Chiral Host–Guest Interaction. A Water-Soluble Calix[4]resorcarene Having L-Proline Moieties as a Non-Lanthanide Chiral NMR Shift Reagent for Chiral Aromatic Guests in Water

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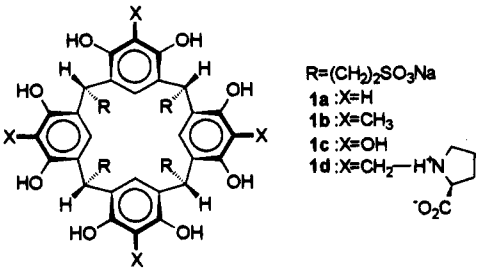
Chiral NMR shift reagents provide a convenient method for the determination of enantiomeric purity and absolute configuration of chiral molecules. A typical example is the paramagnetic lanthanide metal complexes, especially those of Eu^{3+} and Pr^{3+}, having chiral ligands such as camphor derivatives (for use in aprotic solvents)[2] and propylenediamine tetraacetate (for use in water).[3] They give rise to either contact- or pseudocontact-shifted NMR resonances for the substrate bound to the metal center. The shifts are dependent on the chirality of the substrate so as to allow a resolution of enantiomeric resonances. The resolution, however, can be very poor because of line broadening.[2,4]

Water-soluble derivatives **1a–c** of calix[4]resorcarene (resorcinol cyclic tetramer) bind a variety of guest molecules such as mono– and polyols including sugars,[5,6] nucleosides and nucleotides,[5] amino acids,[7] and alkylammonium salts[6] in water. The bound guests exhibit significant ^{1}H NMR upfield shifts due to the ring-current effects of host **1**; the complexation-induced shifts at saturation binding usually fall in the range of 1–3 ppm[5,8] and in some cases exceed 3 ppm.[9–11] Meanwhile, Matsushita and Matsui reported the aminomethylation of calix[4]resorcarene using various secondary amines including L-proline under Mannich conditions.[12] We applied this method to compound **1a**. We report here that the resulting chiral tetra-L-prolinylmethyl derivative **1d** can be used as a chiral NMR shift reagent for aromatic guest molecules in water.[13]

Compound **1d** was obtained from **1a** in a yield of 70%. The ^{1}H NMR spectrum (D_2O) showed the equivalence of the four benzene rings, the four methine groups, and the four prolinylmethyl moieties of **1d**. The IR spectrum (KBr) indicated a zwitterionic nature (NH^+ and CO_2^-) of the proline residue. The CD spectrum (H_2O) showed a positive Cotton effect at 304 nm, indicating that the aromatic cavity of **1d** is in fact in a chiral environment.



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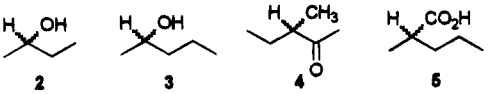

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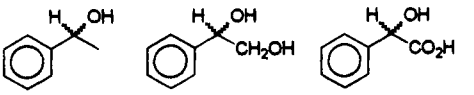

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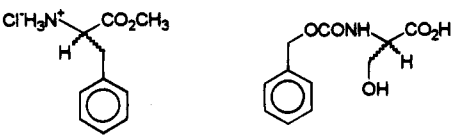

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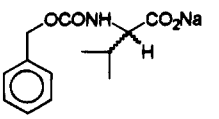

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Host **1d** binds aliphatic alcohols, ketones, and carboxylic acids in a similar manner as host **1a–c**.[5] Figure 1 shows the ^{1}H NMR spectra for 2-butanol (**2**) (10 mM) as a racemic mixture in the absence (a) and presence (b) of **1d** (40 mM). All resonances undergo complexation-induced upfield shifts, while none of them exhibits resolution for enantiomers. This is also true for 2-pentanol (**3**) and 3-methyl-2-pentanone (**4**). In Figure 2 are shown the spectra for 2-methylpentanoic acid (**5**, racemic). In the presence of the host (b), the methyl protons at asymmetric 2-C appear as a pair of doublets, corresponding to the respective enantiomers.

The resolution of resonances for enantiomers turned to be much more satisfactory for aromatic guests such as 1-phenylethanol (**6**), phenylethane–1,2–diol (**7**), mandelic acid (**8**), phenylalanine methyl ester hydrochloride (**9**), *N*-Z-serine (**10**; Z = benzyloxycarbonyl), and *N*-Z-valine sodium salt (**11**). In Figure 3 are shown, as an example, a set of spectra in the aromatic region for guest **10**. The aromatic-proton resonances of free guest (a) not only undergo complexation-induced shifts but also exhibit resolution for the enantiomers (b), as confirmed by examining the spectrum of an optically pure enantiomer (c). In Table 1 are shown the NMR data including complexation-induced shifts (a negative value indicates

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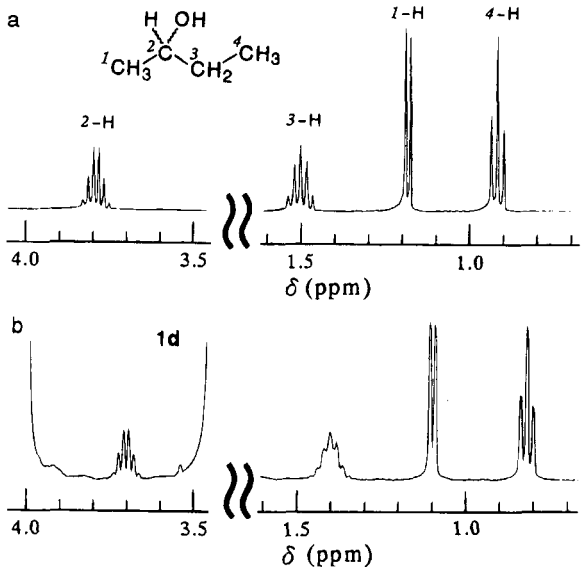

Figure 1. ^{1}H NMR spectra of 2-butanol (**2**, racemic, 10 mM) in the absence (a) and presence (b) of host **1d** (40 mM) in D_2O at 25 °C.

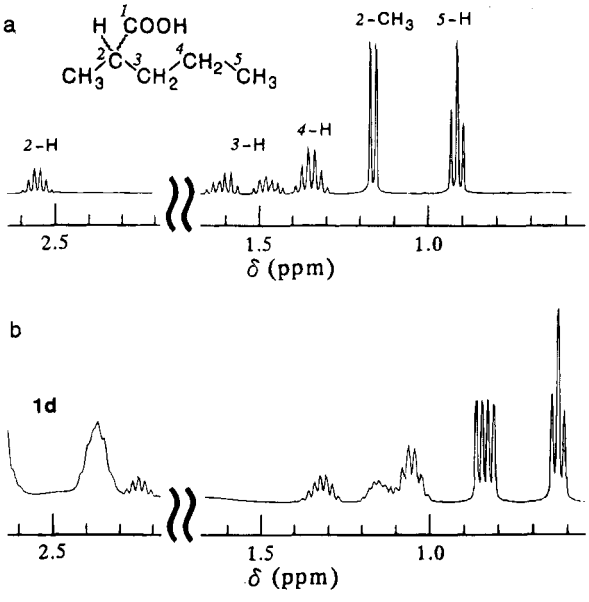

Figure 2. ^{1}H NMR spectra of 2-methylpentanoic acid (**5**, racemic, 10 mM) in the absence (a) and presence (b) of host **1d** (40 mM) in D_2O at 25 °C.

an upfield shift) $\Delta\delta = \delta - \delta_f$ and the extents of enantiomer resolution $\Delta\Delta\delta = \Delta\delta_S - \Delta\delta_R$, where δ and δ_f are chemical shifts of a particular proton in the guest (10 mM) in the presence (40 mM) and absence of host **1d**, respectively. The absolute values of $\Delta\delta$ with respect to enantiomers are $S \geq R$ for guests **6**, **8**, **10**, and **11** but $R \geq S$ for guests **7** and **9**. With respect to various types of protons in a guest, $|\Delta\delta|$ decrease in the order para > meta > ortho > nonaromatic. Clearly, the aromatic cavity of host **1d** preferentially incorporates the aromatic ring of a guest with its para-proton pointing to the bottom of the cavity. On the other hand, the enantiomer resolutions $|\Delta\Delta\delta|$ of the aromatic protons decrease in the order ortho > meta > para, i.e, the order of increasing distances from the chiral center. Guest **9** behaves atypically here again, giving the reverse order para > meta > ortho.

Selected guests such as **6**, **8**, and **10** (1.5 mM) were subjected to full NMR titration. Figure 4 shows how the

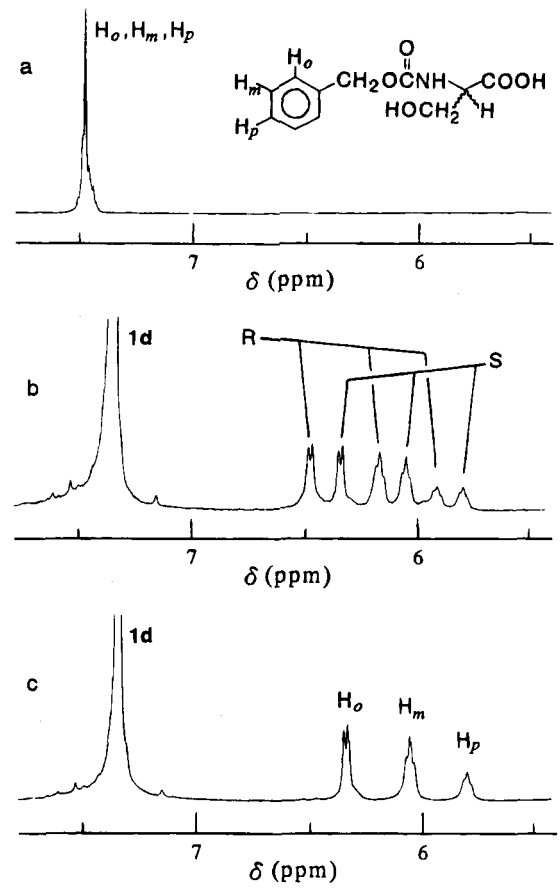

Figure 3. ^{1}H NMR spectra (aromatic region) of *N*-Z-serine (**10**, racemic, 10 mM) in the absence (a) and presence (b) of host **1d** (40 mM) in D_2O at 25 °C and that of optically pure (*S*)-**10** (10 mM) in the presence of **1d** (40 mM) (c).

chemical shifts for the ortho−, meta−, and para-protons of two enantiomers of guest **10** change with changing [**1d**]. The data are consistent with a 1:1 host−guest complexation. The binding constants (K) and the complexation-induced shifts at saturation binding ($\Delta\delta_{sat}$), as determined by Benesi−Hildebrand analysis, are K_S = 70.1 and K_R = 56.0 M^{-1} and $\Delta\delta_{sat.} = -1.69$ (*o*), −2.13 (*m*), and −2.49 (*p*) ppm, respectively, for the *S* enantiomer and $\Delta\delta_{sat.} = -1.61$ (*o*), −2.12 (*m*), −2.49 (*p*) ppm, respectively, for the *R* enantiomer. The binding constants for guests **6** and **8** are also shown in Table 1. The enantioselectivities K_S/K_R are moderate at best.[14]

In summary, host **1d** can be used as a non-lanthanide chiral NMR shift reagent for chiral aromatic guests in water.[13] Although the enantioselectivity is not high, a pair of enantiomers show readily distinguishable NMR shifts for aromatic protons upon complexation.

Experimental Section

^{1}H NMR spectra at 400 MHz were taken with a JEOL JNM-EX 400 spectrometer at 25 °C; HDO (δ_H = 4.80) in D_2O was used as an internal standard. IR and CD spectra were obtained with JASCO IR-810 and JASCO J-500C spectrophotometers, respectively.

Compound **1d** was prepared by a slight modification of the method of Matsushita and Matsui[12] for the aminomethylation of calix[4]resorcarene. Thus, a solution of **1a** (500 mg, 0.45

(14) For an excellent recent review on enantio- and diastereoselective host−guest complexation, see: Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383.

Table 1. ^{1}H NMR Data and Binding Constants for the Complexation of Aromatic Guests with Host 1d in D_2O at 25 °C

		NMR data[a]						binding constants[b]	
		aromatic H							
guest		ortho	meta	para	CH	CH_2	CH_3	K/M^{-1}	K_S/K_R
6	$\Delta\delta_S$	−0.807	−1.142	−1.400	−0.438		−0.269	38.6	
	$\Delta\delta_R$	−0.751	−1.100	−1.381	−0.388		−0.237	35.4	1.09
	$\Delta\Delta\delta$	−0.056	−0.042	−0.019	−0.050		−0.032		
7	$\Delta\delta_S$	−0.750	−1.10	−1.43	*c*	*c*			
	$\Delta\delta_R$	−0.769	−1.10	−1.43	*c*	*c*			
	$\Delta\Delta\delta$	0.019	~0	~0					
8	$\Delta\delta_S$	−0.839	−1.206	−1.432	−0.713			36.6	1.10
	$\Delta\delta_R$	−0.783	−1.162	−1.416	−0.633			33.4	
	$\Delta\Delta\delta$	−0.056	−0.044	−0.016	−0.080				
9	$\Delta\delta_S$	−0.363	−0.644	−0.874	*c*	*c*	−0.14		
	$\Delta\delta_R$	−0.393	−0.706	−0.951	*c*	*c*	−0.14		
	$\Delta\Delta\delta$	0.030	0.062	0.077			~0		
10	$\Delta\delta_S$	−1.283	−1.593	−1.846	*c*	*c*		70.1	1.25
	$\Delta\delta_R$	−1.160	−1.495	−1.755	*c*	*c*		56.0	
	$\Delta\Delta\delta$	−0.123	−0.098	−0.091					
11	$\Delta\delta_S$	−1.114	−1.385	−1.60	*c*	*c*	~0		
	$\Delta\delta_R$	−1.052	−1.368	−1.60	*c*	*c*	~0		
	$\Delta\Delta\delta$	−0.062	−0.017	~0			~0		

[a] [guest] = 10 mM and [**1d**] = 40 mM. [b] [guest] = 1.5 mM. [c] Not observed due to overlap with host proton resonances.

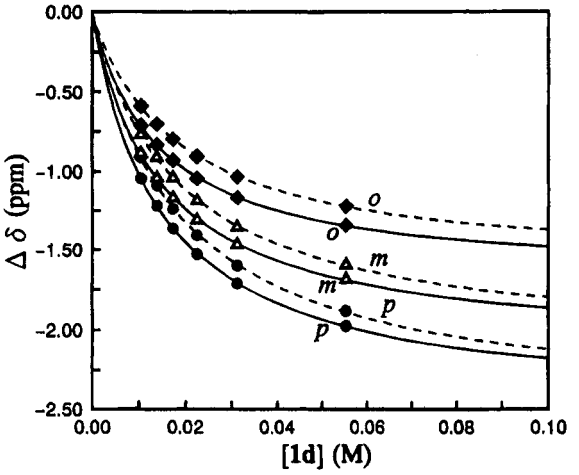

Figure 4. Plots of complexation-induced shifts ($\Delta\delta$) for the aromatic ortho-, meta-, and para-protons of *S*-enantiomer (—) and R-enantiomer (- - -) of guest **10** (1.5 mM) as functions of [**1d**] in D_2O at 25 °C.

mmol), L-proline (260 mg, 2.25 mmol), and formaldehyde (0.22 mL of a 35% aqueous solution, 2.70 mmol) in water (6 mL) was stirred for 48 h at room temperature under nitrogen. Most of the water was removed *in vacuo*. Methanol (50 mL) was added to the residue. The precipitates that resulted were recovered by filtration, washed with methanol, and recrystallized from water–methanol to give very hygroscopic white powders of compound **1d** (580 mg, 70%): mp 175 °C dec; ^{1}H NMR (D_2O) δ 1.87, 2.04, and 2.45 (m, 16 H), 2.62 (q, 8 H), 2.93 (t, 8 H), 3.17 and 3.49 (m, 8 H), 4.05 (dd, 4 H), 4.46 (s, 8 H), 4.71 (t, 4 H), 7.22 (s, 4 H); IR (KBr) 3425 (O—H), 2600 (N^+—H), 1620 and 1400 (CO_2^-), 1180 and 1050 cm^{-1} (S=O); CD (H_2O) $[\theta] = 2.3 \times 10^3$ deg M^{-1} cm^{-1} (λ_{ext} 304 nm). Anal. Calcd for $C_{60}H_{72}N_4O_{28}S_4Na_4 \cdot 13H_2O$: C, 43.26; H, 6.54; N, 3.36. Found C, 43.25; H, 6.42; H, 3.47.

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