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ARTICLES

Photoinduced Decarboxylative Benzylation of Phthalimide Triplets with Phenyl Acetates: a Mechanistic Study

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The photodecarboxylative benzylation of *N*-alkyl, *N*-arylalkyl, and *N*-aryl phthalimides with arylacetic acids in aqueous solution proceeds via electron transfer from the arylalkanoate to the excited triplet state of the phthalimide, either formed directly or upon sensitization with acetone. The rate constant for triplet quenching of *N*-methylphthalimide is $k_q < 10^7$ M^{-1} s^{-1} for 2-phenylacetic acid and $k_q = (1-3) \times 10^9$ M^{-1} s^{-1} for its mono-, di- and trimethoxy-substituted derivatives, suggesting a change of the mechanism for the primary oxidation step from a Photo-Kolbe type reaction yielding an acyloxy radical to a pseudo-Photo-Kolbe process involving the formation of resonance-stabilized zwitterion radicals as intermediates.

1. Introduction

Reports on the phototoxicity of aroyl-substituted 2-arylalkanoic acids, frequently used as nonsteroidal antiinflammatory drugs, have led to a vast research interest in photodecarboxylation reactions.[1] The major fragmentation pathway of the aforementioned compounds at pH > pK_a is the decarboxylation via the excited singlet state, which is assumed to involve the formation of benzyl anions.[2−4]

For nonbenzophenone type 2-arylacetic acids, i.e., phenylacetic acids lacking an aroyl substituent, a different decarboxylation pathway is operative. Previous spectroscopic studies have shown that phenylacetic acids undergo fragmentation in aqueous media upon addition of sulfate radical anions or hydroxyl radicals as well as upon direct biphotonic ionization at $\lambda = 248$ nm, thus yielding benzyl radicals.[5−10] This radical pathway was further confirmed in earlier studies on the photoinduced electron transfer (PET) of phenylacetic acids with acridine.[11,12]

In the course of our continuing research on the photochemistry of cyclic imides, we have recently demonstrated that *N*-methylphthalimide (**1**) is benzylated with high chemical yield upon irradiation at λ_{irr} around 300 nm in the presence of phenylacetic acids.[13] We tentatively proposed that this reaction, which constitutes an efficient and environmentally benign alternative to the Grignard reaction, involves the trapping of benzyl radicals by phthalimide radical anions generated via PET from the arylalkanoates to the triplet state of **1**.

In the current study, we aim to further elucidate the mechanism of this versatile reaction and to rationalize the influence of the substitution pattern of both the phthalimide and the arylalkanoate. For this purpose, we examined the photophysical and photochemical properties of representative *N*-alkyl, *N*-arylalkyl, and *N*-aryl phthalimides (Figure 1) in the presence of 2-phenylacetic acid (D1) and three methoxy-substituted derivatives, namely, 2-(4-methoxyphenyl)acetic acid (D2), 2-(3,4-dimethoxyphenyl)acetic acid (D3), and 2-(3,4,5-trimethoxyphenyl)acetic acid (D4) (Figure 2).

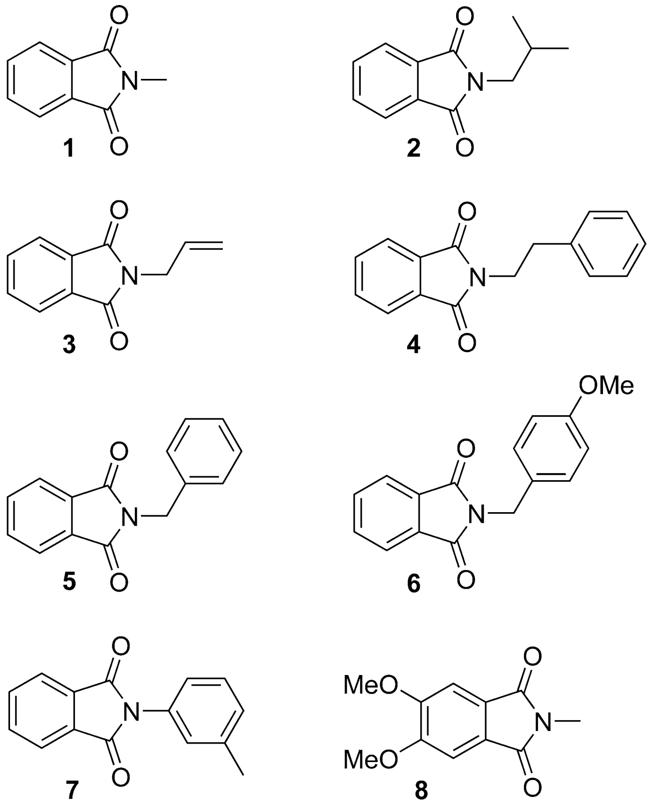

Figure 1. Isoindoline-1,3-diones used as electron acceptors.

2. Experimental Section

Materials. 2-Methylisoindoline-1,3-dione (**1**) and 5,6-dimethoxy-2-methylisoindoline-1,3-dione (**8**) were prepared by

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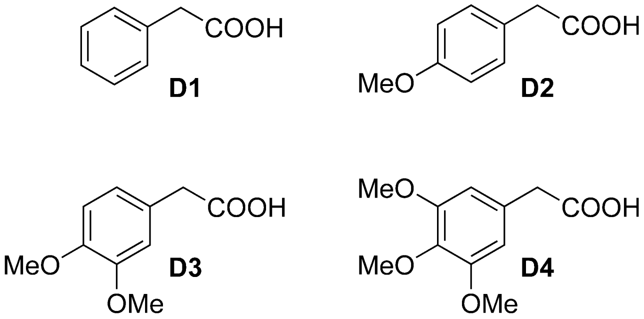

Figure 2. Phenylacetic acids used as electron donors.

the reaction of the respective phthalic anhydrides with *N*-methylformamide.[14] 2-Isobutylisoindoline-1,3-dione (**2**) and 2-allylisoindoline-1,3-dione (**3**) were prepared by heating equimolar amounts of phthalic anhydride with the respective amines in the presence of small amounts of *N*,*N*-dimethylformamide. 2-Phenethyl isoindoline-1,3-dione (**4**), 2-benzylisoindoline-1,3-dione (**5**), 2-(4-methoxybenzyl)isoindoline-1,3-dione (**6**), and 2-*m*-tolylisoindoline-1,3-dione (**7**) were prepared by heating equimolar amounts of phthalic anhydride and the respective amines in a domestic microwave oven (800 W) in five cycles of each 1 min. All phthalimides were recrystallized from ethanol prior to use.

2-Phenylacetic acid (D1), 2-(4-methoxyphenyl)acetic acid (D2), 2-(3,4-dimethoxyphenyl)acetic acid (D3), and 2-(3,4,5-trimethoxyphenyl)acetic acid (D4) were obtained from Acros and used as received. The corresponding methyl esters, methyl 2-phenylacetate (D1a), methyl 2-(4-methoxyphenyl)acetate (D2a), and methyl 2-(3,4-dimethoxyphenyl)acetate (D3a) were prepared from the acids with thionyl chloride in methanol according to standard procedures and purified by column chromatography on silica with cyclohexane/ethyl acetate as the eluent.

Acetonitrile (Merck) was Uvasol quality, and water was used from a Millipore milliQ system.

Instruments and Procedures. The absorption spectra were monitored on a UV/vis spectrophotometer (Hewlett-Packard 8453). The molar absorption coefficient of **1** in acetonitrile at 295 nm is $\epsilon_{295} = 1.5 \times 10^3$ M^{-1} cm^{-1}. Phototransformations on an analytical scale were performed with the 313 nm emission line obtained from a 1000-W Hg lamp and a monochromator at phthalimide concentrations of 1−2 mM and donor concentrations high enough to quench the triplet lifetime to 50−95%. The pH of the unbuffered solutions (initially at 3.2−5) were adjusted by addition of buffers (5 mM), perchloric acid, or aqueous potassium hydroxide. Since *N*-alkylphthalimides are known to hydrolyze slowly in alkaline aqueous solution, continuous irradiation or transient measurements in aqueous solution or acetonitrile−water mixtures at higher pH values were carried out within a few minutes after adjusting the pH to 9−10 and checking the stability of the phthalimides.[15,16] The photolyzates were analyzed by HPLC on a modified N-5-C18 column (0.8 mL min^{-1}) with MeOH−water 2:3 as eluent. The quantum yield for the degradation of the phthalimides, Φ_d, was determined using the aberchrome 540 actinometer.[17]

Cyclovoltammetry. The electrochemical measurements were performed in an airtight cell under an argon atmosphere in anhydrous acetonitrile using an EG&G Potentiostat model 273A. The reference electrode was 0.01 N $AgNO_3$/Ag in acetonitrile electrode. Tetrabutylammonium hexafluorophosphate, NBu_4PF_6, was used as supporting electrolyte. The reference electrode was separated from the sample solution by a fritted glass bridge. The glassy carbon working electrode and the platinum counter electrode were disk electrodes embedded in an insulating polymer. Measurements were carried out at room temperature with a scan rate of 100 mV/s. According to IUPAC recommendations for nonaqueous solvents, the formal potentials $E^{\circ\prime}$ are given as $E^{\circ\prime}_{(Fc)}$ vs the ferrocene/ferricenium (Fc/Fc$^+$) reference redox couple.[18] The formal potential for (Fc/Fc$^+$) in acetonitrile is +0.40 V relative to the aqueous saturated calomel electrode (SCE) at 298 K.[19]

Time-Resolved Absorption Spectroscopy. A XeCl excimer laser (Lambda Physik, EMG 200) with a pulse width of 20 ns and energy 100 mJ was used for excitation at $\lambda = 308$ nm. The absorption signals were measured with two digitizers (Tektronix 7912AD and 390AD); for data handling an Archimedes 440 computer was used as previously described.[20] Absorbances of 1.2−2.8 were used for $\lambda_{exc} = 308$ nm, corresponding to acceptor concentrations of 1−3 mM. Quantum yields for intersystem crossing, Φ_{isc}, were obtained using optically matched solutions, $\Phi_{isc} = 0.8$ for **1** in acetonitrile and assuming that ϵ_T at λ_T are the same. All measurements refer to 24 °C and samples in argon-saturated acetonitrile−water, unless otherwise indicated.

Fluorescence Spectroscopy. The emission and excitation spectra were recorded on a LS50B luminescence spectrometer (Perkin-Elmer) and a Cary Eclipse fluorescence spectrophotometer (Varian). As reference $\Phi_f = 0.9$ for **8** was used. The fluorescence lifetimes (τ_f) were determined from decay kinetics by a fluorimeter (Edinburgh Instr. F900, time resolution 0.2 ns).

3. Results and Discussion

3.1. Transients via Electron Transfer upon Excitation. Excitation of *N*-methylphthalimide (**1**) in argon-saturated acetonitrile by 308 nm laser pulses produces a transient with an absorption maximum at $\lambda_T = 345$ nm, a first-order decay at low pulse intensity, and a lifetime of $\tau_T = 10$ μs. In agreement with previous studies at $\lambda_{exc} = 248$ nm, the observed transient is assigned to the lowest triplet state (^{3}A*).[20−25]

$$A + h\nu \rightarrow {}^1A^* \rightarrow {}^3A^* \qquad (1)$$

Further variation of the alkyl substituent on the phthalimide only has a modest effect, i.e., the rate constant for quenching of the triplet state of **1** and **2** in acetonitrile by oxygen is $k_{ox} = 0.9 \times 10^9$ and 1.6×10^9 M^{-1}, and the quantum yield of intersystem crossing is $\Phi_{isc} = 0.8$ and 0.5, respectively. Similarities of the transient absorption spectra of the other phthalimides suggest that observed main transient in these cases again is the lowest triplet state.

While the triplet properties, namely, λ_T, with an absorption maximum around 325−345 nm, the triplet lifetime τ_T in the 5−20 μs range, and k_{ox} are virtually unaffected by substitution at the imide nitrogen, Φ_{isc} is low for **3**−**5** and 0.02 for **6** and **7**, i.e., when the imide bears an electron-rich methoxybenzyl or an aryl substituent (Tables 1 and 2). In the latter cases, the weak triplet formation observed is most likely to be insufficient to facilitate phototransformations upon direct irradiation of the respective phthalimides.

The addition of water and/or variation of the pH, on the other hand, only leads to a moderate decrease of Φ_{isc} for **1** and the other phthalimides and is thus seemingly tolerable for reactions on a preparative scale.

When **1** is excited in the presence of D3 in argon-saturated acetonitrile/water (100:1 or 1:1), the T−T absorption spectrum at the end of the laser pulse is indistinguishable from that observed in the absence of the dimethoxyphenylacetic acid, but, the ^{3}A* state is quenched (Figure 3).

TABLE 1: Φ_{isc}, τ_T, and Rate Constants ($\times 10^9$ M^{-1} s^{-1}) of Triplet Quenching of Phthalimides by Oxygen, Amines, and D3[a]

acceptor	Φ_{isc}	$\tau_T/\mu s$	k_{ox}	k_q TEA	k_q D3[b]
1	0.8[c]	10	0.9	6 [15][d]	2
2	0.5	10	1.6	6	2
3	0.2	8	1		0.1
4	0.4	10	1		0.1
5	0.2	10	1		2
7	<0.01	10			2
8	<0.02				<0.005

[a] In argon-saturated acetonitrile, $\lambda_{exc} = 308$ nm, [acetone] = 1 M for **7** and **8**. [b] In acetonitrile/water (99:1); in agreement with ΔG_{ET} (vide infra) the rate constants are virtually identical within the range of experimental certainty. [c] Taken from the literature.[20] [d] In brackets: DABCO.

TABLE 2: Triplet State and Radical Anion Properties of Phthalimides[a]

acceptor	Φ_{isc}	λ_T/nm	$\tau_T/\mu s$	λ_{rad}[b]/nm	k_q D3[c]
1	0.7	345	15	390	2.0
2	0.5	325	12	390	2.6
3	0.2	320	12	410	2.5
4	0.2	320		400	2
5	0.1	325, 500[d]	14	400	2
6	<0.02			400	<0.03
7	<0.02	325, 500[d]	10	400	1.5

[a] In argon-saturated acetonitrile/water (1:1, vol), [acetone] = 1 M for **6**−**7** (except for Φ_{isc}), $\lambda_{exc} = 308$ nm. [b] Major maximum at 300 nm. [c] Values for (0.5 mM) D3 ($\times 10^9$ M^{-1} s^{-1}) at pH = 3.5−5. [d] Weak band.

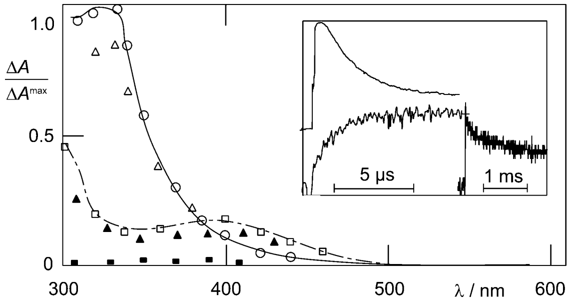

Figure 3. Transient absorption spectra of **1** in argon-saturated acetonitrile−water (1:1, pH 7) in the presence of D3 (0.3 mM) at 20 ns (○), 1 μs (△), 10 μs (□), 1 ms (▲), and 10 ms (■) after the 308 nm laser pulse; insets: kinetics at 400 nm.

TABLE 3: Rate Constant k_q ($\times 10^9$ M^{-1} s^{-1}) of Triplet Quenching of Phthalimides[a]

		acceptor		
donor	% water[b]	**1**	**2**	**7**
D1	50	0.03	<0.002	0.003
D2	1	1.6	1.4	1.3
D3	1	2.4	2.5	2.6
D3	50	2.2	1.8	1.8
D3	95	2.0		
D4	1	2.0	1.2	1.1

[a] In argon-saturated acetonitrile/water, $\lambda_{exc} = 308$ nm, [acetone] = 1 M for **7**. [b] For acetonitrile/water (100:1 and 1:1, vol) pH = 5−7 and 3.2−4, respectively.

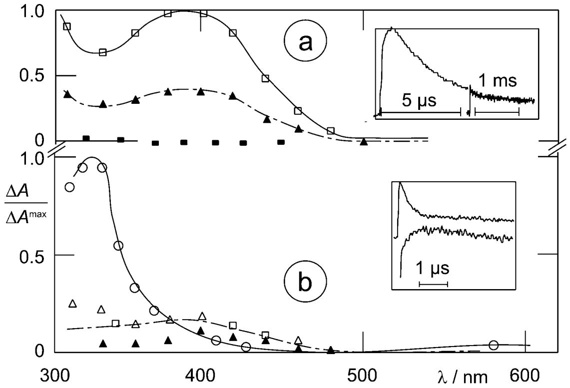

Figure 4. Transient absorption spectra in argon-saturated acetonitrile−water (1:1, pH 7) of (a) **2** and (b) **5** in the presence of D1 (10 mM) at 20 ns (○), 1 μs (△), 10 μs (□), 1 ms (▲), and 10 ms (■) after the 308 nm laser pulse; insets: kinetics at 400 nm.

Quenching of the triplet state of **1** and **2** in acetonitrile was likewise achieved with triethylamine and DABCO. The rate constant, obtained at 340 nm from the linear dependence of $1/\tau_T$ as a function of the DABCO concentration, is $k_q = 1.5 \times 10^{10}$ and 1.6×10^{10} M^{-1} s^{-1} for **1** and **2**, respectively (Table 1). The resulting absorption spectra exhibit a transient with a maximum at $\lambda_{rad} = 390$ nm (Table 2), which we attribute to the phthalimide radical anion ($A^{\bullet-}$) arising from an electron-transfer reaction (eq 2).

$$^3A^* + D \rightarrow A^{\bullet-} + D^{\bullet+} \qquad (2)$$

Taking into account that the laser flash photolysis of *N*-phenyl-2,3-naphthalimide (i.e., an imide with a more extended π-system) in the presence of DABCO yielded the corresponding naphthalimide radical anion with a maximum at 400 nm, this assignment seems plausible.[23,24] The rather short first half-life ($t_{1/2}$) of 20 μs (under our conditions) in a second-order decay kinetics also is in agreement with the proposed photoinduced electron transfer and due to back electron transfer from the phthalimide radical anion ($A^{\bullet-}$) to the DABCO radical cation, which cannot be observed directly here. Similar results are obtained for **1** or **2** with phenylacetic acids in argon-saturated acetonitrile/water (100:1 or 1:1) in the presence of phosphate buffer at pH = 7, i.e., under conditions in which D1−D4 are deprotonated. However, the triplet state of the phthalimides is also quenched at pH = 3, where D1−D4 are present as acids (Tables 2 and 3). The main transient observed a few microseconds after the triplet decay of **1** in the presence of D3 (Figure 3) or **2** in the presence of D1 (Figure 4a) is a long-lived species with an absorption maximum at $\lambda_{rad} = 390$ nm. The decay of this transient is complex and only a part can be fitted by second-order kinetics ($t_{1/2} = 0.2$ ms) under our conditions. We attribute this transient primarily to the phthalimide radical anion and consequently conclude that the triplet quenching of *N*-alkyl phthalimides with D1−D4 does not proceed via energy transfer but is an electron-transfer process with the carboxylates as electron donors (eq 3).

$$^3A^* + R - CO_2^-/R - CO_2H \rightarrow A^{\bullet-} + R - CO_2^{\bullet}/R - CO_2H^{\bullet+} \qquad (3)$$

This assignment is further supported by the finding that traces of oxygen gave rise to a shortening of both components of the observed transient, suggesting that the formation of $O_2^{\bullet-}$ (eq 4) is a major process under these conditions.

$$A^{\bullet-} + O_2 \rightarrow A + O_2^{\bullet-} \qquad (4)$$

For substrates, where the carboxylate itself constitutes the moiety most easily oxidized, the electrochemical one-electron oxidation of carboxylates, commonly known as the Kolbe reaction, as well as its photochemical counterpart, proceeds via direct

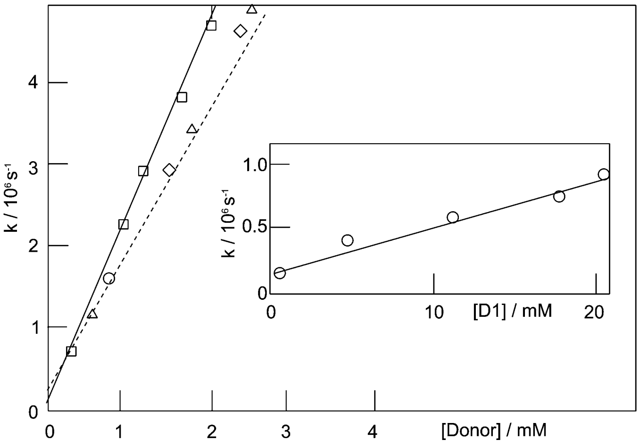

Figure 5. Rate constant for triplet decay of **1** at 340 nm in argon-saturated acetonitrile−water (10:1) as a function of the donor concentration: D1 (○), D2 (△), D3 (□), and D4 (◇).

formation of acyloxy radicals.[26] As confirmed by EPR spectroscopy, the latter undergoes fragmentation with release of CO_2 and gives rise to alkyl radicals (eq 5).[27]

$$R-CO_2^{\bullet} \rightarrow R^{\bullet} + CO_2 \qquad (5)$$

In the case of the phenylacetates, however, the observed variation of triplet quenching rates with the methoxy-substitution of the arene apparently contradicts a direct Kolbe-type mechanism. In the latter case, the methoxyarene would only represent a remote substituent not involved in the primary electron transfer with the phthalimide and thus without any influence on the quenching rate constants. Obviously, this is not the case. From the linear dependence of $1/\tau_T$ at 340 nm as a function of the donor concentration (Figure 5), a rate constant as large as $k_q = (1-3) \times 10^9$ M^{-1} s^{-1} was obtained for the quenching of the triplet of **1** with the methoxy-substituted D2−D4, whereas a much lower rate of $k_q = 3 \times 10^7$ M^{-1} s^{-1} value was found for D1 (Figure 5 inset). For D3, the k_q value is similar in the presence of 0.5 M and ca. 30 M water (Tables 1−3) and in the pH range of 3−7. Triplet quenching thus also takes place when the carboxylic acid is not deprotonated. When D1, D2, or D3 were replaced by the corresponding esters, lower rate constants were found, e.g., $k_q = 1 \times 10^7$ M^{-1} s^{-1} for D1a.[28]

3.2 Transients upon Acetone-Sensitized Excitation. Excitation of acetone (Sens) in argon-saturated acetonitrile by 308 nm laser pulses generates the triplet state ($\lambda_{max} < 330$ nm with small ΔA). The same T−T absorption spectrum appears in aqueous solution at pH 7. Addition of **7** (Figure 6a) to acetone in aqueous solution, acetonitrile, or their mixture leads yields the ^{3}A* state of the phthalimide characterized by the build-up of a transient at $\lambda_T = 325$ and 500 nm (Table 2) within 1 μs and a lifetime of $\tau_T = 5-10$ μs.

$$^3\text{Sens}^* + \text{A} \rightarrow \text{Sens} + {}^3\text{A}^* \qquad (6)$$

The rate constant for energy transfer (eq 6) from ^{3}Sens* (acetone) to **7** is $k_6 = 8 \times 10^9$ M^{-1} s^{-1}, whereas attempts to transfer the triplet energy from benzophenone to **7** failed. This is consistent with the lower triplet energy of benzophenone with respect to $E_T = 293-300$ kJ mol^{-1} for **1**.[24]

The acetone-sensitized excitation of **7** in the presence of electron donors furnishes both quenching of the triplet state of the *N*-aryl phthalimide and the formation of a new transient, as shown for DABCO (Figure 6b) and D3 (Figure 6c). The rate constant of quenching of the ^{3}A* state of **7** is substantial for D2−D4 but much smaller, $k_q = 3 \times 10^6$ M^{-1} s^{-1}, for D1. This and the long-lived transient with $\lambda_{rad} = 390$ nm, which is assigned to the A$^{\bullet-}$ radical, are analogous to nonsensitized photolyses of *N*-alkyl and *N*-arylalkyl phthalimides described above. The presence of water and the pH value only has a marginal influence on the formation of the ^{3}A* state of **7**, and its electron-transfer reactions (eq 2) are only slightly influenced by water. However, the decay kinetics of A$^{\bullet-}$ are complex since also a long-lived component was found for D2−D4. Again, trace amounts of oxygen gave rise to a shortening of both components (eq 4). The triplet state of 4,5-dimethoxy-*N*-methylphthalimide (**8**), populated upon sensitized excitation with acetophenone in acetonitrile, has $\lambda_{max} < 330$ nm and $\tau_T = 4$ μs.

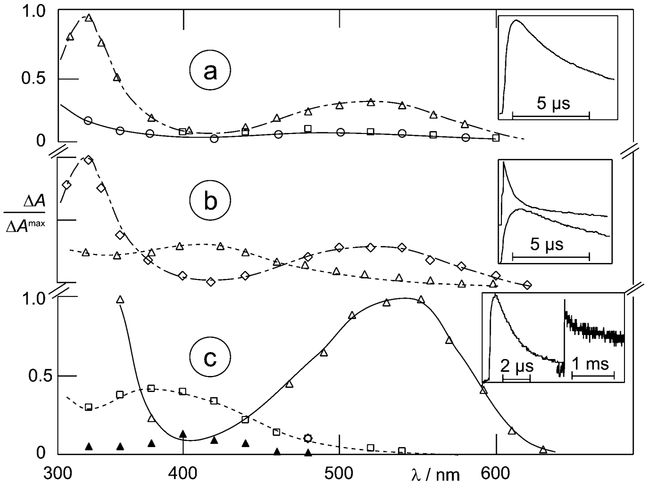

Figure 6. Transient absorption spectra of **7** in argon-saturated acetonitrile−water−acetone (1:1:0.1) (a) neat and in the presence of (b) DABCO (0.1 mM) and (c) D3 (1 mM) at 20 ns (○), 1 μs (△), 10 μs (□), and 1 ms (▲) after the 308 nm laser pulse; insets: kinetics at 400 nm.

3.3 Fluorescence. The significantly large Φ_{isc} (Tables 1 and 2) values indicate that the phthalimides **1**−**7** predominantly react from the triplet state, and in fact fluorescence is not observed for these compounds in the absence or in the presence of potential quenchers under our conditions. The dimethoxy-substituted phthalimide **8**, on the other hand, does exhibit fluorescence with large Φ_f in dichloromethane and acetonitrile.[29,30] The fluorescence lifetime in air-saturated solution in these solvents is $\tau_f = 43$ and 31 ns, respectively.[31] Excitation of **8** in acetonitrile in the presence of D3 results in a decrease of both the fluorescence intensity and the lifetime, which is in agreement with a dynamic fluorescence quenching via electron transfer to the excited singlet state of the phthalimide according to (eq 7).

$$^1\text{A}^* + R-CO_2^-/R-CO_2H \rightarrow \text{A}^{\bullet-} + R-CO_2^{\bullet}/R-CO_2H^{\bullet+} \qquad (7)$$

Preliminary calculations from both methods give a Stern−Volmer constant of ca. 200 M^{-1} corresponding to a rate constant of $k_q = 7 \times 10^9$ M^{-1} s^{-1} for the quenching process (eq 7). Similar values were obtained with D4. Whether the observed quenching eventually furnishes benzylation products similar to P3 and P4 is currently under investigation.[31]

3.4 Continuous Irradiation. The absorbance of **1**, monitored at 300 nm, in argon-saturated acetonitrile−water (pH 2−10) in the presence of D2−D4 decreases upon 313 nm irradiation. The simultaneously observed increase in the absorption at 250 nm suggests the loss of the conjugated imide chromophore. An example of the UV spectra is shown in Figure 7 (inset).

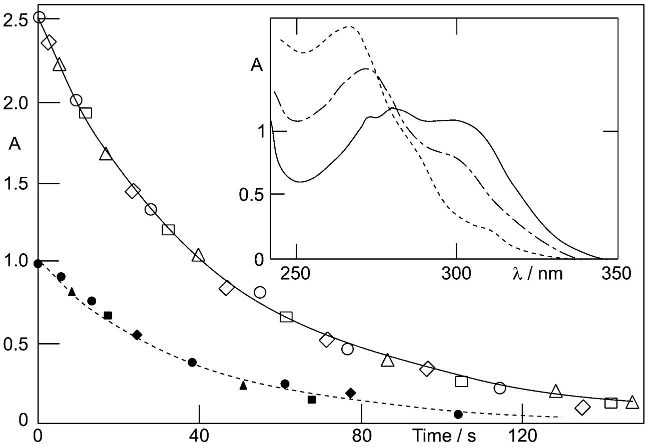

Figure 7. Absorption at 313 nm vs irradiation time for of **1** with D2 (triangles), D3 (squares) and D4 (diamonds) 1 mM; inset: spectrum of **1**/D3 prior to irradiation (full) and at 20 and 100 s (broken).

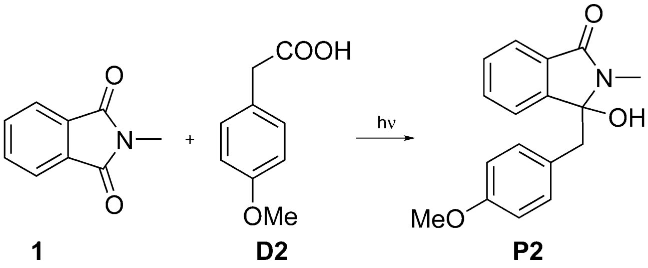

Figure 8. Photodecarboxylative benzylation of **1** with D2.

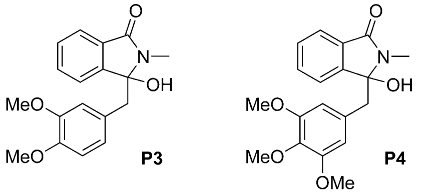

Figure 9. Structures of products from the benzylation of **1** with D3 and D4.

In all cases examined, the photoreaction of **1** with Dn (n = 2−4) chemoselectively gives a single photoproduct Pn. HPLC analysis revealed Pn (n = 2−4) to be identical with samples obtained from preparative irradiation on a multigram scale. The structures of P2 (Figure 8) and the two other products P3 and P4 (Figure 9) were established by NMR spectroscopy and confirmed by X-ray crystallography.[13] While the same photoconversion can be achieved by 308 nm pulses, indicating that a low-intensity irradiation source is not a necessary precondition, irradiation of the **1**/Dn system at 254 nm, although possible in principle, is not advisable due to (i) low donor concentration and (ii) low conversion resulting from large absorption at 254 nm of both Dn and Pn.

The quantum yield Φ_d of decomposition of the phthalimides was determined from plots of the UV changes as a function of the irradiation time (Figure 7), whereas the quantum yield Φ_{prod} of conversion of **1** into the 3-benzyl-3-hydroxy-2-methylisoindolin-1-ones Pn was obtained from plots of the HPLC chromatogram signals vs time (Figure 10).

At least for the **1**/Dn (n = 1−3) system in argon-saturated acetonitrile−water (1:1 and 1:10) at pH 2−8 (Table 4), the Φ_{prod} values were found to be equal to Φ_d or only slightly (3−30%) smaller, indicating that this photobenzylation proceeds without the formation of side products to a significant extent.

The decomposition quantum yield Φ_d increases with the concentration of D3, has a half-value at $[D3]_{1/2}$ = 0.05 mM, and approaches a maximum value Φ_d^{max} (inset Figure 10). $[D3]_{1/2}$ is in agreement with the term $1/(\tau_T k_q)$, using the values of $\tau_T = 10\ \mu s$ and $k_q = 2 \times 10^9\ M^{-1}\ s^{-1}$. The Φ_d^{max} value is 0.3 and similar for D2 and D4 (Table 4). The much larger value $[D1]_{1/2}$ = 50 mM results from the 1000-fold lower k_q value, strongly suggesting that the primary electron transfer to the excited (triplet) state of the phthalimides does not (in all cases) proceed from the donor's identical carboxylate subunit. Interestingly, photoconversion of **1**/Dn into Pn was also observed in the presence of oxygen. In air-saturated acetonitrile−water (1:10, pH 3−4) Φ_d is ca. 0.01 under conditions, where triplet quenching competes with reaction (eq 3), e.g., for a D3 concentration of 1 mM. In contrast to the oxygen-free case, Pn are accompanied by other products not identified yet.

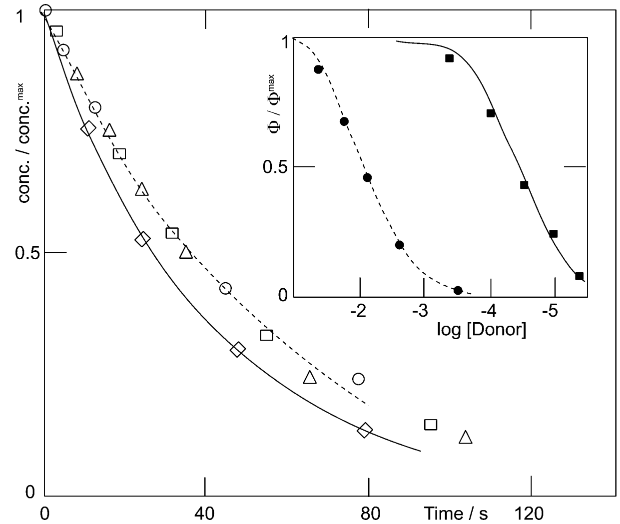

Figure 10. Donor concentrations vs irradiation time for **1** plus 0.03 M D1 (○) and 1 mM D2 (△), D3 (□), and D4 (◇); inset: plots of Φ_d log [donor] for **1**/D1 (●) and **1**/D3 (■).

TABLE 4: Quantum Yield Φ_d of Degradation of 1[a]

donor[b]	% water	pH 2	pH 3−4	pH 6−7
D1	95		0.2	0.2
D2	95	0.1	0.28 (0.25)[c]	0.24 (0.2)
D3	50		0.3	0.3
D3	95	0.1	0.27 (0.23)	0.30 (0.26)
D4	95	0.1	0.26 (0.22)	0.25 (0.22)

[a] In argon-saturated acetonitrile−water, λ_{irr} = 313 nm. [b] Concentrations: 20 mM for D1 and 0.5−1 mM for D2−D4. [c] In parentheses quantum yield of product formation.

Irradiation of **1** in the presence of the methyl esters D2a and D3a results in photodecomposition of the phthalimide, although with k_q values much smaller than for the corresponding acids and furnishes so far no identified products other than P3 and P4.[32]

3.5 Redox Properties of the Phthalimides and the Phenylacetic Acids. In the cyclovoltammetric measurements of all phthalimides in this study, the first wave exhibits almost identical cathodic and anodic peak currents i_p^a, i_p^a while ΔE_p, the difference between the anodic and the cathodic peak potentials E_p^a and E_p^c, typically is in the 70 mV range. Within the limits of experimental uncertainty, this electrode reaction is to be considered reversible. The formal potential is thus given as $E^{\circ\prime} = (E_p^a + E_p^c)/2$. We attribute this first wave to the one-electron reduction of the phthalimide to its corresponding radical anion $A^{\bullet-}$. Additional waves recorded at higher potentials were irreversible but do not play a role for the PET processes under observation (Figure 11).

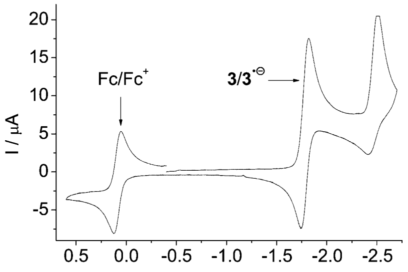

Figure 11. Cyclovoltammogram with reversible one-electron reduction of **3**.

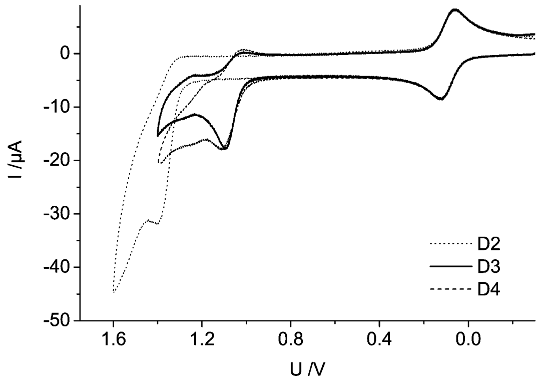

Figure 12. Irreversible oxidation of D2, D3, and D4.

Variation of the substituent on the imide nitrogen of the phthalimide only has a marginal influence on $E^{\circ\prime}$. The reduction potentials vs the ferrocene/ferricenium (Fc/Fc$^+$) redox reference couple is $E^{\circ\prime}_{(Fc)} = -1.87$, -1.86, -1.84, and -1.83 V for **1**, **4**, **5**, and **7**, respectively. The introduction of two methoxy groups to the aromatic core of the phthalimide, on the other hand, substantially changes the spectroscopical properties of the phthalimide and shifts the redox potential by 100 mV, i.e., $E^{\circ\prime}_{(Fc)} = -1.98$ V was measured for the compound **8**.

Under our experimental conditions, the oxidation of the methoxy-substituted phenylacetic acids in acetonitrile was irreversible; the anodic peak potentials E^{a}_{p} were thus used for $E^{\circ\prime}$. Taking the previously reported potential of $E^{\circ\prime}_{(Fc)} = 2.09$ V for toluene as an approximate value for D1, introduction of a methoxy group in the 4-position of phenylacetic acid drastically lowers the potential by 0.78 V, i.e., we measured $E^{\circ\prime}_{(Fc)} = 1.31$ V for D2.[33,34] Further methoxy-substitution in the 3-position again decreases the oxidation significantly by 0.3 V; $E^{\circ\prime}{}_{(Fc)} = 1.02$ V for D3. However, the effect of electron-donating substituents on the oxidation potential is not additive in general (Figure 12). While an 1,2- or 1,4-dimethoxy-substitution pattern allows for the participation of n-orbitals on the oxygen in the efficent delocalization of both charge and spin in a $D^{\bullet+}$ radical cation, little to no additional stabilization is apparently gained in a 1,2,3-trimethoxy-substitution pattern. Consequently, the oxidation potential of D4 ($E^{\circ\prime}_{(Fc)} = 1.00$ V) does not markedly differ from that of D3.

3.6 Mechanistic Considerations. Direct excitation of *N*-alkyl phthalimides **1** and **2** populates the $^3A^*$ state with quantum yields Φ_{isc} high enough to allow for efficent phototransformations in aqueous acetonitrile. Much lower Φ_{isc} are found in the case of the *N*-tolyl phthalimide **7**, where aryl-substitution on the imide nitrogen might lead to small changes in the triplet level not accessible by our means at room temperature. In the case of the 4-methoxybenzyl phthalimide **6**, intramolecular PET, possibly from the singlet state, and immediate electron back transfer, both on a time scale too fast to be monitored with our experimental setup, might be the origin of the low Φ_{isc} found. In all cases, however, these obstacles can be overcome by irradiation in (aqueous) acetone, thus enabling preparative phototransformations of **6** and **7** from the triplet state via sensitization.

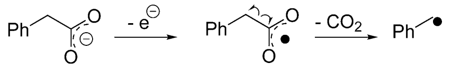

Figure 13. Photo-Kolbe decarboxylation of D1.

Quenching of the triplet state of the phthalimides, generated either by direct irradiation or via triplet sensitization with acetone, with the phenylacetic acids is accompanied by the formation of a new transient, which is assigned to the phthalimide radical anion $A^{\bullet-}$, i.e., the major reaction of $^3A^*$ and Dn is an electron transfer, where the phenylacetic acids act as ground-state electron donors. The transient absorption spectra of the donor radical cations $Dn^{\bullet+}$, typically with absorption bands around 280−310 and 425−455 nm, were not monitored in the current study.[9,10]

$$\Delta G_{ET} = E^{\circ\prime}(D^{\bullet+}/D) - E^{\circ\prime}(A/A^{\bullet-}) - \Delta E_{0,0} + E_{Coulomb} \qquad (8)$$

The thermodynamic driving force ΔG_{ET} for these PET processes can be estimated from the Rehm−Weller equation.[35−37] Using a simplified approach by disregarding the Coulomb term, which is negligible in polar solvents, the free reaction enthalpy ΔG_{ET} was calculated from the redox potentials of the donors and the acceptors, taking the triplet energy of 293 kJ mol^{-1} for **1** as $\Delta E_{0,0}$.

While the reduction of the phthalimides and the oxidation of the electron-rich methoxy-substituted phenylacetic acids could be measured directly (see above), the oxidation potential of the parent D1 could not be determined with our setup. Previously, an anodic peak potential of $E^{a}_{p} = 2.40$ V vs SCE for D1 was reported, which is in good agreement with $E^{\circ\prime}_{(Fc)} = 2.1$ V for toluene.[33] The direct oxidation of alkyl carboxylates to their corresponding acyloxy radical could not be measured either. Instead, a value of $E^{\circ\prime}_{(Fc)} \approx 1.8$ V for the oxidation of propionate in acetonitrile, calculated from a thermodynamic cycle, was used.[38] Taking these electrochemical data into account, the free reaction enthalpies ΔG_{ET} are 89.1, 61.1, 13.8, −14.2, and −16.1 kJ mol^{-1} for the electron transfer from toluene, propionate, D2, D3, and D4 to the triplet-excited state of **1**. While the absolute values might be imprecise due to approximations and difficulties in the determination of data for D1, they still illustrate the observed change in the mechanism while replacing D1 with the electron-rich methoxy-substituted donors.

In the case of D1, the carboxylate rather than the arene is the electroactive, more easily oxidized subunit. PET to the phthalimide thus proceeds in true Photo-Kolbe fashion, i.e., via direct formation of an acyloxy radical and subsequent decarboxylation en route to a benzyl radical (Figure 13). In accordance with this mechanism, propionate itself was shown to undergo decarboxylation and release an ethyl radical under similar conditions.[39]

It is noteworthy that photodecarboxylative benzylation of phthalimides is a very clean reaction. GC/MS analysis of a crude reaction mixture from the irradiation of **2** with D1 shows trace amounts of a side product with $m/z = 182$ and a major fragmentation peak of $m/z = 91$. Addition of dibenzyl to the reaction mixture results in an increase of the total ion current at the same retention time, while the fragmentation pattern remains unchanged. The formation of dibenzyl as the only

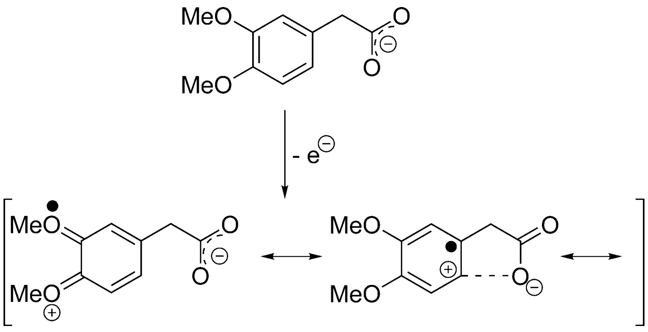

Figure 14. Oxidation of D3.

detectable side product, arising from the dimerization of photogenerated benzyl radicals, further confirms the proposed radical mechanism. The negligible amount formed under our reaction conditions is in good agreement with the concept of a persistent radical effect.[40,41]

The introduction of methoxy substituents to the phenylacetic acid strongly increases the electron density of the aromatic ring. As a result, the primary electron transfer, i.e., the quenching of the phthalimide $^3A^*$ state, is relocated to the arene subunit. Although not directly observed under our conditions, the oxidation of D3 (and D4) is likely to yield delocalized zwitterion radicals, while the carboxylate merely assists in additional stabilization by intramolecular ion pairing and no longer serves as a donor in the primary PET process (Figure 14).

These mechanistic considerations are in full agreement with the quenching rate constants k_q obtained from our laser flash photolysis studies, namely, a value as low as 3×10^6 M^{-1} s^{-1} for D1 and 1000-fold increased rates ($k_q = (1-3) \times 10^9$ M^{-1} s^{-1}) for the electron-rich donors D2−D4. Moreover, the virtually pH-invariant k_q value for D3 over a pH range from 3 to 7 (Table 3) indicates that triplet quenching via PET even occurs when the carboxylic acid initially is not deprotonated and the carboxylate thus cannot serve as an electron donor. Steady-state irradiations showed that, regardless of the particular intermediates initially formed, the oxidation of the phenylacetates eventually furnished benzyl radicals that recombined with the phthalimide radical anions to form a single photoproduct. Under the conditions applied, the quantum yields for the decomposition of the phthalimide Φ_d and the product formation Φ_{prod} are virtually identical, confirming that the reaction constitutes a valuable synthetic method that proceeds with high chemoselectivity and good yields. We had previously developed a photochemical methodology for macrocyclizations based on the intramolecular recombination of alkyl radicals and phthalimide radical anions, generated upon intramolecular PET and decarboxylation of ω-phthalimidoalkanoates.[42−45] Under these conditions, product formation was only observed in the presence of equimolar amounts of base, i.e., at pH > pK_a of the acids. Interestingly, this is not the case for the photoreaction of **1** and D3, where the Φ_d and the Φ_{prod} values remain constant between pH 3 and 7 (Table 4). Generally, decarboxylation of the deprotonated phenylacetate is much faster than that of the corresponding acid, e.g., $k_{dec} = 1.5 \times 10^7$ and 5×10^7 s^{-1} for 4-methylphenylacetic acid at pH 0.3 and pH 2.5.[8] The decarboxylation of D3 is much slower—the rate constants are 5×10^3 and 7×10^4 s^{-1} for the protonated and deprotonated radical cations, respectively. In this case, however, the initial oxidation of the electron-rich dimethoxyarene shifts the pK_a from 4.33 for the acid to 3.49 for the radical cation and thus facilitates the deprotonation and subsequent decarboxylation at a pH lower than expected.[46,47]

4. Conclusion

The photodecarboxylative benzylation of *N*-substituted phthalimides with phenylacetic acid and three methoxy-substituted derivatives in aqueous media was studied. The reaction proceeds from the phthalimide triplet state, either populated upon direct irradiation or by sensitization with acetone (mandatory for **6** and **7**) and furnishes a single photoproduct in good yield. The reaction mechanism includes the release of CO_2 from the electron donor, either upon fragmentation of a PET-generated acyloxy radical (Photo-Kolbe reaction) or, in the case of electron-rich di- and trimethoxyphenylacetic acids, via a previously formed zwitterion radical (pseudo Photo-Kolbe reaction).

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