Tetrahedron: *Asymmetry* 19 (2008) 1790–1796

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Water-soluble calix[4]resorcinarenes as chiral NMR solvating agents for phenyl-containing compounds

Courtney M. O'Farrell, Thomas J. Wenzel *

Department of Chemistry, Bates College, Lewiston, ME 04240, USA

ARTICLE INFO

Article history:
Received 21 May 2008
Accepted 16 July 2008
Available online 8 August 2008

ABSTRACT

Water-soluble calix[4]resorcinarenes with 3- and 4-hydroxyproline substituent groups are evaluated as chiral NMR solvating agents on a series of monosubstituted phenyl-containing compounds. The substrates interact with the calixresorcinarene through insertion of the aromatic ring into the cavity. Cationic, anionic, and neutral substrates were examined, and all exhibited enantiomeric discrimination in the ^{1}H NMR spectrum with one or more of the calixresorcinarenes. The hydroxyproline derivatives were almost always more effective at causing enantiodifferentiation than the corresponding proline derivative. Presumably the hydroxyl group on the proline moieties is involved in interactions with the substituent groups of the substrate that are important in creating chiral recognition. The enantiomeric discrimination in the ^{1}H NMR spectrum is large enough to permit the analysis of enantiomeric purity.

1. Introduction

Enantiomerically pure chiral solvating agents are often used in NMR spectroscopy for the analysis of enantiomeric purity.[1–6] While many compounds have been tested for their utility as chiral NMR solvating agents, the overwhelming majority of these are organic-soluble reagents. Very few water-soluble chiral NMR shift reagents are known. Association of enantiomers with chiral solvating agents involves non-covalent interactions such as hydrogen bonding, other dipole–dipole interactions, and π-stacking between electron-rich and electron-deficient aromatic rings. Steric effects can also be important in the association process. For many chiral solvating agents, polar solvents such as acetonitrile, methanol, acetone, methyl sulfoxide, and water effectively solvate the dipolar groups of the reagent and substrate and reduce formation of the complex that is needed for enantiomeric discrimination. Many pharmaceutical compounds are specifically designed to possess water solubility, and with growing emphasis on the use of water as a solvent in green chemistry, it is important to have water-soluble chiral NMR shift reagents.

Water-soluble lanthanide complexes have been used as chiral NMR shift reagents.[1,7–10] Paramagnetic line broadening can be a problem with lanthanide reagents. Chiral, water-soluble micelles can cause chiral discrimination, although these systems have not been widely studied in NMR applications.[11–13] Another approach is to use water-soluble compounds that have a hydrophobic cavity. Association occurs by insertion of the hydrophobic portion of water-soluble organic salts into the cavity of the solvating agent. Native cyclodextrins,[14–18] trimethyl-β-cyclodextrin,[19–23] and carboxymethylated cyclodextrins[24–29] are one family of water-soluble cavity compounds. The crown ether (18-crown-6)-2,3,11,12-tetracarboxylic acid has been used in water as a chiral solvating agent for primary amines,[30] although the enantiomeric discrimination with the crown ether is better in methanol and acetonitrile.[30–38]

A tetrasulfonated calix[4]resorcinarene which contains enantiomerically pure L-prolinylmethyl groups **1** represents an effective chiral NMR solvating agent for water-soluble substrates with a phenyl or bicyclic aromatic ring.[39–42] A preliminary report of compounds similar to **1** that contain enantiomerically pure hydroxyprolinylmethyl substituents including *cis*-4-hydroxy-D-proline **2**, *cis*-4-hydroxy-L-proline **3**, *trans*-4-hydroxy-L-proline **4**, and *trans*-3-hydroxy-L-proline **5** found that **2**–**5** were more effective chiral NMR solvating agents than **1**.[42] Compounds **1**–**5** adopt a cone configuration in solution or are in rapid exchange among a variety of possible configurations (Fig. 1). Association occurs through insertion of the hydrophobic aromatic ring of the substrate into the well-defined resorcinarene cavity, as evidenced by the large shifts to lower frequencies of the aromatic ring resonances of the substrate caused by shielding from the resorcinol rings. The associated complexes of a pair of enantiomers with **1**–**5** are diastereomers, which can have different chemical shifts in the NMR spectrum. Differences in the association constants of the enantiomers with the reagent may also account for the enantiomeric distinction. These systems are usually under conditions of

* Corresponding author. Tel.: +1 207 786 6296; fax: +1 207 786 8336.
E-mail address: twenzel@bates.edu (T. J. Wenzel).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.07.023

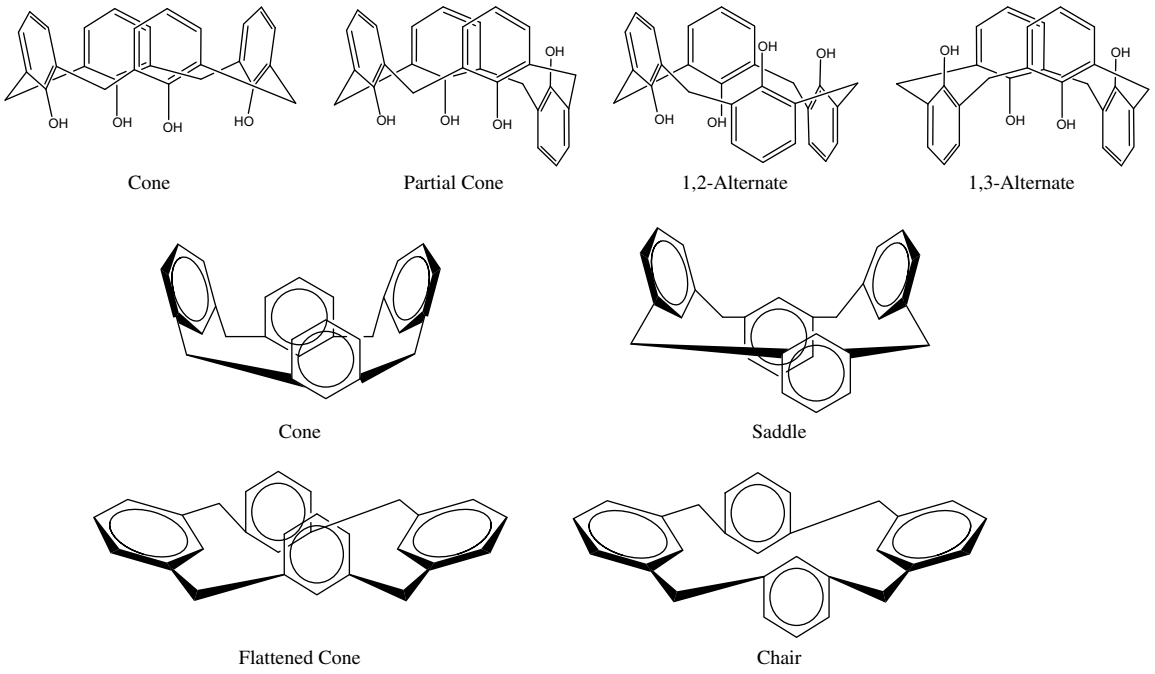
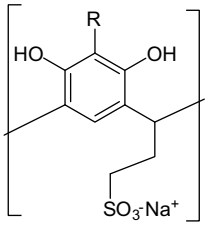
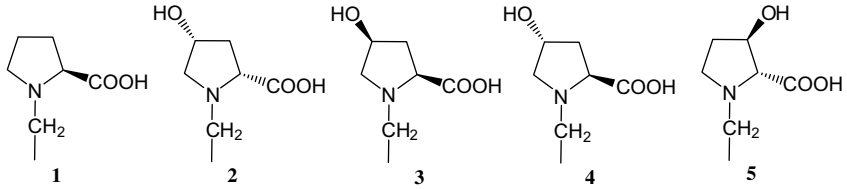
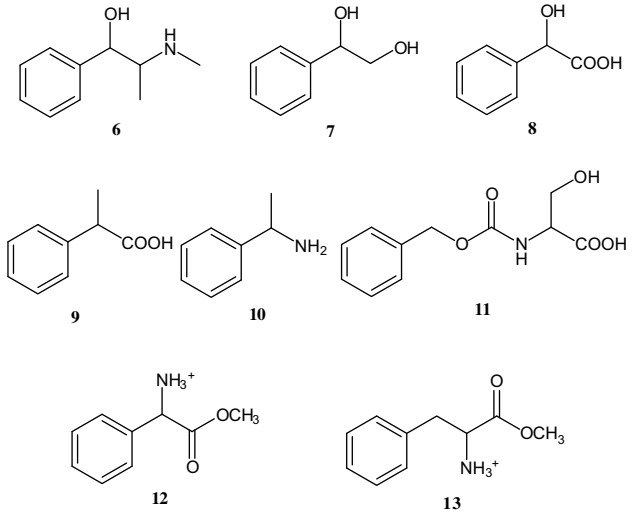


Figure 1. Possible configurations (top) and conformations (bottom) of calix[4]resorcinarenes.







fast exchange such that the NMR spectrum of the substrate is a time average of the bound and unbound forms.

Herein we compare the effectiveness of **1**–**5** as chiral NMR solvating agents for a series of water-soluble, monosubstituted, phenyl-containing compounds **6**–**13**. Compounds **2**–**5** are often superior to **1** as chiral NMR solvating agents.

2. Results and discussion

The effectiveness of **1**–**5** was evaluated with ephedrine **6**, 1-phenyl-1,2-ethanediol **7**, mandelic acid **8**, 1-phenylpropionic acid **9**, 1-phenylethylamine **10**, *N*-CBZ-serine **11**, and the methyl esters of phenylglycine **12** and phenylalanine **13**. These compounds have a range of functionalities in the substituent groups including hydroxyl, ammonium, carboxylate, and ester moieties. Tables 1–8 provide comparative shifts in the ^{1}H NMR spectra of **6**–**13** in the presence of **1**–**5**. The H_o, H_m, and H_p designations refer to positions relative to the substituent groups of the substrates.

Table 1
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **6** (10 mM) in the presence of calixresorcinarenes (40 mM)

	1	2	4	5
H_o	0.35/0.37 (0.02)	0.49	0.60	0.30/0.34 (0.04)
H_m	0.60	0.86	0.97	0.50/0.56 (0.06)
H_p	0.84	1.22	1.23	0.72/0.81 (0.09)
–NMe	0.03/0.04 (0.01)	0.04/0.06 (0.02)	0.07/0.09 (0.02)	0.03/0.04 (0.01)
–CMe	0.12/0.14 (0.02)	0.15/0.16 (0.01)	0.21	0.10/0.11 (0.01)

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

Table 2
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **7** (10 mM) in the presence of calixresorcinarenes (10 mM)

	1	3	4	5
H_o	0.20	0.24	0.26	0.23/0.26 (0.03)
H_m	0.27	0.37/0.39 (0.02)	0.37	0.31/0.34 (0.03)
H_p	0.39	0.53	0.52	0.47

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

Table 3
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **8** (10 mM) in the presence of calixresorcinarenes (10 mM)

	1	3	4	5
H_o	0.29	0.30	0.23/0.26 (0.03)	0.30/0.33 (0.03)
H_m	0.45	0.48	0.39	0.46
H_p	0.58	0.62	0.51	0.60
CH	0.23	0.22	0.18/0.19 (0.01)	0.23/0.24 (0.01)

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

Table 4
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **9** (10 mM) in the presence of calixresorcinarenes (10 mM)

	1	2	4	5
H_o	0.23	0.33	0.35	0.34
H_m	0.29	0.48	0.48	0.46
H_p	0.47	0.70/0.77 (0.07)	0.69	0.66
Me	0.13	0.12/0.13 (0.01)	0.13/0.17 (0.04)	0.17

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

Evidence for host–guest complexation between the substrates and the resorcinarenes is provided by the large shifts to lower frequencies in the ^{1}H NMR spectra of the aromatic resonances of **6**–**13**. The substantial shielding of the aromatic resonances indicates that complexation of **6**–**13** with **1**–**5** proceeds via the insertion of the aromatic ring of the substrate into the resorcinarene cavity. When a phenyl ring is inserted into **1**–**5,** the aromatic hydrogen atoms of the substrate are positioned over the π-electrons of the aromatic rings of the resorcinarene, which accounts for the large shielding. The aromatic resonances of **6**–**13** shift in the order $H_p > H_m > H_o$ with **1**–**5**, indicating that the substrate ring inserts with the hydrogen atom *para* to the substituent group deepest in the cavity. The resonances of hydrogen atoms on the substituent groups of **6**–**13** also shift to lower frequency in the presence of **1**–**5**. These shifts are smaller than those of the aromatic resonances, and diminish the further the hydrogen atom is from the

Table 5
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **10** (10 mM) in the presence of calixresorcinarenes (40 mM)

	1	2	4	5
H_o	0.42/0.44 (0.02)	0.52/0.58 (0.06)	0.56/0.60 (0.04)	0.31/0.36 (0.05)
H_m	0.72	0.90	0.87	0.51/0.53 (0.02)
H_p	0.92	1.15	1.11	0.71
CH	—[a]	0.03/0.04 (0.01)	0.03/0.04 (0.01)	0.05/0.06 (0.01)
Me	0.14	0.17	0.18	0.12/0.13 (0.01)

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.
[a] Overlapped with other resonances.

Table 6
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **11** (10 mM) in the presence of calixresorcinarenes (10 mM)

	1	2	4	5
H_o	0.36/0.42 (0.06)	0.42/0.49 (0.07)	0.39/0.45 (0.06)	0.41/0.47 (0.06)
H_m	0.51	0.56/0.66 (0.10)	0.49/0.59 (0.10)	0.50/0.57 (0.07)
H_p	0.62	0.71/0.81 (0.10)	0.67	0.63/0.70 (0.07)
Ar–CH_2	0.21/0.24 (0.03)	0.20/0.23 (0.03)	0.20/0.23 (0.03)	0.21/0.24 (0.03)

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

Table 7
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **12** (10 mM) in the presence of calixresorcinarenes (40 mM)

	1	2	4	5
H_o	0.30/0.35 (0.05)	0.57	0.56	0.33/0.37 (0.04)
H_m	0.66/0.69 (0.03)	0.96	0.98	0.61/0.66 (0.05)
H_p	0.89	Broadened	1.25	0.78/0.82 (0.10)
CH	0.17	0.21/0.22 (0.01)	0.21/0.23 (0.02)	0.13/0.15 (0.12)
OCH_3	0.06/0.08 (0.02)	0.06/0.09 (0.03)	0.07/0.09 (0.02)	0.08/0.09 (0.01)

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

Table 8
Shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **13** (10 mM) in the presence of calixresorcinarenes (40 mM)

	1	4	5
H_o	0.33/0.36 (0.03)	0.34/0.39 (0.05)	0.26
H_m	0.59/0.65 (0.06)	0.61/0.70 (0.09)	0.42/0.44 (0.02)
H_p	0.74/0.82 (0.08)	0.82/0.94 (0.12)	0.57/0.61 (0.04)
CH	0.09	0.06	0.05
CH_2	0.25	0.02/0.03 (0.01)	0.26
OCH_3	0.09	0.06	0.11

Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

aromatic ring and the cavity. Job plots[43–45] for **8**, **12**, and **13** with **4** and **5** all indicate the formation of a 1:1 complex, which is consistent with all other studies using **1**–**5** as chiral NMR solvating agents.[39–42]

The aromatic resonances of the hydrochloride salt of ephedrine **6** have the largest shifts to lower frequency with **4** (Fig. 2e) and the smallest shifts with **5** (Fig. 2f, Table 1). However, the extent of enantiodifferentiation does not correlate with the magnitude of the shifts caused by the different calixresorcinarenes. Instead, the least amount of enantiomeric discrimination in the ^{1}H NMR spectrum of **6** occurs with **4**, while the largest occurs with **5**. Presumably, the association constant of **6** with **4** is greater than that with **5**, but enantiomeric discrimination is not dependent solely

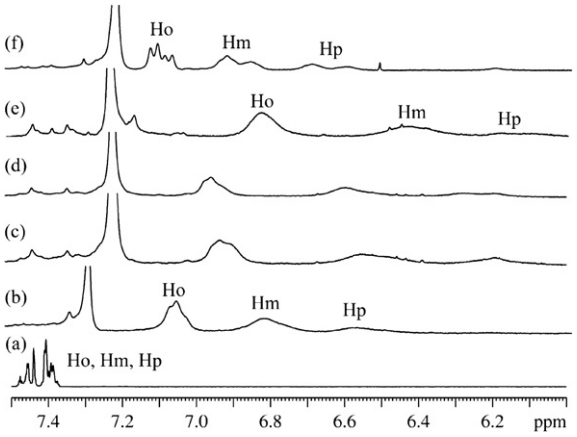


Figure 2. ^{1}H NMR spectrum of the aromatic resonances (400 MHz, D_2O, 23 °C) of (a) **6** (10 mM) enantiomerically enriched (2/3(−)-(1*R*,2*S*), 1/3(+)-(1*S*,2*R*)) with 40 mM (b) **1**, (c) **2**, (d) **3**, (e) **4**, and (f) **5**.

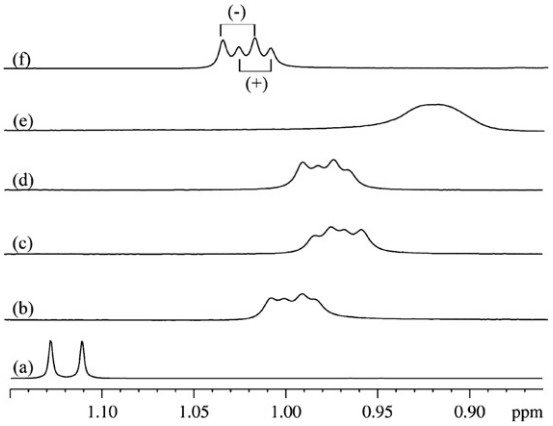


Figure 4. ^{1}H NMR spectrum of the *C*-methyl resonance (400 MHz, D_2O, 23 °C) of (a) **6** (10 mM) enantiomerically enriched (2/3(−)-(1*R*,2*S*), 1/3(+)-(1*S*,2*R*)) with 40 mM (b) **1**, (c) **2**, (d) **3**, (e) **4**, and (f) **5**.

on the magnitude of the association constants. It may also be possible that **6** inserts deeper into the cavity of **4** than **5**, although prior studies found that the magnitude of the shifts correlated with the association constants.[39–42] It is also apparent from the spectra in Figure 2 that the further shifting resonances exhibit more broadening. An intermediate exchange rate of bound and unbound forms such that the peaks in the spectrum no longer represent a single time average of all of the contributing species likely accounts for the broadening. When the broadening is too severe, it reduces the ability to use the peaks for determining the enantiomeric purity. Enantiomeric discrimination is observed for the H_o, H_m, and H_p resonances of **6** with **5** (Fig. 2f), whereas only the H_o resonance exhibits a slight enantiodifferentiation with **1** (Fig. 2b).

The *N*-methyl (Fig. 3) and *C*-methyl (Fig. 4) resonances of **6** show the largest shifts with **4**, and smaller but roughly comparable shifts with **1**–**3** and **5**. While the *N*-methyl resonance shows the least peak broadening and excellent enantiomeric discrimination with **5** (Fig. 3f), even larger enantiodifferentiation occurs with **2** and **3** (Fig. 2c and d). As expected, the positions of the (+)- and (−)- enantiomers are reversed with **2** and **3**. The slight differences in chemical shifts in the spectra with **2** and **3** occur because of small differences in the concentrations of the mixtures. Values for only **2** or **3** are reported in Tables 1–8. The most useful enantiomeric discrimination of the *C*-methyl resonance occurs with **5**. An

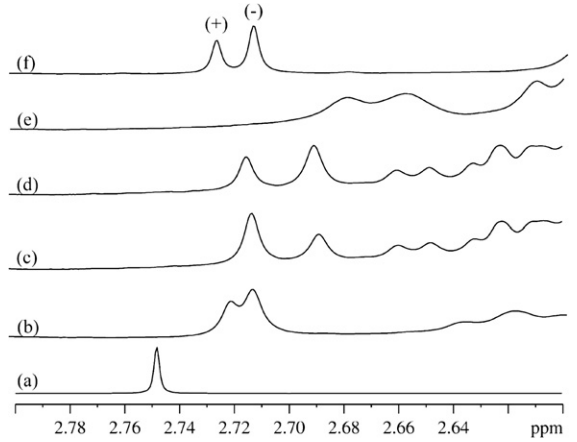


Figure 3. ^{1}H NMR spectrum of the *N*-methyl resonance (400 MHz, D_2O, 23 °C) of (a) **6** (10 mM) enantiomerically enriched (2/3(−)-(1*R*,2*S*), 1/3(+)-(1*S*,2*R*)) with 40 mM (b) **1**, (c) **2**, (d) **3**, (e) **4**, and (f) **5**.

interesting observation is that the H_o, H_m, H_p (Fig. 2f), and *C*-methyl (Fig. 4f) resonances of the (+)-enantiomer of **6** shifts further with **5**, whereas the opposite shift order occurs for the *N*-methyl resonance (Fig. 3f). This indicates that the diastereomeric nature of the host–guest complexes of the two enantiomers of **6** with **5** is more likely to be the cause of the enantiomeric discrimination than any inequivalence in the association constants. The particular effectiveness of **5** with **6** implies that the 3-hydroxy group of the prolinyl portion of the calixresorcinarene is important in distinguishing the enantiomers.

The aromatic resonances of 1-phenyl-1,2-ethanediol **7** exhibit sizeable shifts to lower frequency with **1**–**5** (Table 2). The smallest shifts occur with **1** and those with **2**–**5** are comparable. The H_o resonance of **7** exhibits enantiomeric discrimination with only **5**, whereas the H_m resonance exhibits enantiodifferentiation with **3** and **5**. Since the shifts are fairly comparable with **2**–**5**, the hydroxyl group at the 3-position of **5** must be a significant factor in causing the enantiomeric discrimination. Since the H_m resonance of **7** exhibits enantiomeric discrimination with **3**, but not **4**, the different orientation of the hydroxyl group at the 4-position in **3** and **4** in relation to the resorcarinene cavity must be important in determining the extent of enantiodifferentiation.

The H_o and methine resonances of the sodium salt of mandelic acid **8** exhibit enantiomeric discrimination in the presence of **4** and **5** (Table 3). As with **6** and **7**, the advantage of the hydroxyproline calixresorcinarenes over the proline derivative is apparent, even though the shifts in the spectrum of **8** with **1** are comparable in magnitude to those with **2**–**5**. Presumably, the hydroxyl groups in the *trans*-orientation and their location on the proline moiety of **4** and **5** must be important in causing enantiomeric discrimination. An interesting observation is that the methine resonance of the (*R*)-enantiomer shifts further than that of the (*S*)-enantiomer with **5**, whereas the opposite shift order is observed for **4**. The relative association constants of **8** with **4** ($K_R = 22\ M^{-1}$, $K_S = 32\ M^{-1}$) and **5** ($K_R = 48\ M^{-1}$, $K_S = 37\ M^{-1}$) correlate with the shift order of the methine resonance in both cases. While the relative association constants may explain the enantiomeric discrimination in the spectra of **8** with **4** and **5**, the diastereomeric nature of the associated complexes likely contributes as well.

The shifts to lower frequency of the aromatic resonances of **8** with **1**–**5** are similar in magnitude to those observed in the spectra of **7**. The methine resonance of **7** did not show any enantiomeric discrimination with **1**–**5** as seen with **8**. Similarly, the H_m resonance of **7** exhibits enantiodifferentiation with **3**, but the comparable resonance of **8** does not show any enantiomeric distinction. These differences illustrate the importance that the substituent

groups on the phenyl ring have with regard to interacting with the proline moieties of **1**–**5** and contributing to enantiomeric discrimination.

The sodium salt of 1-phenylpropionic acid **9** is structurally similar to **8** with a methyl group in place of the hydroxyl group. Whereas the H_o resonance of **8** exhibits enantiomeric discrimination with **4** and **5**, among the aromatic hydrogen atoms, only the H_p resonance of **9** exhibits enantiodifferentiation with **2** and **3** (Table 4). Another difference is that the methine resonance of **9** does not exhibit enantiomeric discrimination in the presence of **1**–**5**, contrary to the methine resonance of **8**. However, the methyl resonance of **9** exhibits significant enantiomeric discrimination in the presence of **4** (Fig. 5e), and a small amount of enantiodifferentiation with **2** and **3** (Fig. 5c and d). The large chiral discrimination of the methyl resonance of **9** with **4** relative to the other calixresorcinarenes suggests that the hydroxyl group of **4** is implicated in the mechanism that leads to enantiodifferentiation.

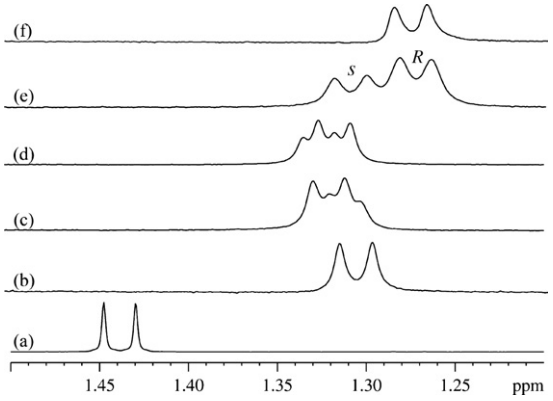


Figure 5. ^{1}H NMR spectrum of the methyl resonance (400 MHz, D_2O, 23 °C) of (a) **9** (10 mM) enantiomerically enriched (2/3-(*R*), 1/3-(*S*)) with 10 mM (b) **1**, (c) **2**, (d) **3**, (e) **4**, and (f) **5**.

The H_o and methine resonances of the hydrochloride salt of 1-phenylethylamine **10** exhibit enantiomeric discrimination with each calixresorcinarene (Table 5). The greatest enantiomeric discrimination for the H_o resonance is observed with **2** and **3**. The enantiomeric discrimination for the methine resonance of **10** is essentially the same for **1**–**5**. However, the ^{1}H NMR spectrum with **5** is more useful because it is not as broadened as those with **2**, **3**, and **4**. Since the resonances of **10** have greater shifts with **2**, **3**, and **4**, the association constants with these pairs are likely greater, accounting for the larger broadening. Another noteworthy observation is that the H_m and methyl resonances of **10** are enantiomerically discriminated only with **5**. Presumably, the enantiomeric distinction of **10** is dependent on the hydroxyl group at the 3-position of **5**.

Previous work had demonstrated that the three aromatic resonances of *N*-CBZ-serine **11** (10 mM) exhibit enantiomeric discrimination in the presence of **1** (40 mM).[39] The addition of **1**–**5** to **11** in a 4:1 ratio caused significant broadening in the aromatic region of the spectra, thus data are reported instead at a 1:1 ratio. At a 1:1 ratio of **11** with **1**, only the H_o resonance exhibits discernable enantiomeric discrimination. While **2**, **3**, and **5** cause shifts to lower frequency in the ^{1}H NMR spectrum of **11** that are comparable to those with **1** (Table 6), these also produce enantiomeric discrimination of the H_m and H_p resonances. Compounds **2**, **3**, and **5** are preferred over **1** because excellent enantiomeric discrimination is observed at much lower concentrations.

The methylene resonances of **11** show similar levels of enantiomeric discrimination in the presence of each of the calixresorcinarenes. The distinction between the enantiomeric discrimination and diastereotopic resolution is confirmed by examining mixtures enriched in one of the enantiomers. An interesting observation is that with **5**, the methylene resonances of the L-enantiomer split further and exhibit diastereotopic resolution as well.

The hydrochloride salts of phenylglycine methyl ester **12** and phenylalanine methyl ester **13** are structurally similar except for the additional methylene group on the aliphatic portion of **13**. Both show sizeable complexation-induced shifts to lower frequency in the ^{1}H NMR spectra with **1**–**5**. For **12**, the shifts in the ^{1}H NMR spectra with **2**, **3**, and **4** are almost double those with **1** and **5** (Table 7), but the aromatic resonances are considerably more broadened with **2**, **3**, and **4** as well. Presumably, stronger association between **12** and **2**, **3**, and **4** causes the broadening.

For **13**, the shifts with **4** and **1** are comparable in magnitude, whereas those with **5** are smaller (Table 8). Data are not reported for **13** with **2** or **3** because only small shifts occur for the aromatic resonances, indicating that weak complexation occurs. These are the only examples for mixtures of **6**–**13** with **1**–**5** where almost no complexation occurs. The shifts in the spectra of **12** and **13** with **1** are similar in magnitude, whereas those caused by **4** and **5** are smaller in the spectra of **13** than those of **12**. The effects of noncovalent interactions between the substituent group of the substrate and proline moieties of **1**–**5** in influencing the magnitude of the shifts are apparent when considering the observations with **12** and **13**.

More significant differences occur in the enantiomeric discrimination of resonances of **12** and **13** in mixtures with **1**–**5**. Even though association of **12** with **2**, **3**, and **4** appears to be greater than with **1** and **5**, enantiomeric discrimination of the aromatic resonances is not observed with **2**, **3**, and **4** (Table 7). Enantiomeric discrimination of the H_o, H_m, and H_p resonances of **12** is observed in the presence of **5**.

Enantiodifferentiation is also observed for the methine (Fig. 6) and methoxy (Fig. 7) resonances of **12** with each of the calix[4]resorcarenes. The greatest discrimination for the methine resonance is observed with **4** and **5** (Fig. 6e and f), yet the greatest discrimination for the methoxy resonance is with **2** and **3** (Fig. 7c and d). Another interesting observation is that the methine resonance of the (*S*)-enantiomer of **12** shifts further with **4**, whereas the reverse shift order occurs for the methoxy resonance. The opposite occurs for **12** with **1**; the methine resonance of the (*R*)-enantiomer shifts further whereas the methoxy resonance of the (*S*)-enantiomer shifts further. However, the spectra for mixtures of **12** with **2**, **3**, and **5** do not show a reversal of the shift order for the methine and methoxy resonances. The diastereomeric nature of the host–

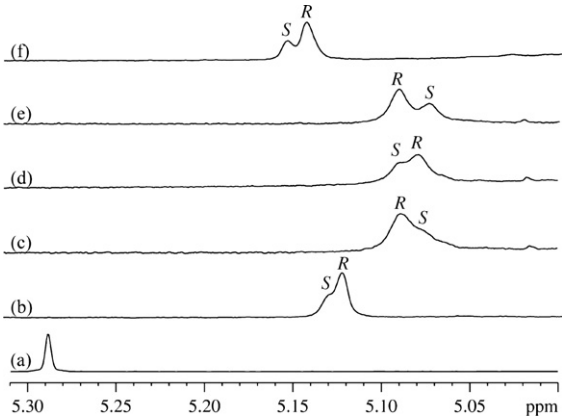


Figure 6. ^{1}H NMR spectrum of the methine resonance (400 MHz, D_2O, 23 °C) of (a) **12** (10 mM) enantiomerically enriched (2/3-(*R*), 1/3-(*S*)) with 40 mM (b) **1**, (c) **2**, (d) **3**, (e) **4**, and (f) **5**.

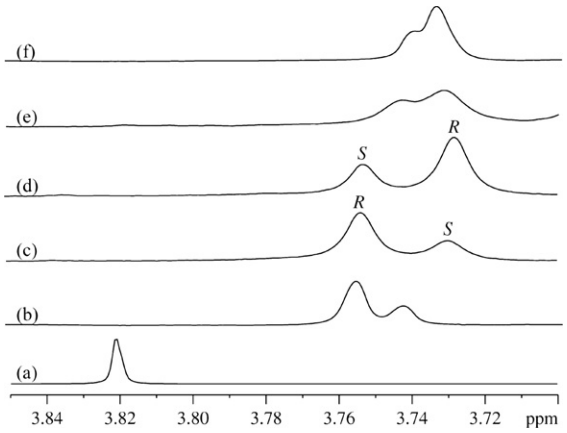


Figure 7. ^{1}H NMR spectrum of the methoxy resonance (400 MHz, D_2O, 23 °C) of (a) **12** (10 mM) enantiomerically enriched (2/3-(*R*), 1/3-(*S*)) with 40 mM (b) **1**, (c) **2**, (d) **3**, (e) **4**, and (f) **5**.

guest complexes of the two enantiomers with **1**–**5** is likely more important in influencing the enantiomeric discrimination than inequivalence in the association constants.

In comparison to **12**, quite different results are observed for the enantiomeric discrimination in the ^{1}H NMR spectrum of **13** with **1**–**5**. Enantiomeric discrimination is much larger for the aromatic resonances of **13** with **1** and **4** than it is with **12** (Table 8, Fig. 8). The enantiodifferentiation of the aromatic resonances of **13** with **4** is especially significant, as observed in Fig. 8c. The methine and methoxy resonances of **13** do not exhibit any enantiomeric discrimination in the presence of **1**–**5**, which is in contrast with the results observed for **12**. Since the shifts of the methine and methoxy resonances of **12** and **13** with **1**, **4**, and **5** are similar in magnitude, the differences in enantiodifferentiation must relate to subtle distinctions in the diastereomeric nature of the substrate–calixresorcinarene complexes.

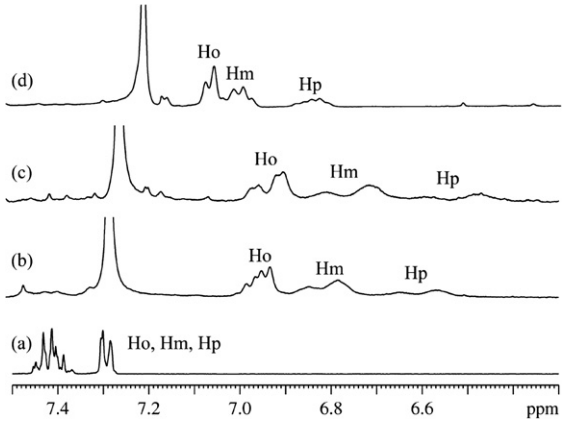


Figure 8. ^{1}H NMR spectrum of the aromatic resonances (400 MHz, D_2O, 23 °C) of (a) **13** (10 mM) enantiomerically enriched (2/3-(*R*), 1/3-(*S*)) with 40 mM (b) **1**, (c) **4**, and (d) **5**.

3. Conclusions

Several prior reports have demonstrated the utility of **1** as a water-soluble chiral NMR solvating agent for aromatic compounds.[39–42] Of the eight substrates examined herein, only a single resonance on two of them (*C*-methyl of **6**, H_o of **12**) exhibits the largest enantiomeric discrimination with **1**. Other resonances of **6** and **12**, as well as all the other substrates, have greater enantiomeric discrimination in the presence of one or more of **2**–**5**. Typical values of enantiodifferentiation with **2**–**5** range from a few hundredths to a tenth of a ppm. The enantiomeric discrimination is often large enough to cause baseline separation of the two resonances, which facilitates the measurement of enantiomeric purity. Presumably, the additional hydroxyl groups on the proline moieties of **2**–**5** provide sites for dipole–dipole interactions or represent steric encumbrances that enhance chiral recognition. Among **2**–**5**, no one compound is consistently the most effectively chiral NMR solvating agent for the substrates examined herein. Each of **2**–**5** has about an equal number of resonances for which it is the most effective reagent.

For several of the substrates, the calixresorcinarene that causes the greatest enantiomeric discrimination varies for different resonances. Compound **12** is an extreme example, in which **1** causes the largest enantiodifferentiation of the H_o resonance, **2** and **3** work the best for the methoxy group, **4** causes the largest enantiomeric discrimination of the methine hydrogen atom, and **5** is best for the three aromatic hydrogen atoms. The importance of the substituent group in influencing the enantiomeric discrimination is apparent when comparing the results for different substrates. Furthermore, the calixresorcinarene that causes the largest shifts in the ^{1}H NMR spectrum of the substrate does not always produce the greatest enantiomeric discrimination. Chiral recognition depends on the differences, either diastereomeric or in association constants, of a pair of enantiomers with the calixresorcinarene, and these differences do not correlate with the magnitude of the shifts with **1**–**5**. Also, the broadening is worse when the shifts are larger, which can reduce the ability to accurately detect distinct resonances for the two enantiomers. While no one of **2**–**5** is consistently most effective, they generally are better chiral NMR solvating agents for phenyl-containing compounds than **1**.

4. Experimental

4.1. Reagents

The prolinylmethyl calix[4]resorcinarene derivatives **1**–**5** were prepared and purified using published procedures.[39,42] Water-soluble derivatives of amines were obtained either by preparation and isolation of the corresponding hydrochloride salt (crystallization from a solution of the amine in methanol saturated with hydrogen chloride gas) or in solution by adding a stoichiometric equivalent of hydrochloric acid in deuterium oxide to the amine. Similarly, water-soluble derivatives of carboxylic acids were obtained either by preparation and isolation of the corresponding sodium salt (crystallization by evaporation of a solution of the acid and a stoichiometric amount of sodium bicarbonate in water) or in solution by adding a stoichiometric amount of sodium hydroxide.

4.2. Procedures

^{1}H NMR spectra were recorded at 400 MHz using 16 scans at ambient probe temperature (23 °C). Samples for NMR spectroscopy were prepared by weighing and dissolving the appropriate amount of substrate in deuterium oxide. Increments of the calixresorcinarene were added either by weight or volumetrically by addition of an appropriate amount of a concentrated stock solution (120 mM or 240 mM). Stoichiometries of complexes were determined using Job's method.[43–45] The concentration of calixresorcinarene and substrate was continuously varied throughout the series while maintaining a total concentration of calixresorcinarene and substrate of 40 mM for each sample. Association constants were determined using the Scatchard method (Foster–Fyfe) of infinite

dilutions of host while maintaining the concentration of substrate at 2 mM.[46–48] The use of the Scatchard method for determining association constants is recommended over other graphical techniques.[49] The concentration of calixresorcinarene was varied from 50 to 1 mM for the series of spectra by diluting with a 2 mM solution of the substrate.

Acknowledgments

We thank the National Science Foundation (Research at Undergraduate Institutions Program, Grants CHE-0244742 and CHE-0653711; Major Instrumentation Program, Grant CHE-0115579), and the Howard Hughes Medical Institute through an institutional award to Bates College for supporting our work.

References

1. Wenzel, T. J. *Discrimination of Chiral Compounds Using NMR Spectroscopy*; John Wiley & Sons: Hoboken, NJ, 2007.
2. Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256–270.
3. Wenzel, T. J. *Encyclopedia of Spectroscopy and Spectrometry*; Academic Press, 2000. pp 411–421.
4. Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383–395.
5. Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1447.
6. Pirkle, W.H.; Hoover, D.J.; in: Eliel, E.L.; Wilen, S.H.; (Eds.), Top Stereochem., Vol. 1, pp 263–331.
7. Kabuto, K.; Sasaki, K.; Sasaki, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 1357–1360.
8. Inamoto, A.; Ogasawara, K.; Omata, K.; Kabuto, K.; Sasaki, Y. *Org. Lett.* **2000**, *2*, 3543–3545.
9. Hazama, R.; Umakoshi, K.; Kabuto, C.; Kabuto, K.; Sasaki, Y. *Chem Commun.* **1996**, 15–16.
10. Sato, J.; Jin, H.; Omata, K.; Kabuto, K.; Sasaki, Y. *Enantiomer* **1999**, *4*, 147–150.
11. Valle, B. C.; Morris, K. F.; Fletcher, K. A.; Fernand, V.; Sword, D. M.; Eldridge, S.; Larive, C. K.; Warner, I. M. *Langmuir* **2007**, *23*, 425–435.
12. Morris, K. F.; Becker, B. A.; Valle, B. C.; Warner, I. M.; Larive, C. K. *J. Phys. Chem. B* **2006**, *110*, 17359–17369.
13. Eckenroad, K. W.; Thompson, L. E.; Strein, T. G.; Rovnyak, D. *Magn. Reson. Chem.* **2007**, *45*, 72–75.
14. MacNicol, D. D.; Rycroft, D. S. *Tetrahedron Lett.* **1977**, 2173–2176.
15. Greatbanks, D.; Pickford, R. *Magn. Reson. Chem.* **1987**, *25*, 208–215.
16. Casy, A. F.; Mercer, A. D. *Magn. Reson. Chem.* **1988**, *26*, 765–774.
17. Aga, D. S.; Heberle, S.; Rentsch, D.; Hany, R.; Müller, S. R. *Environ. Sci. Technol.* **1999**, *33*, 3462–3468.
18. Dodziuk, H.; Sitkowski, J.; Stefaniak, L.; Jurczak, J.; Sybilska, D. *J. Chem. Soc., Chem. Commun.* **1992**, 207–208.
19. Botsi, A.; Yannakopoulou, K.; Hadjoudis, E.; Perly, B. *J. Chem. Soc., Chem. Commun.* **1993**, 1085–1086.
20. Taylor, A.; Williams, D. A. R.; Wilson, I. D. *J. Pharm. Biomed. Anal.* **1991**, *9*, 493–496.
21. Kano, K.; Kato, Y.; Kodera, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1211–1217.
22. Park, K. K.; Park, J. M. *Bull. Korean Chem. Soc.* **1996**, *17*, 1052–1056.
23. Chankvetadze, B.; Burjanadze, N.; Pintore, G.; Strickmann, D.; Bergenthal, D.; Blaschke, G. *Chirality* **1999**, *11*, 635–644.
24. Dignam, C. F.; Randall, L. A.; Blacken, R. D.; Cunningham, P. R.; Lester, S. G.; Brown, M. J.; French, S. C.; Aniagyei, S. E.; Wenzel, T. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1199–1208.
25. Endresz, G.; Chankvetadze, B.; Bergenthal, D.; Blaschke, G. *J. Chromatogr. A* **1996**, *732*, 133–142.
26. Owens, P. K.; Fell, A. F.; Coleman, M. W.; Berridge, J. C. *J. Chromatogr. A* **1998**, *797*, 149–164.
27. Owens, P. K.; Fell, A. F.; Coleman, M. W.; Kinns, M.; Berridge, J. C. *J. Pharm. Biomed. Anal.* **1997**, *15*, 1603–1619.
28. Smith, K. J.; Wilcox, J. D.; Mirick, G. E.; Wacker, L. S.; Ryan, N. S.; Vensel, D. A.; Readling, R.; Domush, H. L.; Amonoo, E. P.; Shariff, S. S.; Wenzel, T. J. *Chirality* **2003**, *15*, S150–S158.
29. Wenzel, T. J.; Amoono, E. P.; Shariff, S. S.; Aniagyei, S. E. *Tetrahedron: Asymmetry* **2003**, *14*, 3099–3104.
30. Machida, Y.; Kagawa, M.; Nishi, H. *J. Pharm. Biomed. Anal.* **2003**, *30*, 1929–1942.
31. Wenzel, T. J.; Thurston, J. E. *J. Org. Chem.* **2000**, *65*, 1243–1248.
32. Wenzel, T. J.; Thurston, J. E. *Tetrahedron Lett.* **2000**, *41*, 3769–3772.
33. Wenzel, T. J.; Thurston, J. E.; Sek, D. C.; Joly, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 1125–1130.
34. Wenzel, T. J.; Freeman, B. E.; Sek, D. C.; Zopf, J. J.; Nakamura, T.; Yongzhu, J.; Hirose, K.; Tobe, Y. *Anal. Bioanal. Chem.* **2004**, *378*, 1536–1547.
35. Lovely, A. E.; Wenzel, T. J. *Org. Lett.* **2006**, *8*, 2823–2826.
36. Lovely, A. E.; Wenzel, T. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2642–2648.
37. Lovely, A. E.; Wenzel, T. J. *J. Org. Chem.* **2006**, *71*, 9178–9182.
38. Lovely, A. E.; Wenzel, T. J. *Chirality* **2008**, *20*, 370–378.
39. Yanagihara, R.; Tominaga, M.; Aoyama, Y. *J. Org. Chem.* **1994**, *59*, 6865–6867.
40. Dignam, C. F.; Richards, C. J.; Zopf, J. J.; Wacker, L. S.; Wenzel, T. J. *Org. Lett.* **2005**, *7*, 1773–1776.
41. Dignam, C. F.; Zopf, J. J.; Richards, C. J.; Wenzel, T. J. *J. Org. Chem.* **2005**, *70*, 8071–8078.
42. O'Farrell, C. M.; Chudomel, J. M.; Collins, J. M.; Dignam, C. F.; Wenzel, T. J. *J. Org. Chem.* **2008**, *73*, 2843–2851.
43. Job, P. *Ann. Chem.* **1928**, *9*, 113–203.
44. Sahai, R.; Loper, G. L.; Lin, S. H.; Eyring, H. *Proc. Nat. Acad. Sci. U.S.A.* **1974**, *71*, 1499–1503.
45. Gil, V. M. S.; Olivceira, N. C. *J. Chem. Ed.* **1990**, 473–478.
46. Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 660–672.
47. Foster, R.; Fyfe, C. A. *Trans. Faraday Soc.* **1965**, *61*, 1626–1631.
48. Foster, R.; Fyfe, C. A. *J. Chem Soc., Chem. Commun.* **1965**, 642.
49. Fielding, L. *Tetrahedron* **2000**, *56*, 6151–6170.