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The role of oxygen acidity on the side-chain fragmentation of ring methoxylated benzocycloalkenol radical cations

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Abstract—The reactivity of 2,2-dimethyl-5-methoxyindan-1-ol (**1**) and 2,2-dimethyl-6-methoxytetral-1-ol (**2**) radical cations has been studied both in acidic and basic solution. At pH ≤ 4 both $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ undergo C_α–H deprotonation as the exclusive reaction with $k=4.6\times10^4$ and 3.2×10^4 s^{-1}, respectively. In basic solution $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ behave as oxygen acids undergoing $^{-}$OH-induced α–OH deprotonation in a diffusion controlled process ($k_{-OH}\approx10^{10}$ M^{-1} s^{-1}). An intermediate alkoxyl radical is formed which undergoes a 1,2-hydrogen atom shift in competition with C–C β-scission (with $\mathbf{1}^{\bullet+}$) or as the exclusive pathway (with $\mathbf{2}^{\bullet+}$). A behavior which is interpreted in terms of the greater ease of ring-opening of a five membered ring as compared to a six-membered one.

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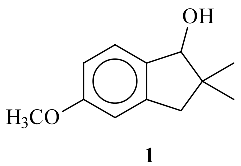
We have recently shown that in acidic aqueous solution 2,2-dimethyl-5-methoxyindan-1-ol (**1**) radical cation undergoes C_α–H deprotonation as the exclusive reaction and that an increase in deprotonation rate results from the alignment between the scissile C–H bond and the π-system imposed by the presence of the five-membered ring, thus providing evidence for the importance of stereoelectronic effects in the deprotonation of alkylaromatic radical cations.[1] In order to obtain additional information on this important topic, we have extended our study to 2,2-dimethyl-6-methoxytetral-1-ol (**2**).[2] Also in $\mathbf{2}^{\bullet+}$ the presence of the six-membered ring prevents a favorable alignment between the scissile C–C bond and the π-system, favoring instead that with the C–H bond.[3]



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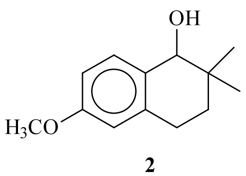

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The recent discovery that 1-(4-methoxyphenyl)alkanol radical cations behave as *carbon acids* in neutral and acidic solution, undergoing C_α–H deprotonation, whereas in basic solution (pH 10) they behave as *oxygen acids* undergoing $^{-}$OH-induced α–OH deprotonation leading, through the intermediacy of a radical zwitterion, to an alkoxyl radical,[4] prompted us to study the reactivity of $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ also in basic solution, in order to obtain information on the role of structural effects on this peculiar mechanistic behavior.

Results and discussion

Generation of the radical cations

Radical cations $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ were generated by oxidation of the neutral substrates employing three different methods: chemical oxidation with potassium 12-tungstocobalt(III)ate ($K_5[Co^{III}W_{12}O_{40}]$, from now on simply indicated as $Co^{III}W$) or oxidation with $SO_4^{\bullet-}$ generated by steady-state photolysis or by pulse radiolysis.

Oxidations induced by $Co^{III}W$. The $Co^{III}W$-induced oxidation of **1** at pH 3.1 has been described previously.[1] $\mathbf{2}^{\bullet+}$ was generated in aqueous solution at pH 3.1 (50 mM citrate buffer) under nitrogen at $T=50$°C by reaction of the substrate (0.5–2 mM) with $Co^{III}W$ (0.5–4 mM). $Co^{III}W$ is a well-known one-electron chemical oxidant able to oxidize methoxybenzene derivatives via outer-sphere electron transfer.[5]

Oxidations induced by $SO_4^{\bullet-}$. $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ were generated in aqueous solution at room temperature by reaction of the substrates with $SO_4^{\bullet-}$. $SO_4^{\bullet-}$ is a strong oxidant which is able to react with aromatic substrates via

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Keywords: radical cation; pulse radiolysis; deprotonation; oxygen acidity; stereoelectronic effect; alkoxyl radical.

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electron transfer to yield the corresponding radical cations with $k \approx 10^9$ M^{-1} s^{-1} (Eq. (1)).[6]

$$SO_4^{\bullet-} + ArCH(X)R \longrightarrow SO_4^{2-} + \overset{\bullet+}{Ar}CH(X)R \tag{1}$$

In the product studies, $SO_4^{\bullet-}$ was generated by steady state photolysis ($\lambda = 254$ nm) of nitrogen saturated aqueous solutions (pH 3.1 or 10.0, citrate or borate buffer, respectively) containing **1** or **2** (2 mM) and $K_2S_2O_8$ (0.1 M) (Eq. (2)).[7]

$$S_2O_8^{2-} \xrightarrow[254\ \text{nm}]{h\nu} 2\ SO_4^{\bullet-} \tag{2}$$

For kinetic studies, $SO_4^{\bullet-}$ was instead generated by pulse radiolysis of argon or oxygen saturated aqueous solutions containing **1** or **2** (0.5–1 mM), $K_2S_2O_8$ (5–10 mM) and 2-methyl-2-propanol (0.1 M) according to Eqs. (3–5).

$$H_2O \rightsquigarrow H^+,\ {}^{\bullet}OH,\ e^-_{aq} \tag{3}$$

$$^{\bullet}OH + CH_3C(CH_3)_2OH \longrightarrow H_2O + {}^{\bullet}CH_2C(CH_3)_2OH \tag{4}$$

$$e^-_{aq} + S_2O_8^{2-} \longrightarrow SO_4^{2-} + SO_4^{\bullet-} \tag{5}$$

Radiolysis of water leads to the formation of the hydroxyl radical ($^{\bullet}OH$) and the hydrated electron (e^-_{aq}) (Eq. (3)). The former is scavenged by 2-methyl-2-propanol (Eq. (4); $k = 6\times10^8$ M^{-1} s^{-1}),[6a] while e^-_{aq} reacts with the peroxydisulfate anion leading to the formation of $SO_4^{\bullet-}$ (Eq. (5); $k = 1.2\times10^{10}$ M^{-1} s^{-1}).[6a]

Product studies

Acidic solution (pH 3.1). The oxidation of **2** was carried out employing $Co^{III}W$ or $SO_4^{\bullet-}$ as the oxidant, showing in both cases the exclusive formation of 2,2-dimethyl-6-methoxytetral-1-one, in line with the results obtained with **1** (exclusive formation of 2,2-dimethyl-5-methoxyindan-1-one).[1] Ketone formation can be explained on the basis of the formation and deprotonation of an intermediate radical cation leading to a carbon centered radical, which is then oxidized to the corresponding ketone, in analogy with one-electron oxidations of arylalkanols.[8] Thus, under these conditions the exclusive reaction of $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ is deprotonation from C-1.

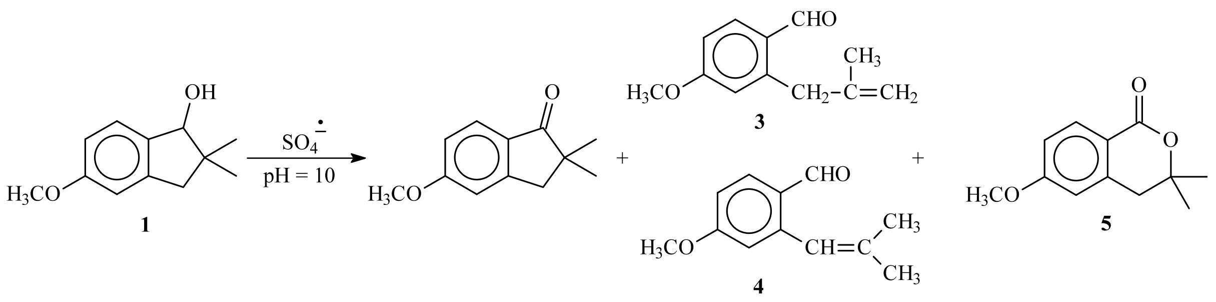
Basic solution (pH 10). The oxidations of **1** and **2** were carried out employing $SO_4^{\bullet-}$ as the oxidant. Oxidation of **1** led the formation of 2,2-dimethyl-5-methoxyindan-1-one as main product (86%) together with 4-methoxy-2-(2-methyl-2-propenyl)benzencarbaldehyde (**3**) (2%), 4-methoxy-2-(2-methyl-1-propenyl)benzencarbaldehyde (**4**) (2%) and 8,8-dimethyl-5-methoxybenzo[c]oxacyclohexan-2-one (**5**) (10%) (Scheme 1).[9]

Oxidation of **2** led instead to the exclusive formation of the corresponding ketone, 2,2-dimethyl-6-methoxytetral-1-one.

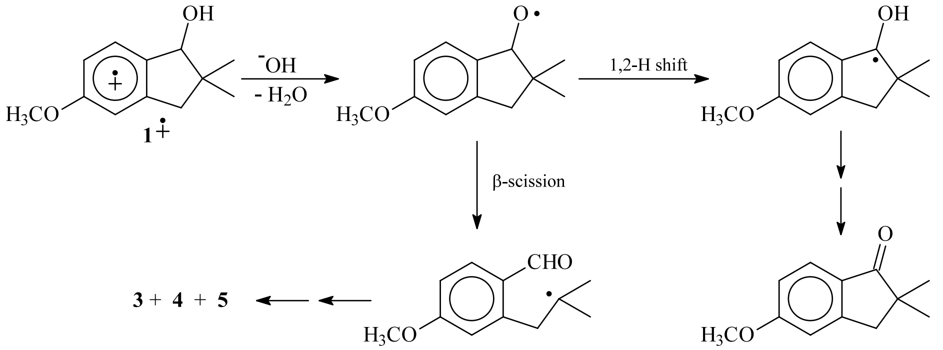
Kinetic studies. These were carried out using the pulse radiolysis technique. The time-resolved absorption spectrum of $\mathbf{2}^{\bullet+}$ at pH 3.3 and room temperature showed the characteristic UV and visible absorption bands of anisole-type radical cations centered at 290 and 460 nm,[4,6b] analogous to those observed previously for $\mathbf{1}^{\bullet+}$.[1]

Acidic solution (pH 3.1). The decay rate of $\mathbf{2}^{\bullet+}$ was measured spectrophotometrically following the decrease in optical density at 460 nm. Under these conditions, $\mathbf{2}^{\bullet+}$ decays with first-order kinetics with $k = 3.2\times10^4$ s^{-1}, in a reaction which, on the basis of product analysis results, is assigned to C–H deprotonation. This value is similar to that obtained for $\mathbf{1}^{\bullet+}$, $k = 4.6\times10^4$ s^{-1},[1] confirming that when the C–H bond is forced into a conformation where it is almost aligned with the π-system as in $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$, the deprotonation rate increases significantly as compared to 1-(4-methoxyphenyl)ethanol radical cation ($k = 7.0\times10^3$ s^{-1}),[4] where all conformations are instead accessible for the scissile C–H bond.

Basic solution. A significant increase in rate was observed when ^-OH was added to the solution. By plotting the observed rate constants for ^-OH-induced decay of the radical cations (k_{obs}) measured at 460 nm, against the concentration of added base, a linear dependence was observed. From the slope of these plots, the second-order rate constants for reaction of ^-OH with $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ (k_{-OH}) were determined as $k_{-OH} = 1.3\times10^{10}$ and 1.1×10^{10} M^{-1} s^{-1}, respectively, values which are indicative of α–OH deprotonation as previously discussed for 1-(4-methoxyphenyl)alkanol radical cations, indicating that under these conditions $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ exhibit *oxygen acidity*.[4]



Scheme 1.



Scheme 2.

On the basis of this observation, the product distribution observed after oxidation of **1** at pH 10 can be explained in terms of the competition between 1,2-hydrogen atom shift and C–C β-scission in an intermediate 2,2-dimethyl-5-methoxyindanyl-1-oxyl radical (or radical zwitterion), formed by $^-$OH-induced α–OH deprotonation of $\mathbf{1}^{\bullet+}$ (Scheme 2). 2,2-Dimethyl-5-methoxyindan-1-one derives from the oxidation of the α-hydroxy indanyl radical formed after 1,2-hydrogen atom shift, whereas products **3**, **4** and **5** from the successive reactions of the carbocation generated by oxidation of the carbon centered radical formed after C–C β-scission.

Interestingly, the observation that 2,2-dimethyl-5-methoxyindan-1-one is the main fragmentation product suggests that in the intermediate 2,2-dimethyl-5-methoxyindanyl-1-oxyl radical, the 1,2-hydrogen atom shift occurs more rapidly than C–C β-scission. Along this line, the exclusive formation of 6-methoxy-2,2-dimethyltetral-1-one in the oxidation of **2** at pH 10 indicates that the intermediate 2,2-dimethyl-6-methoxytetralyn-1-oxyl radical undergoes exclusive 1,2-H atom shift.

Comparison between the results obtained after oxidation of **1** and **2** at pH 10 shows that the importance of the C–C bond cleavage pathway decreases on going from the indane system to the tetralyn one, a result which can be rationalized in terms of the greater ease of ring opening of a cyclopentoxyl radical as compared to a cyclohexoxyl one.[10]

The observation that for both 2,2-dimethyl-5-methoxyindanyl-1-oxyl and 2,2-dimethyl-6-methoxytetralyn-1-oxyl radicals the 1,2-H atom shift occurs more rapidly than C–C β-scission whereas the radical derived from α–OH deprotonation of 1-(4-methoxyphenyl)-2,2-dimethyl-1-propanol radical cation undergoes exclusive C–C bond cleavage,[4] suggests that the conformation imposed by the presence of the five- and six-membered ring plays an important role in the competition between these processes.

In conclusion, this work confirms that in alkylaromatic radical cations overlap between the scissile bond and the π system containing the unpaired electron is a fundamental requisite for the occurrence of bond cleavage. In alkaline aqueous solution $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$ display oxygen acidity undergoing α–OH deprotonation to give an alkoxyl radical from which the observed products of C–H and C–C bond cleavage can be formed. C–C bond cleavage represents however a minor fragmentation pathway for these benzocycloalkenyl-1-oxyl radicals, which mainly undergo a 1,2-H atom shift.

Acknowledgements

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9. **3**, **4**, and **5** were isolated by column chromatography (silica gel, eluent hexane/ethyl acetate, 5:1) and characterized by NMR and GC–MS.
   3: ^{1}H NMR ($CDCl_3$): δ 10.09 (s, 1H, $\mathrm{C}H\mathrm{O}$), δ 7.86–7.82 (d, 1H, $\mathrm{Ar}H$), δ 6.91–6.76 (m, 2H, $\mathrm{Ar}H$), δ 4.85 (m, 1H, $=\mathrm{C}H_2$), δ 3.88 (s, 3H, $\mathrm{OC}H_3$), δ 3.71 (s, 2H, $\mathrm{C}H_2$), δ 1.78 (s, 3H, $\mathrm{C}H_3$). GC/MS (e.i. 70 eV) *m*/*z*: [M$^+$] 190, 176, 175 (100), 158, 148, 147, 129, 128, 115, 103, 91, 78, 77, 51.
   4: ^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H, $\mathrm{C}H\mathrm{O}$), δ 7.89–6.69 (m, 3H, $\mathrm{Ar}H$), δ 6.55 (s, 1H, $\mathrm{ArC}H{=}$), δ 3.87 (s, 3H, $\mathrm{OC}H_3$), δ 1.96 (d, 3H, $=\mathrm{C}(\mathrm{C}H_3)_{trans}$), δ 1.68 (d, 3H, $=\mathrm{C}(\mathrm{C}H_3)_{cis}$). GC/MS (e.i. 70 eV) *m*/*z*: [M$^+$] 190, 176, 175 (100), 158, 148, 147, 132, 115, 103, 91, 78, 77, 51.
   5: ^{1}H NMR ($CDCl_3$): δ 8.07–6.68 (m, 3H, $\mathrm{Ar}H$), δ 3.87 (s, 3H, $\mathrm{OC}H_3$), δ 2.97 (s, 2H, $\mathrm{C}H_2$), δ 1.45 (s, 6H,$\mathrm{C}H_3$). ^{13}C NMR ($CDCl_3$): δ 165 (CO), δ 164 (Ar C-9), δ 140 (Ar C-5), δ 132 (Ar C-4), δ 117 (Ar C-10), δ 113 (Ar C-6), δ 113 (C-3), δ 80 (C-8), 55 (OCH_3), δ 40 (C-7), δ 27 (2 CH_3). GC/MS (e.i. 70 eV) *m*/*z*: [M$^+$] 206, 163, 148 (100), 120, 91, 77, 51.
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