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Determination of Enantiomeric Purity of 1-Phenylalkanols Using a Chiral NMR Shift Reagent

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Synopsis. Addition of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) to solutions of partly active (*S*)-1-phenylalkanols caused large enantiomeric-shift differences ($\Delta\Delta\delta$) in their ^{1}H NMR spectra, which permitted a direct determination of enantiomeric compositions of these alkanols.

Recently, chiral lanthanide shift reagents[1] have been applied to the direct determination of enantiomeric purity of certain organic Lewis bases.

We wish to record a quantitative determination of enantiomeric compositions of a series of partly active 1-phenylalkanols (excess (*S*) isomer), obtained *via* catalytic asymmetric hydrosilylation of the corresponding alkyl phenyl ketones[2] (Eq. 1).

$$\begin{matrix} R \\ \diagdown \\ C{=}O \\ \diagup \\ Ph \end{matrix} + Me_2PhSiH \xrightarrow[\text{catalyst}]{\text{chiral Rh}^+} RPhC^*HOSiMe_2Ph \xrightarrow{OH^-} RPhC^*HOH \qquad (1)$$

(R=Me, Et, *iso*-Pr, and *tert*-Bu)

In ^{1}H NMR spectra of the alkanols, addition of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) (**1**) to the solutions examined caused large enantiomeric-shift differences ($\Delta\Delta\delta$) in the α-proton signals, as for 1-phenylethanol ($\Delta\Delta\delta$=0.30 ppm).[1b,3] The effect of this chiral shift reagent on the alkanol spectra is shown in Table 1.

It is interesting to note that a systematic decrease in the magnitude of downfield paramagnetic-induced shifts ($\Delta\delta$) of alkanol proton signals (*tert*-Bu<*iso*-Pr<Et) can reflect differences in the bulkiness of these alkanols, showing a relationship parallel to the reverse of the degree of asymmetric induction by the hydrosilylation of alkyl phenyl ketones. The fact that all the protons of (*R*)-alkanols resonate definitely at lower fields than those of (*S*)-enantiomers supports the view that the enantiomeric-shift difference can result from the difference in the stability constants of forming diastereoisomeric complexes of **1** with the alkanols[1a] rather than that in magnetic environments of the complexes.[1b,d]

The enantiomeric compositions of the respective alkanols have been determined on the basis of peak areas of completely separated signals due to their α-proton in the lanthanide-assisted spectra. The results are summarized in Table 2, showing exact agreement with those determined from maximum rotations.[4]

Experimental

Complex **1** was prepared by the reaction of 3-trifluoromethylhydroxymethylene-*d*-camphor (**2**) with europium(III) chloride according to the procedure of Goering *et al.*[1b] Diketone **2** was prepared by the following Grignard reaction of *d*-3-bromocamphor with ethyl trifluoroacetate.[5]

A mixture of 23.3 g (0.10 mol) of *d*-3-bromocamphor, 14.5 g (0.105 mol) of ethyl trifluoroacetate, and 2.56 g (0.105 g-atom) of magnesium in 230 ml of anhydrous ether was heated at reflux for 2 hr. The reaction mixture was then hydrolyzed with 10% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. The combined ether solution and extracts were washed twice with saturated sodium chloride solution, and the solvent was

Table 1. Effect of chiral shift reagent (**1**) on the NMR spectra of enantiomeric secondary alcohols

Compound	Proton	Paramagnetic-induced shifts ($\Delta\delta$, ppm)					
		Mole ratio[a] 0.3			Mole ratio[a] 0.5		
		(*R*)	(*S*)	$\Delta\Delta\delta$[b]	(*R*)	(*S*)	$\Delta\Delta\delta$[b]
1-Phenyl-2,2-dimethyl-1-propanol	CH_3	1.20	1.15	0.05	1.69	1.64	0.05
	CH[c]	2.78	2.61	0.17	3.93	3.72	0.21
	H_{ortho}	1.36	1.29	0.07	1.93	1.83	0.10
1-Phenyl-2-methyl-1-propanol	CH_3[d]	1.53	1.44	0.09	2.35	2.24	0.11
	CH_3[d]	2.04	2.01	0.03	2.89	2.85	0.04
	CH[c]	4.32	3.98	0.34	6.25	5.81	0.44
	H_{ortho}	2.06		—	3.04		—
1-Phenyl-1-propanol	CH_3	2.05	2.03	0.02	2.44	2.42	0.02
	CH[c]		—[e]		7.50	7.21	0.29
	H_{ortho}		—[e]		3.57		—

a) **1**/alkanol: stepwise addition of **1** to a solution containing 0.2—0.3 mmol of the alkanol in 0.4 ml of CCl_4 (TMS as an internal standard). b) Differential downfield shifts in ppm. c) Used for quantitative determination of enantiomeric compositions under complete separation of signals. d) Diastereotopic methyls. e) Not measured.

Table 2. Enantiomeric purity of partly active 1-phenylalkanols

Compound	Peak ratio[a] (*S*)/(*R*)	$[\alpha]_D^{20}$, deg	Enantiomeric purity, %[b]
1-Phenyl-2,2-dimethyl-propanol	2.52	−11.20 (*c* 4.1, PhH)	43 (43.3)
1-Phenyl-2-methyl-propanol	2.28	−18.81 (*c* 7.0, Et_2O)	39 (39.4)
1-Phenylpropanol	1.89	−8.47 (neat)	31 (30.2)

a) Determined by cutting out and weighing each peak.
b) Values based on maximum rotations are indicated in parentheses.

removed by evaporation. The residue was fractionally distilled to give 18.9 g (76%) of diketone **2**;[6] bp 62.0—62.5 °C/2 mmHg; n_D^{20} 1.4520; $[\alpha]_D^{20}$ +148° (*c* 4.12, benzene).

The NMR spectra were measured on 0.50—0.75 M-solutions of partly active 1-phenylalkanols[2] in CCl_4 (TMS as an internal standard) using a Varian HA-100 (at 31.4 °C) or a Hitachi R-20B spectrometer. The chiral shift reagent (**1**) was dried *in vacuo* at 60° over phosphorus pentoxide before use. All data are given in Tables 1 and 2.

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References

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3) Other modifications of **1**, in which the trifluoromethyl group was replaced by a *tert*-Bu or C_3F_7 have no advantage in this respect (Ref. 1c).

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6) Although Schurig [*Tetrahedron Lett.*, **1972**, 3297] has recommended the exchange reaction of lanthanide salts with the barium chelate of diketone **2**, the preparation of the free diketone does not seem to be tedious.