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Calix[4]arene-Based Chromogenic Chemosensor for the α-Phenylglycine Anion: Synthesis and Chiral Recognition

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Calix[4]arene-based two-armed chiral anion receptors **3a** and **3b** have been synthesized and examined for their chiral anion-binding abilities by UV/Vis absorption and ^{1}H NMR spectroscopy. The results of nonlinear curve fitting indicate that **3a** and **3b** form 1:1 stoichiometric complexes with the L- or D-α-phenylglycine anion by multiple hydrogen-bonding interactions and exhibit good enantioselective recognition for the enantiomers of the α-phenylglycine anions (**3a**: $K_{ass(L)}/K_{ass(D)}$ = 4.76; **3b**: $K_{ass(D)}/K_{ass(L)}$ = 2.84). The marked colour changes observed for the complexation of **3a** with the chiral anions and the good enantioselective recognition reveal that receptor **3a** could be used as a good chiral chromogenic chemosensor for the enantiomers of the α-phenylglycine anion.

Introduction

Molecular recognition, and in particular chiral recognition, is a fundamental feature of biochemical systems. The study of synthetic model systems could contribute to the understanding of these processes and, at the same time, offer new perspectives for the development of pharmaceuticals, enantioselective sensors, catalysts and other molecular devices.[1] The specific recognition of a certain molecule and the transformation of the recognition event into a signal are crucial points for the molecular design of a chemosensor. Recently, fluorescent and luminescent sensors have been developed for the selective recognition of cations, anions and neutral molecules.[2] However, the use of colorimetric sensors or chromogenic chemosensors has received less attention.[3] The use of such sensors would be a real advantage because the recognition event between host and guest is visible to the naked eye and immune to other factors such as autofluorecence, light scattering as well as electrical interferences. Because of this, several researchers have recently developed optical chemosensor systems for the recognition and monitoring of biologically relevant substrates.[4]

Amino acids and peptides have often been employed as chiral sources in the synthesis of chiral receptors because of their accessibility and biological relevance.[5] Urea, thiourea and amide groups are good hydrogen-bonding donors, thiourea recognition units having an especially strong ability to hydrogen bond to anions, which are widely used in the design and synthesis of artificial receptors for anions.[6] Calixarenes, with their unique three-dimensional structures and almost unlimited scope for derivatization, are important molecular building blocks with a wide range of potential applications.[7]

Phenylglycine is a synthetic amino acid used in the manufacture of β-lactam antibiotics such as semisynthetic cephalosporin and penicillin.[8] Though elegant synthetic methods have been developed for the preparation of phenylglycine derivatives, there is still a need for efficient and rapid monitoring of the amount of each enantiomer of these compounds formed.[9]

Herein, we report the synthesis of two chiral chromogenic receptors (**3a** and **3b**) which contain both thiourea and amino acid binding units. The chiral recognition ability of receptors **3a** and **3b** towards the α-phenylglycine anion was investigated by UV/Vis absorption and ^{1}H NMR spectroscopy. The results reveal that **3a** exhibits good enantioselective recognition for the enantiomers of the α-phenylglycine anion.

Results and Discussion

Synthesis

The synthesis of calix[4]arene derivatives **3a** and **3b** is outlined in Scheme 1. Compounds **1a** and **1b** were synthesized according to literature methods[10] and the intermediates **2a** and **2b** were obtained in high yields (97–98%). Compounds **2a** and **2b** were allowed to react with *p*-nitrophenyl isothiocyanate to give target molecules **3a** and **3b**. Receptors **3a** and **3b** are readily soluble in common organic solvents such as $CHCl_3$, CH_3OH, DMSO and DMF. The structures

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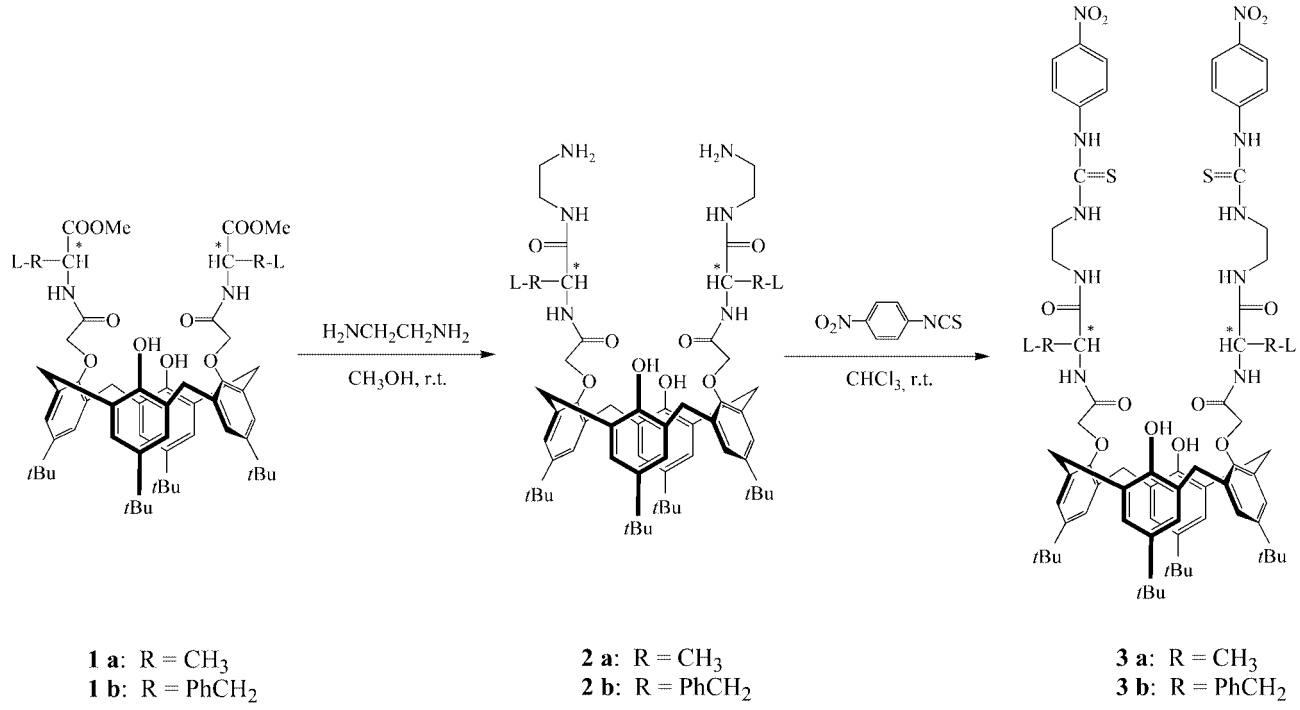
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



1 a: R = CH_3
1 b: R = $PhCH_2$

2 a: R = CH_3
2 b: R = $PhCH_2$

3 a: R = CH_3
3 b: R = $PhCH_2$

Scheme 1. Synthesis of receptors **3a** and **3b**.

of these compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopy, ESI-MS and elemental analysis.

The stereogenic centers of receptors **3a** and **3b** disturb the planar symmetry of the parent rings, resulting in more aromatic carbon signals in the ^{13}C NMR spectra of receptors **3a** and **3b**. This pattern is similar to those observed in the ^{13}C NMR spectra of other chiral calix[4]arenes.[10,11] The ^1H NMR spectra of **3a** and **3b** exhibit two sets of doublets due to the bridging methylene protons and two sets of singlets due to the *tert*-butyl groups. This indicates that the two receptors adopt the cone conformation in $CHCl_3$. The ^1H NMR spectra of **3a** and **3b** also exhibit one set of doublets due to $ArOCH_2$ protons. This splitting pattern may be related to the introduction of chiral moieties into the molecules, as seen with other chiral calix[4]arenes.[10,11]

UV/Vis Spectra Study

A series of UV/Vis spectral titration experiments was undertaken to investigate the possible interactions between the host and each enantiomer of the α-phenylglycine anion. In each case the countercation was tetrabutylammonium.

The UV/Vis absorption spectra of **3a** upon addition of L-α-phenylglycine anions are shown in Figure 1. In the absence of the anion, **3a** has an absorption maximum at 359 nm, which can be assigned to an intramolecular charge-transfer (CT) absorption band. With the addition of the L-α-phenylglycine anion to a solution of receptor **3a** in DMSO (5.0×10^{-5} mol L^{-1}), the characteristic absorption peak of the host at 359 nm gradually decreased with a bathochromic shift (about 5 nm) and a new absorption peak at about 481 nm appeared, illustrating that a complex had formed between the host and guest. Meanwhile, a clear isosbestic point was observed at 380 nm, indicating that there is a balance between the complex and host, guest in solution.[12] Upon gradually increasing the concentration of the L-α-phenylglycine anion, the colour of the solution of **3a** changed from colorless to yellow, which could be observed by the naked eye.

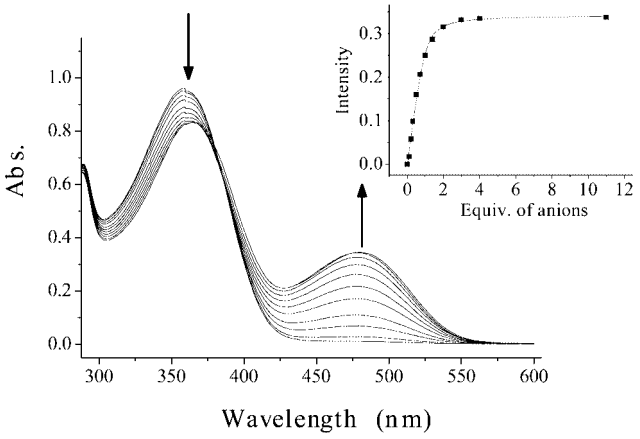


Figure 1. UV/Vis absorption spectra of receptor **3a** in DMSO (5.0×10^{-5} mol L^{-1}) upon the addition of various amounts of the L-α-phenylglycine anion. Anion equivalents: 0, 0.1, 0.2, 0.3, 0.5, 0.7, 1.0, 1.4, 2.0, 3.0, 4.0 and 11.0. Nonlinear curve fitting for the change in absorbance at 481 nm with respect to the amount of L-α-phenylglycine anion added is shown in the inset. The correlation coefficient (R) of the nonlinear curve fitting is 0.9968.

Similar phenomena were observed when D-α-phenylglycine anion was added to a solution of **3a** in DMSO (5.0×10^{-5} mol L^{-1}) (Figure 2). The characteristic absorp-

tion peak of the host at 359 nm gradually decreased with a slight bathochromic shift (about 10 nm) and a new absorption peak appeared at about 481 nm; the intensity of the new peak is greater than that of **3a** with the L-α-phenylglycine anion. In particular, upon gradually increasing the concentration of the D-α-phenylglycine anion, the color of the solution clearly changed from colorless to saffron. This colour change is attributable to an obvious increase of absorption in the visible region at 481 nm. A clear isosbestic point was also observed at 384 nm. The new absorption of the **3a** solution in the visible region can be ascribed to charge-transfer interactions between the electron-rich donor nitrogen atom of the thiourea units and the electron-deficient *p*-nitrophenyl moieties. When the receptor became bound to a L-α-phenylglycine anion, hydrogen bonds were constructed to form stable complexes and the electron density in the supramolecular system was considerably increased. This enhanced the charge-transfer interactions between the electron-rich and -deficient moieties, resulting in a visible color change.[13] When a protic solvent such as methanol was added to the yellow solution of **3a** and the L-α-phenylglycine anion or the saffron solution of **3a** and the D-α-phenylglycine anion in DMSO, the colour of both solutions became colorless. This phenomenon illustrates that the addition of a protic solvent destroyed the complexation between **3a** and the L- or D-α-phenylglycine anion, demonstrating that the interaction between **3a** and the L- or D-α-phenylglycine anion was, in essence, a hydrogen-bonding interaction. The satisfactory nonlinear curve fitting (absorption intensity at 481 nm vs. equivalents of the α-phenylglycine anion; correlation coefficient >0.99) confirmed that receptor **3a** and the L- or D-α-phenylglycine anion formed a 1:1 complex (see the insets of Figure 1 and Figure 2).[14] In addition, the association constants of the two ions with **3a** are very different [$K_{ass(L)} = 2.34 \times 10^5$ M^{-1}; $K_{ass(D)} = 4.91 \times 10^4$ M^{-1}], demonstrating that **3a** exhibits good enantioselective recognition for the enantiomers of the α-phenylglycine anions.

Receptor **3b** showed a similar response to **3a** on addition of the L- or D-α-phenylglycine anion. In the absence of the anion, the UV/Vis spectra of **3b** in DMSO (5.0×10^{-5} mol L^{-1}) exhibited an intramolecular CT absorption band (λ_{max} = 359 nm). With the addition of the L- or D-α-phenylglycine anion, the CT band shifted, respectively, to 373 and 374 nm and a new absorption at 479 nm was observed (see Figure 3 and Figure 4). The color of both solutions changed from colorless to saffron. A clear shift of the isosbestic point was observed from 386 nm to 398 and 395 nm for the L and D enantiomers, respectively. This may be due to different complexation states of the host and guest. Because **3b** has a greater steric hindrance caused by the aryl rings in the chiral units, the two arms in **3b** cannot get close enough to each other to form a good preorganized structure. At lower concentrations of the guest anion, the 1:1 complex may be formed between one arm of **3b** and the guest anion. When the receptor became bound to an anion, the electron density in the supramolecular system increased, which enhanced the charge-transfer interactions between

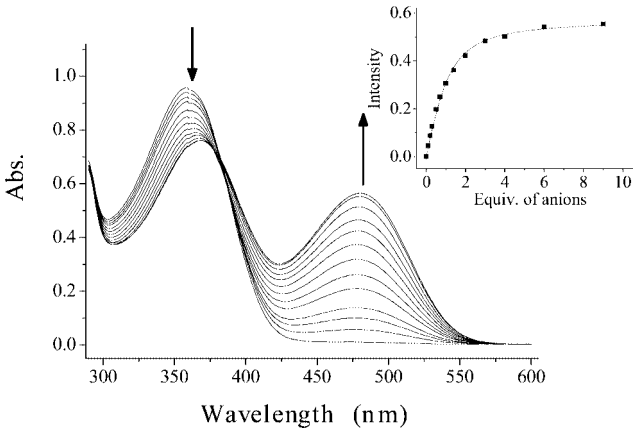


Figure 2. UV/Vis absorption spectra of receptor **3a** in DMSO (5.0×10^{-5} mol L^{-1}) upon the addition of various amounts of the D-α-phenylglycine anion. Anion equivalents: 0, 0.1, 0.2, 0.3, 0.5, 0.7, 1.0, 1.4, 2.0, 3.0, 4.0, 6.0 and 9.0. The nonlinear curve fitting for the change in absorbance at 481 nm with respect to the amount of D-α-phenylglycine anion added is shown in the inset. The correlation coefficient (*R*) of the nonlinear curve fitting is 0.9975.

the electron-rich donor units and the electron-deficient *p*-nitrophenyl moieties, resulting in the new absorption peak. At higher concentrations of the guest anion, the 1:1 complex may be formed between the two arms of **3b** and the guest anion, resulting in an extension of the supramolecular system and increased CT interactions with an enhancement of the absorption at 479 nm. The satisfactory nonlinear curve fitting (absorption intensity at 479 nm vs. equivalents of α-phenylglycine anion; correlation coefficient >0.99) confirmed that receptor **3b** and the L- or D-α-phenylglycine anion formed a 1:1 complex (see the insets of Figure 3 and Figure 4).[14] Receptor **3b** exhibited similar enantioselective recognition for the α-phenylglycine anion as **3a**. The ratio of the association constants for the complex of **3a** and the two α-phenylglycine anions is $K_{ass(L)}/K_{ass(D)}$ = 4.76, while for **3b** $K_{ass(D)}/K_{ass(L)}$ = 2.84. The results illustrate that receptor **3a** exhibits good enantioselective recognition for the enantiomers of the α-phenylglycine anions. The much higher association constants for the complexation of **3a** with the L-α-phenylglycine anion and for the complexation of **3b** with the D-α-phenylglycine anion are probably due to the L- and D-α-phenylglycine anions having a more complementary structure with respect to receptor **3a** and **3b**, respectively.

Continuous variation methods were used to determine the stoichiometric ratios of the complexes formed between the receptors **3a** and **3b** and the anion guests. The total concentration of the host and the α-phenylglycine anion guest was kept constant (1.0×10^{-4} mol L^{-1}) in DMSO, whilst the molar fraction of the guest {[G]/([H]+[G])} was continuously varied. Figure 5 shows the Job plots for **3a** (at 481 nm) and **3b** (at 479 nm) with L- and D-α-phenylglycine anions in DMSO. When the molar fraction of the guest is 0.50, the absorption reaches a maximum, demonstrating that receptors **3a** and **3b** both formed a 1:1 complex with L- or D-α-phenylglycine anions.[15]

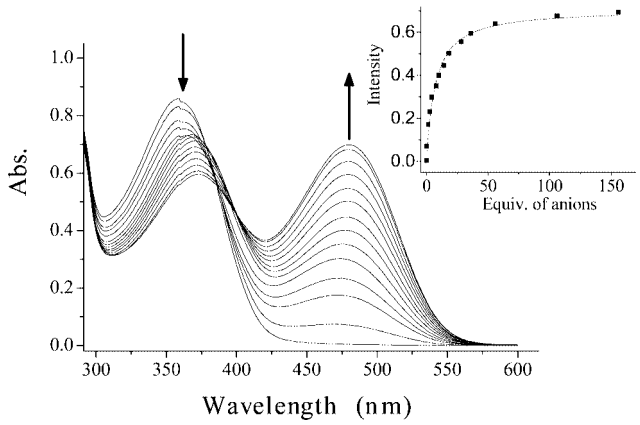


Figure 3. UV/Vis absorption spectra of receptor **3b** in DMSO (5.0×10^{-5} mol L^{-1}) upon the addition of various amounts of the L-α-phenylglycine anion. Anion equivalents: 0, 0.4, 1.4, 3.0, 4.6, 8.2, 10.2, 14.2, 18.2, 28.2, 36.2, 56.2, 106.2 and 156.2. Nonlinear curve fitting for the change in absorbance at 479 nm with respect to the amount of L-α-phenylglycine anion added is shown in the inset. The correlation coefficient (R) of the nonlinear curve fitting is 0.9935.

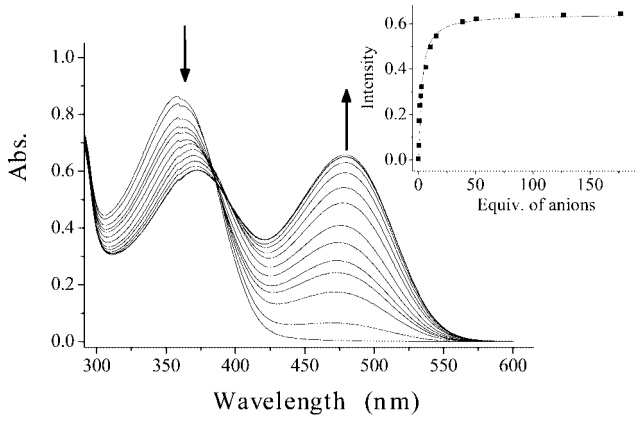


Figure 4. UV/Vis absorption spectra of receptor **3b** in DMSO (5.0×10^{-5} mol L^{-1}) upon the addition of various amounts of D-α-phenylglycine anion. Anion equivalents: 0, 0.4, 0.8, 1.5, 2.0, 2.8, 6.8, 10.8, 15.8, 38.8, 50.8, 86.8, 126.8 and 176.8. Nonlinear curve fitting for the change in absorbance at 479 nm with respect to the amount of D-α-phenylglycine anion added is shown in the inset. The correlation coefficient (R) of the nonlinear curve fitting is 0.9928.

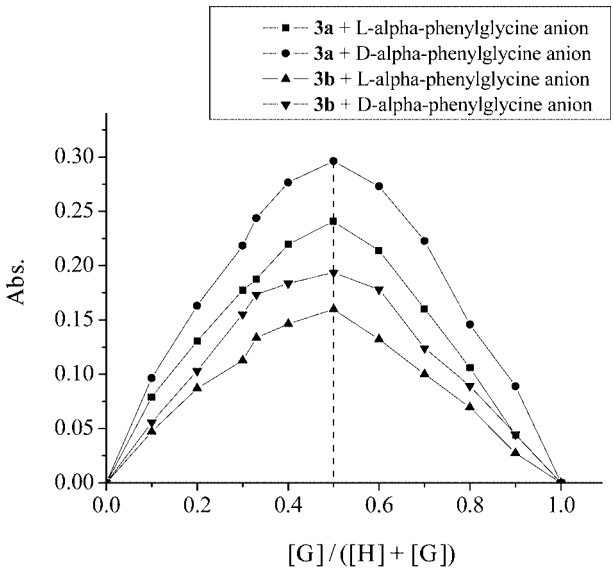


Figure 5. Job plots of **3a** (at 481 nm) and **3b** (at 479 nm) with L- or D-α-phenylglycine anions. The total concentration of the host and guest is 1.0×10^{-4} mol L^{-1} in DMSO.

The interactions between receptor **3a** or **3b** and the enantiomers of the mandelate or dibenzoyl tartrate anion have also been investigated by UV/Vis spectroscopy. The results are listed in Table 1 and show that **3a** and **3b** have lower chiral recognition ability towards the enantiomers of the mandelate and dibenzoyl tartrate anions.

For a complex with a stoichiometry of 1:1, the association constant K_{ass} can be calculated from Equation (1) from the Origin 7.0 package,[14a,16] where X is the absorption intensity and C_H and C_G are the corresponding concentrations of the host and guest anion; C_0 is the initial concentration of the host. The association constants (K_{ass}) and correlation coefficients (R) obtained by a nonlinear least-squares analysis of X versus C_H and C_G are listed in Table 1.

$$X = X_0 + (X_{lim} - X_0)/2\,C_0\{C_H + C_G + 1/K_{ass} - [(C_H + C_G + 1/K_{ass})^2 - 4\,C_H C_G]^{1/2}\} \quad (1)$$

The data in Table 1 illustrate that receptor **3a** has better enantioselective recognition ability towards the enantiomers of the α-phenylglycine anions than receptor **3b**. Receptors

Table 1. Association constants (K_{ass}) and correlation coefficients (R) for complexes formed between receptors **3a** and **3b** and anion guests in DMSO.

Anion[a]	Receptor **3a**		Receptor **3b**	
	K_{ass} [M^{-1}][b][c]	R	K_{ass} [M^{-1}][b][c]	R
L-α-Phenylglycine	$(2.34\pm0.03)\times10^5$	0.9968	$(2.95\pm0.01)\times10^3$	0.9935
D-α-Phenylglycine	$(4.91\pm0.02)\times10^4$	0.9975	$(8.40\pm0.02)\times10^3$	0.9928
L-Mandelate	413.64 ± 2.70	0.9968	194.16 ± 1.81	0.9984
D-Mandelate	166.94 ± 2.53	0.9951	337.51 ± 3.04	0.9946
Dibenzoyl L-tartrate	1560.27 ± 5.52	0.9938	1104.47 ± 4.41	0.9965
Dibenzoyl D-tartrate	1654.36 ± 4.87	0.9942	501.94 ± 3.91	0.9962

[a] Anions were used as their tetrabutylammonium salts. [b] Values of K_{ass} were calculated from UV/Vis titrations in DMSO. [c] All error values were obtained by nonlinear curve fitting.

3a and **3b** also exhibit definite enantioselective recognition towards the enantiomers of the mandelate and dibenzoyl tartrate anions. The association constants for the complexes of **3a** and a range of anions are much higher than those of **3b**, which may be a result of the greater steric hindrance in **3b** caused by the aryl rings in the chiral units. This greater steric hindrance may prevent the two arms in **3b** from getting close enough together to form a good preorganized structure, reducing its selective recognition ability towards guests. Because the receptor **3a** has a relatively rigid structure and a good preorganized structure, receptor **3a** exhibits higher enantioselective recognition for the L- and D-α-phenylglycine anions than **3b**.

^{1}H NMR Study

^{1}H NMR experiments were undertaken to assess the chiral recognition properties between the receptors and the L- or D-α-phenylglycine anions because they can directly provide structural and dynamic information.[17] Chiral recognition studies were carried out using a 300 MHz NMR spectrometer with compounds **3a** and **3b** as the chiral-solvating agents.

Tetrabutylammonium α-phenylglycine was chosen as the probe. The ^{1}H NMR spectrum of racemic α-phenylglycine anions in $CDCl_3$ in the absence of the host exhibited only one singlet (δ = 4.309 ppm) due to the CH proton resonance. The ^{1}H NMR spectra of **3a** (2.0×10^{-3} M) and its complex with equimolar amounts (2×10^{-3} M) of the L-, D- or racemic α-phenylglycine anion were recorded (see the Supporting Information). Two singlet resonances (δ = 4.438 and 4.479 ppm) due to the CH proton of the racemic α-phenylglycine anion were observed in the presence of sensor **3a** with an intensity ratio of about 1:1; the separation between the two peaks is 12.3 Hz. This indicates that the interactions between **3a** and the L and D forms of the α-phenylglycine anion are different, resulting in two singlet resonances for the racemic CH proton. The CH proton singlet resonances of the L- and D-α-phenylglycine anions are shifted downfield by about 0.170 and 0.129 ppm, respectively, in the presence of the sensor **3a**. The different downfield shifts of the CH proton of the two enantiomers reveal that **3a** has good enantioselective recognition ability.

The ^{1}H NMR spectra of **3b** (2.0×10^{-3} M) and its complex with equimolar amounts (2×10^{-3} M) of the L-, D- or racemic α-phenylglycine anion were also recorded (see the Supporting Information). Two singlet resonances (δ = 4.408 and 4.420 ppm) due to the CH proton of the racemic α-phenylglycine anion were observed in the presence of **3b** with an intensity ratio of about 1:1; the separation between the two peaks is 3.6 Hz. This indicates that the interactions between **3b** and the L and D forms of the α-phenylglycine anion are different, resulting in two singlet resonances for the racemic CH proton. The CH proton of the complex between **3b** and the D enantiomer has a larger downfield shift ($\Delta\delta$ = 0.111 ppm) than that of the complex between **3b** and the L enantiomer ($\Delta\delta$ = 0.099 ppm). Hence, in contrast to receptor **3a**, **3b** has a stronger interaction with the D-α-phenylglycine anion than with the L-α-phenylglycine anion.

The ^{1}H NMR spectra of receptors **3a** and **3b** also show other dramatic changes in the presence of a guest. Upon addition of an equimolar amount of the L-α-phenylglycine anion to a solution of **3a**, the two characteristic amide (N**H**) peaks at δ = 9.31 and 9.89 ppm disappeared. Upon addition of an equimolar amount of the D-α-phenylglycine anion to a solution of **3a**, one of the characteristic amide (N**H**) peaks is shifted upfield from 9.31 to 9.30 ppm ($\Delta\delta$ = 0.01 ppm), the other amide (N**H**) peak is also shifted upfield from 9.89 to 9.42 ppm ($\Delta\delta$ = 0.47 ppm) and both of the amide (N**H**) signals become much weaker. In each case, all the signals arising from the thiourea's protons are weakened.

Upon addition of an equimolar amount of the L-α-phenylglycine anion to a solution of **3b**, one of the characteristic amide (N**H**) peaks is shifted upfield from 9.27 to 9.26 ppm ($\Delta\delta$ = 0.01 ppm), the other amide (N**H**) peak is also shifted upfield from 10.11 to 9.63 ppm ($\Delta\delta$ = 0.48 ppm) and both of the amide (N**H**) peaks become much weaker. Upon addition of an equimolar amount of the D-α-phenylglycine anion to a solution of **3b**, the two characteristic amide (N**H**) peaks at 9.27 and 10.11 ppm disappeared. The above result illustrates that the interaction between the host and guest also occurs through multiple hydrogen bonds.

The results of the ^{1}H NMR investigation of the interaction between receptors **3a** or **3b** and the guest indicate that the interaction between **3a** and the L-α-phenylglycine anion is stronger than that between **3a** and the D enantiomer while **3b** exhibited contrasting recognition ability for the enantiomers of the α-phenylglycine anion. Except for the multiple hydrogen-bonding interactions between the host and guest, the steric differences between the hosts **3a** and **3b** may be the main reason for the differences in recognition ability for D- and L-α-phenylglycine anions.[18]

Conclusions

Two chiral chromogenic sensors **3a** and **3b** have been synthesized. The enantioselective recognition ability of the receptors was studied by UV/Vis absorption and ^{1}H NMR spectroscopy. Receptors **3a** and **3b** exhibit different chiral recognition abilities towards the enantiomers of tetrabutylammonium L- and D-α-phenylglycine and formed 1:1 complexes with the guests. Receptor **3a** has a better enantioselective recognition ability than **3b**. Steric effects, a relatively good preorganized structure and the better hydrogen-bonding ability of **3a** may be responsible for its better enantioselective recognition of the α-phenylglycine anions. The good enantioselective recognition and obvious colour change on complexation of **3a** and the α-phenylglycine anion indicate that **3a** could be used as a chiral chromogenic sensor for the enantiomers of the α-phenylglycine anion.

Experimental Section

General: Melting points were determined with a Reichert 7905 melting-point apparatus and are uncorrected. Optical rotations

were recorded with a Perkin–Elmer Model 341 polarimeter. IR spectra were obtained with a Nicolet 670 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian Mercury VX 300-MHz and a Varian Inova 600-MHz spectrometer, respectively. Mass spectra were recorded with a Finnigan LCQ Advantage mass spectrometer. Elemental analysis was performed with a Carlo–Erba 1106 instrument. The UV/Vis spectra were recorded with a TU-1901 spectrophotometer. Ethylenediamine was distilled before use. $CHCl_3$ was washed with water and dried with $CaCl_2$ and Et_3N was dried and distilled from CaH_2. All other commercially available reagents were used without further purification. The anions were used as their tetrabutylammonium salts. Compounds **1a** and **1b** were synthesized according to the method reported in the literature.[10]

General Procedure for the Synthesis of the Calix[4]arene Derivatives 2: A solution (20 mL) of **1a** or **1b** (1.5 mmol) in CH_3OH was added dropwise to a stirred solution of ethylenediamine (0.54 g, 9.0 mmol) in CH_3OH (10 mL). The mixture was stirred for 48 h under N_2 at room temperature. The solvent and excess ethylenediamine were removed under reduced pressure and the residue was dried in vacuo to give product **2a** or **2b** as a yellow solid.

Calix[4]arene Derivative 2a: The pure product was obtained as a yellow powder (1.46 g) in 98% yield; m.p. 154–156 °C. IR (KBr): $\tilde{\nu}$ = 3420, 3049, 2959, 2869, 1659, 1540, 1483, 1391, 1362, 1301, 1232, 1203, 1124, 1042, 982, 872, 819, 593 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.04 (s, 18 H, *t*Bu), 1.26 (s, 18 H, *t*Bu), 1.42 (d, J = 7.2 Hz, 6 H, CCH_3), 2.80–2.94 (m, 8 H, $CH_2CH_2NH_2$), 3.25–3.33 (m, 4 H, $CONHCH_2$), 3.38–3.49 (m, 4 H, $ArCH_2Ar$), 4.17–4.25 (m, 4 H, $ArCH_2Ar$), 4.35 (d, J = 15 Hz, 2 H, OCH_2CO), 4.62–4.69 (m, 2 H, NC*HCO), 4.86 (d, J = 15 Hz, 2 H, OCH_2CO), 6.87 (s, 4 H, ArH), 6.99 (s, 4 H, ArH), 7.87 (s, 2 H, ArOH), 9.42 (d, J = 7.2 Hz, 2 H, CONH), 9.60 (s, 2 H, CONH) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.4, 19.1, 31.2, 31.8, 34.7, 34.3, 40.9, 41.2, 44.8, 46.7, 49.2, 75.1, 125.4, 125.8, 126.1, 126.7, 126.9, 127.2, 132.4, 132.7, 142.8, 143.3, 148.3, 148.5, 149.3, 149.8, 150.2, 150.4, 169.4, 172.6, 173.5 ppm. $C_{58}H_{82}N_6O_8$: C 70.26, H 8.35, N 8.48; found C 70.12, H 8.47, N 8.51.

Calix[4]arene Derivative 2b: The pure product was obtained as a yellow powder (1.66 g) in 97% yield; m.p. 158–160 °C. IR (KBr): $\tilde{\nu}$ = 3314, 3058, 2959, 2865, 1658, 1536, 1483, 1362, 1301, 1260, 1205, 1109, 1041, 870. 848, 727, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 18 H, *t*Bu), 1.08 (s, 18 H, *t*Bu), 2.74–2.96 (m, 8 H, $NCH_2CH_2NH_2$), 3.00–3.05 (m, 4 H, $ArCH_2CH$), 3.27–3.32 (m, 4 H, $CONHCH_2$), 3.53 (d, J = 14.9 Hz, 2 H, $ArCH_2Ar$), 3.87 (d, J = 15 Hz, 2 H, $ArCH_2Ar$), 4.10 (d, J = 15 Hz, 2 H, $ArCH_2Ar$), 4.18 (d, J = 15 Hz, 2 H, $ArCH_2Ar$), 4.93–4.97 (m, 2 H, NC*HCO), 5.10 (d, J = 16 Hz, 2 H, OCH_2CO), 5.23 (d, J = 15.9 Hz, 2 H, OCH_2CO), 6.84 (s, 4 H, ArH), 6.94–7.07 (m, 10 H, ArH), 7.15 (s, 4 H, ArH), 8.22 (s, 2 H, ArOH), 9.28 (d, J = 8.4 Hz, 2 H, CONH), 9.79 (s, 2 H, CONH) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.2, 31.9, 34.1, 32.6, 34.3, 39.8, 41.2, 41.7, 45.0, 46.6, 53.9, 54.7, 75.0, 75.8, 125.1, 125.2, 125.7, 125.9, 126.3, 126.4, 126.7, 126.8, 127.0, 127.5, 128.2, 128.5, 128.8, 129.5, 132.4, 132.9, 136.9, 137.6, 142.4, 147.9, 148.3, 149.3, 150.0, 150.4, 169.3, 169.9, 170.7, 172.1 ppm. $C_{70}H_{90}N_6O_8$: C 73.51, H 7.95, N 7.35; found C 73.25, H 8.13, N 7.29.

General Procedure for the Synthesis of 3: A solution of *p*-nitrophenyl isothiocyanate (0.36 g, 2.0 mmol) in dry $CHCl_3$ (15 mL) was added dropwise to a solution of **2a** or **2b** (1.0 mmol) in dry $CHCl_3$ (15 mL) at room temperature. The reaction mixture was then stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: $CHCl_3$/CH_3CH_2OH).

Calix[4]arene Derivative 3a: The pure product (0.35 g) was obtained by column chromatography on silica gel [eluent: $CHCl_3$/CH_3CH_2OH, 20:1 (v/v)] as a pale yellow powder in 25.9% yield; m.p. 162–164 °C. $[\alpha]_D^{20}$ = +47.76 (c = 0.05, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3335, 2960, 2867, 1655, 1597, 1540, 1484, 1457, 1330, 1302, 1259, 1205, 1123, 1111, 1040, 869, 852, 715, 652, 590 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.00 (s, 18 H, *t*Bu), 1.29 (s, 18 H, *t*Bu), 1.45 (d, J = 5.7 Hz, 6 H, $CHCH_3$), 2.82 (d, J = 5.7 Hz, 4 H, CH_2CH_2NH), 3.40 (d, J = 13.0 Hz, 2 H, $ArCH_2Ar$), 3.48 (d, J = 12.8 Hz, 2 H, $ArCH_2Ar$), 3.65–3.83 (m, 4 H, $CONHCH_2$), 4.18 (d, J = 13.2 Hz, 2 H, $ArCH_2Ar$), 4.23 (d, J = 13.2 Hz, 2 H, $ArCH_2Ar$), 4.36 (d, J = 15.0 Hz, 2 H, OCH_2CO), 4.52–4.70 (m, 2 H, NC*HCO), 4.95 (d, J = 15.0 Hz, 2 H, OCH_2CO), 6.96 (d, J = 6.8 Hz, 4 H, ArH), 7.07 (d, J = 6.8 Hz, 4 H, ArH), 7.38 (br., 2 H, CH_2NHCS), 7.61 (br., 2 H, CSNHAr), 7.78 (d, J = 7.2 Hz, 4 H, O_2N-ArH), 7.96 (s, 2 H, ArOH), 8.06 (d, J = 7.2 Hz, 4 H, O_2N-ArH), 9.31 (d, J = 6.6 Hz, 2 H, CONHCH), 9.89 (s, 2 H, $CONHCH_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.7, 18.9, 31.1, 31.2, 31.6, 31.8, 32.3, 32.6, 32.9, 32.9, 34.2, 34.3, 34.4, 36.6, 39.5, 41.2, 49.4, 50.1, 75.0, 121.5, 124.7, 125.4, 125.7, 126.1, 126.3, 126.4, 126.9, 127.1, 127.3, 127.8, 132.3, 132.5, 132.7, 132.9, 143.4, 143.5, 148.6, 148.9, 149.3, 149.9, 150.3, 162.8, 169.6, 170.4, 173.4, 174.0, 181.3 ppm. ESI-MS: m/z (%) = 1349.4 (100) $[M - 1]^+$. $C_{72}H_{90}N_{10}O_{12}S_2$: C 63.97, H 6.72, N 10.36; found C 63.72, H 6.85, N 10.28.

Calix[4]arene Derivative 3b: The pure product (0.57 g) was obtained by column chromatography on silica gel [eluent: $CHCl_3$/CH_3CH_2OH, 25:1 (v/v)] as a pale yellow powder in 38.0% yield; m.p. 154–155 °C. $[\alpha]_D^{20}$ = +17.39 (c = 0.05, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3314, 2959, 2922, 2865, 1658, 1597, 1515, 1483, 1362, 1330, 1301, 1260, 1205, 1123, 1109, 1041, 870, 848, 809, 727, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.00 (s, 18 H, *t*Bu), 1.11 (s, 18 H, *t*Bu), 2.78–2.96 (m, 4 H, $ArCH_2C$), 2.98–3.10 (m, 4 H, CH_2NHCS), 3.16 (d, J = 12.9 Hz, 2 H, $ArCH_2Ar$), 3.25–3.40 (m, 4 H, $CONHCH_2$), 3.50 (d, J = 14.2 Hz, 2 H, $ArCH_2Ar$), 3.87 (d, J = 13.2 Hz, 2 H, OCH_2CO), 4.05–4.25 (m, 4 H, $ArCH_2Ar$), 4.95–5.10 (m, 2 H, NC*HCO), 5.16 (d, J = 15.9 Hz, 2 H, OCH_2CO), 6.82 (s, 4 H, ArH), 6.92–7.20 (m, 14 H, ArH), 7.55 (br., 2 H, CH_2NHCS), 7.72 (br., 2 H, CSNHAr), 7.82 (d, J = 8.4 Hz, 4 H, O_2N-ArH), 8.08 (d, J = 8.4 Hz, 4 H, O_2N-ArH), 8.33 (s, 2 H, ArOH), 9.26 (d, J = 7.8 Hz, 2 H, CONHCH), 10.10 (br., 2 H, $CONHCH_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.9, 31.1, 31.2, 31.8, 32.1, 32.4, 32.5, 32.9, 34.1, 34.2, 34.4, 37.5, 39.6, 41.2, 54.1, 54.9, 74.0, 75.0, 121.3, 124.8, 125.1, 125.4, 125.7, 126.0, 126.3, 126.4, 126.6, 126.7, 126.9, 127.0, 127.2, 127.3, 127.6, 128.2, 128.6, 128.7, 129.1, 132.3, 132.6, 132.9, 136.3, 136.7, 143.2, 145.9, 148.4, 148.7, 149.2, 149.4, 150.2, 150.3, 170.0, 170.3, 171.9, 172.4, 181.0 ppm. ESI-MS: m/z (%) = 1501.6 (100) $[M - 1]^+$. $C_{84}H_{98}N_{10}O_{12}S_2$: C 67.07, H 6.58, N 9.31; found C 66.78, H 6.63, N 9.28.

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