Electronic Supplementary Information for

Novel Chiral Recognition Beyond the Limitation Due to the Law of Mass Action: Highly Enantioselective Chiral Sensing Based on Non-Linear Response in Phase Transition Events

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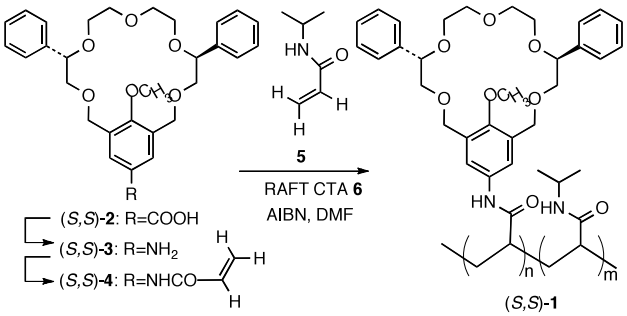
Contents

1. General

^{1}H NMR spectra were recorded with a JEOL GSX-270, a Varian Mercury 300, or a JEOL AL-400 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as an internal standard and *J* values are given in Hz. ^{13}C NMR spectra were recorded at 75.5 MHz with a JEOL GSX-270 spectrometer and chloroform (δ C 77.0) was used as a chemical shift reference. IR spectra were measured on a JASCO FT/IR–410 spectrophotometer. Elemental analyses were performed on a Perkin–Elmer 2400II analyzer. Melting points were measured with a hot-stage apparatus and are uncorrected. Optical rotations were measured using a JASCO DIP–40 polarimeter and [α] values are given in units of 10^{-1} deg cm^2 g^{-1}. MS spectra were recorded with a JEOL JMS-700 spectrometer. Column chromatography and TLC were performed with Merck silica gel 60 (70–230 mesh ASTM) and Merck silica gel 60 F_{254}, respectively. Preparative GPC separation was undertaken with a JAI LC-908 chromatograph using 600 mm×20 mm JAIGEL-1H and 2H GPC columns with $CHCl_3$ as an eluent. All reagents were obtained from commercial suppliers and used as received.



Scheme S1. Synthesis of Chiral Sensor (*S,S*)-**1**

2. Synthetic Procedures of (*S,S*)-1

2-1. Synthesis of (*S,S*)-4 from (*S,S*)-2

A mixture of (*S,S*)-**2** (1.66 g, 3.18 mmol)[1,2] and $SOCl_2$ (0.450 mL, 6.30 mmol) was stirred for 2 h under reflux. After the removal of $SOCl_2$ under reduced pressure, the obtained yellow residue was diluted with acetone (40 mL). NaN_3 (760 mg, 11.7 mmol) was added into the solution. The mixture was stirred for 1 h at room temperature. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in toluene (130 mL) and a 50 % aqueous NaOH solution (70 mL) was added. The resulted mixture was refluxed overnight. After separation of the organic phase, the aqueous phase was extracted with toluene. The combined organic layer was washed with aqueous NaOH solution. After being dried over anhydrous $MgSO_4$, the removal of the solvent gave amine (*S,S*)-**3** (1.48 g) as a colorless solid which was unstable in air: mp 154.0–155.0 °C. Therefore (*S,S*)-**3** was employed for the next amidation reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ 7.34-7.26 (m, 10H), 6.62 (s, 2H), 4.66 and 4.41 (AB, *J*= 11 Hz, 4H), 4.53 (dd, *J*= 2.1, 8.4 Hz, 2H), 4.15 (s, 3H), 3.72-3.43 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 30°C) δ 150.4, 142.8, 139.0, 131.1, 128.4, 127.8, 126.8, 118.4, 81.7, 74.5, 70.1, 69.2, 68.6, 65.0; IR (neat) 3419, 3350, 3061, 3006, 2899, 2861, 1714, 1637, 1613, 1487, 1452, 1343, 1311, 1248, 1228, 1197, 1090, 1027, 1001, 956, 866, 758, 703, 666, 634 cm^{-1}; MS (FAB) *m/z* 516.2 $(M+Na)^+$, HRMS (FAB) *m/z* calcd for $C_{29}H_{35}O_6NNa$ $(M+Na)^+$ 516.2362, found 516.2365; $[\alpha]^{23}_D$= + 121 (*c* 1.03. $CHCl_3$).

To a solution of (*S,S*)-**3** (1.48 g) in CH_2Cl_2 (40 mL) was added slowly acryloylchloride (250 mL, 3.00 mmol) with ice-cooling. Then, the mixture was stirred for 1.5 h at ambient temperature. The reaction mixture was extracted with CH_2Cl_2. The combined extracts were washed with aqueous solution of sodium hydrogencarbonate and brine, and dried over anhydrous $MgSO_4$. Chromatography on silica gel (hexane:ethyl acetate) followed by recrystallization from chloroform:hexane gave (*S,S*)-**4** (1.09 g, 63% yield from (*S,S*)-**2**) as a colorless solid: mp 185.0–186.0 °C: ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ 7.54 (s, 2H), 7.33-7.26 (m, 10H), 6.39 (AB, *J*= 16.8 Hz, 1H), 6.22 (ABX, *J*= 16.8, 9.9 Hz, 1H), 5.72 (AX, *J*= 9.9 Hz,1H), 4.71 and 4.45 (AB, *J*= 10.5 Hz, 4H), 4.53 (dd, *J*= 2.1, 8.7 Hz, 2H), 4.25 (s, 3H), 3.71-3.41 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C) δ 165.6, 155.9, 138.9, 133.0, 132.2, 131.2, 128.4, 127.9, 127.4, 126.9, 123.5, 81.7, 74.4, 70.7, 69.0, 68.3, 65.1; IR (KBr) 3502, 3028, 2868, 2359, 1668, 1608, 1551, 1484, 1452, 1437, 1360, 1343, 1247, 1220, 1091, 1000, 959, 882, 800, 763, 704, 635, 522 cm^{-1}; MS (FAB) *m/z* 570.2 $(M+Na)^+$, HRMS (FAB) *m/z* calcd for $C_{32}H_{37}O_7NNa$ $(M+Na)^+$ 570.2468, found 570.2488; $[\alpha]^{23}_D$= + 108 (*c* 1.08. $CHCl_3$); Anal. Calcd for $C_{32}H_{37}NO_7$: C, 70.18; H, 6.81; N, 2.56. found: C, 70.33; H, 6.56; N, 2.67.

2-2. Synthesis of (*S,S*)-1

A solution of azobisisobutyronitrile (AIBN) (14.6 mg, 0.0889 mmol) in DMF (10 mL) as degassed by bubbling nitrogen for 10 min and a similarly degassed solution of (*S,S*)-**4** (243 mg, 0.443 mmol), *N*-isopropylacrylamide (NIPAM, **5**) (951 mg, 8.40 mmol), and 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid (RAFT CTA, **6**) (42.0 mg, 0.116 mmol) in DMF (2.1 mL) were mixed at 60 ºC under nitrogen, and the mixture was heated at 70 ºC with stirring for 24 h. The copolymer dissolved in DMF was chromatographed by preparative GPC. Removal of the solvent of a high molecular weight fraction (retention time: 31-47 min at a flow rate of 3.8 mL/min) gave yellow solid. The solid was dissolved in acetone, and then purified by reprecipitation by adding to cold diethyl ether. (*S,S*)-**1** (875 mg) was collected by filtration as a colorless powder: ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ 7.31 (m, broad), 6.21 (s, broad), 4.67 (s), 4.53 (d, *J*= 10.8 Hz), 4.43 (s), 4.00 (s), 3.78 (s), 3.72-3.42 (m), 2.27-1.13 (m); M_n = 15000, M_w/M_n = 1.14, SCE with DMF containing 0.01 M LiBr at 40 ºC, flow rate 0.06 mL/min.[3]

2-3. ^{1}H-NMR Spectrum of (*S,S*)-1

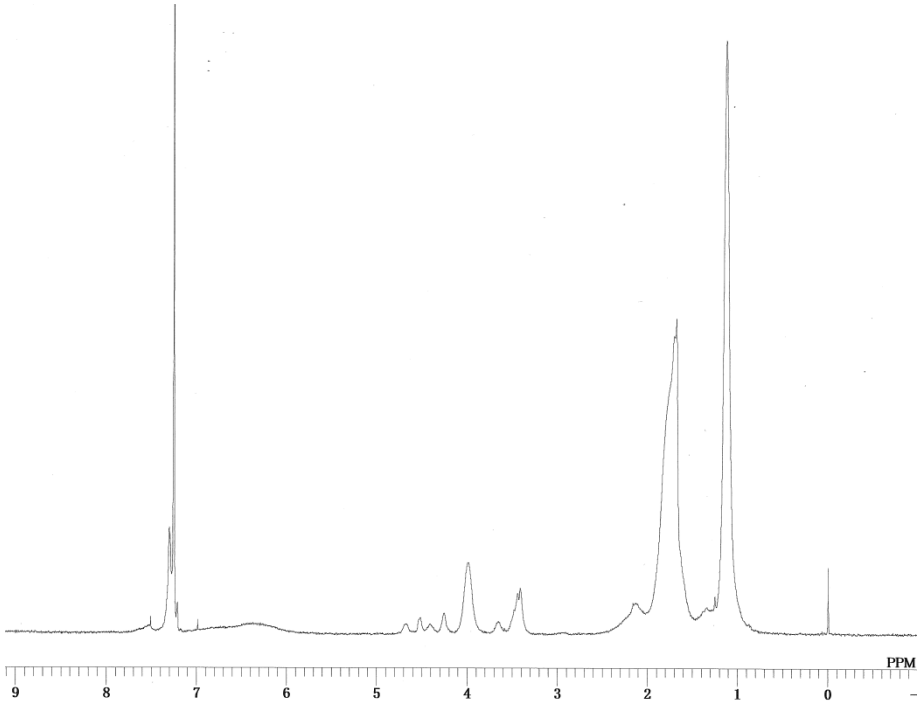


Figure S1. ^{1}H NMR spectrum of (*S,S*)-**1** (400 MHz, $CDCl_3$, 30 ºC).

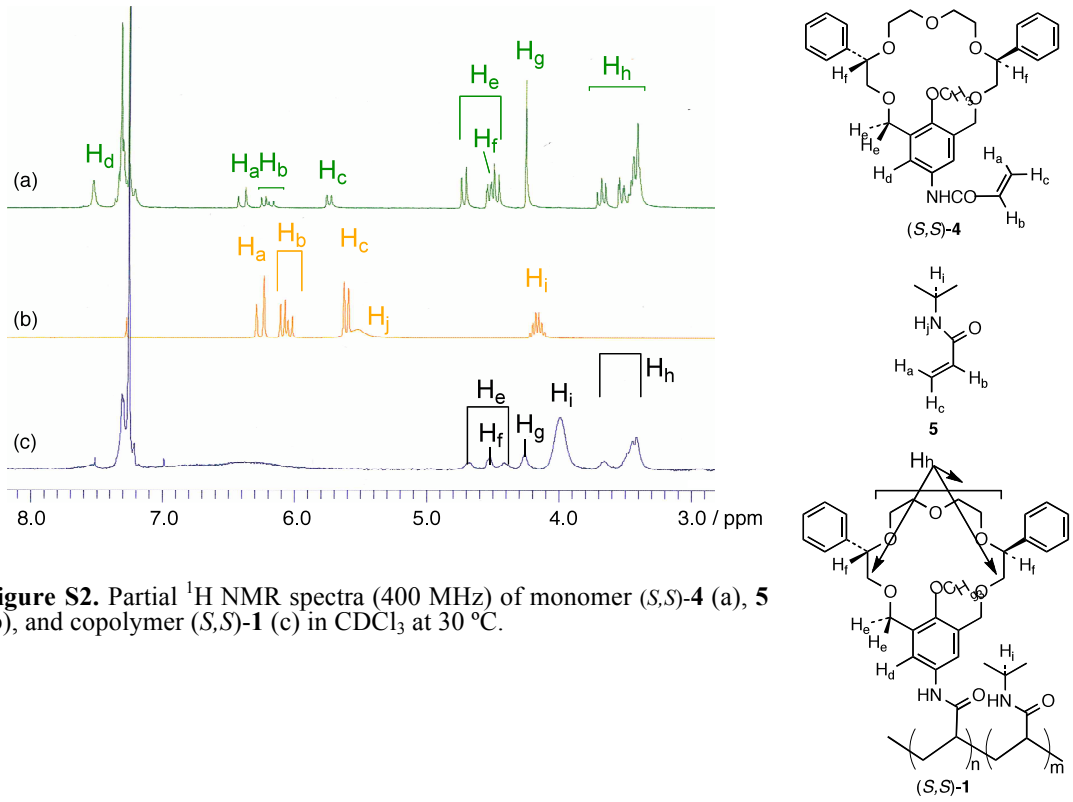


Figure S2. Partial ^{1}H NMR spectra (400 MHz) of monomer (*S,S*)-**4** (a), **5** (b), and copolymer (*S,S*)-**1** (c) in $CDCl_3$ at 30 ºC.

The ^{1}H NMR of (*S,S*)-**1** and monomers (*S,S*)-**4** and **5** are shown in Figure S2 with signal assignments. The signals of the polymer are significantly broadened. The assignments of the signals were carried out using information obtained from H-H COSY spectra shown in Figure S3. The content of the crown ether monomer unit in the polymer was estimated to be 4 mol % based on the integration of the signals for H_g and H_i.

2-4. H-H COSY Spectra of (*S*,*S*)-1

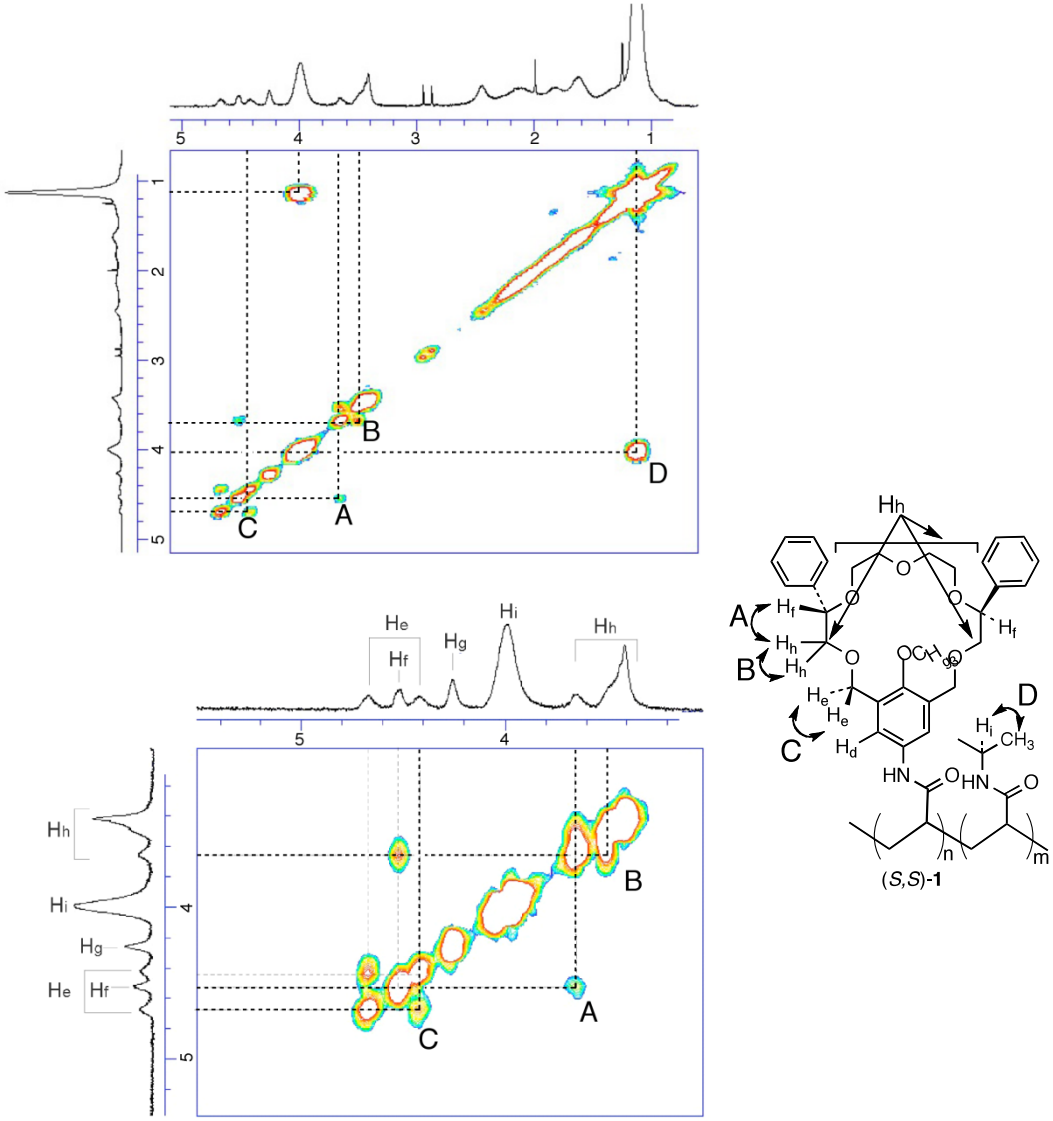
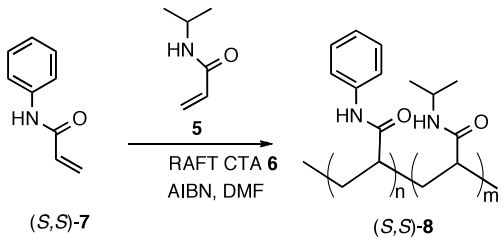


Figure S3. Partial H-H COSY spectra of (*S,S*)-**1** (270 MHz, $CDCl_3$, 30 ºC).

3. Synthetic Procedures of Reference Copolymer (*S,S*)-8

3-1. Synthesis of (*S,S*)-8 from (*S,S*)-7



Scheme S2. Synthesis of Reference Copolymer (*S,S*)-**8**

A solution of AIBN (14.6 mg, 0.0889 mmol) in DMF (10 mL) was degassed by bubbling nitrogen for 10 min and a similarly solution of *N*-phenylacrylamide (**7**) (65.0 mg, 0.442 mmol), NIPAM **5** (950 mg, 8.40 mmol), and RAFT CTA **6** (42.0 mg, 0.114 mmol) in DMF (2.1 mL) were mixed at 60 ºC under nitrogen, and the mixture was heated at 70 ºC with stirring for 36 h. The copolymer dissolved in DMF was purified by reprecipitation by addition to cold diethyl ether. (*S,S*)-**6** (618 mg) was collected by filtration as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ 7.61 (m), 7.06 (m,), 6.41 (s, broad), 3.99 (s), 2.23-1.13 (m); M_n = 21000, M_w/M_n = 1.06, SCE with DMF containing 0.01 M LiBr at 40 ºC, flow rate 0.06 mL/min.[3]

3-2. ^{1}H-NMR Spectrum of (*S,S*)-8

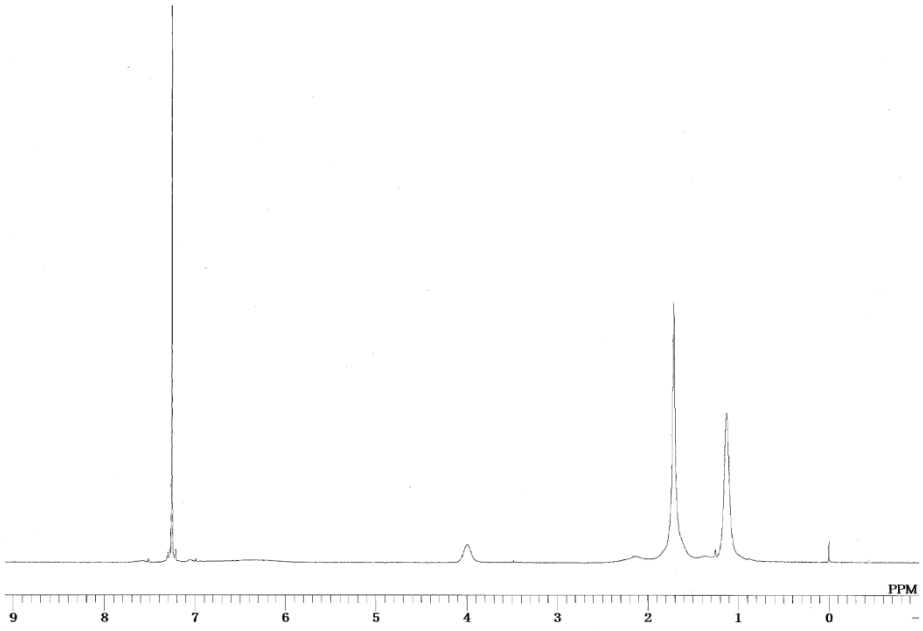


Figure S4. ^{1}H NMR spectrum of (*S,S*)-**8** (400 MHz, $CDCl_3$, 30 ºC).

4. Determination of Binding Constants of (*S,S*)-1

4-1. with (*R*)-NEA·HCl

A solution of host (*S,S*)-**1** (10.0 mg, 3.07 mM of crown ether monomer unit) and a solution of guest (*R*)-NEA·HCl (145.4 mM) each in D_2O were prepared. An initial ^1H NMR spectrum of (*S,S*)-**1** was recorded at 5 ºC. Samples were made by adding each 35, 35, 60, 50, 50, 55, 55, 50, 50, 50, and 50 μL of the guest solutions to 660 μL solution of (*S,S*)-**1**. Then, spectra of these samples were recorded at the same temperature. The binding constant of (*S,S*)-**1** with (*R*)-NEA·HCl was calculated by a non-linear least-squares method to be 6.4 ± 2.7 M^{-1}. The relevant data and the ^1H NMR titration curve, respectively are shown in Table S1 and Figure S5, respectively.

Table S1. Tabulated ^{1}H NMR Titration Tata of (*S,S*)-**1** with (*R*)-NEA·HCl in D_2O at 278 K, Calculated Binding Constant, and Calculated Chemical Shifts of the Complex.

	$[H]_t$ (mM) [a]	$[G]_t$ (mM) [b]	$[G]_t$ / $[H]_t$ [c]	δ (ppm) [d]
1	0.0031	0.0000	0.0	7.010
2	0.0029	0.0073	2.5	6.992
3	0.0028	0.0139	5.0	6.987
4	0.0026	0.0239	9.3	6.975
5	0.0024	0.0312	12.9	6.959
6	0.0023	0.0376	16.5	6.952
7	0.0021	0.0439	20.5	6.950
8	0.0020	0.0494	24.4	6.939
9	0.0019	0.0540	28.0	6.940
10	0.0018	0.0582	31.6	6.933
11	0.0018	0.0620	35.2	6.929
12	0.0017	0.0654	38.8	6.924
				δ_{comp}=6.727
				K=6.4±2.7

[a] Total concentration of crown ether unit of (*S,S*)-**1**

[b] Total concentration of (*R*)-NEA·HCl.

[c] The ratio of crown ether unit of (*S,S*)-**1** over (*R*) -NEA·HCl.

[d] Observed chemical shifts of one of the phenyl protons of (*S,S*)-**1**.

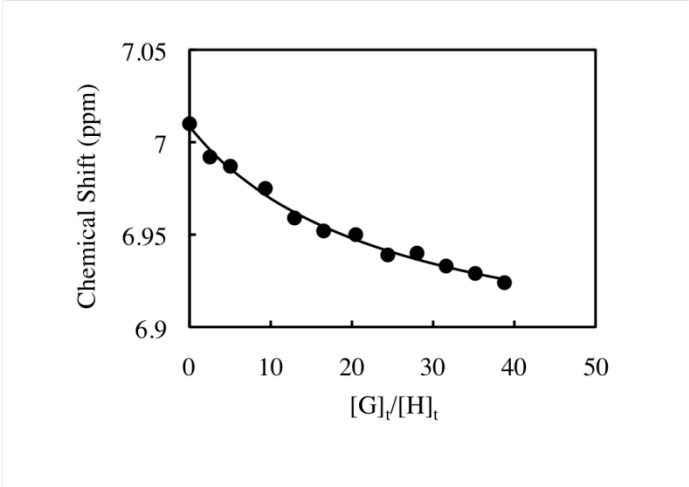


Figure S5. ^{1}H NMR Titration Curve for the Complexation of (*S,S*)-**1** with (*R*) -NEA·HCl at 278 K.

4-1. with (*S*)-NEA·HCl

A solution of host (*S,S*)-**1** (10.0 mg, 3.07 mM of crown ether monomer unit) and a solution of guest (*S*)-NEA·HCl (145.1 mM) each in D_2O were prepared. An initial ^1H NMR spectrum of (*S,S*)-**1** was recorded at 5 ºC. Samples were made by adding each 35, 35, 60, 50, 50, 55, 55, 50, 50, 50, and 50 μL of the guest solutions to 660 μL solution of (*S,S*)-**1**. Then, spectra of these samples were recorded at the same temperature. The binding constant of (*S,S*)-**1** with (*S*)-NEA·HCl was calculated by a non-linear least-squares method to be <1 M^{-1}. The relevant data and the ^1H NMR titration curve, respectively are shown in Table S2 and Figure S6, respectively.

Table S2. Tabulated ^{1}H NMR Titration Data of (*S*,*S*)-**1** with (*S*)-NEA·HCl in D_2O at 278 K, Calculated Binding Constant, and Calculated Chemical Shift of the Complex.

	$[H]_t$ (mM) [a]	$[G]_t$ (mM) [b]	$[G]_t$ / $[H]_t$ [c]	δ (ppm) [d]
1	0.0031	0.0000	0.0	7.002
2	0.0029	0.0081	2.8	6.990
3	0.0027	0.0154	5.6	6.989
4	0.0025	0.0262	10.4	6.968
5	0.0024	0.0339	14.4	6.955
6	0.0022	0.0407	18.4	6.949
7	0.0021	0.0472	22.8	6.938
8	0.0019	0.0530	27.3	6.933
9	0.0018	0.0577	31.3	6.924
10	0.0018	0.0620	35.3	6.921
11	0.0017	0.0658	39.3	6.919
12	0.0016	0.0693	43.3	6.910
				δ_{comp}=4.079
				K <1

[a] Total concentration of crown ether unit of (*S*,*S*)-**1**

[b] Total concentration of (*S*)-NEA·HCl.

[c] The ratio of crown ether unit of (*S*,*S*)-**1** over (*S*) -NEA·HCl.

[d] Observed chemical shifts of one of the phenyl protons of (*S*,*S*)-**1**.

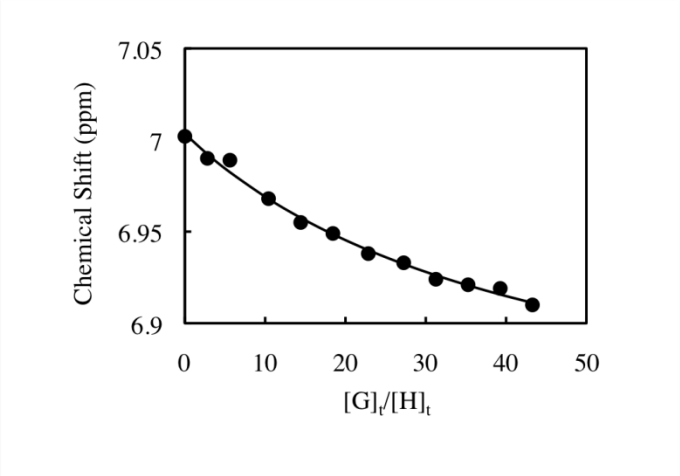


Figure S6. ^{1}H NMR Titration Curve for the Complexation of (*S*,*S*)-**1** with (*S*) -NEA·HCl at 278 K.

5. Phase Separation Experiments

A solution of host chiral sensor (*S,S*)-**1** (0.2 wt% of crown ether monomer unit) and a solution of guest (*R*)-NEA·HCl each in H_2O were prepared. The host (*S,S*)-**1** solution (2.0 mL) was placed in a sample cell. Then, the phase transition was traced by monitoring the transmittance of a 500 nm light beam through a 1 cm sample cell at different temperatures on a specially constructed spectrophotometer (JASCO V-550). The rates of heating up and of cooling down of the sample cells were adjusted at 1 ºC/min.

5-1. Temperature Dependence of the Transmittance at 500 nm of (*S,S*)-1 with NEA·HCl

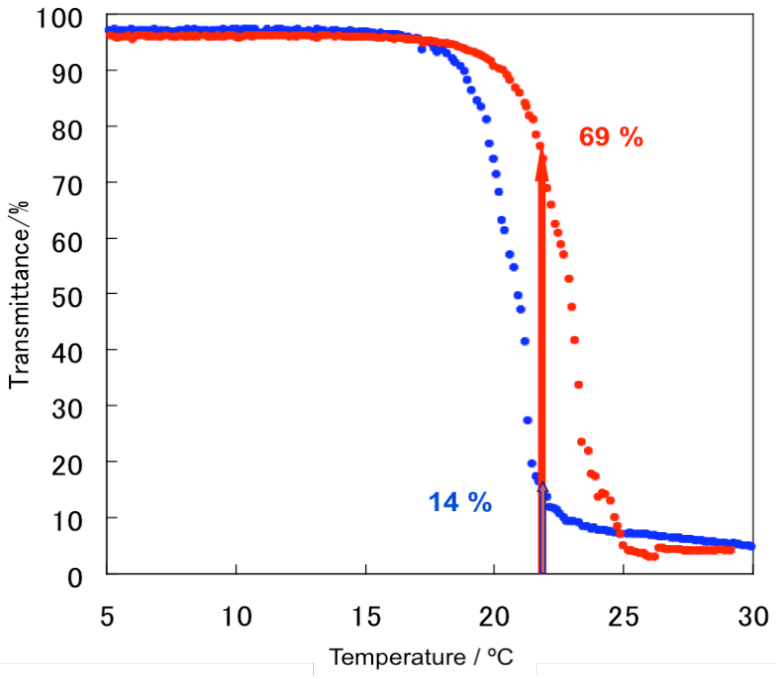


Figure S7. Temperature dependence of the transmittance at 500 nm of 0.2 wt% aqueous solution of (*S,S*)-**1** with 6.0 equivalent of (*S*)-NEA·HCl (red) and that with 6.0 equivalent of (*R*)-NEA·HCl (blue).

5-2. Temperature Dependence of the Transmittance at 500 nm of (*S*,*S*)-1 with PGO·HCl

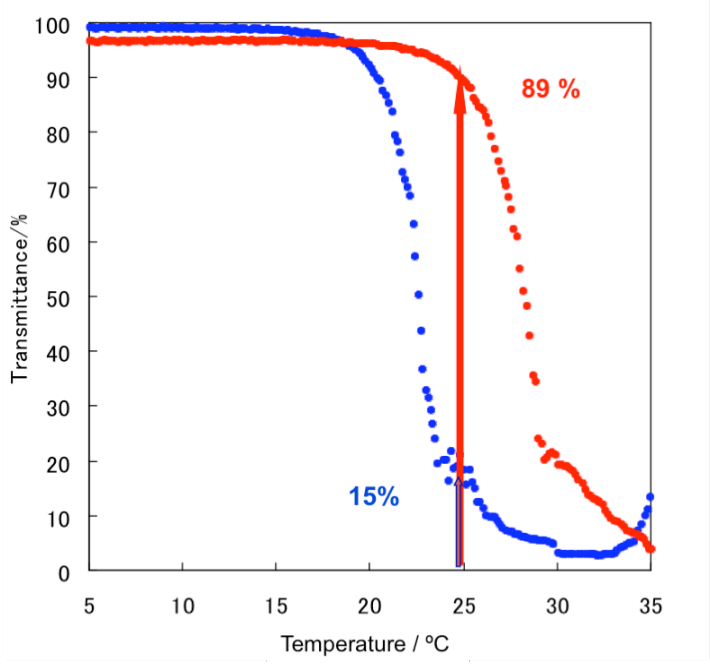


Figure S8. Temperature dependence of the transmittance at 500 nm of 0.2 wt% aqueous solution of (*S*,*S*)-**1** with 6.0 equivalent of (*S*)-PGO·HCl (red) and that with 6.0 equivalent of (*R*)-PGO·HCl (blue).

5-3. Temperature Dependence of the Transmittance at 500 nm of (*S*,*S*)-1 with PEA·HCl

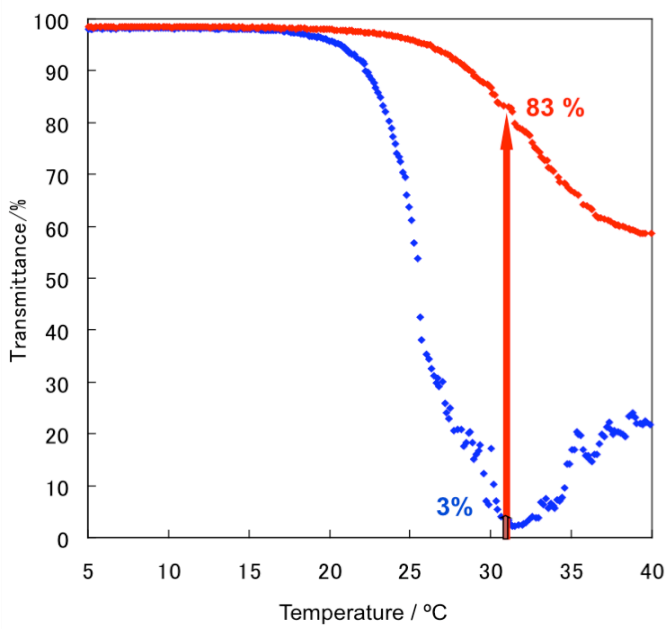


Figure S9. Temperature dependence of the transmittance at 500 nm of 0.2 wt% aqueous solution of (*S*,*S*)-**1** with 6.0 equivalent of (*S*)-PEA·HCl (red) and that with 6.0 equivalent of (*R*)-PEA·HCl (blue).

6. References

(1) Hirose, K.; Nakamura, T.; Nishioka, R.; Ueshige, T.; Tobe, Y. *Tetrahedron Lett.* **2003**, *44*, 1549.

(2) Hirose, K.; Jin, Y. Z.; Nakamura, T.; Nishioka, R.; Ueshige, T.; Tobe, Y. *Chirality* **2005**, *17*, 142.

(3) Ishizone, T.; Ito, M. *J. Poly. Sci. Part A-Poly. Chem.* **2002**, *40*, 4328.