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Water-soluble poly(*p*-phenylene) incorporating methoxyphenol units: Highly sensitive and selective chemodosimeters for hypochlorite

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ABSTRACT

A series of water-soluble poly(*p*-phenylene)s (PPPs), named N-PPPx ($x = 10$, 25 and 50), were directly synthesized by Suzuki coupling in aqueous solution. The structures of the polymers were characterized by ^{1}H NMR and elemental analysis. The polymers exhibit similar absorption and emission spectra with three absorption maxima at *ca.* 205, 290 and 350 nm, and emission maximum at 420 nm in phosphate buffer saline (PBS) solution. Upon addition of hypochlorite, N-PPPx shows a decrease of absorption band at *ca.* 350 nm and a fluorescent quenching. Compared to their model compound PMOPP, N-PPPx shows a significantly amplified fluorescent quenching. Moreover, the K_{sv} is decreased with the increasing content of methoxyphenol moieties in N-PPPx. In view of the sensitivity and selectivity, N-PPP10 and N-PPP25 are very promising polymeric fluorescent probes to hypochlorite under the aqueous condition.

1. Introduction

Water-soluble conjugated polymers (CPs) can combine the advantages of conventional polyelectrolytes and signal amplification of CPs, and thus offer unique potential in fluorescent probes [1–4]. Over the past several years, water-soluble CPs have been widely used in biosensors [5–10]. Recently, chemodosimeters have attracted considerable attention, however a few of chemodosimeters based on water-soluble conjugated polymers have been reported [11–15]. For example, Swager's group reported a poly(*p*-phenyleneethynylene) based chemodosimeter for fluoride ions by using fluoride triggered Si-O bond cleavage [11]; Wang's group reported a water-soluble cationic polyfluorene with boronate-protected fluorescein covalently linking to the polymer backbone for the detection of hydrogen peroxide and glucose in serum [14].

As a kind of reactive oxygen species (ROS), hypochlorous acid (HClO) plays a crucial role in our daily lives and host defense against invading pathogens [16,17]. In living organisms, hypochlorous acid is generated by the reaction of hydrogen peroxide with chloride ions under the catalysis of the heme enzyme myeloperoxidase (MPO), which is synthesized and secreted by activated phagocytes [18–21]. However, because of its high reactivity and non-specificity [22], excessive hypochlorous acid can lead to damage of host tissue that is implicated in a wide range of human diseases, such as kidney disease [23,24], atherosclerosis [25–28], and arthritis [29–31]. Unfortunately the detailed pathogenic mechanism is not fully understood, because of the lack of a feasible method for detecting hypochlorous acid.

Recently, a few probes for hypochlorous acid (HClO) have been reported based on its strong oxidation property [32–39]. For example, Nagano's group [32] and Libby's group [33] reported rhodamine- and fluorescein-based fluorescent probes for HClO, respectively, but the fluorescent probes involved in complicated synthesis; Ma's group also developed two fluorescent probes for HClO [34,35], which works in organic co-solvent system. Moreover, these probes are based on small molecule fluorophores, the sensitivity is still needed to be improved. Considering the signal amplification of conjugated polymers, it will be of significant interest to design a fluorescent polymeric probe for HClO.

Very recently, we have reported a dual-signaling chemodosimeter for HClO based on water-soluble *p*-methoxyphenol derivative probe PMOPP [40]. Based on this research, we designed and synthesized a series of water-soluble CPs by introducing *p*-methoxyphenol moieties into the poly(*p*-phenylene) backbone. We anticipated that the oxidation of *p*-methoxyphenol moieties on the copolymer backbone by HClO would induce an intramolecular charge transfer (ICT), and result in the changes of absorption and fluorescence quenching of the copolymer.

2. Experimental part

2.1. Materials

All chemicals were purchased from commercial sources and were used without further purification unless otherwise noted.

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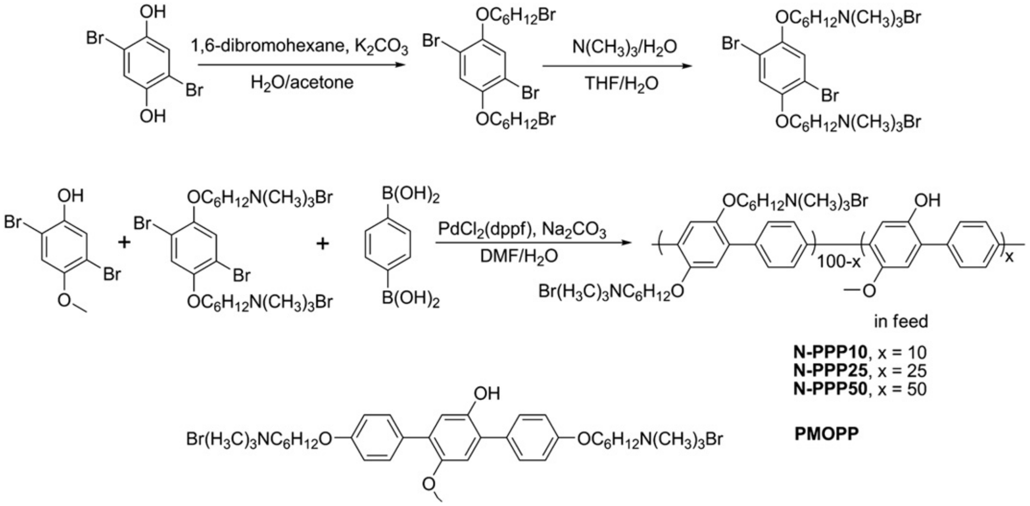

Scheme 1. Synthetic route of the polymers and structure of model compound PMOPP.

2,5-Dibromo-4-methoxyphenol was synthesized according to literature procedures [41]. Dimethylformamide (DMF) was purified by distillation from calcium hydride.

2.2. General methods

^{1}H NMR and ^{13}C NMR spectra were obtained in the indicated solvent with tertramethylsilane as an internal standard on a MECUYRVX300 spectrometer. Mass spectra were measured on a ZAB 3F-HF mass spectrophotometer. Liquid chromatography mass (LC-Mass) spectra were measured on a Waters ZQ-Mass electrospray ionizer (ESI). Elemental analyses of carbon, hydrogen, and nitrogen were performed on a Carlorerba-1106 microanalyzer. Thermogravimetric analysis (TGA) was performed under nitrogen with a NETZSCH STA 449C instrument in the temperature range from 25 to 800 °C at the heating rate of 10 °C min^{-1}. UV–vis absorption measurements were performed on a Shimadzu 2550 spectrophotometer. Fluorescence measurements were performed on a Hitachi F-4500 fluorescence spectrophotometer. All the tests of optical response for ClO$^-$ were carried out after a few seconds of the addition of hypochlorite solution. Testing solutions were prepared by adding 2 or 20 μL of the probe stock solution (5 mM) to 2 mL PBS buffer in a test tube and then adding an appropriate aliquot of each ROS stock solution. The absorption and fluorescence sensing of ROS was run immediately after the ROS were added.

2.3. Synthesis of 1,4-dibromo-2,5-bis(6-bromohexyloxy)benzene

A mixture of 2,5-dibromobenzene-1,4-diol (5.36 g, 20 mmol), 1,6-dibromohexane (12.4 mL, 80 mmol), potassium carbonate (10.00 g, 72 mmol), acetone (10 mL), and water (2.5 mL) was refluxed for 5 h, after which an additional potassium carbonate was added and stirring and reflux continued for 3 h. After filtration, the residue was washed with chloroform and the filtrate was combined. After evaporation of the solvent, excessive 1,6-dibromohexane was removed under reduce pressure, and then the residue was recrystallized from ethanol to afford 1,4-dibromo-2,5-bis(6-bromohexyloxy)benzene as a white solid. Yield: 7.38 g, 62%. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): δ 7.08 (s, 2H), 3.96 (t, $J = 6.3$ Hz, 4H), 3.43 (t, $J = 6.9$ Hz, 4H), 1.90 (m, 4H), 1.80 (m, 4H), 1.53 (m, 8H). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): δ 150.3, 118.7, 111.4, 70.2, 34.1, 32.9, 29.2, 28.1, 25.4. EI-MS: m/z 590 (M$^+$). Anal. Calcd for $C_{18}H_{26}Br_4O_2$: C, 36.40; H, 4.41. Found: C, 36.09; H, 4.03.

2.4. Synthesis of 6,6′-(2,5-dibromo-1,4-phenylene)bis(oxy)bis(N,N,N-trimethylhexan-1-aminium) bromide

To a solution of 1,4-dibromo-2,5-bis(6-bromohexyloxy)benzene (5.94 g, 10 mmol) in tetrahydrofuran (THF) (50 mL) was added trimethylamine aqueous solution (20 mL, 200 mmol). After stirring for 0.5 h, H_2O (10 mL) was added to the mixture. Then additional trimethylamine aqueous (20 mL, 200 mmol) solution was added and the mixture was stirred for 48 h. The solvent was removed by rotary evaporation, and the crude product was recrystallized from ethanol to afford the product as a white solid. Yield: 6.62 g, 93%. ^{1}H NMR (300 MHz, D$_2$O, ppm): δ 7.26 (s, 2H), 3.96 (t, $J = 6.3$ Hz, 4H), 3.16 (t, $J = 8.4$ Hz, 4H), 2.94 (s, 18H), 1.66 (m, 8H), 1.41 (m, 4H), 1.26 (m, 4H). ^{13}C NMR (75 MHz, D$_2$O, ppm): δ 151.3, 118.9, 112.2, 70.3, 66.6, 53.8, 34.5, 33.0, 29.3, 28.4, 25.5. ESI-MS: m/z 275 ((M^{2+}-2Br)/2). Anal. Calcd for $C_{24}H_{44}Br_4N_2O_2$: C, 40.47; H, 6.23; N, 3.93. Found: C, 40.43; H, 5.74; N, 3.62.

2.5. Synthesis of N-PPP10, N-PPP25 and N-PPP50

General procedure for the copolymerization by Suzuki cross-coupling reaction: To a mixture of 6,6′-(2,5-dibromo-1,4-phenylene)bis(oxy)bis(N,N,N-trimethylhexan-1-aminium)

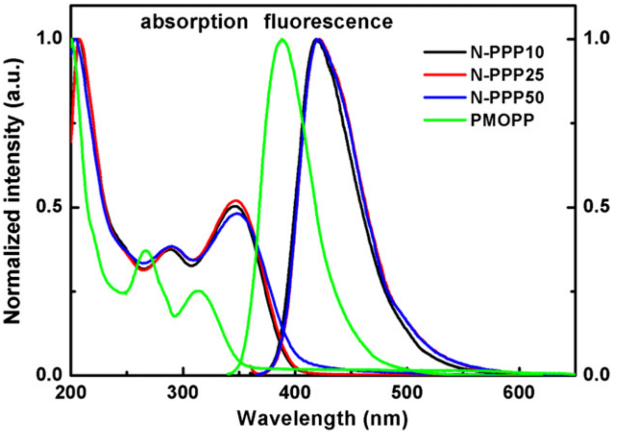

Fig. 1. Normalized UV–vis absorption and fluorescence spectra of the polymers and the model compound PMOPP in PBS solution. Excitation wavelength: N-PPPx, 350 nm; PMOPP, 320 nm.