

Partial Oxidation of 4-*tert*-Butyltoluene Catalyzed by Homogeneous Cobalt and Cerium Acetate Catalysts in the Br⁻/H₂O₂/Acetic Acid System: Insights into Selectivity and Mechanism

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Abstract: The partial oxidation of 4-*tert*-butyltoluene to 4-*tert*-butylbenzaldehyde by hydrogen peroxide in glacial acetic acid, catalyzed by bromide ions in combination with cobalt(II) acetate or cerium(III) acetate, has been studied in detail. Based on the observed differences in reaction rates and product distributions for the different catalysts, a reaction mechanism involving two independent pathways is proposed. After the initial formation of a benzylic radical species, either oxidation of this intermediate by the metal catalyst or reaction with bromine generated in situ occurs, depending on which catalyst is

used. The first pathway leads to the exclusive formation of 4-*tert*-butylbenzaldehyde, whereas reaction of the radical intermediate with bromine leads to formation of the observed side products 4-*tert*-butylbenzyl bromide and its hydrolysis and solvolysis products 4-*tert*-butylbenzyl alcohol and 4-*tert*-butylbenzyl acetate, respectively. The cobalt(II) catalysts Co(OAc)₂ and Co(acac)₂ are able to quickly oxidize the

radical intermediate, thereby largely preventing the bromination reaction (i.e., side-product formation) from occurring, and yield the aldehyde product with 75–80% selectivity. In contrast, the cerium catalyst studied here exhibits an aldehyde selectivity of around 50% due to the competing bromination reaction. Addition of extra hydrogen peroxide leads to an increased product yield of 72% (cerium(III) acetate) or 58% (cobalt(II) acetate). Product inhibition and the presence of increasing amounts of water in the reaction mixture do not play a role in the observed low incremental yields.

Keywords: cerium • cobalt • homogeneous catalysis • oxidation • reaction mechanisms

Introduction

The selective oxidation of hydrocarbons is a major challenge in industrial chemistry. The low reactivity of hydrocarbon substrates requires forcing reaction conditions, which often lead to side reactions and overoxidation of the desired, partially oxidized, product. Mild conditions are mandatory to prevent overoxidation, but the resulting low conversions leave large quantities of hydrocarbon substrate to be recycled continuously in these processes. The ultimate synthetic and industrial aim is high conversion without side reactions under mild reaction conditions with benign oxidants such as

dioxygen or hydrogen peroxide.^[1,2] Transition metal catalyzed oxidation reactions have attracted much recent research interest, as less harsh reaction conditions can be applied to reach conversions similar to those observed in uncatalyzed oxidation reactions. Apart from this, side reactions can be suppressed to some extent, as the relative reactivity of a hydrocarbon substrate and that of its partial oxidation products is known to change considerably in the presence of a catalyst.^[3] Several transition metal catalyzed autoxidation reactions have been applied to industrial processes, for example, the production of terephthalic acid, used in the production of polyesters, from *p*-xylene, which is catalyzed by cobalt(II) acetate bromide, with air as oxidant.^[4]

The cobalt(II) acetate catalyzed oxidation of hydrocarbons with hydrogen peroxide as oxidant, bromide ions as co-catalyst, and acetic acid as solvent has been reported for the partial oxidation of (substituted) toluenes to the corresponding benzaldehydes.^[5–8] This reaction is of significant industrial interest, as 4-*tert*-butylbenzaldehyde is a key intermediate in the production of fragrances.^[8] The aldehyde product can

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be obtained with high selectivity only at low conversion, because the benzoic acid overoxidation product is inevitably formed as the aldehyde product accumulates. Cerium(III) acetate also catalyzes the reaction, albeit with lower conversion and aldehyde selectivity than with cobalt(II) acetate.^[7] No aldehyde product was detected in the absence of bromide ions in this study, and this, together with the fact that 4-*tert*-butylbenzyl bromide was observed as a side product, prompted those authors to suggest that the reaction occurs via a benzylic bromide intermediate.^[7] However, the exact role of cerium and bromide could not be established in that study. The deactivation mechanism of the cobalt(II) catalyzed oxidation of 4-*tert*-butyltoluene was studied by Amin et al.^[8] Water, part of the aqueous hydrogen peroxide solution, was suggested to transform cobalt into a less active form, thereby limiting the overall aldehyde yield. Moreover, accumulation of the 4-*tert*-butylbenzaldehyde product was found to prevent progress of the reaction beyond 50% conversion. Another conclusion from this work was that 4-*tert*-butylbenzyl bromide is not an intermediate in the reaction, in contrast to the reports by Jones et al.^[6] and Auty et al.^[7]

The aim of the present study is to improve cobalt(II)- or cerium(III)-catalyzed toluene oxidation in terms of aldehyde selectivity and conversion through a detailed understanding of the reaction pathway. We studied the differences between the cobalt(II)- and cerium(III)-catalyzed reactions and attempted to identify reaction intermediates and reaction pathways. Based on the catalytic data presented here and those reported previously by others, we propose the existence of two separate reaction pathways, one of which leads to formation of the aldehyde main product, and the other to the side products of this reaction.

Results and Discussion

Results of the catalytic oxidation of 4-*tert*-butyltoluene after 2 h are summarized in Table 1. In the first 40 min of the Ce(OAc)₃-catalyzed reaction (entry 3), 4-*tert*-butylbenzyl bromide is formed rapidly and is the main reaction product (see Figure 1). Formation of this product then ceases and, after reaching a maximum of 0.74 mmol, the amount decreases to 0.62 mmol after 2 h. Benzaldehyde formation starts from the moment of the first hydrogen peroxide addition at a constant, but somewhat slower, rate compared to the formation of the benzylic bromide. Aldehyde formation almost stops after the addition of the last hydrogen peroxide aliquot at *t* = 60 min. The other products of the reaction, 4-*tert*-butylbenzyl alcohol and 4-*tert*-butylbenzyl acetate, are detected merely in small quantities and only during the second hour of the reaction. Interestingly, formation of these products seems to be related to the decrease in the amount of 4-*tert*-butylbenzyl bromide. Indeed, from *t* = 53 min onwards, the combined amounts of benzylic bromide, alcohol, and acetate remain almost constant at around 0.85 mmol (Figure 1b). Formation of the aldehyde product

Table 1. Results after 2 h for the oxidation of 4-*tert*-butyltoluene with different catalysts in the presence of KBr with hydrogen peroxide as oxidant and glacial acetic acid as solvent (*T* = 70°C).

Entry	Catalyst	Conversion [%]	Aldehyde selectivity [%]	Product yields [%]			
				aldehyde 5	bromide 7	alcohol 4	acetate 8
1	–	6.9	31	2.3	3.9	0.4	0.4
2	(NH ₄) ₂ Ce(NO ₃) ₆	28	51	14	11	1.2	1.5
3	Ce(OAc) ₃	28	52	15	10	1.7	1.7
4	Ce(OAc) ₃ ^[a]	35	59	20	7.3	4.2	2.8
5	Ce(OAc) ₃ ^[b]	35	82	28	5.8	0.0	0.4
6	Co(OAc) ₂	47	79	37	2.1	0.0	0.0
7	Co(OAc) ₂ ^[a]	52	79	41	2.9	0.0	1.2
8	Co(OAc) ₂ ^[b]	74	69	51	1.8	0.2	0.4
9	Co(acac) ₂	49	73	36	0.3	2.1	0.3
10	Co(acac) ₂ ^[b]	65	77	50	0.3	2.5	0.2
11	Mn(OAc) ₂	0.2	100	0.2	0.0	0.0	0.0

[a] 0.50 g of water added at the start of the reaction. [b] Double amount of hydrogen peroxide added (addition continued during second hour of reaction).

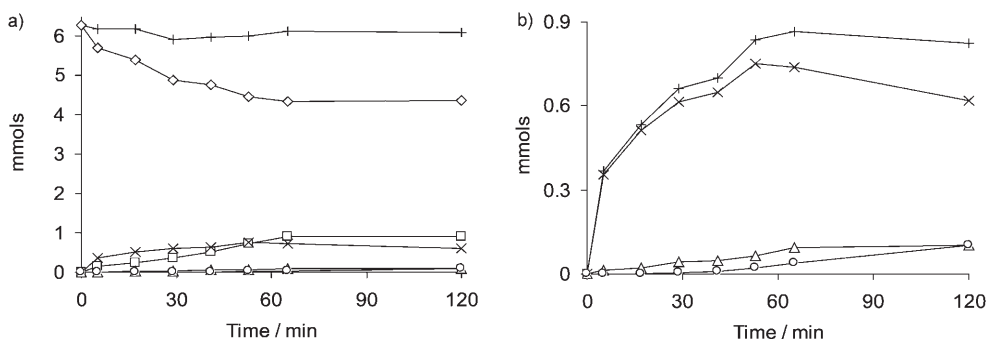


Figure 1. a) Product distribution for the oxidation of 4-*tert*-butyltoluene in acetic acid at 70°C over Ce(OAc)₃ by slow addition of H₂O₂ during the first 60 min. Substrate:Ce:H₂O₂:KBr ratio = 45:1:92:8. Mass balance (+), 4-*tert*-butyltoluene (◇), 4-*tert*-butylbenzaldehyde (□), 4-*tert*-butylbenzyl bromide (×), 4-*tert*-butylbenzyl alcohol (△), and 4-*tert*-butylbenzyl acetate (○). b) Side-product formation. Total amount (+) of 4-*tert*-butylbenzyl bromide (×), 4-*tert*-butylbenzyl alcohol (△), and 4-*tert*-butylbenzyl acetate (○).

appears to follow a course independent of the formation of the bromide, alcohol, and acetate products. A similar pattern of side-product formation was observed by Auty et al. in their study on the $\text{Ce}(\text{OAc})_3$ -catalyzed reaction.^[7]

The result of the $\text{Co}(\text{OAc})_2$ -catalyzed reaction (entry 6, Table 1) is depicted in Figure 2. The aldehyde selectivity is

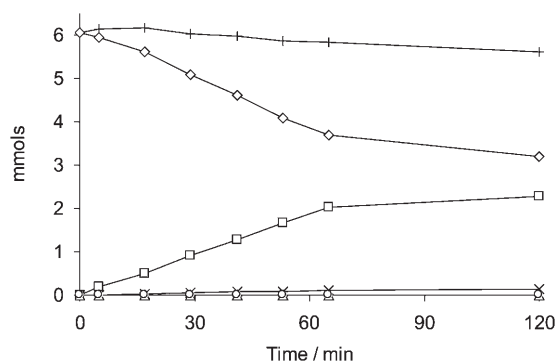


Figure 2. Product distribution for the oxidation of 4-*tert*-butyltoluene in acetic acid at 70°C over $\text{Co}(\text{OAc})_2$ by slow addition of H_2O_2 during the first 60 min. Substrate:Co: H_2O_2 :KBr ratio = 45:1:92:8. Mass balance (+), 4-*tert*-butyltoluene (◇), 4-*tert*-butylbenzaldehyde (□), 4-*tert*-butylbenzyl bromide (×), 4-*tert*-butylbenzyl alcohol (△), and 4-*tert*-butylbenzyl acetate (○).

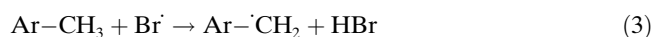
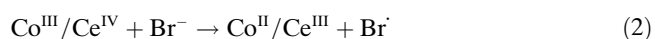
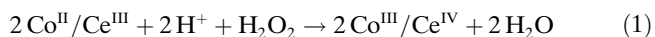
79% at a conversion of 47%, although the mass balance of this reaction was not as good as in the case of $\text{Ce}(\text{OAc})_3$. Only 92% of the starting material could be recovered after 2 h, and the 8% unaccounted for was found to be the over-oxidation product 4-*tert*-butylbenzoic acid (vide infra). Aldehyde formation increased linearly with time during the first hour, during which hydrogen peroxide was added. In contrast to the cerium(III)-catalyzed reaction, hardly any benzylic bromide, alcohol, or acetate was observed in this period. A similar activity was observed with $\text{Co}(\text{acac})_2$: 73% aldehyde selectivity at 49% conversion (Table 1, entry 9), with 11% not detected. The conversion of 4-*tert*-butyltoluene in the presence of $\text{Mn}(\text{OAc})_2$ was negligible (Table 1, entry 11); in fact this “catalyst” is an inhibitor of the reaction, as the blank experiment in which no catalyst was used (entry 1) still resulted in a conversion of 6.9%.

Mechanism: The mechanism of aldehyde formation catalyzed by $\text{Ce}(\text{OAc})_3$ was studied by Auty et al. 4-*tert*-Butylbenzyl bromide was claimed to be a reaction intermediate, which is thought to be subsequently hydrolyzed to the benzylic alcohol, which, in turn, is oxidized to the benzaldehyde by bromine (formed in situ on reaction of hydrogen peroxide with bromide ions).^[7] The evidence for this reaction sequence was an S-shaped curve for aldehyde formation, which indicated that the aldehyde originated from a precursor species formed during the reaction.^[7] The fact that no reaction occurred in the absence of bromide ions supported this interpretation. Our observations with $\text{Ce}(\text{OAc})_3$ as catalyst differ in that the aldehyde product forms gradually

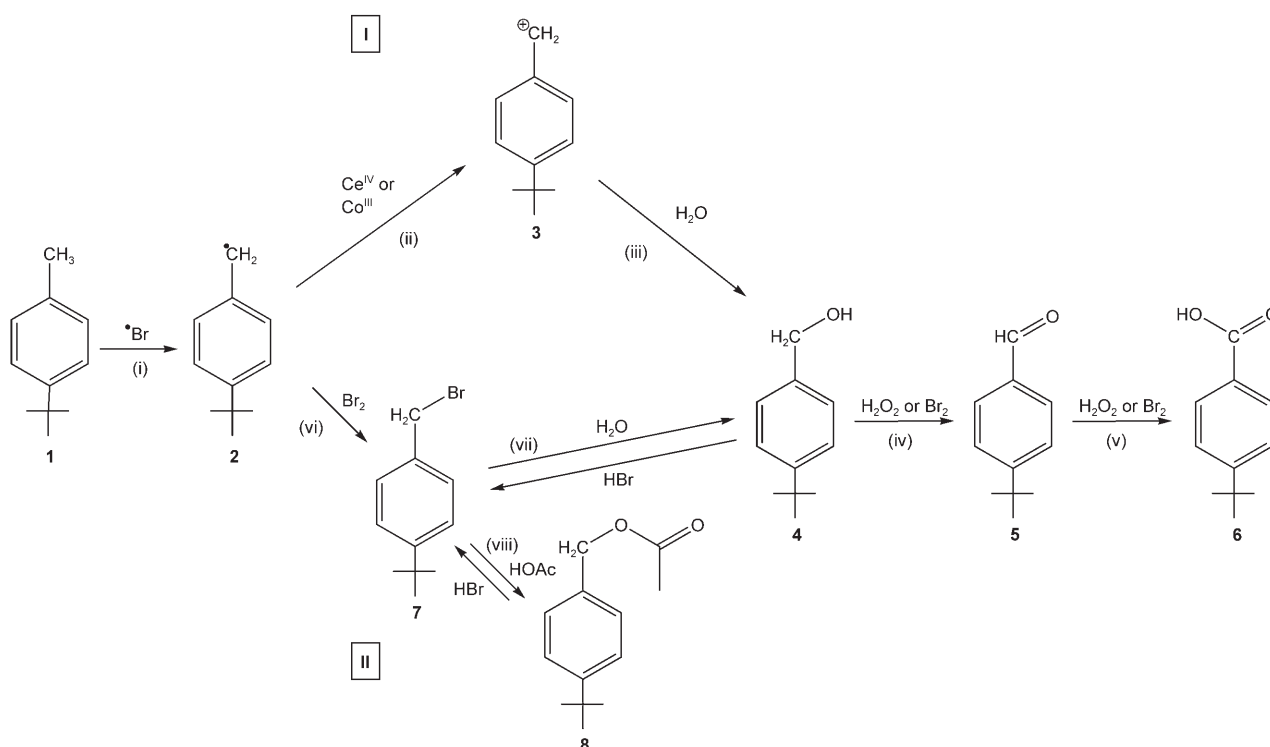
(rather than following an S-shaped curve) during the first hour of the reaction, that is, when hydrogen peroxide was added slowly to the reaction mixture. In contrast to the cerium(III)-catalyzed reaction, hardly any of the bromide, alcohol, or acetate side products are observed in the experiments with $\text{Co}(\text{OAc})_2$ and $\text{Co}(\text{acac})_2$ catalysts. The small amount of benzylic bromide in the cobalt(II)-catalyzed reactions, compared to the cerium(III)-catalyzed case, may originate from fast conversion of the intermediate benzylic bromide to the benzaldehyde product in the cobalt(II)-catalyzed reactions. We tested the hypothesis of a benzyl bromide intermediate by using 4-*tert*-butylbenzyl bromide as substrate in the reaction, with either $\text{Ce}(\text{OAc})_3$, $\text{Co}(\text{OAc})_2$, or no catalyst at all. With $\text{Ce}(\text{OAc})_3$, the aldehyde was produced in 10% yield, which is lower than the 15% yield when 4-*tert*-butyltoluene was used as substrate. The difference in aldehyde yield was even more pronounced when $\text{Co}(\text{OAc})_2$ was used: 13% with the benzylic bromide as substrate, compared to 37% when 4-*tert*-butyltoluene was used. When the reaction was performed without a catalyst, the yield of 4-*tert*-butylbenzaldehyde was still 14%. This blank experiment shows that aldehyde formation from the benzylic bromide occurs to the same extent as in the reactions involving a catalyst, that is, hydrolysis of the benzylic bromide to the alcohol and subsequent oxidation to the aldehyde do not require a metal catalyst. More importantly, the low conversion of the bromide substrate to the aldehyde product in the presence of $\text{Co}(\text{OAc})_2$ suggests that this species is not an intermediate in the Co-catalyzed reaction, as more unconverted bromide would have been found in the reaction mixture when 4-*tert*-butyltoluene was used as substrate. In the $\text{Ce}(\text{OAc})_3$ -catalyzed reaction, aldehyde formation via the benzylic bromide intermediate cannot be ruled out completely, as a significant amount of the benzylic bromide is observed in this reaction.

We propose that 4-*tert*-butylbenzaldehyde and 4-*tert*-butylbenzyl bromide are formed via two different mechanistic pathways. The proposed reaction mechanism is depicted in Scheme 1.

Formation of benzylic radical intermediate 2: The first step in the mechanism is the reaction of a bromine radical with a methyl hydrogen atom of substrate **1** to form a benzylic radical and HBr [Eq. (3), i.e., reaction (i) in Scheme 1]. The bromine radical is formed by reaction of bromide ions with Co^{III} or Ce^{IV} [Eq. (2)] which, in turn, are formed by oxidation of Co^{II} or Ce^{III} by hydrogen peroxide [Eq. (1)].



Evidence for this reaction is the observed color change in the case of $\text{Co}(\text{OAc})_2$ on addition of hydrogen peroxide, from deep blue (tetrahedral Co^{II} species) to blue-green,

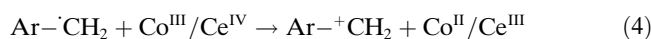


Scheme 1. Proposed reaction mechanism for the oxidation of 4-*tert*-butyltoluene to 4-*tert*-butylbenzaldehyde over cobalt or cerium catalysts, with hydrogen peroxide as oxidant, bromide ions as cocatalyst, and acetic acid as solvent.

where the green color is indicative of Co^{III} species.^[9,10] In the case of $\text{Ce}(\text{OAc})_3$, a change from colorless to orange is observed, which may be indicative of Ce^{IV} species.^[7] This assignment is not unambiguous, however, as the color could also be due to the presence of molecular bromine, formed on reaction of bromide ions with hydrogen peroxide. The UV/Vis spectra of a bromine solution and Ce^{IV} salts in acetic acid both showed absorption maxima in the 375–400 nm region.

Thus, the catalytic species Co^{II} or Ce^{III} undergoes cycles of successive oxidation and reduction, by reducing hydrogen peroxide and by oxidizing bromide ions, respectively. When ceric ammonium nitrate $[(\text{NH}_4)_2\text{Ce}^{\text{IV}}(\text{NO}_3)_6]$ was used, catalytic results similar to those with $\text{Ce}(\text{OAc})_3$ were obtained, that is, the oxidation state of the initial cerium catalyst can be III or IV. Because of the suitability of $\text{Co}^{\text{III}}/\text{Co}^{\text{II}}$ and $\text{Ce}^{\text{IV}}/\text{Ce}^{\text{III}}$ catalysts, a $\text{Mn}^{\text{III}}/\text{Mn}^{\text{II}}$ catalyst was also tested in the oxidation reaction. No substrate conversion was observed at all with $\text{Mn}(\text{OAc})_2$, in contrast to the experiment without any catalyst, which still showed a conversion of 6.9%. This indicates reaction inhibition by the manganese species, probably by catalyzing peroxide decomposition and/or by interfering with the free-radical species involved in the reaction sequence, since manganese complexes are known to act as radical scavengers.^[11] This result is therefore consistent with the free-radical mechanism proposed in Scheme 1. The addition of a radical scavenger, namely, 2,6-di-*tert*-butylphenol, indeed resulted in complete inhibition of the reaction.

Pathway I: formation of 4-tert-butylbenzaldehyde (5) from benzylic radical intermediate 2: The formation of 4-*tert*-butylbenzaldehyde (5) without involvement of benzylic bromide intermediate 7 may involve oxidation of the benzylic radical to benzylic carbocation 3 [Eq. (4), i.e., reaction (ii) in Scheme 1] by Co^{III} or Ce^{IV} .



Both Co^{III} and Ce^{IV} are strong oxidants, capable of oxidizing the benzylic radical. Reaction of benzylic carbocation 3 with water generates 4-*tert*-butylbenzyl alcohol (4), which is quickly oxidized by hydrogen peroxide or bromine (formed in situ on reaction of bromide ions with hydrogen peroxide) to benzaldehyde 5. Other, more complicated reaction sequences from benzylic carbocation 3 to 4-*tert*-butylbenzyl alcohol (4) cannot be excluded, but we have no evidence of such intermediates. Alternative routes may involve a benzylic hydroperoxide intermediate, formed on reaction of 3 with hydrogen peroxide, as this type of species has been reported to give the corresponding benzylic alcohol.^[12] Reaction of benzylic carbocation 3 with bromide ions or acetate appears not to play a significant role here, as formation of benzylic bromide 7 and benzylic acetate 8 as side products appears to occur independently of formation of benzaldehyde product 5.

Pathway II: side-product formation from benzylic radical intermediate 2: In competition with the generation of 4-*tert*-

butylbenzaldehyde, the 4-*tert*-butylbenzyl radical (**2**) may react with molecular bromine (formed on reaction of hydrogen peroxide with bromide ions) to give 4-*tert*-butylbenzyl bromide (**7**) (reaction (vi) in Scheme 1). This side reaction can ultimately lead to 4-*tert*-butylbenzaldehyde (**5**) after hydrolysis of bromide **7**, followed by oxidation with hydrogen peroxide or bromine, as described by Auty et al.^[7] The water needed for hydrolysis is introduced into the reaction in the aqueous hydrogen peroxide solution and is also formed on catalytic decomposition of this reagent. Alternatively, 4-*tert*-butylbenzyl bromide (**7**) may react with the acetic acid solvent to give 4-*tert*-butylbenzyl acetate (**8**).

Product distribution: The aldehyde selectivities in the cobalt- and cerium-catalyzed reactions differ markedly, with the cobalt catalysts showing higher aldehyde selectivity than the cerium ones (75 vs. 50 %, respectively). The aldehyde selectivity in the experiment without a catalyst is only 31 %, much lower than in the catalyzed reactions. These selectivity differences can be understood by considering the proposed reaction scheme: benzylic radical intermediate **2** may be oxidized by Co^{III} or Ce^{IV} to ultimately give benzaldehyde product **5** (Pathway I), or react with bromine to give benzylic bromide **7** and its associated byproducts (Pathway II). The 4-*tert*-butylbenzyl radical (**2**) appears to react much faster with Co^{III} than with Ce^{IV}. In fact, in the case of cobalt, reaction of **2** with bromine according to Pathway II is almost completely suppressed due to the fast oxidation reaction (Pathway I), as hardly any bromide, alcohol, or acetate products are observed. With the cerium catalysts, in contrast, the relatively slow rate of Pathway I allows the side reaction (Pathway II) to occur to a considerable extent, especially in the first 20 min of the reaction. Thus, aldehyde selectivity is favored by fast oxidation of benzylic radical intermediate **2**, that is, by the presence of a strongly oxidizing catalyst. The higher oxidizing power of Co^{III} compared to Ce^{IV} is then the most likely explanation for the higher aldehyde selectivity in the cobalt-catalyzed reaction. In the uncatalyzed reaction, the aldehyde selectivity is still 31 %. In the absence of a metal catalyst, the reaction is not expected

to proceed via Pathway I. Instead, 4-*tert*-butylbenzaldehyde (**5**) formation involves initial formation of the 4-*tert*-butylbenzyl radical (**2**), which is formed on reaction of toluene substrate **1** with bromine radicals, stemming from bromine, or with a hydroxyl radical, which may be formed on decomposition of the added hydrogen peroxide. The radical intermediate then reacts with bromine to give benzylic bromide **7**. The uncatalyzed reaction, which proceeds exclusively through Pathway II, thus results in an aldehyde selectivity of 31 % at 6.9 % conversion.

Formation of benzylic bromide **7** in the Ce-catalyzed reaction slows down significantly after the first 20 min, either due to the lowering of the bromide concentration in the reaction mixture or, possibly, due to the increasing amount of water in the system. The possibility that the presence of water increases 4-*tert*-butylbenzaldehyde selectivity was tested by performing the Ce(OAc)₃-catalyzed reaction in the presence of a small amount of water, added at the start of the reaction (Table 1, entry 4). Indeed, the benzaldehyde yield increased from 15 to 20 %, while the combined yield of the bromide, alcohol, and acetate side products was similar to that of the original experiment (entry 3): 14.3 versus 13.4 %, respectively. The yield of benzylic bromide was reduced to 7.3 %, versus 10 % in the experiment without added water, which is related to the increased amount of benzylic alcohol product, as the extra amount of water is thought to shift the equilibrium of reaction (vii) towards the alcohol product. The change in aldehyde selectivity, from 52 to 59 %, points to the existence of two different pathways, one leading to 4-*tert*-butylbenzyl bromide (**7**) and its hydrolysis and solvolysis products 4-*tert*-butylbenzyl alcohol (**4**) and 4-*tert*-butylbenzyl acetate (**8**), and the other to 4-*tert*-butylbenzaldehyde (**5**).

The effect of water addition on the Co(OAc)₂-catalyzed reaction was also tested (Figure 3). In this case, the rate of aldehyde formation was identical for both reactions. However, in the experiment in which water was added, an increased amount of the bromide product was observed in the early stages of the reaction (see Figure 3). The amount of this side product then decreases, and after 2 h the aldehyde

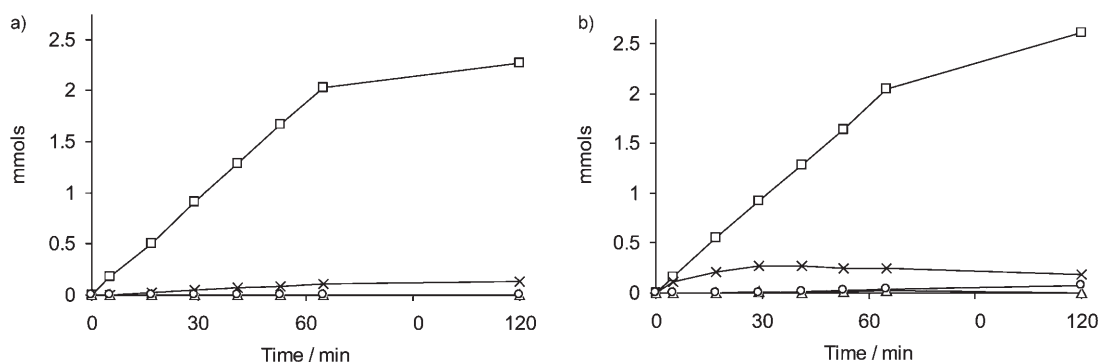


Figure 3. a) Product distribution for the oxidation of 4-*tert*-butyltoluene in acetic acid at 70 °C over Co(OAc)₂ without added water (a) and with addition of 0.50 g water at the beginning of the reaction (b). Substrate:Co:H₂O₂:KBr ratio = 45:1:92:8. 4-*tert*-Butylbenzaldehyde (□), 4-*tert*-butylbenzyl bromide (×), 4-*tert*-butylbenzyl alcohol (△), and 4-*tert*-butylbenzyl acetate (○).

selectivity was 79%, just as in the original experiment. Thus, in the cobalt(II) reaction, addition of water initially favors Pathway II, the opposite to the cerium(III)-catalyzed reaction. Significantly, the reaction mixture to which no water was added had a deep blue color, which slowly changed to brownish pink as the reaction progressed. A much paler blue was observed at the start of the reaction when water was added, and the color change to pink occurred much faster. These observations point to differences in coordination environment for the Co^{II} catalyst, whereby a blue color is indicative of tetrahedral Co^{II} species, and a pink color of octahedral Co^{II} .^[9,10] The different effect of adding water at the start of the cerium- and cobalt-catalyzed reactions illustrates that the observed product distributions are the result of a delicate balance between the two competing reaction pathways presented in Scheme 1. Addition of water changes the relative rates of the two routes in different ways for the two catalysts, and results in increased aldehyde selectivity in the cerium-catalyzed reaction and a decreased aldehyde selectivity in the early stage of the cobalt-catalyzed case.

Overoxidation: Selective oxidation reactions inherently suffer from overoxidation, as the desired (partially oxidized) product is generally more easily oxidized than the substrate. In the oxidation of toluenes to benzaldehydes, formation of the corresponding benzoic acids (reaction (v) in Scheme 1) may reduce the aldehyde yield. The good mass balance (see Figure 1) of the cerium-catalyzed reaction suggests that 4-*tert*-butylbenzoic acid (**6**) is not formed in this case. The relative oxidizabilities of methyl-substituted aromatics and the corresponding benzylic alcohols and benzaldehydes depend on the oxidant and the type of catalyst. For example, in the uncatalyzed autoxidation of methyl-substituted aromatics, the reactivity of the resulting benzaldehyde is much higher than that of the corresponding benzylic alcohol.^[3] In contrast, in the Co/Mn/Br⁻-catalyzed autoxidation reaction, the reactivity of the alcohol is higher than that of the aldehyde, which means that no overoxidation of the aldehyde will occur in the presence of the alcohol, that is, the aerobic oxidation of benzyl alcohol yields benzaldehyde exclusively as long as benzyl alcohol is still present in the system. Only after complete conversion of benzyl alcohol is formation of benzoic acid observed.^[3] The hydrogen peroxide/bromide oxidation system (i.e., in situ generation of bromine) has been studied in detail by Amati et al.^[13] Their investigation revealed that benzylic alcohols are more easily oxidized by hydrogen peroxide/bromide than the corresponding benzaldehydes. This is in agreement with the current study: no overoxidation in the cerium-catalyzed reaction is observed, as a small amount of 4-*tert*-butylbenzyl alcohol is always present in the system due to hydrolysis of the 4-*tert*-butylbenzyl bromide byproduct. As this alcohol is more easily oxidized than 4-*tert*-butylbenzaldehyde, overoxidation of the aldehyde is not expected to occur. In the $\text{Co}(\text{OAc})_2$ -catalyzed reaction, hardly any 4-*tert*-butylbenzyl bromide, and hence no 4-*tert*-butylbenzyl alcohol, is formed, and this suggests that 4-*tert*-butylbenzaldehyde is prone to overoxidation

in this case. This may explain the imperfect mass balance of the $\text{Co}(\text{OAc})_2$ -catalyzed reaction (see Figure 2). As 4-*tert*-butylbenzoic acid could not be analyzed directly by GC-MS, a sample of the reaction mixture was derivatized with BF_3/MeOH to obtain the methyl ester of any 4-*tert*-butylbenzoic acid present. The GC-MS analysis of the derivatized reaction mixture showed the presence of a substantial amount of methyl 4-*tert*-butylbenzoate, that is, overoxidation of 4-*tert*-butylbenzaldehyde had indeed occurred in the $\text{Co}(\text{OAc})_2$ -catalyzed reaction.

Continued peroxide addition: One of the questions remaining is whether the reaction, and in particular the 4-*tert*-butylbenzaldehyde yield, can be improved by the addition of more hydrogen peroxide. In a reaction with $\text{Ce}(\text{OAc})_3$ as catalyst, addition of hydrogen peroxide was continued during the second hour of the reaction (Table 1, entry 5), so the total amount of hydrogen peroxide was twice that used in the standard experiment (Table 1, entry 3). The benzaldehyde yield was 28%, compared to 15% in the original experiment. Higher aldehyde selectivity was observed in the experiment in which peroxide addition was continued (82 vs 52%). This is thought to be due to the extra amount of water present in the reaction (in the form of aqueous hydrogen peroxide solution and its decomposition product), which shifts equilibrium (vii) in Scheme 1 towards benzylic alcohol **4** and thereby reduces the yield of benzylic bromide **7**. Alcohol **4** is subsequently oxidized by the extra equivalent of peroxide to give 4-*tert*-butylbenzaldehyde (**5**). In the reaction in which addition of hydrogen peroxide was continued, 2.5% of starting material was unaccounted for after the reaction, compared to 2.7% in the standard experiment. This may be ascribed to overoxidation of the aldehyde product to the benzoic acid derivative. If this mass-balance difference is added to the aldehyde yield in both cases, the combined product yield (i.e., 4-*tert*-butylbenzaldehyde plus 4-*tert*-butylbenzoic acid) on addition of double the amount of hydrogen peroxide would be 31%, an increase of 72% compared to the 18% obtained in the standard experiment.

The assumption that the differences in mass balance are due to overoxidation of the aldehyde to the benzoic acid is valid, as 1) the methyl ester of this product has been observed with GC-MS after derivatization of the reaction mixtures with BF_3/MeOH ; 2) addition of hydrogen peroxide to a mixture containing bromide ions and 4-*tert*-butylbenzaldehyde is expected to result in 4-*tert*-butylbenzoic acid, as no easily oxidizable 4-*tert*-butylbenzyl alcohol is present. The aldehyde is then the most likely species to be oxidized, as it is more reactive than the 4-*tert*-butyltoluene substrate.

When a second amount of hydrogen peroxide was added during the second hour of the $\text{Co}(\text{OAc})_2$ -catalyzed reaction (Table 1, entry 8), the aldehyde yield was 51% (see Figure 4). This is an increase of only 38% from the 37% aldehyde yield measured in the standard experiment. However, when the decrease in mass balance in both reactions is ascribed to overoxidized 4-*tert*-butylbenzaldehyde, values of 71 versus 45% (aldehyde yield plus unaccounted-for prod-

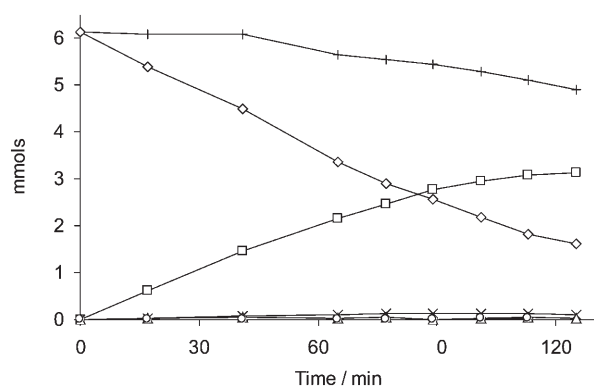


Figure 4. Product distribution for the oxidation of 4-*tert*-butyltoluene in acetic acid at 70°C over $\text{Co}(\text{OAc})_2$ by slow addition of H_2O_2 over 120 min. Substrate:Co: H_2O_2 :KBr ratio = 45:1:184:8. Mass balance (+), 4-*tert*-butyltoluene (◇), 4-*tert*-butylbenzaldehyde (□), 4-*tert*-butylbenzyl bromide (×), 4-*tert*-butylbenzyl alcohol (△), and 4-*tert*-butylbenzyl acetate (○).

uct for 2 and 1 h of hydrogen peroxide addition, respectively) are obtained, which corresponds to an incremental product yield of 58% on continued addition of hydrogen peroxide during the second hour. The aldehyde selectivity drops from 79 to 69% if double the amount of hydrogen peroxide is added. Close inspection of the decrease in amount of substrate in Figure 4 reveals that substrate conversion in the second hour is significantly lower than in the first hour: indeed, 4-*tert*-butyltoluene conversion in the case of $\text{Co}(\text{OAc})_2$ in the second hour was 28%, much less than the 45% converted during the first hour.

These experiments indicate that adding double the amount of hydrogen peroxide to the reaction results in 72% ($\text{Ce}(\text{OAc})_3$ case) or 58% ($\text{Co}(\text{OAc})_2$) more product, if the unaccounted-for amount of material is ascribed to overoxidized product (the benzaldehyde). Thus, the observed lower rate of product formation on addition of the additional amount of hydrogen peroxide during the second hour of the reaction cannot be explained sufficiently by the occurrence of overoxidation and other side reactions, but is due to lower degrees of substrate conversion. The lower conversion in the second hour may be due to the decreased substrate concentration, which has dropped from 6.15 mmol at the start of the reaction to 3.36 mmol after 1 h in the $\text{Co}(\text{OAc})_2$ reaction (entry 8). Alternatively, product inhibition may play a role.

Product inhibition: The possibility of product inhibition was assessed in a reaction in which 2.88 mmol of 4-*tert*-butylbenzaldehyde was added to 6.13 mmol of 4-*tert*-butyltoluene at the start of the reaction (Table 2, entry 1). The results can be compared with the original $\text{Co}(\text{OAc})_2$ experiment

(Table 1, entry 6 and Table 2, entry 2). The combined amount of 4-*tert*-butylbenzaldehyde and 4-*tert*-butylbenzoic acid formed during the reaction was 2.76 mmol, very similar to the value observed for the original experiment (2.74 mmol). This suggests that product inhibition does not play a prominent role in this reaction. In the experiments in which 4-*tert*-butylbenzaldehyde was added at the start of the reaction, the degree of overoxidation is much higher than in the standard experiment. This is as expected, as oxidation of the aldehyde may occur from the first addition of hydrogen peroxide onwards. To investigate the effect of a smaller amount of available substrate and the presence of some product on the rate of substrate conversion, a test reaction was conducted in which 2.64 mmol of 4-*tert*-butyltoluene was mixed with 2.35 mmol of 4-*tert*-butylbenzaldehyde at the start of the reaction (Table 2, entry 3). This starting point is comparable to the situation after one hour in the re-

Table 2. Results for the oxidation of 4-*tert*-butyltoluene over $\text{Co}(\text{OAc})_2$ in the presence of KBr and hydrogen peroxide in glacial acetic acid at 70°C with different compositions of the reaction mixture.

Entry	Catalyst	Amount of 1 at $t=0$ [mmol]	Amount of 5 added at $t=0$ [mmol]	Conversion of 1 [%]	Yield of aldehyde 5 + overoxidized product [mmol (%)]
1	$\text{Co}(\text{OAc})_2$	6.13	2.88	48	2.76 (45)
2	$\text{Co}(\text{OAc})_2$	6.07	–	47	2.74 (45)
3	$\text{Co}(\text{OAc})_2$	2.64	2.35	87	2.20 (84)
4	$\text{Co}(\text{OAc})_2^{[a]}$	3.36 ^[a]	2.16 ^[a]	51 ^[a]	1.71 (51) ^[a]
5	$\text{Co}(\text{OAc})_2$	2.82	–	80	2.16 (77)

[a] Double amount of hydrogen peroxide added (addition continued during second hour of reaction). Amounts of **1** and **5** are those present in the reaction mixture at $t=65$ min. Conversion and yield are calculated over the second hour of the reaction.

action in which addition of hydrogen peroxide was continued in the second hour of the reaction (Table 2, entry 4). After 2 h 2.30 mmol (87%) of substrate was converted, which is more than the 1.73 mmol (51%) of remaining substrate that was converted in the second hour of the experiment involving the double amount of hydrogen peroxide (Table 1, entry 8). The amount of product formed in the test reaction was 2.20 mmol (amount of aldehyde plus benzoic acid products), considerably more than in the second hour of the reaction when the double amount of hydrogen peroxide was used (1.71 mmol). Finally, an experiment involving 2.82 mmol of 4-*tert*-butyltoluene substrate resulted in the formation of 2.16 mmol of product (77%, Table 2, entry 5), comparable to the 2.20 mmol when the aldehyde was added at the start of the reaction. Once again, this result suggests that product inhibition cannot explain the lower conversions observed during the latter stages of the reaction.

Conclusion

The mechanism of the partial oxidation of 4-*tert*-butyltoluene to the corresponding aldehyde in the Co^{II} or $\text{Ce}^{\text{III}}/\text{Br}^-$ /hydrogen peroxide/acetic acid system has been studied in detail. The reaction seems to proceed by two different path-

ways, one of which leads to exclusive formation of 4-*tert*-butylbenzaldehyde, and the other to formation of the benzylic bromide and its hydrolysis, solvolysis, and oxidation products. The role of the metal catalyst is to oxidize the intermediate 4-*tert*-butylbenzyl radical species, whereby the rate of this reaction relative to the side reaction determines the product distribution in the reaction mixture. Cobalt catalysts exhibit higher aldehyde selectivities due to their ability to oxidize the benzylic radical intermediate before it can react with bromine to generate the side products.

Overoxidation of 4-*tert*-butylbenzaldehyde is prevented when a small amount of 4-*tert*-butylbenzyl alcohol is present in the reaction mixture, as this species is more easily oxidized than the aldehyde. Due to the presence of small quantities of the alcohol in the cerium-catalyzed reaction, no overoxidation to the benzoic acid product is observed in that case. Overoxidation does occur to a significant extent in the cobalt-catalyzed reactions due to the high selectivity for the aldehyde product and hence the absence of the alcohol product.

The addition of water at the start of the reaction in the case of $\text{Co}(\text{OAc})_2$ initially leads to decreased aldehyde selectivity. After 2 h, however, conversion and aldehyde selectivity are very similar to those of the experiment without added water. Doubling the amount of added hydrogen peroxide leads to an increase in product yield of 72 ($\text{Ce}(\text{OAc})_3$) and 58% ($\text{Co}(\text{OAc})_2$). The low incremental yield is not due to the presence of increasing amounts of water in the reaction mixture, nor due to the buildup of the aldehyde reaction product. Efforts to reduce the amount of water and aldehyde product in the reaction mixture are thus not expected to result in higher product yields. A possible explanation for the lower rate of product formation on continued peroxide addition is the formation of small amounts of side products such as dialkyl phenol species (not detected in this study) that act as radical scavengers. The ability of this type of phenolic compound to inhibit the reaction completely has been illustrated in this study.

Experimental Section

Starting materials: 4-*tert*-Butyltoluene, 4-*tert*-butylbenzyl bromide, 4-*tert*-butylbenzyl alcohol, 4-*tert*-butylbenzaldehyde (Fluka), hydrogen peroxide (30 wt % aqueous solution, Univar), potassium bromide (Merck), cerium(III) acetate (Aldrich), cerium(IV) ammonium nitrate (Merck), manga-

nese(II) acetate tetrahydrate (Merck), and anhydrous cobalt(II) acetate (Aldrich) were obtained from commercial sources and used as received. Cobalt(II) acetylacetonate ($\text{Co}(\text{acac})_2$) was prepared by following a literature procedure.^[14] 4-*tert*-Butylbenzyl acetate was prepared by esterification of 4-*tert*-butylbenzyl alcohol with acetic acid followed by purification by column chromatography (silica, hexane:ethyl acetate 12:1).

Catalytic testing: In a typical oxidation reaction, 5.4 mmol of 4-*tert*-butyltoluene, 1.0 mmol of KBr, 0.12 mmol of cerium or cobalt catalyst, and chlorobenzene (internal standard for GC analysis) were mixed with 10 mL of glacial acetic acid, and the mixture was heated to 70°C. A 30 wt % aqueous solution of hydrogen peroxide (11.0 mmol) was added to this mixture in six equal aliquots over 1 h, and the mixture was stirred and heated for another hour. The overall molar ratio 4-*tert*-butyltoluene: M^{n+} : H_2O_2 :KBr was 45:1:92:8 in all cases, similar to that in the study by Auty et al.^[7] Samples for GC-MS analysis were taken 5 min after each addition of hydrogen peroxide and after 2 h. The samples were neutralized with aqueous NaOH, extracted with ethyl acetate and toluene, and subsequently analyzed on a Shimadzu GC-MS [QP 2010, using a fused silica Rtx-5Sil MS column (30 m, 0.25 mm i.d.)]. The total flow was 69.3 mL min⁻¹ and a split ratio of 50 was applied. The initial column temperature was 90°C (hold time: 3 min), which was increased to 200°C (ramp rate: 20°C min⁻¹) and held at that temperature for 1.5 min. In some experiments, water or 4-*tert*-butylbenzaldehyde was added at the start of the reaction, and in some other experiments twice the amount of hydrogen peroxide was added by addition of a further six equal aliquots during the second hour of the reaction.

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