Synthesis of Sugar-Substituted Poly(phenylenevinylene)s

Akinori Takasu,* Kazuhiro Iso, Takumi Dohmae, and Tadamichi Hirabayashi

Department of Environmental Technology and Urban Planning, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan

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Sugar-containing PPVs, poly{2-[*O*-(2-acetamido-2-deoxy-*β*-D-glucopyranosyl)]-5-methoxy-*p*-phenylenevinylene-*alt*-*p*-phenylenevinylene} (PPV-GlcNAc) and poly{2,5-bis-[*O*-(*β*-D-glucopyranosyl)]-*p*-phenylenevinylene-*alt*-*p*-phenylenevinylene} (PPV-Glc_2), were synthesized via Heck reaction of *p*-divinylbenzene (DVB) with *O*-glycosylated hydroquinones, 2,5-dibromo-4-methoxyphenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranoside (**3**) and 1,4-bis(*O*-2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-2,5-dibromobenzene (**6**), respectively. Acetyl protecting groups of the PPVs are completely removable under mild conditions (yield 69−87%). The structures were confirmed using ^{1}H NMR and IR spectra. Size exclusion chromatography (SEC) (eluent: DMF, polystyrene standards) measurements indicated that respective M_n and M_w/M_n values of the obtained polymers are 4.49×10^3 and 2.3_5 (PPV-GlcNAc) and 3.86×10^3 and 1.3_9 (PPV-Glc_2). These sugar-containing PPVs are soluble in water/DMF (8/2, v/v) and are recognized by *Concanavalin* A (Con A), D-glucose-binding protein. Blue shift of λ_{max} of the conjugated polymer backbone was confirmed when the glucose-substituted PPV interacts with Con A. Based on those binding properties, these results revealed that the obtained PPVs with pendant sugars have capabilities for detection of biological stimuli.

Introduction

Hybridization of sugars or carbohydrates with conjugated polymers via covalent bonds is an exciting approach to create novel biological sensors and other devices.[1] Carbohydrates and sugars are hydrophilic modules that can render polymers biocompatible and potentially act as biological antennae for sugar-binding proteins including lectin, virus, and *Escherichia coli*. We can expect a red-shift or blue-shift of the absorption maximum wavelength (λ_{max}) of the conjugated polymer backbone when sugar-substituted conjugate polymers bind with sugar-binding proteins. Among conjugated polymers, poly(phenylenevinylene) (PPV) is an extremely interesting electroactive polymer that has demonstrated high conductivity and electroluminescent activity.[2] Numerous approaches have synthesized PPV, and various side groups have been added to the PPV backbones to make them more soluble and processable in some organic solvents.[3] Nevertheless, applications to aqueous sensing have remained limited by strong interactions between hydrophobic backbones and aromatic $\pi-\pi$ stacking, which severely restrict their water solubility. Although several water-soluble PPVs having ionic and nonionic side chains have been reported to date,[4] syntheses of PPVs with carbohydrate or sugar-substituted PPV have not been reported until now. Nonionic PPVs have attracted much interest because water-solubility is not affected by pH or ionic strength. Despite numerous contributions to the biological field of nonconjugated neoglycopolymers,[5] much less is known about sugar-decorated conjugated polymers.[1] Although notable exceptions are sugar-coated polydiacetylenes[1a] and sugar-coated polythiophenes[1b] which have been investigated by Charych et al., the inter-sugar distance is not regulated. Inter-sugar distances are important for affinity with sugar-binding proteins.[6]

This communication reports the first example of production of well-defined glycosylated PPVs using facile Pd-catalyzed synthetic approach, along with explanation of their solubilities in aqueous media and spectroscopic behavior in the presence of lectins. In the structural sense, the glycosidated PPV has an alternating sequence of phenylenevinylene and glycosidated phenylenevinylene units, by which the inter-sugar distance is regulated. Structural accuracy will be examined specifically when the polymer is applied to biosensors to detect biological stimuli.

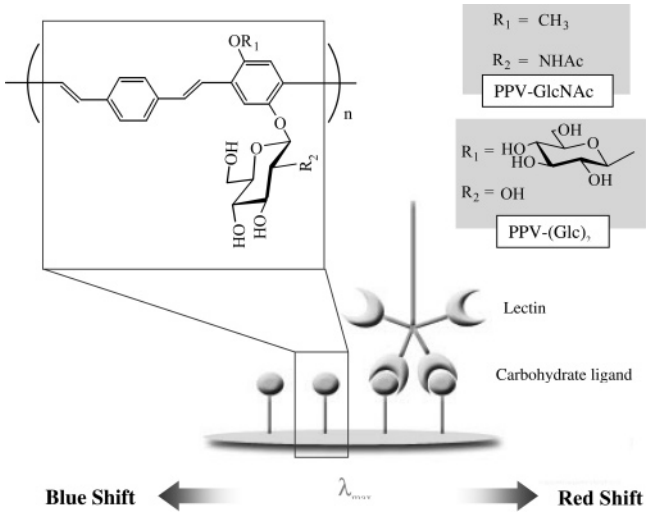

Figure 1. Application of sugar-substitute PPV to biosensors for detection of sugar-binding proteins.

Experimental Section

Materials. *N*-Acetyl-D-glucosamine (GlcNAc) and bromine were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Acetyl chloride, *p*-methoxyphenol, tetrabutylammonium bromide (TBAB), *N*-bromosuccinimide (NBS), hydrazine monohydrate, hydroquinone, silver trifluoromethansulfonate (AgOTf), and boron trifluoride (BF_3)

† To whom correspondence should be addressed. E-mail: takasu.akinori@nitech.ac.jp.

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etherate were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Asahi Kasei Medical Co. Ltd. (Osaka, Japan) supplied *p*-divinylbenzene (DVB). Palladium(II) acetate, tris(2-methylphenyl)phosphine, and triethylamine were purchased from Tokyo Kasei Kogyo Co. Ltd. (Tokyo, Japan). *Concanavalin* A (Con A) and wheat germ agglutinin (WGA) were purchased from Aldrich Co. Ltd and Sigma Co., respectively.

Measurements. FT-IR spectra were recorded in KBr disks using an FT-IR spectrometer (FT/IR-430; Jasco Inc.). The ^{1}H and ^{13}C NMR spectra were measured at 27 °C using a spectrometer (200 MHz for ^{1}H NMR, DPX200; Bruker Analytik). All chemical shifts were expressed as δ downfield from tetramethylsilane (TMS). Average molecular weights (M_n) and polydispersity indexes (M_w/M_n) of polymers were estimated using size exclusion chromatography (SEC) calibrated with polystyrene standards using an HLC 803D (Tosoh Corp.) with an RI-8000 detector (Tosoh Corp.) and TSK-GEL α5000-HXL columns [eluent, DMF + LiBr (0.05 wt %); flow rate, 1.0 mL/min; temperature, 40 °C; Tosoh Corp.]. Ultraviolet measurement was performed using a UV−vis spectrometer (V-550; Jasco Inc.) [10 mM HEPES buffer/DMF (8/2), $[(Glc)_2-PPV]_0 = 20$ μM (40 μM, glucose residue), $[Glucose]_0/[ConA]_0 = 200/1$, at 27 °C]. Fluoresce spectra (excited at 400 nm) was measured by JASCO V-500 spectrometer [10 mM HEPES buffer/DMF (8/2), $[(Glc)_2-PPV]_0 = 2$ μM (4 μM, glucose residue), $[Glucose]_0/[ConA]_0 = 200/1-40/1$, at 27 °C].

Synthesis of Sugar-Substituted Hydroquinones. For 2,5-dibromo-4-methoxyphenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**3**). NBS (1.96 g, 11.6 mmol) was added to **2** (1.5 g, 3.3 mmol) in 1,2-dichloroethane (17.8 mL). The mixture was put into a water bath at 60 °C with vigorous stirring for 336 h. After the reaction, 1,2-dichloroethane (50 mL) was added. Then the mixture was washed with 1.0 M aqueous Na_2SO_3 and distilled water and dried over $MgSO_4$. Subsequently, 1,2-dichloromethane was removed under reduced pressure. The crude product was recrystallized from ethanol to yield 1.01 g (49.8%) of white product. ^{1}H NMR δ ($CDCl_3$) 1.98 (s, 3H, NHCOCH_3), 2.05, 2.06, 2.14 (3s, 9H, OCOCH_3), 3.86 (s, 3H, OCH_3), 3.81−3.90 (m, 1H, H-5), 4.04−4.19 (td, 1H, H-2), 4.22 (d, 1H, 4.5 Hz, H-6), 5.08 (t, 1H, 10.1 Hz, H-4), 5.10 (d, 1H, 8.3 Hz, H-1), 5.43 (dd, 1H, H-3), 5.71 (d, 1H, N*H*COCH_3), 7.04 (s, 1H, aromatic proton), 7.47 (s, 1H, aromatic proton). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 20.7 (OCO*C*H$_3$), 23.4 (NHCO*C*H$_3$), 54.6 (C-2), 56.8 (O*C*H$_3$), 62.4 (C-6), 68.7 (C-3), 71.7 (C-4), 72.1 (C-5), 100.5 (C-1), 110.4 (CH*C*BrCOCH$_3$), 112.5 (CH*C*BrCOCH), 116.0 (CBr*C*HCOCH$_3$), 123.9 (CBr*C*HCO), 147.8 (CBr*C*OCH), 152.6 (CBr*C*OCH$_3$CH), 169.4 (NH*C*OCH$_3$), 170.6 (O*C*OCH$_3$).

Polycondensation of Sugar-Substituted 2,5-Dibromohydroquinones with *p*-Divinylbenzene. For poly[2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-methoxy-*p*-phenylenevinylene-*alt*-*p*-phenylenevinylene] [poly(**3**-*alt*-DVB)]. Triethylamine (0.37 mL, 2.6 mmol) was added to a solution of **3** (610 mg, 1 mmol), DVB (131 mg, 1 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), and tri-*o*-tolylphosphine (81 mg, 0.26 mol) in 6 mL of DMF. The reaction mixture was stirred at 105 °C under N_2 for 66 h and poured into 120 mL of methanol. The precipitate was collected by centrifugation and dried in a vacuum. The purified polymer was dried under reduced pressure to give constant weight (430 mg, yield 73%). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 1.79−2.16 (C*H*$_3$CO), 3.84−3.95 (C*H*$_3$O, H-5), 4.20−4.30 (H-2, H-6), 4.98 (H-4), 5.25 (H-1, H-3), 6.98−7.67 (aromatic protons and vinyl protons), 8.19 (N*H*COCH$_3$). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 20.7 (*C*H$_3$COO), 23.1 (*C*H$_3$CONH), 53.3 (C-2), 56.5 (*C*H$_3$O), 62.4 (C-6), 69.1 (C-3), 71.1 (C-4), 72.5 (C-5), 99.9 (C-1), 108.5, 113.6, 122.0, 127.3, 129.5, 132.5, 137.2, 149.0, 152.7 (aromatic carbons), 126.2, 126.6 (vinyl carbons), 169.8 (CH$_3$*C*ONH), 170.4 (CH$_3$*C*OO). IR (KBr disk, cm^{-1}): 2930 (ν_{C-H}), 1748 [$\nu_{C=O}$(ester)], 1668 ($\nu_{C=C}$), 1235 [ν_{C-O}(ester)].

Deacetylation of Acetylated Sugar-Substituted PPV. For poly-[2-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-5-methoxy-*p*-phenylenevinylene-*alt*-DVB] (PPV-GlcNAc). Hydrazine monohydrate (1.34 mL, 27.68 mmol) was added to a solution of poly(**3**-*alt*-DVB) (200 mg, 0.35 mmol) in 20 mL of THF cooled at 0 °C. The reaction mixture was stirred at room temperature for 6 h. As the reaction proceeded, orange precipitate appeared. The precipitate was collected by centrifugation and purified with methanol for 6 h. The residue was dried under reduced pressure to give a constant weight of 136 mg (yield 87%). ^{1}H NMR [200 MHz, DMSO-d_6/D_2O(1 drop), δ, ppm]: 1.79−2.16 (C*H*$_3$-CO), 3.03−3.84 (H-2,3,4,6), 3.84−3.95 (C*H*$_3$O, H-5), 4.80 (H-1), 5.25 (H-1, H-3), 6.98−7.67 (aromatic protons and vinyl protons), 8.19 (N*H*COCH$_3$).

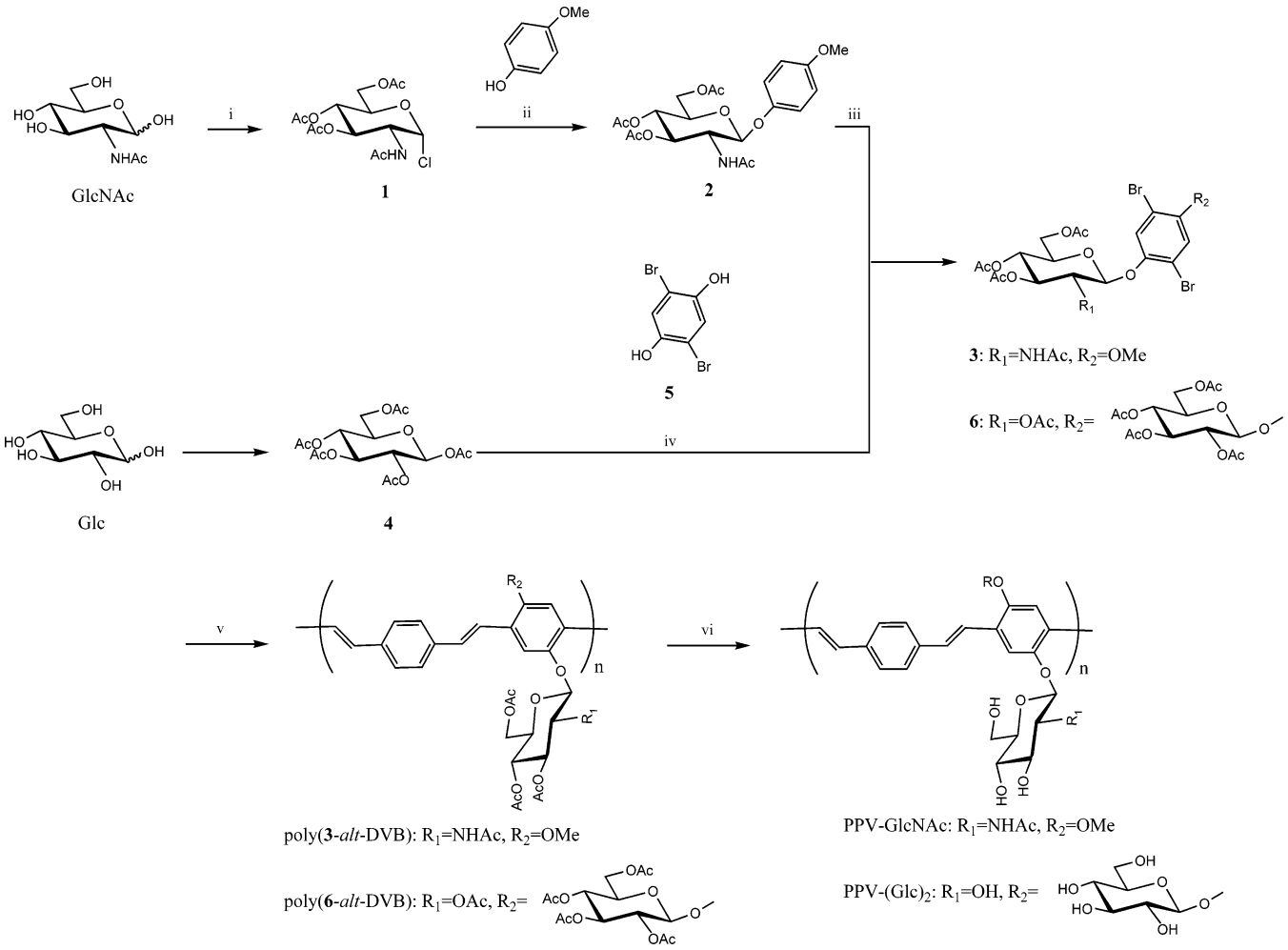
Results and Discussion

Synthesis of Sugar-Substituted Hydroquinones. According to Scheme 1, *O*-glycosylation of 4-methoxyphenol was established by the Koenigs−Knorr[7] reaction using GlcNAc(Ac)$_3$-β-D-Cl[8] (**1**) as the glycosyl donor. The structure of **2**[9] was confirmed using IR and ^{1}H NMR measurements. The NMR assignment was confirmed by ^{1}H−^{1}H COSY NMR measurements. The H-1 proton of **2** was observed at 5.15 ppm (8.2 Hz), indicating that β-selective glycosidation occurred at the anomeric carbon. Successively, dibromination of **2** was carried out using NBS in dichloromethane at 60 °C for 336 h to afford 2,5-dibromo-4-methoxyphenyl β-D-GlcNAc(Ac)$_3$ (**3**) (54% yield). In the ^{1}H NMR spectrum, two singlet signals were assigned to the aromatic proton (7.04 and 7.47 ppm), indicating that the targeted glycosylated monomer **3** had been prepared. Regarding synthesis for diglycosylated monomers **6**, dibromination was carried out before glycosidation because we confirmed that dibromination of diglycosydated hydroquinone required a long time under severe conditions. Therefore, the bromination of hydroquinone proceeded quickly in acetic acid solution at 27 °C according to Traser's reports;[10] the reaction was completed in 2 h. Glycosidation of 2,5-dibromohydroquinone with penta-*O*-acetyl-β-D-glucose in the presence of BF_3-etherate yielded hydroquinone having two glucose residues **6** in 34.5% yield (see Scheme 1).

Polycondensation of Sugar-Substituted 2,5-Dibromohydroquinones with *p*-Divinylbenzene. Reaction of **3** with DVB under standard Pd-catalyzed coupling conditions (in DMF, 105 °C) furnished a red-orange emissive solid in a good yield (73% yield) (Scheme 1). Poly(**3**-*alt*-DVB) was soluble in THF, DMSO, and hot DMF but insoluble in chloroform. The structure was confirmed using IR and ^{1}H NMR spectroscopy. Size exclusion chromatography (SEC) (eluent: DMF + 5% LiBr, polystyrene standards) indicated that M_n and M_w/M_n of the obtained polymer are respectively 6.0×10^3 and 3.4. The acetyl protecting groups of the PPV are completely removable under mild conditions (27 °C for 4.5 h) in a good yield (87%). In the IR and NMR spectra, the characteristic band for the ester C−O stretch and the signal ascribed to the methyl protons of acetoxy groups (C*H*$_3$COO) were not observed at all. The degree of deacetylation was evaluated by ^{1}H NMR as >99%. The M_n and M_w/M_n of the PPV having pendant GlcNAc are respectively 4.49×10^3 and 2.3[5]. The resultant solid material is only slightly soluble (est. 0.1 mg/mL) in water after heating at 60 °C.

Polycondensations of diglycosidated hydroquinone containing two glucose residues (**6**) were also carried out via a Heck coupling reaction and successive deacetylation to improve water solubility. The structure of glucose-substituted PPV (PPV-Glc$_2$) was confirmed using IR and ^{1}H NMR measurements (Supporting Information). SEC (eluent: DMF+5% LiBr, polystyrene

Scheme 1. Synthetic Strategy for Sugar-Substituted PPVs[a]



[a] (i) AcCl, room temperature, 24 h, 61% yield; (ii) *p*-methoxyphenol, TBAB, CH_2Cl_2, 1 N NaOH aq, room temperature, 30 min, 15% yield; (iii) NBS, 1,2-Dichloroethane, 60 °C, 336 h 50% yield; (iv) dichloromethane, 27 °C, 24 h, 35% yield; (v) *p*-divinylbenzene, $Pd(OAc)_2$, NEt_3, DMF, 105 °C; for poly(**3**-*alt*-DVB) 73% yield, for poly(**5**-*alt*-DVB) 83% yield; (vi) NH_2NH_2, MeOH, room temperature. For PPV-GlcNAc 87% yield, for PPV-Glc_2 69% yield.

standards) measurement indicated that respective values of M_n and M_w/M_n in the resultant polymers are 3.86×10^3 and 1.39.

Solubilities in Aqueous Media. Table 1 portrays results of solubility tests in aqueous media. Neither PPV-GlcNAc nor PPV-Glc_2 showed solubility in water or 5−100 mM HEPES buffer solution (r.t. to 60 °C, pH 7.6−9.0). However, they were soluble in water/DMF (9/1, v/v) as well as in DMF and DMSO at room temperature (r.t.). Therefore, we investigated the interaction with lectin in 10 mM HEPES buffer/DMF (8/2, v/v).

Interaction with Lectin (Con A). A recognition test of PPV-Glc_2 with *Concanavalin* A (Con A) (D-glucose-binding protein) was carried out in 10 mM HEPES buffer/DMF (8/2, v/v) at 27 °C for 12 h. After the test, UV−vis measurements were taken to detect interaction with the lectin monitoring λ_{max} change of the PPV backbone. Although we were unable to observe the color change of the aqueous solution, the λ_{max} change was confirmed in UV−vis spectra measurements. Figure 2 shows λ_{max} of PPV-Glc_2 in HEPES buffer/DMF (8/2, v/v), as observed at 430 nm. After addition of Con A for 12 h, the λ_{max} blue-shifted to 420 nm, indicating that interaction with lectin twisted the PPV backbone planarity. After 24 h, the test solution became turbid, indicating that glucose residues in PPV-Glc_2 surely interact with Con A.

In the emission spectrum, quenching of PPV-Glc_2 by Con A was observed in HEPES buffer/DMF (8/2, v/v) at 27 °C. The fluorescent intensity of PPV-Glc_2 decreased with increase of Con A concentration in the range of 2.0×10^{-8}−1.0×10^{-7}

Table 1. Solubility Data of Sugar-Substituted PPVs

conc., mg/mL	solvent	temp., °C	pH	solubility[a] PPV-GlcNAc	solubility[a] PPV-$(Glc)_2$
1.0	5 mM HEPES[b] buffer	r.t.	7.6	−	−
1.0	10 mM HEPES buffer	r.t.	7.5	−	−
1.0	100 mM HEPES buffer	r.t.	7.5	−	−
0.1	5 mM HEPES buffer	r.t.	7.6	−	−
0.1	10 mM HEPES buffer	r.t.	7.5	−	−
0.1	100 mM HEPES buffer	r.t.	7.5	−	−
0.1	100 mM HEPES buffer	40	7.5	−	−
0.1	100 mM HEPES buffer	60	7.5	+	−
0.1	100 mM HEPES buffer	r.t.	8.0	−	−
0.1	100 mM HEPES buffer	r.t.	9.0	−	−
0.01	5 mM HEPES buffer	r.t.	7.6	−	−
0.01	10 mM HEPES buffer/DMF = 9/1	r.t.	7.6	+	+
0.01	10 mM HEPES buffer /DMF = 8/2	r.t.	7.6	+	+
0.01	10 mM HEPES buffer/DMF = 6/4	r.t.	7.6	+	+
0.01	DMF	r.t.		+	+
0.01	DMSO	r.t.		+	+

[a] +, Soluble; -, Insoluble. [b] 2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethanesulfonic acid.

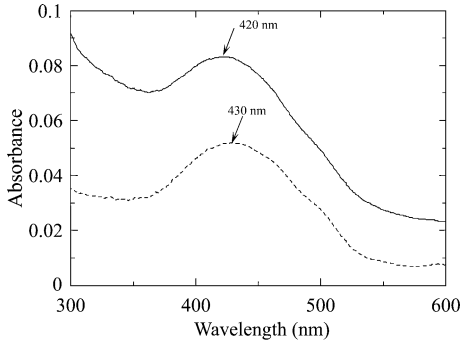


Figure 2. UV−vis spectra of glucose-substituted PPV (PPV-Glc_2) in the presence and absence of Con A [in HEPES/DMF (8/2, v/v), at 27 °C].

(Supporting Information). In the fluorescence spectrum of PPV-GlcNAc, similar quenching was observed on addition of WGA lectin, GlcNAc-binding protein (Supporting Information). These spectroscopic phenomena revealed that the obtained PPVs with pendant sugars (PPV-GlcNAc and PPV-Glc) are capable of detecting biological stimuli.

This study demonstrated the first synthesis of a well-defined poly(phenylenevinylene) having pendant sugar, in which the sugar is attached to the trunk PPV via β-*O*-glycoside linkage, and in which the inter-sugar distance is regulated because the conjugated polymer has an alternating sequence. Structural accuracy will be examined specifically for the polymer's application as a biosensor to detect biological stimuli in water. Optical properties in the presence of a virus or *E. Coli* will be discussed in a forthcoming full paper.

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Supporting Information Available. Experimental Procedure and ^{1}H NMR data of glucose-substituted hydroquinone and Glc-substituted PPVs [PPV−$(Glc)_2$] and fluorescence spectra of PPV-GlcNAc and PPV-Glc_2 in the presence of lectins. These materials are available free of charge via the Internet at http://pubs.acs.org.

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