General Introduction

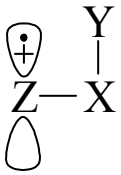
The fragmentation reactions of organic radical cations have been intensively investigated in recent years.[1] The bond more frequently involved is the bond in the β position with respect to the center of positive charge.

Z = Ar, RS, RSe, R_2N

X—Y = C—H, C—C, C—S, C—O, C—Si, C—Sn

Scheme 1

This is due to the considerable degree of overlap achievable between this bond and the SOMO of the radical cation (Scheme 2, where Z is generally an aromatic moiety or a heteroatom, i.e. a species characterized by a relatively low ionization potential) which results in its significant weakening as compared to the neutral substrate.



Scheme 2

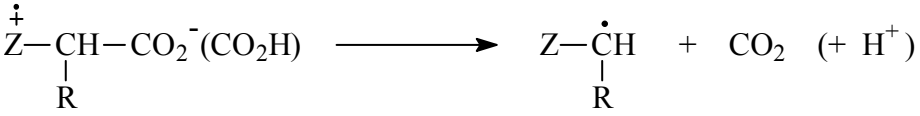
Typical examples are represented by toluene and 1,2-diphenylethane. In the former case, an increase in acidity of approx. 60 pK_a units is observed on going from toluene to the corresponding radical cation, for which a pK_a value between – 11 and – 13 has been estimated in acetonitrile solution.[2] With 1,2-diphenylethane, the CH_2–CH_2 bond dissociation energy (BDE) decreases from 64 kcal mol^{-1} to 29 kcal mol^{-1} on going from the neutral substrate to the corresponding radical cation.[3]

In most cases the initially generated radical cation has the unpaired electron delocalized over the Z moiety and the fragmentation reaction, leading to the formation of a cation and a radical, is accompanied by an intramolecular electron transfer from the scissile bond to the aromatic ring, ultimately resulting in two formal ways of electron apportionment between the fragments which depends on their relative thermodynamic stability. In the *heterolytic* mode

the charge is transferred through the scissile bond while in the *homolytic* mode the spin is transferred across the bond being cleaved. The free energy for radical cation bond cleavage, ΔG_f, can be estimated by means of simple thermodynamic cycles,[1f,4] where, regardless of the cleavage mode, ΔG_f depends on the free energy of homolysis of the radical cation precursor (ΔG_h) and the difference in reduction potentials (ΔE) between the radical cation and the ionic fragment formed: $\Delta G_f = \Delta G_h - \Delta E$.

A great number of fragmentation reactions are thus possible depending on the nature of the bond being cleaved. Most attention has been devoted to the study of the mechanistic[1,5-13] and synthetic[14,15] aspects of reactions involving the cleavage of the C–H and C–C bonds but also fragmentation reactions involving different C–X bonds (X = S, Si, Sn) have attracted considerable interest.[1]

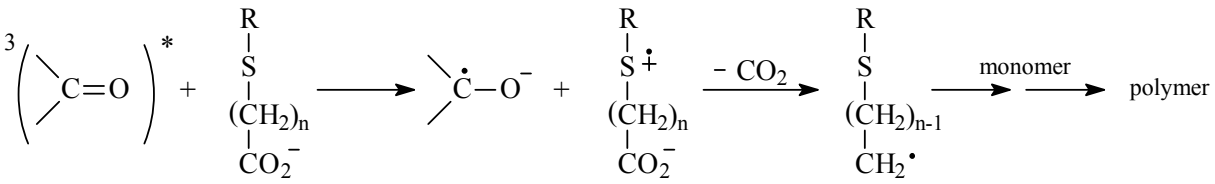
For what concerns the C–C bond cleavage reactions of organic radical cations, a very interesting mode of fragmentation is represented by decarboxylation, observed when a carboxylate or carboxylic group is β with respect to the positive charge (Scheme 3).



Scheme 3

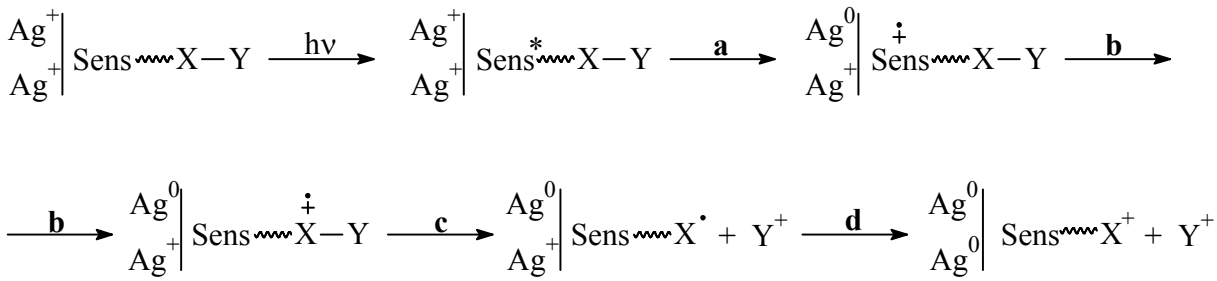
Radical cation decarboxylation has attracted considerable interest,[1a,1b,16-20] as this reaction takes part in several chemical and biological processes,[21] and is involved moreover in important processes such as the initiation of free radical polymerization[22] and the enhancement in the efficiency of silver halide photography (two-electron sensitization).[23,24]

Marciniak and co-workers[22] investigated the reactivity of a series of sulfur-containing carboxylic acids as electron donors in benzophenone photosensitized free-radical polymerization. This process involves the use of light to initiate electron transfer from a donor to an acceptor molecule. The mechanism that emerged from this work was that benzophenone reduction occurs by electron transfer from the donor to give a carboxylated radical zwitterion. This species then undergoes decarboxylation, to yield an alkyl radical that is able to initiate polymerization as described in Scheme 4.



Scheme 4

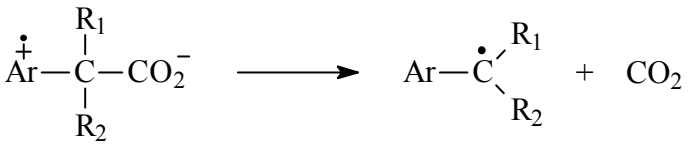
For what concerns the enhancement in the efficiency of silver halide photography, the main drawback associated with conventional silver halide photography is that the oxidized sensitizing dye ($Sens^{\bullet+}$) can undergo return electron transfer in competition with latent image formation, a process that wastes the photon energy and reduces the overall photographic sensitivity. The central idea behind two-electron sensitization (TES) is that the oxidized form of the photographic sensitizing dye ($Sens^{\bullet+}$, formed upon light exposure (Sens*) and electron transfer to silver halide) further oxidizes a fragmentable electron donor X–Y to form the corresponding radical cation $X^{\bullet+}$–Y. Cleavage of $X^{\bullet+}$–Y yields $X^{\bullet}$, which is designed to be a powerful reducing agent capable of injecting another electron into the conduction band of the silver halide. In this way, two electron are transferred per absorbed photon, thus doubling the photographic efficiency (Scheme 5).[23,24]



a Sens* induced reduction of the first Ag^+
b secondary (intramolecular) electron transfer
c $X^{\bullet+}$–Y fragmentation reaction
d $X^{\bullet}$ induced reduction of the second Ag^+

Scheme 5

The decarboxylation of radical zwitterions derived from relatively electron rich arylethanoic acids such as 4-dimethylaminophenylethanoic acid, its α-methyl and α-hydroxy-α-methyl derivatives, and 2,4,5-trimethoxymandelic acid proved to be one of the most useful fragmentation reactions to be applied in the TES process (Scheme 6), given moreover that the corresponding benzyl-type radicals produced in the fragmentation step are characterized by sufficiently negative oxidation potentials.[24]

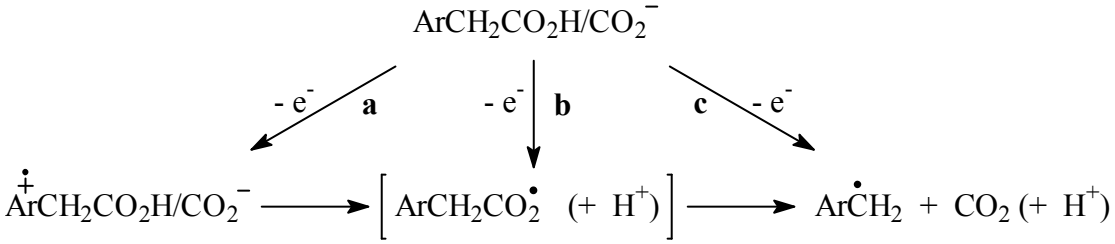


Scheme 6

It is however important to point out that different radical cation fragmentation reactions that can lead to analogous radicals with comparable rates can find application as well in the TES process. For example, aminosilane radical cations that undergo efficient cleavage of the C–Si bond have also been considered for TES.[25]

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 such fragmentation are particularly important.

Along this line, even though a large number of studies on the generation and reactivity of arylalkanoic acid radical cations have been carried out,[26-36] 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 7.



Scheme 7

A problem which 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 7, 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 1-naphthylethanoic acid,[29a] 4-dimethylaminophenylethanoic acid, its α-methyl and α-hydroxy-α-methyl derivatives, and 2,4,5-trimethoxymandelic acid.[23] Along this line, it cannot be

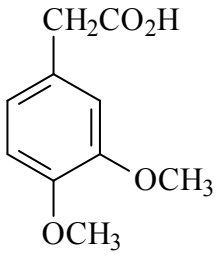
excluded that the one-electron oxidation of arylethanoic acids characterized by higher oxidation potentials, occurs following pathways **b** or **c**.

Moreover, also the nature of the conversion of the intermediate radical cation or radical zwitterion into the decarboxylated benzyl radical has attracted considerable interest,[18,28] since intramolecular electron transfer (from the side-chain to the aromatic π-system) in the radical cation (or radical zwitterion) can be coupled 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.

Additional points of interest concern the the stability of the decarboxylated benzyl radical, the role of the carboxylic proton and possible changes in acid-base behavior on going from the neutral acid to the corresponding radical cation.

Along this line, in order to obtain additional information on the role of structural effects on these processes, we have carried out detailed product and time-resolved studies on the one-electron oxidation of a variety of ring methoxylated phenylethanoic acids, where both number and relative position of the methoxy ring substituents, and the presence of alkyl groups in the α-positions, have been varied.

The results of product and time-resolved kinetic study carried out at different pH values on the one-electron oxidation of a series of ring dimethoxylated phenylethanoic acids (**2**-**5**) are described in Chapter 2.1.



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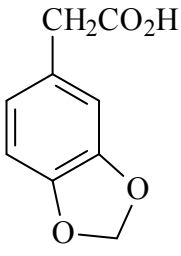

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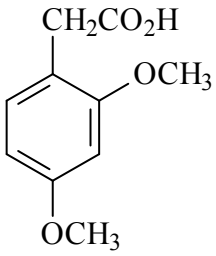

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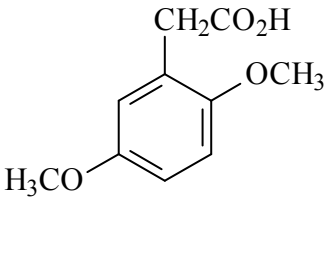

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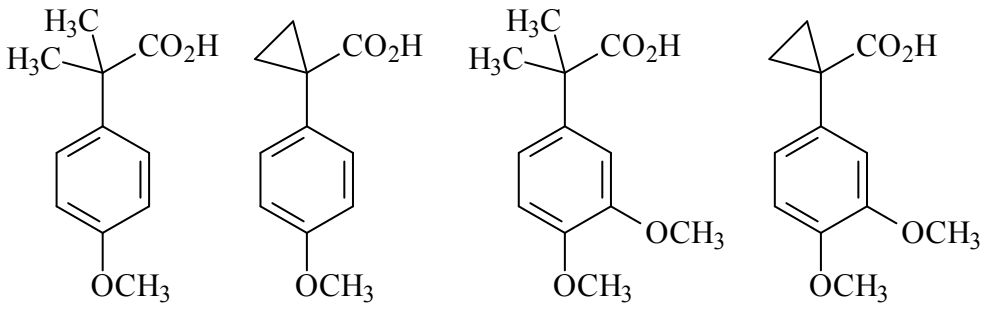
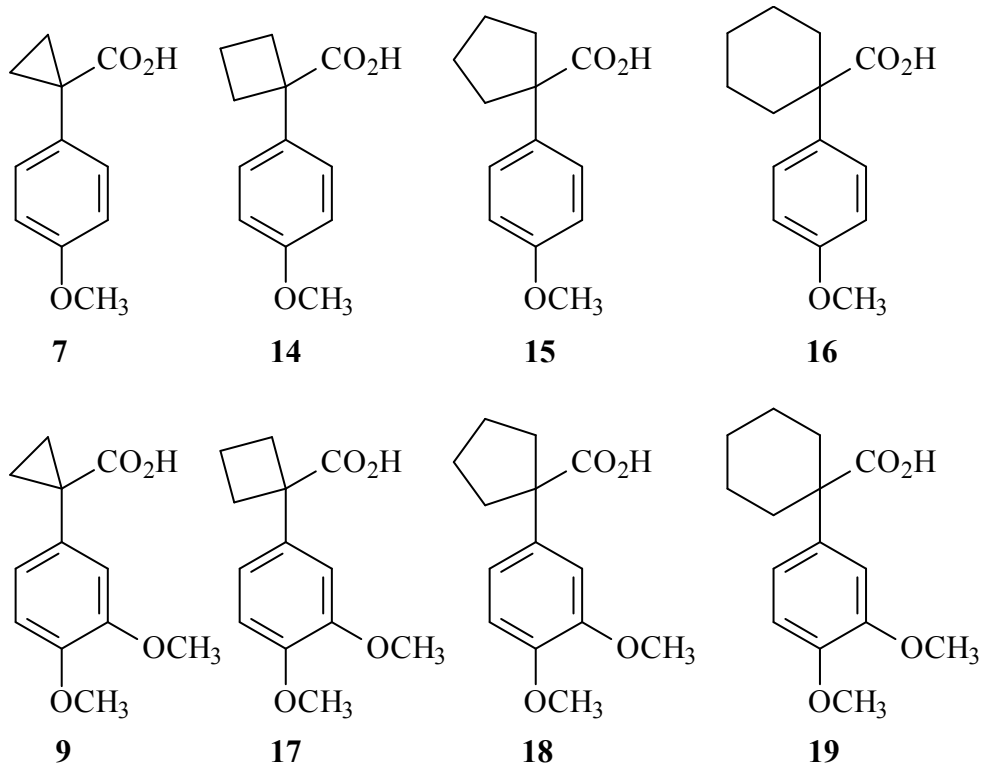
The results of product and time-resolved kinetic study carried out at different pH values on the one-electron oxidation of arylalkanoic acids **6**-**9**, substrates derived from the side-chain modification of 4-methoxyphenylethanoic acid (**1**) and 3,4-dimethoxyphenylethanoic acid (**2**), respectively, are described in Chapter 2.2.



6 **7** **8** **9**

The results of product and time-resolved kinetic study carried out at different pH values on the one-electron oxidation of two related series of 1-arylcycloalkanecarboxylic acids (**7**, **9**, **14-19**) are described in Chapter 2.3.

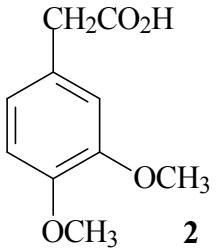


7 **14** **15** **16**

9 **17** **18** **19**

Finally, the observation that no benzylic C–H deprotonation is generally observed after one-electron oxidation of arylethanoic acid radical cations, since with these substrates C–C bond cleavage leads to a very stable fragment (CO_2) and a relatively stable benzyl radical, as described in Scheme 7, prompted us to investigate the possible competition between decarboxylation and benzylic C–H deprotonation and the effect of the distance between the carboxylic group and the aromatic ring. Along this line, we have carried out a product and time-resolved kinetic study over a wide pH range (between 1.7 and 12.5) on the one-electron

oxidation of 3,4-dimethoxyphenylethanoic (**2**), and of arylpropanoic and arylbutanoic acids **20**-**24**. The results of this study are collected in Chapter 3.



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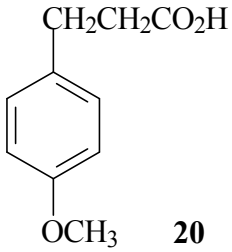

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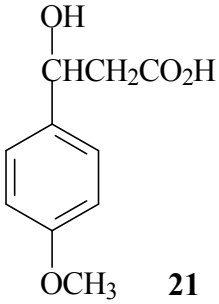

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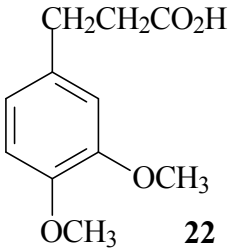

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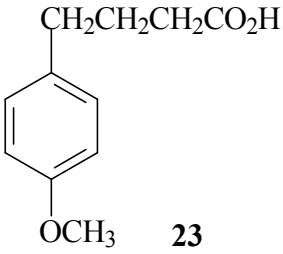

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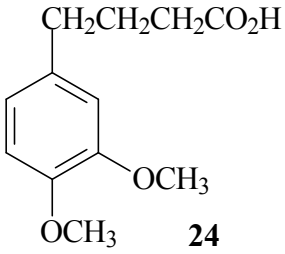

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CHAPTER 1

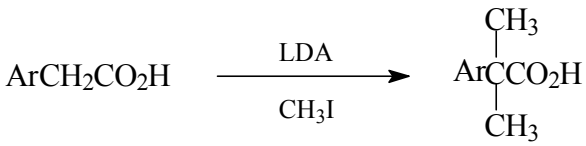
Materials and Methods

1.1 Materials

Commercial samples of potassium peroxydisulfate, thallium(II) sulfate, sodium hydroxide, disodium tetraborate decahydrate, sodiumdihydrogen phosphate, disodiumhydrogen phosphate, perchloric acid and 2-methyl-2-propanol were of the highest commercial quality available. Milli-Q-filtered (Millipore) water was used for all solutions.
Potassium 12-Tungstocobalt(III)ate ($K_5[Co(III)W_{12}O_{40}]$), from now on indicated as Co(III)W, was prepared according to a previously described procedure.[1]

Substrates
Commercial samples of 3,4-dimethoxyphenylethanoic acid (**2**), 3,4-methylenedioxyphenylethanoic acid (**3**), 2,4-dimethoxyphenylethanoic acid (**4**), 2,5-dimethoxyphenylethanoic acid (**5**), 1-(4-methoxyphenyl)cyclopropanecarboxylic acid (**7**), 1-(4-methoxyphenyl)cyclopentanecarboxylic acid (**15**), 1-(4-methoxyphenyl)cyclohexananecarboxylic acid (**16**), 3-(4-methoxyphenyl)propanoic acid (**20**), 4-(4-methoxyphenyl)butanoic acid (**22**), 3-(3,4-dimethoxyphenyl)propanoic acid (**23**) and 4-(3,4-dimethoxyphenyl)butanoic acid (**24**), of the highest available purity were used as received.

1) 2-(4-Methoxyphenyl)-2-methylpropanoic acid (**6**) and 2-(3,4-dimethoxyphenyl)-2-methylpropanoic acid (**8**) were prepared by reaction of 4-methoxyphenylethanoic acid (**1**) and 3,4-dimethoxyphenylethanoic acid (**2**) respectively, with CH_3I in the presence of LDA, according to a previously described procedure. [2]



6: Ar = 4-$MeOC_6H_4$
8: Ar = 3,4-$(MeO)_2C_6H_3$

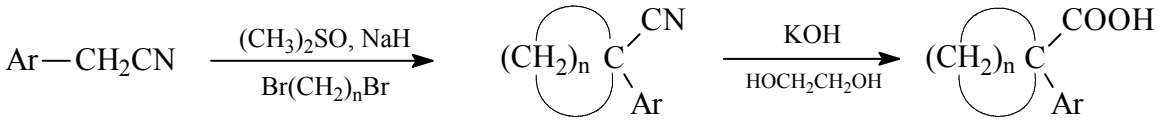
To a solution of LDA (25 mL, 2 M solution) diluted with 50 ml of anhydrous THF at – 5 °C under N_2 was added in small portions 4-metoxyphenylethanoic acid (2.08 g, 12.5 mmol) (or 3,4-dimetoxyphenylethanoic acid) dissolved in 5 ml of THF. The mixture was stirred at – 5 °C for 30 min and then was added with CH_3I (5 mL, 80 mmol). The reaction mixture was

allowed to reach room temperature, stirred for additional 30 min, and then quenched by pouring it into 75 mL of saturated NH_4Cl solution. The aqueous solution was extracted with Et_2O (3 x 25 mL). The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pression. The product was purified by column chromatography (hexane/ethyl acetate 5:1).

2-(4-methoxyphenyl)-2-methylpropanoic acid (**6**)
GC-MS m/z (relative abundance): 194 (M^+), 149 (100), 121, 109, 91.
^{1}H NMR ($CDCl_3$): δ 7.34-7.31 (m, 2H, Ar*H*), 6.89-6.86 (m, 2H, Ar*H*), 3.80 (s, 3H, ArOC*H*$_3$), 1.58 (s, 6H, C*H*$_3$). Yield: 74 %

2-(3,4-dimethoxyphenyl)-2-methylpropanoic acid (**8**)
GC-MS m/z (relative abundance): 224(M^+), 179 (100), 151, 139, 121.
^{1}H NMR ($CDCl_3$): δ 6.95 (d, J = 6.4 Hz, 1H, Ar*H*), 6.93 (s, 1H, Ar*H*), 6.83 (d, J = 6.2 Hz, 1H, Ar*H*), 3.87 (s, 3H, ArOC*H*$_3$), 3.86 (s, 3H, ArOC*H*$_3$), 1.59 (s, 6H, C*H*$_3$). Yield: 63%

2) 1-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid (**9**), 1-(4-methoxyphenyl)-1-cyclobutanecarboxylic acid (**14**), 1-(3,4-dimethoxyphenyl)cyclobutanecarboxylic acid (**17**), 1-(3,4-dimethoxyphenyl)cyclopentanecarboxylic acid (**18**) and 1-(3,4-dimethoxyphenyl)cyclohexanecarboxylic acid (**19**) were prepared by basic hydrolysis of the parent nitriles (**9n**, **14n**, **17n**, **18n**, **19n**), which in turn were prepared by reaction of 4-methoxyphenylethanonitrile (for **14n**) or 3,4-dimethoxyphenylethanonitrile (for **9n**, **17n**, **18n** and **19n**) with the pertinent 1,ω-dibromoalkane in the presence of NaH, according to a previously described procedure.[3]



9: Ar = 3,4-$(MeO)_2C_6H_3$, n = 2
14: Ar = 4-$MeOC_6H_4$, n = 3
17: Ar = 3,4-$(MeO)_2C_6H_3$, n = 3
18: Ar = 3,4-$(MeO)_2C_6H_3$, n = 4
19: Ar = 3,4-$(MeO)_2C_6H_3$, n = 5

Synthesis of nitriles (**9n**, **14n**, **17n**, **18n**, **19n**).

General procedure: a typical three-necked flask was charged under N_2 with 10 ml of anhydrous dimethylsulfoxide and NaH (20 mmol, 50% dispersion in mineral oil). After the vigorous reaction had subsided and cooling to 30 °C, a solution of arylethanonitrile (10 mmol) and 1,ω-dibromoalkane (10 mmol) in 6.5 mL of dry ether was added in small portions. The resulting thick slurry was stirred overnight, cooled in ice-water and 0.5 mL of 2-propanol were added dropwise followed by the addition of 10 mL of water. The mixture was extracted four times with diethyl ether. The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 6:1).

1-(3,4-dimethoxyphenyl)cyclopropanecarbonitrile (**9n**)

GC-MS m/z (relative abundance): 203 (M^+) (100), 172.

1-(4-methoxyphenyl)cyclobutanecarbonitrile (**14n**)

GC-MS m/z (relative abundance): 187 (M^+), 159 (100), 144, 116, 89, 63.

^{1}H NMR ($CDCl_3$): δ 7.35-7.32 (m, 2H, Ar*H*), 6.93-6.90 (m, 2H, Ar*H*), 3.82 (s, 3H, ArOC*H*$_3$), 2.79-2.36 (m, 4H, C*H*$_2$), 2.10-2.02 (m, 2H, C*H*$_2$).

1-(3,4-dimethoxyphenyl)cyclobutanecarbonitrile (**17n**)

GC-MS m/z (relative abundance): 217 (M^+), 189 (100), 174, 146, 128.

1-(3,4-dimethoxyphenyl)cyclopentanecarbonitrile (**18n**)

GC-MS m/z (relative abundance): 231 (M^+) (100), 216, 202, 189.

1-(3,4-didimethoxyphenyl)cyclohexanecarbonitrile (**19n**)

GC-MS m/z (relative abundance): 245 (M^+) (100), 202, 189.

^{1}H NMR ($CDCl_3$): δ 7.03-7.00 (m, 2H, Ar*H*), 6.88-6.85 (m, 1H, Ar*H*), 3.92 (s, 3H, ArOC*H*$_3$), 3.88 (s, 3H, ArOC*H*$_3$), 2.18-2.14 (m, 2H, C*H*$_2$), 1.88-1.68 (m, 7H, C*H*$_2$), 1.28-1.25 (m, 1H, C*H*$_2$).

Synthesis of 1-arylcycloalkanecarboxylic acids (9, 14, 17, 18, 19)

A solution of 1-arylcycloalkylcarbonitrile (5 mmol) and KOH (15 mmol) in 13 mL of ethylene glycol was stirred at reflux temperature for 24 hrs. The solution was poured into 7.5 mL of water and extracted with ether to remove any unreacted nitrile or amide. Then aqueous

solution was acidified with HCl and extracted with diethyl ether. The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 3:1).

1-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid (**9**)
GC-MS m/z (relative abundance): 222 (M^+) (100), 207, 191, 177, 161.
^{1}H NMR ($CDCl_3$): δ 6.91-6.88 (m, 2H, Ar*H*), 6.81-6.78 (m, 1H, Ar*H*), 3.87 (s, 3H, ArOC*H*$_3$), 3.86 (s, 3H, ArOC*H*$_3$), 1.66-1.63 (m, 2H, C*H*$_2$), 1.27-1.23 (m, 2H, C*H*$_2$).

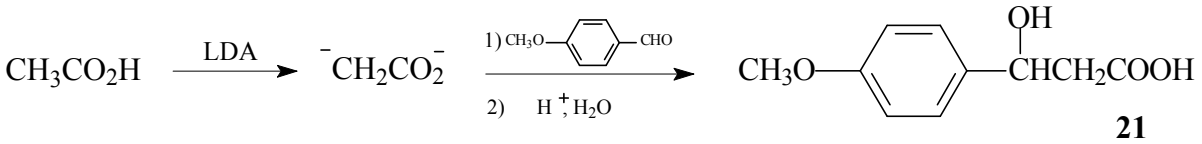
1-(4-methoxyphenyl)cyclobutanecarboxylic acid (**14**)
GC-MS m/z (relative abundance): 206 (M^+), 178 (100), 161, 133, 118, 103, 77.
^{1}NMR ($CDCl_3$): δ 7.23 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 3.79 (s, 3H, ArOC*H*$_3$), 2.85-2.79 (m, 2H, C*H*$_2$),), 2.52-2.45 (m, 2H, C*H*$_2$), 2.08-1.83 (m, 2H, C*H*$_2$).

1-(3,4-dimethoxyphenyl)cyclobutanecarboxylic acid (**17**)
GC-MS m/z (relative abundance): 236 (M^+), 208 (100), 193, 163, 147, 119, 91.
^{1}H NMR ($CDCl_3$): δ 6.88-6.82 (m, 3H, Ar*H*), 6.93-6.90 (m, 2H, Ar*H*), 3.87 (s, 3H, ArOC*H*$_3$), 3.86 (s, 3H, ArOC*H*$_3$), 2.83-2.47 (m, 4H, C*H*$_2$), 2.06-1.88 (m, 2H, C*H*$_2$).

1-(3,4-dimethoxyphenyl)cyclopentanecarboxylic acid (**18**)
GC-MS m/z (relative abundance): 250 (M^+), 205 (100), 164, 151, 191.
^{1}H NMR ($CDCl_3$): δ 6.95-6.92 (m, 2H, Ar*H*), 6.82-6.80 (m, 1H, Ar*H*), 3.87 (s, 3H, ArOC*H*$_3$), 3.85 (s, 3H, ArOC*H*$_3$), 2.64-2.62 (m, 2H, C*H*$_2$), 1.92-1.79 (m, 8H, C*H*$_2$).

1-(3,4-dimethoxyphenyl)cyclohexanecarboxylic acid (**19**)
GC-MS m/z (relative abundance): 264 (M^+), 219 (100), 177, 151, 137.
^{1}H NMR ($CDCl_3$): δ 7.02-6.97 (m, 2H, Ar*H*), 6.88-6.85 (m, 1H, Ar*H*), 3.87 (s, 3H, ArOC*H*$_3$), 3.86 (s, 3H, ArOC*H*$_3$), 2.49-2.44 (m, 2H, C*H*$_2$), 1.78-1.25 (m, 8H, C*H*$_2$).

3) 3-Hydroxy-3-(4-methoxyphenyl)propanoic acid (**21**) was prepared by reaction of 4-methoxybenzaldehyde with the acetic acid dianion produced by reaction of acetic acid with LDA according to a previously described procedure.[4]



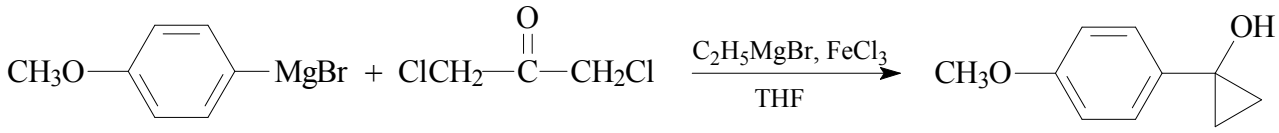
21

To a solution of LDA (11.8 mL, 2 M solution) diluted with 40 ml of anhydrous THF at – 78 °C was slowly added acetic acid (8.88 mmol) in 4 mL of of anhydrous THF. The temperature was allowed to rise to 0 °C and the mixture kept for half an hour. After slow addition of 4-methoxybenzaldehyde (1 g, 7.4 mmol) in 6 mL of anhydrous THF at –78 °C, was stirred at room temperature for 1 hr. Then aqueous solution was acidified with HCl and extracted with diethyl ether. The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting product was purified by crystallization from diethyl ether/hexane and identified by ^{1}H NMR.Yield: 62 %

3-Hydroxy-3-(4-methoxyphenyl)propanoic acid (**21**)

^{1}NMR ($CDCl_3$): δ 7.31 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 5.09 (dd, 1H, J = 9.1, 3.7 Hz), 3.79 (s, 3H), 2.77 (AB portion of an ABX system, 2H, J_{ab} = 16.4, J_{ax} = 9.1, J_{bx} = 3.7, $\Delta\nu_{ab}$ = 30 Hz).

4) 1-(4-Methoxyphenyl)cyclopropanol (**7a**) was prepared by reaction of 1,3-dichloroacetone with 4-methoxyphenylmagnesium bromide in the presence of ethylmagnesium bromide and $FeCl_3$ according to a previously described procedure.[5]



7a

21.6 ml of a 0.5 M solution of 4-methoxyphenylmagnesium bromide in 10 mL of anhydrous THF under N_2 was added slowly dichloroacetone (0.288 g, 10.8 mmol) in 10 mL of anhydrous THF. Next 30 ml of a 2 M a solution of ethyl-magnesium bromide in 40 mL of anhydrous THF was added dropwise, simultaneously with the addition of anhydrous $FeCl_3$ (0.125 g, 0.7 mmol) in 10 mL of anhydrous THF. There was a copious evolution of gas during the addition, which required 2 hrs. After stirring overnight the reaction mixture was poured onto a slurry of ice and 2 M HCl satured with ammonium chloride. The solution was extracted with three portions of diethyl ether The organic extracts were dried (Na_2SO_4) and the solvent

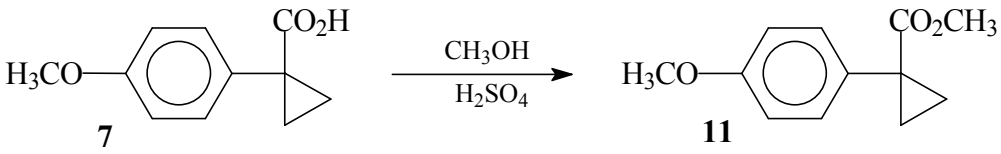
was removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 6:1) and crystallized from pentane to give pure alcohol. Yield: 45 %

1-(4-Methoxyphenyl)cyclopropanol (**7a**)

GC-MS m/z (relative abundance): 164 (M^+), 163, 135 (100), 107, 92, 77, 55.

^{1}H NMR ($CDCl_3$): δ 7.30-7.25 (m, 2H, Ar*H*), 6.90-6.85 (m, 2H, Ar*H*), 3.81 (s, 3H, ArOC*H*$_3$), 1.23-1.18 (m, 2H, C*H*$_2$), 1.00-0.95 (m, 2H, C*H*$_2$).

4) Methyl 2-(4-methoxyphenyl)-2-methylpropionate (**10**), methyl 1-(4-methoxyphenyl)cyclopropanecarboxylate (**11**), and methyl 1-(3',4'-dimethoxyphenyl)cyclopropanecarboxylate (**12**) were prepared by acid catalyzed reaction of the corresponding acids with methanol.



7 **11**

0.1 mL of H_2SO_4 (96%) were added to a solution of the acid (**6**, **7** and **9**) (0.5 mmol) in 1 mL of MeOH. After stirring for 24 hrs an aqueous satured solution of $NaHCO_3$ was added to the reaction mixture. The solution was extracted three times with diethyl ether. The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 2:1). Yield between 90 - 95 %.

Methyl 2-(4-methoxyphenyl)-2-methylpropionate (**10**)

^{1}H NMR ($CDCl_3$): δ 7.34-7.31 (m, 2H, Ar*H*), 6.89-6.86 (m, 2H, Ar*H*), 3.80 (s, 3H, ArOC*H*$_3$), 3.61 (s, 3H, CO_2C*H*$_3$), 1.58 (s, 6H, C*H*$_3$).

GC-MS m/z (relative abundance): 208 (M^+), 149(100), 121, 109, 91.

Methyl 1-(4-methoxyphenyl)cyclopropanecarboxylate (**11**)

^{1}H NMR ($CDCl_3$): δ 7.28-7.25 (m, 2H, Ar*H*), 6.87-6.83 (m, 2H, Ar*H*), 3.80 (s, 3H, ArOC*H*$_3$), 3.62 (s, 3H, CO_2C*H*$_3$), 1.60-1.56 (m, 2H, C*H*$_2$), 1.17-1.13 (m, 2H, C*H*$_2$).

GC-MS m/z (relative abundance): 206 (M^+), 191, 174, 147(100), 131, 91.

Methyl 1-(3,4-dimethoxyphenyl)cyclopropanecarboxylate (**12**)

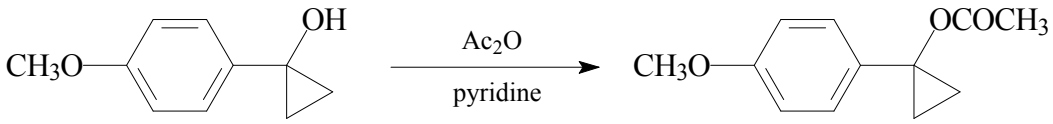
^{1}H NMR ($CDCl_3$): δ 6.92-6.78 (m, 3H, Ar*H*), 3.88 (s, 3H, ArOC*H*$_3$), 3.87 (s, 3H, ArOC*H*$_3$), 3.63 (s, 3H, CO_2CH_3), 1.61-1.56 (m, 2H, C*H*$_2$), 1.21-1.17 (m, 2H, C*H*$_2$).

GC-MS m/z (relative abundance): 236 (M^+), 121, 205, 177(100), 161, 146, 91.

Reaction products

Commercial samples of 3,4-dimethoxybenzyl alcohol, 3,4-methylenedioxybenzyl alcohol, 2,4-dimethoxybenzyl alcohol, 2,5-dimethoxybenzyl alcohol, 3,4-dimethoxybenzaldehyde, 3,4-methylenedioxybenzaldehyde, 2,5-dimethoxybenzaldehyde, 4-methoxyacetophenone, 4-methoxypropiophenone of the highest available purity were used as received. 2-(4-metoxyphenyl)propan-2-ol and 2-(3,4-dimetoxyphenyl)propan-2-ol were available from a previous work.[6] 3-Hydroxy-3-(4-methoxyphenyl)propanoic acid (**21**) was prepared as described above (see pag. 20).

1) 1-(4-Mehoxyphenyl)cyclopropylacetate (**7e**) was prepared by reaction of 1-(4-methoxyphenyl)cyclopropanol (**7a**) with acetic anhydride in pyridine.



7a **7e**

0.38 mL of acetic anhydride (4 mmol) were added dropwise to a solution of 1-(4-methoxyphenyl)cyclopropanol (**7a**) (0. 4 mmol) in 1 mL of pyridine. After stirring for 12 hrs H_2O was added to the reaction mixture. The solution was extracted three times with diethyl ether. The organic extracts were washed three times with 2 M HCl, twice with an aqueous satured solution of $NaHCO_3$ and twice with H_2O. The organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 2:1) and identified by ^{1}H NMR and GC-MS. Yield: 73%

1-(4-Mehoxyphenyl)cyclopropylacetate (**7e**)

^{1}H NMR ($CDCl_3$): δ 7.37-7.34 (d, 2H, *J* = 8.8 Hz Ar*H*), 6.86-6.83 (m, 2H, *J* = 8.8 Hz Ar*H*), 3.79 (s, 3H, ArOC*H*$_3$), 1.99 (s, 3H, OCOC*H*$_3$), 1.25-1.20 (m, 2H, C*H*$_2$), 1.16-1.11 (m, 2H, C*H*$_2$).

GC-MS m/z (relative abundance): 206 (M^+), 163, 135(100), 107, 92, 77.

1.2 Generation of the Radical Cations

The generation of radical cations was carried out according to the following procedures.

Chemical oxidation with Co(III)W

Co(III)W is a well known one-electron oxidant (E^o = 1.00 V/NHE) able to oxidize methoxybenzene derivatives via outer-sphere electron transfer,[1,7] to give the corresponding radical cations (eq. 1.1). In a typical experiment 5 mL of an argon saturated aqueous solution (pH = 1.0 or 6.7) containing the substrate (0.5-5 mM) and Co(III)W (substrate/Co(III)W ratio = 0.3-2) at pH = 1.0 and 6.7 were stirred at T = 25 ºC or 50 ºC until complete conversion of Co(III)W (see later pag. 25).

$$\text{Co(III)W} + \text{ArR} \rightleftharpoons \overset{\cdot}{\underset{+}{\text{Ar}}}\text{R} + \text{Co(II)W} \qquad (1.1)$$

Photochemical oxidation with $SO_4^{\bullet-}$

$SO_4^{\bullet-}$ is a strong oxidant (E^o = 2.7 V/NHE) that is able 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 1.2).[8-10]

$$SO_4^{\cdot -} + \text{ArR} \longrightarrow SO_4^{2-} + \overset{\cdot}{\underset{+}{\text{Ar}}}\text{R} \qquad (1.2)$$

Argon saturated aqueous solutions containing the substrate (0.5-5 mM) were photolysed with UV light in the presence of 0.1 M $K_2S_2O_8$ at pH < 2 and pH ≈ 7. Under these conditions $SO_4^{\bullet-}$ is formed (eq 1.3).[11]

$$S_2O_8^{2-} \xrightarrow{h\nu} 2\ SO_4^{\cdot -} \qquad (1.3)$$

Radiation chemical oxidation with $SO_4^{\bullet-}$, Tl^{2+}

Alternatively, $SO_4^{\bullet-}$ was generated by pulse radiolysis (PR) of argon saturated aqueous solutions containing the substrate (0.2-2 mM), $K_2S_2O_8$ (10 mM) and 2-methyl-2-propanol (0.1 M), according to eqs. 1.4-1.6.

$$H_2O \rightsquigarrow H^+, {}^{\bullet}OH, e^-_{aq} \qquad (1.4)$$

$$^{\bullet}OH + CH_3C(CH_3)_2OH \longrightarrow H_2O + \dot{C}H_2C(CH_3)_2OH \qquad (1.5)$$

$$e^-_{aq} + S_2O_8^{2-} \longrightarrow SO_4^{2-} + SO_4^{\bullet-} \qquad (1.6)$$

Radiolysis of water leads to the formation of the hydroxyl radical ($^{\bullet}$OH) and the hydrated electron (e_{aq}^-) (eq 1.4). The former is scavenged by 2-methyl-2-propanol (eq 1.5; $k = 6 \times 10^8$ $M^{-1}s^{-1}$),[12] while e_{aq}^- reacts with the peroxydisulfate anion leading to the formation of $SO_4^{\bullet-}$ (eq 1.6; $k = 1.2 \times 10^{10}$ $M^{-1}s^{-1}$).[12]

In acid solution (pH < 3.5), Tl^{2+} was also used as the oxidant, produced by PR of N_2O saturated aqueous solutions. The function of N_2O is to scavenge e_{aq}^-, leading to the formation of an additional hydroxyl radical (eq 1.7), with $k = 9.1 \times 10^9$ $M^{-1}s^{-1}$.[13] Tl^{2+} is then produced by oxidation of Tl^+ by $^{\bullet}$OH (eq 1.8) with $k = 1.2 \times 10^{10}$ $M^{-1}s^{-1}$.[14] Also Tl^{2+} reacts with ring methoxylated aromatic substrates by electron transfer to give the corresponding radical cations (eq 1.9) with $k \approx 5 \times 10^8$ $M^{-1}s^{-1}$.[10]

$$e^-_{aq} + N_2O + H_2O \longrightarrow N_2 + {}^{\bullet}OH + {}^-OH \qquad (1.7)$$

$$^{\bullet}OH + Tl^+ + H^+ \longrightarrow Tl^{2+} + H_2O \qquad (1.8)$$

$$Tl^{2+} + ArR \longrightarrow Tl^+ + \dot{A}rR^+ \qquad (1.9)$$

1.4 Product Studies

Oxidations with Co(III)W

5 mL of an argon saturated aqueous solution (pH = 1.0, 1.7 or 6.7) containing the substrate (0.5 -5 mM) and Co(III)W (substrate/Co(III)W ratio = between 0.3 and 2) were stirred at T = 25 ºC or 50 ºC until complete conversion of the oxidant. In the experiment carried out for **7** in AcOH/H_2O 55: 45 at T = 25 ºC in the presence of 0.5 M AcOK, a 10 mM concentration both for **7** and Co(III)W was employed.

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 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, 1.7 or 6.7) containing the substrate (2 mM) and $K_2S_2O_8$ (0.1 M) were irradiated for times varying between 0.5 and 3 minutes. 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 diethyl ether and dried over anhydrous Na_2SO_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-(dimethoxy)benzyl alcohol were used as internal standard. In the ^{1}H NMR experiments diphenylmethanol was used as internal standard. Good to excellent mass balances (≥ 85 %) were obtained in all experiments.

In the reactions of 1-arylcycloalkanecarboxylic acids **14-19** with Co(III)W both at pH = 1.0 and pH = 6.7, the products (corresponding 1-arylcycloalkanol) were identified by GC-MS.

In the reactions of **23** and **24** with Co(III)W both at pH = 1.7 and pH = 6.7, the products (5-(4-methoxyphenyl)oxa-2-cyclopentanone from **23** and 5-(3,4-dimethoxyphenyl)oxa-2-cyclopentanone from **24** were identified by comparison with literature data.[15]

1,6-Bis-(4-methoxyphenyl)hexane-1,6-dione observed in the reaction of **7** and **13** with Co(III)W and $SO_4^{\bullet-}$ was identified by HPLC-MS and ^{1}H NMR by comparison with literature data.[16]

3-Hydroxy-3-(3,4-dimethoxyphenyl)propanoic acid (**22a**) observed in the reaction of **22** with Co(III)W was identified by ^{1}H NMR by comparison with data of corresponding 3-hydroxy-3-(4-methoxyphenyl)propanoic acid (**21**).

1.5 Time-Resolved Studies

Pulse Radiolysis

The pulse radiolysis experiments were performed using a 10 MeV electron linear accelerator which supplied 300 ns pulses with doses such that 1-3 μM radicals were produced. Experiments were performed at room temperature using argon-saturated aqueous solutions containing the substrate (0.5-2.0 mM), peroxydisulfate (2-10 mM) and 2-methyl-2-propanol (0.1 M). Alternatively, N_2O saturated aqueous solutions (pH ≤ 2) containing the substrate (0.5 mM) and thallium(I) sulfate (2.0 mM) were employed. The pH of the solutions was adjusted with NaOH or $HClO_4$. For the experiments at pH ≈ 7 and ≈ 10, 2 mM Na_2HPO_4 or 1 mM $Na_2B_4O_7$, respectively, was added. A flow system was employed in all the experiments. The rate constants were obtained by averaging 5 at least values, and were reproducible to within 10 %.

The second order rate constants for reaction of the radical cations with $^-$OH (k_{-OH}) were measured for **2**, **7**, **9**, **11**, **12**, **20**, **22**, **23** and **24**. The k_{-OH} values were obtained from the slopes of the plots of the observed rates (k_{obs}) *vs* concentration of NaOH. For these experiments the solution containing 0.5-1.0 mM substrate, 10 mM potassium peroxydisulfate and 0.1 M 2-methyl-2-propanol was saturated with argon and 1 mM $Na_2B_4O_7$was added to avoid undesired pH variations upon irradiation.

With methyl ester **11** and **12** the higher value was in all cases < 11.5 in order to prevent basic hydrolysis of the esters.

Laser Flash Photlysis

The radical cations of interest were generated at room temperature by direct laser flash photolysis (LFP) of argon saturated aqueous solutions, containing the substrate (0.2-1.0 mM) and $K_2S_2O_8$ (0.1 M), using the fourth harmonic (266 nm) of a Q-switched Nd:YAG laser providing 8 ns pulses or a 248 nm excimer laser (KrF*) providing 20 ns pulses. The laser energy was adjusted in both cases to ≤ 10 mJ/pulse (output power of the laser) by the use of the appropriate filter. The 266 nm LFP experiments were carried out at T = 25±0.5 °C under

magnetic stirring employing a 3 mL Suprasil quartz cell (10 mm × 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. The 248 nm LFP experiments were carried out at room temperature and the solutions were flowed through a 2 mm (in the direction of the laser beam) by 4 mm (in the direction of the analysing light, 90° geometry) Suprasil quartz cell. Kinetic studies were generally carried out employing 266 nm LFP. Rate constants were obtained by averaging at least 5 values and were reproducible to within 10 %.

The acid-base equilibria between the radical cations (**2**$^{\bullet+}$-**5**$^{\bullet+}$, **20**$^{\bullet+}$, **22**$^{\bullet+}$-**24**$^{\bullet+}$) and the corresponding radical zwitterions ($^{-}$**2**$^{\bullet+}$-$^{-}$**5**$^{\bullet+}$, $^{-}$**20**$^{\bullet+}$, $^{-}$**22**$^{\bullet+}$-$^{-}$**24**$^{\bullet+}$) were studied employing 248 nm LFP. pK_a values were determined by plotting ΔA as a function of pH at a fixed wavelength (where the difference in absorption between radical cation and radical zwitterion is sufficiently large) in the pH range 1-8. The ΔA *vs* pH curve was fitted to the equation: $\Delta A = [\Delta A_o + \Delta A_1 * 10^{(pH - pKa)}]/1 + 10^{(pH - pKa)}$. Two or three independent pK_a determinations were carried out for every radical cation.

1.6 DFT Calculations

Hybrid DFT calculations (UB3LYB) and appropriate geometry optimisations were carried out with GAUSSIAN 03 series of programs using the 6-31G(d) basis set implement therein[17].This method was used because the results it provides for cation radicals and neutral radicals have been found to be reliable.[18]

The calculated spin-squared expectation values ($<S^2>$) were ≤ 0.762 in all cases, in good agreement with the theoretically expected value of 0.75 for a pure doublet state.

The relaxed potential energy surface scan for the internal rotations about the benzylic and the C-CO_2H bonds of 1-(4-methoxyphenyl)-1-cyclopropanecarboxylic acid (**6**), 2-(4-metoxyphenyl)-2-methylpropanoic acid (**8**), and the corresponding radical cations (**6**$^{\bullet+}$, **8**$^{\bullet+}$) were carried out in redundant internal coordinates in step of 30°. On the global minimum found for any conformation search a geometry optimisation was performed.

DFT calculations were also carried out for 4-methoxyphenylcyclopropane, 1-(4-metoxyphenyl)-1-methylethane and the corresponding benzyl carbon radicals (-H$^{\bullet}$). A geometry optimisation was performed on the global minimum found by a preliminary PM3 conformational search.

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