Chapter 2
Synthetic Strategies for the Generation of Molecularly Imprinted Polymers

Xi Wu

2.1 Introduce

Three general approaches, covalent, semi-covalent and non-covalent, are frequently applied in the preparation of MIPs. For the covalent approach, the template is bound to a polymerizable monomer by a labile covalent bond. The template and monomer are copolymerized with a cross-linker in a selected porogenic solvent. A cross-linked polymer is formed around the template which is fixed in the MIPs via labile chemical bond. Then, the bond is broken to remove the template, leaving binding cavities which is uniform in placement of a complementary functional group. However, there are only a limited number of examples that utilize covalent approach in the literature. That is because this approach demands multiple heteroatom functionality to be available in the template.

Because of flexible application and less restrictions, non-covalent imprinting is the most popular imprinting strategy. In the non-covalent approach, the usual preparation process of MIPs could be summarized as polymerization of functional monomer and cross-linker around a template in porogenic solvent. The interactions between the template and MIPs usually are a combination of non-covalent interactions such as H-bonding, electrostatic or π–π interactions. Then, the template is eluted from the MIPs and recognition cavities complementary to the template in chemical functionality, shape and size are formed in the MIPs. These recognition cavities can specifically rebind the template or its analogues from a complex mixture. The main drawback of non-covalent approach is the non-selective binding sites obtained arising from the multitude of complexes with different template-monomer stoichiometry. The pre-polymerization step of non-covalent approach is far from a perfect defined process and it leads to an excess of functional monomer relative to the template exists in the polymerization system. These "free" functional

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monomers are randomly distributed in the polymers and it lead to the non-selective binding sites were formatted.

The third approach is called semi-covalent method and it combines the advantage of both covalent and non-covalent approaches. In the copolymerization step of this strategy, the template interacts with the functional monomer via reversible covalent bond, just as in the covalent approach. Then, the template is removed, leaving an imprint bearing functional groups. In the rebinding step, only non-covalent interactions are exploited, exactly as in the non-covalent approach. The semi-covalent approach is a practical method to obtain MIPs with higher specific recognition ability since it is a feasible way for controlled tailoring of homogeneous binding sites during polymerization.

2.2 Covalent Imprinting

Covalent imprinting approach is a typical method to produce MIPs and it could produce pretty homogeneous recognition sites which exist only in the imprinted cavities in polymer matrix. It demands the template is chemically bound to a monomer by means of a labile covalent interaction. Some reversible condensation reactions such as ketals/acetals, Schiff's base and boronate esters are often utilized to achieve this purpose. However, covalent imprinting is not a common method for the MIPs preparation since the type of reversible condensation reactions is limited.

2.2.1 Covalent Imprinting with Boronate Esters

In covalent imprinting, boronic acids could be used as monomer because the related groups are pretty fit for covalent binding. It can combine with diol-containing molecules to form fairly stable boronic esters. During the reaction, ester formation takes place at relatively low reaction rates and no back reaction occurs in the absence of water. Templates can be removed easily in alcohol or water because boronic esters can be hydrolyzed fastly and completely in these conditions. By contrast, the rebinding of template afterwards is quite slow. Obviously, the rate of equilibration is not satisfying. Luckily, in alkaline solution or in the presence of certain nitrogen bases, esterification reaction of boronic acid with diol occurred, which equilibrate extremely quickly [1, 2]. If the interaction with nitrogen bases takes place intramolecularly, the rate of equilibration would be further accelerated [3].

The boronic acids monomer is very suitable for the template molecule contain diol groups. The template can be bound to the monomer by the boronic ester bond and MIPs with high selectivity could be obtained if all boronic acid binding sites are sufficiently utilized. Wulff and coworker [4, 5] prepared the MIPs using various sugar racemates as templates and boronic acids as functional monomer. The

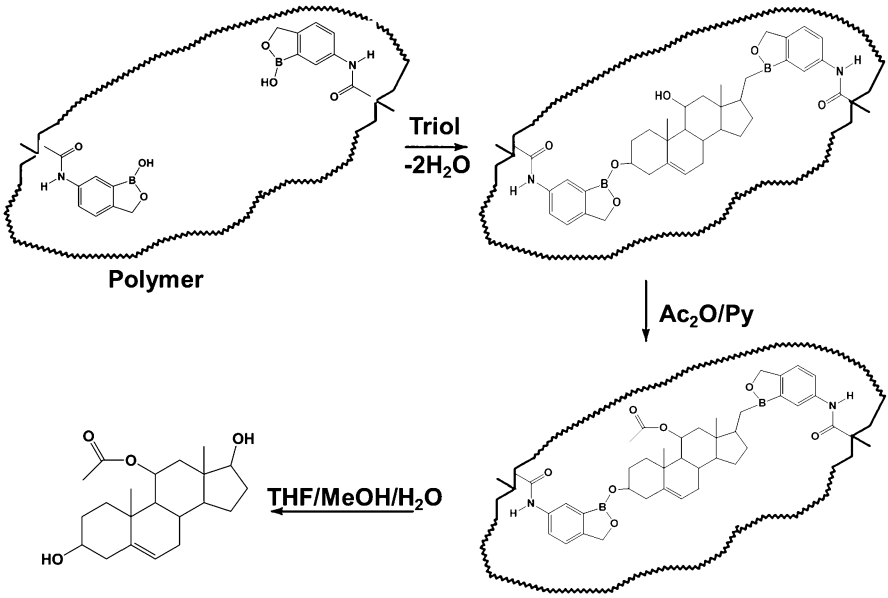

Fig. 2.1 Modification of androst-5-ene-3β,11β,17β-triol on polymer. (Reproduced with permission of Ref. [6])

obtained MIPs were able to resolve racemates of the templates and show a good performance. The boronic acid functional monomer can also be used for binding some other compounds, such as monoalcohols and steroid alcohols (Fig. 2.1) [2, 6].

2.2.2 Covalent Imprinting with Schiff's Bases

Many studies have shown Schiff's bases are also suitable for covalent imprinting [7–9]. The equilibrium rate of the Schiff's bases reaction can satisfy the needs of imprinting with the aid of catalysts or suitable intramolecular neighboring groups. In principle, the active site for covalent imprinting based on Schiff's bases is an amine or an aldehyde. For instance, the aldehyde containing binding sites can be used for the imprinting with amino acid derivatives [7, 8]. The MIPs obtained by covalent imprinting with Schiff's bases have superior selectivity for rebinding the template. That is because two amino groups could be introduced in polymer and two binding groups could provide substrate selectivity. In brief, the selectivity of MIPs obtained by this method is related to the arrangement of the functional groups within the cavity [9].

2.2.3 Covalent Imprinting with Ketals and Acetals

Ketals (Fig. 2.2) for covalent imprinting was also investigated [10–12]. In these researches, diketones with different distances between the keto groups react with polymerizable diols to prepare functional monomers. The MIPs obtained by this strategy showed excellent recognition selectivity with diketones as the template. With these diketones based monomers, the mechanism of the imprinting procedure was studied. The arrangement of functional groups is one major factor that affects performance of the polymer. Furthermore, the size and shape of the template molecules are also important factors for the separability. Similarly, acetals have been successfully employed for the covalent imprinting. A suitable cyclic half-acetal can form full acetals with monoalcohols and this reaction can be used for reversible binding of alcohols.

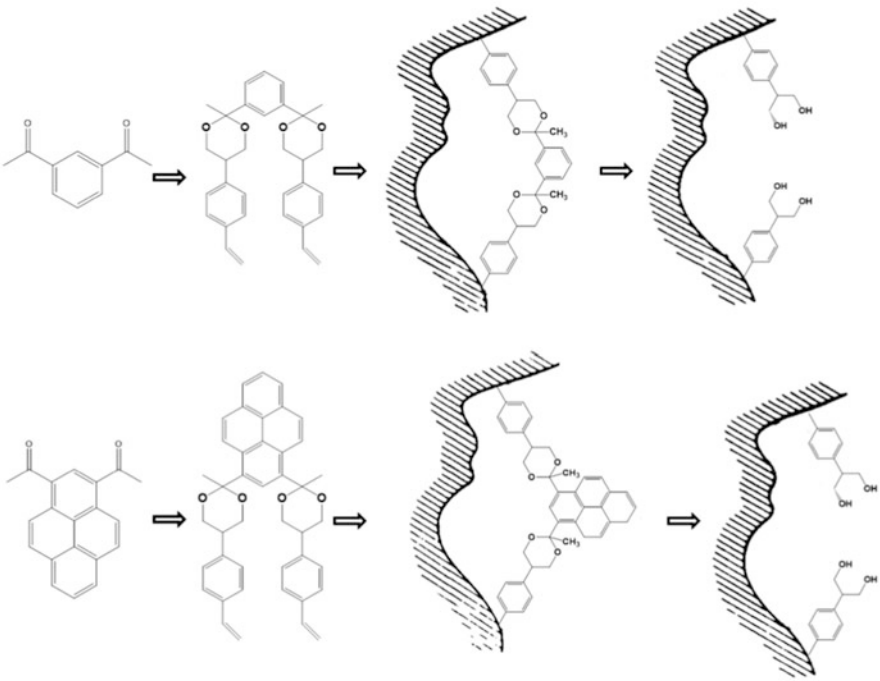

Fig. 2.2 Ketals for covalent imprinting. (Reproduced with permission of Ref. [11])

2.3 Semi-Covalent Imprinting

Both of covalent and non-covalent imprinting methods have its own advantage and disadvantage. Because the template reacts with a certain amount of functional monomer by covalent bond in the polymerization system, the covalent imprinting method remarkably reduced the nonspecific binding sites. It makes that all functional groups present an ideal situation for the imprinting process. However, the complex rebinding process makes covalent imprinting approach not practical for the most applications. Dehydration and hydrolysis reaction for template removal and rebinding template slow the interchange of template with the sites. Furthermore, covalent imprinting is fairly restrictive as it is a challenge to find an appropriate covalent template-monomer complex. Non-covalent imprinting is by far the most important MIPs preparation method. It has many advantages such as simplicity of the synthesis process and broad applicability to a wide range of template structures. The obtained MIPs show excellent properties, such as good mechanical property, high chemical stability and low cost. However, the non-covalent imprinting also has some drawbacks. Since the equilibrium nature of template-monomer interactions, the excess monomer is necessary to displace the equilibrium to form the template-monomer complex. Moreover, the pre-polymerization complexes are formed with an uncontrollable template: monomer stoichiometry. All of these factors can lead to nonspecific binding.

To overcome the problems with covalent and non-covalent approach, a hybrid approach, semi-covalent approach, is proposed. It combines the advantages of covalent and non-covalent method. During the semi-covalent polymerization, the template is bound to a monomer through a reversible covalent bond at first and it can be called template-monomer. After splitting of the template, this step usually achieved by hydrolysis, the generated groups become available to rebinding through non-covalent interactions [13, 14]. Because the imprinting process is covalent, the randomly distributed functional groups from free monomers are limited for the semi-covalent approach and all the binding sites are pretty uniform. Furthermore, template rebinding process is hardly affected by kinetic restrictions.

In the semi-covalent imprinting, template and monomer can be reacted by an ester or amide linkage. The research of Cheong et al. [15] can be considered as a suitable example for this method. At first, the template-monomer was synthesized via esterification of testosterone with methacryloyl chloride in the presence of triethylamine. Then, taken testosterone methacrylate as the template-monomer, EDMA as cross-linker, and chloroform as porogen, the MIPs was synthesized. The obtained MIPs was hydrolyzed with NaOH methanol solution followed by acidification. At last, methacrylic acid residues can be obtained in the polymer and was used for binding testosterone via hydrogen bonding.

For semi-covalent MIPs, removal of the template is achieved by template-monomer hydrolysis. However, template-monomer hydrolysis is usually not easy. Steric crowding is major obstacle in the rebinding process because the steric

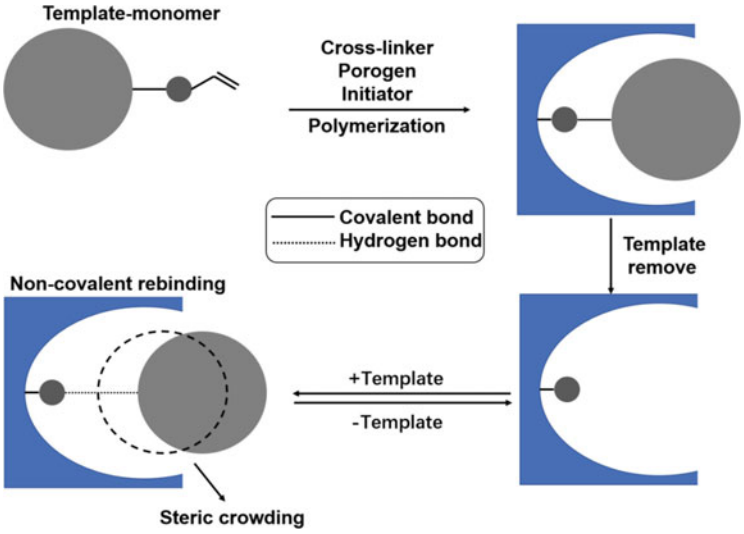

Fig. 2.3 Outline of the semi-covalent imprinting method

requirements of template to monomer in hydrogen bonding contact are different from the corresponding template-monomer (Fig. 2.3).

Hence, some researches about semi-covalent imprinting introduced a linker group which is lost on template removal between the template and the functional monomer to this difficulty [16]. This linker group is known as "spacer" because it works as a spacer between the template and polymer-bound functionality to avoid steric crowding in the process of rebinding.

Chen and coworkers [17] have also adopted semi-covalent imprinting with carbonyl group as sacrificial spacer to synthesis MIP for phenols. In this research, 4-chlorophenyl (4-vinyl)phenyl carbonate was taken as template-monomer, EDMA, 2,2-azobisisobutyronitrile (AIBN), and chloroform was applied as cross-linker, initiator, and porogen, respectively (Fig. 2.4). For removing the template, the MIPs were hydrolyzed using the strategy proposed by Whitcombe and coworkers [14]. The MIPs show superior selectivity for phenols and was successfully applied as HPLC stationary phase in the determination of phenols.

Several other groups can also be used as sacrificial spacers to prepare MIPs. In the research of Chang and coworkers [18], a molecularly imprinted spherical silica particles with controlled sizes was prepared. This material employed carbonyl spacer in template-monomer linked through carbamate linkage. In the presence of dibutyltin dilaurate, the template-monomer complex was synthesized by the reaction of estrone with 3-(triethoxysilyl)propyl isocyanate. Since the bond between template and silica monomer is thermally reversible, the template can be easily removed by thermal reaction.

Furthermore, the template and monomer could also be linked through carbonate. The cholesterol-MIPs were suggested by Lee and coworker [19]. The cholesteryl

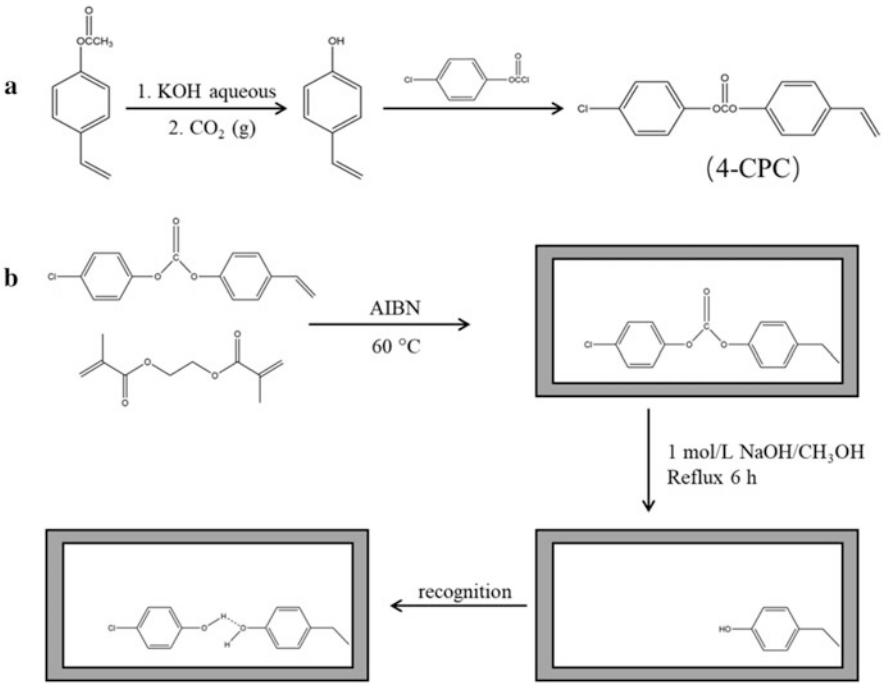

Fig. 2.4 Schematic of the sacrificial semi-covalent method applied in ref. 17. (**a**) The synthesis of template. (**b**) The preparation process of 4-chlorophenol MIPs by semi-covalent method. (Reproduced with permission of Ref. [17])

(4-vinyl) phenyl carbonate which was obtained by the approach of Whitcombe et al. [14] was applied as template-monomer. The MIPs was packed into the HPLC column as stationary phase and the column was used to isolate cholesterol from other steroids. The results also proved that the polymer had a good adsorption capacity for cholesterol.

A variant of the sacrificial spacer approach was employed to imprint pyridine and quinoline via the silyl esters and dimethyl silyl group of silyl ether [20]. In this study, silyl ether derivatized templates were designed for binding nitrogen heterocycles (Fig. 2.5a). The dimethyl silyl group of silyl ether and silyl esters could be acidic hydrolysis or nucleophilic displacement with fluoride ion under mild conditions (Fig. 2.5b). It is means that the templates can be removed easily. In addition, silyl ether chemistry condensed aromatic templates and improved the solubility of templates in nonpolar porogens in MIPs synthesis. The proposed method was successful in creating affinity in MIPs for the nitrogen heterocycles.

There is a method based on urea linkages to introduce amine groups into the MIPs [9]. In this kind of semi-covalent imprinting approach, urea linkage is formed by linking two nitrogen atoms with carbonyl group. The C=O group in urea linkages was applied as sacrificial spacer. In the research of Lubke et al. [21], the bis-N-(4-vinylphenyl)urea derivative of 2,8-dichloro-3,7-diaminodibenzodioxin, used the

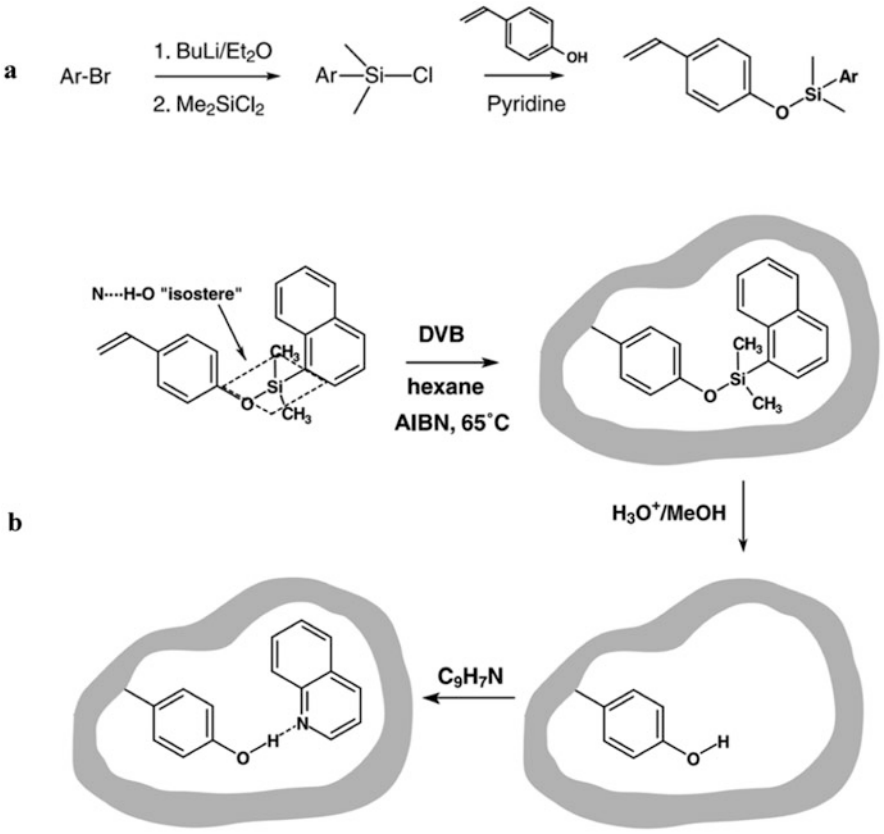

Fig. 2.5 (**a**) Preparation scheme for the synthesis of silyl ether templates. (**b**) Schematic of the imprinting process using a silyl ether as an N···H–O isostere and single atom sacrificial spacer to create recognition sites for nitrogen heterocycles. (Reproduced with permission of Ref. [20])

C=O group spacer to introduce aromatic amines into the MIPs after removal of the template (Fig. 2.6). As a result, MIPs prepared with the diurea template-monomer has very good recognition performance for 2,3,7,8-tetrachlorodibenzodioxin.

Sacrificial spacer gives the semi-covalent imprinting a unique advantage to avoid steric crowding. However, due to the complicated preparation procedure of template-monomer before MIPs polymerization, only a few compounds, such as cholesterol [14, 19], estrone [18], propofol [22, 23], menthol [24, 25], DDT [26], and 2,3,7,8-tetrachlorodibenzodioxin (TCDD) [21], could be imprinted by the semi-covalent method.

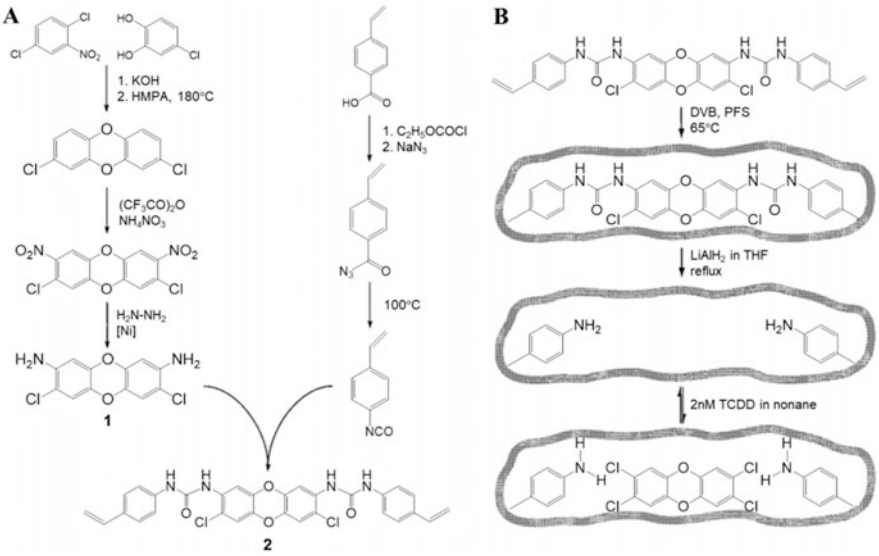

Fig. 2.6 (**a**) Preparation of the diurea template 2 and (**b**) Schematic of the synthesis the template 2 MIPs showing the positioning of aromatic amine groups in the recognition site through the urea functionality (incorporating a carbonyl spacer). (Reproduced with permission of Ref. [21])

2.4 Non-covalent Imprinting

Until now, non-covalent imprinting is the most widely used way for the preparation of MIPs. It is a kind of self-assembly approach and a simplest method to introduce functional groups into the cavities of polymer. The weak non-covalent intermolecular interactions of template-functional monomers have been employed for the template recognition. These are many types of non-covalent interactions and one of the most important is hydrogen bonding interaction due to the specific geometric directionality. The major weakness of non-covalent systems is the heterogeneous binding sites which are obtained from the non-well-defined pre-polymerization step. The formation of template-monomer complexes with different ratios leads to different binding sites, and excess monomers are used in order to form the complexes of template-monomer also might lead to non-selective binding sites [27].

2.4.1 The Nature of the Pre-polymerization Complex

In non-covalent imprinting, it is normally assumed that a pre-polymerization templates-functional monomer complex is formed before the polymerization reaction. Since templates and functional monomers might have multiple binding sites, the

interactions between them could be pretty diversity. It is means that the pre-polymerization complex system is pretty complexity. The interactions between templates and functional monomers could be affected by some factors, such as the property of solvent (the polarity or hydrogen bonding strength) and the reaction temperature. Generally, low polarity solvents and lower temperature are beneficial to the formation of hydrogen bonding interaction in the pre-polymerization complexes and polar solvents are good for ion pair and other strong dipolar interactions. However, it is important to note that the choice of solvent is usually limited. For example, the solubility of the template in solvent must be taken into account in practice and the solvent also has an effect on the structure and porosity of the MIPs. Under these constraints, only a few reagents could be employed as the solvents for MIPs.

The information about the strength and stoichiometry of template-functional monomer interactions helps to understand the nature of the pre-polymerization complex and some experimental studies have been employed to gather the information. Many researches have been proved that the spectroscopic methods, including FT-IR [28], UV-Vis spectrometry [29–31], and nuclear magnetic resonance (NMR) [32–35], are useful to understand the pre-polymerization complex. For instance, by comparing the FT-IR spectra of MIP to the spectra of NIP, whether the molecular imprinting of template occur or not during the preparation can be shown directly [36].

UV-Vis spectrometry is also a well-established method to identify whether the monomer could interact with template and form a stable pre-polymerization complex in a certain solution. Zhang and coworkers [29] have investigated the interaction between MAA and erythromycin by general UV-Vis spectroscopic analysis. The hydroxyl groups and tertiary amine group of the erythromycin can form hydrogen bond and ionic bond with the related monomers, respectively. In this work, MAA was selected as the monomer for the preparation of MIPs. The results proved that the adsorption spectrum of a constant concentration of erythromycin will change with the addition of MAA. If the MAA increased, the adsorption spectrum was found to be red shifted. It is means that new chemical bonds were formed between erythromycin and MAA in the pre-polymerization system. However, FT-IR and UV-Vis spectroscopy are not always sensitive to the changes in the pre-polymerization complex. Application of these two spectroscopic methods is limited in the study of pre-polymerization system.

The NMR technique is the most commonly used for illustrating the interaction type and intensity of the template-monomer complex in non-covalent imprinting systems. The changes of the interactions between template and functional monomer will be reflected in NMR spectrum, because the interaction will lead to local changes in the electronic environment of the parts of the molecules involved. ^{1}H-NMR is currently used in structure analysis of the pre-polymerization complex. In the case of ^{1}H-NMR titrations, chemical shifts in ^{1}H-NMR spectra will change during titrations of the template with the monomer. In the study of Karlsson et al. [37], the bupivacaine MIPs was prepared and a model for the molecular recognition in bupivacaine MIPs has been established based on a series of ^{1}H-NMR titrations.

For simplify the interpretation of the resulting ^{1}H-NMR spectra, acetic acid-d_4 was taken as an analogue for the functional monomer (MAA). Toluene-d_8 and chloroform-*d* were taken as porogens which are commonly used in the preparation of MIPs. The results shown that the chemical shifts of ^{1}H resonances were changed along with the acetic acid-d_4 concentration increase. The resonance from the amide proton of template (bupivacaine) is primarily influenced by acetic acid-d_4. The downfield shift was observed and it was caused by the formation of hydrogen bonding interactions between template and functional monomer analogue.

Work by Bermejo-Barrera and coworkers [38] details the use of NMR and nuclear overhauser effect (NOE) for elucidating the pre-polymerization complex and the interaction type and intensity of the template-monomer preassembled system was investigated. In this research, cocaine hydrochloride (COCH), MAA, and EDMA was taken as template, functional monomer, and cross-linker, respectively. The hydrogen bonding interactions of MAA–COCH and EDMA–COCH were evaluated by NOE NMR. The results proved that the MAA–COCH interaction formed by the interaction between the protonated amino group of COCH and the carbonyl group of MAA. There is an N–H···O hydrogen bond between template and monomer. The interaction of COCH-EDMA was also studied and it is demonstrated that the COCH-EDMA interaction was formed between the amino group of COCH and the ester carbonyl group of EDMA through N–H···O hydrogen bond. Moreover, the selection of the best template-monomer ratio was also achieved with the aid of NMR.

There have been many researches on the characterization of pre-polymerization complex by ^{1}H-NMR [32, 39–41]. However, this method leads to very complicated ^{1}H-NMR spectra with multiplets. The adjacent chemically non-equivalent H atoms will cause the coupling and the splitting of ^{1}H-NMR spectrum. Dubey and coworkers [42] used ^{31}P{^{1}H}NMR to optimize imprinting conditions of derivative of methylphosphonic acid. Since the chemical shift change for the free template and bound monomer template are in proportional to the strength of interactions, the interactions could be monitored by the ^{31}P{^{1}H} NMR analysis of the template which contains P atom. The advantage of ^{31}P{^{1}H} NMR is that the spectrum only displays one single peak for each P atom within the template. Compared to ^{1}H-NMR, ^{31}P{^{1}H} NMR spectrum can be interpreted more easily. Therefore, ^{31}P{^{1}H} NMR could be an alternative tool for the research the template-monomer interactions.

These researches proved that NMR has been shown to be valuable tool for the preparation of MIPs. Furthermore, some new advanced techniques also applied the characterization of pre-polymerization complex. Quartz crystal microbalance (QCM) technique has been usually used to analyte detection of MIPs in recent years [43–46] and surface plasma resonance (SPR) is especially useful for analyzing the thermodynamics and kinetics of intermolecular interactions between biomolecules [47, 48]. These techniques can help to obtain the information of pre-polymerization complex. However, there are still some limitations to them. For example, a template grafting progression is required before the real measurement. Hence, in order to truthfully characterize the interactions in the pre-organization system, these new advanced techniques need further development

in the future. In practice, these instrument analysis techniques mentioned above are frequently used in combination to get as much information of the pre-polymerization complex as possible.

There are many factors that have an effect on the template-monomer interactions. The ratio of template to functional monomer, polymerization temperature and pressure are the important factors and most studies involve the optimization of these factors. A proper proportion of template and functional monomer ensures that high affinity sites can be created in MIPs and nonspecific binding sites can be minimized. Furthermore, the polymerization temperature has been regarded as an important influence on the template-monomer interactions. Since the high temperature is considered to disrupt the interactions, initiator with lower temperatures or photochemical initiation at low temperature is usually employed in practice [49]. It is important to note that free radical polymerization is an exothermic process. Heat management is important for some MIP synthesis methods. For instance, heat convection is severely hampered in the monolithic MIPs or MIPs prepared by bulk polymerization [50]. Meanwhile, because the excess heat can be removed from the MIPs more efficiently, the synthesis methods based on polymerizations in dispersed phases, such as suspension, emulsion, and precipitation polymerization, less affected by exothermic process. The research about effects of pressure on the efficiency of imprinting is relatively small at present. The research by Sellergren et al. [51] shows that the chromatographic capacity factor for an ametryn MIP increases as the pressure of the polymerization increases. However, the studies of the effects of pressure on MIP synthesis are still very limited.

2.4.2 Non-covalent Imprinting with a Single Functional Monomer

The functional monomers play a key role in non-covalent imprinting system. They can form a pre-polymerization complex with the template through functional groups. A suitable functional monomer can strongly interact with the template and it is decisive to generate high affinity binding sites [52, 53]. In most cases, one single functional monomer was employed in the MIPs polymerization. It can be regarded as the simplest and the most widespread method to non-covalent imprinting. However, it does not mean that the character of the pre-polymerization complexes is also simple in this situation. There are some other interactions exist in the pre-polymerization system. For example, the self-association of functional monomer needs to be taken into account.

Since the molecular imprinting technique has been introduced, many functional monomers have been applied in non-covalent imprinting. Some of them have been widely used, while others have only been reported in a few or even one literature. Generally speaking, functional monomers can be classified into acidic, basic, and neutral monomers according to the nature and the acidic monomers, especially

carboxylic acid-based monomers, have been considered as the most successful monomers. For example, methacrylic acid (MAA) can be the most popular functional monomer due to its hydrogen bond donor and acceptor characteristics. In fact, carboxylic acid-based monomers can interact with templates in various ways, includes not only H-bond donors and H-bond acceptors but also ion pair formation, weaker dipole-dipole interactions and so on. The study of Zhang et al. [54] explained in detail why MAA has been considered as a "universal" functional monomer for molecular imprinting. It is important to note that the dimerization was once considered as a drawback of MAA in non-covalent imprinting. However, in this research, it was proved that monomer dimerization can actually improve the imprinting efficiency. Because although the number of template binding sites was reduced by monomer dimerization, the number of non-template binding sites was reduced even more. It leads to that the templated sites were increased in percentage terms. Furthermore, MAA have an effect on the structure and morphology of the resulting MIPs. It has been proved that high molar fractions of MAA would result in the large pore size of MIPs which can help improve the binding capacity of the polymers [55].

Furthermore, in a series of studies, Takeuchi and coworker proved that trifluoromethyl acrylic acid (TFMAA) can be a superior functional monomer for non-covalent molecular imprinting. They indicated that more acidic functional monomers could be preferable for imprinting a basic template molecule [56–58]. Until now, many acidic monomers, such as acrylic acid, itaconic acid, and vinylbenzoic acid, have been applied in non-covalent molecular imprinting researches [59–61]. In general, as the most widely used monomers, they should be highly effective and easily available.

Compared with the acidic monomers, there are by now relatively few literatures using basic monomers. Under the premise, the vinyl pyridines are perhaps the most widely used from the basic monomers. It should be noted that vinyl pyridines are acidic in nature. However, in their basic form, they interact strongly with electron deficient aromatic rings, as well as through acid-base interactions and hydrogen bonding. In many studies, vinyl pyridines have proved useful because they often interact strongly with templates. In the research of Kempe and Mosbach [62], (S)-naproxen MIPs was prepared by using 4-vinyl pyridine as functional monomer. It was assumed that 4-vinyl pyridine interacted with the carboxy group in naproxen by ionic interactions. The resulting MIPs were employed as a chiral stationary phase in HPLC and the resolution of racemic naproxen can be achieved on the MIPs stationary phase efficiently. The major drawback of vinyl pyridines is that the strong k–k interactions results quite high levels of nonspecific binding of templates. Furthermore, vinyl imidazole could be a useful monomer. A porous MIP thin-film was fabricated (Fig. 2.7) and used as a microextraction adsorbent for the selective extraction of trace amounts of polycyclic aromatic sulfur heterocycles (PASHs) from seawater [63]. Taken 1-vinylimidazole as the functional monomer, the optimized MIP thin-film was synthesized. The novel MIP thin-films showed good selectivity, excellent binding behavior, and reproducibility for PASHs. Vinyl imidazole monomers also can be used in metal complexation systems, but beyond that it has been

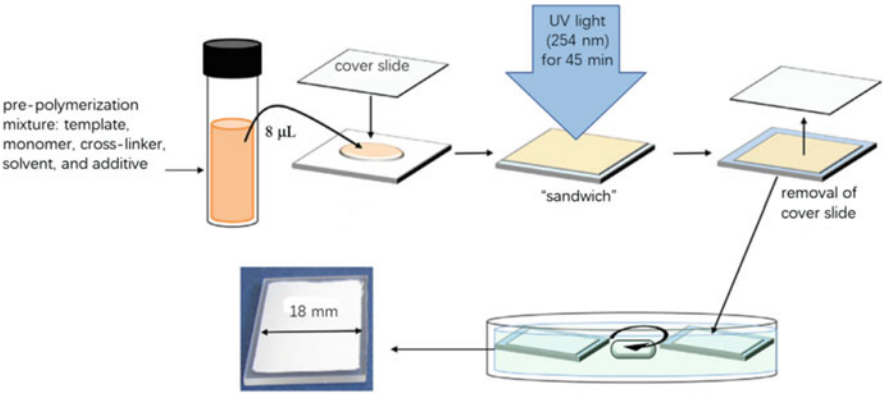

Fig. 2.7 Fabrication process of MIP thin-film on a glass slide. (Reproduced with permission of Ref. [63])

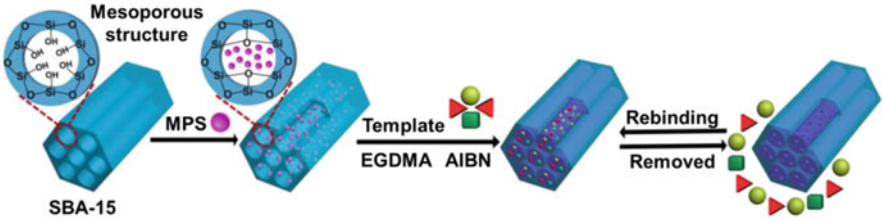

Fig. 2.8 Schematic representation for the preparation of the SBA-15@MT-MIPs. (Reproduced with permission of Ref. [64])

little used. In principle, basic monomers have been effective in some researches, but in general yield less satisfactory results than acidic monomers.

Many neutral monomers have also been widely in molecular imprinting. Acrylamide and its N-alkyl derivatives can be the most successful neutral monomers. In the study of Sun et al. [64], the multi-template MIPs were fabricated using three saponins as multi-template, acrylamide as functional monomer, EGMA as cross-linker, mesoporous silica (SBA-15) as solid support, and ethanol as porogen (Fig. 2.8). The obtained MIPs were reusable and had excellent stability. The materials were employed for the efficient remove impurities and enrichment of the trace level of saponins from plasma samples simultaneously. Furthermore, five different acrylamide-based functional monomers were evaluated by Hayes and coworkers [65]. In this work, myoglobin protein was taken as template and the possible binding interactions between template and the acrylamide-based functional monomers was investigated by using computational technique.

It is worth mentioning that *N*,*O*-bismethacryloyl ethanolamine (NOBE) has aroused extensive interest as a new neutral monomer for molecular imprinting [66]. The NOBE was used to simplify the preparation of MIPs since it combines the functionality of template binding and cross-linking (Fig. 2.9). The corresponding

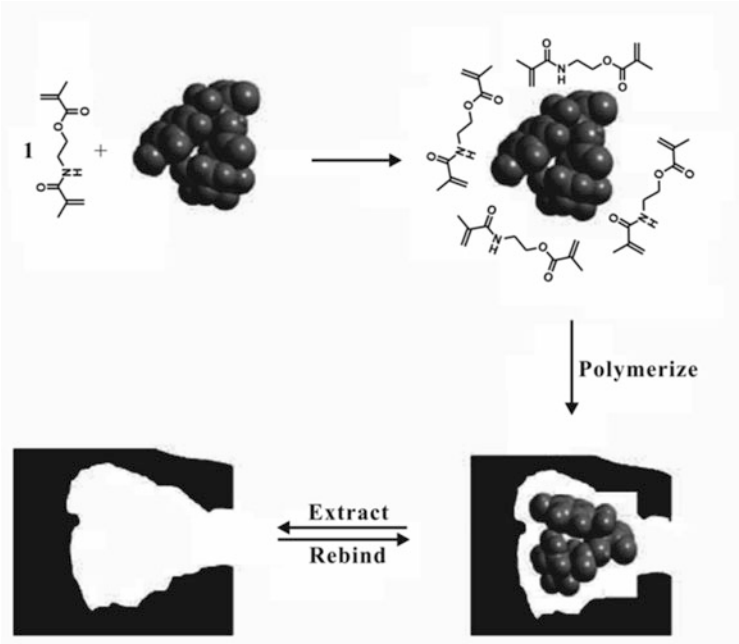

Fig. 2.9 Schematic of the simple OMNiMIP imprinting method with BOC-L-tyrosine as template. (Reproduced with permission of Ref. [69])

studies showed that the higher performance of the one monomer molecularly imprinted polymers (OMNiMIPs) can be achieved compared with the MIPs obtained by the traditional monomer [67–70]. However, this kind of novel monomers for MIPs are still limited by now and more in-depth researches are required.

Some functional monomers have special structures and are hard to categorize according to the criteria mentioned above. For instance, represented by β-cyclodextrins (β-CDs), a series of cyclic oligosaccharides with a hydrophilic exterior and a hydrophobic cavity have been applied as candidate monomers for molecular imprinting [71]. β-CDs can form inclusion complexes with the template through various intermolecular interactions, such as hydrogen bonding, electrostatic interactions, van der Waals forces, and host-guest interactions. In addition, in the presence of a proper cross-linker, the hydroxyl group on β-CDs can take as a polymerization terminal to form a stable polymer matrix. For instance, Liu and coworkers [72] polymerized the aesculin MIPs using β-CD as functional monomers. The study showed that the resulting MIPs have an affinity for template. Moreover, the polymer displayed good controlled release behavior for aesculin.

Miyata and coworkers [73] prepared bisphenol A (BPA) responsive hydrogels with β-CD via MIT. In this work, the β-CDs with acryloyl group were used as ligand (Fig. 2.10). In the pre-polymerization process, a template-functional monomer complex with a sandwich structure, CD-BPA-CD complex, was formed. Moreover,

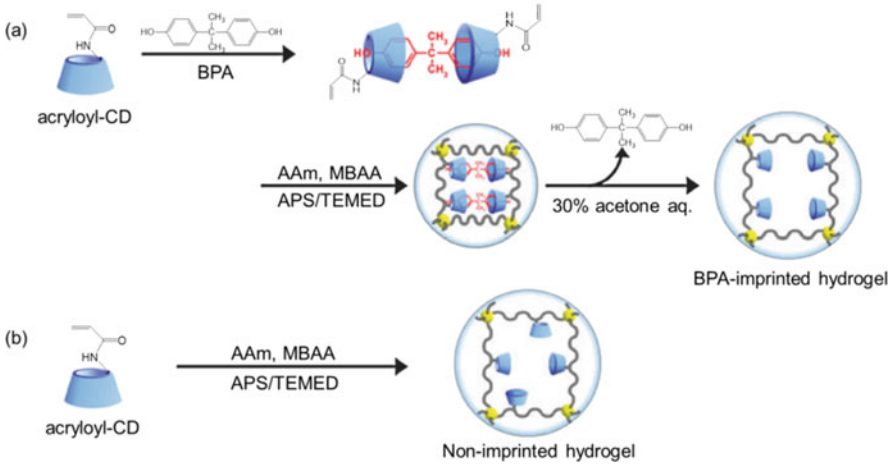

Fig. 2.10 Synthesis of BPA-imprinted (**a**) and non-imprinted hydrogel (**b**). (Reproduced with permission of Ref. [73])

the sandwich-like complex can also act as cross-linker and it makes the apparent cross-linking density of the BPA-imprinted and non-imprinted hydrogels increase.

2.4.3 Imprinting with Combinations of Monomers

The performance of the template-functional monomer interactions is a very important influence to the non-covalent imprinting. The non-covalent interactions can be enhanced by multipoint interactions [74]. Hence, it is very promising to combine the potential specific interaction of different monomers in molecular imprinting. Until now, there are plenty of examples in the literature to demonstrate molecular imprinting by using combinations of two or more functional monomers.

The first application of multi-functional monomer for MIPs was proposed by Mosbach and coworkers [75]. As mentioned above, 2-VP is weakly basic and MAA is acidic. In this study, these two chemically distinct functional monomers were used simultaneously to prepare the MIPs. The resulting MIPs showed improved recognition ability compared with MIPs which were obtained by only one monomer.

Cao and coworkers [76] proposed an efficient strategy for preparation of bifunctional monomers perfluorooctanoic acid (PFOA) MIPs by using 4-vinyl pyridine (4-Vpy) and 2-(trifluoromethyl) acrylic acid (TFMAA) as binary functional monomers (Fig. 2.11). The resulting MIPs was used to specific recognition for PFOA and perfluorooctanesulfonic acid (PFOS) from aqueous solution. The synthesized polymer showed good adsorption capacity and selectivity performance for PFOA and PFOS.

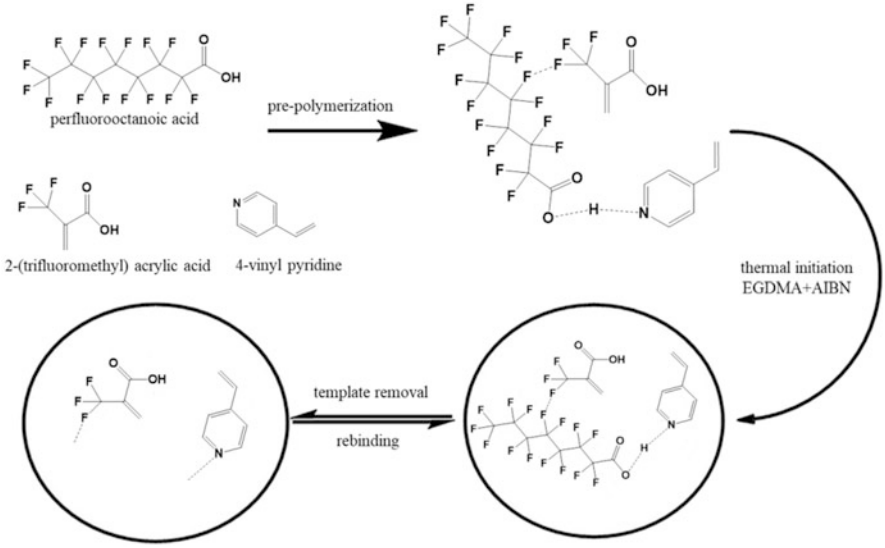

Fig. 2.11 The schematic of the preparation of the binary monomers MIPs. (Reproduced with permission of Ref. [76])

Li et al. [77] prepared MIPs toward norfloxacin (NOR) by using aminopropyltriethoxysilane (3-APTES) and methacryloxypropyltrimethoxysilane (MTEOS) as functional monomers. The MIPs with bifunctional monomer shows a better selectivity for norfloxacin compared with structured analogues and nonstructured analogues. The MIPs was evaluated by various techniques and it was proved that the polymer possessed a good adsorption capacity and an impressive select factor. Of course, there are more applications of MIPs obtained by combinations of functional monomers were proposed by many different research groups [78, 79].

Generally speaking, application of binary functional monomers is more common in the literature. But there are also examples of utilization of multi-functional monomers (more than two) for MIPs. In the study of Haruki and coworker [80], the MIP toward native lysozyme promotes the folding of chemically denatured lysozyme was prepared by using multi-functional monomers (acrylamide, MAA, and 2-(dimethylamino)ethyl methacrylate) as functional monomers. High refolding yield was obtained because of multi-non-covalent interaction between the template and functional monomers.

The application of dual or multiple functional monomers is an effective way to improve the selectivity of MIPs and especially it is a good strategy to imprint macromolecule templates. However, this method should be further improved. For example, the selection of dual/multiple functional monomers for MIP preparation is a hard work due to the complication of pre-polymerization mixture. All kinds of the interactions, such as template-monomer 1, template-monomer 2, and monomer 1-monomer 2, should be considered simultaneously during the optimization.

2.4.4 Custom-Designed Monomers

The common monomers are usually commercially available. However, the performance of these monomers is not good enough for some templates with special structure. The monomers with more hydrogen bonding sites can enhance association constants and the resulting MIPs have more selective recognition sites. For example, a polymerizable bis-urea monomer designed and synthesized by Hall et al. [81]. And the new monomer can interact with the L-glutamyl residue of methotrexate. Barbiturate MIPs were prepared using a new functional monomer by Tanabe et al. [82]. This new monomer, 2,6-bis-acrylamidopyridine, can interact with templates though multiple hydrogen bond. The concave H-bond donor-acceptor-donor configuration of the monomer can match the convex acceptor-donor-acceptor structure of the template. Moreover, the NOBE which is used for the preparation of one monomer MIPs (OMNiMIPs) could be also considered as custom-designed monomers (see Sect. 2.4.2 of this book) [66].

Room temperature ionic liquids (RTILs) could be defined as molten salts with melting points near room temperature. RTILs have been considered as a novel kind of green solvents with interesting and unique property, such as non-volatility, non-volammability, good ion density, and high ionic conductivity etc. RTILs have been increasingly applied in MIT and play multiple roles in MIT. For instance, RTILs are employed as functional monomers and the resulting MIPs have satisfactory recognition ability to template. RTILs could interact with various molecules such as the common organic compounds and biomacromolecules by hydrogen bonding, electrostatic, anion-exchange, π–π interactions and so on [83, 84]. As a "designer solvent," it offers a greater degree of flexibility, which makes RTILs applied for various purposes in MIT. Moreover, many studies have showed that RTIL-based MIPs have excellent performance in aqueous solution.

In the research of Wang's group [85], a new chlorsulfuron MIPs was synthesized by using vinylimidazolium RTIL, 1-vinyl-3-butylimidazolium chloride ([VBIM]Cl), as a unique functional monomer. This kind of new MIPs was prepared by bulk polymerization and showed good selectivity and adsorption/desorption for chlorsulfuron. The binding selectivity of the obtained MIPs was investigated by competitive adsorption using the mixture solution composed of template and related analogues. The novel MIPs revealed good selectivity of 47.2% for template, which was higher than that for the analogues. Furthermore, it is important to notice that low concentration chlorsulfuron could be detected by the proposed MIPs in water solution. Up to now, the studies of the imprinting of normal small organic molecules are very active and plenty of relevant researches have been published. However, fabrication of MIPs for large molecules such as enzyme, polypeptide and proteins has been considered as the toughest challenge in the field of MIPs. Most of the time, this is due to lack of suitable functional monomer for these macromolecules. Fortunately, it is one of effective methods to solve this problem by using RTILs monomers. Thymopentin (TP5) is a biomacromolecule and it is consisted by five amino acids. The purify TP5 is hard to extract from complicated biological samples.

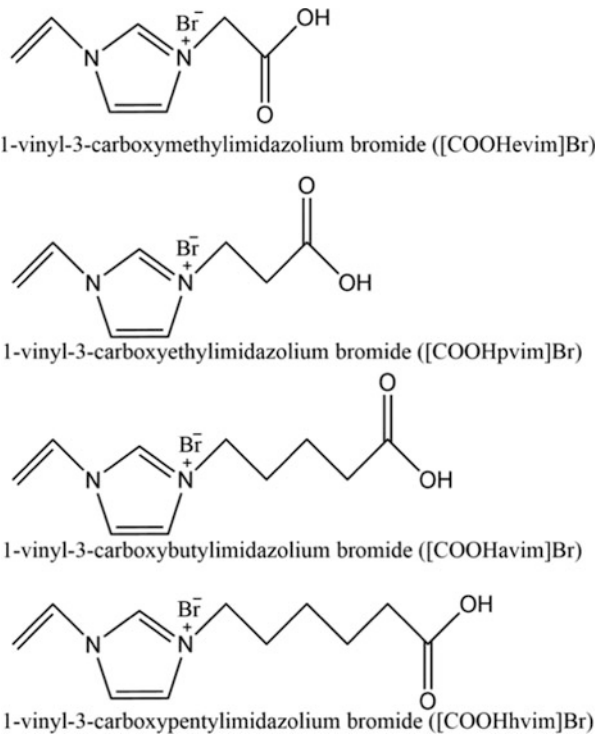

Fig. 2.12 The molecular structure of these four RTIL functional monomers

In a study, a method to prepare TP5 magnetic MIPs by surface-initiated ATRP polymerization was developed [86]. Four candidate RTILs functional monomers, 1-vinyl-3-butyl imidazolium chloride ([VBIM]Cl), 1-vinyl-3-propyl imidazolium chloride ([VPIM]Cl), 1-vinyl-3-ethyl acetate imidazolium chloride and 1-vinyl-3-ethanamide imidazolium chloride, was studied (Fig. 2.12). Molecular dynamics (MD) simulations was employed for computational design of MIPs to find the optimal experimental scheme. In the research, the MD method was employed for investigating the interactions between TP5 and the RTILs monomers.

At last, the TP5 magnetic MIPs were synthesized based on the results of MD simulation. It is proved that the proposed magnetic MIPs prepared with RTILs monomer have excellent specific recognition to TP5.

2.5 Monomer Selection and Optimization Methods

The purpose of molecular imprinting technology is to acquire polymer with high performance. However, it is difficult to predict the performance of any MIPs according to its composition. The optimization of formulation components for MIP preparation is an onerous and time-consuming task. During the optimization

process, lots of variables should be considered simultaneously such as the type and the optimum ratio of formulation components for MIPs. The conventional MIPs synthesis and processing is usually based on the prior literature and this leads to a tendency toward sticking with what has worked in the past. The mechanism of imprints formation and recognition are still not entirely clear. Furthermore, variables influencing performance of MIPs were dependent, making it hard to explain how these variables will interact with each other. Up to date, various approaches have been developed to investigate the related mechanism, such as combinatorial approaches, chemometric methods, and molecular modeling approaches. These methods were used to prepare MIPs with high selectivity easily and employed to simplify the preparation of MIPs.

2.5.1 Combinatorial Approaches to Optimization

Use the imprinting process could be affected by many variables, the optimization needs to be achieved by a multivariate strategy. An optimization approach named combinatorial approach was independently developed by two different teams [87, 88]. This method used an automated system to dispense small volumes of different imprinting mixtures into glass vials. It is means that the composition, such as templates monomers, cross-linkers, solvents, and initiators, is systematically varied. After polymerization and extraction of the template, a solution of template is filled into the vials for adsorption measurements. Then, the affinity of the different MIPs could be determined by analyzing the remaining template concentration in the solution. The key to combinatorial approaches is that a sufficient quantity of polymer compositions is synthesized and evaluated. In the related work [88], 96-well microtiter plates were applied to produce MIPs with different compositions. A fluorescence-based screening method was applied to speed up the evaluation of MIPs performance. The optimized MIPs were prepared by using conventional large-scale synthesis and the results can be validated by screening the "MiniMIP" library. The similar approach has been used to develop optimized MIPs for different templates and application formats [89–92].

However, this approach has not been widely used at present. Because in order to make the process automatic, a complex and costly equipment had to be build or bought. Hence, improvement on the method is very necessary. It is means that a simple and fast screening of MIPs can be achieved. For instance, Bruggemann and coworkers [93] proposed an approach based on ultrafiltration membrane modules. A MIPs membrane was prepared and used for screening procedures. In this approach, the affinity of each MIPs membrane toward the template is studied by pumping a defined amount of the template solution through the MIPs membrane. By measuring the concentration of the template in the permeate solution, the adsorbed amount which is related to the control polymer membrane can be obtained. The results proved that the proposed method can be used for finding optimized template-cross-linker ratios in different porogens by screening MIPs of various compositions.

2.5.2 Chemometric Methods

Chemometrics could be considered as a large class of approaches, which applies the approaches of mathematics, statistics, and computer technology. In practice, chemometric methods are often used to the optimization of system parameters with a significant impact on the synthesis of MIP and corresponding physical and chemical performance [94, 95]. Conventional approaches for MIP optimization only generate limited information although a large amount of experimental research has been made. By contrast, the relevant variables could be optimized systematically and simultaneously with the help of chemometrics in experiment design. Obviously, compared with the conventional univariate experimentations, the experiment designed by chemometrics require less measurements. Furthermore, chemometrics could also be applied to reveal the interaction between the variables. Hence, these advantages of chemometrics makes the optimization process of MIP preparation much efficient and simpler [96].

In the research of Li and coworkers [97], a rational design of photonic MIP films with the aid of chemometrics was proposed. The response surface methodology (RSM) based on central composite design (CCD) was used to the design of the novel photonic materials (Fig. 2.13). RSM was applied to explore the interactive influence of different fabrication parameters and the key parameters related to the sensing performance of the photonic MIP were confirmed with the aid of chemometric method. As a result, the dominant factor (cross-linker) for the preparation of photonic MIPs can be determined and the optimum ratio of monomer, cross-linker and solvent can also be confirmed which made the production of materials the best template molecular recognition abilities. This research proved that the chemometrics can be applied to optimize the factors which were associated with the preparation of photonic MIPs and the optimum formulations of materials can be obtained with fewer experiments.

For the optimization approaches of conventional MIP, univariate experiments must be carried out, which is laborious, time-consuming, and uneconomic. Davies et al. [94] proposed an effective chemometric method for the optimization of MIPs. In the research, a rational design method named three-level full factorial design was applied for the preparation and optimization of sulfonamides MIP. With the aid of the chemometrics, the optimum ratio of template: monomer: cross-linker for the sulfonamides MIP can be predicted exactly. In another work [98], rational design was used to select cross-linker. For the preparation of zidovudine (AZT) MIP, two candidate cross-linkers, divinylbenzene (DVB) and trimethylolpropane trimethacrylate (TRIM), were investigated. The results obtained by adsorption experiments and molecular modeling showed that the DVB cross-linker was more suitable for AZT MIPs. Furthermore, the results obtained by the static adsorption experiments showed that the DVB-based AZT MIPs had the highest imprinting factor. It is means that the optimal cross-linker could be selected based on the strength of the template-cross-linker interaction. In the study of Muhammad et al. [99], a water-compatible MIPs was prepared. To simplify the experimental process,

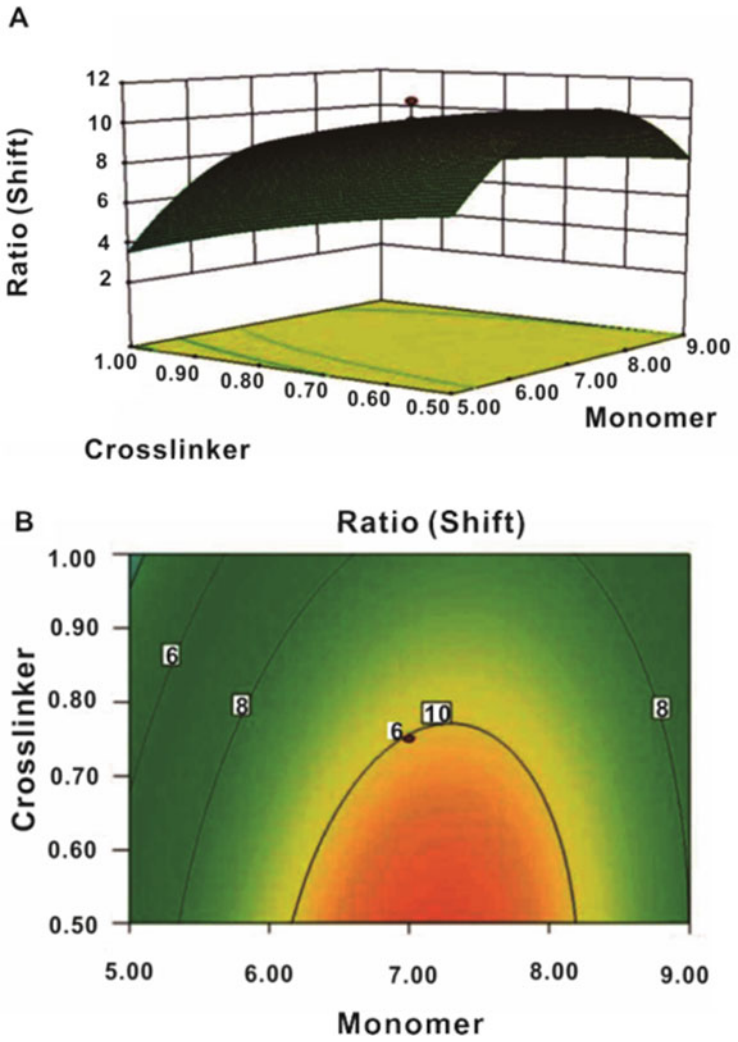

Fig. 2.13 Response surface plot (**a**) and contour plot (**b**) of the combined effects of the monomer and cross-linker on ratio (shift). (Reproduced with permission of Ref. [97])

a new rational design approach based on screening library of non-imprinted polymers (NIPs) was developed. The organized NIP library contains 18 cross-linked co-polymers. These co-polymers were obtained by the monomers which are normal to MIP. In this work, 4-vinylpyridine (4-VP) was selected as the most suitable monomer for preparing amiodarone MIPs by using the proposed method. This research also indicated that a good correlation of the screening tests and modeling of template-monomer interactions can be obtained by the computational approach.

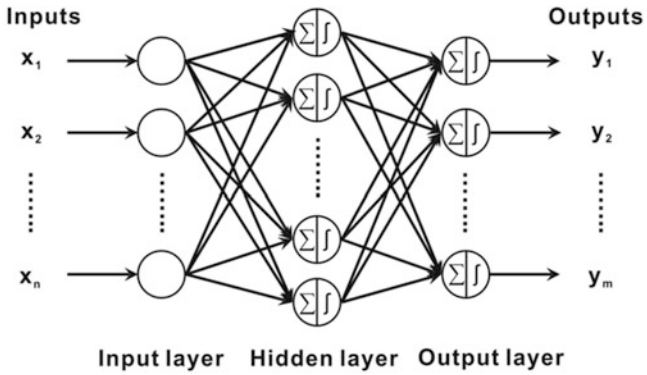

Fig. 2.14 Schematic diagram of a three-layer feed-forward back-propagation neural network used in Ref. [100]. Circles represent neurons and the connection between neurons represents weights. The summation and sigmoid symbol represents summation and sigmoid transfer function, respectively. (Reproduced with permission of Ref. [100])

The results proved that the proposed method is a potential common computational and combinatorial approach for the preparation of MIPs.

Artificial neural networks (ANNs) are a kind of bionic algorithms by imitating biological neural networks and it has found an increasingly wide utilization in many fields. ANN could obtain the best approximation of the practical problems by large learning and training. In the research of Prachayasittikul and coworkers [100], ANN has been brought into the molecular imprinting technique. Briefly, the computed molecular descriptors of template, functional monomer and mobile phase descriptors were chosen according to the magnitude of imprinting factors (IF) of MIP. Then, the IF was calculated by ANN and the results showed that ANN can be considered as a powerful tool for predicting the feasibility of potential template-functional monomer complex before the practical experiments (Fig. 2.14). The unique estimation ability of ANN provided insights on the feasibility of the interaction between template and monomer.

The experiment design has also been applied to optimize the reaction parameters' impact on the performance of template recognition for MIPs preparation.

Kempe and Kempe [101] used multivariate data analysis and the statistical experimental design to optimize the parameters in the model. In their research, MIP bead libraries were built by using the statistical experimental design. The amounts of MAA, TRIM and acetonitrile were taken as the parameters to optimize. The ratio of the amount of free template to the amount binding in the pre-polymerization namely partition coefficient was taken as the response information. Meanwhile, experimental design was achieved by a composite face-centered (CCF) quadratic model. The data were processed by the multiple linear regression (MLR) and the corresponding results were used to demonstrate the prediction and the goodness of fit of this approach.

MIPs usually have a vast range of binding affinities since MIPs have hydrophobic surface and hydrophilic surface simultaneously. Hence, MIPs have specific and

nonspecific binding sites. The balance between electrostatic interactions and hydrophobic would influence the type of binding sites on MIP surface. As a result, it is difficult to discriminate the function from binding data. Moreover, the study on MIPs binding ability with the template is also a very important task for researchers. Nicholls and coworkers [102] used chemometrics to describe and predict the binding extent between template and MIPs for the first time. In this chapter, equilibrium binding study was applied to study the bonding degree of template (bupivacaine) with MIPs and reference polymers. The measuring data is processed by the partial least-squares regression (PLSR) and the corresponding third-degree equations can be obtained. As a result, the corresponding chemometric models were built for describing template binding in the chosen system. The research shows that these models have good correlation and predictive ability. Meanwhile, this study proved that temperature and dielectric constant could be used to describe binding. The results showed that temperature has little impact on the binding ability in the nonpolar and aprotic solution. In contrast, hydrophobic interactions and temperature have important influence on binding in polar solution.

Principal component analysis (PCA) is a kind of effective data compression method. It can compress multidimensional data linearly into lower dimensions with minimal loss of information. In order to identify the most important factor for the rebinding among the template and the corresponding MIPs, Nicholls and coworkers [103] also investigated physical properties of the media on MIP performance by processing rebinding data with PCA. The results proved that polarity of solvent and the dielectric constant (D) have the greatest effects on the binding. At the same time, the chemometrics methods represented by PCA are powerful tools for exploring the true relationship between the corresponding factors and the rebinding ability of MIPs. The mathematical models with good performance for the binding process can be built by chemometrics.

Moreover, the template-functional monomer complex which was formed in the pre-polymerization process has a significant effect on the recognition and morphology of MIPs. PCA was also used to study the effect of template complexation in pre-polymerization mixtures on MIP recognition and morphology [104]. In this study, a series of MIPs which were prepared by changing the ratio of template (bupivacaine): functional monomer (MAA or methyl methacrylate): cross-linker (EGDMA) were obtained. The corresponding MIPs were characterized by swelling studies, gas sorption measurements, and radioligand equilibrium binding experiments. Molecular dynamics (MD) simulation was employed to extract information from pre-polymerization complexes. PCA was applied to process information which was obtained from all-component MD simulation trajectories of a series of MIP pre-polymerization complexes. Furthermore, the data describing the surface characteristics and rebinding behaviors of similar synthesized polymers was also processed by PCA. The above results proved that PCA can be used to reveal relationships between MD-derived descriptions of events in the pre-polymerization complex, recognition performance and morphologies of MIPs.

2.5.3 Molecular Modeling Approaches

Up to now, it turns out that computational calculation is an effective way to reduce experimental trials for preparation of MIPs. Based on practice experience, using efficient molecular modeling to assist the optimization of the imprinting protocol is a very good choice. Molecular dynamics (MD) simulation is considered as a classical computational technique and has been used to simulate and predict the best imprinting protocol. Similarly, density functional theory (DFT) is also usually employed for computational design of the scheme for preparation of MIPs. These molecular modeling approaches have been frequently applied for screening the most suitable functional monomer to a target molecule.

In 2001, Piletsky et al. [105] first proposed a MD-based method for the preparation of ephedrine MIPs. In this method, an artificial library of functional monomers was built at first. Then, this library was screened by using the software of molecular modeling in order to select an optimal monomer for template. An algorithm named LEAPFROG is the core of this approach and it was employed to screen the functional monomers library for study the potential mechanisms between template and functional monomers. The score of empirical binding energy can be obtained after 30,000 runs. This score was evaluated and four functional monomers with the best binding score were selected in this study. The computed results indicated these monomers have the best ability of forming the strongest complexes with the template and they were used for the preparation of MIPs. This research implied that the developed computational approach can be considered as an alternative way for the rational design of MIPs. Moreover, by comparing the corresponding binding scores of different monomers, the specificity and affinity of MIPs can be predicted.

Similar studies were developed by Wei et al. [106]. MD simulation was employed to investigate the template-monomer interaction for optimize the polymerization factors and study the mechanism of recognition in MIPs. By the purposed method, the best monomers for 17-estradiol (BE2) MIPs were selected from a nine functional monomer library by comparing the strength of hydrogen bonding. According to the simulations results, 2-(diethylamino) ethyl methacrylate (DEAEMA), methacrylamide and MAA were recognized as the most suitable monomers for template. The results showed that they have strong affinity to 17-estradiol. The theoretical prediction results were in agreement with previous studies which implied the same functional monomers for the preparation of MIPs. Furthermore, the influence of different temperature and cross-linkers on the performance of the MIPs was studied by Nicholls and coworkers [107]. On the basis of the cross-linkers were different, the template-functional monomer interactions were modeled by MD simulation. The results of simulation explored the most relevant sites of templates which interacted with monomer and it also illustrated the interactions among template, functional monomer, and cross-linker. Furthermore, the interactions between functional monomer and cross-linker were also studied.

In addition to the MIPs design, MIP behavior also can be predicted and explained by the MD methods. For instance, Henthorn and Peppas [108] investigated the

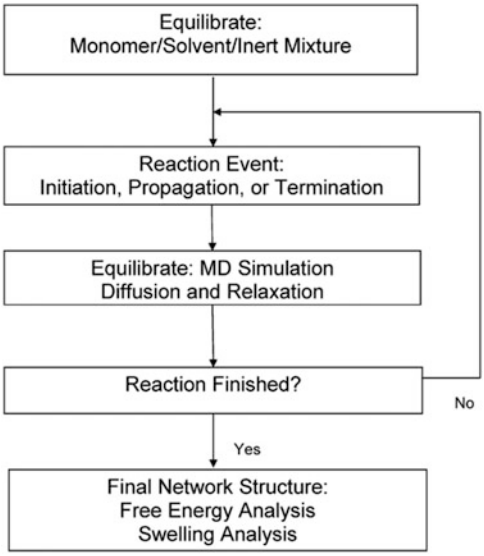

Fig. 2.15 Schematic diagram of kinetic gelation reaction. The reaction is started after the initial equilibration. Radicals are created at every reaction step, allowed to propagate or terminated. Reaction continues until a final conversion is achieved at which time the final network structure is given. (Reproduced with permission of Ref. [108])

densely cross-linked polymeric networks formation mechanism by using a technique named all-atom kinetic gelation which was used to simulate the synthesis system. From beginning to end of this simulation, the interaction and position of all atoms was tracked by an off-lattice method in this work (Fig. 2.15). By using the proposed method, the interactions between the reacting monomers and the recognition mechanism of the polymeric network formation were exploited. It also proved that the network structure of polymers was also effected by templates in this case.

In another study, the interactions between two monomers in an aqueous pre-polymerisation system were studied by using molecular modeling method [109]. In this case, 2, 4-dichlorophenoxyacetic acid (2, 4-D) and 4-VP were taken as the study subjects and the results showed proposed method provided an alternative way to illustrate how MIPs with good performance are prepared in an aqueous solvent.

Another popular quantum method, DFT, also has usually been applied for optimization of geometries of the template-monomers complexes and calculation of interaction energy. It means that DFT can be applied in the design of MIPs. In the study of Ahmadi et al. [110], a methadone MIP was prepared with the help of DFT. According to the calculated results of interaction energy obtained with DFT, MAA was confirmed as the most suitable monomer. This research suggests that the performance of DFT designed MIPs was superior to the MD designed MIPs because the non-covalent template-monomer interactions was represented by DFT. Similarly, with the aid of DFT, MIPs were prepared by Ahmadi et al. [111, 112]. This polymer was applied for the analysis of drugs from plasma. The most suitable monomer for those different drugs were confirmed by the computational methods from DFT. Up to now, DFT is often used to study the interaction of template-monomer complexes to identify the most stable structure [113, 114]. It should be

noted that the solvent is also an important variable. The selection of solvents is another important task for the rational designed MIPs. In computational chemistry, polarizable continuum model (PCM) is also often used to investigate the influence of solvent. PCM is a type of continuum model and has been used in lots of researches [115, 116]. In practice, the computational approaches, such as DFT, MD and PCM, were frequently applied simultaneously in a lot of reported literatures [117–120].

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