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Article

Absolute Configurations and Enantiomeric Compositions of 2-Methyl-1-butanol and 2-Methyl-1-pentanol by ^{1}H-NMR Spectrometry of their Diastereomeric Valine Esters

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Ésteres diastereoméricos da L-valina com o 2-methyl-1-butanol e o 2-methyl-1-pentanol foram examinados como derivados para a análise estereoquímica dos álcoois por ressonância magnética nuclear de prótons. A ausência de racemização, durante suas preparações, e as diferenças de deslocamentos químicos apresentadas por seus epímeros indicam que estes ésteres são derivados úteis para a especificação da configuração e para a determinação da composição enantiomérica do álcool correspondente.

L-valine is examined as a derivatizing agent for the stereochemical analysis of 2-methyl-1-butanol and 2-methyl-1-pentanol, by ^{1}H-NMR spectrometry. Racemization does not occur during derivatization. It is shown that the chemical shift differences of these epimeric esters are useful for the assignment of the configuration and for the determination of the enantiomeric composition of the primary chiral alcohols from which they were prepared.

Keywords: *absolute configuration, optical purity, chiral primary alcohol, NMR*

Introduction

An usual procedure for the stereochemical analysis of secondary chiral alcohols is the conversion of enantiomers into a diastereomeric ester mixture, using an optically pure reagent, followed by analysis of the resulting mixture by gas-liquid partition chromatography (glpc)[1] or by nuclear magnetic resonance (NMR) spectrometry[2]. The glpc technique does not seem to be generally applicable for the resolution of diastereomeric derivatives of chiral primary alcohols. It has been reported that diastereomeric esters of secondary alcohols, derivatized with optically pure acetylated lactic acid, were resolved in a capillary column, while those from primary alcohols having the chiral center at C-2 and C-3 were not[3]. The use of permethylated β-cyclodextrin as stationary phase of capillary glpc columns led to the separation of enantiomers of some secondary chiral alcohols but failed to separate the enantiomers of the primary alcohols 2-methyl-1-butanol and 2-methyl-1-pentanol[4]. More recently, successful glpc resolutions of the enantiomers of 2-methyl-1-butanol and of the trifluoroacetylated 2-methyl-1-pentanol and 2-methyl-1-hexanol by using a trifluoroacetylated γ-cyclodextrin as stationary phase were reported[5].

Nuclear magnetic resonance methods, widely applied to determine enantiomeric composition as well as to infer the configuration of secondary carbinols[6,7], are expected to be applicable similarly for the stereochemical analysis of chiral primary alcohols. However, they have been little used for this purpose. In one report[8], the enantiomeric purities of primary alcohols with the chiral center at C-2 were determined by ^{1}H-NMR (at 90 MHz) using Mosher's derivatizing reagent for their conversion into a diastereomeric mixture, and a lanthanide for induction of larger chemical shifts differences. However, to our knowledge, NMR methods have not been applied for the inference of the configuration of primary carbinols.

We have examined the ^{1}H-NMR spectral characteristics of the above mentioned diastereomeric L-valine esters from 2-methyl-1-butanol and 2-methyl-1-pentanol, at 300 MHz, aiming to investigate their application for the stereochemical analysis of these alcohols. The results of this study are reported herein.

Experimental

Proton magnetic resonance spectra (^{1}H-NMR) were measured on a Varian-Gemini 300 (300 MHz) spectrometer, using approximately 2% solutions in $CDCl_3$, and the following conditions: spectral width 4,500 Hz; pulse width 9.1 μs; flip angle 45°; acquisition time 1.767 s; recycle delay 0 s; number of transients 128. Conditions to optimize integral measurements were not determined. Reported chemical shifts are relative to TMS. Splitting are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; o, octet; m, multiplet. Enantiomeric compositions were based on integration values for non-overlapping peaks of methylenic protons of the diastereomeric derivatives. The integration values, found for peaks from the derivatives present in the sample, were compared with those values found for the same peaks present in an equimolar mixture of the same derivatives. Measurement of peak height gave similar results. Melting points were determined in a Thomas-Hoover apparatus and are uncorrected.

The alcohols, L-valine and p-toluenesulphonic acid used in this study are commercially available (Aldrich Chemical Co.) and were used without further purification. A straightforward literature procedure[10] for the resolution of 2-methyl-1-pentanol, through its easily formed L-valine ester tosylate, have been used for obtaining equimolar as well as partially resolved mixtures of diastereomeric valine esters and valine ester tosylates.

Equimolar mixture of (S,R) plus (S,S) valine 2-methylpentyl ester tosylates

The mixture was obtained by adapting a literature procedure[11]. L-valine (1 g, 8.7 mmol), racemic 2-methyl-1-pentanol (1.5 g, 14.7 mmol), p-toluenesulphonic acid (2 g, 11.6 mmol), benzene (12 mL) and toluene (5 mL), were refluxed, using a Dean-Stark trap for water separation. The cold mixture was filtered to remove excess of acid. From this solution, a crude equimolar mixture of tosylates was obtained as a colorless solid (2.2 g, 5.9 mmol) after removing the solvent and excess alcohol.

Partially resolved (S,R) and (S,S) valine 2-methylpentyl ester tosylates

From 1.1 g of the above equimolar mixture, by kneading the solid under anhydrous ether (3 mL), filtering and washing the less soluble crop with two more portions (3 mL) of ether, 503 mg of a fraction enriched in the (*S*,*R*)-diastereomer was obtained. From the combined mother liquids, after evaporation of the solvent, 506 mg of a crude fraction enriched in the (*S*,*S*)-diastereomer was obtained.

A sample of the less soluble (*S*,*R*)-diastereomer was re-crystallized four times from acetone. The resulting solid, mp 124-128 °C (lit[10]. mp 129-130 °C) was used to produce the corresponding partially resolved (*S*,*R*)-valine ester, as described below.

Equimolar and partially resolved (S,R)- and (S,S)-valine 2-methylpentyl esters

These (*S*)-valine esters were obtained as yellowish liquids (*ca.* 12 mg; 0.06 mmol) through the preparation and subsequent addition of the appropriate tosylate (25 mg; 0.067 mmol) to an excess of a 10% sodium bicarbonate solution (2.5 mL; 3 mmol).

From the above mentioned re-crystallized tosylate, a 90% yield of partially resolved (*S*,*R*)-valine 2-methylpentyl ester was obtained, ^{1}H-NMR (300 MHz, COSY): δ 0.89 (t, 3 H, $\underline{CH_3}CH_2$, J = 7.0), 0.89 (d, 3 H, $\underline{CH_3}CHCH_3$, J = 6.9), 0.92 (d, 3 H, $\underline{CH_3}CH$, J = 6.9), 0.97 (d, 3 H, $CH_3CH\underline{CH_3}$, J = 6.9), 1.08-1.45 (m, 4 H, $\underline{CH_2CH_2}CH3$), 1.49 (br s, 2 H, $\underline{NH_2}$), 1.8 (m, 1 H, $OCH_2\underline{CH}$), 2.03 (d h, 1 H, $CH_3\underline{CH}(CH_3)CH$, J = 4.9 and 6.9), 3.29 (d, 1 H, $CH\underline{CH}N$, J = 4.9), 3.87 (d d, 1 H, $O\underline{CH_2}CH$, ABX system, J = 10.7 and 6.7), 4.01 (d d, 1 H, $O\underline{CH_2}CH$, ABX system, J = 10.7 and 5.9). Differences in signals caused by the minor (*S*,*S*)-valine ester component are more evident in the methylene region: δ 3.91 (d d, 1 H, $O\underline{CH_2}CH$, A<u>B</u>X system, J = 10.7 and 6.7), 3.97 (d d, 1 H, $O\underline{CH_2}CH$, <u>A</u>BX system, J = 10.7 and 5.8).

Equimolar (S,R)- plus (S,S)-, and pure (S,S)-valine 2-methylbutyl ester

Equimolar mixture of diasteromeric esters and pure (*S*,*S*)-valine 2-methylbutyl ester were prepared, respectively, from the racemic and pure (*S*)-alcohol, using the same procedure described above for 2-methylpentyl esters.

The pure ester gave ^{1}H-NMR (300 MHz): δ 0. 90 (d, 3 H, $\underline{CH_3}CHCH_3$, J = 7.0), 0.91 (t, 3 H, $\underline{CH_3}CH_2$, J = 7.0), 0.93 (d, 3 H, $\underline{CH_3}CH$, J = 6.5), 0.98 (d, 3 H, $CH_3CH\underline{CH_3}$, J = 6.5), 1.18 (m, 1 H, $CH\underline{CH_2}CH_3$), 1.42 (m, 1 H, $CH\underline{CH_2}CH_3$), 1.47 (br s, 2 H, $\underline{NH_2}$), 1.71 (m, 1 H, $OCH_2\underline{CH}$), 2.02 (o, 1 H, $CH_3\underline{CH}(CH_3)CH$, J = 6.0), 3.30 (d, 1 H, $CH\underline{CH}N$, J = 6.0), 3.93 (d d, 1 H, $O\underline{CH_2}CH$, A<u>B</u>X system, J = 10.7 and 6.5), 3.98 (d d, 1 H, $O\underline{CH_2}CH$, <u>A</u>BX system, J = 10.7 and 6.0). The equimolar mixture gave the additional ABX system due to epimeric (*S*,*R*) ester at: δ 3.91 (dd, 1 H, $O\underline{CH_2}CH$, J = 10.7 and 6.5), 4.03 (d d, 1 H, $O\underline{CH_2}CH$, J = 10.7 and 6.0).

Results and Discussion

Preliminaries

Equimolar mixtures of *S,R* and *S,S* diastereomers of valine 2-methylbutyl ester and of valine 2-methylpentyl ester were prepared from L-valine and the racemic alcohols, and the ^{1}H-NMR spectra of their solutions in deuterochloroform were obtained at 300 MHz. In these spectra, it was apparent that the diastereotopic methylenic

O-$\underline{CH_2}$-CH protons from the alcoholic moiety showed measurable chemical shift non-equivalencies, allowing a stereochemical analysis of the alcohol from which they were prepared. Although this group gives rise to an ABX system, the resonance signals are observed in a region (near 4 ppm) normally free of overlap with signals from other parts of the molecule. For the pro-*R* and the pro-*S* hydrogens, these methylene group signals consist of two double doublets. The spectra of the resulting diastereomeric esters show, provided no accidental coincidence of chemical shift occurs, one set of two double doublets for the (*S*,*R*)-ester and another set of two double doublets for the (*S*,*S*)-ester.

Methylene resonances of individual diastereomers

The methylene resonances of individual diastereomers of valine 2-methylbutyl esters were identified by comparing the NMR signals presented by the equimolar diastereomeric mixture of (*S*,*R*)- and (*S*,*S*)-valine ester with those shown by the pure (*S*,*S*)-valine ester. This ester was prepared[9] from L-valine and optically pure (*S*)-2-methyl-1-butanol, and the ^{1}H-NMR spectra of its solution in deuterochloroform was determined. The methylene set of signals for this (*S*,*S*)-ester is shown in Fig. 1 a. By simple inspection of the NMR spectrum of the (*S*,*S*)- plus (*S*,*R*)-ester mixture, an external set (not shown), very similar to the outer set of two double doublets presented by the major component in Fig. 1 b, can be assigned to the (*S*,*R*)-ester methylenic protons. Despite the ABX pattern, identification of the signals caused by each diastereomer is a very simple task. Relative to the center of the two systems, the chemical shifts caused by pro-*R* and pro-*S* protons of (*S*,*R*)-ester are farther from each other, while those of (*S*,*S*)-ester are closer.

For diastereomers of valine 2-methylpentyl ester, the methylene resonance was identified by comparing NMR signals representing the major and minor stereoisomer of the two opposite fractions of the partially resolved ester. The methylene signals for these fractions are shown in Figs. 1 b and 1 c. Signals shown in 1 b are due to the fraction enriched in the diastereomer from which the (+)-2-methyl-1-pentanol is obtained[9]. Since the absolute configuration of this alcohol is assigned[10] to the (*R*)-enantiomer, the chemical shifts caused by pro-*R* and pro-*S* protons are farther from each other for the (*S*,*R*)-ester and closer for the (*S*,*S*)-ester, analogously to what has been seen for the methylbutyl ester.

For 2-methylpentyl esters, the observed chemical shift differences ($\Delta\nu_{AB}$) shown by (*S*,*R*)- and (*S*,*S*)-diastereomers were, respectively, 0.14 and 0.06 ppm. For 2-methylbutyl esters these differences were 0.12 and 0.05 ppm. The somewhat larger difference between the 2-methylpentyl (*S*,*R*)- and (*S*,*S*)-diastereomers ($\Delta\Delta\nu_{AB} = 0.08$ ppm) relative to the difference between the corresponding 2-methylbutyl diastereomers ($\Delta\Delta\nu_{AB} = 0.07$ ppm) suggests similar observable behavior for derivatives of other longer chain alcohols.

Correlation between absolute configuration and NMR spectral differences

From the above discussion, an important conclusion is reached. Upon inspection of the chemical shift differences between the pro-*R* and pro-*S* protons of either L-valine 2-methylbutyl or L-valine 2-methylpentyl ester, it is possi-

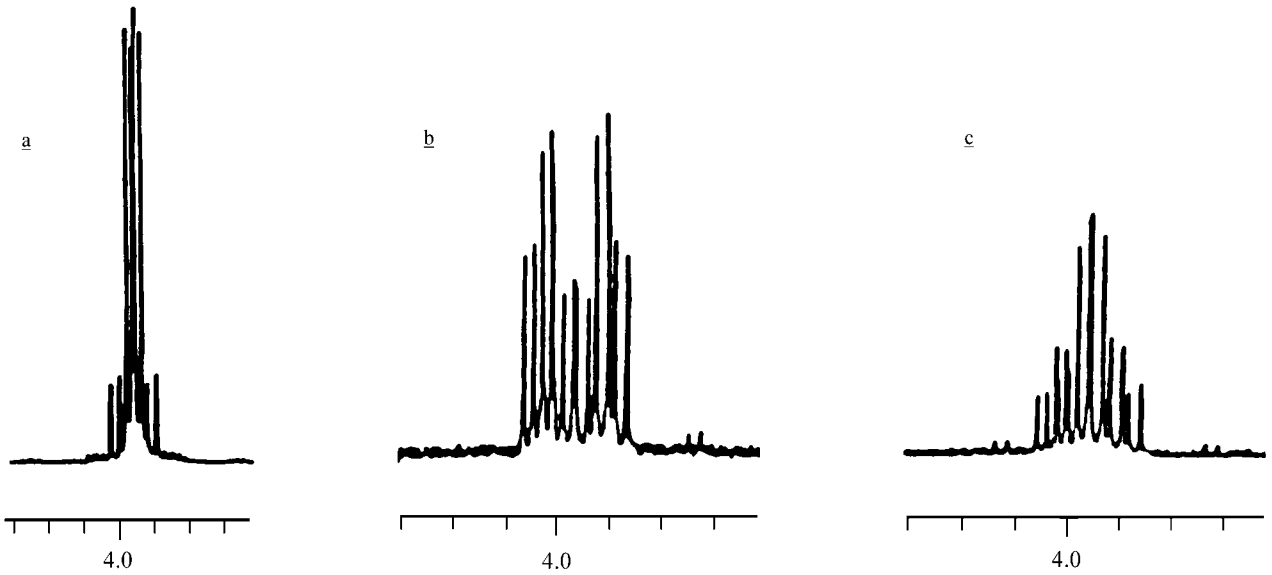
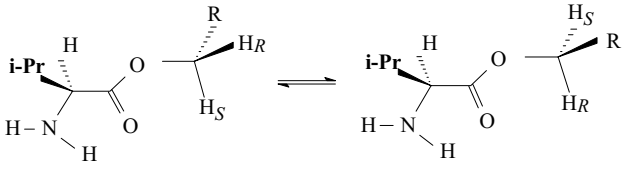


Figure 1. Methylene resonances from a: (*S*,*S*)-valine 2-methylbutyl ester; b: partially resolved (*S*,*R*)-valine 2-methylpentyl ester; c: partially resolved (*S*,*S*)-valine 2-methylpentyl ester.

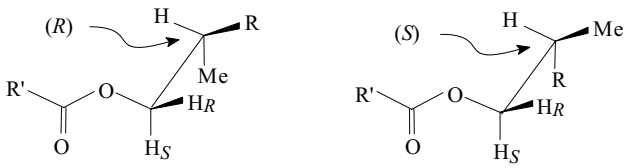
ble to infer the absolute configuration of the alcohols from which they were obtained.

To estimate the possibility of extension of this procedure to other 2-methyl alkanols, we have examined the relationship between configuration and non-equivalencies in NMR spectra of these esters. Substituents in the chiral centers of their acidic and alcoholic moieties, sources of differential shielding effects, contribute to the non-equivalencies of diastereotopic protons H_R and H_S. The examination of substituent effects of the acidic moiety was performed by adapting a model described by Mosher[6] for the inference of configuration of diastereomeric mandelic esters of secondary alcohols. The following conformations for 2-methylalkanol derivatives (**1a** and **1b)** were drawn to fit the model. The isopropyl group in valine esters is substituted for the phenyl group of mandelic esters.



1a **1b**

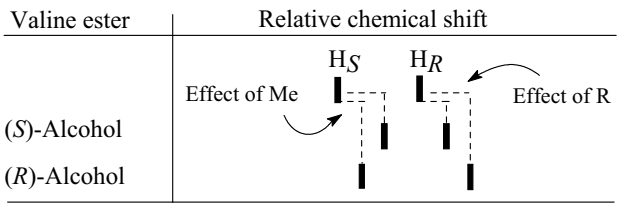
Assuming that the isopropyl group of the acidic moiety is exerting over H_R and H_S an effect similar to that of the phenyl group in mandelic acid esters, *i.e.* a shielding effect, the pro-*R* (H_R) eclipsed proton must be at higher field than pro-*S* (H_S) proton. The effects of groups in the alcoholic moiety can better fit our results if we consider that a greater shielding effect arises from either ethyl or propyl than from methyl, over H_R and H_S, in the more stable eclipsed conformations **2** and **3** of diastereomeric (*S*,*R*)- and (*S*,*S*)-esters of 2-methyl-1-butanol (**2a** and **3a**, R = Et) and 2-methyl-1-pentanol (**2b** and **3b** , R = Pr).



2a **R = Et**
2b **R = Pr**

3a **R = Et**
3b **R = Pr**

The relative chemical shifts, predicted from the above considerations, are shown in Scheme 1. In derivatives **2a** and **2b** of the (*R*)- alcohols, H_R proton should be affected by the group (Et or Pr) which causes the largest shielding effect. The H_S proton is also shielded, but to a lesser extent. In derivatives **3a** and **3b** of the (*S*)-alcohols, the H_S proton is more shielded than H_R proton.



Scheme 1. Relative chemical shifts of pro-*S* (H_S) and pro-*R* (H_R) protons for L-valine esters of (*S*)- and (*R*)-2-methyl-1-butanol and 2-methyl-1-pentanol.

The methodology described herein can be of value for the study of these substituent effects. Other primary chiral alcohols and derivatizing agents must be examined and the study of some of them is now in progress in our laboratory.

Determination of enantiomeric composition of the chiral alcohols

Despite the overlapping of four methylene peaks in the NMR of the (*S*,*R*)- and (*S*,*S*)-diastereomeric derivatives of each alcohol, there is no difficulty in determining the enantiomeric composition, based on measurements of non-overlapping peaks, as described below.

For sake of clarity, we will refer to one peak, of the eight-peaks from the ABX set, by using a left to right ordering number to identify its relative position, and the R or S character indicating to which isomer it corresponds. In Fig. 1b, peaks 1R, 2R, 7R and 8R are the four external peaks from the major component of the partially resolved derivative of (*R*)-2-methyl-1-pentanol. The largest peaks of this set (3R, 4R, 5R and 6R) are overlapped by peaks (1S, 2S, 7S and 8S) of the minor component set from the (*S*)-2-methyl-1-pentanol derivative. The optical purity can be calculated from non-overlapping peaks by comparing their intensities with those caused by the same peaks from the equimolar mixture.

As an example, for the partially resolved (*S*)-valine (*R*)-2-methylpentyl ester, whose methylenic NMR signals are shown in Fig. 1b, integration of peaks R1 and S3 gave the values indicated on the second line of Table 1. For the equimolar diastereomeric mixture, integration of the same peaks gave the values indicated on the third line. The intensity of each peak of partially resolved mixture (PR), relative to the value it should have in the equimolar mixture (EQ), is shown in the next line as PR/EQ values. From these

Table 1. Calculation of optical purity for partially resolved (*S*,*R*)-valine 2-methylpentyl ester.

PEAK	R1	S3
PART. RES.	15.0	11.0
EQUIMOLAR	5.9	13.3
PR / EQ	2.54	0.83
PURITY (%)	75.4	24.6

values, which are proportional to composition of the corresponding isomers, the optical purity (PURITY %) can be calculated.

For a sample of 2-methyl-1-butanol the optical purity can be calculated, similarly, from non-overlapping peaks of the diastereomers, by comparing their intensities with those caused by the same peaks of an equimolar mixture obtained from L-valine and a racemic mixture of the alcohol.

Conclusions

L-Valine can serve as a derivatizing agent for stereochemical analysis of 2-methyl-1-butanol and 2-methyl-1-pentanol by NMR spectrometry. Conversely, pure (*S*)-(-)-2-methyl-1-butanol could serve as a derivatizing agent for the stereochemical analysis of valine.Configurations of these alcohols can be assigned by inspection of the methylenic resonances of their L-valine esters. The methodology described herein can be of value for the study of the nature of the differential shielding effects of substituents bonded to the pertinent chiral centers. The enantiomeric composition can be calculated from non-overlapping peaks, by comparing their intensities with those of the same peaks in the equimolar mixture. A somewhat larger difference between the 2-methylpentyl (*S*,*R*)- and (*S*,*S*)-diastereomers relative to the difference between the corresponding 2-methylbutyl diastereomers suggests that similar observable behavior for derivatives of longer chain 2-methyl-1-alkanols should be expected.

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