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Theoretical and Computational Strategies for the Study of the Molecular Imprinting Process and Polymer Performance

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Abstract The development of in silico strategies for the study of the molecular imprinting process and the properties of molecularly imprinted materials has been driven by a growing awareness of the inherent complexity of these systems and even by an increased awareness of the potential of these materials for use in a range of application areas. Here we highlight the development of theoretical and computational strategies that are contributing to an improved understanding of the mechanisms underlying molecularly imprinted material synthesis and performance, and even their rational design.

Keywords Chemometrics · Molecular dynamics · Molecular imprinting · Multivariate statistical analyses · Quantum mechanics · Rational design

Contents

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1 Introduction

Recent years have seen a rapid increase in both fundamental studies of the molecular imprinting process and in the number of areas in which molecularly imprinted polymer (MIP)-based applications are being explored [1–9]. Major driving forces for this development have been interested in the establishment of in silico rational MIP design strategies, and the interest in tailoring polymers and their formats for particular application areas. This has in turn increased interest in elucidating the physical mechanisms underlying MIP formation and MIP–ligand recognition. This necessitates knowledge of the molecular level events occurring in pre-polymerization mixtures, the polymerization reactions, and of the factors influencing polymer-ligand recognition. Ideally, such insights will lead not only to better-performing polymers, but even to a better understanding of the origin of MIP polyclonality and the often low yields of high-fidelity sites, and the relationship between recognition properties and morphology.

While the molecular imprinting concept is at the surface eye-catching because of its apparent simplicity, researchers have quickly become aware that the complexity of the pre-polymerization mixtures, the heterogeneity of the polymeric recognition sites, and the amorphous nature of the materials together made elucidating mechanisms a challenge. Initially, conclusions regarding the underlying mechanisms were drawn from empirical studies, in particular of ligand-polymer recognition characteristics.

The limits of computational tools for assessing molecularly imprinted polymerization systems led to the earliest attempts to model the molecular imprinting process being based upon the use of thermodynamic models [10–14]. An interesting and relatively recent contribution to the literature in this area reported stochastic simulations being used to study the interaction of pre-polymerization mixture components [15]. Here, monomer-template binding affinities were used in a stochastic algorithm [16] to position the monomer and template units in a lattice matrix. Subsequently, the cross-linker was added, the template removed and the binding sites analyzed for heterogeneity. This modelling resulted in simulated MIPs that display the same trends as MIPs formed under the corresponding imprinting conditions.

The rapid increase in computing power that has taken place over the past decade, and the concurrent establishment of new and improved software, has made the use of simulations based upon mathematical descriptions realizable. Computational techniques can today be used to investigate both polymer performance and intimate aspects of the molecular imprinting process per se. Currently, a broad range of

computational techniques is being used in the study of various aspects of the molecular imprinting [17]. These techniques span from statistical treatments to quantum mechanical simulations. Here we provide a brief background on the use of computational methodologies in the study of molecular imprinting, and we present the state-of-the-art in terms of the types of computational methodologies currently in use. In particular, we address the use of computational means for studying electronic structure and molecular dynamics (MD), and we provide a brief presentation of the use of statistical methods in the study of molecular imprinted polymer systems.

2 Electronic Structure Methods

Computational methods for the study of electronic structure have become increasingly more common in aspects of the design and evaluation of MIPs. This class of methods includes semi-empirical, ab initio, and density functional strategies. In most cases, these methods and basis sets have been developed with the aim of describing a system to a high degree of accuracy, while at a reasonable computational cost. As these methods, in contrast to less sophisticated models and to other theoretical approaches, are able to describe the electronic structure, they generally yield considerably better representations of non-covalent interactions present in the system under study. In most studies these methods have been used to describe interactions present in pre-polymerization mixtures, in particular aiming to investigate the interaction between the template molecule and candidate functional monomers. In some studies, however, their use was extended beyond the pre-polymerization mixture, e.g, where these techniques have also been applied to the evaluation of recognition and rebinding of templates to MIPs.

As stated, the most common application of electronic structure methods in the design of MIPs is in the determination of putative complexes between templates and monomers. Examples of this strategy include the use of the semi-empirical AM1 method for the calculation of a complex between (*S*)–nilvadipine and 4-vinylpyridine (4VP) [18], the optimization of a complex between 2,4,6-trichlorophenol and four molecules of 4VP [19], and the PM3 method for describing two complexes formed between (*S*)-naproxen and one or two molecules of acrylamide, respectively [20]. This strategy was employed in conjunction with density functional methods by Pietrzyk et al. [21] to model a complex between melamine and three functional monomer molecules on a B3LYP/3-21G(d) level of theory. The B3LYP functional was also used by Demircelik et al. [22] with a 6-31G(d,p) basis set, and by Riahi et al. [23], with a 6-311+G(d,p) basis set, for the modelling of template-monomer complexes; the latter study also included the effect of solvent using a polarizable continuum model (PCM). In PCM calculations, the effect of the solvent is approximated by placing the system in a cavity with a surface that is polarizable according to the dielectric constant of the modelled solvent.

More recently, Holdsworth et al. [24] have demonstrated that the binding energies calculated by the AM1 method for complexes of a cocaine molecule and 1–14 molecules of either methacrylic acid (MAA) or 4VP could be used to guide optimization of the polymerization mixture composition (template—functional monomer ratio). The proposed optimal template and functional monomer relationship was subsequently validated both by NMR and rebinding studies on a series of synthesized MIPs, thus confirming the viability of this computational approach.

A number of examples of MIP-design based upon electronic structure techniques have been presented over recent years. The use of binding energies obtained from calculations on complexes between the template and a set of different functional monomers has become a more frequently used strategy for choosing functional monomers. This approach was adopted by Luliński et al. [25] in the design of a dopamine-imprinted polymer system using a PM3 level of theory. Similarly, an AM1 level of theory was used to design a MIP selective for *N*,*O*-dibenzylcarbamate [26], as was the case for studies using theophylline as template [27] in conjunction with the more sophisticated B3LYP/6-31+G**//B3LYP/3-21G level of theory. Other adaptions of this strategy include work by Gholivand et al. [28], using HF/6-31G(d) calculations in the design of a furosemide-imprinted polymer, by Alizadeh [29] for developing a pyridoxime-imprinted polymer using B3LYP/6-31G calculations, by Yao et al. [30], using MP2/6-31++G(d) calculations on an aniline template system, and by Li et al. [31], who chose functional monomers for a polymer system imprinted with chlorophenols based on results from B3LYP/6-31G (d,p) calculations. In a similar study by Kowalska et al. [32], the interactions of harmane various functional monomers were investigated using B3LYP/6-31G(d,p) calculations.

The design of a polymer system imprinted with nicotinamide was undertaken using a broad range of calculations, e.g., different density functional methods and MP2 in combination with different basis sets, by Del Sole et al. [33]. This strategy was also used by Azenha et al. [34] in the design of a silicate-based polymer selective for β-damascenone, in this case using HF and B3LYP in combination with different basis sets.

A growing number of other examples can be found in the literature, including the calculations of the structures of the complexes formed between a series of compounds and two molecules of MAA [35]. In this case, the structural parameters obtained by AM1 calculations could be correlated to the results of experimental data in the form of chromatographic studies. In a study by Lai and Feng [36], molecular geometries of buffer acids and bases optimized on the AM1-level were related to the metformin template binding in the respective media using an assumed mechanism for competitive binding. Moreover, Wu et al. [37] were able to demonstrate a relationship between experimentally determined capacity factors and the binding energies found by MP2/6-31G//HF/6-31G and PM3 calculations of complexes of various functional monomer-templates.

A number of other noteworthy examples include the use of B3LYP/6-311+G**//B3LYP/6-31G* and including solvent effects in the energy calculations of complexes in the pre-polymerization mixture of Diñeiro et al. [38, 39]. Here, the authors

were able to rationally select both the functional monomer and porogen for the successful preparation of a homovanillic acid-imprinted polymer. An extended strategy for optimization of both functional monomer and solvent was presented by Dong et al. [40], who complemented B3LYP/6-31G(d) calculations with a preceding step in which candidate systems were chosen using MD simulations (see later).

Electronic structure methods have also been used for cases where a template that differs from the target structure of the MIP is used. These methods can also assist in the choice of the template itself. One example of such a study, published in 2005 by Rathbone et al. [41], concerned the design of a MIP-based mimic of cytochrome CYP2D6. Here, the templates to be imprinted were chosen on the basis of superposition studies of a series of PM3-optimized candidate molecule geometries on known CYP2D6 substrates with the selected templates.

Quantum chemical calculations have also been used in the design of an ester hydrolysis-catalyzing polymer based on PM3 calculations. These calculations provided support for the hypothesis that the template used in the MIP synthesis is a mimic of the transition state of the reaction to be catalyzed [42]. Finally, using a very different approach, Voshell and Gagné [43] used HF/6-31G* and AM1 computational studies to determine the conformational rigidity of a dendritic system used in the imprinting of BINOL. Based on these results, a more rigid dendrimer structure was identified that afforded enhanced enantioselectivity and decreased binding site heterogeneity.

A significant limitation in the application of electronic structure methods to MIP systems is the difficulty in handling the large numbers of atoms necessary to provide a comprehensive picture of the pre-polymerization or polymer system. One particular complication appears to be the problems that can arise from the lack of an explicit solvent [44, 45]. For electronic structure methods, the inclusion of a reasonable number of solvent molecules makes the calculation rather time- consuming; as a result, solvent effects are often omitted completely. However, methods such as PCM provide the possibility of including solvent effects without the inclusion of explicit solvent molecules [46]. Nonetheless, the validity of this assumption appears limited in light of a recent report [44]. The method was recently applied by Wu et al. [47], in an MP2/6-311+G*//B3LYP/6-311G* study of the pre-polymerization mixture of a nicotinamide imprinted polymer. It was shown that the model works well for predicting the influence of different solvents on the retention and selectivity characteristics of the polymer, as long as the solvent itself is aprotic. A significant limitation of the PCM method is that not all solvents can be modelled adequately due to the inability of the PCM method to include the effect of hydrogen bonds to solvent molecules, which compete with the hydrogen bonds formed between the template and functional monomers. This was also exemplified by Liu et al. [48], who used a B3LYP/6-31+G(d,p) level of theory in which the solvation energies obtained using PCM were compared to the energies' template-solvent molecule interactions. An alternative strategy for using solvation energies obtained from B3LYP/6-31+G(d,p) including a PCM model, was demonstrated by Dong et al. [49]. Here, the solvation

energies of template and functional monomer molecules in various solvents were directly used as a measure of potential competition for interactions from the solvent.

The use of electronic structure methods in the evaluation of a given MIP has been demonstrated by Wang et al. [50]. Based on the optimized geometries and Mulliken charges calculated for a series of substrates using B3LYP/6-311G**, they were able to suggest a recognition mechanism explaining the selectivity of an *N*-(4-isopropylphenyl)-*N′*-butyleneurea imprinted polymer towards such compounds. Jacob et al. [51] were able to propose a model for the interaction between polymer and template using both ab initio and density functional theory (DFT) methods in combination with different basis sets. Similarly, by using PM3 calculations of template-monomer interactions, Wu and Li [52] could explain the failure of the imprinting of picolinamide in an MAA-based polymer. They subsequently developed a Cu(II) complex-based system that did show selectivity for the imprinted compound. The system has also been extended to the recognition of small organic acids [53].

Christoforidis et al. [54] investigated the mode of interaction of semiquinone radicals with an imprinted polymer that was elucidated using a series of B3LYP and MP2 calculations in connection with electron spin echo envelope modulation (ESEEM) spectroscopy. A detailed study on the mechanism of theophylline-polymer recognition was published by Che et al. [55], who had used B3LYP/6-31G (d,p) calculations in combination with 2D IR-spectroscopy.

Of potential importance for many of the new thin film- and surface-based applications of MIPs are computational studies describing adsorption to surfaces. For example, correlations have been found between the PM3-level calculated molecular volume and the adsorption coefficient of bile acids on a film of over-oxidized polypyrrole imprinted with sodium taurocholate [56]. In another study, Mukawa et al. [57] were able to explain the relative selectivities of a polymer synthesized using allyl phenyl disulfide towards phenol and the template analogue thiophenol. In this study, the different strengths of the hydrogen bonds being formed between polymer and ligand were calculated on the HF/6-31G* level of theory. A variation on this theme was used by Meng et al. [58] in the design of a MIP-based transesterification catalyst. Here, the calculation of the AM1 energies was used to examine the various functional monomers under study by probing their interaction with putative reaction intermediates.

To date, only one report has been published where modelling of the properties of an imprinted polymer has been undertaken using electronic structure calculations [59]. Here, the initial step involved PM3-based calculations to model the pre-polymerization complex of nicotinamide or *iso*–nicotinamide with MAA as functional monomer. In a second step, the spatial positions of the functional monomers were fixed and the template molecule removed from the system, thus creating a model for the binding site without the cross-linked polymeric backbone. Finally, a strong correlation with the experimental retention factors of the respective MIPs was observed upon comparison of the interaction energies calculated for a series of substrates with this binding site model.

A notable study is that of Tada et al. [60], who developed an Rh-amine complex imprinted silicate system that displayed shape-selectively in catalysis of hydrogenation reactions. PWC/DNP calculations were conducted on the complexation of the metal center and both the imprinted and catalytically active species were characterized by using these calculations in conjunction with a series of experimental studies.

In summary, recent years have seen an increase in the number of researchers using quantum chemical calculations to address various aspects of MIP science and technology. These approaches have been used primarily for studying interactions in the pre-polymerization mixture, even for explaining recognition phenomena in the finished polymer. Nonetheless, most studies have been focused on single aspects of the process of designing, synthesizing or testing of a system, and the impact on MIP research has so far been rather limited. With the development of refined computational techniques and improved availability of computational power, however, the impact of electronic structure-based calculations can be expected to increase.

3 Molecular Dynamics Simulations

Although there are now many reported protocols describing the successful development of selective MIPs, these protocols typically involve many variables and steps that ideally should be optimized in terms of MIP-template recognition characteristics when translating to other templates. Among these variables, it is generally accepted that the choice of the stoichiometry of polymer components as well as the temperature and pressure during synthesis are factors of major importance [61–63]. With this in mind, the use of in silico techniques for better understanding or optimizing these factors should afford savings in terms of time and cost for MIP production.

A rapidly emerging tool for this task is MD, a computational, force-field-based technique [64]—in particular, its use for simulating and allowing predictions of the nature of the ensemble of non-covalent complexes that are formed between polymer components in a MIP pre-polymerization mixture. Since the pioneering work of Alder and Wainwright in 1957 on the simulation of gaseous argon [65], simulations have progressed such that they nowadays allow for the study of multiple simultaneously interacting atoms. Among the great number of force-fields that exist and that are routinely being used for the study of biomolecules as well as small organic molecules are, for example, AMBER [66], GAFF [67], CHARMM [68], OPLS [69] and GROMOS [70, 71].

Owing to the accuracy of such force-fields, MD simulations have been used to study protein folding [72, 73], conformational changes of DNA [74, 75], orientation of phospholipids in bilayer membranes [76, 77], active transport of drug molecules across membranes [78], physical characteristics of solvents [79] and surfaces [80, 81], as well as biomolecular interactions [82–84].

It is today commonly accepted that the origin of the predetermined recognition in MIPs can be correlated back to the nature and strength of functional monomer-template complexes that are established at the pre-polymerization stage [1, 14, 85–87]. Accordingly, work over the years has been predominantly focused on the development of protocols that can suggest which functional monomer has the highest affinity for the template. The first MD-based protocol with the aim of selecting the best binding functional monomer(s) was reported in 2001 by Piletsky and colleagues [88]. Here, Piletsky and his group developed an approach that was based on a virtual library comprised of a total of 20 different monomers that were screened against one enantiomer of the template ephedrine. In a follow-up work by the group, in order to investigate how the choice of solvent (porogen) and monomers affects functional monomer-template complexation during the pre-polymerization stage, Piletsky and co-workers [88] used a simulated annealing approach to generate low-energy ensembles of ephedrine that was solvated with multiple copies of functional-, cross-linking monomers and explicit solvent molecules. Using this strategy, they later prepared MIPs that have been targeting a series of drugs and pharmaceutically interesting compounds such as simazine [89], cocaine, methadone and morphine [90, 91], creatinine [92], biotin [93], and the cyanobacterial toxin microcystin-LR [94, 95]. It is noteworthy that in the case of microcystin-LR, the use of their approach led to a MIP that demonstrated recognition characteristics similar to those demonstrated by antibodies.

Later, similar strategies utilizing virtual libraries of monomers have been developed by other researchers. Wei et al. [96] imprinted 17β-estradiol after simulating either a monomer-template pair or a single template molecule solvated with eight functional monomers to incorporate also the effect of monomer dimerization on the degree of template complexation. In both these cases, each 17β-estradiol was surrounded by explicit non-polar porogen molecules (acetone or chloroform). The selection of the "best binding" monomer here was made from a virtual library comprised of a total of nine different functional monomers. Here, the use of an MD-based computational screening approach to find the optimal functional monomer suggested that MAA, methacrylamide and 2-(diethylamino)ethyl methacrylate showed the strongest hydrogen bonding interactions to the selected template, with results in accordance with parallel experimental MIP-template batch rebinding studies.

To investigate the impact of the growing polymer chain during polymerization on the stability of functional monomer-template complexation, studies have been performed in which homo- and co-polymeric chains of functional monomers have been used in the search for the optimal monomer. Pavel and Lagowski [97, 98] reported on a strategy where they computed potential energy differences for a series of functional monomer-template complexes. The binding energies were calculated after simulating an ensemble of functional monomers in the absence or presence of the template. Secondly, the effect of polymer chain growth on complex stability was investigated instead, using linear homo- and co-polymer chains. In this, using the target theophylline and a series of structural analogues, they demonstrated that the use of itaconic acid or ethylene dimethacrylate (EDMA) resulted in the best binding

MIP. Later, Pavel and team [99] also reported on the successful virtual screening of a number of warfare agents. These studies were made in order to investigate the character of the non-covalent interactions dictating functional monomer-template complexation. Results from these investigations pointed to the importance of electrostatic interactions as well as the presence of carboxylic and vinyl groups on the functional monomers to drive template complexation.

To study the stability of the complex formed between the template, 2,4-dichlorophenoxyacetic acid and the functional monomer 4VP which is believed to be stoichiometric of type 1:1, Molinelli et al. [100] reported a series of studies inserting a pre-minimized complex that was explicitly solvated by either chloroform or water molecules. From using different starting geometries in the different solvents, hydrogen bond interaction in chloroform and π–π stacking interaction in water, the authors proposed mechanisms to explain the nature of the interactions involved during the pre-polymerization stage as well as during MIP rebinding in aqueous solution.

To develop this strategy further, Monti et al. [101] showed the great potential in using a combination of MD, molecular mechanics (MM), docking and site mapping for obtaining the best functional monomer binding to the template theophylline. Here, the authors demonstrated the presence of a "molecular memory" and a MIP-template selectivity in agreement with experimental data.

In order to investigate the selective adsorption properties of a dimethoate MIP, Lv et al. [102] used a series of simulations to predict the binding energies for a series of homo-polymers and the template. Results from these studies, later supported by chromatographic evaluations, suggested that a homo-polymer built up by butyl methacrylate demonstrated the most selective binding to the template.

Interestingly, MD has also been used to shed light on functional-monomer-template complex stabilities for MIPs prepared in formats other than bulk polymerization, the most commonly used strategy. To investigate the stability of functional monomer-template complexation during pre-polymerization in surface imprinting, Yoshida et al. [103] used simulations to make predictions regarding the stability of functional monomer-template complexation. The corresponding MIP was prepared to demonstrate chiral recognition for tryptophan methyl ester using phenyl phosphonic acid monododecyl ester (n-DDP) as recognition site-members in a water-in-oil emulsion. By studying the dynamics of a single complex (2:1 functional monomer:template stoichiometry), initially in vacuum and later in a toluene-water interface, the authors suggested that the imprinting effect in the prepared MIP was based on the stability of the n-DDP-tryptophan methyl ester complexes formed in the emulsion. In a further development in this field, Toorisaka and co-workers [104] reported on the stability of a complex formed at a water-toluene interface comprised of a cobalt ion, one molecule of alkyl imidazole, and a substrate analogue, *N*α-t-Boc-L-histidine, thus forming a key part in the active site in a catalytic MIP.

The large number of atoms typically present in a MIP pre-polymerization mixture often limits the use of quantum mechanics (QM) for the elucidation of monomer-template binding energies on account of the sheer amount of

computational time that would be required. However, some examples have appeared in the literature where QM has been integrated in the screening process, but with various simplifications being made. Dong et al. [40] reported an MD approach based on a combination of MM and QM for the virtual library screening of the best functional monomer to be used in the imprinting of the herbicide acetochlor. In their approach, the authors initially used a series of MD simulation steps representing a single functional monomer-template complex, surrounded by explicit porogen (either acetonitrile, chloroform or carbon tetrachloride). A measure of the stability of the complex was obtained through calculation of the potential energy for the formed complex using an MM force-field. Secondly, complex energies were computed using DFT and a 6-31G(d) basis set. The presence of an implicit solvent model was, however, computed using a polarizable continuum field. Based on the accuracy obtained from these computations, the top three functional monomers were selected and later used for the imprinting of acetochlor. Notably, this strategy for mixing MM/QM has been found to be successful and also used for the imprinting of rhodamine B [105] and sulfadimidine [106].

Importantly, as already discussed, the diverse nature of the non-covalent interactions that are formed at the pre-polymerization stage makes it necessary to account for all interactions, and not only those formed between functional monomer and the template, to make successful predictions on MIP-template recognition characteristics. To investigate the influence of template and monomer dimerization on final MIP-template recognition, studies on, for example, nicotine dimerization during the pre-polymerization stage helped to explain the unusual behavior observed in final MIP-template rebinding [107, 108]. Notably, in 1999, Katz and Davis [109] proposed that the binding capacity of a MIP that had been imprinted with phenylalanine anilide in either chloroform or acetonitrile originated from the strong degree of template dimerization occurring at the pre-polymerization stage. Recently, the basis of the formation and extent of phenylalanine anilide dimerization previously studied by Katz and Davis was further investigated by Olsson et al. [110] using MD.

To study the impact of functional monomer dimerization on MIP-ephedrine recognition, Ansell and co-workers demonstrated NMR-spectroscopic support for the importance of an all-component treatment of the pre-polymerization mixture [111–113].

To approach a more realistic representation of the “actual” pre-polymerization mixture, a series of efforts has been made towards mimicking the actual pre-polymerization mixture where large multiples of components are present in the stoichiometric ratios representative to the ones being used in typical MIP preparation protocols. O’Mahony et al. [44] used a number of MD simulations to study functional monomer-naproxen complexation and especially the effect of template dimerization on MIP performance. Although these mixtures did not include the initiator, extracted data from simulations suggested not only a high degree of 4VP-naproxen complexation, but also that the cross-linking agent EDMA was found to contribute to the high degree of selectivity demonstrated by the MIP. On the same

theme, the role of template dimerization on final MIP performance was also reported by O'Mahony et al. for imprinting of quercetin using 4VP as functional monomer [114]. In this example, results revealed the formation of sheet-like structures of quercetin-4VP complexes with stabilities typically independent of the concentration of EDMA used. Recently, O'Mahony and colleagues have developed a 4-VP-based MIP that was imprinted with hydroquinone and capable of extracting the endocrine disruptor Bisphenol-A from milk [115]. In this case, however, the group used a novel approach in which the template's capacity to dimerize (through hydrogen bonding) to later facilitate the formation of imprints for binding the target, Bisphenol-A, through a predicted 2:1 functional monomer-target complex.

By also including the initiator and multiple templates in correct stoichiometries to represent an actual pre-polymerization system, Karlsson et al. [45] were able to present a comprehensive investigation of all non-covalent interactions taking place in a bupivacaine imprinting procedure. Interestingly, the authors reported both a correlation between results obtained from a series of NMR spectroscopic studies on monomer-template complex stability and simulated data, and also the origin of the recognition-site heterogeneity frequently demonstrated in MIPs (see Fig. 1). This binding-site heterogeneity and possible consequences for polymer morphology and template rebinding in bupivacaine MIPs was later also investigated by Golker et al. [116, 117]. Here, the authors performed a large number of MD simulations and physical characterizations of polymer morphologies and template rebinding capacities using different polymer compositions (increasing molar fraction of the functional monomer MAA). Correlations between the nature and extent of the non-covalent interactions present at the pre-polymerization stage and the final polymer performance could be made. The success in using MD-based approaches for predicting MIP-template rebinding performance prompted a recently reported study to investigate the role of the cross-linking monomer (EDMA or TRIM) in (*S*)-propranolol MIPs [118]. This type of use of MD in the study of MIPS was further extended in an investigation of the role of π–π stacking interactions for establishing molecular memory in MIPs imprinted with polychlorinated benzenes such as 1,2,3-trichlorobenzene [119].

Up to this point in time, most MD-based studies aimed at predicting MIP recognition behavior have been focused on the interactions taking place during the pre-polymerization stage, i.e., prior to polymer formation. To eliminate the problems related to simulating the polymerization process, which requires a QM treatment of the simulated mixture, and the difficulties in obtaining information on polymer micro- and macrostructure due to heterogeneity, some interesting recent attempts have been made to model imprints in the final MIP through building rough models of chains of polymer.

To better understand the origin to the molecular memory in MIPs and to demonstrate the importance of pores on MIP-template recognition, Srebnik and colleagues [120–122] performed a series of MD studies to investigate the mechanisms to the imprinting effect. To shed light on the influence of pore formation, Youngermann and Srebnik [123] investigated factors contributing to binding-site imperfections

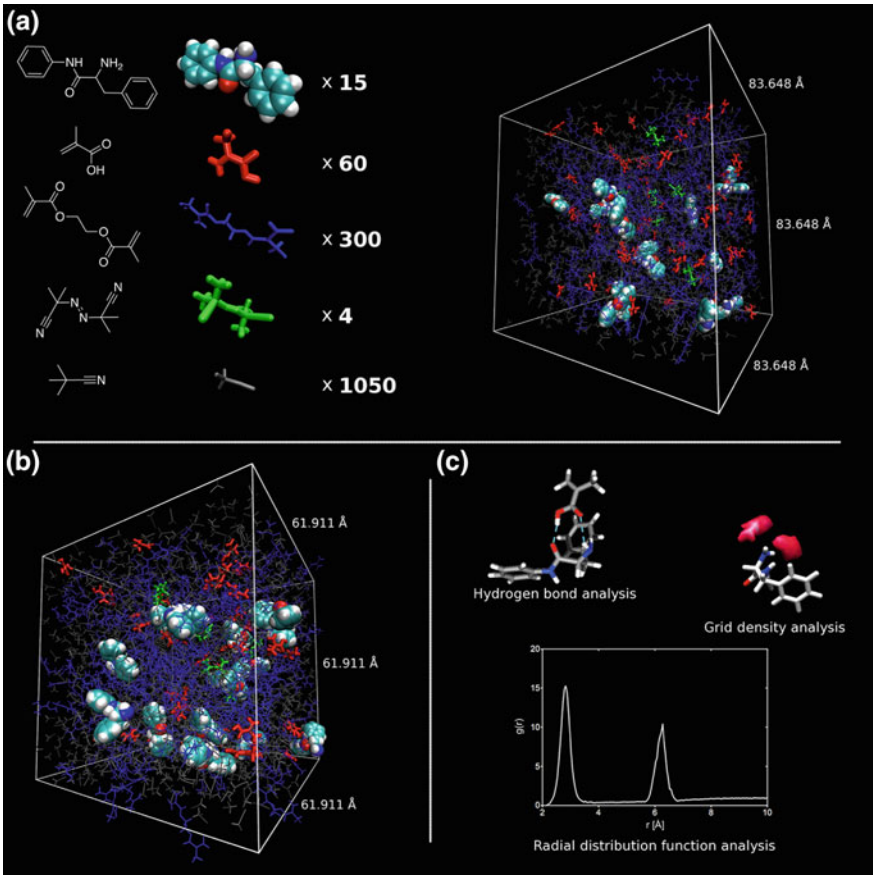

Fig. 1 The strategy used for all-component MD simulations, here for a bupivacaine MIP pre-polymerization mixture [115]. **a** The system is constructed using all the components used in the MIP synthesis and in the same stoichiometry as the synthesis. For small molecule templates, at least 10 template structures are generally used. Randomized initially packing geometries are used [110]. **b** After a series of energy minimization steps and equilibration, first at NVT and then at NPT, the collection of production-phase data is undertaken (for small organic templates, typically 5–10 ns production-phase at NVT, and generally >5 systems run in parallel). **c** Study of the interactions of the components in the pre-polymerization mixture is performed by examining the trajectories of all the components in the system over the production-phase, e.g., using radial distribution functions and hydrogen bond analyses. The prevalence of a given type of component around a particular element is illustrated using 3D grid density analyses

leading to the recognition-site heterogeneity using a series of coarse-grained MD simulations. Through topological analyses of a modelled cross-linked polymer network, before and after template removal, they suggested that the typically low yield of imprints (10–15 %) was a result of the quality of generated pores. They also proposed that when considering both the size and shape of the template, the best

performing MIP should have a high degree of cross-linkage (90 %) and that the low quality of the imprints induced by the templates resulted from the aggregation of template during the pre-polymerization stage.

Finally, to shed further light on the physical characteristics of the MIP matrix, MD simulations have also been used to study the role of the solvent during template rebinding as well as to simulate the dynamics of the final MIP. In a study by Zhao et al. [124], a cubic model of a MIP was built to represent a hydrogel network. This model polymer matrix was studied in the presence of the template, cholesterol, and the dynamics of this polymeric hydrogel as well as its interactions with explicit solvent molecules were evaluated. The authors modelled this highly cross-linked infinite polymer network based on a dummy cube inserting various numbers of single polymeric chains of poly-methacrylic acid. Results obtained from their simulations and subsequent analyses of the dynamics of the polymer and its interactions with surrounding water molecules revealed a highly ordered structure of water solvating the hydrogel. From these observations they concluded that by adjusting the amount of carboxyl groups incorporated in the polymer matrix, they could control the water structure and thereby the diffusion of water through the polymer. The authors found a good correlation between experimental template (cholesterol) diffusion data as compared with results obtained by simulation. In subsequent work by the same group, the effect of charge on the functional monomers positioned in a cubic methacrylate-based MIP model was investigated through artificially changing the charge of the carboxylic acid functionalities incorporated in the cubic lattice [125]. Results from these studies suggest that the diffusion of the target molecule cholesterol was not affected by the polymer network structure, and the authors notably concluded that the recognition process is solely governed by the mesh size of the network. Interestingly, the authors also suggested that the effect of increasing charge in the system resulted in an enhanced polymeric structure.

Xerogels have been the subject of another recent study, where the role of adding polyethylene glycol (PEG) for tuning the porosity of the final polymeric material was explored by Azeha et al. using MD simulations [126]. They also examined the sol-gel phase separation of the various components present in the damascenone imprinted xerogel pre-gelification stage. Results presented suggested that the presence of PEG in these mixtures had an adverse effect on template-functional monomer association and hence no improvement in the imprinting effect of damascenone was proposed—which was shown to be in accordance with experimental findings. Notably, the addition of PEG had no effect on the interactions related to the network structuring, and the authors proposed that the PEG molecules were pushed out into the aqueous-methanolic sol-phase when added to the pre-gelification mixture.

Taken together, the examples provided above clearly illustrate that MD-based studies can provide valuable insights into pre-polymerization systems in particular, but even into physical characteristics of the final MIP matrix.

4 Multivariate Statistical Analyses

The application of mathematical and statistical methods to chemical data is a discipline within computational science referred to as chemometrics [127–129]; its development has led to improved or simplified selection of optimal experimental parameters as well as the extraction of significant information generated from multivariate data analysis. It is important to note that in the field of chemometrics it is recommended to use an experimental design, in which the factors are systematically and simultaneously varied. Through experimental design, a minimal number of experiments can be used in order to extract a maximal amount of information. In essence, the concept involves changing all relevant factors simultaneously over a series of planned experiments and then interpreting the results using mathematical models. Traditionally, the different experimental design methods applied to the analysis of different aspects of MIP systems are considered to be fractional factorial [130–135], full factorial [136–140], central composite [134, 137, 138, 140, 141], Box-Behnken [142] and Doehlert [132, 133, 135, 139, 143]. The fundamental differences between these designs are that they differ in terms of how factors are varied and the number of experiments required. The experimental designs discussed above may be schematically illustrated, as shown in Fig. 2. There are no limitations, other than practical, in terms of the number of factors that can be used in an experimental design. Full and fractional designs are primarily used if the objective of the study is screening, and Box-Behnken and Doehlert are used for surface modelling while central composite design is an extension of the factorial designs intended for both optimization and surface modelling. The molecular imprinting literature includes a growing number of papers and even a range of different chemometric methods. We provide below a short description of the different uses to highlight the potential of these methods.

Within the field of molecular imprinting, the synthesis of MIPs, as well as rebinding of the template to the MIP, are good examples of experimental endeavors that may be addressed using chemometric approaches. Examples of factors that can be varied when working with MIPs include the types and amounts of monomer, template, cross-linker, porogen and initiator. Other factors that can be of relevance can include polymerization temperature, the ratio of the various reaction mixture components (stoichiometry), and the ligand recognition or rebinding environment. Chemometric strategies can be a powerful complement to traditional MIP analysis, which is generally univariate in nature, i.e., first one parameter is optimized and then that value is used to optimize the next parameter. By using the univariate approach, the optimum found could be false. Even so, only a few efforts have been reported on the use of chemometrics in the optimization of the MIP binding parameters [132–135, 139–142, 144–147], and in the optimization of polymer composition [130, 131, 136–138, 143, 148, 149].

A number of statistical methods are available for the analysis of experimental data. A quite common example is analysis of variance (ANOVA) that is used to analyze observations that depend on the variation of one or more factors. However,

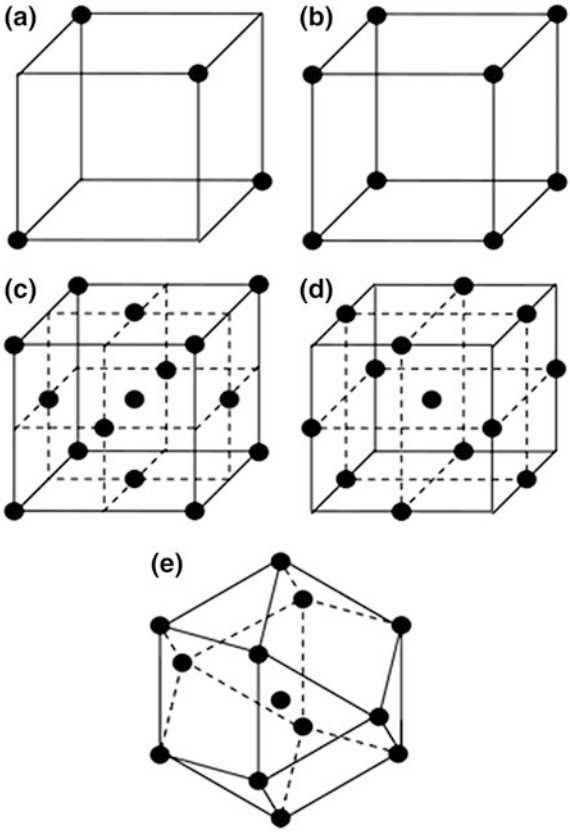

Fig. 2 Schematic illustration of the experimental designs used in the analysis of MIPs. The controlled variables in the studies are called factors and could be, for example, the amount of functional monomer, cross-linker and porogen. Points represent experimental runs of a three-factor **a** fractional factorial, **b** full factorial, **c** central composite, **d** Box-Behnken, and **e** Doehlert design

as ANOVA is a univariate method, it cannot take into account the covariance of different variables. Principal component analysis (PCA) is used in the classification of data. The principle by which PCA functions is to find the so-called principal components (PCs). The various PCs are graphically represented by vectors, where the first PC approximates the maximum variance direction in the data. The second PC is chosen so that it is orthogonal to the first PC and approximates the second maximum variance direction, and so forth. Through the identification of the PCs describing most of the variation, patterns in the data may be revealed as well as the factors that have the most influence on the variance. Different methods used in multivariate calibration of data include partial least squares regression (PLSR), principal component regression (PCR), and multiple linear regression (MLR) [127]. The major differences between these calibration methods are found in how they handle covariance. If the variables are independent, MLR is the preferred regression method, while PCR and PLSR handle covariance better.

Another method used to calibrate data is artificial neural network (ANN) construction [150]. The neural network is comprised of different layers and it functions as an associative memory by using experimental data to program itself. The input

layer receives input data, the hidden layer performs processing and transformation of the input data and the output layer processes the final results [17]. Numerical values, known as weights, are assigned to the connections between nodes of the various layers. These express the relative strength of the input data. The commonly used "back-propagation of error" algorithm is a supervised learning method used in ANN, meaning that it requires both the input and output to be known in advance. The weights are adjusted accordingly with respect to the error, which is calculated from the difference between the actual and predicted values.

The optimization of the composition of MIPs has been combined with different chemometric approaches in several papers. For example, PLSR was used to analyze a first order model for the composition of a bisphenol A-imprinted polymer [130]. By varying the amount of template, monomer (MAA or 4VP), cross-linker [EDMA or trimethylpropane trimethacrylate (TRIM)], initiator (2,2′-azobis(isobutyronitrile, AIBN), porogenic solvent (tetrahydrofuran, chloroform, toluene or acetonitrile) and the polymerization method (thermal or UV), mini-MIPs were prepared and evaluated through rebinding experiments in acetonitrile. After identification of the polymer composition that yielded the maximum specific binding, it was prepared on a larger scale in order to validate the prediction power of the model. It is important to note that validation is a critical step in the optimization process, although in this work it had its weakness in that only one part of the model (the optimum) was validated. The screening and evaluation of a small library of small-scale piroxicam-imprinted polymers was performed by Navarro-Villoslada and Takeuchi [131]. They did this by using a fractional factorial design for polymer compositions, and varying the amount of monomer (4VP), cross-linker (EDMA, TRIM, divinylbenzene or bisphenol A dimethacrylate), template (piroxicam), initiator (AIBN), porogenic solvent (acetonitrile), and polymerization method (thermal or UV). A first order calibration curve was used for the fitting of the experimental data and for cross-validation.

A central composite design was used by Kempe and Kempe [137] in another approach for the optimization of polymer composition—in this case for propranolol-imprinted polymer beads. They used the regression method MLR to analyze the variable factors: amount of monomer (MAA), cross-linker (TRIM), and porogenic solvent (acetonitrile). Propranolol rebinding was measured by a binding assay and the resulting quadratic model was validated. Davis et al. concluded in another paper that difficulties arise when using commonly used protocols when introducing new templates into molecular imprinting [136]. Consequently, they proposed a chemometric approach for the design of a polymer imprinted with sulfamethazine. They based their experimental study on an HPLC multi-analyte competition rebinding assay. A three-level full factorial design was used for the experimental setup, and a quadratic regression model containing squared terms was used for data fitting. Two factors [amount of monomer (MAA) and cross-linker (EDMA)] were considered. ANOVA was subsequently used for validating the model.

It is important to note that a chemometrics-based approach to polymer composition optimization provides no guarantee of finding the optimal MIP design. A general problem in this regard is evident in cases when the optimum is found in a

corner of the experimental region [130, 131, 136, 143, 148, 149]. In such cases, extension of the experimental region until a local optimum can clearly be seen as important in order to allow the drawing of more conclusions regarding MIP design.

Parameter analysis with respect to ligand rebinding to a MIP offers further opportunities for the optimization of molecular imprinting systems. One of the strengths of chemometrics is that the analysis methods can handle a great number of variables while also selecting the most important ones. Baggiani et al.used the semi-empirical quantum-chemical method AM1 for geometry optimization of the molecules studied and, on the basis of the optimized structures, molecular descriptors were calculated and used as variables in the chemometric methods [144]. The thermally polymerized pentachlorophenol MIP was comprised of 4VP as the functional monomer and EDMA as the cross-linking monomers, respectively. An analysis of the correlation of HPLC column selectivity with molecular descriptors was performed with PCA and PCR. The results obtained in this study showed that the pentachlorophenol-imprinted polymer demonstrates a pattern of selectivity towards several related phenols, and which steric and electronic molecular descriptors could be used to explain the selectivity. In another study, the binding of bupivacaine to imprinted polymers in different solvent mixtures and at various temperatures using equilibrium binding studies was investigated by Rosengren et al. [145]. By using PLSR, it was shown that binding could be described in terms of temperature and dielectric constant following a third-degree equation with cross-terms. The models developed in this work were validated using independent binding data obtained with a separate batch of polymers. Moreover, the complexity of the relationship highlighted the necessity for a robust validation process when building models.

The rebinding of chloroguaiacol to a MIP by utilizing a flow pre-concentration system coupled to amperometric detection was the subject of a study by Tarley et al. [132]. A fractional factorial design was initially used to establish an experiment for the study of the influence of the mobile phase physical properties (pH, flow rate, KCl concentration, elution flow rate and eluent volume). Analysis of these factors identified those most important with respect to rebinding. A Doehlert design yielded a quadratic model with cross terms and was used for the final optimization of the rebinding with the most important factors (pH and KCl concentration).

Nantasenamat et al. used literature data as the basis for a similar approach [146, 151]. They applied ANN to correlate imprinting factors from diverse published HPLC studies with molecular descriptors and mobile phase compositions [152]. The mobile phase descriptors were measured (pH and ionic strength) or taken from the literature (dielectric constant). Back-propagation of error algorithm was then used to calculate the model. The data-set was subsequently divided into two groups that were analyzed separately. Interestingly, one group consisted of data from uniformly sized MIPs and the other consisted of data from irregularly sized MIPs.

An interesting contribution to the literature involved the use of a stochastic simulation to examine the interaction between the components present in the pre-polymerization mixture [15]. Here, monomer-template binding affinities were used

in a stochastic algorithm [16] to position the monomer and template units in a lattice matrix. Subsequently, the cross-linker was added, the template removed, and the binding sites analyzed for heterogeneity. This modelling resulted in simulated MIPs that display the same trends as the MIPs formed under the corresponding imprinting conditions.

5 Conclusions and Future Perspectives

Recent years have witnessed exceptional growth in the number of studies using computational and theoretical techniques for describing, predicting and analyzing molecular imprinting systems. In many respects, the improvements in the accessibility of computational power and software have helped drive the development of MIP science and technology. As we can anticipate further improvements in computer hardware and software technologies, it is reasonable to assume that this trend will continue, and new, as well as barely addressed aspects of molecular imprinting, e.g., the investigation of relationships between morphology and polymer composition, may be studied, and steps taking us closer to truly rationally designed MIPs will be demonstrated.

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