

Determination of Enantiomeric Purity of Polar Substrates with Chiral Lanthanide NMR Shift Reagents in Polar Solvents¹

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Received September 17, 1986

The proton NMR spectra of 19 1,2- and 1,3-dioxygenated compounds were studied in deuteriated acetonitrile, acetone, and chloroform in the presence of chiral lanthanide NMR shift reagents tris(3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato)europium(III) (1) and tris(((trifluoromethyl)hydroxymethylene)-*d*-camphorato)europium(III) (2). Enantiotopic *OH*, *CH*, and *CH*₃ NMR resonances were best resolved in acetonitrile; line broadening obscured the scalar coupling. Enantiomeric excesses as high as 98% can be determined for 16 of these compounds in this polar solvent.

Chiral synthons are often smaller polar molecules, and it is useful to have a simple method of determining their optical purity. Methods based on chiral lanthanide shift reagents often fail with these substances² for several reasons. They may be contaminated with water and sparingly

soluble in the nonpolar solvents normally used with shift reagents (CDCl₃, CD₂Cl₂). In these solvents, their strong binding to the lanthanide ion (often a reflection of chelation by multiple polar functions) gives broad resonances and, as a consequence, poor resolution between enantiotopic resonances in the NMR spectrum.³ We have re-

(1) Supported by the National Science Foundation, Grants CHE 85-08702 and NIH GM 30367.

(2) For references to non lanthanide based methods, see: Luchinat, C.; Roelans, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873-4878.

(3) Sullivan, G. R. *Top. Stereochem.* **1979**, *10*, 287-329. Fraser, R. R. *Asymmetric Synth.* **1983**, *1*, 173-196. McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038-1054.

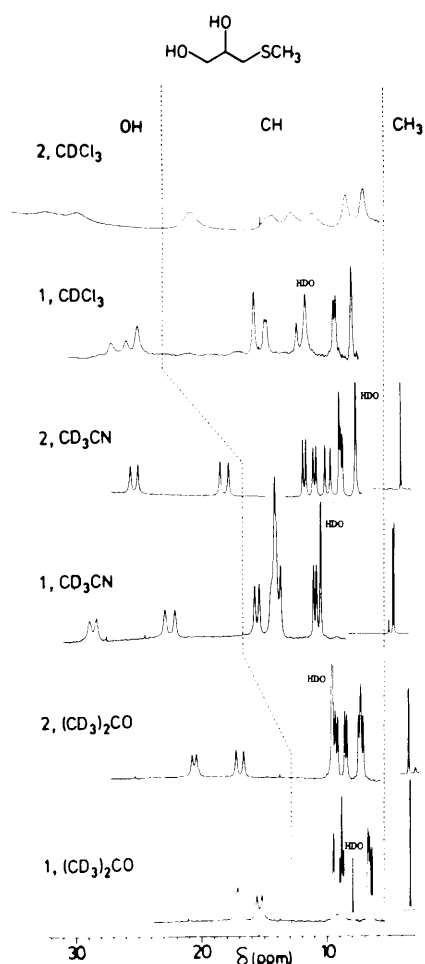


Figure 1. Proton NMR spectra of 0.2 M 3-(methylthio)propane-1,2-diol in the presence of 0.2 M shift reagents 1 and 2 in CDCl_3 , CD_3CN , and $(\text{CD}_3)_2\text{CO}$.

cently reported that the enantiomeric excess of one representative molecule of this type, 3-chloropropane-1,2-diol, could be determined by the nonequivalence of enantiotopic OH resonances by using tris(3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato)europium(III) (1) in the polar, coordinating solvent acetonitrile.⁴ This observation was interesting both for its suggestion of broad utility for chiral shift reagents in polar solvents and for the spectroscopic observation of enantiotopic hydroxyl groups. We have examined the generality of this observation and find that a wide variety of 1,2- and 1,3-dioxygenated compounds exhibit well-resolved enantiotopic protons (OH, CH, and CH_3) in the presence of 1 or tris(((trifluoromethyl)hydroxymethylene)-*d*-camphorato)europium(III) (2) in acetonitrile or acetone. Acetonitrile consistently permits resolution of enantiotopic protons of 1,2- and 1,3-diols more completely than either chloroform or acetone; the less polar carbonyl compounds are resolved equally well in chloroform.

Results and Discussion

Sensitivity of Enantiotopic Shifts to Structure. We summarize the spectral results obtained with a number of polar substances with chiral europium shift reagents in acetonitrile and acetone in Table I and compare those results with similar experiments conducted with chloroform as a solvent. Figures 1–3 give representative spectra.

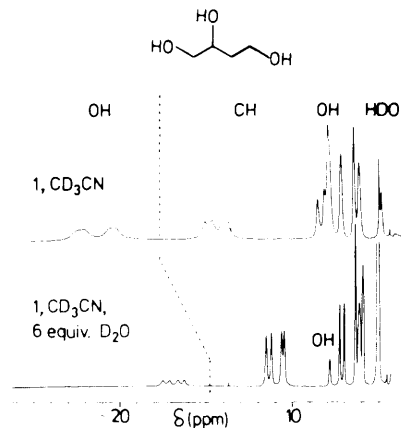


Figure 2. Proton NMR spectra of 0.2 M butane-1,2,4-triol in the presence of 0.2 M shift reagent 1 in acetonitrile- d_3 : “anhydrous” (upper) and in the presence of D_2O (lower; 6 molar equiv of D_2O /mol of substrate added).

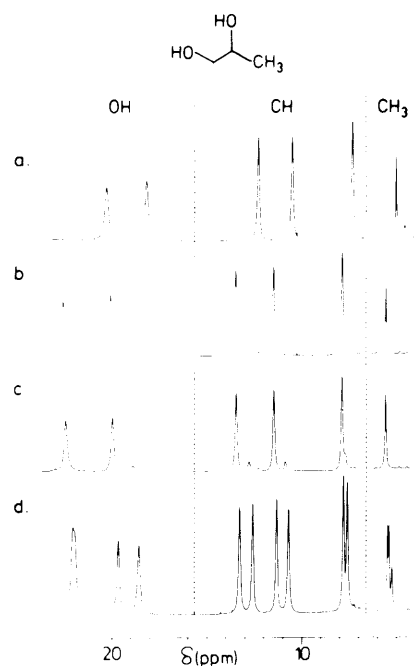



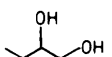
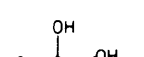
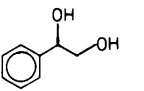
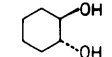
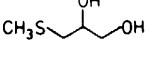
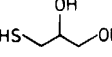
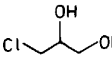
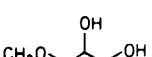
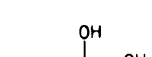
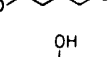

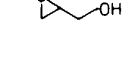



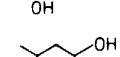
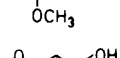

Figure 3. Proton NMR spectra of 0.2 M propane-1,2-diol in the presence of 0.2 M shift reagent 2 in acetonitrile- d_3 . (a) *R* isomer, prepared from glucose by fermentation using *Clostridium thermosaccharolyticum* (ATCC 31960). (b) *R* isomer, prepared by reduction of hydroxyacetone by fermenting *Saccharomyces cerevisiae*. This sample has traces of impurities. (c) A mixture of 90% *R* from b and 10% racemic, prepared by volume with use of micropipettes. (d) Racemic. The small differences in chemical shift for the enantiomers between samples is caused primarily by small differences in concentration. A shift-reagent peak overlaps the CH_3 signal in each case.

Table I summarizes qualitatively the ease of discrimination of enantiotopic protons. We estimate that if the valley between two enantiotopic resonances in the racemic mixture is less than 5%, an enantiomeric excess of 98% or less can be determined; such “base-line” resolution for at least one pair of enantiotopic resonances is indicated by “++”. “Useful” resolution corresponds to a <15% valley and is indicated by “+”; such resolution would permit determination of enantiomeric excess of up to 90%. A “–” indicates that enantiotopic protons are resolved, but too poorly for use in a quantitative determination of enantiomeric excess. A “—” indicates that no enantiotopic protons were resolved.

We conclude that the enantiomeric purity of 1,2-dioxygenated compounds and 1,3-diols is best determined

(4) Crans, D. C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 7019–7927.

Table I. Ability of Chiral Shift Reagents 1 and 2 To Induce Shift Differences between Enantiotopic Protons in Some Polar Organic Compounds^a

Shift Reagent	Chloroform-d		Acetonitrile-d ₃		Acetone-d ₆	
	1	2	1	2	1	2
Substrate						
	-	--	+ h	++ h	+	++ h
	-	--	++	++ h	+	++ h
	-	--	++	++ h	++	++ h
	+	-	++	++ h	+	++
	+	--	- p	++ h	-	+
	-	--	++ h	++ h	+	++ h
	-	--	++ h	++ h	++	++ h
	-	--	++ h	+ h	++ h	+ h
	- i	- i	+	+ h	-	+ h
	i	i	+	+ h	++	++ h
	i	i	-	-	-	+
	++	-	++	++ h	-	+ h
	++	++	++	++	-	-
	-	--	++	+	++	-
	++	--	++ h	++ h	-	-
	++	--	++ p	++	-	-
	++ h	+	++ h	++ h	-	-
	+	--	++ h	++	-	-
	++	--	++	++ h	-	--

^a ++ = "base-line" resolution, + = "useful" resolution, - = poor resolution, -- = no resolution of enantiotopic protons; see text for details. h = enantiotopic hydroxyl proton(s) resolved with less than a 15% valley between resonances (may be less than a 5% valley). i = not completely soluble; results, where given, are for substrate concentrations less than 0.2 M. p = separation of a second small, denser liquid phase.

in acetonitrile. Acetone is also an effective solvent for the 1,2-diols. For less polar compounds, chloroform also

permits "base-line" resolution of enantiotopic resonances; others have found that chloroform and carbon tetrachloride are effective solvents for determining the enantiomeric purity of less polar diols.⁵ The binding of the materials in Table I to the shift reagent is much stronger than that of monofunctional substrates. As a result, the hydroxyl resonances typically reach chemical shifts of over 15 ppm, the methine and methylene from 4 to 15 ppm (with no overlap of OH and CH for each substrate), and the CH₃ resonances from 2 to 7 ppm; the latter sometimes overlap the CH or the shift reagent. Plots of the chemical shifts as a function of the ratio of concentrations of lanthanide to substrate (*L/S*) (0.2 M substrate) indicate that the complexes have 1:1 stoichiometry;⁶ the chemical shift differences between enantiomers and the shifts themselves change very little between *L/S* 0.7 and 2.0. Figure 1 shows spectra typical of those observed under conditions used to obtain the data summarized in Table I. We note particularly that enantiotopic OH resonances are commonly observed, especially with 2 in acetonitrile; we have found only one other example of enantiotopic OH resonances exhibiting nonequivalence in a chiral medium.⁷ Previous studies of lanthanide shift reagents have concentrated on uncoupled methyl groups because the CH and OH resonances have been too broad for enantiotopic resonances to be resolved. In our solutions, the shift differences were often great enough to exceed the broadening. The broadening did, however, obscure the spin-spin coupling information; as a result, it was not possible to assign the resonances without systematically varying the *L/S* ratio. It is clear from an inspection of the spectra that the splittings observed are differences in chemical shifts rather than scalar coupling; the splittings are much too large to be proton-proton couplings (the enantiotopic CH's of 3-(methylthio)propane-1,2-diol with 2 in CD₃CN (Figure 1), for example, are separated by 100 Hz), all are doublets, and they scale with the magnetic field (for those samples tested). Methyl groups and weakly binding substrates frequently show both coupling and chemical-shift differences. The results for glycerol indicate that the resonances of the secondary CHOH protons are shifted more than the resonances of the primary CH₂OH protons.

The shift differences for a particular substrate-shift reagent pair are reduced in the more strongly coordinating acetone; however, acetone dissolves more polar substances that are only sparingly soluble in acetonitrile. Acetone solutions of the shift reagents produced well-resolved and strongly shifted spectra of several derivatives of carbohydrates;⁸ this observation suggests that shift reagents in acetone might be useful in defining structures for derivatives of carbohydrates.

Overall, our results indicate an order of strength of binding of substrate to shift reagent of 1,2-diols > other 1,2-dioxygen-containing species ≥ 1,3-dioxygen-containing species. The poor results for 3-methoxypropane-1,2-diol, excellent results for glycidol, and the similarity of bu-

(5) Jakovac, I. J.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165-2168. Johnson, P. Y.; Jacobs, I.; Kerkman, D. J. *J. Org. Chem.* **1975**, *40*, 2710-2720.

(6) Monofunctional substrates form both 1:1 and 2:1 complexes; it appears that the dioxygenated compounds occupy two sites on the octacoordinate europium(III).

(7) Sweeting, L. M.; Anet, F. A. L. *Org. Magn. Reson.* **1984**, *22*, 539-452.

(8) Carbohydrate derivatives examined in acetone included 1,2-*O*-isopropylidene- α -D-glucopyranose, 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose, and 4,6-*O*-benzylidene-1-*O*-methyl- β -D-glucopyranose, which are insufficiently soluble in acetonitrile to give useful spectra. Unfortunately, glyceraldehyde did not dissolve sufficiently in acetone to yield useful spectra.