JOC The Journal of Organic Chemistry

Article

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Enantioselective Recognition for Many Different Kinds of Chiral Guests by One Chiral Receptor Based on Tetraphenylethylene Cyclohexylbisurea

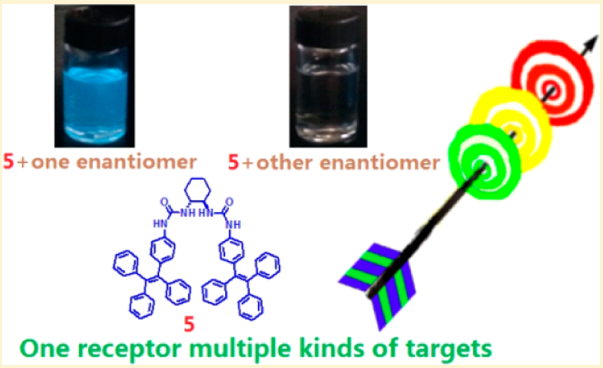
Jia-Bin Xiong,[†] Wen-Zhao Xie,[†] Jian-Ping Sun,[†] Jin-Hua Wang,[†] Zhi-Hua Zhu,[†] Hai-Tao Feng,[†] Dong Guo,[‡] Hui Zhang,[‡] and Yan-Song Zheng*[,†]

[†]Key Laboratory for Chemistry of Energy Conversion and Storage Materials, Ministry of Education, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, People's Republic of China

[‡]College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, People's Republic of China

Supporting Information

ABSTRACT: A neutral chiral receptor based on TPE cyclohexylbisurea was synthesized and could discriminate the enantiomers of many different kinds of chiral reagents, including chiral acidic compounds, basic compounds, amino acids, and even neutral alcohols. The ^{1}H NMR spectra disclosed that the ability of chiral recognition could be ascribed to the multiple hydrogen bonds and CH−π interactions between the TPE urea receptor and the enantiomer of the chiral guest, which led to the selective aggregation of the receptor with one of the two enantiomers. This result exhibited a great potential in enantiomer discernment and high-throughput analysis of enantiomer composition of these chiral analytes by one chiral AIE molecule.



INTRODUCTION

Most drug molecules are chiral, and their enantiomers often show different physiological activity. Therefore, a single enantiomer must be obtained and the enantiomeric purity must be known in the research and development of chiral drugs. Although there already are many methods for measurement of enantiomeric purity,[1,2] the fluorescent spectroscopic approach is the most promising due to its cost effectiveness, accuracy, and sensitivity, which are very necessary for high-throughput screening of potential chiral drugs.[2] In this context, fluorescent receptors for discrimination and analysis of enantiomers are attracting more and more attention. Up to now, a large number of excellent fluorescent receptors exist for the analysis of enantiomers of one class of chiral compounds, but discrimination of enantiomers of different kinds of chiral molecules with one fluorescent receptor is rare,[3] although other methods such as NMR and circular dichroism probes often have the efficiency of "one stone, two birds".[4,5]

Recently, a new class of organic compounds with amazing aggregation-induced emission (AIE) effects, that is, having no fluorescence in solution but emitting strong light in the aggregation state, are rapidly making progress because they can overcome the disadvantages of aggregation-caused quenching (ACQ) of most fluorophores in the solid state and show a remarkable potential in optoelectronic materials.[6] Meanwhile, the fluorescence change from AIE effects also makes the organic compounds of this class versatile and exceptional chemo-/biosensors.[6,7] By introduction of optically pure groups into the AIE molecules, the prepared chiral AIE molecules may become excellent chiral sensors for discrimination and analysis of enantiomers of chiral analytes.[8−12,15] For example, AIE compounds bearing a chiral carboxylic group can enantioselectively form a suspension with one enantiomer but a clear solution with the other enantiomer of chiral amines, in which the suspension emits strong fluorescence but the solution has no emission.[8] In a similar way, the chiral AIE amine can discriminate the two enantiomers of chiral acidic compounds by enantioselective aggregation.[9] Pu and Hou et al. also reported that one 1,1′-bi-2-naphtholamine receptor could enantioselectively induce precipitation and enhance solid-state fluorescence with one enantiomer of α-hydroxycarboxylic acids.[10] In 2014, Tang and Wong found that a AIE silole bearing two optically pure thiourea groups could form helical aggregates with the enantiomers of chiral carboxylic acids and emit complexation-induced circularly polarized luminescence (CPL) in the solid thin film state.[11] Very recently, our group reported that AIE macrocycles bearing an optically pure diphenyldiaminoethylene group displayed enantiomer discrimination not only for chiral acidic compounds but also for unprotected α-amino acids.[12] Here a chiral AIE receptor based on tetraphenylethylene (TPE) cyclohexylbisurea was synthesized and could discriminate enantiomers of acidic compounds, basic compounds, amino acids, and even neutral alcohols.

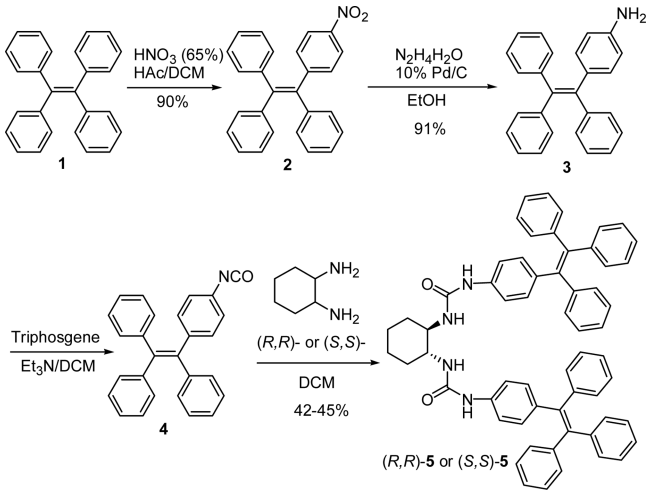
Received: February 20, 2016
Published: March 31, 2016

DOI: 10.1021/acs.joc.6b00371
J. Org. Chem. 2016, 81, 3720−3726

RESULTS AND DISCUSSION

The chiral TPE receptor was synthesized by the reaction route shown in Scheme 1. TPE **1** could be selectively nitrated to give

Scheme 1. Synthesis of the Chiral TPE Cyclohexylbisurea 5



mononitroTPE **2** in excellent yield (90%) with nitric acid in a mixed solvent of acetic acid and dichloromethane as long as the temperature and the amount of the nitrating agent were properly controlled. Then the mononitroTPE **2** was reduced to TPE monoamine **3** in 91% yield by hydrazine hydrate in the presence of Pd/C, which was further transformed into isocyanate **4**. Without being purified, the isocyanate **4** underwent a condensation reaction with optically pure (1*R*,2*R*)- or (1*S*,2*S*)-1,2-cyclohexanediamine to offer the target product chiral TPE cyclohexylbisurea **5** in 42% or 45% yield.

The chiral TPE cyclohexylbisurea **5** was soluble in convenient organic solvents such as chloroform, 1,2-dichloroethane, and THF but insoluble in hexane and water. After **5** was dissolved in 1,2-dichloroethane, the resultant solution (1.0×10^{-4} M) did not emit fluorescent light. When an 80% fraction of hexane was added to the solution and turbidity appeared, the solution started to give fluorescent emission. As the hexane fraction was continually increased and the solution become more turbid, the fluorescent intensity increased rapidly. At a 95% fraction of hexane, the intensity was increased by 203-fold in comparison with the solution without added hexane (Figure 1). Therefore, the chiral TPE cyclohexylbisurea **5** is an AIE compound.

Interestingly, when the concentration of (*R*,*R*)- or (*S*,*S*)-**5** in 1,2-dichloroethane was increased to 1.0×10^{-2} M from 1.0×10^{-4} M, the solution became a transparent gel after it stood at room temperature for several minutes. Upon heating, the gel went back into solution but became a gel again after the heated solution was cooled to room temperature (Figure 2A). This process could be reversed many times. Meanwhile, while the solution did not display emission, the gel showed strong fluorescence under a portable 365 nm UV lamp. This result indicated that the chiral TPE cyclohexylbisurea **5** tended to aggregate at high concentration, probably due to the two urea groups, which easily formed multiple hydrogen bonds between molecules. This is in accordance with the literature reports in which one urea group that is conjugated to long aliphatic chains can easily form a stable gel because of hydrogen-bonding interactions between urea groups.[13] However, TEM images

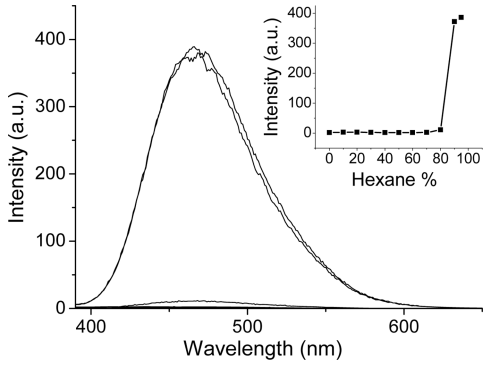


Figure 1. Change in the fluorescence spectrum of (*S*,*S*)-**5** (1.0×10^{-4} M) in 1,2-dichloroethane with added hexane. Conditions: λ_{ex} 366 nm, ex/em slits 3/3 nm. Inset: curve of fluorescent intensity vs hexane percentage in 1,2-dichloroethane measured at 468 nm.

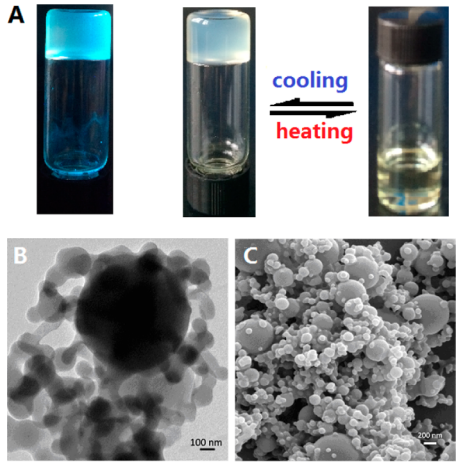


Figure 2. (A) Photos of the gel formed by 10 mg of (*R*,*R*)-**5** in 1.0 mL of 1,2-dichloroethane under a portable 365 nm UV lamp (left) and interconversion of the gel and solution by cooling and heating (right). (B) TEM image and (C) FE-SEM image of the gel.

disclosed that the gel was composed of nanospheres with a diameter of 50−500 nm, and SEM images also confirmed the formation of nanospheres with a similar diameter range of 50−500 nm (Figure 2B,C). In general, organic gels are often formed by nanofibers which could interdigitate to produce many micro-3D spaces and immobilize the solvent. Gels formed by nanospheres are very rare.[14]

Although the morphology of the aggregates of **5** in 1,2-dichloroethane was nanospheres, the circular dichroism (CD) spectra of the solution of **5** at different concentrations was measured (Figure S9 in the Supporting Information). When the concentration of (*S*,*S*)-**5** was 1.0×10^{-4} M or less, no CD signal was observed, demonstrating that (*S*,*S*)-**5** was completely dispersed into 1,2-dichloroethane, which is in accordance with the fluorescence test. After the concentration was increased to 5.0×10^{-4} M, a broad CD band with a negative Cotton effect between 365 and 260 nm appeared, and it became stronger at 1.0×10^{-3} M (Figure S9 and Figure 3). When the concentration reached 5.0×10^{-3} M, at which point a gelatinous solid started to appear in the solution, the CD signal was not only very strong but also displayed many fine peaks. Because only the aggregation led to CD signals, the aggregates should possess helical chirality which could result from the helical stacking of (*S*,*S*)-**5** in one direction. At $1.0 \times$

DOI: 10.1021/acs.joc.6b00371
J. Org. Chem. 2016, 81, 3720−3726

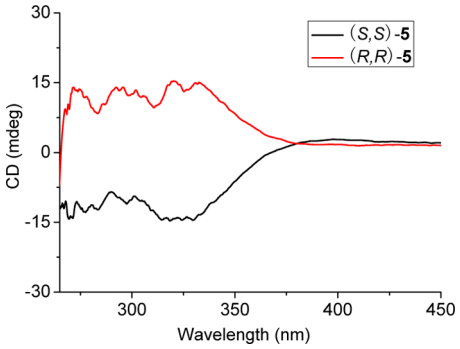


Figure 3. CD spectra of (*R*,*R*)-**5** and (*S*,*S*)-**5** in 1,2-dichloroethane, respectively, at 1.0×10^{-3} M.

10^{-3} M, the solution of (*R*,*R*)-**5** instead of (*S*,*S*)-**5** in 1,2-dichloroethane showed a broad CD band with a positive Cotton effect between 365 and 260 nm, which was the mirror image of that of (*S*,*S*)-**5** (Figure 3). Therefore, the configuration of **5** determined the handed direction of the helical chirality and the CD sign of the aggregates. Due to easily formed aggregation, the chiral **5** could display CD signals in solution, while other all chiral AIE compounds that have been reported up to now often only exhibit CD signals in solid or in polymer film.[11,15]

To measure the ability of the chiral recognition of the chiral TPE **5**, the effect of enantiomers of a wide variety of chiral analytes on the aggregation of **5** in solution was tested. It was surprisingly found that the enantiomers of not only chiral acidic compounds but also chiral basic amines, zwitterionic amino acids, and even completely neutral chiral alcohols could selectively affect the aggregation of **5**. When the nonsolvent hexane was added to a solution of the enantiomers of 2-chloromandelic acid **6** and (*R*,*R*)-**5** in 1,2-dichloroethane, it was found that the mixture of (*S*)-**6** and (*R*,*R*)-**5** led to aggregation and resulted in a suspension but a mixture of (*R*)-**6** and (*R*,*R*)-**5** was still a solution. The suspension emitted strong fluorescence, while the solution showed very weak emission (Figure 4), and the fluorescence intensity ratio or enantioselectivity ($I_{(S)\text{-}6}/I_{(R)\text{-}6}$) of the suspension to the solution was 8.8 (Table 1). Similarly, among the two enantiomers of mandelic acid **7**, (*S*)-**7** led to aggregation of (*R*,*R*)-**5** but (*R*)-**7** did not, which gave rise to an enantioselectivity ($I_{(S)\text{-}7}/I_{(R)\text{-}7}$) of 5.9. For other chiral carboxylic acids, such as 1,2,3,4-tetrahydronaphthoic acid **8**, 2,3-dibenzoyltartaric acid **9**, and 2,3-di-*p*-toluoyltartaric acid **10**, (*R*,*R*)-**5** also exhibited an ability to discriminate their two enantiomers. Noticeably, for camphorsulfonic acid **11** with strong acidity, (*R*,*R*)-**5** displayed very high enantioselectivity ($I_{\text{L-}11}/I_{\text{D-}11}$) of 63 (Figure S10 in the Supporting Information and Table 1).

For chiral amines, their enantiomers could be also discriminated by (*R*,*R*)-**5** (Figure S10 in the Supporting Information and Table 1). When the nonsolvent hexane was added to a solution of the enantiomers of phenylglycinol **12** and (*R*,*R*)-**5** in 1,2-dichloroethane, a mixture of (*S*)-**12** and (*R*,*R*)-**5** gave rise to suspension, but a mixture of (*R*)-**12** and (*R*,*R*)-**5** remained in solution, which resulted in a fluorescence intensity ratio ($I_{(S)\text{-}12}/I_{(R)\text{-}12}$) of 9.2 for the *S* and *R* enantiomers. In similar way, the *S*,*S* isomer of 1,2-diphenylethanediamine **13** and 1,2-cyclohexanediamine **14** induced the aggregation of (*R*,*R*)-**5**, but their *R*,*R* isomers did not cause aggregation of (*R*,*R*)-**5**, which gave enantioselectivities of 2.4 and 33 for **13** and **14**, respectively.

Due to the greater polarity of amino acids, the mixed solvent THF/water instead of 1,2-dichloroethane/hexane was used for testing the enantioslective aggregation. After D- or L-leucine **15** was added to (*R*,*R*)-**5** in a mixed solvent of THF and water, only the mixture of (*R*,*R*)-**5** and L-**15** was a suspension and emitted strong fluorescence but the interaction of (*R*,*R*)-**5** with D-**15** gave a solution which emitted almost no fluorescence (Figure S10 in the Supporting Information). The enantioselectivity ($I_{\text{L-}15}/I_{\text{D-}15}$) was up to 156. For other α-amino acids, including phenylalanine **16**, tryptophan **17**, proline **18**, threonine **19**, arginine **20**, and histidine **21**, their enantiomers could be discriminated by the chiral TPE bisurea (*R*,*R*)-**5** with good enantioselectivity (Figure S10 and Table 1).

Very outstandingly, for neutral chiral alcohols, (*R*,*R*)-**5** could also display a obvious chiral recognition between their enantiomers (Figure S10 and Table 1). When a nonsolvent was added to a mixture of (*R*,*R*)-**5** and the enantiomers of menthol **22** in THF, a mixture of (*R*,*R*)-**5** and L-**22** gave rise to a suspension but that of (*R*,*R*)-**5** and D-**22** led to a solution, which offered an enantioselectivity ($I_{\text{L-}22}/I_{\text{D-}22}$) of 2.5. In the same mixed solvent, the enantioselectivity was 2.0 ($I_{(R)\text{-}23}/I_{(S)\text{-}23}$) for binol **23**. For methyl mandelate **24** and diethyl tartarate **25**, (*R*,*R*)-**5** showed high enantioselectivities of 55 ($I_{(S)\text{-}24}/I_{(R)\text{-}24}$) and 3.3 ($I_{\text{L-}25}/I_{\text{D-}25}$), respectively, in a mixed solvent of hexane and 1,2-dichloroethane.

Because of inherent chiral recognition, when (*S*,*S*)-**5** was used as a receptor, the interaction of chiral analytes with (*S*,*S*)-**5** resulted in contrary enantioselective aggregation in comparison with (*R*,*R*)-**5**. Therefore, by using (*R*,*R*)-**5** and (*S*,*S*)-**5**, the

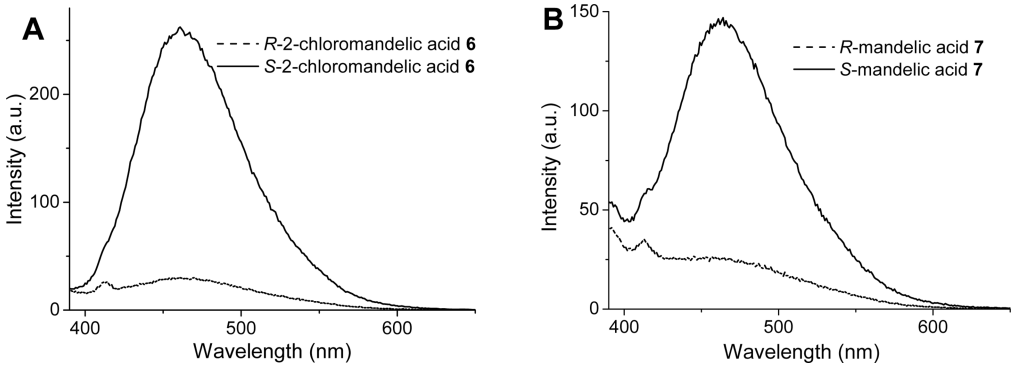
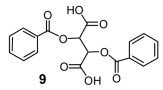
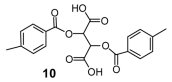
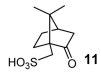
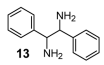
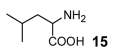
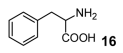
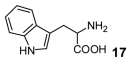
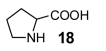
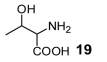
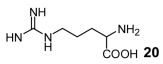
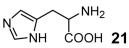
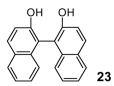
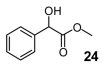
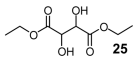


Figure 4. Fluorescence spectra of a mixture of an enantiomer of a chiral analyte and (*R*,*R*)-**5** in organic solvent(s): (A) 7.8×10^{-5} M in hexane/1,2-dichloroethane 3.5/1; (B) 1.0×10^{-4} M in hexane/1,2-dichloroethane 2.7/1. [(*R*,*R*)-**5**] = [analyte].

DOI: 10.1021/acs.joc.6b00371
J. Org. Chem. 2016, 81, 3720−3726

Table 1. Fluorescence Intensity Ratio and State of the Mixture of Enantiomer of Analyte with (*R*,*R*)-5 in Solvent(s)

Entry	Analytes	I_1/I_2	State[a]	Solvent[b]
1	 **6**	8.8 (S/R)	Sus/Sol	7.8×10^{-5} M in hexane/DCE 3.5:1
2	 **7**	5.9 (S/R)	Sus/Sol	1.0×10^{-4} M in hexane/DCE 2.7:1
3	 **8**	3.6 (R/S)	Pre/Sol	8.9×10^{-5} M in hexane/DCE 4.0:1
4	 **9**	3.8 (D/L)	Pre/Sol	8.0×10^{-5} M in hexane/ DCE 5.5:1
5	 **10**	9.2 (D/L)	Sus/Sol	8.0×10^{-5} M in hexane/DCE 4.0:1
6	 **11**	63 (L/D)	pre/sol	8.5×10^{-5} M in hexane/DCE 5.9:1
7	 **12**	9.3 (S/R)	Sus/sol	7.6×10^{-5} M in hexane/DCE 4.0:1
8	 **13**	2.4 (SS/RR)	Sus/Sol	7.4×10^{-5} M in hexane/DCE 3.9:1
9	 **14**	33 (SS/RR)	Sus/Sol	5.4×10^{-5} M in hexane/DCE 6.0:1
10	 **15**	156 (L/D)	Sus/Sol	1.0×10^{-4} M in H_2O/THF 4.0:1
11	 **16**	9.1 (L/D)	Sus/Sol	1.0×10^{-4} M in H_2O/THF 1.6:1
12	 **17**	6.2 (L/D)	Sus/Sol	4.5×10^{-5} M in H_2O/THF 1.9:1
13	 **18**	2.6 (D/L)	Sus/Sol	1.0×10^{-4} M in H_2O/THF 1.4:1
14	 **19**	3.6 (D/L)	Sus/Sol	1.0×10^{-4} M in H_2O/THF 1.7:1
15	 **20**	15.8 (L/D)	Sus/Sol	1.2×10^{-4} M in H_2O/THF 1.6:1
16	 **21**	49 (L/D)	Sus/Sol	1.0×10^{-4} M in H_2O/THF 1.5:1
17	 **22**	2.5 (L/D)	Sus/Sol	1.3×10^{-4} M in H_2O/THF 1.7:1
18	 **23**	2.0 (R/S)	Sus/Sol	1.2×10^{-4} M in H_2O/THF 1.9:1
19	 **24**	55 (S/R)	Sus/Sol	5.8×10^{-5} M in hexane/DCE 3.6:1
20	 **25**	3.3 (L/D)	Sus/Sol	8.1×10^{-5} M in hexane/DCE 4.0:1

[a]Enantiomer 1/enantiomer 2. Abbreviations: Pre, precipitates; Sus, suspension; Sol, solution. [b]Volume ratio of solvents. DCE = 1,2-dichloroethane; [(*R*,*R*)-**5**] = [analyte].

enantiomeric purity of the chiral analyte could be quantitatively measured, which was demonstrated by the example shown in Figure 5. When the concentration of the chiral receptor **5** and the total concentration of the two enantiomers of 2-chloromandelic acid **6** were made invariant (7.8×10^{-5} M), with (*S*,*S*)-**5** as receptor, the fluorescence intensity increased with an increase in the molar percent of (*R*)-**6** in enantiomer composition. In contrast, with (*R*,*R*)-**5** as receptor, the fluorescence intensity decreased with an increase in the molar percent of (*R*)-**6**. The resultant two standard curves could be used to determine the enantiomeric purity of chiral carboxylic acid **6**. This has a great potential for high-throughput analysis of the enantiomeric purity of chiral drugs and reagents.

To get insight into the interaction mechanism of (*R*,*R*)-**5** with the chiral acid **6**, the ^{1}H NMR spectra of a mixture of (*R*,*R*)-**5** and (*R*)-/(*S*)-**6** and the NMR titration of (*R*,*R*)-**5** with *R*-**6** or *S*-**6** in $CDCl_3$ were recorded. When (*R*,*R*)-**5** was mixed with 0.5 equiv of (*R*)-**6** and 1 equiv of (*S*)-**6**, the proton signals

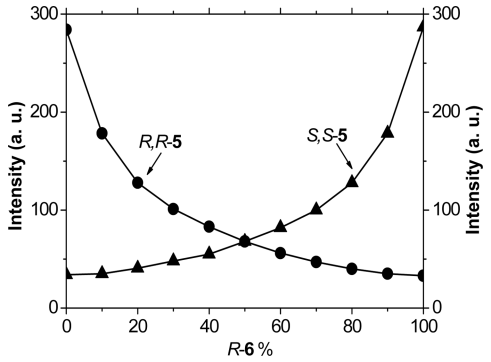


Figure 5. Change in fluorescence intensity of a mixture of (*R*,*R*)-**5** or (*S*,*S*)-**5** and 2-chloromandelic acid **6** with enantiomer content in hexane/1,2-dichlororethane 3.5/1. [*R*,*R*-**5**] = [*S*,*S*-**5**] = [*R*-**6**] + [*S*-**6**] = 7.8×10^{-5} M.

DOI: 10.1021/acs.joc.6b00371
J. Org. Chem. 2016, 81, 3720−3726

of both the urea **5** and the chiral acid **6** showed obvious changes (Figure 6). With respect to the chiral acid **6**, the signals

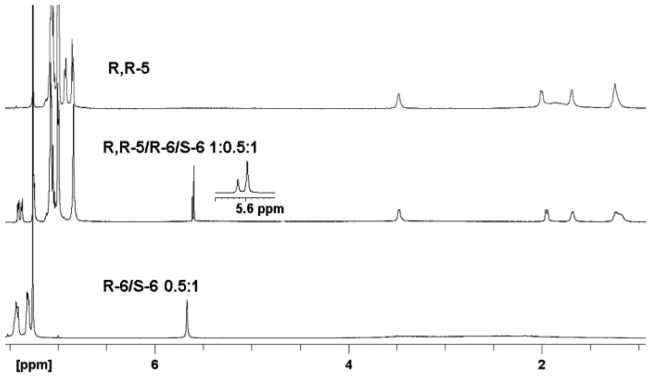


Figure 6. ^{1}H NMR spectra of (*R*,*R*)-**5**, a mixture of (*R*,*R*)-**5**, (*R*)-**6**, and (*S*)-**6** (molar ratio 1:0.5:1), and a mixture of (*R*)-**6** and (*S*)-**6** (molar ratio 0.5:1) in $CDCl_3$. [(*R*,*R*)-**5**] = 3.0 × 10^{-3} M.

of aromatic protons had an upfield shift of about 0.05−0.06 ppm from 7.31 to 7.25 ppm and from 7.42 ppm to 7.37 ppm. The methine proton also displayed an upfield shift from 5.66 to 5.61 ppm for (*R*)-**6** and upfield one from 5.66 to 5.59 ppm for (*S*)-**6**, indicating that (*S*)-**6** had a 0.02 ppm greater upfield shift than (*R*)-**6** and these two enantiomers could be discriminated in NMR spectra. With respect to the receptor (*R*,*R*)-**5**, the proton signals of the urea groups were not easily observed because of the fast exchange with carboxylic protons or protons of water that were not completely removed from the solvent. However, the proton signals of the aniline rings of the TPE unit appeared to have the largest upfield shift of 0.08 ppm, while the protons of other phenyl rings showed almost no signal change. In addition, it was the β-methylene protons rather than the α-methine proton connected to the amino group in the cyclohexyl unit that displayed a significant upfield shift of 0.06 ppm because only a 0.003 ppm upfield shift came from the α-methine proton. The distinct upfield shift of both the aniline protons and the β-methylene protons of (*R*,*R*)-**5** implied that they were placed in the shielded area of the phenyl ring of the guest acid and showed obvious CH−π interactions due to attractions of the hydrogen bonds of the carboxylic group and those of urea (Figure 7).

The NMR titration of (*R*,*R*)-**5** with (*R*)-**6** or (*S*)-**6** further demonstrated that the obvious proton signal change was an upfield shift with the addition of the guest acid (Figure 8). From the Job plots of the ^{1}H NMR titration, it was found that both (*R*)-**6** and (*S*)-**6** formed a 1:1 complex with (*R*,*R*)-**5** (Figures S11 and S12 in the Supporting Information). By nonlinear fitting analysis, the association constants of (*R*,*R*)-**5**−(*R*)-**6** and (*R*,*R*)-**5**−(*S*)-**6** complexes were 67 ± 16 and 83 ± 8.0 M^{-1}, respectively (Figure S13 and Figure S14 in the Supporting Information). From Figure 7, the interaction difference of (*R*)-**6** and (*S*)-**6** with (*R*,*R*)-**5** should come from the different binding position when (*S*)-**6** was replaced with (*R*)-**6** or the position of any two substituents at the chiral carbon of **6** was exchanged. Although the binding force from hydrogen bonds and CH−π interactions is much less than the Coulomb attraction of a basic receptor with an acidic guest, which usually led to an association constant at the level of tens of thousands,[9] the interaction difference of (*R*)-**6** and (*S*)-**6** with (*R*,*R*)-**5**, respectively, was enough to result in different polarity and solubility of the diastereomers (*R*,*R*)-**5**−(*S*)-**6** and

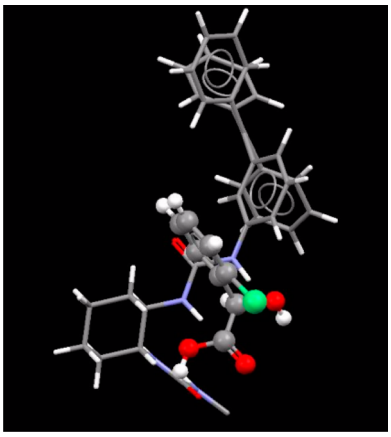


Figure 7. Diagram of both the aniline protons and the β-methylene protons of (*R*,*R*)-**5** that were placed in the shielded area of the phenyl ring of the guest acid (*S*)-**6**. (*S*)-**6** is drawn as a ball and stick diagram; (*R*,*R*)-**5** is drawn in stick form with omission of one TPE unit for clarity.

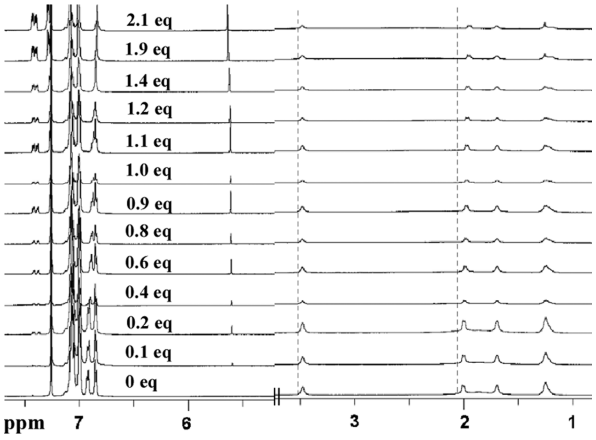


Figure 8. Changes in the ^{1}H NMR spectra of (*R*,*R*)-**5** with increasing (*S*)-**6** in $CDCl_3$. [(*R*,*R*)-**5**] = 3.0 mM; the number over the spectrum is the molar ratio of (*S*)-**6** to (*R*,*R*)-**5**.

(*R*,*R*)-**5**−(*R*)-**6** complex in the mixed solvent due to different interaction forces of (*R*,*R*)-**5** with (*S*)-**6** and (*R*)-**6**. The diastereomeric (*R*,*R*)-**5**−(*S*)-**6** complex had less solubility and was more easily aggregated than the diastereomeric complex (*R*,*R*)-**5**−(*R*)-**6**; therefore, the (*R*,*R*)-**5**−(*S*)-**6** complex emitted stronger fluorescence, which led to enantioselectivity.

■ CONCLUSIONS

In conclusion, a neutral chiral receptor based on TPE cyclohexylbisurea was synthesized and easily formed aggregates in 1,2-dichloroethane, which resulted in both AIE effects and distinct CD signals. The aggregation could be selectively triggered by only one enantiomer but could not be triggered by the other enantiomer of a wide variety of chiral reagents, including chiral acidic compounds, basic compounds, amino acids, and even neutral alcohols. ^{1}H NMR spectra disclosed that the multiple hydrogen bonds and CH−π interactions between the TPE urea receptor and the enantiomer of the chiral guest played key roles in the selective aggregation. This result exhibits a great potential for enantiomer discernment and high-throughput analysis of the enantiomer composition of many chiral analytes by one chiral AIE compound.

DOI: 10.1021/acs.joc.6b00371
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EXPERIMENTAL SECTION

^{1}H NMR titration was carried out by addition of a concentrated solution of chiral acid **6** into the solution of receptor **5** in $CDCl_3$. To keep the concentration of sensor **5** constant and account for dilution effects during titration, a solution of **6** was prepared with a solution of **5** at its initial concentration as a solvent. The association constants were calculated by nonlinear curve fitting in Origin 7.5 using the equation[16]

$$\delta_{obs} = \delta_{H} + \frac{([H] + [G] + 1/K_a) - \sqrt{([H] + [G] + 1/K_a)^2 - 4[H][G]}}{2[H]} (\delta_{com} - \delta_{H})$$

where δ_{obs} is the chemical shift of the β-methylene protons in the cyclohexyl unit of (*R*,*R*)-**5** after the enantiomer of **6** was gradually added, δ_H is the chemical shift of the β-methylene protons in the cyclohexyl unit of (*R*,*R*)-**5** without **6**, δ_{com} is the chemical shift of the β-methylene protons in the cyclohexyl unit of (*R*,*R*)-**5** in the **5**−**6** complex, [H] is the molar concentration of (*R*,*R*)-**5**, and [G] is the molar concentration of enantiomer of **6** added during titration.

Synthesis of Compound 2.[17] In a flask were placed tetraphenylethylene **1** (2.64 g, 8 mmol), glacial acetic acid (1.9 mL, 32 mmol), and dichloromethane (80 mL). After the solution was cooled to −15 °C with an ice−salt bath, concentrated nitric acid (1.6 mL, 24 mmol) was added with rigorous magnetic stirring. The reaction solution was stirred for about 15 min at the ice temperature and then was quenched with cold water. The organic phase was immediately separated and washed with water three times (3 × 50 mL). Upon drying over anhydrous Na_2SO_4 and filtration, the solution was evaporated to dryness under vacuum. The yellow residue was recrystallized from MeOH to give **2** as a yellow powder (2.25 g, 90%).

Synthesis of Compound 3.[18] In a flask were placed mononitroTPE **2** (1.2 g, 3.18 mmol), 10% Pd/C (100 mg), and EtOH (100 mL), and the mixture stirred for 15 min at room temperature. Then 85% hydrazine hydrate (5.4 mL, 95.4 mmol) was added and this mixture refluxed for 4 h. After it was cooled to room temperature, the reaction mixture was diluted with dichloromethane (30 mL) and filtered through a layer of Celite. After the solvent was removed under vacuum, the resultant white solid was dissolved in dichloromethane (50 mL) and washed with water three times (3 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was recrystallized with MeOH to give **3** as a white solid (1.02 g, 91%).

Synthesis of Compound (*R*,*R*)-5. TPE amine **3** (1.0 g, 2.88 mmol) and Et_3N (0.48 mL, 3.54 mmol) were dissolved in dichloromethane (50 mL), and the solution was cooled to 0 °C in an ice bath with stirring. After a solution of triphosgene (342 mg, 1.15 mmol) in dichloromethane (10 mL) was added dropwise within 15 min, the reaction solution was stirred for 2 h until complete disappearance of **3** and no further increase of **4**. Then (1*R*,2*R*)-cyclohexanediamine (164 mg, 1.44 mmol) was added and the mixture stirred overnight at ambient temperature. The solution was washed with water three times and dried over anhydrous Na_2SO_4. Upon filtration, the solvent was removed under vacuum and the resident was purified by flash chromatography (silica gel; eluent dichloromethane/methanol 80/1) to give (*R*,*R*)-**5** as a white solid (0.52 g, 42%): $[\alpha]^{20}_D$ = +38.8 (10 mg/mL, $CHCl_3$); mp 251−252 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−6.90 (m, 30H), 6.87 (d, *J* = 8.4 Hz, 4H), 6.80 (d, *J* = 8.5 Hz, 4H), 5.80−5.50 (w, 2H), 3.60−3.35 (w, 2H), 2.20−1.85 (m, 4H), 1.75−1.60 (m, 2H), 1.30−1.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 143.9, 143.7, 140.5, 140.4, 138.5, 136.9, 132.1, 131.4, 131.3, 127.7, 127.6, 127.6, 126.4, 126.4, 126.3, 119.3, 54.5, 33.0, 24.9; IR (KBr) ν 3337, 3078, 3053, 2931, 2857, 1656, 1593, 1551, 1444, 1404, 1316, 1225, 1182, 1154, 1117, 1074, 1029, 912, 847, 821, 757, 698, 626 cm^{-1}; ES$^+$ HRMS *m*/*z* calcd for $C_{60}H_{53}N_4O_2$ 861.4169 [M + H], found 861.4220 [M + H].

Synthesis of (*S*,*S*)-5. (*S*,*S*)-**5** was synthesized by the same procedure used for (*R*,*R*)-**5**. (*S*,*S*)-**5** was obtained as a white solid (0.56 g, 45%): $[\alpha]^{20}_D$ = −43.6 (10 mg/mL, $CHCl_3$); mp 252−253 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−6.93 (m, 30H), 6.87 (d, *J* = 8.4 Hz, 4H), 6.79 (d, *J* = 8.5 Hz, 4H), 5.90−5.59 (w, 2H), 3.55−3.35 (w, 2H), 2.36−2.06 (w, 2H), 2.06−1.90 (m, 2H), 1.78−1.59 (m, 2H), 1.33−1.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 143.8, 143.7, 140.5, 140.3, 138.5, 136.8, 132.1, 131.4, 131.3, 127.7, 127.65, 127.61, 126.4, 126.38, 126.31, 119.3, 54.5, 32.9, 24.9; IR (KBr) ν 3329, 3078, 3052, 2934, 2857, 1655, 1594, 1561, 1404, 1316, 1250, 1226, 762, 689, 628 cm^{-1}; ES$^+$ HRMS *m*/*z* calcd for $C_{60}H_{53}N_4O_2$ 861.4169 [M + H], found 861.4174 [M + H].

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00371.

^{1}H and ^{13}C NMR, IR, and HRMS spectra and nonlinear fittings for the association constant (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail for Y.-S.Z.: zyansong@hotmail.com

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the National Natural Science Foundation of China (21072067) and the HUST Interdisciplinary Innovation Team (2015ZDTD055) for financial support and thank the Analytical and Testing Centre at the Huazhong University of Science and Technology for measurements.

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