Electronic supplementary materials *Mendeleev Commun.*, 2019, **29**, 260–262

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

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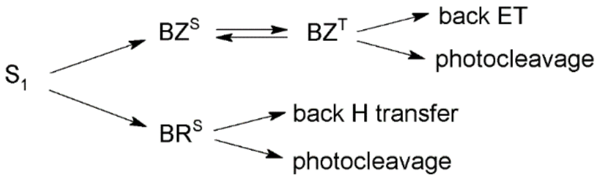
Contents

1. Experimental details

The procedures for the synthesis of diastereomers (*R*,*S*)-**1** and (*S*,*S*)-**1** were published.[1] Stock solutions for NMR measurements were prepared in the following solvents: a mixture of deuterobenzene (D 99.8%) and deuteroacetonitrile (D 99.9%); both solvents from Aldrich. ^{1}H NMR spectroscopy experiments were performed using a Bruker AVHD spectrometer (500 MHz ^{1}H operating frequency, *t*(90) 11.2 ms). Samples in standard 5 mm Pyrex NMR tubes were deoxygenated by argon bubbling for 15 min immediately before irradiation and then irradiated using a Lambda Physik EMG 101 MSC excimer laser (λ 308 nm, 100 mJ at the output window).

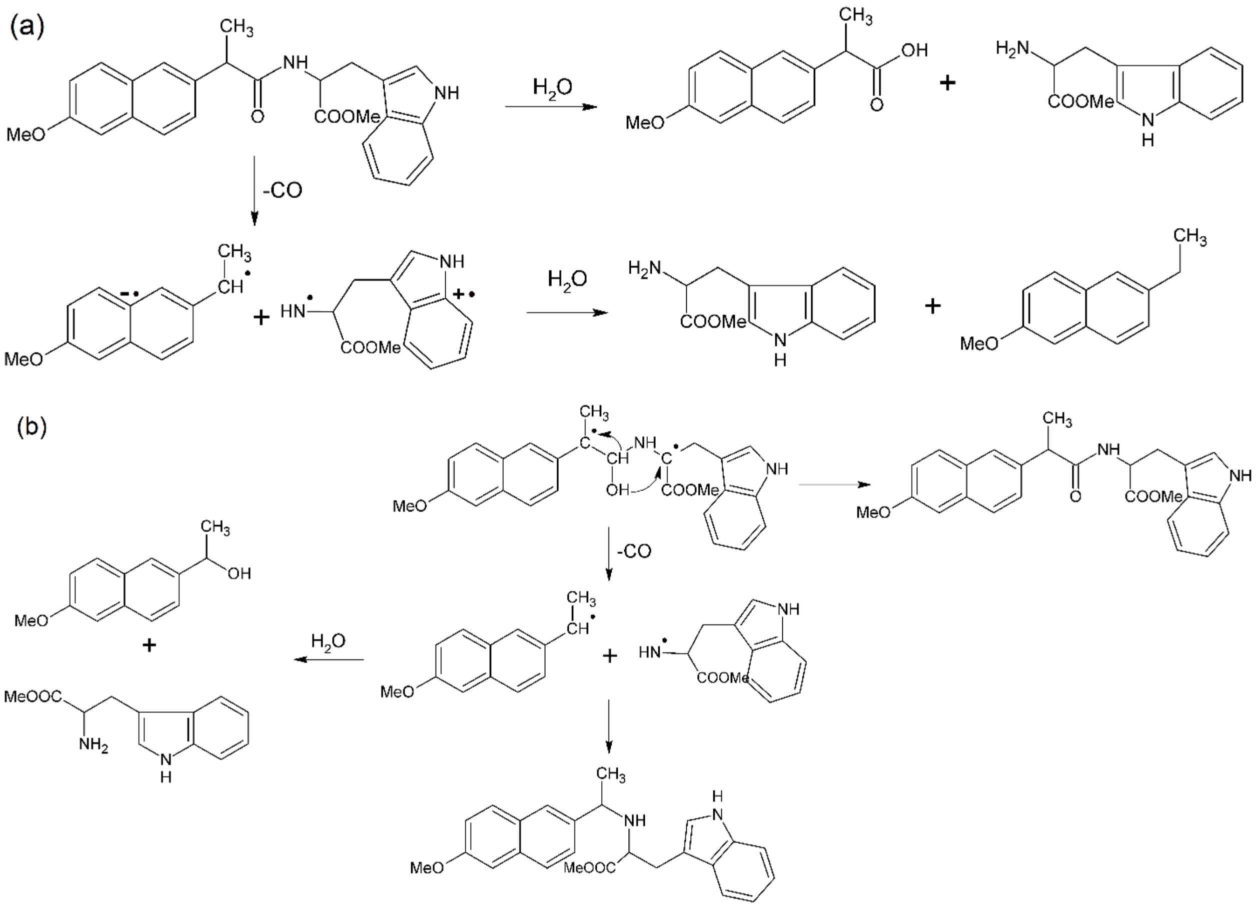
2. Photoinduced processes in NPX–Trp linked system



Scheme S1 Photoinduced transformation of NPX–Trp linked system, according to:[1] S_1 is singlet excited state of the system, ET is electron transfer, BZ is biradical-zwitterion, BR is biradical.

3. Reference data about photolysis of amides and additional experimental data

According to published data the photodegradation of both NPX and Trp moieties in linked systems includes a variety of reactions.[2] The products could be formed by several ways from both BZ and BR of the linked systems according to Scheme 2 (a,b) adopted from[2,3] to the case of NPX–Trp system.



Scheme S2 Mechanisms of NPX–Trp photocleavage from (*a*) BZ, (*b*) BR.

Besides, the reference data on photoinduced processes in amides, to which the NPX–Trp linked system can be attributed, let us to expect the formation of the following products: glycine, methylenindoline, oxindole and kynurenine, derivatives of naproxen and tryptophan.[2,3]

Below are the ^{13}C NMR spectra of diastereomers of the NPX–Trp linked system.

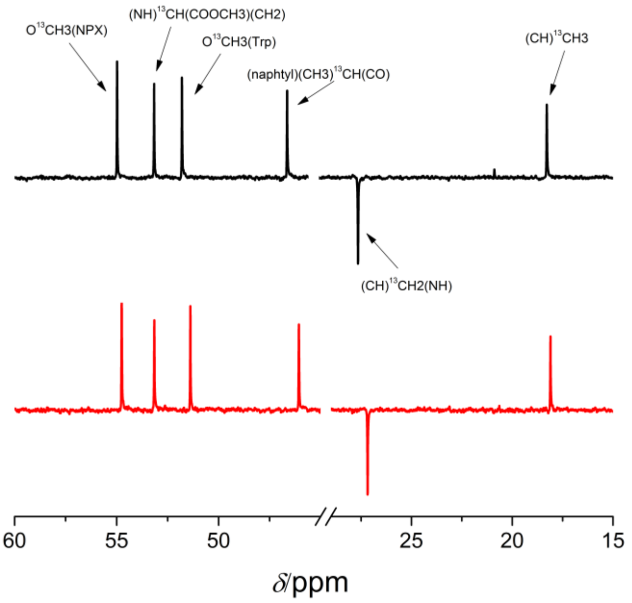


Figure S1 Aliphatic region of ^{13}C DEPT-135 spectra of 10 mM solution of compound (*R*,*S*)-**1** (black) and 10 mM solution of compound (*S*,*S*)-**1** (red). The most prominent difference in chemical shift is observed for the chiral carbon of the Trp part (Δδ ~30 Hz).

We used the ^{1}H NMR spectra for the identification of diastereomers, since in their ^{13}C spectra signals differ only for carbon atom of Trp chiral center (Figure S2). As can be seen from the figures, the ^{1}H NMR signals of hydrogen atoms bonded with chiral carbon are the most suitable for analysis. As regards the aromatic protons, in the naproxen part the signals of the (*R*,*S*) and (*S*,*S*) configurations do not differ from each other and the exception is only the protons of the indole ring. But in the region of indole protons other products of the NPX–Trp photolysis are accumulated (see Figure S2).

The addition of the kynurenine to the product of the photolysis did not allow one to reveal its presence. The location of other products signals in NMR spectra are shown in the picture below.

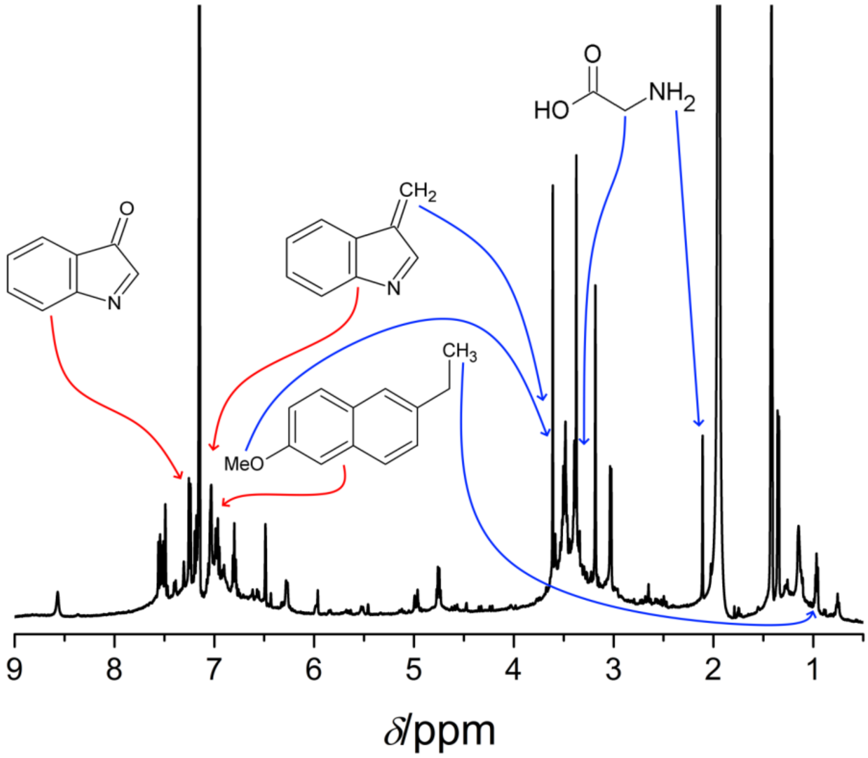


Figure S2 ^{1}H-NMR of 10 mM solution of compound (*R*,*S*)-**1** in 40% CD_3CN 60% C_6D_6 after 45 min of photolysis. The positions of expected products (oxyindole, 3-methyleneindolenine, glycine and 2-ethyl-6-methoxynaphthalene) signals are labelled by arrows.

Figure S2 shows that aliphatic protons of these products should be located in the region of C*H* Me and C*H*$_2$(CH) protons of NPX–Trp diastereomers. It is confirmed by the comparison of the time dependence of these signals intensities with those of the other protons of NPX–Trp diastereomers (Figure S3).

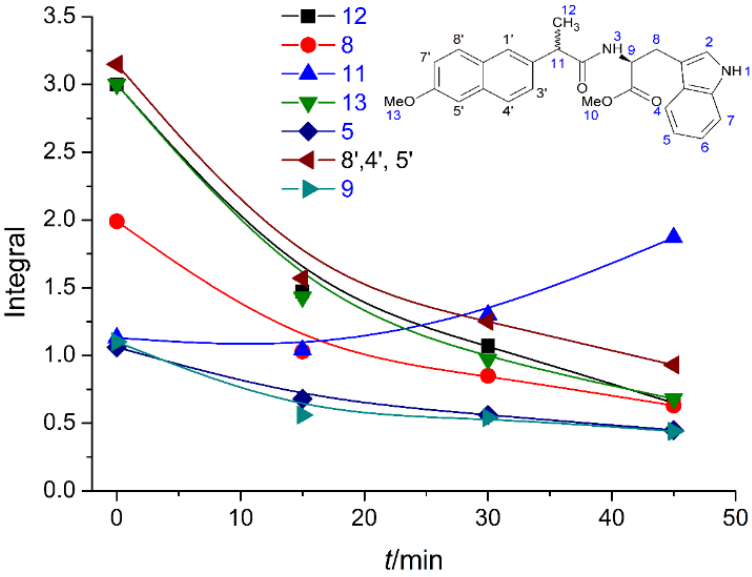


Figure S3 Time dependences of NMR signals of compound (*R*,*S*)-**1** photolysis products.

Thus, in the region of C*H*Me and OMe (13) protons, the decay rates are the smallest, as compared to those for *Me*(CH) and aromatic protons (8',4',5') of the naproxen fragment. The maximum concentration of products is in the region of the resonance of C*H*(CH_2) (8), indole (5) and C*H*Me (11) protons. In the latter case, an increase in intensity is observed with exposure time.

Comparison of the integral intensities of the new, referred to (*S*,*S*)-diastereomer, signals: *Me*(CH) and C*H*$_2$(CH), with the corresponding signals of the initial (*R*,*S*)-diastereomer shows that the degree of conversion is 2–3%.

References

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2. C. Schöneich, *J. Pharm. Pharmacol.*, 2018, **70**, 655.
3. J. D. Coyle, *Pure Appl. Chem.*, 1988, **60**, 941.