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First immobilization of a glycoluril-derived molecular clip on Merrifield resin: facile separation of dihydroxybenzenes by affinity chromatography

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ABSTRACT

A practical method for the separation and purification of dihydroxybenzenes from phenol-dihydroxybenzene, methoxyphenol-dihydroxybenzene, and isomeric dihydroxybenzene mixtures was developed on the basis of affinity chromatography using a functionalized Merrifield resin. The resin was obtained by immobilization of a glycoluril-derived clip on Merrifield resin. This recyclable resin was repeatedly used for convenient and rapid separation of dihydroxybenzenes from the above-mentioned mixtures.

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Affinity chromatography, as a powerful method for probing small molecule biomacromolecule interactions by immobilizing either on a solid support, has been applied successfully in rapid selection and purification of compounds from complex mixtures.[1] Although this technique is primarily intended for isolation and purification of complex biological mixtures,[2] it has also been shown to be a very powerful and predictive technique to monitor ligand–protein, substrate–enzyme, inhibitor–enzyme, and ligand–receptor interactions.[3–7] Therefore, continued efforts to develop novel receptors to meet the demand of high selectivity and good versatility are important.

In recent years, a series of organic receptors based on diphenylglycoluril, commonly referred to as 'molecular clips' have been introduced and developed by Nolte's group.[8] These molecules possess a well-defined and rigid U-shaped cavity, which is formed by the glycoluril framework and two aromatic side-walls. With their preorganized clefts, they are excellent receptors for dihydroxybenzene guest molecules through hydrogen bonds, π–π stacking interactions, and a so-called 'cavity effect'.[9–12] The binding strength of these types of guests within the host can span a wide range (K_a = 0–10^5 M^{-1}), which vary with a simple modification of either the host or guest molecule.[13]

Here we report the first immobilization of a glycoluril-derived molecular clip on Merrifield resin. Bearing in mind the strong binding interactions between dihydroxybenzenes and the glycoluril clips, we designed an affinity chromatography separation strategy. The new functionalized resin is able to separate isomeric dihydroxybenzenes, phenol-dihydroxybenzene, and methoxyphenol-dihydroxybenzene mixtures efficiently and rapidly.

The synthesis of the functionalized resin **5** was achieved as depicted in Scheme 1. Following a published procedure, we prepared the clip molecule **3** in two steps via TFA-catalyzed condensation of the commercially available 4,4′-dimethoxybenzil (**1**) with urea followed by amidoalkylation of the resulting 4,4′-bis(methoxyphenyl) glycoluril (**2**) with 1,2-bis(bromomethyl)benzene in DMSO.[14] The resulting clip **3** was then demethylated with pyridine·HCl according to a procedure developed in our laboratory to yield the hydroxy-containing clip **4**.[15]

Compound **4** was immobilized on Merrifield resin (Fluka, cross-linked with 2% divinylbenzene, ~1.4 mmol/g Cl loading, 200–400 mesh) by agitating a mixture of **4** and the resin in the presence of pyridine in DMF at 60 °C for 7 days.[16] Extensive washing of **5** was then performed to remove physisorbed species. The beads of **5** were washed with DMF, water, MeOH, and CH_2Cl_2, and then dried in vacuo. Elemental analysis (C, 85.87; H, 7.01; N, 1.48) indicated a loading of 0.28 mmol of **4** per 1 g of resin. IR (KBr, cm^{-1}): 2940, 1715, 1610, 1496, 1460, 1455, 1262, 752, 685.

We initially demonstrated the affinity chromatography approach by separating phenol from a mixture containing a dihydroxybenzene compound (catechol, resorcinol, or hydroquinone). Considering the high affinity of glycoluril clips for dihydroxybenzenes, we expected to separate the dihydroxybenzene compound (DHB) from the mixture via its host–guest complexation with the immobilized clip. Separation was achieved by packing **5** (10 g) in a 2 × 25 cm column, loading the mixture as a methanolic solution

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Scheme 1. Reagents and conditions: (i) urea, TFA, toluene, Dean-Stark apparatus; (ii) KOH, DMSO, 1,2-bis(bromomethyl)benzene, 120 °C, 2 h; (iii) pyridine·HCl, 180–190 °C, 4 h; (iv) (resin)–CH_2Cl, pyridine, DMF, 60 °C, 7 d.

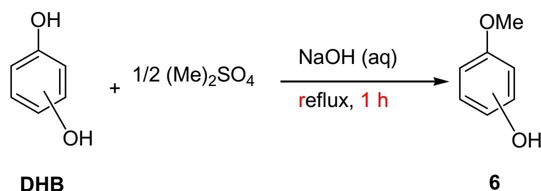
Table 1
The solvent systems for elution of the components of the phenol–DHB mixtures

Mixture	Eluted components			
	$MeOH/CHCl_3$ (5:95, v/v)	$MeOH/CHCl_3$ (10:90, v/v)	$MeOH/CHCl_3$ (12:88, v/v)	$MeOH/CHCl_3$ (15:85, v/v)
Phenol, catechol	Phenol	—	Catechol	—
Phenol, resorcinol	Phenol	—	—	Resorcinol
Phenol, hydroquinone	Phenol	Hydroquinone	—	—

Table 2
The solvent systems for elution of the components of the isomeric DHB mixtures

Mixture	Eluted components		
	$MeOH/CHCl_3$ (10:90, v/v)	$MeOH/CHCl_3$ (12:88, v/v)	$MeOH/CHCl_3$ (15:85, v/v)
Catechol, resorcinol	—	Catechol	Resorcinol
Catechol, hydroquinone	Hydroquinone	Catechol	—
Resorcinol, hydroquinone	Hydroquinone	—	Resorcinol

(1 mL, 0.005 M for each of the solutes), and washing the column with $MeOH–CHCl_3$ solution (5:95, v/v) at a flow rate of 1.5 mL/min. Next, the resin-bound DHB was released from the column by elution with the more polar eluent (Table 1). After each separation, the column was regenerated by washing with methanol.



Scheme 2.

To check the scope of the molecular clip in the affinity chromatography of various DHB mixtures, we loaded a methanolic sample (1 mL) containing two isomeric DHBs (concentration was 0.005 M for each solute) on the modified resin **5**. Separation was performed using a suitable eluent as described above (Table 2).

We also investigated the separation of these mixtures using a traditional column containing Silica Gel 60 (0.040–0.063 mm, Merck) as a stationary phase. The results indicated that the isomeric DHBs could not be separated from each other.

In a subsequent series of experiments, we examined the performance of our column in a practical situation. Therefore, we monomethylated DHBs as follows: at 10 °C dimethyl sulfate (0.64 mL, 7.0 mmol) was added dropwise to a solution containing the DHB (1.5 g, 13.6 mmol), sodium hydroxide (0.54 g, 13.5 mmol), and water (5 mL). The reaction mixture was refluxed for 1 h with

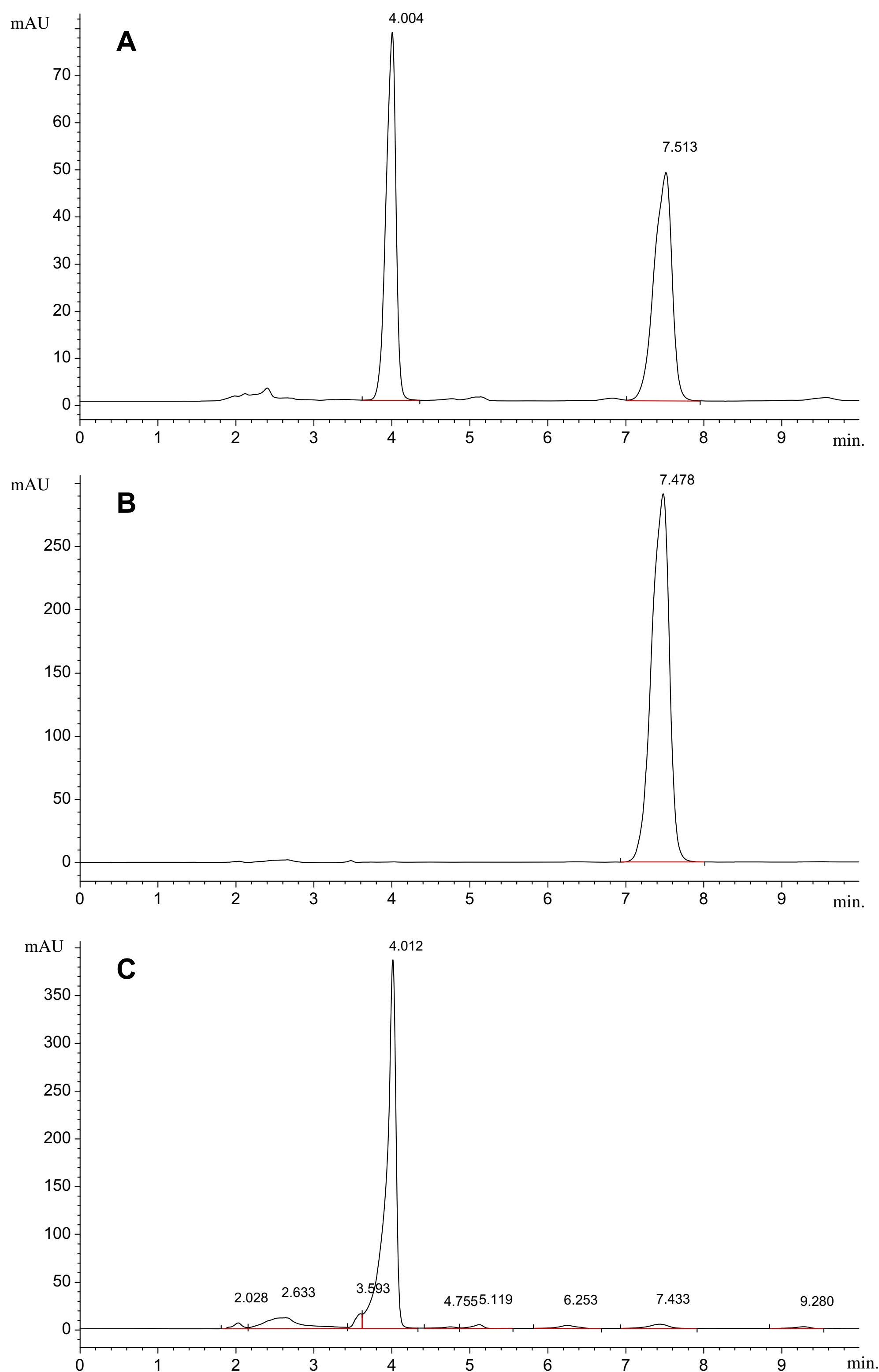


Figure 1. HPLC chromatograms of (A) the reaction mixture of 3-methoxyphenol and resorcinol before separation, (B) the recovered component (3-methoxyphenol) of the mixture by elution with MeOH/$CHCl_3$ (5:95, v/v), (C) the recovered component (resorcinol) of the mixture by elution with MeOH/$CHCl_3$ (15:85, v/v), (D) a standard sample of 3-methoxyphenol, and (E) a standard sample of resorcinol.

stirring. After removal of the solvent under reduced pressure, a crude residue that contained mainly methoxyphenol **6**, and the unreacted DHB was obtained (Scheme 2). A small amount of this residue was dissolved in MeOH (1 mL), loaded onto the column, and eluted with the appropriate solvent (Table 3).

All the collected fractions were analyzed by HPLC and/or TLC. As an example, the HPLC chromatograms of the reaction mixture for the mono-methylation of resorcinol before and after separation indicated that pure 3-methoxyphenol and unreacted starting material (resorcinol) were recovered from the reaction mixture (Fig. 1).

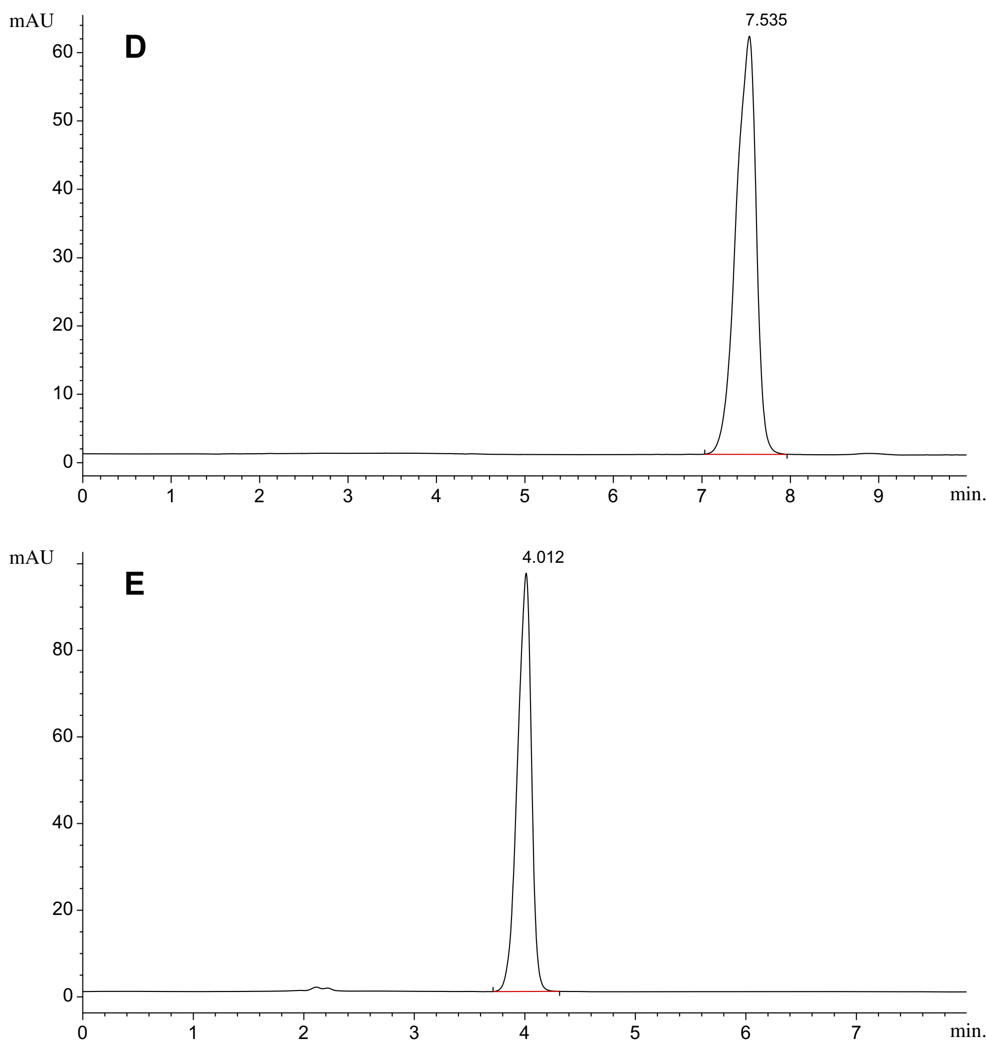


Fig. 1 (*continued*)

Table 3
The solvent systems for elution of the components of the reaction mixtures

Reaction mixture	Eluted components			
	MeOH/$CHCl_3$ (5:95, v/v)	MeOH/$CHCl_3$ (10:90, v/v)	MeOH/$CHCl_3$ (12:88, v/v)	MeOH/$CHCl_3$ (15:85, v/v)
Catechol, 2-methoxyphenol	2-Methoxyphenol	—	Catechol	—
Resorcinol, 3-methoxyphenol	3-Methoxyphenol	—	—	Resorcinol
Hydroquinone, 4-methoxyphenol	4-Methoxyphenol	Hydroquinone	—	—

In conclusion, a practical method for the separation and purification of dihydroxybenzene compounds has been developed. The approach is based on affinity chromatography using a recyclable glycoluril clip-functionalized Merrifield resin. Current work in our laboratory is directed toward the application of this functionalized resin (or Merrifield resins with higher density of the immobilized clip) for the separation and purification of naturally occurring and biologically important dihydroxybenzenes.

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16. A mixture of Merrifield resin (10 g), compound **4** (3.52 g, 6.64 mmol), and pyridine (2.2 mL) in DMF (70 mL) was heated at 60 °C for 7 d. After cooling, the brown solid was filtered and washed sequentially with DMF (50 mL), H_2O (50 mL), MeOH (50 mL), and CH_2Cl_2 (50 mL), and finally dried in voccuo.