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ARTICLE

Synthesis of Functional Catechols as Monomers of Mussel-Inspired Biomimetic Polymers

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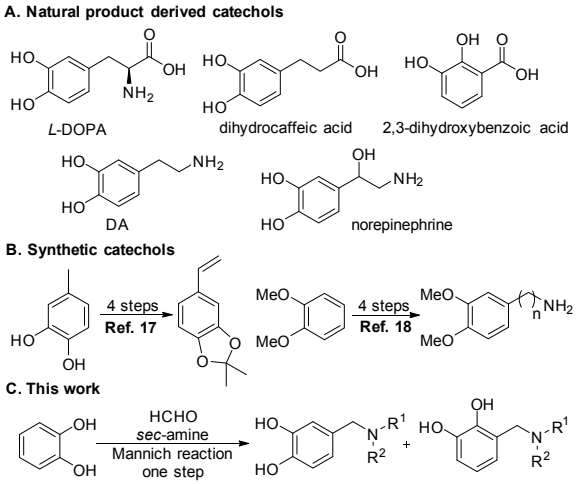
Catechol-containing polymers have attracted much attention in recent years because of their versatile mussel-inspired adhesive function. We report herein the facile synthesis of 4-/3-substituted catechols using the Mannich reaction of catechol with formaldehyde and secondary amines. The reaction proceeds smoothly in water without any catalyst. Separation of the desired products is important to the success of this methodology, and was achieved by a pH-controlled solvent extraction and recrystallization process. The synthesized functional catechols not only exhibited dopamine-like oxidative cross-linking, but also possessed functional groups that are useful for synthesis of catechol-containing polymers. As a proof-of-concept application, two functional catechols, one bearing monohydroxyl and the other dihydroxyl groups at the 4-aminomethyl substituent, were incorporated into polyacrylate and polyurethane backbones, respectively, endowing these polymers with excellent coatability on various surfaces.

Introduction

Mussel-inspired biomimetic polymers are a class of catechol-containing polymers that possess versatile potential applications as biomimetic adhesives, coatings, and hydrogel materials.[1] The design of such polymers is inspired by adhesive mussel foot proteins (Mfps), which are rich in *L*-3,4-dihydroxyphenylalanine (*L*-DOPA) and secreted by marine mussel byssi to adhere strongly to various surfaces in saline and wet environments.[2,3] To date, various naturally occurring catechol-containing products have been derived and incorporated into synthetic polymers to mimic the functions of Mfps, including *L*-DOPA,[4,5] dihydrocaffeic acid,[6] 2,3-dihydroxybenzoic acid (a siderophore scaffold),[7,8] dopamine (DA),[9,10] and norepinephrine[11] (**Scheme 1A**). DA is the simplest mimic of Mfps and has been widely used to construct polymers.[1,12] These natural catechol-containing products are mainly obtained through a variety of biochemical processes. For example, *L*-DOPA is produced via the tyrosine phenol lyase-catalyzed conversion of catechol and propionic acid, and subsequent treatment of *L*-DOPA with *L*-DOPA decarboxylase affords DA;[13] dihydrocaffeic acid is obtained from the catalytic hydrogenation of caffeic acid;[14] norepinephrine is generated by β-hydroxylation of DA with dopamine β-monooxygenase;[15] and 2,3-dihydroxybenzoic acid can be obtained through a modified enzymatic Kolbe–Schmitt carboxylation of catechol with bicarbonate.[16] These naturally occurring catechols provide promising biomimetic functions when incorporated into polymer backbones. However, this research direction often faces challenges because of the limited types of catechols available and high cost of large-scale production of such biomimetic polymers.

Scheme 1. Natural product-derived and synthetic catecholic scaffolds



One approach to circumvent these issues is to chemically synthesize polymerizable catechols. Recently, Leibig and coworkers reported the synthesis of catechol-containing vinyl monomers using 4-methylcatechol as a raw material through a four-step procedure involving catecholic hydroxyl protection, methyl bromination, Wittig reaction, and subsequent deprotection.[17] Hu and colleagues developed a four-step process to obtain 3,4-dihydroxyphenylalkylamines starting with 1,2-dimethoxybenzene via Friedel–Crafts acylation, carbonyl deoxygenation, cyanide substitution, and reduction (**Scheme 1B**).[18] These approaches involve lengthy synthetic

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routes, require harsh reaction conditions, and give the target products with low atom economy. Moreover, these methods may be difficult to scale up to realize the practical application of catecholic biomimetic polymers.

In view of the role of natural catechols in polymers, the catechol unit is deemed essential but the necessity of the amino group is under debate.[17,19,20] For example, regarding DA, the amino group is mostly grafted to the polymer backbone or mounted with a linking handle for polymerization, rather than acting as an adhesion functionality.[1,12] Accordingly, if one functional group could be introduced as a polymerizable handle on the catechol ring through a facile and inexpensive method, the scaled-up synthesis and application of biomimetic polymers would be possible. We envisioned that the Mannich reaction of catechol, which features readily available raw materials and a simple reaction process, may provide this solution. As a congener of catechol, phenol readily undergoes the three-component Mannich reaction with formaldehyde and secondary amines. This approach has been used to synthesize benzylamines,[21] benzoxazine urea–aldehyde resins,[22] and fluorescent bioconjugates.[23] However, the use of this reaction to obtain functional catechols has not been reported, possibly because of the multiple highly reactive sites of catechol and the difficulty of product purification. Catechols with an additional substituent have been used to simplify the Mannich reaction; for example, in the synthesis of catechol-bearing polypeptide conjugates starting with 3-methylcatechol.[24]

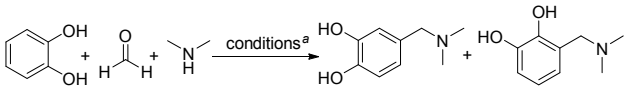
In this work, we take advantage of the Mannich reaction of catechol with formaldehyde and secondary amines to develop a green and facile method for the synthesis of 4-/3-functionalized catechols (**Scheme 1C**). This method is highly atom-economic and can be conducted in water at ambient temperature. Furthermore, two polyethylene glycol (PEG)-containing polymers, one polyacrylate and the other polyurethane with incorporated monohydroxyl and dihydroxyl catechols, respectively, are synthesized, and their coatability on various surfaces is evaluated.

Results and discussion

Optimization of Reaction Conditions

The three-component Mannich reaction of catechol with formaldehyde and a secondary amine is an electrophilic substitution process, in which an iminium ion is first produced by condensation of formaldehyde and the amine. The iminium ion then attacks the *ortho* and *para*-hydroxyl sites of the catechol ring, giving different aminomethylation products. We used the reaction of catechol with formaldehyde and dimethylamine (**1a**) as a model reaction to investigate the feasibility of synthesizing 4- and 3-(*N,N*-dimethylaminomethyl)catechol (**2a**-4/-3). The effects of the reaction conditions on the reaction conversion rate and product yields were evaluated; the results are listed in **Table 1**. The reaction was first attempted using methanol as the solvent according to the analogous reaction conditions of phenolic compounds.[21] When conducted at 25 °C under N_2 until there was no obvious change in product composition as determined by thin layer chromatography (ca. 4 h), the reaction gave a low conversion rate of 60% for catechol with yields of 30% and 26% for the products **2a**-4 and **2a**-3, respectively (**Table 1**, entry 1) (conversion rate determination and product isolation are discussed below). Other solvents including 1,4-dioxane, acetonitrile, THF, isopropanol, DMF, DMSO, and water were then examined. The reaction in 1,4-dioxane for 6 h afforded catechol conversion of 43% and the products **2a**-4 and **2a**-3 in yields of 23% and 16%, respectively (entry 2). In acetonitrile, THF, or isopropanol, the reaction gave similar results to those in methanol (entries 3–5). Additionally, when the reaction was conducted in DMF or DMSO, no marked improvements of the conversion rate and yield were found (entries 6 and 7). Fortunately, when the reaction was performed in H_2O, a high conversion rate of 88% for catechol and high yield of 68% for **2a**-4 were achieved, while the yield of **2a**-3 was depressed to 12% (entry 8). Elevating or lowering the temperature did not improve the outcome of the reaction in H_2O; whereas conducting the reaction in air resulted in decreased yields.

Table 1. Optimization of Mannich Reaction Conditions.



1a **2a**-4 **2a**-3

entry	solvent	time(h)	conversion (%)[b]	yields of **2a**-4/-3 (%)[c]
1	Methanol	4	60	30 / 26
2	1,4-dioxane	6	43	23 / 16
3	Acetonitrile	6	54	26 / 22
4	THF	6	50	24 / 18
5	Isopropanol	6	56	28 / 21
6	DMF	6	52	22 / 28
7	DMSO	6	50	23 /17
8	H_2O	2	88	68 / 12

[a]Reaction conditions: catechol (0.02 mol), dimethylamine (0.02 mol, 33 wt% aqueous), formaldehyde (0.02 mol, 37 wt% aqueous), solvent (30 mL), N_2 atmosphere, 25 °C. [b]The conversion rate of catechol was calculated based on the recovered amount of catechol. [c]Yield of isolated product.

The above results revealed that water was the optimal reaction medium and markedly improved the conversion rate and regioselectivity for the 4-position. Water has a much higher isoelectric constant than those of the organic solvents used here, which not only promotes the formation of the N,N-dimethyliminium cation, but is also favorable to generate the catechol anion, which in turn improves the regioselectivity. Because catechol has two acidity constants (pKa_1 9.2 and pKa_2 13.0), as predicted with ChemDraw software,[25] it is reasonable that one of the two catechol hydroxyl groups dissociates to generate a certain amount of catechol anion during the reaction with a pH range 8–9 because of the presence of dimethylamine. As a result, water enhances the electronic effects of the intermediate N,N-dimethyliminium cation and catechol anion, facilitating this electrophilic substitution with high regioselectivity.

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pH-Controlled Extraction and Recrystallization

During the optimization of reaction conditions, the separation and purification of the products was found to be important to the success of this three-component Mannich reaction. Initially, we tried typical methods such as column chromatography and recrystallization to isolate the reaction products **2a**-4 and **2a**-3 from the reaction mixture, but none were successful. When attempting column chromatography, the strong adhesion of the reaction mixture to silica gel led to severe loss of the products. Recrystallization attempts gave an inseparable mixture because of the strong interactions between the reactants, products, and some byproducts as well as possibly their similar solubilities.

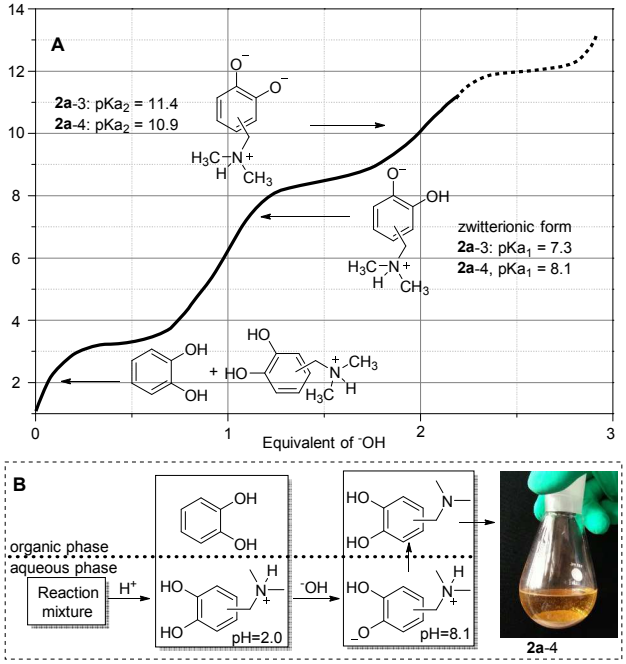

Figure 1. (A) Schematic titration curve of compounds **2a**-4/-3 and their predicted states at different pH. (B) Purification process of **2a**-4 via pH-controlled extraction and recrystallization.

The products **2a**-4 and **2a**-3 have two acidic catecholic hydroxyl moieties and one tertiary amino group. The three acidity constants of **2a**-4 were predicted to be pKa_1 (-OH) 8.1, pKa_2 (-OH) 10.9, and pKa_3 ($-N^+HR_2$) 15.2 using ChemDraw software;[25] while the corresponding values for **2a**-3 are 7.3, 11.4, and 15.2. We hypothesized that separation and isolation of the products from the reaction mixture might be achievable using a method analogous to the extraction of natural amino acids, which involves solution pH adjustment.[26] Thus, a schematic titration curve was drawn (**Figure 1A**), including the predicted existing states of **2a**-4/-3. According to the pH-dependent states, we designed the pH-controlled extraction/recrystallization procedure shown in **Figure 1B** and found that it was able to purify the products. Thus, after reaction, the solution was adjusted to pH 2, where the unreacted catechol should exist as free catechol and **2a**-4/-3 as ammonium salts. Extraction with ethyl acetate recovered catechol and the reaction conversion rate was calculated (**Table 1**). Next, the solution pH was adjusted to 8.1, where the desired products were converted to zwitterionic forms with a reasonable yield. At this stage, we speculated that the zwitterionic states of the products might have relatively low solubilities in water and become extractable with ethyl acetate. Furthermore, once entering the organic phase, the products may convert to their neutral forms with high solubility. We found that several extractions with ethyl acetate recovered most of the desired products from the aqueous phase. The neutral states of **2a**-4/-3 can be inferred from their ^{1}H NMR spectra recorded in DMSO-*d6*, which displayed normal proton signals of two catecholic hydroxyl and aminomethyl groups (Supporting Information) as compared with the predicted spectra for the zwitterionic states of the products. This pH-controlled solvent extraction process removed most of the reactants and byproducts and afforded a clean solution of the product mixture of **2a**-4/-3, enabling recrystallization to be performed in CH_3CN and giving the desired product **2a**-4 as crystals with adequate purity, as confirmed by ^{1}H NMR spectroscopy. The mother liquor, after removal of CH_3CN, furnished the minor product **2a**-3 as a liquid, which was able to be purified by column chromatography on silica gel.

Synthesis of Functional Catechols

Having obtained the optimal reaction conditions and purification method for the model reaction, we then sought to expand the reaction substrate scope to include a number of secondary amines bearing monohydroxyl, dihydroxyl, and ester groups to produce monomers that can be used to synthesize catecholic polymers. It was found that the selected secondary amines (**1b–e**) could be used with acceptable conversion rates of catechol and gave satisfactory yields of the 4-substituted catechols **2b–e**-4 as major products in addition to 3-substituted catechols **2b–e**-3 as minor products (**Table 2**, entries 1–4). Steric hindrance seemed to have a certain effect on the reaction; for example, the conversion rate and yield of 85% and 61%, respectively, for diethanolamine to give **2b**-4 (entry 1) decreased to 69% and 49%, respectively, for diisopropanolamine to afford the corresponding **2d**-4 (entry 3). For the even larger diethoxycarbonylethylamine (**1e**), a conversion rate of 68% and yield of 63% of **2e**-4 were obtained without producing **2e**-3 (entry 4).

The dihydroxyl-containing catechols **2b**-4/-3 and **2d**-4/-3 can be directly embedded into polyurethanes. Monohydroxyl **2d**-4/-3 are useful in polyacrylates after acrylation. Amino-containing **2a**-4/-3 can also be used as monomers by introducing polymerizable functional groups onto the amino groups. Meanwhile, the diester-bearing **2e**-4 may be used as a diacid monomer in polyester synthesis after hydrolysis. It is noted that the principal products **2a–e**-4 are reminiscent of DA with a 4-substitution pattern, while the minor products **2a–d**-3 have a structural resemblance to the siderophore scaffold 2,3-dihydroxybenzoic acid and another class of natural products called urushiols. Urushiols are 3-substituted catechol derivatives and their syntheses are difficult and tedious.[27,28] Therefore, the protocol established here for the facile

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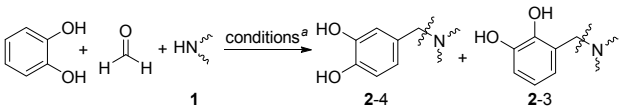
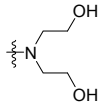
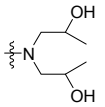
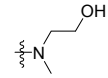
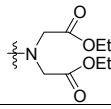
synthesis of functional catechols provides a viable approach for the practical synthesis of various biomimetic polymers. In addition, ten-fold scale-up syntheses of **2b**-4 and **2c**-4 were performed, giving yields of 60% and 71%, respectively, demonstrating the scalability of this Mannich reaction.

Table 2. Synthesis of Functional Catechols



entry	product	conversion[b] and yield[c]	entry	product	conversion and yield
1		85% **2b**-4 (61%) **2b**-3 (10%)	3		69% **2d**-4 (49%) **2d**-3 (16%)
2		87% **2c**-4 (70%) **2c**-3 (12%)	4		68% **2e**-4 (63%) **2e**-3 (trace)

[a]Reaction conditions: catechol (0.02 mol), amine 1 (0.02 mol), formaldehyde (0.02 mol, 37 wt% aqueous), H_2O (30 mL), N_2 atmosphere, 25 °C. [b]The conversion rate of catechol was calculated based on the recovered amount of catechol. [c]Yield of isolated product.

Electrochemical Oxidative Cross-linking

One of the fascinating functions of catechols is their oxidative cross-linking, which is important to enhance the adhesion of catechol-containing polymers.[29] Oxidative cross-linking is easily induced either via aerobic oxidation or through electrochemical initiation. To determine whether the synthesized functional catechols have such oxidative coupling ability, two representative materials, **2b**-4 and **2c**-4, as well as DA, were characterized using cyclic voltammetry (**Figure 2**). DA displays typical two-step redox characteristics on a gold electrode with one pair at 0.218 V/0.095 V and the other at −0.229 V/−0.321 V (vs sat. Hg/Hg_2Cl_2) (**Figure 2A**), similar to those reported previously.[30] The former pair is presumably caused by the catechol/quinone redox cycle, while the latter is related to the redox behavior of 5,6-indolequinone, a species formed by the intramolecular cyclization of DA.[30] Furthermore, the peak currents decrease rapidly with increasing potential scan number, and drop to nearly zero after ten scans, suggesting the formation of an insulating polydopamine film.[30] Both **2b**-4 and **2c**-4 exhibited only one strong oxidation peak at around 0.220 V during the first potential scan, which decreased rapidly to nearly zero for **2b**-4 (**Figure 2B**) and to a small value for **2c**-4 (**Figure 2C**). Because **2b**-4 and **2c**-4 possess tertiary instead of primary amines, no 5,6-indolequinone-like species should be generated, which explains the lack of redox peaks at −0.229 V/−0.321 V like those observed for DA. The irreversible oxidation of **2b**-4 and **2c**-4 and the quickly decreasing peak currents suggest the rapid formation of insulating polymer films, which probably result from intermolecular quinone-like cross-linking occurring during the electrochemical process.[31,32]

The formation of insulating films of **2b**-4 and **2c**-4 was characterized by impedance analysis. Both the films exhibited typical impedance curves (**Figure 2D**). Using the equivalent circuit model shown in the inset of **Figure 2D**, the calculated charge transfer resistances of the **2b**-4 and **2c**-4 films were 1.5 and 1.1 MΩ, respectively. These values are comparable to that of the polydopamine film (1.3 MΩ). The high oxidative cross-linking polymerization ability of **2b**-4 and **2c**-4 is promising for their potential application in mussel-inspired biomimetic polymers.

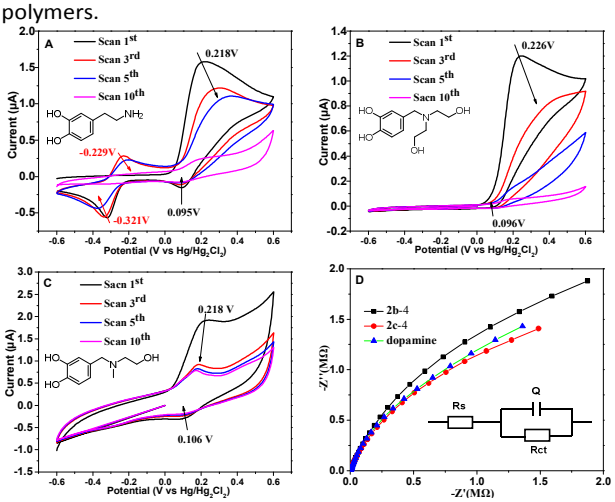


Figure 2. Cyclic voltammograms of (A) dopamine (DA), (B) 4-**2b**, and (C) 4-**2c** in PBS at pH 8.0 with a concentration of 2.0 mM, and (D) impedance curves of the resulting insulating films of DA, 4-**2b**, and 4-**2c**. Working electrode: gold; scan range: −0.6–0.6 V (vs. sat. Hg/Hg_2Cl_2); scan rate: 20 mV/s; scan numbers 1, 3, 5, and 10 are shown. The arrows indicate the trends of peak currents.

Synthesis of Catecholic Polymers

To verify the biomimetic functions of the functional catechols in polymers, **2b**-4 and **2c**-4 were incorporated into two PEG-containing polymers, polyurethane and polymethacrylate, respectively, as a proof-of-concept application of the functional catechols. The strategies for polymer synthesis were based on the reported methods for DA-containing polymers.[9,33] **2b**-4-containing polyurethane, denoted DEPU, was synthesized through the prepolymerization of isophorone diisocyanate (IPDI) and PEG diol (Mn=1000) followed by chain extension with **2b**-4. Meanwhile, **2c**-4-containing polymethacrylate, denoted DEPA, was obtained via the methacrylation of **2c**-4 followed by copolymerization with PEG-methacrylate (Mn=300) using 2,2-azodiisobutyronitrile (AIBN) as an initiator (**Scheme 2**).

In the synthesis of DEPU, chain extension only occurred between isocyanates and the alkyl hydroxyls of **2b**-4; the catecholic hydroxyl groups did not participate in the reaction, as evidenced by ^{13}C NMR spectra, which revealed no marked chemical shift change of the carbon of the catecholic hydroxyl group of **2b**-4 before and after polymerization (145.1 vs. 143.6 ppm, **Figure S1**). The intact catecholic hydroxyls after urethane linkage formation are also used as an indicator of the successful synthesis of DA-containing polyurethanes.[33] The ^1H NMR spectrum of DEPU contains the characteristic peaks of the catechol unit (6.60–6.95 ppm), methyl and methylene

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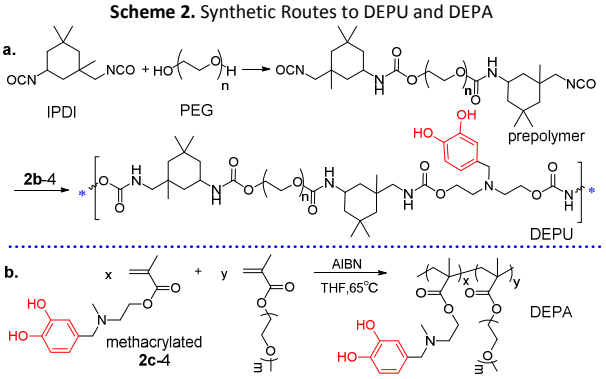
groups of IPDI (0.85–1.70 ppm), and methylene unit of the PEG chain (-O-CH_2-CH_2-O, 3.30–3.75 ppm; -CH_2-OC(=O)-, 4.10–4.45 ppm) (**Figure S2**). In the synthesis of DEPA, AIBN was used as an initiator for the copolymerization of methacrylated **2c**-4 and PEG-methacrylate. The catecholic hydroxyls did not prevent this polymerization; a similar result was found for the radical polymerization of acrylated DA.[9,34,35] The ^{1}H NMR spectrum of DEPA exhibited the characteristic peaks of the catechol unit (6.40–7.20 ppm) and the methylene group of PEG (-O-CH_2-CH_2-O, 3.30–3.75 ppm; -CH_2-OC (=O)-, 4.05–4.45 ppm) (**Figure S3**).

Scheme 2. Synthetic Routes to DEPU and DEPA



The ^{1}H NMR signal intensities of catechol and methylene of PEG in DEPU and DEPA were used to calculate the relative compositions of the individual monomers, giving catechol unit contents of 14.3% for DEPU and 48.1% for DEPA. These compositions can be easily tuned by varying the monomer ratio in polymer synthesis or choosing PEG with a different chain length. Gel permeation chromatography (GPC) measurements were also performed to characterize the polymers (**Figure S4**). DEPU exhibited a number-average molecular weight Mn of 18.6 kDa and polydispersity of 1.23, while DEPA had an Mn of 9.3 kDa and polydispersity of 1.77. The compositions and GPC data are summarized in **Table 3**.

Table 3. Compositions and Molecular Weights of DEPU and DEPA.

polymer	Catechol (%)	PEG (%)	Mn (kDa)	Mw (kDa)	PDI
DEPU	14.3	42.9	18.6	23.0	1.23
DEPA	48.1	51.9	9.3	16.5	1.77

Universal Coatability and Antifouling Properties

The aim of incorporating catechol moieties into polymers is to impart these materials with Mfp-like adhesive properties and coatability, not only on common inorganic and organic substrates with intrinsically different wettability, but even on surfaces that are highly resistant to coating such as polytetrafluoroethylene (PTFE).[36,37]

DEPU and DEPA coatings were deposited by dip-coating on various substrates, including glass, silicon, gold, stainless steel, and PTFE. The surface coatability was reflected by the change in water wettability and antifouling effect resulting from the nature of PEG chains in the polymers upon coating formation. Both DEPU and DEPA were capable of forming coatings rapidly (within 30 min) from polymer solutions with a concentration of 1 mg/mL in THF. The DEPU coatings displayed static contact angles of 42°–54° on glass, silicon, gold, and stainless steel, and the DEPU coatings showed contact angles in the range of 28°–33° on the same substrates (**Figure 3**). The polymers also exhibited good coatability on PTFE, an inert and highly hydrophobic surface, decreasing the water contact angle from the original 116° to 68° for DEPU and 54° for DEPA for coatings formed using 3-mg/mL polymer solutions and a deposition time of 2 h. On the one hand, the wettabilities of substrates upon coating with a polymer film are generally altered to approximately the intrinsic wettability of the polymer regardless of the initial substrate wettability. On the other hand, the coating may not be able to reach the polymer intrinsic wettability because of the influence of substrate-dependent morphology, which may depend on the substrate because of the varied aggregation of PEG-containing polymers.[18,38] Consequently, the substrate-dependent polymer morphologies would result in different wettabilities on different substrates coated with the same polymer; this is reflected by the contact angles of DEPU and DEPA coatings on different substrates exhibiting a narrow range instead of a fixed value. In addition, although both DEPU and DEPA contain PEG chains, they still displayed different morphologies on silicon, as revealed with scanning electron microscopy (SEM), for which structure-dependent microscale aggregation states were clearly seen (**Figure S5**). Nevertheless, the wettability variation trends of the polymer coatings suggest the strong coating abilities of the synthesized polymers.

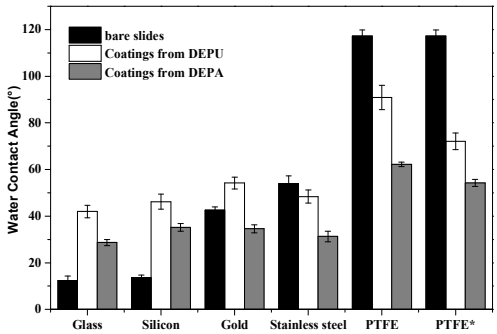


Figure 3. Wettabilities of various substrates without and with the coatings formed by immersing in DEPU and DEPA solutions at 1 mg/mL for 30 min. For PTFE, the coating time was 2 h and the polymer concentration was 3 mg/mL.

The polymers containing catechol and PEG units have wide-ranging potential applications as biomaterials. Their antifouling effect is one important feature, which takes advantage of the coatability of catechol and protein adsorption resistance of PEG chains.[5] The antifouling test can be used to validate not only the formation of coatings, but also the feasibility of biomaterial applications. In the present work, the protein adsorption resistance of DEPU and DEPA coatings on a gold surface was investigated using surface plasmon resonance (SPR). The chosen proteins were bovine serum albumin (BSA) and human plasma fibrinogen (Fib), which are typical model

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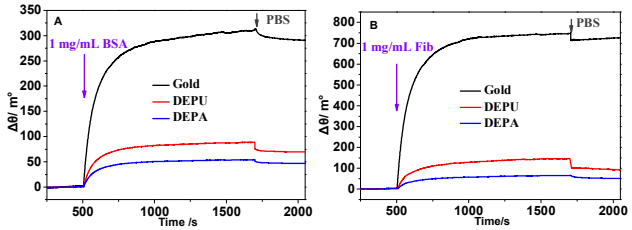

Figure 4. SPR sensorgrams of adsorption of the proteins (a) BSA and (B) Fib (B) on gold (black line) and the DEPU (red line) and DEPA (blue line) coatings.

proteins used for antifouling assessment. The SPR sensorgrams presented in **Figure 4** show that the amounts of BSA and Fib adsorbed on the DEPU coating are 60 and 78 ng/cm^2, respectively, whereas the corresponding values for the DEPA coating are 32 and 46 ng/cm^2, respectively. These values are comparable to the antifouling capacity of a recently developed DA-grafted branched polyglycerol coating (49.6 ng/cm^2 for Fib),[39] illustrating the excellent antifouling abilities of the DEPU and DEPA coatings.

Conclusions

A facile green approach to synthesize 4-/3-substituted catechols using the inexpensive Mannich reaction of catechol with formaldehyde and various secondary amines was developed. The key to the success of this approach was the use of a pH-controlled solvent extraction and subsequent recrystallization process for product purification, which overcame the difficulties associated with general chromatography and recrystallization. The developed method provided 4-substituted catechols as the major product, which resembled DA in their substitution pattern, and 3-substituted catechols as a minor product, which are structurally similar to natural 2,3-dihydroxybenzoic acid and urushiols. Furthermore, the catechols possessed functionalities such as alkyl hydroxyl, amino, and ester groups for easy incorporation into polymer backbones, and their synthesis is scalable, facilitating the practical application of catechol biomimetic polymers. The present work also demonstrated that incorporation of dihydroxyl and monohydroxyl catechols into polyurethane and polymethacrylate resulted in their favorable coatability on various surfaces and excellent antifouling behavior. Therefore, this work provides a new methodology for the scale-up synthesis and applications of mussel-inspired polymers, which is important to decrease the need for precious DA-like catechols of natural origin.

Experimental

Materials. Catechol, formaldehyde (37 wt% aqueous), diethanolamine, N-methylethanolamine, and diisopropanolamine were purchased from Aladdin Reagent Co., Ltd. (China). IPDI and diethyl iminodiacetate were purchased from Adamas-beta (China). Dimethylamine (30 wt% aqueous) came from Sinopharm Chemical Reagent Co., Ltd. PEG diol (Mn = 1000, Aldrich) was dehydrated by heating at 100 °C for 2 h under vacuum. AIBN, ω-methyl PEG methacrylate (PEGMA, Mn = 300), Fib, and BSA were purchased from Sigma Aldrich. The proteins were dissolved in phosphate-buffered saline (PBS; pH 7.4) at a concentration of 1 mg/mL. All other reagents were of the highest purity available commercially.

General procedure for synthesis of functional catechols. Formaldehyde (20 mmol, 37 wt% aqueous) was added to a solution of a secondary amine (20 mmol) in distilled water (30 mL). The mixture was stirred at room temperature for 30 min. A solution of catechol in water (20 mmol, 10 mL) was then added dropwise under N_2 and the resultant solution was stirred for 4 h. The solution pH was adjusted to about 2 using dilute hydrochloric acid and then the solution was extracted with ethyl acetate three times to recover catechol. The aqueous phase was adjusted to pH 8 with aqueous NaOH and then extracted using 50 mL of ethyl acetate three to five times. The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated to afford the product mixture. The mixture was dissolved in a suitable amount of acetonitrile and then recrystallized to give the expected 4-substituted catechol. The mother liquor was evaporated to give a liquid, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 1:5) to afford the 3-substituted catechol.

4-(*N*,*N*-Dimethylaminomethyl)benzene-1,2-diol (**2a**-4). Yellow solid (2.27 g, 68%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.78 (s, 2H), 6.66 (s, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 3.17 (s, 2H), 2.08 (s, 6H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 145.8 (s), 123.3 (s), 119.7 (s), 118.9 (s), 116.2 (s), 115.2 (s), 61.5 (s), 44.6 (s). HRMS (ESI-TOF): calcd for [$C_9H_{13}NO_2$ + H^+] 168.1019, found 168.1018.

3-(*N*,*N*-Dimethylaminomethyl)benzene-1,2-diol (**2a**-3).[40] Yellow oil (0.40 g, 12%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.65 (d, *J* = 7.1 Hz, 1H), 6.54 (t, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 6.2 Hz, 1H), 3.54 (s, 2H), 2.23 (s, 6H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ145.4 (s), 119.6 (s), 123.3 (s), 118.9 (s), 116.2 (s), 115.2 (s), 61.5 (s), 44.6 (s). HRMS (ESI-TOF): calcd for [$C_9H_{13}NO_2$ + H^+] 168.1019, found 168.1018.

4-(*N*,*N*-Bis(2-hydroxyethyl)aminomethyl)benzene-1,2-diol (**2b**-4). Yellow solid (2.77 g, 61%). ^{1}H NMR (600 MHz, DMSO-*d6*) δ 6.62 (d, *J*=11.9Hz, 1H), 6.52 (s), 6.49(d, *J* = 8.0 Hz, 1H), 4.57(s, 2H), 3.75 (s, 2H), 3.52 (s, 4H), 2.61 (s, 4H), 2.21 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ 145.2 (s), 143.6 (s), 130.2 (s), 119.3 (s), 116.1 (s), 115.6 (s), 63.3 (s), 54.7 (s), 53.4 (s). HRMS (ESI-TOF): calcd for [$C_{11}H_{17}NO_4$ + H^+] 228.1235, found 228.1236.

3-(*N*,*N*-Bis(2-hydroxyethyl)aminomethyl)benzene-1,2-diol (**2b**-3). Yellow oil (0.45 g, 10%).^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.64 (d, J = 7.6 Hz, 1H), 6.54 (t, J = 7.6 Hz, 1H), 6.48 (d, J = 6.9 Hz, 1H), 3.64 (s, 2H), 3.56 (t, *J* = 5.9 Hz, 2H), 2.53 (t, *J* = 5.9 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 141.6 (s), 141.5 (s), 119.8 (s), 115.6 (s), 114.7 (s), 111.0 (s), 56.3 (s), 54.7 (s), 53.4 (s), 52.0 (s). HRMS (ESI-TOF): calcd for [$C_{11}H_{17}NO_4$ + H^+] 228.1235, found 228.1236.

4-(*N*-(2-Hydroxyethyl)-*N*-methylaminomethyl)benzene-1,2-diol (**2c**-4). Yellow solid (2.76 g, 70%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.01 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 2H), 3.78 (t, *J* = 7.4 Hz, 2H), 2.81 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 145.6 (s), 145.4 (d, *J* = 23.5 Hz), 127.6 (s), 121.0 (s), 117.5 (s), 115.8 (s), 61.4 (s), 58.5 (d, *J* = 14.6 Hz), 41.8 (s). HRMS (ESI-TOF): calcd for [$C_{10}H_{15}NO_3$ + H^+] 197.1132, found 198.1134.

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3-(*N*-(2-Hydroxyethyl)-*N*-methylaminomethyl)benzene-1,2-diol (**2c**-3). Yellow oil (0.47 g, 12%). ^{1}H NMR (600 MHz, DMSO-*d6*) δ 7.38 (s, 2H), 6.65 (d, J = 7.7 Hz, 1H), 6.54 (t, J = 7.6 Hz, 1H), 6.49 (d, *J* = 7.2 Hz, 1H), 3.65 (s, 2H), 3.56 (t, *J* = 5.8 Hz, 2H), 2.54 (t, *J* = 5.8 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ 141.7 (s), 141.4 (s), 119.2 (s), 115.5 (s), 114.7 (s), 111.1 (s), 56.2 (s), 54.9 (s), 54.4 (s). HRMS (ESI-TOF): calcd for [$C_{10}H_{15}NO_3$ + H^+] 197.1132, found 198.1134.

4-(*N,N*-Bis(2-hydroxypropyl)aminomethyl)benzene-1,2-diol (**2d**-4). Yellow solid (2.49 g, 49%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.67 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 3.82 (s, 2H), 3.74 – 3.65 (m, 2H), 2.74 – 2.38 (m, 4H), 1.02 (d, *J* = 8.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 145..0 (s), 129.8 (s), 123.6(s), 123.5(s), 119.4 (s), 115.7 (s), 64.3 (s), 62.6(s), 57.4 (s), 20.53 (s). HRMS (ESI-TOF): calcd for [$C_{13}H_{21}NO_4$ + H^+] 256.1563, found 256.1566.

3-(*N,N*-Bis(2-hydroxypropyl)aminomethyl)benzene-1,2-diol (**2d**-3). Yellow oil (0.82 g, 14%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.67 (d, *J* = 7.7 Hz, 1H), 6.54 (t, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 7.2 Hz, 1H), 3.80 (s, 2H), 3.79 – 3.62 (m, 2H), 2.39 (m, 4H), 1.05 (m, *J* = 5.4 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 145.0 (s), 145.0 (s), 123.6 (s), 123.5 (s), 119.4 (s), 119.4 (s), 64.3 (s), 62.5 (d, J=20.1 Hz), 60.0 (s), 22.1 (t, *J*= 20.4 Hz), 20.48 (s). HRMS (ESI-TOF): calcd for [$C_{13}H_{21}NO_4$ + H^+] 256.15.63, found 256.1566.

4-(*N,N*-Bis(ethoxycarbonylmethyl)aminomethyl)benzene-1,2-diol (**2e**-4). Colorless solid (3.92 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 4.15 (d, *J* = 7.1 Hz, 4H), 3.74 (s, 2H), 3.50 (s, 4H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (151 MHz, DMSO) δ 162.8 (s), 135.2 (s), 135.0 (s), 121.1 (s), 119.4 (s), 112.7 (s), 107.5 (s), 106.2 (s), 51.9 (s), 45.4 (s), 41.02 (s). HRMS (ESI-TOF): calcd for [$C_{15}H_{21}NO_6$ + H^+] 312.1442, found 312.1447.

Scale-up synthesis of 2b-4 **and 2c**-4**.** Ten-fold scale-up syntheses of **2b**-4 and **2c**-4 were performed using the standard reaction conditions and the pH-controlled solvent extraction and recrystallization procedure, giving **2b**-4 with a yield of 60% (13.6 g) and **2c**-4 with a yield of 71% (13.8 g).

Synthesis of catecholic polymers. The catechol-containing polyurethane (DEPU) based on IPDI, PEG, and **2b-**4 as a chain extender was synthesized by a two-step procedure. First, the dehydrated PEG diol (2.0 g, 2.0 mmol) was dissolved in DMF and then IPDI (0.89 g, 4.0 mmol) was added with mechanical stirring under N_2 at 80 °C. After the -NCO content reached the theoretical value (determined by dibutylamine titration using bromophenol blue as an indicator), the expected prepolymer was formed. The solution was then cooled to room temperature and **2b**-4 (0.47 g, 2.1 mmol, OH/NCO = 1.05) was added. The reaction mixture was heated at 60 °C for 2 h. The solution was cooled to room temperature and then a suitable amount of anhydrous ethyl ether was added to form a suspension. The suspension was centrifuged to give the polymer DEPU as a light brown viscous liquid, which was dried under vacuum at 40 °C for 48 h before use. Yield: 72%. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 6.6–7.1 (br, Ar-H), 4.1–4.5 (br, -CH_2-OC(=O)-), 3.3–3.8 (br, polyether backbone), 0.8–1.7 (br, methyl and methylene of IPDI).

To synthesize catechol-containing polymethacrylate (DEPA), an intermediate methacrylated **2c**-4 was synthesized first, which was achieved by reacting **2c**-4 with methacrylic anhydride using trimethylamine as a catalyst. The catechol-containing polymethacrylate DEPA was then synthesized as follows. The monomers methacrylated **2c**-4 (0.265 g, 1.0 mmol) and PEGMA (0.30 g, 1.0 mmol) were dissolved in anhydrous THF (30 mL) and then AIBN (16.4 mg, 0.1 mmol) was added. The solution was heated at 65 °C for 12 h with magnetic stirring under N_2. A suitable amount of hexane was added and subsequent centrifugal precipitation gave the polymer DEPA as a light brown viscous liquid, which was dried under vacuum at 40 °C for 24 h before use. Yield: 65%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.4–6.8 (br, Ar-H), 3.4–3.8 (br, polyether backbone), 0.8–2.2 (br, polymethacrylate main chain).

Structural data, including ^{1}H NMR spectra and GPC, for DEPU and DEPA are provided in the Supporting Information (**Figure S1–S4**).

Coating preparation. Substrate cleaning was performed before coating. A gold substrate (standard SPR sensor chip with a 50-nm gold film on quartz) was immersed in 30% H_2O_2 and then 1% aqueous $NaBH_4$ for 10 min, rinsed with water, and then treated with H_2 plasma in a Harrick plasma cleaner (Sterilizer PDG-32G) for 10 min. A silicon wafer was treated by immersion in piranha solution (H_2SO_4/H_2O, 3:1) for 10 min, then ultrasonically cleaned in acetone and Milli-Q water in sequence, and finally treated with H_2 plasma in the Harrick plasma cleaner for 10 min. Stainless steel and glass substrates were ultrasonically cleaned in ethanol, acetone, and ultra-pure water for 10 min each, and then treated with H_2 plasma for 10 min.

Coatings were fabricated on the various substrates by a dip-coating method. The clean substrates were immersed in a solution of DEPU or DEPA (1 mg/mL) in THF for 30 min. The coatings on PTFE were formed by immersion for 2 h in a polymer solution with a concentration of 3 mg/mL. The coating on the SPR sensor chip was formed by a spin-coating method involving low-speed spinning at 600 rpm for 15 s followed by high-speed spinning at 1200 rpm for 60 s using a polymer solution (1 mg/mL) in THF. The prepared coatings were rinsed with ethanol and then blown dry with an N_2 stream.

Characterization. NMR spectra were recorded on a Varian NMR spectrometer (Mercury plus-600 or plus-400) using DMSO-*d6*, methanol-*d4*, or $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to tetramethylsilane. High-resolution ESI mass spectra were obtained on an Agilent 6530 accurate-mass Q-TOF spectrometer. GPC was performed on a PerkinElmer Series 200 using DMF/LiBr (0.01mol/L) as the eluent. The sample concentration was 1.0 mg/mL in THF, and the flow rate was 1.0 mL/min. Molecular weight was calibrated using polystyrene standards. The water static contact angles of various coatings were measured with a contact angle system (OCA 20, Data Physics, Germany) at room temperature. A water droplet with a volume of 3 μL was added to a surface and allowed to equilibrate for 15 s. Five measurements at different locations were averaged to give the reported value. The surface morphology of coatings on silicon wafers was analyzed using a Zeiss Ultra Plus field-emission SEM with an accelerating voltage of 15 kV. Antifouling properties were

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measured with an Autolab Springle SPR system (Echo Chemie B.V., the Netherlands). A polymer-coated sensor chip was mounted in the flow cell and the measurement was performed as follows. PBS (pH 7.4) was flowed over the modified SPR sensor surface until a stable baseline was achieved. A solution of a protein (BSA or Fib; 1 mg/mL) in PBS was then flowed over the sensor for 20 min. Finally, PBS was introduced again to flush away weakly bound protein molecules. The correlation between the shift in SPR angle (θ_{SPR}) before and after protein exposure and the amount of adsorbed protein was calculated according to the manufacturer's instruction that an increase of θ_{SPR} of 120 m° approximately equals a protein density of 100 ng/cm^2.

Conflicts of interest

There are no conflicts to declare.

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Table of contents

Synthesis of Functional Catechols as Monomers of Mussel-Inspired Biomimetic Polymers

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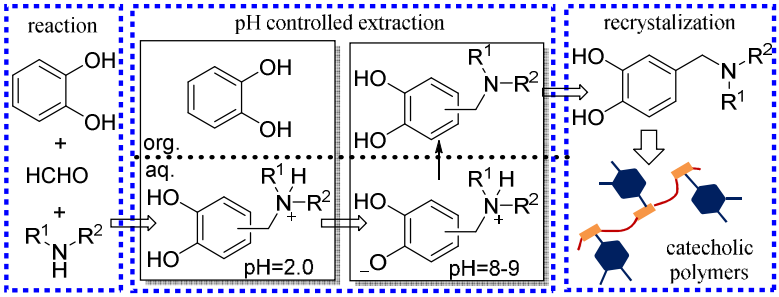

A Mannich reaction was developed to synthesize functional catechols as a facile route to catecholic polymers with versatile bioinspired properties.