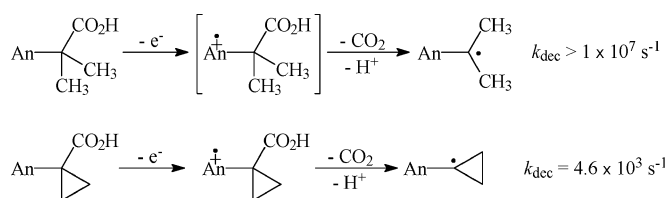# One-Electron Oxidation of 2-(4-Methoxyphenyl)-2-Methylpropanoic and 1-(4-Methoxyphenyl)cyclopropanecarboxylic Acids in Aqueous Solution. The Involvement of Radical Cations and the Influence of Structural Effects and pH on the Side-Chain Fragmentation Reactivity

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A product and time-resolved kinetic study on the one-electron oxidation of 2-(4-methoxyphenyl)-2-methylpropanoic acid (**2**), 1-(4-methoxyphenyl)cyclopropanecarboxylic acid (**3**), and of the corresponding methyl esters (substrates **4** and **5**, respectively) has been carried out in aqueous solution. With **2**, no direct evidence for the formation of an intermediate radical cation **2**$^{\bullet+}$ but only of the decarboxylated 4-methoxycumyl radical has been obtained, indicating either that **2**$^{\bullet+}$ is not formed or that its decarboxylation is too fast to allow detection under the experimental conditions employed ($k > 1 \times 10^7$ s^{-1}). With **3**, oxidation leads to the formation of the corresponding radical cation **3**$^{\bullet+}$ or radical zwitterion $^-$**3**$^{\bullet+}$ depending on pH. At pH 1.0 and 6.7, **3**$^{\bullet+}$ and $^-$**3**$^{\bullet+}$ have been observed to undergo decarboxylation as the exclusive side-chain fragmentation pathway with rate constants $k = 4.6 \times 10^3$ and 2.3×10^4 s^{-1}, respectively. With methyl esters **4** and **5**, direct evidence for the formation of the corresponding radical cations **4**$^{\bullet+}$ and **5**$^{\bullet+}$ has been obtained. Both radical cations have been observed to display a very low reactivity and an upper limit for their decay rate constants has been determined as $k < 10^3$ s^{-1}. Comparison between the one-electron oxidation reactions of **2** and **3** shows that the replacement of the C(CH$_3$)$_2$ moiety with a cyclopropyl group determines a decrease in decarboxylation rate constant of more than 3 orders of magnitude. This large difference in reactivity has been qualitatively explained in terms of three main contributions: substrate oxidation potential, stability of the carbon-centered radical formed after decarboxylation, and stereoelectronic effects. In basic solution, $^-$**3**$^{\bullet+}$ and **5**$^{\bullet+}$ have been observed to react with $^-$OH in a process that is assigned to the $^-$OH-induced ring-opening of the cyclopropane ring, and the corresponding second-order rate constants (k_{OH}) have been obtained. With $^-$**3**$^{\bullet+}$, competition between decarboxylation and $^-$OH-induced cyclopropane ring-opening is observed at pH ≥ 10, with the latter process that becomes the major fragmentation pathway around pH 12.

Introduction

The decarboxylation of organic radical cations is an important reaction that has attracted considerable interest.[1-5] This reaction takes part in several chemical and biological processes,[6] and is involved in particular in important processes such as the initiation of free radical polymerization[7] and the enhancement in the efficiency of silver halide photography (two-electron sensitization (TES)).[8,9] In the latter process, the decarboxylation of radical zwitterions derived from relatively electron rich arylethanoic acids such as 4-dimethylaminophenylethanoic acid,

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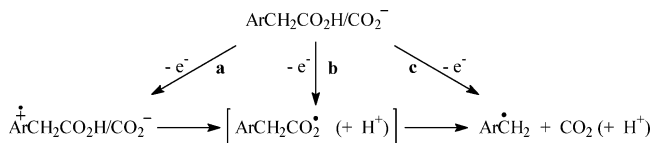
SCHEME 1

$$Ar-\overset{+}{\underset{R_2}{\overset{R_1}{C}}}-CO_2^- \longrightarrow Ar-\overset{\bullet}{\underset{R_2}{\overset{R_1}{C}}} + CO_2$$
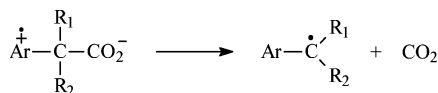
its α-methyl and α-hydroxy-α-methyl derivatives, and 2,4,5-trimethoxymandelic acid proved to be one of the most useful reactions (Scheme 1).

Control over the decarboxylation rate constant of the intermediate radical cation (or radical zwitterion) represents a key issue for the development of these processes, and accordingly studies aimed at the quantification of the factors that govern this fragmentation are particularly important.

However, even though a large number of studies on the generation and reactivity of arylalkanoic acid radical cations have been carried out,[10−21] several mechanistic aspects of these processes are still not fully clarified. A variety of alternative mechanistic pathways for the one-electron decarboxylative oxidation of arylethanoic acids are described in Scheme 2.

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SCHEME 2

$$ArCH_2CO_2H/CO_2^-$$

$$\overset{-e^-}{\underset{a}{\swarrow}} \quad \overset{-e^-}{\underset{b}{\downarrow}} \quad \overset{-e^-}{\underset{c}{\searrow}}$$

$$\overset{+}{Ar}CH_2CO_2H/CO_2^- \longrightarrow \left[ArCH_2CO_2^{\bullet}\ (+\ H^+) \right] \longrightarrow Ar\overset{\bullet}{C}H_2 + CO_2\ (+\ H^+)$$
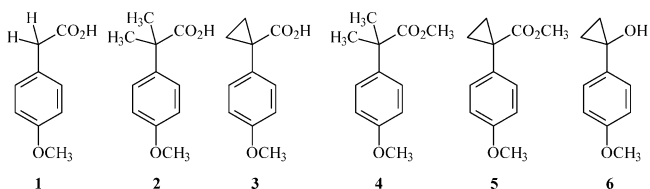
A point that has attracted considerable attention has been that of establishing the actual role of intermediate radical cations. In this respect, the generally accepted mechanism for the one-electron oxidation of arylethanoic acids involves the formation of an aromatic radical cation (or radical zwitterion) that then undergoes decarboxylation to give the corresponding benzyl radical (Scheme 2, path a). However, in aqueous solution direct evidence in this respect has been obtained only in the oxidation of relatively electron rich substrates such as 4-dimethylaminophenylethanoic acid, its α-methyl and α-hydroxy-α-methyl derivatives, 2,4,5-trimethoxymandelic acid,[9] ring-dimethoxylated phenylethanoic acids,[11] and 1-naphthylethanoic acid.[14a] Along this line, it cannot be excluded that the one-electron oxidation of arylethanoic acids, characterized by higher oxidation potentials, occurs following pathways b or c, i.e. bypassing radical cation formation, as suggested recently for the one-electron oxidation of 4-methoxyphenylethanoic acid (**1**).[12]

Moreover, also the nature of the conversion of the intermediate radical cation (or radical zwitterion) into the decarboxylated benzyl radical has attracted considerable interest,[3,13,22] since intramolecular electron transfer (from the side-chain to the aromatic π-system) in the radical cation (or radical zwitterion) can be coupled to or followed by bond cleavage: in other words decarboxylation can occur directly from the radical cation (or radical zwitterion) or from an intermediate arylacetoxyl radical.

An additional point of interest is represented by the stability of the decarboxylated benzyl radical, which is expected to influence the decarboxylation rate constant.[3]

Along this line, in view of the importance of these processes and in order to obtain a deeper understanding on the role of structural effects on the one-electron oxidation of arylethanoic acids and in particular on the possible involvement of aromatic radical cations, we have carried out a product and time-resolved kinetic study at different pH values on the one-electron oxidation of 2-(4-methoxyphenyl)-2-methyl propanoic acid (**2**) and 1-(4-methoxyphenyl)cyclopropanecarboxylic acid (**3**), two structurally related substrates derived from the side-chain modification of 4-methoxyphenylethanoic acid (**1**), whose structures are displayed in Chart 1. To obtain additional information, we have also studied the one-electron oxidation of the methyl esters of acids **2** and **3** (substrates **4** and **5**, respectively), and of 1-(4-methoxyphenyl)cyclopropanol (**6**).

CHART 1

Results

Spectral Properties. Argon- or nitrogen-saturated aqueous solutions of substrates **2**−**6** (0.5−2 mM) were photolyzed in

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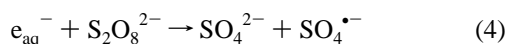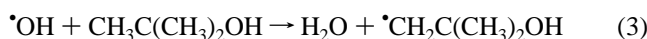**FIGURE 1.** Time-resolved absorption spectra observed after 266 nm LFP of a nitrogen-saturated aqueous solution ($T = 25$ °C, pH 1.7) containing 0.1 M $K_2S_2O_8$ and 2 mM 2-(4-methoxyphenyl)-2-methyl propanoic acid (**2**), recorded at 37 (filled circles), 60 (empty circles), 140 (f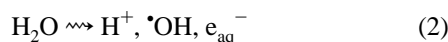illed squares), and 300 ns (empty squares) after the 8 ns, 10 mJ laser flash. Insets: (a) Time-resolved absorption spectrum observed after 266 nm LFP of a nitrogen-saturated aqueous solution ($T = 25$ °C, pH 1.7) containing 0.1 M $K_2S_2O_8$ recorded 90 ns after the 8 ns, 10 mJ laser flash. (b) First-order decay of absorption monitored at 450 nm. (c) Corresponding first-order buildup of absorption monitored at 290 nm, measured under argon (filled circles) and oxygen (empty circles).

the presence of 0.1 M $K_2S_2O_8$ at pH ≤ 2 and pH ~ 7, employing 266 nm laser flash photolysis (LFP). Under these conditions $SO_4{}^{\bullet-}$ is formed (eq 1).[14a]

$$S_2O_8{}^{2-} \xrightarrow{h\nu} 2SO_4{}^{-\bullet} \qquad (1)$$
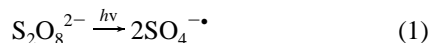
Alternatively, $SO_4{}^{\bullet-}$ was generated by pulse radiolysis (PR) of argon-saturated aqueous solutions containing substrates **2**−**6** (0.2−2 mM), $K_2S_2O_8$ (10 mM), and 2-methyl-2-propanol (0.1 M), according to eqs 2−4.

$$H_2O \rightsquigarrow H^+, \, {}^\bullet OH, \, e_{aq}{}^- \qquad (2)$$

$${}^\bullet OH + CH_3C(CH_3)_2OH \rightarrow H_2O + {}^\bullet CH_2C(CH_3)_2OH \qquad (3)$$

$$e_{aq}{}^- + S_2O_8{}^{2-} \rightarrow SO_4{}^{2-} + SO_4{}^{\bullet-} \qquad (4)$$

Radiolysis of water leads to the formation of the hydroxyl radical (${}^\bullet OH$) and the hydrated electron ($e_{aq}{}^-$) (eq 2). The former is scavenged by 2-methyl-2-propanol (eq 3; $k = 6 \times 10^8$ M^{-1} s^{-1}),[23] while $e_{aq}{}^-$ reacts with $S_2O_8{}^{2-}$ leading to the formation of $SO_4{}^{\bullet-}$ (eq 4; $k = 1.2 \times 10^{10}$ M^{-1} s^{-1}).[23] $SO_4{}^{\bullet-}$ is a strong oxidant that is known to react with ring-methoxylated aromatic substrates via electron transfer to yield the corresponding radical cations with $k \geq 5 \times 10^9$ M^{-1} s^{-1} (eq 5).[24−26]

$$SO_4{}^{\bullet-} + ArR \rightarrow SO_4{}^{2-} + {}^{\bullet+}ArR \qquad (5)$$
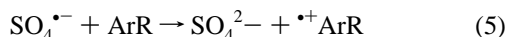
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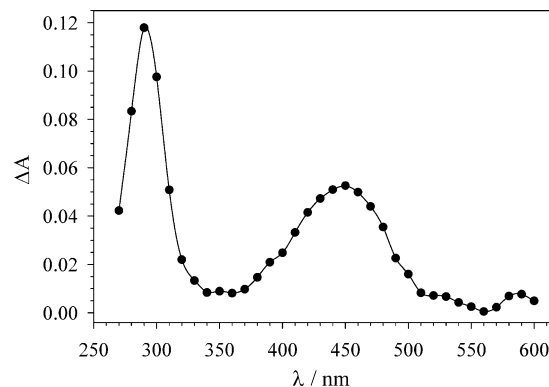
FIGURE 2. Time-resolved absorption spectrum observed after 266 nm LFP of a nitrogen-saturated aqueous solution ($T = 25$ °C, pH 7.0) containing 0.1 M $K_2S_2O_8$ and 0.2 mM methyl 2-(4-methoxyphenyl)-2-methylpropanoate (**4**), recorded 2.1 μs after the 8 ns, 10 mJ laser flash.

Figure 1 displays the time-resolved absorption spectra observed after LFP of a nitrogen-saturated aqueous solution (pH 1.7) containing 2-(4-methoxyphenyl)-2-methylpropanoic acid (**2**) (2.0 mM) and $K_2S_2O_8$ (0.1 M).

The spectrum recorded 37 ns after the laser flash (filled circles) shows the formation of a broad absorption band between 350 and 510 nm, characterized by a maximum at 450 nm, that, by comparison with literature data,[14a,27] and with the time-resolved absorption spectrum of $SO_4{}^{\bullet-}$, obtained after 266 nm LFP of a nitrogen-saturated aqueous solution (pH 1.7) containing 0.1 M $K_2S_2O_8$ (inset **a**), can be reasonably assigned to $SO_4{}^{\bullet-}$, formed as described in eq 1. The decay of this band (inset b) occurs with $k\downarrow(450 \text{ nm}) = 1.0 \times 10^7$ s^{-1} and is accompanied by the formation of a species ($k\uparrow(290 \text{ nm}) = 1.1 \times 10^7$ s^{-1}) characterized by an absorption band in the UV region of the spectrum extending from <290 to 340 nm (an isosbestic point is visible at 330 nm), whose decay is accelerated by the presence of oxygen (inset c), and in an oxygen-saturated solution occurs with an observed rate constant $k_{obs} = 2.2 \times 10^6$ s^{-1}. Given that the solubility of oxygen in water is reported as 1.27×10^{-3} M at $T = 25$ °C,[28] a second-order rate constant for reaction of this transient species with oxygen can be derived as $k = 1.7 \times 10^9$ M^{-1} s^{-1}.

The time-resolved absorption spectrum observed after 266 nm LFP of a nitrogen-saturated aqueous solution (pH 7.0) containing 0.1 M $K_2S_2O_8$ and 0.2 mM methyl 2-(4-methoxyphenyl)-2-methylpropanoate (**4**) is shown in Figure 2. Visible are two bands, centered at 290 and 450 nm, that are very similar to those observed previously for the radical cations of 4-methoxyalkylbenzenes and 1-(4-methoxyphenyl)alkanols.[24,29−31] An identical spectrum was also obtained after PR of an argon-saturated aqueous solution (pH 7.0) containing 10 mM $K_2S_2O_8$, 0.2 mM **4**, and 0.1 M 2-methyl-2-propanol. On the basis of these observations, this species can be reasonably assigned to the radical cation **4${}^{\bullet+}$**, formed by $SO_4{}^{\bullet-}$-induced one-electron oxidation of the neutral substrate **4** as described in Scheme 3.

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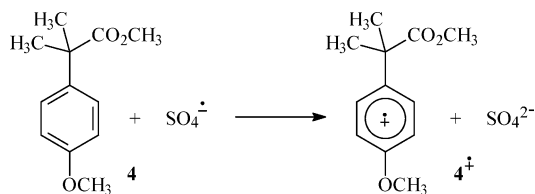(28) Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*, 2nd ed.; Marcel Dekker: New York, 1993.

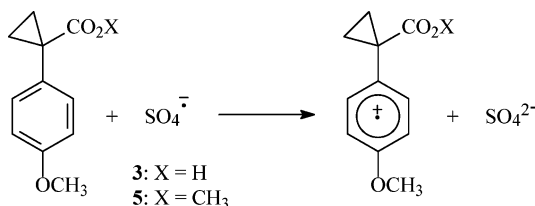(29) Baciocchi, E.; Bietti, M.; Ercolani, G.; Steenken, S. *Tetrahedron* **2003**, *59*, 613−618.

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SCHEME 3

SCHEME 4

3: X = H
5: X = CH$_3$

The time-resolved absorption spectrum observed after PR of an argon-saturated aqueous solution containing 1-(4-methoxyphenyl)cyclopropanecarboxylic acid (**3**) (0.5 mM), K$_2$S$_2$O$_8$ (10 mM), and 2-methyl-2-propanol (0.1 M) at pH 1.7 (filled circles) displayed in Figure 2 shows UV and visible absorption bands centered at 320 and 500 nm whose decay is not affected by the presence of oxygen. An analogous spectrum was observed after LFP of an argon-saturated aqueous solution (pH 1.7) containing **3** (1 mM) and K$_2$S$_2$O$_8$ (0.1 M) (see the Supporting Information (SI), Figure S1).

A similar spectrum, characterized by UV and visible absorption bands centered at 300 and 500 nm, was also observed after PR of an argon-saturated aqueous solution (pH 4.0) containing methyl 1-(4-methoxyphenyl)cyclopropanecarboxylate (**5**) (0.2 mM), K$_2$S$_2$O$_8$ (10 mM), and 2-methyl-2-propanol (0.1 M) (see SI, Figure S2).

It is well-known that in organic media arylcyclopropane radical cations are characterized by an absorption band in the visible region of the spectrum centered between 510 and 580 nm depending on the nature of the aromatic ring substituent.[32,33] Along this line, the UV and visible absorption bands described above for the transients observed in the oxidation reactions of substrates **3** and **5** can be reasonably assigned to the radical cations **3**$^{•+}$ and **5**$^{•+}$, formed by one-electron oxidation of the neutral substrates as described in Scheme 4.

By increasing the pH of the solution to ~7, the spectrum obtained after SO$_4$$^{•-}$-induced one-electron oxidation of **3** was similar to that obtained in acidic solution. However, as described previously for ring-methoxylated phenylalkanoic acid radical cations,[11,34] a broadening of the radical cation visible absorption band, accompanied by a 20 nm red-shift in its position was observed (Figure 3, empty circles). This behavior is attributed to the formation of the radical zwitterion $^-$**3**$^{•+}$ as described in Scheme 5.[35] Quite importantly, no significant spectral variation was instead observed for **5**$^{•+}$ between pH 4 and 10.

The one-electron oxidation of 1-(4-methoxyphenyl)cyclopropanol (**6**) was studied employing both PR and LFP. PR of an argon-saturated aqueous solution (pH 5.0) containing 2 mM **6**,
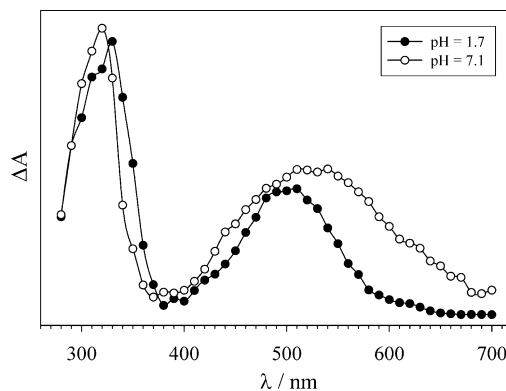
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(35) This notation represents an oversimplification because, as compared to the radical cations, the corresponding radical zwitterions lack the presence of the carboxylic proton.

FIGURE 3. Time-resolved absorption spectra observed on reaction of SO$_4$$^{•-}$ with **3** (0.5 mM) recorded after PR of argon-saturated aqueous solutions at pH 1.7 (filled circles) and 7.1 (empty circles), containing 0.1 M 2-methyl-2-propanol and 10 mM K$_2$S$_2$O$_8$, 2 μs after the 300 ns, 10 MeV electron pulse.

SCHEME 5
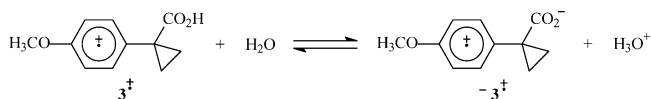
0.1 M 2-methyl-2-propanol, and 10 mM K$_2$S$_2$O$_8$ did not provide evidence for the formation of an intermediate radical cation, showing instead the fast formation of a product absorbing at λ < 370 nm, a result that suggests that **6**$^{•+}$ is either not formed under these conditions or that its rate of decay exceeds the time resolution of the PR equipment employed. Unfortunately, 266 nm LFP experiments carried out on **6** showed the formation of transient species derived from the direct photochemistry of the substrate and no further LFP investigation was carried out.

Product Studies. The one-electron oxidation reactions of substrates **2**−**6** were carried out in argon-saturated aqueous solution (pH 1.0 or 6.7) at $T = 25$ or 50 °C, employing SO$_4$$^{•-}$ (generated by steady-state photolysis as described in eq 1) and/or potassium 12-tungstocobalt(III)ate (from now on simply indicated as Co(III)W) as the oxidant. Co(III)W is a well-known one-electron oxidant able to convert ring-methoxylated aromatic substrates into the corresponding radical cations via outer-sphere electron transfer.[36−38] The Co(III)W-induced oxidations were generally carried out until complete conversion of the oxidant. In the SO$_4$$^{•-}$-induced oxidations, irradiation times were generally chosen in such a way as to avoid complete substrate consumption. After workup, the reaction mixtures were analyzed by GC, GC-MS, and ^{1}H NMR, and the reaction products were generally identified by comparison with authentic samples and quantitatively determined by GC or ^{1}H NMR.

With 2-(4-methoxyphenyl)-2-methylpropanoic acid (**2**), product studies, carried out at both pH 1.0 and 6.7 with Co(III)W as the oxidant, showed the exclusive formation of 2-(4-methoxyphenyl)propan-2-ol (**2a**), as described in Scheme 6.

When SO$_4$$^{•-}$ was used as the oxidant, the reaction of **2**, at both pH 1.0 and 6.7, showed the formation of **2a** as the major product accompanied by 4-methoxyacetophenone. The relative amount of 4-methoxyacetophenone was observed to increase on going from pH 1.0 to pH 6.7. The product distributions

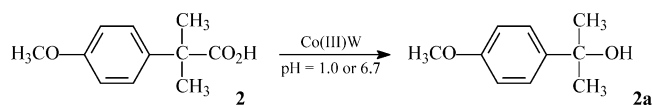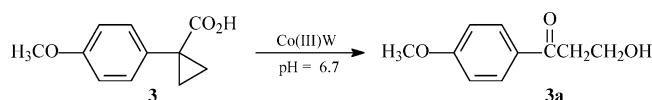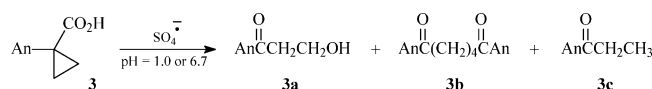(36) Weinstock, I. A. *Chem. Rev.* **1998**, *98*, 113−170.
(37) Baciocchi, E.; Bietti, M.; Mattioli, M. *J. Org. Chem.* **1993**, *58*, 7106−7110.
(38) Eberson, L. *J. Am. Chem. Soc.* **1983**, *105*, 3192−3199.

TABLE 1. Product Distributions Observed in the Co(III)W and SO$_4^{\bullet-}$-Induced Oxidation of 2-(4-Metoxyphenyl)-2-methylpropanoic Acid (2), Carried out in Aqueous Solution[a]

entry	oxidant	pH[b]	recovered substrate (2) (%)	AnC(CH$_3$)$_2$OH[c] (2a) (%)	AnCOCH$_3$[c] (%)
1[d]	Co(III)W	1.0	53	47	
2[d]	Co(III)W	6.7	40	60	
3[e]	SO$_4^{\bullet-}$	1.0		98	2
4[f]	SO$_4^{\bullet-}$	6.7		89	11

[a] Good to excellent mass balances ($\geq$90%) were observed in all experiments. [b] pH 1.0 (HClO$_4$ 0.1 M); pH 6.7 (NaH$_2$PO$_4$ 0.1 M, adjusted with NaOH). [c] An = 4-MeOC$_6$H$_4$. [d] [substrate] = 5 mM, [Co(III)W] = 5 mM, T = 50 °C. [e] [substrate] = 2.5 mM, [K$_2$S$_2$O$_8$] = 0.1 M, T = 25 °C, irradiation time = 30 s. [f] [substrate] = 2.5 mM, [K$_2$S$_2$O$_8$] = 0.1 M, T = 25 °C, irradiation time = 20 s.

SCHEME 6

SCHEME 7

SCHEME 8

observed in the one-electron oxidation reactions carried out for substrate **2** are collected in Table 1.

The Co(III)W-induced oxidation of 1-(4-methoxyphenyl)-cyclopropanecarboxylic acid (**3**) was studied at pH 1.0 and 6.7. At pH 1.0 a very slow reaction was observed (after 48 h at T = 50 °C, >95% of the substrate was recovered from the reaction mixture). At pH 6.7 a significantly faster reaction was observed, showing the exclusive formation of 1-(4-methoxyphenyl)-3-hydroxypropan-1-one (**3a**) as described in Scheme 7.

The SO$_4^{\bullet-}$-induced oxidation of **3** was studied at both pH 1.0 and 6.7. The analysis of the reaction mixture showed the formation of **3a**, 1,6-bis(4-methoxyphenyl)hexane-1,6-dione (**3b**), and 4-methoxypropiophenone (**3c**) as described in Scheme 8 (An = 4-MeOC$_6$H$_4$).

The product distributions observed in the one-electron oxidation reactions carried out for **3** are collected in Table 2.

The Co(III)W-induced oxidation of **3** was also studied in AcOH/H$_2$O 55:45 at T = 50 °C, in the presence of 0.5 M AcOK. Under these conditions, the analysis of the reaction mixture showed the formation of **3a**, 1-(4-methoxyphenyl)cyclopropyl acetate (**3d**), and **3c**. No quantitative analysis was carried out under these conditions.

With 1-(4-methoxyphenyl)cyclopropanol (**6**), product studies, carried out at pH 6.7 with Co(III)W or SO$_4^{\bullet-}$ as the oxidant, showed the formation of **3a**, **3b**, and **3c**, i.e., of the same products observed in the SO$_4^{\bullet-}$-induced oxidation of **3** described above in Scheme 8 and Table 2. The product distributions observed in the one-electron oxidation reactions carried out for **6** are collected in Table 3.

The one-electron oxidations of methyl 2-(4-methoxyphenyl)-2-methylpropanoate (**4**) and methyl 1-(4-methoxyphenyl)cyclo-

TABLE 2. Product Distributions Observed in the Co(III)W and SO$_4^{\bullet-}$-Induced Oxidation of 1-(4-Methoxyphenyl)cyclopropanecarboxylic Acid (3), Carried out in Aqueous Solution[a]

entry	oxidant	pH[b]	recovered substrate (3) (%)	3a (%)	3b (%)	3c (%)
1[c]	Co(III)W	1.0	>95	d		
2[c]	Co(III)W	6.7	55	45		
3[e,f]	SO$_4^{\bullet-}$	1.0	90	3	4	3
4[e,g]	SO$_4^{\bullet-}$	6.7	90	1	6	4
5[e,h]	SO$_4^{\bullet-}$	6.7	70	4	20	6
6[e,i]	SO$_4^{\bullet-}$	6.7	38	7	46	9

[a] Good to excellent mass balances ($\geq$85%) were observed in all experiments. [b] pH 1.0 (HClO$_4$ 0.1 M); pH 6.7 (NaH$_2$PO$_4$ 0.1 M, adjusted with NaOH). [c] [substrate] = 2.5 mM, [Co(III)W] = 2.5 mM, T = 50 °C. [d] An almost complete recovery of the substrate was observed after 48 h and only traces of **3a** were observed. [e] [substrate] = 2.5 mM, [K$_2$S$_2$O$_8$] = 0.1 M, T = 25 °C. [f] Irradiation time = 60 s. [g] Irradiation time = 30 s. [h] Irradiation time = 120 s. [i] Irradiation time = 360 s.

TABLE 3. Product Distributions Observed in the Co(III)W and SO$_4^{\bullet-}$-Induced Oxidation of 1-(4-Methoxyphenyl)cyclopropanol (6), Carried out in Aqueous Solution (pH 6.7) at T = 25 °C[a]

entry	oxidant	recovered substrate (6) (%)	3a (%)	3b (%)	3c (%)
1[b]	Co(III)W	74	11	9	6
2[c]	SO$_4^{\bullet-}$	70	1	22	7

[a] Good to excellent mass balances ($\geq$95%) were observed in all experiments. [b] [substrate] = 2 mM, [Co(III)W] = 2 mM. [c] [substrate] = 1.5 mM, [K$_2$S$_2$O$_8$] = 0.1 M, irradiation time = 40 s.

propanecarboxylate (**5**) were carried out in argon-saturated aqueous solution (pH 6.7) at T = 50 °C, employing Co(III)W as the oxidant. Under these conditions complete recovery of the parent compound was observed for all substrates after reaction times $\geq$24 h. This observation clearly indicates that methyl esters **4** and **5** are essentially unreactive under these experimental conditions. The lack of reactivity of these substrates is also evidenced by the fact that no change in color was observed for the Co(III)W/methyl ester reaction mixtures, whereas when the Co(III)W-induced oxidation reaction of aromatic compounds takes place, it is always accompanied by a color change from yellow to blue (indicative of the conversion of Co(III)W into its reduced form Co(II)W).[37,38]

Time-Resolved Kinetic Studies. As mentioned above, no intermediate radical cation was detected in the time-resolved studies carried out for 2-(4-methoxyphenyl)-2-methylpropanoic acid (**2**) and 1-(4-methoxyphenyl)cyclopropanol (**6**). Even though the mechanistic aspects of the one-electron oxidation of **2** and **6** will be discussed in detail later on, it is important to point out that with **2** the kinetic data obtained by LFP indicate that if a radical cation is actually formed after one-electron oxidation, its decay rate constant must exceed 1×10^7 s^{-1}, whereas with **6** the kinetic data obtained by PR indicate that if a radical cation is actually formed, its decay rate constant must exceed 1×10^6 s^{-1}.[39]

The decay of the radical cation **3**$^{\bullet+}$ and of the corresponding radical zwitterion $^-$**3**$^{\bullet+}$ was measured spectrophotometrically in aqueous solution (T = 25 °C, pH 1.7 and $\sim$7, respectively) following the decrease in optical density at the corresponding

(39) It is important to point out that the time-resolution of the LFP equipment used in this study (8 ns laser pulse) is significantly higher than that of the PR equipment (300 ns electron pulse).

TABLE 4. First-Order Rate Constants (k) for the Decay of Radical Cations and Radical Zwitterions Generated after PR and/or LFP of the Parent Substrates 3–5 in Aqueous Solution, Measured at $T = 25$ °C

substrate	pH[a]	transient	generation	λ_{det}[b]/nm	k/s^{-1}
3	1.7	**3**•+	PR, SO$_4$•−, Ar	500	4.7×10^3
	1.7	**3**•+	PR, SO$_4$•−, O$_2$	500	4.4×10^3
	1.7	**3**•+	LFP, SO$_4$•−, N$_2$	500	4.5×10^3
	7.0	−**3**•+	PR, SO$_4$•−, Ar	520	2.2×10^4
	7.0	−**3**•+	LFP, SO$_4$•−, N$_2$	520	2.4×10^4
4	7.0	**4**•+	PR, SO$_4$•−, Ar	450	$<10^{3\,c}$
5	7.2	**5**•+	PR, SO$_4$•−, Ar	500	$<10^{3\,c}$

[a] pH 1.7 (adjusted with HClO$_4$); pH ~7 (NaH$_2$PO$_4$ 2 mM, adjusted with NaOH). [b] Monitoring wavelength. [c] The decay of the radical cation was observed to be influenced by the radiation chemical dose, and only an upper limit for the decay rate constant could be determined.

FIGURE 4. Plot of k_{obs} against concentration of NaOH for the reaction of radical zwitterion −**3**•+ with −OH. From the linear regression analysis: intercept = 1.6×10^4 s^{-1}, slope = 6.9×10^6 M^{-1} s^{-1}, r^2 = 0.9968.

visible absorption band maximum (500 and 520 nm, respectively). In both cases the decay was observed to follow first-order kinetics, and the rate constants thus obtained are collected in Table 4.

The decay of the radical cations **4**•+ and **5**•+ was measured spectrophotometrically in aqueous solution ($T = 25$ °C, pH ~7) following the decrease in optical density at the corresponding visible absorption band maximum (450 and 500 nm, respectively). With these radical cations the decay was observed to be influenced by the radiation chemical dose and accordingly, only an upper limit for their decay rate constant could be determined. The upper limits to the rate constants thus obtained are also collected in Table 4.
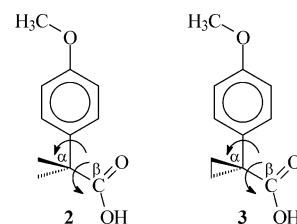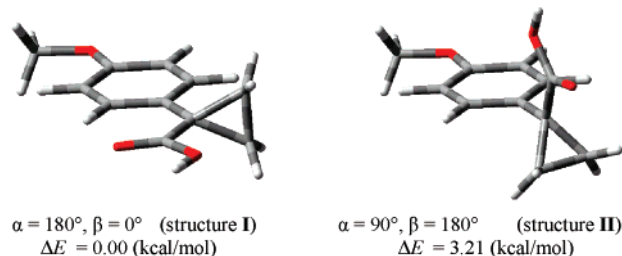
By monitoring the decay of the radical zwitterion −**3**•+, and of the radical cation **5**•+ at the visible absorption band maximum (520 and 500 nm, respectively) a significant increase in rate was observed when −OH was added to the solution, and by plotting the observed rates (k_{obs}) vs concentration of added base, a linear dependence was observed (Figure 4 and Figure S3, showing the k_{obs} vs [−OH] plots for the reactions of −**3**•+ and **5**•+, respectively). From the slopes of these plots, the second-order rate constants for reaction of −OH with −**3**•+ and **5**•+ (k-OH) were determined. The rate constants thus obtained are collected in Table 5.

DFT Calculations. Hybrid density functional (DFT) calculations with unrestricted MO formalism [UB3LYP/6-31G(d)] were

TABLE 5. Second-Order Rate Constants for the −OH-Catalyzed (k-OH) Decay of Radical Zwitterion −3•+ and Radical Cation 5•+ Generated by PR of the Parent Substrates in Aqueous Solution, Measured at $T = 25$ °C

transient[a]	pH range[b]	k_{OH}[c] (M^{-1} s^{-1})
−**3**•+	10.2–12.3	7.1×10^6
5•+	10.0–11.3[d]	5.4×10^7

[a] −**3**•+ and **5**•+ were generated by PR (dose ≤5 Gy/pulse) of argon saturated aqueous solutions containing the substrate (0.4–1.0 mM), K$_2$S$_2$O$_8$ (10 mM), 2-methyl-2-propanol (0.1 M), and Na$_2$B$_4$O$_7$ (1 mM). [b] pH range employed for the determination of k_{OH}. [c] Obtained from the slopes of the k_{obs} vs [NaOH] plots, where k_{obs} was obtained following the decay of absorption at the radical cation or radical zwitterion visible absorption band maximum (500 and 520 nm, respectively). Average of three independent determinations. Error ≤10%. [d] The pH was limited to 11.3 because at pH >11.5 ester hydrolysis was observed

SCHEME 9

CHART 2

$\alpha = 180°$, $\beta = 0°$ (structure **I**) $\alpha = 90°$, $\beta = 180°$ (structure **II**)
$\Delta E = 0.00$ (kcal/mol) $\Delta E = 3.21$ (kcal/mol)

carried out for **2**•+ and **3**•+. The potential energy surface scans for the internal rotations about the C$_{Ar}$−C (α) and C−CO$_2$H (β) bonds (depicted for the sake of clarity in Scheme 9 for **2** and **3**, showing the situation where $\alpha = 0°$ and $\beta = 0°$) calculated for **2**•+ and **3**•+ are shown in the SI, Figures S4 and S5, respectively.

With the neutral substrates **2** and **3**, the most stable conformations were those characterized by dihedral angle values of $\alpha = 60°$, $\beta = 90°$ and $\alpha = 89°$, $\beta = 180°$, respectively (see SI).
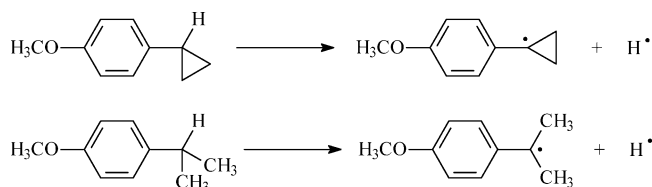
The potential energy surface calculated for **3**•+ (SI, Figure S5) is strongly influenced by the relative orientation of the cyclopropyl and carboxylic groups. Accordingly, the most stable conformation for **3**•+ is the one where the plane of the aromatic ring bisects the plane of the cyclopropane ring ($\alpha = 180°$, $\beta = 0°$: *bisected* conformation) (Chart 2, structure **I**).

This result is in line with the well-known conformation-dependent donor properties of the cyclopropyl group.[40,41] In this conformation, $\sigma-\pi$ overlap between the cyclopropane σ bonds and the aromatic π-system is maximal and electron donation can efficiently occur. Quite interestingly, in this conformation

(40) Dinnocenzo, J. P.; Merchán, M.; Roos, B. O.; Shaik, S.; Zuilhof, H. *J. Phys. Chem. A* **1998**, *102*, 8979−8987.
(41) Tanko, J. M.; Li, X.; Chahma, M.; Jackson, W. F.; Spencer, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 4181−4192. Drumright, R. E.; Mas, R. H.; Merola, J. S.; Tanko, J. M. *J. Org. Chem.* **1990**, *55*, 4098−4102.

SCHEME 10

the carboxylic group is coplanar with the aromatic ring, resulting in efficient orbital overlap between the carbonyl π-system and the cyclopropane σ bonds. In the alternative *perpendicular* conformation (Chart 2, structure **II**), the cyclopropyl group is orthogonal to the π-system and no such overlap can be achieved.

As compared to the potential energy surface calculated for **3**$^{•+}$, the potential energy surface calculated for **2**$^{•+}$ (SI, Figure S4) appears to be relatively flat, and significantly smaller energy differences between the alternative conformations were calculated (see SI, Scheme S1) indicating that in this case the relative arrangement of the aromatic ring and the C(CH$_3$)$_2$ moiety plays a minor role.

To obtain information on the relative stabilities of the 1-(4-methoxyphenyl)cyclopropyl and 4-methoxycumyl radicals, DFT calculations at the UB3LYP/6-31G(d) level of theory were also carried out to determine the gas-phase bond dissociation enthalpies (BDEs) of the benzylic C−H bond in 4-methoxycyclopropylbenzene and 4-methoxycumene (Scheme 10).

BDEs calculated at this level of theory are sufficiently reliable for the discussion presented herein because it has been pointed out both that the B3LYP functional offers an attractive and seemingly accurate alternative to the expensive conventional ab initio methods for the computation of BDEs,[42] and that, thanks to the cancellation of errors, differences in BDEs (ΔBDEs) within a closely related family of compounds are much more reliable than the absolute values.[43] BDE values were thus obtained from the enthalpy differences between the radicals produced by homolitic C−H bond cleavage and the parent substrate (BDE(R-H) = E(R$^•$) + E(H$^•$) − E(R-H), where R-H = 4-methoxycyclopropylbenzene or 4-methoxycumene). BDE values of 99.0 and 90.1 kcal mol^{-1} were calculated for the benzylic C−H bond of 4-methoxycyclopropylbenzene and 4-methoxycumene, respectively.

Discussion

Product studies carried out on 2-(4-methoxyphenyl)-2-methylpropanoic acid (**2**) showed the formation of 2-(4-methoxyphenyl)propan-2-ol (**2a**) as the exclusive or predominant reaction product as described in Scheme 6 and Table 1. This product clearly derives from the oxidation of an intermediate 4-methoxycumyl radical formed after oxidative decarboxylation of **2**, as described previously for the one-electron oxidation of 4-methoxyphenylethanoic acid (**1**) in acidic aqueous solution.[12,14a] Along this line, the formation of 4-methoxyacetophenone in the SO$_4$$^{•-}$-induced oxidation of **2**, and the observation that the relative amount of 4-methoxyacetophenone was observed to increase on going from pH 1.0 to pH 6.7, can be explained in terms of the further oxidation of the first formed alcohol **2a**,

via an intermediate radical cation **2a**$^{•+}$, a process that is known to be favored by the presence of a base.[44]

LFP experiments carried out at pH 1.7 did not provide any direct evidence for the formation of an intermediate radical cation **2**$^{•+}$, showing instead the initial formation of SO$_4$$^{•-}$ whose decay (occurring with an observed rate constant $k_↓$(450 nm) = 1.0×10^7 s^{-1}) is accompanied by a corresponding buildup in absorption in the UV region of the spectrum ($k_↑$(290 nm) = 1.1×10^7 s^{-1}) of a transient species (Figure 1). The decay of this species is accelerated by oxygen occurring with a second-order rate constant $k = 1.7 \times 10^9$ M^{-1} s^{-1}, a value that is similar to those measured previously for the reactions of carbon-centered radicals with oxygen.[45−47] On the basis of these observations and of the results of product studies described above this transient can be assigned to the 4-methoxycumyl radical.

Overall, these results are consistent with those obtained previously for the one-electron oxidation of 4-metoxyphenylethanoic acid (**1**), where no direct evidence for the formation of an intermediate radical cation **1**$^{•+}$ but only of the 4-methoxybenzyl radical was obtained.[12,14a] The mechanism of the one-electron oxidation of **2** can be thus suggested to occur according to Scheme 11, where electron removal from **2** is coupled with the decarboxylation reaction, directly leading to the 4-methoxycumyl radical. Oxidation of this radical in the reaction medium gives **2a**.

However, even though no intermediate radical cation **2**$^{•+}$ was detected in the LFP experiments, the kinetic data do not allow the possible intermediacy of **2**$^{•+}$ to be excluded, because its lifetime could be too short to allow detection under the experimental conditions employed: in other words, the decay of **2**$^{•+}$ (if actually formed) is fast compared with its rate of formation by reaction of **2** with SO$_4$$^{•-}$, and only a lower limit for its decarboxylation rate constant ($k > 1 \times 10^7$ s^{-1}) can be given.[48]

At least partial support to this hypothesis comes from the observation that the second-order rate constant for reaction of SO$_4$$^{•-}$ with **2**, derived from the rate constant measured for the decay of SO$_4$$^{•-}$ ($k_↓$(450 nm) = 1.0×10^7 s^{-1}) and the concentration of **2** (2.0×10^{-3} M) as $k = 5.0 \times 10^9$ M^{-1} s^{-1}, is very similar to the rate constants measured previously for reaction of SO$_4$$^{•-}$ with monomethoxylated benzene derivatives,[24−26] thus indicating that electron removal is very likely to occur from the aromatic nucleus. The possibility that electron removal occurs instead from the carboxylic (or carboxylate) function, directly leading to an acyloxy radical, can be discarded on the basis of the second-order rate constants determined for the reaction of SO$_4$$^{•-}$ with ethanoic acid at pH ∼0 and 6.8: $k = 8.8 \times 10^4$ and 5.0×10^6 M^{-1} s^{-1}, respectively.[49,50]

With methyl 2-(4-methoxyphenyl)-2-methyl propanoate (**4**), direct evidence for the formation of an intermediate radical cation **4**$^{•+}$ after one-electron oxidation was obtained by LFP

(42) Bally, T.; Borden, W. T. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; Wiley-VCH: New York, 1999; Vol. 13, pp 1−97.

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(44) Baciocchi, E.; Bietti, M.; Lanzalunga, O.; Steenken, S. *J. Am. Chem. Soc.* **1998**, *120*, 11516−11517.

(45) Font-Sanchis, E.; Aliaga, C.; Cornejo, R.; Scaiano, J. C. *Org. Lett.* **2003**, *5*, 1515−1518.

(46) Scaiano, J. C.; Tanner, M.; Weir, D. *J. Am. Chem. Soc.* **1985**, *107*, 4396−4403.

(47) Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095−5099.

(48) An analogous situation has been described previously for the SO$_4$$^{•-}$-induced oxidation of 4-methylphenyl- and 4-methoxyphenylethanoic acids in aqueous solution (see ref 14a).

(49) Neta, P.; Huie, R. E.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1988**, *17*, 1027−1284.

SCHEME 11

SCHEME 12

and PR, as clearly shown by the time-resolved spectrum shown in Figure 2. $4^{\bullet+}$ displayed a very low reactivity, evidenced by the lack o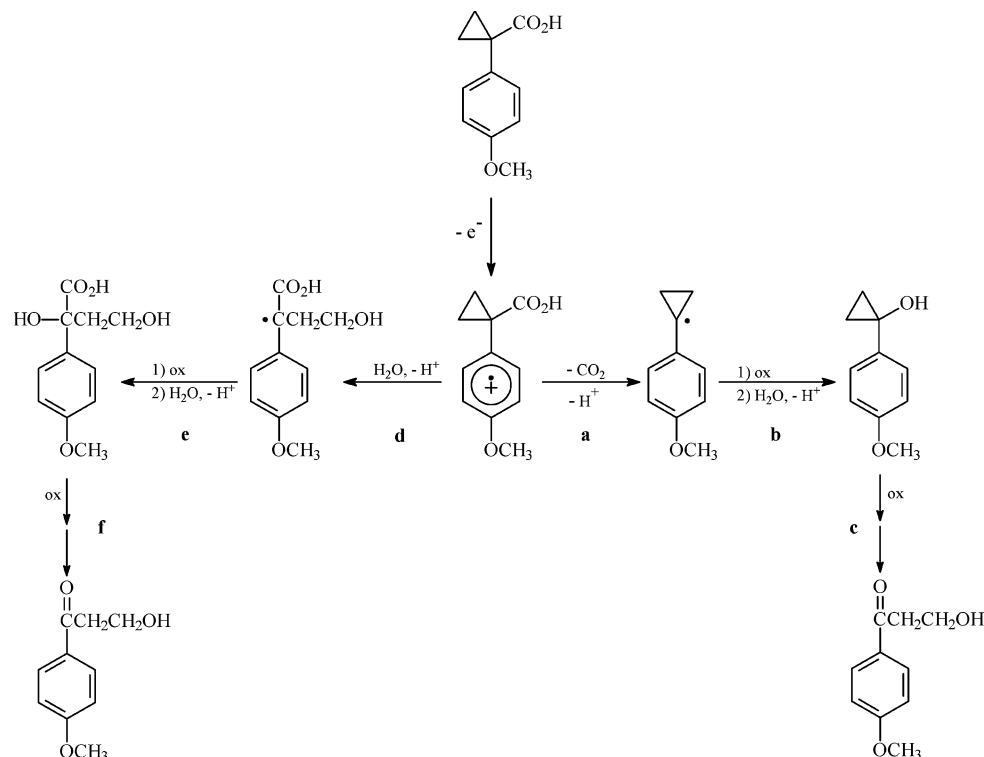f reaction observed when **4** was reacted with Co(III)W, and by the upper limit determined for its decay rate constant ($k < 10^3$ s^{-1}). With this substrate, the presence of the CO$_2$Me group prevents the decarboxylation reaction of the corresponding radical cation, thus determining a dramatic depression in its reactivity as compared to **2**. Moreover, the presence of the two methyl groups in the α position precludes the possibility of benzylic C−H deprotonation as an alternative decay pathway of $4^{\bullet+}$.

With 1-(4-methoxyphenyl)cyclopropanecarboxylic acid (**3**), direct evidence for the formation of an intermediate radical cation $3^{\bullet+}$ or radical zwitterion $^-3^{\bullet+}$ after one-electron oxidation was obtained by both LFP and PR, as clearly shown by the time-resolved spectra displayed in Figures 3 and S1. The Co-(III)W-induced oxidation of **3** showed, at pH 6.7, the formation of 1-(4-methoxyphenyl)-3-hydroxypropan-1-one (**3a**) as the exclusive reaction product (see Scheme 7 and Table 2). The

same product, accompanied by 1,6-bis(4-methoxyphenyl)hexane-1,6-dione (**3b**) and 4-methoxypropiophenone (**3c**), was also observed after SO$_4^{\bullet-}$-induced oxidation of **3** at pH 1.0 and 6.7 (see Scheme 8 and Table 2).

Two possible mechanistic pathways can in principle be proposed in order to explain the formation of **3a** from $3^{\bullet+}$ (Scheme 12). In the mechanism described in paths a−c, the initially formed radical cation $3^{\bullet+}$ undergoes decarboxylation to give the 1-(4-methoxyphenyl)cyclopropyl radical (path a). Oxidation of this radical followed by reaction with the solvent water gives 1-(4-methoxyphenyl)cyclopropanol (**6**) (path b) whose subsequent oxidation finally leads to **3a** (path c).

As it is well-known that arylcyclopropane radical cations can undergo a facile ring-opening reaction by nucleophilic attack at the C$_\beta$ carbon of the cyclopropane ring,[33,51−53] a possible mechanistic alternative is that described in paths d−f of Scheme 12. $3^{\bullet+}$ undergoes a water-induced ring-opening reaction to give a stabilized benzylic radical (path d). Oxidation of this radical followed by reaction with water gives 2,4-dihydroxy-2-(4-

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(50) It is important to point out that whereas the results of an indirect kinetic study on the Co(III)W-induced oxidation of **1** were interpreted in terms of a rate-determining electron transfer from **1** to the relatively weak oxidant Co(III)W, leading to the conclusion that no aromatic radical cation $1^{\bullet+}$ was formed as a reaction intermediate (see reference 12), the mechanistic picture may be different with the significantly stronger oxidant SO$_4^{\bullet-}$.

(51) Wang, Y.; Tanko, J. M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2705−2711.
(52) Wang, Y.; Tanko, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 8201−8208.
(53) Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. Soc.* **1997**, *119*, 987−993.

methoxyphenyl)butanoic acid (path e) whose subsequent oxidative decarboxylation finally leads to **3a** (path f).

However, the latter pathway can be discarded on the basis of the observation that methyl 1-(4-methoxyphenyl)cyclopropanecarboxylate (**5**), whose radical cation **5**$^{•+}$ would be expected to display a reactivity toward ring-opening comparable to that of **3**$^{•+}$, showed instead a significantly lower reactivity (see Table 4), thus indicating that water is not sufficiently reactive to promote the nucleophilic ring-opening of the cyclopropane ring in the radical cation.

Also the observation that the decay rate constant increases on going from **3**$^{•+}$ to $^-$**3**$^{•+}$ is in line with a decarboxylation reaction (path a), as described previously for the one-electron oxidation of arylethanoic acids, where the decarboxylation rate constants were observed to increase by at least 1 order of magnitude on going from the radical cations to the corresponding radical zwitterions.[11] Last but not least, the formation of products **3b** and **3c** cannot be explained in terms of the mechanism described by paths d–f.
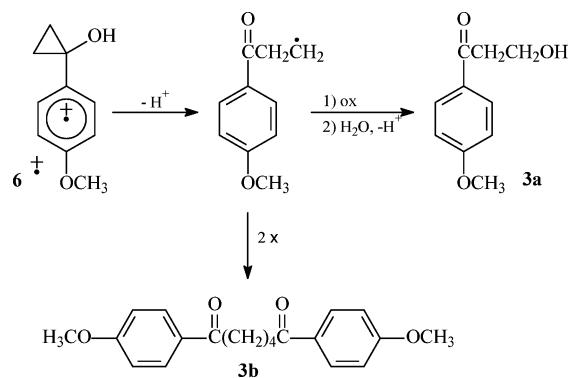
On the other hand, in the one-electron oxidation of **3**, 1-(4-methoxyphenyl)cyclopropanol (**6**) was never detected among the reaction products. This observation is, however, not surprising because **6** was observed to be significantly more reactive than **3**, and in particular, given that the decarboxylation rate constants for **3**$^{•+}$ and $^-$**3**$^{•+}$ were measured as 4.6×10^3 and 2.3×10^4 s^{-1}, respectively (from the average of the PR and LFP data, see Table 4), the kinetic data obtained by PR indicate that if **6**$^{•+}$ is actually formed, its decay rate constant must be $> 1 \times 10^6$ s^{-1}. Indirect evidence in favor of the intermediacy of **6** comes from the observation that the same products (**3a**, **3b**, and **3c**) were formed after one-electron oxidation of **3** and **6**, and, more importantly, from the observation that 1-(4-methoxyphenyl)cyclopropyl acetate (**3d**) was detected among the reaction products when the Co(III)W-induced oxidation of **3** was carried out in AcOH/H$_2$O 55:45, in the presence of AcOK. The formation of **3d** under these conditions can be explained according to Scheme 12, path b, where oxidation of the 1-(4-methoxyphenyl)cyclopropyl radical leads to an intermediate 1-(4-methoxyphenyl)cyclopropyl cation that can react with water to give **6** and with acetate to give **3d**. The observation that **3d** but not **6** was observed among the reaction products is in full agreement with the previous indication that the conversion of 4-methoxybenzyl alcohol into its acetate determines a significant decrease in side-chain fragmentation reactivity of the corresponding radical cations.[37] Taken together, this evidence provides strong support to the hypothesis that the one-electron oxidation of **3** proceeds through the mechanism described by paths a–c in Scheme 12, via decarboxylation of a first formed radical cation **3**$^{•+}$.

Quite interestingly, the data discussed above also provide indirect evidence on the involvement of an intermediate 1-(4-methoxyphenyl)cyclopropyl cation in this process.[54]

The formation of 1,6-bis(4-methoxyphenyl)hexane-1,6-dione (**3b**) can be explained according to Scheme 13, where **6**$^{•+}$ undergoes ring-opening to give a radical that can either dimerize to give **3b** or become oxidized in the reaction medium finally leading to **3a**.

SCHEME 13

Concerning 4-methoxypropiophenone (**3c**), it is well-known that this product can derive from the acid-catalyzed or thermal rearrangement of **6**.[59] Blank experiments showed the stability toward rearrangement of **6** at pH ≥ 3. Accordingly, the observation that in aqueous solution (pH 6.7) the Co(III)W-induced oxidation of **3** led to the exclusive formation of **3a** (Scheme 6), whereas **3c** was also observed among the reaction products when the reaction was carried out in AcOH/H$_2$O 55:45, indicates that in the latter experimental conditions the acid-catalyzed rearrangement of **6** is operating.

On the other hand, the formation of **3c** following SO$_4$$^{•-}$-induced oxidation of **3** at pH 6.7 (see Table 2) requires a different explanation and additional experiments in this respect will be necessary.

Comparison between the one-electron oxidation reactions of **2** and **3** shows that the replacement of the C(CH$_3$)$_2$ moiety with a cyclopropyl group determines a decrease in decarboxylation rate constant in the corresponding radical cations of more than 3 orders of magnitude![60] This large difference in reactivity can be qualitatively explained in terms of three main contributions: substrate oxidation potential, stability of the carbon-centered radical formed after decarboxylation, and stereoelectronic effects.

It is well-known that the decarboxylation rate constants of arylalkanoic acid radical cations are influenced by the substrate oxidation potential.[9,11] In particular, with ring dimethoxylated phenylethanoic acid radical cations, the decarboxylation rate constant was observed to decrease by increasing radical cation stability.[11] Clearly, an increase in radical cation stability determines an increase in the height of the kinetic barrier for side-chain to ring intramolecular electron transfer associated to decarboxylation (Scheme 2) resulting in a corresponding decrease in decarboxylation rate constant.

Comparison between the oxidation potentials of cyclopropylbenzene and cumene clearly shows that the former compound

(54) The involvement of a highly reactive 1-(4-methoxyphenyl)cyclopropyl cation has been also proposed in the alcoholisys of 1-(4-methoxyphenyl)cyclopropyl halides.[55] In this respect, it is important to point out that clear evidence in favor of the formation of a cyclopropyl cation has been obtained when this species is condensed in a rigid ring system,[56,57] or when the cationic center is bound to a strongly stabilizing ferrocenyl group.[58]

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(60) On the basis of the assumption that if **2**$^{•+}$ is actually formed after one electron oxidation, it undergoes decarboxylation with $k > 1 \times 10^7$ s^{-1}.

is more easily oxidizable than the latter one,[61] a behavior that can be ascribed to the well-known electron-donating properties of the cyclopropyl group.[40,41] Accordingly, it is reasonable to propose that $3^{\bullet+}$ will be thermodynamically more stable than $2^{\bullet+}$, on the basis of the lower oxidation potential that can be expected for 3 as compared to 2.[66] Evidence in favor of the electron-donating ability of the cyclopropyl group is also provided by the analysis of the time-resolved spectra obtained for $3^{\bullet+}$, shown in Figures 3 and S1, that resemble the spectra observed for arylcyclopropane radical cations,[32,33,40] rather that those observed for anisole derivatives.[24,26,29–31]

Another important factor is represented by the stability of the carbon-centered radical formed after decarboxylation. In this context, Gould and Farid have clearly shown that in the decarboxylation of radical cations of anilino biscarboxylates characterized by comparable stabilities, the decarboxylation rate constants were influenced by the stability of the product radical, increasing with increasing radical stability.[3] Accordingly, as a consequence of the Hammond postulate,[67] an increase in stability of the product radical determines an increase in the reaction exothermicity and a corresponding decrease in activation energy. Along this line, the difference between the BDEs calculated for 4-methoxycyclopropylbenzene and 4-methoxycumene (99.0 and 90.1 kcal mol^{-1}, respectively, ΔBDE = 8.9 kcal mol^{-1}) allows the assessment of the relative stabilities of the 1-(4-methoxyphenyl)cyclopropyl and 4-methoxycumyl radicals,[43] indicating that the 4-metoxycumyl radical appears to be significantly more stable that the 1-(4-methoxyphenyl)cyclopropyl radical,[68] in line with the relatively low stability reported for cyclopropyl radicals.[69–71]

A final point of interest is represented by the possible role of stereoelectronic effects in these processes. It is well-known that the side-chain fragmentation reactivity of alkylaromatic

radical cations can be influenced by the relative orientation between the scissile bond and the π system (stereoelectronic effect),[72–75] with the most suitable orientation for cleavage being the one where the dihedral angle between the plane of the aromatic ring and the plane defined by the scissile bond and the atom of the aromatic ring to which this bond is connected is 90°. In this conformation the scissile bond is aligned with the π system bearing the unpaired electron, and the best orbital overlap for bond cleavage can be achieved. Along this line, in the most stable conformation calculated for $3^{\bullet+}$ (Chart 2, structure **I**, $\alpha = 180°$, $\beta = 0°$), the carboxylic group is coplanar with the plane of the aromatic ring, and no efficient overlap between the scissile C–CO$_2$H bond and the π system can be achieved. To reach the most stable conformation where the scissile bond is perpendicular to the plane of the aromatic ring (most suitable orientation for bond cleavage: structure **II**, $\alpha = 90°$, $\beta = 180°$) an energy barrier of at least 4.6 kcal mol^{-1} has to be overtaken (see SI, Figure S5 and Scheme S2).

On the other hand, in the most stable conformation calculated for $2^{\bullet+}$ (see SI, Scheme S1: structure **V**, $\alpha = 130°$, $\beta = 356°$), the scissile C–CO$_2$H bond is very close to the most suitable orientation for cleavage (SI, Scheme S1: structure **VI**, $\alpha = 90°$, $\beta = 210°$). In this case, moving on a relatively flat potential energy surface, in order to reach the most suitable orientation for C–CO$_2$H bond cleavage an energy barrier $\leq$1.8 kcal mol^{-1} has to be overtaken (see SI, Figure S4). Thus, even though the observed differences in energy are relatively small, stereoelectronic requirements for decarboxylation appear to disfavor C–CO$_2$H bond cleavage in $3^{\bullet+}$ as compared to $2^{\bullet+}$.

In summary, when comparing the one-electron oxidation reactions of 2 and 3, the discussion presented above clearly indicates that the stability of the radical cation, the stability of the carbon radical formed after decarboxylation, and stereoelectronic requirements for fragmentation all exert their effect in the same direction, that is by decreasing the decarboxylation rate constant of $3^{\bullet+}$ as compared to that of $2^{\bullet+}$.

Table 5 displays the second-order rate constants for reaction of radical zwitterion $^{-}3^{\bullet+}$ and of the corresponding methyl ester radical cation $5^{\bullet+}$ with $^{-}$OH: $k_{OH} = 7.1 \times 10^6$ and 5.4×10^7 M^{-1} s^{-1}, respectively. At pH $\sim$7 $^{-}3^{\bullet+}$ was observed to undergo decarboxylation with $k = 2.3 \times 10^4$ s^{-1} (Table 4), whereas $5^{\bullet+}$ displayed a significantly lower reactivity and only an upper limit for its decay rate constant could be obtained ($k < 10^3$ s^{-1}). In $5^{\bullet+}$ the presence of the CO$_2$Me group prevents the decarboxylation reaction and, moreover, the presence of the cyclopropyl group in the α position precludes the possibility of benzylic C–H deprotonation as an alternative decay pathway. As mentioned above, nucleophilic ring-opening of the cyclopropane ring was not observed at pH $\sim$7, indicating that water is not sufficiently reactive to promote this reaction. In basic solution, however, a different situation was observed with k_{OH} increasing on going from $^{-}3^{\bullet+}$ to $5^{\bullet+}$. In order to explain this behavior it is reasonable to propose that under these conditions $^{-}3^{\bullet+}$ and

(61) Cyclopropyl benzene: $E° = 1.91$ V ($E_p = 1.97$ V: sweep rate 150 mV/s).[32] Cumene: $E° = 2.17$ V[62,63] ($E_p = 2.27$ V,[64] 2.32 V[62]: sweep rates 100 mV/s). All values are in V vs SCE in acetonitrile.

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(63) In ref 62, the value of the standard oxidation potential for cumene is given in trifluoroacetic acid (TFA) as 2.29 V vs SCE. The value of 2.17 V vs SCE in acetonitrile derives from the application of the corrective factor previously determined for the oxidation potentials of alkylbenzenes ($E°_{MeCN} = E°_{TFA} - 0.12$ V).[65]

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(66) Also the adiabatic ionization potentials that can be obtained on the basis of the computed energy differences between the most stable structures of $2^{\bullet+}$ and 2 and of $3^{\bullet+}$ and 3 (7.48 and 7.33 eV, respectively, see the Supporting Information) point in this direction.

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(68) It is, however, important to point out that this approach is based on the assumption that 4-methoxycyclopropylbenzene and 4-methoxycumene are characterized by the same energies. In order to validate this assumption, we have calculated, at the UB3LYP/6-31G(d) level of theory, the energy difference between products and reagents for the isodesmic reaction shown below (An = 4-MeOC$_6$H$_4$). The energy difference thus obtained ($\Delta E = -3.1$ kcal mol^{-1}) is significantly smaller than the ΔBDE of $\approx$9 kcal mol^{-1} reported above, and confirms that the 4-metoxycumyl radical is more stable than the 1-(4-methoxyphenyl)cyclopropyl radical.
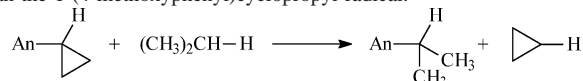
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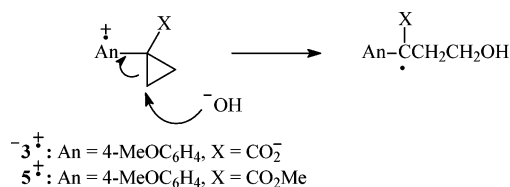(71) Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625–1651.

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SCHEME 14

$^-\mathbf{3}^{\ddagger\cdot}$: An = 4-MeOC$_6H_4$, X = CO$_2^-$
$\mathbf{5}^{\ddagger\cdot}$: An = 4-MeOC$_6H_4$, X = CO$_2$Me

$\mathbf{5}^{\bullet+}$ both undergo a $^-$OH-induced ring-opening of the cyclopropane ring, as described in Scheme 14.

Quite interestingly, the intercept of the k_{obs} against [NaOH] plot for the reaction of $^-\mathbf{3}^{\bullet+}$ (1.6×10^4 s^{-1}, see Figure 4), which represent the rate constants for the *uncatalyzed* reaction of $^-\mathbf{3}^{\bullet+}$, is very close to the decarboxylation rate constant measured for this radical zwitterion at pH 7.0 ($k = 2.3 \times 10^4$ s^{-1}, see Table 4). On the basis of this observation it is reasonable to propose that at pH ≥ 10 $^-\mathbf{3}^{\bullet+}$ undergoes competition between decarboxylation and $^-$OH-induced ring-opening of the cyclopropane ring, with the latter process that becomes the major fragmentation pathway around pH 12. In this context, it has been shown that arylcyclopropane radical cations are characterized by a certain extent of positive charge at the C$_\beta$ carbon of the cyclopropane ring, and that nucleophilic attack generally occurs at this position.[33,40] Along this line, the k_{-OH} values reported above can be rationalized in terms of the effect of the aromatic ring and of the cyclopropane ring substituent (CO$_2^-$ or CO$_2$-Me) on the stabilization of an incipient positive charge at C$_\beta$, and consequently on the rate constant for the $^-$OH-induced reaction. CO$_2$Me is a relatively strong electron-withdrawing group that is expected to increase the extent of positive charge at C$_\beta$ whereas the CO$_2^-$ group is expected to exert a negligible effect in this respect, in full agreement with the increase in k_{-OH} observed on going from radical zwitterion $^-\mathbf{3}^{\bullet+}$ to the corresponding methyl ester radical cation $\mathbf{5}^{\bullet+}$.

In conclusion, by means of product and time-resolved kinetic studies additional information on the role of structural effects on the one-electron oxidation of ring-methoxylated arylethanoic acids has been obtained. Decarboxylation was observed as the exclusive fragmentation pathway after one-electron oxidation of both 2-(4-methoxyphenyl)-2-methylpropanoic acid and 1-(4-methoxyphenyl)cyclopropanecarboxylic acid; however, direct evidence for the involvement of an intermediate radical cation was obtained only for the latter substrate. Replacement of the C(CH$_3$)$_2$ moiety with a cyclopropyl group determines a decrease in decarboxylation rate constant of more than 3 orders of magnitude, a behavior that has been rationalized in terms of differences in substrate oxidation potential, stability of the carbon-centered radical formed after decarboxylation, and stereoelectronic requirements for fragmentation. Very interestingly, with the 1-(4-methoxyphenyl)cyclopropanecarboxylic acid radical cation, competition between decarboxylation and $^-$OH-induced cyclopropane ring-opening is observed above pH 10.

Experimental Section

Product Studies. (a) Oxidations with Co(III)W. A 5 mL sample of an argon-saturated aqueous solution (pH 1.0 or 6.7) containing equimolar amounts of the substrate and Co(III)W (between 2 and 5 mM) was stirred at $T = 25$ or 50 °C until complete conversion of the oxidant. In the experiment carried out for **3** in AcOH/H$_2$O 55:45 at $T = 50$ °C in the presence of 0.5 M AcOK, a 10 mM concentration of both the substrate and Co(III)W was employed.

(b) Oxidations with SO$_4^{\bullet-}$. Irradiations were performed employing a photochemical reactor equipped with 8×15 W lamps with emission at 254 nm. The reactor was a cylindrical flask equipped with a water cooling jacket thermostated at $T = 25$ °C. Irradiation times were generally chosen in such a way as to avoid complete substrate consumption. In a typical experiment 20 mL of an argon-saturated aqueous solution (pH 1.0 or 6.7) containing the substrate (1.5–2.5 mM) and K$_2$S$_2$O$_8$ (0.1 M) were irradiated for times varying between 20 and 360 s. Blank experiments performed in the absence of irradiation showed the formation of negligible amounts of reaction products.

With both oxidizing systems, the reaction mixture was acidified with 2 N HCl (only for the experiments at pH 6.7), extracted with ethyl ether, and dried over anhydrous Na$_2$SO$_4$. The reaction products were identified by GC, GC-MS, and ^{1}H NMR, by comparison with authentic samples. The quantitative analysis was carried out by GC or ^{1}H NMR. In the GC experiments 3,4-(methylendioxy)benzyl alcohol or 3,4-dimethoxybenzyl alcohol was used as internal standard. In the ^{1}H NMR experiments diphenylmethanol was used as internal standard. Good to excellent mass balances ($\geq 85\%$) were obtained in all experiments.

Time-Resolved Studies. (a) Pulse Radiolysis. The pulse radiolysis experiments were performed with a 10 MeV electron linear accelerator that supplied 300 ns pulses with doses such that 1–3 μM radicals were produced. Experiments were performed at room temperature with argon-saturated aqueous solutions containing the substrate (0.2–2.0 mM), peroxydisulfate (10 mM), and 2-methyl-2-propanol (0.1 M). For the experiments carried out at pH 1.7, the pH of the solutions was adjusted with HClO$_4$. For the experiments carried out at pH $\sim$7, 2 mM Na$_2$HPO$_4$ was added and the pH was adjusted with NaOH. A flow system was employed in all the experiments. Rate constants were obtained following the decrese in absorbance at the radical cation visible absorption maxima, by averaging at least 8 values, and were reproducible to within 10%.

The second-order rate constants for reaction of $^-\mathbf{3}^{\bullet+}$ and $\mathbf{5}^{\bullet+}$ with $^-$OH (k_{-OH}) were obtained from the slopes of the plots of the observed rates (k_{obs}) vs concentration of NaOH. For these experiments argon-saturated solutions containing 0.4–1.0 mM substrate, 10 mM potassium peroxydisulfate, 0.1 M 2-methyl-2-propanol, and 1 mM sodium tetraborate were employed. k_{-OH} values were obtained from the average of three independent determinations and were reproducible to within 10%.

(b) Laser Flash Photolysis. Experiments were carried out by direct laser flash photolysis (LFP) of argon-saturated aqueous solutions, containing the substrate (0.2–2.0 mM) and K$_2$S$_2$O$_8$ (0.1 M), using the fourth harmonic (266 nm) of a Q-switched Nd:YAG laser providing 8 ns pulses. The laser energy was adjusted to ≤ 10 mJ/pulse (output power of the laser) by the use of the appropriate filter. The concentration of K$_2$S$_2$O$_8$ was such that this species absorbed most of the 266 nm radiation. Experiments were carried out at $T = 25 \pm 0.5$ °C under magnetic stirring employing a 3 mL Suprasil quartz cell (10 mm $\times$ 10 mm). The stability of the solutions to the experimental conditions was checked spectrophotometrically comparing the spectrum of the solution before irradiation with that obtained after irradiation. Rate constants were obtained by averaging at least 8 values and were reproducible to within 10%.

Computational Details

Hybrid DFT calculations have been carried out at the UB3LYP/6-31G(d) level of theory, using the Gaussian 03 program package.[76] All species have been fully geometry optimized in the gas phase and the Cartesian coordinates of the global minima thus obtained are supplied in the SI. The calculated spin-squared expectation values ($\langle S^2 \rangle$) were, after spin annihilation, ≤ 0.751 in all cases, in good agreement with the theoretically expected value of 0.75 for a pure doublet state.

The potential energy surface scans for the internal rotations about the benzylic and the C–CO$_2$H bonds of $\mathbf{2}^{\bullet+}$ and $\mathbf{3}^{\bullet+}$ (see SI) were

carried out in redundant internal coordinates in steps of 30°. A geometry optimization was performed on the global minimum found for any conformation.

Gas-phase bond dissociation enthalpies (BDEs) relative to the benzylic C−H bond in 4-methoxycyclopropylbenzene and 4-methoxycumene were also calculated by geometry optimization of the involved species at the UB3LYP/6-31G(d) level of theory (BDE-$(R-H) = E(R^\bullet) + E(H^\bullet) - E(R-H)$).

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Supporting Information Available: Details on the synthesis and characterization of substrates **2** and **4**−**6** and of reaction products **3a**, **3b**, and **3d**, time-resolved absorption spectra observed after LFP of substrate **3** and PR of substrate **5**, Plot of k_{obs} vs [NaOH] for **5**$^{\bullet+}$, optimized Cartesian coordinates and potential energies calculated for the global minima of **2**, **2**$^{\bullet+}$, **3**, **3**$^{\bullet+}$, 4-methoxycyclopropylbenzene, 1-(4-methoxyphenyl)cyclopropyl radical, 4-methoxycumene, and 4-methoxycumyl radical, and Potential energy surface scans for **2**$^{\bullet+}$ and **3**$^{\bullet+}$, calculated at the UB3LYP/6-31G(d) level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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