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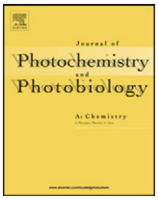

Photolysis dynamics of diastereoselectivity in the photocyclization of *o*-ethoxybenzophenone and *o*-2,2,2-trifluoroethoxybenzophenone

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ABSTRACT

The photochemical reactions of *o*-ethoxybenzophenone (**R-1**) and *o*-2,2,2-trifluoroethoxybenzophenone (**R-2**) in cyclohexane solutions of 0.7 M pyridine have been investigated using time-resolved laser flash photolysis to understand diastereoselectivity in the photocyclization of the two compounds. Whereas the formation times of biradical intermediates (7 ns) are the same for the two compounds, the lifetime of the biradical intermediate of **R-2** (200 ns) is eight times larger than that of **R-1** (25 ns), explaining why diastereoselectivity is much lower in the photocyclization of **R-2**.

1. Introduction

Photocyclization reactions *via* intramolecular hydrogen abstraction have been studied extensively for decades [1–3]. In the course of photocyclization reactions, the formation of unwanted diastereomers by the bond rotation of a biradical intermediate before or during cyclization is unavoidable if the two radical centers of the intermediate are prostereogenic. Thus, it is well known that the diastereoselectivity of solids is high owing to the restricted rotational motions of reaction intermediates, whereas that of solutions is low owing to the high rotational flexibility of reaction intermediates [4,5]. However, high diastereoselectivity in solutions can be achieved under certain conditions such as high strain energy associated with hydrogen abstraction, large steric hindrance between two radical moieties, and restricted rotational motion of C–C bonds in reaction intermediates [6–9]. In the field of pharmaceuticals, the synthesis of diastereomerically pure compounds is very important because the biological activities of synthetic drugs are stereoselective in many cases [10–12].

Substituent groups attached to radical centers greatly influence the diastereoselectivity of a cyclization reaction [13,14]. Kim and Park have reported that *o*-ethoxybenzophenone (**R-1**) undergoes a photochemical reaction in benzene *via* hydrogen abstraction to produce diastereomeric dihydrobenzofuranols (**P-1**) with a *Z*/*E* ratio of 11:1 in benzene. On the other hand, *o*-2,2,2-trifluoroethoxybenzophenone (**R-2**) produces 2-trifluoromethyl-3-phenyldihydrobenzofuran-3-ols (**P-2**) with a *Z*/*E* ratio of 2:1, as shown in Fig. 1 [15]. They have proposed that a sufficiently long lifetime of the biradical intermediate of **R-2** (**BR-2**) allows its C–C single bonds to rotate, yielding thermally equilibrated diastereomers before cyclization. They have attributed the long lifetime of the biradical intermediate of **BR-2** to a combination of hyperconjugation and captodative effects arising from alkoxy and trifluoromethyl substituents.

In this paper, we have studied the photolysis dynamics of **R-1** and **R-2** to report their time-resolved transient-absorption spectra as well as kinetic profiles. We have found that the different lifetimes of two biradical reaction intermediates appearing during their photolysis reactions explain the reason for the difference in the diastereoselectivities of the photoproducts of the two compounds.

2. Materials and methods

R-1 and **R-2** were synthesized, purified and confirmed by ^{1}H NMR, as described in Ref. [15]. An actively/passively mode-locked Nd:YAG laser (Quantel, YG 701) with the pulse duration

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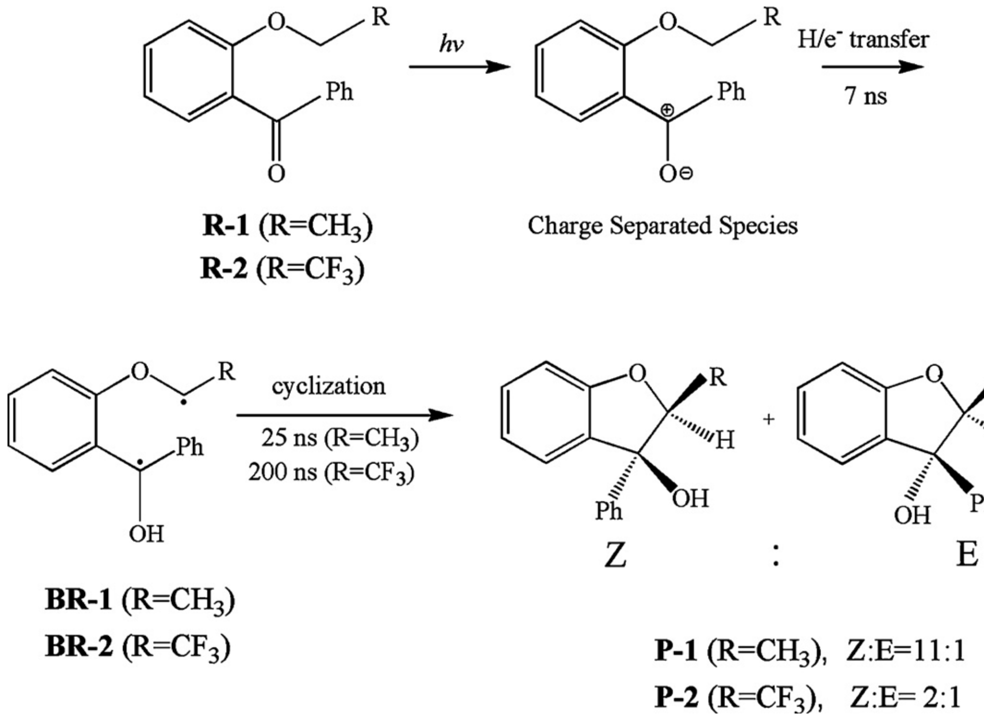

Fig. 1. Photochemical reaction scheme of *o*-ethoxybenzophenone (**R-1**) and *o*-2,2,2-trifluoroethoxybenzophenone (**R-1**) in cyclohexane solutions of 0.7 M of pyridine.

of 25 ps was employed for picosecond fluorescence and transient-absorption kinetic measurements. Samples were excited with 355 nm laser pulses. Fluorescence was collected from the front surface of the sample excitation. Fluorescence kinetic profiles were obtained with a 10 ps streak camera (Hamamatsu, C2830) attached with a CCD (Princeton Instruments, RTE-128-H). The transient absorption of a sample was probed using fluorescence from an organic dye excited with the pulses split from sample-excitation pulses. The comparison of dye-emission kinetic profiles measured with streak camera without and with sample excitation yields transient-absorption kinetic profiles. Fluorescence and transient-absorption kinetic constants were extracted by fitting measured kinetic profiles to computer-simulated kinetic curves convoluted with temporal response functions. Transient-absorption spectra were obtained by monitoring the transmittance changes of samples excited made with 355 nm pulses from a 6 ns Q-switched Nd:YAG laser (Quanta System, HYL-101). Probe pulses emitted from an organic dye excited by pulses split from sample excitation pulses were detected with a CCD (Princeton Instruments, ICCD-576-G) attached to a 0.5 m spectrometer (Acton Research, SpectroPro-500).

3. Results and discussion

Fig. 2 shows the fluorescence kinetic profiles of **R-1** and **R-2** in cyclohexane solutions of 0.7 M pyridine, measured at 550 nm after excitation at 355 nm. We have added pyridine to the cyclohexane solutions in order to impede the disproportionation reaction of the biradical intermediates (**BR-1** and **BR-2**) back to the reactant compounds (**R-1** and **R-2**) and to enhance the quantum efficiency of cyclization [16]. It should be noted that pyridine should be carefully used since biradical intermediates might be trapped when the concentration of pyridine is high. As compared to the best-fit curve, the kinetic profile of **R-1**, as shown in Fig. 2a, exhibits biexponential decays of 50 ps (60%) and 800 ps (40%), while the kinetic profile of **R-2** in Fig. 2b exhibits biexponential decays of 50 ps (88%) and 800 ps (12%). The faster decay component is attributed to the S_1 decay of the two reactants that leads to the S_1 state of the charge-separated species, while the slower component is attributed to the S_1 decay of the charge-separated species that leads to the formation of its T_1 state.

Fig. 3 shows time-resolved transient-absorption spectra of the two reactants in cyclohexane solutions of 0.7 M pyridine, measured at two different time delays after excitation at 355 nm. The absorption band at 550 nm in Fig. 3a is ascribed to the biradical intermediate (**BR-1**) because *o*-(benzyloxy)benzophenone, which is structurally analogous to **R-1**, exhibits absorption bands at 540 and 550 nm resulting from the triplet-state charge-separated species and the subsequent formation of the biradical intermedi-

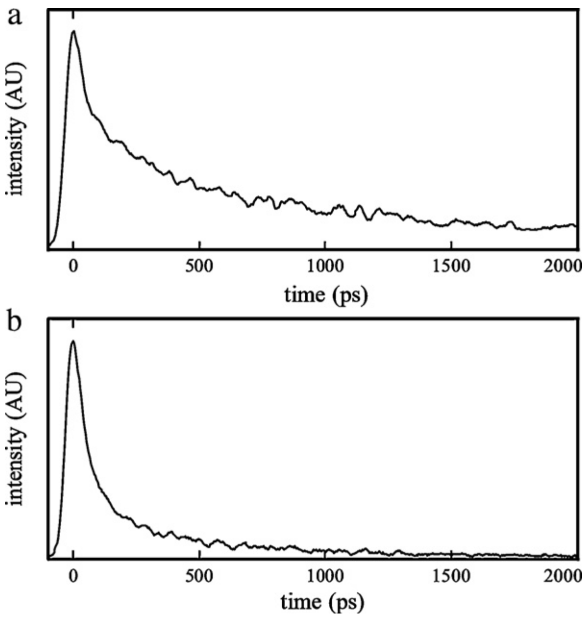

Fig. 2. Fluorescence kinetic profiles, excited at 355 nm and monitored at 550 nm, of 5 mM *o*-ethoxybenzophenone (a) and *o*-2,2,2-trifluoroethoxybenzophenone (b) in cyclohexane solutions of 0.7 M pyridine.

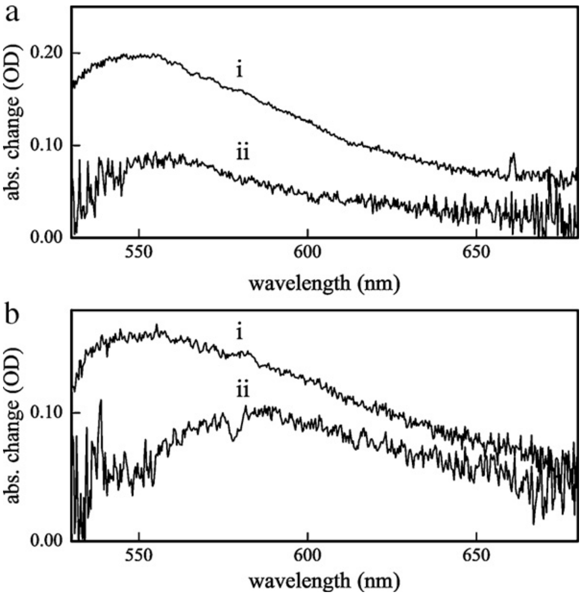

Fig. 3. Time-resolved transient absorption spectra of 5 mM *o*-ethoxybenzophenone (a) and *o*-2,2,2-trifluoroethoxybenzophenone (b) in cyclohexane solutions of 0.7 M pyridine, measured at time delays of 2 ns (i) and 50 ns (ii) after excitation at 355 nm.

ate, respectively [17,18]. The transient-absorption spectra of **R-2** in Fig. 3b exhibit two absorption bands at 550 nm and 580 nm. The 550 nm absorption band is ascribed to the triplet-state charge-separated species leading to the formation of **BR-2** because it decays faster than the 580-nm absorption band arising from **BR-2**. The kinetic profile in Fig. 4b (see below) agrees well with the two absorption bands with a fast component (7 ns) and a slow component (200 ns) resulting from the triplet-state charge-separated species and the biradical intermediate, respectively. We attribute the red shifts of **BR-2** and the triplet-state charge-separated species to electronegative fluorines.

Fig. 4 shows the transient-absorption kinetic profiles of biradical intermediates derived from the reactant compounds in cyclohexane solutions of 0.7 M pyridine, measured at 550 nm after excitation at 355 nm. The best-fit curve of the kinetic profile in Fig. 4a exhibits a single rise (7 ns) and a single decay (25 ns) while that in Fig. 4b exhibits biexponential decays (7 ns and 200 ns). It is well established that the lifetime of a biradical intermediate depends on the spin–orbit coupling that, in turn, strongly depends on orientation and distance between two radical moieties [19–21]. We have reported that the lifetime of the biradical intermediate of 1-(*o*-tolyl)-1-benzoylcyclopropane, which transforms into a five-membered ring, is 20 ns [22,23]. This indicates that the kinetic profile in Fig. 4a arises from a biradical intermediate because distance and orientation between the radical centers of **R-1** are quite similar to respective ones between the radial centers of 1-(*o*-tolyl)-1-benzoylcyclopropane. In addition, these radicals do not have a strong electron-withdrawing or donating group that might increase or decrease the lifetime of the biradical intermediate by the synergistic effect discussed later in this paper. Therefore, the single decay of 25 ns, as shown in Fig. 4a, should be ascribed to the decay time of **BR-1**. The 7 ns rise time of the kinetic profile in Fig. 4a corresponds to the decay time of the triplet-state charge-separated species leading to the subsequent formation of **BR-1**. The formation rates of **BR-1** and **BR-2** are faster than those of acyclic analogues because the phenyl group between carbonyl and CH_2 increases the conformational rigidity, thus reducing unfavorable rotational conformations in the transition state [24]. The faster decay time of the kinetic profile in Fig. 4b is ascribed to the triplet-state charge-separated species because its decay time of 7 ns is in good agreement with the decay time of the triplet decay time of the charge separated species of **R-1**. It is not surprising that the formation times of the biradical intermediates of two structurally analogous compounds are the same because hydrogen abstraction from CH_2 depends strongly on the distance and orientation between oxygen and hydrogen atoms in a triplet state [25,26]. The slow decaying component in Fig. 4b is ascribed to the decay time of **BR-2**. The decay times of the two distinct components are consistent with the time-resolved transient absorption spectra shown in Fig. 3b. The photolysis mechanisms of **R-1** and **R-2** are summarized in Fig. 1.

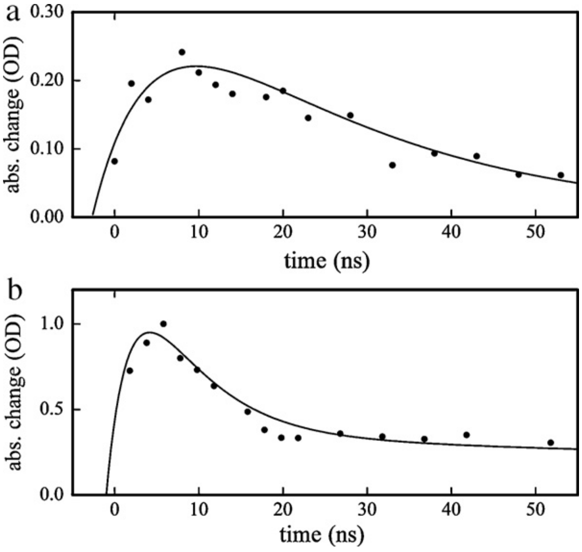

Fig. 4. Transient-absorption kinetic profiles, excited at 355 nm and monitored at 550 nm, of 5 mM *o*-ethoxybenzophenone (a) and *o*-2,2,2-trifluoroethoxybenzophenone (b) in cyclohexane solutions of 0.7 M pyridine.

There have been several studies on the effect of substituent groups attached to carbon-centered radicals [27–30]. They have revealed that synergistic (captodative) effect caused by an electron donor-acceptor pair directly attached to a $CH^\bullet$ radical enhances the stability of the radical to a greater extent, as compared to a donor–donor pair or an acceptor–acceptor pair. We believe that a combination of CF_3 (electron acceptor) and OR (electron donor) attached to the $CH^\bullet$ radical enhances the stability of **BR-2** and extends its biradical lifetime by a factor of eight as compared to the stability of **BR-1**. It should be noted that as the opposite partial charges on the two radical centers of **BR-2** because of CF_3 and OH/Ph increase the spin–orbit coupling, they are expected to reduce the lifetime of **BR-2**. However, this effect seems insignificant as compared to the synergistic effect discussed above [31].

The diastereomeric ratio of **P-1** and **P-2** can be explained in terms of their relative energies produced by the steric effects between the phenyl and methyl groups as well as their transition states leading to cyclization. Our preliminary calculations suggest that the diastereoselectivity of the photoproducts exists in the biradical intermediate before cyclization because the energy difference between the two diastereomeric products is smaller than the energy difference between their transition states leading to the diastereomeric products. The energy difference between *Z* (**P-1**) and *E* (**P-1**) is 0.9 kcal/mol, whereas the energy difference between the transition states leading to *Z* (**P-1**) and *E* (**P-1**) is 19.1 kcal/mol at the B3LYP/3-21G computational level. Under these circumstances, diastereoselectivity is pronounced if the rotational barrier is high and the lifetime of the biradical intermediate is short because a conformational equilibrium is not achieved within a short lifetime.

The rotation time of the C–C bond arising from a phenyl-$CH^\bullet$ radical has been deduced from the mechanistic study of *o*-alkylphenyl ketones to be 30–50 ns [32]. In the present study, the rotation of the C–C bond between the hydroxybenzyl radical and the benzene ring in both **BR-1** and **BR-2** is expected to be slow owing to the partial double bond character resulting from the extended π-electron delocalization effect. Therefore, it is unlikely that **BR-1** can establish a conformational equilibrium within 25 ns, whereas **BR-2** is speculated to have enough time to rotate its C–C bond for establishing a conformational equilibrium, resulting in low diastereoselectivity. It should be mentioned that when the lifetime of a biradical intermediate is long enough for establishing a conformational equilibrium, the energy difference between two rotational conformers of the biradical intermediate affects the diastereoselectivity of the final products. However, this effect seems insignificant for **BR-2** because the hydroxyl group is as bulky as the phenyl group when they are solvated by hydrogen bonding [25]. Therefore, we believe that the difference in the lifetimes of the biradical intermediates influences the diastereoselectivity of the photoproducts of the two reactants.

4. Conclusions

In conclusion, from transient absorption kinetic profiles, we find that the formation times of the biradical intermediates of **R-1** and **R-2** are 7 ns whereas the decay times of **BR-1** and **BR-2** are 25 ns and 200 ns, respectively. We consider that the low diastereoselectivity of **P-2** originates from the long lifetime of its biradical intermediate that allows a conformational equilibrium to be established before cyclization.

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