NMR Chiral Analysis of Aromatic Hydrocarbons by Using Permethylated β-Cyclodextrin as Chiral Solvating Agent

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Received July 20, 1995

Introduction

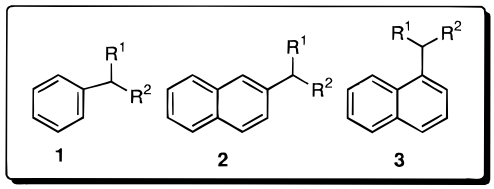
The separation and stereochemical characterization of chiral substances is a current challenge in asymmetric synthesis. Chiral solvating agents (CSAs) for NMR spectroscopy[1] permit a practical and direct solution: in many cases they can interact with the two enantiomers of the analyte and form short-lived diastereoisomeric adducts having anisochronous NMR resonances, the integration of which directly leads to the enantiomeric composition. Even if the majority of CSAs are used for the chiral analysis of compounds having polar functional groups,[1,2] there is a great demand for ones suitable for substrates devoid of such functionalities. In this respect cyclodextrins seem to be very promising,[3] because of their ability to accommodate apolar groups into their apolar cavities by virtue of only hydrophobic attractive interactions.[4] Recently, we have used the permethylated β-cyclodextrin (TRIMEB) as an efficient CSA for the chiral analysis in the CD_3OD solution of trisubstituted allenes devoid of polar functional groups.[5]

We are now reporting that TRIMEB can to be used to determine the enantiomeric purities of chiral aromatic hydrocarbons $ArCHR^1R^2$ (R^1, R^2 = alkyl, Ar = phenyl, 2-naphthyl, 1-naphthyl) (Chart 1), an important class of apolar compounds for which no general direct NMR method of enantiomeric purity determination has been proposed till now.

Results and Discussion

We have analyzed the ^1H NMR spectra of CD_3OD solutions containing the free chemically pure (GLC, ^1H NMR) racemic hydrocarbons **1a-d**, **2a-c**, **3a-c** (Chart 1) and their mixtures with permethylated β-cyclodextrin. Practically in every case we have found that TRIMEB produced the doubling of the proton resonances of the hydrocarbons, the entity of which was enhanced by adding further equivalents of the cyclodextrin, by lowering the temperature or by increasing the total concentration.

Chart 1



	a	b	c	d
R^1	Bu^t	Pr^i	Et	Bu^t
R^2	Me	Me	Me	Et

In Figure 1 the proton spectrum of the mixture containing the racemic compound **1a** and 3 equiv of TRIMEB, recorded at −20 °C is reported. The spectrum shows two separate singlets at 0.90 and 0.91 ppm corresponding to the *tert*-butyl resonances, two doublets centered at 1.31 and 1.32 ppm due to the methyl protons, two partially superimposed quartets at 2.59 and 2.61 ppm arising from the methine proton, and, finally, a complicated signal pattern between 7.18 and 7.30 ppm due to the phenyl protons, which is not shown in the Figure 1. The intense resonances included in the region from 3.0 to 5.2 ppm are due to the cyclodextrin. In Figure 2 the spectral regions including the *tert*-butyl and methyl absorptions of **1a** in the free state (Figure 2a), in the mixtures containing racemic **1a** (Figure 2b) and (*R*)-**1a** (Figure 2c) in the presence of TRIMEB (molar ratio hydrocarbon/CSA 1:1) are shown. The mixture, containing the enantiomerically enriched compound, shows (Figure 2c) two sets of signals which have relative intensities corresponding to the optical purity of **1a** (op 68%), and the most intense *tert*-butyl and methyl absorptions are at higher frequencies relatively to the less intense ones. Therefore, the two sets of signals are, respectively, due to the enantiomers of the hydrocarbon, which are fast exchanging between the free and complexed states, with the resonance at higher frequency corresponding to the (*R*) configuration.

The nonequivalences measured at room temperature and in the presence of 1 equiv of TRIMEB are rather small; they progressively increase when temperature is lowered or further equivalents of the CSA are added (Table 1). In any case, the presence in the hydrocarbon of suitable probes, like *tert*-butyl or methyl groups (which give rise to simple NMR signals: singlets or doublets), even makes small nonequivalences useful; indeed the enantiomeric composition can be confidently evaluated by comparing the heights of the diastereotopic signals, provided their line widths are comparable.

As an alternative, the nonequivalences can be affected by varying the total concentration of the solutions, and the data in Table 2 show that a two-fold increase of the nonequivalence is achieved for **1a** by increasing the total concentration from 20 to 80 mM, in the presence of 2 equiv of TRIMEB.

Finally, Table 3 summarizes the nonequivalence induced in the alkyl protons of the compounds **1-3** (80 mM, −20 °C) in the equimolar mixtures hydrocarbon/TRI-

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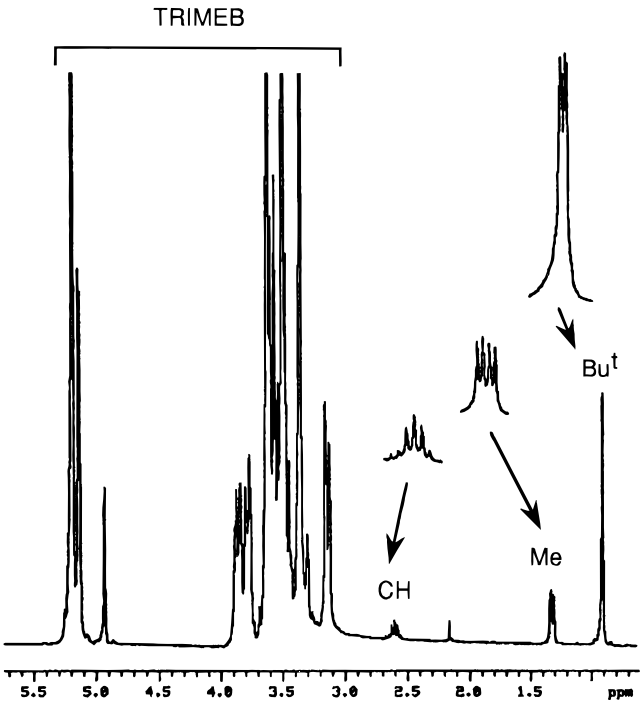

Figure 1. ^{1}H NMR spectrum (300 MHz, CD_3OD, −20 °C) of racemic **1a** (20 mM) in the presence of 3 equiv of TRIMEB.

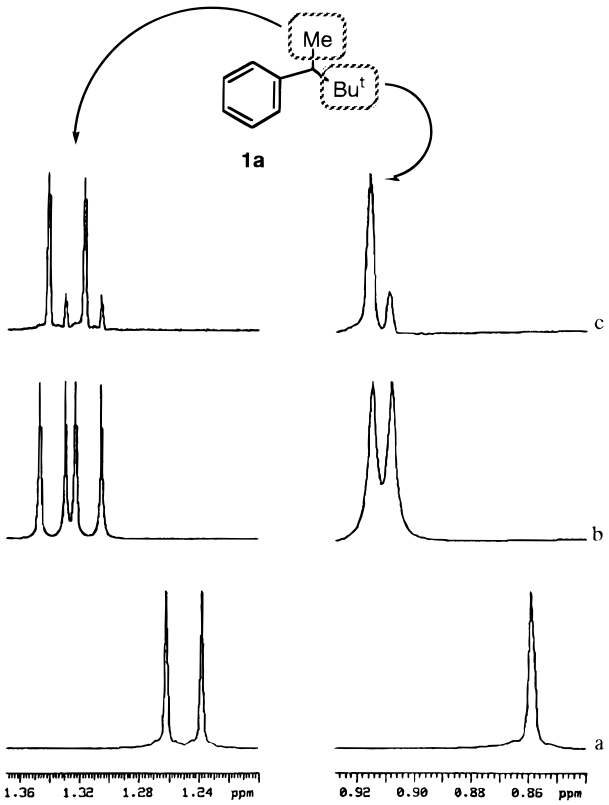

Figure 2. ^{1}H NMR (300 MHz, CD_3OD, −20 °C) spectral regions corresponding to the *tert*-butyl and methyl proton absorptions of **1a** (80 mM) for (a) the free compound, (b) the mixture (*R*,*S*)-**1a**/TRIMEB (1:1), (c) the mixture (*R*)-**1a**/TRIMEB (1:1) (op 68%).

MEB. An important observation arises from the comparison between these data: TRIMEB discriminates the two enantiomers of all the hydrocarbons bearing a phenyl or 2-naphthyl aromatic nucleus, irrespective to the nature of the alkyl groups bound to the chiral center. On the contrary, when the aromatic nucleus is a 1-naphthyl, the structure of the alkyl groups becomes critical: only the two enantiomers of the very crowded substrate **3a** are discriminated by the cyclodextrin, and no nonequivalence can be detected in the case of **3b** and **3c** bearing an isopropyl or ethyl group. Unfortunately, attempts to obtain information on the nature of the cyclodextrin−hydrocarbon interaction by intermolecular NOE measurements failed, probably as a consequence of the lability of the complexes formed, which is also well reflected in the small complexation shifts measured in the mixtures relatively to the free compounds.

Even though the nonequivalences obtained are rather small, great attention must be paid to the fact that no alternative direct method for their ee determination exists; also the gas chromatographic approach which could be promising in principle[6] fails in generality: only **1a**, **1b**, and **3a** were separated well enough by GLC analysis using permethylated *β*-cyclodextrin as chiral stationary phase (Table 4) and no correlation to the hydrocarbon structure (phenyl, 1- or 2-naphthyl) has been found.

In conclusion TRIMEB, a commercially available product, seems to be a useful CSA for apolar chiral phenyl or 2-naphthyl derivatives irrespective to the alkyl groups, whereas, in the case of 1-naphthyl hydrocarbons, the success depends on the structure of the alkyl groups.

Table 1. Nonequivalence ($\Delta\delta\delta$,[a] 300 MHz, CD_3OD) Induced in the Alkyl Protons of 3,3-Dimethyl-2-phenylbutane (1a) (80 mM) in the Presence of TRIMEB, as a Function of the Temperature and of the Molar Ratio 1a/TRIMEB

	molar ratio 1:1			molar ratio 1:2		
	25 °C	0 °C	−20 °C	25 °C	0 °C	−20 °C
Bu^t	0.9	1.4	2.1	1.3	1.9	2.5
Me	1.3	2.1	3.5	1.6	2.8	3.8
CH	2.8	4.7	6.9	5.0	7.4	9.3

[a] $\Delta\delta\delta = |\delta_S - \delta_R|$, difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of TRIMEB.

Table 2. Nonequivalence ($\Delta\delta\delta$,[a] 300 MHz, 25 °C, CD_3OD) Induced in the Alkyl Protons of 3,3-Dimethyl-2-phenylbutane (1a) in the Presence of 2 Equiv of TRIMEB, as a Function of the Concentration (mM)

proton	20	80
Bu^t	0.6	1.3
Me	0.9	1.6
CH	2.1	5.0

[a] $\Delta\delta\delta = |\delta_S - \delta_R|$, difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of TRIMEB.

Table 3. Nonequivalence ($\Delta\delta\delta$,[a] 300 MHz, −20 °C, CD_3OD) Induced in the Alkyl Protons of Hydrocarbons 1a-d, 2, and 3a-c (80 mM) in the Equimolar Mixtures Hydrocarbon/TRIMEB

	a			b				c			d		
	Bu^t	Me	CH	Me[b]	Me[c]	Me	CH	Me[d]	Me	CH	Bu^t	Me[d]	CH
1	2.1	3.5	6.9	0.6	1.1	3.0	0	1.6	0	0	2.0	1.8	4.5
2	4.6	4.3	8.5	1.5	3.0	6.7	4.2	1.7	2.2	1.7			
3	2.9	3.8	4.8	–	–	–	–	–	–	–			

[a] $\Delta\delta\delta = |\delta_S - \delta_R|$, difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of TRIMEB. [b] Low-frequency methyl of the isopropyl group. [c] High-frequency methyl of the isopropyl group. [d] Methyl of the ethyl group.

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Table 4. Gas Chromatographic Separations of Aromatic Hydrocarbons 1a, 1b, and 3a on Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (CYDEX-B) Stationary Phase

compd	k' [a]	α	column temperature, °C
1a	17.50	1.03	65
1b	11.97	1.02	60
3a	22.34	1.01	130

[a] The capacity factor of the first-eluted enantiomer.

However, considering also what has been previously reported in the case of the trisubstituted allenes[5] and α-pinene[3d] the permethylated β-cyclodextrin seems a versatile and promising CSA for the NMR ee determination of apolar chiral substrates.

Experimental Section

The ^{1}H NMR measurements have been performed at 300 MHz in CD_3OD; the temperature was controlled to ±0.1 °C. For the gas chromatographic analyses fused silica columns DB-1 (30 m, i.d. 0.25 mm, film thickness 0.25 μm), CYDEX-B (25 m, i.d. 0.33 mm, film thickness 0.25 μm) and helium as carrier gas (12 and 10 psig, respectively) have been employed. Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) and *sec*-butylbenzene (2-phenylbutane, **1c**) were purchased from Sigma. Racemic **1**-**3** were prepared according to reported procedures[7,8] for the corresponding optically active compounds.

(*R*,*S*)-3,3-Dimethyl-2-phenylbutane (1a):[7] ^{1}H NMR δ 0.86 (9H, s), 1.25 (3H, d, J = 7.3 Hz), 2.50 (1H, q, J = 7.3 Hz), 7.08−7.30 (5H, m).

A sample of (−)-(*R*)-**1a** having $[\alpha]^{25}_D$ = 17.48 (neat) and ee 68.4% (GLC) was also prepared.

3-Methyl-2-phenylbutane (1b):[7] 66% yield, ^{1}H NMR δ 0.72 (3H, d, J = 6.7 Hz), 0.94 (3H, d, J = 6.7 Hz), 1.22 (3H, d, J = 7.1 Hz), 1.75 (1H, m), 2.37 (1H, m), 7.08−7.30 (5H, m). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.03; H, 10.97.

2-Phenylbutane (1c): ^{1}H NMR δ 0.79 (3H, t, J = 7.3 Hz), 1.21 (3H, d, J = 7.0 Hz), 1.58 (1H, m), 1.60 (1H, m), 2.56 (1H, m), 7.08−7.30 (5H, m).

2,2-Dimethyl-3-phenylpentane (1d):[7] ^{1}H NMR δ 0.65 (3H, t, J = 7.2 Hz), 0.87 (9H, s), 1.69 (1H, m), 1.84 (1H, m), 2.22 (1H, dd, J_1 = 12.1 and J_2 = 3.1 Hz), 7.08−7.30 (5H, m). Anal. Calcd for $C_{13}H_{20}$: C, 88.57; H, 11.43. Found: C, 88.53; H, 11.47.

3,3-Dimethyl-2-(2-naphthyl)butane (2a):[8b] ^{1}H NMR δ 0.91 (9H, s), 1.35 (3H, d, J = 7.3 Hz), 2.74 (1H, q, J = 7.3 Hz), 7.34 (1H, dd, J_1 = 8.8 and J_2 = 1.8 Hz), 7.37−7.46 (2H, m), 7.60 (1H, d, J = 1.8 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.74−7.84 (2H, m). Anal. Calcd for $C_{16}H_{20}$: C, 90.51; H, 9.49. Found: C, 90.48; H, 9.52.

3-Methyl-2-(2-naphthyl)butane (2b):[8b] ^{1}H NMR δ 0.76 (3H, d, J = 7.0 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.32 (3H, d, J = 7.0 Hz), 1.88 (1H, m), 2.56 (1H, m), 7.33 (1H, dd, J_1 = 8.4 and J_2 = 1.5 Hz), 7.37−7.46 (2H, m), 7.58 (1H, d, J = 1.5 Hz), 7.72−7.84 (3H, m). Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.83; H, 9.17.

2-(2-Naphthyl)butane (2c):[8a] ^{1}H NMR δ 0.83 (3H, t, J = 7.3 Hz), 1.31 (3H, d, J = 7.0 Hz), 1.69 (2H, m), 2.75 (1H, m), 7.34 (1H, dd, J_1 = 8.8 and J_2 = 1.8 Hz), 7.36−7.46 (2H, m), 7.59 (1H, d, J = 1.8 Hz), 7.70−7.84 (3H, m). Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.22; H, 8.78.

3,3-Dimethyl-2-(1-naphthyl)butane (3a):[8b] ^{1}H NMR δ 0.91 (9H, s), 1.37 (3H, d, J = 7.3 Hz), 3.68 (1H, q, J = 7.3 Hz), 7.36−7.52 (4H, m), 7.69 (1H, dd, J_1 = 5.5 and J_2 = 4.1 Hz), 7.82 (1H, dd, J_1 = 8.1 and J_2 = 1.8 Hz), 8.24 (1H, dd, J_1 = 9.2 and J_2 = 1.5 Hz). Anal. Calcd for $C_{16}H_{20}$: C, 90.51; H, 9.49. Found: C, 90.51; H, 9.49.

3-Methyl-2-(1-naphthyl)butane (3b):[8b] ^{1}H NMR δ 0.83 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.33 (3H, d, J = 7.0 Hz), 2.02 (1H, m), 3.39 (1H, m), 7.34−7.54 (4H, m), 7.68 (1H, dd, J_1 = 7.7 and J_2 = 1.1 Hz), 7.84 (1H, dd, J_1 = 7.7 and J_2 = 1.8 Hz), 8.13 (1H, dd, J_1 = 8.5 and J_2 = 1.1 Hz). Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.87; H, 9.13.

2-(1-Naphthyl)butane (3c):[8a] ^{1}H NMR δ 0.90 (3H, t, J = 7.3 Hz), 1.35 (3H, d, J = 7.0 Hz), 1.74 (1H, m), 1.82 (1H, m), 3.53 (1H, m), 7.32−7.54 (4H, m), 7.67 (1H, dd, J_1 = 7.7 and J_2 = 1.1 Hz), 7.83 (1H, dd, J_1 = 8.0 and J_2 = 1.8 Hz), 8.13 (1H, dd, J_1 = 8.1 and J_2 = 1.1 Hz). Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.27; H, 8.73.

JO951314L

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