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Tetrahedron
Tetrahedron 61 (2005) 919–926

Cyclodextrin assisted enantiomeric recognition of benzo[*de*]isoquinoline-1,3-dione derived amino acids

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Received 20 July 2004; revised 3 November 2004; accepted 5 November 2004

Available online 30 November 2004

Abstract—Spectroscopic evidence for enantiomeric recognition of properly modified amino acids through the cyclodextrin assisted formation of polymer like self-assemblies is presented. The requirements for the formation of these assemblies through aromatic π–π stacking are discussed. It is suggested that this approach can be used for enantiomeric separation of chiral compounds that contain both electron-rich and electron-poor moieties.

1. Introduction

It is now well accepted that marketing only one enantiomer of a chiral drug is crucial for the pharmaceutical industry.[1] There are two commonly used approaches for preparing the enantiomerically pure compounds needed for chiral drug marketing. These approaches include; (a) development of preparation procedures that yield only the desirable enantiomer[2] and (b) using preparation procedures that generate both enantiomers and then purifying the racemic mixture using expensive chiral separation techniques. The first approach is very expensive because it is necessary to use either chiral intermediates or chiral catalysts to obtain the desired enantiomerically pure product, while the second approach, which results in the production of racemates, causes problems with waste management and chiral separations. Therefore, it would be ideal to develop new chemistry that can address both of these problems by applying inexpensive preparation procedures for the production of racemic products, which can then be transferred from a racemic mixture to the desired enantiomerically pure targeted compound.

There are many drugs that have aromatic moieties and are currently marketed as racemic mixtures. These drugs include Prozac, Escitalopram, and Clopidogrel to name a few.[1d] It is also known that cyclodextrins are capable of forming stable complexes with aromatic compounds.[3] Therefore, it is reasonable to propose that cyclodextrins can form diasteriomeric inclusion complexes with racemic aromatic compounds. Based on the knowledge that diasteriomers have different physical properties, it is reasonable to expect that one of the diasteriomeric inclusion complexes will crystallize out from the racemic aqueous cyclodextrin solution more readily.

It has also been well established that stronger enantiomeric recognition can be accomplished if two enantiomers compete to bind to a multi-chiral resolving molecule.[4] The same effect should be present if two enantiomers are competing to bind to a homochiral self-assembly polymer made from one of the enantiomers. There are many nonbonding interactions (such as hydrogen bonding, electrostatic interactions, π–π-aromatic stacking. dipole–dipole, etc.) responsible for the formation of molecular associates.[5] Aromatic π–π stacking interactions are crucial for formation of molecular associates, interactions between substrate and enzymes, biomolecular associates, organic molecule conformation, etc.[6] Furthermore, multi-chirality and multi-point interactions are very important for enantiomeric recognition.[7]

The ideal cyclodextrin assisted molecular associate, which has all of these requirements, is presented in Figure 1. Molecule **M** has four moieties that should be essential for the formation of homochiral polymer-like molecular associates. The two aromatic moieties are complementary to one another, and are the electron-donor and the electron-acceptor. This aromatic complementarity enables the molecule to form molecular associates through π–π stacking. In general, the π–π stacking of aromatic complexes are very weak, therefore these complexes should

Keywords: Enantiomers; Enantiomeric recognition; Cyclodextrin complexation.
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doi:10.1016/j.tet.2004.11.021

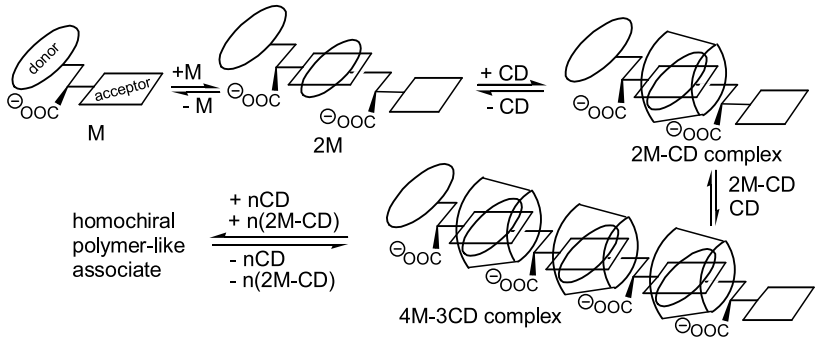


Figure 1. Possible pathway to cyclodextrin assisted formation of homochiral polymer-like associate.

be stabilized through their binding into the cyclodextrin cavity (Fig. 1). During the formation of this cyclodextrin assisted molecular associate, two aromatic moieties, each from different **M** molecules, are now ready to form a new cyclodextrin inclusion complex and molecular associate with a new **M** molecule. In this way, the polymer-like molecular associate would be formed.

The presence of polar groups, such as carboxylates, enable this polymer-like associate to interact with water surroundings. On the other hand, chirality of **M** makes the molecular associate diasteriomeric and stereoselective for incorporating only one enantiomer of **M** into the homochiral molecular associate.

To test the validity of the proposed cyclodextrin assisted self-assembly approach to enantiomeric recognition, the proper molecular system must be selected. Amino acids seem to be the best molecular choice for this study, provided that the amino acids have both electron-rich and electron-poor aromatic moieties. None of the natural amino acids satisfy this requirement; therefore, through simple chemical modifications of natural amino acids this requirement can be achieved. For instance, simple aromatic molecules such as methylindole, toluene, and methylbenzoisoquinoline-1,3-dione (Fig. 2) have a noticeable difference in aromatic electronic properties (Fig. 2). The AM1[11] computed frontier molecular orbital (HOMO–LUMO) energies suggest that toluene is electronically neutral, indole is electron rich and, benzoisoquinoline-1,3-dione is electron poor (Fig. 2). If these molecular moieties are incorporated into amino acids, then the requirement for molecule **M** has been accomplished.

Three amino acids were selected to test the validity of this hypothesis: alanine (without aromatic moiety), phenylalanine (neutral aromatic electronic properties), and trypthophan (electron-rich electronic properties). Through amino group replacement with benzo[*de*]isoquinoline-1,3-dione, new molecular systems **1a**, **1b**, and **1c** were generated. As expected, the LUMO orbital energy for all these three molecules is similar (because each has the same electron poor aromatic moiety) while the HOMO energies vary dramatically (Fig. 3) with the expected best complementarily of HOMO–LUMO interactions with **1c**. The AM1 estimated LUMO–HOMO energy difference as measured for π–π aromatic stacking capabilities are 8.00, 7.85, and 7.69 eV for **1a**, **1b**, and **1c**, respectively (the lower LUMO–HOMO energy gap the higher capability to form molecular associates through π–π molecular stacking[8]).

The synthetic conditions for the preparation of these amino

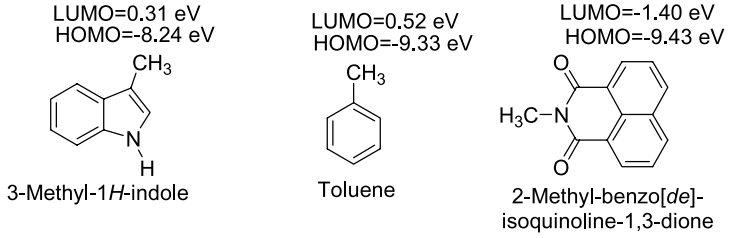


Figure 2. The AM1 estimated HOMO–LUMO energies for the aromatic moieties.

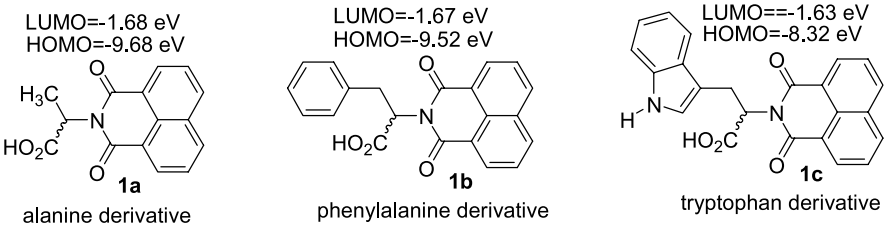
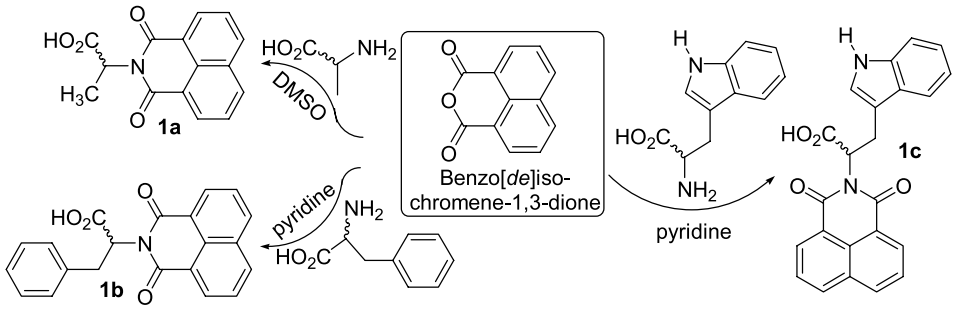


Figure 3. The AM1 estimated HOMO–LUMO energies for three modified amino acids.



Scheme 1. Preparation of electron-deficient alanine, phenylalanine, and tryptophan.

acid derivatives are presented in Scheme 1. Reactions are performed with the amino acid and benzo[*de*]isochromene-1,3-dione in DMSO for alanine and pyridine for phenylalanine and tryptophan (Scheme 1). The isolated yields range between 80 and 95%.

To demonstrate the existence of weak nonbonding interactions, as well as enantiomeric recognition when one of the enantiomers acts as resolving agent,[9] spectroscopic studies of racemic and non-racemic highly concentrated solutions of **1a**, **1b**, and **1c** were studied. These compounds are soluble in DMSO, therefore this was our solvent of choice. Both concentration (0.0001–0.3 M) and molar ratio (1:10, 1:5, 1:1, 5:1, and 10:1) of the *S* and *R* enantiomers were varied. In none of our NMR studies with all three compounds were we able to observe any NMR evidence for enantiomeric recognition.

For the study of the cyclodextrin assisted molecular complexes, water is a much better solvent of choice. However, none of the studied compounds is sufficiently soluble in water to perform reliable NMR studies. Therefore, sodium salts of **1a**, **1b**, and **1c** were used for the NMR spectroscopic studies. Neither **1a** nor **1b** non-racemic mixtures at any concentration range up to 0.1 M and any enantiomeric ratio show spectroscopic recognition. On the other hand, there is NMR enantiomeric recognition of non-racemic **1c** (Fig. 4). The spectroscopic recognition is not due to the formation of molecular associates through hydrogen bonding, nor through electrostatic interactions between the carboxylate group and sodium, because these interactions are also present in **1a** and **1b**. The only reasonable explanation is that molecule **1c** can form molecular associates through π–π stacking between the indole and benzo[*de*]isochromene-1,3-dione moieties.[10]

If this nonbonding π–π stacking is responsible for enantiomeric recognition, then the presence of cyclodextrin will enhance NMR spectroscopic recognition. This is due to the fact that both aromatic moieties tend to bind into the cyclodextrin cavity, and then orient themselves in the proper way for the aromatic stacking and for strong homochiral molecular associates. This is perfectly demonstrated in Figure 5 for γ-cyclodextrin assisted enantiomeric recognition of the racemic **1c**. The best results are obtained in γ-cyclodextrin in comparison with β-cyclodextrin, while no enantiomeric recognition was observed in α-cyclodextrin. This finding is not surprising considering that the cyclodextrin cavity must be large enough to accommodate two aromatic rings.

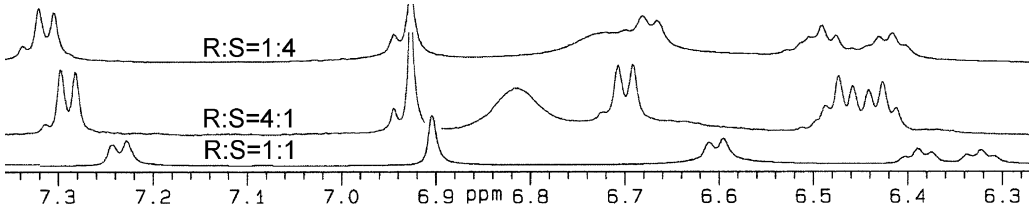


Figure 4. The NMR spectra of aromatic portion of **1c** (0.1 M) in aqueous $NaHCO_3$ (0.3 M) with different enantiomer ratios.

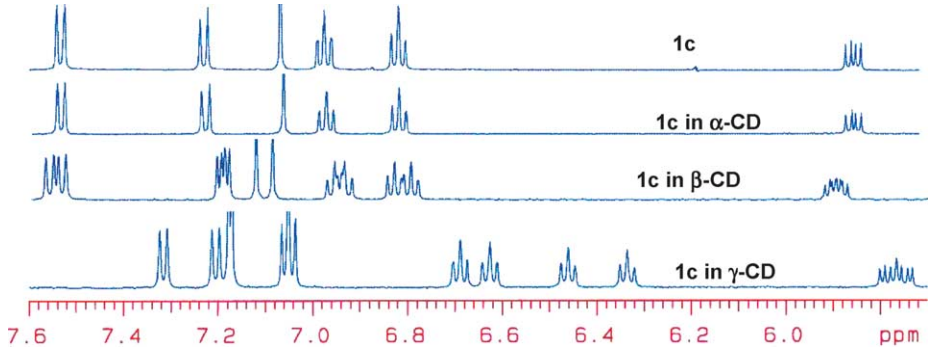


Figure 5. A portion of NMR spectra of racemic **1c** (0.001 M) in aqueous $NaHCO_3$ (0.003 M) with α, β, and γ-CD (0.01 M), respectively.

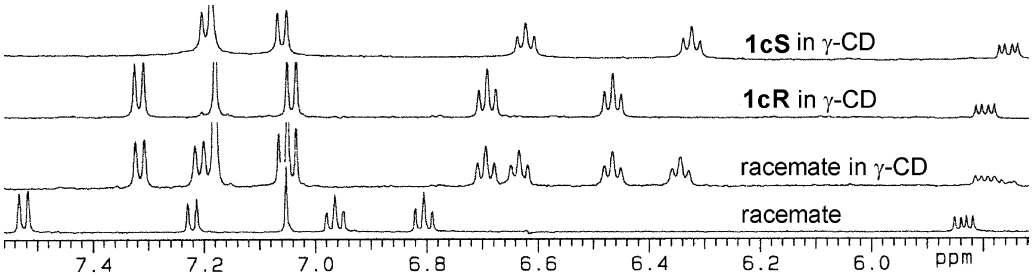


Figure 6. A portion of NMR spectra of **1c** (0.001 M) in aqueous $NaHCO_3$ (0.003 M) and γ-CD (0.01 M).

There are two sets of peaks in racemate NMR in presence of γ-CD. It is also possible to easily recognize each enantiomer peak if individual enantiomers NMR in γ-CD compared with the racemate NMR in γ-CD (Fig. 6).

Enantiomeric recognition can be observed even if there is no formation of the molecular associates described in Figure 1. The enantiomer binding into the cyclodextrin cavity can initiate the chiral environment necessary to observe spectroscopic differences. In α-cyclodextrin no NMR spectroscopic recognition was observed due to fact that neither the indole nor benzo[*de*]isochromene-1,3-dione aromatic moieties can bind into the α-cyclodextrin cavity. The β-cyclodextrin cavity is sufficiently large to accommodate the indole ring. If there is formation of molecular associates higher than the 1:1 cyclodextrin complex with respect to **1c**, we should observe this in electrospray mass spectroscopy. By performing this experiment it is clearly demonstrated that the cyclodextrin inclusion complex with **1c** was formed (Fig. 7) but no higher order (1:2 or 2:1) complex between β-CD and **1c** was observed.

Now we turn our attention to the molecular system that shows the best NMR enantiomeric recognition; γ-CD complexes with **1c** (Fig. 5). The electrospray mass spectra clearly shows the formation of 2:1 and 1:2 γ-CD complexes with **1c** (signals at 1488 and 1032, Fig. 8). All the other molecular complexes are present as well.

These are very encouraging results, but there is no experimental evidence for the formation of polymer-like cyclodextrin assisted molecular assemblies presented in Figure 1. For this reason, we performed MALDI MS spectra analysis of the aqueous γ-cyclodextrin solution of **1c**. If the structural patterns presented in Figure 1 are present, then typical fragmentation similar to the fragmentation of polymers should be observed in the MALDI MS spectra. All possible fragments were detected with lower intensity for larger molecular fragments (Fig. 9).

To better understand the binding of these guest compounds with host cyclodextrins, association constants (K, M^{-1}) were measured by ^{1}H NMR (500 MHz) at different temperature. In Table 1 are listed association constant K, standard free energy ΔG°, standard entropy term $T\Delta S^\circ$ and standard enthalpy ΔH° of guest **1c** with β and γ cyclodextrin. The chemical shift change of NMR signal of guest **1c** in presence of α cyclodextrine was too small to measure (as shown in Fig. 5). So the association constant is too small to measure practically. The solution of **1c**

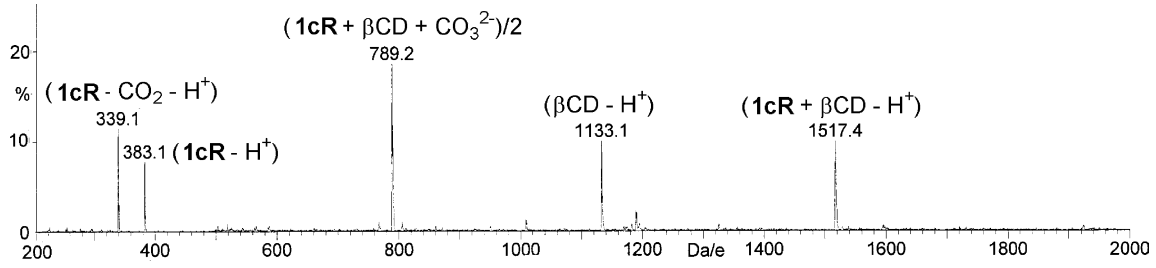


Figure 7. Negative electrospray mass spectrophotometry of **1c***R* (0.001 mol) in aqueous $NaHCO_3$ (0.003 M) and β-cyclodextrin (β-CD, 0.01 M).

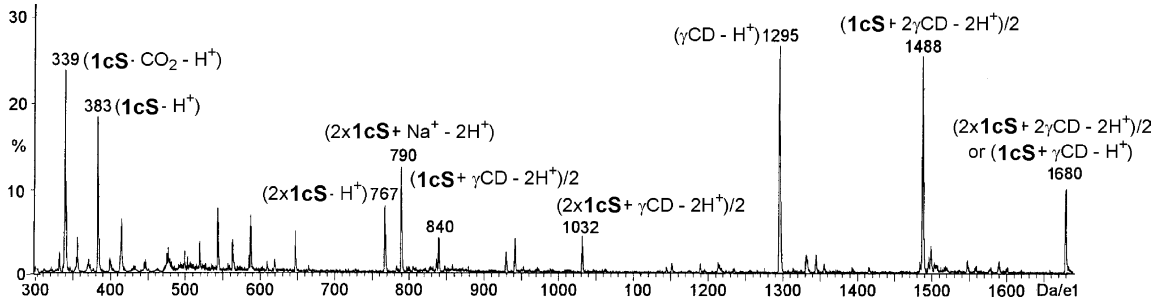


Figure 8. Negative electrospray mass spectra of **1c***S* (0.001 M) in aqueous $NaHCO_3$ (3×10^{-3} M) and γ-cyclodextrin (γ-CD, 10^{-2} M).

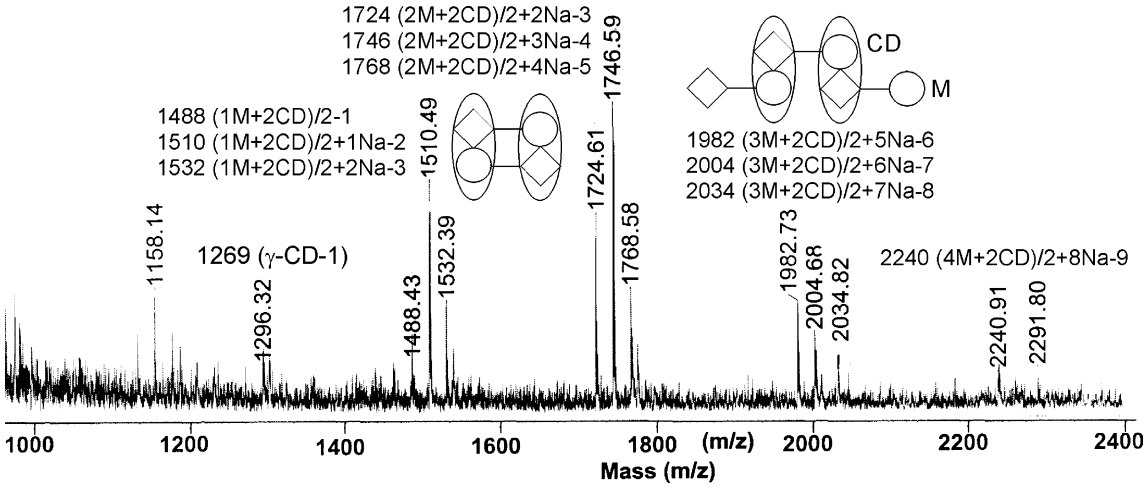


Figure 9. Positive MALDI-MS spectra of aqueous γ-CD and **1c**.

Table 1. Optical rotations of guest compounds **1a**, **1b** and **1c**

Guest compound	Optical rotation	
	L-enantiomer	D-enantiomer
1a	−19.5 (*c* 0.1, MeOH)	+18.0 (*c* 0.1, MeOH)
1b	−31.6 (*c* 1, MeOH)	+28.4 (*c* 1, MeOH)
1c	−17.0 (*c* 0.1, H_2O)	+16.2 (*c* 0.1, H_2O)

(0.001 M) in aqueous $NaHCO_3$ (3×10^{-3} M) was titrated with host solution at different temperature. Each time the change in chemical shift was measured. Non-linear regression analysis using origin 6.1 (Aston Scientific Ltd) was used to generate the association constant K_a according to the equation[12]:

$$\Delta = \frac{\Delta_{max} K_a[H]}{1 + K_a[H]}$$

where Δ, the peak shift in ppm, Δ_{max}, the maximum peak shift in ppm, and [H], the concentration of host. At least two experiments were performed for each system. Standard free energy was calculated using $\Delta G^\circ = -RT \ln K_a$ equation. Standard enthalpy ΔH° was determined according to the Van't Hoff equation: $d \ln K/d(1/T) = -\Delta H^\circ/R$ where $R = 8.3144\ J\ K^{-1}\ mol^{-1}$ and ΔH° in $J\ mol^{-1}$. $T\Delta S^\circ$ was calculated using $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ equation.

As shown in Table 2, the association constant of guest **1c** is more than seven times higher for γ-CD compare to the association constant for β-CD. These results are consistent with what we understand from Figure 5. The cyclodextrin cavity must be large enough to accommodate two aromatic rings which γ-CD have. Also the association constant for L-enantiomer is higher than that of D-enantiomer.

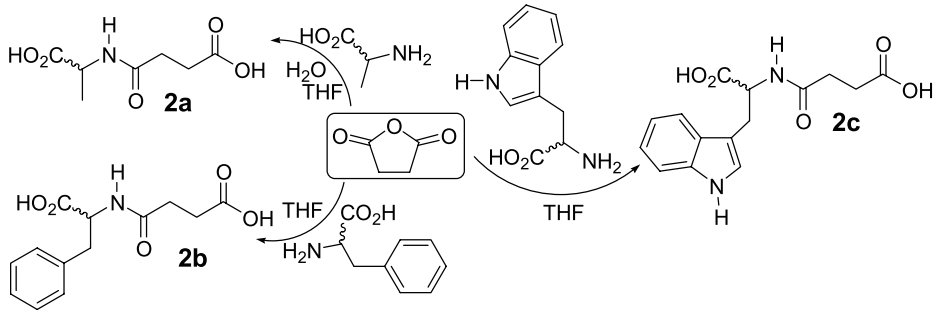
To show that the presence of the electron-poor aromatic moiety is crucial for the formation of the molecular assemblies discussed above, as well as make the amino acid derivative very soluble in water, mono amino acid amides with succinic acid were prepared (Scheme 2). Each and every of these reactions requires specific conditions, which were optimized by monitoring the reaction by NMR spectroscopic studies. After all reaction conditions were optimized, the isolated yields were higher than 85% (Table 3).

All of these compounds are very soluble in water, which makes it possible to perform the NMR spectroscopic studies in DMSO, $CDCl_3$, and water. We did not observe NMR enantiomeric recognition in DMSO and water, as well as in aqueous cyclodextrins. We were able to detect through electrospray MS spectroscopic study the formation of β-CD inclusion complexes with both **2b** and **2c**. It seems obvious that these cyclodextrin inclusion complexes cannot produce the different NMR environment to cause the NMR spectroscopic recognition. When two aromatic rings are together in the γ-CD cavity, as is the case with **1c**, the currency of one

Table 2. ^1H NMR derived thermodynamic parameters for the binding of guest molecule **1c** to host β and γ-CD

Temperature (K)	L-enantiomer		D-enantiomer	
	β-CD	γ-CD	β-CD	γ-CD
298	$K=63.02\pm19.63$	$K=413.03\pm21.45$	$K=47.26\pm6.72$	$K=320.93\pm19.5$
	$\Delta G^\circ=-10.27\pm0.7$	$\Delta G^\circ=-14.93\pm0.13$	$\Delta G^\circ=-9.56\pm0.3$	$\Delta G^\circ=-14.31\pm0.15$
	$T\Delta S^\circ=-4.84\pm2.9$	$T\Delta S^\circ=-9.7\pm0.12$	$T\Delta S^\circ=-28.89\pm1.5$	$T\Delta S^\circ$ -18.71 ± 3.5
313	$K=42.57\pm10.34$	$K=262.26\pm11.95$	$K=19.88\pm3.61$	$K=210.7\pm5.73$
	$\Delta G^\circ=-9.22\pm0.6$	$\Delta G^\circ=-13.81\pm0.11$	$\Delta G^\circ=-7.41\pm0.4$	$\Delta G^\circ=-13.26\pm0.07$
	$T\Delta S^\circ=-5.76\pm3.1$	$T\Delta S^\circ=-10.83\pm0.11$	$T\Delta S^\circ=-31.05\pm1.6$	$T\Delta S^\circ=-19.76\pm3.4$
343	$K=26.94\pm3.39$	$K=113.35\pm4.86$	$K=6.12\pm1.26$	$K=59.26\pm12.93$
	$\Delta G^\circ=-8.16\pm0.3$	$\Delta G^\circ=-11.73\pm0.11$	$\Delta G^\circ=-4.49\pm0.5$	$\Delta G^\circ=-10.12\pm0.49$
	$T\Delta S^\circ=-6.84\pm3.4$	$T\Delta S^\circ=-12.9\pm0.1$	$T\Delta S^\circ=-33.95\pm1.7$	$T\Delta S^\circ=-22.9\pm3.8$
	$\Delta H^\circ=-15\pm3.7$	$\Delta H^\circ=-24.63\pm0.01$	$\Delta H^\circ=-38.4\pm1.2$	$\Delta H^\circ=-33\pm3.4$

All K, ΔG°, $T\Delta S^\circ$, ΔH° values are in kJ/mol unit.



Scheme 2. Preparation of acid-amides of alanine, phenylalanine, and tryptophan.

Table 3. Optical rotations of guest compounds **2a**, **2b**, and **2c**

Guest compound	Optical rotation	
	L-enantiomer	D-enantiomer
2a	+22.0 (*c* 1, MeOH)	−21.6 (*c* 1, MeOH)
2b	−14.9 (*c* 1, MeOH)	+13.4 (*c* 1, MeOH)
2c	+37.1 (*c* 1, MeOH)	−32.8 (*c* 1, MeOH)

ring causes a change of magnetic properties on the other ring, which is easily detected through NMR spectroscopic studies, resulting in spectroscopic recognition of two enantiomers.

2. Conclusion

In conclusion we can state that there are spectroscopic evidences for the formation of chiral cyclodextrin assisted polymer-like aggregates with γ-cyclodextrin that accommodate two aromatic rings and modified chiral amino acids. For successful cyclodextrin assistance in the formation of these kinds of aggregates, modified amino acids must contain both electron-poor and electron-rich aromatic moieties. Cyclodextrin with a sufficiently large cavity, such as γ-cyclodextrin must be used to be able to bind both aromatic rings involved in aromatic π–π stacking.

3. Experimental

3.1. General

Melting points were taken on an Electrothermal IA 9000 Digital Melting Point Apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were run on Varian Unity 400 and Varian INOVA 500 MHz spectrophotometer with DMSO-d_6 as a solvent and internal standard (2.50 and 35.91 ppm for ^{1}H and ^{13}C NMR, respectively). The mass spectra were recorded on a Micromass Quattro 2 Triple Quadropole Mass Spectrometer; Optical rotations of guest compounds were detected at 25 °C with the light of sodium D-line (589 nm) using Autopo III automatic polarimeter Rudolph Research, Flanders, New Jersy. Elemental Analysis was performed by Atlantic Microlab, Inc., Norcross, GA.

3.1.1. Preparation of (*S*)-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)propionic acid (1a*S*). Dimethyl sulfoxide (30 mL) solution of benzo[*de*]isochromene-1,3-dione (1.98 g; 0.01 mol) and alanine (0.89 g; 0.01 mol) was refluxed for 1 h. Reaction mixture was cooled to room temperature and slowly added into stirring water (200 mL). Formed precipitate was separated by filtration, washed with water (3×30 mL) and dried at 110 °C for a few hours to afford 2.15 g (80%) pure product. Mp 257–261 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ ppm: 8.51 (dd, 4H, J_1=10.5 Hz; J_2=7.5 Hz), 7.89 (t, 2H, J=7.5 Hz), 5.54 (q, 1H, J=7 Hz), and 1.53 (d, 3H, J=6.5 Hz). ^{13}C NMR (DMSO-d_6, 500 MHz) δ ppm: 171.4, 162.9 (carbonyls), 134.7, 131.3, 131.1, 127.4, 121.7 (aromatic carbons), 48.5 (chiral carbon CH), 14.5 (methylene carbon). MS-ES$^+$ (CH_3OH) *m/z* 292.2 (65%, M+Na$^+$), 324.1 (85%, M+CH_3OH+Na$^+$), 561.3 (100%. 2M+Na$^+$), and 829.8 (50%, 3M+Na$^+$). Anal. Calcd for $C_{15}H_{11}NO_4$ (269.07): C, 66.91; H, 4.12; N, 5.20 Found: C, 66.85; H, 4.21; N, 5.11.

3.1.2. Preparation of (*R*)-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)propionic acid (1a*R*). The stereoisomer *R* was prepared in 87% yield by following procedure for preparation of *S* isomer. The NMR and MS-ES spectra of *R* and *S* stereoisomers are identical.

3.1.3. Preparation of (*S*)-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-phenyl-propionic acid (1b*S*). Pyridine solution (150 mL) of benzo[*de*]isochromene-1,3-dione (0.99 g; 5 mmol) and L-phenylalanine (0.825 g; 5 mmol) was refluxed for 6 h. Volume of the reaction mixture was reduced to ~5 mL and hot reaction mixture was added to ice cooled aqueous hydrochloric acid (150 mL water and 50 concd HCl). Formed solid precipitate was separated by filtration, washed with water (3×20 mL) and dried at 110 °C for a few hours to afford 1.6 g (93%) pure product. Mp 250–252 °C ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.41 (d, 2H naphthalene ring, J=7 Hz), 8.37 (d, 2H naphthalene ring, J=7 Hz), 7.78 (t, 2H naphthalene ring, J=7.5 Hz,), 7.14 (d, 2H, J=7.5 Hz), 7.07 (2H, t, J=7.5 Hz) 7.00 (t, 1H, J=7.5 Hz) 5.92 (dd,1H, J_1=10 Hz; J_2=5.5 Hz) 3.58 (dd, 1H, J_1=14 Hz; J_2=5.5 Hz), and 3.39 (dd,1H, J_1=14.5 Hz; J_2=10 Hz). ^{13}C NMR (DMSO-d_6, 500 MHz) δ ppm: 171.8, 163.0 (carbonyls), 137.9, 134.7, 131.2, 129.0, 128.1, 127.5, 127.3, 127.2, 126.3, 121.2 (10 aromatic carbons), 53.9 (chiral carbon CH), and 24.3 (methylene carbon). MS-ES$^-$ *m/z* 344 (100% M−H$^+$). Anal. Calcd for $C_{21}H_{15}NO_4$ (345.10): C, 70.03; H, 4.38; N, 4.06. Found: C, 69.91; H, 4.42; N, 3.95.

3.1.4. Preparation of (*R*)-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-phenyl-propionic acid (1b*R*). Stereoisomer *R* was prepared in 91% yield and has same spectroscopic characteristics as stereoisomer *S*.

3.1.5. Preparation of (*S*)-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-(1*H*-indol-3-yl)-propionic acid (1c*S*). Dimethyl sulfoxide (30 mL) solution of benzo[*de*]isochromene-1,3-dione (0.99 g; 5 mmol) and L-tryptophan (1.04 g; 5 mmol) was heated at 150 °C for 30 min. Red colored reaction mixture was slowly added into stirring water (200 mL). Formed yellow precipitate was separated by filtration, washed with water (3×20 mL) and dried at 110 °C to give 1.6 g (83%) of pure product. Mp 235–239 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 12.80 (br s, 1H), 10.63 (1H, s), 8.44 (dd, 4H, J_1=4.4 Hz, J_2=7.2 Hz), 7.85 (t, 2H, J=7.6 Hz), 7.46 (d, 1H, J=8.0 Hz), 7.17 (d, 1H, J=7.6 Hz), 6.99 (s, 1H,), 6.92 (t, 1H, J=7.6 Hz), 6.79 (t, 1H, J=7.2 Hz), 5.88 (dd, 1H, J_1=9.6 Hz, J_2=5.6 Hz), 3.65 (dd, 1H, J_1=14.8 Hz, J_2=5.6 Hz), 5.54 (dd, 1H, J_1=14.8 Hz, J_2=9.6 Hz), ^{13}C NMR (DMSO-d_6, 500 MHz) δ ppm: 171.0, 163.1, 135.9, 134.7, 131.2, 127.4, 127.2, 123.5, 121.4, 120.8, 118.2, 118.0, 111.3, 110.3, 53.7, and 24.0 ppm. ESI$^+$ (CH_3CO_2H) *m*/*z* 385 (100, M+H$^+$) and 769 (45%, 2M+H$^+$). Anal. Calcd for $C_{23}H_{16}N_2O_4$ (384.38): C, 71.87; H, 4.20; N, 7.29 Found: C, 71.55; H, 4.31; N, 7.18.

3.1.6. Preparation of (*R*)-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-(1*H*-indol-3-yl)-propionic acid (1c*R*). The *R* stereoisomer has same spectroscopic characteristics as *S* isomer and is prepared in 87% isolated yield by following the *S* preparation procedure.

3.1.7. Preparation of (*S*)-*N*-(1-carboxyethyl)succinamic acid (2a*S*). Water solution (5 mL) of *S*-alanine (1.5 g; 0.017 mol) was slowly added into stirring tetrahydrofuran solution (200 mL) of succinic anhydride (1 g; 0.01 mol). Resulting suspension was stirred at 30 °C for 1 h. Solid was separated by filtration and filtrate was evaporated under reduced pressure. Liquid residue was mixed with ethyl acetate and the resulting mixture was dried over anhydrous sodium sulfate. Drying reagent was removed by filtration and filtrate was evaporated to solid residue and solid residue was slurred in petroleum ether. Product was isolated by filtration of white suspension in 79% yield. Mp 152–155 °C. ^{1}H NMR (D_2O, 500 MHz) δ ppm: 4.35 (q, 1H, chiral CH; J=7 Hz), 2.69 (s, 4H, two CH_2 groups of the succinic acid moiety) and 1.42 (d, 3H, J=7.5 Hz). ^{13}C NMR (D_2O, drop of DMSO-d_6 added for reference, 500 MHz) δ ppm: 177.5, 177.4, 175.2 (carbonyl carbon), 49.4, 30.5, 29.8, 29.5 (four aliphatic carbon). ES-MS$^-$ *m*/*z* 188.1 (85%, M−H$^+$), 377.3 (100%, 2M−1H$^+$), and 566.0 (30%, 3M−H$^+$). Anal. Calcd for $C_7H_{11}NO_5$ (189.06): C, 44.45; H, 5.86; N, 7.40 Found: C, 44.37; H, 5.98; N, 7.33.

3.1.8. Preparation of (*R*)-*N*-(1-carboxyethyl)succinamic acid (2a*R*). The *R* isomer was prepared by following the same synthetic procedure with 83% isolated yield. The spectroscopic characteristics are identical to the *S* isomer.

3.1.9. Preparation of (*S*)-*N*-(1-carboxy-2-phenylethyl)-succinamic acid (2b*S*). Tetrahydrofuran (500 mL) suspension of phenylalanine (1.65 g; 0.01 mol) and succinic anhydride (1.0 g; 0.01 mol) was refluxed until the suspension becomes clear solution (approximately 30 h). Solvent was evaporated under reduced pressure. Solid residue was scurried in petroleum ether (100 mL), separated by filtration, and washed with petroleum ether (3×20 mL) and dried at 60 °C for a few hours. The isolated yield is 2.5 g (95%) of pure product. Mp 127–129 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.15 (d, 1H, amide NH, J=8 Hz) 7.25 (m, 5H benzene ring), 4.50 (ddd, 1H chiral), 3.05 (dd, 1H, J_1=13.5 Hz; J_2=5 Hz), 2.86 (dd, 1H, J_1=13.5 Hz; J_2=9.5 Hz), and 2.35 (s, 4H aliphatic two CH_2 group). ^{13}C NMR (DMSO-d_6, 500 MHz) δ ppm: 73.8, 173.1, 171.1 (carbonyls), 129.2, 128.2, 126.4 (aromatic carbons), 53.6, 37.0, 29.9, and 29.1 (four aliphatic carbon). MS-ES$^+$ *m*/*z* 266.1 (22%, M+H$^+$) and 288.1 (100%, M+Na$^+$). Anal. Calcd for $C_{13}H_{15}NO_5$ (265.10): C, 58.86; H, 5.70; N, 5.28 Found: C, 58.92; H, 5.77; N, 5.15.

3.1.10. Preparation of (*R*)-*N*-(1-carboxy-2-phenylethyl)-succinamic acid (2b*R*). The *R* stereoisomer was prepared in 93% isolated yield by following the procedure described for the *S* stereoisomer. The spectral characteristics for this compound are identical to the spectral characteristics of the *S* stereoisomer.

3.1.11. Preparation of (*S*)-*N*-[1-carboxy-2-(1*H*-indol-3-yl)ethyl]succinamic acid (2c*S*). Tetrahydrofuran (1 L) suspension of tryptophan (2 g; 0.01 mol) and succinic anhydride (1 g; 0.01 mol) was refluxed until it became solution (approximately 40 h). Solvent was evaporated and solid residue was mixed with petroleum ether (200 mL). Solid material was separated by filtration, washed with petroleum ether (3×20 mL), and dried at 60 °C for several hours to afford 2.8 g (92%) of pure product. Mp (hydroscopic). ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 10.82 (s, 1H the pyrrole ring NH) 8.15 (d, 1H amide hydrogen, J=7.5 Hz), 7.52 (d, 1H benzene ring H, J=7.5 Hz), 7.32 (d, 1H, J=8 Hz), 7.14 (s, 1H the pyrrole ring CH) 7.05 (t, 1H, J=7 Hz) 6.97 (t, 1H, J=7 Hz) 4.46 (ddd, 1H) 3.14 (dd, 1H, J_1=14 Hz; J_2=5.5 Hz) 3.00 (dd, 1H, J_1=14 Hz; J_2=8 Hz), 2.35 ppm (s, 4H aliphatic two CH_2 group hydrogen). ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 173.8, 173.5, 171.1 (carbonyls), 136.1, 127.3, 123.6, 121.0, 118.4, 118.2, 111.4, 109.9 (eight aromatic carbons), 53.1, 29.9, 29.1, and 27.2 ppm (four aliphatic carbon). MS-ES$^-$ *m*/*z* 303.1 (35%, M−H$^+$), 431.3 (15%, 3M−CO_2−2H$^+$), and 607.1 (100%, 2M−H$^+$). Anal. Calcd for $C_{15}H_{16}N_2O_5$ (304.30): C, 59.21; H, 5.30; N, 9.21 Found: C, 59.15; H, 5.38; N, 9.16.

3.1.12. Preparation of (*R*)-*N*-[1-carboxy-2-(1*H*-indol-3-yl)ethyl]succinamic acid (2c*R*). The *R* stereoisomer was prepared in 96% yield by following same procedure outlined for the *S* stereoisomer. All spectra of *R* stereoisomer are identical to the *S* stereoisomer spectra.

Acknowledgements

We thank the Louisiana Board of Reagents for their financial support (LEQSF (2001-04)-RD-B-12) for this work.

References and notes

1. For instance see (a) *Chiral Drugs*; Challener, C. A., Ed.; Gower: New York, 2002. (b) *The Impact of Stereochemistry on Drug Development and Use*; Aboul-Enein, H. Y., Wainer, I. W., Eds.; Wiley: New York, 1997. (c) Rouhi, A. M. 'Chiral Business', Chemical and Engineering News; 2003. May 5, pp 45–55. (d) Rouhi, A. M. 'Chirality at Work', Chemical and Engineering News; 2003, May 5, pp 55–61.
2. For definition of stereochemistry see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
3. For more information regarding cyclodextrin complexes see: (a) Schneider, H.-J.; Hacket, F.; Rüdiger, V. *Chem. Rev.* **1998**, *98*, 1755–1785. (b) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1917. (c) Song, L.; Purdy, W. C. *Anal. Chem.* **1992**, *64*, 1405–1412.
4. *Chirality in Natural and Applied Sciences*; Lough, W. J., Wainer, I. W., Eds.; CRC: Boca Raton, FL, 2002.
5. (a) Boeyens, J. C. A. Intermolecular bonding In *Inermolecular Interactions*; Plenum: New York, NY, 1998. (b) Soltis, R. D.; Hasz, D. Studies on the nature of intermolecular bonding in antigen–antibody complexes *Immunology* **1982**, *46*, 175–181.
6. (a) Guan, L.; Hu, Y.; Kaback, H. R. *Biochemistry* **2003**, *42*, 1377–1382. (b) Lawrence, A. J. *Chem. Rev.* **1954**, *54*, 713–776. (c) Cubberley, M. S.; Iverson, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 7560–7563. (d) Guckian, K. M.; Schweitzer, B. A.; Ren, R. X.-F.; Sheils, C. J.; Tahmassebi, D. C.; Kool, E. T. *J. Am. Chem. Soc.* **2000**, *122*, 2213–2222. (e) Ilhan, F.; Gray, M.; Blanchette, K.; Rotello, V. M. *Mocromolecules* **1999**, *32*, 6159–6162.
7. Bentley, R. *Arch. Biochem. Biophys.* **2003**, *414*, 1–12.
8. For frontier orbital interactions see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.
9. For similar enantiomeric recognition through hydrogen bonding interactions in highly concentrated chloroform solutions see: (a) Jursic, B. S.; Goldberg, S. I. *J. Org. Chem.* **1992**, *57*, 7172–7174. (b) Jursic, B. S.; Goldberg, S. I. *J. Org. Chem.* **1992**, 7270–7372. (c) Jursic, B. S.; Zdravkovski, Z. *J. Org. Chem.* **1993**, *58*, 5245–5250. (d) Jursic, B. S.; Zdravkovski, Z.; Zuanic, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1711–1716.
10. For π–π aromatic stacking in enantiomeric recognition see: Jursic, B. S. *J. Chem. Soc. Perkin Trans. 2* **1994**, 961–969. For enantiomeric recognition in molecular aggregates such as micelles see: Jursic, B. S. *Tetrahedron Lett.* **1993**, *34*, 963–966.
11. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
12. Connors, K. A. *Binding Constants*; Wiley: New York, 1987.