Kinetic and Product Studies on the Side-Chain Fragmentation of 1-Arylalkanol Radical Cations in Aqueous Solution: Oxygen versus Carbon Acidity

Enrico Baciocchi,*[a] Massimo Bietti,[b] and Steen Steenken*[c]

Abstract: A kinetic and product study of the side-chain fragmentation reactions of a series of 1-arylalkanol radical cations ($4\text{-MeOC}_6\text{H}_4\text{CH(OH)R}^{\bullet+}$) and some of their methyl ethers was carried out; the radical cations were generated by pulse radiolysis and γ radiolysis in aqueous solution. The radical cations undergo side-chain fragmentation involving the C_α–H and/or C_α–C_β bonds, and their reactivity was studied both in acidic (pH ≤ 4) and basic (pH 10–11) solution. At pH 4, the radical cations decay with first-order kinetics, and the exclusive reaction is C_α–H deprotonation for $1^{\bullet+}$, $2^{\bullet+}$, and $3^{\bullet+}$ (R = H, Me, and Et, respectively) but C_α–C_β bond cleavage for $5^{\bullet+}$, $6^{\bullet+}$, and $7^{\bullet+}$ (R = tBu, CH(OH)Me, and CH(OMe)Me, respectively). Both types of cleavage are observed for $4^{\bullet+}$ (R = iPr). The radical cations of the methyl ethers $8^{\bullet+}$, $9^{\bullet+}$, and $10^{\bullet+}$ (R = H, Et, and iPr, respectively) undergo exclusive deprotonation, whereas C–C fragmentation predominates for $11^{\bullet+}$ (R = tBu). Large C_α deuterium kinetic isotope effects (4.5 and 5.0, respectively) were found for $1^{\bullet+}$ and

its methyl ether $8^{\bullet+}$. Replacement of an α-OH group by OMe has a very small effect on the decay rate when the radical cation undergoes deprotonation, but a very large, negative effect in the case of C–C bond cleavage. It is suggested that hydrogen bonding of the α-OH group with the solvent stabilizes the transition state of the C–C bond fragmentation reaction but not that of the deprotonation process; however, other factors could also contribute to this phenomenon. The decay of the radical cations is strongly accelerated by HO^-, and all the α-OH substituted radical cations react with HO^- at a rate ($\approx 10^{10} \text{M}^{-1}\text{s}^{-1}$) very close to the limit of diffusion control and independent of the nature of the bond that is finally broken in the process (C–H or C–C). The methyl ether $8^{\bullet+}$, which exclusively undergoes C–H bond cleavage, reacts significantly slower (by a factor of ca. 50) than the correspond-

ing alcohol $1^{\bullet+}$. These data indicate that 1-arylalkanol radical cations, which display the expected carbon acidity in water, become oxygen acids in the presence of a strong base such as HO^- and undergo deprotonation of the O–H group; diffusion-controlled formation of the encounter complex between HO^- and the radical cation is the rate-determining step of the reaction. It is suggested that, within the complex, the proton is transferred to the base to give a benzyloxyl radical, either via a radical zwitterion (which undergoes intramolecular electron transfer) or directly (electron transfer coupled with deprotonation). The latter possibility seems more in line with the general base catalysis ($\beta \approx 0.4$) observed in the reaction of $5^{\bullet+}$, which certainly involves O–H deprotonation. The benzyloxyl radical can then undergo a β C–C bond cleavage to form 4-methoxybenzaldehyde and $R^\bullet$ or a formal 1,2-H shift to form an α-hydroxybenzyl-type radical. The factors of importance in this carbon/oxygen acidity dichotomy are discussed.

Keywords: alcohols · cleavage reactions · pulse radiolysis · radical cations · radical reactions

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Introduction

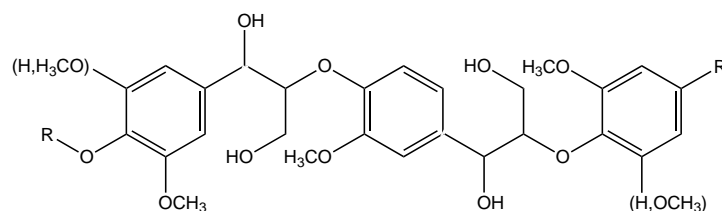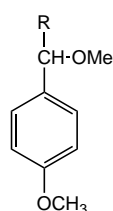The degradation of lignin, a three-dimensional polymer composed of phenylpropane units (Figure 1), is a process of

Figure 1. Schematic representation of lignin showing the β-O-4 inter-unit linkages and the presence of benzyl alcohol groups.
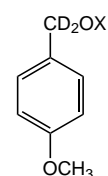
enormous practical importance both for the production of cellulose in the pulp and paper industry and for preparing useful aromatic compounds from a continuously renewable source.[1] Recently, the use of lignin-degrading fungi has generated much interest, and most attention has been focused on the white-rot fungus *Phanerochaete chrysosporium*, which secretes lignin peroxidase (LiP), a ferric hemoprotein that depolymerizes both lignin and its model compounds.[2] Convincing evidence exists that this enzyme unergoes an electron-transfer reaction to form radical cations that structurally resemble the 1-arylalkanol radical cations **A**⁺ where R can be a complex group, for example, CH(CH₂OH)Ar or CH(CH₂OH)OAr. The key step in the degradation process is then the cleavage of the C–R bond [Eq. (1)], a typical side-chain fragmentation reaction of alkylaromatic radical cations.[3] Very likely, this reaction also plays a major role when lignin is degraded by industrial chemical[4] or electrochemical[5] oxidations.
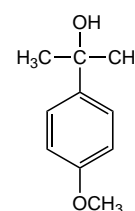
R
CH·OH
(ring)
OCH₃
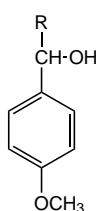
1: R = H
2: R = Me
3: R = Et
4: R = *i*Pr
5: R = *t*Bu
6: R = CH(OH)Me
7: R = CH(OMe)Me

R
CH·OMe
(ring)
OCH₃

8: R = H
9: R = Et
10: R = *i*Pr
11: R = *t*Bu

CD₂OX
(ring)
OCH₃

12: R = H
13: R = Me

OH
H₃C–C–CH₃
(ring)
OCH₃

14

R
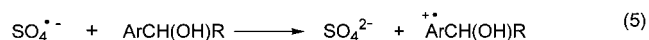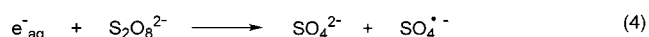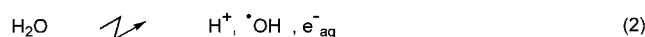CHOH
(ring)
•+
OCH₃
OCH₃

→

CHO
(ring)
OCH₃
OCH₃

+ R• + H⁺   (1)

A•⁺
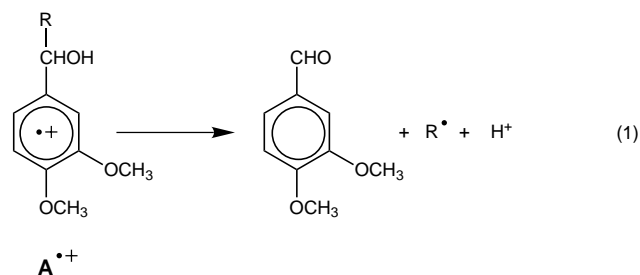
The presence of α-OH groups is a structural feature of fundamental importance in lignin and in the model compound **A**⁺. The OH group strongly favors cleavage of the side-chain C_α–C_β bond (simply referred to as C–C bond in the following) in aromatic radical cations [Eq. (1)].[6] Clear evidence in this respect comes from our previous study on the fragmentation reactions of 1- and 2-arylalkanol radical cations.[7] The important role of the α-OH group was evident in the significantly higher rate of potassium 12-tungstocobalt(III)ate (Co(III)W) induced oxidation of 4-MeOC₆H₄CH(OH)*t*Bu relative to its methyl ether. On the basis of a pulse radiolysis study of the reactivity of the 4-MeOC₆H₄CH(OH)CH₂Ph radical cation, it was suggested that the favorable effect of the α-OH group is mainly due to the stabilization by hydrogen bonding of the transition state that leads to C–C bond cleavage.

Given our continuing interest in the reactivity of alkylaromatic radical cations and the importance of Equation (1) with respect to the catalytic reactivity of LiP, we felt that further investigation of the effects of structure and the basicity of the medium on the reactivity of benzyl alcohol and α-alkylbenzyl alcohol radical cations was necessary. We now report on a pulse and steady-state radiolysis study of the fragmentation reactions of several 1-(4-methoxyphenyl)alkanol radical cations and some of their methyl ethers (substrates **1–14**), in the pH range 3.5–11.[8] This study was carried out in

water (the solvent in which LiP operates) with 4-methoxyl-substituted substrates; the methoxyl group results in radical cations that absorb in the UV/Vis region of the spectrum and have a lifetime sufficient for detection by pulse radiolysis.
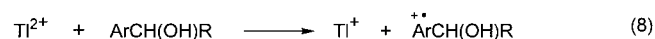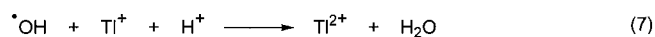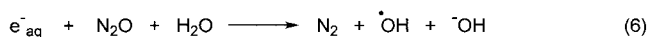
Results

Generation of the radical cations: Radical cations of substrates **1–14** were generated in aqueous solution either by pulse radiolysis or steady-state γ radiolysis with sulfate radical anion $SO_4^{\bullet-}$ or Tl^{2+} as the oxidant. In the former case (method 1) Equations (2)–(5) apply. Radiolysis of water

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

$$^\bullet OH + CH_3C(CH_3)_2OH \longrightarrow H_2O + \;^\bullet CH_2C(CH_3)_2OH \qquad (3)$$

$$e^-_{aq} + S_2O_8^{2-} \longrightarrow SO_4^{2-} + SO_4^{\bullet-} \qquad (4)$$

$$SO_4^{\bullet-} + ArCH(OH)R \longrightarrow SO_4^{2-} + \overset{+\bullet}{Ar}CH(OH)R \qquad (5)$$

leads to formation of hydroxyl radicals ($^\bullet OH$) and hydrated electrons (e^-_{aq}) [Eq. (2)]. The former is scavenged by 2-methyl-2-propanol [Eq. (3); $k = 6 \times 10^8 \, M^{-1} s^{-1}$],[9] while e^-_{aq} reacts with the peroxodisulfate anion to yield $SO_4^{\bullet-}$ [Eq (4); $k = 1.2 \times 10^{10} \, M^{-1} s^{-1}$].[9] Then $SO_4^{\bullet-}$ reacts with the aromatic compounds[10] to form the corresponding radical cations [Eq (5); $k = 5 \times 10^9 \, M^{-1} s^{-1}$ for anisole and derivatives[7, 11]].

For reactions carried out at pH ≤ 4, Tl^{2+}, produced by irradiating N₂O-saturated aqueous solutions of Tl^+ [Eqs. (2), (6)–(8)] was used as oxidant (method 2). The role of N₂O is

$$e^-_{aq} + N_2O + H_2O \longrightarrow N_2 + \;^\bullet OH + \;^- OH \qquad (6)$$

$$^\bullet OH + Tl^+ + H^+ \longrightarrow Tl^{2+} + H_2O \qquad (7)$$

$$Tl^{2+} + ArCH(OH)R \longrightarrow Tl^+ + \overset{+\bullet}{Ar}CH(OH)R \qquad (8)$$

to scavenge e^-_{aq} ($k = 9.1 \times 10^9 \, M^{-1} s^{-1}$),[12] leading to formation of hydroxyl radicals [Eq. (6)]. Oxidation of Tl^+ by $^\bullet OH$[13] produces Tl^{2+} [Eq (7); $k = 1.2 \times 10^{10} \, M^{-1} s^{-1}$],[14] which is known to react with aromatic compounds by one-electron

transfer to give the corresponding radical cations [Eq (8); $k \approx 5 \times 10^8 \, M^{-1} \, s^{-1}$].[11]

Product analysis: It is well known that two fragmentation pathways are possible for 1-arylalkanol radical cations (Scheme 1, R ≠ H): heterolytic cleavage of the C_α–H bond (path **a**; from now on, C_α–H is referred to as C–H) and homolytic cleavage of the C–C bond (path **b**).[15–17]
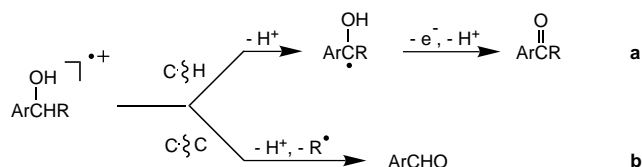
Scheme 1. The two possible fragmentation pathways for 1-arylalkanol radical cations.

For path **a**, an α-hydroxybenzyl-type radical is formed that, under oxidizing conditions (vide infra), undergoes oxidation followed by proton loss to give the corresponding ketone. Path **b** leads directly to an aromatic aldehyde. Hence, the study of the reaction products provides quantitative information on the relative importance of the two fragmentation pathways of 1-arylalkanol radical cations.

The reaction products of radical cations $2^{\cdot+}$–$5^{\cdot+}$ and $9^{\cdot+}$–$11^{\cdot+}$ were analyzed after steady-state γ radiolysis, using method 1 to produce the radical cations. Argon-saturated aqueous solutions containing 0.5–5.0mM substrate, 0.2–1.0mM $K_2S_2O_8$, and 0.2–1.0M 2-methyl-2-propanol were irradiated at room temperature with a ^{60}Co γ source at dose rates of 0.5 Gys^{-1} until 40% conversion with respect to peroxodisulfate was attained. In order to minimize over-oxidation of the initial products, all experiments were carried out with a substrate/oxidant ratio ≥ 2. The product distribution was studied at pH ≈ 4 and 11. Products were identified and quantitatively determined by HPLC (comparison with authentic samples). The results are collected in Table 1.

It is evident that at pH 4 deprotonation is the exclusive reaction of the α-alkylbenzyl alcohol radical cations $2^{\cdot+}$ and $3^{\cdot+}$ (R = Me and Et, respectively), whereas $5^{\cdot+}$ (R = tBu) undergoes almost exclusively C–C bond cleavage. For $4^{\cdot+}$ (R = iPr), both C–C and C–H bond cleavage are observed. The methyl ethers $9^{\cdot+}$ and $10^{\cdot+}$ (R = Et and iPr, respectively) undergo exclusively deprotonation, whereas with $11^{\cdot+}$ (R = tBu) partitioning between the two pathways occurs. The C–C bond cleavage is the only pathway for $6^{\cdot+}$ and $7^{\cdot+}$, in which an OX group (X = H, Me) is present in the β position of the side chain.

When the reactions are carried out in the presence of 1mM NaOH (pH 11), there is a significant increase in the extent of C–C bond cleavage, which becomes the main path for $3^{\cdot+}$ (R = Et) and the almost exclusive path for $4^{\cdot+}$ (R = iPr).

Pulse radiolysis: The radical cations were produced by methods 1 and 2 with a 300 ns, 3 MeV electron pulse. In all cases they exhibited the characteristic UV/Vis absorption bands, centered around 290 and 440–450 nm, of anisole-type

Table 1. Product distributions obtained from the decomposition of 4-MeOC$_6$H$_4$CH(X)R radical cations in aqueous solution.[a]

	R	X	pH[b]	Aldehyde [%]	Ketone [%]
$2^{\cdot+}$	Me	OH	4	< 0.1	> 99.9
			11	< 0.1	> 99.9
$3^{\cdot+}$	Et	OH	4	0.5	99.5
			11	70.0	30.0
$9^{\cdot+}$	Et	OMe	4	0.5	99.5
$6^{\cdot+}$	CH(OH)Me	OH	[c]	≥ 99.5	–
$7^{\cdot+}$	CH(OMe)Me	OH	[c]	≥ 99.5	–
$4^{\cdot+}$	iPr	OH	4	11.0	89.0
			11	95.0	5.0
$10^{\cdot+}$	iPr	OMe	4	1.5	98.5
$5^{\cdot+}$	tBu	OH	4	> 95	[d]
			11	> 95	[d]
$11^{\cdot+}$	tBu	OMe	4	88	12

[a] The radical cations were generated at room temperature by method 1, by steady-state ^{60}Co γ radiolysis of argon-saturated aqueous solutions containing 0.5–5.0mM substrate, 0.2–1.0mM $K_2S_2O_8$, and 0.2–1.0M 2-methyl-2-propanol (substrate/oxidant ratio between 2 and 5). The reported values are the average of two to four experiments. [b] The pH of the solution was adjusted to 4 or 11 with $HClO_4$ or NaOH. [c] The oxidation reactions were carried out in 55/45 AcOH/H_2O at 50 °C with Co(III)W as oxidant (ref. [7] and unpublished results). [d] A small amount of ketone (< 5%) was observed under all conditions. The fact that this amount is not influenced significantly by the presence of the base is probably due to the existence of a background hydrogen atom abstraction reaction by $SO_4^{\cdot-}$ that eventually leads to formation of the ketone. In agreement with this hypothesis is the observation that in the oxidation of **5** by Co(III)W, a well-known outer sphere one-electron oxidant but not an H atom abstractor,[18, 19] the only observed product was 4-methoxybenzaldehyde.[7, 20]

radical cations.[7, 11] The rates of decay of the radical cations were determined spectrophotometrically by measuring the decrease in optical density at 440–450 nm or by monitoring the production of H$^+$ by the ac-conductance technique.

In acid media (pH ≤ 4), the latter technique was generally preferred, and radical cations were more often generated by method 2 than by method 1. The conductance technique has higher sensitivity under our pulse-radiolysis conditions and hence allows the use of significantly lower dose/pulse ratios than the spectrophotometric technique. The advantage of method 2 is that scavenging of ·OH by 2-methyl-2-propanol is not necessary, so that the high concentration of ·CH$_2$C(CH$_3$)$_2$OH radicals formed in this process [Eq. (3)] is avoided. Use of low doses and thus low concentrations of radicals in solution is particularly important when dealing with long-lived radical cations (lifetime ≥ 0.1 ms) for which decay by second-order radical–radical reactions begins to compete with unimolecular decay.[21] This problem is much less important in basic media, in which decomposition of the radical cations is significantly faster. Therefore, under basic conditions, the radical cations were always generated by method 1, and the rates were monitored by spectrophotometry.

As an example, the time-resolved spectra obtained for the oxidation of **2** at pH 3.9 are shown in Figure 2, in which the characteristic absorptions due to the radical cation $2^{\cdot+}$, centered at 290 and 440 nm,[7, 11] are clearly visible. These absorptions reach a maximum 5 μs after the pulse [completion of radical cation formation, Eq. (5)] and then decrease according to first-order kinetics (see inset a for absorption at 440 nm) that reflects the decay of the radical cations. This
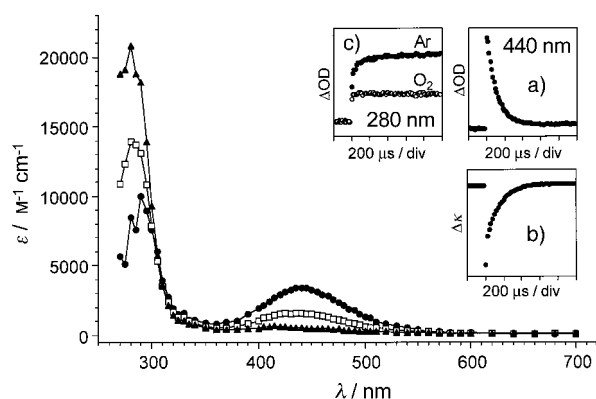
Figure 2. Time-resolved absorption spectra for the reaction of SO$_4^{\cdot-}$ with **2** (0.2 mM) recorded on pulse radiolysis of an Ar-saturated aqueous solution (pH 3.9) containing 0.1 M 2-methyl-2-propanol and 10 mM K$_2$S$_2$O$_8$, at 5 (●), 200 (□), and 700 μs (▲) after the 300 ns, 3 MeV electron pulse. Insets: a) First-order decay of **2**$^{\cdot+}$ monitored at 440 nm; b) Buildup of conductance (due to production of H$^+$) in the decay of **2**$^{\cdot+}$; c) Buildup of absorption at 280 nm due to formation of 4-MeOC$_6$H$_4$C$^{\cdot}$(OH)CH$_3$ (Ar, ●), which is scavenged by O$_2$ (○). For the determination of the extinction coefficient, G(radical cation) $= G$(SO$_4^{\cdot-}$) $= 3.1 \times 10^{-7}$ mol J^{-1} was used.[22]

decay is accompanied (inset c) by a corresponding buildup of optical density around 280 nm, which indicates the formation of a product that absorbs at this wavelength more strongly than the radical cation itself (an isosbestic point is visible at $\approx$ 310 nm). In this case, the decay of the radical cation was also followed by monitoring the production of H$^+$ by the conductance technique (inset b), and the first-order rate constant obtained in this way was the same as that obtained by measuring the decrease in absorption at 440 nm (inset a).

Inset c shows that the absorption buildup at 280 nm is no longer observed when O$_2$ is present, and this indicates that the species responsible for this absorption is rapidly scavenged by oxygen. This suggests that this species is a carbon-centered radical and that therefore the decay of the radical cation involves C$-$H deprotonation (Scheme 1, path **a**) to give the 4-methoxy-α-hydroxybenzyl-type radical 4-MeOC$_6$H$_4$-CH$^{\cdot}$(OH)CH$_3$, as is also indicated by the products (Table 1).

Similar results were obtained with the other substrates, with the exception of **5**$^{\cdot+}$, **6**$^{\cdot+}$, and **7**$^{\cdot+}$. In the case of **5**$^{\cdot+}$, decay of the radical cation led to the formation of a species which has a strong absorption at 285 nm and does not react with oxygen. This species was identified as 4-methoxybenzaldehyde, formed by homolytic C$-$C bond fragmentation of the radical cation (Scheme 1, path **b**), again in agreement with the study of the reaction products.[7]

The decay of **6**$^{\cdot+}$ and **7**$^{\cdot+}$ led to the formation of a species that absorbs strongly around 280 nm and is quenchable by oxygen. This species was identified as the 4-methoxy-α-hydroxy benzyl radical 4-MeOC$_6$H$_4$CH$^{\cdot}$(OH), formed by heterolytic C$-$C bond fragmentation of the radical cations (Scheme 2: Ar $=$ 4-MeOC$_6$H$_4$; X $=$ H, Me).

$$\overset{\cdot+}{\text{ArCH(OH)CH(OX)Me}} \longrightarrow \overset{\cdot}{\text{ArCHOH}} + \overset{+}{\text{CH(OX)Me}}$$
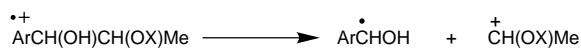
Scheme 2. Heterolytic C$-$C bond fragmentation of the radical cations (Ar $=$ 4-MeOC$_6$H$_4$; X $=$ H, Me).

For **6**$^{\cdot+}$ and **7**$^{\cdot+}$, the decay rate of the radical cation is very high. It is therefore necessary to find conditions under which formation of the radical cation [Eq. (5)] is not rate-determining. This requirement is satisfied at concentrations of the parent substrates of $\geq$ 7 mM and 1 mM for **6**$^{\cdot+}$ (Figure 3) and
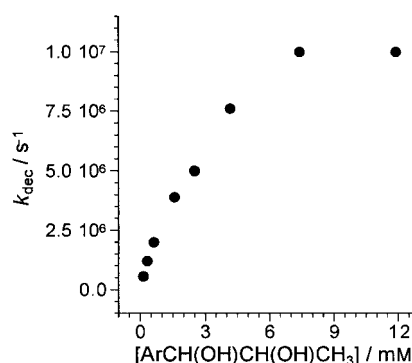

Figure 3. Plot of k_{dec} versus [**6**]. The radical cation was generated by method 1 from an argon-saturated aqueous solution containing (0.1 – 12 mM) **6**, 20 mM K$_2$S$_2$O$_8$, and 0.2 M 2-methyl-2-propanol, and its decay was monitored at 450 nm (Ar $=$ 4-MeOC$_6$H$_4$).

7$^{\cdot+}$, respectively. Thus, for **6**$^{\cdot+}$ and **7**$^{\cdot+}$, the decay rates obtained after reaching the plateau in the plots of k_{dec} versus substrate concentration were taken as the unimolecular decomposition rates. (In all other cases, the decay rates are much smaller than the formation rates even at lower substrate concentrations.)

The first-order rate constants for decay in water at pH 4 of the investigated radical cations are listed in Table 2. These

Table 2. Rate constants k_{dec} for the uncatalyzed decay of radical cations **1**$^{\cdot+}$–**14**$^{\cdot+}$, generated by pulse radiolysis of the parent substrate 4-MeOC$_6$H$_4$CH(X)R in aqueous solution (pH $\leq$ 4) at 25 °C.

	R	X	k_{dec} [s^{-1}] [a]	Bonds cleaved
1$^{\cdot+}$	H	OH	1.5×10^4 1.8×10^{4}[b]	C$-$H
12$^{\cdot+}$	D	OH	3.3×10^3	C$-$D
8$^{\cdot+}$	H	OMe	1.5×10^4	C$-$H
13$^{\cdot+}$	D	OMe	3.0×10^3	C$-$D
2$^{\cdot+}$	Me	OH	7.0×10^3 9.0×10^{3}[b]	C$-$H
3$^{\cdot+}$	Et	OH	5.4×10^3	C$-$H
9$^{\cdot+}$	Et	OMe	1.6×10^3	C$-$H
4$^{\cdot+}$	iPr	OH	3.5×10^3	C$-$H, C$-$C
10$^{\cdot+}$	iPr	OMe	1.1×10^3	C$-$H
5$^{\cdot+}$	tBu	OH	1.5×10^{5}[b]	C$-$C
11$^{\cdot+}$	tBu	OMe	23	C$-$H, C$-$C
6$^{\cdot+}$	CH(OH)Me	OH	1.0×10^{7}[b, c]	C$-$C
7$^{\cdot+}$	CH(OMe)Me	OH	1.0×10^{6}[b]	C$-$C
14$^{\cdot+}$	Me,Me[d]	OH	2.9×10^2	C$-$C

[a] The radical cations were generated by method 2, with doses such that $\leq$ 1 μM of radicals were produced. Rates of decay were measured by monitoring the increase in conductance at pH $\approx$ 3.5. [b] The radical cations were generated by method 1 in argon-saturated aqueous solutions containing 0.1 – 1.0 mM substrate, 2.0 mM K$_2$S$_2$O$_8$, and 0.1 M 2-methyl-2-propanol, the pH was adjusted to about 4 with HClO$_4$, and the rates of decay were measured by monitoring the decrease in optical absorption at 440 – 450 nm: dose $\approx$ 1 Gy per pulse. [c] Obtained by using 7 – 12 mM of substrate (see text). The pulse width was reduced to 25 ns. [d] 4-Methoxycumyl alcohol (4-MeOC$_6$H$_4$C(OH)Me$_2$), in which the second α-hydrogen atom is also replaced by a methyl group.

rate constants did not change in the pH range 3–5, but significantly increased on addition of HO⁻. This effect was studied quantitatively for the radical cations $1^{\cdot+}$–$5^{\cdot+}$, $8^{\cdot+}$, and $12^{\cdot+}$–$14^{\cdot+}$, the decay rates of which were measured spectrophotometrically at 440–450 nm as a function of the HO⁻ concentration. Clean first-order decays were observed, and linear dependencies of the observed rates (k_{obs}) on the concentration of HO⁻ were found. From the slope of these plots, the second-order rate constants (k_{HO^-}) for the reaction of HO⁻ with the radical cations were determined (Table 3).

Table 3. Rate constants (k_{OH^-}) for the ⁻OH-promoted decay of radical cations 4-MeOC₆H₄CH(X)R$^{\cdot+}$ generated by pulse radiolysis of the parent substrate in aqueous solution at 25 °C.[a]

	R	X	k_{OH^-} [M⁻¹s⁻¹][b]	Bonds cleaved
$1^{\cdot+}$	H	OH	1.2×10^{10}[c]	C–H
$12^{\cdot+}$	D	OH	1.1×10^{10}[c]	C–D
$8^{\cdot+}$	H	OMe	2.5×10^{8}	C–H
$13^{\cdot+}$	D	OMe	1.4×10^{8}	C–D
$2^{\cdot+}$	Me	OH	1.4×10^{10}[c]	C–H
$3^{\cdot+}$	Et	OH	1.2×10^{10}	C–H, C–C
$4^{\cdot+}$	iPr	OH	1.2×10^{10}	C–H, C–C
$5^{\cdot+}$	tBu	OH	1.3×10^{10}[c]	C–C
$14^{\cdot+}$	Me, Me[d]	OH	1.2×10^{10}[c]	C–C

[a] The radical cations were generated by method 1 from oxygen-saturated aqueous solutions containing 1.0 mM substrate, 10 mM K₂S₂O₈, and 0.1 M 2-methyl-2-propanol with doses such that ≤3 μM of radicals were produced. 1 mM Na₂B₄O₇ was added to buffer the pH of the solution. [b] The observed rates were measured by monitoring the decay of the optical absorption at 440–450 nm. The pH of the solution was varied between 8.5 and 10.5, and the second-order rate constants for reaction of the radical cations with HO⁻ were obtained from the slope of the plots of the observed rates k_{obs} versus the NaOH concentrations. [c] Lower rates were observed in the presence of 0.5 M Na₂SO₄ (negative salt effect).[8] See also Table 4. [d] 4-Methoxycumyl alcohol (4-MeOC₆H₄C(OH)Me₂), in which the second α-hydrogen atom is also replaced by a methyl group.

Discussion

Studies in water at pH 4: The results of product studies and pulse-radiolysis experiments (Tables 1 and 2) show that the decay of radical cations $1^{\cdot+}$–$4^{\cdot+}$, $8^{\cdot+}$–$10^{\cdot+}$, $12^{\cdot+}$, and $13^{\cdot+}$ proceeds by cleavage of the C–H bond. This is well supported by the large deuterium kinetic isotope effect ($k_H/k_D = 4.5$ for $1^{\cdot+}/12^{\cdot+}$ and $k_H/k_D = 5.0$ for $8^{\cdot+}/13^{\cdot+}$). Probably, H₂O is the proton-abstracting base as the rate constants did not change between pH 3 and 5.

Replacement of an α-OH group by an α-OMe group has a very small effect upon the deprotonation rate, as shown by the fact that the reactivities of $1^{\cdot+}$, $3^{\cdot+}$, and $4^{\cdot+}$ are similar to those of the corresponding methyl ethers $8^{\cdot+}$, $9^{\cdot+}$, and $10^{\cdot+}$. This situation, however,

is drastically different for C–C bond cleavage. The rate of this process is slowed down by almost four orders of magnitude on going from the alcohol radical cation $5^{\cdot+}$ to its methyl ether $11^{\cdot+}$. This rate effect is particularly striking if one considers that $5^{\cdot+}$ and $11^{\cdot+}$ have very similar C–C bond dissociation energies (BDE).[23]

This large difference between the effects of α-OH and α-OMe on the cleavage of the C–C bond was already noted by us, although indirectly, in a study of the chemical oxidation of **5** and **11**. It was suggested that the OH group permits a strong stabilization of the transition state of the C–C bond fragmentation reaction by engaging in hydrogen bond formation with solvent molecules.[7] This concept can be extended to explain the intriguing fact that, in contrast to C–C cleavage, there is no significant difference between α-OH and α-OMe when the cleavage of the radical cation involves the C–H bond.

Scheme 3 (Ar = 4-MeOPh) illustrates, with the mesomeric structures **a**–**e**, how the α-OH group may engage in hydrogen-bond stabilization of the transition state in the homolytic C–C bond cleavage reaction. Mesomer **c**, with a positively charged oxygen atom and a fully formed C=O double bond, should be particularly important, and for this structure strong stabilization by hydrogen bonding with the solvent water is anticipated.

In contrast, the transition state for the C–H bond cleavage (Scheme 4; the proton-accepting base H₂O is also shown) is envisaged as a resonance hybrid of structures **f**–**j**. The most important structure is probably **j**, which represents the heterolytic cleavage of the C–H bond, whereas structure **h** (corresponding to **c** in Scheme 3) should be unimportant since it involves unfavorable homolytic cleavage of the C–H bond.

An additional aspect is that OH ($\sigma^+ = -0.92$)[25] is a significantly more efficient electron donor than OMe ($\sigma^+ = -0.78$).[25, 26] This difference in the ability for electron donation is likely to be felt more in the transition state of the C–C bond cleavage that in that for C–H cleavage, since there is evidence that a greater accumulation of positive charge (by bond delocalization) is required in the former transition state than in the latter.[27–29]
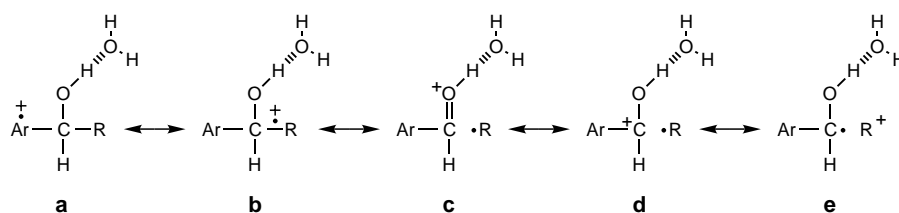
Scheme 3. The transition state for the homolytic C–C bond cleavage reaction (Ar = 4-MeOPh).
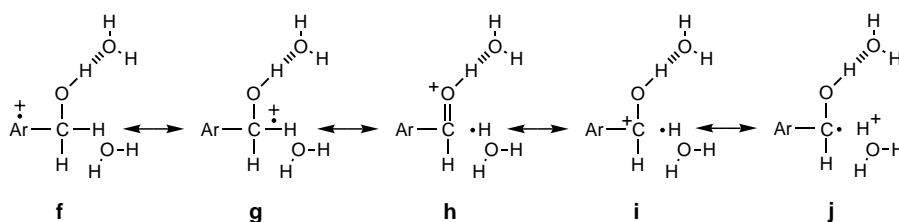
Scheme 4. The transition state for the C–H bond cleavage with the proton-accepting base H₂O.

Savéant et al. recently pointed out that the (rate-determining) C−C bond cleavage step in a radical cation may be reversible. If so, the overall rate will be high only if the subsequent reactions of the cleavage fragments are sufficiently fast.[30] This is certainly the case for $5^{\cdot+}$, which gives rise to 4-MeOC$_6$H$_4$CH$^+$OH, from which deprotonation to 4-MeOC$_6$H$_4$CHO should be extremely rapid, but not for $11^{\cdot+}$, which yields 4-MeOC$_6$H$_4$CH$^+$OMe, a stabilized carbocation that cannot deprotonate. Therefore $5^{\cdot+}$ should be more reactive than $11^{\cdot+}$, as is observed (Table 2).

For the radical cations with an OX group (X = H, Me) in the β position, such as $6^{\cdot+}$ and $7^{\cdot+}$, a different situation applies since the C−C bond cleavage is now heterolytic (Scheme 2). At first sight, this observation is surprising, as the oxidation potentials in MeCN of $\cdot$CH(OX)Me (X = H, Me: − 0.45 V vs. SCE)[31] and 4-MeOC$_6$H$_4$CH$\cdot$OH (− 0.51 V vs. SCE)[32, 33] suggest a slight preference for homolytic cleavage. However, in H$_2$O the difference in solvation energy between 4-MeOC$_6$H$_4$CH$^+$OH and the smaller and less delocalized carbocation $^+$CH(OX)Me should be much larger than in MeCN.[34] Hence, in H$_2$O the oxidation potential of $\cdot$CH(OX)Me (X = H, Me) is likely to be significantly more negative than that of 4-MeOC$_6$H$_4$CH$\cdot$OH, and heterolytic C−C bond cleavage is therefore the favored pathway for $6^{\cdot+}$ and $7^{\cdot+}$.

The above-mentioned difference in the electronic effects of OH and OMe may also explain the higher reactivity of $6^{\cdot+}$ compared with $7^{\cdot+}$.[35, 36] On the same basis, the observation that $7^{\cdot+}$ fragments more rapidly than $5^{\cdot+}$ suggests that the OMe group is more effective than two methyl groups in stabilizing the partial positive charge that develops on the scissible C−C bond in the transition state for C−C bond cleavage.

Finally, information on the effect of the α-alkyl group upon the rate of C−H cleavage is provided by comparison of the radical cations $1^{\cdot+}$–$4^{\cdot+}$, which undergo C−H bond cleavage (Table 1) exclusively ($1^{\cdot+}$-$3^{\cdot+}$) or as the main reaction path ($4^{\cdot+}$). The kinetic data in Table 2 show that by changing the α-alkyl group the deprotonation rate decreases in the order H > Me > Et > iPr, as expected on the basis of stereoelectronic effects.[37, 38] The bulkier the alkyl group, the more energetically costly it is to reach the conformation most suitable for bond cleavage, that is, one in which the C−H bond is collinear with the π-electron system. The differences in rate for the three alkyl groups are rather small, but this is not surprising since when dealing with steric effects in the alkyl-group series, drastic changes are generally observed only on going from iPr to tBu.[39] Probably, this holds also in the present case, but unfortunately we were unable to determine a reliable reaction rate for the deprotonation of $5^{\cdot+}$, since it undergoes almost exclusively C−C bond cleavage (see footnote [d] in Table 1).

Reactions in the presence of HO$^-$: Remarkably, all α-OH-substituted radical cations react with HO$^-$ at the same rate (Table 3), that is, that of a diffusion-controlled reaction ($\approx 10^{10}$ M^{-1}s^{-1}),[40] independent of the nature of the bond eventually broken in the process (C−H or C−C). In line with this, comparing $1^{\cdot+}$ with its C$_\alpha$-deuterated counterpart $12^{\cdot+}$ reveals no deuterium kinetic isotope effect.

There is a decrease in reaction rate (ca. 50-fold) on going from $1^{\cdot+}$ to its methyl ether $8^{\cdot+}$, which undergoes C−H bond cleavage and accordingly has a k_H/k_D value of 1.8 (cf. $8^{\cdot+}$ and $13^{\cdot+}$). The difference in reactivity of $1^{\cdot+}$ and $8^{\cdot+}$ cannot be attributed to a difference in the electronic effects of OH and OMe, since in acid medium the influence of these groups on C−H deprotonation is very similar (see previous section). Hence, this observation together with the very similar reactivity of $1^{\cdot+}$ and $5^{\cdot+}$, in spite of the different types of side-chain fragmentation, point to a mechanism in which the α-OH group plays a key and specific role.

The high (diffusion-controlled) rates are typical of thermodynamically favored proton-transfer reactions between electronegative atoms.[41] The most reasonable conclusion is that in the radical cations with α-OH substituents, the reaction center is the α-OH group itself. In other words, these radical cations, which in water display the expected carbon acidity, become oxygen acids in the presence of a strong base such as HO$^-$ and undergo OH deprotonation as the first step of the decay process.

The fact that the deprotonation rate is diffusion-controlled indicates that the interaction between HO$^-$ and the radical cation to form the encounter complex is the rate-determining step of the reaction.[41] Therefore, the radical cation must be a stronger oxygen acid than H$_2$O, that is, its pK_a must be much smaller than 15.7.[42] Once the complex is formed, several pathways linking the complex to the observed C−C and C−H fragmentation products can be envisaged (Scheme 5, Ar = 4-MeOC$_6$H$_4$).
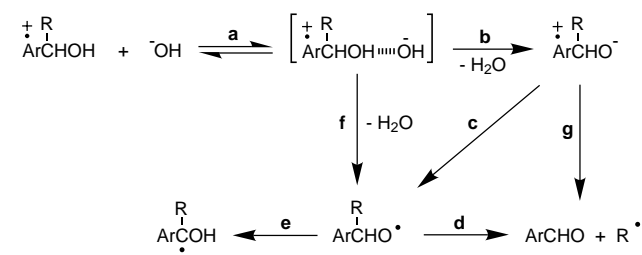

Scheme 5. Possible pathways linking the complex to the observed C−C and C−H fragmentation products (Ar = 4-MeOC$_6$H$_4$).

Within the complex, the proton may be transferred to the base to give a benzyloxyl radical directly (intramolecular electron transfer concerted with deprotonation, path **f**), or via a radical zwitterion which undergoes intramolecular electron transfer (paths **b**, **c**). Two routes are then available for the benzyloxyl radical: β C−C bond cleavage to form 4-methoxybenzaldehyde and the radical R$\cdot$ (path **d**), or a formal 1,2-H shift to give an α-hydroxybenzyl-type radical (path **e**).

Both C−C β cleavage[44] and 1,2-H shift reactions[45] are well-known processes for alkoxyl radicals. The latter seem to be limited to aqueous solution[46] and require the participation of solvent molecules (a direct shift of the H atom from carbon to oxygen would have too high an energetic cost).[47] The competition in the benzyloxyl radical between β cleavage and 1,2-H shift should depend on the stability of R$\cdot$. Hence, our experimental observations (Table 1) lead to the conclusion

that when R is H or Me, the 1,2 shift is the exclusive pathway, whereas when R is *t*Bu, only β cleavage occurs. An intermediate situation apparently holds for R = Et and *i*Pr.

A further alternative is concerted electron transfer and side-chain fragmentation in the zwitterion (path **g**). Thus, the products might be formed without the intermediacy of the benzyloxyl radical. Intramolecular electron transfer coupled with side-chain fragmentation was suggested to occur in the reactions of aromatic radical anions.[48, 49] However, we were recently able to directly observe the 4-methoxycumyloxyl radical in the HO⁻-promoted C−C bond fragmentation of the 4-MeOC₆H₄C(CH₃)₂OH radical cation **14**·⁺ to form 4-MeOC₆H₄COCH₃ (Scheme 6).[50] Since **14**·⁺ also reacts with HO⁻ at a diffusion-controlled rate (see Table 3), it is very likely that this reaction occurs with the mechanism shown in Scheme 5 (paths **a–d** or alternatively **a, f, d**).
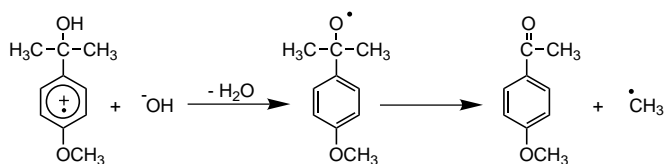
Scheme 6. The 4-methoxycumyloxyl radical as intermediate in the HO⁻-promoted C−C bond fragmentation of the 4-MeOC₆H₄C(CH₃)₂OH radical cation.

These data support the hypothesis of the formation of an intermediate benzyloxyl radical in the HO⁻-promoted decay of 1-arylalkanol radical cations. However, some caution has to be exerted with respect to the generality of this conclusion. The results for cumyl alcohol refer to a system in which intramolecular electron transfer in the radical zwitterion leads to a relatively stable benzyloxyl radical as its fragmentation produces the methyl radical, that is, the least stable alkyl radical.

To obtain further information on the detailed mechanism of the O−H deprotonation process, we studied the decay of **1**·⁺, **2**·⁺, **5**·⁺, and **8**·⁺ in buffer systems. At constant pH, the rates depended upon the buffer concentration, indicating general base catalysis. The second-order rate constants for the reactions with AcO⁻, HCO₃⁻, and HPO₄²⁻ are listed in Table 4, together with those for the reaction with HO⁻.

Table 4. Second-order rate constants for reaction of **1**·⁺, **2**·⁺, **5**·⁺, and **8**·⁺, generated by pulse radiolysis in aqueous solution, with different bases at 25 °C.[a]

	k(AcO⁻) [M⁻¹s⁻¹]	k(HCO₃⁻) [M⁻¹s⁻¹]	k(HPO₄²⁻) [M⁻¹s⁻¹]	k(HO⁻) [M⁻¹s⁻¹][b, c]
1·⁺	2.8×10^5	6.0×10^5	2.7×10^6	$5.4 \times 10^{9[d]}$
2·⁺	7.8×10^4	7.3×10^5	9.9×10^5	$5.3 \times 10^{9[d]}$
5·⁺	8.0×10^4	7.2×10^5	1.5×10^6	6.0×10^9
8·⁺	4.2×10^5	7.0×10^5	1.9×10^6	2.0×10^8

[a] The radical cations were generated by method 1, with doses such that ≤ 3 μM of radicals were produced. The ionic strength of the solution was buffered with 0.5 M Na₂SO₄. In the experiments with NaOAc, NaHCO₃, and Na₂HPO₄, the pH of the solution was kept constant (5.5, 7.0, and 8.0 respectively). [b] The pH of the solution was varied between 8.5 and 10.5, and 1 mM Na₂HPO₄ was added to avoid undesired pH changes. [c] The values are lower than those reported in Table 3 due to the presence of 0.5 M Na₂SO₄, which exerts a negative salt effect. [d] Saturated with oxygen.

Satisfactory linear Brønsted plots were obtained from these data, and the reactions of the α-OH-substituted radical cations **1**·⁺, **2**·⁺, and **5**·⁺ have practically the same β value (ca. 0.4), a value higher than that of 0.25 for the reaction of the methyl ether **8**·⁺, whose deprotonation involves the C−H bond. However, it has to be pointed out that with the buffer bases the rate constants for reaction with **8**·⁺ and the α-OH-substituted radical cations are very similar so that the β values are practically determined by the rate constants for the HO⁻-induced reaction, which are in all cases similar. Thus, we cannot be sure whether, with weaker bases than HO⁻, **1**·⁺ and **2**·⁺ undergo C−H or O−H deprotonation, and a meaningful discussion of their β values is therefore not possible. This, however, is not the case for the reaction of **5**·⁺, which should undergo O−H deprotonation. The fact that with the buffer bases the rate of this reaction is much lower than the diffusion-controlled limit suggests that with the weaker bases the proton transfer is thermodynamically uphill. This is because the benzyl alcohol-type radical cations are weaker oxygen acids than the conjugate acids of the buffers. Interestingly, the Brønsted value is smaller than unity, the value expected for uphill proton transfer between oxygen atoms.[41] This may mean that proton transfer is not the only process involved in the rate-determining step,[51] but that it is coupled with intramolecular electron transfer that leads directly to the oxyl radical (Scheme 5, step **f**). However, deprotonation coupled to some extent with C−C bond cleavage may also be consistent with the above results. At present no clear-cut choice between these alternatives is possible, and further studies with a wider range of structures and redox properties of the substrates are necessary.

Regardless of the detailed mechanism by which the encounter complex is converted into the products, our results clearly indicate that benzyl alcohol radical cations exhibit the expected carbon acidity in water (pH ≤ 4), but become oxygen acids in the presence of HO⁻. This shift from carbon to oxygen acidity, unprecedented in the chemistry of aromatic radical cations, is both interesting and surprising, since only the C−H but not the O−H bond can overlap efficiently with the π system of the aromatic radical cation and, from the (thermodynamic) acidity point of view, the deprotonation of the side-chain α carbon atom (carbon acidity pK_a = − 7.5 in MeCN)[24, 34] is strongly favored over deprotonation at oxygen.[42] We feel that an explanation may be found in terms of the concept of hard and soft acids and bases. The O−H group is a much harder acid center than C−H, and its hardness is probably also increased by the presence of the positive charge in the ring. Thus, the interaction of the O−H group with the charged hard base HO⁻ might be particularly favorable owing to an effective electrostatic interaction to form a relatively stable hard−hard complex.[52] With the uncharged base H₂O, no favorable electrostatic interaction can occur and reaction takes place at the softer acid center C−H.

The problem can also be dealt with in terms of the Marcus theory of proton-transfer reactions on the basis of the fact that carbon acids have a much larger intrinsic barrier for proton transfer than oxygen acids.[53] In particular, Savéant has recently shown for the case of radical cations from NADH

analogues and alkylaromatic compounds that the intrinsic barrier for C−H deprotonation correlates with the homolytic bond-dissociation energy.[54] Thus, when a very weak base (H₂O) is involved, the effect of the much larger driving force of C−H deprotonation predominates, whereas the intrinsic barrier that favors O−H deprotonation comes into play when the base is strong (HO⁻).

Further work, including theoretical calculations, aimed at a better understanding of this mechanistic dichotomy is under way.

Conclusions

The results presented above have unveiled the existence of a hitherto unknown mechanistic dichotomy for the reactions of α-R-substituted (R = H, Me, Et) benzyl alcohol radical cations. In water, in the absence of any other base, these species display the expected carbon acidity of alkylaromatic radical cations and undergo C_{α}−H deprotonation with formation of an α-hydroxyl-substituted carbon radical. However, when HO⁻ is present, they behave as oxygen acids, and deprotonation involves the alcoholic C_{α}−OH bond. It is possible that a benzyloxyl radical is formed via a radical zwitterion that undergoes an intramolecular electron transfer or directly (concerted proton transfer and intramolecular electron transfer). The latter possibility seems more in line with the general base catalysis observed in the reaction of 5·⁺ ($\beta \approx 0.4$), a process that certainly involves deprotonation of the O−H group. Once formed, the benzyloxyl radical undergoes a 1,2-H shift to give an α-hydroxyl-substituted carbon radical. When R ⧧ H, the benzyloxyl radical can also undergo β cleavage of the C−C bond. This mechanism accounts well for the products and is also supported by the direct observation of the 4-methoxycumyloxyl radical in the HO⁻-promoted reaction of the radical cation of 4-methoxycumyl alcohol. However, at present the possibility that side-chain fragmentation is to some extent concerted with OH deprotonation cannot be excluded, at least as far as C−C bond cleavage is concerned. The observed shift from carbon acidity in water to oxygen acidity in the presence of HO⁻ can be interpreted in terms of the concept of hard and soft acids and bases as well as by the Marcus theory.

Another interesting result is that when water is the only base present, the α-OH group exerts a large favorable effect upon the decay rate of α-alkylbenzyl alcohol radical cations if the decay involves cleavage of the C−C bond but not in the case of C−H deprotonation. By considering the structures that contribute to the transition states of the two processes, we have noticed that only in the former case does the presence of the α-OH group allow significant stabilization of the transition state by hydrogen bonding. Other factors of importance include the different electronic effects of OH and OMe as well as the different reactivity of the fragments formed in the cleavage.

Experimental Section

Reagents: Potassium peroxodisulfate, potassium dihydrogenphosphate, disodium hydrogenphosphate, sodium acetate, sodium hydrogencarbonate, sodium hydroxide, disodium tetraborate decahydrate, potassium thiocyanate, thallium(I) sulfate, perchloric acid, and 2-methyl-2-propanol were of the highest commercially available quality. Milli-Q-filtered (Millipore) water was used for all solutions. 4-Methoxybenzyl alcohol (**1**; Aldrich) and 1-(4-methoxyphenyl)ethanol (**2**; Aldrich) were used as received. 1-(4-Methoxyphenyl)-1-propanol (**3**), 1-(4-methoxyphenyl)-2-methyl-1-propanol (**4**), 1-(4-methoxyphenyl)-2,2-dimethyl-1-propanol (**5**), *threo*-1-(4-methoxyphenyl)-1,2-propanediol (**6**), 1-(4-methoxyphenyl)-2-methoxy-1-propanol (*erythro/threo* mixture) (**7**), and the methyl ethers **9 – 11** were prepared according to literature procedures.[7, 55] α,α-[D₂]-4-Methoxybenzyl alcohol (**12**) was synthesized by reduction of 4-methoxybenzoic acid with LiAlD₄.[56] The corresponding methyl ether (**13**) was prepared by reaction of the alcohol **12** with methyl iodide and sodium hydride in anhydrous THF. Both compounds had the expected ¹H NMR and MS spectra.

Reaction products: 4-Methoxybenzaldehyde, 4-methoxyacetophenone, and 4-methoxypropiophenone (Aldrich) were used as received. 4-Methoxyisobutyrophenone and 4-methoxyphenyl-*tert*-butyl ketone were prepared according to literature procedures.[55]

Product analysis: γ irradiation was carried out with a panorama ⁶⁰Co γ source (Nuclear Engineering) at dose rates of $0.5 \, \mathrm{Gy\,s^{-1}}$. In a typical experiment, 5 mL of an argon-saturated aqueous solution containing the substrate (0.5 – 5.0 mM), potassium peroxodisulfate (0.2 – 1.0 mM) (substrate/oxidant ratio: 2 – 5) and 2-methyl-2-propanol (0.2 – 1.0 M) was irradiated at room temperature ($\approx 25\,^{\circ}$C) until 40 % conversion of peroxodisulfate was attained. Reaction products were identified and quantitatively determined by HPLC (comparison with authentic samples) on a Shimadzu LC 6A instrument equipped with a Shimadzu SPD 6A UV/Vis detector (wavelength of detection 285 nm) and a Nucleosil-5-C18 column (125 × 4.6 mm; Macherey & Nagel). Solvent: methanol/water 1:1 (0.8 mL min⁻¹). Blank experiments were performed under all conditions and showed the presence of negligible amounts of products. Two to four experiments were performed under all conditions with very good reproducibility (within 5 %) and mass balance.

Pulse radiolysis: The pulse-radiolysis experiments were performed with a 3 MeV van de Graaff accelerator which supplied 300 ns pulses with doses such that $0.5 – 3 \, \mu\mathrm{M}$ of radicals were produced. A temperature-controlled continuous-flow cell was employed in all experiments. The pulse-radiolysis setup and the methods of data processing are described elsewhere.[57] Dosimetry was performed with N₂O-saturated 10 mM KSCN aqueous solutions with $G(\cdot\mathrm{OH}) = 6.0 \times 10^{-7} \, \mathrm{mol\,J^{-1}}$ and $\varepsilon[(\mathrm{SCN})_2^{\cdot-}] = 7600 \, \mathrm{M^{-1}\,cm^{-1}}$ at 480 nm.[58] Experiments were performed in argon-saturated aqueous solutions containing the substrate (0.1 – 1.0 mM), peroxodisulfate (2 – 10 mM) and 2-methyl-2-propanol (0.1 M). Alternatively, N₂O-saturated aqueous solutions (pH ≤ 3.5) containing the substrate (0.1 – 0.2 mM) and thallium(I) sulfate (0.5 – 2.0 mM) were employed. The pH of the solutions was adjusted with NaOH or HClO₄. The temperature of the solutions was kept constant at 25 ± 0.2 °C. Rate constants were obtained by averaging 8 – 14 values, each of which consisted of the average of 10 – 30 shots and was reproducibile to within 3 %.

The second-order rate constants for reaction of the radical cations with HO⁻ ($k_{\mathrm{OH^-}}$) were obtained from the slopes of the plots of the observed rates (k_{obs}) versus the concentration of NaOH. For these experiments the solution containing 0.5 – 1.0 mM substrate, 10 mM potassium peroxodisulfate, and 0.1 M 2-methyl-2-propanol was saturated with argon or oxygen, and 1 mM sodium tetraborate was added to avoid undesired pH variations upon irradiation.

The second-order rate constants for reaction of the radical cations with different bases (k_{base}) were obtained from the slope of the plots of the observed rate constants (k_{obs}) versus the concentration of the added base. For these experiments the ionic strength of the solution was buffered with 0.5 M sodium sulfate and the pH of the solution was adjusted with NaOH or HClO₄ to 5.5, 7.0, or 8.0 for the experiments with NaOAc, NaHCO₃, and Na₂HPO₄, respectively. In these experiments the following base concentrations were employed: NaOAc, 0 – 100 mM; NaHCO₃, 0 – 70 mM; Na₂HPO₄, 0 – 50 mM. In the experiments with NaOH, 1.0 mM Na₂HPO₄ was added to avoid undesired pH variations, and the pH of the solution was varied between 8.5 and 10.5.

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