

Chemical Shift Nonequivalence of Enantiomers of Amino Acid Derivatives in ^1H NMR and ^{19}F NMR Spectroscopy Induced by *L*-Chirasil-Val.

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Dedicated to Prof. Dr. Ernst Bayer on the occasion of his 65th birthday

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Enantiomers of N-trifluoroacetyl-amino acid methyl esters in CCl_4 solution, after addition of the chiral polysiloxane (*L*)-Chirasil-Val, display a chemical shift nonequivalence $\Delta\delta$ in both ^1H NMR and ^{19}F NMR spectroscopy. The effects found for the leucine and valine derivatives can be correlated with the thermodynamic parameters of interaction in the undiluted system, as determined by gas chromatography. In CDCl_3 solution, no peak splitting was observed. The method is potentially useful for the determination of the enantiomeric purity of substrates of low volatility.

A convenient method of establishing the enantiomeric purity (e.e.) by NMR spectroscopy is based on the addition of a chiral solvation agent (CSA) [1]. Thus, the originally external enantiotopic nuclei of an enantiomeric pair become diastereotopic by formation of nonisolable diastereomeric solvates. Usually, high concentrations and strong intermolecular forces, such as π - π [2] and acid-base [3] interactions, are necessary to achieve sufficient peak resolution. Detailed insight into the mechanism of such interactions led to the invention of highly efficient chiral stationary phases (CSPs) in HPLC [4]. Here we report on a reversal of this strategy, *i.e.*, the application of a CSP successful in chromatography, as a CSA in NMR spectroscopy.

The polymeric CSP (*L*)-Chirasil-Val (**1**) is widely used in GC to resolve enantiomers of many classes of compounds [5]. Among these, N-acyl amino acid esters, owing to the particularly high resolution factors (α) found in GC, *e.g.*, $\alpha = 1.90 \pm 0.04$ extrapolated to 298 K for the leucine derivative (**2**), are most promising candidates for discrimination studies by NMR spectroscopy. After addition of no more than 0.6 equivalents of (*L*)-**1** to a solution of (D,L)-**2** in CCl_4 , the N-H proton doublet of the enantiomers of **2** is split into two completely separated sets, as depicted in Fig. 1. Both the relative shift $\Delta\delta$ and the difference $\Delta\Delta\delta$ are strongly dependent on the concentration of

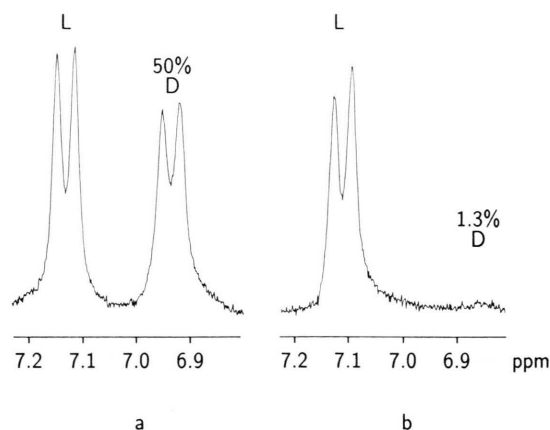
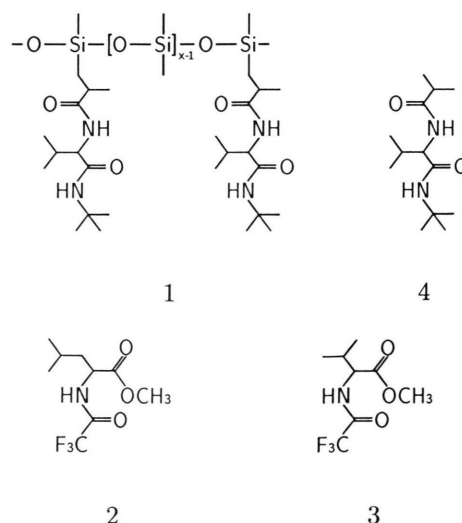


Fig. 1. Chemical shift nonequivalence of (D)- and (L)-**2** (24 mM solution in CCl_4) in the presence of 0.62 equivalents of *L*-**1** (loading $1/x = 0.20$), in the ^1H NMR spectrum (250 MHz), internal lock C_6D_{12} , NS = 64.



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(L)-**1**, as compiled in Table I. Thus, relatively small concentrations of the polymeric chiral selector are already sufficient to effect a baseline split of the N–H signal. Fortunately, the substrate N–H region remains uncongested by the complex pattern of the selector N–H signals [6].

The sense and degree of enantiomer discrimination in CCl_4 solution, as displayed in ^1H NMR spectroscopy, appears to parallel previous findings for the undiluted system by gas phase calorimetry [7]. Chiral recognition in this selector-selectand-system is strongly propagated by hydrogen bonding, as indicated by the marked low field shift, $\Delta\delta(\text{L}) > \Delta\delta(\text{D})$, of the substrate amide protons. A comparison of the entries **2** and **3** is given in Table I.

As compared to the leucine derivative (**2**), the valine derivative (**3**) displays relatively small differences in the chemical shift $\Delta\delta$, as well as in the gas phase calorimetric properties $\Delta\Delta S$ and $\Delta\Delta H$ [8], because of steric hindrance of the intermolecular interaction. After correction for this effect, however, the degree of diastereoselectivity, mirrored by the chiral recognition factor (χ), ends up higher for **3**, as expected from a qualitative comparison of the intramolecular constraints operating.

Although signal separation in ^1H NMR spectroscopy is excellent, the determination of e.e. is hampered by the broad shape of the N–H signal. Integration is more facile in the ^{19}F NMR spectrum (see Fig. 2). The sharp CF_3 singlets of the enantiomers are nicely separated, and the polymeric selector remains invisible. All e.e. values measured by this method are in good accordance with GC analysis.

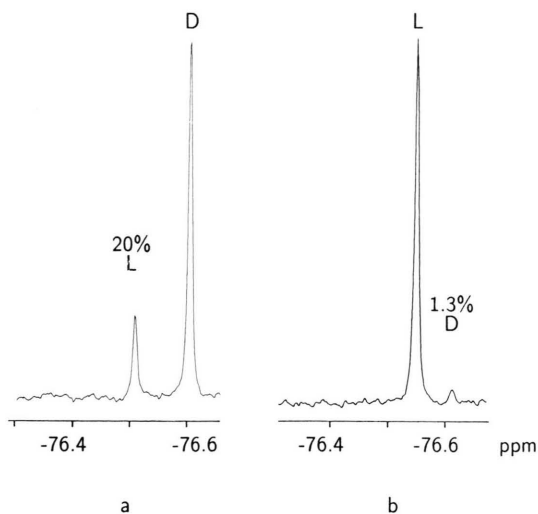


Fig. 2. Chemical shift nonequivalence of (D)- and (L)-**2** (conditions similar to Fig. 1) in the ^{19}F NMR spectrum (376.5 MHz), internal standards $\text{CF}_3\text{COOCH}_3$ and CFCl_3 , NS = 64.

In the more polar solvent CDCl_3 , (D,L)-**2** does not show any signal split after addition of (L)-**1**, although differences in the chemical shift of isolated selectand enantiomers were reported for low molecular weight selector analogues [9, 10]. We have investigated the analogue (L)-**4** in CCl_4 as the solvent; however, due to its poor solubility **4** appears to be unsuitable as a CSA. Thus, the polymer backbone has several functions. Besides a solubilizing effect, self-association [11] of the chiral diamide moieties is suppressed, and cooperative binding of the substrate [5] due to an entropy effect may be assumed. It should be noted that the self-induced nonequivalence in enantiomers of N-acyl

Equiv. 1 added	$^3J_{\text{HH}}(\text{L})$	$^3J_{\text{HH}}(\text{D})$	$\Delta\delta(\text{L})$	$\Delta\delta(\text{D})$	$\Delta\delta$	$\Delta\Delta\delta$
N–TFA–Leu–OMe (2)						
0.25	7.8	7.5	0.11	0.01	0.06	0.10
0.99	8.2	8.0	0.50	0.25	0.38	0.25
1.61	8.2	8.2	0.72	0.39	0.55	0.33
4.33	8.2	8.5	1.12	0.70	0.91	0.42
N–TFA–Val–OMe (3)						
0.23	–	–	0.08	0.06	0.07	0.02
0.93	–	–	0.23	0.18	0.21	0.05
1.52	8.2	8.0	0.32	0.25	0.29	0.07
4.07	8.2	8.5	0.51	0.41	0.46	0.10

Table I. Effects of the CSA (L)-Chirasil-Val (**1**) on the ^1H NMR Spectral Properties of (D,L)-N–TFA–Leu–OMe (**2**) and (D,L)-N–TFA–Val–OMe (**3**), respectively, 0.24 M in CCl_4 ; $\Delta\delta$ in ppm relative to 6.79 ppm for pure **2**, and 6.67 ppm for pure **3**; $\Delta\Delta\delta$ in ppm, chiral recognition factor $\chi = \Delta\Delta\delta/\Delta\delta$ without dimension; $^3J_{\text{HH}}$ (coupling constant of N–H with $\text{C}^\alpha\text{--H}$) in Hz.

amino acid esters is much smaller, and only observed under special conditions [12].

In addition to the chromatographic techniques nowadays in use, the determination of e.e. by NMR in the presence of a CSA is still a valuable complement. Due to their unique properties, soluble chiral polymers bearing functions well-de-

signed for specific multiple interactions with groups near the stereogenic center of the target molecule offer a promising alternative.

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