The selective oxidation of toluenes to benzaldehydes by cerium(III), hydrogen peroxide and bromide ion

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Abstract

4-t-Butyltoluene can be oxidised in acetic acid to 4-t-butylbenzaldehyde by hydrogen peroxide in a process catalyzed by cerium(III) and bromide ions. The conversion proceeds via benzylic bromination, hydrolysis of the bromide to alcohol and the rapid oxidation of the alcohol to the aldehyde by bromine. The reaction is ineffective in the absence of bromide but is also inhibited by significant quantities of the ion, apparently because the hydrolysis step is reversible. The role of the cerium has not been clearly established. Cerium(IV) is formed in the system but the first step appears not to involve electron transfer from the aromatic ring. Nor can simple radical bromination explain the rate of formation of benzylic bromide.

1. Introduction

Traditionally benzene derivatives with substituents on a side chain have been obtained by the oxidation of the parent hydrocarbon. For instance the classic method for converting toluene to benzoic acid is to use a powerful oxidant such as chromic acid or potassium permanganate [1]. From an industrial point of view such methods have several disadvantages. They use relatively expensive reagents, they result in the production of transition metal co-products the safe disposal of which can be expensive, and they are unselective.

The first two of these problems have largely been overcome by use of catalytic systems using small amounts of metal salts and oxygen as the primary oxidant. For instance the manufacture of terephthalic acid can be achieved in good yield by the use of cobalt(II) salts, usually the acetate [2,3]. Under mild conditions the product is 4-methylbenzoic acid, the second methyl group being much more resistant to oxidation than the first, presumably through deactivation by the carboxyl group [4].

The addition of bromide ions to the system improves significantly the conversion to terephthalic acid [3,5]. Reaction can be carried out at lower temperatures and at atmospheric pressure. It is also possible to use hydrogen peroxide in

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place of air [6]. This allows even lower temperatures to be employed and a mixture of aldehyde and acid is obtained.

Now the conversion of an aromatic hydrocarbon directly to an aldehyde has considerable commercial attractions. The drawback to the cobalt(II) ion/bromide ion/hydrogen peroxide system is twofold. Carboxylic acids are invariably produced as by-products and cobalt(III), the active oxidation state of the metal, is deactivated by the presence of water from the aqueous solution of hydrogen peroxide. An alternative is the use of peroxysalts in place of hydrogen peroxide: this is reported to give improved conversions to aldehydes [7].

Several other transition metal ions behave in a similar way to cobalt(III). For instance manganese(III) is very similar in its chemistry and again, bromide ions have a positive effect on the reaction [8]. Unfortunately it is a less powerful oxidant than cobalt(III) and reaction fails with many substrates.

Cerium(IV) is another possibility [9]. Reports suggest that this strong oxidant can be employed in the presence of bromide ions for the benzylic bromination of substituted methylbenzenes [10]. It has been claimed that the metal oxidant oxidises the bromide ion to bromine atoms and it is bromine which reacts with the substrate to give the corresponding benzylic bromide (Scheme 1). Cerium(IV) is expensive but it can certainly be used in catalytic quantities in conjunction with sodium bromate for the
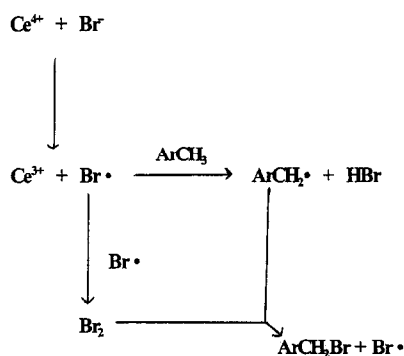
selective oxidation of benzylic alcohols to aldehydes [11].

This paper describes an attempt to combine these earlier observations with the aim of developing a means of selectively oxidising toluenes to benzaldehydes using a cheap oxidant and catalytic amounts of metal salt. The substrate chosen for study was 4-t-butyltoluene, the aldehyde from which is an important flavour and fragrance intermediate.

2. Results and discussion

Oxidation of 4-t-butyltoluene (1) was carried out by adding 35% aqueous hydrogen peroxide solution, dropwise over 1 h, to a stirred solution of cerium(III) acetate and sodium bromide in acetic acid at 70°C. When addition was complete the mixture was heated for a further hour and then analyzed. The reagents were employed in the molar ratio [aromatic substrate:hydrogen peroxide:sodium bromide:cerium(III)] of 45:90:8:1. The results, set out in Table 1 (experiment 1), show that the major product was 4-t-butylbenzaldehyde (2) with lesser amounts of 4-t-butylbenzyl bromide (3), 4-t-butylbenzyl alcohol (4), and 4-t-butylbenzyl acetate (5). That all three of the reagents are necessary to oxidise the aromatic substrate in good yield is shown by the results of experiments 2–4 in which cerium(III), peroxide and bromide were omitted in turn.

Reaction still occurs in the absence of cerium(III) but on a much reduced scale and with the aldehyde now being a minor product. No reaction products were observed when the bromide was omitted but surprisingly a small conversion was seen in the absence of hydrogen peroxide. That this is due to slow autoxidation of the hydrocarbon is shown by experiment 5 in which the reaction was carried out under a nitrogen atmosphere. Repeating the first oxidation under nitrogen (experiment 6) gave very similar results to those obtained earlier.

Ce⁴⁺ + Br⁻

$$Ce^{4+} + Br^-$$

$$Ce^{3+} + Br\cdot \xrightarrow{ArCH_3} ArCH_2\cdot + HBr$$

$$Br\cdot$$

$$Br_2 \longrightarrow ArCH_2Br + Br\cdot$$

Scheme 1.

Table 1
Products from the oxidation of 4-*t*-butyltoluene by cerium(III) acetate, hydrogen peroxide and sodium bromide in acetic acid at 70°C [a]

Experiment	Ce(III)	H$_2$O$_2$	NaBr	Conversion [b] (%)	Product yields (%)				Selectivity [c] (%)
					(2)	(3)	(4)	(5)	
1	✓	✓	✓	37	19	10	5	3	51
2	—	✓	✓	21	6	8	trace	2	29
3	✓	—	✓	10	4	2	2	trace	40
4	✓	✓	—	10	trace	0	0	0	—
5 [d]	✓	—	✓	0	0	0	0	0	—
6 [d]	✓	✓	✓	41	24	9	6	3	59

[a] Molar ratio of 4-*t*-butyltoluene:cerium(III) acetate:hydrogen peroxide:sodium bromide was 45:1:90:8.
[b] Substrate conversion defined as percentage of starting material not recovered at the end of the reaction.
[c] Selectivity defined as yield of aldehyde as a percent of substrate conversion.
[d] Reaction carried out under nitrogen.

Bromide is the only halide ion we have found to be effective in the oxidation. Sodium bromide can be replaced by hydrobromic acid or even by bromine with little change in conversion though the yield of benzylic bromide is increased. Using potassium iodide or iodine resulted in very little oxidation of the substrate with the benzylic acetate being the only significant product. Similarly, using sodium chloride as the halide source, little oxidation occurred, only trace quantities of benzaldehyde and a small amount of what appears, by GC–MS, to be a ring-chlorinated product were detected.

Three other observations are worthy of note before considering potential mechanisms for the oxidation. Firstly, on addition of hydrogen peroxide to the reaction system the solution turns from pale yellow to an orange colour. This might be ascribed solely to the formation of bromine (see below) were it not for the fact that the omission of bromide ions lead to the same colour change. Monitoring of the UV–visible spectrum showed a reduction in the intensity of a band with λ_{max} at 253 nm, ascribed to cerium(III), and the formation of a new absorption band of λ_{max} 307 nm, a similar wavelength to the absorption shown by cerium(IV) species. We presume that cerium(IV) is formed in our systems.

The second observation was that an orange–red colour is seen above the reaction mixture during the course of reaction presumably due to

the expected formation of bromine under the conditions used. Finally the product distribution as a function of reaction time is shown in Fig. 1.
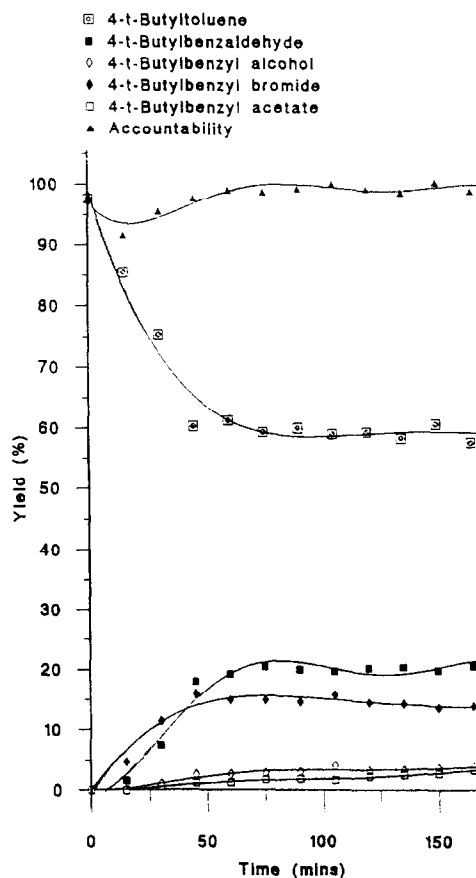

Fig. 1. Product distribution as a function of time in the oxidation of 4-*t*-butyltoluene by the Ce(OAc)$_3$/H$_2$O$_2$/NaBr system.

From this it can be seen that the reaction is very rapid being essentially complete at the end of hydrogen peroxide addition (i.e. after 60 min). After this time the only significant change is the slow depletion of the benzylic bromide and its replacement by alcohol and acetate suggesting that these last two compounds stem from solvolysis of the bromide. However two other points are apparent from Fig. 1. Firstly accountability of the system is high throughout the reaction period but, more significantly, initially 4-t-butylbenzyl bromide is the major product. The yield of the aldehyde follows the typical S-shaped curve expected of a product derived from an intermediate formed during reaction. A logical conclusion would be that intermediate is the benzylic bromide.

Two possible mechanisms can be envisaged for the oxidation. The first, Scheme 2, is an electron-transfer process, effected by the cerium(IV) in the system. The second, Scheme 3, involves hydrogen atom abstraction followed by solvolysis of the resultant bromide.

Of course neither of these schemes explains the formation of the major product of the reactions, the aldehyde, but they can easily be modified to do so. 4-t-Butylbenzyl alcohol appears to be formed only slowly as the reaction proceeds.

Scheme 2.
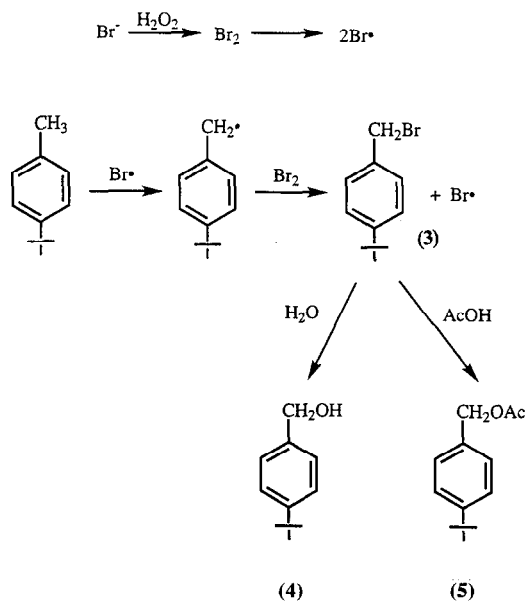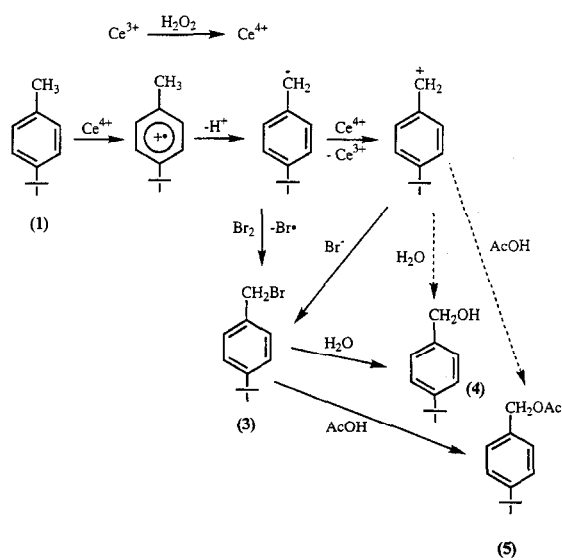
However further experiments, detailed in Fig. 2 and Table 2, show that the alcohol is oxidised rapidly to the aldehyde under the reaction conditions. For this step to occur the presence of cerium ions is not essential but both bromide and hydrogen peroxide must be there. Probably the effective oxidant is bromine. The relatively high yields of acetate in experiments 9 and 10 presumably stem from the slow esterification of the alcohol. In contrast to the alcohol the acetate is relatively inert to oxidation, only 14% of aldehyde being formed under conditions in which the alcohol gave 70% conversion.

It is believed therefore that the route to aldehyde involves the sequence shown in Scheme 4. The formation of benzylic acetate is a side reaction which results in a lowering of the overall yield of aldehyde. Unfortunately it is probably not possible to avoid this since attempts to use alternative solvents, including methanol, t-butanol and acetonitrile, proved fruitless. Carboxylic acids are the only solvents found in which reaction proceeds.

Two questions remain. The first is whether the alcohol results from hydrolysis of bromide during the course of reaction. At first sight it is surprising that a benzylic bromide is solvolyzed
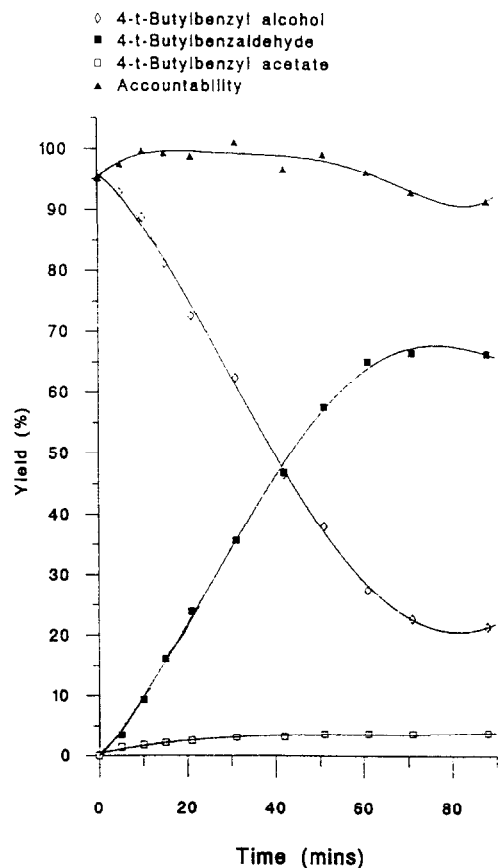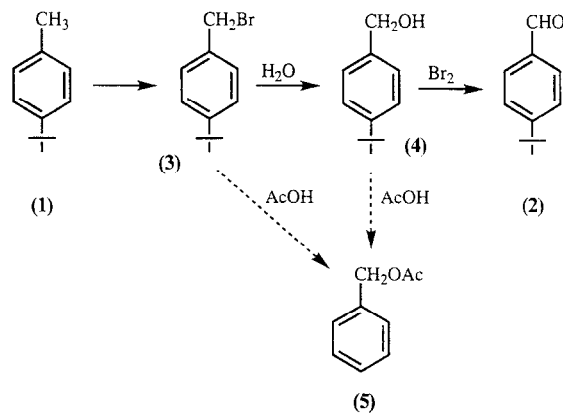
Scheme 3.

◊ 4-t-Butylbenzyl alcohol
■ 4-t-Butylbenzaldehyde
□ 4-t-Butylbenzyl acetate
▲ Accountability

Fig. 2. Product distribution as a function of time in the oxidation of 4-t-butylbenzyl alcohol by the Ce(OAc)$_3$/H$_2$O$_2$/NaBr system.

only slowly under these conditions. However when 4-t-butylbenzyl bromide was reacted under the standard conditions very little conversion was indeed observed (experiment 11).

Scheme 4.

An explanation is provided by the results of experiment 12 in which sodium bromide was omitted from the system. Given the small amount of bromide added to the reactions detailed in Table 1 (molar ratio of hydrocarbon:bromide ion is 45:8), the use of the benzylic bromide as substrate introduces much greater concentrations of bromide ion into the system. The crucial factor then behind the apparent slow conversion of benzylic bromide to further products may be the fact that hydrolysis is reversible leading to a relatively low concentration of alcohol in the system (reaction 1).
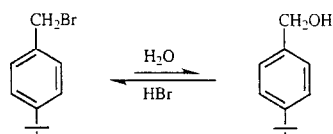
$$(1)$$

Table 2

Products from the oxidation of 4-t-butylbenzyl alcohol (4) and 4-t-butylbenzyl bromide (3) by cerium(III), hydrogen peroxide and sodium bromide in acetic acid at 70°C [a]

Experiment	Substrate	Ce(III)	H$_2$O$_2$	NaBr	Conversion [b] (%)	Product yields (%)			
						(2)	(3)	(4)	(5)
7	4	✓	✓	✓	79	68	—	21	4
8	4	—	✓	✓	100	70	—	0	5
9	4	✓	—	✓	37	0	—	63	31
10	4	✓	✓	—	32	trace	0	68	25
11	3	✓	—	✓	17	5	83	0	8
12	3	✓	✓	✓	41	15	59	0	12

[a] Molar ratio of aromatic substrate:cerium(III) acetate:hydrogen peroxide:sodium bromide was 45:1:90:8.
[b] Substrate conversion defined as percentage of starting material not accounted for at the end of the reaction.

The water in the system comes from the aqueous hydrogen peroxide and from the breakdown of that oxidant. Displacing the equilibrium to the right, by the addition of extra water, should increase the conversion to aldehyde and that is indeed what is observed (Table 3).

One problem with this system is that yields of aldehyde are not as high as might be wished. However the catalytic system still remains active and the addition of two further quantities of hydrogen peroxide (54 mmol) and sodium bromide (2.5 mmol) at two hourly intervals gave yields of aldehyde of 50% with 73% selectivity as Fig. 3 shows.

There remains the problem of how the first step of the reaction, the conversion of 4-t-butyltoluene to 4-t-butylbenzyl bromide occurs. Two have been suggested: an electron transfer mechanism followed by deprotonation of the resultant radical cation, or hydrogen atom abstraction from the hydrocarbon.

The latter process is unlikely to involve bromine radicals as the abstracting agent since, in the absence of cerium(III), the reaction proceeds to a much reduced extent. In addition it has been shown, with the cobalt(II) acetate/sodium bromide system which presumably is akin to the cerium(III) reaction, that electron withdrawing groups in toluene stop the reaction of that compound altogether whereas substituents such as a 4-nitro group might have been expected to stabilise a benzylic radical [9].

That would leave an electron transfer reaction as the most likely route were it not for the fact that cerium(III) and hydrogen peroxide —
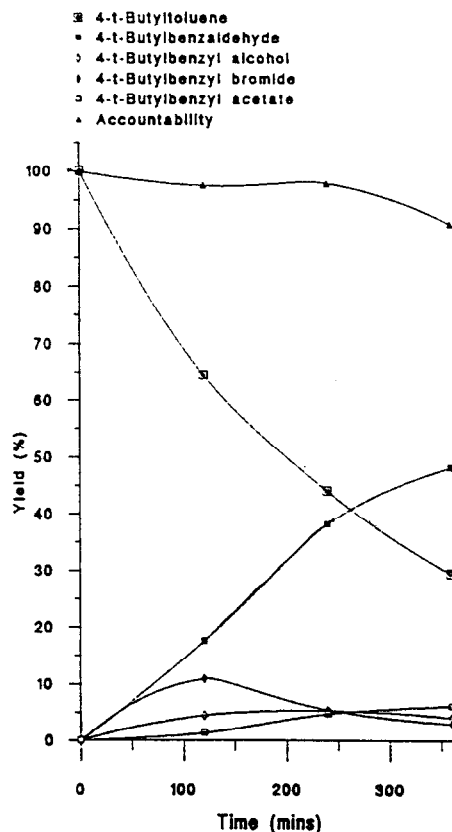

Key:
- ⊒ 4-t-Butyltoluene
- ● 4-t-Butylbenzaldehyde
- ⊃ 4-t-Butylbenzyl alcohol
- ⊩ 4-t-Butylbenzyl bromide
- ⊐ 4-t-Butylbenzyl acetate
- ▲ Accountability

Fig. 3. Effect of multiple additions of H_2O_2 and NaBr on the oxidation of 4-t-butyltoluene by $Ce(OAc)_3$.

which give cerium(IV) — alone bring about no reaction. Even if the absence of bromide ion precludes the formation of the benzylic bromide and products derived therefrom, one might have expected at least other products of radical cation formation, such as those from nuclear acetoxylation. None were observed.

Table 3
The effect of water on the oxidation, in acetic acid at 70°C, of 4-t-butyltoluene by cerium(III), hydrogen peroxide and sodium bromide [a]

Experiment	Added H_2O (cm^3)	Conversion [a] (%)	Product yields (%)				Selectivity [b] (%)
			(2)	(3)	(4)	(5)	
1	0	37	19	10	5	3	51
13	5	42	26	3	9	4	62
14	10	44	28	trace	10	3	64

[a] Reagent ratios as in Table 1 and 2.
[b] Conversion and selectivity as defined in Table 1.

In order to investigate whether aromatic radical cations could be formed in the system, substrates with lower ionisation potentials, which would be expected to form radical cations more easily than 4-*t*-butyltoluene, were oxidised. The oxidation of 4-methoxytoluene gave very little aldehyde (reaction 2). Some 66% of the starting material was recovered and the major product was 3-bromo-4-methoxytoluene.
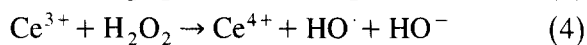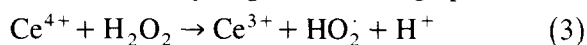

(2)
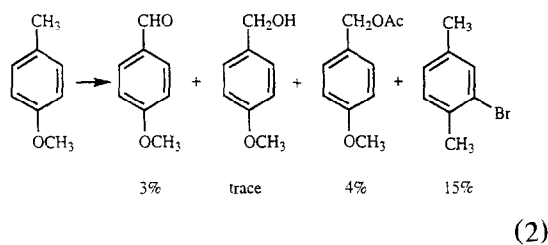
2,3-Dimethoxytoluene gave a single product, 4-bromo-2,3-dimethoxytoluene. No product of side-chain oxidation was observed. Similarly 1,4-dimethoxybenzene gave 2-bromo-1,4-dimethoxybenzene as the major product accompanied by trace quantities of 2,5-dimethoxyphenyl acetate and a dibromodimethoxybenzene. Both substrates should form radical cations readily.

It could be argued that the ring-brominated products are derived from nucleophilic attack by bromide ion on radical cations but, given that bromine is present in the system, it is at least equally likely that they stem from electrophilic substitution of the highly activated rings by the halogen. To check on this point a competitive reaction of 1,3- and 1,4-dimethoxybenzenes was carried out. Towards electrophiles the 1,3-isomer is much the more reactive (ca. 10^5 times more reactive to bromination in acetic acid) [12]. However the ionisation potential of the 1,4-isomer (7.80 eV) is significantly less than that of the 1,3-isomer (8.16 eV) [13] so that the former undergoes electron-transfer processes more easily [14].

Oxidation of a mixture of the two compounds using the cerium(III)/H_2O_2/NaBr system gave only products derived from 1,3-dimethoxybenzene despite the fact that the 1,4-isomer clearly can react under these conditions. (The only product found was 4-bromo-1,3-dimethoxybenzene.) We conclude therefore that the ring brominated products stem solely from electrophilic bromination.

In the absence of any evidence for electron transfer reactions involving the aromatic substrate and with the fact that simple radical substitution involving bromine appears not to be fast enough under the reaction conditions to account for the product yields obtained, we must seek some other explanation. One possibility is that a peroxy or a hydroxyl radical initiates radical substitution. Cerium(IV) is alleged to react with hydrogen peroxide to produce hydroperoxy radicals (reaction 3) [15]. Hydroxyl radicals are also likely to be present stemming from cerium(III) catalyzed decomposition of hydrogen peroxide (reaction 4). One other possibility is that a bromine radical anion, formed from reaction of bromine atoms with bromide ions at diffusion controlled rates (reaction 5) is the hydrogen abstracting species [16].

$$Ce^{4+} + H_2O_2 \rightarrow Ce^{3+} + HO_2^{\cdot} + H^+ \qquad (3)$$

$$Ce^{3+} + H_2O_2 \rightarrow Ce^{4+} + HO^{\cdot} + HO^- \qquad (4)$$

$$Br^{\cdot} + Br^- \rightarrow Br_2^{\cdot -} \qquad (5)$$

Whilst the nature of this initial step still remains to be clarified we can nevertheless say that Scheme 4 is the likely route by which 4-*t*-butyltoluene is converted to 4-*t*-butylbenzaldehyde by the cerium(III)/H_2O_2/NaBr system. The experiments already detailed demonstrate that this catalytic process can be developed into a highly selective method of converting methyl-substituted benzene derivatives into aromatic aldehydes providing the ring is not strongly activated toward electrophilic substitution.

3. Experimental

3.1. Analytical procedures

Gas chromatographic analysis was carried out on a Hewlett Packard 5710A gas chromatograph

fitted with a 25 m × 0.4 mm SE-54 capillary column and a flame ionisation detector. Peak area measurements were obtained on a Hewlett Packard 3392A integrator and converted to percentage yields using an internal standard.

Mass spectra were recorded on a V.G. Autospec instrument operated in EI mode at 70 eV. The spectrometer was directly coupled to a Hewlett Packard 5890 series II gas chromatograph via a heated inlet system. Compounds were identified by comparison of their retention times and mass spectra with those of authentic materials or by comparison of the mass spectra with those stored in the V.G. Opus data system controlling the mass spectrometer.

UV–visible spectra were recorded on a Shimadzu 160A UV spectrometer.

3.2. Authentic compounds

Hydrogen peroxide (35% w/w in water) was supplied by Solvay-Interox. 4-*t*-Butylbenzaldehyde and bromine were purchased from Lancaster Chemicals. All other compounds used were commercial materials purchased from Aldrich, with the exception of 4-*t*-butylbenzylacetate which was prepared by reaction of 4-*t*-butylbenzyl alcohol with acetyl chloride and the product purified by distillation.

3.3. Oxidation procedure

The standard oxidation procedure, typified by that of 4-*t*-butyltoluene, was carried out as follows. 4-*t*-Butyltoluene (4.00 g, 27 mmol), cerium(III) acetate hydrate (0.20 g, 0.60 mmol) and sodium bromide (0.50 g, 5.00 mmol) were weighed into a flask and acetic acid (50 cm^3) added. The resulting mixture was stirred, heated to 70°C and 35% hydrogen peroxide solution (5.20 g, 54 mmol) was added dropwise over a period of 60 min. After 1 h further stirring the reaction mixture was allowed to cool, and a small sample was removed and analyzed for residual peroxide. A known weight of an inter-

nal standard (1,4-dibromobenzene) was added to the reaction mixture which was then analyzed by GC and GC–MS. Substrate accountability was almost always greater than 95%.

In some experiments one or other of the reagents were omitted. In other experiments the 4-*t*-butyltoluene was replaced by other substrates always employing 27 mmol of the compound. In a few experiments the sodium bromide was replaced by other halogen species but always in the appropriate proportion.

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