10-Hydroxyacenaphtho[1,2-*b*]quinoline (13): light yellow solid; mp 309–310 °C (ethyl acetate); yield 92%; ^{1}H NMR (DMSO-d_6) δ 7.4–8.5 (m, 10 H), 8.95 (s, 1 H) ppm.

Anal. Calcd for $C_{19}H_{11}NO$: C, 84.7; H, 4.1; N, 5.2. Found: C, 84.6; H, 4.0; N, 5.0.

General Method for the Preparation of Quinones 7 and 14. To an aqueous solution of Fremy's salt $(SO_3K)_2NO$ (3.9 mmol) in 100 mL of 0.16 M KH_2PO_4 at 5 °C was added dropwise with stirring a solution of the phenol (6 or 13) in 50 mL of HMPA. The mixture was stirred at 5–7 °C for 2–2.5 h and then left overnight at 0 °C. The solid separated was filtered, washed well with water, and dried.

10,11-Dioxo-10,11-dihydrodibenz[*a*,*h*]acridine (7): purple violet solid; mp 235–237 °C dec; yield 97%; IR (KBr) ν_{max} 1615, 1645, 1660 cm^{-1}.

Anal. Calcd for $C_{21}H_{11}NO$: C, 81.5; H, 3.5; N, 4.5. Found: C, 81.3; H, 3.4; N, 4.2.

10,11-Dioxo-10,11-dihydroacenaphtho[1,2-*b*]quinoline (14): brick red solid; mp >350 °C; yield 100%; IR (KBr) ν_{max} 1615, 1640, 1655 cm^{-1}.

Anal. Calcd for $C_{19}H_9NO_2$: C, 80.5; H, 3.2; N, 5.0. Found: C, 80.3; H, 2.9; N, 4.7.

General Procedure for the Preparation of the *trans*-Dihydrodiols 8 and 15. To a suspension of the quinone (7 or 14) (0.3 mmol) in ethanol (15 mL) was added an excess of $NaBH_4$ (200 mg). The mixture was stirred at 25 °C for 48 h with a constant blow of oxygen and keeping the volume of solvent constant by addition of ethanol. The color of the reaction mixture changed from orange to faint yellow during this time. After decomposing the complex with ice–water, the organic portion was extracted with an ethyl acetate–ether mixture, washed with water, and dried ($MgSO_4$). Removal of solvent in vacuo followed by purification by preparative TLC (silica gel/ethyl acetate–ether, 1:1) furnished the *trans*-diols.

***trans*-10,11-Dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (8)**: faint yellow solid; mp 226–229 °C (lit.[10] mp 230–231 °C; yield 25%; MS (*m*/*e*) 313 (M$^+$); ^{1}H NMR (DMSO-d_6 + D_2O) δ 4.3 (d, 1 H), 4.9 (d, 1 H), 6.1 (dd, 1 H), 7.6–8.5 (m, 8 H), 8.9 (d, 1 H), 9.7 (s, 1 H) ppm.

***trans*-10,11-Dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]quinoline (15)**: faint yellow solid; mp 225–227 °C; yield 40%; ^{1}H NMR (DMSO-d_6 + D_2O) δ 4.1 (m, 1 H), 5.2 (d, 1 H, J = 7 Hz), 6.5 (m, 1 H), 7.2 (d, 1 H, J = 7 Hz), 7.3–8.5 (m, 5 H), 8.6 (d, 1 H, J = 6 Hz), 9.1 (s, 1 H) ppm.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 79.4; H, 4.5; N, 4.9. Found: C, 79.1; H, 4.3; N, 4.5.

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A Case of Self-Induced Anisochrony in the Proton Nuclear Magnetic Resonance Spectra of 1,5-Benzothiazepines

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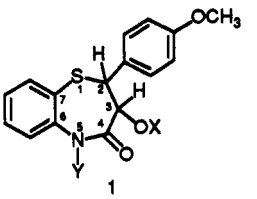
The NMR spectra of enantiomers may be different when they are of solutions in a nonracemic chiral solvent[1a] or of solutions in an achiral solvent containing a nonracemic chiral additive, such as a lanthanide shift reagent.[1b] In the absence of any added nonracemic chiral substance, the notion that enantiomers and racemates show identical NMR spectra holds true only at high dilution. To the extent that there is some degree of solute aggregation, they may exhibit different NMR spectra.[1a,2-8] Generally, the differences under such circumstances are so small that they are not detectable.

Now, we report a new example of the self-discrimination of enantiomers which can be conveniently used for the determination of the enantiomeric purity of 1,5-benzothiazepines 1 (Figure 1) by ^{1}H NMR methods. In this case, enantiomeric purity is of particular importance because



1

X=OCCH$_3$	Y=CH$_2$CH$_2$N(CH$_3$)$_2$·HCL	Cis	2S,3S	(+)-1a
X=H	Y=H	Cis	2S,3S	(+)-1b
X=H	Y=H	Cis	2R,3R	(-)-1b
X=OCCH$_3$	Y=H	Cis	2S,3S	(+)-1c
X=OCCH$_3$	Y=H	Cis	2R,3R	(-)-1c
X=H	Y=CH$_3$	Cis	2S,3S	(+)-1d
X=H	Y=CH$_3$	Cis	2R,3R	(-)-1d
X=H	Y=H	Trans	2S*,3R*	(+)-1e
X=H	Y=H	Trans	2S*,3R*	(-)-1e

Figure 1.

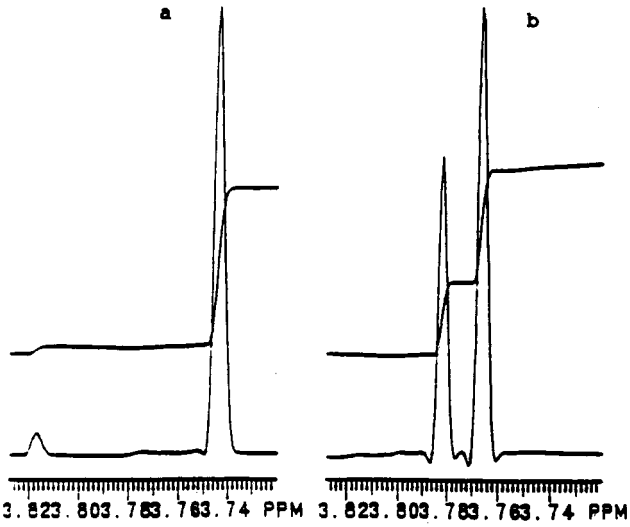


Figure 2. *p*-Methoxy proton resonances of (a) 95% (+)-**1b**, 5% (-)-**1b**, and (b) 60% (+)-**1b**, 40% (-)-**1b**.

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Table I. ^{1}H NMR Spectral Data (300 MHz) of Pure (+)-1b, Pure (−)-1b, and Mixtures of Different Concentrations in $CDCl_3$ at 22 °C. Chemical Shifts (δ, ppm) of the *p*-Methoxy Group Protons

	chemical shift: δ, ppm				
(+)-1b:(−)-1b	9.3×10^{-2} M	4.6×10^{-2} M	9.3×10^{-3} M	9.3×10^{-4} M	9.3×10^{-5} M
100:0	3.741	3.758	3.797	3.816	3.819
90:10	3.747, 3.811	3.763, 3.812	3.790, 3.817	3.813, 3.820	3.819
80:20	3.753, 3.800	3.765, 3.805	3.800, 3.816	3.813, 3.818	3.820
50:50	3.774	3.783	3.808	3.818	3.820
20:80	3.800, 3.755	3.806, 3.769	3.815, 3.799	3.819, 3.814	3.819
10:90	3.810, 3.748	3.810, 3.760	3.817, 3.800	3.821, 3.814	3.819
0:100	3.741	3.756	3.798	3.817	3.820

the 1,5-benzothiazepines (+)-**1b**[9] and (+)-**1c** (Figure 1) are intermediates in the synthesis of diltiazem [(+)-**1a**], an enantiomerically pure drug with calcium antagonist activity.[9]

Enantiomerically pure (+)-**1b** or (−)-**1b** and a racemic mixture of the two show nonequivalence of ^{1}H NMR spectra at the same concentration in chloroform-*d* solution (Table I). When the proportions of (+)-**1b** and (−)-**1b** in a mixture deviate from 1:1, two sets of signals appear for both the *p*-methoxy group protons and the aromatic protons. The ratio of the integrals of the two sets of signals gives the enantiomeric ratio. The signals that best define the nonequivalence of the spectra of the enantiomers are those due to the *p*-methoxy group protons (Figure 2), for those of the aromatic protons overlap. The chemical shifts of the protons of the *p*-methoxy group of the pure enantiomers, the racemate, and mixtures thereof, recorded at different concentrations, are shown in Table I.

An analysis of the data reveals the following. (i) The difference in the values of the chemical shift (Δδ) of the two *p*-methoxy group proton signals decreased as the mixture approached racemic composition. (ii) Δδ was concentration dependent: at higher concentrations, correspondingly larger Δδ were observed, whereas at high dilution (9.3×10^{-5} M), Δδ was too small to be detected (Table I). (iii) The chemical shift of the protons of the racemic mixture differed from that of the pure enantiomers. (iv) The pure enantiomers and mixtures equally enriched by one enantiomer or the other showed identical spectra: the signals due to the protons of the enantiomer present in the higher concentration always appeared at higher field. (v) There was a linear relationship ($R = 0.999$) between enantiomeric purity and Δδ[10] (Table I).

These findings have analytical significance: for a saturated (9.3×10^{-2} M) solution in $CDCl_3$ of a mixture of (+)-**1b** and (−)-**1b**, the concentration ratio of the enantiomers could be determined from 99:1 to 54:46 with an accuracy of ±1. The same result was obtained by the use of a chiral shift reagent like $Pr(hfbc)_3$. However, the reagent caused splitting of the *p*-methoxy group proton signals, with broadening of the signals.

The phenomenon was strongly solvent dependent. Halogenated solvents (CCl_4, CD_2Cl_2, $CDCl_3$) and aromatic solvents (benzene, toluene) were useful for the detection of the phenomenon, but $CDCl_3$ was the solvent of choice for solubility reasons. In contrast, the phenomenon was not observed in *N*,*N*-dimethylformamide-*d*, dimethylsulfoxide-d_6, or methanol-*d*.

We attribute the manifestation of two signals to a fast exchange of monomers among dimers of the type *RR*, *RS*, and *SS*. Thus, at a slow exchange rate, there should be two signals, one (A) for the hetero dimer RS (or its equivalent, *SR*) and one (B) for the sum of the homo dimers *RR* + *SS*. In this case, integration of the signals would not match the relative proportions of *R* and *S*. When, on the other hand, the exchange rate is fast, there is a coalescence of peaks proportional to their contribution to each of the static peaks. Because peak B, the peak due to the homo dimer, is the sum of the signals for *RR* and *SS*, and because the spectrum of *R* (or *S*) at a fast exchange rate would be affected only by the equilibrium *RS* ⇄ *RR* (or *SR* ⇄ *SS*), it can be seen that, for an unequal amount of *R* and *S*, two peaks would be predicted for the fast exchange limit. Integration of the signals would now reflect the relative proportions of *R* and *S*.

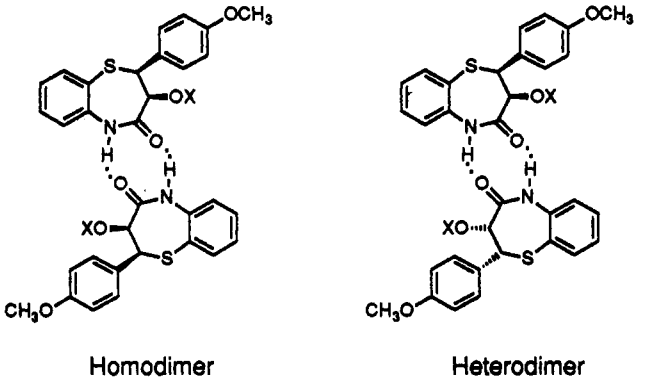

Figure 3.

In order to obtain information on the influence of substituents on this self-discrimination, we investigated the ^{1}H NMR behavior of the *O*-acetyl [(+)- and (−)-**1c**] and *N*-methyl [(+)- and (−)-**1d**] derivatives (Figure 1). Compounds **1c** showed the phenomenon, but it was of reduced magnitude. Thus, for a 9.3×10^{-2} M solution in $CDCl_3$ at 22 °C, $\Delta\delta = 0.03$ ppm. In contrast, compounds **1d** did not display self-discrimination under a large variety of conditions of concentration, solvent, and temperature. The different spectroscopic behavior of **1c** and **1d** suggested that N–H, and not O–H, hydrogen bonding permitted the molecular associations depicted in Figure 3.

Moreover, solute aggregation in solution also depended on the relative configurations of C-2 and C-3. Thus, in contrast to the cis isomers [(+)- and (−)-**1b**], the trans isomers [(+)- and (−)-**1e**][11] did not display the phenomenon under a large variety of conditions.

Experimental Section

NMR spectra were recorded with a Varian XL 300 spectrometer at 300 MHz for ^{1}H and at 75.4 MHz for ^{13}C. The temperature was controlled to ±1 °C. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer 241 polarimeter. Merck silica gel (230–400 mesh) was used for flash column

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(10) In contrast to Horeau's prediction (*Tetrahedron Lett.* **1969**, 3121), a linear relationship between $[\alpha]^t_D$ and ee at a given concentration in $CHCl_3$ was found.

(11) The enantiomerically pure trans isomers (+)-**1e** and (−)-**1e** are described here for the first time (see Experimental Section). The absolute configurations (2*R*,3*S*; 2*S*,3*R*) have not been assigned.

chromatography. Melting points were determined with a Kofler apparatus and are uncorrected. Isobutane chemical ionization mass spectra were recorded at 110 eV with a Finnegan MAT 8220 instrument equipped with a Data General Nova 4X data system. References to the removal of solvents under reduced pressure mean the evaporation of the solvent at ca. 20 mmHg with a Büchi rotary evaporator. The solutions for ee determinations were prepared by mixing, or by mixing and diluting with $CDCl_3$, 9.3 $\times 10^{-2}$ M solutions of enantiomerically pure (+)-**1b** and (−)-**1b** in $CDCl_3$.

Compounds (+)-1b and (−)-1b. Compounds (+)-**1b** and (−)-**1b** were prepared by a literature method.[9] (+)-**1b**: mp 207–210 °C (lit.[9] mp 208–210 °C); $[\alpha]^{25}_D$ = +55.2° (*c* 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 4.48 (d, 1 H, B part of an AB system, J = 6.88 Hz), 5.08 (d, 1 H, A part of an AB system, J = 6.88 Hz), 6.9–7.7 (8 H, aromatic H), 8.2 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.20 (q), 57.50 (d), 69.30 (d), 113.64 (d), 123.06 (d), 126.28 (s), 126.89 (d), 127.36 (s), 130.03 (d), 131.12 (d), 134.70 (d), 140.34 (s), 159.93 (s), 173.7 (s); CI MS m/e 302 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.02; N, 4.65; O, 10.64; S, 15.93. Found: C, 63.75; H, 5.01; N, 4.63; O, 10.62; S, 15.87.

Compounds (+)-1c and (−)-1c. Acetic anhydride (1.73 g, 17 mmol) was added to a suspension of (+)-**1b** or (−)-**1b** (5 g, 16.6 mmol) in toluene (15 mL). The mixture was refluxed for 2 h. The mixture was then cooled to room temperature and was poured into 10% aqueous sodium carbonate (40 mL). The organic layer was separated, washed with water, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash chromatography to give pure (+)-**1c** or (−)-**1c** (5.14 g, 15 mmol), in 90% yield. (+)-**1c**: mp 153–155 °C (lit.[12] mp 152–153 °C); $[\alpha]^{20}_D$ = +40° (*c* 0.5; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 3.69 (s, 3 H), 5.17 (d, 1 H, B part of an AB system, J = 7.1 Hz), 5.33 (d, 1 H, A part of an AB system, J = 7.1 Hz), 6.7–7.7 (8 H, aromatic H), 8.4 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.19 (q), 54.98 (q), 54.98 (d), 71.08 (d), 113.50 (d), 123.33 (d), 126.47 (d), 126.75 (s), 126.84 (s), 130.28 (d), 130.38 (d), 134.48 (d), 140.82 (s), 159.53 (s), 169.19 (s), 169.56 (s); CI MS m/e 344 $(M + 1)^+$. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.95; H, 4.99; N, 4.08; O, 9.34; S, 18.64. Found: C, 62.07; H, 5.04; N, 4.03; O, 9.11; S, 19.35.

Compounds (+)-1d and (−)-1d. Methyl iodide (1.37 g, 9.6 mmol) was added to a stirred mixture of (+)-**1b** or (−)-**1b** (1 g, 3.32 mmol) and potassium carbonate (1 g, 7.25 mmol) in acetone (8 mL). The reaction mixture was stirred at 50 °C for 18 h. The mixture was then cooled to room temperature, poured into water (30 mL), and extracted with methylene chloride (2 × 30 mL). The combined extracts were dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave (+)-**1d** or (−)-**1d** in 95% yield. (+)-**1d**: mp 87–92 °C; $[\alpha]^{20}_D$ = +85° (*c* 0.5; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.52 (s, 3 H), 3.83 (s, 3 H), 4.37 (d, 1 H, B part of an AB system, J = 6.8 Hz), 4.95 (d, 1 H, A part of an AB system, J = 6.8 Hz), 6.9–7.7 (8 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 36.3 (q), 55.18 (q), 56.74 (d), 69.29 (d), 113.58 (d), 123.65 (d), 126.19 (s), 127.25 (d), 127.96 (s), 130.32 (d), 131.20 (d), 135.09 (d), 145.96 (s), 159.80 (s), 171.55 (s); CI MS m/e 316 $(M + 1)^+$. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.71; H, 5.43; N, 4.44; O, 10.17; S, 15.22. Found: C, 64.53; H, 5.48; N, 4.48; O, 10.12; S, 15.39.

Compounds (+)-1e and (−)-1e. Sodium bicarbonate (4.2 g, 50 mmol) and 2-aminothiophenol (31.4 g, 251 mmol) were added under nitrogen to a stirred suspension of (±)-*trans*-2,3-epoxy-3-(4-methoxyphenyl)propionic acid methyl ester (50 g, 240 mmol) in methanol (500 mL). The mixture was stirred for 3 h at room temperature and then poured into a 0.1 M potassium phosphate buffer (pH 7) (100 mL). The methanol was evaporated under reduced pressure, and the residue was diluted with water and extracted with methylene chloride (2 × 100 mL). The combined extracts were dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a solid residue (83 g, 240 mmol). Sodium hydroxide (12 g, 300 mmol) was added, with vigorous stirring, at 25 °C to a suspension of the residue (83 g, 240 mmol) in water (415 mL). The mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the mixture was extracted with methylene chloride (2 × 100 mL). Aqueous 1 N HCl (250 mL) was added to the aqueous phase, which had been diluted with water (500 mL). The precipitate that formed was collected by filtration, washed with water, and dried under reduced pressure. (*R*)-(+)-Phenylethylamine (20.8 g, 172 mmol) was added to the solid (50 g, 156 mmol) suspended in water (990 mL). The suspension was refluxed, with stirring, until a transparent solution was produced. The solution was then cooled to 20 °C over 2 h. The solid that precipitated from the cooled solution was collected by filtration and recrystallized three times from water (800 mL). Aqueous HCl, 1N (90 mL), was added to a suspension of the solid in water (1.8 L), and the suspension was stirred at room temperature for 1 h. The mixture was then filtered, and the solid that was collected was washed with water (200 mL). The solid was dried under reduced pressure to give pure *erythro*-(+)-3-((2-aminophenyl)thio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid (14 g, 44.0 mmol). An analytical sample of the acid was treated with diazomethane to give the corresponding methyl ester, which was enantiomerically pure by ^1H NMR analysis in the presence of Pr(hfbc)$_3$. A stirred suspension of the acid (14 g, 44.0 mmol) in xylene (210 mL) was refluxed for 10 h. The reaction mixture was then cooled to room temperature, and the suspended solid was collected by filtration and dried under reduced pressure to afford (−)-**1e** (9.8 g, 32.5 mmol): mp 194–200 °C; $[\alpha]^{20}_D$ = −720° (*c* 0.5; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 4.26 (d, 1 H, B part of an AB system, J = 10 Hz), 4.32 (d, 1 H, A part of an AB system, J = 10 Hz, 6.85–7.7 (8 H, aromatic H), 8.2 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.37 (q), 57.69 (d), 72.04 (d), 114.28 (d), 123.28 (d), 126.11 (s), 127.36 (d), 128.32 (d), 130.46 (d), 134.65 (s), 135.82 (d), 139.63 (s), 159.38 (s), 173.94 (s); CI MS m/e 302 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.02; N, 4.65; O, 10.64; S, 15.93. Found: C, 63.67; H, 4.99; N, 4.63; O, 10.62; S, 15.82. (+)-**1e** (mp 195–200 °C; $[\alpha]^{20}_D$ = +721° (*c* 0.5; $CHCl_3$)) was prepared in a similar manner, using (−)-(*S*)-phenylethylamine in place of (+)-(*R*)-phenylethylamine in the resolution step.

Acknowledgment. We thank Mr. R. Casagrande for technical assistance and Professor Jay S. Siegel of the University of California for stimulating discussions.

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