Structural Effects on the OH^--Promoted Fragmentation of Methoxy-Substituted 1-Arylalkanol Radical Cations in Aqueous Solution: The Role of Oxygen Acidity

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Abstract: A kinetic and product study of the OH^--induced decay in H_2O of the radical cations generated from some di- and tri-methoxy-substituted 1-arylalkanols ($ArCH(OH)R^{\bullet+}$) and 2- and 3-(3,4-dimethoxyphenyl)alkanols has been carried out by using pulse- and γ-radiolysis techniques. In the 1-arylalkanol system, the radical cation $3,4\text{-}(MeO)_2C_6H_3CH_2OH^{\bullet+}$ decay at a rate more than two orders of magnitude higher than that of its methyl ether; this indicates the key role of the side-chain OH group in the decay process (oxygen acidity). However, quite a large deuterium kinetic isotope effect (3.7) is present for this radical cation compared with its α-dideuterated counterpart. A mechanism is suggested in which a fast OH deprotonation leads to a radical zwitterion which then undergoes a rate-determining 1,2-H shift, coupled to a side-chain-to-ring intramolecular electron transfer (ET) step. This concept also attributes an important role to the energy barrier for this ET, which should depend on the stability of the positive charge in the ring and, hence, on the number and position of methoxy groups. On a similar experimental basis, the same mechanism is suggested for $2,5\text{-}(MeO)_2C_6H_3CH_2OH^{\bullet+}$ as for $3,4\text{-}(MeO)_2C_6H_3CH_2OH^{\bullet+}$, in which some contribution from direct C–H deprotonation (carbon acidity) is possible. In fact, the latter process dominates the decay of the trimethoxylated system $2,4,5\text{-}(MeO)_3C_6H_2CH_2OH^{\bullet+}$, which, accordingly, reacts with OH^- at the same rate as that of its methyl ether. Thus, a shift from oxygen to carbon acidity is observed as the positive charge is increasingly stabilized in the ring; this is attributed to a corresponding increase in the energy barrier for the intramolecular ET. When $R = t$Bu, the OH^--promoted decay of the radical cation $ArCH(OH)R^{\bullet+}$ leads to products of C–C bond cleavage. With both Ar = 3,4- and 2,5-dimethoxyphenyl the reactivity is three orders of magnitude higher than that of the corresponding cumyl alcohol radical cations; this suggests a mechanism in which a key role is played by the oxygen acidity as well as by the strength of the scissile C–C bond: a radical zwitterion is formed which undergoes a rate-determining C–C bond cleavage, coupled with the intramolecular ET. Finally, oxygen acidity also determines the reactivity of the radical cations of 2-(3,4-dimethoxyphenyl)ethanol and 3-(3,4-dimethoxyphenyl)propanol. In the former the decay involves C–C bond cleavage, in the latter it leads to 3-(3,4-dimethoxyphenyl)propanal. In both cases no products of C–H deprotonation were observed. Possible mechanisms, again involving the initial formation of a radical zwitterion, are discussed.

Keywords: acidity · alcohols · electron transfer · pulse radiolysis · radical ions

Introduction

Recently, we found convincing evidence that the OH^--promoted decay of the 4-methoxybenzyl alcohol radical cation to the α-hydroxy-4-methoxybenzyl radical does not involve the expected C_α–H deprotonation (carbon acidity), but is initiated by deprotonation at the alcoholic OH group (oxygen acidity).[1, 2] The mechanism reported in Scheme 1 (R = H) was suggested, in which the radical cation and the OH^- first form an encounter complex, which is then O–H deprotonated to produce a benzyloxyl radical, presumably through a radical zwitterion (paths **b** and **c**).

The benzyloxyl radical undergoes a formal 1,2-H atom shift (from here on indicated as 1,2-H shift) to form the α-hydroxy carbon radical (path **d**).[3, 4] The same mechanism holds for

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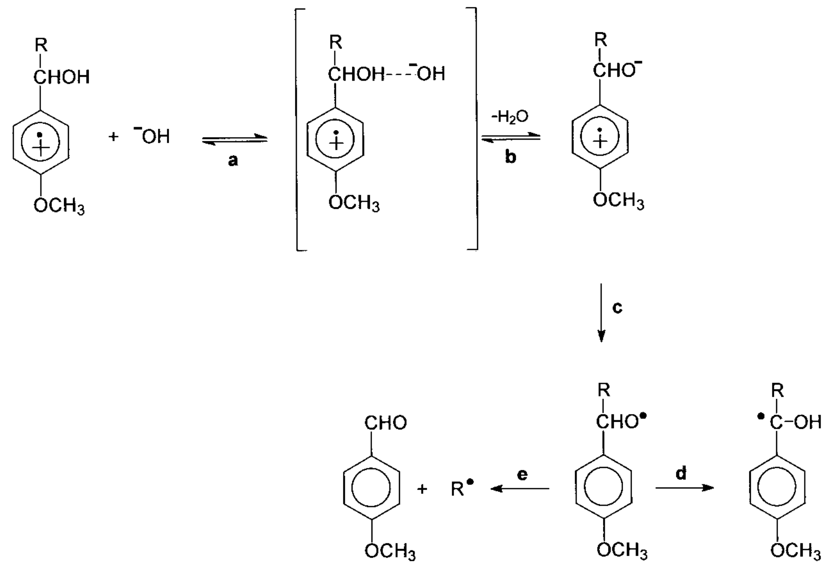
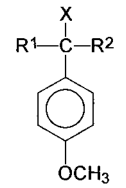


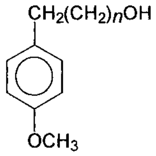
Scheme 1. Proposed mechanism for the OH^--promoted decay of 1-(4-methoxyphenyl)alkan-1-ol radical cations.

R = Me, whereas when R = Et, *i*Pr or *t*Bu, the benzyloxyl radical can also undergo a β-fragmentation reaction producing 4-methoxybenzaldehyde and an alkyl radical (path **e**).

The evidence supporting the main features of this mechanism, and particularly the role of the OH group, is as follows: a) the reaction of both the 4-methoxybenzyl alcohol and the 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol radical cations ($\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$, respectively) with OH^- takes place at a diffusion-controlled rate ($k = 1.2 \times 10^{10}\,\mathrm{M^{-1}s^{-1}}$),[2] as expected for a process that involves an oxygen acid; b) a significant lowering of reactivity ($k = 2.5 \times 10^{8}\,\mathrm{M^{-1}s^{-1}}$)[2] is observed on going from $\mathbf{1}^{\bullet+}$ to the corresponding methyl ether radical cation ($\mathbf{3}^{\bullet+}$) which can only undergo direct C_α–H bond cleavage and c) formation of the 4-methoxycumyloxyl radical is observed when the 4-methoxycumyl alcohol radical cation ($\mathbf{4}^{\bullet+}$) is reacted with OH^-.[5] More importantly, the reaction of $\mathbf{4}^{\bullet+}$ with OH^- is diffusion controlled as is that of $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$. The cumyloxyl radical then undergoes a β-fragmentation reaction leading to 4-methoxyacetophenone by loss of Me• (Scheme 2).



1: R1 = R2 = H, X = OH
2: R1 = H, R2 = *t*Bu, X = OH
3: R1 = R2 = H, X = OMe
4: R1 = R2 = Me, X = OH

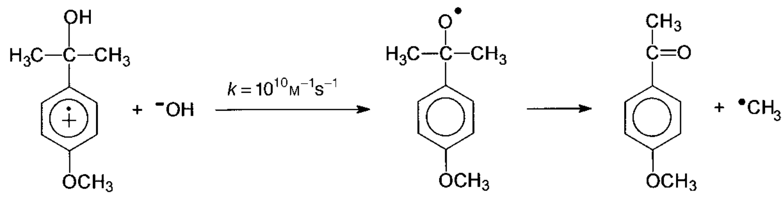


5: *n* = 1
6: *n* = 2

The oxygen acidity was even found to play a role when the OH group was in a more remote position with respect to the ring.[6] Thus, the 2-(4-methoxyphenyl)ethanol radical cation ($\mathbf{5}^{\bullet+}$) reacted with OH^- at an almost diffusion-controlled rate and formed products of β-C–C bond cleavage, whereas 3-(4-methoxyphenyl)propanol ($\mathbf{6}^{\bullet+}$) was converted into 3-(4-methoxyphenyl)propanal. In the former case, intramolecular electron transfer (ET) coupled to C–C bond cleavage either in the encounter complex or in the radical zwitterion was considered as a possible mechanism. In the second case, formation of an alkoxyl radical,[6] which then undergoes a 1,2-H atom shift, was suggested.

In order to extend our investigation to systems other than monomethoxylated ones, we also studied the OH^--induced decay of 3,4-dimethoxybenzyl alcohol (veratryl alcohol) and 1-(3,4-dimethoxyphenyl)-2,2-dimethylpropan-1-ol radical cations ($\mathbf{7}^{\bullet+}$ and $\mathbf{8}^{\bullet+}$, respectively, see below) in aqueous solution. This study produced results quite similar to those obtained with the monomethoxylated systems and led us to suggest that the mechanism reported in Scheme 1 also holds true for the more stable radical cations.[7] An intriguing result was, however, that the reactivity of $\mathbf{7}^{\bullet+}$ was significantly smaller than that of $\mathbf{8}^{\bullet+}$ and, hence, below the diffusion limit. This contrasts with the situation observed in the monomethoxylated systems, where the reactions of both $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ were diffusion controlled.[2]

Oxygen acidity represents a really novel aspect of the side-chain reactivity of arylalkanol radical cations and the definition of its scope and mechanism is certainly worth further investigation. Thus, it seemed appropriate to get a deeper mechanistic insight into the OH^--promoted reactions of ring-substituted di- and trimethoxybenzyl alcohol radical cations with the aim of determining if and how oxygen acidity is influenced by the number and position of ring methoxy groups. An additional motive of interest is that dimethoxylated benzyl alcohol radical cations (particularly the 3,4-dimethoxy systems) are structurally very closely related to the radical cations supposed to be key intermediates in the oxidative degradation of lignin,[7, 8] which is indeed triggered

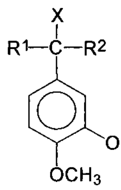


$\mathbf{4}^{\bullet+}$

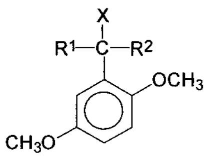
Scheme 2. Formation of an intermediate cumyloxyl radical in the reaction of the 4-methoxycumyl alcohol radical cation with OH^- leading to 4-methoxyacetophenone.

by the simple fragmentation reactions of these species. Thus, this study could also have a bearing on lignin degradation, a process of enormous practical importance.

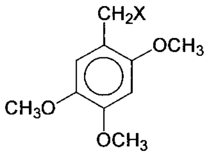
In this paper we report on a pulse- and γ-radiolysis study of the reactions of a number of radical cations generated from 1-arylalkanols and some of the corresponding methyl ethers (compounds **7**–**18**), 2-(3,4-dimethoxyphenyl)ethanol (**19**) and 3-(3,4-dimethoxyphenyl)propanol (**20**). For comparison purposes, the reactivity of 3,4- and 2,5-dimethoxytoluene radical cations ($\mathbf{10}^{\bullet+}$ and $\mathbf{15}^{\bullet+}$, respectively) under the same reaction conditions was also investigated.



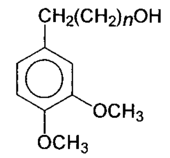
7: R¹ = R² = H, X = OH
8: R¹ = H, R² = *t*Bu, X = OH
9: R¹ = R² = H, X = OMe
10: R¹ = R² = X = H
11: R¹ = R² = Me, X = OH



12: R¹ = R² = H, X = OH
13: R¹ = H, R² = *t*Bu, X = OH
14: R¹ = R² = H, X = OMe
15: R¹ = R² = X = H
16: R¹ = R² = Me, X = OH



17: X = OH
18: X = OMe



19: *n* = 1
20: *n* = 2

Results

Generation of the radical cations: Radical cations of substrates **7**–**20** were generated in aqueous solution either by pulse radiolysis or steady state γ-radiolysis, with a sulfate radical anion ($SO_4^{\bullet-}$) as the oxidant [Eqs. (1)–(4)].

$$H_2O \rightsquigarrow H^+, {}^{\bullet}OH + e^-_{(aq)} \qquad (1)$$

$$OH^{\bullet} + CH_3C(CH_3)_2OH \rightarrow H_2O + {}^{\bullet}CH_2C(CH_3)_2OH \qquad (2)$$

$$e^-_{(aq)} + S_2O_8^{2-} \rightarrow SO_4^{2-} + SO_4^{\bullet-} \qquad (3)$$

$$SO_4^{\bullet-} + ArCH(OH)R \rightarrow SO_4^{2-} + {}^{\bullet+}ArCH(OH)R \qquad (4)$$

Radiolysis of water leads to the formation of the hydroxyl radical (${}^{\bullet}OH$) and the hydrated electron ($e^-_{(aq)}$) [Eq. (1)]. The former is scavenged by 2-methylpropan-2-ol [Eq. (2); $k = 6 \times 10^8\,M^{-1}s^{-1}$][9] while $e^-_{(aq)}$ reacts with the peroxydisulfate anion; this leads to the formation of $SO_4^{\bullet-}$ [Eq. (3); $k = 1.2 \times 10^{10}\,M^{-1}s^{-1}$].[9] $SO_4^{\bullet-}$ then reacts with aromatic compounds[10] to form the corresponding radical cations [Eq. (4); $k = 5 \times 10^9\,M^{-1}s^{-1}$ with anisole and derivatives[11, 12]].

Product analysis: Product analysis of the oxidation reactions of 1-arylalkanols was carried out after steady-state γ-radiolysis of Ar-saturated aqueous solutions (pH ≈ 10) of 1.0–2.0 mM substrate, 0.5–2.0 mM $K_2S_2O_8$ and 0.2 M 2-methyl-2-propanol at room temperature for the time necessary to obtain a 40–60 % conversion with respect to peroxydisulfate. In order to minimize overoxidation of the first-formed products, most experiments were carried out with a substrate/oxidant ratio ≥2:1.

Product distributions of the oxidation reactions of the 4-methoxyphenyl derivatives **1**–**4** and the 3,4-dimethoxyphenyl derivatives **7**–**9**, under analogous experimental conditions, have been described previously.[2, 5–7]

The reaction of **11** led to 3,4-dimethoxyacetophenone (yield 5 %, with respect to $SO_4^{\bullet-}$) as the exclusive product; whereas, under the same reaction conditions, **16** was practically unreactive.

Compounds **12**, **13**, and **14** gave 2,5-dimethoxybenzaldehyde as the exclusive product, with the yields (52 %, 85 %, and 4 %, respectively) reflecting the different reactivities of the substrates (see later).[2] Compounds **17** and **18** led to 2,4,5-trimethoxybenzaldheyde.

The reaction of **19** led to 3,3′,4,4′-tetramethoxybibenzyl and 2-methyl-4-(3,4-dimethoxyphenyl)-2-butanol as the main products. Traces of 3,4-dimethoxybenzaldehyde were also formed. These products clearly indicate that the radical cation undergoes C–C bond cleavage that leads to the 3,4-dimethoxybenzyl radical. Compound **20** gave 3-(3,4-dimethoxyphenyl)propanal as the exclusive product (yield 10 %, with respect to $SO_4^{\bullet-}$).

Pulse-radiolysis studies: The radical cations were produced according to Equations (1)–(4). In all cases they exhibited the characteristic UV and visible absorption bands of methoxybenzene-type radical cations,[11, 12] at around 290–310 and 425–455 nm depending on the substitution pattern.

As an example, the time-resolved spectra obtained by oxidation of **13** at pH 10.4 are given in Figure 1. The spectra

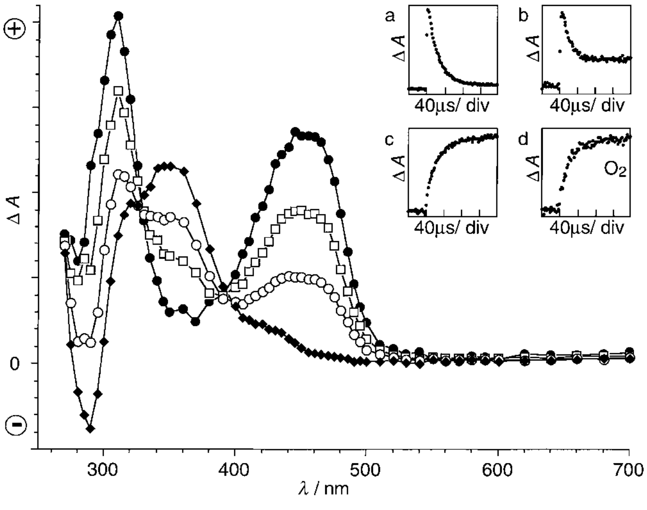


Figure 1. Time-resolved absorption spectra observed on reaction of $SO_4^{\bullet-}$ with **13** (0.1 mM) and recorded by pulse radiolysis of an argon-saturated aqueous solution (pH 10.4) containing 2-methylpropan-2-ol (0.1 M) and $K_2S_2O_8$ (10 mM), at 4 (●), 15 (□), 30 (○) and 140 µs (◆) after the 300 ns, 3 MeV electron pulse. Insets: a) First-order decay of $\mathbf{13}^{\bullet+}$ monitored at 455 nm. b) First-order decay of $\mathbf{13}^{\bullet+}$ monitored at 310 nm (the residual absorption is due to the formation of 2,5-dimethoxybenzaldehyde). c) Buildup of absorption at 360 nm due to formation of 2,5-dimethoxybenzaldehyde (Ar), which is unchanged in the presence of O_2 (inset d).

show the characteristic absorptions due to $\mathbf{13}^{\bullet+}$: the bands being centered at 310 and 455 nm. These absorptions reach a maximum at 4 μs after the pulse due to completion of radical cation formation [Eq. (4)] and then decrease (see Figure 1 insets a and b) as a consequence of the first-order decay of the radical cation. This decay is accompanied (inset c) by a corresponding build up of optical density centered at 360 nm; this indicates that a product is formed that has a higher absorption at this wavelength than the radical cation itself (two isosbestic points are visible at $\approx$330 and 390 nm). Inset d shows that the absorption build up at 360 nm is unaffected by O_2; this suggests that the species responsible is not a radical. It was identified as 2,5-dimethoxybenzaldehyde, formed after C–C bond cleavage in $\mathbf{13}^{\bullet+}$ (Scheme 1), in agreement with product studies (see above).

The rates of decay of the radical cations were measured spectrophotometrically by monitoring the decrease in optical density at the visible absorption maximum of the radical cations. The rates significantly increased upon addition of OH^-. Clean first-order decays were observed and linear dependencies were obtained of the observed rates (k_{obs}) on the concentrations of added OH^-. From the slopes of these plots, the second-order rate constants for reaction of OH^- with the radical cations (k_{OH^-}) were obtained. The data are listed in Tables 1 and 2 in which previously determined kinetic constants for the monomethoxylated systems and for some 3,4-dimethoxy substituted compounds are also displayed.

The second order rate constants for reaction of $\mathbf{19}^{\bullet+}$ and $\mathbf{20}^{\bullet+}$ with OH^- were measured analogously and are listed in Table 3.

Discussion

Benzyl alcohol radical cations: In Table 1, the kinetic data for the dimethoxy- and trimethoxy-substituted benzyl alcohol radical cations, whose decay ultimately involves the cleavage of the C–H bond, can be compared with those of their methyl ethers as well as with those of the previously investigated 4-methoxy-substituted system.[2] Considering the results for the 3,4-dimethoxybenzyl alcohol radical cation ($\mathbf{7}^{\bullet+}$), one very striking observation is that a significant kinetic deuterium isotope effect (KDIE, $k_H/k_D = 3.7$) is found when $\mathbf{7}^{\bullet+}$ is compared with its α-dideuterated counterpart. This indicates that substantial cleavage of the β-C–H bond occurs in the rate-determining step of the reaction. This conclusion is not consistent with our previous suggestion that the mechanism proposed for $\mathbf{1}^{\bullet+}$, formation of a base/radical-cation encounter complex in the rate-determining step (Scheme 1), can be extended to $\mathbf{7}^{\bullet+}$. In the case of $\mathbf{1}^{\bullet+}$, the reaction was diffusion controlled and, evidently, no KDIE was observed.

The most simple explanation would be that $\mathbf{7}^{\bullet+}$, which is a more stable radical cation and therefore a somewhat weaker acid than $\mathbf{1}^{\bullet+}$, no longer exhibits a kinetic oxygen acidity. Thus, the reaction with OH^- might occur by direct C–H deprotonation. However, this conclusion contrasts sharply with the observation that the corresponding methyl ether radical cation ($\mathbf{9}^{\bullet+}$) reacts with OH^- by C–H deprotonation with a rate constant more than two orders of magnitude smaller than that measured for $\mathbf{7}^{\bullet+}$ (7.9×10^6 versus $1 \times 10^9\,\mathrm{M^{-1}s^{-1}}$); this clearly indicates that the OH group also plays a crucial role in the dimethoxylated system. Accordingly, in acidic solution ($pH \leq 5$), where C–H deprotonation is taking place exclusively, $\mathbf{7}^{\bullet+}$ and $\mathbf{9}^{\bullet+}$ exhibit a very similar reactivity.[7] A different mechanism for the OH^--promoted decay of $\mathbf{7}^{\bullet+}$ and $\mathbf{9}^{\bullet+}$ is also indicated by the substantial difference in the KDIE values: 3.7 for $\mathbf{7}^{\bullet+}$ and 1.4 for $\mathbf{9}^{\bullet+}$. Thus it is possible to suggest that the OH^--promoted decay of $\mathbf{7}^{\bullet+}$ is also initiated by OH deprotonation even though the observed KDIE tells us that substantial C–H bond cleavage has occurred in the transition state of the rate-determining step of the overall deprotonation process.

Table 1. Second-order rate constants (k_{OH^-} [$\mathrm{M^{-1}s^{-1}}$]) for the OH^--promoted decay of ring methoxylated radical cations $ArR^{\bullet+}$, generated by pulse radiolysis of the parent substrate in aqueous solution, measured at $T = (25 \pm 0.1)$ °C.

Ar/R	CH_3	CH_2OH	CD_2OH	CH_2OMe	CD_2OMe
$4\text{-}MeOC_6H_4$	$5.5 \times 10^{7[a]}$	$1.2 \times 10^{10[b]}$	$1.1 \times 10^{10[b]}$	$2.5 \times 10^{8[b]}$	$1.4 \times 10^{8[b]}$
		$k_H/k_D = 1.1$		$k_H/k_D = 1.8$	
$3,4\text{-}(MeO)_2C_6H_3$	2.1×10^6	$1.0 \times 10^{9[c]}$	2.7×10^8	$7.9 \times 10^{6[c]}$	5.8×10^6
		$k_H/k_D = 3.7$		$k_H/k_D = 1.4$	
$2,5\text{-}(MeO)_2C_6H_3$	1.2×10^5	2.9×10^6	9.3×10^5	4.5×10^5	2.8×10^5
		$k_H/k_D = 3.2$		$k_H/k_D = 1.6$	
$2,4,5\text{-}(MeO)_3C_6H_2$	–	7.3×10^4	–	6.7×10^4	–

[a] From ref. [6]. [b] From ref. [3]. [c] From ref. [7].

Table 2. Second-order rate constants (k_{OH^-} [$\mathrm{M^{-1}s^{-1}}$]) for the OH^--promoted decay of methoxy-substituted 1-aryl-2,2-dimethylpropan-1-ol and cumyl alcohol radical cations, generated by pulse radiolysis of the parent substrate in aqueous solution, measured at $T = (25 \pm 0.1)$ °C.

Ar/R	CH(OH)*t*Bu		$C(CH_3)_2OH$	
$4\text{-}MeOC_6H_4$	($\mathbf{2}^{\bullet+}$)	$1.3 \times 10^{10[a]}$	($\mathbf{4}^{\bullet+}$)	$1.2 \times 10^{10[b]}$
$3,4\text{-}(MeO)_2C_6H_3$	($\mathbf{8}^{\bullet+}$)	$8.3 \times 10^{9[c]}$	($\mathbf{11}^{\bullet+}$)	5.6×10^6
$2,5\text{-}(MeO)_2C_6H_3$	($\mathbf{13}^{\bullet+}$)	1.5×10^8	($\mathbf{16}^{\bullet+}$)	1.6×10^5

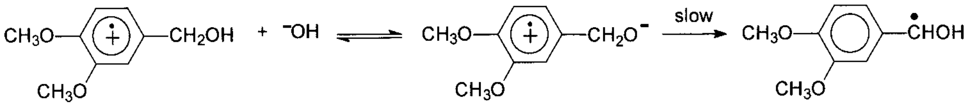
[a] From ref. [2]. [b] From ref. [5]. [c] From ref. [7].

Table 3. Second-order rate constants (k_{OH^-} [$\mathrm{M^{-1}s^{-1}}$]) for the OH^--promoted decay of 2- and 3-arylalkanol radical cations generated by pulse radiolysis of the parent substrate in aqueous solution, measured at $T = (25 \pm 0.1)$ °C.

substrate		k_{OH^-} [$\mathrm{M^{-1}s^{-1}}$]
$4\text{-}MeOC_6H_4CH_2CH_2OH^{[a]}$	($\mathbf{5}^{\bullet+}$)	8.3×10^9
$4\text{-}MeOC_6H_4CH_2CH_2CH_2OH^{[a]}$	($\mathbf{6}^{\bullet+}$)	1.7×10^9
$3,4\text{-}(MeO)_2C_6H_3CH_2CH_2OH$	($\mathbf{19}^{\bullet+}$)	3.4×10^8
$3,4\text{-}(MeO)_2C_6H_3CH_2CH_2CH_2OH$	($\mathbf{20}^{\bullet+}$)	2.1×10^8

[a] From ref. [6].

The simplest way to deal with this apparently contradictory situation is by saying that, with $\mathbf{7}^{\bullet+}$, the benzyloxyl radical is formed in a fast step followed by a rate-determining 1,2-H shift (Scheme 1, path **d**), a completely reversed situation from that observed for $\mathbf{1}^{\bullet+}$. However, this possibility appears unlikely as it would have allowed us to observe the buildup of the intermediate benzyloxyl radical, which was not the case. Thus, the most reasonable hypothesis that would accommodate both the observed C–H KDIE and a mechanism involving oxygen acidity is that a radical zwitterion is first formed in a fast step and is then converted to the carbon-centered radical by a rate-determining process in which intramolecular ET is coupled to a 1,2-H shift (Scheme 3).



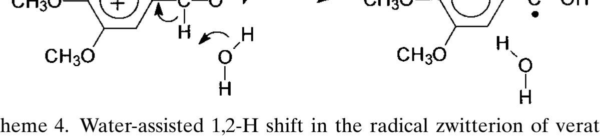
Scheme 3. Proposed mechanism for the OH$^-$-promoted decay of the veratryl alcohol radical cation.

The difference in the mechanistic behavior of the two radical cations **1**$^{\cdot+}$ and **7**$^{\cdot+}$ may be attributed to the greater energy barrier for the intramolecular side-chain-to-ring electron transfer, which has to accompany the OH deprotonation in order to produce the benzyloxyl radical, in the dimethoxylated system than in the monomethoxylated one—the ring-localized positive charge being more efficiently stabilized in the former system than in the latter.[13] Thus, in the radical zwitterion formed from **7**$^{\cdot+}$ the energetic cost for this intramolecular ET is likely to be so high as to require assistance from the 1,2-H shift. With the coupled intramolecular ET-1,2-H shift the (stabilized) benzyl radical is formed directly, bypassing the less-stable benzyloxyl radical. In other words, while **1**$^{\cdot+}$ undergoes stepwise intramolecular ET and 1,2-H shift, in **7**$^{\cdot+}$ the two processes are coupled, due to the higher barrier for the intramolecular ET.[15]

In this respect, it is interesting to note that the role of the energy associated with the intramolecular ET in determining the reaction paths of radical zwitterions has already been recognized in a study concerning the conversion of aromatic carboxylate radical zwitterions into the corresponding acyloxyl radicals.[16] It was observed that this process is much more efficient with the benzoate radical zwitterion than with the 4-methoxybenzoate one. In that case too, the difference was attributed to an energetically more costly intramolecular ET in the methoxylated system.

The 1,2-H shift suggested to occur in the radical zwitterion formed from **7**$^{\cdot+}$ is unprecedented. However, it has features similar to those of the well-established 1,2-H shift in alkoxyl radicals[3, 4, 17] being favored by the solvent water as illustrated in Scheme 4.

As a matter of fact, the proposed mechanism (Scheme 3) differs from the mechanism in Scheme 1 in that it incorporates the electronic and structural reorganization necessary to convert the radical zwitterion into the carbon-centered radical in only one step . Therefore, if the above hypothesis is correct, the value (3.7) of the KDIE measured for **7**$^{\cdot+}$ would pertain to the 1,2-H shift in the zwitterion, a process which reasonably should exhibit features different from those of a direct OH$^-$-induced C–H deprotonation.[19, 20]



Scheme 4. Water-assisted 1,2-H shift in the radical zwitterion of veratryl alcohol.

Passing on to examine the results obtained with 2,5-dimethoxybenzyl alcohol (**12**), we first noted that the decay of **12**$^{\cdot+}$ is much slower (about 300 times) than that of **7**$^{\cdot+}$. However, the reaction exhibits a KDIE value ($k_H/k_D = 3.2$, from the comparison of **12**$^{\cdot+}$ with its α-dideuterated counterpart) which is very close to that observed for **7**$^{\cdot+}$. In this case too, the value is significantly different from that found for the corresponding methyl ether **14**$^{\cdot+}$ (1.6), which can only undergo direct C–H deprotonation. As expected, the latter value is very similar to that observed for **9**$^{\cdot+}$, the methyl ether of **7**$^{\cdot+}$. It is also found that **12**$^{\cdot+}$ is more reactive than **14**$^{\cdot+}$, however the difference is much smaller than that observed between **7**$^{\cdot+}$ and **9**$^{\cdot+}$.

Thus, we also suggest that the OH$^-$-promoted decay of **12**$^{\cdot+}$ involves initial OH deprotonation, the mechanism being the same as that proposed for **7**$^{\cdot+}$. The lower reactivity with respect to **7**$^{\cdot+}$ is probably due to the larger stabilization of the positive charge in the 2,5-dimethoxy system as compared with the 3,4-dimethoxy one.[22, 23] In other words, the intramolecular ET coupled to the 1,2-H shift should require more energy in the radical zwitterion derived from **12**$^{\cdot+}$ than in that derived from **7**$^{\cdot+}$. Even though OH deprotonation seems to remain the main reaction channel for the decay of **12**$^{\cdot+}$, the possibility that direct C–H deprotonation begins to compete with this system cannot be excluded. As already noted, this possibility is suggested by the relatively small difference in reactivity between **12**$^{\cdot+}$ and its methyl ether **14**$^{\cdot+}$. If this is actually the case, it would indicate that the stabilization of the positive charge in the ring depresses the oxygen acidity more than the C–H acidity. Also in line with this conclusion is the observation that **12**$^{\cdot+}$ is about 300 times less reactive than **7**$^{\cdot+}$, whereas when direct C–H deprotonation occurs (methyl ethers and toluenes), the difference in reactivity between the 3,4- and the 2,5-dimethoxy system is less than 20. (Compare **9**$^{\cdot+}$ with **14**$^{\cdot+}$ and **10**$^{\cdot+}$ with **15**$^{\cdot+}$.)

The results obtained with the 2,4,5-trimethoxybenzyl alcohol radical cation (**17**$^{\cdot+}$) are also consistent. With this substrate, no difference in reactivity between **17**$^{\cdot+}$ and its methyl ether (**18**$^{\cdot+}$) is observed (Table 1); this indicates that both species react by direct C–H deprotonation, with no role played by the OH group. Practically, in **17**$^{\cdot+}$ the positive charge is so efficiently stabilized by the three methoxy groups[24] that intramolecular ET in the radical zwitterion is very unfavorable. It is possible that the OH group is still involved in a side process, but the progress of the reaction is predominantly determined by C–H deprotonation.

The observation that the stabilization of the positive charge in the ring affects oxygen more than carbon acidity can reasonably be explained by the fact that, in the latter case, there is a direct overlap between the C–H bond and the aromatic π-system. This might significantly lower the energetic barrier for the intramolecular ET and make it fairly insensitive to the effect of electron-donating substituents in the ring. In the radical zwitterion, on the other hand, the negatively charged oxygen and the positively charged aromatic ring are separated by a methylene group and a higher energy barrier for the intramolecular ET is expected.

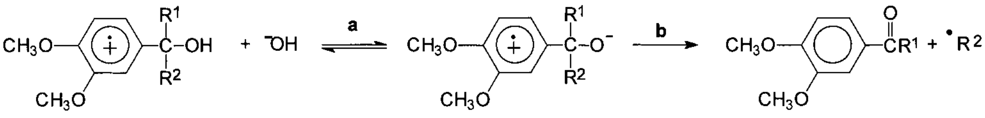
We have already discussed the competition between oxygen and carbon acidity in 1-(4-methoxyphenyl)alkanol radical cations.[2] Our conclusion was that with relatively weak bases, the largely thermodynamically favored C–H deprotonation prevails; with strong bases, however, the driving force is no longer a problem and the route involving OH deprotonation takes over, due to the lower intrinsic barrier of this process with respect to that of C–H deprotonation.[25–29] In the light of the present results this view has to be somewhat modified, the main effect of the base being that of promoting the formation of the radical zwitterion in a process with a low intrinsic barrier. Hence, the follow-up of the reaction seems to depend upon the energetics of the intramolecular side-chain-to-ring electron transfer in the radical zwitterion. When the energy barrier for the intramolecular ET is relatively low, the reaction proceeds via the radical zwitterion, as suggested for mono- and dimethoxy-substituted benzyl alcohol radical cations, and the reaction is controlled by oxygen acidity. However, when this barrier becomes high (2,4,5-trimethoxy substituted system), the radical zwitterion is still formed but it is no longer a productive reaction intermediate and direct C–H deprotonation in the radical cation takes over.

Oxygen acidity and C–C bond cleavage: The effects discussed above also have a significant bearing on the OH^--promoted C–C bond cleavage reaction of 1-arylalkanol radical cations illustrated in Schemes 1 (paths **e**) and 2. Accordingly, for this process as well, the introduction of a second methoxy group induces a change in mechanism. This can be clearly seen by the fact that in the cumyl alcohol series, **11**$^{\bullet+}$ and **16**$^{\bullet+}$ are converted into the corresponding acetophenones at a much lower rate (more than three orders of magnitude) than the monomethoxylated **4**$^{\bullet+}$ (Table 2). The latter reacts with OH^- at a diffusion-controlled rate,[5] whereas the rate constants for **11**$^{\bullet+}$ and **16**$^{\bullet+}$ are as low as 5.6×10^6 and $1.6 \times 10^5\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, respectively. Moreover, while formation of the intermediate benzyloxyl radical was clearly observed in the reaction of **4**$^{\bullet+}$, no such evidence was obtained for either **11**$^{\bullet+}$ or **16**$^{\bullet+}$. This indicates that with the last two radical cations an intermediate benzyloxyl radical is either not formed at all or it decomposes at a rate much faster than that of its formation. If the latter possibility is true, the much smaller reactivity of **11**$^{\bullet+}$ and **16**$^{\bullet+}$ compared with **4**$^{\bullet+}$ can be explained by an increase in the rate of β-fragmentation of the intermediate benzyloxyl radical as well as by a decrease in the OH-deprotonation rate of the radical cations themselves. However, both hypotheses are unlikely. An increase in the rate of β-cleavage of the intermediate benzyloxyl radical as we move from **4**$^{\bullet+}$ to **11**$^{\bullet+}$ and **16**$^{\bullet+}$ can be excluded since the rates of β-cleavage of some ring-substituted cumyloxyl radicals have been found to be practically unaffected by the nature and number of substituents.[30] Likewise, a significantly lower rate of OH deprotonation with **11**$^{\bullet+}$ and **16**$^{\bullet+}$ than with **4**$^{\bullet+}$ is made unlikely by the results obtained with the α-*tert*-butyl derivatives **8**$^{\bullet+}$ and **13**$^{\bullet+}$ which were found to react with OH^- at rates three orders of magnitude higher than those measured for **11**$^{\bullet+}$ and **16**$^{\bullet+}$, respectively (Table 2). This large difference in rate is incompatible with a slow OH-deprotonation step as very similar oxygen acidities can be assumed for **8**$^{\bullet+}$ and **11**$^{\bullet+}$ as well as for **13**$^{\bullet+}$ and **16**$^{\bullet+}$.

Thus, it seems reasonable to suggest a mechanism resembling that proposed for **7**$^{\bullet+}$ and **12**$^{\bullet+}$. As illustrated in Scheme 5 for the 3,4-dimethoxy derivatives, OH deprotonation leads to a radical zwitterion that undergoes intramolecular ET coupled with C–C bond cleavage in the slow step and forms the carbonyl product directly. Through this concerted process the energy of the transition state can be lowered by partial formation of a ring-conjugated C=O double bond. As observed for **4**$^{\bullet+}$, no benzyloxyl radical is formed, probably due to the higher energy barrier for intramolecular ET in dimethoxylated radical zwitterions already discussed. Since C–C bond cleavage has progressed to some extent in the transition state of the rate-determining step, the observation that the radical cations undergoing C–*t*Bu cleavage (**8**$^{\bullet+}$ and **13**$^{\bullet+}$) are much more reactive than those undergoing C–Me cleavage (**11**$^{\bullet+}$ and **16**$^{\bullet+}$) is easily accounted for on the basis of the much higher stability of *t*Bu$^\bullet$ as compared with Me$^\bullet$.

The higher reactivity of **11**$^{\bullet+}$ relative to **16**$^{\bullet+}$ is also consistent with the above proposal since, as already discussed, the intramolecular ET should be energetically more costly in the radical zwitterion from the latter than in that from the former. In this respect, it is noteworthy that practically the same difference in reactivity is also observed for **8**$^{\bullet+}$/**13**$^{\bullet+}$.

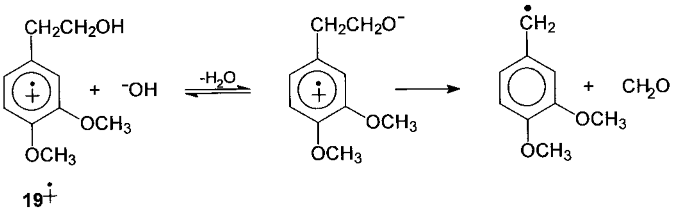
Reactivity of 2- and 3-(3,4-dimethoxyphenyl)alkanol radical cations: The data displayed in Table 3 clearly show that the OH group continues to play a key role in the OH^--induced decay of 3,4-dimethoxy-substituted phenylalkanol radical cations even when two or three methylene groups are interposed between the OH group and the ring. Accordingly, both **19**$^{\bullet+}$ and **20**$^{\bullet+}$ are about 100 times more reactive than the 3,4-dimethoxytoluene radical cation (**10**$^{\bullet+}$) which decays by C–H deprotonation. Further strong support for the hypothesis of OH deprotonation comes from the nature of the reaction products—with **19**$^{\bullet+}$ products derived from C–C bond cleavage in the radical cation are observed, whereas the



Scheme 5. Proposed mechanism for the OH^--promoted decay of the 3,4-dimethoxycumyl alcohol radical cation.

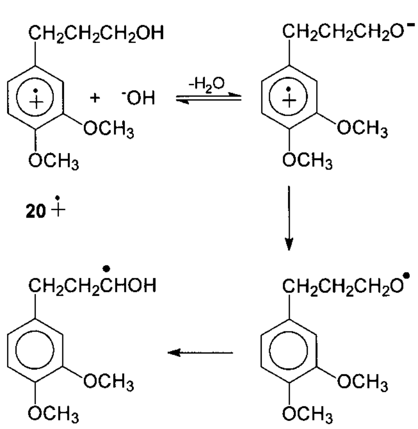
decay of $\mathbf{20}^{\bullet+}$ leads to 3-(3,4-dimethoxyphenyl)propanal. No product coming from α-C–H deprotonation was observed with either radical cation.

A very similar outcome has been observed for the reactions of the corresponding 4-methoxy derivatives $\mathbf{5}^{\bullet+}$ and $\mathbf{6}^{\bullet+}$; this suggests that the main features of the mechanisms proposed for these compounds should also hold true when a second methoxy group is added to the aromatic ring.[6] For $\mathbf{19}^{\bullet+}$, formation of a radical zwitterion, which then undergoes a rate-determining C–C bond cleavage coupled with intramolecular ET, can be suggested (Scheme 6).



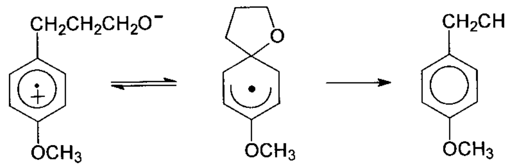
Scheme 6. Proposed mechanism for the OH⁻-promoted decay of the 2-(3,4-dimethoxyphenyl)ethanol radical cation.

With $\mathbf{5}^{\bullet+}$, the rate of reaction with OH⁻ is diffusion controlled, probably owing to the lower energetic cost of the intramolecular ET in the radical zwitterion formed from the monomethoxylated system. The possible mechanism for $\mathbf{20}^{\bullet+}$ is illustrated in Scheme 7.



Scheme 7. Proposed mechanism for the OH⁻-promoted decay of the 3-(3,4-dimethoxyphenyl)propan-1-ol radical cation.

A radical zwitterion is formed, from which an alkoxyl radical is produced; this then undergoes a 1,2-H shift leading to an α-hydroxy carbon radical, the precursor of the final 3-arylpropanal.[6] However, in view of the previous discussion, it is difficult to imagine that the radical zwitterion is converted into an alkoxyl radical by a side-chain-to-ring intramolecular ET. In line with this, such a possibility was excluded for the zwitterions formed from 1-(3,4-dimethoxyphenyl)alkanol radical cations and a fortiori it should be excluded when the negatively charged oxygen is further removed from the aromatic ring. Thus, as already suggested, the sequence of ring-closing/ring-opening equilibria illustrated in Scheme 8 appears to be a more likely possibility for the conversion of the zwitterion from $\mathbf{20}^{\bullet+}$ (and perhaps also that from $\mathbf{6}^{\bullet+}$) into the alkoxyl radical.[6, 31, 32]

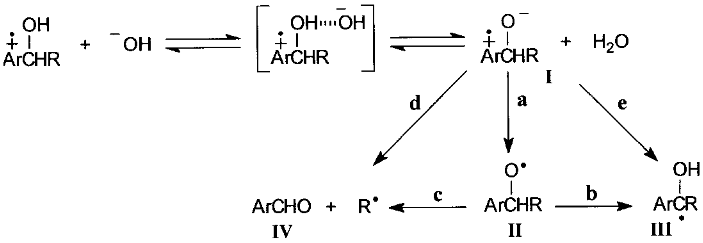


Scheme 8. Proposed ring-closing/ring-opening mechanism for the conversion of the 3-(4-dimethoxyphenyl)propan-1-ol radical zwitterion into the alkoxyl radical.

Conclusion

From the results reported in this paper it is evident that oxygen acidity plays an important role in the OH⁻-promoted decay of dimethoxy-substituted 1-arylalkanol radical cations [ArCH(OH)R$^{\bullet+}$], a reaction which is also likely to play an important role in the oxidative degradation of lignin in alkaline aqueous solution.

More importantly, these results have provided a more complete mechanistic picture for the fragmentation of 1-arylalkanol radical cations in alkaline aqueous solution in which, as illustrated in Scheme 9, a key role is played by the radical zwitterion intermediate **I**, as well as by the energy barrier for the side-chain-to-ring intramolecular ET in the zwitterion itself. Such a barrier, the height of which should depend upon the degree of stabilization of the positive charge on the aromatic ring, appears to determine the concerted or stepwise (via the oxyl radical **II**) nature of the conversion of **I** into a carbon radical (**III**) or a carbonyl compound (**IV**). On this basis, when the energy barrier for the intramolecular ET is relatively small (Ar = 4-MeOC$_6$H$_4$), conversion of **I** into **III** or **IV** occurs via **II** (path **a**), which then undergoes a 1,2-H shift and/or β-fragmentation (paths **b** or **c**, respectively).



Scheme 9. General mechanistic Scheme for the fragmentation of 1-arylalkanol radical cations in alkaline aqueous solution.

When Ar = 3,4- or 2,5-(MeO)$_2$C$_6$H$_3$, the energy barrier for the conversion of **I** into **II** is higher, and the reaction proceeds through paths **e** and **d**, in which the intramolecular ET is concerted with bond breaking. Finally, when Ar = 2,4,5-(MeO)$_3$C$_6$H$_2$, the energy barrier for the intramolecular ET becomes so high that carbon acidity (direct C – H deprotonation) takes over, the radical zwitterion being formed only in an unproductive side-equilibrium, if at all.

Oxygen acidity appears to also play a major role in the reactivity of 2- and 3-arylalkanol radical cations, in which the OH group is separated from the ring by two or three methylene groups, respectively. With these substrates, the same reaction mechanism is suggested for both 4-methoxy- and 3,4-dimethoxy-substituted systems.

Experimental Section

Reagents: Potassium peroxydisulfate, sodium hydroxide, disodium tetraborate decahydrate, potassium thiocyanate, and 2-methyl-2-propanol were of the highest commercial quality available. Milli-Q-filtered (Millipore) water was used for all solutions.

3,4-Dimethoxytoluene (**10**), 2,5-dimethoxybenzyl alcohol (**12**), 2,5-dimethoxytoluene (**15**), 2,4,5-trimethoxybenzyl alcohol (**17**), 2-(3,4-dimethoxyphenyl)ethanol (**19**) and 3-(3,4-dimethoxyphenyl)propanol (**20**) (Aldrich) were used as received. 3,4-Dimethoxybenzyl alcohol (**7**) was purified by distillation. 1-(3,4-Dimethoxyphenyl)-2,2-dimethylpropan-1-ol (**8**) was available from previous work.[7]

3,4-Dimethoxycumyl alcohol (**11**) and 2,5-dimethoxycumyl alcohol (**16**) were prepared by reaction of the pertinent arylmagnesium bromide with acetone in anhydrous tetrahydrofuran, purified by column chromatography (silica gel, eluent hexane/ethyl acetate 3:1) and identified by GC-MS and ^{1}H NMR.

1-(2,5-Dimethoxyphenyl)-2,2-dimethylpropan-1-ol (**13**) was prepared by reduction of 2,5-dimethoxyphenyl *tert*-butyl ketone with $NaBH_4$[33], purified by column chromatography (silica gel, eluent hexane/ethyl acetate in gradient), and identified by GC-MS. ^{1}H NMR ($CDCl_3$): $\delta = 0.93$ (s, 9H; $3CH_3$), 3.77 (s, 6H; $2OCH_3$), 6.77–6.88 (m, 3H; $2,5\text{-}MeOC_6H_3$). 2,5-Dimethoxyphenyl *tert*-butyl ketone was synthesized by a literature procedure.[34]

α,α-[D_2]-3,4-Dimethoxybenzyl alcohol and α,α-[D_2]-2,5-dimethoxybenzyl alcohol were synthesized by reduction of the pertinent benzoic acid with $LiAlD_4$.[33] The corresponding methyl ethers were prepared by reaction of these alcohols with methyl iodide and sodium hydride in anhydrous tetrahydrofuran.

The same procedure was used for the synthesis of methyl ethers **9**, **14**, and **18** from the corresponding alcohols (**7**, **12**, and **17**, respectively). All methyl ethers showed the expected GC-MS and ^{1}H NMR spectra.

Product analysis: γ-Irradiations were carried out with a panorama ^{60}Co γ-source (Nuclear Engineering) at dose rates of $\sim 0.5\,Gy\,s^{-1}$. In a typical experiment, 5 mL of an argon-saturated aqueous solution (pH $\approx$ 10) containing the substrate (1.0–2.0 mM), potassium peroxydisulfate (0.5–2.0 mM), disodium tetraborate decahydrate (1.0 mM) and 2-methylpropan-2-ol (0.2 M) was irradiated at room temperature for the time necessary to obtain a 40–60 % conversion of peroxydisulfate. Reaction products were identified and quantitatively determined by GC-MS and HPLC (comparison with authentic samples). Blank experiments were performed under every condition and showed the presence of only negligible amounts of products.

Pulse Radiolysis: The pulse-radiolysis experiments were performed by using a 3-M eV van de Graaff accelerator which supplied 300 ns pulses with doses such that 1–3 μM radicals were produced. A thermostatable continuous-flow cell was employed in all experiments. The pulse-radiolysis setup and the methods of data handling have been described elsewhere.[35] Dosimetry was performed with N_2O-saturated KSCN aqueous solutions (10 mM) by taking $G(^{\cdot}OH) = 6.0 \times 10^{-7}\,mol\,J^{-1}$ and ε $((SCN)_2^{\cdot-}) = 7600\,M^{-1}\,cm^{-1}$ at 480 nm.[36] Experiments were performed by using argon-saturated aqueous solutions containing the substrate (0.2–1.0 mM), peroxydisulfate (10 mM), and 2-methylpropan-2-ol (0.1 M). The pH of the solutions was adjusted with NaOH or $HClO_4$ and sodium tetraborate (1 mM) was added to avoid undesired pH variations upon irradiation. The temperature of the solutions was kept constant at 25 ± 0.1 °C. The observed rates (k_{obs}) were obtained by averaging eight to 14 values, each consisting of an average of ten to 30 shots, and were reproducible to within 3 %.

The second order rate constants for reaction of the radical cations with OH^- (k_{OH^-}) were obtained from the slopes of the plots of k_{obs} versus the concentration of NaOH.

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[20] We have also measured the solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) for the decay of $\mathbf{7}^{\cdot+}$ and found a (preliminary) value of about 0.7, which might be consistent with a fast pre-equilibrium involving the formation of the radical zwitterion (specific base catalysis).[21] Instead a k_{H_2O}/k_{D_2O} value of 1.5 has been observed for the 1,2-H shift in the benzyloxyl radical. See ref. [18].

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