Photoinduced Hydrogen Abstraction

Diastereomeric Differentiation in the Quenching of Excited States by Hydrogen Donors**

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Photoinduced hydrogen transfer and electron transfer to excited states of carbonyl compounds are two of the most intensively investigated fundamental processes in photochemistry.[1–3] Numerous studies have been performed to elucidate the mechanisms as well as to determine ways to control these processes, and have involved variation of the electronic nature of the excited state (n,π* versus π,π*)[4,5] and its multiplicity, that is, singlet- versus triplet-state photochemistry.[6,7] Electronic donor properties, such as bond dissociation energies and ionization potentials,[1,4,7,8] structural features, namely, stereoelectronic and steric hindrance effects,[9,10] and the influence of the chemical surrounding (solvent polarity, hydrogen bonding) have also been investigated.[11–14]

However, relatively little is known about diastereomeric differentiation in the intramolecular quenching of excited states, which is basically related to the search for asymmetric photoreactions, and is another phenomenon which could control the kinetics of hydrogen- or electron-transfer processes.[15–17] Recently, studies were performed on the intramolecular exciplex-mediated quenching of triplet states in diastereomeric dyads consisting of 2-arylpropionic acid derivatives and electron donors of biological importance, namely, tyrosine and tryptophan.[18,19] Other studies focused on the chiral control of intramolecular charge-transfer quenching of ketone triplets in solution and in the solid state.[20,21] Reports on related intermolecular quenching are rather scarce and are also focused mainly on exciplex-mediated processes.[22,23]

Although the possibility of conformational control of photoinduced hydrogen abstractions in Norrish type II reac-

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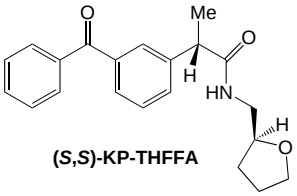
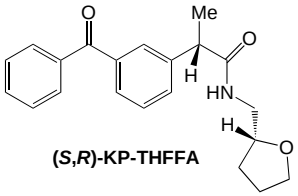
tions[24,25] or photoenol formation[26] has been reported, diastereomeric differentiation of a hydrogen donor by an excited chromophore remains unprecedented. Just recently such an effect was observed in hydrogen abstractions in dyads comprised of a chiral benzophenone derivative, namely, (*S*)-ketoprofen (KP), and a chiral 1,4-cyclohexadiene.[27] Unfortunately, the lifetime of the triplet state of ketoprofen in the investigated dyads was too short for direct kinetic characterization. Thus, a hydrogen donor with lower interaction efficiency, that is, a chiral tetrahydrofuran derivative, seemed to be a promising choice to circumvent this problem. The intermolecular rate constant for the triplet quenching of benzophenone by this ether is known to be 30 times lower than for 1,4-cyclohexadiene ($9.6\times10^{6}\,\text{M}^{-1}\,\text{s}^{-1}$ versus $2.9\times10^{8}\,\text{M}^{-1}\,\text{s}^{-1}$) in benzene.[28] Furthermore, a higher selectivity in the quenching reaction can be anticipated as a result of the lower reactivity of tetrahydrofuran which might result in a significant discrimination between both diastereomers (similar to the reactivity-selectivity principle).

Ketoprofen is a known photosensitizer similar to benzophenone which is photophysically well-characterized,[29] with special emphasis devoted to its photobiological importance.[30] Since benzophenone can be considered as the classical carbonyl chromophore, our investigations regarding diastereomeric differentiation during hydrogen-abstraction reactions are expected to provide deeper insights into a photochemical mechanism of general interest.

The dyads (*S*,*S*)-KP-THFFA and (*S*,*R*)-KP-THFFA were synthesized from (*S*)-ketoprofen (KP) and (*S*)- or (*R*)-tetrahydrofurfurylamine ((*S*)- or (*R*)-THFFA) by condensation in the presence of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide (EDC) in dichloromethane. Analysis of the products by ^{1}H and ^{13}C NMR spectroscopy confirmed their identity. The UV/Vis absorption spectra of both isomers in acetonitrile are characterized by a weak absorption at 338 nm, which corresponds to the n,π* transition, and a much stronger band at 254 nm, which is typical for the π,π* absorption. These bands are similar to those obtained for the benzophenone chromophore.



(*S*,*S*)-KP-THFFA



(*S*,*R*)-KP-THFFA

Laser flash photolysis studies on the nanosecond timescale using the 355-nm output of a Nd:YAG laser (full width of half maximum height: ca. 10 ns, 10 mJ pulse^{-1}) were performed to clarify the role of diastereomeric differentiation in the primary step of the photoreduction of the carbonyl function, namely, transfer of a hydrogen atom to the triplet-excited chromophore. A transient with absorption maxima at 325 and 530 nm was formed immediately in both cases (Figure 1, inset) upon excitation of nitrogen-bubbled solutions of the diastereomers (9.5×10^{-4} M) in acetonitrile. The

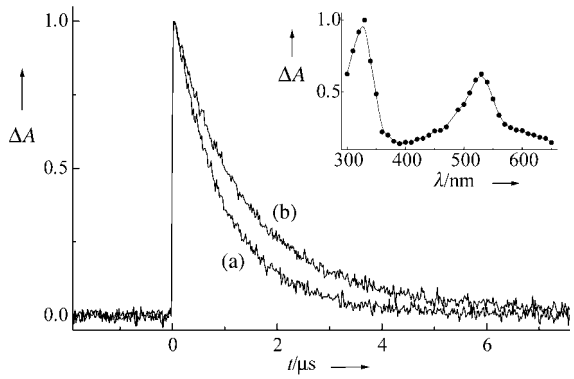


Figure 1. Transient decay for solutions of a) (*S*,*S*)-KP-THFFA and b) (*S*,*R*)-KP-THFFA in acetonitrile (9.5×10^{-4} M) under nitrogen at 525 nm upon excitation at 355 nm. The inset shows the corresponding transient spectrum of (*S*,*S*)-KP-THFFA 20–120 ns after the laser flash.

position of these bands and the ratio between their intensities (A_{325}/A_{530} ca. 1.6:1) lead to an unambiguous assignment of this transient to the triplet–triplet absorption (the triplet state) of the ketoprofen chromophore.[29–31] The ketyl radical of ketoprofen has similar absorption maxima (330 and 540 nm), but with a much larger ratio of the intensities of the two bands. The kinetics of the transient was measured at $\lambda_{obs}=525$ nm and shown to consist of a major fast component and a minor slow component (lifetime ca. 3.4–3.8 μs). The latter might be caused by the decay of biradicals formed as a result of hydrogen abstraction. Based on the transient spectrum, the major fast component can be ascribed to the triplet decay, which is significantly different for the two diastereomers: $\tau_T=0.95$ μs for (*S*,*S*)-KP-THFFA and 1.20 μs for (*S*,*R*)-KP-THFFA. The corresponding decay traces are shown in Figure 1. This result provides kinetic evidence for diastereomeric differentiation in the photoinduced hydrogen-transfer process. The triplet lifetime of ketoprofen itself under the same experimental conditions is $\tau_0=1.32$ μs. The intramolecular rate constant for hydrogen abstraction (k_H) was determined from the following relationship [Eq. (1)].

$$k_H = 1/\tau_T - 1/\tau_0 \qquad (1)$$

A unimolecular rate constant of $k_H=3.0\times10^{5}\,\text{s}^{-1}$ is found for the *S*,*S* diastereomer, while the *S*,*R* diastereomer reacts four times slower ($k_H=7.5\times10^{4}\,\text{s}^{-1}$).

To rule out the possibility that the diastereomeric differentiation found for the dyads simply reflects the result of different conformational pre-organization of the diastereomers, the intermolecular triplet quenching of (*S*)-KP by the acetamides of (*S*)- and (*R*)-THFFA was examined. Remarkably, true chiral recognition was actually observed in this experiment. The respective bimolecular quenching rate constants were 3.8×10^{7} and $2.0\times10^{7}\,\text{M}^{-1}\,\text{s}^{-1}$, thus, the enantioselectivity factor was 1.9. Although this value is smaller than that found in the intramolecular case, as would be expected from the higher degrees of freedom, it is still quite substantial and deserves further investigation. This chiral recognition could be associated with restricted approach geometries, probably as a result of hydrogen-bonding interactions

between the carboxy group of (*S*)-KP and the NH group of the acetamides of (*S*)- and (*R*)-THFFA.

The ketyl radicals formed (biradicals in the case of an intramolecular hydrogen transfer) remain difficult to assign in the transient spectrum for the following reasons: 1) the ketyl radical is generated only in a relatively small amount (maximum 30% quenching effect for (*S*,*S*)-KP-THFFA) and 2) a significant amount of long-lived light-absorbing transients (LAT) is formed during irradiation of the dyads, as evidenced by an increase in the absorbance at approximately 330 nm (Figure 2).[32] However, although LAT complicate the analysis of the transient spectra, they provide clear-cut evidence for the hydrogen-transfer process.

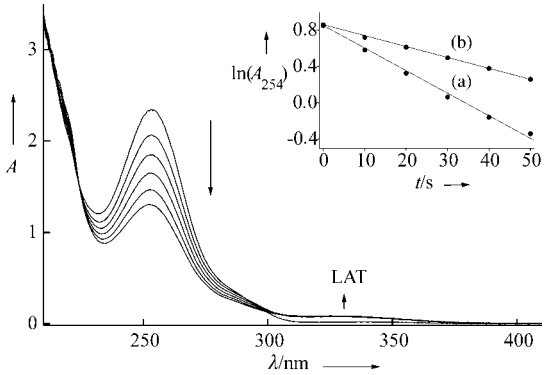
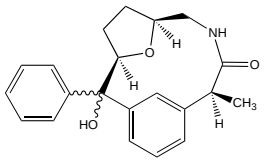


Figure 2. Steady-state irradiation of a solution of (*S*,*R*)-KP-THFFA in nitrogen-bubbled acetonitrile at $\lambda_{exc} = 254$ nm. The UV/Vis spectra were taken in time intervals of 10 s. The inset shows the respective plots for the decrease of the absorbance at 254 nm for a) (*S*,*S*)-KP-THFFA and b) (*S*,*R*)-KP-THFFA.

The influence of stereochemistry on the decomposition of the dyads under steady-state irradiation was tested in an additional experiment. The decay of the band at 254 nm in nitrogen-saturated solutions was followed during the irradiation time (Figure 2). Significant differences were noted between the two diastereomers, similar to the situation for the analogous ketoprofen–cyclohexadiene dyad,[27] with (*S*,*R*)-KP-THFFA being more photostable than the *S*,*S* diastereomer. Logarithmic plots of absorbance versus irradiation time yielded straight lines (Figure 2, inset), whose slopes point to a difference factor of 2. Again, similar to the kinetic observation of the triplet, the *S*,*S* compound reacts more efficiently, although with a somewhat lower differentiation.

Finally, isolation of the major photoproducts was accomplished by means of preparative HPLC. The NMR data (see Supporting Information) confirm the unambiguous formation of biradical recombination products, as reported for other benzophenone–hydrogen-donor dyads.[27,33] Hydrogen is surprisingly not abstracted from the more highly substituted OCHR group, but from the OCH_2 group. Molecular modeling studies (ab initio B3LYP6-31G* DFT and semiempirical AM1 calculations; see Supporting Information) on the transition states for both pathways revealed a higher activation energy (by 1.8 kcal mol^{-1}) for hydrogen abstraction from the methine group, presumably as a result of a higher ring strain in the resulting cyclophane-like photoproduct (Scheme 1).



Scheme 1. Diastereomeric photoproducts of (S,S)-KP-THFAF.

In conclusion, kinetic evidence for diastereomeric differentiation is presented for a classical textbook example of a hydrogen-abstraction process. The concept is supported by photoproduct studies and quantum-chemical calculations.

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