

Computational Design and Fabrication of Enantioselective Recognition Sorbents for L-phenylalanine Benzyl Ester on Multiwalled Carbon Nanotubes Using Molecular Imprinting Technology

Sajini T, Thomas Renjith, Mathew Beena

Cite this article as:

Sajini T, Thomas Renjith, Mathew Beena. Computational Design and Fabrication of Enantioselective Recognition Sorbents for L-phenylalanine Benzyl Ester on Multiwalled Carbon Nanotubes Using Molecular Imprinting Technology[J]. *Chinese J. Polym. Sci.*, 2019, 37(12): 1305-1318. doi: 10.1007/s10118-019-2282-4

View online: <https://doi.org/10.1007/s10118-019-2282-4>

Articles you may be interested in

[Novel Terpolymers of Poly\(*p*-dioxanone-*co*-trimethylene carbonate-*co*-L-phenylalanine\): Synthesis, Characterization, Thermal Properties and Copolymerization Mechanism](#)

Chinese J. Polym. Sci. 2016, 34(5): 594 <https://doi.org/10.1007/s10118-016-1777-5>

[A Review Featuring Fabrication, Properties and Applications of Carbon Nanotubes \(CNTs\) Reinforced Polymer and Epoxy Nanocomposites](#)

Chinese J. Polym. Sci. 2018, 36(4): 445 <https://doi.org/10.1007/s10118-018-2045-7>

[Boc-phenylalanine Grafted Poly\(3,4-propylenedioxythiophene\) Film for Electrochemically Chiral Recognition of 3,4-Dihydroxyphenylalanine Enantiomers](#)

Chinese J. Polym. Sci. 2019, 37(5): 451 <https://doi.org/10.1007/s10118-019-2211-6>

[侧链带有L-氨基酸乙酯的螺旋聚苯乙炔衍生物的手性识别能力研究](#)

CHIRAL RECOGNITION OF HELICAL POLY(PHENYLACETYLENE) DERIVATIVES BEARING L-AMINO ACID ETHYL ESTER PENDANTS

高分子学报. 2013(6): 811 <https://doi.org/10.3724/SP.J.1105.2013.13054>

[交联剂含量对憎水改性缔合型增稠剂性能的影响](#)

IMPACT OF CROSS-LINKER AMOUNT ON THICKENING PERFORMANCE IN ASSOCIATIVE LATEX THICKENERS

高分子学报. 2012(4): 475 <https://doi.org/10.3724/SP.J.1105.2012.11391>

[离子液体作为功能单体制备溶菌酶分子印迹复合膜的研究](#)

Lysozyme Molecular Imprinted Membranes with Ionic Liquids as Functional Monomer

高分子学报. 2015(3): 259 <https://doi.org/10.11777/j.issn1000-3304.2015.14224>

Computational Design and Fabrication of Enantioselective Recognition Sorbents for L-phenylalanine Benzyl Ester on Multiwalled Carbon Nanotubes Using Molecular Imprinting Technology

T Sajini^{a,b}, Renjith Thomas^a, and Beena Mathew^{b*}

^a Research & Post Graduate Department of Chemistry, St. Berchmans College (Autonomous), Affiliated to Mahatma Gandhi University, Changanassery 686101, India

^b School of Chemical Sciences, Mahatma Gandhi University, Priyadarsini Hills P O, Kottayam 686560, India

Abstract Computational strategies have been employed to investigate the influence of the nature of monomers and cross-linker in order to design three dimensional imprinted polymers with selective recognition sites for L-phenylalanine benzyl ester (L-PABE) molecule. Here, computational chemistry methods were applied to screen the molar quantity of functional monomers that interact with one mole of the template molecule. Effects of the nature of functional monomer, cross-linker, and molar ratio were determined computationally using density functional calculations with B3LYP functional and generic 6-31G basis set. Methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) were used as the functional monomer and crosslinking agent, respectively. L-PABE imprinted polymer layered on multiwalled carbon nanotube (MWCNT) and conventional bulk MIP were synthesised and characterized as well. To investigate the influence of pre-organization of binding sites on the selectivity of L-PABE, respective non-imprinted polymers were also synthesised. MWCNT-MIPs and MIPs exhibited the highest adsorption capacity towards L-PABE. The synthesized polymers revealed characteristic adsorption features and selectivity towards L-PABE in comparison with those of its enantiomer analogues.

Keywords Molecular imprinting; L-phenylalanine benzyl ester; Density functional theory; Monomer; Cross-linker; Selectivity

Citation: Sajini, T.; Thomas, R.; Mathew, B. Computational design and fabrication of enantioselective recognition sorbents for L-phenylalanine benzyl ester on multiwalled carbon nanotubes using molecular imprinting technology. *Chinese J. Polym. Sci.* 2019, 37, 1305–1318.

INTRODUCTION

Molecular imprinting technology is an exploring technique to fabricate artificial sorbents of a template or target molecule for the selective and specific recognition of the imprinted template molecule *via* simple polymerization method.^[1,2] Among the various imprinting strategies like covalent, non-covalent, and semi-covalent imprinting, non-covalent imprinting involves the self-assembly of complexes of the template and functional monomers *via* non-covalent interactions such as hydrogen bonding, π - π interaction, van der Waals force, *etc.*, and this methodology has got much attention in the design of molecularly imprinted polymers (MIPs). After the synthesis of the pre-organized complex of functional monomer and template, polymerization will happen in the presence of a cross-linker and initiator which results in the covalent stabilisation of these pre-organized complexes in highly cross-linked polymer matrices.^[3–5] Finally, extraction of the target molecule gives rise to the binding sites which are complementary to the template molecule (Scheme 1).

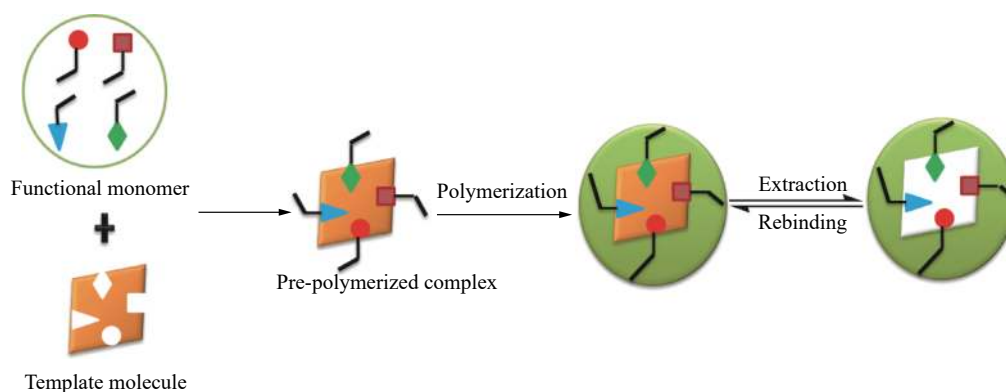
Some disadvantages in molecular imprinting technology

are their low adsorption rate and low kinetic response towards a target molecule.^[6–8] The imprinting of molecular recognition sites at nanostructures results in homogeneous binding cavities on polymer matrix and thus greatly enhances the easy removal of templates, excellent binding capacities, and better kinetics of molecular recognition compared with the traditional imprinted bulky materials.^[9] Multiwalled carbon nanotubes (MWCNTs), which exhibit extremely large surface area, should be an excellent candidate as the support material in molecular imprinting technology. Preparation of MIPs on the surface of MWCNTs would endow MIPs with large surface area; consequently, the binding sites in the outer layer of the composite would improve the accessibility of template molecule and reduce the binding time.^[10–14] To facilitate the easy recognition of binding sites with high selectivity and uniform layering of MIP on MWCNTs, it is necessary to modify MWCNTs with carboxyl functional groups by strong acid treatment to obtain vinyl group-functionalized MWCNTs. The copolymerization of these vinyl groups with the cross-linker and monomer would result in the imprinted polymer layer on the surface of MWCNTs.^[7,15]

Generally, MIP preparation is simple, but finding the best functional monomer (FM) with effective interaction with the template to achieve high selectivity, specificity, and rebinding

* Corresponding author: E-mail beenams@cs@gmail.com

Received March 25, 2019; Accepted April 22, 2019; Published online June 18, 2019



Scheme 1 Schematic representation of molecular imprinting process

ing capacity is of great importance in separation science. The experimental methodologies to find the most suitable FM, cross-linker, and molar ratio are commonly tedious and time-consuming, while molecular modelling offers a complementary tool for understanding the prevalent molecular interactions, and provides a powerful pre-selection tool for identifying suitable functional monomers and cross-linker.^[16,17] A wide range of computational techniques have been used in the study of numerous characteristic features of the molecular imprinting technology.^[18–21] Among these, combinatorial chemistry and molecular modelling are the most auspicious tools for the development of MIPs with enriched recognition properties.^[22–25] Various applications of computational modelling in molecular imprinting technology have been progressively developed and they are capable of designing efficient pre-polymerization system and hence demonstrating the potential of molecular modelling towards rational design of MIP.^[26,27] According to certain recent literatures, the applications of density functional theory (DFT) have got much attention in various fields of MIPs such as for the designing of chromatographic, electrophoretic, and enantioselective separation techniques.^[28–31] In the DFT methods, the effects of electron correlation is determined, which are usually applied in MIP studies because of their high accuracy of information, reliability, and cost-effective nature.^[18,32]

The amino acid benzyl ester, L-phenylalanine benzyl ester (L-PABE), was chosen as template molecule in the present work. It can prevent sickling of erythrocytes from sickle cell disease patients and hence acts as an antisickling agent.^[33,34] This study focused on selecting an appropriate functional monomer (FM) and a cross-linker for L-PABE using DFT calculations of structural and energetic parameters, finding the most stable molar ratio between FM and the template molecule, synthesis and characterization of MWCNT-MIP, MWCNT-NIP, MIP, and NIP by Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), and transmission electron microscopy (TEM), and determining the adsorption parameters and selectivity of designed imprinted polymers.

MATERIAL AND INSTRUMENTS

L-phenylalanine benzyl ester and D-phenylalanine benzyl ester were obtained from Alfa Aesar, India. MWCNTs with

diameter of 10–15 nm were purchased from Reinsto Nano Ventures Private Limited, New Delhi, India. Cross-linkers such as ethylene glycol dimethacrylate (EGDMA), *N,N*-ethylene bismethacrylamide (EBMAA), and *meta*- and *para*-divinylbenzene (DVB) were purchased from Sigma Aldrich, Germany. Functional monomers such as methacrylic acid (MAA), itaconic acid (IA), acrylamide (AAM), acrylic acid (AA), and 4-vinyl pyridine (4-VP) were purchased from Alfa Aesar, India. The initiator, 2,2'-azobis-isobutyronitrile (AIBN), was from Merck, India. The solvent methanol was of analytical grade and was purchased from Merck, India.

A Fourier transform infrared spectrometer 8400S (DIN 206-72400, Shimadzu, Japan) was used to record FTIR spectra of the samples. Binding studies were carried out on a Shimadzu UV-Vis spectrophotometer model 2450. For the morphological studies of the polymer samples, transmission electron microscopy (TEM, Facility-JEOL JEM-2100) and scanning electron microscopy (SEM, JEOL-JSM-6390A) were used. PAN analytical X'PERT PRO was used for X-ray diffraction studies of polymers.

Hardware and Software

Calculations reported in this article were performed using Gaussian 09W 64 bit^[35] software with Gauss View 5.0^[36] as the GUI. The calculations were performed on Intel processed workstation with 32 GB RAM.

Geometry Optimisation and Energy Calculation

The 3D chemical structures of the monomer, template, and cross-linker were generated using Gauss View 5.0 software and subjected to series of initial optimisations using Gaussian 09 software, which is an electronic structure package capable of guessing properties such as energies, structures, and vibrational frequencies of atoms, molecules, and reactive systems.^[18] Here, overall frequency optimisations and energy calculations were executed and each species was found to be at the minima by having no negative values in the frequency calculation. DFT method was chosen to set up the calculations and the geometry optimizations were performed at the B3LYP functional and generic 6-31G basis set.

In order to screen out the most suitable functional monomer, binding energies of six commonly used functional monomers such as methacrylic acid (MAA), itaconic acid (IA), acrylamide (AAM), *m*-divinylbenzene (*m*-DVB), acrylic acid (AA), and 4-vinylpyridine (4-VP) (Fig. 1) with the

template molecule L-PABE were determined computationally using DFT with B3LYP functional and generic 6-31G basis set. Template to functional monomer stoichiometry was found out in the same manner as described above using the selected monomer.

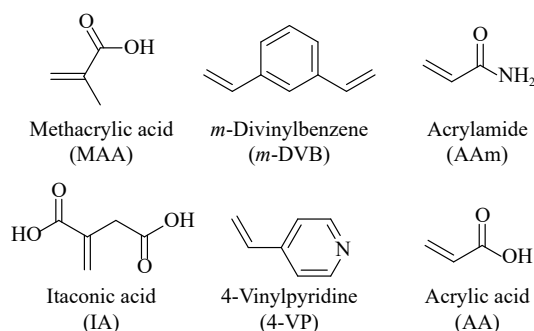


Fig. 1 Functional monomers for screening with L-PABE for the design of MIPs

To discover the appropriate cross-linkers, binding energies of three commonly used cross-linkers, ethylene glycol dimethacrylate (EGDMA), *N,N*-ethylene bismethacrylamide (EBMAA), and *p*-divinylbenzene (*p*-DVB), with the template and the chosen monomer were determined computationally using DFT with B3LYP functional and generic 6-31G basis set (Fig. 2).

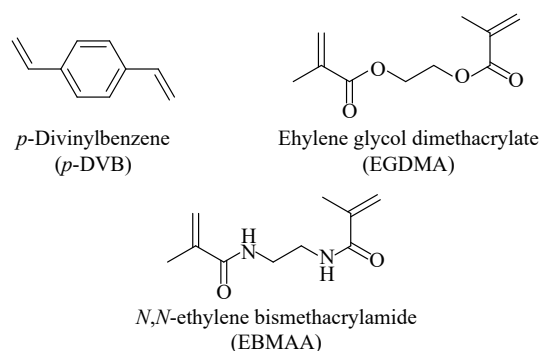


Fig. 2 Cross-linkers for screening with L-PABE for the design of MIPs

The binding energies between L-PABE and the functional monomers as well as cross-linkers were calculated using the following Eqs. (1)–(3) via DFT approximation, where T is the template, FM is functional monomer, and CL is cross-linker.

$$\Delta E_{T-FM} = E_{\text{template, monomer}} - (E_{\text{template}} + E_{\text{monomer}}) \quad (1)$$

$$\Delta E_{T-CL} = E_{\text{template, cross-linker}} - (E_{\text{template}} + E_{\text{cross-linker}}) \quad (2)$$

$$\Delta E_{FM-CL} = E_{\text{monomer, cross-linker}} - (E_{\text{monomer}} + E_{\text{cross-linker}}) \quad (3)$$

EXPERIMENTAL

Synthesis of Imprinted and Non-imprinted Polymers on Vinyl-functionalized MWCNTs

L-phenylalanine benzyl ester imprinted polymer layered on MWCNT was prepared by polymerizing vinyl groups anchored on MWCNT with MAA and EGDMA in the pre-

sence of L-PABE. For MIP synthesis, MWCNT-CH=CH₂ (0.02 g) was added to 30 mL of methanol in a 250 mL round-bottom (RB) flask and purged with N₂ under magnetic stirring. L-PABE (0.05 mmol) and MAA (0.10 mmol) dissolved in 5 mL of methanol were added to the RB flask and mixed for 30 min to form a complex of template and functional monomer. The initiator AIBN (10 mg) and cross-linker EGDMA (1.25 mmol) were then added. The temperature of the pre-organized mixture was raised to 65 °C, and the reaction was allowed to proceed for 8 h. The resulting product was collected by centrifugation and washed thoroughly with ethanol to discard unreacted monomer and template molecule. The template molecule was eluted by methanol until no L-PABE could be detected by UV-Vis spectroscopy (257 nm) in the eluent. The same procedure was used for the synthesis of MIPs with different FMs such as itaconic acid (IA), acrylamide (AAM), *m*-divinylbenzene (*p*-DVB), acrylic acid (AA), and 4-vinylpyridine (4-VP). In accordance with computational data, a 1:2 molar ratio of template to functional monomers was used in order to saturate all functional binding sites in the template. After the identification of better monomer, both MWCNT-MIP and MIPs were prepared using the selected monomer with different cross-linkers such as *N,N*-ethylene bismethacrylamide (EBMAA) and *p*-divinylbenzene (*p*-DVB). For comparison, blank polymers (MWCNT-NIP) were prepared by the same procedure, without adding template molecule in the polymerization process. L-PABE non-imprinted polymers (NIP) without MWCNTs were also prepared and analyzed. Schematic representations of the fabrication of MWCNT-MIP and MIP are depicted in Scheme 2.

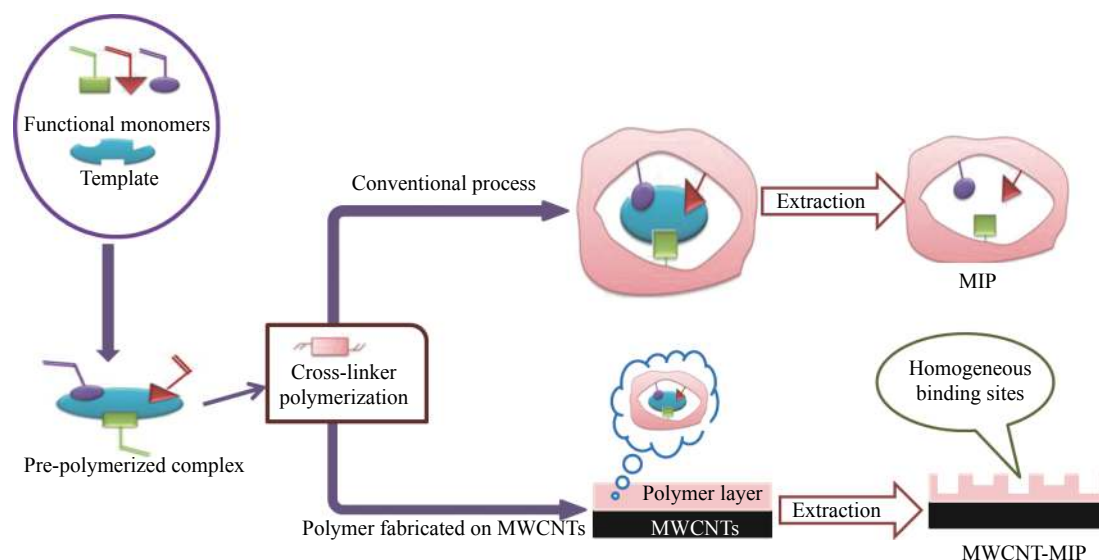
Adsorption Mechanism and Selectivity Studies of L-PABE Imprinted Polymers

The adsorbed amount of L-PABE on each polymer was monitored by a UV-Vis spectrophotometer at 257 nm. For this, 10 mg of each polymer were transferred into a tube containing 7.0 mL of methanol with specific initial concentrations of L-PABE ranging from 0.05 mmol·L⁻¹ to 0.35 mmol·L⁻¹ and equilibrated for about 3 h at 28 °C. The mixture was centrifuged at 15000 r·min⁻¹ for 5 min. Finally, the extracted solution was monitored by a UV-Vis spectrophotometer and the concentration of free L-PABE in the supernate was measured. The amount of L-PABE adsorbed onto the polymer, Q_e (μmol·g⁻¹) was determined according to the following equation:^[37]

$$Q_e = \frac{(c_i - c_f) \times V}{m} \quad (4)$$

where c_i (mg·mL⁻¹) and c_f (mg·mL⁻¹) represent the initial and final solution concentrations of L-PABE. V (mL) is the sample volume and m (g) is the mass of the polymer.

In order to obtain the thermodynamic parameters, the experiments were carried out at three different temperatures (291, 301, and 311 K) for 10 min to 180 min. The time taken for the saturated rebinding specificity was investigated by incubating an equal amount of polymer in template solution of the known concentration of L-PABE at these temperatures. The amount of L-PABE adsorbed by each polymer was measured using similar procedure for binding studies. The



Scheme 2 Schematic representation of synthesis of conventional molecularly imprinted polymer (MIP) and imprinted polymer on vinyl-functionalized MWCNTs (MWCNT-MIP)

sorption kinetic data of L-PABE on MWCNT-MIP was analyzed using the pseudo-second-order rate equation as follows:^[38]

$$\frac{t}{Q_t} = \frac{1}{k_2 \times Q_e^2} + \frac{t}{Q_e} \quad (5)$$

where k_2 is the rate constant of pseudo-second-order sorption.

The mechanism of adsorption process can be determined based on the change of adsorption enthalpy and adsorption entropy because the change of adsorption enthalpy can indirectly define the inducement between imprinted polymers and the template molecule, and a larger adsorption enthalpy displays a stronger binding capacity towards the template molecule.^[39] Also, the adsorption entropy is a function of the disordered state before and after adsorption, which reflects the change of template molecule from the solution to the surface of the imprinted polymer.^[40] Established on the thermodynamic theory, the correlation relationship of imprinted and non-imprinted polymers can be expressed as follows:^[41]

$$\ln\left(1 - \frac{Q_T x w}{n_0}\right) = \frac{\Delta H_{ad}}{RT} - \frac{\Delta S_{ad}}{R} \quad (6)$$

where n_0 is the initial molar number of the adsorbate, w is the mass of MIPs, ΔH_{ad} and ΔS_{ad} are the adsorption enthalpy and adsorption entropy, respectively, and T (K) is the absolute temperature of the adsorption process.

For the selectivity studies, to the template desorbed polymer, equal volume of the template solutions and the enantiomer (D-PABE) solution having an equal concentration were added into different tubes and the difference in the binding extent was estimated spectrophotometrically. The imprinting factor or separation factor (α), which represents the effect of the imprinting process, is the amount ratio of substrate bounded by MIP to that bounded by the corresponding NIP.

$$\alpha_{\text{Template}} = \frac{K_{\text{MIP}}}{K_{\text{NIP}}} \quad (7)$$

$$K = \frac{\text{Template}_{\text{Bound}}}{\text{Template}_{\text{Free}}} \quad (8)$$

The selectivity of the imprinted polymer towards the template was calculated in terms of selectivity factor (α).

$$\alpha = \frac{\alpha_{\text{Template}}}{\alpha_{\text{Analogue}}} \quad (9)$$

RESULTS AND DISCUSSION

Computational Studies

Selection of the optimal functional monomer for the synthesis of MIPs for L-PABE

Selection of the most suitable functional monomer by template interaction analysis permits the choice of high affinity MIP towards L-PABE. From the optimized structure of L-PABE template molecule in Fig. 3, it reveals that the chemical structure of L-PABE encompasses a collection of heterogeneous interaction sites able to form hydrogen bonds with the functional monomer. To achieve the strongest affinity binding sites, the electrostatic potential energy contour onto the molecular surface of L-PABE was measured. Figs. 3(a) and 3(b) show the frequency optimized geometry of L-PABE along with the contours of electrostatic potential energy. The most significant interaction between L-PABE and FM in the MIP will occur at the regions marked with green numbers in Fig. 3(a) which contain regions around one

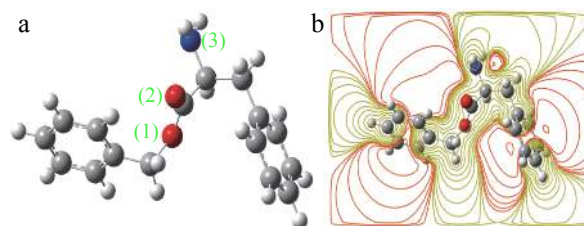


Fig. 3 (a) Frequency optimized structure of L-PABE (Green colored numbers show the most significant interactive sites of L-PABE) and (b) electrostatic potential contours of L-PABE

nitrogen and two oxygen heteroatoms.

After knowing the strongest interactive sites of L-PABE, the next step is to evaluate the affinity binding of each FM (MAA, IA, AAm, *m*-DVB, AA, and 4-VP) with the template molecule L-PABE leading to 1:1 complexes. The B3LYP/6-31G optimized structures for template and functional monomer complexes are shown in Fig. 4. In these energy optimized complexes, hydrogen bonds and dipoles are drawn in yellow line and red arrow, respectively, to facilitate visualization. The establishment of hydrogen bond in four complexes (L-PABE/AA, L-PABE/AAm, L-PABE/IT, and L-PABE/MAA) could be noticed. In L-PABE/MAA, L-PABE/IT, and L-PABE/AA complexes, hydrogen bonds were formed between hydrogen of hydroxyl group of the functional monomer and carboxyl oxygen of the template molecule. In L-PABE/AAm complex, hydrogen bond formation occurs at carboxyl oxygen of acrylamide and hydrogen from amino group of template molecule. These results show that the strongest interaction between FMs and L-PABE is through hydrogen bonding.

The calculated B3LYP binding energies of the complexes (ΔE) are presented in Table 1. From the values, it can be observed that three monomers, namely methacrylic acid, acrylic acid, and itaconic acid, possess lower binding energies and

hence formed more stable complexes with L-PABE, among which methacrylic acid and itaconic acid were found to keep the strongest affinity for L-PABE. The carboxylic functional group of acidic functional monomers is an excellent hydrogen bond donor-acceptor group which would participate in the formation of hydrogen bonding interactions with the template. In the present study, the selection of the best monomer is in good agreement with the basic criteria of molecular imprinting “an acidic functional monomer was the best monomer for the imprinting of an basic template molecule”.[32]

In order to determine the effect of monomers on adsorption process, batch adsorption experiments were carried out for MWCNT-MIP and MIP which were synthesised using these six monomers. The results obtained are plotted in Fig. 5. The plot indicates that MWCNT-MIP and MIP prepared using methacrylic acid and itaconic acid showed similar and better recognition of L-PABE template molecule. In our system, hydrogen bonding interactions between carboxyl oxygen of L-PABE and hydroxyl group of MAA and IA are predominant compared to other monomers. The higher hydrogen bonding ability of the carboxyl oxygen enhances the strength of the hydrogen-bonding interaction between the template molecule and the carboxyl oxygen functional group, creating specific recognition sites within the polymer

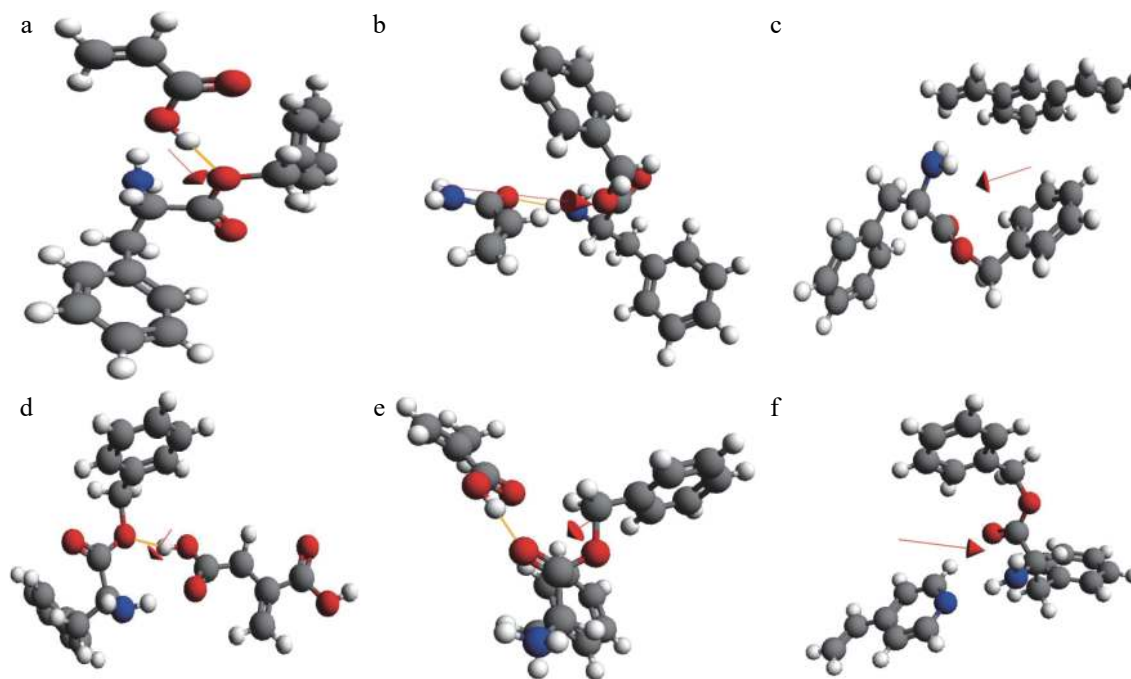


Fig. 4 B3LYP/6-31G energy optimized structures for template and FM complexes: (a) L-PABE/AA, (b) L-PABE/AAm, (c) L-PABE/*m*-DVB, (d) L-PABE/IT, (e) L-PABE/MAA, and (f) L-PABE/4-VP

Table 1 Screening of virtual library of functional monomers for molecular imprinting of L-phenylalanine benzyl ester ($E_{\text{L-PABE}} = -824.9303$ au)

Functional monomer	E_{monomer} (au)	$E_{\text{template/FM complex}}$ (au)	Binding energy (au)	Binding energy ($\text{kJ}\cdot\text{mol}^{-1}$)
Methacrylic acid (MAA)	-306.388	-1131.339	-0.021	-54.548
Acrylic acid (AA)	-267.077	-1092.027	-0.019	-52.390
Acryl amide (AAm)	-247.222	-1072.164	-0.012	-31.259
Itaconic acid (IA)	-494.882	-1319.834	-0.021	-56.301
<i>m</i> -Divinylbenzene (<i>m</i> -DVB)	-386.964	-1211.898	-0.003	-9.013
Vinylpyridine (VP)	-325.599	-1150.542	-0.013	-34.087

tive charges in comparison with those of MAA. It reveals that L-PABE has the capacity to act as a nucleophile and also MAA has the ability to act as the electrophile.

Effective template to functional monomer stoichiometry

During the imprinting process, there must be a specific molar amount of functional monomer that interact with the template molecule to ensure more binding sites on imprinted polymer.^[24] Molar ratio optimization of template-monomer complex was carried out in order to determine the influence of increased functional monomer concentration on the selected template-monomer complexes. B3LYP/6-31G optimized structures of FM (indicated moles) that bind with one mole of L-PABE are shown in Fig. 8 and the corresponding binding energies are presented in Table 2.

By analysing Table 2, it is clear that the ΔE values of template-monomer complex increased up to a ratio of 1:2, after which it decreased and then slightly increased in 1:4 complex. By comparing these four complexes, 1:2 molar ratio gave the higher binding energy and greater stability towards L-PABE.

In order to confirm the optimal molar ratio for L-PABE to MAA, MIPs with varied imprinting ratios were prepared. For that, MAA was used as the functional monomer and EGDMA was used as the cross-linker. As shown in Fig. 9, the MIPs, whose molar ratio for L-PABE to MAA is 1:2, exhibits the maximum adsorption and the greatest affinity towards the binding sites formed in polymer matrix. The order of adsorption quantity in different molar ratios is 1:2 > 1:4 > 1:3 > 1:1, indicating that the appropriate reaction ratio of L-PABE to MAA is 1:2, which is in agreement with the result obtained in computational studies. Among MWCNT-MIPs and MIPs, polymer imprinted on MWCNTs has the strongest affinity towards L-PABE due to the homogeneous distribution of binding sites.

Selection of suitable cross-linker for the maximum adsorption of L-PABE

The selection of the most suitable cross-linker is another crucial parameter in MIP synthesis because effective cross-linker in the polymeric network helps to maintain the specific sites of functional group in FM and preserve the structure of binding cavities.^[44] The molecules of DVB, EGDMA, and EBMAA are commonly used cross-linkers for the preparation of MIPs. The binding energies (ΔE) between L-PABE and MAA/cross-linkers were calculated at the B3LYP/6-31G level and are presented in Table 3. Their energy optimized structures are depicted in Fig. 10.

As shown in Table 3, the ΔE values between L-PABE and different cross-linkers are in the increasing order of $\Delta E(\text{L-PABE-EBMAA}) < \Delta E(\text{L-PABE-DVB}) < \Delta E(\text{L-PABE-EGDMA})$ and the ΔE values between MAA and different cross-linkers in the decreasing order of $\Delta E(\text{MAA-DVB}) > \Delta E(\text{MAA-EBMAA}) > \Delta E(\text{MAA-EGDMA})$.

These results show that the ΔE value ($-2.2853 \text{ kJ}\cdot\text{mol}^{-1}$) between L-PABE and EGDMA is the largest, and the ΔE value between MAA and EGDMA ($-18.604 \text{ kJ}\cdot\text{mol}^{-1}$) is the smallest. As a result, the interaction between EGDMA and L-PABE is the weakest and the interaction between EGDMA and MAA is the strongest. This is in good agreement with the rule that the strength of the interaction between template and cross-linker should be weak and that between functional monomer and cross-linker should be strong.^[43] This is again confirmed with the experimental evidence obtained from these cross-linkers as shown in Fig. 11.

Evaluation of the amount of cross-linker

To fabricate the MIPs with stable and ordered binding sites, certain rigidity is required. That is, to enable the template molecule to enter the imprinted cavities easily, certain extent of flexibility is required. Increasing the extent of cross-

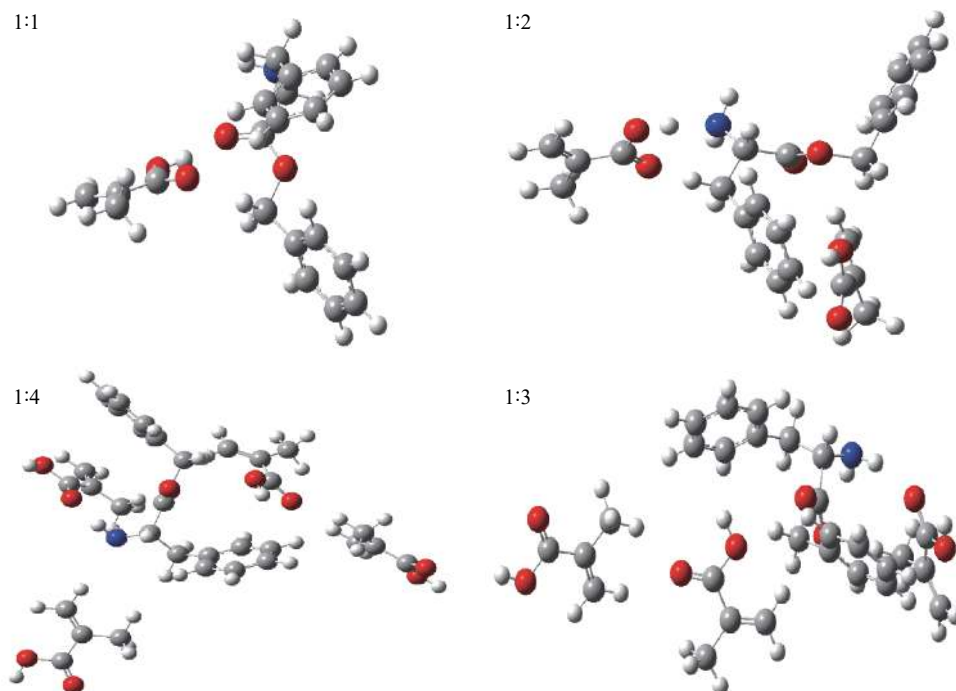
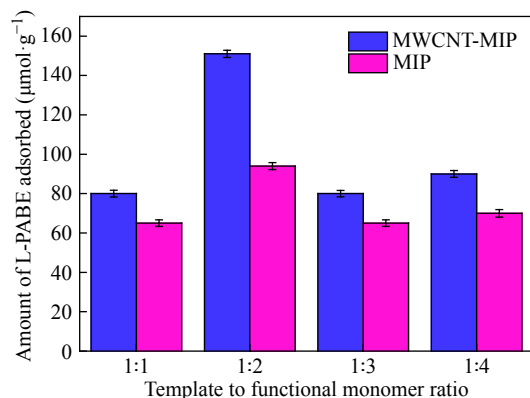


Fig. 8 Models of complexes formed from L-PABE and MAA at different molar ratios: 1:1, 1:2, 1:3, and 1:4

Table 2 Binding energies of template and monomer complexes ($E_{\text{monomer}} = -306.3878$ au, $E_{\text{template}} = -824.9303$ au)

Molar quantity of monomer	$E_{\text{T-FM complex}}$ (au)	Binding energy (au)	Binding energy ($\text{kJ}\cdot\text{mol}^{-1}$)
1	-1131.339	-0.021	-54.548
2	-1437.739	-0.034	-88.969
3	-1744.116	-0.022	-58.358
4	-2050.509	-0.027	-71.969

**Fig. 9** The adsorption of L-PABE with varying template to functional monomer ratios in methanol**Table 3** Binding energies (ΔE) between L-PABE as well as MAA and different cross-linkers at the B3LYP/6-31G level ($\text{kJ}\cdot\text{mol}^{-1}$)

System	DVB	EGDMA	EBMAA
L-PABE	-14.317	-9.562	-72.364
MAA	-25.234	-77.839	-50.089

linking of polymers would reduce the flexibility and decrease the contribution of specific binding to imprinted receptor sites.^[43] Thus, it is very important to decide the amount of cross-linker needed for the preparation of MIPs with a high adsorption capacity and selectivity. In this system, ethylene

glycol dimethacrylate (EGDMA) was used as the cross-linker. MWCNT-MIPs and MIPs were prepared by changing the amount of EGDMA in the range of 0.10–0.40 mmol and their adsorption properties were determined. As shown in Fig. 12, when the amount of EGDMA is 0.25 mmol, both MWCNT-MIP and MIP reveal very high adsorption capacity. The reason is that when the amount of EGDMA is lower than 0.25 mmol, the imprinted cavities would be movable, easily deformed, and could not fix the binding sites. When the amount of EGDMA is higher than 0.25 mmol, the existence of the non-covalent interaction between EGDMA and the functional monomer would deteriorate the imprinting efficiency. Hence, the amount of EGDMA to be added was fixed as 0.25 mmol.

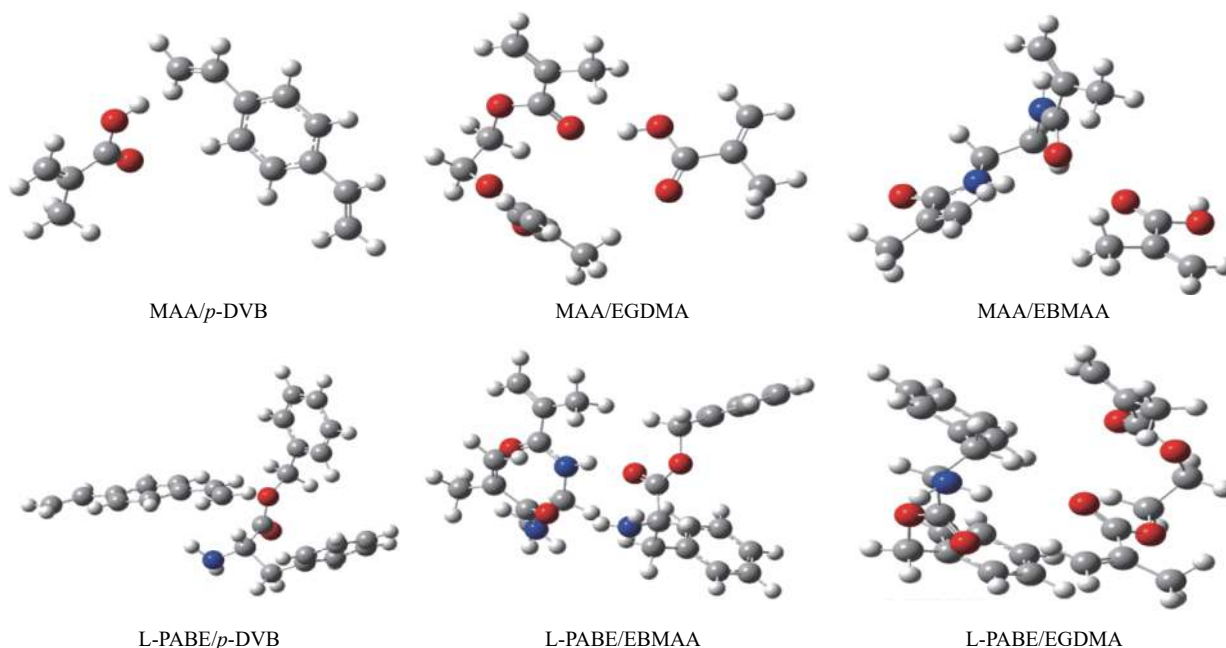
Characterization of L-PABE Imprinted and Non-imprinted Polymers

FTIR

The synthesis of MWCNT-MIP from the functional monomer MAA and crosslinking agent EGDMA was primarily confirmed by FTIR spectroscopy. The FTIR spectra of vinyl functionalised MWCNT, MIP, and MWCNT-MIP are shown in Fig. 13.

The vibrational bands corresponding to each spectrum are given below: (a) 2924 cm^{-1} $\equiv\text{C-H}$ stretching, 1701 cm^{-1} $>\text{C=O}$ stretching, 1653 cm^{-1} $>\text{C=C}<$ stretching, 1262 cm^{-1} $\equiv\text{C-O}$ symmetric stretching (ester), 1005 cm^{-1} out of plane $\equiv\text{C-H}$ bending vibration; (b) 1730 cm^{-1} $>\text{C=O}$ stretching, 1021 cm^{-1} C-N stretching, 1296 cm^{-1} $\equiv\text{C-O}$ symmetric stretching (ester), 1193 cm^{-1} $\equiv\text{C-O}$ asymmetric stretching (ester), 957 cm^{-1} $-\text{O-H}$ bending; (c) 2952 cm^{-1} $\equiv\text{C-H}$ stretching, 1730 cm^{-1} $>\text{C=O}$ stretching, 1021 cm^{-1} C-N stretching, 1296 cm^{-1} $\equiv\text{C-O}$ symmetric stretching (ester), 1193 cm^{-1} $\equiv\text{C-O}$ asymmetric stretching (ester), 959 cm^{-1} $-\text{O-H}$ bending.

The vibrational bands at 2924, 1701, 1653, 1262, and

**Fig. 10** B3LYP/6-31G optimised structures of L-PABE/cross-linker complexes

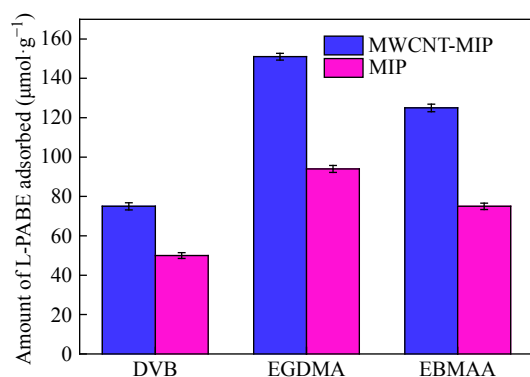


Fig. 11 Effect of cross-linkers on the amount of L-PABE bound on MWCNT-MIP and MIP

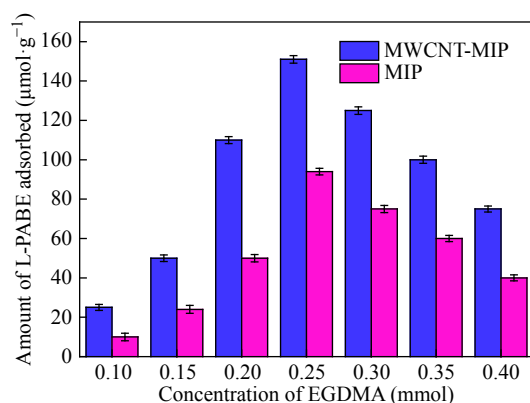


Fig. 12 Dependence of EGDMA cross-linked on L-PABE binding by MWCNT-MIP and MIP

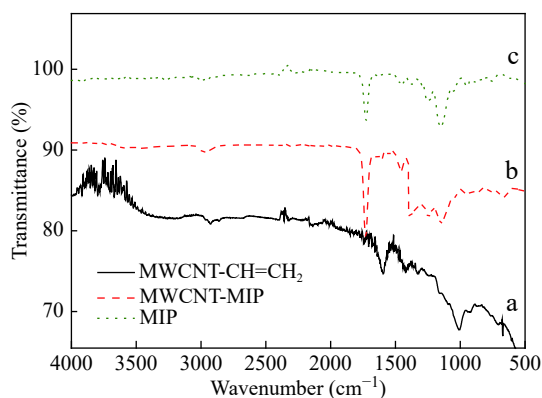


Fig. 13 FTIR spectra of (a) vinyl-functionalized MWCNT, (b) MWCNT-MIP, and (c) MIP

1005 cm^{-1} observed in the spectrum (a) indicate the successful incorporation of vinyl group on the surface of MWCNT. The characteristic bands of neat MIP also appear in the spectrum of MWCNT-MIP, which reveals the successful fabrication of MWCNT-MIP.

X-ray diffraction analysis

X-ray diffraction (XRD) technique was used to examine the crystalline nature of MWCNT-MIP synthesised from MAA and EGDMA. Fig. 14 shows the XRD patterns of MWCNT-MIP, MWCNT, and MIP. XRD pattern of neat MWCNTs shows four characteristic peaks at 25.3° (002), 43.7° (101),

51.0° (004), and 72.7° (110) [JCPDS 41-1487]. The (002) reflection peak can be observed at the same 2θ values in both MWCNT and MWCNT-MIP patterns. The intensities of diffraction peaks in MWCNT-MIP are decreased as compared to those of MWCNT. The conventional MIP could scatter the X-ray beams to give a very broad peak ($2\theta = 5^\circ\text{--}20^\circ$), which is the characteristic peak of its amorphous nature. This is a good indication of the successful fabrication of MIP layer on the surface of MWCNT. From XRD patterns, it could be concluded that MWCNT retains the same cylindrical wall structure and inter planar spacing after the attachment of MIP layer on it. The spatial extent of stacking of graphene layers is calculated using Scherrer's formula ($L = 0.9\lambda/B\cos\theta$), where L is the mean size of the MWCNT-MIP particles, λ is the X-ray wavelength (Cu $K\alpha$, $\lambda_{K\alpha} = 0.1542$ nm), $\theta_{\max}$ is the maximum angle of the (002) peak, and $B(2\theta)$ is the half-peak width for MWCNT-MIP (002) in radians. The value of L is found to be approximately 24.5 nm, which is in good agreement with TEM results.

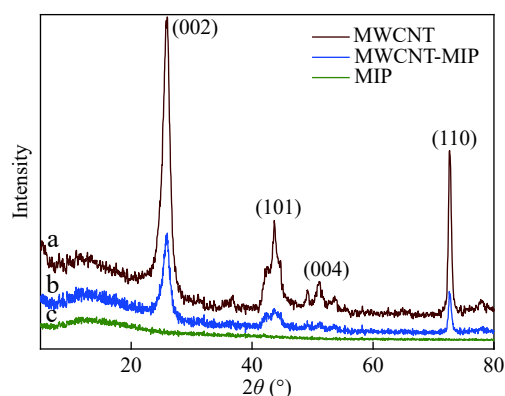


Fig. 14 X-ray diffraction patterns of (a) MWCNT, (b) MWCNT-MIP, and (c) MIP

Scanning electron microscopic analysis

Morphological characteristics of MWCNT-MIP and MIP were examined by SEM technique. In Fig. 15, MWCNT-MIP shows thread-like nanotube structure moieties with an average size about 22–31 nm. Generally, MIPs have a rough surface morphology because of the extraction of template

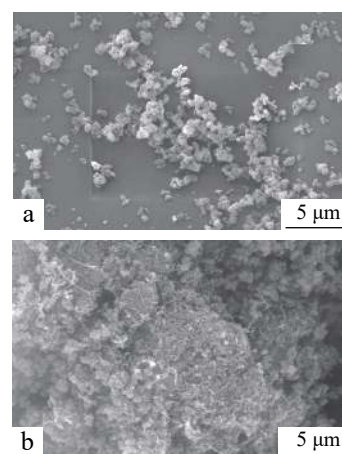


Fig. 15 SEM images of (a) MIP and (b) MWCNT-MIP

molecule from its polymer matrix. Here, the conventional MIPs also display an agglomerated morphology, which could be significantly converted into thread-like tubular forms through the incorporation of MWCNT into the polymer matrix. Further TEM analysis narrates the tubular nature of MWCNTs.

Transmission electron microscopic analysis

In order to know the detailed surface morphology, crude MWCNTs, vinyl functionalized MWCNT, and MWCNT-MIP were characterized with TEM. TEM micrographs of crude MWCNTs before and after fabrication of MIP are shown in Fig. 16. The image of MWCNTs reveals that the crude multiwalled nanotubes are entangled with one another and form a cross-linked structure due to the presence of impurities. Their average diameter is about 15 nm and the length is several micrometers. Compared to crude MWCNTs, the outer wall thickness of MWCNTs increases in MWCNT-MIP and it also preserves the nanofibrillar morphology. The average diameter is increased to 25 nm, which indicates the fact that an imprinted layer with thickness about 5–10 nm was successfully wrapped around the vinyl functionalized MWCNTs.

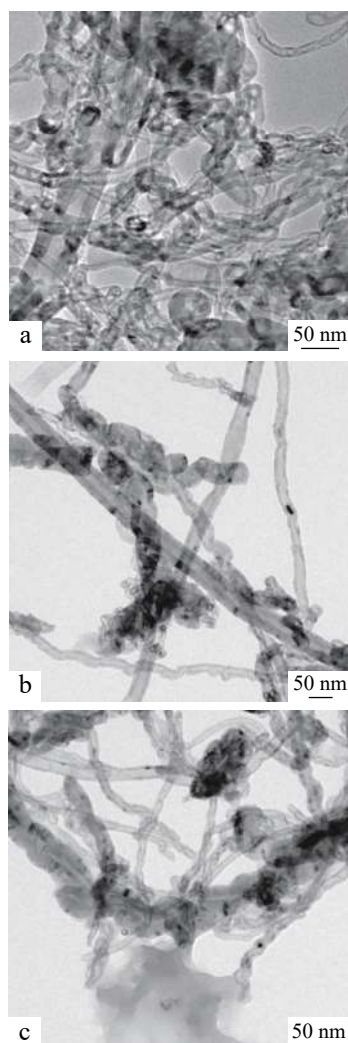


Fig. 16 TEM images of (a) MWCNT, (b) Vinyl functionalized MWCNT, and (c) MWCNT-MIP

Binding Experiments

In order to observe the binding performance of the surface imprinted MIP on MWCNTs against MWCNT-NIP control, an equilibrium binding analysis was carried out. The binding isotherm depicts a saturation curve which indicates that a finite number of binding sites exist in the imprinted polymer. As shown in Fig. 17, the adsorption capacity of MWCNT-MIP is much higher than that of MIP. This reveals that MWCNT-MIP has a distinctive capacity for L-PABE, which could be attributed to the presence of complementary cavities in the MWCNT-MIP materials. The surface-imprinted MWCNT-MIP has a higher binding capacity than that of MWCNT-NIP. The weak adsorption of L-PABE to MWCNT-NIP might be attributed to the non-specific interaction in the non-imprinted polymer matrix.

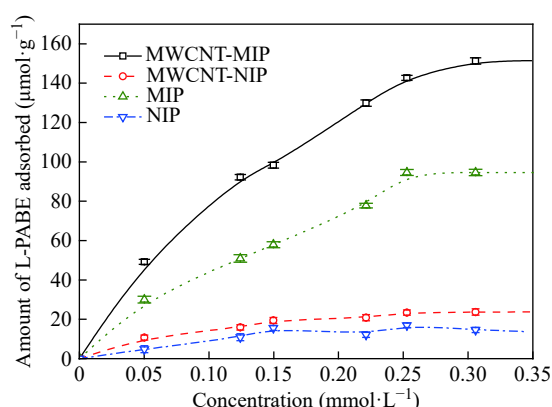


Fig. 17 Binding isotherm of MWCNT-MIP, MWCNT-NIP, MIP and NIP

Adsorption Dynamics and Kinetics

Fig. 18 shows the time dependence of the adsorption capacities of L-PABE towards imprinted polymer at three different temperatures. It reveals that the amount of adsorption increased with the increasing temperature or adsorption time. As shown, L-PABE adsorption initially increased but the growth trend slowed down with the time extension. In the case of MWCNT-MIPs, after 50 min the adsorption process reached equilibrium, whereas for MIPs, this did not happen

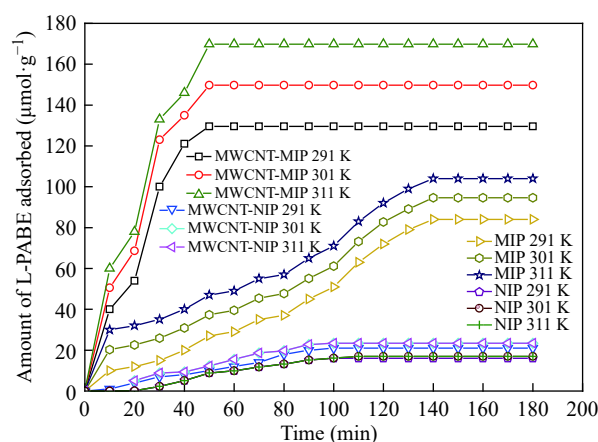


Fig. 18 Adsorption kinetics on MWCNT-MIP, MWCNT-NIP, MIP, and NIP at different temperatures

until 160 min. This is probably due to high complexation between L-PABE molecules and L-PABE binding cavities in the imprint polymer structure. At the initial stage a large number of imprinted cavities existed on the support, so L-PABE molecule could readily reach the specific binding sites. When the recognition cavities were filled up, the rate of adsorption dropped significantly and then the adsorption process achieved equilibrium. The increased adsorption rate also implied that the imprinted cavities situated on the surface made recognition more accessible for the template molecule and hence shortened the time required to reach adsorption equilibrium.

The plot of t/Q_t against t given in Fig. 19 has a high correlation coefficient (0.9992), which reveals that the L-PABE adsorption using MWCNT-MIP is in good agreement with the pseudo-second order kinetics reaction with rate constant $k_2 = 0.2413 \text{ mol}^{-1} \cdot \text{min}^{-1}$.

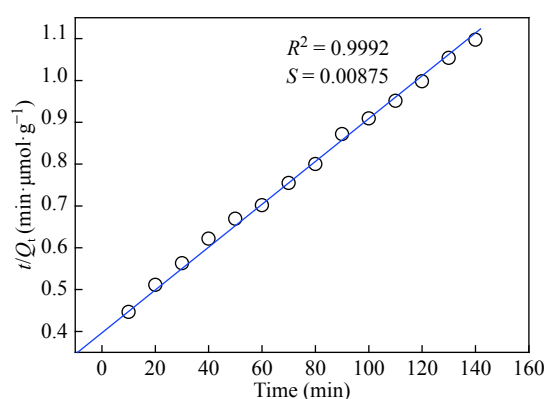


Fig. 19 Second order kinetics of the experimental data for MWCNT-MIP at 301K

Thermodynamic Studies

Since the adsorption by imprinted molecule is a result of induced molecular memory, the adsorption enthalpy obtained by changing internal-energy is more or less dependent on the interaction between sorbent and substrate. Hence, the change of adsorption enthalpies could be indirectly related to the induced interaction between MIP and substrates. The adsorption entropy is a measure of disorders before-and-after adsorption that reflects the change of molecular motions from the free space to a two-dimensional surface.^[41] Hence, based on Eq. (6), $\ln(1 - Q_T \cdot w/n)$ is plotted against $(1/T)$ in Fig. 20 in which the plots are normally expected to be a straight line. Compared with the non-imprinted polymers, the imprinted polymers show a significantly different adsorption behavior for L-PABE. The thermodynamic parameters are collected in Table 4. Among MWCNT-MIP and MIPs, polymer layered on nanotubes shows greater enthalpy value which will enhance the inducement of polymer for L-PABE. Conversely, the adsorption entropy of the imprinted polymers is lower than that of non-imprinted polymers. The change in adsorption entropy, which reveals a difference in the adsorption behavior of polymer fabricated on MWCNTs and on conventional polymer matrix, might result from the increased interaction between molecules due to high specific imprint and the larger restriction on molecular motions due to bin-

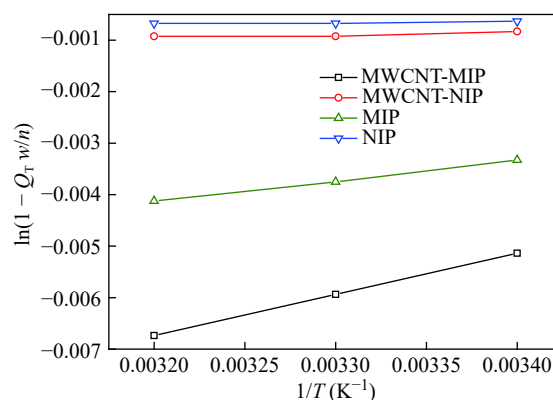


Fig. 20 Thermodynamic correlation for the relative adsorption of L-PABE

Table 4 ΔH_{ad} and ΔS_{ad} values of imprinted and non-imprinted polymer

Polymer	$\Delta H_{ad} (\text{kJ} \cdot \text{mol}^{-1})$	$\Delta S_{ad} (\text{kJ} \cdot \text{mol}^{-1} \cdot \text{K}^{-1})$
MWCNT-MIP	66.512	10.929
MIP	32.840	13.941
MWCNT-NIP	39.533	20.482
NIP	16.503	26.888

ding. These results indicate that the L-PABE adsorption on the MWCNT-MIP was a spontaneous process of enthalpy control.

Selectivity of the L-PABE Imprinted and Non-imprinted Polymers

The chiral recognition ability of the synthesized MWCNT-MIP was estimated using its enantiomer D-LABE. The concentration of D- and L-enantiomers was chosen as $0.2528 \text{ mmol} \cdot \text{L}^{-1}$, which is the maximum adsorption concentration of L-PABE revealed from binding analysis. Fig. 21 suggests that the non-imprinted polymer prepared without the template molecule is not able to recognize the chirality. This is ascribed to the production of non-specific binding sites in the polymer matrix. The maximum adsorption quantity of synthesised MWCNT-MIP towards L-PABE and D-LABE is about 149.7 and $25.8 \mu\text{mol} \cdot \text{g}^{-1}$, respectively.

A proposed mechanism for the selective and specific binding of L-PABE in MIP and MWCNT-MIP is depicted in Scheme 3. The interactions between the functional monomer

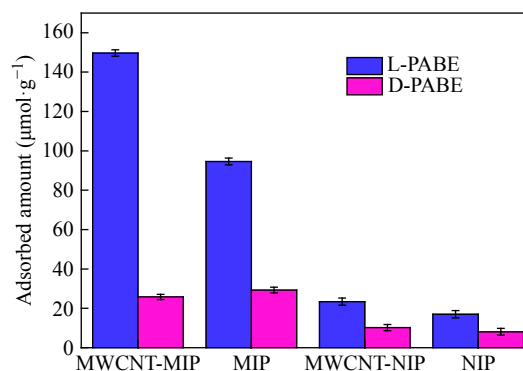
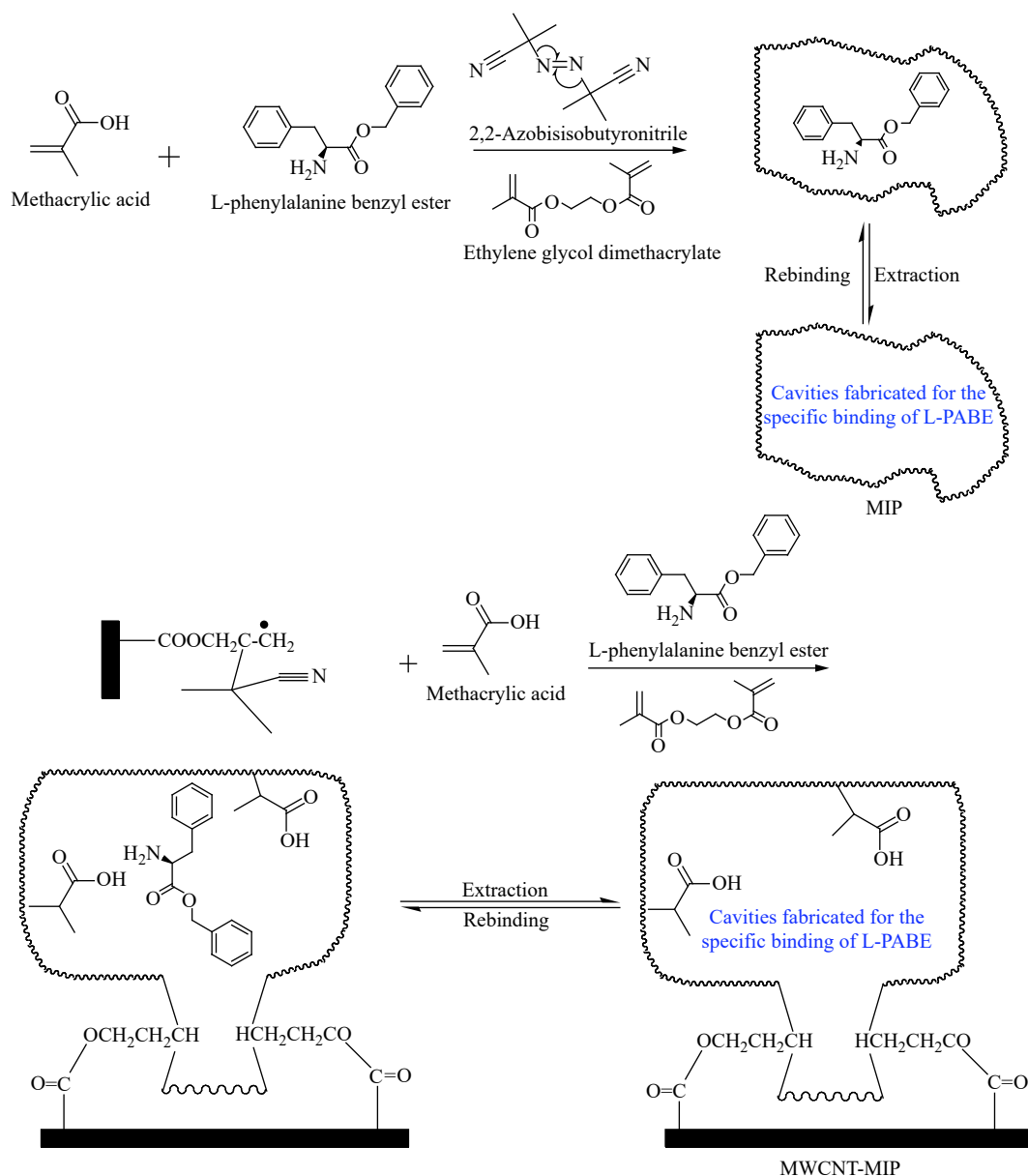


Fig. 21 Evaluation of selectivity of the L-PABE imprinted polymer



Scheme 3 Proposed mechanism for the selective and specific binding and rebinding of L-PABE in MIP and MWCNT-MIP

and the template have a crucial effect on creating highly specific adsorption sites in polymer network. The geometry of the sites constructed on the polymer surface is complementary to the imprinted L-PABE which plays a vital role in recognizing the chiral molecule. Heterogeneous binding sites and highly selective homogeneous chiral cavities of L-PABE were formed in MIP and MWCNT-MIP, respectively.

As depicted in Table 5, imprinted polymer on MWCNT

has higher selectivity factor towards target L-PABE molecule than conventional MIP. This again indicates the formation of homogenous binding site on the surface of MWCNT. A large number of template recognition cavities with high binding capacities towards L-PABE have been formed on the surface of MWCNT-MIP. The high specificity is mainly attributed to the specific binding of the template molecule.

Table 5 Selectivity and separation factors of MWCNT-MIP and MIP

	Separation factor of L-PABE	Separation factor of D-PABE	Selectivity factor, $\alpha = \frac{\alpha_{\text{template}}}{\alpha_{\text{analogue}}}$
$\alpha_{\text{template}} = \frac{K_{\text{MWCNT-MIP}}}{K_{\text{MWCNT-NIP}}}$	14.235	2.703	5.266
$\alpha_{\text{template}} = \frac{K_{\text{MIP}}}{K_{\text{NIP}}}$	8.295	3.272	2.535

CONCLUSIONS

In the current work, we designed a novel chiral sorbent for the enantioselective recognition for L-PABE using computational modelling and successfully fabricated the designed sorbents on vinyl functionalized MWCNT via molecular imprinting approach. Here, computational aspects helped us to choose the most suitable monomer and cross-linker for the synthesis of L-PABE imprinted polymers. Methacrylic acid and EGDMA were chosen as the best monomer and cross-linker, respectively, based on DFT with B3LYP functional and generic 6-31G basis set. The most appropriate template to functional monomer ratio was determined to be 1:2. FTIR spectra, XRD, SEM, and TEM confirmed the homogeneous binding sites on MWCNT-MIP. The results of the high adsorption of L-PABE on MWCNT-MIP suggested that the nanolayer MIP preparation on the surface of MWCNTs could enhance the porous site availability compared to that of bulk polymerization. Thermodynamic studies revealed the spontaneous nature of adsorption. The high separation factor suggested that non-covalent molecular imprinting with MWCNTs as supporting material is a promising method for analyzing chiral compounds.

REFERENCES

- Ertürk, G.; Mattiasson, B. Molecular imprinting techniques used for the preparation of biosensors. *Sensors* **2017**, *288*, 1–17.
- Shah, N.; Haneef, M.; Park, J.; Ul-Islam, M. A brief overview of molecularly imprinted polymers: From basics to applications. *J. Pharm. Res.* **2012**, *5*, 3309–3317.
- Ou, J.; Dong, J.; Tian, T.; Hu, J.; Ye, M.; Zou, H. Enantioseparation of tetrahydropalmatine and Tröger's base by molecularly imprinted monolith in capillary electrochromatography. *J. Biochem. Biophys. Methods* **2007**, *70*, 71–76.
- Lu, Y.; Li, C.; Zhang, H.; Liu, X. Study on the mechanism of chiral recognition with molecularly imprinted polymers. *Anal. Chim. Acta* **2003**, *489*, 33–43.
- Mahony, J. O.; Karlsson, B. C. G.; Nicholls, I. A. Correlated theoretical, spectroscopic and X-ray crystallographic studies of a non-covalent molecularly imprinted polymerisation system. *Analyst* **2007**, *132*, 1161–1168.
- Sajini, T.; Gigimol, M. G.; Mathew, B. A brief overview of molecularly imprinted polymers supported on titanium dioxide matrices. *Mater. Today Chem.* **2019**, *11*, 283–295.
- Zhong, C.; Yang, B.; Jiang, X.; Li, J. Critical reviews in analytical chemistry current progress of nanomaterials in molecularly imprinted electrochemical sensing current progress of nanomaterials in molecularly imprinted electrochemical sensing. *Crit. Rev. Anal. Chem.* **2018**, *48*, 15–32.
- Rezaei, B.; Rahmadian, O. Direct nanolayer preparation of molecularly imprinted polymers immobilized on multiwalled carbon nanotubes as a surface-recognition sites and their characterization. *J. Appl. Polym. Sci.* **2012**, *125*, 798–803.
- Jacobs, C. Nanotube based electrochemical sensors for biomolecules. *Anal. Chim. Acta* **2010**, *662*, 105–127.
- Anirudhan, T. S.; Alexander, S. Synthesis and characterization of vinyl-functionalized multiwalled carbon nanotubes based molecular imprinted polymer for the separation of chlorpyrifos from aqueous solutions. *J. Chem. Technol. Biotechnol.* **2013**, *88*, 1847–1858.
- Xu, L.; Xu, Z. Molecularly imprinted polymer based on multiwalled carbon nanotubes for ribavirin recognition. *J. Polym. Res.* **2012**, *19*, 1–6.
- Kan, X.; Zhao, Y.; Geng, Z.; Wang, Z.; Zhu, J. Composites of multiwalled carbon nanotubes and molecularly imprinted polymers for dopamine recognition. *J. Phys. Chem. C* **2008**, *112*, 4849–4854.
- Scida, K.; Stege, P. W.; Haby, G.; Messina, G. A.; García, C. D. Recent applications of carbon-based nanomaterials in analytical chemistry. *Anal. Chim. Acta* **2011**, *691*, 6–17.
- Prasad, B. B.; Srivastava, A.; Pandey, I.; Tiwari, M. P. Electrochemically grown imprinted polybenzidine nanofilm on multiwalled carbon nanotubes anchored pencil graphite fibers for enantioselective micro-solid phase extraction coupled with ultratrace sensing of D- and L-methionine. *J. Chromatogr. B* **2013**, *912*, 65–74.
- Datsyuk, V.; Kalyva, M.; Papagelis, K.; Parthenios, J.; Tasis, D.; Siokou, A.; Kallitsis, I.; Galiotis, C. Chemical oxidation of multiwalled carbon nanotubes. *Carbon* **2008**, *6*, 2–9.
- Nicholls, I. A.; Andersson, H. S.; Golker, K.; Henschel, H.; Karlsson, B. C. G.; Olsson, G. D.; Rosengren, A. M.; Shoravi, S.; Suriyanarayanan, S.; Wiklander, J. G.; Wikman, S. Rational design of biomimetic molecularly imprinted materials: Theoretical and computational strategies for guiding nanoscale structured polymer development. *Anal. Bioanal. Chem.* **2011**, *400*, 1771–1786.
- Meier, F.; Schott, B.; Riedel, D.; Mizaikoff, B. Computational and experimental study on the influence of the porogen on the selectivity of 4-nitrophenol molecularly imprinted polymers. *Anal. Chim. Acta* **2012**, *744*, 68–74.
- Riahi, S.; Edris-Tabrizi, F.; Javanbakht, M.; Ganjali, M. R.; Norouzi, P. A computational approach to studying monomer selectivity towards the template in an imprinted polymer. *J. Mol. Model.* **2009**, *15*, 829–836.
- Cowen, T.; Karim, K.; Piletsky, S. Computational approaches in the design of synthetic receptors—A review. *Anal. Chim. Acta* **2016**, *936*, 62–74.
- Nicholls, I. A.; Chavan, S.; Golker, K.; Karlsson, C. G.; Olsson, G. D.; Rosengren, A. M. Theoretical and computational strategies for the study of the molecular imprinting process and polymer performance. *Adv. Biochem. Eng. Biotechnol.* **2015**, *150*, 25–50.
- Batra, D.; Shea, K. J. Combinatorial methods in molecular imprinting. *Curr. Opin. Chem. Biol.* **2003**, *7*, 434–442.
- Sajini, T.; Aravind, K.; Mathew, B. Theoretical and computational strategies for the fabrication of enantioselective recognition site on molecularly imprinted polymers. *Int. J. Curr. Adv. Res.* **2017**, *6*, 6334–6336.
- Nicholls, I. A.; Andersson, H. S.; Charlton, C.; Henschel, H.; Karlsson, B. C. G.; Karlsson, J. K.; Mahony, J. O.; Rosengren, A. M.; Rosengren, K. J.; Wikman, S. Theoretical and computational strategies for rational molecularly imprinted polymer design. *Biosens. Bioelectron.* **2009**, *25*, 543–552.
- Tadi, K. K.; Motghare, R. V. Computational and experimental studies on oxalic acid imprinted polymer. *J. Chem. Sci.* **2013**, *125*, 413–418.
- Riahi, S.; Eynollahi, S.; Ganjali, M. R.; Norouzi, P. Computational approach to investigation of template/monomer complex in imprinted polymers; dinitrobenzene sensor. *Int. J. Electrochem. Sci.* **2010**, *5*, 509–516.
- Khan, M. S.; Wate, P. S.; Krupadam, R. J. Combinatorial screening of polymer precursors for preparation of benzo. *J. Mol. Model.* **2012**, *18*, 1969–1981.
- Nicholls, I. A.; Karlsson, C. G.; Olsson, G. D.; Rosengren, A. M. Computational strategies for the design and study of molecularly imprinted materials. *Ind. Eng. Chem. Res.* **2018**, *10*, 27.
- McCormick, T. M.; Bridges, C. R.; Carrera, E. I.; Dicarmine, P. M.; Gibson, G. L.; Hollinger, J.; Kozycz, L. M.; Seferos, D. S. Conjugated polymers: Evaluating DFT methods for more ac-

- curate orbital energy modeling. *Macromolecules* **2013**, *46*, 3879–3886.
- 29 Singh, A. K.; Singh, M. Designing L-serine targeted molecularly imprinted polymer via theoretical investigation. *J. Theor. Comput. Chem.* **2016**, *15*, 1650014.
- 30 Mojica, E. R. E. Screening of different computational models for the preparation of sol-gel imprinted materials. *J. Mol. Model.* **2013**, *19*, 3911–3923.
- 31 Silva, C. F.; Borges, K. B.; Soares, C. Rational design of a molecularly imprinted polymer for dinotefuran: Theoretical and experimental studies aimed at the development of an efficient adsorbent for microextraction by packed sorbent. *Analyst* **2018**, *143*, 141–149.
- 32 Pardeshi, S.; Patrikar, R.; Dhodapkar, R.; Kumar, A. Validation of computational approach to study monomer selectivity toward the template Gallic acid for rational molecularly imprinted polymer design. *J. Mol. Model.* **2012**, *18*, 4797–4810.
- 33 Acquaye, C. T. A.; Gorecki, M.; Wilchek, M.; Votano, J. R.; Rich, A. Antisickling activity of amino acid benzyl esters. *Proc. Natl. Acad. Sci.* **1980**, *77*, 181–185.
- 34 Acquaye, C. T. A.; Young, J. D.; Ellory, J. C.; Gorecki, M.; Wilchek, M. Mode of transport and possible mechanism of action of L-phenylalanine benzyl ester as an anti-sickling agent. *Biochim. Biophys. Acta* **1982**, *693*, 407–416.
- 35 Frisch, G. E. S. M. J.; Trucks, G. W.; Schlegel, H. B.; Robb, B. M. M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, H. P. H. G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Izmaylov, M. H. A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Ehara, T. N. M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Honda, J. Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, E. B. J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Kudin, J. N. K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Raghavachari, J. T. K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Cossi, J. B. C. M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Bakken, R. E. S. V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Yazyev, J. W. O. O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Martin, G. A. V. R. L.; Morokuma, K.; Zakrzewski, V. G.; Salvador, A. D. D. P.; Dannenberg, J. J.; Dapprich S.; Farkas, D. J. F. O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J. Gaussian 09 Revis. D.01, **2013**.
- 36 Dennington, R.; Keith, T.; Millam, J. Semichem Inc. Shawnee Mission, KS, **2016**.
- 37 Polimer, P.; Molekul, C. Synthesis and characterization of a molecularly imprinted polymer for Pb²⁺ uptake using 2-vinylpyridine as the complexing monomer. *Sains. Malaysiana* **2010**, *39*, 829–835.
- 38 Zakaria, N. D.; Yusof, N. A.; Haron, J.; Abdullah, A. H. Synthesis and evaluation of a molecularly imprinted polymer. *Int. J. Mol. Sci.* **2009**, *10*, 354–365.
- 39 Zhang, W.; Li, Q.; Cong, J.; Wei, B.; Wang, S. Mechanism analysis of selective adsorption and specific recognition by molecularly imprinted polymers of Ginsenoside Re. *Polymers* **2018**, *10*, 216.
- 40 Yuan, H.; Ma, X.; Xu, Z. Pore structure analysis of PFSA/SiO₂ composite catalysts from nitrogen adsorption isotherms. *Sci. China Chem.* **2011**, *54*, 257–262.
- 41 Li, S.; Huang, X.; Zheng, M.; Li, W.; Tong, K. Molecularly imprinted polymers: Thermodynamic and kinetic considerations on the specific sorption and molecular recognition. *Sensors* **2008**, *8*, 2854–2864.
- 42 Karim, K.; Breton, F.; Rouillon, R.; Piletska, E. V.; Guerreiro, A.; Chianella, I.; Piletsky, S. A. How to find effective functional monomers for effective molecularly imprinted polymers? *Adv. Drug Deliver. Rev.* **2005**, *57*, 1795–1808.
- 43 Liu, J.; Wang, Y.; Tang, S. Theoretical guidance for experimental research of the dicyandiamide and methacrylic acid molecular imprinted polymer. *New J. Chem.* **2017**, *41*, 13370–13376.
- 44 Muhammad, T.; Nur, Z.; Piletska, E. V.; Piletsky, S. A. Rational design of molecularly imprinted polymer: The choice of cross-linker. *Analyst* **2012**, *137*, 2623–2628.