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Determination of the absolute configuration of a secondary alcohol by NMR spectroscopy using difluorodinitrobenzene

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Abstract

A versatile method was developed to determine the absolute configuration of a secondary alcohol using the characteristic functions of 1,5-difluoro-2,4-dinitrobenzene (FFDNB). In this method, a secondary alcohol reacted first with FFDNB under mild basic conditions, and 1-phenylethylamine was then introduced into the secondary alcohol-FDNB derivative for the recognition by the NMR spectral method. Because the conformations of the resulting derivatives are rigidly fixed by the dinitrobenzene plane, the absolute configuration at the asymmetric carbon of the secondary alcohol tested can be definitively deduced using the NMR anisotropic effect. © 1999 Elsevier Science Ltd. All rights reserved.

Several methods have been used for the determination of the absolute configuration of the α-carbon of secondary alcohols by NMR spectroscopy. Of these, the modified Mosher method has been widely used for this purpose.[1] This method is based on the derivatization of the compound to be tested with the two enantiomers of a chiral anisotropic reagent, methoxytrifluoromethylphenylacetic acid (MTPA), and comparison of the chemical shifts of the resulting diastereomers. This methodology can be regarded to consist of two processes: the freezing of the conformation of the resulting diastereomer and the recognition of the desired conformation based on the influence of the NMR anisotropy effect. However, to the best of our knowledge, no suitable method has been developed for the first process; therefore, the conformation of the resulting diastereomer is always open to discussion. For example, Riguera et al. pointed out that MTPA esters comprise three main conformers in close populations and that MPA (methoxyphenylacetic acid) is superior to MTPA based on the results of extensive conformational studies.[2] Although they recommended a single derivatization method using MPA in combination with low-temperature measurement, they needed to also discuss the detailed conformation.[3]

Ideally, an appropriate derivatization reagent should be used for the first process, which reacts with a compound to form two diastereomers each with a fixed conformation that can be readily confirmed. For the second process, a recognition system composed of plural methods such as NMR, HPLC and CD

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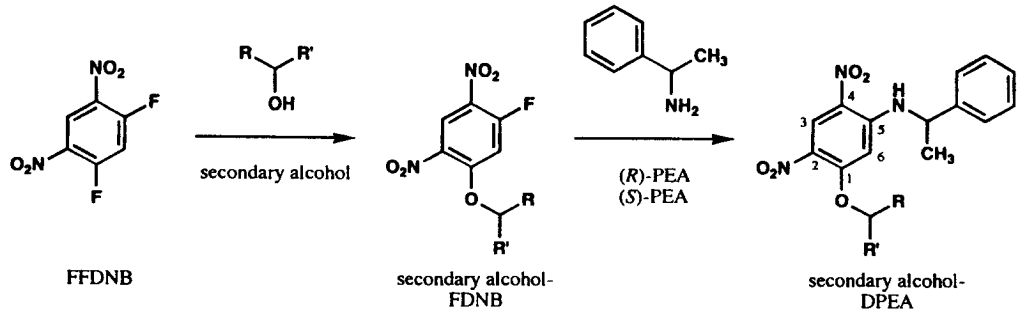

Figure 1. Derivatization procedure for determination of absolute configuration of secondary alcohol

should be established. In a previous study we have demonstrated that 1-fluoro-2,4-dinitrophenyl-5-(*R*,*S*)-phenylethylamine ((*R*,*S*)-FDPEA) is very useful as a chiral anisotropic reagent for the determination of the absolute configuration of primary amino compounds.[4] The obtained $\Delta\delta$ values using this reagent are approximately 5 times larger than those determined by the modified Mosher method,[5] indicating that the desired fixed conformation is formed and an anisotropic effect is consequently more effective in this method. Additionally, this conformation could be readily confirmed by a UV spectral analysis and an NOE experiment.[6] If the FDPEA method can be applied to the determination of the absolute configuration of the α-carbon of a secondary alcohol, it would provide a more definite conclusion compared with conventional methods. In order to develop this method, the following two problems must be overcome: (i) is it possible to prepare the desired DPEA derivative of a secondary alcohol?, and (ii) is the prepared DPEA derivative in the desired conformation?

Although a secondary alcohol was directly derivatized with FDPEA, the desired secondary alcohol derivative could not be prepared. Based on the reactivity of 1,5-difluoro-2,4-dinitrobenzene (FFDNB), the reaction sequence was changed to obtain the desired secondary alcohol derivative. That is, the tested secondary alcohol reacted first with FFDNB to give quantitatively the secondary alcohol-FDNB derivative, in which a strong NOE was observed between the H-6 of FDNB and the α-proton of the secondary alcohol.[7] 1-Phenylethylamine (PEA) was then introduced quantitatively into the resulting secondary alcohol-FDNB derivative (Fig. 1). The derivatization procedure for secondary alcohols was finally optimized as follows: a secondary alcohol reacted with FFDNB and triethylamine (molar ratio of 1:8:8) in dichloromethane at 40°C for 24 h. In order to remove the excess FFDNB, the reaction mixture was applied to an ODS cartridge. The resulting secondary alcohol-FDNB derivative reacted with PEA in 1% triethylamine–acetonitrile at 40°C for 1 h. After elimination of the excess reagents, the desired derivatives were subjected to NMR measurement.

The planar structures of the resulting derivatives were confirmed using FAB mass and various 2D NMR spectra, and the conformation was examined using UV and NOE difference spectra. As shown in Fig. 2(a), very strong NOEs were observed between the H-6 of DNB and the α-proton of the tested secondary alcohol and the α-proton of the introduced primary amine.[8] These experimental results indicated that the resulting conformation is quite similar to those of DLA (2,4-dinitrophenyl-5-leucinamide) and the DPEA derivatives of the primary amines, including amino acids,[6,9] and this rigid conformation can be formed even without hydrogen bonding between the nitro group at C-2 and the introduced hydroxyl groups.[10] Thus, it was confirmed that this method is able to determine the absolute configuration of secondary alcohols using the following NMR spectral method [Fig. 2(b)]. When (*R*)-FDPEA is used, the R substituent is more strongly affected by the phenyl group, whereas the opposite phenomenon occurs in the case of (*S*)-FDPEA. Here, the $\Delta\delta$ value is defined as ($\Delta\delta=\delta_R-\delta_S$), where δ_R is the chemical shift of each proton in the (*R*)-DPEA derivative and δ_S is the chemical shift of each

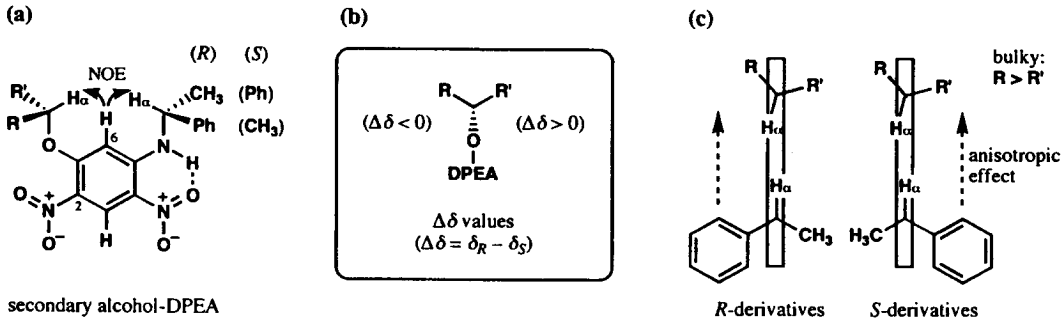

Figure 2. (a) Conformation of the secondary alcohol-DPEA derivatives, (b) $\Delta\delta$ values of the DPEA derivatives and (c) conformation of the sterically hindered secondary alcohol-DPEA derivative

Table 1
$\Delta\delta$ values in ^{1}H NMR spectra of (*S*)-2-butanol-, (*S*)-2-pentanol- and (*S*)-2-octanol-(*R*,*S*)-DPEA derivatives (400 MHz, $CDCl_3$)

	Position	(*S*)-2-butanol	(*S*)-2-pentanol	(*S*)-2-octanol
Secondary alcohol	H-1	0.5405	0.5485	0.5440
	H-2	–0.0980	–0.1180	–0.1090
	H-3	–0.2455	–0.2730	–0.2210
		–0.3535	–0.2800	–0.2800
	H-4	–0.2490	–0.2470	–0.2090
			–0.2880	–0.2510
	H-5		–0.2110	–0.2090
				–0.1230
	H-6			–0.1230
	H-7			–0.0460
	H-8			–0.0230
DNB	H-6	0.0360	0.0510	0.0570
PEA	NH	–0.0075	–0.0070	–0.0075
	CH_3	0.0015	0.0000	0.0005
	Hα	–0.0020	0.0010	–0.0030

$\Delta\delta$: $\delta_R - \delta_S$ (ppm)

proton in the (*S*)-DPEA derivative. As is obvious from Fig. 2(b), the $\Delta\delta$ values for the protons oriented on the left side of the DNB plane are all negative, while those located on the right side of the DNB plane are positive.

The established method was applied to acyclic and cyclic secondary alcohols. Table 1 shows the $\Delta\delta$ values of the DPEA derivatives of (*S*)-2-butanol, (*S*)-2-pentanol and (*S*)-2-octanol. While the $\Delta\delta$ values of H-6 of DNB, H_{NH}, H_{CH_3} and Hα of PEA are nearly zero, the signs of the $\Delta\delta$ values for the alcohol moiety are clearly separated on the boundary of a carbon atom bearing the hydroxyl group [Fig. 2(b)] and their values become smaller with an increase in the distance from the asymmetric carbon, indicating that the desired conformation is favorably formed.[6,9] Although the $\Delta\delta$ values for H-2 of these compounds should be ideally zero, any H-2s show negative values (Table 1). Because this may be mainly caused by steric hindrance at C-1 and C-3, the H-2 tends to usually give the same sign as the protons at the bulkier carbon [Fig. 2(c)]. These experimental results strongly supported the fact that the present method is applicable to the determination of the absolute configuration of a secondary alcohol as well as a primary amine.

The present method was also applied to cyclic secondary alcohols, (–)-menthol, and cholesterol and

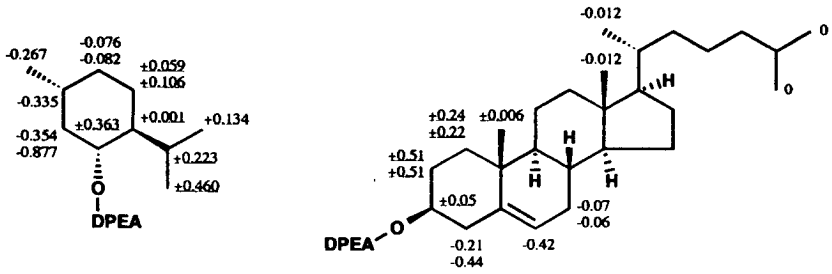

Figure 3. $\Delta\delta$ values of (−)-menthol- and cholesterol-DPEA derivatives

the obtained $\Delta\delta$ values are shown in Fig. 3. The values of the (−)-menthol-DPEA derivative are greater than those with MTPA[1] and MPA[11] and are superior to those with the napthyl derivatives, particularly at remote protons from the asymmetric center.[11] An additional characteristic feature of the proton at C-1 of menthol is that the +0.363 $\Delta\delta$ values can be regarded as the steric hindrance at C-2 as mentioned above, and the isopropyl group at C-2 contributes prominently to this result (Fig. 3). As expected, the obtained $\Delta\delta$ values for cholesterol are also larger than that of the corresponding MTPA derivative. In contrast to the case of menthol, the $\Delta\delta$ values of the proton at C-3 of cholesterol are almost zero because the reduced bulkiness at both of the β-carbons is almost the same.

In the present study, we have established a versatile method for the determination of the absolute configuration of the α-carbon of secondary alcohols using the characteristic functions of FFDNB and NMR spectroscopy. In this method, a secondary alcohol reacted first with FFDNB under mild basic conditions and 1-phenylethylamine was then introduced into the secondary alcohol-FDNB derivative for the recognition. Because the conformation of the resulting DPEA derivative is definitely fixed by the characteristic hydrogen bonding and arrangement of the related functional groups, the $\Delta\delta$ values obtained by this method are larger than those by the conventional methods such as the modified Mosher method. Additionally, such conformation can be easily confirmed using UV spectral analyses and NOE measurements, indicating that a detailed discussion of the derivatives conformation is unnecessary.

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7. Approximately 15% NOEs (400 MHz) were observed between the H-6 of FDNB and the α-proton of the secondary alcohol.
8. Approximately 19% and 13% NOEs (400 MHz) were observed between the H-6 of DNB and the Hα of the secondary alcohols tested (linear alcohols and menthol) and the Hα of PEA, respectively. In the case of cholesterol, 12% and 9% NOEs (600 MHz) were observed between the H-6 of DNB and the Hα of the secondary alcohol and the Hα of PEA, respectively.
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10. The NHs of PEA forming the intramolecular hydrogen bonding appear around 8.76 ppm in all secondary alcohols tested in this study.
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