Preparation and Structural Study of the Enantiomers of α,α′-Bis(trifluoromethyl)-9,10-anthracenedimethanol and Its Perdeuterated Isotopomer, Highly Effective Chiral Solvating Agents

M. Pomares, F. Sánchez-Ferrando, A.Virgili,* A. Alvarez-Larena,† and J. F. Piniella†

Departament de Química and Departament de Geología, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

albert.virgili@uab.es

Received July 20, 2001

Enantiopure forms of α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol and the corresponding perdeuterated isotopomers were prepared. The conformational study was carried out by ^{1}H NMR, and the absolute configuration was determined by the X-ray study of the crystallized diastereoisomeric carbamate derivative. This compound was tested as a chiral solvating agent (CSA). The results showed very good discrimination for several racemic mixtures that improved other classical methods. The study of diastereomeric complexes was carried out by determination of the stoichiometry of the complex and the binding constant of the equilibrium.

Introduction

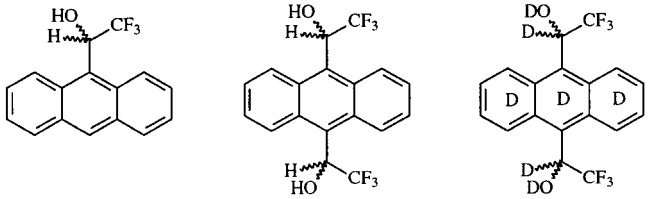
Arylcarbinols and arylamines are widely used as chiral solvating agents[1] (CSA). Since they render differences in the NMR spectra of enantiomers, they reveal the enantiomeric purity of a sample. The study of diastereomeric complexes and the preparation of new, stronger, and more general agents is an important target of research.[2]

Some difunctional compounds[3] have been tested as CSA with satisfactory results. With the aim to improve the chiral recognition capacity of Pirkle's alcohol (2,2,2-trifluoro-1-(9-anthryl)ethanol) **1**,[4] one of the most used CSA, we synthesized the difunctional analogue α,α′-bis-(trifluoromethyl)-9,10-anthracenedimethanol **2**, which behaved as a very effective chiral solvating agent. Moreover, as its active enantiomers have a C_2 symmetry their NMR spectra lead to the clearest final analysis (Chart 1).

In this paper, we describe the preparation of **2**, the isolation of its enantiomers; (*R*,*R*)-**2**, (*S*,*S*)-**2**, and *meso*-**2** by direct chromatography separation on a chiral column and their structural study. We have tested its capacity for chiral induction (as a CSA) in the presence of several racemic mixtures of acids, alcohols, amines, epoxides, etc., and we have measured the corresponding equilibrium constants.

Because deuterated chiral agents[5] are also used to measure enantiomeric mixtures, without external interferences, by ^{1}H and ^{13}C NMR spectroscopy, we also synthesized and studied the corresponding perdeuterio analogue **3**.

Chart 1. Structures of Compounds 1−3



1 **2** **3**

Results and Discussion

Synthesis, Resolution, and Structural Studies. The diastereomeric mixture of α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol **2** was obtained by $LiAlH_4$ reduction of 9,10-trifluoroacetylanthracene **4**, which was prepared by a process based on the reaction of the lithium derivative[6] of 9,10-dibromoanthracene with trifluoroacetic anhydride (TFAA) in a 40% yield (Scheme 1).

The intermediate product 9,10-trifluoroacetylanthracene **4** was also isolated and characterized by NMR. Reduction of **4** with $LiAlH_4$ gives a mixture of diastereoisomers: *meso*-**2** and racemic (*RR*,*SS*)-**2** in a good yield.

The perdeuterated isotopomer (**3**) was prepared in the same way starting with 9,10-dibromoperdeuterioanthracene (**5**) prepared by dibromination of perdeuterioanthracene. The synthetic reactions were monitored by the ^{1}H NMR spectra of residual monoprotonated molecules and by the ^{2}H NMR.

† Departament de Geología.

(1) (a) Pirkle, W. H.; Hoover D. J. *Top. Stereochem*. **1982**, *13*, 263. (b) Parker, D. *Chem. Rev*. **1991**, *91*, 1441−57. (c) Weisman, G. R. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 1, Chapter 8.

(2) (a) Kühn, M.; Buddrus, J. *Tetrahedron: Asymmetry* **1993**, *4*, 207. (b) Moragas, M.; Cervelló, E.; Jaime, C.; Virgili, A.; Ancian, B. *J. Org. Chem*. **1998**, *63*, 8689−8695. (c) Almer, S.; Cervelló, E.; Jaime, C.; Virgili, A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3719−3725.

(3) (a) Fulwood, R.; Parker, D. *Tetrahedron*: *Asymmetry* **1992**, *3*, 25−28. (b) Toda, F.; Toyotaka, R.; Fukuda, H, *Tetrahedron*: *Asymmetry* **1990**, *1*, 303. (c) Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A.; Oomine, K.; Fiji, K. *Chem. Lett*. **1988**, *131*. (d) Bilz, A.; Stork, T.; Helmchen, G. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3999−4002.

(4) Pirkle W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150.

(5) Gil, J.; Virgili, A. *J. Org. Chem*., **1999**, *64*, 7277−7280. (b) Muñoz, A.; Sánchez, M.; Junk, T.; Virgili, A. *J. Org. Chem*. **2000**, *65*, 5069−5071.

(6) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1363−1370.

10.1021/jo015957e CCC: $22.00
Published on Web 01/04/2002

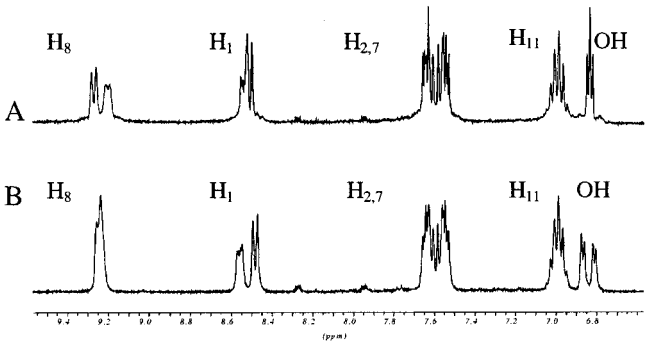
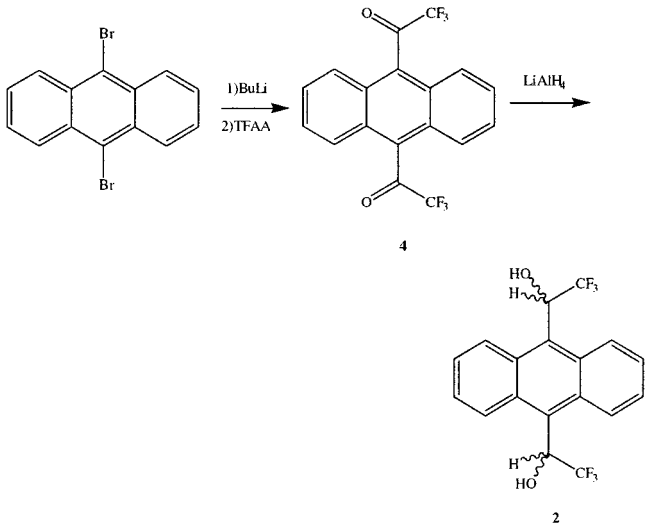


Figure 1. ^{1}H NMR spectra (in CD_3COCD_3) of *meso*-(**2**) (A) and *rac*-(**2**) (B) at 240 K.

Scheme 1. Synthesis of Compound 2



The acetate derivatives of **2** and **3** (**6** and **7**, respectively) were prepared quantitatively by treatment with acetyl chloride and were used to isolate pure enantiomers by preparative HPLC on a Whelk-O1 chiral HPLC column[7] using hexane/isopropyl alcohol (98:2) as the elution solvent (3 mL/min). The first compound eluted was (−)-**6** ((*R*,*R*)-**6** as the X-ray described below shows); the second one was the optically inactive (*meso*)-**6** and the third one was (+)-**6** ((*S*,*S*)-**6**). Saponification of each separated ester with K_2CO_3 (1 M) gave the enantiomers (*R*,*R*)-**2** and (*S*,*S*)-**2** as well as (*meso*)-**2** respectively. Enantiomers of **3** were obtained in the same way.

Room-temperature ^{1}H NMR spectra of (*R*,*R*)-**2** and (*S*,*S*)-**2** enantiomers and their diasteoisomer *meso*-**2** show slow rotation around C_9-C_{11} resulting in broad resonances for H_1 and H_8 (and their equivalents H_4 and H_5). At lower temperatures, the internal rotation is frozen and the proton pairs H_1, H_8 and H_2, H_7 become anisochronous (as well as their corresponding isochronous H_4, H_5 and H_3, H_6). At 250 K, these signals are markedly separated.

At 240 K, spectra of enantiomers of alcohol (*R*,*R*)-**2** and (*S*,*S*)-**2** are slightly different from *meso* (*R*,*S*)-**2** (Figure 1). The racemate (or each enantiomer) gave two signals (area ratio 1.5/1) for H_1 and two doublets (area ratio 1.5/1) for hydroxyl protons. In the meso isomer, it is the H_8 nucleus that appears as a pair of signals (relative integral ratio 1/1).

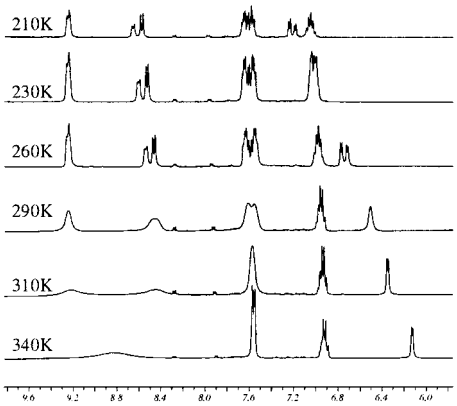
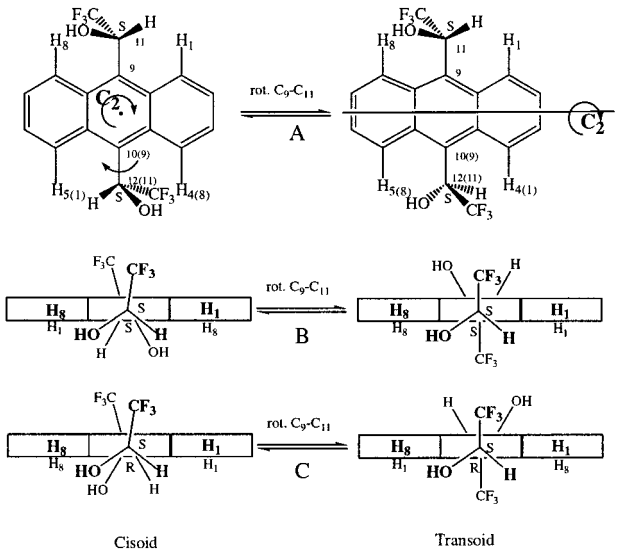


Figure 2. Variable-temperature ^{1}H NMR (in CD_3COCD_3) spectra of (*R*,*R*)-**2**.

Scheme 2. Conformational Equilibrium of (*S*,*S*)-2 and *meso*-2: (A) Frontal Vision for (*S*,*S*)-2 Structure, (B) Vertical Vision for (*S*,*S*)-2, and (C) Vertical Vision for *Meso*-2



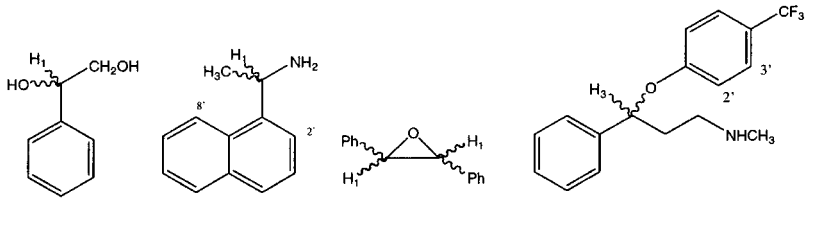
Taking into consideration that the mean conformation of the benzylic bond maintains the $C-CF_3$ bond in a perpendicular position with respect to the anthracene plane, one can consider two relative situations[8] for the two substituents of the anthracene ring: a transoid and a cisoid situation (Scheme 2). The symmetry of both is not the same, and their NMR spectra are different. In the racemic isomer *rac*-**2**, the difference between the protons near H_{11} (H_1 type) is greater than the difference between the protons near the OH group (H_8 type). In *meso*-**2**, the main difference is in the H_8-type protons.

Figure 2 displays NMR spectra of enantiomer (*R*,*R*)-**2** at several temperatures. The coalescence between H_1 and H_8 was observed at 330 K and that between H_2 and H_7 at 285 K. The rotation barrier was measured by a ^{1}H DNMR complete line-shape analysis (CLSA) (or considering T_C) performed on the temperature dependence of protons H_1 and H_8. It could be also calculated with the two resonances (cisoid and transoid) of protons H_1 or H_8 of the *rac*-**2** or the *meso*-**2**, respectively. The $\Delta G^{\ddagger}$ value of the process was calculated using the Eyring equation

(7) Pirkle, W. H.; Kosho, M. E.; Wu, Z. *J. Chromatogr.* **1996**, *91*, 726.

(8) Casarini, D.; Lunazzi, L.; Gasparini, F.; Villani, C. *J. Org. Chem.* **1995**, *60*, 97−102. Casarini, D.; Lunazzi, L.; Alcaro, S.; Gasparini, F.; Villani, C. *J. Org. Chem.* **1995**, *60*, 5515−5519.

Chart 2. Compounds Assayed in the Enantiodiscrimination Tests



9 **10** **11** **12**

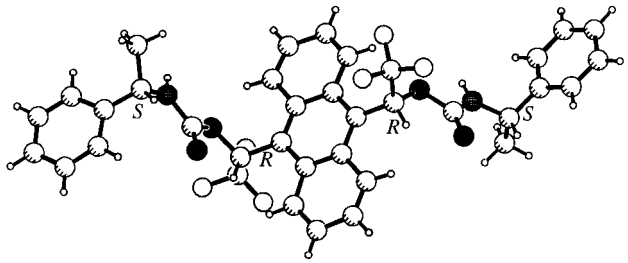


Figure 3. X-ray structure of dicarbamate **8** with (*R*,*R*) configuration of chiral centers of the alcohol part.

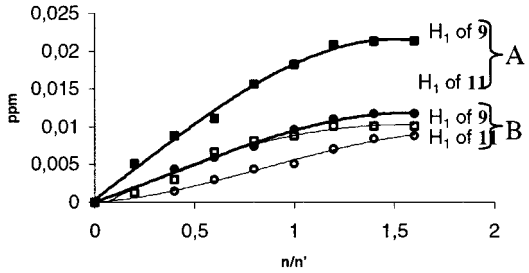


Figure 4. Evolution of the enantiodifferentiation at 300 K of protons of **9** and **11** when (*R*,*R*)-**2** (A) or (*R*)-**1** (B) is added at several molar relations (n/n' = [CSA]/[subs]).

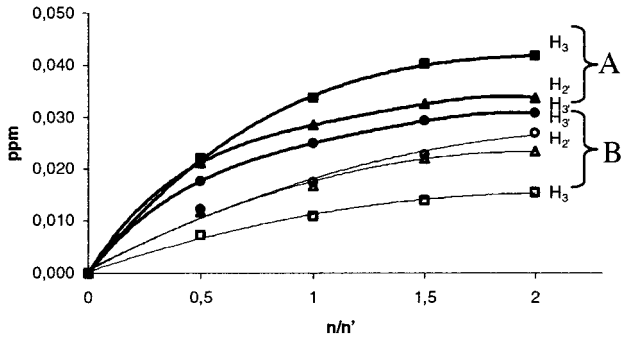


Figure 5. Evolution of the enantiodifferentiation at 300 K of several protons of **12** when (*R*,*R*)-**2** (A) or (*R*)-**1** (B) is added at several molar relations (n/n' = [CSA]/[subs]).

($\Delta G^{\ddagger}_{330} = 15.08 \pm 0.8$ kcal/mol). This value is consistent with the calculated barrier for Pirkle's alcohol described earlier.[9]

The configuration of the enantiomers was determined by X-ray analysis of the dicarbamate derivative (**8**) obtained[10] by reaction of the first eluted enantiomer with 2 equiv of (−)-1-phenylethylisocyanate of absolute configuration *S*. Figure 3 demonstrates that the compound used (the first eluted one, the levorotatory) corresponds to the (*R*,*R*) enantiomer.

One can see that in compound **8** the two trifluoromethyl groups lie in the opposite side of the anthracene plane adopting a transoid relative distribution. Moreover, two phenyl rings are quasi parallel to the anthracene part, the angles of anthracene ring with each of phenyl groups are 14.1 and 4.2. The structure affords a maximum longitude. Both carbamates are in an anti arrangement.

Chiral Induction Activity. The behavior as a chiral solvating agent was tested with several racemic mixtures. Although both enantiomers of **2** were used, as the behavior of two enantiomers is symmetrical against the same racemic, the results are always referred to those obtained with the (*R*,*R*)-**2** enantiomer. The *meso*-derivative (*meso*-**2**) was also assayed giving, as expected, no enantiodifferentiation.

The following racemic mixtures were used: phenylethanediol (**9**), 1-(1-naphthyl)lethylamine (**10**), *trans*-stilbene oxide (**11**), and fluoxetine (**12**) (Chart 2).

In all cases, the experiments were carried out adding portions of CSA to a solution (0.05 M) of the racemic substrate until a maximum increase of nonequivalence was obtained (2 equiv). For comparison, the same treatment was done using Pirkle's alcohol because of its known excellent results and its structural similarity to our compound. Figures 4 and 5 represent typical curves obtained for this experiments corresponding to **9**, **11**, and **12**, compounds that aid in viewing the data trends.

In all cases, the increase of the enantiodiscrimination with the concentration of CSA is higher if enantiomer (*R*,*R*)-**2** is used instead of (*R*)-**1**. Moreover, the maximum values obtained are also much greater using **2**. Only in the case of epoxide (**11**) is the difference moderate. In the other cases, the use of **2** provides significant improvements.

The enantiodifferentiation of **12** (Figure 5) was observed on three protons, in the case of H_3 the effect was triple when compound **2** was used.

In the case of **10**, very substantial values of $\Delta\delta$ were obtained when **2** was used. Whereas using **1** allows only the enantiodiferentiation of H_1, by using **2**, several individual resonances could be resolved for each enantiomer of **10** without interfering signals. Previously, comparable results on **10** could only be obtained by using perdeuterated Pirkle's alcohol.[5] The evolution of the signals for **10** is described in Figure 6, in which one observes a general increase of the enantioseparation compared with the published[11] results using perdeuterio Pirkle's alcohol.

(9) (a) Ben Hassine, B.; Gorsane, M.; Pecher, J.; Martin, R. H.; Defay, N.; Ottinger, R. *Bull. Soc. Chim. Belg.* **1985**, *94*, 425−430. (b) Jaime, C.; Virgili, A.; Claramunt, R. M.; López, C.; Elguero, J. *J. Org. Chem.* **1991**, *56*, 6521−6523.

(10) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904−6.

(11) Muñoz, A.; Virgili, A. *Enantiomer* **2001**, *6*, 235−244.

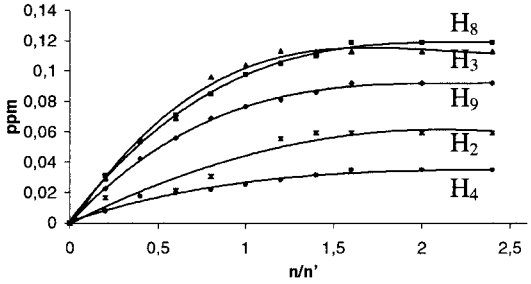


Figure 6. Evolution of the enantiodifferentiation at 300 K of several protons of **10** when (*R,R*)-**2** is added at several molar relations.

Table 1. Maximum Enantiodifferentiation of Compounds 9−12 When 2 Equiv of CSA ((A) (*R*)-1, (B) (*R,R*)-2) Are Added[a]

substrate	obsd resonance	A Δδ/ ppm	B Δδ/ppm
9	H_1	0.010	0.021
10	H_9	0.069	0.092
10	H_2	0.060[b]	0.050
10	H_3	0.052[b]	0.113
10	H_4	0.017[b]	0.035
10	H_8	0.114[b]	0.119
11	H_1	0.011	0.012
12	H_3	0.017	0.042
12	$H_{2'}$	0.026	0.034
12	$H_{3'}$	0.029	0.031

[a] In all cases, concentration of CSA was 0.1 M. [b] Values were obtained when perdeuterated (*R*)-**1** was used.

Results of H_3 and H_4 are doubled, meaning that they are particularly affected by the proximity of the second chiral group of compound **2**.

Table 1 presents the maximum enantiorecognition of compounds **9**−**12**. In all cases, values refer to the addition of (*R,R*)-**2** and are compared with the addition of (*R*)-**1**. The values were observed after using (*R,R*)-**2** in a molar relation (CSA/sample) of 2/1. Table 1 shows that when a chiral solvating agent is needed, the use of (*R,R*)-**2** improves the general method of analysis of enantiomers. The quantitative separation of enantiomers is better and in most cases much better than using (*R*)-**1**. Moreover, the obtained spectra were cleaner in the aromatic region.

We studied the stoichiometry of the complex due to the difunctionality of compound **2** and a possible 2:1 association. The use of the Job[12] equation and its plots allowed the determination of the molar ratio of the associated complex. The variation of the chemical shift changing the concentration of the racemic compound with respect to the total concentration (which is maintained constant) was traced (Figure 7). All quadratic curves corresponding to several protons present a maximum value at 0.5, meaning a 1/1 complex**.**

The measurements of binding constants were carried out using the equimolecular method.[13] This is the result obtained when several variable solutions of identical concentration of racemic and CSA compounds are studied.

The variation of chemical shifts (Δδ) under these conditions could be analyzed as a function of the concentration (*S*°) giving the linear relation $\Delta\delta = \delta_c - (\delta_c/K)^{1/2}(\Delta\delta/S°)^{1/2}$, where δ_c is the chemical shift of the complex. From the slope and the intercept of the straight line with the abscissa found for each of the protons, one can obtain a mean value of the equilibrium constant (*K*) at several temperatures.

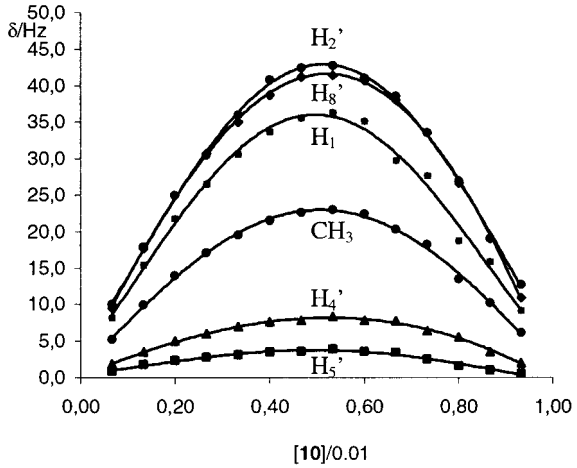


Figure 7. Job plots of the complex formation of compound **10** when **2** is used

Table 2. Equilibrium Constants of the Complex Formation of the Enantiomers of 10 with (*R,R*)-2 Measured by the Equimolecular Method[a]

	(*R*)-**10** + (*R,R*)-**2**		(*S*)-**10** + (*R,R*)-**2**	
T/K	K/M^{-1}	Δ*G*°/kJ/mol	K/M^{-1}	Δ*G*°/kJ/mol
253	136.3	−10.3	180.5	−10.9
268	82.13	−9.8	116.3	−10.6
283	49.4	−9.1	55.5	−9.4
298	35.2	−8.8	35.8	−8.9
	(21.8)	(−7.6)	(22.8)	(−7.7)

[a] The values obtained if (*R*)-**1** was used are shown in parentheses.

Table 3. Equilibrium Constants Measured by the Equimolecular Method of the Complex Formation of the Enantiomers of 9 with (*R*)-1 and (*R,R*)-2 at 298 K

	(*R*)-**9** + (*R*)-**1**	(*S*)-**9** + (*R*)-**1**	(*R*)-**9** + (*R,R*)-**2**	(*S*)-**9** + (*R,R*)-**2**
K/M^{-1}	3.7	3.8	2.4	2.4
Δ*G*°/ kJ/mol	−3.2	−3.3	−2.1	−2.1

The binding constants of the association of **9** and **10** with **2** or **1** show the similarity of the thermodynamic factors of both enantiomers. We obtained these parameters for each pure enantiomer of **9** and **10** in a separate experiment, using (*R*)-**1** or (*R,R*)-**2** as a chiral inductor. The results are expressed in Tables 2 and 3, which show uniformity in each series.

Because the binding constants corresponding to any enantiomer of **9** are very similar if (*R*)-**1** or (*R,R*)-**2** are used, the stability of the corresponding complexes should be also comparable. In the case of compound **10**, the measured constants are much greater if the difunctional compound (*R,R*)-**2** is used, meaning a greater efficacy in the formation of complex when (*R,R*)-**2** is applied. This can be explained by the involvement of the hydroxyl group in the formation of the association is in the complexes of compound **10**, while in those of **9** the interaction between the aromatic rings, should be the main driving force of the complex formation.

(12) (a) Job, P. *Ann. Chem.* **1928**, *9*, 113−125. (b) Djedaini, F. *J. Pharm. Sci.* **1990**, *79*, 643−646.

(13) (a) Bouquant, J.; Chuche, J. *Tetrahedron Lett.* **1972**, *23*, 2337−2340. (b) Raber, D. J.; Hardee, L. E., *Org. Magn. Reson.* **1982**, *20*, 125−132. (c) Fielding L. *Tetrahedron* **2000**, *56*, 6151−6170.

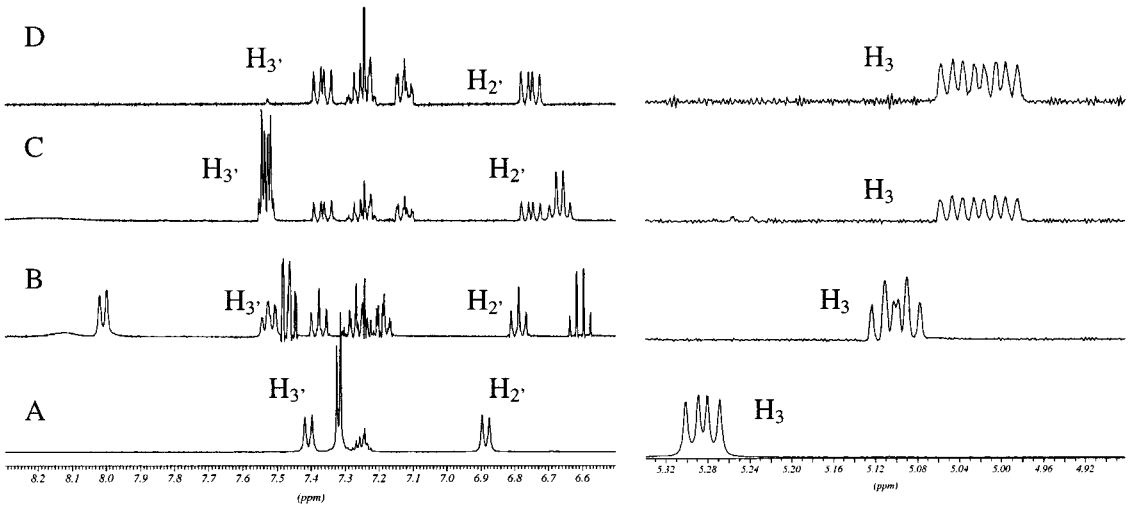


Figure 8. Part of the ^{1}H NMR spectra (300 K) of racemic fluoxetine (**12**) (A) when chiral solvating agent **1** (B), **2** (C), or **3** (D) was added (2 equiv).

Since the differences between the constants of each pair of enantiomers are very small, one can conclude that the greater enantiodifferentiation observed when (*R*,*R*)-**2** is used, is caused by differences in the geometry of the complexes rather than by the displacement of the equilibrium. Decreasing the temperature, this difference becomes more important and the equilibrium factor increases, along with its importance in the capacity of differentiation of enantiomers.

Perdeuterated Analogue. As the previously described, perdeuterio-2,2,2-trifluoro-1-(1-pyrenyl)ethanol and perdeuterio-2,2,2-trifluoro-1-(9-anthryl)ethanol (the perdeuterated homologue of **1**),[5] the new α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol (**3**) also shows absence of the signals in the ^{1}H and ^{13}C NMR spectra, as well as a high capacity in the separation of enantiomers.

Figure 8 displays the NMR spectra of mixtures of racemic of fluoxetine with compounds (*R*)-**1**, (*R*,*R*)-**2,** and deuterated (*R*,*R*)-**3**. The advantage of (*R*,*R*)-**3** is clearly demonstrated in Figure 8, which shows the same separation as when (*R*,*R*)-**2** is used, but with no other signals in the spectrum.

We have previously shown that addition of enantiopure perdeuterated Pirkle's alcohol to racemic, undeuterated Pirkle's alcohol (**1**), results in an enantiodifferentiation of some proton NMR signals of the latter.[5] However, a similar behavior could not be confirmed for the deuterio enantiomer (*R*,*R*)-**3**. Thus, the ^{1}HNMR spectra of mixtures of racemic **2** with enantiopure perdeuterio derivative (*R*,*R*)-**3** showed an extensive overlapping of signals, at all temperatures tested, which could not be analyzed. A possible reason for this difference could be that the presence of a second CF_3CHOH unit in both the protio racemate and the deuterio CSA results in a tremendous increase in the number of conformations accessible to the complex.

Experimental Section

NMR spectra were recorded at 400.13 MHz for ^{1}H. The temperature was controlled to 0.1 °C. Chemical shifts are reported in parts per million relative to internal TMS. The complete identification of the NMR signals was carried out with the aid of several 1D (NOE) and 2D (COSY, HMQC, and HMBC) spectra. Chiral semipreparative HPLC is carried out using a (*R*,*R*)-Whelk-O1 column (250 mm × 10 mm).

The NMR titration method was carried out with 0.4−0.5 mL of a solution 0.03−0.05 M of the compound (**9**−**12**). After addition (at constant volume) of several portions of 0.2−0.5 equiv of CSA (**1**, **2**, or **3**), NMR spectra were measured and the variations of the chemicals shifts calculated for each addition. The measures were done until a maximum enantiodiscrimination (1.5−2.5 equiv). The comparative experiments were carried out in identical conditions.

Binding constants were determined (equimolecular method) measuring chemical shifts of an equimolecular solution in $CDCl_3$ of each compound (**9** or **10**) and the corresponding chiral solvating agent (**9** or **1**). From 0.5 mL of an initial concentration of 0.05 M of each and after four additions of 0.1 mL of solvent we obtained five values of chemical shift (δ) correlated with the corresponding concentration (S). In the case of compound **10** the measures were carried out at five temperatures after each dilution.

Crystallographic Data. The X-ray data for **8** were collected on an Enraf-Nonius diffractometer [λ(Mo Kα) = 0.710 69 Å, graphite monochromator, $\omega/2\theta$, T = 293 K]. $C_{36}H_{30}F_6N_2O_4$, colorless crystals, M = 668.62, crystal dimensions 0.58 × 0.14 × 0.09 mm^3, tetragonal, $P4_3$ (No. 78), a = 13.446(9) Å, c = 18.416(17) Å, V = 3330(4) Å^3, Z = 4, ρ_{calcd} = 1.334 Mg m^{-3}, μ = 1.09 mm^{-1}. Data collection range 2° < 2θ < 50°, 3031 unique reflections, 1203 observed [$I > 2\sigma(I)$]. The structure was solved by direct methods (SHELXS-86[14]) and refined by full-matrix least-squares refinement on F^2 for all reflections (SHELXL-97[15]). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with isotropic displacement parameters fixed at 1.5 (methyl H) or 1.2 (the rest) times the U_{eq} of corresponding carbons or nitrogens. Refined parameters, 433; geometric restrictions were applied. Goodness-of-fit on F^2, 0.814. $R_w(F^2)$ = 0.189 for all data, $R(F)$ = 0.079 for the observed reflections.

9,10-Trifluoroacetylanthracene (4). A solution (1.6 M) of butyllithium in hexane (4.8 mL, 7.68 mmol) was slowly added to a diethyl ether (30 mL) solution of 9,10-dibromoanthracene (1 g, 2.97 mmol) kept under N_2 with continuous stirring at room temperature. The reaction was completed after 20 min, the mixture was cooled to −78 °C, and an excess of trifluoro-

(14) Sheldrick, G. M. *SHELXS-86. Crystallographic Computing 3*; Sheldrick, G. M., Krüger, C., Goddard, R., Eds.; Oxford University Press: Oxford, 1985.

(15) Sheldrick, G. M. *SHELXL-97, Program for the Refinement of Crystal Structures*, Göttingen, 1997.

acetic anhydride was added dropwise (7 mL, 50.4 mmol). After 3 h, the reaction was quenched and the mixture was washed with a solution of saturated NH_4Cl (2 × 50 mL), a solution of 10% NaOH (2 × 50 mL), and finally water (2 × 50 mL). The organic layer was separated, dried, and concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane 80/20 v/v) to give yellow needles (0.325 g 30% yield). Mp: 160−161 °C. IR (KBr) ν: 3085, 1750-(C═O), 1152−1216−1279 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm) 7.88 (4H, m), 7.95 (4H, m). ^{13}C NMR ($CDCl_3$) δ (ppm) 124.9 (C2), 127.9 C9a), 129.4 (C1), 131.5 (C9), 177.2 (C═O). EM *m*/*z*: 370 (31), 301 (90), 204 (100), 176 (96), 88 (94).

α,α′-Bis(trifluoromethyl)-9,10-anthracenedimethanol (2). A diethyl ether solution (20 mL) of **4** (300 mg, 0.81 mmol) was slowly added to a diethyl ether slurry (10 mL) of $LiAlH_4$ (74.84 mg, 1.98 mmol) and kept under N_2 with continuous stirring at room temperature. After 4 h, reduction was completed. The reaction was quenched and the organic layer was separated, dried, and concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane 60/40 v/v) to give white needles (0.210 g, 70% yield). IR (KBr) ν: 3472−3388, 2924, 1264, 1173−1124 cm^{-1}. ^1H NMR ($CDCl_3$, 298 K) δ (ppm): 6.73 (2H, q, J = 7.2 Hz), 7.56 (4H, m), 8.4 (2H, broad), 9.2 (2H, broad). EM *m*/*z*: 374 (48), 305 (63), 258 (100), 176 (20). Anal. Calcd for $C_{18}H_{12}F_6O_2$: C, 57.76; H, 3.23. Found: C, 57.77; H, 3.17.

***(R,R)*-2.** $[\alpha]^{20} = -27°$ (c = 2.00, ethanol). Mp: 174−174.5 °C. ^1H NMR (acetone-d_6, 240 K) δ (ppm) (major isomer, cisoid or transoid): 7.23 (2H, d, J = 6.2 Hz, OH), 7.04 (2H, q, J = 7.6 Hz, H_9), 7.59 (4H, m, H_2, H_3, H_6, H_7), 8.57(2H, d, J = 9.1 Hz, H_1), 9.23 (2H, s, H_8); (minor isomer, transoid or cisoid) 7.18 (2H, d, J = 6.2 Hz, OH), 7.04 (2H, q, J = 7.6 Hz, H_9), 7.66 (4H, m, H_2, H_3, H_6 and H_7), 8.65 (2H, dd, J = 2.9 Hz, J = 9.9 Hz, H_1), 9.25 (2H, s, H_8). ^{13}C NMR (acetone-d_6, 240 K) δ (ppm) (major isomer, cisoid or transoid): 69.51 (C_{11}), 124.0 (C_1), 125.2 (C_2), 127.2 (C_7), 129.56 (C_8 and C_9), 131.5(C_{9a}), 131.8 (C_{9b}); (minor isomer, transoid or cisoid) 69.51 (C_{11}), 124.8 (C_1), 126.9 (C_2), 125.4 (C_7), 128.8 (C_8) 129.5 (C_9)130.8(C_{9a}), 131.8 (C_{9b}).

***(S,S)*-2.** $[\alpha]^{20} = +28°$ (c = 2.00, ethanol).

***(R,S)*-2.** Mp: 172−173 °C. ^1H NMR (acetone-d_6, 240 K) δ (ppm) (cisoid or transoid): 7.23 (2H, d, J = 3.5 Hz, OH), 7.06 (2H, q, J = 8.2 Hz, H_9), 7.62 (4H, m, H_2, H_3, H_6, H_7), 8.62 (2H, d, J = 8.8 Hz, H_1), 9.27 (2H, d, J = 8.7 Hz, H_8); (transoid or cisoid): 7.23 (2H, d, J = 3.5 Hz, OH), 7.06 (2H, q, J = 8.2 Hz, H_9), 7.58 (4H, m, H_2, H_3, H_6, H_7), 8.60 (2H, s, J = 9.9 Hz, H_1), 9.20 (2H, s, H_8). ^{13}C NMR (Acetone-d_6, 240 K) δ (ppm) (cisoid or transoid): 69.0 (C_{11}), 123.9 (C_1), 125.1 (C_2), 127.2 (C_7), 129.5 (C_8) 129.2 (C_9), 131.0 (C_{9a}), 131.5 (C_{9b}); (transoid or cisoid) 69.1 (C_{11}), 124.7 (C_1), 126.9 (C_2), 125.3 (C_7), 128.9 (C_8), 129.2 (C_9), 130.7 (C_{9a}), 131.8 (C_{9b}).

α,α′-Bis(trifluoromethyl)-9,10-anthracenedimethyl Diacetate (6). To a mixture of **2** in dichloromethane (200 mg, 0.53 mmol) was added 0.028 g of (dimethylamino)pyridine (DMAP) (0.28 mmol), 1 mL of triethylamine, and 0.4 mL of acetyl chloride (5.6 mmol). After 6 h, the reaction was finished. The organic layer was washed with water (2 × 25 mL), HCl 1 M (2 × 25 mL), and a solution of 10% $NaHCO_3$ (2 × 25 mL). The organic layer was separated, dried, and concentrated. The solid residue (0.225 g, 0.53 mmol, 90%) was purified by chromatography on silica gel (hexane/dichloromethane 1/1 v/v). Mp: 160−162 °C. ^1H NMR ($CDCl_3$) δ (ppm): 1.53 (6H, s), 7.59 (4H, m), 7.87 (2H, q, J = 7.3 Hz), 8.41(2H, s), 8.79 (2H, s). IR (KBr) cm^{-1}: 3022, 1764, 1271, 1215−1124. MS *m*/*z*: 458 (4), 258 (16), 178 (10), 43 (100).

***(R,R)*-α,α′-Bis(trifluoromethyl)-9,10-anthracenedimethyl Di(1-phenylethyl)carbamate (8).** Enantiomer (*R*,*R*)-**2** (300 mg, 0.8 mmol) and (S)-(−)-1-phenylethylisocyanate 99% (0.7 mL, 4.8 mmol) were mixed and heated to 80 °C while protected by a drying tube for 72 h, according to the literature.[10] The mixture was then chromatographed with hexane/dichloromethane (1/1). Recrystallization from dichloromethane gave white needles, 428 mg (80% yield). Mp: 146−148 °C. IR (KBr) ν cm^{-1}: 3406, 3301, 2966, 1695, 1528, 1500, 1252. ^1H NMR ($CDCl_3$, 298 K) δ (ppm) minor rotamer: 1.57 (6H, d, J = 7.2 Hz), 4.86 (2H, d, J = 7.2 Hz), 7.1−7.4 (4H, m), 8.41 (2H, s), 8.74 (2H, s); major rotamer 1.23 (6H, d, J = 6.8 Hz), 6.46 (2H, d, J = 6.8 Hz), 7.1−7.4 (4H, m), 7.84 (2H, s), 7.57 (2H, s). $[\alpha] = -44.8$ (c = 2.05, CH_2Cl_2).

Perdeuterio 9,10-Dibromoanthracene (5). A CCl_4 solution (10 mL) of Br_2 (0.62 mL, 11.66 mmol) was slowly added dropwise to a solution that contained anthracene-d_{10} (1.50 g, 7.97 mmol) and $AlCl_3$ (353 mg, 2.65 mmol) in CCl_4 (30 mL). The addition took 1 h, and the mixture was kept under N_2 and cooled to 0 °C. One hour later, the reaction was finished. The crude was washed with 10% NaOH (2 × 50 mL) and water (2 × 50 mL). The organic layer was dried with anhydrous $MgSO_4$. The brown solid was then chromatographed with hexane, and a yellow solid was obtained (1.57 g, 4.55 mmol, 57% yield). Mp: 219−221 °C. IR (KBr) cm^{-1}: 2966−2924, 892, 693. EM *m*/*z*: 344 (91), 265 (9), 184 (100), 92 (72). Residual ^1H NMR ($CDCl_3$) δ (ppm): 7.63 (s), 8.59 (s).

The synthesis of the deuterated analogues of 9,10-trifluoroacetylanthracene (**4**), α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol (**3**) and α,α′-bis(trifluoromethyl)-9,10-anthracenedimethyl acetate (**7**) were prepared in the same way as the protonated ones.

Perdeuterio 9,10-Trifluoroacetylanthracene. Mp: 159−160 °C. IR (KBr) ν cm^{-1}: 2282 (CD), 1750 (st C═O), 1152−1216−1279 (st CF), 1215 (st CO). MS (70 eV) *m*/*e*: 378 (M^+, 31), 309 (90), 204 (100), 184 (96). Residual ^1H NMR ($CDCl_3$) δ (ppm): 7.65 (s), 7.79 (s).

Perdeuterio α,α′-Bis(trifluoromethyl)-9,10-anthracenedimethanol (3). Mp: 172−174 °C. IR (KBr) ν cm^{-1}: 3472−3388, 2278, 1264, 1173−1124. MS (70 eV): *m*/*e*: 384 (M^+, 100), 315(71), 268 (82), 187 (99). Residual ^1H NMR ($CDCl_3$): δ (ppm): 6.73 (H_{11}, s), 7.56 (H_2 and H_3, s).

Perdeuterio α,α′-Bis(trifluoromethyl)-9,10-anthracenedimethyl Diacetate (7). Mp: 160−162 °C. IR (KBr) ν cm^{-1}: 2278 (st C−D), 1764 (st C═O), 1271, 1215−1124. MS (70 eV) *m*/*e*: 468 (M^+, 20), 357 (15), 268 (11), 43 (100).

Acknowledgment. Financial support from CICYT (project PPQ3000-369) is gratefully acknowledged. M.P. thanks the CIRIT for a research fellowship. M.P. thanks the CIRIT for a predoctoral fellowship.

JO015957E