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COMMUNICATION

Amplification of enantioselectivity and sensitivity based on non-linear response of molecular wire bearing pseudo-18-crown-6 to chiral amines†‡

Keiji Hirose,* Shintaro Miura, Yui Senda and Yoshito Tobe*

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Exploiting a non-linear response for chiral discrimination, an intelligent system capable of chirality amplification was designed and constructed as poly(phenyleneethynylene) having chiral pseudo-18-crown-6. Both sensitivity and selectivity were amplified from those limited by the law of mass action.

Because of the importance of chirality in pharmaceutical and biological chemistry, the development of methodologies for measurement of enantiomeric purity is an important issue. Despite the efficiencies of modern chiral chromatographic techniques,[1] optical spectroscopies including NMR spectroscopy,[2] mass spectrometry,[3] UV-vis (in solution,[4] liquid crystals,[5] gels,[6] and suspensions[7]), or fluorescence[8] and IR spectrometry[9] are among the frequently used alternatives due to easy performance and accessibility. Although significant development of chirality indicators has been achieved, the creation of highly enantioselective as well as highly sensitive chirality recognition systems remains still difficult and is one of the most challenging and important goals of molecular recognition.[8c] The signals of chiral chromogenic indicators and fluorogenic indicators with a static or dynamic quenching mechanism are proportional to the amount of the diastereomeric host–guest complexes according to the law of mass action, providing a limitation in apparent enantioselectivity.[10] In order to surmount this limitation, intelligent systems capable of chirality amplification based on non-linear response[7] need to be developed.[11] Here we report highly enantioselective chirality recognition, which exceeds the above limitation, based on fluorescence quenching phenomena exhibiting non-linear intensity changes.

We designed a molecular wire type chirality indicator (*S*,*S*)-**1** composed of a poly(phenyleneethynylene) (PPE) chain and a chiral pseudo-18-crown-6 ether connected by a triple bond which permits effective transfer of binding information to the conjugated polymer chain.[12] PPEs are chemically stable, and can be made either water- or organo-soluble by simple chemical modification. In general, they are strongly fluorescent with emission maxima ranging from 420 to 600 nm.[13] Such conjugated polymers are attractive as active transducers for chirality indicators,[14] though the amplification mechanisms of molecular wire type chirality indicators are diverse and not always obvious. The chiral pseudo-18-crown-6 ethers were selected as recognition sites due to their high affinity for chiral primary and secondary amines as well as ammonium salts.[15] We envisioned that a PPE such as (*S*,*S*)-**1** incorporating the chiral pseudo-18-crown-6 ether would exhibit not only enough enantioselective complexation ability but also show non-linear response of fluorescent intensities toward complexations with diastereomeric chiral amine substrates. Chemosensors (*S*,*S*)-**2** and (*S*,*S*)-**3** bearing single recognition sites were also synthesized as reference compounds (Fig. 1).

Syntheses of chirality indicators (*S*,*S*)-**1**, (*S*,*S*)-**2** and (*S*,*S*)-**3** were carried out as shown in Scheme 1. Crown ether (*S*,*S*)-**5** was obtained through selective demethylation of the known chiral pseudo-18-crown-6 (*S*,*S*)-**4**[16] in 71% yield. Sonogashira coupling of (*S*,*S*)-**5** with (trimethylsilyl)acetylene followed by deprotection gave (*S*,*S*)-**6** in 85% (2 steps), which was coupled with bromide **7** to give (*S*,*S*)-**8** in 81% yield. Selective deprotection of the TMS group of (*S*,*S*)-**8** with K_2CO_3 in MeOH followed by coupling with **10** and subsequent deprotection of TIPS gave monomer **11** in 43% (3 steps). Polymerization reaction of monomer **11** catalyzed by $Pd(PPh_3)_4$ in the presence of CuI and $(i\text{-Pr})_2NH$ in toluene afforded (*S*,*S*)-**1** in 91% yield. The detail of the syntheses of (*S*,*S*)-**2** and (*S*,*S*)-**3** are described in ESI.†

(*S*,*S*)-**1** has a polydispersity (M_w/M_n = 1.9) with a molecular weight of M_n = 22 700 as determined by SEC. The UV-vis spectrum of (*S*,*S*)-**1** was measured in CH_2Cl_2 together with those of (*S*,*S*)-**2**, and (*S*,*S*)-**3** (Fig. S3-1, ESI†). Extension of the conjugated π-system of (*S*,*S*)-**2** to (*S*,*S*)-**1** induced a bathochromic shift of the absorption assigned to the phenol moiety from 350 to 319 nm. The emission spectra of (*S*,*S*)-**1**, (*S*,*S*)-**2** and (*S*,*S*)-**3**

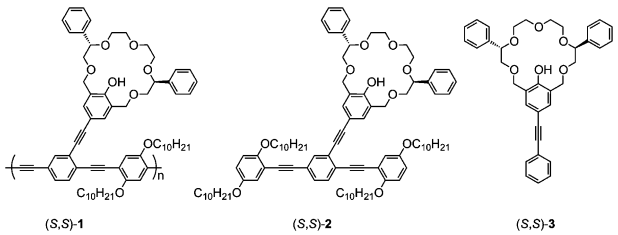

Fig. 1 Structures of polymer and monomer-type chiral chemosensors (*S*,*S*)-**1**–**3**.

Division of Frontier Materials Science, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan. E-mail: hirose@chem.es.osaka-u.ac.jp, tobe@chem.es.osaka-u.ac.jp; Fax: +81-6-6850-6229; Tel: +81-6-6850-6228

† Electronic supplementary information (ESI) available: Details of polymer and model syntheses, determination of binding constants and Stern–Volmer constants. See DOI: 10.1039/c2cc30417a

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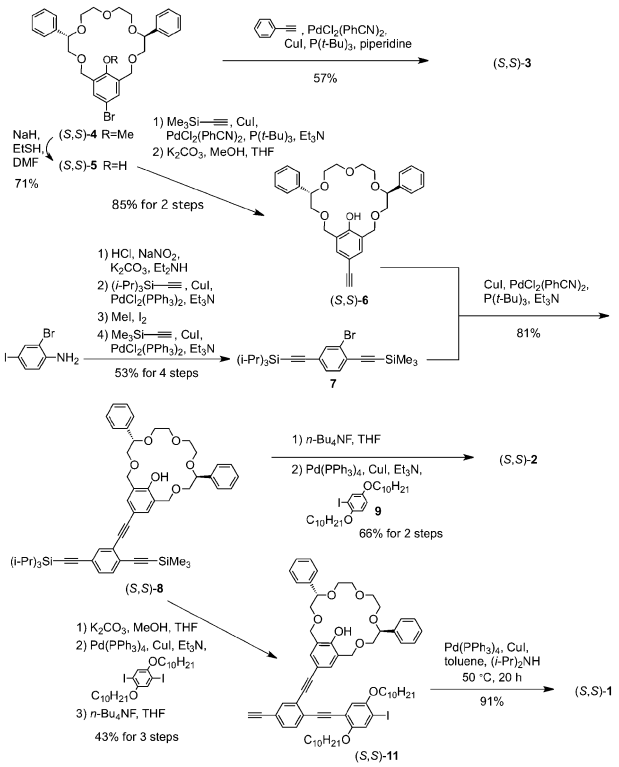

Scheme 1 Synthesis of chiral sensors (*S*,*S*)-**1**–**3**.

measured in CH_2Cl_2 exhibit maxima at 463 nm, 432 nm and 342 nm, respectively (Fig. S3-2, ESI†). The shape of the fluorescence emission band of molecular wire (*S*,*S*)-**1** is sharp, which is a characteristic feature of molecular wires.

The binding constants of monomer-type chemosensors (*S*,*S*)-**3** and (*S*,*S*)-**2** with ethanolamine derivatives, 2-amino-1-propanol (2APO), 1-amino-2-propanol (1APO), and valinol (VLO) were determined by titration experiments conducted using ^{1}H NMR and UV-vis spectroscopy.[17] Stern–Volmer constants were also determined by fluorescent titration of (*S*,*S*)-**2** and (*S*,*S*)-**1** (Table 1). The binding constants of (*S*,*S*)-**3** with 2APO, 1APO, and VLO were found to range from 3.4 to 5.5 × 10 M^{-1} and the enantioselectivities ($K_{(R)}/K_{(S)}$) were high (4.8, 2.2, 3.7, respectively). All of the binding constants of (*S*,*S*)-**2** for the guests were in the same order of magnitude but appreciably larger than the corresponding binding constants of (*S*,*S*)-**3**, because of small substituent effects of conjugate systems of (*S*,*S*)-**2** and (*S*,*S*)-**3** on binding properties of phenolic crown ethers.[19] The enantioselectivities ($K_{(R)}/K_{(S)}$) of (*S*,*S*)-**2** for the guests were moderate (3.6, 1.3, 3.4, respectively).

The fluorescence quenching behaviors of (*S*,*S*)-**2** and (*S*,*S*)-**1** upon formation of host–guest complexes with the primary amines were also examined. In Fig. 2, the vertical axis of the graph (I_0/I) represents a ratio of the fluorescence intensities, and the horizontal axis corresponds to the concentration of an amine at an equilibrium. The obtained plots of (*S*,*S*)-**2** with (*R*)-2APO and (*S*)-2APO were approximated by straight lines according to the Stern–Volmer equation.[20] The obtained quenching constants from the slope for (*S*,*S*)-**2** were $K_{SV(R)}$ = 1.4 × 10^2 M^{-1} and $K_{SV(S)}$ = 3.7 × 10 M^{-1}, respectively, which were in good agreement with the corresponding binding constants obtained by UV-vis titration ($K_{(R)}$ = 1.1 × 10^2 M^{-1} and $K_{(S)}$ = 3.0 × 10 M^{-1}, respectively (Table 1)). Therefore, it is deduced that quenching of the monomer model (*S*,*S*)-**2** occurs with a static quenching mechanism. Thus, the enantioselectivity did not change by changing the detection method from UV-vis to fluorescence spectroscopy.

Next, the fluorescence quenching behavior of the molecular wire (*S*,*S*)-**1** (2.0 × 10^{-6} M)[21] upon complexation with the same primary amines was examined. As shown in Table 1, the quenching constants of (*S*,*S*)-**1** are about 5 to 10 times greater than those of (*S*,*S*)-**2**. Therefore, sensitivity of the molecular wire (*S*,*S*)-**1** was significantly improved from that of the monomer model (*S*,*S*)-**2**. For example, at 6.7 × 10^{-4} M of 2APO, the quenching degree (I_0/I) of monomer (*S*,*S*)-**2** is 1.064 for (*R*)-2APO and 1.018 for (*S*)-2APO. The complexation ratios under these conditions are 6.1% ((*R*)-2APO) and 1.8% ((*S*)-2APO). The enantioselectivity ($K_{SV(R)app}/K_{SV(S)app}$) was 3.6. On the other hand, (I_o/I) of the polymer (*S*,*S*)-**1** was significantly amplified (2.5 for (*R*)-2APO and 1.2 for (*S*)-2APO). The apparent K_{SV} at the guest concentration of 6.9 × 10^{-4} M were 2.3 × 10^3 M^{-1} and 3.0 × 10^2 M^{-1}, respectively. The enantioselectivity was improved to be 7.8. Photographs of an effective fluorescent quenching in complexation of (*S*,*S*)-**1** with (*R*)-2APO is shown in Fig. S5 (ESI†). At a lower concentration (1.3 × 10^{-4} M) of the guest, the apparent K_{SV} ($K_{SV\,app}$) were 1.2 × 10^3 M^{-1} for (*R*)-2APO and 3.5 × 10 M^{-1} for (*S*)-2APO and the enantioselectivity reached 35.

Similarly, $K_{SV\,app}$ of (*S*,*S*)-**1** for (*R*)- and (*S*)-1APO (1.4 × 10^3 M^{-3} and 1.2 × 10^3 M^{-1}, respectively) increased from those of (*S*,*S*)-**2** (7.9 × 10 M^{-1} and 6.2 × 10 M^{-1}, respectively). However, the enantioselectivity ($K_{SV(R)app}/K_{SV(S)app}$) was not improved (1.2). This is due to the fact that the sensitivity for

Table 1 Binding constants (*K*), Stern–Volmer constants (K_{SV}), and the enantioselectivities of (*S*,*S*)-**1**, (*S*,*S*)-**2** and (*S*,*S*)-**3** with 2-amino-1-propanol, 1-amino-2-propanol, and valinol at 30 °C

	2-Amino-1-propanol (2APO)			1-Amino-2-propanol (1APO)			Valinol (VLO)		
Host	$K_{(R)}$	$K_{(S)}$	$K_{(R)}/K_{(S)}$	$K_{(R)}$	$K_{(S)}$	$K_{(R)}/K_{(S)}$	$K_{(R)}$	$K_{(S)}$	$K_{(R)}/K_{(S)}$
(*S*,*S*)-**3**	(5.5 ± 0.3)[a] × 10	(1.1 ± 0.1)[a] × 10	4.8	(3.0 ± 0.2)[a] × 10	(1.4 ± 0.1)[a] × 10	2.2	(1.2 ± 0.1)[a] × 10	3.4 ± 0.1[a]	3.7
(*S*,*S*)-**2**	(1.1 ± 0.1)[b] × 10^2	(3.0 ± 0.1)[b] × 10	3.6	(6.8 ± 0.4)[b] × 10	(5.5 ± 0.8)[b] × 10	1.3	(2.4 ± 0.5)[b] × 10	7.0 ± 2.7[b]	3.4
(*S*,*S*)-**2**	(1.4 ± 0.1)[c] × 10^2	(3.7 ± 0.1)[c] × 10	3.6	(7.9 ± 0.1)[c] × 10	(6.2 ± 0.1)[c] × 10	1.3	(2.7 ± 0.1)[c] × 10	(1.0 ± 0.1)[c] × 10	2.6
(*S*,*S*)-**1**[18]	2.3 × 10^3[d]	3.0 × 10^2[d]	7.8	1.4 × 10^3[f]	1.2 × 10^3[f]	1.2	5.1 × 10^2[g]	1.0 × 10^2[g]	5.1
	1.2 × 10^3[e]	3.5 × 10[e]	35						

[a] *K* by ^{1}H NMR titration in $CDCl_3$. [b] *K* by UV-vis titration in CH_2Cl_2. [c] K_{SV} by fluorescent titration in CD_2Cl_2. [d] Apparent K_{SV} ($K_{SV\,app}$) at [guest] = 6.9 × 10^{-4} M. [e] Apparent K_{SV} ($K_{SV\,app}$) at [guest] = 1.3 × 10^{-4} M. [f] Apparent K_{SV} ($K_{SV\,app}$) at [guest] = 1.1 × 10^{-3} M. [g] Apparent K_{SV} ($K_{SV\,app}$) at [guest] = 4.1 × 10^{-3} M.

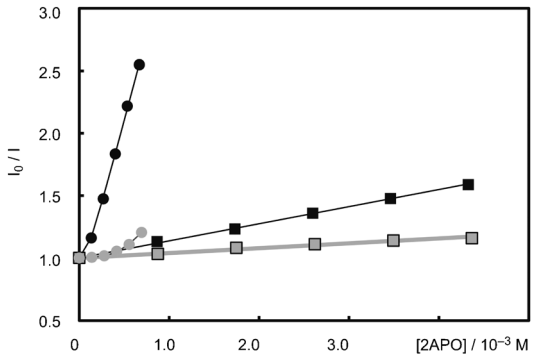

Fig. 2 Stern–Volmer plot for the quenching of the fluorescence of (*S*,*S*)-**1** (●) and (*S*,*S*)-**2** (■) with (*R*)- (black) and (*S*)-2-amino-1-propanol (gray) in CH_2Cl_2 at 20 °C.

both enantiomers was amplified by similar magnitude as shown in Fig. S4-25 in ESI.† For VLO, $K_{SV\ app}$ of (*S*,*S*)-**1** (5.1×10^2 M^{-3} and 1.0×10^2 M^{-1}) increased by one order of magnitude (2.7×10 M^{-3} and 1.0×10 M^{-1}). In addition, the enantioselectivity ($K_{SV(R)\,app}/K_{SV(S)\,app}$) improved from 2.6 to 5.1. Although the fluorescent quenching mechanism of (*S*,*S*)-**1** was not clearly determined,[22] the quenching efficiency is enhanced compared to that of the corresponding monomer (*S*,*S*)-**2**. More interestingly, the apparent enantioselectivity of the polymer can be significantly enhanced at relatively low guest concentration as exemplified for 2APO and VLO.

In conclusion, based on the nonlinear response of molecular wire (*S*,*S*)-**1** as exemplified in Fig. 2, we have demonstrated a highly selective chirality recognition of chiral amine guests in homogeneous solution by binding constants and the ratios shown in Table 1. The fluorescence of (*S*,*S*)-**1** was quenched upon complexation with amine guests. At relatively low guest concentration, the molecular wire showed both amplified sensitivity and enantioselectivity compared to the model monomer (*S*,*S*)-**2**.

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20 $(I_0/I) = 1 + K[G]$. When (I_0/I) is proportional to $[G]$, K_{sv} is obtained from the slope K. Apparent K_{sv} ($=K_{sv\,app}$) is obtained from $((I_0/I) - 1)/[G]$ for (*S*,*S*)-**1** with guest concentration.
21 UV-vis spectra of (*S*,*S*)-**1** in CH_2Cl_2 were not affected by concentration in the range of 2.0×10^{-6}–4.0×10^{-5} M.
22 The Stern–Volmer plots of (*S*,*S*)-**1** with (*S*)- and (*R*)-2APO show positive deviations from predictive linear behaviours. In order to determine the mechanism, curve approximations were carried out by applying a static quenching model, a dynamic quenching model, and the combined model of static and dynamic mechanisms. Models of the Förster resonance energy transfer mechanism and Dexter energy transfer mechanism for fluorescent quenching were also applied assuming that the binding constant (K) of one receptor site in (*S*,*S*)-**1** is same as that of (*S*,*S*)-**2**. However, none of the models fit the experimental data.

