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Water-Soluble Calix[4]resorcarenes as Enantioselective NMR Shift Reagents for Aromatic Compounds

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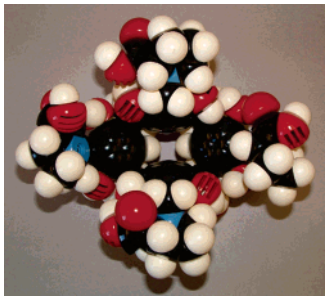

A tetra L-prolinylmethyl derivative of a tetra-sulfonated calix[4]resorcarene (**1**) is an effective chiral NMR solvating agent for water-soluble compounds with phenyl, pyridyl, bicyclic aromatic, or indole rings. These aromatic compounds form host−guest complexes with the calix[4]resorcarene in water. Complexation of substrates with the calix[4]resorcarene is likely promoted by hydrophobic effects, and bicyclic substrates have association constants with the calix[4]resorcarene larger than those of similar phenyl-containing compounds. Aromatic resonances of the substrates show substantial upfield shifts because of shielding from the aromatic rings of the calix[4]resorcarene, and several resonances in the ^{1}H NMR spectra typically exhibit enantiomeric discrimination. The extent of enantiomeric discrimination depends in part on interactions of the substituent groups of the substrates with the prolinylmethyl groups of the calix[4]resorcarene. The effectiveness of a calix[4]-resorcarene prepared from *N*-methyl-L-alanine (**2**) as a chiral NMR discriminating agent is compared to the L-prolinylmethyl derivative.

Introduction

NMR spectroscopy is one of the more common ways of determining ee and assigning absolute configurations of chiral compounds.[1] The strategy involves the use of either a chiral derivatizing or chiral solvating agent. Chiral derivatizing agents are optically pure compounds that are covalently attached to the enantiomers of interest. Differences in chemical shifts of the resulting diastereomeric complexes can be used to determine ee. If the distinction between enantiomers shows a consistent pattern, chiral derivatizing agents can then be used to assign absolute configurations of the enantiomers.[2] The most notable example among these is the use of α-methoxy-α-trifluoromethylphenylacetic acid to assign the absolute configurations of carbinols and amines.[3]

Chiral solvating agents associate with the enantiomers in solution, usually under conditions of fast exchange of the bound and unbound forms. In this case, noncovalent intermolecular interactions including hydrogen bonds and charge-transfer complexation between electron-rich and electron-deficient aromatic rings are usually important. Steric effects are often significant as well in causing distinctions between the enantiomers. Discrimination can occur because of distinctions in the spectra of the resulting diastereomeric complexes or because of the different time-averaged solvation environments caused by the unequal association constants of the enantiomers with the chiral solvating agent. Chiral solvating agents are usually used for determining ee, although if the mode of association and relative shifts of the two enantiomers

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exhibit a systematic pattern, absolute configurations can sometimes be assigned as well.

Some chiral solvating agents are host compounds, the most widely known of which are cyclodextrins[4] and crown ethers.[5] Two other families of potential chiral host compounds are calixarenes and calixresorcarenes.[6] Calixarenes are prepared by the condensation of phenols and formaldehyde, where the reaction conditions can be varied to alter the number of phenol units in the ring. Calixresorcarenes are prepared by the condensation of resorcinol with formaldehyde or other aldehydes, preferentially forming compounds with four resorcinol units. Derivatives that have the potential to be used for chiral discrimination are prepared by attachment of an optically pure substituent group to the calixarene or calixresorcarene unit,[7] although the applications of these for chiral discrimination in NMR spectroscopy are relatively limited in scope. One reason is that in organic-soluble systems favorable solvation of the enantiomers and calixarene or calixresorcarene does not promote host−guest complexation.[6e,8] Expansion and immobilization of the cavity of calix[4]resorcarenes by using 2,3-dichloropyrazines, 2,3-dichloroquinoxalines, or other bis-electrophiles to bridge adjacent hydroxyl groups on the resorcinol rings creates derivatives with stronger complexation properties in organic solvents.[9]

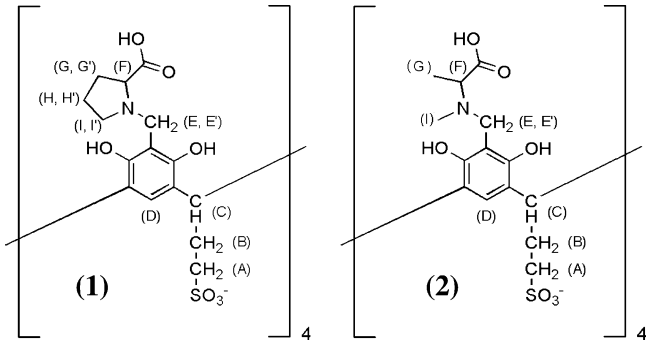

FIGURE 1. Structures of L-prolinylmethyl (**1**) and *N*-methyl L-alaninylmethyl (**2**) sulfonated resorcarene derivatives.

In contrast to findings in organic solvents, water-soluble calixarenes often associate more strongly with organic substrates.[10] Relevant to the work herein, the water-soluble resorcarene **1** prepared by the attachment of L-prolinylmethyl groups to a sulfonated calix[4]-resorcarene (Figure 1) is an exceptional chiral NMR solvating agent for water-soluble substrates with an aromatic ring.[11] Presumably the unfavorable solvation environment for hydrophobic organic salts in water promotes host−guest complexation with **1**. Large ring-induced upfield shifts occur for the aromatic resonances of substrates that associate with **1**. In a recent report, we noted that **1** is an exceptionally effective chiral NMR solvating agent for bicyclic ring compounds including propranolol hydrochloride, 1-(1-naphthyl)ethylamine hydrochloride, and tryptophan.[12] The purpose of this study was to examine derivatives similar to **1** in which certain *N*-methyl amino acids are attached instead of L-proline. Also, the applicability of **1** for other types of water-soluble organic salts is described.

Results and Discussion

Compound **1** has been shown in prior work to form host−guest complexes with substrates of the general motifs shown in Figure 2.[11,12] Large upfield shifts in the ^{1}H NMR spectra of the aromatic resonances of the substrates indicate that complexation of compounds with

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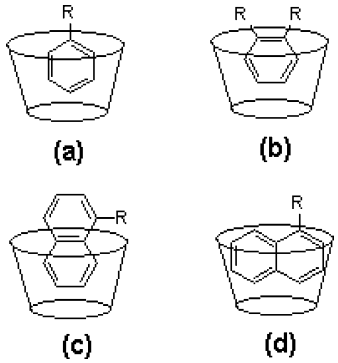

FIGURE 2. Possible geometries of association of substrates with **1**.

1 involves insertion of the aromatic portion of the guest into the resorcarene cavity. The ability of naphthyl-containing compounds such as 1-(1-naphthyl)ethylamine hydrochloride (**3**) (Figure 2c) and propranolol hydrochloride (**4**) (Figure 2d) to complex with **1** was rather surprising, and it was proposed that **1** adopts a flattened-cone conformation to accommodate a guest such as **4**.[12] The flattened-cone conformation creates a cleft-like cavity that can accommodate a naphthyl ring in the manner illustrated in Figure 2d.

The procedure for coupling proline to the sulfonated calix[4]resorcarene is generally applicable to secondary amines.[13] A derivative with L-*N*-methyl alanine (**2**) was prepared and evaluated for its utility as a chiral NMR solvating agent. Two additional derivatives using L-*N*-methyl valine and L-*N*-methyl leucine were explored. The progress of the coupling reactions is conveniently monitored by following the loss of the upfield singlet in the aromatic portion of the ^{1}H NMR spectrum. In the cases of the *N*-methyl-L-valine and *N*-methyl-L-leucine derivatives, tremendous broadening in the ^{1}H and ^{13}C NMR spectra made characterization difficult, and as neither couple acted efficiently as a chiral NMR discriminating agent, further analysis was not pursued. An interesting difference is observed when comparing the ^{1}H NMR spectrum of **1** to that of **2**. The ^{1}H NMR spectrum of **1** exhibits sharp resonances, indicating that the compound is either in the symmetrical cone conformation or undergoes a rapid exchange between several conformations. In contrast, the ^{1}H NMR spectrum of **2** shows considerable broadening, indicating that several conformations of these compounds undergo an intermediate rate of exchange in deuterium oxide. A similar observation is made when comparing the ^{13}C NMR spectrum of **1** to **2**. Warming a solution of **2** up to 70 °C in an attempt to increase the rate of conformational exchange does not appreciably diminish the broadening in the ^{1}H NMR spectrum.

Comparative shifts in the ^{1}H NMR spectra of substrates with **1** and **2** do not show a consistent pattern. For example, the shifts in the ^{1}H NMR spectrum of mandelic acid (**7**) with **2** are considerably less than those with **1**, whereas the shifts in the ^{1}H NMR spectra of doxylamine succinate **5**, phenyl alanine methyl ester hydrocloride **6**, and phenyl glycine methyl ester hydrochloride (**8**) are reasonably similar with those of **1** and **2**. The relative order of shifts in the spectra of **5**, **6**, **7**, and **8** with **1** and **2** are similar, indicating that the geometry of association of these substrates is comparable with **1** and **2**. The general shift order of $H_p > H_m > H_o$ for these substrates is consistent with the geometry shown in Figure 2a. Neither **1** nor **2** causes enantiomeric discrimination in the ^{1}H NMR spectrum of **7**. For **5**, **6**, and **8** the presence of **1** causes far greater enantiomeric discrimination than **2** in the ^{1}H NMR spectra.

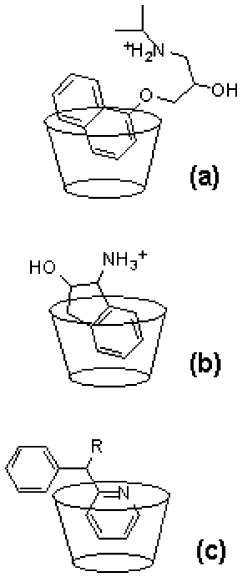

FIGURE 3. Geometries of association of (a) **4** with **2**, (b) **15** with **1**, (c) pyridyl ring of **5**, **16**, **17**, **18**, and **19**, with **1**.

In earlier work, we showed that the association constants of the bicyclic **3** and **4** with **1** were considerably larger than those for compounds with a phenyl ring.[12] The greater shifts in the ^{1}H NMR spectra of **3** and **4** relative to those of **5**, **6**, **7**, and **8** with **2** indicate that bicyclic aromatic compounds also associate more strongly than monocyclic aromatic compounds with **2**. The shifts in the ^{1}H NMR spectrum of **3** with **1** and **2** are quite comparable in magnitude. The relative magnitudes of the shifts in the ^{1}H NMR spectrum of **3** support the geometry of association shown in Figure 2c, in which the ring without the aliphatic substituent group preferentially binds in the cavity of **1** and **2**. The enantiomeric discrimination for the H_6, H_7, and H_8 resonances of **3** with **2** is quite similar to that observed with **1**. The resonance of H_4 shows enantiomeric discrimination with **1** but not **2**, whereas the resonance of H_5 is discriminated with **2** but not **1**. Although the geometry of association of **3** with **1** and **2** is generally similar, the differences in enantiomeric discrimination of H_4 and H_5 show that there are also some subtle distinctions between the two.

The H_3, H_4, H_5, and H_6 resonances of **4** exhibit relatively large shifts with **1**, which supports the geometry of association illustrated in Figure 2d. A markedly different shift order is observed in the ^{1}H NMR spectrum of **4** with **2**. In this case, the resonances for H_3 and H_4 show the largest shifts, followed by H_2 and H_5. Furthermore, the shifts of the H_2, H_3, H_4, and H_5 resonances with **2** are larger than those with **1**. These shifts imply that the naphthyl ring is tipped in the cavity as illustrated in Figure 3a. The H_2 resonance is the only one that

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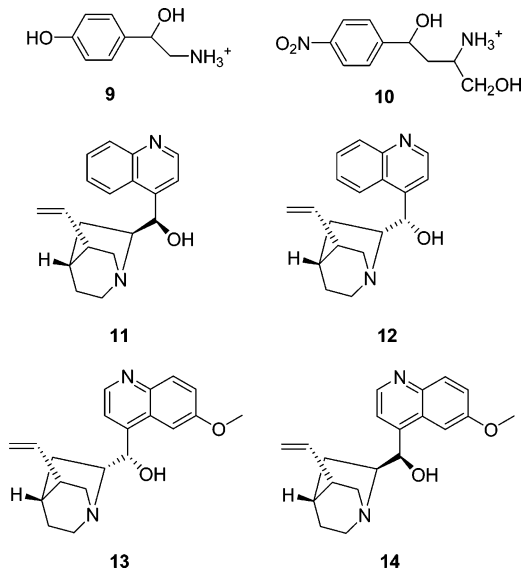

FIGURE 4. Structures of **9**−**14**.

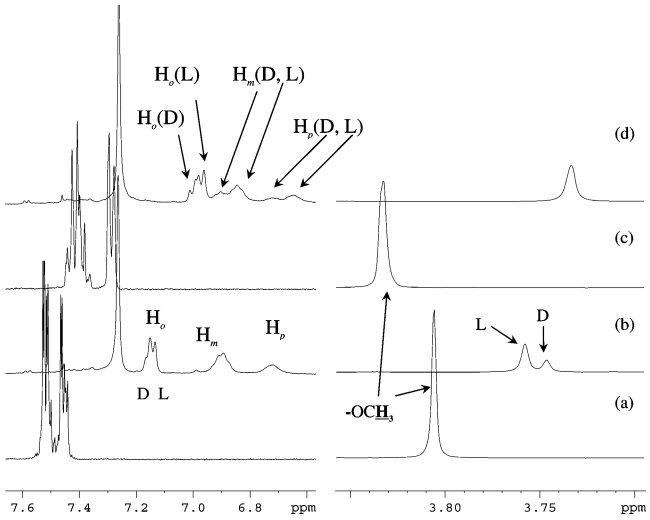

FIGURE 5. ^{1}H NMR spectra (400 MHz, D_2O, 23 °C) of (a) **8** (10 mM), (b) **8** (10 mM) with **1** (30 mM), (c) **6** (10 mM), and (d) **6** (10 mM) with **1** (30 mM).

exhibits enantiomeric discrimination in the presence of **2**, and it is slightly larger than that with **1**. The presence of **1** also causes enantiomeric discrimination of the H_3 and H_4 resonances.

Compound **2** is the best chiral NMR discriminating agent of the three *N*-methyl amino acid derivatives we studied, but its use is still not favored over that of **1**, which generally induced enantiomeric discrimination of greater magnitude in more hydrogen resonances of the substrates.

Chiral Discrimination Studies with 1. Several additional substrates were examined to further assess the range of functionalized aromatic compounds that associate with **1**. The shifts in the aromatic portion of the ^{1}H NMR spectra of two water-soluble compounds with a *p*-substituted aromatic ring, 1-aminoethyl-4′-hydroxybenzyl alcohol hydrogen chloride (**9**) and 2-amino-1-(4-nitrophenyl)-1,3-propanediol hydrogen chloride (**10**) (Figure 4), are quite small (less than 0.05 ppm for the aromatic resonances). The implication is that a *para*-substituted aromatic ring is too hindered to insert into the cavity of **1**.

Not surprisingly, ^{1}H NMR spectra of the enantiomeric pair of water-soluble hydrogen chloride salts of (+)-cinchonine (**11**) and (−)-cinchonidine (**12**) (Figure 4) exhibit no significant shifts in the presence of **1**. The substitution pattern on the quinoline ring likely inhibits inclusion in the cavity of **1**. Quinine (**13**) and quinidine (**14**) (Figure 4) have a relatively unhindered quinoline ring that should be able to form an inclusion complex with **1**, but no shifts are observed in the ^{1}H NMR spectra of the hydrochloride salts of these in solutions with **1**. Presumably, steric hindrance between the proline residues and the large aliphatic substituent group on the quinoline ring accounts for the lack of host−guest complex formation with **13** and **14**.

Shifts and enantiomeric discrimination in the ^{1}H NMR spectrum of 1-amino-2-indanol hydrogen chloride (**15**) in the presence of **1** are provided in Table 2. The magnitude of the shifts indicates that hydrogens H_4, H_5, and H_6 of **15** are deepest in the cavity of **1** and supports the geometry of association in Figure 3b, in which the ring is slightly tipped. Presumably the steric effect of the ammonium group causes the asymmetrical insertion of **15** into the cavity. The significant degree of enantiomeric discrimination of H_5 with **1** likely reflects differences in the diastereomeric nature of the complexes rather than differences in association constants of the two enantiomers, especially given the relatively small enantiomeric distinctions for the other hydrogen resonances of the aromatic ring.

Figure 5 provides a comparison of the shifts and extent of enantiomeric discrimination in the ^{1}H NMR spectra of **6** and **8** with **1**. The aromatic resonances of the two substrates show reasonably comparable shifts, but the enantiomeric discrimination of the aromatic resonances of **6** is far greater than that in the corresponding resonances of **8** (Table 1). Presumably, interaction of the larger substituent group of **6** relative to **8** with the proline moieties of **1** is responsible for the greater discrimination in the aromatic region of **6**. The methine and methoxy resonance of **6** are not enantiomerically discriminated in the presence of **1**, whereas the same resonances of **8** exhibit a small extent of discrimination with **1**. The aliphatic hydrogen atoms of **8** are closer to the aromatic cavity of **1** than those in **6**, which likely explains the greater enantiomeric discrimination. For the methoxy group of **8**, the resonance of the D-enantiomer shifts further, whereas for every other hydrogen resonance of **6** and **8** that shows enantiomeric discrimination, the resonance of the L-enantiomer shifts further. The reversal in shift order means that the diastereomeric nature of the complexes with **1** is responsible for the distinction of the methoxy resonances of **8** rather than differences in association constants between the two enantiomers.

The compounds **5**, pheniramine maleate (**16**), chloropheniramine maleate (**17**), bromopheniramine maleate (**18**), and carbinoxamine maleate (**19**) are water-soluble cationic species that have an aromatic and pyridyl ring, each of which has the potential to insert into the cavity of **1** (Figure 6). The shifts in the ^{1}H NMR spectra of **5**, **16**, **17**, **18**, and **19** (10 mM) that occur on complexation with **1** (10 mM) are provided in Figure 6. The magnitude

TABLE 1. Comparative Shifts (Δδ) and Enantiomeric Discrimination (ΔΔδ) in ppm in the ^{1}H NMR Spectrum (400 MHz) of Substrates (S) in the Presence of 1 and 2

	[**1** or **2**/S]	Δδ (**1**)	ΔΔδ(**1**)	Δδ(**2**)	ΔΔδ(**2**)
1-(1-Naphthyl)ethylamine Hydrochloride (**3**)					
H_4	0.5:1	0.33/0.39	0.06	0.24	0
H_5		0.47	0	0.35/0.45	0.10
H_6		0.55/0.71	0.16	0.59/0.72	0.13
H_7		0.41/0.55	0.14	0.47/0.59	0.12
H_8		0.25/0.35	0.10	0.30/0.38	0.08
Propranolol Hydrochloride (**4**)					
H_2	0.5:1	0.35/0.39	0.04	0.56/0.62	0.06
H_3		0.48/0.53	0.05	0.82	0
H_4		0.48/0.53	0.05	0.90	0
H_5		0.54	0	0.63	0
H_6		0.49	0	0.37	0
H_7		0.51	0	0.38	0
H_8		0.20	0	0.25	0
Doxylamine Succinate (**5**)					
H_2	1:1	0.20	0	0.21	0
H_3		0.32	0	0.21	0
H_4		0.44	0	0.34	0
H_3'		0.28/0.52	0.24	0.37	0
H_4'		0.33/0.96	0.63	0.46/0.54	0.08
H_5'		0.71	0	0.50	0
H_6'		0.23/0.28	0.05	0.21	0
Phenyl Alanine Methyl Ester Hydrochloride (**6**)					
H_o	4:1	0.33/0.36	0.03	0.34	0
H_m		0.59/0.65	0.06	0.56	0
H_p		0.74/0.82	0.08	0.65	0
CH		0.09	0	0.12	0
CH_2		0.25	0	0.20	0
CH_2'		0.16	0	0.16	0
$-OCH_3$		0.09	0	0.08	0
Mandelic Acid (**7**)					
H_o	4:1	0.70	0	0.33	0
H_m		1.07	0	0.52	0
H_p		1.33	0	0.67	0
CH		0.47	0	0.33	0
Phenyl Glycine Methyl Ester Hydrochloride (**8**)					
H_o	4:1	0.30/0.35	0.05	0.28	0
H_m		0.66/0.69	0.03	0.65	0
H_p		0.89	0	0.81	0
CH		0.17	0	0.15	0
$-OCH_3$		0.05/0.08	0.03	0.08	0

of the shift of the H_4 resonance in both **5** and **16** and the relative shift order $H_4 > H_3 > H_2$ indicates that the aromatic ring of these two substrates does bind within the cavity of **1**. For mixtures of **17**, **18**, and **19** with **1**, the shift of the H_2 resonance is larger than that of H_3, which contrasts with the observation for **5** and **16**. Furthermore, the magnitude of the shifts of the H_2 resonance in **17**, **18**, and **19** is larger than that of the corresponding hydrogen atom in **5** and **16**, whereas just the opposite trend occurs for the H_3 resonances. These data for **17**, **18**, and **19** indicate that the halogen atom inhibits complexation of the aromatic ring of these substrates with **1**.

The magnitudes of the shifts of the hydrogen resonances indicate that the pyridyl ring of **5**, **16**, **17**, **18**, and **19** binds in the cavity of **1**. The ability of pyridyl rings to associate with **1** extends the range of compounds for which **1** can be used as a chiral NMR solvating agent. The consistently larger shifts of H_4' and H_5' relative to H_3' and H_6' for each of the five substrates support the geometry of association illustrated in Figure 3c. This geometry reduces steric repulsion of the substrate with

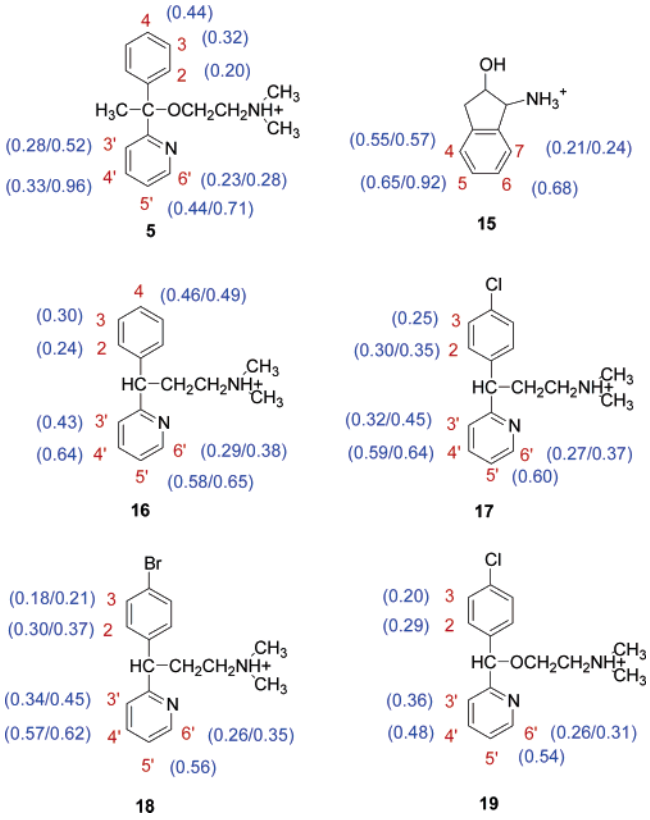

FIGURE 6. Upfield changes in chemical shifts in the ^{1}H NMR spectra (400 MHz, D_2O, 23 °C) of **5**, **15**, **16**, **17**, **18**, and **19** with **1**. Two values indicate that the resonance exhibited enantiomeric discrimination. The substrate concentration was 10 mM. The concentration of **1** was 10 mM with **5**, **16**, **17**, **18**, and **19** and 40 mM with **15**.

the cavity of **1** and electron−electron repulsion between the lone pair of electrons of the pyridyl nitrogen and the π electrons of the aromatic rings of **1**. Both rings of **5** and **16** bind within the cavity of **1**. It is most likely that complexation of **5** and **16** with **1** involves binding of only one ring at a time, thereby creating a situation of competing equilibria between the two rings and the cavity. The relative magnitude of the shifts in the NMR spectra of **5** and **16** with **1** suggest a slight preference for binding of the pyridyl ring over the aromatic ring in the cavity. Although it is unlikely, CPK models of **1** in a flattened-cone conformation indicate that simultaneous binding of both rings within the cavity is possible, even though the two rings are twisted relative to each other and not in the same plane.

Several resonances in the ^{1}H NMR spectra of **5**, **16**, **17**, **18**, and **19** are enantiomerically discriminated in the presence of **1** (Table 2). For example, the enantiomeric discrimination of the H_3' and H_4' resonances of **5** with **1**, as shown in the spectrum in Figure 7b, is quite significant when compared to the same resonances in the spectra of **16**, **17**, **18**, and **19**. Presumably, the C-methyl group of **5**, which is unique among the compounds in this series, has a significant role in the binding with **1** that is responsible for the enantiomeric discrimination of the H_3' and H_4' resonances. The H_6' resonances of **16**, **17**, and **18** are especially useful for the determination of ee, but interestingly the H_6' resonance of **5** shows much less enantiomeric discrimination of the compounds studied.

TABLE 2. Enantiomeric Discrimination (ΔΔδ) in ppm in the ^{1}H NMR Spectrum (400 MHz) of Substrates in the Presence of 1

	[**1**/substrate]	ΔΔδ(**1**)	ΔΔδ(**1**) (50 °C, 4:1 ratio)
	Doxylamine Succinate (**5**)		
H_2			0.05
H_3			0.11
H_4			0.12
H_3'	0.4:1	0.10	
H_4'	0.4:1	0.15	0.26
H_5'			0.20
H_6'	4:1	0.08	0.06
CH_3	0.8:1	0.05	
	1-Amino-2-indanol (**15**)		
H_4	4:1	0.02	
H_5	4:1	0.28	
H_7	4:1	0.03	
	Pheniramine Maleate (**16**)		
H_2	4:1	0.04	
H_4	4:1	0.05	
H_5'	4:1	0.12	
H_6'	4:1	0.15	
	Chloropheniramine Maleate (**17**)		
H_2	4:1	0.04	
H_3	4:1	0.08	
H_4'	1:1	0.05	
H_6'	4:1	0.14	
	Bromopheniramine Maleate (**18**)		
H_2	1:1	0.06	
H_3	1:1	0.03	
H_3'	4:1	0.09	
H_6'	4:1	0.14	
	Carbinoxamine Maleate (**19**)		
H_6'	1:1	0.05	
CH	1:1	0.03	

The ^{1}H NMR spectrum of **19** in the presence of **1** shows an unusual degree of broadening compared to the other compounds and significantly less enantiomeric discrimination than occurs with the other compounds. Obviously the aliphatic group of these substrates and its interaction with the proline residues have a significant effect on the extent of enantiomeric discrimination.

The ^{1}H NMR spectra of compounds in the presence of **1** sometimes show significant levels of broadening. Obtaining the spectra at higher temperatures reduces the broadening by speeding up the exchange rate of association and dissociation. Higher temperatures also reduce the association constants of the substrates with **1**. Even though the shifts and enantiomeric discrimination in the ^{1}H NMR spectra of compounds with **1** are reduced at elevated temperatures, the enantiomeric discrimination is often still significant enough for the determination of ee. For example, Figure 7c and d shows a comparison of the aromatic region of the ^{1}H NMR spectra of **5** (10 mM) with that of **1** (40 mM) at ambient probe temperature and 50 °C. The reduced broadening at 50 °C is apparent, as is the enantiomeric discrimination of resonances of H_2, H_3, H_4, H_4', H_5' and H_6'. The enantiomeric discrimination of the hydrogen resonances of **5** with **1** at 50 °C is reported in Table 2.

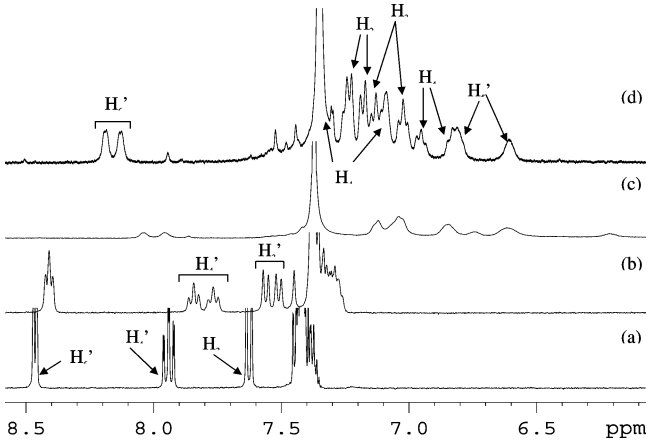

FIGURE 7. ^{1}H NMR spectra (400 MHz, D_2O) of **5** (10 mM) (a) at 23 °C, (b) with **1** (2 mM) at 23 °C, (c) with **1** (40 mM) at 23 °C, and (d) with **1** (40 mM) at 50 °C.

TABLE 3. Shifts (Δδ) in ppm in the ^{1}H NMR Spectrum (400 MHz) of 1 (5 mM) in the Presence of Different Substrates (10 mM)

		Δδ						
	δ_o	**20**	**21**	**16**	**17**	**18**	**3**	**4**
H_A	2.57	0.03	0.10	0.16	0.13	0.13	0.14	0.15
H_B	2.89	-0.01	0.02	0.03	0.01	0.01	0.02	0.02
H_C	4.67	0.01	0.01	0.05	0.03	0.04	0.05	0.04
H_D	7.18	0.08	0.17	0.28	0.24	0.25	0.28	0.34
H_E	4.40	−0.10	−0.21	−0.31	−0.33	−0.30	−0.40	−0.40
H_E'	4.40	−0.20	−0.36	−0.44	−0.44	−0.42	−0.68	−0.58
H_F	4.01	−0.03	−0.08	−0.10	−0.10	−0.09	−0.19	−0.20
H_G	2.40	0	−0.01	−0.01	0	−0.01	−0.13	−0.11
H_G'	1.84	0.01	−0.03	−0.04	−0.04	−0.04	−0.17	−0.14
H_H	2.02	0.01	−0.02	−0.02	−0.02	−0.02	−0.10	−0.07
H_H'	2.02	0.01	−0.02	−0.02	−0.02	−0.02	−0.20	−0.18
H_I	3.46	−0.03	−0.13	−0.16	−0.14	−0.14	−0.34	−0.30
H_I'	3.15	−0.02	−0.09	−0.09	−0.12	−0.12	−0.24	−0.24

Effects of Complexation on the ^{1}H NMR Spectrum of 1. Dimerization of a calix[4]arene with alanine substituent groups has been observed in methanol.[14] This was the first report of such a dimerization in a protic solvent. Addition of guest compounds resulted in the disassembly of the dimer. Evidence for dimerization involved the observation that the chemical shifts in the NMR spectrum of the calix[4]arene changed with concentration. We observe a similar effect with **1** in D_2O. Increasing the concentration of **1** in D_2O from 1 to 40 mM leads to slight (0.03−0.07 ppm) upfield shifts of several resonances of the prolinylmethyl moieties and slight downfield shifts of the resonances of the aromatic hydrogen and sulfonate bridge hydrogen nuclei. Job plots for complexes of a variety of substrates with **1** all clearly indicate only 1:1 complexation, suggesting as in prior work that the presence of the guest compounds leads to disassembly of the dimer species.

The shifts in the ^{1}H NMR spectrum of **1** (5 mM) in the presence of **3**, **4**, **16**, **17**, **18**, **20**, and **21** (10 mM) are listed in Table 3. Recording the shifts in the spectrum of **1** at a 2:1 substrate/resorcarene ratio enhances the complexation of **1** and the magnitude of the shifts. As the concentration of **1** is made increasingly greater than that of the substrate, the shifts in the NMR spectrum of the substrate become larger, but the shifts of the resonances of **1** gradually approach those of the uncomplexed species.

(14) Brewster, R. E.; Shuker, S. B. *J. Am. Chem. Soc.* **2002**, *124*, 7902−7903.

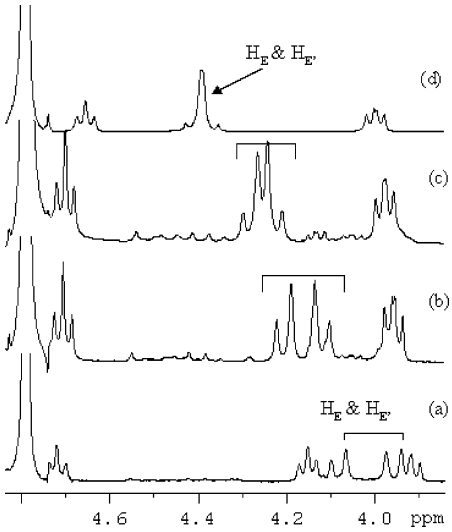

FIGURE 8. ^{1}H NMR spectra (400 MHz, D_2O, 23 °C) of **16** (10 mM) with added amounts of **1** at (a) 5, (b) 10, (c) 20, (d) 30, and (d) 40 mM.

This is especially apparent with the H_E and H_E' resonances of **1**, as shown in the series of spectra in Figure 8).

The aromatic resonance of **1** (H_D) exhibits a downfield shift in the presence of the substrates. The geometries of the complexes (Figure 2) do not situate the face of the aromatic ring of the substrate in a position to shield the aromatic hydrogen atoms of **1**. Instead, the aromatic hydrogen atoms of **1** are positioned to the side of the aromatic ring of the substrate, hence the deshielding and downfield shift on complexation. The shifts in the NMR spectrum of **1** with **3** and **4** are quite comparable. The similarity of the shifts in the spectrum of **1** with **16**, **17**, and **18** suggests that the structure of the host−guest complexes are similar and that insertion of the aromatic ring of **16** has a similar effect on **1** as does insertion of the pyridyl ring. The general trend of the shifts of the resonances of **1** with the substrates is **3**, **4** > **16**, **17**, **18** > **21** > **20**, which correlates with the relative association constants of the substrates (361 and 595 M^{-1} for the *R*- and *S*-enantiomer of **5**; 258 and 482 M^{-1} for the *R*- and *S*-enantiomer of **4**; 68 and 97 M^{-1} for the *R*- and *S*-enantiomer of **20**; and 59 and 113 M^{-1} for the *R*- and *S*-enantiomer of **21**).[12] A Job plot indicates that the stoichioimetry of the complex of *R*-**17** with **1** is one-to-one. The association constant of *R*-**17** with **1** is 301 M^{-1}, which correlates with the trend of induced shifts in the ^{1}H NMR spectrum of **1**.

The resonances of the hydrogen atoms of the bridging sulfonate groups (H_A, H_B, and H_C) exhibit relatively small shifts, which is consistent with association of compounds in the cavity defined by the resorcinol rings and prolinylmethyl units. The behavior of the diastereotopic H_E and H_E' atoms is especially interesting (Figure 8). The resonances of these two hydrogen atoms have coincident chemical shifts in the NMR spectrum of **1**. Complexation of a substrate causes these resonances to show substantial diastereotopic resolution and appear as two distinct doublets in the spectrum. These resonances also shift upfield the furthest of any in **1**. The significant upfield shifts for the H_E and H_E' resonances of **1** are not surprising given their location adjacent to the resorcinol rings and expected proximity to the aromatic ring of the substrates in the complexes. The next largest upfield shifts occur for the H_F, H_I, and H_I' resonances, and smallest for H_G, H_G', H_H, and H_H', all of which is consistent with the geometries proposed in Figure 2. Furthermore, the differences in upfield shifts for the diastereotopic pairs of hydrogen atoms in **1** (H_E, H_E'; H_G, H_G'; H_H, H_H'; and H_I, H_I') when complexed with substrates are consistent with a geometry in which one hydrogen atom of each diastereotopic pair points in toward the cavity and experiences greater shielding from the aromatic ring of the substrate than the other hydrogen atom that points away from the cavity.

There are also certain subtleties in the shifts in the NMR spectrum of **1** in the presence of substrate compounds that further support the geometries proposed in Figure 2. For example, the resonances for H_G, H_G', H_H, and H_H' with **16**, **17**, **18**, **20**, and **21** exhibit almost no shift, an observation consistent with a geometry in which the aromatic ring of these substrates is embedded within the resorcarene cavity and not situated in such a way as to shield these hydrogen atoms of the proline units. The resonances of the diastereotopic H_H and H_H' atoms are resolved in the presence of **3** and **4** but not in the presence of **2** and **21**, a reasonable observation considering the larger ring size and larger association constants of **3** and **4**. The shifts in the NMR spectrum of **1** with the sodium salt of tryptophan (**22**) are not reported, but unlike the situation with **21**, in which the H_H and H_H' resonances are not resolved, complexation of **22** causes the largest diastereotopic resolution of the H_H and H_H' resonances (0.19 ppm) of any of the substrates studied. Furthermore, one of the resonances exhibits a slight downfield shift (0.04 ppm), whereas the other exhibits an upfield shift (−0.15 ppm). The comparative effects of complexation of **21** and **22** on the diastereotopic H_H and H_H' hydrogen atoms of **1** further demonstrates the importance of the substituent group of the substrate in influencing the exact nature of binding, enantiomeric discrimination, and resulting shifts in the NMR spectrum. Both steric and dipole−dipole effects, including ion pairing between cationic moieties of the substrate and carboxylate groups of the proline residues of **1**, are likely significant in the binding.[15]

Comparison of 1 with Other Chiral Solvating Agents. Suitable chiral NMR solvating agents for water-soluble substrates are relatively uncommon. The best known examples are the cyclodextrins.[4] Water-soluble chiral lanthanide complexes have also been reported, although these are primarily used for the discrimination of amino acids.[1] Compound **1** avoids the paramagnetic line broadening caused by lanthanide shift reagents. The shifts and enantiomeric discrimination in the ^{1}H NMR spectra of substrates with cyclodextrins are much smaller than those observed with **1**. For example, only a slight enantiomeric discrimination of 0.01 ppm or less is observed for several resonances in the ^{1}H NMR spectra of **16**, **17**, **18**, and **19** in the presence of β-cyclodextrin.[4c] Slightly larger enantiomeric discrimination was observed for the H_3' (0.02 ppm), H_4' (0.03 ppm), and H_5' (0.02 ppm)

(15) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373−382.

resonances of **5** in the presence of β-cyclodextrin, although these are considerably less than those in the presence of **1** (Table 2).[4c] A prior report noted a small amount of enantiomeric discrimination (2.4 Hz at 400 MHz) in the resonance of one of the methylene hydrogen atoms of **4** with β-cyclodextrin.[4b] The same resonance exhibited discrimination of 4.9 Hz at 400 MHz in the presence of γ-cyclodextrin. Neither of these values is comparable to the discrimination of three aromatic resonances of **4** in the presence of **1** (Table 1).[12]

The compound (18-crown-6)-2,3,11,12-tetracarboxylic acid (**23**) is an effective chiral NMR discriminating agent for protonated amines in methanol.[5i,j] The enantiomeric discrimination in the ^{1}H NMR spectra of **3**, **6**, **8**, and **15** in the presence of **23** has been previously reported.[5i,l] In some instances, certain resonances of substrates: H_1 (0.16 ppm) and H_7 (0.12 ppm) of **15**; CH (0.28 ppm) of **8**; CH_3 (0.08 ppm) and CH (0.19 ppm) of **3**, show larger enantiomeric discrimination in the presence of **23**. However, the general observation is that addition of **1** to these substrates causes larger shifts and greater enantiomeric discrimination of more hydrogen resonances than occurs with **23**.

Conclusions

Compound **1** is an important chiral solvating agent to consider for water-soluble compounds that contain phenyl, pyridyl, and bicyclic aromatic rings. Substitution on the aromatic ring has an important influence on the ability of a substrate to associate with **1**, as *para*-substituted rings are too hindered to fit into the cavity. The aromatic region of the spectrum of substrates that complex with **1** show large ring-induced upfield shifts (up to 2 ppm). The enantiomeric discrimination depends on interactions of the substituent groups with the prolinylmethyl moieties of **1** but in many cases are quite pronounced and occur for several resonances of the substrate. For those substrates that do associate with **1**, the shifts and enantiomeric discrimination are usually greater than those observed with other potential chiral NMR shift reagents including cyclodextrins, crown ethers, and water-soluble lanthanide complexes.

Experimental Section

Reagents. The sulfonated resorcarene and its prolinylmethyl derivative were prepared and purified as described in a published procedure.[11] 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 in solution. 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.

Synthesis of *N*-Methyl-L-alanine Derivatized Sulfonated Calix(4)resorcarene (2). A 0.5 g (0.45 mmol) portion of the tetrasulfonated calix[4]resorcarene[11] and 0.23 g (2.25 mmol)of *N*-methyl-L-alanine were dissolved in 6 mL of water and heated to 70 °C. Once fully dissolved, 0.22 mL (2.7 mmol) of 35% formaldehyde was added, and the reaction mixture was stirred for 48 h. The reaction was dried by rotary evaporation and redissolved in 1 mL of water. The pure product was obtained by trituration with methanol and collected by vacuum filtration (0.178 g, 28.7% yield). ^{1}H NMR (400 MHz,D_2O): δ 7.5 ppm (s, 4H, aromatic), 6.45 (s, 4H, N*H*), 4.63 (s, broad, 4H, Ar-*CH*-Ar), 4.32 (s, broad, 4H, N-CH_2-Ar), 3.85 (s, broad, 4H, N-CH_2-Ar), 2.72 (s, broad, 16H, CH-CH_2-CH_2-SO_3), 2.69 (s, 12H, N-CH_3), 1.5 (d, J = 4 Hz, 12H, CH-CH_3). ^{13}C NMR (D_2O, all signals broad): δ 179 ppm (*C*OOH), 156, 131, 128, 107 (aromatic), 69 (*C*HCH_3), 46 (*C*H on SO_3 chain), 38 (CH_2N), 35 (NCH_3), 37, 34 (CH$CH_2CH_2SO_3$), 15 (CHCH_3). Anal. Calcd for $C_{56}H_{72}N_4Na_4O_{28}S_4 \cdot 16H_2O$: C, 38.26; H, 5.96; N, 3.19; Na, 5.24. Found: C, 38.29; H, 5.63; N, 3.04; Na, 5.37.

Apparatus. NMR spectra were recorded on a 400 MHz spectrometer. All spectra were recorded using 16 scans at ambient probe temperature (23 °C) unless otherwise specified. When necessary, assignments were confirmed by COSY spectra.

Procedures. Samples for NMR spectroscopy were prepared by weighing and dissolving the appropriate amount of substrate in deuterium oxide. Increments of the calix[4]resorcarene were added either by weight or volumetrically by addition of an appropriate amount of a concentrated stock solution (120 mM). Stoichiometries of complexes with **1** were determined using Job's method.[16] The concentrations of **1** and substrate were continuously varied throughout the series while maintaining a total concentration of **1** and substrate of 40 mM for each sample. Association constants were determined using the Scatchard method (Foster−Fyfe) of infinite dilutions of host (**1**) while maintaining the concentration of substrate at 2 mM.[17] The use of the Scatchard method for determining association constants is recommended over other graphical techniques in a recent review article.[18] The concentration of **1** was varied from 50 to 1 mM for the series of spectra by diluting with a 2 mM solution of the substrate.

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