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A Water-Soluble Calix[4]resorcinarene with α-Methyl-L-prolinylmethyl Groups as a Chiral NMR Solvating Agent

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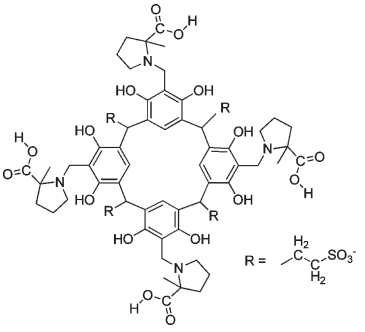
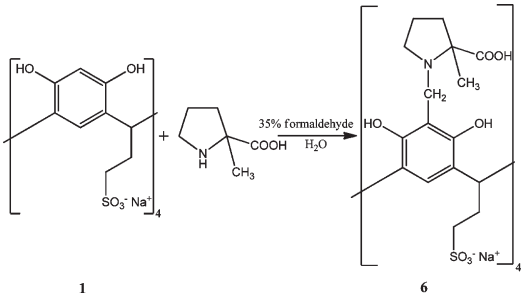
Received November 3, 2010



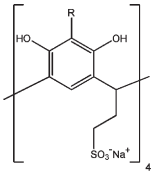
A water-soluble calix[4]resorcinarene containing α-methyl-L-prolinylmethyl groups is synthesized and evaluated as a chiral NMR solvating agent. Aryl-containing substrates with substituted amines are studied.

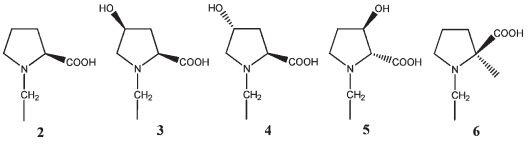
A series of water-soluble, sulfonated calix[4]resorcinarenes with prolinylmethyl (**2**−Pro)[1−3] and hydroxyprolinylmethyl (*cis*-4-hydroxy-L-proline (**3**−c4L), *trans*-3-hydroxy-L-proline (**4**−t3L), and *trans*-4-hydroxy-L-proline (**5**−t4L)) substituent groups are effective water-soluble chiral NMR solvating agents for substrates with mono- and *ortho*-substituted phenyl rings as well as naphthyl and anthryl rings with suitable substitution patterns to minimize steric hindrance.[4−7] Host−guest complexes form by insertion of the aromatic ring into the cavity of the calix[4]resorcinarene. Evidence for this mode of complexation involves the substantial shielding that occurs for most hydrogen atoms of the substrate and especially for those on the aromatic ring. This shielding occurs because hydrogen atoms of the substrate within the cavity are positioned over the aromatic rings of the calix[4]-resorcinarene. The hydroxyproline analogues (**3**−**5**) are usually more effective than the proline derivative (**2**) as chiral NMR solvating agents.[4−7] Herein we report on the utility of an α-methyl-L-prolinylmethyl analogue (**6**−αMP) of the sulfonated calix[4]resorcinarene as a chiral NMR solvating agent.

SCHEME 1. Synthesis of 6



1 **6**





2 **3** **4** **5** **6**

Water-soluble **6** is synthesized in two steps (Scheme 1).[1,4] The attachment of proline and hydroxyproline moieties to **1** described in prior reports involved a reaction at room temperature for 48 h.[1,4] Reaction of α-methyl-L-proline with **1** for 48 h resulted in only partial substitution of the amino acid with an unacceptably high number of unsubstituted resorcinol rings.[4] Performing the reaction at elevated temperatures leads to the attachment of an α-methyl-L-prolinylmethyl unit on every resorcinol ring, but the ^{1}H NMR spectra are severely broadened, suggesting that **6** is in several of the possible allowed configurations.[8] Performing the reaction at room temperature for 2 weeks or longer leads to the desired compound (**6**−αMP) with a ^{1}H NMR spectrum not significantly compromised by broadening. Rotary evaporation does not increase the broadening in the spectrum. Concentrated stock solutions of αMP used for NMR studies exhibit the same spectra for at least 2 weeks, although the spectra eventually broaden if αMP is retained in solution for too long. The compound can sit in the solid state for months and be redissolved in water for use as a chiral NMR solvating agent.

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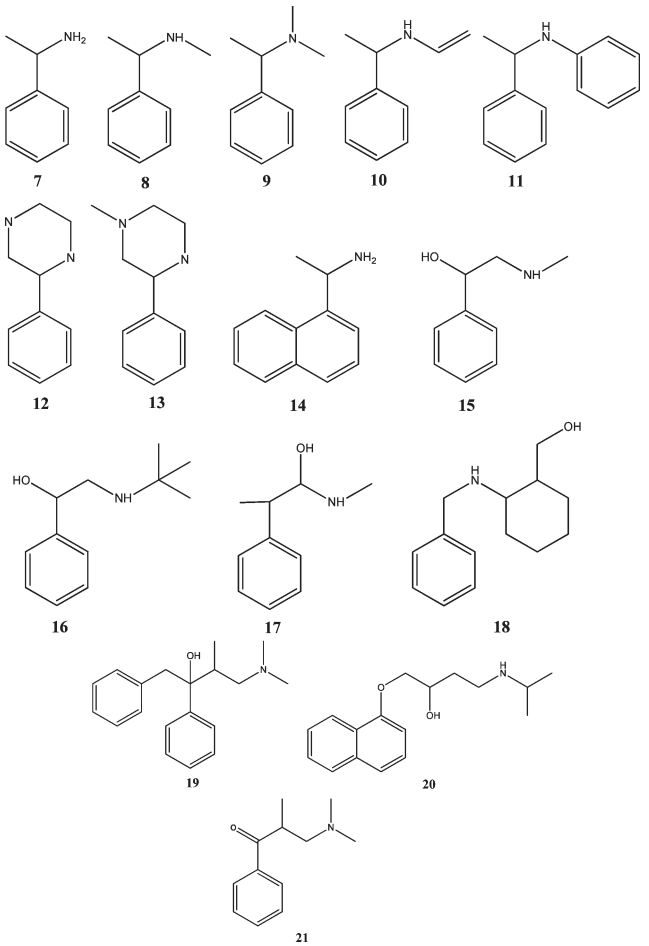
Published on Web 01/04/2011 DOI: 10.1021/jo102197w

Prior studies of **2**−**5** have shown that 1:1 complexes occur with aryl-containing substrates[2,4] and that any aggregation of the calix[4]resorcinarene does not hinder its effectiveness as a chiral NMR solvating agent.[4] Water-solubility of the aryl-containing substrates examined herein is achieved by examining the compounds as their ammonium salts. The best strategy for conducting NMR studies is to maintain the substrate at a fixed concentration (10 mM) and add increasing amounts of the calix[4]resorcinarene either as a solid or as an aliquot from a concentrated stock solution. The resonances of the substrate sometimes exhibit broadening in mixtures with αMP. This likely occurs because of an intermediate rate of exchange of the bound and unbound form of the substrate. When the broadening is too excessive, determining chemical shifts and enantiomeric discrimination is often impractical. Studies with **2** have shown that it is possible to reduce the broadening by recording the NMR spectra at 45 °C.[3] Raising the temperature also reduces the perturbations in chemical shifts and magnitude of the enantiomeric discrimination, but the sharper spectra facilitates assignment of the resonances. All of the results reported herein were obtained at ambient temperatures.



Tables 1 and 2 provide the enantiomeric discrimination in the NMR spectra of **7**−**21** with αMP and with one of the previously studied calix[4]resorcinarenes. The values represent the largest enantiomeric discrimination that was achieved with the other reagents and with αMP. Data with αMP is only reported for hydrogen atoms where the resonances of both enantiomers do not overlap with any other resonance.

TABLE 1. Enantiomeric Discrimination (ΔΔδ) in ppm in the ^{1}H NMR Spectrum (400 MHz, D_2O, 23 °C) of 7−14 in the Presence of Different Calix[4]resorcinarenes

7			**11**		
	t3L 40 mM	αMP 40 mM		t3L 10 mM	αMP 40 mM
H*o*	0.049	**0.088**	CCH_3		**0.019**
H*m*	0.018	**0.085**	$ArCH_2$		**0.061**
H*p*		**0.106**	CCH_3	**0.011**	
CH	0.011	**0.093**			
CH_3	0.009	**0.017**			
8			**12**		
	c4L 10 mM	αMP 10 mM		t4L 6 mM	αMP 15 mM
H*o*	**0.019**		H*o*		**0.015**
H*m*	**0.019**				
H*p*	**0.020**				
9			**13**		
	t4L 10 mM	αMP 20 mM		t4L 10 mM	αMP 10 mM
H*m*	**0.034**		NCH_3	**0.093**	
H*p*	**0.040**				
CCH_3	0.006	**0.020**			
10			**14**		
	t4L 10 mM	αMP 20 mM		c4L 25 mM	αMP 2 mM
H*o*		**0.093**	H4	**0.109**	
H*m*		**0.078**	H5		**0.108**
H*p*		**0.089**	H6	**0.159**	0.109
CCH_3		**0.107**	H7	**0.171**	0.122
			H8	**0.128**	0.083
			CH	**0.049** 10 mM	
			CH_3	**0.041** 10 mM	

TABLE 2. Enantiomeric Discrimination (ΔΔδ) in ppm in the ^{1}H NMR spectrum (400 MHz, D_2O, 23 °C) of 15−21 in the Presence of Different Calix[4]resorcinarenes

15			**19**		
	t3L 10 mM	αMP 10 mM		t4L 10 mM	αMP 10 mM
H*o*	**0.019**		H*o*	**0.019**	0.018
H*m*	**0.034**		H*m*	**0.070**	0.016
H*p*	**0.053**		H*p*	**0.098**	0.037
NCH_3	**0.050** 40 mM	0.028	$ArCH_2$		**0.019** 8 mM
			CCH_3	**0.021**	
16			**20**		
	t4L 10 mM	αMP 10 mM		Pro 10 mM	αMP 20 mM
H*o*	**0.080**		H2	0.057	**0.102**
H*m*	**0.100**		H3	**0.064**	
H*p*	**0.102**		H4	0.059	**0.105**
t-Bu	0.035 40 mM	**0.054**	H5		**0.045**
			H8		**0.028**
17			**21**		
	t3L 40 mM	αMP 50 mM		t4L 40 mM	αMP 10 mM
H*o*	**0.040**	0.025	H*o*	**0.156****	
H*m*	**0.058**	0.053	H*m*	**0.105**	
H*p*	0.086	**0.092**	H*p*	**0.120**	
NCH_3	0.018*	**0.034**	NCH_3	**0.023**	
CCH_3	0.011	**0.028**	CCH_3	0.013	**0.042**
18					
	t3L 10 mM	αMP 15 mM			
H*o*		**0.018** 6 mM			

*Data reported for t4L (40 mM). **Data reported for t3L (40 mM).

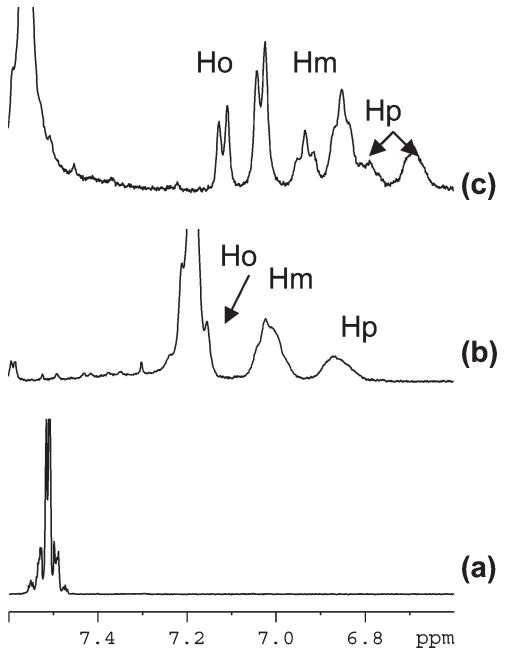


FIGURE 1. ^{1}H NMR spectrum of the aromatic resonances (400 MHz, D_2O, 23 °C) of (a) **7** (10 mM) enantiomerically enriched (2/3-(*S*), 1/3-(*R*)) with (b) t3L (30 mM) and (c) αMP (30 mM).

Compounds **7**−**11** (Table 1) include 1-phenylethylamine (**7**) and four derivatives in which the amine group has an aliphatic (**8**, **9**), olefinic (**10**), or aromatic (**11**) substituent group. αMP produces the largest enantiomeric discrimination for all five of the ^{1}H resonances of **7** of all of the calix[4]resorcinarenes. Figure 1 provides a comparison of the aromatic region of the ^{1}H NMR spectrum of **7** (10 mM) with t3L (30 mM) and αMP (30 mM) that demonstrates the significant improvement in enantiomeric discrimination observed with αMP over the other calix[4]resorcinarenes.

Incorporating substituent groups onto the amine moiety of **7** has a significant influence on the enantiomeric discrimination observed with the different calix[4]resorcinarenes and especially with αMP. No enantiomeric discrimination of the H*o*, H*m*, and H*p* resonances (positions relative to the substituent group on the ring) of **8** and **9** is observed with αMP. For **9**, αMP does produce larger enantiomeric discrimination of the *C*-methyl resonance than any of **2**−**5**.

Compounds **2**−**5** do not cause enantiomeric discrimination of any of the resonances of **10**, whereas αMP causes significant enantiomeric discrimination of the aromatic hydrogen resonances. A comparison of the effect of αMP and t4L on the aromatic region (Figure 2) and *C*-methyl resonance (Figure 3) of **10** shows the enhanced utility of αMP over **2**−**5**.

αMP is unique in causing enantiomeric discrimination of the methine and methylene resonances of **11**, whereas t3L causes enantiomeric discrimination of the *C*-methyl resonance that is not observed with αMP. Subtleties in the interaction of the substituent groups of **7**−**11** with the α-methyl group of αMP likely account for the differences in enantiomeric discrimination that occur.

Compounds **2**−**5** do not cause enantiomeric discrimination in the ^{1}H NMR spectrum of **12**, whereas αMP produces enantiomeric discrimination of the H*o* resonance (Table 1). For **13**, αMP is ineffective at causing enantiomeric discrimination of any resonances, whereas t4L produces enantiomeric discrimination of the *N*-methyl resonance.

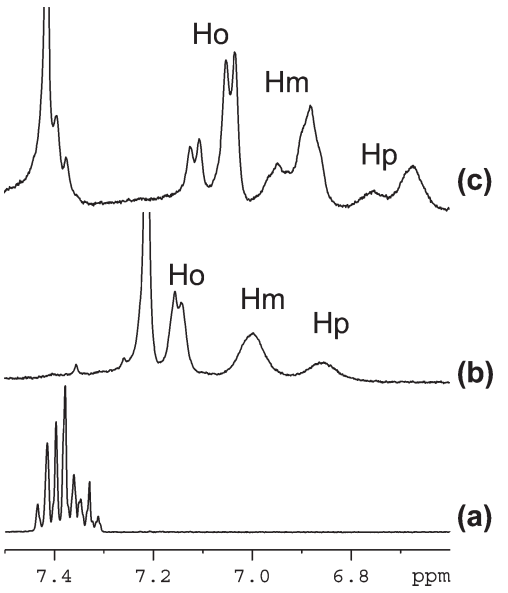


FIGURE 2. ^{1}H NMR spectrum of the aromatic resonances (400 MHz, D_2O, 23 °C) of (a) **10** (10 mM) enantiomerically enriched (2/3-(*S*), 1/3-(*R*)) with (b) t4L (10 mM) and (c) αMP (10 mM).

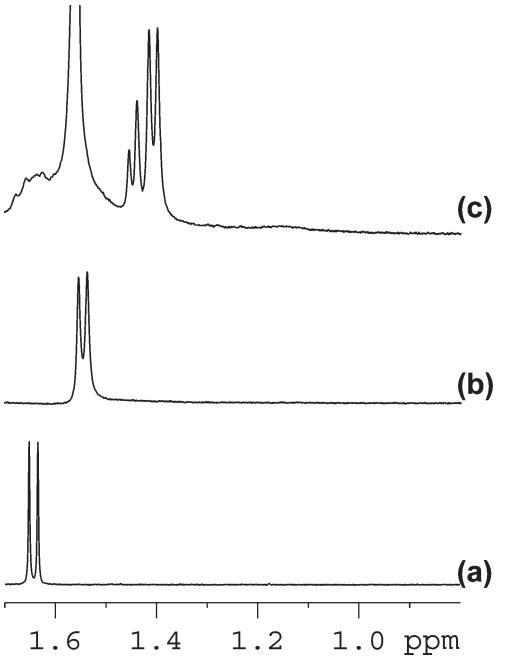


FIGURE 3. ^{1}H NMR spectrum of the *C*-methyl resonance (400 MHz, D_2O, 23 °C) of (a) **10** (10 mM) enantiomerically enriched (2/3-(*S*), 1/3-(*R*)) with (b) t4L (10 mM) and (c) αMP (10 mM).

Prior studies have shown that naphthyl rings of water-soluble substrates fit into the cavity of **2**-**5** and have higher association constants than substrates with phenyl rings.[2−4] The perturbations in chemical shifts for **14** with αMP are very large and significant broadening occurs in the spectra at the higher concentrations of αMP. The data for **14** in Table 1 is for αMP at 2 mM. Substantial enantiomeric discrimination is observed for the H5, H6, H7, and H8 resonances.

Relative to c4L, the enantiomeric discrimination with αMP is much larger at proportional concentrations. αMP is unique among **2**−**6** in causing enantiomeric discrimination in the H5 resonance of **14**.

Compounds **15**−**20** have hydroxyl groups in addition to the amine moiety. For **15** and **16**, αMP causes no enantiomeric discrimination of the aromatic resonances but does cause discrimination for certain of the aliphatic resonances (Table 2). The enantiomeric discrimination of the *tert*-butyl resonance of **16** is larger with αMP. For **17** and **19**, the enantiomeric discrimination of specific aliphatic resonances is substantially larger with αMP than with **2**−**5**. Compounds **2**−**5** do not cause any enantiomeric discrimination in the ^{1}H NMR spectrum of **18**, whereas αMP does cause enantiomeric discrimination of the H*o* resonance. αMP is unique in causing enantiomeric discrimination of the H5 and H8 resonances of **20**. Furthermore, the enantiomeric discrimination for H2 and H4 of **20** is larger with αMP than observed with **2**−**5**. Compound **21** has a ketone moiety and αMP causes the largest enantiomeric discrimination of the *C*-methyl resonance.

In conclusion, a sulfonated calix[4]resorcinarene with α-methyl-L-prolinylmethyl moieties is an effective water-soluble chiral NMR solvating agent for amine and amino alcohol substrates with phenyl or naphthyl rings. Enantiomeric discrimination that is large enough to determine enantiomeric purity is often observed. For 12 of the 15 substrates examined herein, αMP causes larger enantiomeric discrimination of one or more resonances than observed with previously reported proline and hydroxyproline calix[4]resorcinarenes. For three of the substrates, αMP is unique in causing enantiomeric discrimination of any of the resonances.

Experimental Section

Reagents. The sulfonated calix[4]resorcinarene (**1**), prolinylmethyl derivative (**2**), and hydroxyprolinylmethyl derivatives (**3**−**5**) were prepared and purified as their hydrated species as described previously.[1,4] 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.

Synthesis of the Tetra-α-methyl-L-prolinylmethyl Derivative (6). Tetrasulfonated calix[4]resorcinarene (**1**) (250 mg, 0.248 mmol) and α-methyl-L-proline (128.1 mg, 0.992 mmol) were dissolved in distilled water (3 mL). Once fully dissolved, formaldehyde (37%, 0.110 mL) was added. The reaction mixture was purged with nitrogen gas and then allowed to stir under a nitrogen atmosphere. Reaction progress was monitored by removing a small aliquot of the reaction mixture, adding it to deuterium oxide, and recording an NMR spectrum. After 2 weeks, the reaction was dried by rotary evaporation and allowed to further dry by vacuum desiccation to yield hydrated **6** (0.446 g, 95% yield). To purify, solid **6** was dissolved in a minimal amount of distilled water (approximately 0.5 mL) and allowed to stir. The purified solid was triturated from solution with methanol, collected by vacuum filtration, and further dried in a vacuum desiccator. ^{1}H NMR (400 MHz, D_2O, HOD reference): δ 7.36 (s, 4H), 4.80 (t, 4H). 4.30 (s, 8H), 3.44 (m, 4H), 3.26 (m, 4H), 2.95 (t, 8H), 2.68 (m, 8H), 2.26 (m, 4H), 2,10 (m, 8H), 1.85 (m, 4H), 1.57 (s, 12H). ^{13}C NMR (100 MHz, D_2O. TMS reference): δ 179.9, 154.5, 128.0, 127.7, 127.3, 110.20, 77.3, 73.2, 54.8, 51.6, 47.6, 38.2, 25.8, 23.9. Anal. Calcd for $C_{64}H_{80}N_4O_{28}S_4Na_4 \cdot 18H_2O$: C, 40.50; H, 6.16; N, 2.95. Found: C, 40.30; H, 6.21; N, 3.18.

Acknowledgment. We thank the National Science Foundation (Research at Undergraduate Institutions Program, Grant CHE-0653711; Major Research Instrumentation Program, Grant CHE-0115579) for supporting our work.

Supporting Information Available: Procedures for obtaining NMR spectra, ^{1}H NMR spectrum for compound **6**, perturbations in chemical shifts of **7**−**21** in the presence of **2**−**6**, and additional examples of NMR spectra for substrate mixtures with **2**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.