Determination of the Enantiomeric Purity and Absolute Configuration of α-Deuteriated Primary Alcohols

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Summary The enantiomeric purity and absolute configuration of α-deuteriated primary alcohols can be ascertained by n.m.r. spectroscopy of the corresponding esters with camphanic acid in the presence of $Eu(dpm)_3$.

RECENT studies on a variety of chiral shift reagents have shown that such compounds are capable of inducing differential pseudo-contact shifts for the n.m.r. signals of corresponding protons in both enantiomers of certain organic Lewis bases.[1] The ability of these reagents to differentiate between reflection equivalent (enantiotopic) protons in certain compounds by n.m.r. spectroscopy was recognized and observed experimentally.[2] Earlier, differentiation of enantiotopic groups by n.m.r. spectroscopy was accomplished by conversion of the reflection symmetric compound into a chiral derivative, thus converting enantiotopic groups into configurationally different (diastereotopic) ones.[3] This technique may be greatly improved in the case of esters of primary alcohols with (−)-camphanic acid by making use of a normal achiral shift reagent such as $Eu(dpm)_3$. These esters are readily prepared by treating the alcohol in pyridine at room temperature for 30—120 min with excess of (−)-camphanoyl chloride[4] followed by hydrolysis and isolation of the neutral reaction product. Esters of (−)-camphanic acid with ethanol (m.p. 59—60°), 2,2-dimethylpropanol (m.p. 77—78°), benzyl alcohol (m.p. 103—105°), 3-methylbut-2-enol (m.p. 37—39°), and geraniol (oil) have been prepared and their n.m.r. spectra in CCl_4 recorded in the presence of 10—40 mol % $Eu(dpm)_3$. Pseudo-contact shift differences of 0·4—0·5 p.p.m. for the signals due to the α-methylene protons in the primary alcohol fraction are easily achieved. The Figure shows the well-resolved AB part of an ABX_3 system due to the methylene hydrogens of the ethoxy-group in camphanic acid ethyl ester. Other chiral derivatives of primary alcohols such as 1-phenylethylcarbamates or esters of 2-methoxy-2-trifluoromethylphenylacetic acid and 2-methoxyphenylacetic acid do not show comparable effects in their n.m.r. spectra on addition of equal amounts of shift reagent.

The exceptional behaviour of (−)-camphanic acid esters may be due to the fact that they can act with the two adjacent ester functions as bidentate ligands. Recently europium shift reagents have been shown to form 2:1 complexes with monodentate Lewis bases.[5] Addition of 2,2-dimethylpropanol (−)-camphanic acid ester to $Eu(fod)_3$ in CCl_4 produces an induced circular dichroism associated with the weak 525 nm transition (ϵ 0·1) of europium. A 1:1 ratio of ester to $Eu(fod)_3$ gives the maximal molecular ellipticity (−5 deg cm^2 dmol^{-1}). Higher ratios do not enhance this value. Lower ratios give proportionately smaller ellipticities. These results are compatible with the assumed 1:1 ratio between camphanic acid ester and europium in the complex.

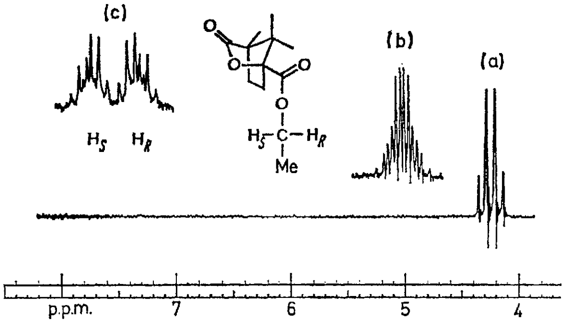

FIGURE. ^{1}H *N.m.r. spectrum* (100 MHz) *of* (−)-*camphanic acid ethyl ester in* CCl_4 *showing the changes in the signals of the α-methylene protons:* (a) *without;* (b) *with* 10 mol %; (c) *with* 35 mol % $Eu(dpm)_3$.

The ability to differentiate between the α-hydrogens of a primary alcohol may be used to determine the enantiomeric purity of alcohols where one of these hydrogens has been replaced by deuterium. The enantiomeric composition of such chiral α-deuteriated primary alcohols will be given by the relative, integrated intensity of the α-methylene hydrogen signals in the n.m.r. spectra of their camphanic acid esters. Samples of (*R*)-[1-^{2}H]ethanol,[3]† (*S*)-2,2-dimethyl[1-^{2}H]propanol,[3] (*R*)-[1-^{2}H]benzyl alcohol,[3] (*R*)-3-methyl-[1-^{2}H]but-2-enol,† and (*R*)-[1-^{2}H]geraniol[3]† have been checked by this procedure. Because the absolute configuration of these α-deuteriated alcohols is known, it was possible to assign the remaining n.m.r. signal of the α-hydrogen in the alcohol fraction to either H_S or H_R. In all the five esters of ($-$)-camphanic acid investigated, the n.m.r. absorption caused by the *pro-R* hydrogen occurs at higher frequencies than that due to the *pro-S* hydrogen. Apparently the relative position of these signals does not depend upon the nature of the substituent R in the alcohol part of the ester. There are good reasons to believe that all such esters assume similar conformations in the complex with Eu(dpm)$_3$. It is therefore very likely that the H_R signal will always appear at higher field because the *pro-R* hydrogen is less distant from the central ion than the *pro*-S hydrogen. This regularity may be used to assign absolute configurations to α-monodeuteriated primary alcohols having structures similar to those investigated. Conversion of these alcohols into esters of ($-$)-camphanic acid followed by an investigation of their n.m.r. spectra in the presence of Eu(dpm)$_3$ seems to be a general method for the determination of their absolute configurations and enantiomeric composition. Preliminary experiments with α-deuteriated primary amines suggest that the method may also be applied to this class of chiral compounds.

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† Prepared according to a procedure of H. Simon *et al.*[6] by exchange of the *pro-R* hydrogen with deuterium, catalysed by liver alcohol dehydrogenase. The stereochemistry of the hydrogen transfer catalysed by this enzyme has been elucidated with (*R*)-[1-^{3}H] geraniol.[7]

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