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Light-Induced Decarboxylation of (*o*-Acylphenyl)acetic Acids

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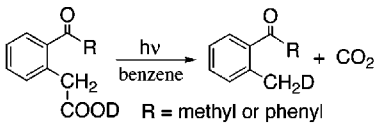
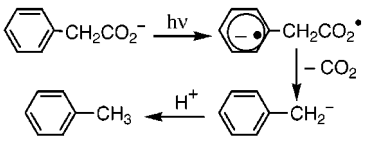
ABSTRACT



Near-UV irradiation of both *o*-acetylphenyl- and *o*-benzoylphenylacetic acids in benzene solution results in their efficient decarboxylation. Their meta and para isomers do not undergo this process. The O-deuterated acids yield deuterated *o*-acyltoluene products, suggesting the possibility of an intramolecular proton transfer step in the decarboxylation process, although intermolecular deuteration would achieve the same result. The corresponding esters and amides are essentially photoinert and, like the acids, do not undergo the benzocyclobutenol formation expected of *o*-alkylphenyl ketones.

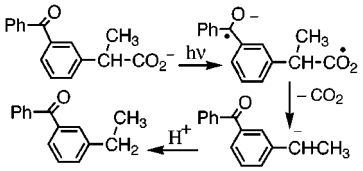
The light-induced decarboxylation of various α-arylcarboxylic acids has received a good deal of attention, especially since several NSAIDs are α-arylpropionate salts.[1] In the case of the parent phenylacetic acid, two mechanisms have been identified that involve the π,π^* excited singlet state of the aromatic moiety:[2]

(1) In polar protic solvents, electron transfer from the carboxylate anion site to the benzene ring is followed by rapid loss of CO_2 from the carboxy radical site, the resulting benzyl anion then being protonated by solvent.



(2) In less polar solvents photoionization induces homolytic cleavage, which generates benzyl radicals that both dimerize and abstract hydrogen atoms from solvent.

Ketoprofen, sodium α-(3-benzoylphenyl)propionate, also undergoes decarboxylation only in protic solvents,[3] apparently also by internal electron transfer to the n,π^* singlet and/or triplet states of its ketone chromophore.[4]



We now report another such photodecarboxylation of (acylphenyl)acetic acids, one that proceeds by a different mechanism that may include but is not initiated by electron transfer. UV-irradiation of both (*o*-acetylphenyl)acetic acid **1** and (*o*-benzoylphenyl)acetic acid **2** in benzene causes loss of CO_2 and leaves *o*-acyltoluenes as products. Our discovery of this process resulted from studies of substituent effects on the Yang photoenolization of *o*-alkylphenyl ketones.[5] Having shown that a variety of *o*-acyltoluenes substituted on the benzylic carbon undergo stereoselective photocyclization to benzocyclobutenols via γ-hydrogen abstraction by excited n,π^* states,[6] we were disappointed to find that neither

(1) Kochevar, I. E.; Hoover, K. W.; Gawienowski, M. *J. Invest. Dermatol.* **1984**, *82*, 214. Ljunggren, J. *J. Photodermatol.* **1985**, *2*, 3. Navaratman, S.; Hughes, J. L.; Parsons, B. J.; Phillips, G. O. *Photochem. Photobiol.* **1985**, *41*, 375. Encinas, S.; Miranda, M. A.; Marconi, G.; Monti, S. *Photochem. Photobiol.* **1998**, *67*, 420.

(2) Budac, D.; Wan, P. *J. Photochem. Photobiol., A* **1992**, *67*, 135. Epling, G. A.; Lopes, A. *J. Am. Chem. Soc.* **1976**, *99*, 2700.

(3) Bosca, F.; Miranda, M. A.; Carganico, G.; Mauleon, D. *Photochem. Photobiol.* **1994**, *60*, 96. Constanzo, L. L.; DeGuidi, G.; Condorelli, G.; Cambria, A.; Fama, M. *Photochem. Photobiol.* **1989**, *50*, 359.

(4) Martinez, L. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 11066 and references therein.

(5) Yang, N. C.; Rivas, C. *J. Am. Chem. Soc.* **1961**, *83*, 2213.

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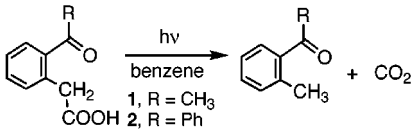
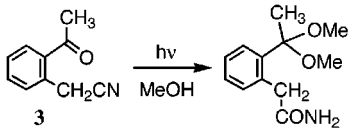
esters nor amides of **1** and **2** do so. (They do form some as yet unidentified products in very low chemical and quantum yields.) Knowing the rapidity of γ-hydrogen abstraction in *o*-alkylphenyl ketones[7] and the 10- to 30-fold extent to which γ cyano and carboxy groups lower rates of Norrish type II hydrogen abstraction,[8] we were certain that the esters and amides of **1** and **2** should undergo very efficient triplet state γ-hydrogen abstraction to form *o*-xylylenols. Knowing that the *o*-xylylenol intermediates undergo rapid acid-catalyzed reketonization,[9] we suspected that trace amounts of acid in the esters and amides might be responsible for the lack of cyclization products, and so we studied **1** and **2** themselves.

NMR tubes containing benzene-d_6 solutions 0.01 M in **1** or **2** were irradiated for 20−30 min at 40 °C in a Rayonet reactor with 300-nm lamps, after which ^{1}H NMR analysis revealed that the 3.5 or 3.8 ppm methylene singlet of the reactant had disappeared to be replaced by a 2.2 or 2.5 ppm singlet characteristic of the benzylic methyl of *o*-acyltoluenes. The acyltoluene products were isolated from preparative scale irradiations; their NMR spectra, mass spectra, and GC retention times were identical to those of pure samples. The time required for complete conversion, when compared to that for the photocyclizations of similar compounds, indicated quantum yields in the 50% range. A benzene solution of **1** in a sealed IR cell was irradiated, after which the sample contained a bubble and showed an intense new peak at 2340 cm^{-1} characteristic of CO_2 and greatly diminished intensities of the acid carbonyl and hydroxyl peaks.



As with the esters and amides, no trace of a benzocyclobutenol could be observed. Unreacted ketoacid must catalyze reketonization of any *o*-xylylenol products before they can cyclize. Apparently even the low concentration of ketoacid reactant remaining after >95% complete reaction is sufficient to prevent any photocyclization of the acyltoluene products, which form benzocyclobutenols quite efficiently in the absence of acid.[6a]

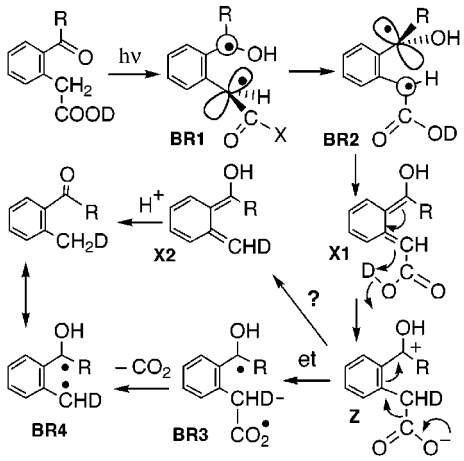
As for the mechanism of this decarboxylation, it clearly cannot be due to electron transfer from carboxyl to excited carbonyl, for several reasons. First, we found no such decarboxylation by the meta and para isomers of **1**, which should undergo electron transfer as readily as their ortho isomer. (We have not yet studied their behavior in protic solvents but do not anticipate behavior much different from that of ketoprofen.) Second, for other α-aryl acids, including ketoprofen, electron transfer does not occur in hydrocarbon solvents. The knowledge that cyclization of any *o*-xylylenol would be prevented by the acid can be combined with revealing studies on the behavior of *o*-acetylphenylacetonitrile **3**. Park found that upon irradiation in methanol **3** forms its amide; he proposed hydrogen abstraction as the first step.[10] Agosta and co-workers studied this process independently and showed convincingly that in methanol triplet **3** undergoes the expected γ-hydrogen abstraction, which is followed by a very plausible series of ionic reactions of the resulting *o*-xylylenol.[11]



The key revelations that the above facts provide are (1) if **3** forms an *o*-xylylenol, then so should **1** and **2**, which in the case of their esters and amides mainly revert to ketone; and (2) if traces of **1** or **2** can cause *o*-xylylenols to revert to starting material by *intermolecular* catalysis, then *intramolecular* protonation of xylylenols might also occur. To test the validity of these conclusions, we prepared and irradiated the O-deuterated versions of **1** and **2**. In both cases the benzylic methyls of the acyltoluene products were deuterated, as indicated by both ^{2}H NMR peaks and split ^{1}H NMR peaks at 2.2 or 2.5 ppm and by large M + 1 and M + 2 mass spectral peaks in the case of **2**. This alone does not prove intramolecular benzylic deuteration.

We propose the mechanism for decarboxylation depicted in Scheme 1. First the n,π^* excited ketone chromophore

Scheme 1



abstracts a hydrogen atom from the ortho benzylic carbon to generate an excited xylylenol **BR1** that relaxes via rearranged **BR2** to a ground-state xylylenol **X1**, the well-known mechanism for photoenolization of *o*-alkylphenyl

(6) (a) Wagner, P. J.; Subrahmanyam, D.; Park, B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 709. (b) Wagner, P. J.; Sobczak, M.; Park, B.-S. *J. Am. Chem. Soc.* **1998**, *120*, 2488.

(7) $k_H > 10^9$ s^{-1}: Wagner, P. J.; Chen, C.-P. *J. Am. Chem. Soc.* **1976**, *98*, 239.

(8) Wagner, P. J.; Kemppainen, A. E. *J. Am. Chem. Soc.* **1972**, *94*, 7495.

(9) Scaiano, J. C.; Wintgens, V.; Netto-Ferreira, J. C. *Tetrahedron Lett.* **1992**, *33*, 5905.

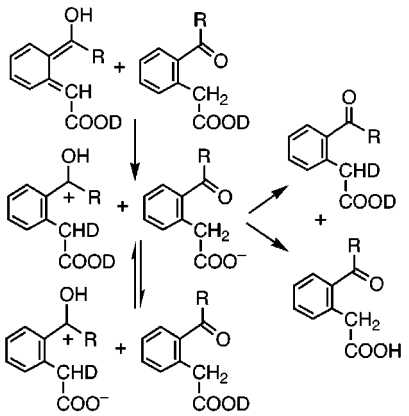
(10) Park, B.-S., Ph.D. Thesis, Michigan State University, 1992.

(11) Lu, A. L.; Bovonsombat, P.; Agosta, W. C. *J. Org. Chem.* **1996**, *61*, 3729.

ketones.[6,12] Next a carboxyl group protonates the xylylenol to generate a zwitterionic species **Z**, which then can decarboxylate by one of two pathways: a one-electron transfer to generate a biradical **BR3** that undergoes the rapid decarboxylation expected of carboxyl radicals, generating xylylenol **X2** via the singlet biradical **BR4**, or a two-electron decarboxylation that generates **X2** directly. **X2** then undergoes, from any proton source, acid-catalyzed ketonization to final product.

With a $\sim 10^3$ M^{-1} s^{-1} rate constant for protonation of *o*-xylylenols by acetic acid,[9] the pseudo-unimolecular rate constant for bimolecular protonation of **X1** by 0.01 M ketoacid is 10 s^{-1}. Thus formation of **Z** probably involves some protonation of **X1** by a second ketoacid molecule, followed by rapid proton exchange. However, reprotonation of the ketocarboxylate anion by the hydroxy-carbocation is more likely and would explain the formation of doubly deuterated acyltoluenes, as shown in Scheme 2. It is not clear to what extent the dimerization of acids in hydrocarbon solvents would affect bimolecular protonation; how rapid intramolecular 1,3-proton transfer might be also awaits determination.

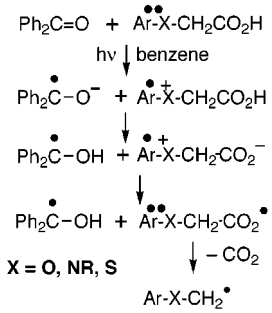
Scheme 2



We do not have specific experimental evidence for an electron-transfer step, other than knowledge of the facility with which carboxylate anions undergo one-electron oxidation by excited states. Precedent for the **Z** → **BR3** pathway for decarboxylative electron transfer is afforded by earlier reports of sensitized decarboxylation of carboxylic acids, but *only* those containing readily oxidizable groups. The process is induced by one-electron transfer to excited ketones, as shown in Scheme 3.[13] Direct hydrogen atom abstraction from a carboxyl group cannot be involved.

A key feature of Scheme 1 is the geometry of **BR2**, which determines which isomers of **X1** are formed and thus the selectivity of further reactions. We have already noted how the geometric preferences of such biradicals dominate their

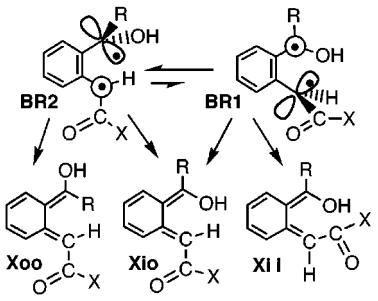
Scheme 3



further behavior, one very relevant example being the nearly complete lack of photoreactivity of *o*-benzylacetophenone.[6b] The biradical it forms by γ-hydrogen abstraction relaxes to a geometry with the OH pointed in and both xylylenols formed from it maintain that feature, which results in rapid and exclusive reversion to starting ketone.[14] It struck us that similar behavior by the various *o*-acylphenylacetic acid derivatives could provide another explanation for their lack of benzocyclobutenol formation. That would be the case if carboxyl and cyano groups were better than a methyl/hydroxyl combination at stabilizing one radical site on these triplet biradicals, a possibility that seemed reasonable enough to investigate.

We performed computations at a variety of levels,[15] all of which indicate that the lowest energy geometry of triplet **BR2** from both **1** and **2** is that drawn in Scheme 1, with the α-hydroxyl radical site twisted 90° out of conjugation with the center benzene ring and the enolate radical site conjugated with the benzene ring. As shown in Scheme 4, this geometry

Scheme 4



collapses to two ground-state *o*-xylylenols with the carboxyl group pointing out, **Xoo** with the OH pointing out, **Xio** with OH in.[6b] The latter reverts rapidly to starting ketone by a 1,5-sigmatropic H shift, whereas the former lives long enough to undergo protonation either by its own or another molecule's carboxyl group.

It is noteworthy that the methyl/hydroxyl combination is predicted to stabilize a radical site better than does a cyano

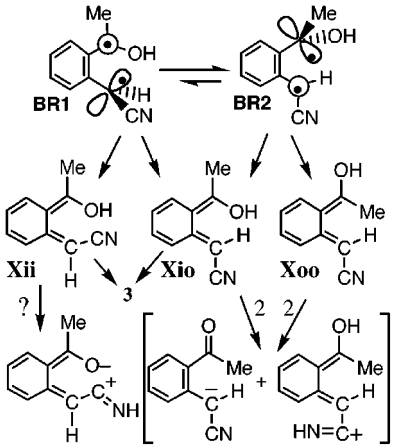
(12) Small, R. D., Jr.; Scaiano, J. C. *J. Phys. Chem.* **1977**, *81*, 2126.
(13) (a) Davidson, R. S.; Harrison, K.; Steiner, P. R. *J. Chem. Soc. C* **1971**, 3480. (b) Cohen, S. G.; Ojampera, S. *J. Am. Chem. Soc.* **1975**, *97*, 5633.
(14) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595.
(15) UHF/PM3, 6-31G*, Dft.

or carbonyl group. The calculations indicate a 2.8 kcal/mol gap between the energies of **BR1** and **BR2**, which would provide only 1% population of **BR1** at thermal equilibrium. It thus appears that the lack of cyclization of the various derivatives of **1** cannot be blamed on exclusive xylylenol formation from the initial **BR1** geometry. If the triplet biradical preferred the **BR1** geometry with the carboxyl radical site twisted, only xylylenols with the OH in would be formed[6b] and most or all would revert to starting ketone, in which case the decarboxylation of **1** and **2** could not display anything close to the measured ~50% quantum efficiency.

A thoughtful referee has suggested that the benzylic deuteration could be due to an inter- or intramolecular H/D exchange between a carboxyl and an enolic hydroxyl group on xylylenol **Xii** or **Xio**, followed by internal protonation by the ennolic OD group. Such a process would indeed deuterate the benzylic carbon but in doing so would merely regenerate reactant and thus prevent decarboxylation, which requires total loss of the carboxyl proton. The idea is doubly unlikely given that the computations suggest that xylylenol **Xii** is not formed.

Internal protonation of the **Xii** xylylenol from **3** has been suggested to initiate amide formation.[11] It is hard to picture this happening unless xylylenols are formed mainly from the **BR1** geometry. Scheme 5 shows both intra- and intermolecular protonation processes that may compete in the xylylenols formed from **3**. **Xio** can only revert to **3** intramolecularly. It is not clear how well a 1,7-proton transfer to nitrogen would compete with the known rapid 1,5-transfer to carbon in **Xii**. However, both **Xio** and **Xoo** can protonate another xylylenol by the bimolecular process that causes the slow reversion of other **Xoo** xylylenols to ketone.[14] Bimolecular processes are probably at least partially involved in all protonations of these photoproduced xylylenols.

Scheme 5



Since *o*-alkylacetophenones react from both singlet and triplet excited states,[7,14] it is likely that both biradical conformers are populated enough to form all possible xylylenols. However, we found little difference in the behavior of **1** and **2**, although benzophenones react only from their triplet states. We shall perform more quantitative measurements on these compounds in order to provide better information about intermediates and the extent of bimolecular protonations in these reactions.

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