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An Enantioselective NMR Shift Reagent for Cationic Aromatics

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ABSTRACT

The water-soluble tetra L-prolinylmethyl derivative of a tetrasulfonated calix[4]resorcarene is an effective chiral NMR solvating agent for compounds with bicyclic aromatic or indole rings. Complexation of bicyclic substrates with the calix[4]resorcarene is likely promoted by hydrophobic effects. The bicyclic substrates have larger association constants with the calix[4]resorcarene than similar phenyl-containing compounds. Substantial enantiomeric discrimination is observed for several resonances in the ^{1}H NMR spectra of these substrates.

Nuclear magnetic resonance (NMR) spectroscopy is often used to determine enantiomeric excess (ee) and assign absolute configurations of chiral compounds.[1] A common strategy is to use a chiral solvating agent that associates with the enantiomers in solution. Some chiral solvating agents, most notably cyclodextrins[2] and crown ethers,[3] operate through the formation of host−guest complexes. Two series of host compounds that would seem to offer interesting potential as chiral solvating agents are calixarenes and calix[4]resorcarenes.[4] Unfortunately, calixarene and calix[4]resorcarene derivatives do not function that effectively as hosts for organic substrates in organic solvents. For example, we examined a series of organic-soluble calix[4]arene and calix[4]resorcarene derivatives and found only weak association of substrate compounds and poor enantiomeric discrimination.[5] Other chiral calixarene and calix[4]resorcarene systems have been developed, but these are also of rather limited utility for chiral discrimination and the NMR spectroscopic applications are not especially noteworthy.[6]

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In these cases, organic solvents effectively solvate the guest and occupy the relatively hydrophobic cavity of the host, thereby reducing the formation of host−guest complexes.[4e,7] Association of organic compounds with calix[4]-arenes is more favorable in water-soluble systems.[8] Similarly, a water-soluble sulfonated resorcarene rendered chiral through the attachment of L-prolinylmethyl residues to each of the aromatic rings (Figure 1) induces sizable upfield shifts in

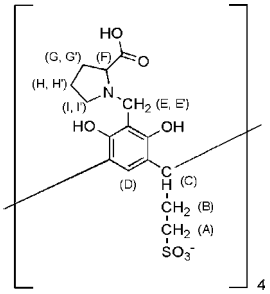

Figure 1. Structure of L-prolinylmethyl derivative of sulfonated calix[4]resorcarene (**1**).

the aromatic resonances of compounds such as 1-phenylethanol, mandelic acid, phenylalanine, and carbobenzyloxy derivatives of amino acids.[9] Presumably these compounds form a host−guest complex with **1** by inclusion of the aromatic ring in the resorcarene cavity. Ring shielding effects from the aromatic residues of the resorcarene on the aromatic hydrogen atoms of the substrate are responsible for the substantial upfield shifts.

In further exploration of the use of **1** as a chiral NMR solvating agent, we have found rather surprisingly that water-soluble organic compounds containing bicyclic naphthyl or indole rings such as 1-(1-naphthyl)ethylamine hydrochloride, propranolol hydrochloride, and tryptophan associate even more strongly with **1** than compounds with a phenyl ring. Association of these bicyclic aromatic compounds with **1** most likely occurs when a cleft-like cavity is created by the flattened cone as opposed to the symmetrical cone conformation of the resorcarene (see graphical abstract).[4e]

Representative ^{1}H NMR spectra of 1-phenylethylamine hydrochloride (**2**) and 1-(1-naphthyl)ethylamine hydrochloride (**3**) in the presence of **1** are provided in the Supporting Information.

The upfield shifts induced in the ^{1}H NMR spectra of several substrates in the presence of **1** are provided in Figure 2. The magnitude of the shifts in the ^{1}H NMR spectra of these substrates demonstrates the ability of water-soluble phenyl- and naphthyl-containing compounds to form host−guest complexes with **1**. The extensive shielding of the

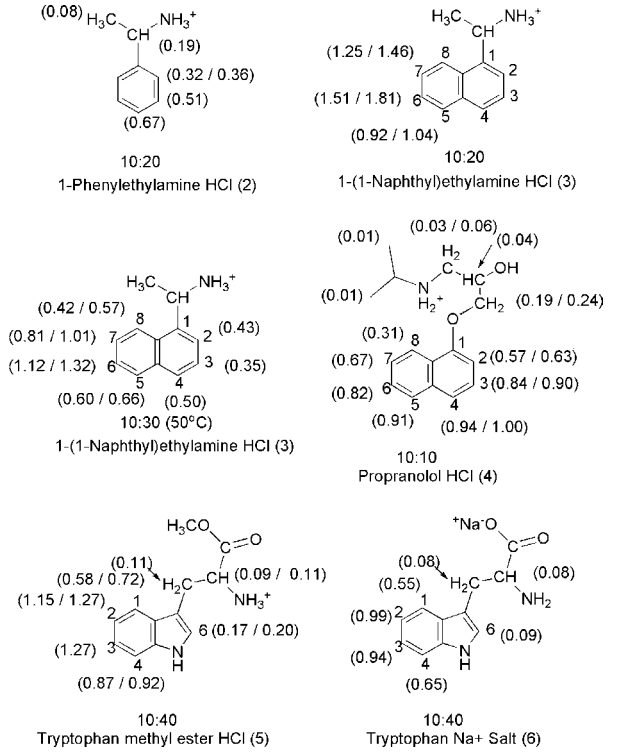

Figure 2. Upfield changes in chemical shifts in the ^{1}H NMR (400 MHz, D_2O, 23 °C unless indicated otherwise) spectra of different substrates. Two values indicate that the resonance exhibited enantiomeric discrimination.

aromatic hydrogen atoms of the guest compounds upon insertion into **1** is apparent from the magnitude of the upfield shifts in the spectra, which can be as high as 2 ppm.

Addition of **1** at concentrations up to 40 mM in D_2O produced no discernible change in the pH of the solution. Similarly, the shifts in the NMR spectrum of a mixture of carbobenzyloxy-DL-serine and **3** in the presence of **1** were essentially identical at pH 5.5 and 2. This suggests that no special steps need to be taken to control the pH when using **1** as a chiral NMR discriminating agent.

The shifts of the resonances of **3** with **1** are about three times larger than those in the spectrum of **2** with **1** (Figure 2), implying that there is a preference for association of the naphthyl-containing compound over that of the phenyl-containing compound. The stoichiometry of the complexes of **2** and **3** with **1**, determined by using Job's method,[10] is found to be 1:1. Association constants for **2** and **3** with **1**, measured with a Scatchard method (Foster−Fyfe), are reported in Table 1.[11,12] Comparing **3** and **2**, there is a clear connection between the relative magnitude of the shifts and the association constants. Similarly, the order of shifts for

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Table 1. Association Constants (M^{-1}) in D_2O at 23 °C of Compounds with **1**

	R-enantiomer	*S*-enantiomer
1-phenylethylamine HCl (**2**)	68	97
1-(1-naphthyl)ethylamine HCl (**3**)	361	595
propranolol HCl (**4**)	258	482
tryptophan methyl ester HCl (**5**)	59	113
sodium tryptophan (**6**)	67	40

the *S*- and *R*-enantiomers in the discriminated spectra of **2** and **3** agree with the magnitudes of the association constants. The larger association of **3** compared to **2** is likely caused by the relative hydrophobicities of the substrates. Since a naphthyl ring is more hydrophobic than a phenyl ring, there is a greater driving force for host−guest complexation in water.

The shifts caused by **1** in the NMR spectrum of **2** vary in the order $H_p > H_m > H_o$, indicating that the geometry of association most likely involves insertion of the phenyl ring into the cavity as shown in Figure 3a. The H_6 and H_7

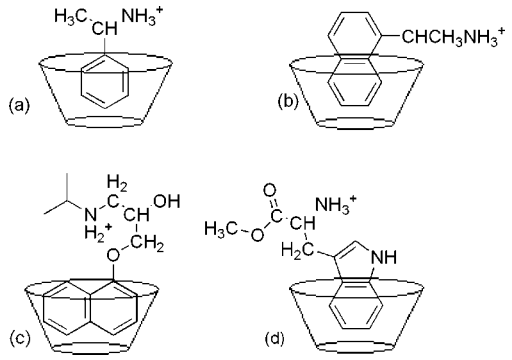

Figure 3. Geometries of (a) **2**, (b) **3**, (c) **4**, and (d) **5** and **6** with **1**.

resonances of **3** exhibit the largest shifts in the presence of **1**, followed by H_5 and H_8, and then H_2, H_3, and H_4. The pattern of these shifts is strongly suggestive of the association geometry shown in Figure 3b, in which only the unsubstituted ring of the naphthyl group is inserted into the cavity.

The slightly larger shifts of the resonances of H_5 relative to H_8 and H_6 relative to H_7 in the spectrum of **3** might indicate a slight tipping of the ring in the cavity toward deeper insertion of H_5 and H_6. Presumably the protonated amine group of **3** is involved in dipole−dipole interactions with the proline residues and perhaps the hydroxyl groups of the resorcinol rings of **1**.

The addition of **1** causes not only larger upfield shifts in the spectrum of **3** than **2**, but also substantially greater enantiomeric discrimination (Table 2). The series of spectra for **3** in the presence of **1** shown in Figure 4 illustrates the extent of enantiomeric discrimination that occurs for some

Table 2. Enantiomeric Discrimination ($\Delta\Delta\delta$) in ppm in the ^1H NMR Spectrum (400 MHz, D_2O, 23 °C) of Substrates in the Presence of **1**

		$\Delta\Delta\delta$	**1**:substrate
1-phenylethylamine HCl (**2**)	H_o	0.05	3:1
1-(1-naphthyl)ethylamine HCl (**3**)	H_4	0.07	1:1
	H_5	0.12	2:1
	H_6	0.23	2:1
	H_7	0.21	2:1
	H_8	0.16	1:1
	CH	0.06	2:1
	CH_3	0.05	2:1
Propranolol HCl (**4**)	H_2	0.06	1:1
	H_3	0.06	1:1
	H_4	0.06	1:1
tryptophan methyl ester HCl (**5**)	H_1	0.14	4:1
	H_2	0.12	4:1
	H_4	0.05	4:1
	H_6	0.03	4:1
	CH	0.02	4:1
	OCH_3	0.04	4:1

of the resonances. Five of the seven aromatic resonances of **3** exhibit readily discernible enantiomeric discrimination in the presence of **1**. Furthermore, the methine and methyl resonances of **3** show enantiomeric discrimination in the presence of **1**, which is not observed for the corresponding resonances of **2**. In all cases, the resonances of the *S*-enantiomer for **2** and **3** shift further in the presence of **1**.

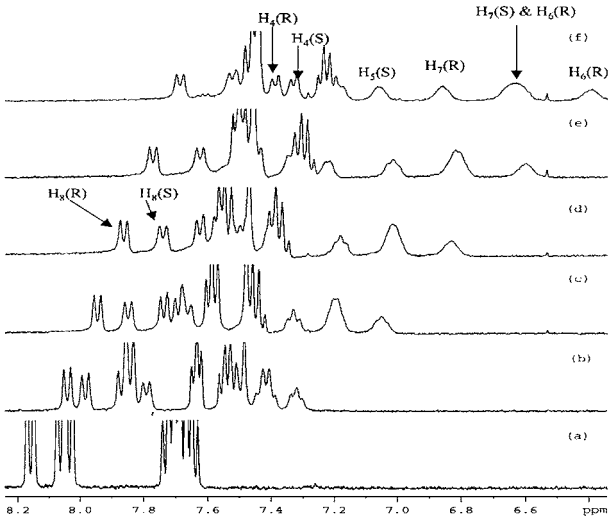

Figure 4. ^1H NMR spectra (400 MHz, D_2O, 23 °C) of (a) **3** (10 mM) with added amounts of **1** at (b) 2, (c) 4, (d) 6, (e) 8, and (f) 10 mM.

Job plots indicate a 1:1 stoichiometry of the complex of propranolol hydrochloride (**4**) with **1**. The association constants for *R*- and *S*-**4** (Table 1) with **1** are larger than

those reported for compounds with a phenyl ring.[9] The H_4, H_5, H_6, and H_7 resonances of **4** exhibit shifts in the presence of **1** that are quite large and similar in magnitude (Figure 2). The shifts of the H_2 and H_7 resonances are smaller, and the shift of H_8 in the presence of **1** is the smallest of the aromatic hydrogen atoms. The pattern of shifts in the spectrum of **4** with **1** is quite different from those in the spectrum of **3** with **1**. For **4**, the shifts are consistent with the association geometry illustrated in Figure 4c and the graphical abstract, in which both rings of the naphthyl group are inserted into the cavity. Steric effects caused by the larger aliphatic substituent of **4** compared to **3** are most likely responsible for the different orientation of the two compounds in the cavity of **1**, although differences in the dipole−dipole interactions of the substituent groups with the proline and resorcinol hydroxyl residues cannot be ruled out as a causative factor. It is especially interesting to find that a naphthyl ring can fit into the cavity of **1** in the manner observed for **4**.

Indole rings such as that found in tryptophan also form inclusion complexes with **1**. A series of spectra for tryptophan methyl ester hydrochloride (**5**) with increasing concentrations of **1** is provided in the Supporting Information. Large upfield shifts are observed for H_1, H_2, H_3, and H_4 (Figure 2), and four of the five aromatic resonances exhibit enantiomeric discrimination (Table 2). The methine and methoxy resonances shift much less than the aromatic resonances, yet also exhibit enantiomeric discrimination. Job plots show that **5** forms a 1:1 complex with **1**, and the association constant for the L-enantiomer is considerably larger than that for the D-enantiomer (Table 1).

A noteworthy observation is the difference in shift order between the L- and D-enantiomers for several of the resonances in the presence of **1**. For H_2, H_4, and H_6, the resonances of the D-enantiomer shift further in the presence of **1** than that of the L-enantiomer, whereas the opposite order is observed for H_1 and the methoxy resonance. This implies that the diastereomeric nature of the host−guest complexes of the two enantiomers with **1** is more significant in causing the enantiomeric discrimination than the inequivalence in association constants.

The pattern of shifts for **5** with **1** is consistent with a geometry in which the phenyl ring inserts into the cavity of **1** as shown in Figure 3d. Similar to the situation with **3**, the somewhat larger shift of H_4 relative to H_1 might indicate that the ring is slightly tipped when inserted into the cavity. The geometry of the complex between **5** and **1** is more similar to that of **3** than that of **4**. Presumably the repulsive forces of the lone pair on the nitrogen atom in the indole ring inhibit insertion of the heterocyclic ring of **5** into the cavity of **1**.

The shifts in the NMR spectrum of the sodium salt of tryptophan (**6**) in the presence of **1** are somewhat less than those in the spectrum of **5** (Figure 2), although the relative magnitudes of the shifts suggest that the geometries of association of **6** and **5** with **1** are similar. Addition of **6** (10 mM) to **1** (5 mM) causes the aliphatic CH and CH_2 resonances of **6** to shift upfield by approximately 0.5 and 0.2 ppm, respectively. These upfield shifts are indicative of protonation of the amine functionality of **6** with likely deprotonation of proline carboxylic acid functionalities of **1**, thereby producing the zwitterionic tryptophan species in solution. The larger association constants for the enantiomers of **5** compared to **6** likely occur because the methyl ester group of **5** is less favorably solvated in water than the zwitterionic form of **6**, but ion pairing effects may be significant as well.[13]

Of further interest is the comparison of the enantiomeric discrimination of **5** and **6** in the presence of **1**. Whereas the spectrum of **5** with **1** shows considerable enantiomeric discrimination for all but one of the aromatic resonances, the spectrum of **6** with **1** only shows a slight degree of enantiomeric discrimination for H_1 and H_4. Even more interesting are the association constants of the L- and D-enantiomers of **6** with **1** (Table 1). In this case, the D-enantiomer of **6** has the higher association constant with **1**, which is the opposite of what was found with **5**. The importance of the aliphatic substituent group and potential ion-pairing interactions in influencing the extent of enantiomeric discrimination of guest compounds in the presence of **1** is apparent when comparing the results with those of **5** and **6**.

Suitable chiral NMR solvating agents for water-soluble substrates are relatively uncommon, and are mostly limited to cyclodextrins[2] and water-soluble lanthanide complexes.[1] The shifts with **1** are much larger than those with cyclodextrins and avoid the paramagnetic line broadening caused by lanthanide shift reagents. Compound **1** is an important chiral solvating agent to consider for water-soluble compounds that contain phenyl and bicylic aromatic rings.

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for **2**, **3**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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