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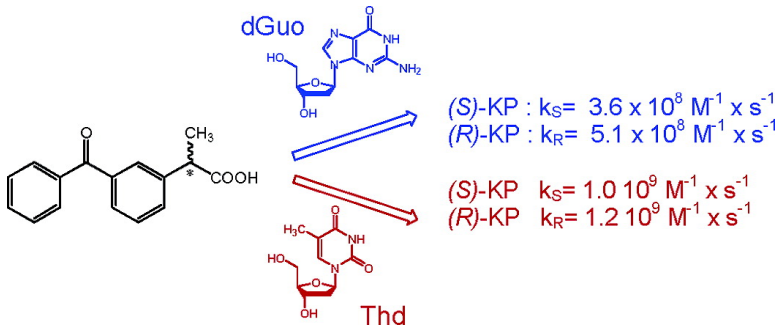

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Excited State Enantiodifferentiating Interactions between a Chiral Benzophenone Derivative and Nucleosides

Virginie Lhiaubet-Vallet, Susana Encinas, and Miguel A. Miranda*

Instituto de Tecnología Química UPV-CSIC, Universidad Politécnica de Valencia, Avda de Los Naranjos s/n, 46022 Valencia, Spain

Received May 30, 2005; E-mail: mmiranda@qim.upv.es

Asymmetric photochemistry has attracted considerable attention.[1,2] Research efforts have mainly focused on photochirogenesis[2] and photoresolution of racemic mixtures;[3] however, direct photophysical evidence for chiral discrimination in the triplet excited states has only been found in a few cases.[4]

Supramolecular photochemistry within chiral environments[5] provided by biomolecules is of special interest, as a detailed knowledge of stereodifferentiating photoprocesses is essential for the design of new chiral drugs and therapeutic agents.[6] In this context, the possibility of stereodifferentiating interactions between drug triplet excited states and biomolecules or their simple building blocks remains practically unexplored.

Actually, stereoselectivity is becoming an important issue in pharmaceutical chemistry. There is an increasing trend to synthesize and commercialize pure enantiomers in order to suppress the toxic effects induced by the less active forms. Ketoprofen (KP) has been recognized to be the strongest photosensitizer among non-steroidal anti-inflammatory drugs (NSAID).[7] Although it was only commercialized as the racemic form, the pharmacologically active *S*-stereoisomer (dexketoprofen) has recently been introduced in the market. Unambiguous evidence for the photosensitivity side effects associated with both the racemate and the *S*-enantiomer has been obtained at the clinical level.[7,8]

The photosensitizing properties of racemic KP toward biomolecules are now well established; they have been attributed to its benzophenone chromophore.[9] Photosensitization of DNA by KP involves two major types of mechanism: (1) triplet−triplet energy transfer leading to thymine dimerization and (2) electron-transfer oxidation of the guanine nucleobase.[10,11] Moreover, formation of oxetanes has recently been proposed to explain the high rate constant for quenching of the KP nπ* triplet state by thymidine (Thd).[12] This result has been discussed in connection with thymidine (or thymine) photosensitization by benzophenone (BP) that has been intensively investigated.[12,13] Irradiation of a short double-stranded oligonucleotide, including a benzophenone immobilized in the major groove, gives rise to interstrand cross-linking by oxetane formation between thymidine and BP.[14]

In the present work, the possible enantiodifferentiation during DNA photosensitization by drugs has been investigated by examining the interaction between the triplet excited state of enantiopure (*R*)- or (*S*)-KP and two relevant nucleosides, namely, Thd and 2′-deoxyguanosine (dGuo).

Nanosecond laser flash photolysis (LFP) studies were performed at 355 nm (Nd:YAG), in nitrogen-bubbled acetonitrile:water (4:1) solutions. The characteristic spectra of KP triplet−triplet transition (λ_{max} = 320 and 520 nm)[9] were observed immediately after the laser pulse (Figure 1a, inset). The triplet state of KP (^{3}KP) was quenched by addition of Thd (Figure 1a); measurement of its lifetime as a function of Thd concentration allowed us to obtain the Stern−Volmer plots (Figure 1b) and to calculate the quenching

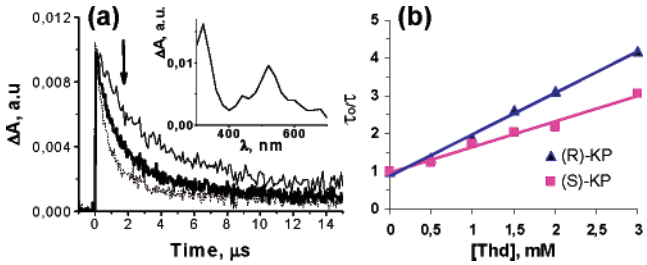

Figure 1. (a) ^{3}KP decay at 520 nm in the presence of increasing amounts of Thd (0−1.5 mM) after laser excitation at 355 nm. Inset: Laser flash photolysis spectrum of KP 0.15 μs after the laser pulse, showing the typical benzophenone triplet−triplet transition. (b) Stern−Volmer plots of ^{3}KP quenching by Thd.

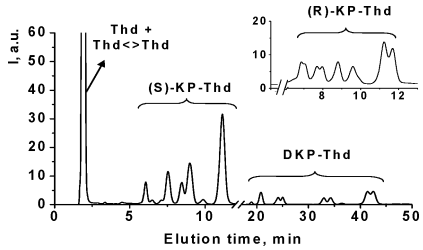

Figure 2. UV chromatograms obtained at 210 nm from the HPLC−MS analysis of the reaction mixtures obtained after irradiation of Thd in the presence of (*S*)-KP (ratio 3:1). Inset: Same experiment performed with (*R*)-KP + Thd.

rate constants by linear regression. They were found to be k_S(Thd) = (3.6 ± 0.2) × 10^8 and k_R(Thd) = (5.1 ± 0.2) × 10^8 M^{-1}•s^{-1} for (*S*)- and (*R*)-KP, respectively. Hence, the enantioselectivity factor for triplet deactivation by Thd was ca. 1.4. Under these conditions, no signal corresponding to Thd triplet (λ = 370 nm)[15] or KP ketyl radical (λ = 330 and 545 nm) was detected. In a control experiment to confirm the obtained trend, an analogous enantiodifferentiation was observed during quenching of (*S*)-KP by the natural D-thymidine or by its antipode, L-thymidine. It was found that the triplet lifetime of (*S*)-KP in the presence of 2 mM L-Thd was 0.6 μs. This value was identical to that found with the equivalent combination (*R*)-KP/D-Thd (0.6 μs) and significantly different from that of (*S*)-KP/D-Thd (0.8 μs). To get further insights into the mechanism involved in the photoreaction, deaerated mixtures of (*R*)- or (*S*)-KP and Thd (relative ratio of 1:3) were UVA-irradiated, and the complex photoproduct mixtures were analyzed by reverse phase HPLC coupled with electrospray detection (Figure 2). Four groups of photoproducts were detected: (i) thymidine dimers with *m*/*z* = 507 (242 × 2 + Na^+), (ii) the different regio- and stereoisomers of KP−Thd oxetanes with *m*/*z* = 519 (242 + 254 + Na^+), (iii) the different regio- and stereoisomers of the oxetanes formed between decarboxylated KP and Thd (DKP−Thd) with *m*/*z* = 475 (242 + 254 − 44 + Na^+), and (iv) decarboxylated KP with

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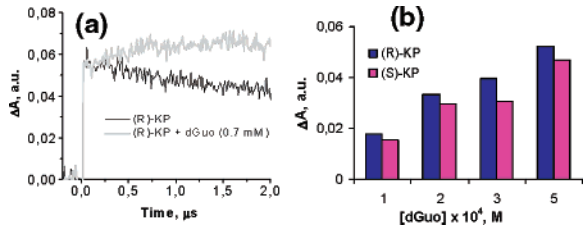
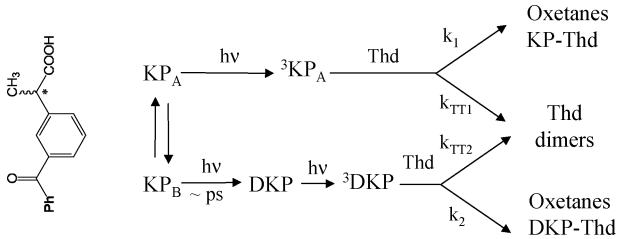


Figure 3. (a) Kinetic traces (decay or growth) measured at 320 nm for (*R*)-KP solutions with or without dGuo after laser flash photolysis at 355 nm. (b) Comparison of the amount of ketyl radical formation for (*R*)- and (*S*)-KP as a function of dGuo concentration.

Scheme 1. Mechanistic Pathways Explaining Formation of the KP Thd Photoproducts



m/z = 233 (254 − 44 + Na^+). Formation of the different photoproducts can be explained by the mechanistic pathways summarized in Scheme 1. The excited triplet state of the protonated form (^3KP_A) would react with Thd by a Paterno−Büchi mechanism (k_1), leading to formation of KP−Thd oxetanes; alternatively, a triplet−triplet energy-transfer mechanism would give rise to thymidine dimerization (k_{TT1}). Deprotonated KP (KP_B) is known to photodecarboxylate in the picosecond range;[16] the resulting DKP would, in turn, react with Thd, giving rise to DKP−Thd oxetanes (k_2), or photosensitize thymine dimer formation (k_{TT2}). Considering the benzophenone-like structure of KP and DKP, the values given in the literature for BP can provide an indication about the competition between the two types of processes: the rate constant of Paterno−Büchi photocycloaddition (k_1 and k_2) should be around 10^8−10^9 $M^{-1}\cdot s^{-1}$, 1 order of magnitude higher than the rate constant k_{TT1} and k_{TT2} of triplet−triplet energy transfer.[12,17] Thus, the enantioselective quenching of the chiral KP triplet state by Thd can be associated with formation of the C−O bond, the first step of oxetane formation, rather than with energy transfer leading to Thd dimerization. Actually, the latter process was expectedly slow, as the triplet energy of BP derivatives (ca. 290 kJ·mol^{-1}) is slightly lower than that of Thd (ca. 310 kJ·mol^{-1}).[18] Hence, dimer formation would require thermal activation and higher Thd concentration to increase the efficiency of ^{3}Thd generation and its quenching.

A similar quenching study was performed with 2′-deoxyguanosine, the most easily oxidizable nucleoside. Concomitantly with the decrease of ^{3}KP, the growth of a transient species corresponding to KP ketyl radical (λ = 330 and 545 nm) was observed. Figure 3a shows the decay of ^{3}KP in the absence of dGuo and the formation of ketyl radical after dGuo addition, both at 320 nm. In this case, the quenching rate constants were k_S(dGuo) = (1.00 ± 0.05) × 10^9 $M^{-1}\cdot s^{-1}$ and k_R(dGuo) = (1.23 ± 0.09) × 10^9 $M^{-1}\cdot s^{-1}$. It is noteworthy that the amount of (*R*)- and (*S*)-KP ketyl radical formation (Figure 3b) follows the same tendency as the enantiodifferentiation observed in the quenching of ^{3}KP. Detection of the ketyl radical, obtained by protonation of the KP radical anion, can be considered as proof for the electron-transfer photoreaction between ^{3}KP and dGuo (eq 1).

$$KP + dGuo \rightarrow KP^{\bullet -} + dGuo^{+\bullet};\ KP^{\bullet -} + H^+ \rightarrow KPH^{\bullet} \quad (1)$$

Taking into account the redox potentials (E(KP/KP$^{\bullet -}$) = −1.24 V and E(dGuo/dGuo$^{+\bullet}$) = 1.05 V vs SCE)[11] and the KP triplet energy, the process would be exergonic (ΔG = ca. −70 kJ·mol^{-1}), according to the Rehm−Weller equation.

In summary, a significant enantiodifferentiation is observed in the quenching of ^{3}KP by Thd and dGuo that can be correlated with the Paterno−Büchi photoreaction and ketyl radical formation, respectively. The biological implications of this finding are currently under study.

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Supporting Information Available: ^{1}H NMR spectra and HPLC traces of BP/Thd and KP/Thd photomixtures, and isolated photoproducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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