The First Chiral Solvating Agent (CSA) without ^{1}H NMR Signals: the Perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol. Preparation and Chiral Induction on Protonated Pirkle Alcohol

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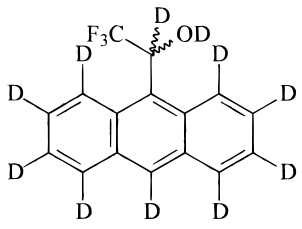
Received June 4, 1999

Chiral solvating agents[1] (CSA) are used to measure the enantiomeric composition of chiral compound samples containing unknown amounts of each enantiomer, coming from a stereoselective synthesis, a natural source, or other origins. Both enantiomers of 2,2,2-trifluoro-1-(9-anthryl)ethanol (**1**) (Pirkle alcohol)[2] have been widely used to distinguish enantiomers of several kinds of compounds: acids, alcohols, amines, epoxides, sulfoxides, lactones,[3] etc. Other anthracene derivatives containing bulky substituents, such as the *tert*-butyl group, have also been found useful.[4] Often, successful analysis of a mixture of enantiomers requires a high CSA:substrate ratio (up to 5:1 or more). Thus, in the NMR spectra, the signals from the CSA can obscure those coming from the enantiomers being analyzed.

To overcome this problem, we have synthesized a CSA devoid of any signal in its ^{1}H NMR spectrum, namely, perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol (**2**), the fully deuterated Pirkle alcohol analogue. The very low proton content (2% approximately) of **2** results in a ^{1}H NMR spectrum with very weak singlets in the aromatic region, observable only after long accumulations. Thus, the use of **2** for measuring the enantiomer ratio in real samples could benefit from a considerable sensitivity improvement via an increase of the dynamic range of the NMR detector. Formula of compound 2



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The use of deuterated Pirkle alcohol **2** for the determination of enantiomer ratios should be applicable to the same wide range of compounds successfully resolved using ordinary Pirkle alcohol. Before comparing both the protio (**1**) and the deuterio (**2**) compounds as CSA with a variety of substrates, we found that enantiopure **2** induces a rather large separation on some of the NMR signals of racemic **1** at usual concentration, although both compounds differ only in the isotopic composition. In contrast, addition of one enantiomer of ordinary Pirkle alcohol to its own racemic, under the same conditions, did not produce any enantioseparation at any temperature. The observed phenomenon would be very similar to the self-discrimination. Few examples of self-discrimination under fast exchange conditions have appeared in the literature;[5] it is considered as exceptional. The described cases are mostly due to the formation of diastereoisomeric dimers of chiral compounds, and most of them are observed at high concentration. As the difference is a manifestation of two signals in a fast exchange between monomers (enantiomers) and dimers (diastereoisomers), only for nonracemic mixtures a difference of homodimer (dimer formed by two homochiral molecules) and heterodimer is observed. In the present paper we report these results in detail.

Results and Discussion

The preparation of racemic perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol (**2**) was carried out as previously described for ordinary Pirkle alcohol.[6] Thus, reaction of perdeuterioanthracene with trifluoroacetic anhydride gave the perdeuterioanthryltrifluoromethyl ketone (**3**) in a quantitative yield. Reduction of **3** with deuterated lithium aluminum hydride, also quantitative, furnished the desired racemic compound, **2**. Direct resolution of racemic alcohol **2** into its enantiomers was unsuccessfully attempted by means of preparative HPLC on a chiral stationary phase. Finally, the acetate derivatives of **2** (**4**) (prepared quantitatively by treatment with acetic anhydride) were separated, using a semipreparative Whelk-O1 column, with a flow of 3 mL/min of a mixture of hexane/isopropyl alcohol (97:3), showing the same retention times as ordinary Pirkle alcohol acetates. The first eluted compound was the (*R*)-(−)-acetate (**4R**), while the (*S*)-(+)-acetate (**4S**) was obtained 9.8 min later.

Saponification of each ester with 1 M K_2CO_3 gave the enantiomers of perdeuterio-2,2,2-trifluoro-1-(9-anthryl)-ethanol[7] **2R** and **2S** in 91% yield.

Proton NMR spectra of common Pirkle alcohol **1** (5 mg, 0.018 mmol, 3.6×10^{-2} M), containing varying amounts of the perdeuterated enantiomer **2S**, were recorded at 400 MHz in $CDCl_3$, under saturation of the exchanging hydroxyl signal. Figure 1 shows the evolution of the signals of protons H_{10} and H_{11} for racemic **1** at increasing concentrations of **2S**. As the ratio **2S**/**1** increases, the H_{11} quartet splits into two quartets of increasing separation. Analogously, the H_{10} singlet gives rise to two overlapping

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10.1021/jo990917k CCC: $18.00
Published on Web 08/21/1999

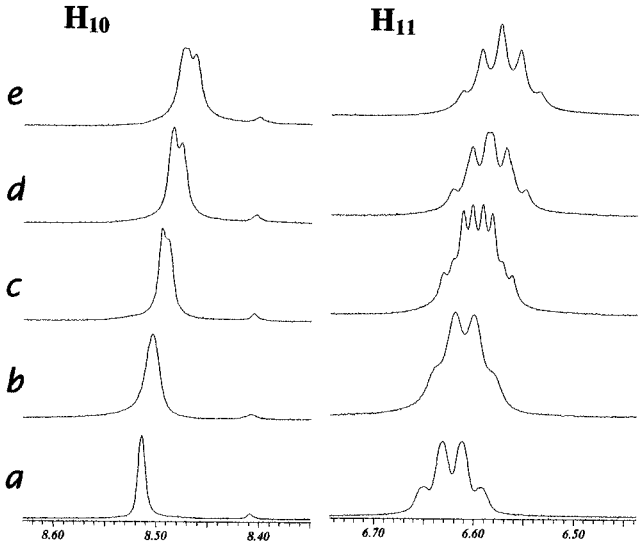

Figure 1. Part of the ^{1}H NMR spectra of **1**(**R,S**) at 300 K: (a) without **2S**, (b) after addition of 0.72 equiv of **2S**, (c) after addition of 1.45 equiv of **2S**, (d) after addition of 2.18 equiv of **2S**, (e) after addition of 2.90 equiv of **2S**.

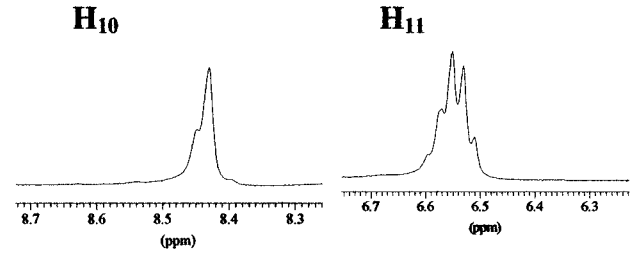

Figure 2. Part of the ^{1}H NMR spectra of a mixture of **1R** and **1S** (1:3) at 300 K after addition of 2.90 equiv of **2S**.

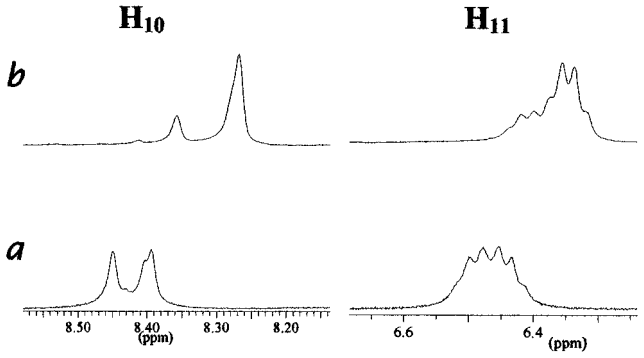

Figure 3. Part of the ^{1}H NMR spectra of **1** at 230 K (a) of a racemic mixture, **1**(**R,S**), after addition of 1.4 equiv of **2S** and (b) of a enriched mixture, **1R**:**1S** = 1:3, after addition of 2.9 equiv of **2S**.

singlets corresponding to the two enantiomers of **1**. No significant increase in the separation of two signals was observed when more then 3 equiv of **2S** was added (Figure 4).

As partially protonated compounds are present, when high concentrations are used, their resonances are discernible, principally at H_{10} absorption.

To assign the now resolved H_{10} and H_{11} signals to each enantiomer of Pirkle alcohol **1**, 1 equiv of enantiopure **1S** was added to a sample containing 1 equiv of racemic **1** and 2.90 equiv of **2S**. The resulting spectrum, shown in Figure 2, displayed resolved pairs of signals of unequal

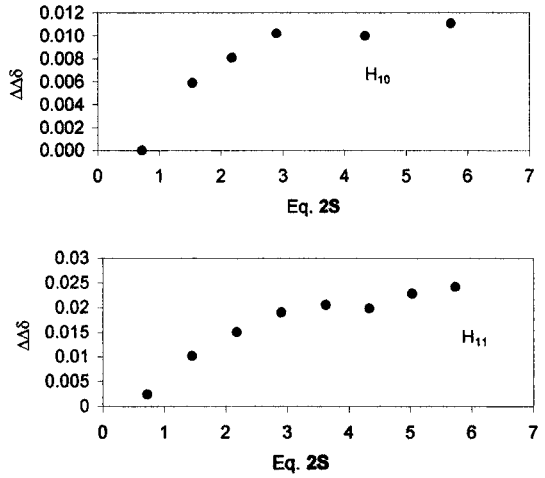

Figure 4. Evolution (at 300 K) of the difference of the chemical shifts between **1R** and **1S** vs the concentration of **2S**.

intensities, from which the chemical shifts for enantiomers **1S** ($\delta(H_{10})$ = 8.44 ppm; $\delta(H_{11})$ = 6.55 ppm) and **1R** ($\delta(H_{10})$ = 8.46 ppm; $\delta(H_{11})$ = 6.58 ppm) could be assigned.

Lowering the temperature resulted in a considerable increase of these chemical shift differences, as shown in Figure 3. At 230 K the sample consisting of racemic **1** with 1.4 equiv of **2S** already showed two perfectly resolved singlets for H_{10}. The same was observed for the sample consisting of a 1:3 mixture of **1R/1S** with 2.9 equiv of **2S**. These effects result from the temperature dependence of two processes, namely, the intermolecular association and the rotation around the $C_{10}-C_{11}$ bond. The dynamics of both should have a strong influence in the formation and stability of the complex responsible for the chiral induction.

To the best of our knowledge, the above results, the preparation of a perdeuterated chiral solvating agent and the chiral induction of a compound by the corresponding perdeuterated isotopomer, have been observed and reported here for the first time. This last distinction seems to be very near to chiral autorecognition between the enantiomers of a molecule. The concentration used in the NMR experiment, the same as that of a routine spectrum, and the observation of the separation for any relation of enantiomers (including the racemic mixture), converts the described fact as an important one. Indeed, the *RS* and *RR* (or *SS*) dimers of a compound can be regarded as diastereoisomeric; one can think about their possible differentiation. Since, under the same conditions, the ^{1}H NMR spectrum of a nonracemic mixture of the enantiomers of Pirkle alcohol does not show any signal resolution, it is concluded that the isotopic enrichment itself is responsible for the different behavior of the aggregate species, because of the atomic or molecular weight differences, and ruling out electronic reasons. Parameters such as the carbon−hydrogen bond length, shorter for the deuterium isotope, or the force of the hydrogen bond, or other factors, can determine these phenomena.

The observed chemical shift is the weighted average between those of the free species and the complex. In the addition of **2S** to racemic **1**, the corresponding protons of **1S** are more shielded than those of **1R**. Considering a similar geometry for the association, we can suppose that complex **1S2S** is more stable than **1R2S**.

The crystalline structure of the enantiomer **1S** and racemic **1(R,S)** has been published[8] showing several differences in the packing of two crystals. In all cases (but not in all molecules of the crystal) one can find a parallelism between the aromatic rings and some nonclassical hydrogen bonding (hydroxylic proton/fluorine or hydroxylic proton/π system).

In solution, the structure and dynamics of the complex cannot be easily solved. To explain the large change in the chemical shifts of protons H_{10} and H_{11} (exalted at low temperatures) and any additional changes, one should consider the planar association between two anthracene rings in a face to face $\pi-\pi$ stacking association and, possibly, in a head to tail fashion relative to central substituents. Of course, differential properties of the $\pi-\pi$ interactions[9] of deuterated compounds should be assumed to justify the chiral induction.

Experimental Section

NMR spectra were recorded at 400.13 MHz for ^{1}H and 61.40 MHz for ^{2}H. The temperature was controlled to 0.1 °C. Chemical shifts are reported in parts per million relative to internal TMS for proton and to external $CDCl_3$ for deuterium. Chiral semipreparative HPLC is carried out using a (R,R) Whelko-O1 column (250 mm × 10 mm). The elemental analysis could be modified by the presence of the residual protonated molecules.

Perdeuterio-9-anthryltrifluoromethyl Ketone (3). Perdeuterated anthracene (0.50 g, 2.66 mmol) and trifluoroacetic anhydride (1.67 g, 7.95 mmol) were added to 5 mL of deuterated benzene in a 50 mL pressure resistant reactor. The mixture is heated at 200 °C and after 8 days is cooled, the reactor is carefully opened, and the mixture is purified by flash column chromatography and crystallized in methanol, obtaining 0.74 g (2.60 mmol, 98% yield) of **3**: mp 78−81 °C; IR (KBr) 2282, 1744 cm^{-1}; residual[10] ^{1}H NMR ($CDCl_3$) δ (ppm) 7.53 (s, $H_{3/6}$, 14%), 7.57 (s, $H_{2/7}$, 14%), 7.73, (s, $H_{1/8}$, 19.5%), 8.07 (s, $H_{4/5}$, 19%), 8.62 (s, H_{10}, 33.5%); ^{2}H NMR ($CHCl_3$) δ (ppm) 7.54 ± 0.11 ($D_{3/4/6/7}$), 7.72 ± 0.08 ($D_{1/8}$), 8.06 ± 0.07 ($D_{4/5}$), 8.61 ± 0.06 (D_{10}); MS (EI) *m/e* (%) 283 (30), 214 (100), 186 (77), 158 (24). Anal. Calcd for $C_{16}D_9F_3O$: C, 67.83; D, 6.39. Found: C, 67.63; D, 6.48.

(±)-Perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol (2). A solution of 1.00 g (3.53 mmol) of perdeuterio-9-anthryltrifluoromethyl ketone (**3**) in 25 mL of ether was added to a mixture of 0.030 g (7.15 mmol) of $AlLiD_4$ in 100 mL of ether under nitrogen. After 1 h, the mixture was treated with ethyl acetate and water. The organic phase was dried with $MgSO_4$, evaporated, and crystallized with methanol, obtaining 0.95 g (95% yield) of perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol (**2**): mp 124−126 °C; IR (KBr) 3560, 2274 cm^{-1}; residual[10,11] ^{1}H NMR ($CDCl_3$) δ (ppm) 3.01 (s, O−H), 7.48 (s, $H_{3/6}$, 13%), 7.55 (s, $H_{2/7}$, 12%), 8.02 (s, $H_{4/5}$, 30%), 8.54 (s, H_{10}, 45%); ^{2}H NMR ($CHCl_3$) δ (ppm) 6.57 ± 0.10 (D_{11}), 7.50 ± 0.16 ($D_{3/4/6/7}$), 8.01 ± 0.08 ($D_{4/5}$), 8.53 ± 0.08 (D_{10}). Anal. Calcd for $C_{16}D_{11}F_3O$: C, 66.88; D, 7.71. Found: C, 67.60; D, 7.68. After saponification of **4R** and **4S**, **2R** showed $[\alpha]^{25}_D = -26°$, and compound **2S** showed $[\alpha]^{25}_D = +27°$.

(±)-Perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol Acetate (4): mp 97−99 °C; IR (KBr) 2960, 2278, 1759 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm) 2.19 (s, 3H, O−CH3); residual[10,11] signals 7.48 (s, $H_{3/6}$, 17%), 7.55 (s, H_2, 6%), 7.62 (s, H_7, 8%), 8.02 (s, $H_{4/5}$, 27%), 8.34 (s, H_8, 15%); 8.56 (s, H_{10}, 17%), 8.73 (s, H1 10%). Anal. Calcd for $C_{16}D_{11}F_3O$: C, 65.85; D + H, 7.97. Found: C, 65.95; D + H, 8.00. After separation, **4R** showed $[\alpha]^{25}_D = -23°$, and compound **4S** showed $[\alpha]^{25}_D = +24°$.

Acknowledgment. Financial support was received from DGICYT (Projects PB95-0636 and PB96-1181). The Universitat Autonoma de Barcelona (UAB) is gratefully acknowledged for fellowships (J.G.). We thank the "Servei de Ressonància Magnètica Nuclear" of UAB for allocating spectrometer time.

JO990917K

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(10) In parentheses is given the percent of total integration of aromatic signals. It depends on the degree of deuteration of the starting compound (94−98%).

(11) H_1 and H_8 are not observed in **2** by the fast interchange, and H_{11} was not detected by the complete deuteration.