Research Article

Rational Design and Experimental Research on the Self-Assembled System of Thermosensitive Molecularly Imprinted Polymers Formed by α -Lipoic Acid and N-Vinyl Caprolactam

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In this paper, the main work was to study the theoretical self-assembly process of thermosensitive molecularly imprinted polymers (MIPs) for α -lipoic acid and to investigate thermosensitive functional monomers through density functional theory calculations (DFT) and intermolecular weak interaction analysis. The M06-2X/6-311+G (d, p) level was used to study the structural parameters, bonding sites, natural population analysis, binding energies (ΔE), atom in molecules (AIM), independent gradient model (IGM), and imprinted molar ratio. The results revealed that α -lipoic acid mainly interacted with N-vinyl caprolactam (NVCL) by weak hydrogen bonds, and the best conditions for MIP synthesis were an optimum molar ratio of 1:4 (α -lipoic acid/NVCL). The thermosensitive properties showed that the highest adsorption was at 40°C and the lowest adsorption was at 20°C; also, the MIPs released the intercepted α -lipoic acid inside polymers, and the lower critical solution temperatures (LCST) of MIPs and nonimprinted polymers (NIPs) are 25.7°C and 19.4°C, respectively. In this study, the thermosensitive MIPs displayed a different adsorption capacity towards NVCL, which could be applied for controlled separation and release of α -lipoic acid in different temperatures in a complex matrix.

1. Introduction

It is well known that α -lipoic acid (ALA) is a multifunctional therapeutic compound that exists mainly in the liver tissue of animals and plants and shows activity in both vitro and vivo experimental studies [1, 2]. ALA and its reduced state substance, DHLA, have become a research spot in the field of food science and medicine in recent years because of its high antioxidant property [3]. ALA/DHLA is one of the strongest natural antioxidants which exhibit the ideal antioxidant property in almost all kinds of situations, hence its reputation as the “universal antioxidant” [4, 5]. It can deactivate a variety of free radicals including the hydroxyl radical ($\cdot\text{OH}$), singlet oxygen ($^1\text{O}_2$), peroxyxynitrite ion (ONOO^-), superoxide anion ($\text{O}_2^{\cdot-}$), and hypochlorous acid (HClO) [6–8]. Thus, ALA was used as a dietary supplement of vitamin E and vitamin C, added into cosmetic as a sensitizer, or utilized as medicine for a variety of diseases [9–12]. However, there exists

some unknown safety issue with the ALA synthesized by the chemical approach which limits the application of ALA in the field of food [13]. Thus, finding an efficient separation, purification, and controlled release technology for natural ALA is significant for its further utilization, especially in the food area.

With continuing development and improvement, molecular imprinting technique (MIT) has been successfully utilized in various fields, including solid phase extraction, chiral separation, drug delivery, biomimetic sensors, and antibody and enzyme mimics and membranes [14–17]. Furthermore, the stimulus-responsive technology has been applied in imprinted polymers including but not limited to responding to chemical (pH) and physical condition (temperature) [18, 19]. This kind of polymer has been applied to controlled drug release, tissue engineering, and gene transfection. In particular, in the case of thermosensitive polymers, the lower critical solution temperature (LCST)

decides the thermosensitive property through the phase transition at a specific temperature [20]. As the phase transition of N-vinyl caprolactam (NVCL) happens near the range of physiological temperature (32–34°C), it was chosen as both the functional monomer and the thermosensitive monomer in this study.

In order to improve adsorption selectivity, and exploring the recognition mechanism of MIPs at the molecule level, the density functional theory (DFT) calculation has been chosen to study the ALA-MIP due to its accuracy in the computation of weak intermolecular interactions [21, 22]. The choice of calculated methods has a significant influence on the accuracy of the calculated results, and it has been deployed in the previous investigations on MIPs. To be specific, Khan et al. built a computational model to understand the nature of weak interactions between the template molecule and the functional monomers using the B3LYP method, which is the most comprehensively utilized in the studies so far [23]. Liu et al. applied the LC-WPBE, CAM-B3LYP, and other methods to stimulate the structure of salbutamol, methacrylic acid, and other molecules and used the PBE1PBE method to investigate the interaction between melamine and acrylamide in the MIPs [24]. Nevertheless, the wB97XD [25] and M06-2X [23–26] methods have also been utilized in the former study of MIPs and showed a better performance on the calculation of weak molecule interaction rather than B3LYP.

Based on the above considerations, we demonstrated a strategy that combined the theoretical calculation and the best conditions for MIP synthesis, and NVCL was carried out as the thermosensitive functional monomer for the specific recognition of ALA. By using the determined DFT method at the M06-2X/6-311+G (d, p) level, we evaluated the interaction and quantitative relationship between the template and monomers. To further investigate the thermosensitive property of the MIPs, the effects of different temperatures on the adsorption selectivity were studied.

2. Experimental

2.1. Materials and Reagent. For the synthesis of MIPs, the following reagents were employed: N-vinyl caprolactam (NVCL, functional monomers), α -lipoic acid (ALA, template), ethylene glycol dimethacrylate (EGDMA, 98%, cross-linking agent), dihydrolipoic acid (DHLA), 3-phenylbutanoic acid (PBA), and 2,2-azobisisobutyronitrile (AIBN, radical initiator) were obtained from Sigma-Aldrich which were of reagent grade. Acetic acid was obtained from the (Tianjin, China). HPLC-grade acetonitrile (ACN) and methanol were purchased from AppliChem. All other chemicals were of analytical grade with the highest purity available.

2.2. Instrumentation

2.2.1. Chromatographic Conditions. An Agilent high-performance liquid chromatography (HPLC) model 1260 Infinity II system (Agilent Technologies, USA) and a UV detector model 1260 were used for chromatographic analysis. All chromatographic procedures were conducted at $30 \pm 3^\circ\text{C}$,

and the ZORBAX Extend-C18 column was used to perform analytical results. The mobile phase consists of a matrix of acetonitrile:water (adjusted with phosphoric acid to a pH of 3.5) (50:50, v/v) at the flow rate of $1\text{ mL}\cdot\text{min}^{-1}$. The injection volume was $20\text{ }\mu\text{L}$ for standards and samples.

2.2.2. MIP and NIP Characterization. The Frontier FTIR (PerkinElmer, USA) was used to investigate the FT-IR spectra of the polymers between 4000 and 500 cm^{-1} with the potassium bromide tableting method. The morphology of the polymers was determined by an S-3400N scanning electron microscope (SEM) (Hitachi, Japan) at 30.0 kV . The differential scanning calorimetry (DSC) (Nanjing, China) model DSC-100 was used to investigate the thermosensitive property of the polymers between 0°C and 90°C . Approximately 20 mg of polymer was placed in the DSC-200L furnace with an aluminium crucible, and the heating rate was $5^\circ\text{C}\cdot\text{min}^{-1}$.

2.3. Computational Methods

2.3.1. Geometrical Optimization and Imprinted Reaction Site Prediction. To explore the optimize structure of ALA, the B3LYP, B2PLYPD, PBE1PBE, CAM-B3LYP, wB97XD, and M06-2X methods with 6-311+G (d, p) basis were compared, then all the calculated structure parameters were compared to existing experimental data for suitable method selection [27]. After determining the computational method, the conformations of the template molecule (ALA), functional monomers (NVCL), and their self-assembly precomplexes were optimized and confirmed with no imaginary frequency.

To predict the reactive sites of ALA and NVCL which determine the shape and size of the imprinting complex, the natural population analysis (NPA) and molecular electrostatic potentials (MEPs) were calculated under the determined levels.

2.3.2. The Better Ratios and Self-Assembly Mechanism. As many reports shows [28, 29], the MIPs with the better ratio were the complexes with the lowest value of binding energy ($\Delta E_{\text{binding}}$) and proper intermolecular weak interaction. The atom in molecule (AIM) theory and independent gradient model (IGM) were widely used in the intramolecular interaction analysis.

Similar to reduced density gradient function, the independent gradient model (IGM) also was a method to analyze noncovalent interactions based on the electron density topology [30]. Define the iso surfaces as function S , and so,

$$S = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla\rho(r)|}{(\rho(r))^{4/3}}, \quad (1)$$

where $\rho(r)$ represents the electron density (ED) and $|\nabla\rho(r)|$ stands for the norm of the ED gradient vector. The basis of the independent gradient model (IGM) is also the ED gradient in terms of atomic components. In $|\nabla\rho(r)|$ IGM, SIGM with S largest deviation occurs in key point (BCP). Set the difference as function δg , $\delta g(r) = |\nabla\rho(r)|_{\text{IGM}} - |\nabla\rho(r)|$. δg can

divided into intramolecular interaction (δg intra) and intermolecular interaction (δg inter) [31].

Bader's atoms in molecules (AIM) hold that the electron density distribution was related to the chemical-bonding type. The bond critical point (BCP) occurs between attractive atom pairs. For intramolecular hydrogen bond topological analysis, the Laplacian ($\nabla^2 \rho$) plays a very important role in the characterization of chemical bonding. The relationships between energetic topological parameters and the $\nabla^2 \rho(r)$ at BCPs are shown as [32]

$$\frac{1}{4} \nabla^2 \rho(r) = 2G(r) + V(r), \quad (2)$$

where $G(r)$, $V(r)$, and $\rho(r)$ are the kinetic energy, potential energy, and total electron energy densities, respectively. For the closed shell system, the positive $\nabla^2 \rho$ indicate the hydrogen bond. The bond energy E_{HB} can be described as $E_{\text{HB}} = 1/2V(r_{\text{BCP}})$; the unit is kJ/mol.

The binding energy was calculated through Equation (1). Moreover, the basis set superposition error (BSSE) existing in calculation results will lead to overestimation of the interaction energy and sometimes take a decisive proportion in the interaction energy of a weak interaction system [33]. Herein, the BSSE was eliminated to correct the energies of the complexes by using the counterpoise correction method in the following equation [34]:

$$\Delta E_{\text{binding}} = E_{\text{complex}} - E_{\text{template}} - \sum E_{\text{binding}}, \quad (3)$$

where $\Delta E_{\text{binding}}$, E_{complex} , E_{template} , and $\sum E_{\text{binding}}$ represent the binding energy of the complex, the total energy of the complex, the energy of the template, and the total energy of the functional monomers, respectively.

The binding energy of different ratios of the ALA and NVCL complex was performed on Gaussian 16 packages which were supported by the high-performance computing platform of Guizhou University [35]. At the same calculation level, the binding energy decomposition at the molecular force field, bond critical point (BCP) analysis with atom in molecule (AIM) theory, and weak interaction maps at the independent gradient model (IGM) for different ratios of the ALA and NVCL self-assembly complex were calculated on the Multiwfn 3.6 packages [36].

2.4. Experimental Methodology

2.4.1. MIP and NIP Syntheses. The MIPs was prepared using a bulk polymerization method. In a typical synthesis, the template (ALA, 0.52 g) and the functional monomer with different molar ratios were added into 15 mL of acetonitrile and dissolved at room temperature. The matrix was incubated for 24 h. After that, 7.5 mL of cross-linker (EGDMA) and 0.02 g of initiator (AIBN) were added into the matrix and stirred for 20 min. For complete dissolution of the solids, the matrix was placed in an ultrasonic treatment for 10 min and then was purged with nitrogen for 5 min to remove oxygen dissolved in the matrix, and this procedure was repeated for three times. Then, the matrix was sealed and incubated in a

thermostatic bath at 60°C for 24 h. As a reference, the NIPs are also polymerized using a similar procedure without the presence of a template.

2.4.2. Template Molecule Removal. The obtained polymers were grounded and collected through a 75 μm sieve and washed and stirred by methanol/acetic acid solutions (9:1, v/v) for three times. Then, the polymers were extracted by Soxhlet extraction with methanol/acetic acid solutions (9:1, v/v) until no template molecule was detected in the effluent by an UV/visible spectrophotometer in order to obtain free-template MIPs. To remove acetic acid from the system, the methanol solution was loaded continuously for 4 h. Finally, the collected polymers were dried at 50°C. The NIPs were treated with the same processes for analysis purpose.

2.4.3. Equilibrium Adsorption Quantity. In a typical process, the powder of MIPs and NIPs (20.0 mg) was immersed in an ALA acetonitrile solution (5.00 mL, 200 mg/L) in an Erlenmeyer flask to find out the static adsorption performance of MIPs and NIPs. The Erlenmeyer flask was oscillated at 40°C for 24 h and then centrifuged immediately at 10000 rpm for 10 min at room temperature. The supernatant solution was filtered using a membrane filter (0.22 μm) and then analysed to investigate the remaining concentration of ALA. The concentration of ALA was determined by monitoring the absorbance at a wavelength of 215 nm using the HPLC-UV method. The equilibrium adsorption quantity (Q , mg/g) was calculated according to the change of the ALA concentrations before and after absorption by

$$Q = \frac{C_0 - C}{W}, \quad (4)$$

where C_0 (mg/L) and C (mg/L) are the initial and equilibrium concentrations of ALA, respectively. V (mL) is the volume of acetonitrile the ALA solution, and W (mg) is the mass of MIPs or NIPs.

2.4.4. Static Adsorption Experiments. The selectivity of MIPs was investigated by using DHLA and PBA as interfering agents owing to the similar molecular structure with ALA. MIPs (20 mg) were added to 5 mL of the DHLA or PBA acetonitrile solution with an initial concentration of 200 mg/L, and the static adsorption experiments were performed. The selectivity factor (α) was obtained according to Equation (5) as follows:

$$\alpha = \frac{Q_i}{Q_j}, \quad (5)$$

where Q_i (mg/g) and Q_j (mg/g) are the adsorption quantities of ALA and its structural analogue, respectively.

3. Result and Discussion

3.1. Theoretical Studies

3.1.1. Geometrical Optimization and Selection of Appropriate Calculated Method. In order to find a proper DFT calculation

TABLE 1: The calculated bond lengths and bond angles of ALA [using the B3LYP, B2PLYPD, PBE1PBE, wB97XD, M06-2X, and CAM-B3LYP methods with the 6-311+G (d, p) basis set] and available experimental data.

Species	B3LYP	B2PLYPD	PBE1PBE	wB97XD	M06-2X	CAM-B3LYP	Experimental
R (Å)							
C1-C2	1.55	1.56	1.54	1.54	1.54	1.54	1.51
C2-C3	1.55	1.56	1.54	1.54	1.54	1.54	1.55
C3-C11	1.53	1.54	1.52	1.53	1.53	1.52	1.53
C11-C14	1.54	1.54	1.53	1.53	1.53	1.53	1.51
C14-C17	1.53	1.54	1.52	1.53	1.53	1.53	1.53
C17-C20	1.53	1.54	1.52	1.52	1.53	1.52	1.55
C20-C23	1.51	1.54	1.50	1.51	1.51	1.50	1.50
S9-C1	1.84	1.75	1.82	1.83	1.83	1.83	1.79
S10-C3	1.85	1.75	1.84	1.84	1.83	1.84	1.82
S9-S10	2.11	2.03	2.08	2.09	2.09	2.09	2.05
O24-C23	1.21	1.26	1.20	1.20	1.20	1.20	1.20
O25-C23	1.36	1.43	1.35	1.35	1.35	1.35	1.31
Φ (°)							
C1-C2-C3	113.12	106.88	112.59	112.71	112.44	112.77	112.61
C2-C3-C11	114.47	111.28	114.26	113.84	113.66	114.13	112.89
C3-C11-C14	113.32	109.47	113.05	112.71	112.39	113.10	115.38
C11-C14-C17	112.48	109.47	112.43	112.32	112.10	112.40	109.28
C14-C17-C20	112.42	109.47	112.39	112.13	111.99	112.31	110.39
C17-C20-C23	113.63	109.47	113.41	113.40	112.74	113.39	112.99
C20-C23-O24	126.38	120.00	126.09	126.13	125.94	126.21	124.89
C20-C23-O25	111.30	120.00	111.48	111.53	111.60	111.59	113.39
O24-C23-O25	122.32	120.00	122.43	122.34	122.46	122.20	121.89
C2-C1-S9	110.00	107.29	109.64	109.85	109.67	109.86	112.61
C1-S9-S10	91.06	87.38	90.80	91.23	90.83	91.12	95.56
S9-S10-C3	90.71	87.46	90.60	90.71	90.46	90.81	92.84
S10-C3-C2	107.60	107.19	107.54	107.61	107.49	107.68	106.78
S10-C3-C11	110.22	115.31	110.33	110.58	110.45	110.36	111.37

method to be applied in this research system, we simulated the conformational parameters of ALA using the B3LYP, B2PLYPD, PBE1PBE, wB97XD, M06-2X, and CAM-B3LYP methods with the 6-311+G (d, p) basic set due to various applications of DFT calculations in the different research areas.

As presented in Table 1, the computational and experimental values of bond lengths and bond angles are very similar, which indicate that the DFT method is reliable as well as efficient in the calculation of the geometry structures of molecules. Comparing with the other methods, the M06-2X method presented the calculation parameters closer to the existing experimental data in both the bond lengths and the bond angles. For example, the experimental bond angle of C17-C20-C23 is 112.99°, and the data given by M06-2X method is 112.74°. In contrast, the data presented by the B3LYP, PBE1PBE, wB97XD, and CAM-B3LYP methods are 113.63°, 113.41°, 113.40°, and 113.39°, respectively, and the one from B2PLYPD is even 109.47°. Similarly, the experimental bond length of S10-C3 is 1.82 Å, and the data given by M06-2X method is 1.83 Å. The other methods all indicate

the value of 1.84 Å, except for B3LYP which is 1.85 Å, and B2PLYPD which is 1.75 Å. As a result, the M06-2X/6-311+G (d, p) level was carried out as the appropriate calculation level.

3.1.2. Analysis of the Imprinted Reaction Sites. The NPA charges and MEPs indicated the potential electrophilic and nucleophilic reactive sites of the ALA and NVCL molecules by using the M06-2X/6-311+G (d, p) method. With the help of the distribution of the electron cloud, the active sites of the ALA and NVCL molecules can be easily predicted through MEPs. According to Figure 1, the atom surrounded by red color shows the electronegativity. Hence, the atoms O24, S9, and S10 of ALA could easily lose an electron during the interaction, which indicates that they are potential proton acceptors. On the contrary, the blue color represents the positive electricity, which means those atoms could be proton donors. Therefore, the H26 atom of ALA exhibits obviously positive charges, which reveals that it is the proton donor. Similarly, it can be concluded that the O1 atom is the proton donor and H18 and H21 are potential proton acceptors, in NVCL.

FIGURE 1: The MEP and NPA population of ALA (a) and NVCL (b).

FIGURE 2: Color scaling of weak interaction of template-monomer mixture.

TABLE 2: The binding energies ($\Delta E_{\text{binding}}$) and the basis set superposition error (BSSE) of ALA and NVCL in different imprinted molar ratios at the M06-2X/6-311+G (d, p) level ($\text{kJ}\cdot\text{mol}^{-1}$).

Molar ratio	$\Delta E_{\text{binding}}$	E_{BSSE}
1 : 1	-11.07	-0.89
1 : 2	-17.89	-1.06
1 : 3	-27.89	-3.88
1 : 4	-29.97	-4.46
1 : 5	-37.11	-5.55

In NPA, the hydrogen atom and oxygen atom in the hydroxyl group of ALA could be a proton donor and proton receptor, respectively, which means that the ALA molecule could be both the proton donor and receptor. Furthermore, the S9 and S10 atoms show charges of 0.079 and 0.092, respectively, which mean that their ability to form a hydrogen bond is much lesser than that of O24. Similarly, the H18 and H21 with NPA charges of 0.164 and 0.150 in NVCL could also be the potential proton receptors.

3.1.3. The Better Ratios and Self-Assembly Mechanism

(1) *IGM Analysis.* Different ratios (1 : 1, 1 : 2, 1 : 3, 1 : 4, and 1 : 5) of ALA and NVCL were simulated based on the results of NPA charges and MEPs. Based on the optimized structures, the intermolecular weak interaction iso surface map was firstly performed. By mapping the δg descriptor with the sign function $\text{sign}(\lambda_2)\rho$, then getting the noncovalent interaction iso surface in Figure 2, the green colors are identified as Van der Waals interaction and the blue colors are identified as the hydrogen bond. Through the different color distribution in Figure 2, there exist two kinds of interaction between the ALA and NVCL, hydrogen bonds and Van der Waals force [37]. Figure 2 also shows that different ratios of the ALA and NVCL complex have the same number of blue hydrogen bonds. In the ESP and imprinted reaction site analysis, the interaction between the H26 atom of ALA and the O1 atom of NVCL was a hydrogen bond; this was consistent with the Figure 2 IGM iso-surface map results. When the molar ratio is 1 : 5, one functional monomer becomes superfluous and no longer participates in the formation of hydrogen bonds. However, it attracts other monomers through Van der Waals forces.

(2) *Binding Energy and Energy Decomposition.* According to the IGM iso surface maps above, it was clear that the main intermolecular force for the ALA-NVCL self-assembly system was the same, but their strength was unknown, so the binding energy with the BSSE correction of the complex was calculated at the M062X/6-311+G (d, p) level, and the result is shown in Table 2. From Table 2, the binding energy between ALA and NVCL has significant influence on the recognition property; the $\Delta E_{\text{binding}}$ values gradually decrease along with the increase of the imprinting ratio and the 1 : 5 ratio with the lowest $\Delta E_{\text{binding}}$ values. Compared with other research, the $\Delta E_{\text{binding}}$ of this study is slightly higher which

TABLE 3: The energy decomposition of ALA-NVC complex.

	Electrostatic	Repulsion	Dispersion
Ratio 1 : 1			
ALA-NVCL	-35.41	26.49	-27.33
Ratio 1 : 2			
ALA-NVCL	-43.5	53.3	-65.33
NVCL-NVCL	-2.57	17.39	-30.63
Total	-46.07	70.69	-95.96
Ratio 1 : 3			
ALA-NVCL	-35.53	82.09	-106.46
NVCL-NVCL	-7.56	28.51	-54.56
Total	-43.09	110.6	-161.02
Ratio 1 : 4			
ALA-NVCL	-41.67	107.49	-144.9
NVCL-NVCL	-7.93	28.3	-54.5
Total	-49.6	135.79	-199.4
Ratio 1 : 5			
ALA-NVCL	-47.51	119.13	-166.98
NVCL-NVCL	-7.38	50.74	-92.08
Total	-54.89	169.87	-259.06

FIGURE 4: FT-IR spectra of MIPs (a), NIPs (b), and LA (c).

explained the lower adsorption quantity [38]. Therefore, the energy decomposition of all different ratios of the ALA and NVCL self-assembly complex was calculated based on the GAFF molecular force field at the M062X/6-311+G (d, p) level, and the results are in Table 3. The nature of the hydrogen bond is electrostatic interaction, and the dispersion force was also a kind of electrostatic interaction, but it was very much weaker than the hydrogen bond. In Table 3, the total binding for ratio 1 : 1, 1 : 2, and 1 : 3 was also much lower than 1 : 4 and 1 : 5, which was consistent with the Table 2 binding energy result. So here, we focused on the ratios 1 : 4 and 1 : 5. The electrostatic items of ratios 1 : 4 and 1 : 5 were more than

TABLE 4: The BCP analysis of intramolecular hydrogen bond of ALA-NVCL complex.

Ratio	Bond	ρ	$\nabla^2\rho$	V	G	H_{BCP}	E_{HB}	Distance	Angle
1:1	O25-H26-H27	68.37	488.53	-100.61	111.37	10.76	-50.31	2.731	1.897
1:2	O25-H26-H27	72.69	540.60	-113.10	124.12	11.03	-56.55	2.701	3.240
1:3	O25-H26-H27	70.63	532.37	-108.44	120.77	12.32	-54.22	2.712	3.405
1:4	O25-H26-H27	70.73	533.64	-108.74	121.07	12.33	-54.37	2.711	3.382
1:5	O25-H26-H27	71.20	539.32	-110.08	122.45	12.37	-55.04	2.708	3.369

FIGURE 3: The SEM photograph of MIPs and NIPs.

ratios 1:3 and 1:4, respectively; this was at the molar of 1:4 and 1:5; the additional NVCL molecule formed more electrostatic interaction. For the electrostatic items, the values between ALA and NVCL increased 5.84 kJ/mol from ratios 1:4 to 1:5, and the values between NVCLs did not change much. However, the spatial repulsion item values have increased 34.08 kJ/mol for ratios 1:5 to 1:4; this shows that for molar ratios of 1:5 and higher, the hydrogen bonds are the same number as those of 1:4, and the steric effect became more significant, which was inefficient for polymerization and the self-assembly process [39].

(3) *BCP Analysis*. In order to further explore the IGM results and the hydrogen bond strength, the bond critical point (BCP) search and intramolecular hydrogen-bond analysis of MIPs have been obtained in Table 4. Note that ρ is the electron density (kJ/mol), $\nabla^2\rho$ is the Laplacian of electron density (kJ/mol), G is the Lagrangian kinetic energy (kJ/mol), H is the Hamiltonian kinetic energy (kJ/mol), and V is the potential energy density (kJ/mol). Lipkowski's hydrogen bonding qualitative standards were ρ (5.251~105.02 kJ/mol) and $\nabla^2\rho$ (52.51~393.825 kJ/mol) [40]. Based on the studies of Rozas et al., the strength of hydrogen bonds can be classified into three types as follows: weak hydrogen bond ($E_{HB} < 50.208$ kJ/mol, $\nabla^2(rBCP) > 0$, $G(rBCP) + V(rBCP) > 0$), medium hydrogen bond ($50.208 < E_{HB} < 100.416$ kJ/mol, $\nabla^2(rBCP) > 0$, $G(rBCP) + V(rBCP) < 0$), and strong hydrogen bond ($E_{HB} > 100.416$ kcal/mol, $\nabla^2(rBCP) < 0$, $G(rBCP) + V(rBCP) < 0$) [41].

From Table 3, different ratios of ALA-NVCL complexes have different hydrogen bond strength; this was consistent with the Khan and Pal research on the dioxin-imprinted

FIGURE 5: Adsorption capacities of MIPs and NIPs with different molar ratios.

TABLE 5: The selectivity factor α of the MIPs and NIPs.

	MIPs		NIPs	
	$Q(\text{mg/g})$	α_1	$Q(\text{mg/g})$	α_1
ALA	6.53	—	2.71	—
DHLA	2.86	2.28	2.25	1.20
PBA	2.41	2.71	2.34	1.15

FIGURE 6: Adsorption quantity of MIPs in different molar ratios of 1 : 1 (A), 1 : 2 (B), 1 : 3 (C), 1 : 4 (D), and 1 : 5 (E) in different temperatures.

polymer AIM analysis result [42]. The hydrogen bonding at ratio 1 : 1 in one template molecule is stronger than the others. For ratios 1 : 3 and 1 : 4, the E_{HB} values were very similar, but the energy composition shows that the ratio 1 : 4 system contributed more electrostatic attraction than ratio 1 : 3, which indicates that the ratio 1 : 4 was much better than 1 : 3. For the 1 : 5 ratio, the NVCL can bind one more ALA than ratio 1 : 4, but the E_{HB} values were much lower. Combined with the Table 4 energy decomposition results, there were lower hydrogen bond strength and more repulsion at ratio 1 : 5, so we conclude that the best ratio for the ALA-NVCL self-assembly system was 1 : 4.

3.2. Experimental Studies

3.2.1. SEM Analysis. The SEM demonstrated the morphology of the MIPs and NIPs in Figure 3. We can find out that the SEM micrographs of self-assembled MIPs and NIPs exhibit great difference, especially in porous texture and material distribution. The NIPs show a plate-like and relatively smooth surface in multiple layers, whereas the MIPs are more heterogeneous, showing an irregular surface with the porous structure, which indicates that the existing template molecule could significantly influence the morphology of imprinted polymers. Herein, the MIPs show a better adsorption property by increasing the specific surface area which provides a larger quantity of imprinting caves than the NIPs.

3.2.2. FT-IR Analysis. In Figure 4, the FT-IR spectra reflected the structural difference of ALA-MIPs and NIPs, but the location, width, and strength of the C=O vibration peak of NIPs and ALA-MIPs shift from 1735 to 1729 cm^{-1} , and the O-H shifts from 3451 to 3443 cm^{-1} which indicates the formation of a hydrogen bond. Noticeable, the vibration peak of C-H shifts from 2959 to 2952 cm^{-1} in NIPs and ALA-MIPs. Therefore, the results coordinate with the active sites of the ALA and NVCL molecules in Figure 1, which indicate that the C-H group could potentially be a part of the hydro-

gen bond formation. These redshifts of vibration frequency are mainly caused by the formation of a hydrogen bond inside polymers and different complex structures between MIPs and NIPs.

3.2.3. Adsorption Property of the MIPs. To investigate the result of computer-aided design and theoretical simulation, the MIPs and NIPs with different proportions (1 : 1, 1 : 2, 1 : 3, 1 : 4, and 1 : 5) for ALA and NVCL were polymerized to study the adsorption property. The adsorption capacities of MIPs and NIPs in different ratios are shown in Figure 5. The MIPs with the molar ratio of 1 : 4 has the maximum adsorption quantity, which is consistent with the binding energy analysis and calculated results. Thus, theoretical simulation can provide a trustworthy strategy for polymerization of MIPs.

Moreover, the adsorption quantity of NIPs under all molar ratios is substantially lower than that of MIPs according to experimental data. However, the maximum adsorption of NVCL-MIPs, 6.53 $\text{mg}\cdot\text{g}^{-1}$, was lower than MIPs of other monomers in former research [27], and it also consists of a lower binding energy ($-29.97 \text{ kJ}\cdot\text{mol}^{-1}$) in the simulation. The quantum chemical simulation does show a great ability in prediction of performance of MIPs. On the other hand, 3D caves formed during polymerization can specifically recognize the shape, size, molecule conformation, and active sites of ALA in preferred proportion.

3.2.4. Adsorption Selectivity. The adsorption selectivity of MIPs towards the ALA, DHLA, and PBA is concluded in Table 5. The result shows that the best adsorption ability was listed as ALA (6.53 mg/g), DHLA (2.86 mg/g), and PBA (2.41 mg/g) which showed a significant affinity for ALA in MIPs. The NIPs showed the similar affinity for both three materials and the highest absorption for ALA. The selectivity factors (α) of DHLA and PBA against ALA in MIPs were 2.28 and 2.71, respectively, indicating that MIPs have better adsorption selectivity to ALA. This result indicated that the

FIGURE 7: The DSC curve of MIPs and NIPs.

MIPs had a higher molecular recognition selectivity to the template and the polymer had specific recognition sites.

3.2.5. Thermosensitive Property of the MIPs. As shown in Figure 6, the adsorption curves of MIPs with different molar ratios (1:1, 1:2, 1:3, 1:4, and 1:5) exhibit a rather fluctuated trend. In general, the MIPs achieved the highest adsorption quantity at about 40°C and the lowest at 20°C approximately. The adsorption property of MIPs with the molar ratio of 1:4 is greater than other proportions in most temperatures and drops dramatically when the temperature comes to 20°C, which is much lower than others (0.21 mg/g). What is worth mentioning is that the negative adsorption value in 20°C may due to the extension of the molecular structure under LCST which leads to the release of the ALA intercepted by a polymer. On the contrary, although all the MIPs show the lowest adsorption quantity at 20°C, the MIPs with a proportion of 1:1 exhibit a rather gentle trend under different situations which mean that the MIP cannot form enough recognition sites for ALA due to the low proportion of NVCL, and it was also short of poly (NVCL) to exhibit the thermosensitive property.

The DSC curve is shown in Figure 7. In NIPs, due to the absence of the ALA molecule, the LCST was presented at the temperature of 19.4°C, which is consistent to the lowest adsorption quantity at 20°C in the adsorption study. And it reached the lowest point at 80°C with a smooth drop. Nevertheless, the curve of MIPs is fluctuating and dropping above its LCST and then rises back with the fluctuation. This fact can be explained as the formation of the selective curve of MIPs and its irregular surface with the porous structure. When the temperature rises up to the LCST, the monomer of MIPs pushes the polymer to change its geometric structure. The LCST of MIPs ascends to 25.7°C compared with NIPs. This result can be illustrated as the existence of ALA in MIPs because the LCST will increase by the addition of hydrophilic groups.

4. Conclusions

In this paper, we investigated the nature of imprinted polymers and recognition mechanism through theoretically calculating the structural parameters, binding energies, and potential active sites of ALA and NVCL in different molar ratios at M06-2X/6-311+G (d, p) level. The calculation results forecast that the MIPs with the molar ratio of 1:4 exhibit the highest adsorption quantity and show the lowest effective binding energy, which are consistent with the experimental data. Furthermore, the adsorption quantity at different temperatures indicates that the MIPs (1:4) have the highest adsorption at 40°C and the lowest adsorption at 20°C, which are 6.53 mg·g⁻¹ and 0.21 mg·g⁻¹, respectively. And the LCST of MIPs and NIPs are 25.7°C and 19.4°C. Herein, the MIPs can be used to separate and release the ALA on the basis of temperature changes. In addition, the selectivity of MIPs towards the ALA, DHLA, and PBA is ALA > DHLA > PBA. The NIPs in all proportions have a lower recognition property compared with MIPs. This paper indicates that theoretical calculation can be used in the rational design of MIP and NVCL which can be utilized as a functional monomer and thermosensitive monomer which could respond to temperature changes.

Data Availability

All data, models, and code generated or used during the study appear in the submitted article.

Conflicts of Interest

All authors declare no conflict of interest, particularly no financial and personal relationships with other people or organizations that could inappropriately influence this work.

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