Base-Catalyzed C−H Deprotonation of 4-Methoxybenzyl Alcohol Radical Cations in Water: Evidence for a Carbon-to-Oxygen 1,2-H-Shift Mechanism

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Fragmentation reactions of radical cations, and particularly those involving C−H and C−C bond cleavage, are attracting continuous interest due to their many practical and theoretical implications.[2] In this research area, we recently reported that, in aqueous solution, the cleavage of a C−C bond in alkyl-aromatic radical cations is assisted by the presence of an α-OH group.[3] Base catalysis was observed, and a hydrogen-bonded transition state was suggested. In an effort to throw more light on this phenomenon, we have now discovered that an α-OH group can assist as well the cleavage of a C−H bond (C−H deprotonation). The results of our study, which permit more general conclusions to be drawn on the nature of the α-OH group assistance in fragmentation reactions of radical cations, are presented herewith.

The starting point was the similar effect of OH^- on the fragmentation reactions of the radical cations $1^{\bullet+}$ and $2^{\bullet+}$, the former of which involves the cleavage of the C−C bond (eq 1, B symbolizes a base) and the latter one, however, that of the C−H bond (eq 2).
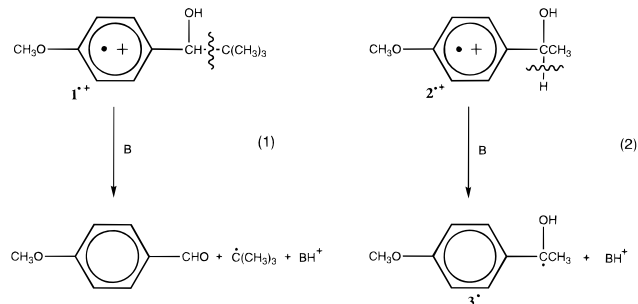

The two radical cations were generated in H_2O from **1** or **2** using $SO_4^{\bullet-}$, and their reactions were studied by the pulse radiolysis technique, as previously described.[3] Both radical cations showed the characteristic absorption bands centered around 290 and 450 nm.[4] It was observed that $1^{\bullet+}$ decayed to form 4-methoxybenzaldehyde (absorption at 285 nm) by cleav-

age of the C−C bond according to eq 1. In contrast, the decay of $2^{\bullet+}$ leads to the α-hydroxybenzyl type radical $3^{\bullet}$ (λ_{max} at 300 nm), *via* cleavage of the C−H bond (eq 2). In agreement with the pulse radiolysis results, steady state γ-irradiation of **1** and **2** gave 4-methoxybenzaldehyde and 4-methoxyacetophenone, respectively, the latter deriving from oxidation of $3^{\bullet}$, in the presence of $S_2O_8^{2-}$.[5]

The rate constants of reactions 1 and 2 in water, measured by the decrease of the 450 nm absorption of the radical cation,[6] turned out to be 1.8×10^5 and 3.7×10^4 s^{-1}, respectively; i.e., the C−C bond cleavage (of $1^{\bullet+}$) is *ca.* 5 times faster than the deprotonation reaction (of $2^{\bullet+}$). With both $1^{\bullet+}$ and $2^{\bullet+}$, the decay rates were found to increase in the presence of OH^- (Figure 1), whereby the rate constants for the OH^--catalyzed process are almost identical ($k \approx 5 \times 10^9$ M^{-1} s^{-1}) for the two radical cations. At first sight, this is a very surprising result in view of the fact that with $1^{\bullet+}$ the base catalysis can only involve the O−H bond whereas with $2^{\bullet+}$ the C−H bond is expected to be involved.

To gain further information on this phenomenon, we also studied the radical cations $4^{\bullet+}$ and $5^{\bullet+}$, where the only possible fragmentation reaction is C−H deprotonation, as described in eqs 3 and 4 and as experimentally observed.[7]
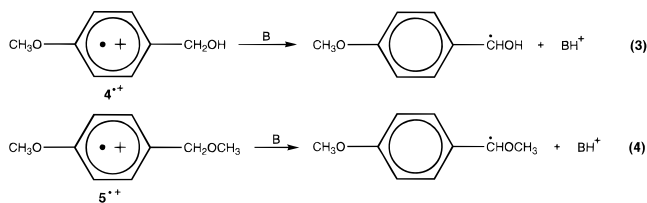
The kinetic study of these reactions showed that in the absence of NaOH the rate of deprotonation of $4^{\bullet+}$ (7.5×10^4 s^{-1}) is similar to that of $5^{\bullet+}$ (1.0×10^5 s^{-1}), as expected since the OH and OMe α-substituents should exhibit very similar electronic effects. However, the OH^--catalyzed reaction is drastically different for the two compounds as clearly visible from the slopes of the corresponding plots in Figure 1. The OH^--catalyzed deprotonation of $4^{\bullet+}$ (squares) is 27 times faster than that of $5^{\bullet+}$ (triangles) (5.4×10^9 *vs* 2.0×10^8 M^{-1} s^{-1}), although with $4^{\bullet+}$ and $5^{\bullet+}$ the same bond is (finally) broken. Even more interestingly, the second-order rate constant for the OH^--catalyzed decay of $4^{\bullet+}$ is almost identical with those for the case of $1^{\bullet+}$ and $2^{\bullet+}$, as indicated above. These values (5×10^9 M^{-1} s^{-1}) are characteristic for reaction of OH^- with protons bonded to a heteroatom such as oxygen.[8] The kinetic isotope effect was also studied, using 4-MeOC$_6$H$_4$−CD$_2$OH and −CD$_2$OMe instead of **4** and **5**. With the radical cation from the alcohol (−CD$_2$OH), the rate constant for reaction with OH^- was 5.3×10^9 M^{-1} s^{-1}, i.e., the same as that from the

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(5) Irradiations were carried out on argon-saturated aqueous solutions containing the substrate, $K_2S_2O_8$ (substrate/oxidant ratio ≥2), and 0.2 M 2-methyl-2-propanol at room temperature, using a ^{60}Co γ-source at dose rates of 0.3−0.9 Gy s^{-1}, for the time necessary to obtain a 40% conversion with respect to peroxydisulfate. Products were identified and quantitatively determined by HPLC (comparison with authentic samples).

(6) Experiments were carried out at 25 °C by pulse-irradiating argon-saturated aqueous solutions containing the substrate, peroxydisulfate, and 2-methyl-2-propanol. For the kinetic study of the radical cation decay, the ionic strength of the solution was buffered with 0.5 M Na_2SO_4, and 1 mM Na_2HPO_4 was added to avoid undesired pH changes upon irradiation. The decay followed first-order kinetics. Second-order rate constants for the base-induced process were obtained from the slope of the plots of k_{obs} *vs* [NaOH].

(7) The two radical cations were generated from **4** and **5**, respectively, and their decay kinetically studied as described in ref 6. In both cases, the decay of the radical cation, monitored at 450 nm, produced the corresponding carbon-centered radical (absorption at about 300 nm), as described in eqs 3 and 4.

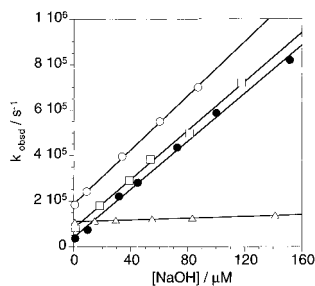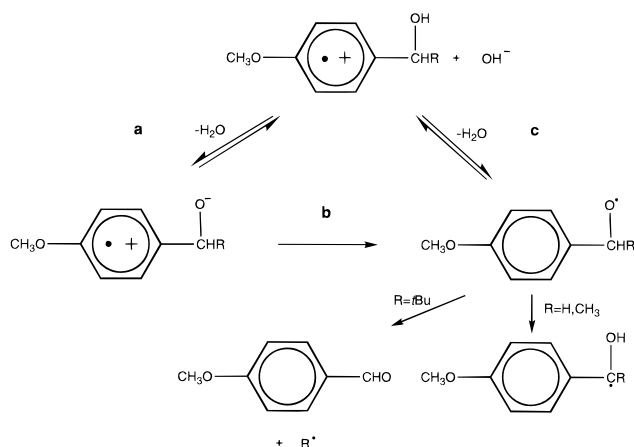(8) Eigen, M. *Angew. Chem.* **1963**, *75*, 489−508.

Figure 1. Effect of [OH$^-$] on the rate of decay of **1$^{\bullet+}$** (open circles), **2$^{\bullet+}$** (full circles), **4$^{\bullet+}$** (squares), and **5$^{\bullet+}$** (triangles).

Scheme 1

*non*deuterated compound, which means that $k(H)/k(D) = 1.0$, whereas for the ether ($-CD_2OMe$), $k(H)/k(D)$ was determined to be 1.8.

These observations clearly indicate that the OH$^-$-catalyzed decays of the radical cations **1$^{\bullet+}$**, **2$^{\bullet+}$**, and **4$^{\bullet+}$**, all of which bear an OH group on the α-carbon, have a fundamental mechanistic feature in common, independent of whether C$-$C or C$-$H bond cleavage eventually occurs. It is reasonable to assume and supported by the high rate constant of 5×10^9 M^{-1} s^{-1} that this common mechanistic feature involves the interaction of the base with the α-OH group, as detailed in Scheme 1.

The first step is deprotonation at the OH group, leading to a radical zwitterion (step a). In the second step the radical zwitterion undergoes an intramolecular electron transfer, forming a benzyloxyl radical (step b), analogous to that for the intramolecular electron transfer converting a 4-methoxybenzoate radical zwitterion into a benzoyloxyl radical.[9] The reorganization energy needed for this process could be quite high. An alternative is that the conversion of the radical cation into the benzyloxyl radical takes place in a single step. In other words, deprotonation and intramolecular electron transfer may be concerted (step c).

The fate of the benzyloxyl radical depends on the nature of R, as illustrated in Scheme 1. When, as in **1$^{\bullet+}$** (R = *t*Bu), R can give rise to a stabilized carbon radical such as *t*Bu$^{\bullet}$, a β-fragmentation reaction follows, and 4-methoxybenzaldehyde is formed.[10] This pathway is energetically less feasible when R is H or Me, (**4$^{\bullet+}$** and **2$^{\bullet+}$**). In these cases we suggest that the benzyloxyl radical is converted into the observed α-hydroxy carbon radical *via* a 1,2-hydrogen atom shift, a process which is well documented for alkoxyl radicals in aqueous solution.[11] Such a shift is expected to be very fast, and the same holds for

the β-fragmentation reaction, so it is not surprising that no spectral evidence was found for the presence of the benzyloxyl radical (λ_{max} around 560 nm).[12]

The mechanism discussed above nicely accounts for the experimental facts, particularly the kinetic isotope effect data, presented in this paper. In this case it is perfectly understandable that the rate constants for catalysis concerning the radical cations **1$^{\bullet+}$**, **2$^{\bullet+}$**, and **4$^{\bullet+}$** and its deuterated analogue are practically the same: accordingly, very similar pK_a and intramolecular electron transfer energies are foreseeable for these species.[13]

Possibly, the mechanism of Scheme 1 holds only for reactions with OH$^-$ (or bases of similar or greater strength); different mechanisms might operate with weaker bases. For example, in water, C$-$C bond cleavage in **1$^{\bullet+}$** might be assisted by hydrogen bond formation as previously suggested,[3] without involving complete OH deprotonation. For **2$^{\bullet+}$** and **4$^{\bullet+}$** in the absence of OH$^-$, direct attack to the C$-$H bond might occur, in agreement with the observation that, under these conditions, **2$^{\bullet+}$** and **4$^{\bullet+}$** decay with a rate similar to that of **5$^{\bullet+}$**, whose deprotonation can only involve the cleavage of the C$-$H bond.[14] On the other hand, in an alkylaromatic radical cation, the kinetic acidity of a β-C$-$H bond is expected to be significantly higher than that of a γ-O$-$H bond since only the former bond can interact with the SOMO of the radical cation which resides on the aromatic ring. Thus, it is reasonable that, in the presence of so weak a base as water, the deprotonation of the radical cation mainly involves the C$-$H bond. In the presence of the strong base OH$^-$, however, OH deprotonation becomes predominant and the mechanism changes to that of Scheme 1.

In conclusion, we have presented data indicating that the OH$^-$-induced deprotonation of α-hydroxy-substituted alkylaromatic radical cations in water to form the corresponding carbon radical does not involve the direct attack of the base at the C$-$H bond, as generally believed. We suggest that in the first step the base deprotonates the α-OH bond to produce a benzyloxyl radical, either directly or via a radical zwitterion which then undergoes an intramolecular (side chain to nucleus) electron transfer. The resulting benzyloxyl radical is then converted into the carbon radical by a 1,2-hydrogen atom shift, this reaction constituting the α-deprotonation.

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(13) It is evident that the observed catalytic effect of OH$^-$ (taking into account that the *k* value of 5×10^9 M^{-1} s^{-1} indicates interaction with the OH group) cannot be explained *solely* on the basis of the formation of a zwitterion (i.e., *without* intramolecular electron transfer occurring, giving the benzyloxyl radical) which then undergoes (**2$^{\bullet+}$** and **4$^{\bullet+}$**) C$-$H bond cleavage, since the conversion of the OH function into the *less* electron-withdrawing O$^-$ function would *decrease* the acidity of the radical cation, leading to a *negative* catalytic effect, in contrast to the experimental observation.

(14) It should be noted that, for this comparison, the values reported in the text for **4$^{\bullet+}$** and **5$^{\bullet+}$** have to be divided by 2 (statistical correction).