Efficient Photodecarboxylation of Trifluoromethyl-substituted Phenylacetic and Mandelic Acids

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ABSTRACT

A total of eight CF₃-substituted phenylacetic and mandelic acids are shown to undergo efficient photodecarboxylation (PDC; $\Phi = 0.37$ -0.74) in basic aqueous solution to give the corresponding trifluoromethyltoluenes or trifluoromethylbenzyl alcohols. The products are consistent with the almost exclusive formation of benzylic carbanions that subsequently react with water, with minor amounts (\leq 5%) of radical-derived products detected. Quenching studies indicate that the reaction likely proceeds from the singlet excited state. This work demonstrates that the CF₃ group greatly facilitates the excited state ionic PDC of phenylacetic acids.

INTRODUCTION

Photodecarboxylation (PDC) reactions have been of interest for decades, partly because of the central role they play in the photodecomposition of a number of pharmaceutical and agricultural compounds (1). For example, ketoprofen (1), a nonsteroidal anti-inflammatory drug (NSAID), undergoes loss of CO_2 when irradiated in neutral aqueous solution to give a short-lived carbanion (2) that reacts with water to produce 3ethylbenzophenone (3) (Eq. 1) (2–7), a reaction that has been linked to the phototoxic effects of this drug (8).



The mechanism of PDC for arylacetic acids such as ketoprofen is strongly dependent on the nature of the other substituents on the aryl ring (1). Arylacetic acids that lack a strong electron withdrawing group (EWG) on the ring (a good example is ibuprofen, another NSAID), will generally undergo PDC *via* an inefficient homolytic pathway that produces radical intermediates (9). However, arylacetic acids that

*Corresponding author email: mlukeman@acadiau.ca (Matthew Lukeman) © 2010 The Authors. Journal Compilation. The American Society of Photobiology 0031-8655/10 contain the strongly electron withdrawing keto or nitro groups attached to the aromatic ring follow a heterolytic pathway similar to that in Eq. 1, and produce carbanion intermediates with high quantum yield (10-13). Heterolytic PDC reactions are of particular current interest as they have been exploited in the design of new photoremovable protecting groups (PPGs) with very promising properties (14,15). Benzophenone and xanthone-based arylacetic acids (4) with leaving groups substituted β to the benzylic carbon undergo heterolytic PDC to generate carbanion 5, which rapidly eliminates the leaving group $(k > 10^9 \text{ s}^{-1})$ to give alkene 6 (Eq. 2). In addition to the fast rates of substrate release, other advantages associated with carbanion-mediated PPGs are high quantum vield ($\Phi > 0.6$), good aqueous solubility and good absorption above 300 nm. They have been shown to be capable of releasing a variety of leaving groups, including halides, carboxylic acids, amines (via the carbamate) and alcohols.





We are interested in finding new chromophores capable of undergoing efficient heterolytic PDC, primarily so that they might be exploited in the design of future PPGs related to 4 but also because of our fundamental interest in the mechanism of PDC reactions in general. Because nitro and keto functional groups are well known to mediate efficient heterolytic PDC (and several other excited state reactions that produce benzylic carbanions [16-20]), we became interested as to whether the trifluoromethyl (CF₃) group, another ground state EWG, might also be able to promote ionic excited state reactions. The CF₃ group would represent an attractive alternative to the keto and nitro substituents in PPG applications, as these latter groups have a tendency to undergo competing photoinduced hydrogen abstraction (especially when substituted in the ortho position), and electron transfer chemistry. While CF₃ substituents are reasonably strong EWGs in the ground state $(\sigma_{\rm m} = 0.43, \sigma_{\rm p} = 0.54)$ (21), it was not initially clear whether

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this would translate into good electron withdrawing ability in the excited state. EWGs that engage in conjugation with aryl rings (such as the nitro and keto groups) generally experience an enhancement of their ability to withdraw electron density via resonance on excitation, producing an excited state that is much more polar than the corresponding ground state. Because the CF₃ group is saturated and cannot engage in direct conjugation with aryl rings to which it is attached, it might not experience a sufficient enhancement of its electron withdrawing properties to mediate ionic excited state reactions. While there are no reports available to our knowledge that clearly demonstrate that the CF₃ group can mediate excited state ionic reactions, Seiler and Wirz showed that ortho, meta and *para* trifluoromethylphenols have pK_a^* values (in S₁) that are around two units more acidic than that of unsubstituted phenol (22), a fact which could be taken as evidence for the existence of enhanced electron withdrawing ability of the CF₃ group in S_1 . To explore whether the CF_3 group is capable of mediating heterolytic PDC of phenylacetic acids, the photochemistry of five CF₃ substituted phenylacetic acids (7-11) and three CF₃ substituted mandelic acids (12-14) was investigated in aqueous solution. In this work we demonstrate that all eight derivatives undergo PDC efficiently to give products consistent with the initial formation of benzylic carbanions.





7 $R_1 = H, R_2 = COOH$ 12 $R_1 = OH, R_2 = COOH$ 15(-D) $R_1, R_2 = H(D)$ 15(-D) $R_1, R_2 = H(D)$ 20(-D) $R_1 = OH, R_2 = H(D)$

9 $R_1 = H, R_2 = COOH$ **13** $R_1 = OH, R_2 = COOH$ **17(-D)** $R_1, R_2 = H(D)$ **21(-D)** $R_1 = OH, R_2 = H(D)$



CF₃ CF₃

10 R₁ = H, R₂ = COOH **18(-D)** R₁, R₂ = H(D) **11** $R_1 = H, R_2 = COOH$ **14** $R_1 = OH, R_2 = COOH$ **19(-D)** $R_1, R_2 = H(D)$ **22(-D)** $R_1 = OH, R_2 = H(D)$

Structure 1.

MATERIALS AND METHODS

All phenylacetic and mandelic acids (7–14) were purchased from Oakwood Chemicals and used as received. Authentic samples of 15, 17, 20 and 21, and 19 were also purchased from Oakwood Chemicals and used for comparison in GCMS studies. NMR experiments were performed on a Bruker AVANCE 300 (300 MHz) spectrometer using deuterated solvents purchased from Norell, Inc. All other fine chemicals were purchased from Sigma Aldrich Canada. Photolyses were carried out in a LuzChem LZC-Org photochemical reactor equipped with 10 low-pressure mercury lamps (254 nm output, dose = 75 W m⁻²), in most cases in quartz NMR tubes (also purchased from Norell). UV–Vis spectra were recorded on a CARY 100 spectrometer.

The photolysis procedure involved making a solution of the requisite phenylacetic or mandelic acid in a 1:1 (vol/vol) mixture of CD₃CN and D₂O containing NaOH (0.16 M), and transferring 0.8 mL

of this solution to a quartz NMR tube. The solution was then bubbled with N_2 or argon via a stainless steel needle for 5 min and capped tightly. Typically, four to eight such tubes were prepared and irradiated simultaneously for periods of 3–20 min in a merry-goround apparatus to ensure that all tubes received the same light dose. Quantum yield measurements were made by comparison of integrations of the peaks in the ¹H NMR spectra for samples of 7–14 with those of ketoprofen (1) (3) irradiated simultaneously. For solubility reasons, photolyses of ketoprofen were carried out in 1:1 CD₃CN-D₂O (containing 0.16 NaOH) rather than in purely aqueous solution in which its quantum yield is reported. We have measured the quantum yield for PDC of ketoprofen under these modified conditions to be 87% of that in pH 7 buffer, or 0.65, and we used this value to determine the quantum yields of 7–14. Reported quantum yields are the average of three to five runs.

RESULTS

Product studies

7
$$\frac{hv}{pD \ 13}$$
 15-D (3)
1:1 D₂O-CD₃CN

Carbanions generated from ionic PDC of 7-14 were expected to react rapidly with water to give the corresponding trifluoromethyl-substituted toluenes (15-19 from 7-11, respectively) or benzyl alcohols (20-22 from 12-14, respectively). Due to the expected volatility of some of these products, photolyses of 7-14 were carried out in quartz NMR tubes which allowed identification and quantification of the photoproducts without workup, thereby eliminating product loss. Irradiation of 7 (50 mм, LuzChem LZC-ORG photochemical reactor, 10 UVC lamps, argon bubbled) for 3 min in 1:1 CD₃CN-D₂O (containing 0.16 M NaOH) resulted in 22% conversion to trifluoromethyltoluene 15 with one benzylic hydrogen replaced with deuterium (i.e. 15-D, Eq. 3), as evidenced by the appearance of a new peak at 2.45 ppm in the ¹H NMR spectrum (Fig. S1, Table S1). Photolysis for longer periods of time led to higher conversions, with >90% conversion reached after 20 min (Fig. 1), and with no other primary or secondary photoproducts observed by ¹H NMR spectroscopy. The formation of the monodeuterated trifluoromethyltoluene 15-D is entirely consistent with the initial formation of a carbanion intermediate that subsequently reacts with the D₂O solvent. No other products (such as dimers) (10,12) were observed in the ¹H NMR spectra, suggesting a clean ionic reaction pathway rather than a radical pathway. Irradiation of 8-11 gave similar results, each giving efficient conversion to its corresponding trifluoromethyltoluene photoproduct (i.e. 16-D-19-D from 8-11, respectively). Irradiation of 12-14 was carried out in the same manner in order to determine the effect of the α -hydroxyl group on the reaction efficiency. Each of 12-14 underwent efficient PDC as well, with the corresponding deuterium containing trifluoromethylbenzyl alcohol (20-D-22-D) obtained as the only reaction product (Eq. 4) observable by ¹H NMR spectroscopy. Photolyses were repeated for 7–14 under conditions identical to those described above, but with the base (NaOH) omitted. Under these conditions, the carboxylic acid functionality is expected to exist primarily in its undissociated form. Even after irradiation for 20 min, no evidence for product formation was apparent in the ¹H NMR spectra, indicating that the carboxylic acid group must be ionized in order for the reaction to take place. Also, samples of 7-14 dissolved in neutral or basic solution showed no observable decarboxylation (by NMR spectroscopy) when kept in the dark for a period of 2 h.



In order to probe for trace side products not visible by ¹H NMR analysis, higher conversion photolyses were carried out for 7-14 (same conditions as above, irradiation time = 20 min), and the photolysates were analyzed by GC-MS. For 7-14, the major products observed via this method of analysis in all cases were the corresponding toluenes and benzyl alcohols 15-22, as indicated by their mass spectra. We also ran authentic samples of 15, 17, 20 and 21 by GCMS for comparison, and they matched those produced photochemically in both their retention times and mass spectra. In addition to these primary product peaks, small peaks were observed in the photolysis runs for all cases that had retention times and mass spectra consistent with dimeric photoproducts. Due to our inability to detect these by ¹H NMR spectroscopy, and because of their small relative peak integrations in the GC-MS chromatograms, we estimate that they account for $\leq 5\%$ of the product obtained in all cases. The presence of dimeric products in the photolysate suggests that in addition to the primary heterolytic PDC, a much less efficient homolytic pathway is available that produces benzylic radicals. These dimeric photoproducts are unlikely to be secondary photoproducts resulting from excitation of primary products 15-22; the photochemistry of trifluoromethyltoluenes has been examined in detail, and the major reaction is phototransposition (with low Φ) which does not lead to dimer formation (23).



Figure 1. Plot of percent decarboxylation of 7 (50 mM in 1:1 [vol/vol] CD₃CN-D₂O, 0.16 M NaOH) with irradiation time. The error associated with each point is estimated to be $\pm 5\%$. The curve was drawn to run through the points and is not the result of a least-squares fitting analysis.

Table 1. Quantum yields for photodecarboxylation (in neutral or basic aqueous solution) of 7–14 and for selected arylacetic acids for comparison. Estimated errors are $\pm 10\%$.

Substrate	Фрdc	Reference
7	0.46	
8	0.41	
9	0.37	
10	0.74	
11	0.56	
12	0.53	
13	0.37	
14	0.69	
Phenylacetic acid	0.04*	(24)
Mandelic acid	0.4	(25)
2-Nitrophenylacetic acid	0.04	(10)
3-Nitrophenylacetic acid	0.63	(10)
4-Nitrophenylacetic acid	0.59	(10)
2.4-Dinitrophenylacetic acid	0.04	(10)
3-Benzovlphenvlacetic acid	0.66	(11)
4-Benzovlphenvlacetic acid	0.62	(11)
3-Acetylphenylacetic acid	0.6	(12)
4-Acetylphenylacetic acid	0.22	(12)
2-Xanthoneacetic acid	0.67	(12) (13)
3-Xanthoneacetic acid	0	(13)
4-Xanthoneacetic acid	0.61	(13)

*In basic methanol.

Quantum yields for PDC of 7–14 in basic D_2O-CD_3CN (0.16 M NaOH) were measured using the PDC reaction of ketoprofen ($\Phi = 0.75$) (3) as a secondary reference standard. The results appear in Table 1 along with selected examples of quantum yields for PDC reactions of other arylacetic acids. The quantum yields measured for 7–14 span the range from 0.37 to 0.74, demonstrating that the CF₃ group is able to mediate the PDC reaction nearly as well as a nitro or keto group (Table 1), placing it among the very best excited state activating groups. All arrangements of the CF₃ group gave high quantum yields, whereas the keto and nitro groups give low yields when the EWG is in the *ortho* position due to competing intramolecular hydrogen abstraction (Table 1).

To gather information regarding the multiplicity of the reactive excited state, two samples for each of 7-14 were simultaneously irradiated as before in which one sample per pair contained 10 mm potassium sorbate, and the extents of conversion were determined by ¹H NMR spectroscopy. The sorbate ion is a potent triplet quencher, and is known to quench the triplet states of other arylacetic acids with rate constants approaching the diffusion limit $(k_q = 7 \times$ $10^9 \text{ m}^{-1}\text{s}^{-1}$ for ketoprofen) (6). Assuming a similar quenching rate constant for the triplet states of 7-14, the presence of 10 mm sorbate in our samples was expected to quench at least 50% of triplet states with lifetimes 14 ns or longer. Due to competitive absorption of the 254 nm incident light by sorbate ions, some reduction in the photodecarboxlyation yields of 7-14 was expected, and this expected drop was calculated from the extinction coefficients and concentrations employed. For all of 7-14, the presence of 10 mm sorbate caused no additional drop in reaction efficiency beyond that expected because of competitive absorption, suggesting that the PDC of all derivatives proceeds either through the singlet state or through a very short-lived triplet («10 ns). In an effort to sensitize the reaction, and thus provide evidence for a triplet pathway, solutions of 7–14 were irradiated in a basic 1:1 D_2O -acetone- d_6 solution at 300 nm, where the solvent absorbs strongly, but 7–14 do not. Even after extended photolysis (>20 min) under these conditions, complete recovery of starting material was realized for all compounds, lending further support for a singlet pathway.

DISCUSSION

The proposed mechanism for the PDC of 7 based is presented in Scheme 1. Direct excitation of the acid form of 7 does not lead to any observable reaction, indicating that the carboxylate form is required for efficient PDC. Excitation of the carboxvlate form in aqueous solution (pH > 7) produces a singlet excited state which undergoes C-C bond heterolysis to generate a benzylic carbanion and CO₂. Our inability to quench the reaction with sorbate or to sensitize the reaction with acetone argues against PDC occurring from a triplet state. While we cannot definitively rule out the reaction occurring from a very short-lived triplet state, singlet reactivity has the added appeal of enabling production of the singlet carbanion directly in one step via a spin-allowed process. The carbanion produced can then react with water (or D_2O) to give the toluene product 12 (or 12-D). Because trace amounts of dimer were observed by GC-MS, we propose a second minor pathway from the excited carboxylate 7^{-*}: ejection of an electron to produce the radical 7. (and a solvated electron), which then loses CO_2 to generate the trifluoromethyl-substituted benzyl radical which subsequently dimerizes. The eventual fate of the solvated electron is unknown, although it represents a minor pathway. Related derivatives 8-14 are assumed to follow the same mechanism as 7 due to their similarity in reaction products, quenching and sensitization behavior.



A major conclusion from this work is that the CF₃ group is clearly able to mediate the ionic PDC of phenylacetic acids in aqueous solution (pH > p K_a), regardless of whether it is positioned *ortho*, *meta* or *para* to the acetic acid functional group. On comparing the PDC efficiencies of 7–9, there is only a small difference in reaction efficiency between the three isomers, although the *meta* derivative gives the most efficient reaction, followed by *ortho*, and with the *para* position being least reactive. The enhanced reactivity from the *meta* isomer is mirrored in the reaction efficiency of mandelic acids 12 and 13, and is reminiscent of the "*meta* effect" proposed by Zimmerman and Sandel (26), which is simply the observation that substituents on aromatic rings will exert a much greater influence on the reaction center in photochemical reactions when they are located at the *meta* position than when located in the *para* position. If the small difference in reactivity between 7–9 does result from the *meta* effect, it certainly is not as pronounced as it is in the case of xanthone acetic acids, in which case the *meta* derivative undergoes PDC with a quantum yield of 0.64 and the *para* derivative does not undergo PDC at all (13). Further, on comparison of 10 and 11, both of which contain two CF₃ groups, the di-*meta* derivative undergoes PDC with an efficiency which is less than the *orthopara* derivative, which would run contrary to expectations based on the *meta* effect.

Comparing the PDC efficiency of 12-14 with the corresponding phenylacetic acids 7, 9 and 11, it is apparent that the presence of the *a*-hydroxyl group modestly increases the reaction efficiency for all but the para arrangement, presumably because the electronegative oxygen atom can assist in stabilizing the incipient carbanion on the α -carbon. However, the enhancement offered by the α -hydroxyl group is very modest when one considers its effect on unsubstituted phenvlacetic acid. While the PDC efficiency of phenylacetate in basic solution is marginal ($\Phi \sim 0.04$, Table 1) (24), addition of the hydroxyl group to the benzylic position to give the mandelate ion leads to a 10-fold increase in PDC quantum yield ($\Phi = 0.40$, Table 1) (25). A similarly large enhancement is not observed for 12-14, and the PDC quantum yield of 13 is essentially the same as that of unsubstituted mandelic acid. This result seems to indicate that the enhancements in PDC efficiency provided by the trifluoromethyl substituents and α hydroxy substituents are not additive, particularly in the para case. Derivatives 10, 11, and 14 containing two CF₃ groups show the highest yields of the eight studied, suggesting that multiple CF₃ groups do act cooperatively in the excited state to give an overall additive effect.

We propose that the CF_3 group is able to enhance the PDC efficiency of phenylacetic acids to which it is attached because of enhanced resonance electron-withdrawing capabilities of this group in the excited state. For EWGs that are directly conjugated with an aromatic system, an increase in their electron withdrawing abilities in S₁ can be rationalized with HMO theory (26). HMO calculations predict a larger electron density on the EWG in the LUMO compared to the HOMO for substituted benzyl anions, so when an electron is excited from the HOMO to the LUMO, electron density shifts onto the EWG, increasing its apparent withdrawing ability. Despite being saturated, the CF₃ group does exert resonance effects (R = 0.16, ref. 21) via hyperconjugation, and its electronwithdrawing ability via resonance may be greater in S_1 due to a similar electron-density shift. This would allow a portion of the developing negative charge on the benzylic carbon during the transition state of the PDC step to be delocalized onto the CF₃ group, thus facilitating the reaction.

Hydrogen bonding is likely to be of significant importance in at least some PDC reactions, although its role is not well understood. Keto-substituted phenylacetic acids typically show a strong solvent dependence, with efficient reaction often only observed in aqueous solution (2-7,11-13). A notable exception to this generalization is the efficient PDC of 2-acetylphenylacetic acid in benzene (27), although this reaction is believed to be assisted by intramolecular hydrogen bonding, only available in this example because of the proximate positioning of the ketone and acetic acid functionalities (28). The PDC efficiencies of several keto-substituted phenylacetic acids show significant solvent isotope effects when D_2O is used in place of water, in some cases as high as 4.2 (29), indicating that the decarboxylation step is very sensitive to the surrounding solvent, and that in some cases, a formal proton transfer might occur to the substrate on loss of CO₂. In such cases, it is probable that solvent hydrogen bonding with the carbonyl group of the keto substituent is the important interaction, as it is well established that aromatic ketones become more basic in the excited state (30,31). Discrete proton transfer to the keto group during the PDC step would also favor the reaction by avoiding a carbanion intermediate altogether and directly generating a neutral enol. The PDC reactions of 7-14 collectively provide an interesting case for comparison because the CF₃ group in these compounds cannot engage in significant hydrogen bonding interactions with water. Clearly, the absence of hydrogen bonding to the aryl substituent does not preclude efficient PDC for phenylacetic acids in general. Indeed, the reliance of efficient heterolytic PDC on substituent hydrogen bonding might be peculiarity specific to keto-substituted phenylacetic acids.

An important consideration in the reaction mechanism concerns whether the ion-derived products are the result of a true heterolytic process, or whether they might arise from an initial homolysis to produce a radical pair, which then converts to an ion pair after an electron transfer. Pincock et al. have proposed that the homolysis-electron transfer mechanism is an important source of the ion-derived products in the photohydrolysis of benzylacetates (32-35). Peters and others have investigated the mechanism of photosolvolysis of a variety of benzyl compounds, and in several cases the formation of ion pairs from radical pairs was directly monitored using picosecond and femtosecond time-resolved techniques (36-38). In one such case (38), a derivative containing a trifluoromethylphenyl group was included in the study, although it was not designed to give rise to carbanion intermediates. In all examples investigated by Pincock and Peters, the ion pairs in question involved benzylic carbocations, and it is not clear whether conclusions can be drawn from this work about the production of benzylic carbanions. Nevertheless, it remains a distinct possibility that the "apparent" heterolytic PDC of 7-14 actually occurs as a result of initial homolysis followed by electron transfer.

In summary, we report for the first time the ability of the CF_3 group to mediate the formation of benzylic carbanions *via* the heterolytic PDC of phenylacetic and mandelic acids with remarkably high quantum efficiency. The results suggest that the CF_3 group might be able to mediate many other ionic excited state reactions such as the photoaddition of water and alcohols to styrenes, photo-retro-aldol reactions of 2-phenyl-ethanols and nucleophilic aromatic substitution.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. ¹H NMR spectra of irradiated samples of 7–14. **Table S1.** Summary of ¹H NMR data for 7–14.

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