The Determination of Enantiomeric Purity Using Chiral Lanthanide Shift Reagents[1]

Sir:

Tris[*tert*-butylhydroxymethylene-*d*-camphorato]europium(III) (**1**) induces contact and/or pesudocontact shifts of different magnitudes in corresponding protons

of certain enantiomeric Lewis bases.[2,3] This observation demonstrates that nmr spectroscopy using chiral lanthanide chelates can in principle be employed to establish absolute enantiomeric purity; in practice, the utility of **1** is restricted to applications involving relatively basic and unhindered substrates (*e.g.*, primary and secondary amines), and fails with less basic substances. Here we wish to report the synthesis of the chiral shift reagents **2–7** and to outline data demonstrating the general applicability of these materials to the determination of the enantiomeric purity of relatively nonbasic substances.

The β-diketone ligands from which these complexes are derived were prepared either by procedures analogous to that described previously for **1**[3] (for **2** and **3**), or by slow addition of the methyl ketone derived from R″ to a refluxing solution of the acid chloride derived from R′ in dimethoxyethane containing *ca.* 1 equiv of suspended sodium hydride and a catalytic amount of *tert*-butyl alcohol (for **4–7**).[4] Conversions of these
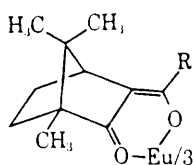
1, R = R₁
2, R = R₂
3, R = 77% R₁ + 23% R₂
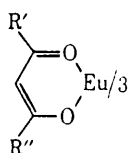
4, R′ = R₂; R″ = R₂
5, R′ = R₂; R″ = R₁
6, R′ = 77% R₁ + 23% R₂; R″ = R₁
7, R′ = R₂; R″ = 77% R₁ + 23% R₂

R₁ = C(CH₃)₃

R₂ =

R₃ =

R₄ =
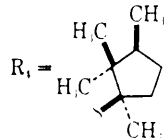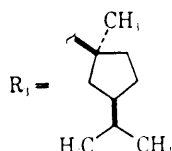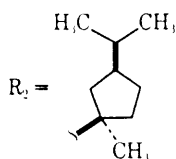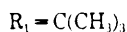
β-diketones to the europium complexes **2–7** were accomplished as described previously;[2,5] crude complexes were purified by sublimation.

The *collective* utility of compounds **2–7** in separating the resonances of enantiomeric amines, alcohols, ketones, esters, and sulfoxides appears to be quite general; one or another of these shift reagents has induced shifts between enantiomers present in samples of the majority of these substances that we have examined. However, no single one of these reagents appears to be clearly superior to the others for every application.

(2) G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, **92**, 6979 (1970).

(3) The utility of lanthanide chelates as shift reagents was first demonstrated by C. C. Hinckley, *ibid.*, **91**, 5160 (1969).

(4) Fenchoic acid was obtained from fenchone and campholic acid from camphor using standard procedures: *cf.* F. W. Semmler, *Chem. Ber.*, **39**, 2577 (1906); K. E. Hamlin and A. W. Weston, *Org. React.*, **9**, 1 (1957); F. E. L. Humbert, *Bull. Soc. Chim. Fr.*, 2867 (1966). The *d*-fenchone used in this study contained 23% of the *l* enantiomer. Carboxylic acids were converted to the corresponding methyl ketones and acid chlorides by standard procedures, using methyllithium and thionyl chloride, respectively.

(5) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).
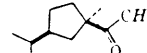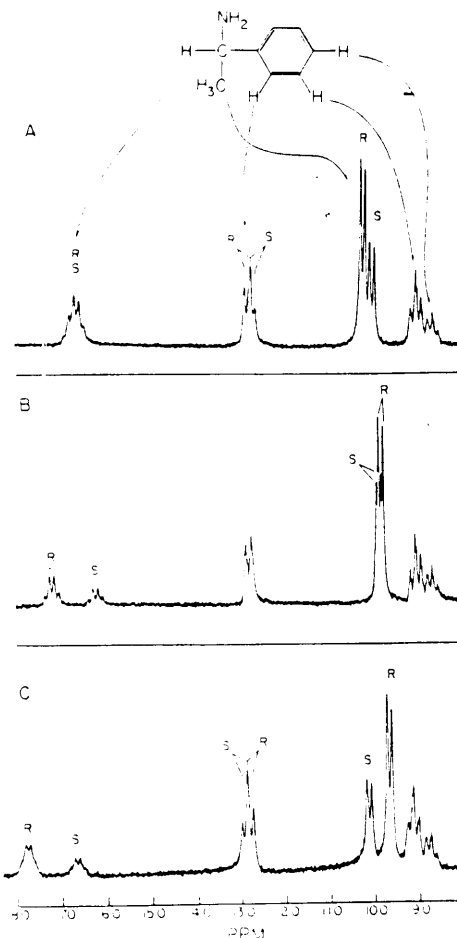

Figure 1. Spectra of solutions prepared from mixtures of (*R*)- and (*S*)-1-phenylethylamine in CCl₄ containing the chiral shift reagents **3** (0.20 *M*) (A), **2** (0.19 *M*) (B), and **7** (0.15 *M*) (C). In each solution the *R* enantiomer is present in higher concentration than the *S*. Solutions are approximately 0.35 *M* in 1-phenylethylamine. The conditions under which these spectra were obtained are not necessarily those in which the enantiomeric shift differences are maximized.

Thus, representative data obtained for typical substrates with reagents **2** and **7** (Table I), and the full spectra shown in Figure 1, demonstrate an appreciable (and presently unpredictable) sensitivity of the shifts between resonances of enantiomers to changes in the structure of the shift reagent.

Table I. Differences in Resonance Fequencies (ΔΔδ, ppm) between Corresponding Protons of Enantiomers in the Presence of Shift Reagents **2** and **7**

Compound	ΔΔδ 2[a]	ΔΔδ 7[b]
C₆H₅C*H*(CH₃)NH₂	1.13	1.65
C₆H₅CH(C*H₃*)NHCH₃	0.28	0.46
C₂H₅CHNH₂C*H₃*	0.20	0.64
CH₃C*H*NH₂CO₂C₂H₅	0.75	0.97
C₆H₅CC*H₃*(C₂H₅)OH	0.32	0.25
C₅H₁₁CHOHC*H₃*	0.10	0.00
C₆H₅C*H₂*SOCH₃	0.32	0.40
C₂H₅CH(O₂CC*H₃*)CH₃	0.00	0.075
C₂H₅CH(O₂CH)C*H₃*	0.00	0.10
CH₃COCH(C*H₃*)C₂H₅	0.00	0.058
⬡CH₃ (structure)	0.00	0.050

[a] Spectra were obtained in CCl₄ solutions *ca.* 0.4 *M* in shift reagent and 0.3 *M* in substrate. [b] Solutions in CCl₄, *ca.* 0.25 *M* in shift reagent.

Two features of the presently available data suggest that the association and conformational equilibria responsible in part for the enantiomeric shift differences are complex. First, there is no apparent correlation between the magnitudes of the shifts induced in chemically distinct sets of enantiomeric protons and the structure of the shift reagents. Thus, the shift between the methyl protons of (R)- and (S)-1-phenylethylamine is small in solutions of 2 but moderately large in the presence of 3, while the CH protons in the same samples show the opposite behavior (Figure 1). Second, the *sense* of the shift difference need not be the same for all the protons in enantiomeric substrates; each proton in (R)-1-phenylethylamine falls at lower field than the corresponding proton of the S enantiomer in solutions containing 1,[2] while the protons of the methyl group of the R enantiomer resonate at *higher* field, and the CH of this enantiomer at *lower* field, than the analogous S protons, in the presence of 2 and 7. Since the shielding experienced by protons in complexes of lanthanide shift reagents with substrates is a sensitive function of the geometry of these complexes,[6,7] and since the diastereomeric complexes formed as the result of coordination of enantiomeric bases to chiral chelates need not necessarily have closely related geometries, these observations are not surprising. However, they do suggest that *prediction* of the sense and relative magnitudes of shifts between enantiomers in these systems will be difficult,[8] and that in practical applications it may accordingly be worthwhile to examine several different chiral shift reagents to find empirically the one giving the most useful spectra.[8a]

Acknowledgment. We wish to thank Professor Harlan Goering for communicating results prior to publication[9] and for samples, and Hoffmann-LaRoche, Inc., for gifts of optically active compounds.

(6) B. L. Shapiro, J. R. Hlubucek, C. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971); P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *ibid.*, **92**, 5734, 5737 (1970), and references in each.

(7) For recent structural data on tris(β-diketo)lanthanide complexes, see J. C. A. Boeynes, *J. Chem. Phys.*, **54**, 75 (1971); W. D. Horrocks, Jr., J. P. Sipe III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258 (1971), and references in each.

(8) The prospects for utilizing chiral shift reagents to determine *absolute* configurations presently appear very dim. For successful applications of nmr spectroscopy in chiral solvents to determination of absolute configurations, see W. H. Pirkle, R. L. Muntz, and I. C. Paul, *ibid.*, **93**, 2817 (1971).

(8a) Note Added in Proof. Additional evidence supporting the hypothesis that the conformation of the β-diketone ligands around the europium ion is fairly flexible is provided by the observation by M. McCreary that it is possible to *induce* chirality in Eu(DPM)$_3$ by coordination with a chiral amine. Thus, a $\Delta\Delta\delta$ of 0.36 ppm is observed for the CHNH$_2$ resonance of racemic 1-phenylethylamine (0.45 M) in a CDCl$_3$ solution containing Eu(DPM)$_3$ (0.45 M) and (R)-N-methyl-1-phenylethylamine (0.64 M).

(9) H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *ibid.*, **93**, 5913 (1971).

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