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# Stereoselective intramolecular hydrogen abstraction by a chiral benzophenone derivative

**Miguel A. Miranda,* Luis A. Martínez, Abdelouahid Samadi, Francisco Boscá and Isabel M. Morera**
*Departamento de Química—Instituto de Tecnología Química UPV—CSIC, Universidad Politécnica de Valencia, Camino de Vera s/n 46071. Valencia, Spain. E-mail: mmiranda@qim.upv.es; Fax: +34 96 3877349; Tel: +34 96 3877344*

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**An unprecedented stereoselective photoreduction of a chiral BZP is observed in steady state as well as in time-resolved studies.**

Hydrogen abstraction by benzophenone (BZP) from suitable donors has attracted considerable attention in the last two decades and is one of the most general and best-known photochemical reactions. The transient species detected upon laser flash photolysis of BZP include its triplet, the ketyl radical ($BZPH^{\cdot}$) and the radical anion ($BZP^{\cdot -}$). Reaction of BZP n–π* triplets with allylic hydrogens gives $BZPH^{\cdot}$, which may form benzhydrol $BZPH_2$, dimerize to pinacol $(BZPH)_2$ or yield cross-coupled dimers.[1]

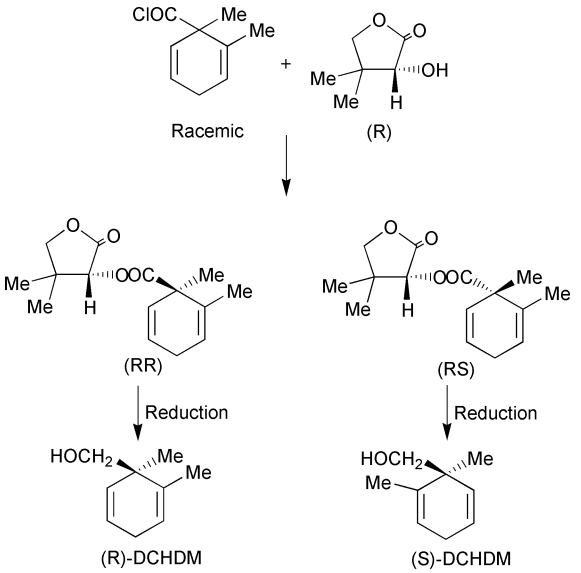
A photochemical reaction may be stereoselective when a chiral sensitizer is involved in the process.[2] Previously, it has been shown that bichromophoric compounds containing covalently linked sensitizer and substrate-derived substructures can be useful for modeling photochemical enantioselective events. Thus, in the electron transfer between excited π–π* ketones and amino acids a high degree of enantioselective discrimination has been achieved; this has been related to the possible enantioselectivity of the photobiological properties of drugs.[3]

Ketoprofen (KP, 2-(3-benzoylphenyl)propionic acid), a currently used nonsteroidal anti-inflammatory drug containing the BZP chromophore,[4] behaves as a photosensitizing agent in humans.[5] Hydrogen abstraction from and formation of adducts to target biomolecules appear to be the main processes responsible for KP-induced phototoxicity and photoallergy. The former process is known to play a key role in the photodynamic lipid peroxidation leading to cell membrane lysis, where polyunsaturated fatty acids serve as hydrogen source.[6]

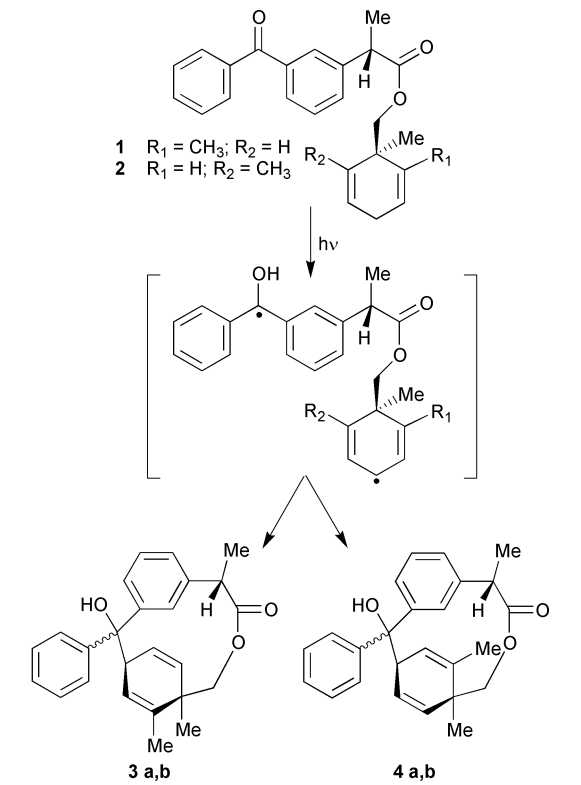
In connection with the potential enantioselectivity of drug-photosensitized lipid peroxidation, we have prepared two diastereomeric bichromophores starting from (*S*)-KP and a chiral cyclohexa-1,4-diene moiety containing the double allylic system present in linoleic acid and other polyunsaturated fatty acids.

1,2-Dimethylcyclohexa-2,5-dienecarboxylic acid was synthesized through Birch reduction and subsequent methylation of *o*-toluic acid.[7] Esterification (*via* the acid chloride) with (*R*)-pantolactone produced a diastereomeric mixture (Scheme 1), which was resolved into its individual components by a combination of fractioned recrystallization and column chromatography. The structure of a crystalline sample corresponding to the *RS* isomer was established by X-ray diffraction. Reduction of the separated isomers by $LiAlH_4$ followed by semi-preparative HPLC, using acetonitrile : water : acetic acid as eluent, yielded the pure enantiomers of 1,2-dimethylcyclohexa-2,5-diene-1-methanol (DCHDM). They were reacted with the acid chloride of (*S*)-KP to give the corresponding esters **1** and **2**.

Independent photolysis of **1** and **2** in argon-bubbled acetonitrile solution yielded **3** or **4**, respectively. In each case, a pair of diastereomers was obtained (**3a**,**b or 4a**,**b**, Scheme 2), whose separation was achieved by sequential column chromatography and HPLC. In both cases, the **a** : **b** ratio was *ca.* 1. Their characterization was based on NMR ($^1H$ and $^{13}C$) as well as MS spectral data. The stereochemistry of the intramolecular coupling products **3a**,**b** and **4a**,**b** is inherited from that of the pure enantiomeric reactants (KP and DCHDM). Thus, the generation




**Scheme 1**




**Scheme 2**

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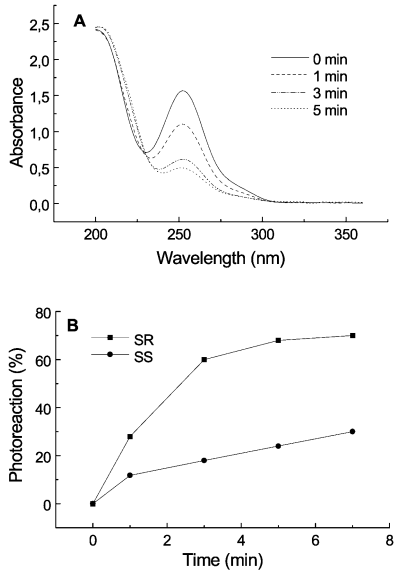


**Fig. 1** Photocyclization of bichromophores **1** and **2**. A: monitoring of BZP absorption band disappearance for the *SR* isomer. Similar spectra were obtained for the *SS* isomer, although reaction times were higher. B: comparison of the results obtained for both diastereomers.

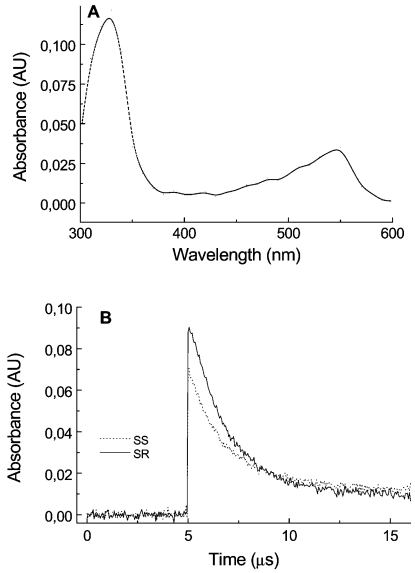


**Fig. 2** Photophysical studies on bichromophores **1** and **2**. A: Transient absorption spectrum for the *SR* isomer upon 355 nm laser excitation. A similar spectrum was obtained for the *SS* isomer. B: Decay traces observed for both isomers at 330 nm.

of a new asymmetric center upon cyclization (*i.e.* the reduced carbonyl carbon) is responsible for the formation of a pair of diastereomers starting either from **1** or from **2**.

Remarkably, the rate of photocyclization upon steady state photolysis was clearly higher in the case of **1** (*SR* diastereomer). The reaction was followed by monitoring the disappearance of the typical BZP absorption band centered at *ca.* 254 nm. This is shown in Fig. 1A. Fig. 1B compares the results obtained for the *SR* and *SS* bichromophores. Thus, after 5 min of irradiation in acetonitrile solution, more than 60% of starting **1** was consumed while under similar conditions only 20% of *SS* isomer **2** had reacted. As the coupling products are generated upon intramolecular cyclization of an intermediate biradical, these results suggest that the key hydrogen abstraction process is stereoselective.

In order to gain some mechanistic insight, photophysical studies were also carried out on both bichromophores. Upon laser excitation (Nd:YAG, 355 nm) of $10^{-3}$ M acetonitrile solutions of both esters, the recorded transient spectra showed two bands with maxima at *ca.* 330 and 540 nm (Fig. 2A). The decay traces at 330 nm (see Fig. 2B) allowed to determine the lifetimes ($\tau$ = 1.8 and 1.6 μs for **1** and **2**, respectively). The transients were assigned as the biradicals formed upon intramolecular hydrogen abstraction. In connection with the stereoselectivity of the photoreduction process, it was very interesting to realize that biradical formation was *ca.* 30% more efficient for the *SR* isomer. This explains the results obtained in the steady-state experiments.

The observed stereoselectivity may be due to the fact that, according to 3D models, the methyl group at C-2 of (*S*)-DCHDM hinders both hydrogen abstraction and cyclization of the resulting biradical as compared to (*R*)-DCHDM. The destabilizing interaction between this methyl group and the α-carbonyl methyl can also be clearly observed in the models of the final products **3** and **4**.

Summarizing, this work reports an unprecedented stereoselective photoreduction of a chiral BZP upon intramolecular hydrogen abstraction. This stereoselectivity is observed in the steady state as well as in time-resolved studies. Since KP is a chiral photosensitizing drug, our results suggest that the initiation step of photodynamic lipid peroxidation, and thus cell membrane disruption, might be more easily promoted by one of the drug enantiomers. Hence, although the results here obtained with the intramolecular process in model systems should not be overemphasized, it appears that photooxidation of polyunsaturated fatty acid may be a stereoselective process.

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