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Photodecarboxylation of 2-Phenylpropionic Acid in Solution and Included within β-Cyclodextrin

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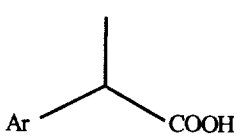
Abstract: Photolysis of 2-phenylpropionic acid (**1**) in acetonitrile, methanol or benzene leads to ethylbenzene (**2**), 2,3-diphenylbutane (**3***d,l* and *meso*), 1-(2-ethylphenyl)-1-phenylethane (**4**), 1-(4-ethylphenyl)-1-phenylethane (**5**) and acetophenone (**6**). In cyclohexane or carbon tetrachloride, solvent derived products are formed. These results involve homolytic cleavage of the C-C bond α to the carboxy group, which affords 1-phenylethyl radical (PER) as key intermediate. The α,α coupling of PER in solution to give **3** is nonstereoselective; by contrast, formation of the *meso* isomer is preferred upon inclusion of **1** within β-cyclodextrin. This is attributed to the coupling of two long-lived PER-CD units

INTRODUCTION

The photochemistry of 2-arylpropionic acids has attracted considerable attention in connection with the photosensitizing properties of nonsteroidal anti-inflammatory drugs (NSAID's) such as benoxaprofen, naproxen, ketoprofen, tiaprofenic acid, carprofen or suprofen.[1-4] The most general photoprocess of these compounds is decarboxylation, wich leads to products with an ethyl side chain or their oxyfunctionalized derivatives.[5-8] The observed photobiological effects have been attributed in part to the involvement of 1-arylethyl radicals, which appear to be key intermediates in the photodecarboxylation.[1,2,8] Surprisingly, there is no report dealing with the photochemistry of 2-phenylpropionic acid (**1**), in spite of its potential interest as the simplest analogue of the above mentioned drugs.



Ar = phenyl	(**1**)
2-(4-chlorophenyl)benzoxazol-5-yl	(benoxaprofen)
6-methoxy-2-naphtyl	(naproxen)
3-benzoylphenyl	(ketoprofen)
4-benzoyl-2-thienyl	(tiaprofenic acid)
6-chlorocarbazol-2-yl	(carprofen)
4-(2-thenoyl)phenyl	(suprofen)

Besides, the expected formation of 1-phenylethyl radical (PER) as primary intermediate might be related with the generation of an identical species by photolysis of other precursors (for instance, 2,4-diphenyl-3-pentanone), wich is well substantiated in the literature.[9-13] In this context, we have undertaken a systematic study on the photochemistry of 2-phenylpropionic acid (**1**) in different media. The results can contribute to gain a deeper insight into the molecular bases of photosensitization by this family of NSAID's.

RESULTS AND DISCUSION

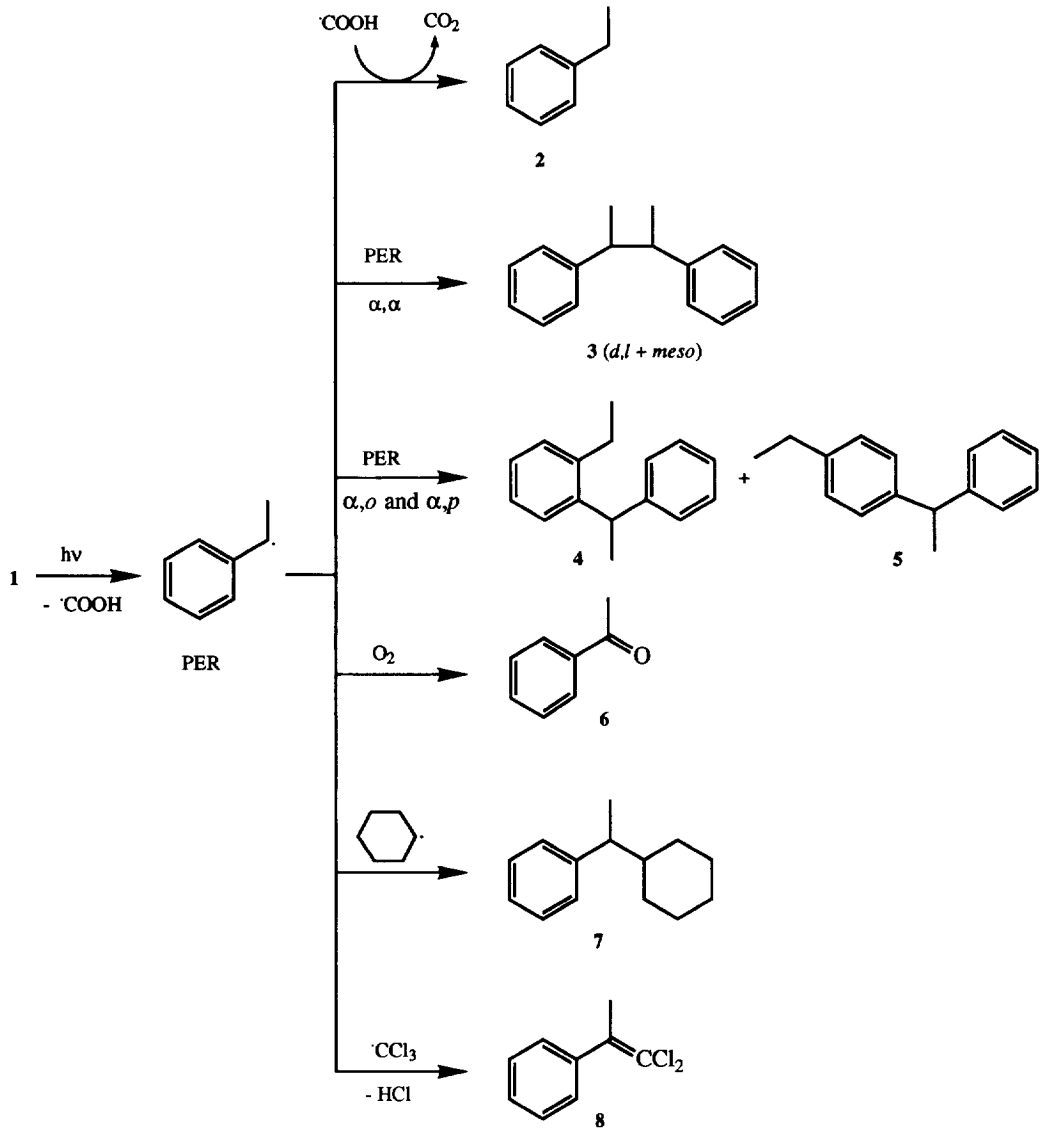
Irradiation of **1** led to photomixtures whose composition depended on the reaction conditions (Table 1). When acetonitrile was used as solvent, the major products under inert atmosphere (entry 1) were the *d,l* and *meso* isomers of 2,3-diphenylbutane (**3**). Ethylbenzene (**2**) was also obtained, as well as minor amounts of 1-(2-ethylphenyl)-1-phenylethane (**4**) and 1-(4-ethylphenyl)-1-phenylethane (**5**). These results clearly indicate that primary homolytic cleavage of the C-C bond α to the carboxy group gives rise to the 1-phenylethyl radical, which subsequently undergoes dimerization or hydrogen abstraction. The α,α- dimers **3** have been previously reported to be the major products (93% overall yield) in the photolysis of 2,4-diphenyl-3-pentanone.[9] In the same work, an additional unidentified dimer (5%) was detected by GC/MS, whose structure might well be that of compound **5**. Since the spin density of the benzylic radical must be also significant at the *o*- and *p*- positions, the formation of α,*o*- and α,*p*- coupling products is reasonable. Concerning the hydrogen abstraction process leading to **2**, two possibilities can be considered: (i) an intermolecular pathway involving the solvent as donor and (ii) disproportionation within the initially formed radical pair, with evolution of carbon dioxide. To check these hypotheses, the experiment was performed in perdeuterated acetonitrile. The fact that no deuterium atom was found in the resulting ethylbenzene allowed to rule out the operation of pathway (i). This is further supported by calculations based on bond energies, which predict that hydrogen abstraction by PER from the carboxyl radical would be strongly exothermic (77.4 kcal/mol), while the analogous process involving acetonitrile as donor would be endothermic by 7-8 kcal/mol.[14-16]

Table 1. Photodecarboxylation of 2-Phenylpropionic Acid

			Product Distribution (%)						
Entry	Conditions	Conversion	**2**	3*d,l*	3*meso*	**4**	**5**	**6**	Others
1	CH_3CN/Ar	76	13	40	41	1	5	-	-
2	CH_3OH/Ar	37	8	41	42	1	7	-	-
3	C_6H_6/Ar	27	25	33	34	1	7	-	-
4	C_6H_{12}/Ar	13	20	34	36	1	6	-	3[a]
5	CCl_4/Ar	12	-	-	-	-	-	-	100[b]
6	CH_3CN/O_2	27	-	-	-	-	-	100	-
7	H_2O,CD/Ar	49	-	34	66	-	-	-	-

[a] Compound **7**, [b] Compound **8**.

When photolysis of **1** was carried out using methanol as solvent, the product distribution was very similar, although the degree of conversion was lower (entry 2). Parallel irradiation of the deuterated acid **1D** in monodeuterated methanol (CH_3OD) led to ethylbenzene labelled at the benzylic position (**2D**). This constitutes an additional evidence against intermolecular hydrogen abstraction (i) and is compatible with the disproportionation pathway (ii). Taking into account the corresponding bond energies, process (i) would be disfavoured by at least 8 kcal/mol.[14-16]



Scheme 1

In benzene and cyclohexane (entries 3 and 4), most of the starting material was recovered unreacted from the photolysate. However, the nature of the photoproducts and their relative ratios were analogous to those found with the previous solvents. In the case of cyclohexane, a minor product was 1-cyclohexylethylbenzene (**7**).[17] The use of carbon tetrachloride (entry 5) produced a dramatic change of the reaction course. Instead of the usual products, only a solvent-derived adduct (**8**) was obtained.[18] The formation of **7** and **8** must involve coupling of PER with cyclohexyl or trichloromethyl radical, respectively.[14-16]

In agreement with the proposed generation of PER as key intermediate, the photolysis of **1** under aerobic conditions (entry 6), led to efficient trapping of the radical site by molecular oxygen, affording acetophenone (**6**) as single photoproduct.

In connection with the possible biological implications of these results, it was also of interest to perform the photolysis of **1** in aqueous medium. Unfortunately, the scarce solubility of this compound in water did not allow the preparation of clear solutions of the appropriate concentrations. However, the 2-arylpropionic acids benoxaprofen, naproxen and ketoprofen have been reported to form soluble complexes with β-cyclodextrin (CD), whose reduced photohemolytic activities are very interesting within the framework of skin photosensitization.[19,20] This led us to examine the photochemical behaviour of the parent compound **1** in aqueous solution as the CD complex (entry 7). Under these conditions, the α,α-dimers **3** were again obtained; however, a marked stereoselectivity was observed for the *meso* isomer.

In order to account for this observation, it must be considered that the lifetime of PER within β-cyclodextrin (PER-CD) is known to be extremely long (up to several days).[13] Since free PER is much shorter-lived in solution, the relative concentration of PER-CD must be markedly higher. Thus, the α,α-dimers **3** probably arise from coupling of two PER-CD units. In principle, the stereochemical control observed in this medium might be attributed either to the chiral nature of CD or to the translational and rotational constraints imposed by this host molecule to the photochemically generated PER intermediates. Although both possibilities appear reasonable, it is interesting to note that identical *meso* selectivities for the α,α-dimeric products **3** were achieved starting from the optically active R or S enantiomers of 2-phenylpropionic acid (**1**) (data not shown in Table 1). This lack of stereospecificity was indeed foreseable, in view of the long lifetime reported for PER within CD, which allows efficient stereoequilibration of this species. Thus, the most simple explanation of these experimental results appears to be the preferred geometrical arrangement for the approach of two PER-CD units, which has antiperiplanar methyl groups and can be considered a precursor of the *meso* diasteroisomer (Figure 1).

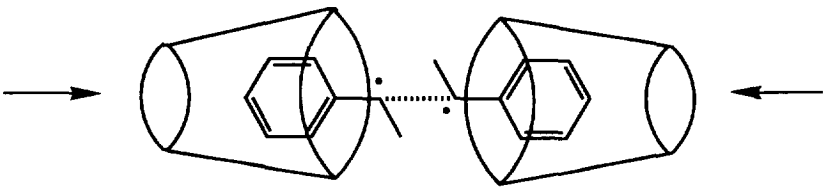


Figure 1

In summary, PER is the key intermediate in the photochemistry of **1**, and its chemical behaviour is strongly modified by inclusion within CD. This must be connected with the reduced photohemolytic activity of

nonsteroidal anti-inflammatory 2-arylpropionic acids upon complexation with CD, since most of the photobiological properties of these drugs have been attributed to the generation of 1-arylethyl radicals.

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EXPERIMENTAL

General irradiation procedure

Irradiation in organic solvents. Solutions of **1** (20 mg) in the corresponding solvent (2 ml) were placed into quartz tubes surrounding a centrally positioned quartz cooling jacket containing a 125 W medium pressure Hg lamp, and irradiated for 2 h.

Irradiation in the presence of β-cyclodextrin. A solution of **1** (20 mg) and CD (850 mg) in distilled water (100 ml) was irradiated for 10 h using the quartz-filtered light of a 125 W medium pressure Hg lamp. The reaction mixture was extracted three times with ether, dried over $MgSO_4$ and concentrated to dryness under reduced pressure.

Analysis of the photomixtures

The photolysates were analyzed by GC/MS, using a Hewlett-Packard 5988 A spectrometer with a Ultra 2 column (cross-linked 5% phenyl methyl silicone, dimensions 25 m x 0.2 mm x 0.33 μm). Authentic samples of the compounds **2-8** were purchased or synthesized by known procedures,[17,18,21-23] in order to compare their physical and spectral data with those of the photolysis products.

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