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NMR investigation of photoinduced chiral inversion in (*R*)/(*S*)-naproxen–(*S*)-tryptophan linked system

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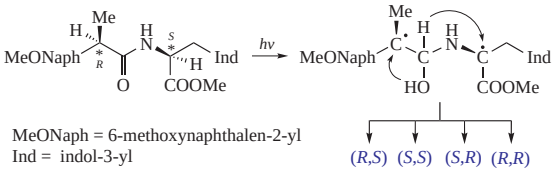
The inversion of the chiral centers in (*R*)/(*S*)-naproxen–(*S*)-tryptophan linked system under UV irradiation has been detected by the ^{1}H NMR spectroscopy as an example of the (*R*,*S*)-diastereomer transformation into (*S*,*S*) analogue in an achiral environment.



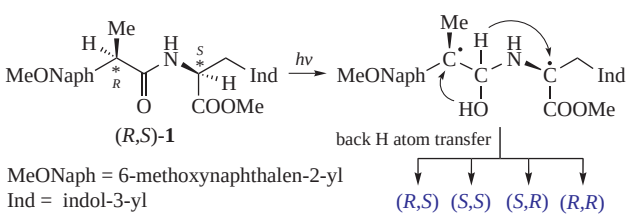
Chiral inversion is a conversion of an enantiomer or a chiral moiety into its antipode, resulting from the interaction of chiral molecules with enzymes, transport proteins, chemical reagents, or under other conditions.[1] The chiral inversion can be affected by solvents, temperature or UV irradiation.[1–3] In addition to the fundamental interest in the mechanism of this phenomenon, there is also practical significance, since spontaneous chiral inversion (SCI) can result in lowering the effect of chiral drug on a living organism or directly influence the pharmacological properties of the drug.[1] An important example of pharmaceuticals that undergo SCI is the 2-arylpropionate subclass of nonsteroidal anti-inflammatory drugs (NSAIDs).[4–6]

Mechanism of chiral inversion in 2-arylpropionates is a current issue.[1,4] The enzymatic version of the process was supposed to occur through the formation of an activated thioester derivative with coenzyme A (CoA) followed by interaction with epimerase accompanied by reversible deprotonation of the drug moiety chiral center in the CoA thioester.[7,8]

The reversible H atom transfer was also observed upon the UV irradiation of N^{α}-(2*R*/*S*)-2-(6-methoxynaphthalen-2-yl)-propionyl-(*S*)-tryptophan methyl ester **1** in solution.[9] It was demonstrated using chemically induced dynamic nuclear polarization analysis that the transfer occurred in the intermediate biradical with paramagnetic centers located on chiral atoms (Scheme 1).[9]

This observation allowed us to suppose that the back transfer of hydrogen atom in the biradical leads to SCI at the prochiral paramagnetic centers according to Scheme 1. The investigation of ketoprofen–aminocholestene system photolysis, where the transformation of the intermediate biradical also resulted in the formation of new chiral centers,[10] supported our hypothesis.

To check whether this scheme of back transfer is valid for photolysis of compound **1**, we employed NMR as one of widely



Scheme 1 Hydrogen atoms transfer in biradical formed from compound (*R*,*S*)-**1**.

accepted methods for drug chiral analysis.[11] It was found that the ^{13}C NMR signals for the diastereomers of compound **1** differ only for carbon atom of tryptophan chiral center (see Online Supplementary Materials), therefore ^{1}H NMR spectroscopy was chosen for further experiments. The signals of aliphatic hydrogen atoms at the chiral centers are the most suitable for analysis (Figure 1). Contrary to that, the aromatic protons in the naproxen moiety do not show difference for compounds (*R*,*S*)-**1** and (*S*,*S*)-**1**. The protons of the indole ring reveal some difference, but unfortunately the signals of numerous photolysis by-products are present in this region (see Online Supplementary Materials).

Upon UV irradiation of compound (*R*,*S*)-**1**† the multiplets are observed, whose spin-spin coupling constants coincide with those for the protons near the chiral centers of compound (*S*,*S*)-**1**.

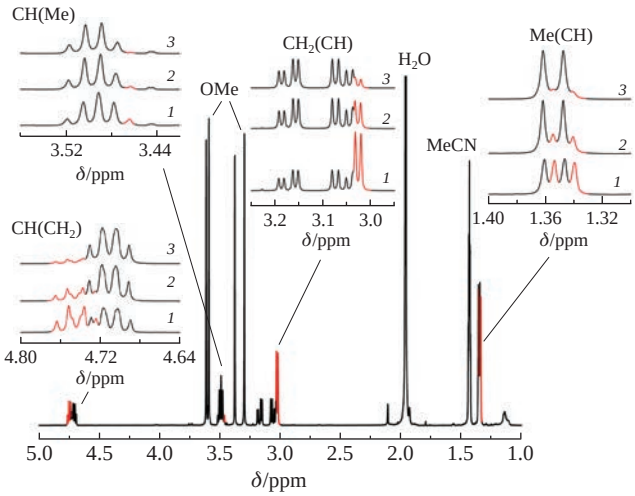


Figure 1 The aliphatic region of the ^{1}H NMR spectra for initially prepared diastereomeric mixtures of compounds (*R*,*S*)-**1** (black) and (*S*,*S*)-**1** (red), with expanded regions for protons bound with chiral centers. The (*R*,*S*)-**1**/(*S*,*S*)-**1** concentration ratio is: (*1*) 1 : 1; (*2*) 3 : 1; (*3*) 5 : 1. For C*H*(CH_2) protons the signals of diastereomer (*R*,*S*)-**1** are in a high field (right side); for C*H*(Me), *Me*(CH) and CH_2(CH) protons the signals of this diastereomer are in a low field (left side).

† ^{1}H NMR experiments were performed on a Bruker AVHD spectrometer [500 MHz, *t*(90) 11.2 ms] in the CD_3CN–C_6D_6 (2 : 3) solution under laser irradiation with 308 nm wavelength.

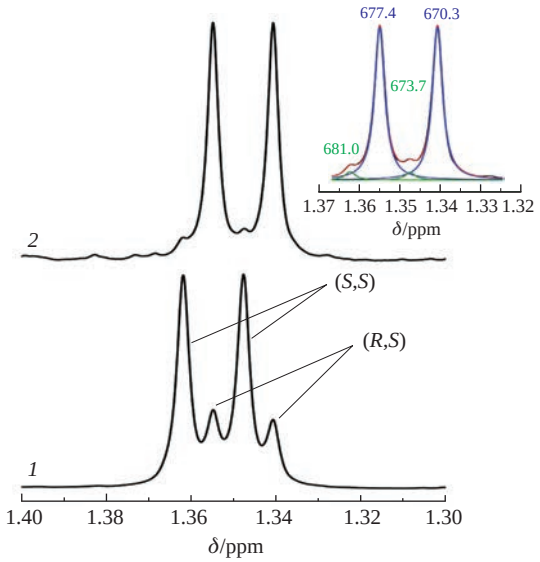


Figure 2 ^{1}H NMR signals of *Me*(CH) protons for (*1*) the (*S*,*S*)-**1**/(*R*,*S*)-**1** mixture (concentration ratio 3 : 1) and (*2*) pure compound (*R*,*S*)-**1** after 15 min of UV irradiation. Inset: NMR line shape fitting of *Me*(CH) protons for photolysis products of compound (*R*,*S*)-**1**.

It turned out that for methyl and methylene protons at the chiral carbon atoms, the appearance of isomeric product was observed as separate lines (Figures 2, 3). At the same time, for C*H*Me and C*H*(CH_2) protons (Figures 4, 5), the formation of another isomer led to fine changes in the signal pattern discussed below.

As evident from Figure 2, the lines of *Me*(CH) protons for the diastereomer (*S*,*S*)-**1** are separated from those of the initial diastereomer (*R*,*S*)-**1**.

For CH_2(CH) protons both chemical shifts and signal patterns are different: the signal for diastereomer (*R*,*S*)-**1** is a doublet and for diastereomer (*S*,*S*)-**1** the signal represents two doublets of doublets (Figure 3). The latter signal pattern is a result of the distinction between the two protons $H^{\beta1}$ and $H^{\beta2}$ in the triptophan moiety of compound (*S*,*S*)-**1**. It is worth mentioning that there is also a small amount of tryptophan by-product (see Online Supplementary Materials), its CH_2(CH) signals have the same pattern as those of compound (*S*,*S*)-**1**, and the high-field components of CH_2(CH) tryptophan multiplet overlap with the low-field component of diastereomer (*S*,*S*)-**1** multiplet (Figure 3). Therefore, the intensity of the two components of compound (*S*,*S*)-**1** multiplet (se Figure 3, spectrum *1*) differ due to the contribution from tryptophan by-product to the left component.

The estimation of the diastereomer (*R*,*S*)-**1** conversion into its (*S*,*S*)-counterpart using intensities of *Me*(CH) and CH_2(CH) signals at the identical irradiation time gave a conversion value of 2–3%.

Figure 4 demonstrates that in the resonance region of C*H*Me protons the signals of several by-products are present. Structureless lines can belong to methylene protons of glycine, 3-methyleneindolenine or other compounds (see Online Supplementary Materials). Reference data on photoinduced processes in amides indicate the possibility of formation of the following by-products as derivatives of naproxen and tryptophan: glycine, 3-methyleneindolenine, oxyindole, kynurenine and 2-ethyl-6-methoxynaphthalene.[12–14]

In addition to the two above mentioned separate signals, the spectra contain multiplets, whose deconvolution with the Lorenz function reveals that they can be the result of overlapping signals of C*H*Me protons for compounds (*R*,*S*)-**1** and (*S*,*S*)-**1** (Figure 4). For the fitting procedure, the spin–spin coupling constants *J* of diastereomer (*S*,*S*)-**1** were used. For the quartet of the proton at naproxen chiral center ^3J value is 7.1 ± 0.1 Hz.

The correspondence of the multiplet on the left side to the C*H*Me protons of the diastereomer (*S*,*S*)-**1** was proved by the addition of this isomer to the reaction mixture after photolysis [Figure 4(*b*)].

Lorentz fitting deconvolution of a signal of C*H*(CH_2) proton at the chiral center of diastereomer (*R*,*S*)-**1** was carried out on the assumption that this signal represents superposition of CH protons from both isomers. It is worth mentioning that the signal after photolysis differs from the signal of the original compound (*R*,*S*)-**1** in width and shape of the multiplet components (Figure 5). Fitting shows that this can result from differences in the signals patterns for the diastereomers. So, for compound (*R*,*S*)-**1** the C*H*(CH_2) signal is a multiplet with the following constants: $^3J_{H^\alpha H^\beta}$ 5.9 Hz, $^3J_{H^\alpha NH}$ 7.6 Hz [Figure 5(*a*)]. The corresponding signal for compound (*S*,*S*)-**1** is a quartet.

To reproduce the intensity of multiplets related to the CH protons in both chiral centers, it was necessary to have a much greater signal intensity than that required to quantify isomer (*S*,*S*)-**1**. The similarity of emerged signal patterns to that for compounds (*R*,*S*)-**1** and (*S*,*S*)-**1** allows us to suggest that other diastereomers are also formed (see Scheme 1) during photolysis, and their chemical shifts partially coincide with those of diastereomers (*S*,*S*)-**1** and (*R*,*S*)-**1**. However, the reliable detection

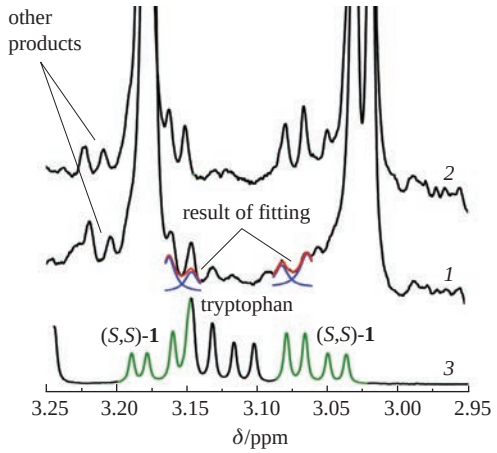


Figure 3 The CH_2(CH) protons resonance region of ^{1}H NMR spectra for (*1*) compound (*R*,*S*)-**1** after 45 min of photolysis, (*2*) the same with subsequent addition of compound (*S*,*S*)-**1**, and (*3*) the mixture of compound (*S*,*S*)-**1** (green lines) and tryptophan (black line refers to the triptophan multiplet located in a high field).

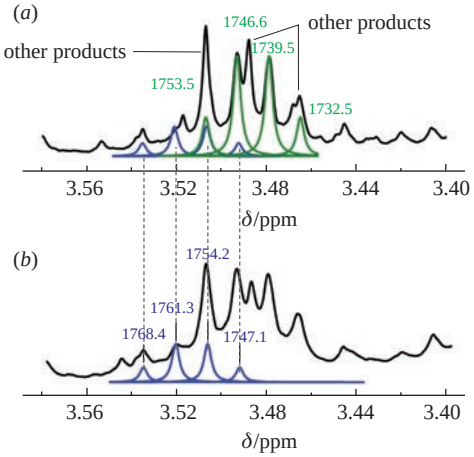


Figure 4 The C*H*Me proton resonance region of ^{1}H NMR spectra for (*a*) compound (*R*,*S*)-**1** after 15 min of UV irradiation and (*b*) with addition of compound (*S*,*S*)-**1** to the reaction mixture. The line shape fitting is shown with initial diastereomer (*R*,*S*)-**1** signals in green and product diastereomer (*S*,*S*)-**1** signals in blue.

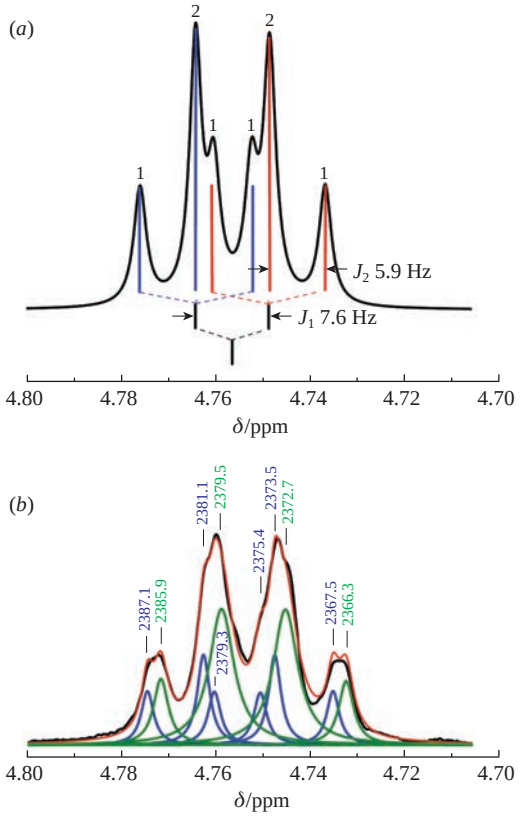


Figure 5 The C*H*(CH_2) proton resonance region of ^{1}H NMR spectra for compound (*R*,*S*)-**1** (*a*) before and (*b*) after 30 min of UV-irradiation. The line shape fitting is shown with the initial diastereomer (*R*,*S*)-**1** signals in green and the product diastereomer (*S*,*S*)-**1** signals in blue.

of these diastereomers in the reaction mixture is hampered at the moment by the absence of reference compounds.

In the photolysis of diastereomer (*S*,*S*)-**1** new signals similar to the signals of compound (*R*,*S*)-**1** also appear, but to a lesser extent, and SCI cannot be reliably determined because of the signals of by-products.

In summary, the existence of diastereomer (*S*,*S*)-**1** among the photolysis products of compound (*R*,*S*)-**1** testifies in favour of suggestion that the SCI process here is the result of the back H-transfer in the intermediate biradical. This represents the unidirectional conversion of (*R*)-naproxen moiety into its (*S*)-analogue which is typical of 2-arylpropionate NSAIDs in general and is described for *in vitro* and *in vivo* reactions with participation of α-methylacyl-CoA racemase (AMACR, EC 5.1.99.4).[7]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.006.

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