Journal of Photochemistry and Photobiology A: Chemistry 204 (2009) 52–62

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

# Photodecarboxylation of benzoyl-substituted biphenylacetic acids and photo-retro-Aldol reaction of related compounds in aqueous solution. Acid and base catalysis of reaction

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ARTICLE INFO

*Article history:*
Received 3 December 2008
Received in revised form 20 January 2009
Accepted 3 February 2009
Available online 24 February 2009

*Keywords:*
Benzyl carbanion
Acid catalyzed photodecarboxylation
Photo-retro-Aldol
Extended enols/enolates

ABSTRACT

To further explore the structural effects on efficiency of photodecarboxylation of Ketoprofen-type molecules the photodecarboxylation of two "extended" benzoyl-substituted acetic acids, 3′-benzoyl and 4′-benzoyl-4-biphenylacetic acids (**2** and **3**, respectively) have been studied in aqueous solution. In these systems, the benzoyl or benzophenone activating chromophore is distal to the phenylacetic acid moiety, separated by a phenyl spacer. Both of these compounds were found to undergo efficient ($\Phi$ = 0.3–0.7) photodecarboxylation in solutions of various pHs, giving rise to very broad long wavelength transient absorptions in laser flash photolysis studies (at pH > p$K_a$) that have been assigned as the corresponding highly conjugated benzylic carbanions/enolates. The photodecarboxylation of the corresponding parent benzophenone systems was also studied as a function of pH for comparison as are two photo-retro-Aldol reactions of benzophenone alcohols. Photo-retro-Aldol reaction requires base-catalysis but surprisingly, photodecarboxylation can also be mediated in acidic pH for some of the studied phenylacetic acids. The acid-catalyzed pathway requires prior protonation of the photoexcited benzophenone oxygen and has precedent in the acid catalyzed photohydration and intramolecular photoredox chemistry of benzophenones. These and other new mechanistic insights discovered in this work show that the benzophenone chromophore can activate decarboxylation over much longer molecular distances as well as induce new types of ionic chemistry.



## 1. Introduction

Photodecarboxylation is a simple but fundamentally important reaction that has been studied by many groups over the last several decades [1]. Some time ago, we wrote a review summarizing examples and the various mechanistic possibilities for loss of carbon dioxide (generally in a primary photochemical step) from an electronically excited organic compound [2]. Notable advances since the review was written are two reports in which a photodecarboxylation is used as the critical step in the photorelease of protected organic compounds (photocaging) [3,4]. In addition, continuing work [5], notably by Scaiano and workers, has increased our understanding and extending one of the most intriguing and efficient of all photodecarboxylations, namely, that involving Ketoprofen (**1**), initially reported by Costanzo et al. [6] (Eq. (1)), which reacts (at least formally) via benzyl carbanion **1a**. It seems clear that in these photodecarboxylation, the benzophenone (or related moiety, e.g., xanthone or acetophenone) chromophore is essential for reaction (via benzyl carbanions, many of which have been detected by laser flash photolysis (LFP)), although these observations seem inconsistent with the known propensity of benzophenone excited states to react via radical-type intermediates.

Other reported "ionic" photochemistry of benzophenone and derivatives (acid catalyzed photohydration (Eq. (2)) [7] and intramolecular photoredox reaction (Eq. (3)) [8]) in aqueous solution indicate that the benzophenone chromophore may be viewed as an enhanced electron-withdrawing group in the triplet excited state capable of inducing acid–base chemistry resulting in overall ionic chemistry. This type of behaviour is unprecedented and may open up further new types of photoreactions for one of most studied of all functional groups in organic photochemistry.

In this work, we explore the possibility of using the benzophenone chromophore to induce photodecarboxylation through a more extended aromatic system in benzoyl biphenylacetic acids **2** and **3**. Although many additional isomers are available for study based on this structural motif, we chose these compounds for initial studies due to their ease of synthesis (vide infra). We address the question of whether the enhanced electron withdrawing ability of the benzophenone excited state can be transmitted through what is formally a biphenyl system. We find that both **2** and **3** are very reactive

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doi:10.1016/j.jphotochem.2009.02.011

and moreover, display acid catalysis of photodecarboxylation. This latter finding prompted us to re-examine the photodecarboxylation of the "parent" compounds **4** and **5** as a function of pH. In addition, to gauge the extent of the ability of the benzophenone excited state to act as photoexcited "leaving group" (as a benzyl carbanion), the possibility of retro-Aldol type reaction of **6** (base-catalyzed elimination of formaldehyde) and **7** (base-catalyzed elimination of benzaldehyde) were also explored to complete the study.

## 2. Experimental details

### 2.1. General

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC 300 (300 MHz for $^1$H), and in some cases, on a Bruker AC 360 (360 MHz for $^1$H) instrument, in commercially available $D_2O$, $CDCl_3$ or $CD_3CN$ as solvents. Low resolution mass spectra (MS) were taken on a Finnigan 3300 (CI). High resolution mass spectra (HRMS) were recorded on a Kratos concept 1H (EI) mass spectrometer. Product studies were carried out in 100 mL quartz tubes in a Rayonet RPR photochemical reactor equipped with 254, 300 or 350 nm lamps. UV–vis spectra were recorded on a Varian Cary 5 spectrophotometer. Melting point measurements were made on a Gallenkamp melting point apparatus. Preparative thin layer chromatography (TLC) was performed utilizing 20 cm × 20 cm silica gel plates from Analtech and the solvent systems listed in each experiment. $CH_3CN$ used for the fluorescence studies was dried over $CaH_2$ and distilled before use. Readily available inorganic and organic reagents were purchase from Aldrich and used as received.

### 2.2. Materials

#### 2.2.1. 3- and 4-benzoylphenylacetic acids *4* and *5*

The general procedure is described as follows. The starting materials 3-methylbenzophenone (**8**) and 4-methylbenzophenone (**9**) (Aldrich, 5 mmol) were dissolved in 100 mL $CCl_4$ containing 5.2 mmol NBS and a pinch of benzoyl peroxide. The solution was refluxed for 2 h with irradiation using a halogen lamp. The monobromination products (>95% yield) were obtained after removal of the solvent by vacuum. This material was immediately treated with an 1.1 equimolar amount of NaCN in 10% $H_2O$–$CH_3CN$ at 50 °C for 4 h, which converted the bromides to the corresponding cyano derivatives (>95% yield) which, without purification, were converted to the corresponding acetic acids by acid hydrolysis in conc. HCl. Pure samples of the phenylacetic acids derivatives were obtained by base extraction of the acid followed by acidification and re-crystallization from toluene/hexane.

*3-Benzoylphenylacetic acid (**4**).* $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.71 (s, 2H, $ArCH_2$–), 7.41–7.54 (m, 4H, ArH), 7.55–7.61 (m, 1H, ArH), 7.65–7.81 (m, 4H, ArH), 12.5 (in $d_6$-acetone, br, –COOH); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 40.8 (–$CH_2$–), 128.5, 128.8, 129.4, 130.3, 131.2, 132.7, 133.6, 133.8, 137.6,138.1, 176.8 (–COOH), 196.6 (C=O). M.p. 96–98 °C, lit. [9] 112–114 °C, HRMS $C_{15}H_{12}O_3$: calc. 240.0788, found 240.0786.

*4-Benzoylphenylacetic acid (**5**).* $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 3.74 (s, 2H, $ArCH_2$–), 7.40 (d, $J$ = 8 Hz, 2H, ArH), 7.46 (t, $J$ = 8 Hz, 2H, ArH), 7.53–7.61 (m, 1H, ArH), 7.73–7.81 (m, 4H, ArH), 12.4 (in $d_6$-acetone, br, –COOH); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$: 41.1 (–$CH_2$–), 128.5, 129.6, 130.2, 130.7, 132.7, 136.8, 137.7, 138.1, 177.1 (–COOH), 196.5 (C=O). M.p. 111–112 °C, Lit. [10] 107–110 °C; HRMS $C_{15}H_{12}O_3$: calc. 240.0788, found 240.0786.

#### 2.2.2. 3′-Benzoyl and 4′-benzoyl-4-biphenylacetic acids *2* and *3*

*2.2.2.1. 4′-Benzoyl-4-biphenylacetic acid (**3**).* The synthetic steps are shown in Scheme 1. 4-Hydroxybenzophenone (**10**) (Aldrich, 3.96 g, 20 mmol) was dissolved in 150 mL of distilled $CH_2Cl_2$ in a 250 mL round bottom flask. After addition of 8 mL of pyridine (25 mmol) the solution became clear and was cooled to 0 °C and trifluoromethylsulfonic anhydride (Aldrich, 30 mmol, 1.5 equiv., 7.1 g) in a 20 mL of distilled $CH_2Cl_2$ was added via a 50-mL dropping funnel over 20 min. The solution was then allowed to warm to room temperature and stirred overnight. The reaction was worked up by pouring the organic solution into 200 mL ice-water and then extracting with 200 mL $CH_2Cl_2$ twice and washed with water. The organic layer was combined and dried with anhydrous Magnesium sulfate. After evaporation of pyridine, the crude triflate **11** was taken to next step coupling reaction without further purification.

The triflate **11** was coupled with 4-methylphenylboronic acid (Aldrich) under Suzuki reaction conditions as follows. 4-Methylphenylboronic acid (30 mmol, 1.5 equiv.) was dissolved in 300 mL of deoxygenated toluene in a 500 mL three-neck round bottom flask containing 8.3 g (60 mmol, 2 equiv.) $K_2CO_3$ along with all the triflate **11** (~20 mmol). The flask was fitted with a reflux condenser and a stirring bar. After flushing with $N_2$, the catalyst $Pd(PPh_3)_4$ (1.5 mole% based on triflate **11**) was added through the side arm. The mixture was then purged again with $N_2$ and allowed to stir at reflux temperature overnight. The solution was cooled and any inorganic precipitated from toluene was removed by vacuum filtration. After decoloration through carbon powder and filtration, a clear yellow toluene solution was obtained. Removal by evaporation gave a light yellow solid which was recrystallized from 9:1 toluene:hexane, producing a white solid, *4-Methyl-4′-benzoylbiphenyl (**12**)* (4.3 g, 82% yield), $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.40 (s, 3H, $ArCH_3$), 7.28 (d, $J$ = 8 Hz, 2H, ArH), 7.46–7.62 (m, 5H, ArH), 7.69 (d, $J$ = 8 Hz, 2H, ArH), 7.82 (d, $J$ = 8 Hz, ArH), 7.88 (d, $J$ = 8 Hz, 2H, ArH); mass (CI, $m/z$): 273 ($M^+$+1).

The synthetic procedure used to take **12** to the corresponding acid was identical to the general procedure employed for **4** and **5** described above. The pure sample was obtained by base solution extraction, re-acidification and recrystallization from toluene/hexane, to give pure *4′-benzoyl-4-biphenylacetic acid (**3**)* in 60% overall yield, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.78 (s, 2H, $ArCH_2$–), 7.40 (d, $J$ = 8 Hz, 2H, ArH), 7.42–7.46 (m, 2H, ArH), 7.54–7.58 (m, 3H, ArH), 7.65 (d, $J$ = 8 Hz, 2H, ArH), 7.85 (d, $J$ = 8 Hz, 2H, ArH), 7.95 (d, $J$ = 8 Hz, 2H, ArH), 12.4 (in $d_6$-acetone, br, –COOH), HRMS $C_{21}H_{16}O_3$ calc. 316.1099, found: 316.1103.

*2.2.2.2. 3′-Benzoyl-4-biphenylacetic acid (**2**).* An analogous synthetic route was followed based on Scheme 1 with similar yields. In the first step, 3-hydroxylbenzophenone (Aldrich) was used in place of 4-hydroxylbenzophenone (**10**). The final product **2** was initially obtained as an oil. It was transformed to its methyl ester by dissolving in MeOH along with 1 mL conc. $H_2SO_4$. The methyl ester was purified by column chromatography ($CH_2Cl_2$, silica). After saponification in basic aqueous MeOH, followed by acidification and column chromatography, the acid **2** was obtained a yellow solid.

*4-Methyl-3′-benzoylbipheny (**13**).* $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.40 (s, 3H, $ArCH_3$), 7.28 (d, $J$ = 8 Hz, 2H, ArH), 7.42–7.61 (m, 6H, ArH), 7.70–7.74 (m, 2H, ArH), 7.82 (d, $J$ = 8 Hz, 2H, ArH), 8.08 (s, 1H, ArH). Mass (CI, $m/z$) 273 ($M^+$+1).

*3′-Benzoyl-4-biphenylacetic acid (**2**).* $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.80 (s, 2H, $ArCH_2$–), 7.30 (d, $J$ = 8 Hz, ArH), 7.38–7.56 (m, 6H, ArH), 7.68–7.72 (m, 2H, ArH), 7.77 (d, $J$ = 8 Hz, 2H, ArH), 7.93 (s, 1H, ArH), 12.5 (in $d_6$-acetone, br, –COOH). HRMS $C_{21}H_{16}O_3$ calc. 316.1099, found 316.1102.

#### 2.2.3. Benzophenone alcohols *6* and *7*

*2-(3′-Benzoyl)phenethyl alcohol (**6**).* This alcohol was made via simple $BH_3$/THF reduction of acid **4** at 0 °C (70% yield), $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.68 (s, 1H, –OH), 2.93 (t, 2H, $J$ = 7 Hz, $ArCH_2$–), 3.90 (t, 2H, $J$ = 7 Hz, –$CH_2O$–), 7.37–7.49 (m, 4H, ArH), 7.54–7.65 (m,

2H, ArH), 7.75–7.92 (m, 2H, ArH); HRMS $C_{15}H_{14}O_2$ calc. 226.0994, found 226.0996.

*1-Phenyl-2-(4′-benzoylphenyl)ethanol (**7**).* The synthesis of this alcohol required initial conversion of acid **5** (5 mmol) to its acid chloride in 20 mL $SOCl_2$ followed by reflux for 4 h under $N_2$. The acid chloride was reacted with benzene in the presence of 1.4 g $AlCl_3$ at 50 °C for 4 h (Friedel–Crafts reaction) to give the corresponding diketone in 70% yield This was reduced with $NaBH_4$ which upon column chromatography (to separate the mixture of alcohols) and final recrystallization (9:1 toluene/hexane) gave the required **7** (60% yield), $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.96 (d, 1H, $J$ = 3 Hz, –OH), 3.11 (d, 2H, $J$ = 8 Hz, $ArCH_2$–), 4.95 (t, 1H, ArCH–), 7.26–7.31 (m, 3H, ArH), 7.31–7.38 (m, 4H, ArH), 7.43–7.50 (m, 2H, ArH), 7.53–7.61 (m, 1H, ArH), 7.70–7.80 (m, 4H, ArH); HRMS $C_{21}H_{18}O_2$ calc. 302.1299, found 302.1298.

### 2.3. Product studies

Preparative photolyses were carried out with 20–50 mg samples dissolved in 40–100 mL of the appropriate solvents (e.g., 1:1 $H_2O$–$CH_3CN$, $D_2O$–$CH_3CN$). If solution pH is cited, it refers to the aqueous portion. The solution was irradiated at 254, 300 or 350 nm with continuous cooling (by a cold finger) and purging by a stream of $N_2$. Photolysis times ranged from 2 to 20 min. After photolysis, the solutions were worked up initial acidification with aq HCl to pH 2 (for neutral and basic pH runs) followed by extraction with $CH_2Cl_2$. Some analytical photolysis runs were carried out directly in NMR tubes in 1:1 $D_2O$–$CD_3CN$ (300 or 350 nm irradiation) and the progress monitored at selected intervals by NMR.

#### 2.3.1. Photolysis of 3-benzoylphenylacetic acid (*4*)

Phenylacetic acid **4** (20 mg) was dissolved in 80 mL 1:1 $H_2O$–$CH_3CN$, pH 7.5 in a 100 mL quartz tube. Upon work-up as described above, and upon removal of $CH_2Cl_2$ the NMR of the crude material showed 70% conversion to 3-methylbenzophenone (**8**), which was subsequently confirmed by isolation by preparative TLC (silica, $CH_2Cl_2$), as being identical to authentic material, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.40 (s, 3H, $ArCH_3$), 7.33–7.39 (m, 2H, ArH), 7.41–7.45 (m, 2H, ArH), 7.55–7.60 (m, 3H, ArH), 7.80 (d, $J$ = 8 Hz, 2H, ArH); mass (EI): 196 ($M^+$). Evidence for formation of benzyl a carbanion intermediate was obtained by photolysis in 1:1 $CH_3CN$–$D_2O$ (pD ~ 8 adjusted with NaOD), which gave exclusively **8**-$\alpha D$, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.40 (br, 2H, $ArCH_2D$), 7.35–7.40 (m, 2H, ArH), 7.42–7.45 (m, 2H, ArH), 7.56–7.60 (m, 3H, ArH), 7.80 (d, $J$ = 8 Hz, 2H, ArH); mass (CI, $m/z$): 198 ($M^+$+1).

#### 2.3.2. Photolysis of 4-benzoylphenylacetic acid (*5*)

Photolysis of **5** as described above gave *4-methylbenzophenone* (***9***), which was identical to authentic material, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.45 (s, 3H, $ArCH_3$), 7.28 (d, $J$ = 8 Hz, 2H, ArH), 7.48 (t, $J$ = 4 Hz, 2H, ArH), 7.58–7.63 (m, 1H, ArH), 7.70 (d, $J$ = 8 Hz, 2H, ArH), 7.80 (d, $J$ = 8 Hz, 2H, ArH); mass (EI): 196 ($M^+$). Photolysis in 1:1 $D_2O$–$CH_3CN$ gave **9**-$\alpha D$, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.45 (br, 2H, $ArCH_2D$), 7.28 (d, $J$ = 8 Hz, 2H, ArH), 7.48 (t, $J$ = 8 Hz, 2H, ArH), 7.58–7.64 (m, 1H, ArH), 7.70 (d, $J$ = 8 Hz, 2H, ArH), 7.80 (d, $J$ = 8 Hz, 2H, ArH); mass (CI, $m/z$): 198 ($M^+$+1).

#### 2.3.3. Photolysis of 4′-benzoyl-4-biphenylacetic acid (*3*)

Photolysis of **3** gave exclusively *4-methyl-4′-benzoylbiphenyl* (***12***) as identified by comparison with an authentic sample (vide supra). Photolysis in 1:1 $D_2O$–$CH_3CN$ gave **12**-$\alpha D$, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.40 (br, 2H, $ArCH_2D$), 7.28 (d, $J$ = 8 Hz, 2H, ArH), 7.46–7.62 (m, 5H, ArH), 7.69 (d, $J$ = 8 Hz, 2H, ArH), 7.82 (d, $J$ = 8 Hz, 2H, ArH), 7.88 (d, $J$ = 8 Hz, 2H, ArH); mass (CI, $m/z$) 274 ($M^+$+1).

#### 2.3.4. Photolysis of 3′-benzoyl-4-biphenylacetic acid (*2*)

Photolysis of **2** gave exclusively *4-methyl-3′-benzoylbiphenyl* (***13***) as identified by comparison with an authentic sample (vide supra). Photolysis in 1:1 $D_2O$–$CH_3CN$ gave **13**-$\alpha D$, $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.40 (2H, br, $ArCH_2D$), 7.28 (d, $J$ = 8 Hz, 2H, ArH), 7.42–7.61 (m, 6H, ArH), 7.70–7.75 (m, 2H, ArH), 7.82 (d, $J$ = 8 Hz, 2H, ArH), 8.08 (s, 1H, ArH); MS (CI, $m/z$) 274 ($M^+$+1).

#### 2.3.5. Photolysis of 1-phenyl-2-(4′-benzoylphenyl)ethanol (*7*)

The photo-retro-Aldol reaction of **7** could be conveniently monitored by UV–vis spectrophotometry. Solutions of substrate (ca. $10^{-4}$ M) were prepared in 3 mL cuvettes at pH 12 and purged with $N_2$ prior to photolysis at 300 nm. UV–vis spectra were taken at various time intervals. Photolysis of **7** was also carried out in 1:1 $D_2O$–$CH_3CN$ (pD 12), which gave exclusively **9**-$\alpha D$.

#### 2.3.6. Photolysis of 2-(3′-benzoyl)phenethyl alcohol (*6*)

Photolysis of **6** in 1:1 $H_2O$–$CH_3CN$, pH 12 gave exclusively 3-methylbenzophenone (**8**), by comparison with an authentic sample (vide supra). Photolysis in 1:1 $D_2O$–$CH_3CN$, pD 12 gave exclusively **8**-$\alpha D$.

### 2.4. Photodecarboxylation quantum yields

Quantum yields were measured using the reaction of Ketoprofen (**1**) as a secondary standard, with a reported quantum yield of 0.75 at pH 7 [6]. $N_2$-purged solutions of the substrates along with an identical solution of **1** were photolyzed at pH 7.5 at 300 nm. Photolysis times were kept short to such that conversions were <15%. The relative yields were calculated by $^1$H NMR and converted to quantum yields.

### 2.5. Triplet sensitization and quenching experiments

For triplet sensitization experiments, acetone ($E_T$ ~ 78 kcal/mol, [11]) was used in place of $CH_3CN$ as cosolvent with photolysis at 254 nm. At this wavelength, it was estimated that acetone would absorb >90% of the exciting light under the conditions employed when the substrate concentrations were kept at ca. $10^{-3}$ M. Sodium sorbate (estimated $E_T$ ~ 60 kcal/mol, based on the known value for trans-piperylene [11]) and 1,3-cyclohexadiene ($E_T$ ~ 53 kcal/mol, [11]) were used as triplet quenchers for quenching experiments with photolysis at 300 nm. All triplet quenching experiments were analyzed using fluorene (reference $^1$H NMR peak at $\delta$ 3.8 ($CH_2$)) as an external standard, added after photolysis. The maximum quencher concentration that could be employed for of 1,3-cyclohexadiene was $10^{-2}$ M due to its relatively low solubility in 1:1 $H_2O$–$CH_3CN$.

### 2.6. Laser flash photolysis

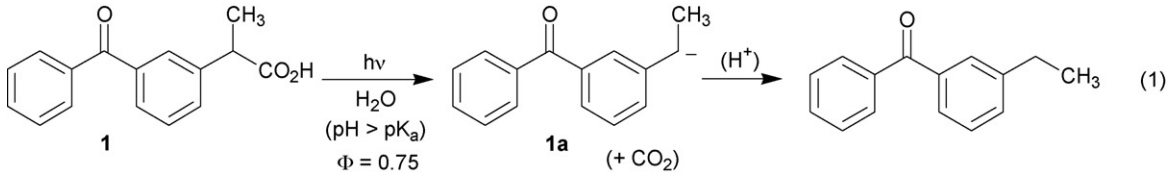
LFP experiments were carried out at the University of Victoria LFP Facility. A Spectra-Physics excimer laser (308 nm, ~10 ns, <30 mJ/pulse) and Nd:YAG Laser (266 nm, Spectra-Physics Quanta-Ray GCR, 10–25 mJ/pulse, ~10 ns) were employed for excitation. In order to avoid multiphoton processes, the laser pulse energies were adjusted to lower than 20 mJ/pulse through the use of neutral density filters in the case of the excimer laser or attenuation of power for the YAG laser. The monitoring UV–vis beam utilized was a pulsed 150 W or a 75 W xenon short arc lamp. Sample solutions were prepared with OD ~ 0.3 in 7 mm × 7 mm quartz flow cells. Before applying the laser shots, the solution was first purged with either oxygen or $N_2$ prior to and during experiments. All experiments were carried out at 20 ± 2 °C.

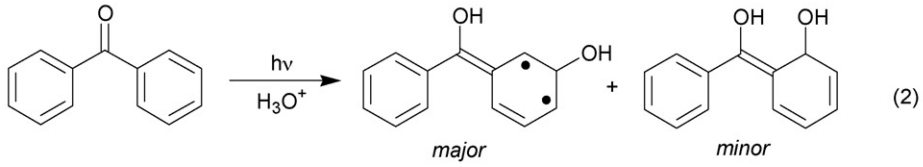
## 3. Results and discussion

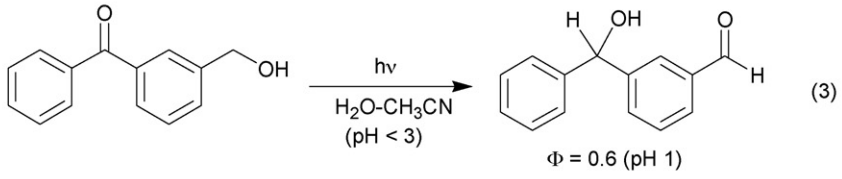
### 3.1. Product studies

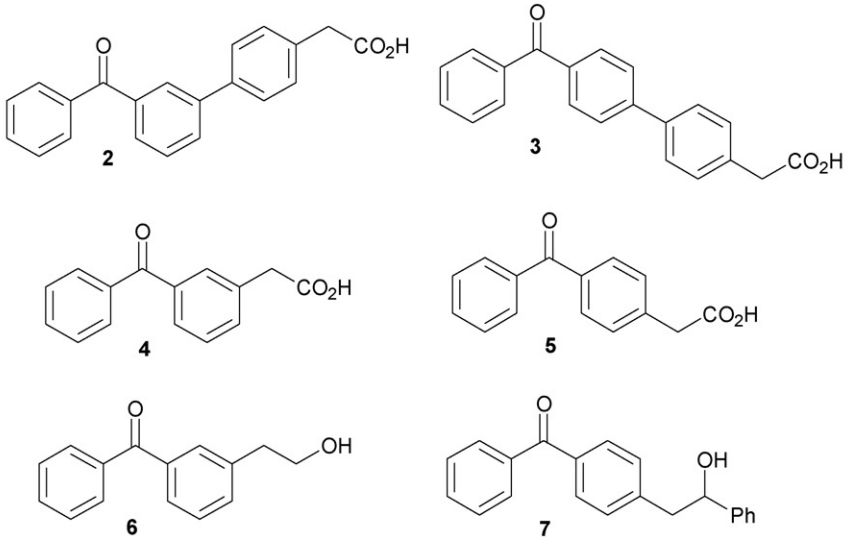
As **4** is structurally almost identical to Ketoprofen (**1**), one would expect efficient photodecarboxylaton from this compound. However, it is less clear that the para isomer **5** would be as reactive. Photolysis of both **4** and **5** in 1:1 $H_2O$–$CH_3CN$ ($\sim 10^{-3}$ M, pH 7, $N_2$ purged) gave exclusively the corresponding methylbenzophenones **8** and **9**, respectively (Eq. (4)), with a lower quantum yield for reaction for **5** (vide infra). Quantitative yield was achievable on prolonged photolysis. Photolysis in the presence of oxygen ($O_2$ purged solutions) had only a minor effect in the isolation of a side product (the corresponding benzoylbenzaldehydes, <10% yield), with **8** and **9** being still the major products. In order to show that the reaction proceeds via a benzylic carbanion (or equivalent intermediate), product studies in 1:1 $D_2O$–$CH_3CN$ (pD 7) were carried out which showed exclusively incorporation of a deuterium atom at the requisite α-carbon of the photoproducts (viz., formation of **8**-*αD* amd **9**-*αD*). Quantum yields (vide infra) are lower in $D_2O$ consistent with proton transfer in the product determining step.

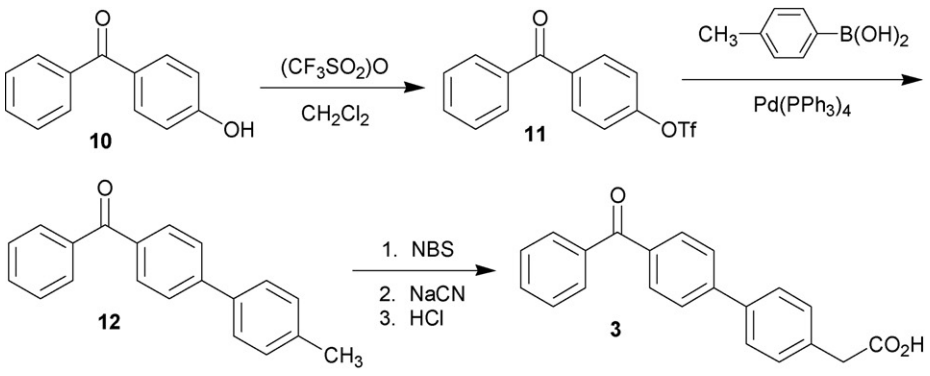
To our pleasant surprise, photolysis of biphenylacetic acids **2** and **3** also led to efficient and clean decarboxylation (Eq. (5)), with quantitative conversions observed on extended photolysis. Additionally, photolysis in 1:1 $D_2O$–$CH_3CN$ (pD 7) also gave the corresponding α-deuterated products (**12**-*αD* and **13**-*αD*) indicative of analogous benzyl carbanions as intermediates. To our knowledge, this is first evidence that the benzophenone moiety can exert its electronic influence through a biphenyl (phenylene) ring system, to induce efficient decarboxylation of a distal phenylacetic acid moiety. We had reported [12] that the nitro group is able to do this (Eq. (6)) but prior to the present discovery, it was thought the nitro group is a much more powerful electron-withdrawing group than the benzoyl group, in both ground and excited states. Evidently, this is not true in the excited triplet (or singlet) state and the aromatic ketone (benzoyl) moiety may act like a nitro group in these reactions. This is further demonstrated below.



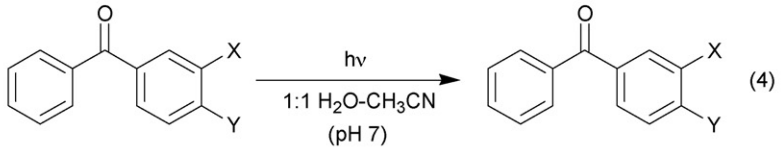



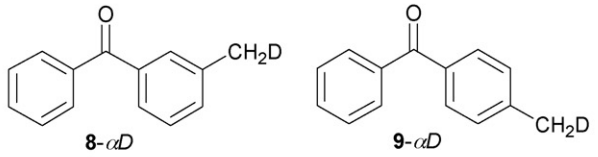


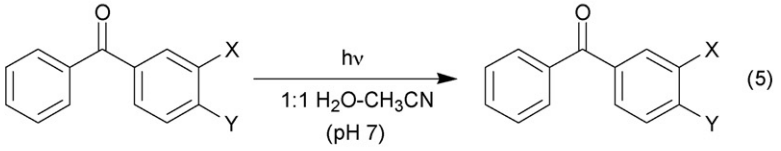

**Scheme 1**




**4** X = $CH_2CO_2H$; Y = H
**5** X = H; Y = $CH_2CO_2H$

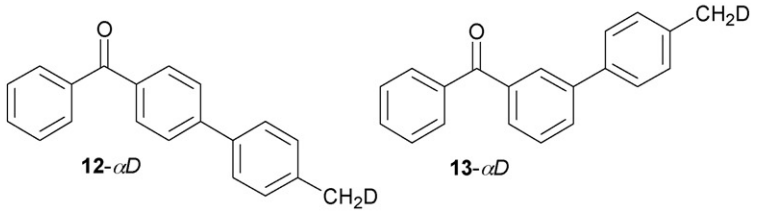
**8** X = $CH_3$; Y = H
**9** X = H; Y = $CH_3$

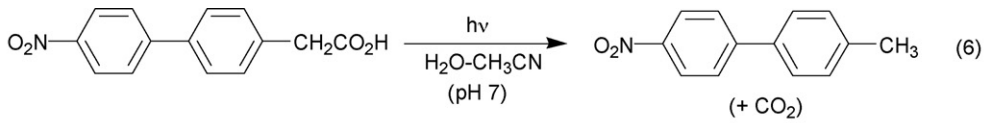


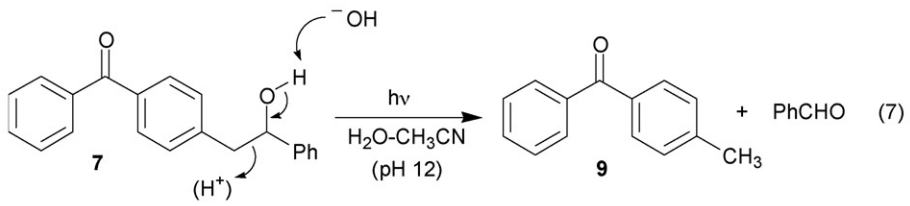



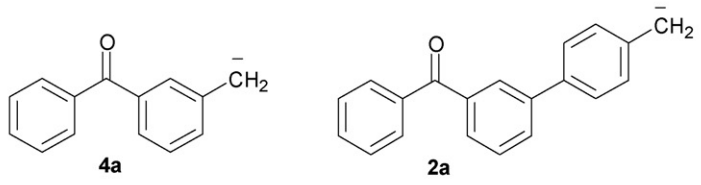

**2** X = p-$PhCH_2CO_2H$; Y = H
**3** X = H; Y = p-$PhCH_2CO_2H$

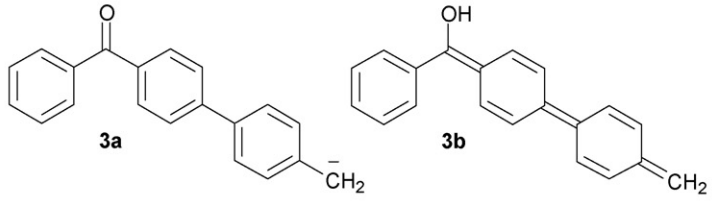
**13** X = p-$PhCH_3$; Y = H
**12** X = H; Y = p-$PhCH_3$

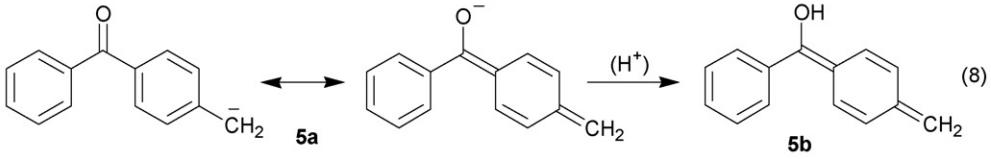


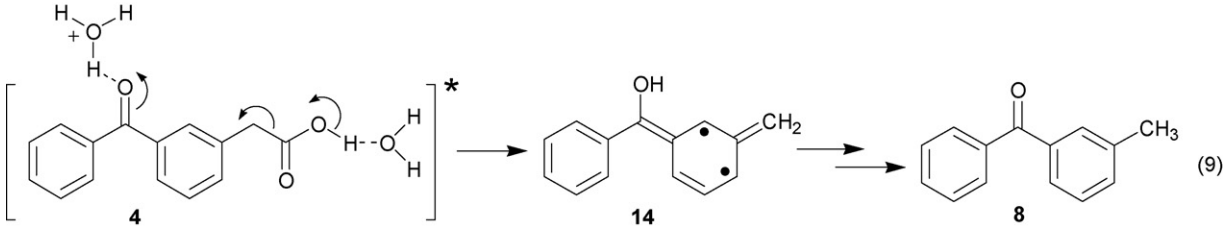



The potential photo-retro-Aldol type reactions of benzophenone alcohols **6** and **7** would further demonstrate that the benzoyl moiety is indeed acting as powerful electron withdrawing group, and inducing C–C bond heterolysis at the benzylic moiety in which the benzyl carbanion becomes a photoactivated leaving group on photolysis. This would mirror what was observed by Wan and Muralidharan [13] for several *m*,*p*-nitrophenylethanols and related compounds that readily undergo base-catalyzed retro-Aldol type reactions upon irradiation, via the corresponding nitrobenzyl carbanions. Photolysis of **6** and **7** in 1:1 $H_2O$–$CH_3CN$, pH 12 gave clean and efficient conversion to the corresponding methylbenzophenones as the only isolated products (Eq. (7)). Retro-Aldol reaction from **7** should also give rise to benzaldehyde but this compound was not readily isolable due to its high volatility and ready oxidation. Instead, formation of benzaldehyde was confirmed below.

UV–vis spectrophotometry was also used to follow the photo-retro-Aldol reaction of **7** since benzaldehyde is one of the expected photoproducts which can be easily monitored by UV–vis ($\lambda_{max} \sim 254$ nm). As shown in Fig. 1, photolysis of **7** in basic $H_2O$–$CH_3CN$ resulted in an increase in optical density at ~254 nm, with a broad shoulder peak at ~265 nm as the reaction progressed. The UV–vis trace after 9 min photolysis was essentially identical to that of an equimolar mixture of authentic benzaldehyde and 4-methylbenzophenone (**8**) (inset, Fig. 1). Moreover, in analytical runs carried out in an NMR tube in $D_2O$–$CD_3CN$ (pD 12), the growth of a $^1H$ NMR signal at $\delta$ 10.1 (aldehyde CHO) on photolysis also confirmed that benzaldehyde is produced on photolysis, in addition to the growth of the methylene protons at $\delta$ 2.42 for **9**-$\alpha D$.

In this method, purging the NMR tube with argon was essential, as trace amounts of oxygen readily consumed benzaldehyde that is formed, as demonstrated by runs saturated with $O_2$ which produced no detectable benzaldehyde although the photo-retro-Aldol reaction proceeded as evidenced by formation of **9**-$\alpha D$.

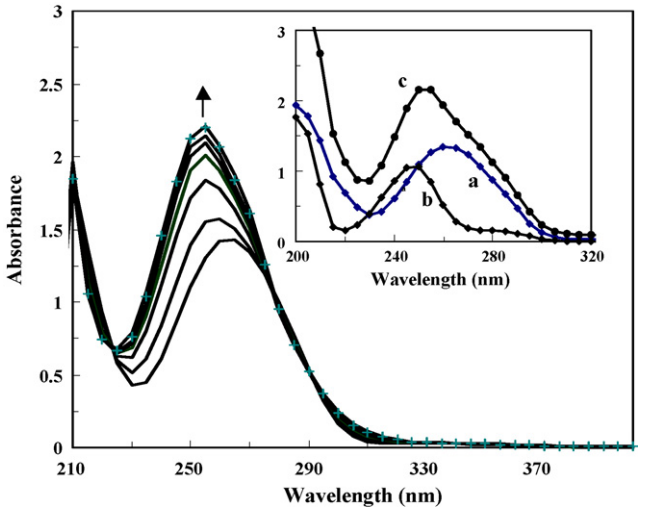



**Fig. 1.** UV–vis spectra for photolysis of **7** (1:1 $H_2O$–$CH_3CN$, pH 12, $N_2$ purged, $\lambda_{ex}$ 300 nm). Each trace represents about 1 min of photolysis time. Inset: UV spectra of authentic samples of expected photoproducts from photo-retro-Aldol reaction for comparison: (a) absorption curve for authentic 4-methylbenzopheone (**9**), (b) absorption curve for authentic benzaldehyde, and (c) absorption spectrum observed for a equimolar solution of benzaldehyde and **9**, the expected reaction mixture, which was essentially identical to the "final" spectrum observed on photolysis of **7**.

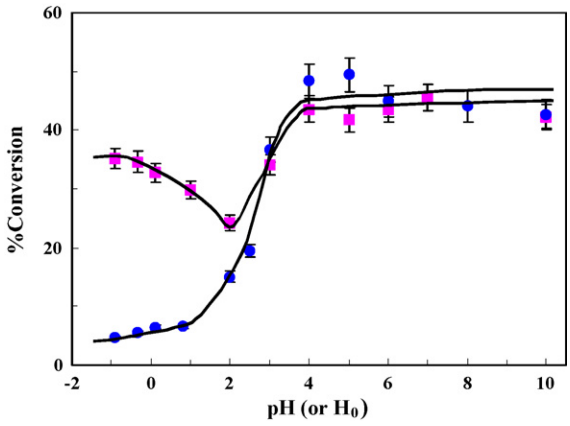



**Fig. 2.** pH dependence of photodecarboxylation efficiency for **4** (squares) and **5** (circles) in 1:1 $H_2O$–$CH_3CN$, ~$10^{-3}$ M, $N_2$ (pH or $H_0$ refers to the aqueous portion).

### 3.2. Quantum yield and pH effects

Product studies have already indicated efficient photodecarboxylation (at pH 7) for all of **2–5**. This is confirmed in quantum yield measurements (Table 1).

As shown in Table 1, the "parent" phenylacetic acids **4** and **5** have essentially the same photodecarboxylation quantum yield (at pH 7), and only slightly lower than that reported for Ketoprofen (**1**) itself, showing no evidence of a "meta" effect that might have been expected [14]. However, there is a significant difference in quantum yields for the biphenylacetic acids **2** and **3** that might be interpreted as a "meta" effect if one argues that the location of the phenylacetic acid moiety on the benzophenone ring determines the extent of activation by the ketone. More notably is the exceptionally high quantum efficiency ($\Phi = 0.73$) displayed by **2**, with its carboxyl group significantly further away than the parent systems.

Quantum yields were also measured in 1:1 $D_2O$–$CH_3CN$ (pD 7) to give solvent deuterium isotope effects ($\Phi_H/\Phi_D$) for photodecarboxylation at pH(D) 7. The data show that for the parent systems **4** and **5** photodecarboxylation is less efficient by 10–20% in $D_2O$ whereas for the more extended systems **2** and **3**, the effect of $D_2O$ is much more dramatic, especially for **2** where a reduction in quantum yield of up to four-fold. Although a detailed analysis of isotope effects on these photochemical reactions is beyond the scope of the present study, the results may be interpreted as due to differences in the extent of proton transfer (from water) in the product forming (decarboxylation) step in these reactions. For the parent systems **4** and **5**, the relatively small effect is consistent with transition states for decarboxylation that is "early" in the bonding to water at the carbonyl oxygen, to give intermediate enols (vide infra). In contrast, the more extended conjugated systems **2** and **3** have transition states that are probably more symmetrical with respect to proton transfer from water to the carbonyl oxygen. This seems reasonable considering that these systems require a much greater degree of charge transfer through the $\pi$ system in the excited state to induce reaction, hence requiring greater assistance at the carbonyl oxygen end in the transition state.

**Table 1**
Quantum yields[a] of photodecarboxylation in $H_2O$ and $D_2O$ for arylacetic acids 2–5.

| Substrates | $\Phi_H$ | $\Phi_D$ | $\Phi_H/\Phi_D$ |
|---|---|---|---|
| **4** | 0.66 | 0.53 | 1.2 |
| **5** | 0.63 | 0.55 | 1.14 |
| **3** | 0.30 | 0.13 | 2.3 |
| **2** | 0.73 | 0.17 | 4.3 |

[a] $\Phi_H$ ($\Phi_D$) refers to the quantum yields measured in $H_2O$ ($D_2O$)–$CH_3CN$, pH or pD 7; estimated error ±0.04.

It is now well-known that photodecarboxylation of Ketoprofen (**1**) takes place via the carboxylate form [5], that is, in water with pH > p$K_a$, although photodecarboxylation can also be observed when the carboxylate form is generated in other solvents [5d,e,f]. Up until now, no evidence for photodecarboxylation of a Ketoprofen-like molecule has been reported in acid solution or in organic solvents where the compound is in the acid form. This seems reasonable since the carboxylate ion is much more likely to induce formation of the corresponding benzyl carbanion on photolysis. However, we now show that another mechanism can operate: photoprotonation of the distal benzophenone carbonyl oxygen in the excited state can also induce decarboxylation.

As shown in Fig. 2, the photodecarboxylation efficiency vs pH observed for 4-benzoylphenylacetic acid (**5**) displays the expected trend (a normal titration curve for the carboxylic acid moiety) in which the acid form is unreactive and the carboxylate form reacts with no pH dependence above pH 5. From the titration curve, the p$K_a$ of **5** can be estimated to be about 3.5, a value close to the reported p$K_a$ of 3.7 for phenylacetic acid itself. The photodecarboxylation efficiency vs pH for 3-benzoylphenylacetic acid (**4**) resembles that observed for **5** in the pH 2–10 region but below pH 2, the efficiency increases, levelling off at $H_0 = -1$, indicative of an acid catalyzed mechanism for photodecarboxylation. To ensure that the same reaction is occurring in acid, photolysis was also carried out in acidic $D_2O$–$CH_3CN$ which resulted in exclusive formation **8**-*αD*, confirming that the mechanism of photodecarboxylation takes place via a mechanism in which the benzylic carbon is protonated by solvent (carbanion or equivalent intermediate such as an enol). Dark reactions carried out for both substrates in both basic and acidic solutions showed on reaction.

The effect of pH on the photodecarboxylation efficiency of biphenylacetic acids **2** and **3** is shown in Fig. 3. Both of these compounds displayed acid-catalysis of reaction although the pH onset of this is quite different, very early (ca. pH 4) for **3** and ca. pH 1 for **2**. In both of these compounds, the products observed in acidic solution were the same as those observed in basic pH confirming that the mechanism of photodecarboxylation at all pHs involves eventual protonation of the benzylic position (via a benzylic carbanion or equivalent).

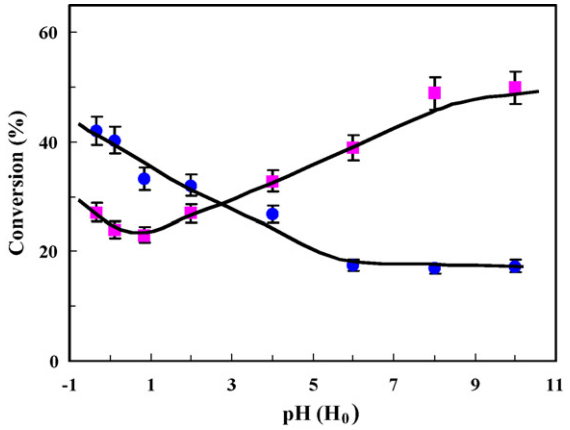



**Fig. 3.** pH dependence of photodecarboxylation efficiency for **2** (squares) and **3** (circles) in 1:1 $H_2O$–$CH_3CN$, ~$10^{-3}$ M, $N_2$ (pH or $H_0$ refers to the aqueous portion).

In view of the pH dependence observed for the above acids, we have examined the effect of pH ($H_0$) for the photo-retro-Aldol reaction of **6**. No reaction was observed in the pH 2–11 region. In more basic solution, (pH 12–13), a clean and efficient photo-retro-Aldol reaction was observed (giving **9**) indicative of a base-catalyzed reaction. Surprisingly, when the acidity of solution increased from pH 2 to $H_0 = -1.5$, the photo-retro-Aldol became increasingly efficient indicative of an acid-catalyzed pathway. Unfortunately, the same pH effect study could not be carried out for **7** due to a lack of compound; we anticipate this will be done in future studies.

### 3.3. Triplet sensitization and quenching studies

The well-known high intersystem crossing yield of benzophenones and simple derivatives would suggest that photodecarboxylation of these compounds is probably via the triplet excited state although evidence for singlet state reactivity has been presented [5j,k]. For the analogous reaction with a xanthone system, singlet reactivity has been confirmed [5a]. Among several possible triplet sensitizers, acetone was chosen as it has a high excited triplet energy ($E_T \sim 78$ kcal/mol [11]), miscible with water and able to act as a good cosolvent, and relatively unreactive photochemically.

Acetone triplet sensitized experiments were carried out for the parent benzoylphenylacetic acids **4** and **5**. In experiments conducted in which acetone absorbed >90% of the exciting light (at 254 nm), the photodecarboxylation proceeded with almost the same efficiency compared to irradiation without sensitizer. Unlike direct photolysis runs, the presence of oxygen in sensitization experiments resulted in a drastic reduction in conversion due to triplet quenching of acetone by oxygen. These results imply that the excited triplet states of **4** and **5** are reactive with respect to photodecarboxylation.

Triplet quenching experiments can in principle determine the ratio of singlet vs triplet pathways. Fig. 4 shows typical results for triplet quenching experiments for **4** and **5** using sodium sorbate. In all cases, good linear Stern–Volmer plots were obtained. Although not shown in the plots, use of higher concentrations of sodium sorbate completely quenched the photodecarboxylation reaction for both **4** and **5**. From the slopes of the quenching plots, it was estimated that the reactive triplet lifetimes of **4** and **5** were 3 ns and 20 ns, respectively, assuming the bimolecular triplet quenching rate constant is diffusion-controlled in water ($5 \times 10^9$ $M^{-1}$ $s^{-1}$ [11]).

Sodium sorbate was also employed in quenching experiments for biphenylacetic acids **2** and **3** (Fig. 5). In contrast to the results observed for **4** and **5**, the Stern–Volmer plots were biphasic. After initial (linear) quenching at low concentrations of sodium sorbate, the photodecarboxylation reached a plateau region, with

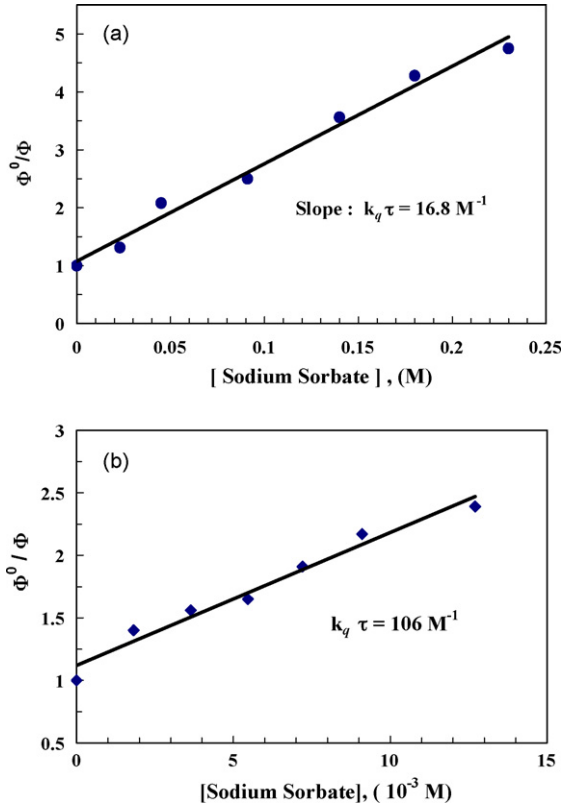



**Fig. 4.** Stern–Volmer plots of quenching of photodecarboxylation for **4** (a) and **5** (b) in the presence of sodium sorbate. $\Phi^0/\Phi$ refers to the yields in the absence and presence of quencher.

$\Phi^o/\Phi \sim 4.5$ and ~3 for **2** and **3**, respectively, at higher quencher concentrations. These values can be interpreted to mean that with respect to photodecarboxylation, about 20% of **2** and 30% of **3** of the reaction cannot be quenched by sodium sorbate. We interpret this to mean that about 80% and 70% of the decarboxylation of **2** and **3**, respectively, is via the triplet excited state and the remaining fraction arise via an "unquenchable" state, most likely the singlet excited state (although we cannot rule out the possibility of another triplet state that is much shorter lived). From the initial linear region of the quenching plots, we estimated that the reactive triplet lifetimes of **2** and **3** are 100 ns and 60 ns, respectively.

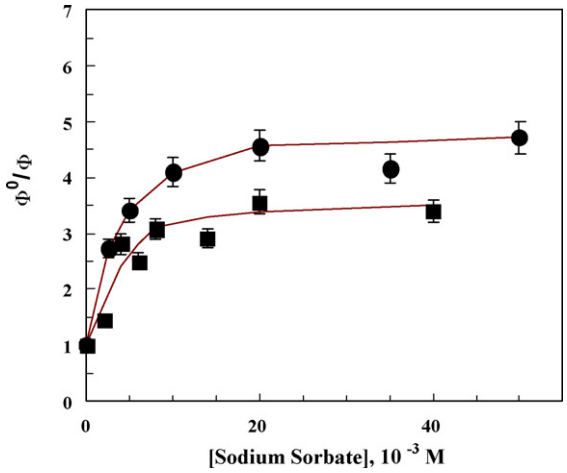



**Fig. 5.** Stern–Volmer plot of quenching of photodecarboxylation for **2** (circles) and **3** (squares) in the presence of sodium sorbate. $\Phi^0/\Phi$ refers to the yields in the absence and presence of quencher.

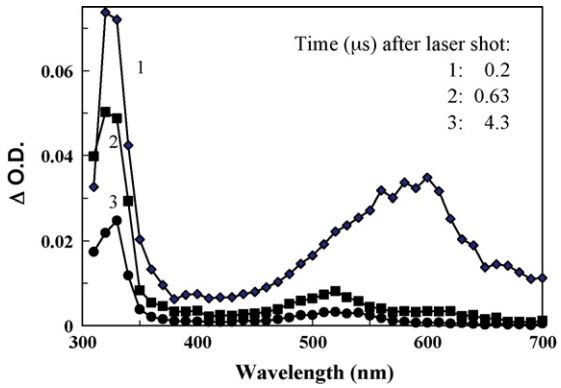



**Fig. 6.** Transient spectra observed on LFP (308 nm) of **4** in 1:1 $H_2O$–$CH_3CN$ ($N_2$ purged), pH 7.5 (aqueous portion).

### 3.4. Laser flash photolysis

In this work, LFP studies were restricted to the readily accessible pH 2–12 region since prior literature data are available to help in the interpretation of observed transients [5]. As anticipated, LFP of 3-benzoylphenylacetic acid (**4**) (which differs from **1** only by the presence of an α-methyl group) in 1:1 $H_2O$–$CH_3CN$ (pH 7.5, $N_2$ purged) gave similar spectra to those already reported for Ketoprofen (**1**) by Scaiano [5d–k] and Monti et al. [5l] (Fig. 6). The transient observed immediately after the laser pulse showed strong absorptions at 330, 525 and 600 nm. In the presence of $N_2$, the decay at ~600 nm was fitted to a single exponential with a short lifetime ~100 ns. The presence of oxygen quenched the weak band at 525 nm, suggesting it is likely due to the triplet excited state. The decays at 330 nm and 525 nm were both well-fitted to a bi-exponential function, providing a short lifetime ~100 ns (same lifetime as that of the 600 nm decay) and a long lifetime of about 3.7 μs (triplet excited state). Based on prior work [5d–k] on **1** it seems reasonable to assign the 600 nm as the benzyl carbanion **4a** which would be the expected intermediate in a simple decarboxylation step from the carboxylate form of **4**.

LFP of 3-benzoylbiphenylacetic acid **2** in 1:1 $H_2O$–$CH_3CN$, pH 8 gave transient spectra that resembled that observed for **4** (Fig. 7). Under $N_2$, the transient spectrum had absorptions at 370, 430 and 560 nm. A lifetime of 4.1 μs was obtained for the transient at 370 and 560 nm, and a second lifetime of 6 μs was obtained for the 430 nm band. The 430 nm absorption band was quenched in $O_2$, suggesting that it is due to the triplet excited state. It seems reasonable that the anticipated carbanion **2a** (370 and 560 nm) would have similar absorption bands compared to **4a** although the presence of an extra benzene ring would be expected to perturb the conjugation.

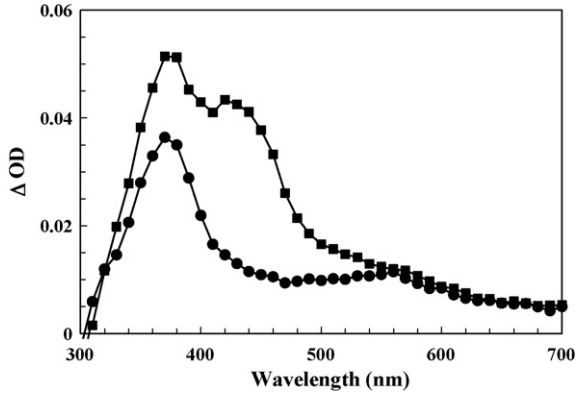



**Fig. 7.** Transient spectra observed on LFP of **2** in 1:1 $H_2O$–$CH_3CN$ (pH 8), under $N_2$ (squares) and under $O_2$ (circles), recorded 0.54 μs after the laser shot.

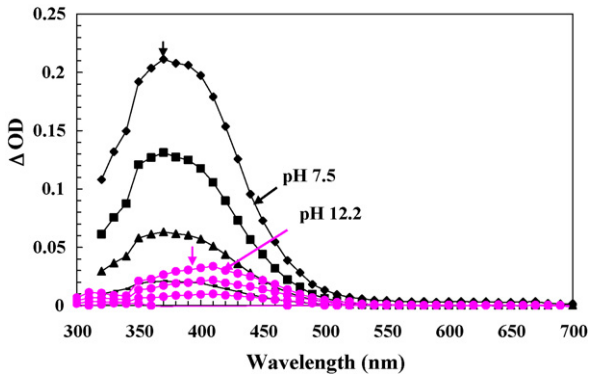



**Fig. 8.** Transient spectra observed from LFP of **5** at pH 7.5 (squares; enol **5b**) and 12 (circles; enolate/carbanion **5a**) (1:1 $H_2O$–$CH_3CN$, $O_2$ purged). Spectra recorded at 0.20, 0.63, 1.6, 4.3 μs and at 0.65, 2.3, 5.8, 40 μs after 308 nm laser shots for pH 7.5 and pH 12.2, respectively.

Further evidence of assignment of the above transients to simple benzyl carbanions comes from solvent isotope effects for their decay, which gave small normal ($k_H/k_D$ < 1.3) isotope effects consistent with a highly reactive carbanion that is protonated quickly by water in an early transition state.

LFP results for the parent 4-benzoylphenylacetic acid (**5**) indicate a different course of reaction compared to **2** and **4**, by virtue of the para substitution pattern in **5** that allows for formation of a stable enol intermediate that is not available for either **2** or **4**. Thus, LFP of **5** in 1:1 $H_2O$–$CH_3CN$, pH 7.5 gave a strong broad absorption band spanning 320–500 nm with a maximum at 390 nm (Fig. 8). The decay kinetics of this intermediate vs pH has been studied in depth by us [5b] and can be confidently assigned as due to enol **5b** (Eq. (8)) that is formed via protonation of the benzyl carbanion/enolate **5a** at the carbanion oxygen. Although the extent of direct carbanion protonation (to form **9** directly) cannot be directly estimated, it is believed to be minor. That is, the major pathway in the photodecarboxylation of **5** is via the enol **5b**, which subsequently ketonizes to **9** in a thermal reaction. The p$K_a$ of the enolic OH has been estimated to be ca. 7.7 [5b] (very acidic enol); hence, LFP at pH 12 (Fig. 8) gave a transient that is assigned to the red-shifted enolate/carbanion **5a**. No direct evidence for such an enol pathway was evident for the meta isomers **2** and **4** although the corresponding non-Kekulé enols would be difficult to detect spectroscopically. Moreover, such intermediates would be very high energy species and if formed would be very short-lived.

The question arises whether an analogous enol **3b** (vs **3a**) is on the photodecarboxylation pathway for the extended para system **3**. LFP of **3** in 1:1 $H_2O$–$CH_3CN$ (pH 8) gave a strong broad absorption band in the 350–700 nm region, with a maximum at 520 nm (Fig. 9), consistent with a species that has extended conjugation. Across the spectrum, the decay of the transient was fitted well to a single exponential, with a lifetime of ~0.5 μs. LFP of **3** at pH 12 provided essentially the same transient spectrum (lifetime ~0.3 μs) from that observed at pH 8 (Fig. 9) indicating that the same species is observed at both pH, unlike the case observed for **5**. However, the p$K_a$ of the enolic OH of **3b** would be expected to be even lower (more acidic) than that estimated for **5b** (vide supra) and therefore one would not expected changes in UV–vis absorptions at pHs 8 and 12. We argue that based on the solvent deuterium isotope effects (Table 1), the most reasonable assignment for the observed transient is to extended enol **3b**.

### 3.5. Mechanisms of reaction

Although decarboxylation is fundamentally a simple reaction, this work has shown that the mechanistic possibilities for

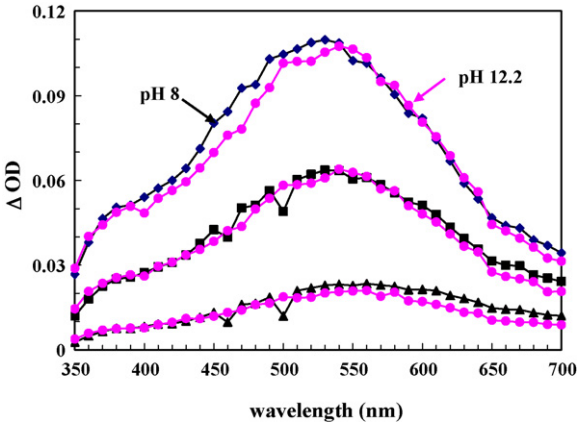



**Fig. 9.** Transient spectra observed on LFP of **3** at pH 8 (squares) and pH 12 (circles) (1:1 $H_2O$–$CH_3CN$, $O_2$ purged). Spectra recorded at 0.15, 0.52, 1.2 μs and 0.08, 0.26, 0.63 μs for spectra of pH 8 and pH 12.2.

photodecarboxylation of benzoyl-substituted phenylacetic acids is surprisingly more complex, with the possibility of decarboxylation via the carboxylic acid form in an acid-catalyzed process, and the possibility of direct formation of extended enols rather than a simple benzylic carbanion for all substrates. These new mechanistic possibilities would not have been predicted based on the what is know for the photodecarboxylation of Ketoprofen (**1**) which reacts via formation of the expected benzyl carbanion **1a**.

An examination of the calculated HOMO/LUMO coefficients (Chem 3D/MOPAC, AM1) for some the compounds studied is informative. The electronic distribution of the excited state can be qualitatively predicted by examining changes in HOMO/LUMO coefficients since the simplest picture of an electronically excited state can be visualized as being obtained by promotion of an electron from the HOMO to the LUMO (Fig. 10). The following general observations can be made from these calculations: (1) in the biphenyl systems there is a tendency to planarize the two rings since there is bonding character between the two carbon atoms joining the rings in the LUMO but not in the HOMO. This will have the effect of enhancing electronic communication between the ketone and the distal carboxylic acid group in the excited state and hence promoting reaction, (2) there is extensive charge migration (on electronic excitation), from the benzene ring containing the $CH_2CO_2H$ group, with significant reduction in charge at the ring carbon attached to the $CH_2CO_2H$ group. This enhances decarboxylation, and (3) there is migration of charge to the ketone and the benzene ring not containing the $CH_2CO_2H$ group. This promotes protonation of the ketone and hence the acid-catalyzed pathway and water-assisted mechanism in neutral pH.

We have also calculated the HOMO/LUMOs for the corresponding carboxylate ions as this would also be informative since some of these acids have been reported to be reactive only in the carboxylate form. In the carboxylate form, the HOMO and HOMO-1 are almost exclusively localized on the carboxylate group with the LUMO heavily localized on the carbonyl and the mono-substituted (with C=O) benzene ring. This shows that there would be expected significant charge transfer from the carboxylate to the carbonyl on electronic excitation of the carboxylate form which would results in formally a radical on the carboxylate and a radical ion on the carbonyl. This would also induce efficient decarboxylation.

The above results indicate that these compounds are intrinsically reactive and undergo decarboxylation via a number of different mechanisms depending on structure and pH. The simplest mechanism appears to be that followed by Ketoprofen (**1**), **2** and **4** in their carboxylate forms (pH > p$K_a$). Here, the mechanism appears to be simple loss of $CO_2$ to form the corresponding benzylic carbanion **1a**, **2a** and **4a**, respectively. In acid, we have found that **2**, **3** and **4** can photodecarboxylate via their acid (protonated) forms. The data is less clear whether **5** can photodecarboxylate in the acid form since the catalysis may be small and hence not readily observable (Fig. 2). Note that the quantum yield for photodecarboxylation does not go to "zero" for **5** in acid, which is consistent

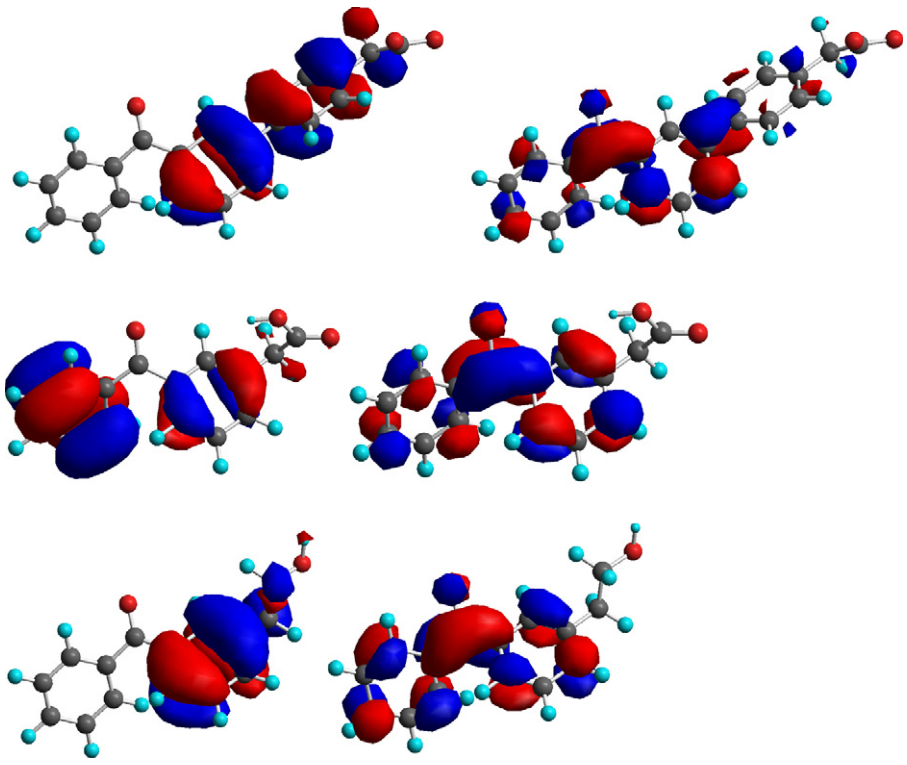


**Fig. 10.** Calculated HOMOs (left) and LUMOs (right) (chem 3D/MOPAC, AM1) for benzoylphenylacetic acids **2** (top) and **4** (middle), and benzoylphenethyl alcohol **6** (bottom).

with some reactivity in acid, although the catalysis, if it exists, is clearly not as great as that observed for the other compounds. One mechanism that can visualized for reaction in acid is loss of $CO_2$ concerted with protonation of the ketone oxygen (Eq. (9)). This pathway avoids direct formation of a carbanion intermediate but would involve formation of a non-Kekulé structure (for the meta substituted compounds) **14** that would eventually lead to **8**. A photodecarboxylation mechanism involving the exclusive formation of an elongated enol **5b** has been documented for the **5** [5b]. At sufficient high pHs, the mechanism of reaction is via benzyl carbanion **5a**. Accordingly, the mechanism for photodecarboxylation of **3** is most likely via extended enol **3b** in analogy with **5**. Notably, **3** also reacts via an acid-catalyzed mechanism for which intermediate **3b** is formally required although proof requires a detailed study of its decay vs pH. These and other aspects including detailed studies of the related photo-retro-Aldol reactions of **6** and **7** are topics for continuing work.

## 4. Conclusions

In summary, we have synthesized a number of benzophenone derivatives to investigate the possibility of using the benzophenone chromophore to induce decarboxylation and related retro-aldol chemistry in aqueous solution. We have been successful in each case showing that (i) the benzophenone triplet excited state (and possibly the singlet as well) can induce decarboxylation over a long distance through biphenyls with no significant decrease in quantum efficiency, (ii) acid-catalyzed photodecarboxylation from the acid form is observable in some substrates, particularly the biphenyl (extended) systems since these are predicted to be more polarized in the excited state, having a greater "pool" of $\pi$ electrons, and (iii) base-catalyzed photo-retro-Aldol reactions have been observed for suitably designed systems. These results offer new insights into the new area of "ionic" photochemistry of benzophenones and new discoveries are anticipated for this much-studied chromophore.

## Acknowledgment

Support of this research by NSERC (Canada) and the University of Victoria is gratefully acknowledged. M.L. thanks NSERC for a postgraduate scholarship.

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