# CHAPTER 3

Reactivity and Acid-Base Behavior of Ring-Methoxylated Arylalkanoic Acid Radical Cations and Radical Zwitterions in Aqueous Solution. The Influence of Structural Effects and pH on the Benzylic C−H Deprotonation Pathway

Introduction

In chapter 2.1, we have shown that in aqueous solution the one-electron oxidation of ring-dimethoxylated phenylethanoic acids leads to the formation of aromatic radical cations or radical zwitterions depending on pH, providing moreover pK_a values for their acid-base equilibria. The radical cations were observed to undergo exclusive decarboxylation to give the corresponding benzyl radicals (as shown in Scheme 3.1 for 3,4-dimethoxyphenylethanoic acid radical cation ($2^{\bullet+}$)) with rate constants that are influenced by the substitution pattern of the aromatic ring, and a significant increase in decarboxylation rate constant was observed on going from the radical cations to the corresponding radical zwitterions.
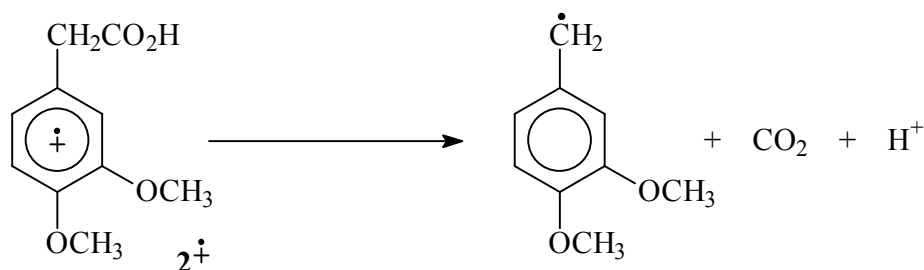
Scheme 3.1

These results have been interpreted in terms of the reorganization energy required for the side-chain to ring intramolecular electron transfer associated to decarboxylation, which is influenced by the extent of stabilization of the positive charge on the aromatic ring and hence by the relative position of methoxy ring substituents. In this study, no evidence for the formation of products deriving from benzylic C–H deprotonation in the radical cations or in the radical zwitterions was obtained.

Along this line, in order to obtain more information on the role of structural effects on the acid-base behavior of arylalkanoic acid radical cations and on the possible competition between decarboxylation and benzylic C–H deprotonation, we have investigated the effect of the distance between the carboxylic group and the aromatic ring through a product and time-resolved kinetic study at different pH values on the reactivity of the radical cations generated after one-electron oxidation of 3-(4-methoxyphenyl)propanoic (**20**), 3-hydroxy-3-(4-methoxyphenyl)propanoic (**21**), 3-(3,4-dimethoxyphenyl)propanoic (**22**), 4-(4'-methoxyphenyl)butanoic (**23**) and 4-(3,4-dimethoxyphenyl)butanoic acid (**24**) (Chart 3.1).
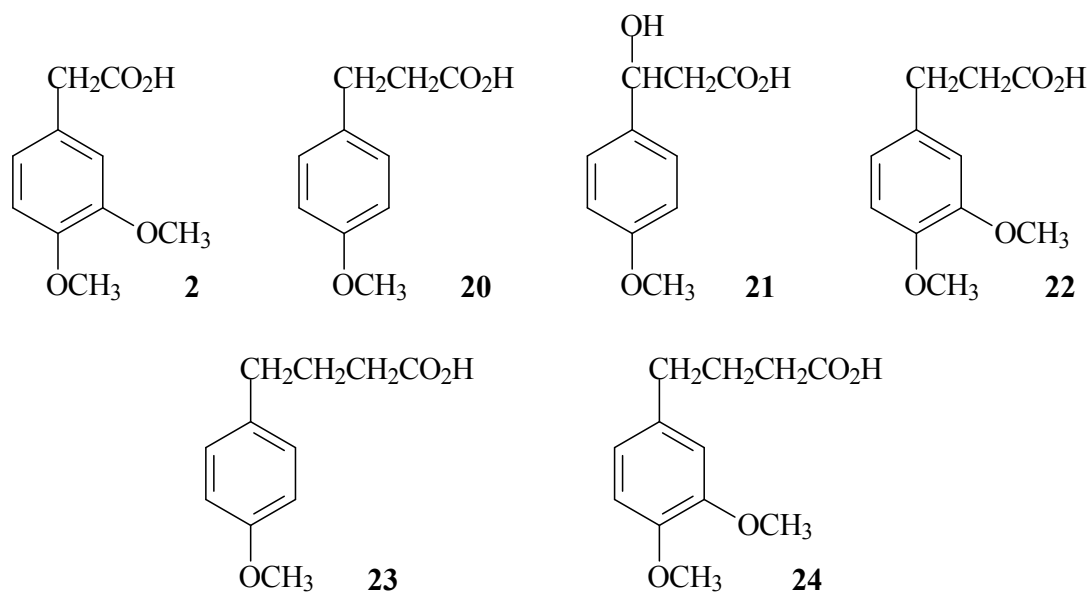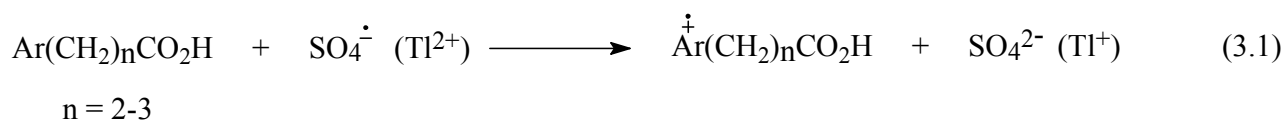
CH₂CO₂H ... OCH₃ OCH₃ **2**

CH₂CH₂CO₂H ... OCH₃ **20**

OH CHCH₂CO₂H ... OCH₃ **21**

CH₂CH₂CO₂H ... OCH₃ OCH₃ **22**

CH₂CH₂CH₂CO₂H ... OCH₃ **23**

CH₂CH₂CH₂CO₂H ... OCH₃ OCH₃ **24**

Chart 3.1

Results and Discussion

Spectral properties and acid-base behavior. The transients produced after PR or LFP of acidic aqueous solutions (pH $\leq$ 2) containing substrates **20-24** showed UV and visible absorption bands centered around 290-310 and 420-450 nm which are analogous to those observed for the corresponding mono- and dimethoxylated aromatic radical cations,[1-3] and are thus assigned to the arylalkanoic acid radical cations **20$^{\bullet+}$-24$^{\bullet+}$**, formed by SO$_4^{\bullet-}$ or Tl^{2+} induced one-electron oxidation of the neutral substrates as described in eq 3.1.

$$\text{Ar(CH}_2)_n\text{CO}_2\text{H} \ + \ \text{SO}_4^{\bullet-} \ (\text{Tl}^{2+}) \longrightarrow \ \overset{\bullet+}{\text{Ar}}(\text{CH}_2)_n\text{CO}_2\text{H} \ + \ \text{SO}_4^{2-} \ (\text{Tl}^+) \quad\quad (3.1)$$

$$n = 2\text{-}3$$

By increasing the pH of the solution to $\approx$ 7, the spectra obtained after SO$_4^{\bullet-}$ induced one-electron oxidation of acids **20-24** were similar to those obtained in acidic solution.[4] However, as described previously for ring-methoxylated phenylethanoic acid radical cations (see Chapter 2.1), a broadening of the radical cation visible absorption band was observed. This behavior is attributed to the formation of the radical zwitterions $^-$**20$^{\bullet+}$**-$^-$**24$^{\bullet+}$**.[6] As an example, Figure 3.1 shows the

time-resolved absorption spectra observed after 248 nm LFP of argon-saturated aqueous solutions containing **20** (1 mM) and $K_2S_2O_8$ (0.1 M) at pH = 2.0 (filled circles) and pH = 7.0 (empty circles). A broadening of the visible absorption band is observed on going from **20**$^{\bullet+}$ to $^-$**20**$^{\bullet+}$. Identical spectra were obtained after PR of argon saturated aqueous solutions (pH = 2.0 and 7.3) containing $K_2S_2O_8$ (5 mM), 2-methyl-2-propanol (0.1 M) and **20** (0.5 mM).

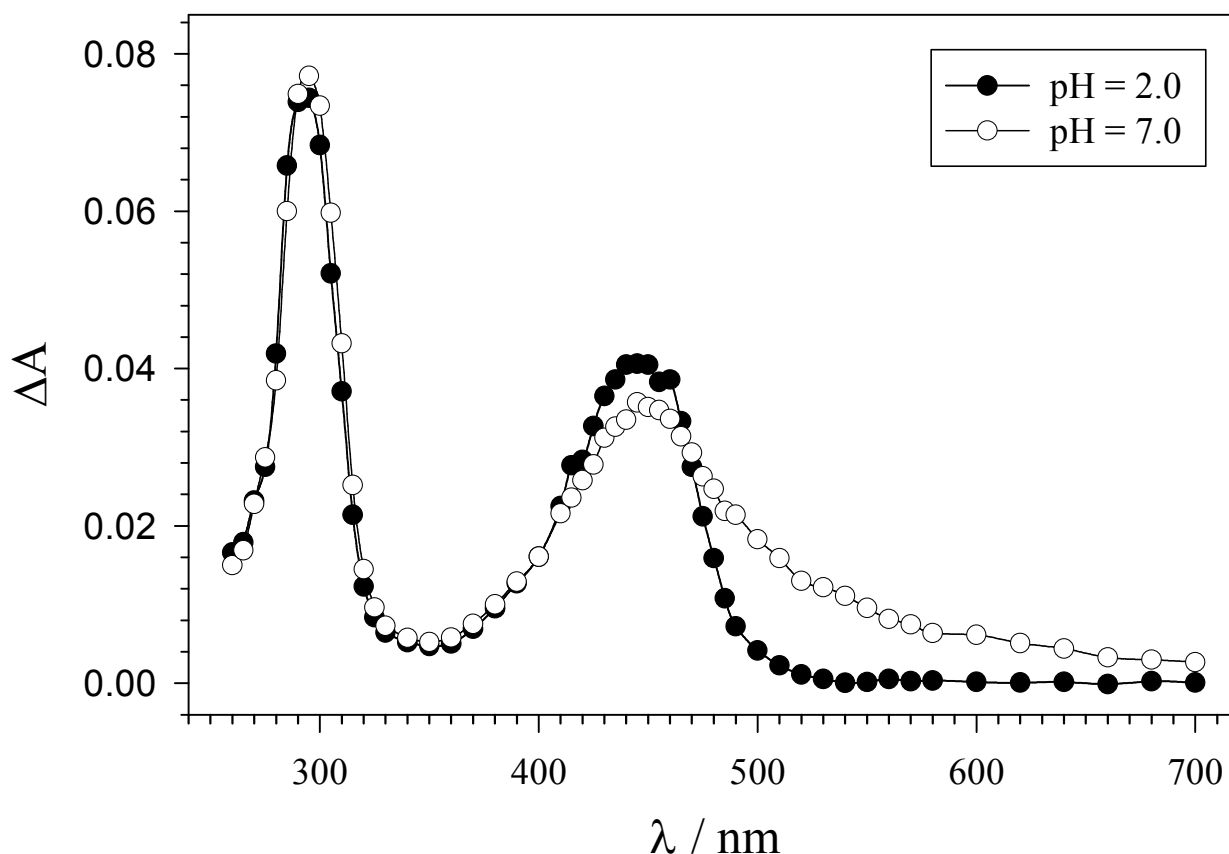**Figure 3.1**. Time-resolved absorption spectra observed after 248 nm LFP of argon-saturated aqueous solutions containing 0.1 M $K_2S_2O_8$ and 1 mM 3-(4'-methoxyphenyl)propanoic acid (**20**), recorded at pH = 2.0 (filled circles), and pH = 7.0 (empty circles), 1 μs after the 20 ns, 10 mJ laser flash.

By measuring the absorption at a suitable wavelength (where the difference in absorption between radical cation and radical zwitterion is sufficiently large) as a function of pH, the pK_a values for the acid-base equilibria between the radical cations and the corresponding radical zwitterions (eq 3.2) were determined.
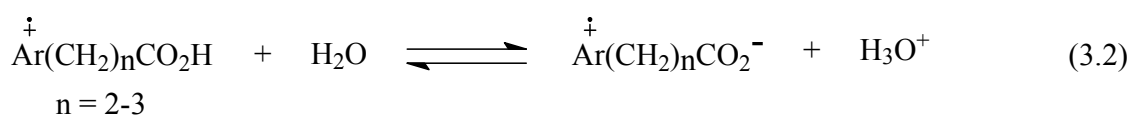
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$$\overset{\text{\textbullet}+}{Ar}(CH_2)_nCO_2H \quad + \quad H_2O \quad \rightleftharpoons \quad \overset{\text{\textbullet}+}{Ar}(CH_2)_nCO_2^- \quad + \quad H_3O^+ \qquad (3.2)$$

$$n = 2\text{-}3$$

Figure 3.2 shows the plot of ΔA (monitored at 510 nm) *vs* pH for the acid-base equilibrium between $20^{\text{\textbullet}+}$ and $^-20^{\text{\textbullet}+}$. Qui verificare la possibilità di inserire un'analoga figura per un butanoico ok per 23 e 24
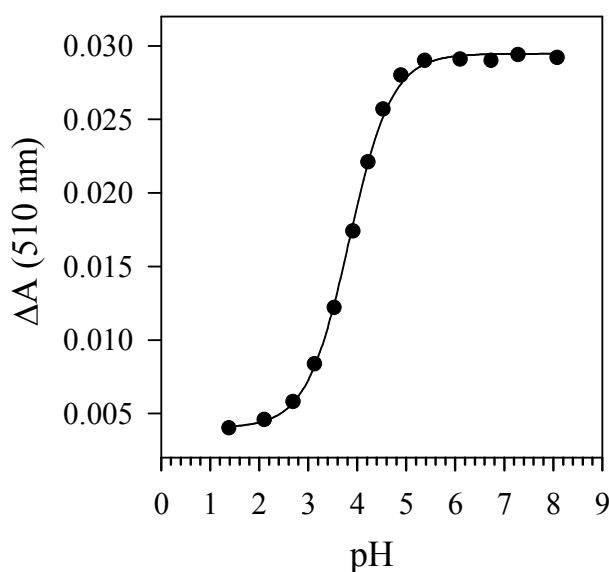
Figure 3.2. Plot of ΔA monitored at 510 nm *vs* pH for $20^{\text{\textbullet}+}$, generated after 248 nm LFP of an argon-saturated aqueous solution containing 0.1 M $K_2S_2O_8$ and 1 mM **16**. From the curve fit: pK_a = 3.84±0.02 (r = 0.9995).

The pK_a values thus obtained for $20^{\text{\textbullet}+}$-$24^{\text{\textbullet}+}$ are collected in Table 3.1 together with the radical cation visible absorption band maxima and the pK_a values of the neutral acids **20-24**. As a matter of comparison, the corresponding data for 3,4-dimethoxyphenylethanoic acid (**2**) and for its radical cation (**2$^{\text{\textbullet}+}$**) are also included (see Chapter 2.1).

Table 3.1. Visible absorption band maxima for radical cations **20**, **22**$^{\bullet+}$-**24**$^{\bullet+}$ and corresponding pK_a values for their acid-base equilibria, measured at room temperature.

radical cation [a]	λ_{max} (vis) [b] (nm)	λ_{monit} [c] (nm)	pK_a [d] (radical cation)	pK_a [e] (neutral acid)	ΔpK_a [f]
2$^{\bullet+}$	420 (450) [g]	460	3.49±0.05	4.33	0.84
20$^{\bullet+}$	445	510	3.87±0.03	4.69	0.82
22$^{\bullet+}$	420	450	4.12±0.04	4.69 [h]	0.57
23$^{\bullet+}$	450	480	4.28±0.03	4.76 [i]	0.48
24$^{\bullet+}$	420	450	4.44±0.03	4.76 [i]	0.32

[a] Generated by 248 nm LFP as described above (eqs 8 and 9). [b] Radical cation visible absorption band maxima. [c] Monitoring wavelength for pK_a determination. [d] Based on the average of at least two independent measurements. [e] Taken from ref. 7. [f] ΔpK_a = pK_a (neutral acid) − pK_a (radical cation). [g] Visible absorption band maximum for the corresponding radical zwitterion $^-$**2**$^{\bullet+}$. [h] This value refers to 3-(4'-methoxyphenyl)propanoic acid (**20**). However, on the basis of the very similar pK_a values measured for **20** and for 3-phenylpropanoic acid (pK_a = 4.69 and 4.66, respectively), and for 4-methoxyphenylethanoic acid (**1**) and 3,4-dimethoxyphenylethanoic acid (**2**) (pK_a = 4.36 and 4.33, respectively) the same pK_a value (pK_a = 4.69) can be reasonably assumed for **20** and **22**. [i] This value refers to 4-phenylbutanoic acid. However, on the basis of the considerations outlined in footnote h above, the same pK_a value (pK_a = 4.76) can be reasonably assumed also for **23** and **24**.

With 3,4-dimethoxyphenylethanoic acid (**2**) the increase in acidity of the carboxylic proton observed on going from the neutral substrate (pK_a = 4.33) to the corresponding radical cation **2**$^{\bullet+}$ (pK_a = 3.49) has been rationalized in terms of the increased electron withdrawing effect determined by the presence of an electron hole on the aromatic ring. Along this line, the observation that in the ring dimethoxylated arylalkanoic acid series the radical cation pK_a value increases on going from **2**$^{\bullet+}$ to **24**$^{\bullet+}$ can be explained analogously in terms of a decrease in the electron withdrawing effect as the distance between the carboxylic group and the electron deficient aromatic ring increases. Accordingly, on the basis of the pK_a values available for the neutral substrates: 4.33 for **2**, 4.69 for **22**, and 4.76 for **24** (see Table 3.1), the difference in pK_a between the neutral substrates and the corresponding radical cations (ΔpK_a) decreases progressively on going from **2**$^{\bullet+}$ to **24**$^{\bullet+}$: ΔpK_a = 0.84, 0.57 and 0.32 for **2**$^{\bullet+}$, **22**$^{\bullet+}$ and **24**$^{\bullet+}$,

respectively. Quite interestingly the ΔpK_a value obtained for **24/24$^{\bullet+}$** shows that even though small, an effect on acidity is still present when the positively charged aromatic ring is in the γ position with respect to the carboxylic function. As a matter of comparison, a similar effect on acidity has been also observed when comparing butanoic acid ($pK_a = 4.82$) with 4-chlorobutanoic acid ($pK_a = 4.52$).[8]

A slight decrease in acidity is also observed on going from the monomethoxylated radical cations to the dimethoxylated ones (compare **20$^{\bullet+}$** with **22$^{\bullet+}$** and **23$^{\bullet+}$** with **24$^{\bullet+}$**), a behavior that reasonably reflects the fact that the presence of two methoxy ring substituents as in **22$^{\bullet+}$** and **24$^{\bullet+}$** allows a greater extent of positive charge stabilization as compared to **20$^{\bullet+}$** and **23$^{\bullet+}$**, resulting in a weaker electron withdrawing effect.

Product studies. The oxidation reactions of substrates **20-24** were carried out in argon saturated aqueous solution (pH = 1.7 or 6.7) at room temperature, employing $SO_4^{\bullet-}$ as the oxidant, generated by steady state 254 nm photolysis as described in eq 1.3. Irradiation times were chosen in such a way as to avoid complete substrate consumption. In some experiments, potassium 12-tungstocobalt(III)ate (Co(III)W) was used as the oxidant.
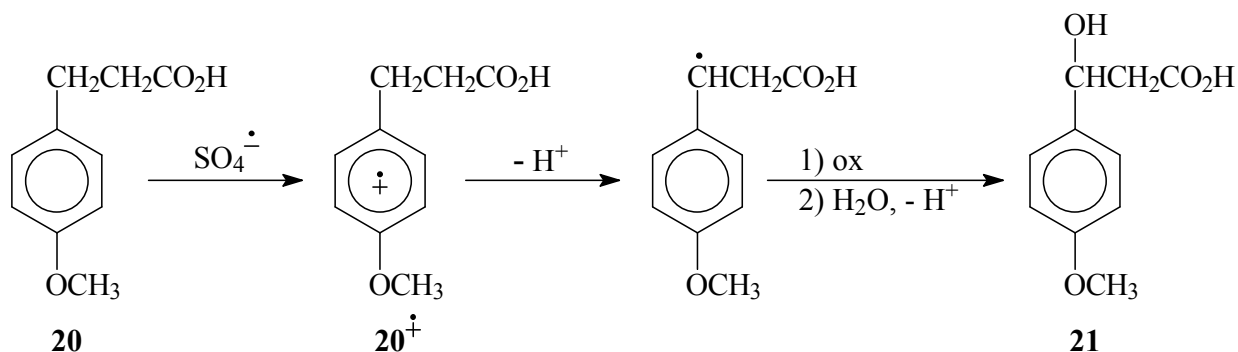
After workup, the reaction mixtures were analyzed by ^{1}H NMR using diphenylmethanol as internal standard and the reaction products were generally identified by comparison with authentic samples.

At pH = 1.7 the reaction of **20** led to a 60 % substrate conversion after 1.5 min of irradiation (mass balance > 99 %). Formation of 3-hydroxy-3-(4'-methoxyphenyl)propanoic acid (**21**), was observed accompanied by a small amount ($\approx$ 2 % of the reaction products) of 4-methoxyacetophenone (Scheme 3.2).[9] An analogous product distribution was observed when the irradiation was carried out at pH = 6.7.
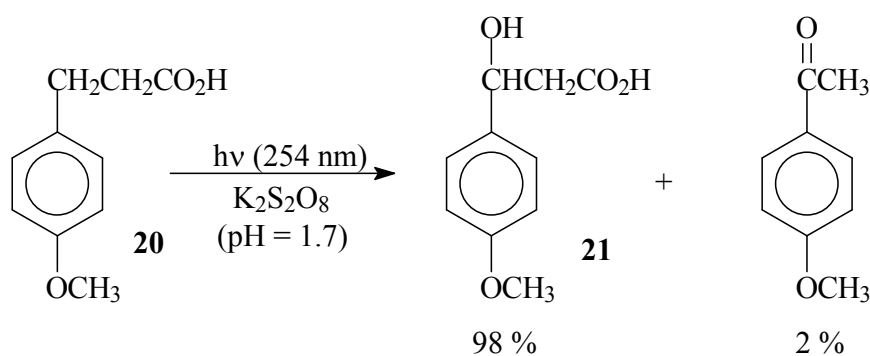
Scheme 3.2

The formation of **21** can be explained in terms of benzylic C–H deprotonation of the radical cation **20**$^{•+}$ (generated by SO$_4$$^{•-}$ induced oxidation of **20** as described in eq. 3.1) to give a substituted benzyl radical. Oxidation of this radical in the reaction medium followed by reaction with the solvent water leads to **21**, as shown in Scheme 3.3, in line with the deprotonation reactions of a variety of alkylaromatic radical cations described previously.[10-16]
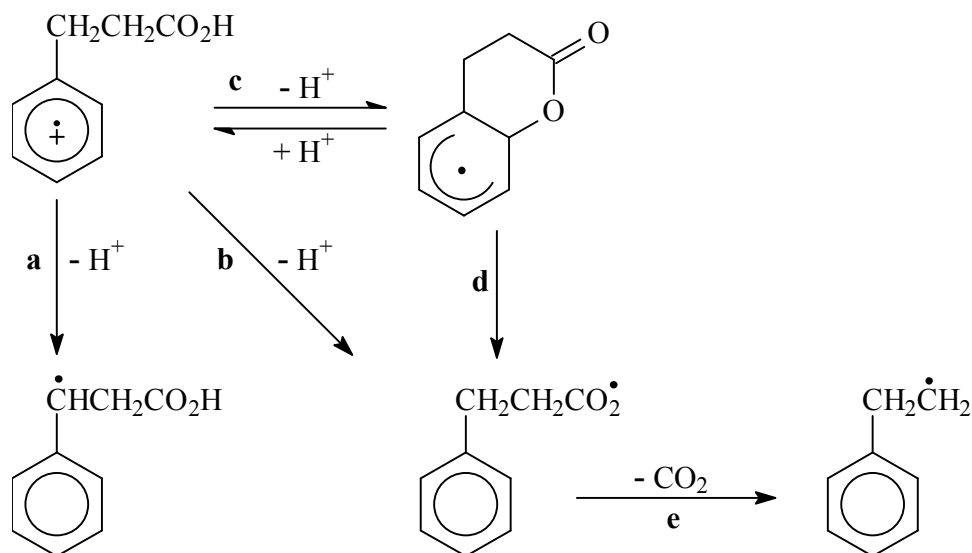

Scheme 3.3

The formation of 4-methoxyacetophenone in small amount can be instead explained in terms of the further oxidation of the first formed β-hydroxy acid **21** (see below).

Quite interestingly, previous studies carried out on 3-phenylpropanoic acid radical cation showed the formation of products deriving from both the decarboxylation and benzylic C–H deprotonation pathways.[17-19] In particular, by means of product studies Walling observed the formation of styrene, ethylbenzene, β-phenylethyl acetate, phenylacetaldehyde and 2-chromanone as major reaction products after one-electron oxidation of 3-phenylpropanoic acid in acetic acid and acetonitrile.[19] It was proposed that styrene, ethylbenzene, β-phenylethyl acetate and phenylacetaldehyde derive from the decarboxylation of the first formed radical cation,[20] whereas 2-chromanone derives from the C–H deprotonation pathway.[21] Gilbert carried out instead an EPR study at different pH values on the one-electron oxidation of 3-phenylpropanoic acid promoted by $^{•}$OH or SO$_4$$^{•-}$.[17,18] The signals deriving from the C–H deprotonated benzylic radical (PhCH$^{•}$CH$_2$CO2H) were observed at pH < 1.8 with $^{•}$OH and < 1.5 with SO$_4$$^{•-}$. Above these pH values, these signals were replaced in both cases by those assigned to the decarboxylated radical PhCH$_2$CH$_2$$^{•}$. This behavior was explained in terms of the formation of an aromatic radical cation which, depending on pH, undergoes C–H deprotonation (Scheme 3.4,

path **a**) or intramolecular electron transfer from the carboxyl group to the ring (either direct (path **b**) or via formation of a discrete σ-bonded cyclic intermediate (paths **c-d**)) to give an acyloxyl radical, precursor of the decarboxylated radical PhCH$_2$CH$_2$$^\bullet$ (path **e**).

Scheme 3.4

According to this picture, the observation that **20**$^{\bullet+}$ undergoes instead exclusive benzylic C–H deprotonation at both pH 1.7 and 6.7 can be rationalized in terms of the increased stability of **20**$^{\bullet+}$ as compared to 3-phenylpropanoic acid radical cation determined by the presence of a methoxy ring-substituent. This increased stabilization of the positive charge on the aromatic ring results in an increase of the energy barrier for the intramolecular electron transfer step (Scheme 3.4, path **b** or **c-d**) thus disfavoring the formation of the intermediate acyloxyl radical and hence of the products deriving from the decarboxylation pathway.

At pH = 1.7 the reaction of **21** led to a 35 % substrate conversion after 30 s of irradiation (mass balance > 99 %). Formation of 3-oxo-3-(4'-methoxyphenyl)propanoic acid (**21k**) as the major reaction product, accompanied by 4-methoxyacetophenone was observed. The ^{1}H NMR analysis of the reaction mixture showed a decrease in the amount of **21k** on standing at room temperature, accompanied by a corresponding increase in the amount of 4-methoxyacetophenone.

In particular, the ^{1}H NMR spectrum recorded immediately after workup of the reaction mixture (Figure 3.3, spectrum **a**, showing the 2.5-5.2 ppm range) shows the presence of the substrate **21** (65 %: characterized by the double doublet at 5.09 ppm, the singlet at 3.79 ppm and the multiplet

at 2.77 ppm) accompanied by **21k** (33 %: characterized by the singlets at 4.00 and 3.89 ppm) and 4-methoxyacetophenone (2 %: characterized by the singlets at 3.87 and 2.55 ppm). The ^{1}H NMR spectrum recorded after heating the same sample for 1 hour at $T = 50$ °C (Figure 3.3, spectrum **b**) shows in addition to the signals due to **21** the almost complete disappearance of the signals due to **21k** (2 %), accompanied by an increase in intensity of the signals due to 4-metoxyacetophenone (33 %).
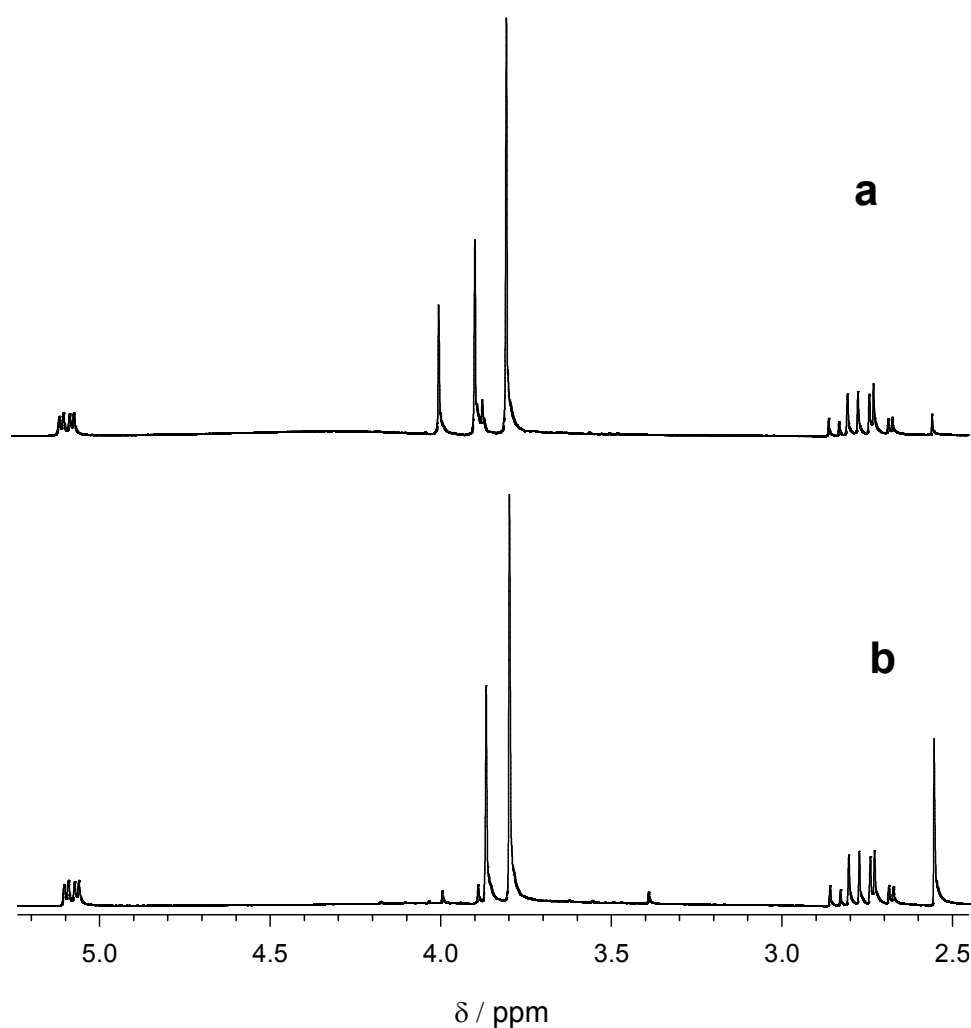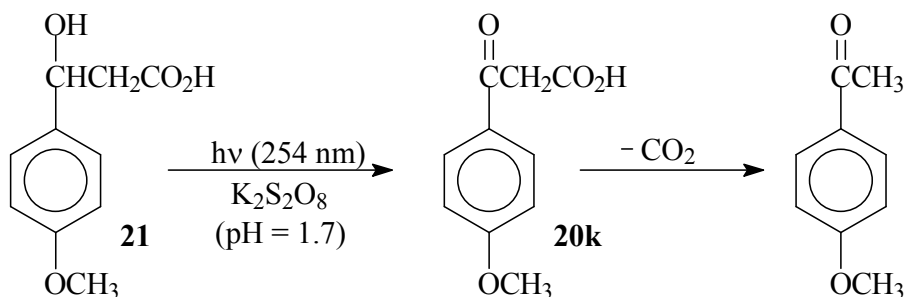

Figure 3.3. ^{1}H NMR spectra recorded in CDCl$_3$ after 254 nm steady state photolysis of an aqueous solution (pH = 1.7) containing 2 mM 3-hydroxy-3-(4'-methoxyphenyl)propanoic acid (**21**) and 0.1 M K$_2$S$_2$O$_8$. **a**) Spectrum recorded immediately after workup of the reaction mixture. **b**) Spectrum recorded on the same solution as in **a** after heating for 1 hour at $T = 50$ °C.

This behavior strongly suggests that 4-methoxyacetophenone derives from the spontaneous decarboxylation of the first formed β-keto acid **21k**, as described in Scheme 3.5, in full
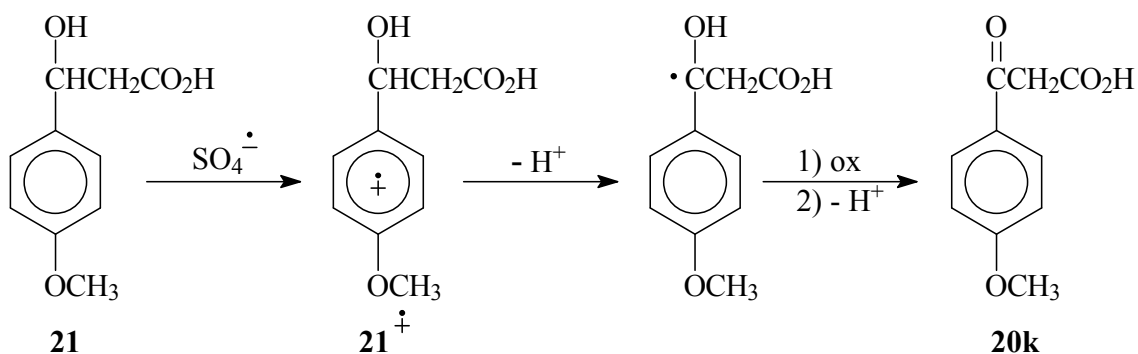
agreement with the reported decarboxylation kinetics of **21k** (in aqueous solution at $T = 35.6$ °C, $\tau = 1930$ s).[23]

Scheme 3.5

An analogous behavior was observed when **21** was irradiated at pH = 6.7 even though, as compared to the reaction carried out at pH = 1.7, a significantly higher substrate conversion was observed (85 % after 30 s irradiation).
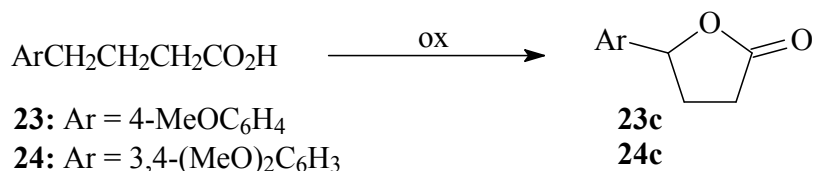
The formation of **21k** after one-electron oxidation of **21** can be explained in terms of C–H deprotonation of the radical cation **21**$^{\bullet+}$ (generated by $SO_4^{\bullet-}$ induced oxidation of **21** as described in eq. 3.1) to give a substituted α-hydroxy benzyl radical. Oxidation of this radical in the reaction medium followed by deprotonation leads to **21k**, as shown in Scheme 3.6, in line with the deprotonation reactions of a variety of 1-arylalkanol radical cations described previously.[1,10,24-26]
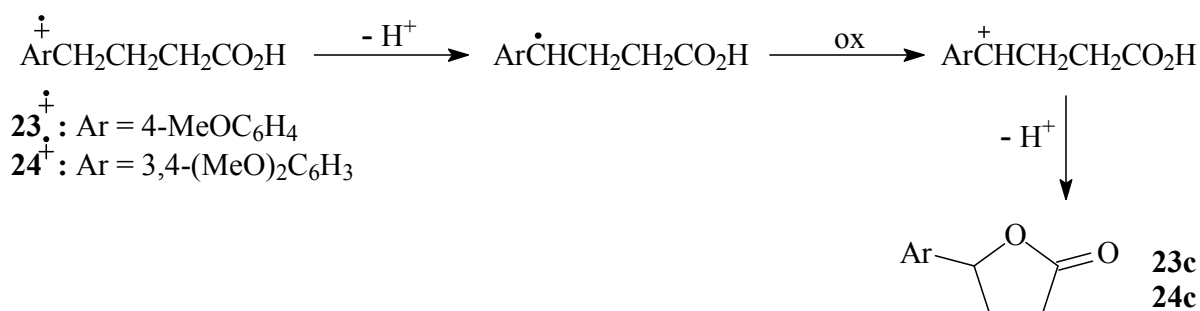

Scheme 3.6

At pH = 1.7 the reaction of **23** led to a 60 % substrate conversion after 1.5 min of irradiation (mass balance > 99 %). The exclusive formation of 5-(4'-methoxyphenyl)oxa-2-cyclopentanone (**23c**) was observed. Formation of the same product was also observed when the oxidation of **23**

was carried out at pH = 1.7 or 6.7 employing Co(III)W (Scheme 3.7: Ar = 4-MeOC$_6$H$_4$, ox = hv/K$_2$S$_2$O$_8$ or Co(III)W).

$$ArCH_2CH_2CH_2CO_2H \xrightarrow{\text{ox}} \text{Ar-}\begin{subarray}{c}O\\ \\ \end{subarray}\text{=O}$$

23: Ar = 4-MeOC$_6$H$_4$ **23c**
24: Ar = 3,4-(MeO)$_2$C$_6$H$_3$ **24c**

Scheme 3.7

The formation of **23c** following one-electron oxidation of **23** can be explained in terms of C−H deprotonation of the radical cation **23$^{\bullet+}$** to give a substituted benzyl radical. Oxidation of this radical in the reaction medium followed by intramolecular nucleophilic attack leads to **23c**, (Scheme 3.8, Ar = 4-MeOC$_6$H$_4$), as described previously for the one-electron oxidation of 4-phenylbutanoic acid.[27-29]

$$\overset{\bullet+}{Ar}CH_2CH_2CH_2CO_2H \xrightarrow{- H^+} Ar\overset{\bullet}{C}HCH_2CH_2CO_2H \xrightarrow{\text{ox}} Ar\overset{+}{C}HCH_2CH_2CO_2H$$

23$\overset{\bullet+}{}$: Ar = 4-MeOC$_6$H$_4$
24$\overset{\bullet+}{}$: Ar = 3,4-(MeO)$_2$C$_6$H$_3$

                                                            $- H^+ \downarrow$

$$\text{Ar-}\begin{subarray}{c}O\\ \\ \end{subarray}\text{=O} \quad \begin{array}{c}\textbf{23c}\\ \textbf{24c}\end{array}$$

Scheme 3.8

At pH = 1.7, 1.5 min irradiation of the ring-dimethoxylated acids **22** and **24** in the presence of K$_2$S$_2$O$_8$ resulted in both cases in an almost quantitative (≥ 95 %) recovery of the parent compound. No oxidation products were detected under these conditions. The reactions of **22** and **24** were thus carried out employing Co(III)W as the oxidant.

The reaction of **22** with Co(III)W was carried out only at pH = 1.7 and the exclusive formation of 3-hydroxy-3-(3',4'-dimethoxyphenyl)propanoic acid (**22a**) (see for analogy Scheme 3.2 describing the reaction of **20**) was observed. Formation of **22a** can be explained in terms of C−H deprotonation of the radical cation **22$^{\bullet+}$** as described in Scheme 3.3 for the oxidation of **20**.

The reaction of **24** with Co(III)W was carried out at pH = 1.7 and 6.7. In both cases the exclusive formation of 5-(3',4'-dimethoxyphenyl)oxa-2-cyclopentanone (**24c**) was observed (Scheme 3.7:

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Ar = 3,4-(MeO)$_2$C$_6$H$_3$, ox = Co(III)W). Formation of **24c** can be explained in terms of C–H deprotonation of **24**$^{\bullet+}$ (Scheme 3.8: Ar = 3,4-(MeO)$_2$C$_6$H$_3$, ox = Co(III)W), as discussed above for the corresponding reaction of **23**.

Time-resolved kinetic studies.

Acidic solution (pH ≈ 1.7). The decay rates of the radical cations **20**$^{\bullet+}$-**24**$^{\bullet+}$ were measured spectrophotometrically following the decrease in optical density at the visible absorption band maxima (between 420 and 450 nm). With **20**$^{\bullet+}$, **21**$^{\bullet+}$ and **23**$^{\bullet+}$ the decay was observed to follow first order kinetics, in a reaction that, on the basis of the product analysis results described above, is assigned to benzylic C–H deprotonation.

The decay of radical cations **22**$^{\bullet+}$ and **24**$^{\bullet+}$ was instead observed to be influenced by the radiation chemical dose or laser intensity and accordingly, only an upper limit for their decay rate constant could be determined. Also the decay of **22**$^{\bullet+}$ and **24**$^{\bullet+}$ is assigned to benzylic C–H deprotonation on the basis of the product analysis results described above. The rate constants thus obtained are collected in Table 3.2.

Table 3.2. First order rate constants (k) measured following the decay of radical cations **20**$^{\bullet+}$-**24**$^{\bullet+}$ generated by PR or LFP of the parent substrates in aqueous solution (pH ≈ 1.7), measured at T = 25 °C.

radical cation	oxidant	k / s^{-1} [a]
20$^{\bullet+}$	Tl^{+2} [b]	1.5×10^3
	SO$_4$$^{\bullet-}$ [c]	1.8×10^3
21$^{\bullet+}$	SO$_4$$^{\bullet-}$ [c]	6.5×10^3
22$^{\bullet+}$	Tl^{+2} [b]	$< 5 \times 10^2$
	SO$_4$$^{\bullet-}$ [c]	< 50
23$^{\bullet+}$	Tl^{+2} [b]	1.7×10^3
	SO$_4$$^{\bullet-}$ [c]	2.1×10^3
24$^{\bullet+}$	Tl^{+2} [b]	$< 5 \times 10^2$
	SO$_4$$^{\bullet-}$ [c]	< 50

[a]Monitored following the decay of absorption at the radical cation visible absorption band maxima (between 420 and 450 nm). Error ≤ 10%. [b]Generated by PR (dose ≤ 1 Gy/pulse) of N$_2$O saturated aqueous solutions containing the substrate (0.5 mM) and Tl$_2$SO$_4$ (2.0 mM) as described in eqs 1.4, 1.7-1.9. [c]Generated by LFP of argon saturated aqueous solutions containing the substrate (0.1-1.0 mM) and K$_2$S$_2$O$_8$ (0.1 M) as described in eqs 1.2 and 1.3.

Quite interestingly, the rate constants measured for $20^{\bullet+}$ and $23^{\bullet+}$ and for $21^{\bullet+}$ are very similar to those measured previously in acidic aqueous solution for benzylic C–H deprotonation of the structurally related radical cations 4-MeOC$_6$H$_4$(CH$_2$)$_3$OH$^{\bullet+}$ and 4-MeOC$_6$H$_4$(CH$_2$)$_4$OH$^{\bullet+}$ (k = 1.8 × 10^3 and 1.4 × 10^3 s^{-1}, respectively),[30] and for 4-MeOC$_6$H$_4$CH(OH)CH$_2$CH$_3$$^{\bullet+}$ (k = 5.4 × 10^3 s^{-1}).[25] The similarity of these values provides additional support to the assignement of the rate constants displayed in Table 3.2 to the benzylic C–H deprotonation reaction. For what concerns instead the dimethoxylated radical cations $22^{\bullet+}$ and $24^{\bullet+}$, even though due to instrumental limits only an upper limit for their deprotonation rate constants could be determined, the limits reported in Table 2 ($k < 50$ s^{-1}) can be reasonably compared with the rate constant obtained for α-C–H deprotonation of 3,4-dimethoxybenzylalcohol radical cation (k = 17 s^{-1}). As discussed previously for alkylaromatic radical cations,[1,11,12,24] stabilization of the radical cation (that is on going from the monomethoxylated radical cations $20^{\bullet+}$ and $23^{\bullet+}$ to the corresponding dimethoxylated ones $22^{\bullet+}$ and $24^{\bullet+}$) leads to a significant decrease in the deprotonation rate constant.

Basic solution (pH > 10). By monitoring the decay of radical zwitterions $^-2^{\bullet+}$, $^-20^{\bullet+}$, $^-22^{\bullet+}$, $^-23^{\bullet+}$ and $^-24^{\bullet+}$ at the visible absorption band maxima (between 420 and 450 nm) 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 for all radical zwitterions (Figure 3.4, showing the plot for the reaction between $^-2^{\bullet+}$ and $^-$OH).
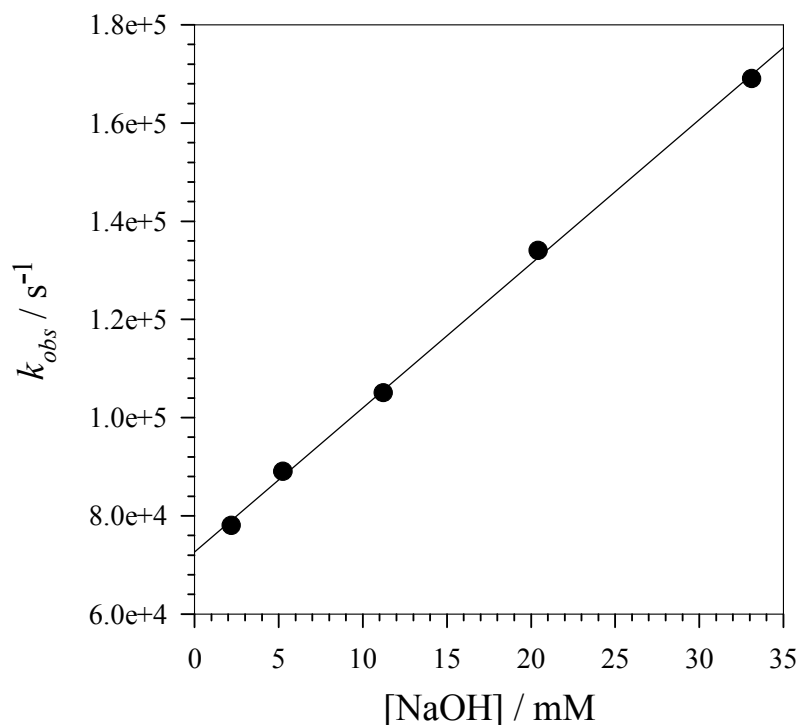
Figure 3.4. Plot of k_{obs} against concentration of NaOH for the reaction of radical zwitterion $^-2^{\bullet+}$. From the linear regression analysis: intercept = 7.2×10^4 s^{-1}, slope = 2.9×10^6 M^{-1} s^{-1}, r^2 = 0.9991.

From the slopes of these plots, the second-order rate constants for reaction of $^-$OH with the radical zwitterions (k_{-OH}) were determined. The rate constants thus obtained are collected in Table 3.3.

Table 3.3. Second-order rate constants for the $^-$OH-catalyzed (k_{-OH}) decay of radical zwitterions $^-2^{\bullet+}$, $^-20^{\bullet+}$, $^-22^{\bullet+}$-$^-24^{\bullet+}$ generated by pulse radiolysis of the parent substrates in aqueous solution, measured at $T = 25$ °C.

radical zwitterion [a]	pH range [b]	k_{-OH} [c] (M^{-1} s^{-1})
$^-2^{\bullet+}$	11.3-12.6	2.9×10^6
$^-20^{\bullet+}$	10.3-11.4	2.8×10^7
$^-22^{\bullet+}$	11.2-12.5	9.0×10^5
$^-23^{\bullet+}$	10.3-11.4	4.4×10^7
$^-24^{\bullet+}$	11.2-12.5	8.5×10^5

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The data collected in Table 3.3 show that very similar second-order rate constants k_{-OH} have been obtained for the monomethoxylated radical zwitterions $^-\mathbf{20}^{\bullet+}$ and $^-\mathbf{23}^{\bullet+}$, as well as for the dimethoxylated ones $^-\mathbf{22}^{\bullet+}$ and $^-\mathbf{24}^{\bullet+}$. These values are similar to those determined previously for the $^-$OH-induced α-C–H deprotonation of 4-methoxytoluene and 3,4-dimethoxytoluene radical cations ($k_{-OH} = 5.5 \times 10^7$ and 2.1×10^6 M^{-1} s^{-1}, respectively),[2c] and can be thus assigned to the same process i.e. $^-$OH-induced benzylic C–H deprotonation in $^-\mathbf{20}^{\bullet+}$-$^-\mathbf{24}^{\bullet+}$.

With $^-\mathbf{2}^{\bullet+}$ the second-order rate constant for reaction with $^-$OH has been determined as $k_{-OH} = 2.9 \times 10^6$ M^{-1} s^{-1}, a value that is very similar to the one determined previously for the $^-$OH-induced α-C–H deprotonation of 3,4-dimethoxytoluene radical cation discussed above.[2c] Quite importantly, the intercept of the k_{obs} against [NaOH] plot (7.2×10^4 s^{-1}, see Figure 4), that represents the rate constant for the *uncatalyzed* reaction of $^-\mathbf{2}^{\bullet+}$, is very close to the decarboxylation rate constant measured previously for this radical zwitterion between pH 6 and 10 ($k = 6.5 \times 10^4$ s^{-1}).[32] On the basis of these observations it is reasonable to propose that above pH 11 $^-\mathbf{2}^{\bullet+}$ undergoes competition between benzylic C–H deprotonation and decarboxylation, with the former process that becomes the major fragmentation pathway around pH 12.5.

In conclusion, by means of product and time-resolved studies additional information on the acid-base behavior and side-chain fragmentation reactivity of ring-methoxylated arylpropanoic and arylbutanoic acid radical cations and radical zwitterions in aqueous solution have been obtained. The radical cation pK_a values increase by increasing the number of methoxy ring substituents and by increasing the distance between the carboxylic group and the aromatic ring. The radical cations or radical zwitterions undergo benzylic C–H deprotonation as the exclusive side-chain fragmentation pathway over the pH range 1.7-12.5. Very interestingly, with 3,4-dimethoxyphenylethanoic acid radical zwitterion, that was previously observed to undergo

decarboxylation as the exclusive fragmentation pathway up to pH 10, competition between decarboxylation and benzylic C–H deprotonation is observed above pH 11.

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(3) **21$^{\bullet+}$** was generated exclusively by 266 nm LFP of an argon saturated aqueous solutions (pH = 1.7 or 6.6) containing **21** (1.0 mM) and $K_2S_2O_8$ (0.1 M), and showed in both cases UV and visible absorption bands centered at 290 and 445 nm.

(4) It is important to point out that at pH ≈ 7 one-electron oxidation occurs on the deprotonated acids and not on the neutral substrates **20**-**24**. However, on the basis of the spectroscopic evidences presented, that are indicative of the formation of aromatic radical zwitterions under these conditions, the direct oxidation of the carboxylate function to give an acyloxyl radical can be excluded. In addition, as it is well known that acyloxyl radicals undergo very rapid decarboxylation (see for example ref. 5), also the lack of decarboxylation products observed after one-electron oxidation of the acids at pH ≈ 7 (see the product studies described below) points against direct one-electron oxidation of the carboxylate function.

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(9) It is important to point out that when the reaction mixture of **20** was analyzed by GC and GC-MS, the formation of 4-methoxystyrene as major product, accompanied by smaller amounts of 4-methoxybenzaldehyde, 4-methoxyacetophenone and 4-methoxyphenylacetaldehyde was observed. No evidence for the formation of hydroxy acid **21** was instead obtained. A similar outcome was also observed when an authentic sample of **21** was analyzed by GC and GC-MS. Accordingly, the formation of the products described above from the reaction mixture of

20 under these analytical conditions can be reasonably explained in terms of the thermal decomposition of the first formed **21**.

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