Chirality-Sensing Binaphthocrown Ether–Polythiophene Conjugate

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Abstract: An enantiomeric binaphthyl unit was tethered to adjacent thiophenes with oxyethylene linkers to give a chiral polythiophene with binaphthocrown ether cavities. Upon inclusion of a chiral cationic guest in the cavity of the chiral crown ether–polythiophene conjugate, the bithiophene unit was twisted to shorten the effective conjugation length of polythiophene backbone, enabling us to sense the guest binding by reading out the amplified optical signal gains arising from

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the backbone structure change. This strategy allowed us to discriminate the guest chirality without using chiroptical signals or a circular dichroism spectrometer to achieve the highest enantioselectivity of 7.3 for valine methyl ester with a 40-fold enhanced sensitivity compared with the corresponding monomeric sensor.

Introduction

A chemical sensor serves as a versatile tool for detecting a range of pollutants in the environment,^[1] explosives that threaten homeland security, and hazardous materials for human health,^[2] and hence, is one of the most vital and challenging topics in current chemistry. The supramolecular approaches to such sensory systems using polymers are of particular significance not only for fundamental science but also for a number of practical applications,^[3] since a conjugated polymer is capable of amplifying the binding events, for example, the efficient quenching of fluorescent polymers, to greatly enhance the signal gain upon interaction with target analytes.^[4]

Chirality-sensing supramolecular systems have recently attracted much attention with increasing demand for enantiomerically pure compounds in various areas of science and technology.^[5] We have reported the synthesis, separation, and chiral recognition behavior of novel inherently chiral molecular clips as supramolecular chirality sensors, which bind the HCl salt of tryptophan methyl ester with moderate enantioselectivity (K_p/K_L) of up to 3.5.^[6]

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In the present study, to develop a chirality-sensing supramolecular system incorporating conjugated polymer, we chose polythiophene as the backbone, a crown ether derivative of which was demonstrated to show remarkably high sensitivities and selectivities toward achiral cations by Swager et al.^[7] As a chirality-sensing moiety, enantiopure binaphthyl was attached to a bithiophene monomer through two oxyethylene linkers, which was then polymerized to give a novel binaphthocrown ether fused polythiophene (BPT), as shown in Figure 1. Although a variety of crown ether-appended polymers with inherent or guest-induced optical activity are known,^[5,8] the chiral signal gain obtained in the present polymer is based not on the conventional manipulation of binaphthyl chirality upon complexation of a chiral



Figure 1. Concept and mechanism of enantioselective signal transfer and propagation in optically active binaphthylcrown ether–bithiophene conjugate BPT upon inclusion of a chiral guest.

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guest but on the chirality propagation to and amplification in the conjugated polymer chain.

The basic idea for enhancing the chirality sensing ability adopted in BPT is illustrated in Figure 1. The polythiophene moiety, which is originally planar, is expected to be twisted upon inclusion of a chiral guest by the oxyethylene moieties, with accompanying hypsochromic shift and induced chiroptical signals. The present strategy for sensing the guest chirality is different from those commonly employed in conventional chiroptical sensors^[5] in which the direct chiroptical signal changes of a chiral chromophore are intended to be read out, although sophisticated imprinting polymers and cyclodextrin-appended polymers have also been reported by Shimizu and Greene^[9] and Yashima et al.,^[10] respectively, as a tool for visual detection. In contrast, the backbone of the present polymer sensor is inherently achiral, but its guestchirality-dependent conformational changes upon interaction with a chiral guest can be analyzed by the change in absorbance without using a circular dichroism (CD) spectrometer.

Results and Discussion

BPT was synthesized in 22 % yield based on the monomer units through polymerization with $[Fe(acac)_3]$ (acac=acetylacetonate) catalyst of the corresponding monomer, which was prepared from 3-bromothiophene in 6 steps, as shown in Scheme 1.^[11] The structure of BPT was fully characterized by comparing the ¹H and ¹³C NMR spectra with those of the monomer, as shown in Figure 2. The numbers of aromatic and of aliphatic protons in the monomer are 16 and 24, respectively. As the number of oxyethylene protons does not



Scheme 1. Synthesis of a novel binaphthyl-appended polythiophene (BPT).

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grated area of the aliphatic protons was used as a reference to determine the number of aromatic protons in BPT as 14. This indicates that the polymerization occurred efficiently and selectively at the highly reactive α position of the bithiophene monomer unit. Furthermore, ¹³C NMR spectra gave more detailed structural information. For simplicity, only the bithiophene carbon atoms are labeled in Figure 2. Importantly, the C_a and C_m signals appeared at different positions in the monomer and were merged to give a single signal of C_{a'}+C_{m'} in BPT, indicating that these carbon atoms become magnetically equivalent in agreement with the polymer structure shown (Figure 2, bottom). This clearly demonstrates that polymerization occurred at the α position of the bithiophene retaining the remaining monomer structure.

change during the polymerization of the monomer, the inte-

The number average molecular weight (M_n) and the polydispersity index (PDI) of BPT were determined as 3400 and 1.6, respectively, by gel permeation chromatography (GPC) measurements relative to the polystyrene standard. It should be noted, however, that a higher-molecular-weight component was detected above the upper limit of the GPC column used, and therefore, the real M_n may be higher, as was the case with the achiral crown ether-appended polythiophene.^[7a] We tentatively assigned the higher-molecularweight component to self-assembled aggregates due to strong interchain interactions.

The chiroptical properties of BPT and the corresponding monomer as a reference were examined in acetonitrile and dichloromethane by UV/Vis and CD spectroscopies. Since BPT was not soluble in methanol, acetonitrile, or methylcyclohexane, the UV/Vis and CD spectra of the monomer in acetonitrile were recorded for comparison purposes to show the typical exciton couplet at the ¹B_b band, as shown in Figure 3a. As can be seen from Figure 3b, the major ${}^{1}B_{b}$ band of the binaphthyl chromophore in the monomer and BPT exhibited an intense negative exciton couplet in the CD spectrum, while the UV/Vis spectrum of BPT showed a π - π^* transition at 400–680 nm, which is characteristic of polythiophene. However, the CD spectrum in this region showed an extremely weak positive induced Cotton effect, suggesting that the polymer backbone is not appreciably twisted, probably due to the flexible oxyethylene linkers connecting the bithiophene and binaphthyl moieties in BPT. A significant difference was observed in exciton coupling amplitude of the major ¹B_b band^[12] between the monomer and BPT, indicating altered dihedral angles of the binaphthyl moiety. Since the molar circular dichroism ($\Delta \varepsilon$) at 240 nm $(-133 \,\mathrm{M}^{-1} \mathrm{cm}^{-1})$ of BPT is smaller than that $(-200 \,\mathrm{M}^{-1} \mathrm{cm}^{-1})$ of the monomer, the dihedral angle is deduced to be wider for BPT. This is probably due to the easier rotation around the arylic bond for polythiophene than for bithiophene, implying a more flexible planar structure of the former. As the Cotton effects on the ¹L_a and ¹L_b bands are usually independent of the dihedral angle, the molar ellipticities of BPT for these bands were comparable to those of the monomer and hence the exciton coupling at the ¹B_b band of the bi-



Figure 2. a) 1 H NMR spectra in CD₂Cl₂ and b) 13 C NMR spectra in CDCl₃ at room temperature. Top: The structure and NMR spectra of the monomer. Bottom: The structure and NMR spectra of BPT.

naphthyl pendant is crucial in deducing the conformation of this polymer.

To assess the chiral discrimination ability, we investigated the binding behavior of BPT with methyl esters of enantiopure alanine (Ala-OMe+HCl), valine (Val-OMe+HCl), leucine (Leu-OMe·HCl), proline (Pro-OMe·HCl), and phenylalanine (Phe-OMe·HCl) as cationic chiral guests in dichloromethane. For comparison, we first examined the complexation of the monomer with L- and D-Ala-OMe+HCl. Upon addition of L- or D-Ala-OMe•HCl to a 0.13 mM solution of the monomer in dichloromethane at 25 °C, the anisotropy factor $(g = \Delta \varepsilon / \varepsilon)$ at 243 nm decreased with an accompanying isoanisotropic point at 272 nm (see Figure 4), indicating that the binaphthyl moiety in the monomer becomes more planar upon inclusion of the guest.^[13] Nonlinear least-squares fit of the titration data (Figure 4), assuming 1:1 stoichiometry, gave the association constants for D- and L-Ala-OMe+HCl: $K_{\rm p} = (2320 \pm 480) \,\mathrm{m}^{-1}, K_{\rm p} = (1090 \pm 70 \,\mathrm{m})^{-1}$. Thus, the enantioselectivity $(K_{\rm p}/K_{\rm L})$ and differential free energy change $(\Delta\Delta G_{p-1}^{\circ})$ were calculated to be 2.1 and -1.9 kJ mol^{-1} , respectively; see Table 1. These results indicate that the monomer functions as a good chirality-sensing host for the cationic guest in dichloromethane.

As shown in Figure 5a, gradual addition of D-Ala-OMe-HCl (0–78.7 μ M) to a solution of BPT (19 μ M in monomer units) in dichloromethane caused a small but steady hyperchromic effect at shorter wavelengths, but a hypochromic effect at longer wavelengths with accompanying isosbestic point at 395 nm in the UV/Vis spectra, with accompanying hypsochromic shift of the CD extremum at 240 nm (Figure 5, inset). These hypsochromic shifts indicate that the polymer backbone is twisted upon inclusion of the chiral guest as illustrated in Figure 1.^[14] We can thus determine from the UV/Vis signal gain upon complexation of a chiral

Table 1. Association constants (K_a) , enantioselectivities (K_v/K_i) , free energy changes $(-\Delta G^\circ)$, and differential free energy changes $(\Delta \Delta G^\circ_{v-t})$ for 1:1 complexation of HCl salts of amino acid methyl esters and acetylcholine chloride (ACh-Cl) with BPT and the corresponding monomer unit in dichloromethane at 25°C.

Host	Guest ^[a]	Enantio- mer	$K_{ m a} \ [{ m M}^{-1}]^{[{ m b}]}$	$K_{ m d}/K_{ m L}$	$-\Delta G^{\circ}$ [kJ mol ⁻¹]	$\Delta\Delta G^{\circ}_{\scriptscriptstyle \mathrm{D-L}}$ [kJ mol ⁻¹]
monomer ^[c]	Ala	L	1090	2.1	17.3	-1.9
		D	2320 ^[d]		19.2	
BPT ^[e]	Ala	L	38 500	2.4	26.2	-2.2
		D	93 500		28.4	
	Val	L	21500	7.3	24.7	-5.0
		D	158000		29.7	
	Leu	L	21800	20	24.8	-3.3
		D	83900	3.0	28.1	
	Pro	L	33800	0.8	25.8	0.4
		D	28400		25.4	
	Phe	L	11400	1.3	23.1	-0.7
		D	15000		23.8	
	ACh•Cl	[f]	26700	[f]	25.3	[f]

[a] All amino acids used were HCl salts of the methyl esters. [b] Error in K_a was <8.5%, unless noted otherwise. [c] 0.13 mm. [d] The error in K_a was 21%. [e] 19–23 μ M. [f] Not applicable.

guest with the present polymer sensor BPT, and a nonlinear least-squares fit of the UV/Vis titration data (Figure 5b), assuming 1:1 stoichiometry, the association constant for D-Ala-OMe-HCl ($K_{\rm D} = (93500 \pm 5400) \,\mathrm{M^{-1}}$), which is 40-fold higher than that for the monomeric sensor. Similar treatments of the UV/Vis titration data gave the association constants listed in Table 1.^[15]

It is interesting to compare the enantioselectivities and sensitivities obtained for Ala-OMe upon complexation with the monomer and BPT sensors. Employing the same sensing unit, both sensors showed comparable enantioselectivities of 2.1 and 2.4. However, the actual quantity of analyte needed for appreciable detection is two orders of magnitude smaller

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Figure 3. a) UV/Vis and CD spectra of the monomer (0.0398 mM), measured in a 2 mm cell, in acetonitrile at 25 °C. b) UV/Vis and CD spectra of BPT (57.9 μ M in monomer unit: solid line), measured in a 2 mm cell, and the monomer (23.4 μ M: dashed line), measured in a 1 cm cell, in dichloromethane at 25 °C; the insets show UV/Vis and CD spectra of BPT (0.252 mM in monomer unit) in dichloromethane at 25 °C, measured in a 1 cm cell.

for BPT than for the monomer. Intriguingly, only Pro-OMe-HCl exhibited inverted enantioselectivity to favor the L form, for which the cyclic secondary amine structure of Pro is likely to be responsible.^[16] These results indicate that BPT functions as a high-sensitivity, chirality-sensing polymer for amino acid derivatives, in particular, for Val-OMe-HCl, which showed the highest $K_{\rm p}/K_{\rm L}$ of 7.3 or $\Delta\Delta G_{\rm D-L}^{\circ}$ of -5.0 kJ mol⁻¹ among the amino acid guests examined



Figure 4. Top: Anisotropy (g) factor profiles of a solution of the monomer (0.13 mM) in dichloromethane upon gradual addition of a) L-Ala-OMe·HCl (0-2.24 mM) and b) D-Ala-OMe·HCl (0–5.55 mM) at 25 °C, measured in a 2 mm cell. Bottom: Results of nonlinear least-squares fitting analyses, assuming 1:1 stoichiometry, to determine the association constants at 25 °C: a) $K_{\rm L} = (1090 \pm 70) \,{\rm M}^{-1}$ and b) $K_{\rm D} = (2320 \pm 480) \,{\rm M}^{-1}$.

(Table 1). It is noteworthy that BPT exhibited a high affinity of $K_a = 26700 \text{ m}^{-1}$, or $-\Delta G^\circ = 25.3 \text{ kJ mol}^{-1}$, for acethylcholine chloride (ACh-Cl), which plays an important role in neurotransmitter.



Figure 5. a) UV/Vis spectral changes of a solution of BPT (19 μ M in monomer units) in dichloromethane upon gradual addition of D-Ala-OMe+HCl (0-78.7 μ M; from gray to black) at 25 °C, measured in a 1 cm cell, while the inset shows the CD spectral changes. b) Nonlinear least-squares fit, assuming 1:1 stoichiometry, to determine the association constant.

Conclusion

We developed a novel chirality-sensing polythiophene that affords a chiral signal gain based on the conformational change of the polymer backbone upon inclusion of chiral analyte. It is noteworthy that the present polymer sensor has a microgram sensitivity and good enantioselectivities of up to 7.3. We have also demonstrated that the present strategy to analyze the chiral host–guest interactions through the UV/Vis absorption changes, rather than the CD spectral changes, works well and may be expanded to other chiralitysensing systems.

Experimental Section

Instruments: Melting point was measured with a Büchi B-545 apparatus. FAB and EIMS spectra were obtained by using a JEOL JMS-DX303 instrument. ¹H NMR spectra (400 MHz), ¹³C NMR spectra (100 MHz), and 2D-COSY, HSQC, and HMBC spectra (400 MHz) were recorded in CD_2Cl_2 or $CDCl_3$ on a JEOL EX400 spectrometer. UV/Vis and CD spectra were measured in a quartz cell (with light path of 2 or 10 mm) by using JASCO V-560 and J-720WI spectrometers equipped with an ETC-505T temperature controller. GPC purification of the monomer was run on a JAIGEL column eluted by chloroform at a flow rate of 3.5 mLmin^{-1} under isocratic conditions, by using a JASCO LC-908 instrument fitted with a UV detector (254 nm). Molecular weights of the polymer were determined relative to the polystyrene standards by using ana-

lytical GPC with a Shodex K-803 L column at 40 °C eluted by chloroform at a flow rate of 1.0 mLmin^{-1} under isocratic conditions.

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