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Water-Soluble Calix[4]resorcinarenes with Hydroxyproline Groups as Chiral NMR Solvating Agents for Phenyl- and Pyridyl-Containing Compounds

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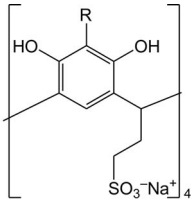
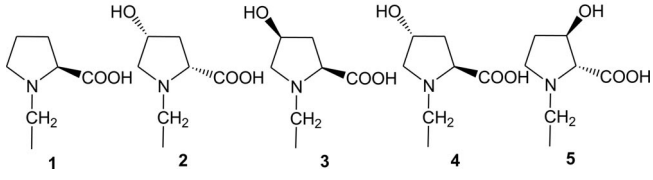
A series of water-soluble sulfonated calix[4]resorcinarenes with L-proline, *cis*-4-hydroxy-D- and -L-proline, *trans*-4-hydroxy-L-proline and *trans*-3-hydroxy-L-proline are evaluated as chiral NMR solvating agents. The changes in chemical shifts and enantiomeric discrimination in the ^{1}H NMR spectra of a variety of phenyl- and pyridyl-containing compounds are reported. Substrates associate by insertion of the phenyl or pyridyl ring into the cavity of the calix[4]resorcinarene. Series of compounds with methylbenzylamine and benzyl alcohol units are among those examined. For many compounds, the calix[4]resorcinarenes with the hydroxyproline groups are more effective chiral NMR solvating agents than the corresponding proline derivative. The *trans*-4- and *trans*-3-hydroxy-L-proline derivatives are especially effective as chiral NMR solvating agents. Enantiomeric discrimination in the ^{1}H NMR spectra is often large enough to facilitate the analysis of enantiomeric purity.

Introduction

An extensive number of chiral reagents have been developed and used with NMR spectroscopy for the determination of enantiomeric purity and assignment of absolute stereochemistry.[1–6] The overwhelming majority of these reagents are useful in organic solvents. Water-soluble chiral NMR solvating agents are far less common. The most widely studied and broadly applicable water-soluble chiral NMR shift reagents include native cyclodextrins[7–11] and certain water-soluble cyclodextrin derivatives.[12–24] Given the growing emphasis on the use of water as a green solvent in synthetic chemistry and the importance of water solubility for pharmaceuticals, there is a need for additional water-soluble chiral NMR shift reagents.

A water-soluble reagent prepared by the attachment of L-prolinylmethyl groups to a sulfonated calix[4]resorcinarene (SCR-Pro, **1**) has been shown to be an effective chiral NMR solvating agent for compounds with phenyl, naphthyl and pyridyl rings.[25–27] SCR-Pro exists in aqueous solution in a cone-shaped configuration with a well-defined cavity. Water-soluble organic salts with mono- or *ortho*-substituted phenyl rings and mono- or 2,3-disubstituted naphthyl rings form host–guest complexes by insertion of the aromatic ring into the cavity of SCR-Pro.[28] Substantial shielding of the aromatic hydrogen atoms of the substrate by the π-electrons of the calix[4]resorcinarene cavity provides evidence for the mode of host–guest complexation.





In subsequent reports, we have shown that similar water-soluble calix[4]resorcinarenes with (hydroxyprolinyl)methyl groups that include *cis*-4-hydroxy-D-proline (SCR-c4D, **2**), *cis*-4-hydroxy-L-proline (SCR-c4L, **3**), *trans*-4-hydroxy-L-proline (SCR-t4L, **4**) and *trans*-3-hydroxy-L-proline (SCR-t3L, **5**) moieties are often more effective chiral NMR shift reagents than SCR-Pro for phenyl[28,29] and bicyclic[29,30] aromatic compounds. Herein we provide a further comparison of the effectiveness of SCR-Pro and the corresponding derivatives with hydroxyproline groups as chiral NMR shift reagents for water-soluble compounds with phenyl or pyridyl rings. In many cases, the hydroxyproline derivatives produce enantiomeric discrimination in more resonances of substrates and of greater magnitude than SCR-Pro.

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Results and Discussion

The effectiveness of the calix[4]resorcinarenes will be compared for a variety of phenyl-containing substrates (**6**–**24**). These compounds have a range of functional groups in the substituent attached to the phenyl ring and include series of compounds with methylbenzylamine (**6**–**10**) and benzyl alcohol (**11**–**15**) units. Compounds **6** and **13**–**15** have been previously studied with these calix[4]resorcinarenes, and certain data is included herein for comparative purposes.[29] Compounds **20**–**24** have a pyridyl ring that is also capable of association within the cavity of the calix[4]resorcinarenes.[27] The shielding of the aromatic hydrogen atoms of every substrate with a monosubstituted phenyl ring (**6**–**21**) in the presence of each calix[4]resorcinarene vary in the order H*p* > H*m* > H*o*, where these refer to the positions relative to the substituted carbon atom of the ring. The especially large shielding of the hydrogen atoms of the aromatic rings combined with the order of perturbations of chemical shifts indicates that the association geometry involves insertion of the aromatic ring into the cavity with the H*p* position being deepest. The substituent group of the substrate is then positioned to interact with the proline moieties.

Table 1 compares the changes in chemical shifts and enantiomeric discrimination for **6**–**10** in the presence of SCR-t4L. In all cases, a series of spectra were recorded with increasing concentrations of the calix[4]resorcinarene. The data presented herein do not necessarily represent the largest enantiodifferentiation for a particular resonance but are reported at a consistent ratio for comparative purposes among the different calix[4]resorcinarenes. Compounds **6**–**8** differ only in the number of methyl groups on the nitrogen atom. A general observation is that the substituent groups of **6**–**8** do not have that much influence on the changes in chemical shifts in the presence of SCR-t4L. The values for the aromatic protons of **6** and **7** are comparable, whereas the changes in chemical shifts in the spectrum of **8** are slightly smaller. Even though the perturbations in chemical shifts are smallest for **8**, the enantiomeric discrimination is the largest for the H*m* and H*p* resonances with SCR-t4L, perhaps because the larger substituent group relative to **6** and **7** enhances the chiral recognition. The changes in chemical shifts for **10** are largest among **6**–**10**, but no enantiomeric discrimination is observed. Presumably, interactions of the substituent groups of the substrate and moieties of the proline groups are especially important in influencing the extent of enantiomeric discrimination.

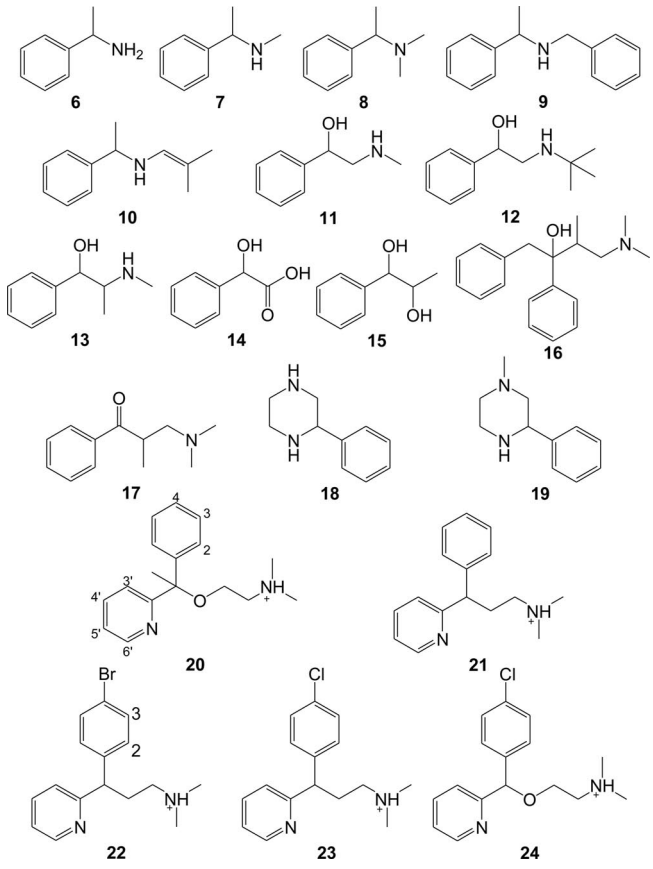

Table 2 provides the changes in chemical shifts and enantiomeric discrimination in the spectra of **7**–**9** in the presence of the four calix[4]resorcinarenes. The changes in chemical shifts and magnitude of enantiomeric discrimination are the same for SCR-c4D and SCR-c4L except for a reversal in order of the resonances of the two enantiomers. Therefore, data are only provided for SCR-c4L throughout. Data is not provided for **10**, because enantiomeric discrimination is not observed in any of the combinations. The changes in chemical shifts in the NMR spectrum of **7** in the presence of SCR-Pro and SCR-c4L are comparable. Perturbations with SCR-t3L are somewhat smaller, whereas those with SCR-t4L are the largest. However, the larger changes in chemical shift with SCR-t4L do not translate into greater enantiomeric discrimination in the NMR spectrum as generally comparable levels of enantiomeric discrimination occur in the H*o*, H*m*, and H*p* resonances with SCR-c4L, SCt4L and SCR-t3L. SCR-Pro only causes enantiomeric discrimination of the H*o* resonance and is less effective than

Table 1. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **6**–**10** (10 mM) in the presence of SCR-t4L (10 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	H*o*	H*m*	H*p*	*C*Me
6	0.230	0.355	0.484	0.047
7	0.254/0.273 (0.019)	0.375/0.393 (0.018)	0.486/0.504 (0.018)	0.052
8	0.229	0.298/0.332 (0.034)	0.393/0.433 (0.040)	0.167/0.173 (0.006)
9	–	–	–	0.154/0.162 (0.008)
10	0.353	0.491	0.641	0.123

Table 2. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **7**–**9** (10 mM) in the presence of calix[4]resorcinarenes (10 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	SCR-Pro	SCR-c4L	SCR-t4L	SCR-t3L
7				
H*o*	0.212/0.229 (0.017)	0.188/0.207 (0.019)	0.254/0.273 (0.019)	0.179/0.195 (0.016)
H*m*	0.318	0.290/0.309 (0.019)	0.375/0.393 (0.018)	0.262/0.274 (0.012)
H*p*	0.414	0.406/0.426 (0.020)	0.486/0.504 (0.018)	0.359/0.376 (0.017)
8				
H*o*	0.156	0.210	0.229	0.147
H*m*	0.210	0.310	0.298/0.332 (0.034)	0.207
H*p*	0.257	0.407	0.393/0.433 (0.040)	0.277
*N*Me	0.117	0.155	0.145	0.125/0.131 (0.006)
*C*Me	0.138	0.172	0.166/0.173 (0.007)	0.098
9				
*C*Me	0.128	0.096/0.107 (0.011)	0.154/0.162 (0.008)	0.089/0.100 (0.011)

SCR-c4L, SCR-t4L and SCR-t3L. None of the calix[4]resorcinarenes cause enantiomeric discrimination of the *C*- or *N*-methyl groups.

The extent of enantiomeric discrimination in the NMR spectrum of **8** with the calix[4]resorcinarenes is quite different than that of **7**. Whereas SCR-Pro, SCR-c4L and SCR-t3L cause enantiomeric discrimination of some or all of the aromatic resonances of **7**, they are ineffective with the aromatic resonances of **8**. Changes in the chemical shifts are quite comparable for SCR-Pro and SCR-t3L, slightly larger with SCR-c4L, and larger still for SCR-t4L. The enhanced enantiomeric discrimination with SCR-t4L is more likely the result of differential interactions of the proline hydroxy group rather than the larger perturbations in chemical shifts, because, as already noted herein and from previous studies,[28–30] larger shifts with the different calix[4]-resorcinarenes often do not correlate with enhancements in enantiomeric discrimination. Substantial enantiomeric discrimination of the H*m* and H*p* resonances only occurs in the presence of SCR-t4L. SCR-t3L is unique in causing a small degree of enantiomeric discrimination in one of the two diastereotopic *N*-methyl resonances. Similarly, SCR-t4L is unique in causing a small extent of enantiomeric discrimination in the *C*-methyl resonance.

The aromatic resonances of the two phenyl rings of **9** overlap in its NMR spectrum, and all move to lower frequency on addition of the calix[4]resorcinarenes, indicating that both rings insert into the cavity. The aromatic resonances continue to overlap throughout the series of spectra with every calix[4]resorcinarene making it impractical to determine whether any enantiomeric discrimination occurs. SCR-c4L, SCR-t4L and SCR-t3L do produce a small degree of enantiomeric discrimination for the *C*-methyl resonance of **9**, whereas SCR-Pro does not, demonstrating the enhanced effectiveness of the hydroxyproline derivatives over the proline derivative.

Table 3 provides a comparison of the data for the aromatic resonances of **11**–**15** with SCR-t3L. These data show that the magnitudes of the changes in chemical shifts do not correlate with the degree of enantiomeric discrimination. Changes in chemical shifts in the spectra of **11** and **13** with SCR-t3L are the two smallest of the group, yet these combinations show the largest enantiomeric discrimination. Subtleties of the interaction of the aliphatic groups of **11**–**15** with the 3-hydroxy group of SCR-t3L must be important in distinguishing the different changes in chemical shift and enantiomeric discrimination.

Table 3. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **11**–**15** (10 mM) in the presence of SCR-t3L (10 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	H*o*	H*m*	H*p*
11	0.339/0.358 (0.019)	0.556/0.590 (0.034)	0.776/0.829 (0.053)
12	0.440	0.669	0.931
13	0.260/0.296 (0.036)	0.426/0.484 (0.058)	0.628/0.709 (0.081)
14	0.543/0.565 (0.022)	0.852	1.080
15	0.503/0.542 (0.039)	0.703/0.726 (0.023)	0.943

Table 4 provides changes in chemical shifts and enantiomeric discrimination of the aromatic resonances of **11** and **12** in the presence of the four calix[4]resorcinarenes. There is considerable variability in the changes in chemical shifts for **11** in the presence of the different calix[4]resorcinarenes, as values with SCR-Pro and SCR-t3L are much smaller than those with SCR-c4L and SCR-t4L. Yet, SCR-t4L and SCR-t3L are the only two that cause observable enantiomeric discrimination in the aromatic signals of **11**. The enantiomeric discrimination in the spectrum of **11** is best with SCR-t3L, and presumably the hydroxy group at the 3-position of the proline is significant in influencing the extent of enantiomeric discrimination. All of the calix[4]resorcinarenes cause enantiodifferentiation of the *N*-methyl resonance [a comparison of the effect of the various calix[4]resorcinarenes (10 mM) on the *N*-methyl resonance of **11** (10 mM) is shown in the Supporting Information]. Larger enantiomeric

Table 4. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **11** and **12** (10 mM) in the presence of calix[4]resorcinarenes (30 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	SCR-Pro	SCR-c4L	SCR-t4L	SCR-t3L
11				
H*o*	0.370	0.456	0.498/0.514 (0.016)	0.339/0.358 (0.019)
H*m*	0.597	0.767	0.794/0.813 (0.019)	0.556/0.590 (0.034)
H*p*	0.817	1.054	1.105/1.153 (0.048)	0.776/0.829 (0.053)
N-Me[a]	0.036/0.065 (0.029)	0.050/0.089 (0.039)	0.065/0.114 (0.049)	0.060/0.110 (0.050)
12				
H*o*	0.366	0.388	0.565/0.645 (0.080)	0.440
H*m*	0.615	0.655	0.899/0.999 (0.100)	0.669
H*p*	0.867	0.926	1.253/1.355 (0.102)	0.931
C-Me[a]	0.150	0.084	0.150/0.185 (0.035)	0.076

[a] Concentration of calix[4]resorcinarenes is 40 mM.

discrimination of the *N*-methyl resonances occurs with SCR-t4L and SCR-t3L relative to the other calix[4]resorcinarenes.

Changes in chemical shifts in the aromatic portion of the spectrum of **12** with SCR-Pro, SCR-c4L and SCR-t3L are fairly similar, and no degree of useful enantiomeric discrimination is observed. SCR-t4L, on the other hand, causes significantly larger perturbations of the chemical shifts and substantial enantiomeric discrimination for all three of the aromatic and *tert*-butyl resonances. A comparison of the *tert*-butyl resonance of **12** in the presence of the different calix[4]resorcinarenes is provided in the Supporting Information. Figure 1 shows a series of spectra for the aromatic resonances of **12** with increasing concentrations of SCR-t4L. Presumably, dipole–dipole interactions between the substituent group of **12** and the hydroxy group of SCR-t4L are important in accounting for the larger changes in chemical shifts and enantiomeric discrimination relative to the other calix[4]resorcinarenes.

The aromatic resonances of both phenyl rings of **16** are shielded in the presence of the calix[4]resorcinarenes, indicating that each ring inserts into the cavity. The resonances of the two phenyl rings are distinct in the initial spectrum, and one set exhibits enantiodifferentiation in the presence of SCR-t4L and SCR-t3L (Table 5). The *C*-methyl resonance shows enantiomeric discrimination in the presence of SCR-Pro, SCR-t4L and SCR-t3L. Enantiomeric discrimination in the spectrum of **16** with SCR-t4L is markedly superior to that with the other calix[4]resorcinarenes.

The aromatic resonances of **17** exhibit enantiomeric in the presence of all of the calix[4]resorcinarenes (Table 5). The *N*-methyl and *C*-methyl resonances also show enantiomeric discrimination, although these are smaller in magnitude than observed for the aromatic hydrogen atoms. Whereas the enantiodifferentiation of **17** is fairly similar for the different calix[4]resorcinarenes, more resonances exhibit the best results with SCR-t4L. Figure 2 shows a series of spectra for the aromatic resonances of **17** with increasing concentrations of SCR-t4L. The enantiomeric discrimination of the H*o*, H*m*, and H*p* resonances is apparent. The H*o* resonance is especially useful for determining the enantiomeric purity of **17**.

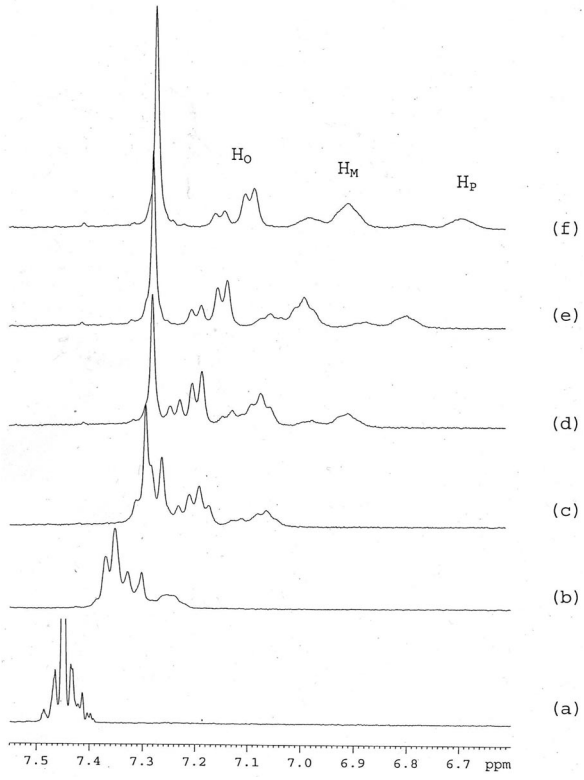

Figure 1. ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of the H*o*, H*m*, H*p* resonances of (a) **12** (10 mM) enantiomerically enriched [2/3 (–), 1/3 (+)] with SCR-t4L at (b) 2 mM, (c) 4 mM, (d) 6 mM, (e) 8 mM and (f) 10 mM.

Compounds **18** and **19** have two nitrogen atoms. Hydrochloric acid concentrations of 12 and 22 mM were used to dissolve these substrates (10 mM) with the expectation that mono- and diprotonated species predominate at the two respective concentrations. No differences in enantiomeric discrimination occur at the two different concentrations of hydrochloric acid, and data for **19** (Table 5) are at 12 mM hydrochloric acid. Data are not included for **18** because no enantiomeric discrimination is observed in the NMR spectrum. The phenyl ring of **18** and **19** inserts in the calix[4]-resorcinarene cavity. The phenyl resonances of **18** and **19**

Table 5. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **16**, **17** and **19** (10 mM) in the presence of calix[4]resorcinarenes (10 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	SCR-Pro	SCR-c4L	SCR-t4L	SCR-t3L
16				
H*o*	0.143	0.146	0.175/0.194 (0.019)	0.109/0.128 (0.019)
H*m*	0.187	0.239	0.235/0.305 (0.070)	0.159/0.170 (0.011)
H*p*	0.251	0.317	0.321/0.419 (0.098)	0.232
*C*Me	0.102/0.118 (0.016)	0.089	0.108/0.129 (0.021)	0.064/0.071 (0.007)
17[a]				
H*o*	0.663/0.785 (0.122)	0.781/0.900 (0.119)	0.935/1.070 (0.135)	0.645/0.801 (0.156)
H*m*	0.905/1.001 (0.096)	1.097/1.189 (0.092)	1.214/1.319 (0.105)	0.866/0.965 (0.099)
H*p*	1.298	1.445/1.553 (0.108)	1.606/1.726 (0.120)	1.163/1.274 (0.111)
*N*Me	0.212	0.017/0.024 (0.007)	0.039/0.062 (0.023)	0.048/0.060 (0.012)
*C*Me	0.074/0.088 (0.014)	0.074/0.086 (0.012)	0.104/0.117 (0.013)	0.069/0.080 (0.011)
19				
H*o*	0.219	_[b]	0.260	0.192
H*m*	0.359	0.364	0.397	_[b]
H*p*	0.462	0.481	0.513	0.386
*N*Me	0.028/0.107 (0.079)	0.005/0.077 (0.072)	0.064/0.157 (0.093)	0.014/0.101 (0.087)

[a] Concentration of calix[4]resorcinarenes is 30 mM for the aromatic resonances. [b] Obscured by other resonances.

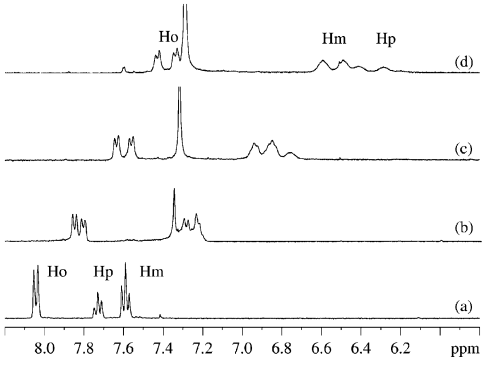

Figure 2. ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of the H*o*, H*m*, H*p* resonances of (a) **17** (10 mM) with SCR-t4L at (b) 4 mM, (c) 10 mM and (d) 20 mM.

exhibit comparable changes in chemical shifts with the different calix[4]resorcinarenes, but no enantiomeric discrimination. The piperidine ring resonances are complex, and many overlap with resonances of the calix[4]resorcinarenes, precluding the opportunity to observe enantiomeric discrimination. The *N*-methyl singlet of **19** shows a significant degree of enantiodifferentiation in the presence of all of the calix[4]resorcinarenes, with the largest value occurring with SCR-t4L.

Compounds **20**–**24** have a phenyl and pyridyl ring, although the phenyl ring is unsubstituted in **20** and **21** and *para*-substituted in **22**–**24**. Prior studies of **22**–**24** with SCR-Pro indicated that the phenyl ring was inhibited from associating with the cavity because of the halide atom.[27] Association of **22**–**24** involved insertion of the pyridyl ring into the cavity in such a manner that the changes in chemical shifts for H4′ and H5′ were greater than those of H3′ and H6′. Compounds **21** and **22** were shown to associate with SCR-Pro through insertion of both the phenyl and pyridyl ring, although binding through the pyridyl ring was more favorable. Geometries in which both rings insert simultaneously into a single calix[4]resorcinarene cavity seemed improbable, and binding likely involved one ring or the other with a rapid exchange between the two possibilities.[27] The perturbations of chemical shifts and enantiomeric discrimination of the resonances of **20**–**24** with the calix[4]resorcinarenes are reported in Tables 6 and 7. The patterns of changes in chemical shifts of **20**–**24** with SCR-c4L, SCR-t3L, and SCR-t4L are comparable to those with SCR-Pro and imply the same geometry of association for the aromatic and pyridyl rings.

The changes in chemical shifts for the resonances of doxylamine succinate (**20**) are generally similar with the various calix[4]resorcinarenes. The H6′ doublet splits into two distinct resonances with the different calix[4]resorcinarenes (see Figure in Supporting Information). Figure 3 shows a comparison of the enantiodifferentiation of the H3′ and H4′ resonances of **20** with the different calix[4]resorcinarenes. The H3′ and H4′ resonances of **20** exhibit substantial broadening in the presence of SCR-t3L (Figure 3e). Broadening such as this is usually indicative of an intermediate rate of exchange between the bound and unbound forms of the substrate. In this and other studies using these calix[4]-resorcinarenes as chiral NMR discriminating agents, larger changes in the chemical shifts of the resonances of the substrate are often accompanied by greater broadening.[26–30] The best calix[4]resorcinarene is the one that produces adequate changes in chemical shifts with suitable enantiomeric discrimination and acceptable levels of broadening. As seen by the spectra in Figure 3, SCR-Pro is the best reagent for

20. The enantiodifferentiation of the H4′ resonance of **20** is especially large with SCR-Pro. With SCR-Pro, the enantiomeric discrimination of the H3′, H4′ and H6′ resonances of **20** is large enough with sufficiently minimal broadening to be able to accurately determine enantiomeric purity. However, SCR-t3L is unique among the calix[4]resorcinarenes in causing enantiomeric discrimination of the H4 and H5′ resonances.

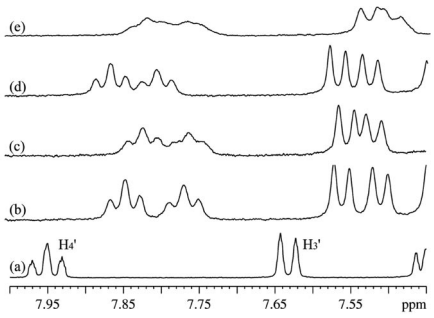

Figure 3. ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of the H3′ and H4′ resonances of (a) **20** (10 mM) with 2 mM (b) SCR-Pro, (c) SCR-c4L, (d) SCR-t4L and (e) SCR-t3L.

The changes in chemical shifts that occur in the ^{1}H NMR spectrum of **21** with the calix[4]resorcinarenes are slightly larger than those for **20** (Table 6). The relative shifts in the spectra of **20** and **21** in the presence of the calix[4]-resorcinarenes indicate comparable binding geometries in which both the phenyl and pyridyl rings insert into the cavity. Whereas the H3′ and H4′ resonances of **20** exhibit substantial enantiomeric discrimination in the presence of each of the calix[4]resorcinarenes, these same two resonances usually exhibit no enantiomeric discrimination in the spectra of **21**. In contrast, the enantiomeric discrimination of the H2, H3, H5′ and H6′ resonances of **21** are generally greater than the same resonances of **20**. The importance of dipole–dipole or steric interactions of the substituent groups on the proline residues with the aliphatic groups of **20** and **21** must have a significant role in explaining the subtle distinctions in enantiomeric discrimination between the two similar substrates.

Brompheniramine maleate (**22**) and chlorpheniramine maleate (**23**) differ only in the halogen atom on the aromatic ring. The halogenated ring does not insert into the cavity of the calix[4]resorcinarenes as indicated by the pattern of changes in chemical shifts (H2 > H3) and the considerably smaller shielding of the phenyl ring relative to the pyridyl ring. The changes in chemical shifts in the spectra of **22** and **23** in the presence of the calix[4]resorcinarenes are quite similar. Furthermore, there is not much variability in the magnitudes of the changes in chemical shifts for each specific proton of **22** and **23** with the calix[4]resorcinarenes. Examining the extent of enantiomeric discrimination in the spectra of **22** and **23** with the different calix[4]resorcinarenes shows that no one of them is consistently the most effective. Each one of the different calix[4]resorcinarenes produces the largest enantiodifferentiation for at least one resonance. SCR-t3L is unique in causing enantiomeric discrimination for the H5′ and methine resonances of **22** and methine resonance of **23**. Figure 4 shows the ^{1}H NMR spectra of the H2 and H3 resonances of **22** with increasing concentrations of SCR-t4L. Both show appreciable enantiomeric discrimination and the resonances of the (*S*) enantiomer exhibit the greater perturbations in chemical shifts.

Table 6. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **20** and **21** (10 mM) in the presence of calix[4]resorcinarenes (10 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	SCR-Pro	SCR-c4L	SCR-t4L	SCR-t3L
20				
H2	0.202	0.209	0.194	0.221
H3	0.319	0.250	0.222	0.269
H4	0.443	0.513	0.437	0.409/0.443 (0.034)
H3′	0.283/0.520 (0.237)	0.369/0.541 (0.172)	0.320/0.551 (0.231)	0.352/0.522 (0.170)
H4′	0.328/0.961 (0.633)	0.481/0.908 (0.427)	0.429/0.849 (0.420)	0.447/0.849 (0.402)
H5′	0.708	0.674	0.628	0.484/0.593 (0.109)
H6′	0.234/0.293 (0.059)	0.312/0.344 (0.032)	0.237/0.292 (0.055)	0.226/0.268 (0.042)
Me	0.131	0.102/0.112 (0.010)	0.128/0.139 (0.011)	0.136/0.146 (0.010)
21				
H2	0.244	0.288	0.303/0.329 (0.026)	0.320/0.362 (0.042)
H3	0.308	0.410	0.369/0.407 (0.038)	0.419/0.455 (0.038)
H4	0.460/0.492 (0.032)	0.603	0.592	0.606/0.657 (0.051)
H3′	0.426	0.502	0.623	_[a]
H4′	0.641	_[a]	_[a]	0.654/0.723 (0.069)
H5′	0.577/0.647 (0.070)	0.803/0.880 (0.077)	0.837	0.641/0.722 (0.081)
H6′	0.263/0.352 (0.089)	0.411/0.484 (0.073)	0.390/0.482 (0.092)	0.318/0.367 (0.049)
CH	0.188	_[a]	0.236	0.252/0.263 (0.016)

[a] Obscured by other resonances.

Table 7. Changes in chemical shifts ($\Delta\delta$) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of **22**–**24** (10 mM) in the presence of calix[4]resorcinarenes (10 mM). Two values indicate that enantiomeric discrimination occurs. Values in parentheses are the enantiomeric discrimination in ppm.

	SCR-Pro	SCR-c4L	SCR-t4L	SCR-t3L
22				
H2	0.305/0.374 (0.069)	0.332/0.371 (0.039)	0.338/0.403 (0.065)	0.376/0.418 (0.042)
H3	0.178/0.219 (0.041)	0.153/0.189 (0.036)	0.194/0.230 (0.036)	0.200/0.241 (0.041)
H3′	0.345/0.454 (0.109)	0.358/0.444 (0.086)	0.411/0.540 (0.129)	_[a]
H4′	0.568/0.617 (0.049)	_[a]	_[a]	0.439/0.484 (0.045)
H5′	0.557	0.703	0.705	0.443/0.488 (0.045)
H6′	0.261/0.353 (0.092)	0.335/0.410 (0.075)	0.327/0.405 (0.078)	0.228/0.265 (0.037)
CH	_[a]	_[a]	0.162	0.150/0.193 (0.043)
CH_2	0.031/0.044 (0.013)	0.051	0.052/.060 (0.008)	0.053/0.097 (0.044)
23				
H2	0.298/0.347 (0.049)	0.217/0.273 (0.056)	0.270/0.302 (0.032)	0.295/0.325 (0.030)
H3	0.251	0.142/0.158 (0.016)	0.210	0.248/0.289 (0.041)
H3′	0.320/0.455 (0.135)	0.352/0.435 (0.083)	0.543	_[a]
H4′	0.591/0.637 (0.046)	_[a]	0.646	0.494/0.530 (0.036)
H5′	0.602	0.680/0.714 (0.034)	0.709	0.488/0.543 (0.055)
H6′	0.271/0.371 (0.100)	0.331/0.441 (0.110)	0.329/0.413 (0.084)	0.243/0.282 (0.039)
CH	0.077	0.143	0.162	0.176/0.216 (0.040)
CH_2	0.012/0.034 (0.022)	0.043/0.052 (0.009)	0.051	0.087/0.095 (0.008)
24				
H2	0.292	0.328/0.352 (0.024)	0.463	0.410/0.437 (0.027)
H3	0.201	0.247/0.284 (0.037)	0.326/0.357 (0.031)	0.277/0.303 (0.026)
H3′	0.359	0.571/0.578 (0.007)	0.724	0.403/0.426 (0.023)
H4′	0.477	_[a]	_[a]	0.545/0.571 (0.026)
H5′	0.538	0.892	0.885	0.524/0.548 (0.024)
H6′	0.265/0.316 (0.051)	0.483/0.505 (0.022)	0.408/0.513 (0.105)	0.262/0.287 (0.025)
CH	0.164/0.185 (0.021)	0.180	0.228/0.263 (0.035)	0.171/0.182 (0.011)
CH_2	0.062	0.073/0.080 (0.007)	0.104	0.088/0.111 (0.013)

[a] Obscured by other resonances.

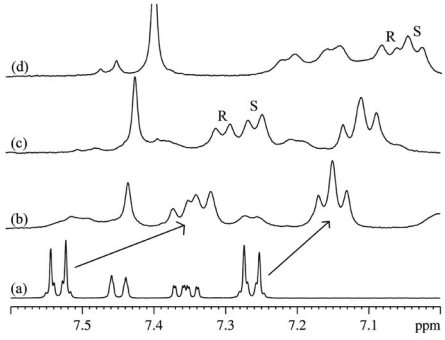

Figure 4. ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of the aromatic region (δ_{H2} = 7.54 ppm, δ_{H3} = 7.26 ppm) of (a) **22** (10 mM) enantiomerically enriched [2/3 (*S*), 1/3 (*R*)] with SCR-t4L at (b) 4 mM, (c) 6 mM and (d) 10 mM.

Chlorpheniramine (**23**) and carbinoxamine (**24**) are structurally similar except that **24** has an additional ether oxygen atom in the aliphatic group. The changes in chemical shifts in the spectrum of **24** with the calix[4]resorcinarenes are almost all larger than those of **23**, and the ^{1}H NMR spectra of **24** are considerably more broadened than occurs with **23** (Table 7). Enantiomeric discrimination is almost always smaller with **24** than with **23**. The only exception is the larger enantiodifferentiation of the H6′ resonance of **24** with SCR-t4L. SCR-t3L is unique in causing enantiomeric discrimination of every aromatic resonance of **24**. Only SCR-t4L and SCR-t3L cause a discernible level of enantiomeric discrimination for the methine resonance of **24**, although the shift order for the enantiomers is reversed in the two spectra (see Figure in Supporting Information). The hydroxy groups on the proline moieties of the different calix[4]resorcinarenes must play an important role in contributing to enantiomeric discrimination and accounting for such a reversal in shift order in the spectra.

Conclusions

The sulfonated calix[4]resorcinarenes with prolinylmethyl and (hydroxyprolinyl)methyl substituents are excellent water-soluble chiral NMR solvating agents for compounds with a monosubstituted phenyl or pyridyl ring. For substrates with methylbenzylamine (**6**–**9**), benzyl alcohol (**11**–**15**), or phenyl (**16**, **17** and **19**) moieties, the calix[4]resorcinarenes with a (hydroxyprolinyl)methyl group are more effective than the derivative with a prolinylmethyl group. The *trans*-4-hydroxyproline and *trans*-3-hydroxyproline derivatives usually cause the largest enantiodifferentiation of **6**–**19**. For **20**–**24**, no one calix[4]resorcinarene is consistently the most effective. SCR-t3L usually causes enantiodifferentiation of most of the resonances of **20**–**24**, although SCR-

Pro often causes the largest enantiomeric discrimination for those resonances that are differentiated.

Experimental Section

Reagents: The prolinylmethyl calix[4]resorcinarene derivatives **1**–**5** were prepared and purified using published procedures.[25,28] Substrates were purchased as protonated salts when available. For those substrates only available in neutral form, hydrochloride salts were obtained in solution by adding a stoichiometric equivalent of hydrochloric acid in deuterium oxide.

Procedure: ^{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. A series of spectra were then measured with increasing concentrations of the calix[4]-resorcinarene added either by weight or volumetrically using an appropriate quantity of a concentrated stock solution (120 mM or 240 mM).

Supporting Information (see footnote on the first page of this article): Additional figures that compare the effectiveness of the different calix[4]resorcinarenes as chiral NMR solvating agents.

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