PERKIN 2

Oxidative decarboxylation of 4-methoxyphenylacetic acid induced by potassium 12-tungstocobalt(III)ate. The role of intramolecular electron transfer

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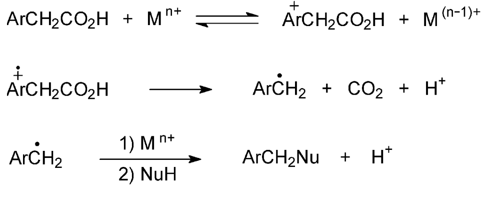
A kinetic study of the oxidation of 4-methoxyphenylacetic acid ($\mathrm{AnCH_2CO_2H}$: An = 4-$\mathrm{MeOC_6H_4}$) with potassium 12-tungstocobalt(III)ate ($\mathrm{K_5[Co^{III}W_{12}O_{40}]} \equiv \mathrm{Co^{III}W}$) has been carried out in aqueous solution at different pH values (between 2.15 and 4.98). The reaction proceeds *via* a rate determining electron transfer, followed by a fast decarboxylation step leading to a 4-methoxybenzyl radical. From the analysis of the kinetic data the rate constants for reaction of $\mathrm{Co^{III}W}$ with $\mathrm{AnCH_2CO_2H}$ and $\mathrm{AnCH_2CO_2^-}$ respectively, k_1 and k_2, have been derived as $k_1 = 0.109$ $\mathrm{M^{-1}\ s^{-1}}$ and $k_2 = 2.948$ $\mathrm{M^{-1}\ s^{-1}}$, indicating that in the oxidation of 4-methoxyphenylacetic acid by $\mathrm{Co^{III}W}$, ionization of the carboxylic group results in an almost 30-fold acceleration of the decarboxylation rate. In order to explain this behavior, it is proposed that no aromatic radical cation is formed as a reaction intermediate, electron removal from the aromatic ring being instead concerted with an intramolecular side-chain to nucleus electron transfer, directly leading to a carboxyl radical which then undergoes rapid decarboxylation to give the 4-methoxybenzyl radical.

The oxidative decarboxylation of arylalkanoic acids is an important reaction both in chemistry and biology.[1,2] As an example, most non-steroidal anti-inflammatory drugs have an α-arylacetic or an α-arylpropionic acid structure, and it is possible that these drugs are metabolized *via* an oxidative decarboxylation pathway.[3] Moreover, many drugs, herbicides and pesticides containing a carboxylic group can produce *via* decarboxylation potentially toxic radical intermediates.[2]

The oxidative decarboxylation of arylacetic acids by cobaltic acetate,[4] ceric ammonium nitrate (CAN)[5] and potassium 12-tungstocobalt(III)ate ($\mathrm{K_5[Co^{III}W_{12}O_{40}]}$, from now on indicated as $\mathrm{Co^{III}W}$)[6] as the oxidants has been kinetically investigated using the competitive method. A mechanism involving a direct interaction between the carboxylic group and the metal complex was suggested, but it was also proposed that in the presence of electron releasing ring substituents, like a *para*-methoxy group, an electron transfer mechanism could operate (Scheme 1).



Scheme 1

The formation of an intermediate aromatic radical cation, which then undergoes rapid decarboxylation leading to a benzylic radical was also the conclusion of Steenken and Gilbert who studied the oxidative decarboxylation of 4-methyl- and 4-methoxyphenylacetic acids by laser flash photolysis.[7] Lower limits for the decarboxylation rate of 4-methylphenylacetic acid were provided ($k_{\mathrm{dec}} > 10^7\ \mathrm{s^{-1}}$), following the formation of the 4-methylbenzyl radical, and it was also shown that the rate constant increases with increasing pH, indicating that decarboxylation is faster when the carboxyl group is ionized. 4-Methoxyphenylacetic acid was studied only under conditions where the carboxylate anion predominates and an upper limit for decarboxylation ($k_{\mathrm{dec}} \geq 5 \times 10^7\ \mathrm{s^{-1}}$) was established. However, no evidence for the formation of an intermediate radical cation was provided.

More recently Kochi studied the decarboxylation of arylacetates by photoinduced electron transfer in charge transfer ion pairs between arylacetate anions and a cationic acceptor in aqueous solution, providing absolute rates of decarboxylation: $k_{\mathrm{dec}} \approx 10^9\ \mathrm{s^{-1}}$.[8] Also in this case, no evidence for the involvement of aromatic radical cations was provided.

In this context, several questions concerning the mechanism of the oxidative decarboxylation of arylacetic acids remain unanswered. Apart from the fact that there is no clear evidence for the involvement of aromatic radical cations, another aspect of interest is whether decarboxylation occurs directly from the radical cation or from an intermediate acyloxyl radical, as clearly shown in the case of benzoic acids.[9] The acyloxyl radical, in turn, might be formed directly or following intramolecular electron transfer in an intermediate radical cation.

In order to obtain more information about this complex mechanistic picture, we have carried out a kinetic study, at different pH values, of the oxidation of 4-methoxyphenylacetic acid ($\mathrm{AnCH_2CO_2H}$: An = 4-$\mathrm{MeOC_6H_4}$) with the well known outer sphere one-electron oxidant $\mathrm{Co^{III}W}$.[10,11] By this study it has been possible to determine the reaction rate for both the neutral and ionized form of 4-methoxyphenylacetic acid and to get a further insight into the reaction mechanism.

Results and discussion

The oxidation of $\mathrm{AnCH_2CO_2H}$ by $\mathrm{Co^{III}W}$ has been studied in water at T = 20 °C. Product analysis has shown the formation of 4-methoxybenzyl alcohol as the exclusive product.[6,12] The kinetic study of the reaction has been carried out spectrophotometrically, following the decrease in absorbance of $\mathrm{Co^{III}W}$ at 390 nm. The pH has been varied between 2.15 and 4.98 using a NaOH–citric acid buffer, and the ionic strength of the solution has been buffered with $\mathrm{NaClO_4}$. From the analysis of the

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Table 1 k_{obs} values for the $\mathrm{Co^{III}W}$ induced oxidation of 4-methoxyphenylacetic acid in water at $T = 20$ °C at pH = 2.58 and 4.50

pH	$[\mathrm{Co^{III}W}]$/M	$k_{obs}/\mathrm{s^{-1}}$ [a]
2.58	0.0005	6.6×10^{-3}
		6.4×10^{-3} [b]
2.58	0.001	6.4×10^{-3}
2.58	0.0015	7.1×10^{-3}
		6.0×10^{-3} [b]
4.50	0.0003	6.3×10^{-2}
		6.5×10^{-2} [b]
4.50	0.0005	6.4×10^{-2}
		6.2×10^{-2} [b]
4.50	0.001	6.5×10^{-2}
4.50	0.0015	6.7×10^{-2}
		6.0×10^{-2} [b]

[a] Measured as described in eqn. (1). Each value is the average of 3–5 experiments: error ≤ 5%. [b] Reaction carried out in the presence of $\mathrm{Co^{II}W}$.

Table 2 k_{obs} values for the $\mathrm{Co^{III}W}$ induced oxidation of 4-methoxyphenylacetic acid in water at $T = 20$ °C at different pH values

pH	$k_{obs}/\mathrm{s^{-1}}$ [a]
2.15	5.0×10^{-3}
2.58	6.4×10^{-3}
3.04	1.0×10^{-2}
3.59	2.1×10^{-2}
4.03	3.8×10^{-2}
4.50	6.5×10^{-2}
4.98	8.6×10^{-2}

[a] Measured as described in eqn. (1). Each value is the average of 3–5 experiments: error ≤ 5%.

kinetic data a second order equation is obtained showing that, due to the very fast decarboxylation step, the reaction proceeds *via* a rate determining electron transfer. Working with a substrate excess, excellent first-order kinetics were observed, allowing us to determine rate constants (k_{obs}) by eqn. (1).

$$[\mathrm{Co^{III}W}] = [\mathrm{Co^{III}W}]_0 \exp(-k_{obs}t) \qquad (1)$$

The values of k_{obs} thus obtained are displayed in Tables 1 and 2.

It was found that k_{obs} is unaffected by the concentration of the oxidant ($\mathrm{Co^{III}W}$) as well as by the concentration of its reduced form ($\mathrm{Co^{II}W}$). The lack of a kinetic effect by $\mathrm{Co^{II}W}$ clearly indicates that if an electron transfer step is occurring it is the rate determining one.[11,13]

It was also observed that k_{obs} increases with increasing pH, going from $5.0 \times 10^{-3}\ \mathrm{s^{-1}}$ at pH = 2.15 to $8.6 \times 10^{-2}\ \mathrm{s^{-1}}$ at pH = 4.98 (Table 2), which can reasonably be explained by assuming that the reaction rate is determined by the sum of two contributions, that due to the oxidation reaction of the neutral acid (v_1) and that due to the reaction of the carboxylate anion (v_2) (eqns. (2) and (3), respectively, where the factor 2 takes into account the fact that two moles of oxidant are consumed for each mole of substrate. k_1 and k_2 are the rate constants for electron transfer from $\mathrm{AnCH_2CO_2H}$ and $\mathrm{AnCH_2CO_2^-}$, respectively, to $\mathrm{Co^{III}W}$).

$$v_1 = 2k_1[\mathrm{AnCH_2CO_2H}][\mathrm{Co^{III}W}] \qquad (2)$$

$$v_2 = 2k_2[\mathrm{AnCH_2CO_2^-}][\mathrm{Co^{III}W}] \qquad (3)$$

It is thus possible to write for k_{obs}:

$$k_{obs} = 2(k_1[\mathrm{AnCH_2CO_2H}] + k_2[\mathrm{AnCH_2CO_2^-}]) \qquad (4)$$

From the equilibrium constant for the dissociation of 4-methoxyphenylacetic acid: $K_a = [\mathrm{AnCH_2CO_2^-}][\mathrm{H^+}]/[\mathrm{AnCH_2CO_2H}]$ we obtain:

$$k_{obs}/[\mathrm{AnCH_2CO_2^-}] = 2(k_2 + k_1[\mathrm{H^+}]/K_a) \qquad (5)$$

which predicts a linear correlation between $k_{obs}/[\mathrm{AnCH_2CO_2^-}]$ and $[\mathrm{H^+}]$, with $2k_1/K_a$ as the slope and $2k_2$ as the intercept. By plotting $k_{obs}/[\mathrm{AnCH_2CO_2^-}]$ against $[\mathrm{H^+}]$ a very good linear correlation is indeed observed (Fig. 1), and given that $K_a = 4.36 \times 10^{-5}$ M,[14,15] from the slope and intercept, the rate constants for reaction of $\mathrm{Co^{III}W}$ with $\mathrm{AnCH_2CO_2H}$ and $\mathrm{AnCH_2CO_2^-}$ respectively, k_1 and k_2, can be derived.

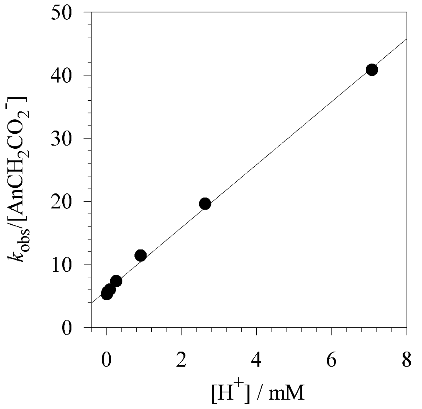
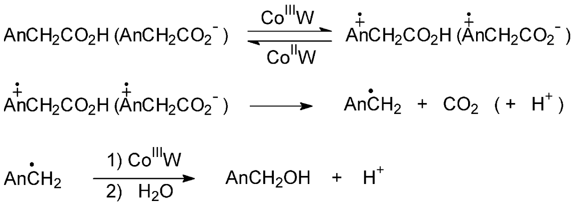


Fig. 1 Plot of the $k_{obs}/[\mathrm{AnCH_2CO_2^-}]$ ratio *vs.* concentration of $\mathrm{H^+}$ for the reactions of 4-methoxyphenylacetic acid with $\mathrm{Co^{III}W}$ in $\mathrm{H_2O}$ (NaOH–citric acid buffer) at $T = 20$ °C. $r^2 = 0.998$.

The values thus obtained: $k_1 = 0.109\ \mathrm{M^{-1}\ s^{-1}}$ and $k_2 = 2.948\ \mathrm{M^{-1}\ s^{-1}}$, indicate that in the oxidation of 4-methoxyphenylacetic acid by $\mathrm{Co^{III}W}$, ionization of the carboxylic group results in an almost 30-fold acceleration of the decarboxylation rate.

At first sight, these kinetic results might be interpreted on the basis of the generally accepted mechanism for the oxidative decarboxylation of electron rich phenylacetic acids (Scheme 2),



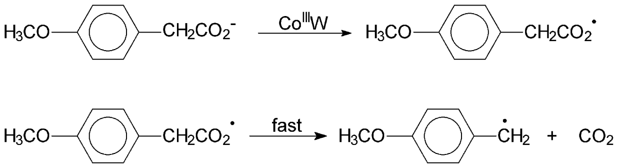
Scheme 2

provided that the radical ion or radical zwitterion intermediate is formed in the slow step.

However, the observed large difference in reactivity (30 fold) between the ionized and the neutral form of the acid, while understandable if one considers the decarboxylation step, is difficult to explain when, as indicated by the present kinetic results, the rate determining step is the formation of the radical cation. Accordingly, we cannot imagine a difference in stability between $\mathrm{An^{\cdot+}CH_2CO_2^-}$ and $\mathrm{An^{\cdot+}CH_2CO_2H}$ (the difference in electronic effect between $\mathrm{-CH_2CO_2^-}$ and $\mathrm{-CH_2CO_2H}$ is only 0.1 σ units)[16] so significant as to justify the observed difference in oxidation rate between $\mathrm{AnCH_2CO_2^-}$ and $\mathrm{AnCH_2CO_2H}$. It would require an unreasonably large (*ca.* − 15) ρ value for the oxidation reaction.

The possibility of a change in the site of oxidation from the aromatic ring in $\mathrm{AnCH_2CO_2H}$ to the carboxylate in $\mathrm{AnCH_2CO_2^-}$ is also highly unlikely, as clearly shown by Gilbert in the oxidation of phenylalkanoic acids with $\mathrm{SO_4^{\cdot-}}$.[17]

Thus, in consideration also of the fact that no direct evidence for the formation of a radical cation in the oxidative decarboxylation of arylacetic acids has been so far provided,[7,8] the only reasonable explanation which can be presently put forward to explain the above results is that *no radical cation intermediate* is actually formed, electron removal from the aromatic ring being concerted with the intramolecular side-chain to nucleus electron transfer, so directly leading to the carboxyl radical which then undergoes fast decarboxylation to give the 4-methoxybenzyl radical (Scheme 3).



Scheme 3

In other words, the rate determining electron transfer occurs from the CO_2^- or CO_2H group, but it requires the mediation of the aromatic ring which acts as a *redox relay*. Thus, the energetics of the oxidation is determined by both the ease of electron abstraction from the aromatic ring and the height of the kinetic barrier for the intramolecular electron transfer. The latter should certainly be higher for the CO_2H group as compared to CO_2^-, since an additional proton transfer to the medium is required, thus accounting for the significantly slower decarboxylation rate measured for $AnCH_2CO_2H$ as compared to $AnCH_2CO_2^-$. Of course, it is possible that with arylacetic acids more electron rich than those hitherto studied, a mechanistic changeover may occur with formation of an intermediate radical cation. Work is in progress to look for this possibility.[18]

Experimental

Materials

Citric acid, sodium hydroxide, sodium perchlorate and 4-methoxybenzyl alcohol were of the highest commercial quality available. HPLC grade water was used for all solutions. 4-Methoxyphenylacetic acid (Fluka) was recrystallized twice from water. $Co^{III}W$ was prepared according to a previously described procedure.[19]

Product analysis

The oxidations of 4-methoxyphenylacetic acid induced by $Co^{III}W$ were performed in aqueous solution (pH = 3 or 5) at T = 25 °C. In a typical experiment, 5 mL of an argon saturated solution containing the substrate (0.02 M) and $Co^{III}W$ (0.02 M) were stirred until complete conversion of the oxidant. Workup was performed as described previously.[19] 4-Methoxybenzyl alcohol (identified by comparison with an authentic sample) was the exclusive reaction product.

Kinetic studies

All the kinetics studied were carried out in a 1 cm quartz cuvette previously flushed with argon. The solvent mixtures (citric acid–NaOH buffer solutions, pH 2.15–4.98) were thoroughly purged with argon and the ionic strength of the solutions was buffered with 0.1 M $NaClO_4$. The stability of $Co^{III}W$ to reaction conditions was checked for every reaction mixture. A cuvette containing 1 ml of a 4-methoxyphenylacetic acid (0.020 M) solution in the pertinent buffer was placed in a thermostated compartment of a UV–vis spectrophotometer. After thermal equilibration at T = 20 °C, the reaction was started by rapid addition of the $Co^{III}W$ solution (0.021 M in the pertinent buffer: final $Co^{III}W$ concentration in the cuvette between 0.0003 and 0.0015 M).[20] The rate of disappearance of $Co^{III}W$ was followed spectrophotometrically by measuring the absorbance of $Co^{III}W$ at 390 nm. The absorbance A was recorded up to when a constant value was reached (A_∞; conversion $Co^{III}W > 99\%$), and was related to the extent of reaction as $[Co^{III}W]/[Co^{III}W]_0 = (A_t - A_\infty)/(A_0 - A_\infty)$. Excellent first-order kinetics have been observed and the observed rates (k_{obs}) have been derived applying eqn. (1) to the experimental data. Each value is the average of 3–5 experiments: error ≤ 5%.

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