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Using Molecularly Imprinted Polymer for Protecting Functional Group in Organic Reaction

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ABSTRACT: In this study, a novel method of selective protecting group based on molecularly imprinted polymer for regioselective organic reaction is reported. The simplicity, convenience and feasibility of this method may be illustrated by the protection of hydroxyl group at C17 or C3 of β-estradiol in the reaction between β-estradiol and diphenylphosphinic chloride. Polymers to protect hydroxyl group at C17 or at C3, both demonstrated excellent protection effect. In polymers imprinted with 2-methyl-cyclopentanol template to protect hydroxyl group at C17, the proportion of 3-phosphate was almost as high as 100%. In molecularly imprinted polymer synthesized using 5,6,7,8-Tetrahydro-2-naphthol as a template to protect hydroxyl group at C3, the proportion of 17-phosphate reached 98.2%. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 130: 595–602, 2013

KEYWORDS: separation techniques; recycling; molecular recognition; functionalization of polymers; adsorption

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INTRODUCTION

Protecting group strategies are indispensable to the general pursuit of organic synthetic reaction.[1] The choice of protecting groups is one of the decisive factors in the successful realization of a complex, demanding synthetic project. As a consequence of the great importance of protecting groups in organic chemistry, a multitude of blocking techniques have been developed for a wide range of functional groups.[2,3] However, selective derivatization/protection of one of two same functional groups in the same molecular is still difficult and requires careful control of experimental conditions.[4,5] For example, two hydroxyl groups such as those in β-estradiol are often hard to differentiate.

The technique of molecular imprinting, which may be traced back to the early 1970s,[6] has received much attention in recent years[7,8]; and, it is a powerful method for preparing artificial recognition sites with predetermined selectivity for a wide range of target molecules.[9–17] Consequently, the imprinted polymers have become increasingly attractive in many fields of chemistry and biology, particularly as tailor-made separation materials,[18] antibody and receptor binding site mimics, enzyme mimics[19] and recognition elements.[20–22] Hamase et al. employed polymers imprinted with L-phenylaniline anilide as protecting groups during derivatization of D- or L-phenylalanine anilide with a fluorescent label, dansyl chloride.[23] This reaction generated considerably less (46%) of the L-isomer than the D-analogue. The acylation of di- and trihydroxysteroids bound to polymers imprinted with structurally related diols was also investigated by Alexander et al.[24]

Here, we describe a method of selective protection of groups using molecularly imprinted polymers (MIPs) imprinted with one part of the structure of the compound. Other part can also be used as a template to synthesize MIPs to protect the corresponding group. Conventional synthesis methods for MIPs often result in materials exhibiting poor site accessibility for the target molecule. Recently, surface imprinting method was developed to improve the ability of MIP to identify target molecule by designing the molecular recognition sites on the surfaces of imprinted materials. In this method, double bonds were first immobilized on the surface of macroporous aminomethyl resin, followed by grafting MIPs. The double bond could guide easily the formation of MIPs at the solid support surface by radical polymerization. So, we used macroporous aminomethyl resin with a double bond as solid support to synthesize MIP.

To explore the feasibility of this approach, we selected β-estradiol as a model to react with diphenylphosphinic chloride (Figure 1). Figure 2 shows the strategy for the protection of β-estradiol with MIPs. MIPs were synthesized from double-bond-functionalized macroporous aminomethyl resin as solid support using 2-methyl-cyclopentanol as a template, MAA as a functional monomer and ethylene glycol dimethacrylate (EGDMA) as a crosslinker which is able to provide sufficient rigidity of the crosslinked polymer.

Additional Supporting Information may be found in the online version of this article.

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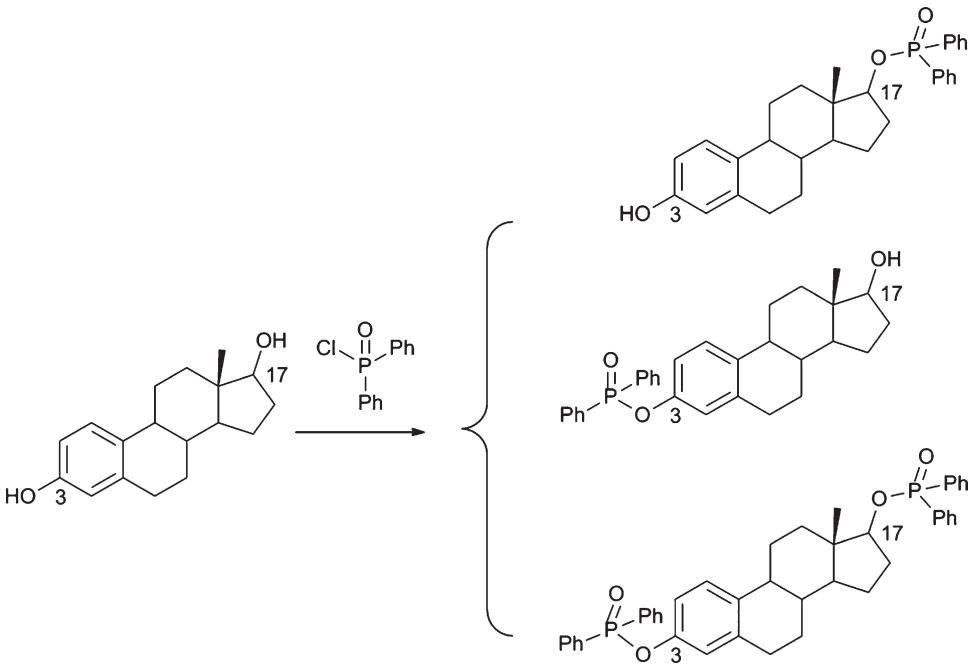

Figure 1. Reactive route of β-estradiol and diphenylphosphinic chloride.

After removing the template, the synthesized MIPs were used for adsorption of β-estradiol. The hydroxyl group at C17 of β-estradiol bound in the matched sites of MIPs and this would leave hydroxyl group at C3 available for organic reaction with diphenylphosphinic chloride [Figure 2(a)]. Conversely, MIPs using 5,6,7,8-tetrahydro-2-naphthol as a template were synthesized in the same manner, only but functional monomer was 4-vinyl pyridine. After β-estradiol was adsorbed by the synthesized MIPs, hydroxyl group at C3 of β-estradiol bound in the matched sites of MIPs and 17-hydroxyl group was leaved available for reaction with diphenylphosphinic chloride [Figure 2(b)].

EXPERIMENTAL

Materials

Methacrylic acid (Alfa Aesar 98%), 4-vinyl pyridine (Alfa Aesar 98%), *N*-hydroxysuccinimide (Alfa Aesar 98%), 1-ethyl-3,(3-dimethylaminopropylcarbodiimide)hydrochloride (Alfa Aesar 98.5%), 2-methyl-cyclopentanol (Alfa Aesar 98%), ethylene glycol dimethacrylate (Alfa Aesar 99%), azobisisbutyronitrile (Alfa Aesar), 5,6,7,8-tetrahydro-2-naphthol (Alfa Aesar 98%), β-estradiol(Alfa Aesar 99%), diphenylphosphinic chloride (Alfa Aesar 98%), 4-dimethylamiopryidine (Alfa Aesar), triethyl amine (Alfa Aesar) were used as received.

Modification of HC4021-2 Macroporous Aminomethyl Resin

The double bond could guide the formation of MIPs at the solid support surface by radical polymerization.[16] To modify HC4021-2 macroporous aminomethyl resin with a double bond, 5.114 mL methacrylic acid (MAA) was dropwise added into the phosphate buffer solution (50 mL, PH = 6.1) containing *N*-hydroxysuccinimide (NHS, 16.57 g) and 1-ethyl-3,(3-di-methyl-aminopropylcarbodiimide)hydrochloride (EDC, 13.80 g) and the reaction was kept for 1 h at 4°C. Then the prepared solution was dropped into the 25 g swollen HC4021-2 resin and stirred overnight at room temperature. The product was separated, washed by acetonitrile and dried in vacuum for 24 h at room temperature.

Polymerization

MIPs were synthesized using 2-methyl-cyclopentanol as a model template and MAA as a complementary functional monomer which has hydrogen bond effect with the template, ethylene glycol dimethacrylate (EGDMA) as a crosslinker which is able to provide sufficient rigidity of the crosslinked polymer. Double-bond-functionalized HC4021-2 macroporous aminomethyl resin (25g) were dispersing into 300 mL acetonitrile. Then, 2-methyl-cyclopentanol (2 mmol), MAA (8 mmol) and EGDMA (40 mmol) were dissolved in the solution. The molar ratio of template/monomer/crosslinker was 1 : 4 : 20. The mixture solution was stirred for 2 h at room temperature for the self-assembly formation of a complex of model template and monomer. At last initiating agent azobisisbutyronitrile (AIBN, 200 mg) were dropped into the solution. Polymerization was carried out in an oil bath at 60°C for 24 h under nitrogen atmosphere.[10,25] The microspheres were separated from the reaction mixture by centrifugalization and were washed with a mixture solvent of methanol and acetic acid (9 : 1, v/v) for several times to extract the template molecules until the eluent was free from template as detected by UV–vis spectrometry. The obtained polymers were finally rinsed with ethanol to remove the remaining acetic acid and dried in vacuum at RT for 24 h. Molecularly imprinted polymers using 5,6,7,8-tetrahydro-2-naphthol as a template were synthesized in the same manner, while functional monomer and crosslinker were 4-vinyl pyridine (8 mmol) and EGDMA (64 mmol). The molar ratio of template/monomer/crosslinker was 1 : 4 : 32. 4-vinyl pyridine has hydrogen bond and conjugate effect with the template. Nonimprinted polymers were prepared also in the same manner, without the addition of the template molecule.

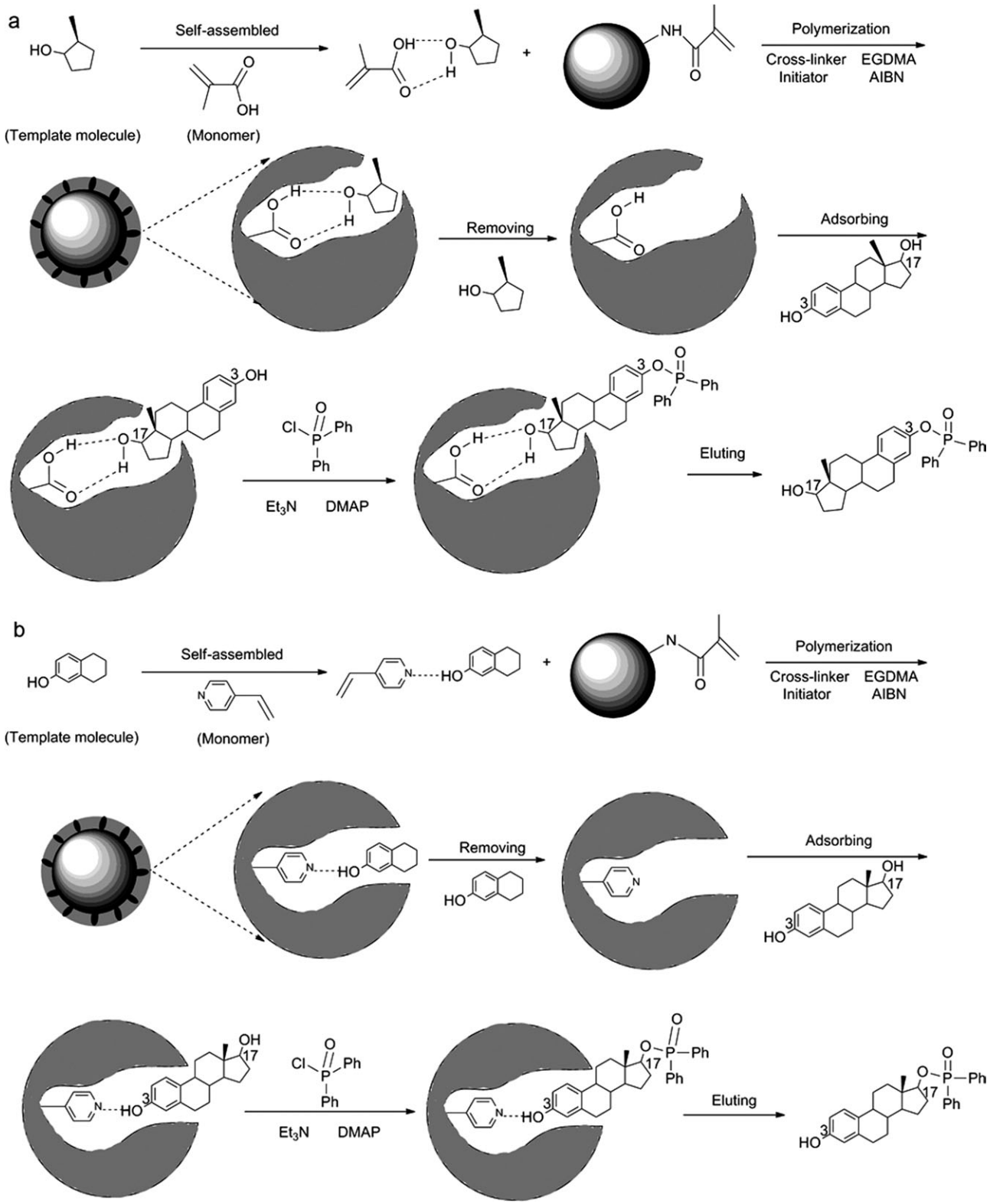

Figure 2. Strategy for the protection of β-estradiol with MIPs: (a) Hydroxyl group at C17 of β-estradiol was protected with MIPs and 3-hydroxyl group reacted with diphenylphosphinic chloride. (b) Hydroxyl group at C3 of β-estradiol was protected with MIPs and 17-hydroxyl group was left available for reaction with diphenylphosphinic chloride.

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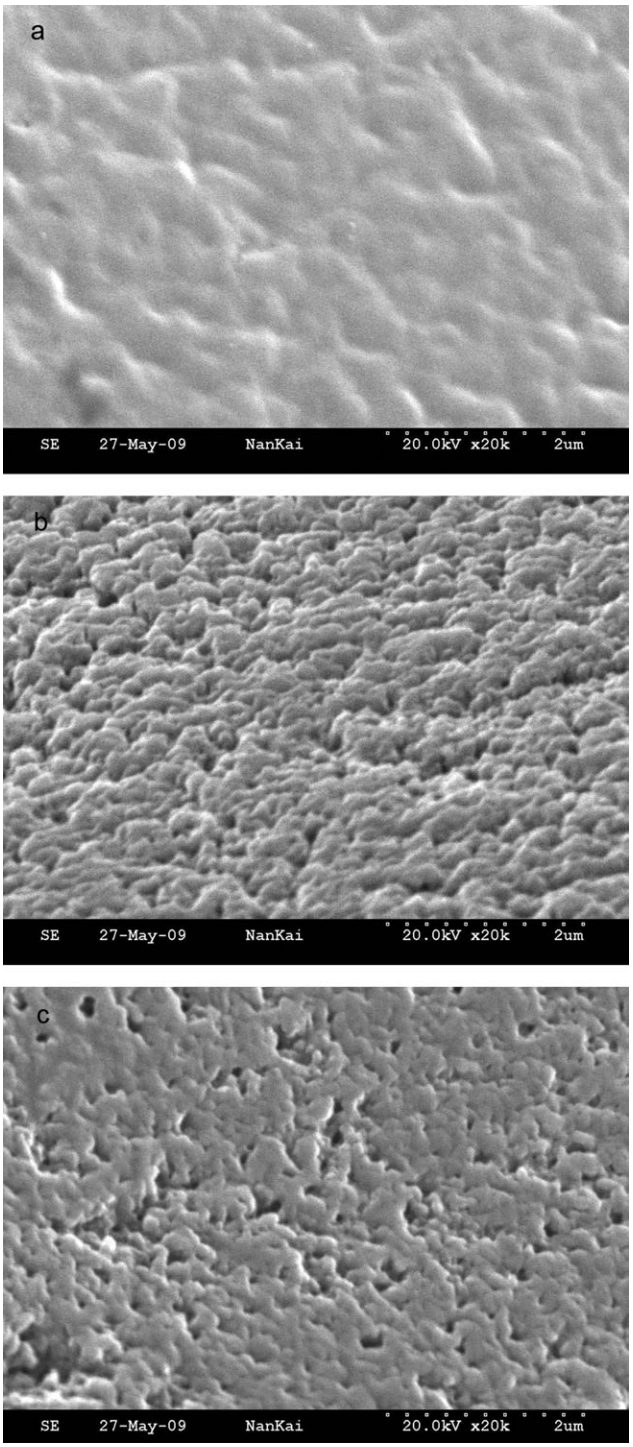

Figure 3. Scanning electron micrographs of MIPs and macroporous aminomethyl resin spheres: (a) MIPs using 2-methyl-cyclopentanol as a template; (b) MIPs using 5,6,7,8-tetrahydro-2-naphthol as a template; (c) macroporous aminomethyl resin spheres.

Adsorption of β-Estradiol

MIPs were incubated with β-estradiol in acetonitrile for 24 h. The microspheres were centrifugalized and washed with acetonitrile twice. The concentration of β-estradiol in the supernatant or eluent was measured by UV spectrometry (at 281 nm) and the adsorption quantity in MIPs was then calculated according to the standard curve of β-estradiol.

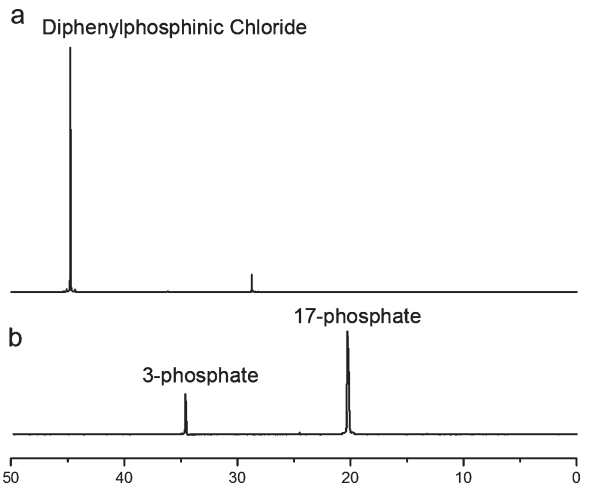

Figure 4. ^{31}P-NMR spectra of phosphate without protecting hydroxyl groups at C3 and C17: (a) pure diphenylphosphinic chloride peak at δp: 44.83. (b) Two peaks emerge, one peak at δp: 33.11 attributed to 3-phosphate and the other at δp: 20.08 attributed to 17-phosphate.

Synthesis of Phosphinate Esters Between Diphenylphosphinyl Chloride and β-Estradiol Binding to MIPs

According to the adsorption quantity in MIPs, DMAP (5 equiv.) and triethyl amine (3 equiv.) were added to the mixture of MIPs in 300 mL anhydrous acetonitrile at 0°C.[26,27] Diphenylphosphinyl chloride (1 equiv.) was added dropwise into the solution and stirred for 30 min. The reaction mixture was warm to room temperature and then stirred for 18 h. Then the supernatant was reserved. The microspheres were washed with acetonitrile for three times every 2 h. The eluent was collected. After this step, the microspheres were washed again with a mixture solvent of methanol and acetic acid (9 : 1, v/v) for several times

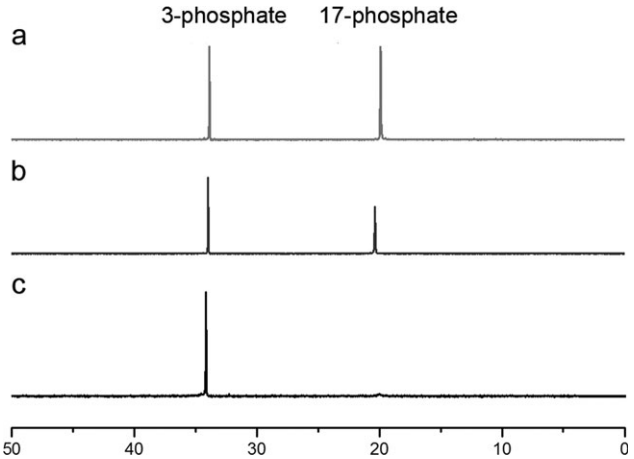

Figure 5. ^{31}P-NMR spectra of phosphate production after protecting hydroxyl group at C17: (a) spectrum of supernatant. (b) spectrum of acetonitrile eluent. (c) spectrum of methanol: acetic acid = 9 : 1 (volume ratio) eluent.

Table I. The Proportion of Product in The Reaction by Protection of β-Estradiol with MIPs

Eluent	MIP_1	MIP_2
	3-Phosphate (%)	17-Phosphate (%)
Supernatant	57.5	86.2
Acetonitrile	68.0	87.5
Mixture of methanol and acetic acid	100	98.2

MIP_1 imprinted with 2-methyl-cyclopentanol template. MIP_2 imprinted with 5,6,7,8-tetrahydro-2-naphthol template.

to extract the phosphinate ester product until the eluent was free from product which can be measured by UV spectrometry. Finally, the supernatant, eluent washing with acetonitrile or with a mixture of methanol and acetic acid was evaporated in vacuum, respectively. After acetic acid were got rid of with saturated sodium carbonate, the product was extracted by ethyl acetate, then dried by magnesium sulfate and evaporated in vacuum. 3-phosphate was characterized by FTIR and ^{1}H-NMR. FTIR cm^{-1}: 3460.13, 3057.15, 2939.04, 2863.81, 2702.32, 1219.4, 1120.03; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 0.64 (3H, J = 2.0 Hz, d), 1.06–1.37 (7H, m), 1.55–1.57 (1H, m), 1.75–1.86 (3H, m), 2.05–2.11 (1H, J = 11.4 Hz, m), 2.21–2.24 (1H, d), 2.72 (2H, J = 9.5, 5.2 Hz, dd), 3.48–3.52 (1H, J = 8.5, t), 4.45–4.52 (1H, br), 6.98–7.01 (2H, J = 10.2 Hz, d), 7.18–7.19 (1H, J = 8.4 Hz, d), 7.54–7.62 (6H, m), 7.87–7.92 (4H, m). 17-phosphate was also characterized by FTIR and ^{1}H-NMR. FTIR cm^{-1}: 3468.49, 3057.09, 2938.83, 2863.92, 1696.20, 1491.16, 1129.28; ^{1}H-NMR (DMSO-d6, 400MHz): δ 0.66 (3H, s), 1.14–1.23 (7H, m), 1.68 (1H, m), 1.88–1.99 (3H, J = 12.1 Hz, d), 2.02 (1H, m), 2.16–2.18 (1H, J = 12.6 Hz, d), 2.65 (2H, m), 3.50–3.66 (1H, J = 19.2, 7.6, 6.4 Hz, dq), 7.02–7.07 (2H, m), 7.14–7.16 (1H, J = 8.7 Hz, d), 7.37–7.52 (6H, m), 7.79–7.94 (4H, m), 10.06–10.07 (1H, s).

Crystal Characterization

XRD patterns were recorded on a Rigaku Saturn724 CCD X-ray diffractometer (MoK\a radiation, λ = 0.7107 Å), in a 2θ angular range of 2–28°. The XRD profiles were refined using the BrukerAxs program SHELXL-97 (Sheldrick, 1997).

RESULTS AND DISCUSSION

Surface Characterization of MIP

Scanning electron micrographs of MIPs are shown in Figure 3. The surface of MIP is smooth, using 2-methyl-cyclopentanol as a template and MAA as a functional monomer [Figure 3(a)] because MAA has the shorter side group of carboxyl group. The surface of MIP using 5,6,7,8-tetrahydro-2-naphthol as a template and 4-vinyl pyridine as a functional monomer is scraggy because of the rigid structure of 4-vinyl pyridine [Figure 3(b)]. In the polymerization process, the rigid pyridine ring can better maintain the shape of the template which ensures the stability of the spatial structure of the recognition sites on the surface of MIP. Such surface can provide greater space and more accessibility to the recognition site of MIP for target molecule.

Effect of Protecting Hydroxyl Group at C17 Using MIP with 2-Methyl-cyclopentanol Template or C3 Using MIP with 5,6,7,8-Tetrahydro-2-naphthol as Template

To determine whether the groups could be protected effectively, the reaction between β-estradiol and diphenylphosphinic chloride was established as the basis of comparison. As shown in Figure 4(a), ^{31}P-NMR spectroscopy of pure diphenylphosphinic chloride shows a peak at δp: 44.83. While in ^{31}P-NMR spectrum of the product of the reaction between β-estradiol and diphenylphosphinic chloride, the original pure peak disappeared and two new peaks emerge, one peak at δp: 33.11 attributed to 3-phosphate and the other at δp: 20.08 attributed to 17-phosphate. Based on integral data, the proportion of 3-phosphate is 18.1% and the proportion of 17-phosphate reached 81.9% [Figure 4(b)].

Table II. Crystal Data and Structure Refinement for 3-Phosphinate and 17-Phosphinate

Compound	3-Phosphinate	17-Phosphinate
Empirical formula	$C_{30}H_{33}O_3P$	$C_{30}H_{33}O_3P$
Formula weight	472.53	472.53
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic
Space group	P2(1)2(1)2(1)	P2(1)2(1)2(1)
Unit cell dimensions (Å)	a = 11.830(4)	a = 11.786(3)
	b = 14.144(4)	b = 14.087(4)
	c = 15.169(4)	c = 15.181(4)
Volume/Å^3	2538.0(13)	2520.6(11)
Z	4	4
Crystal size (mm^3)	0.24 × 0.20 × 0.18	0.20 × 0.18 × 0.10
FinalR indices [I > 2σ(I)]	R_1 = 0.0527, wR_2 = 0.1142	R_1 = 0.0502, wR_2 = 0.0989
R indices (all data)	R_1 = 0.0577, wR_2 = 0.1169	R_1 = 0.0548, wR_2 = 0.1009
Absolute structure parameter	−0.04(9)	0.07(9)
Largest diff peak and hole (e. Å^{-3})	0.568 and −0.261	0.166 and −0.298

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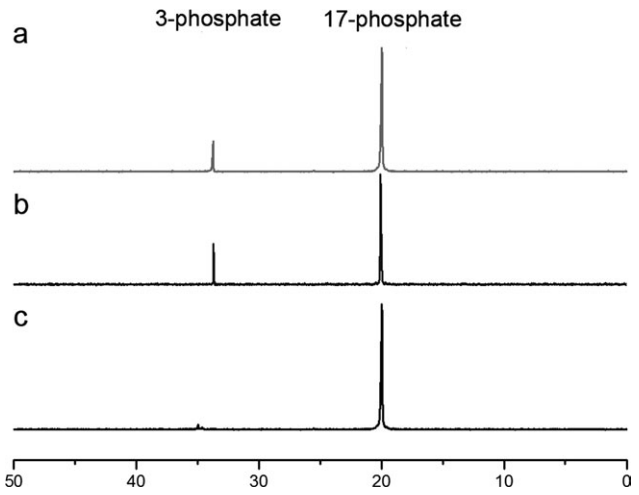

Figure 6. ^{31}P-NMR spectra of phosphate production after protecting hydroxyl group at C3: (a) spectrum of supernatant. (b) spectrum of acetonitrile eluent. (c) spectrum of methanol: acetic acid = 9 : 1 (volume ratio) eluent.

Next we sought to prove the effect that the functional group was protected with MIPs, according to Figure 2(a), when hydroxyl group at C17 of β-estradiol was protected with MIPs imprinted with 2-methyl-cyclopentanol template, 3-hydroxyl group reacted with diphenylphosphinic chloride. As shown in Figure 5, the proportion of 3-phosphate was 57.5, 68.0, and 100%, respectively from Figure 5(a–c). Pure 3-phosphate was got in eluent of mixture of methanol and acetic acid (Table I). The crystal of 3-phosphate was obtained by liquid phase diffusion of hexane to a solution of 3-phosphate in ethyl acetate at room temperature and determined by single-crystal X-ray diffraction (XRD) [Figure 7(a)]. According to XRD experimental data, cell parameters of a = 11.830(4) Å, b = 14.144(4) Å, and c = 15.169(4) Å were calculated (CCDC 862863) (Table II). XRD patterns and corresponding analysis confirmed the formation of 3-phosphate. These results proved that the molecular β-estradiol bound to specific recognition sites of MIPs imprinted with 2-methyl-cyclopentanol template so that hydroxyl group at C17 of β-estradiol was protected during the organic reaction. Furthermore, β-estradiol entered the cavities in MIPs deeper, the

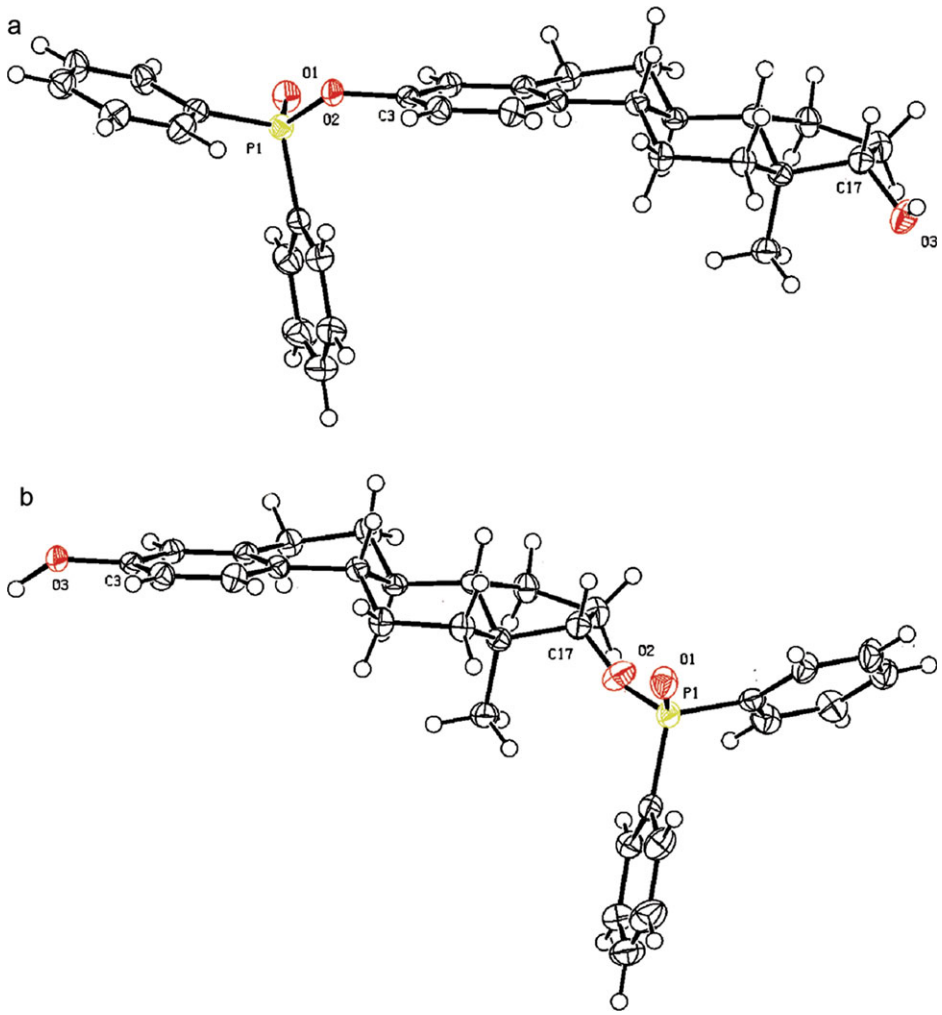

Figure 7. Molecular structure of 3-phosphinate (a) and 17-phosphinate (b). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

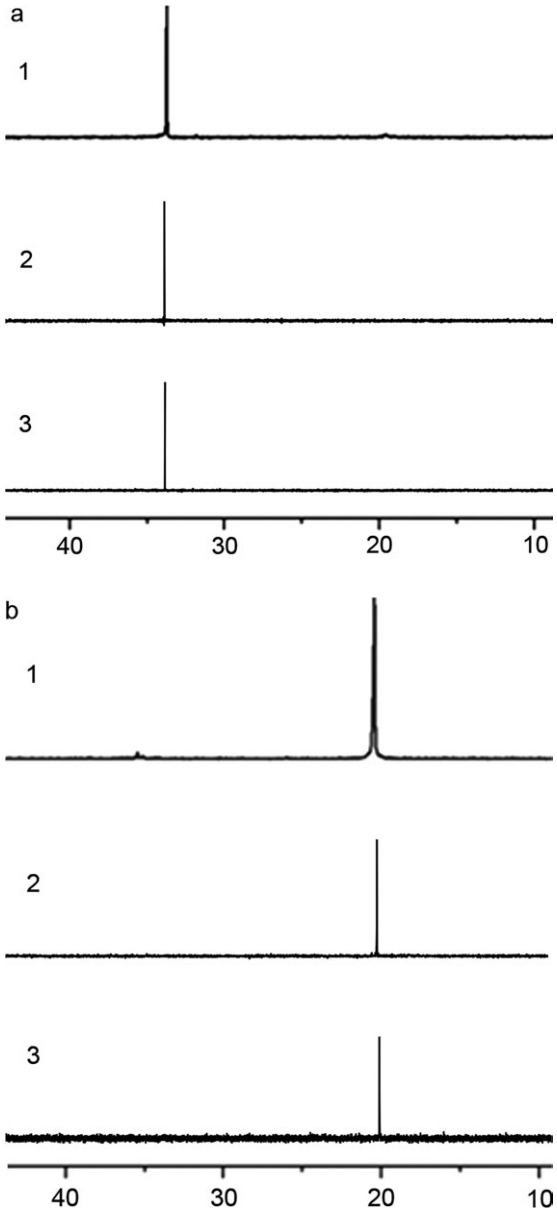

Figure 8. Protection of functional group of β-estradiol using the MIP in triplicate. The products in eluent of mixture of methanol and acetic acid were analyzed with ^{31}P-NMR: (a) Spectra of phosphate after introduction of protecting hydroxyl group at C17. (b) Spectra of phosphate after introduction of protecting hydroxyl group at C3.

protection effect of hydroxyl group was better. As control, adsorption test with nonimprinted polymers without 2-methyl-cyclopentanol template was performed and the result showed that no β-estradiol was adsorbed. Furthermore, MIP was used to directly adsorb the products of the reaction between β-estradiol and diphenylphosphinic chloride and the result showed that no 3-phosphate was obtained in eluent of mixture of methanol and acetic acid. This indicated that the acquisition of pure 3-phosphate by the MIP was not due to the selectively purify effect, but rather to protection of the hydroxyl group at C17 (Supporting Information).

To provide further evidence for feasibility of the method of selective protection of functional group in organic reaction, experiments were going on in accordance with Figure 2(b), when hydroxyl group at C3 of β-estradiol was protected with MIPs imprinted with 5,6,7,8-tetrahydro-2-naphthol template, 17-hydroxyl group reacted with diphenylphosphinic chloride. As shown in Figure 6, the proportion of 17-phosphate was 86.2, 87.5, and 98.2%, respectively from Figure 6(a–c). High purity 17-phosphate was got in eluent of mixture of methanol and acetic acid (Table I). The crystal of 17-phosphate was obtained by liquid phase diffusion of cyclopentane to a solution of 17-phosphate in ethyl acetate at room temperature and determined by XRD [Figure 7(b)]. The crystal data and structure refinement for 17-phosphate were collected (Table II) giving calculated cell parameters of $a = 11.786(3)$ Å, $b = 14.087(4)$ Å, and $c = 15.181(4)$ Å (CCDC 862862). XRD patterns and corresponding analysis confirmed the formation of 17-phosphate. It established that hydroxyl group at C3 of β-estradiol was protected during the organic reaction. Importantly, it confirmed that the method of selective protection of functional group with MIPs is feasibility. As control, adsorption test between nonimprinted polymers without 5,6,7,8-tetrahydro-2-naphthol template was performed and the result showed that no β-estradiol was adsorbed. In addition, MIPs were used to adsorb directly the products of the reaction between β-estradiol and diphenylphosphinic chloride and the result showed that no 17-phosphate was obtained in eluent of mixture of methanol and acetic acid. This indicated that the acquisition of pure 17-phosphate by the MIP was not due to the selectively purify effect, but rather to protection of the hydroxyl group at C3 (Supporting Information).

Reproducibility of MIP

As a protecting group material through noncovalent bonds, the MIP was reusable. Figure 8 shows that the protection efficiency of the MIP is highly repeatable. In the reaction step, the yield of 3-phosphate in eluent of mixture of methanol and acetic acid was 33, 31, and 28%, respectively from the first time to the third time [Figure 8(a)] and the yield of 17-phosphate in eluent of mixture of methanol and acetic acid was 30, 28, and 25%, respectively from the first time to the third time [Figure 8(b)].

CONCLUSIONS

In conclusion, a novel, efficient and mild method for selective protection of functional groups is developed employing MIPs as a protecting group for regioselective organic reaction. In polymers imprinted with 2-methyl-cyclopentanol template to protect hydroxyl group at C17, the proportion of 3-phosphate was almost as high as 100%. In polymers synthesized using 5,6,7,8-tetrahydro-2-naphthol as a template to protect hydroxyl group at C3, the proportion of 17-phosphate reached 98.2%. Furthermore, 3-phosphate and 17-phosphate obtained by MIPs were characterized by ^{1}H-NMR, ^{31}P-NMR and XRD and they proved that selective protecting group based on molecularly imprinted polymer was feasible. In previous work, Hamase and Alexander groups employed the imprinted polymers as protecting groups, but they prepared the imprinted polymers by using the whole reaction compound or the compound only lacking of a functional group than the reaction compound as template.[23,24] In

this article, we chose the molecular which is structurally similar to a part of the reaction compound as a template to prepare the imprinted polymers as protecting groups. Different from previous covalent binding protection techniques, the method protects functional groups through noncovalent bonds, therefore protecting group is reusable. MIPs as protecting groups have other advantages, for instance, easy preparation, chemical stability and low cost. In addition, MIPs as solid-phase support possess screening effect for organic reaction occurring on its solid surface. This strategy may open a new route in the study of blocking techniques.

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