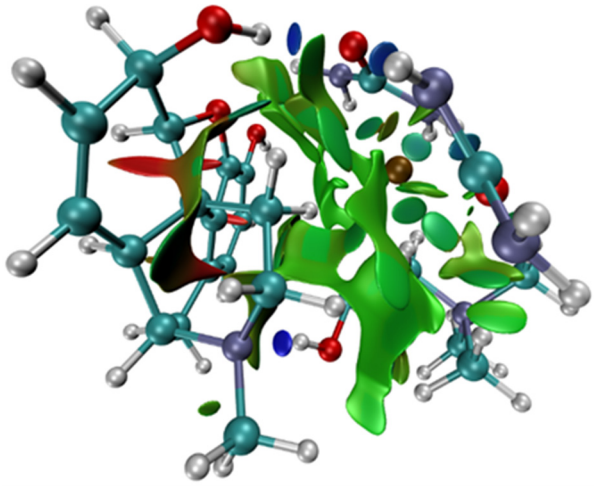

Fig 9. MO-DES IRI isosurface map

The formulas used are:

$$\Delta E = E_{complex} - [E_{TM} + nE_{FM}] \quad (2)$$

$$\Delta G = G_{complex} - [G_{TM} + nG_{FM}] \quad (3)$$

Where:

ΔE represents the binding energy,

$E_{complex}$ is the energy of the combined template and monomers,

E_{TM} and E_{FM} are the energy of the template and functional monomers, respectively,

n is the molar ratio of functional monomers to template molecules,

ΔG is the Gibbs free energy of the complex,

$G_{complex}$, G_{TM}, G_{FM} are the Gibbs free energy of the comples, template, and monomers, respectively.

Due to the high computational resource requirements of calculations, most studies on pre-polymerized mixtures have traditionally focused on non-solvated molecular complexes in vacuum. However, as computational capabilities expand and innovative hybrid methods emerge, integrating electronic structure with molecular imprinting simulations, QM simulation methods are increasingly applied in designing and studying molecularly imprinted systems.

Currently, multi-molecule simulations that include monomers, templates, and explicit solvents typically utilize MD simulations. MD simulations are especially well-suited for analyzing liquid systems[76] and are predominantly used for pre-polymerization simulations. These simulations provide valuable insights into the types and strengths of pre-polymerization interactions by analyzing computational data and molecular trajectories, thereby enhancing our understanding of the recognition performance of MIPs.

Due to their lower cost compared to QM methods, MD simulations are particularly effective for large polymeric systems that include solvent molecules. One notable application by Xi et al.[77] involved optimizing the three-dimensional structures of six functional monomers to identify the best candidate based on proton-donating abilities, as shown in figure 12. They used Discovery Studio's steepest descent and conjugate gradient methods to minimize system energy, resulting in optimized structures. Semi-flexible docking was then performed using the CDOCKER force field, which involves fixing the protein conformation while allowing ligand conformations to vary within a certain range, based on geometric and energy matching. This approach identified methacrylamide (MAC) as the optimal functional monomer, forming the most stable complex at a 1:7 docking ratio with the template molecule, as shown in figure 11. This methodology is now a standard practice in analyzing the pre-polymerization processes of MIPs [34,78,79], often combining electronic structure and molecular dynamics simulations.

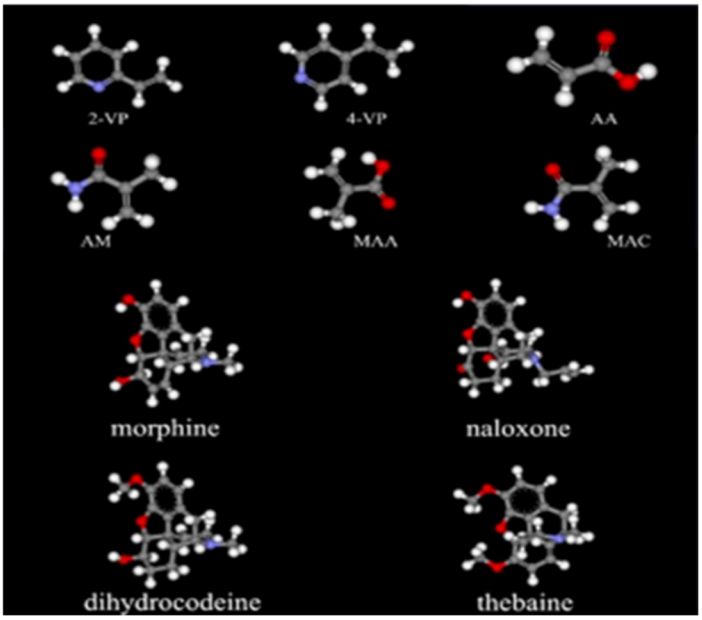

Fig 10. The 3D models of six functional monomers, MO and candidate templates in minimum energy conformation [77]

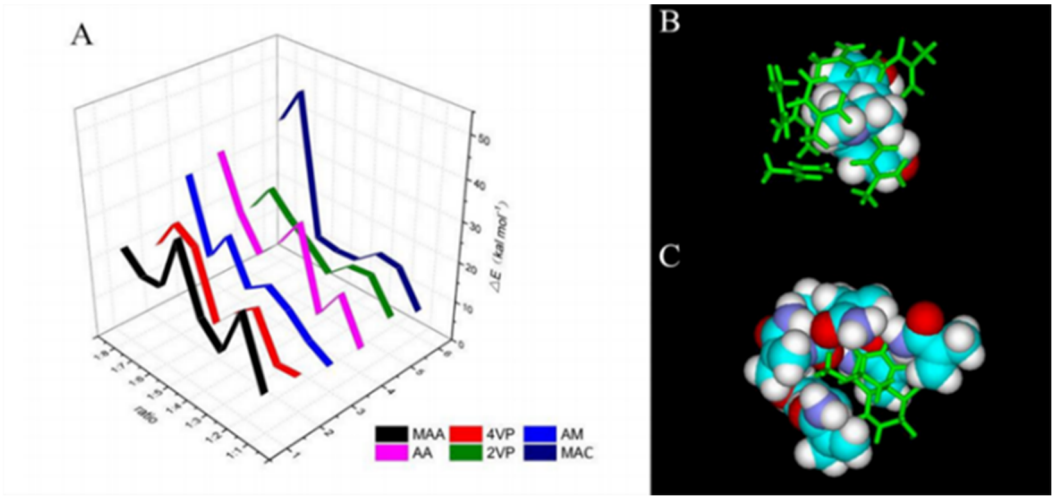

Fig 11. (A) The △E of six different monomers in different ratio, (B and C) two computationally simulated formed by MAC as the monomer and MO as the template at the ratio of 7:1[77]

Traditionally, computer simulations in the pre-polymerization phase of MIPs have focused on optimizing one variable at a time. However, the outcomes from single-variable optimizations can often be suboptimal. Thus, multivariable optimization has emerged as a preferred method. For example, Mamo SK et al.[58] used DFT to screen a library of functional monomers, determining the optimal template to monomer ratio via DFT calculations, as shown in figure 12. They calculated an ideal imprinting ratio of 2:4:40 (functional monomer: cross-linker: perrhenate ion template) using MM+ force field with the NVT-Molecular Dynamics in a periodic boundary to ascertain the minimal simulation time needed for achieving energy equilibrium in the pre-polymerization complex. This approach reflects a broader trend in optimizing polymer compositions or synthesis methods through various multivariate techniques and experimental designs [80-83].

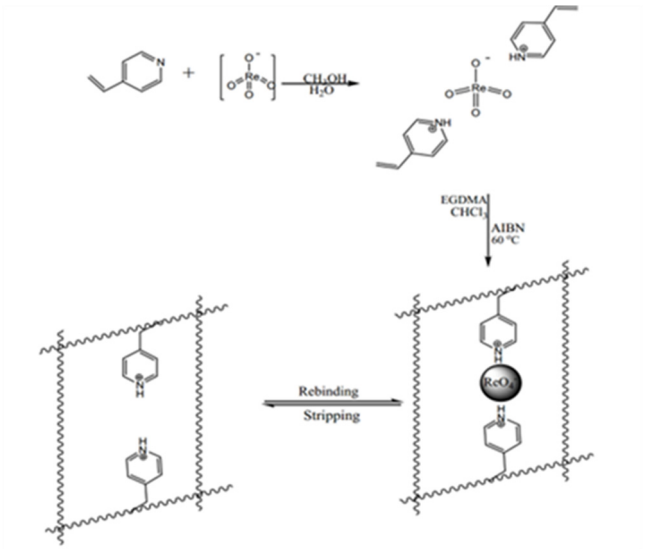

Fig 12. Imprinting mechanism of the ReO4- ion imprinted polymer [58].

4.2. Selection of Solvent and Crosslinking Agent

The selection of solvents and crosslinking agents plays a pivotal role in the pre-polymerization simulations of molecular imprinting, traditionally conducted in a vacuum to optimize the interaction ratios between template molecules and functional monomers. However, incorporating spatial media effects, such as solvents, into simulations can yield results that are more consistent with experimental outcomes. Solvents specifically influence the system's energy during MIP synthesis. The binding energy in the presence of solvents is calculated using the following equation (4):

$$\Delta E_{solvent} = E_{(template\text{-}functional\ complex\ in\ the\ gas\ phase)} - E_{(template\text{-}monomer\ complex\ in\ solvent\ (pore\text{-}forming\ agent))} \quad (4)$$

Where $\Delta E_{solvent}$ is the energy difference between complexs in solution and vacuum environment. During the polymerization process of MIPs, the influence of the solvent on non-covalent interactions is weak, a higher $\Delta E_{solvent}$ suggests that the solvent provides an environment for polymerization, leading to more effective molecular imprinting[84,85].

The polarizable continuum model (PCM) is generally employed to simulate the impact of solvents. This model calculates the molecular Gibbs free energy in a molecular solution by summing the contributions from electrostatics (G_{es}), dispersion-repulsion(G_{dr}), and cavity formation(G_{cav}):

$$G_{sol} = G_{es} + G_{dr} + G_{cav} \quad (5)$$

PCM assumes a uniform distribution of molecules around the solvated system[73,86,87], effectively modeling the environmental influence as interaction with a continuous medium. This approach circumvents the need for explicit sampling of liquid structures and allows for repeated quantum mechanical calculations within the modeled environment[88]. For instance, Ahmadi F et al. [89] used the PCM model to assess the interaction energies between the template molecule of 3,4-methylenedioxymethamphetamine (MDMA) and MAA monomers in the various solvents such as chloroform, tetrahydrofuran, acetone, methanol, and acetonitrile. Their calculations indicated that chloroform provided the most stable environment for these interactions. The PCM model considers only the dielectric constants and sizes of solvent molecules, thus excluding hydrogen bonding effects—necessitating experimental validation of these computational predictions. For most neutral molecules and those with no significant local ionic character, the impact of adding a solvent model during structural optimization can generally be ignored. However, in cases involving significant local charges, such as when using DES, which contain molecules with notable local charges, as functional monomers to simulate the pre-polymerization with template molecules, ignoring the solvent model during structure optimization can lead to structures that deviate significantly from their actual

configuration in a solvent environment. This discrepancy could result in qualitatively incorrect results.

Crosslinkers, crucial for polymerizing functional monomers into rigid, highly crosslinked polymers, influence the template-functional monomer binding[90]. MD simulations can elucidate the effects of crosslinkers during MIP synthesis. For example, research by Yu et al.[91] demonstrated that the number of hydrogen bonds formed in the presence of crosslinkers significantly differed from those formed without crosslinkers, highlighting the complex role of crosslinkers in the polymerization process. In order to achieve a good blotting effect, the reactivity of between crosslinkers should be close to that of between crosslinkers and the functional monomer. Otherwise the polymerization of the monomer or the crosslinker will be dominant, and the copolymerization reaction of crosslinkers and monomers cannot be fully completed. Additionally, the morphology and structural stability of the polymers are strongly dependent on the amount of cross-linking agents used in the entropic polymerization. The cross-linking ratio in MIPs synthesis plays a critical role in balancing structural stability and the functionality of active sites. A low cross-linking ratio may compromise the polymer's stability, whereas an excessively high ratio can occupy too many active sites, thereby diminishing the capacity and selectivity of the MIPs [92,93]. It is crucial to select a cross-linker that not only provides sufficient rigidity to maintain the structural integrity of the cavities but also allows flexibility to enhance the accessibility to the binding sites, improving the MIPs' binding efficiency [94]. Currently, the optimization of cross-linker type and concentration through computer simulations in MIP synthesis is underexplored, indicating a need for more comprehensive research in this area.

5. Conclusion

In the preparation of MIPs, the binding properties of template molecules to functional monomers need to be considered. The type and amount of solvent and crosslinker can also affect polymer synthesis. In order to better understand the mechanism of polymer synthesis at the molecular level and guide the synthesis and design of polymers, computer simulation technology has been applied to each step of the preparation process of MIPs.

Previously, we discussed the role of computer-aided design in MIP prepolymerization, which involves selecting the most suitable simulation methods based on the molecular properties of the components, choosing optimal functional monomers, solvents, and cross-linkers through simulations, and streamlining other processes, such as simulating of optimal functional monomers(fig.5) and DESs(fig.8) of MO, docking of nattokinase with small molecules(fig.7). Despite its benefits, this emerging technology still requires further refinement and development.

(a) The efficacy of computer simulations depends on advancements in computer hardware and the evolution of molecular imprinting simulation theories. Molecular simulations have become a cornerstone in the screening and optimization of materials, drastically reducing the time and costs associated with developing effective MIP adsorbents and cutting down on the use of organic solvents. The development of theoretical models and detailed atomic and electronic level calculations further elucidate the specific recognition mechanisms of imprinted materials.

(b) Experimentally determining the optimal functional monomers involves complex, multilevel considerations. Computer simulations align with green chemistry principles and provide insights into the intermolecular interactions within molecularly imprinted polymers. This understanding is crucial for the application of MIPs in bioseparation and sensor technologies.

(c) Among the computational techniques available, quantum mechanics simulations are the most precise, though they require significant computational resources. QM remains the preferred method in MIP simulations for its accuracy.

(d) Molecular mechanics and molecular dynamics are methods based on electrostatic molecular mechanics. These techniques simplify computations by focusing on atoms rather than electrons, which accelerates computational speeds. MD simulations are particularly suited for macromolecular systems in liquid solvents, effectively identifying the lowest-energy conformations during the annealing process.

In summary, a variety of simulation methods are instrumental in the design and optimization of MIPs, complementing each other to ensure comprehensive and precise results. As technology progresses, the gap between simulation outcomes and experimental results continues to narrow, highlighting the growing reliability of computer simulations in this field.

Acknowledgments

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