Correlation of Configuration of Chiral Secondary Carbinols by Use of a Chiral Lanthanide Nuclear Magnetic Resonance Shift Reagent[1]

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The nmr chemical shifts induced in a series of 12 pairs of enantiomers of secondary carbinols of known configuration by the chiral shift reagent tris[(3-heptafluorobutyryl)-*d*-camphorato]europium(III), *d*-Eu(HFC)$_3$, have been measured and correlated. In the presence of this chiral shift reagent at least one signal from each carbinol serves to distinguish one enantiomer from the other. Thus this reagent can be used for the determination of enantiomeric purity of these secondary carbinols. The signal from the carbinyl proton uniformly has the largest europium-induced chemical shift ($\Delta\delta$) and generally but not always is the signal for which the largest chemical shift difference between enantiomers ($\Delta\Delta\delta_{R-S}$) is observed. A direct correlation between configuration and chemical shift differences, $\Delta\Delta\delta_{R-S'}$, for the proton attached to the carbinyl carbon in the secondary carbinols RCHOHR′ was not observed. However, there was a consistent pattern to the chemical shift differences for the protons in either R or R′. This study reveals that great care will be required in the application of chiral shift reagents for the establishment of configurations based on empirical correlations.

Since the first report of a chiral lanthanide shift reagent[2] (LSR), a wide variety of such chiral reagents have been synthesized and used with many compounds. It has been shown that in the presence of these reagents the nmr signals of enantiotopic groups on virtually all chiral molecules containing the necessary functionalities can be distinguished under the appropriate conditions.[3-15] This technique has been generally accepted for the direct determination of enantiomeric purity. Recently, the use of these reagents for the correlation of configuration in closely related compounds has been demonstrated for a series of α-amino esters,[3] a series of 1-deuterio primary alcohols,[4] and a series of alkyl aryl carbinols.[15] Whitesides[5] and Goering[6] have also considered the possible use of chiral shift reagents for configuration correlation but have not explored it further.

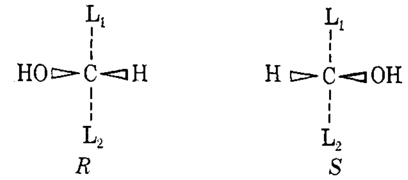
The use of the chiral europium shift reagent tris[(3-heptafluorobutyryl)-*d*-camphorato]europium(III), *d*-Eu(HFC)$_3$, for this purpose has now been extended to the 12 chiral secondary alcohols shown in Table I. The groups L$_1$ and L$_2$ in this table are specified such that L$_1$ has the lower priority in the Cahn, Ingold, and Prelog nomenclature scheme.[16] This is an arbitrary assignment which in the absence of heteroatoms in either R group generally designates the less bulky group as L$_1$. In Table I are listed the lanthanide-induced shifts (LIS or $\Delta\delta$) of the signals for the enantiomers, the differences in the lanthanide-induced shifts (ΔLIS or $\Delta\Delta\delta$) for the *R* and *S* enantiomers, and the molar ratios (LSR/substrate) at which the spectra were recorded.

There are basically three series represented by the compounds in Table I. In the first series L$_1$ is equal to methyl, while L$_2$, the larger group, is varied; in the second series L$_2$ is equal to phenyl (generally the more bulky group), while L$_1$ is varied. The third series comprises the four examples containing a *tert*-butyl group, namely, the last two entries and the member of each of the other series which contains a *tert*-butyl group. There is a definite correlation in the configuration of the carbinol and the sense of nonequivalence in the europium-induced shift difference ($\Delta\Delta\delta_{R-S}$) for the L$_1$ and L$_2$ proton resonances. Without exception the $\Delta\Delta\delta_{R-S}$ values for the protons on the L$_1$ substituents were negative. The corresponding values for the L$_2$ substituents were also negative where a difference was observed, but in the latter case four examples failed to show any difference. However, the $\Delta\Delta\delta_{R-S}$ values for the signals from the protons on the carbinyl carbon did not show this uniformity; four were zero, five were positive, and three were negative. It may be significant that the three examples with negative $\Delta\Delta\delta_{R-S}$ values for the carbinyl proton signals were substituted *tert*-butylcarbinols (methyl, *n*-butyl, and phenyl).

These limited results indicate that a reliable configurational correlation for secondary carbinols, L$_1$CHOHL$_2$, in general cannot be based on the $\Delta\Delta\delta_{R-S}$ value for the proton on the carbinyl carbon, contrary to the suggestion of Červinka, *et al.*[15] However, the uniformly negative $\Delta\Delta\delta_{R-S}$ values for the proton signals on the L$_1$ and L$_2$ substituents, when observable, indicate that the correlation of these signals with configuration may be general. Such a correlation should prove reliable and valuable when applied within a closely related series and with due consideration for the nature of the substituent groups. Secondary carbinols which have L$_1$ and L$_2$ substituents which are unsaturated or contain heteroatoms very likely will constitute special cases. By studying several members of a coherent series of such compounds, however, a suitably specialized correlation might emerge.

There seems to be no readily apparent direct relationship between the difference in steric requirements of L$_1$ and L$_2$ and the *magnitude* of the $\Delta\Delta\delta_{R-S}$ values, as one might have anticipated. There is a hint that as the substrate becomes more sterically hindered around the carbinol carbon by virtue of increasing size of both L$_1$ and L$_2$ the $\Delta\Delta\delta_{R-S}$ values increase. This is seen in progressing from methylethylcarbinol to methyl-*tert*-butylcarbinol and finally to *n*-butyl-*tert*-butylcarbinol. However, a similar progression is not followed in the alkylphenylcarbinol series. Under comparable conditions the largest induced shift difference, $\Delta\Delta\delta_{R-S}$, reported in Table I is −0.65 ppm for the carbinyl proton signal of (*R*)- and (*S*)-*n*-butyl-*tert*-butylcarbinol. This might be rationalized by postulating that the steric hindrance of the *n*-butyl group some distance from the site of the complexation of the europium to the oxygen was more important in determining the magnitude of enantiomer chemical shift differences than steric requirements closer to the carbinyl carbon. However, this is not borne out by the negligible $\Delta\Delta\delta$ value for the corresponding signal in methyl-*n*-hexylcarbinol. It is possible that the effect may be present in the methylene signals of the *n*-hexyl group (L$_2$), but the complex nature of the signals in this region renders such an analysis of the 100-MHz spectrum impractical. We conclude that the overall conformational fit of the chiral shift reagent with the *R* *vs.* *S* enantiomers is very specific and so sensitive to small steric and electronic differences in the substrate ligands that any *simple quantitative* correlation of magnitudes of $\Delta\Delta\delta_{R-S}$ values is not possible.

Table I
Chemical Shift Differences Induced by the Chiral Shift Reagent *d*-Eu(HFC)$_3$ in Enantiomeric Secondary Carbinols



Registry no.		L_1CHOHL_2		Carbinyl proton			L_1			L_2			LSR/ RCHOHR′ molar ratio[c]
R	*S*	L_1	L_2	$\Delta\delta_R$[a]	$\Delta\delta_S$	$\Delta\Delta\delta_{R-S}$[b]	$\Delta\delta_R$	$\Delta\delta_S$	$\Delta\Delta\delta_{R-S}$	$\Delta\delta_R$	$\Delta\delta_S$	$\Delta\Delta\delta_{R-S}$	
14898-79-4	4221-99-2	CH_3	C_2H_5	9.55	9.55	0.0	5.09	5.15	−0.06	3.14[d]	3.14[d]	0.0	0.53
1572-93-6	1517-66-4	CH_3	*i*-Pr	12.29	12.29	0.0	6.51	6.58	−0.07	4.31[d]	4.32[d]	−0.01	0.56
1572-96-9	1517-67-5	CH_3	*t*-Bu	12.49	12.90	−0.41	6.61	6.65	−0.04[e]	4.53	4.66	−0.13	0.56[e]
5978-70-1	6169-06-8	CH_3	*n*-Hex	11.37	11.37	0.0	6.10	6.14	−0.04				0.62
3539-97-7	17628-73-8	CH_3	CF_3	6.17	5.91	0.26	3.14	3.20	−0.06				0.58
1517-69-7	1445-91-6	CH_3	C_6H_5	10.17	9.83	0.34	5.43	5.49	−0.06	4.44[f]	4.44[f]	0.0	0.52[g]
1565-74-8	613-87-6	C_2H_5	C_6H_5	10.81	10.54	0.27				4.66[f]	4.66[f]	0.0	0.57
22144-60-1	22135-49-5	*n*-Pr	C_6H_5	9.59	9.15	0.44	1.29[d]	1.32	−0.03	4.00[f]	4.00[f]	0.0	0.50
14898-86-3	34857-28-8	*i*-Pr	C_6H_5	9.73	9.44	0.29	3.51[h]	3.54	−0.03	3.98[f]	4.06[f]	−0.08	0.57[g]
23439-91-0	15914-85-9	*t*-Bu	C_6H_5	7.83	7.92	−0.09	2.57	2.71	−0.14	3.20[f]	3.44[f]	−0.22	0.52[g]
51716-29-1	35147-17-2	*n*-Bu	*t*-Bu	9.98	10.63	−0.65				3.30	3.56	−0.26	0.55
51773-31-0	51773-32-1	*t*-Bu	CF_3	4.24	4.24	0.0	1.40	1.49	−0.09				0.59

[a] $\Delta\delta$ is the amount of shift induced by addition of the designated molar ratio of *d*-Eu(HFC)$_3$ in parts per million downfield from TMS (not the chemical shift). [b] $\Delta\Delta\delta_{R-S}$ is the difference between the signals of the enantiomers ($\Delta\delta_R - \Delta\delta_S$) induced by the addition of the designated molar ratio of *d*-Eu(HFC)$_3$. [c] Refers to the ratio of the lanthanide shift reagent Eu(HFC)$_3$ to substrate. It should be noted that these ratios were only convenient values and were not chosen for maximum or optimum $\Delta\Delta\delta$. [d] This value refers to the CH_3 signal of the ethyl, *n*-propyl, or isopropyl groups. [e] At LSR/substrate molar ratios of 0.3 or less the $\Delta\delta_R - \Delta\delta_S$ values for the CH_3 group (L_1) were positive instead of negative. [f] This value refers to the ortho protons on the phenyl ring. [g] These examples have been reported previously with another chiral shift reagent in a different solvent and at lower LIS/substrate ratios by Červinka, *et al.*[15] [h] This value refers to the methyl signals of the isopropyl group. The internally diastereotopic methyl signals were also separated, thus giving four signals; for both sets of enantiomeric methyl signals $\Delta\delta_R - \Delta\delta_S$ was −0.03.

Others have reported that, as increasing amounts of chiral lanthanide shift reagents are added to some chiral substrates, the sense of nonequivalence (sign of $\Delta\Delta\delta$) for some signals is reversed.[5-7] This phenomenon was observed only for the methyl signal of methyl-*tert*-butylcarbinol among the compounds reported in Table I. At molar ratios of Eu(HFC)$_3$ to methyl-*tert*-butylcarbinol of 0.3 or below, $\Delta\Delta\delta_{R-S}$ was positive; in higher molar ratios the signals cross, leading to the negative value as reported in Table I at the 0.56 ratio. It is obviously crucial for correlation purposes to make such comparisons in any series of compounds at closely comparable LIS/substrate ratios. It should also be emphasized that the sign of $\Delta\Delta\delta_{R-S}$ is frequently not the same for signals from the various ligands of a given substrate. This substantiates the conclusion made by others[5,6] that a difference in the equilibrium constants for diasteriomeric forms of the complex is not necessarily the primary cause of the nonequivalence in the lanthanide-induced shift differences for enantiomeric substrates.

A problem in the study of the correlation of chemical shift differences of natural products by this method is that both enantiomers of the substrate are usually not available. In such cases a study of correlation of configuration with $\Delta\Delta\delta$ can be accommodated by the use of both enantiomeric forms of the chiral shift reagent rather than the substrate. Several enantiomeric shift reagents have been described by Whitesides and coworkers.[5] Since *l*- as well as *d*-camphor is available, the others bearing the *l*-camphorato group are potentially available. A study of this type should prove valuable.

Experimental Section

All nmr spectra were obtained with a Varian HA-100 nmr spectrometer. The *d*-Eu(HFC)$_3$ was purchased from Willow Brook Labs, Inc., and was stored *in vacuo* over P_4O_{10}. The substrate concentrations were 0.19–0.25 *M* in $CDCl_3$. Spectra were obtained by preparing a substrate solution from partially active material of known configuration[17,18] and enantiomeric composition. The nmr chemical shift differences were followed by incremental addition of *d*-Eu(HFC)$_3$, thereby shifting the signals progressively downfield from TMS. As observed by Whitesides and coworkers[5] at molar ratios of *ca.* 1.0, some broadening often occurred owing to a fine white precipitate which could be removed *via* filtration through a plug of glass wool, thereby restoring the resolution of the signals.

References and Notes

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