A New Case of Chiral Recognition between Isotopomers. Preparation and Study of (*R*) and (*S*) Perdeuterio 2,2,2-Trifluoro-1-(1-pyrenyl)ethanol

Anna Muñoz,[†] Marta Sánchez,[†] Thomas Junk,[‡] and Albert Virgili*[,†]

Unitat de Química Orgànica, Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain, and Department of Chemistry, University of Lousiana at Monroe, Monroe, Louisiana 71209-0530

albert.virgili@uab.es

Received March 23, 2000

Introduction

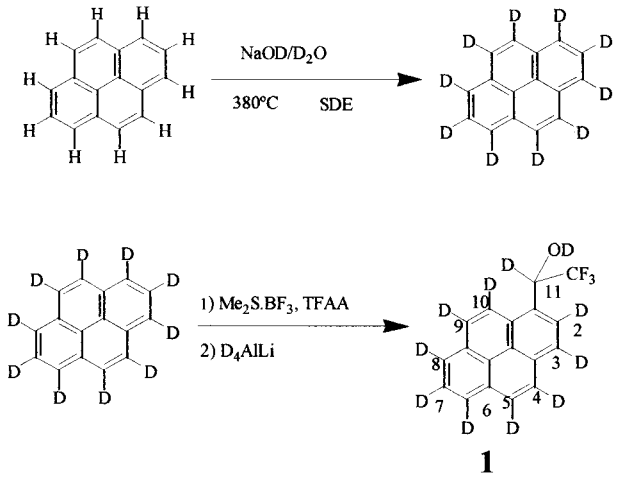
The analysis of enantiomers using a chiral solvating agent[1] (CSA) is becoming a very common methodology in the observation and determination of the enantiomer composition of a compound. Recently we reported[2] the preparation and use of the perdeuterio 2,2,2-trifluoro-1-(9-anthryl)ethanol (**3**), which is the result of replacing proton atoms by the deuterium atoms in the Pirkle alcohol, the most common of the CSA's. Compound **3** is the first compound of this type that does not present signals in the NMR spectra (^{1}H and ^{13}C), affording the advantage that we can see the NMR spectrum of each enantiomer alone, without interfering signals. We have also demonstrated[2] that this compound (**3**), besides being a very useful CSA, can distinguish two enantiomers of Pirkle alcohol (**4**). This is the first time that this phenomenon has been described.

In the present paper we describe a second case of this particular enantio-differentiation, that demonstrates, at least in the area of used compounds, the generalization of this "chiral self-discrimination:[3] the chiral recognition of a compound by the same perdeuterated enantiopure compound. A more extensive overview would require the study of several molecules where the association would be governed by other binding forces.

Results and Discussion

Scheme 1 affords the preparation (74% yield) of racemic compound **1**.[4] The deuteration of pyrene was carried out by supercritical deuterium exchange[5] (SDE) using NaOD /D_2O as deuterium source. The intermediate ketone was isolated, purified, and reduced to racemic alcohol. The chiral HPLC allowed us to obtain the separated enantiomers.

Scheme 1. Preparation of Compound 1



1

The absolute configuration was established by comparison of the optical activity with that described[6] for the perprotio compound. The first enantiomer eluted was *S*(+) ($[\alpha]^{25}_D = +20°$, $c = 0.5$, CH_2Cl_2) and the second was *R*(−) ($[\alpha]^{25}_D = -20°$, $c = 0.5$, CH_2Cl_2).

The perprotio compound[4] (**2**) was obtained in the same way and used as racemic compound.

Proton NMR spectra of **2** (5 mg, 0.017 mmol, 4.2×10^{-2} M) containing varying amounts of perdeuterated enantiomers **1S** or **1R** were recorded at 400 MHz in $CDCl_3$, under saturation of the exchanging hydroxyl signal (Figure 1). The two enantiomers of **2** were distinguished by the presence of the enantiomer **1S**. This is observed by the protons H_9, H_{10}, and H_{11}, and it increases with the ratio [**1S**]/[**2**]. As the concentration of **1S** increases, the doublets corresponding to H_9 and H_{10} split into two doublets and the H_{11} quartet split into two quartets. No more signals other than those corresponding to **2** are observed. Therefore, the spectra obtained correspond to the each enantiomer. Similar results were achieved when **1R** is used. When we used known nonracemic mixtures of **2** we assigned the signals of each enantiomer as indicated in Figure 1.

Lowering of the temperature resulted in a considerable increase in chemical shift differences. Figure 2 shows the ^{1}H NMR spectra of racemic **2** at four temperatures in the presence of 3 equiv of perdeuterated **1S**, and values are plotted in Figure 3. At low temperature the protons H_5 and H_7 are also enantio-differentiated, and even at 270 K the H_2 is duplicated. The arrangement of Figure 4, a hypothetical dimer in a head-to-tail, face-to-face $\pi-\pi$ stacking association, could explains the shifts observed in the protons, as happens in Pirkle alcohol.[2] As in this case of isotopomeric chiral recognition[2] of Pirkle alcohol, when **1S** is used, protons of enantiomer **2S** are shifted to higher field than enantiomer **2R**. This means that the associated complex **1S2S** could be more stable than the associated **1S2R**. In the same way, using **1R**, the complex **1R2R** is more shielded (more stable too) than **1R2S**.

For comparison, if the two compounds were the same isotopomer, the SS or RR association between two identi-

[†] Universitat Autònoma de Barcelona.
[‡] University of Lousiana at Monroe.

(1) (a) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem*. **1982**, *13*, 263−331 (b) Weisman, G. R. *Asymmetric Synthesis*; Academic Press: New York, 1983; Vol. 1, Chapter 8. (c) Parker, D. *Chem. Rev*. **1991**, *91*, 1441−1457.
(2) Gil, J.; Virgili, A. *J. Org. Chem*. **1999**, *64*, 7277−7280.
(3) (a) Luchinat, C.; Roelens, S. *J. Am. Chem. Soc*. **1986**, *108*, 4873 and citations therein. (b) Dobashi, A.; Saito, N.; Yuuichi, M.; Hara, S. *J. Am. Chem. Soc*. **1986**, *108*, 307 (c) Giordano, C.; Restelli A.; Vila, M. *J. Org. Chem*. **1991**, *56*, 2270 and citations therein.
(4) Kiselyov, A. S.; Hervey, R. G. *Tetrahedron Lett*. **1995**, *36*, 4005.
(5) Junk, T.; Catallo, W. J. *Chem. Soc. Rev*. **1997**, *26*, 401−406.
(6) Kato, K.; Katayama, M.; Fujii, S.; Kimoto, H. *Biosci. Biotech. Biochem*. **1997**, *61*, 194.

10.1021/jo0004411 CCC: $19.00
Published on Web 07/20/2000

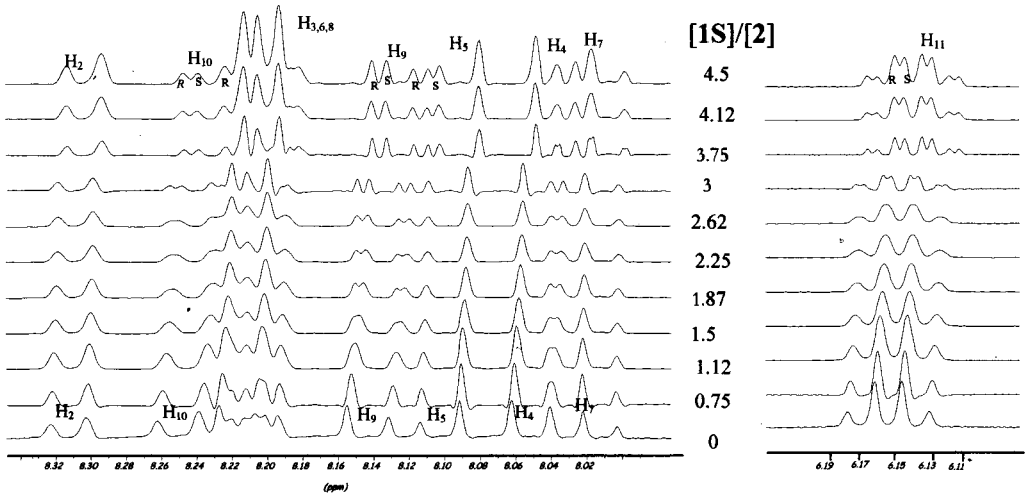


Figure 1. ^{1}H NMR spectra (300 K) of racemic 2,2,2-trifluoro-1-(1-pyrenyl)ethanol (**2**) in the presence of (*S*)-perdeuterated-2,2,2-trifluoro-1-(1-pyrenyl)ethanol (**1S**) at several [**1S**]/[**2**] ratios.

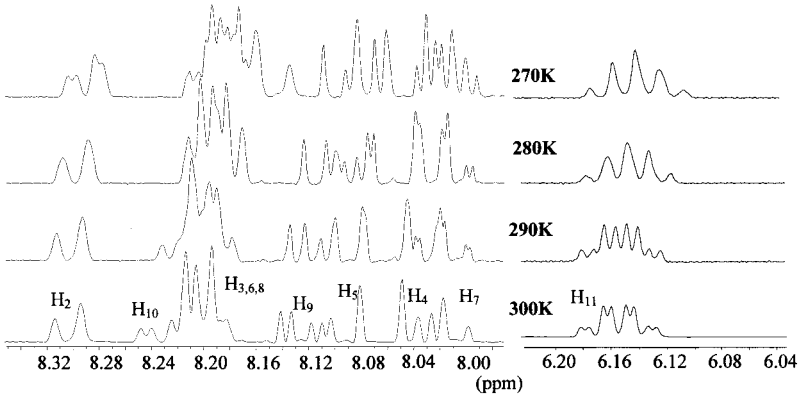


Figure 2. ^{1}H NMR spectra of chiral recognition of enantiomers of **2** by **1S** (3 equiv) at several temperatures.

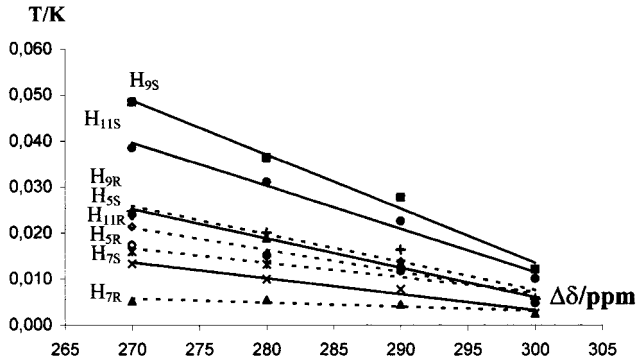


Figure 3. Variation with the temperature of the chemical shifts of protons of each enantiomer of **2** when 3 equiv of **1S** was added.

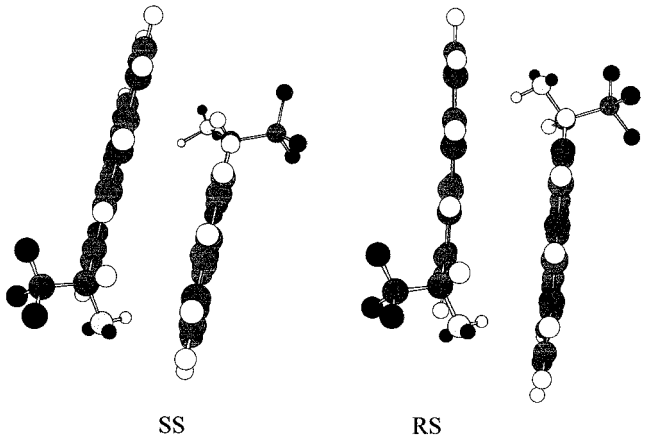


Figure 4. Proposed dimers of **2** SS and RS associations obtained by Molecular Mechanics.

cal molecules, would be more stable than the SR one. Only the fast and averaged equilibrium hinder the separation of signals when a nonracemic mixture is studied.

Experimental Section

NMR spectra were recorded with at 400.13 MHz for ^{1}H and 61.40 MHz for ^{2}H. The temperature was controlled to 0.1 °C. Chemical shift are reported in ppm relative to internal TMS for the proton and to external $CDCl_3$ for the 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 molecules with some hydrogen atoms.

Simple Molecular Mechanics calculations were carried out with CS Chem-3D Pro (v. 5) program using the internal standard conditions

Perdeuterio Pyrene. A 1.1 g (5.4 mmol) amount of pyrene was placed in a Hastelloy C-22 autoclave with 1 mL of a solution of Na(OD)/D_2O (1 mM). The mixture is heated to 380 °C for 24 h. Perdeuterated pyrene was isolated after extraction with dichloromethane and purified by flash chromatography. The compound (1.1 g, 5.2 mmol, 96% yield) was characterized by GC/MS, and ^{1}H NMR (of residual proton-containing compound).

Perdeuterio 2,2,2-Trifluoro-1-(1-pyrenyl)ethanol (1). At 195 K and under argon atmosphere a solution of 1.64 g (7.76 mmol) of trifluoroacetic anhydride in 1 mL of anhydrous methylene chloride is added to a solution of 1.01 g (7.76 mmol) of boron trifluoride−methyl sulfide complex ($Me_2S{\cdot}BF_3$) in 5.2 mL of the same solvent. After 15 min of gently stirring the mixture is added to a solution of 0.40 g (1.94 mmol) of perdeuterio pyrene in 1.2 mL of anhydrous methylene chloride, and the resulting solution was stirred at 195 K for an additional 15 min. The solution was allowed to warm to room temperature and stirred for 24 h. After a conventional treatment ($NaHCO_3$ and CH_2Cl_2 extraction), the mixture was purified by flash chromatography. A 0.22 g (0.73 mmol) amount (38% yield) of perdeuterio-1-pyrenyltrifluoromethyl ketone was obtained, and 0.21 g (0.99 mmol) of deuteriopyrene was recovered: mp 125−126 °C; IR (KBr) 2260, 1690 cm $^{-1}$; residual ^{1}H NMR ($CDCl_3$) δ (ppm) 8.01 (H_4, s, 1%), 8.07 (H_7, s, 10%), 8.12 (H_3, s, 26%), 8.18 (H_5, s, 1%), 8.25−8.26 ($H_{6,8,9}$, w, 51%), 8.50 (H_2, s, 11%), 9.10 (H_{10}, s, 1%); MS (EI) *m*/*e* (%) 307 (48), 306 (28), 238 (100). Anal. Calcd for $C_{18}D_9F_3O$: C, 70.35; D 5.90. Found: C, 70.38; D, 5.76.

A solution of 0.15 g (0.49 mmol) of obtained ketone in 25 mL of anhydrous ethylic ether was added, under nitrogen at 0 °C, to 0.06 g (1.46 mmol) of $AlLiD_4$ in 15 mL of the same solvent. After 30 min the mixture was treated with ethyl acetate and water. The organic phase was dried with MgSO4, evaporated and crystallized with EtOAc/pentane, obtaining 0.14 g (0.45 mmol) (90% yield) of **1**: mp 138−139 °C; IR (KBr) 2279, 1244, 1195 cm $^{-1}$; residual ^{1}H NMR ($CDCl_3$) δ (ppm) 6.14 (H_{11}, s, 1%), 8.02 (H_7, s, 9%), 8.05 (H_4, s, 2%), 8.10 (H_5, s, 2%), 8.14 (H_9, s, 2%), 8.20 (H_6, H8, s, 23%), 8.21 (H_3, s, 50%), 8.240 (H_{10}, s, 1%), 8.31 (H_2, s, 11%). MS (EI) *m*/*e* (%) 310 (84), 309 (46), 241 (93), 211 (100). Anal. Calcd for $C_{18}HD_{10}F_3O$: 69.66%C, 6.81% (D + H). Found: 69.67% C, 6.96% (D + H).

Enantiomers of **1** were obtained by chiral HPLC using hexane/2-propanol 92/8 as liquid phase. λ = 290 nm, flow 2.8 mL/min. K_S = 6.8, K_R = 8.8, α = 1.3.

JO0004411