Inhibition of the Cobalt Acetate/Bromide-Catalyzed Hydrogen Peroxide Oxidation of 4-*tert*-Butyltoluene

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Abstract:

The hydrogen peroxide oxidation of 4-*tert*-butyltoluene to 4-*tert*-butylbenzaldhyde, an important fragrance intermediate, catalyzed by cobalt acetate and bromide in acetic acid was investigated again. The initial stages of the reaction appear to be rapid and quantitative, but after approximately 25−30% conversion, the process ceases. Overoxidation to 4-*tert*-butylbenzoic acid does not occur. It appears that both water and the aldehyde product itself inhibit further oxidation. An engineering solution to remove the product continuously seems required for process optimization.

Introduction

The partial oxidation of 4-*tert*-butyltoluene to 4-*tert*-butylbenzaldehyde is of interest for the use of the aldehyde as an intermediate in the production of 4-*tert*-butyl-α-methyldihydrocinnamaldehyde, trade names Lilestral (BBA) or Lilial (Givaudan), an important fragrance compound used in large quantities in soap and cosmetic perfumes.

Various methods have been investigated. Gerber et al.[1] applied the cobalt(II) acetate−bromide-catalysed air oxidation system that has been intensively examined and applied for the autoxidation of alkyl aromatics to aromatic carboxylic acids, especially *p*-xylene to terephthalic acid.[2] By using lower temperatures than those applied for the oxidation to carboxylic acids, they were able to achieve a selectivity to the benzaldehyde of 70% with conversions of 50% of the substrate. Naturally enough, however, there was overoxidation to the benzoic acid which increased as the aldehyde accumulated.

Electrochemical methods have been employed. Bosma et al.[3] used direct oxidation on graphite electrodes in methanol to obtain high yields of the dimethyl acetal, which could be hydrolyzed to the aldehyde product. Bejan and co-workers have described electrochemical assisted air oxidation which increases the rate of the autoxidation reaction.[4,5] The end product of the oxidation is still the benzoic acid, but the aldehyde concentration can be maximized.[6]

In the direct antecedent to the present work, Jones et al. described the use of peroxide oxidants for selective oxidation to benzaldehydes catalyzed by cobalt acetate and bromide ion.[7] In their hands, sodium perborate monohydrate was more effective than aqueous hydrogen peroxide, and benzyl bromide was suggested as an important intermediate. There was little overoxidation to benzoic acids under the mild conditions used at 45 °C.

Further to our interest in cobalt acetate complexes,[8] we have investigated the hydrogen peroxide oxidation of 4-*tert*-butyltoluene with the ultimate goal of identifying the active catalytic species. Here, we report observations on the stoichiometry and rate of the reaction.

Experimental Section

Materials. Chemicals were used as received from the following suppliers: 4-*tert*-butyltoluene, 4-*tert*-butylbenzaldehyde, 4-*tert*-butylbenzoic acid, 4-*tert*-butylbenzyl bromide, and manganese(II) acetate tetrahydrate (Fluka); 4-*tert*-butylbenzyl alcohol, 4-*tert*-butylphenol, benzophenone, cobalt(II) acetate, cobalt(III) acetate tetrahydrate, and sodium perborate monohydrate (Aldrich); hydrogen peroxide (29−32% w/w), glacial acetic acid, and acetic anhydride (AJAX Chemicals); and sodium bromide (May and Baker).

Hydrogen peroxide was standardized prior to use with a standard potassium permanganate solution supplied by Merck.

Reaction Procedures. In a typical experiment, a 100 mL round-bottom flask was equipped with a water cooling condenser, water bath, thermometer, nitrogen inlet and outlet, overhead stirrer, glass stirrer rod, and poly(tetrafluoroethylene) paddle. It was charged with glacial acetic acid (50 g), sodium bromide (4.8 mmol), and cobalt(II) acetate tetrahydrate (2.0 mmol). The system was then purged with nitrogen at ambient temperature for 15 min. Substrate (32.9 mmol) was added to the mixture. The dark blue solution was warmed to 45 °C, and the peroxygen source was then added over 0, 15, 30, 60, or 120 min. Aqueous hydrogen peroxide (50, 75, 100, or 200 mmol) was added by a peristaltic pump, while sodium perborate monohydrate was added through the nitrogen inlet in four aliquots. In some experiments, the reaction was left to proceed at 45 °C for a further 2 h after the final addition of peroxide. The solutions were subsequently cooled to ambient temperature and analyzed by HPLC.

In various experiments, the temperature, time of reaction, cobalt(II) acetate tetrahydrate and sodium bromide catalyst

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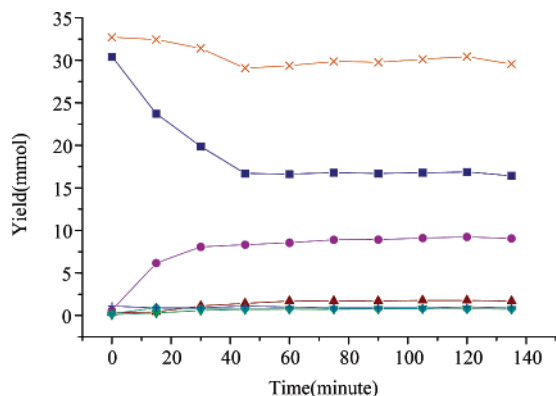
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Figure 1. Mass−time data for the oxidation of 33 mmol of 4-*tert*-butyltolune by the addition of 50 mmol of H$_2$O$_2$ over 60 min: (×) mass balance, (■) 4-*tert*-butyltoluene, (●)4-*tert*-butylbenzaldehyde, (▲) 4-*tert*-butylbenzoic acid, (▼)4-*tert*-butylphenol, (◆)4-*tert*-butylbenzyl bromide, and (+)4-*tert*-butylbenzyl alcohol.

concentrations, and oxidant type and concentration were changed or one of the reagents was omitted. In other experiments, 4-*tert*-butyltoluene was replaced by other substrates or was mixed with expected products. In a few experiments, the solvent was replaced or mixed with acetic anhydride or water.

Analytical Methods. The HPLC instrument comprised the Waters 600 controller, Rheodyne 7725 rotary injection valve, and Waters 486 tunable absorbance detector operating at 210 nm. The data were collected through a Waters Millennium HPLC. Serva Octadecyl Si = 100 or Altech Altima C18-086 columns were used. The flow rate was 1.0 mL/min. The mobile phase A was water with 0.05% (v/v; 4 mM) trifluoroacetic acid; the mobile phase B was acetonitrile with 0.05% (v/v; 4 mM) trifluoroacetic acid. The solvent program with the Octadecyl Si = 100 column was started at A:B (50:50) for 8 min and then stepped to A:B (40:60) held for 12 min and then to A:B (50:50) for another 10 min. The solvent program with the Altech Altima C18-086 column was started at A:B (50:50) for 10 min, then stepped to A:B (20:80), held for 20 min, and then stepped to A:B (50:50) for another 15 min. Benzophenone was used as the internal standard.

Product identification was by the use of authentic compounds and retention times. Mixtures of all the expected products and the substrate in different concentrations were injected to the HPLC system, and standard curves were obtained. The unconverted substrate and the yield of all products were measured by comparing the peak area of each compound with the peak area of the standards.

Results

General. Figure 1 illustrates many of the principal features of the results. It shows the mass balance, remaining substrate, and products observed when 50 mmol of hydrogen peroxide were added gradually over 60 min to oxidize 32.9 mmol of 4-*tert*-butyltoluene and the reaction was then allowed to continue for another 75 min.

The mass balance is reasonably good, with over 90% of the starting material accounted for. There may be some

significance that the unaccounted material disappears when the reaction becomes inhibited, but no unidentified peaks in the HPLC traces were observed at this point.

The minor oxidation products 4-*tert*-butylbenzyl bromide, 4-*tert*-butylbenzyl alcohol and 4-*tert*-butylphenol were all observed at less than 1 mmol each. These products never appeared in more than these small quantities.

The yield of the over-oxidation product 4-*tert*-butylbenzoic acid also remained small at less than 2 mmol under these and most of the other conditions investigated. It only increased to about 5 mmol when a large excess of H$_2$O$_2$ was added slowly over an hour. It also increased to 4 mmol when the temperature was raised from 45 to 60 °C, without any increase in the yield of aldehyde, so 45 °C was used as the temperature for the remaining experiments.

The most striking features of these results is the rapid but incomplete formation of the 4-*tert*-butylbenzaldehyde product. The stoichiometry of the reaction requires 2 mol of hydrogen peroxide to produce 1 mol of aldehyde from the toluene substrate. Under the conditions of this experiment, the 50 mmol of peroxide should produce 25 mmol of aldehyde, leaving 8 mmol of unoxidized toluene. But only 9 mmol of aldehyde are formed, and this almost all appears in the first 30 min when only 25 mmol of peroxide had been added. Indeed, in the first 15 min, the yield of aldehyde was virtually quantitative, with 12 mmol of peroxide producing almost 6 mmol of aldehyde.

The effect of the rate of addition of hydrogen peroxide on the yield of aldehyde was examined. If the 50 mmol of peroxide were added all at once at the start of the reaction, the yield was only about 3 mmol. But if they were added gradually over 15, 30, 60, or 120 min, just 7−9 mmol of aldehyde were produced, most in the early stages as described above. It appears that, after the initial almost quantitative reaction, the process is inhibited and the remaining peroxide is ineffective for the oxidation of the toluene. Neither, however, does it oxidize the aldehyde further to the benzoic acid.

Increasing the amount of hydrogen peroxide to 75, 100, or 200 mmol did not improve the yield of aldehyde, and at the higher concentrations there was considerable loss of material to unidentified products, with poor mass balances.

Catalysts. Both bromide ion and a source of cobalt are required for the catalytic oxidation. In the absence of bromide, no products were observed. With 1 mmol sodium bromide, about 5 mmol of aldehyde were produced, while, with 2−6 mmol of bromide, the maximum yield of 8−9 mmol was found, decreasing to 7 mmol of aldehyde with 8 mmol of added bromide. Hence, the turnover number of the bromide as cocatalyst is no more than 5.

The benzylic bromide compound 4-*tert*-butylbenzylbromide, however, is not an intermediate in the reaction. When 16.5 mmol were used under the same conditions, in place of the toluene substrate, less than 1 mmol each of the aldehyde, acid, and phenol products were found, with 12.5 mmol of the bromide recovered unchanged.

In the absence of cobalt(II) acetate, less than 1 mmol of aldehyde was produced, together with 2 mmol of 4-*tert*-
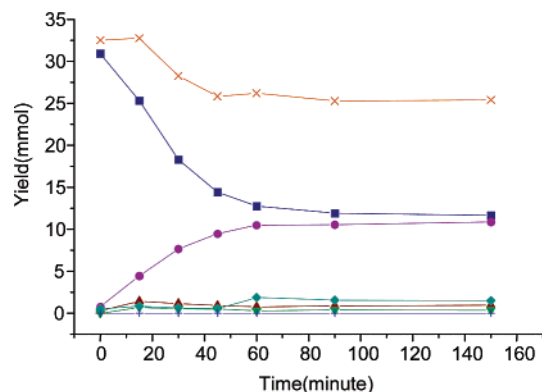
Figure 2. Effect of the presence of 75 mmol of acetic anhydride on the conditions shown in Figure 1.

Figure 3. Effect of the presence of 100 mmol of H₂O on the conditions shown in Figure 1.

butylbenzyl bromide and a trace of the benzyl alcohol. With 1 mmol of cobalt(II) acetate, the yield of the aldehyde was about 4 mmol, increasing to 10 mmol with 2 mmol cobalt-(II) and decreasing to 8 mmol with 3 mmol of cobalt. Here again, the turnover number with respect to cobalt is no greater than 5.

The cobalt can be supplied as cobalt(III). Crude "cobalt-(III) acetate" prepared by ozone oxidation was equally effective as the equivalent amount of cobalt(II).

Manganese(II) acetate is not a cocatalyst, unlike its effect in cobalt acetate/bromide autoxidation reactions conducted at higher temperatures. Addition of 2 mmol of manganese-(II) acetate completely inhibited the reaction, and manganese-(II) acetate in place of cobalt(II) also produced no products.

Search for Inhibitors. Water appears to be an inhibitor of the oxidation reaction. A solution of cobalt(II) acetate in acetic acid is pink, indicative of octahedral cobalt(II). Addition of bromide ion causes the solution to turn blue, indicative of tetrahedral cobalt(II). As the reaction approaches the inhibition point, it turns pink again.

This is not due to a loss of bromide ion, for the effect is independent of the bromide concentration over the range 2−6 mM.
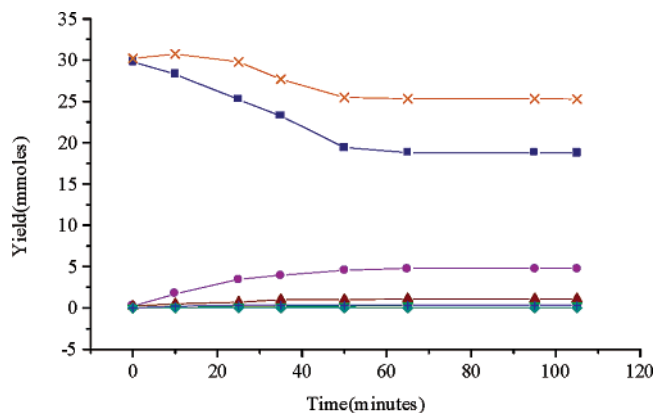
Water is a product of the reaction, according to the stoichiometry

$$ArCH_3 + 2H_2O_2 \rightarrow ArCHO + 3H_2O$$
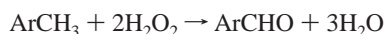
Hence, the formation of the maximum amount of approximately 10 mmol of aldehyde produces 30 mmol of water. But in addition as 20 mmol of H₂O₂ are being added, another 88 mmol of water are introduced with the 30% H₂O₂ reagent. (The 2 mmol of cobalt(II) acetate also contribute 8 mmol of water as the tetrahydrate.) Thus, approximately 100 mmol of water appear to be sufficient to convert an active tetrahedral cobalt(II) catalyst into an inactive octahedral form.

Attempts to sequester the water with acetic anhydride were unsuccessful, as the reaction between water and acetic anhydride is much slower than the oxidation reaction. The presence of acetic anhydride, however, did affect the reaction profile, slowing the initial rate of benzaldehyde product formation but not affecting the final yield of ∼10 mmol (Figure 2).

Deliberate addition of 100 mmol of water to the reaction system reduced the yield of aldehyde to 5 mmol but did not inhibit the reaction completely. This was despite the observation that the addition of this water converted the blue cobalt-(II) species to a pink one. The rate profile was altered, with formation of the aldehyde product again occurring more slowly over the full 60 min of peroxide addition (Figure 3). Hence, it appears that the oxidation is not completely inhibited by water but that it converts the cobalt to a less active form.

Jones et al. made an indirect test of this hypothesis by comparing the reactivity of sodium perborate monohydrate and sodium perborate tetrahydrate on the conversion and aldehyde yield of this oxidation. The monohydrate gave higher conversion (38.6 to 26.5%) and higher selectivity to the aldehyde (75.5 to 66.7%), consistent with its lower water content. They also reported that the perborates gave considerably higher selectivity to the aldehyde than they found with 35% hydrogen peroxide (75.5 and 66.7 vs 40.5%). We did not observe this. Under similar conditions the sodium perborate monohydrate yielded only 6.4 mmol of aldehyde with a selectivity of 54% compared with hydrogen peroxide oxidation which yielded 9.4 mmol of aldehyde with a selectivity of 80%.

The above observations indicate that the presence of water is not sufficient to inhibit the reaction completely, so the search was continued for other inhibitors. 4-*tert*-Butylphenol is observed as a minor product and could act as a free radical trap inhibitor of the oxidation process. But, addition of 5 mmol of the phenol did not completely inhibit the reaction, which still produced 2 mmol of the benzaldehyde product, while adding 1 mmol of phenol gradually with the hydrogen peroxide over 60 min yielded 7.5 mmol of aldehyde. Hence, the trace amounts of phenol produced in the reaction are insufficient to cause the inhibition. (The reaction was completely inhibited, however, in the presence of 1.3 mmol of TEMPO, a more efficient free radical trap.)

The presence of 10 mmol of the other minor products 4-*tert*-butylbromide or 4-*tert*-butylbenzoic acid had no effect on the formation of the benzaldehyde product. When 10 mmol of the product 4-*tert*-butylbenzaldhyde were treated over 120 min in the absence of the toluene, 9.4 mmol were recovered, confirming the evidence shown in Figure 1 that the aldehyde is not oxidized further under these conditions.

But, when 5 mmol of the aldehyde product were added to the toluene oxidation system, only 7 mmol of toluene oxidation occurred; when 10 mmol of aldehyde were added, only 4 mmol of toluene oxidation were observed, and when 20 mmol of aldehyde were added, the oxidation of toluene to aldehyde ceased, although there was considerable unaccounted loss of the toluene substrate.

These observations suggest that the 4-*tert*-butylbenzaldehyde product is also an inhibitor of the oxidation of the toluene. They are consistent with additional observations of the oxidation of 4-*tert*-butylalcohol. When 20 mmol of the alcohol were oxidized, 14 mmol of aldehyde were produced, only 1 mmol of unreacted alcohol was recovered and 5 mmol of material were lost. When 10 mmol of the alcohol were added to the toluene oxidation, only 14 mmol of aldehyde were found, again suggesting that the rapid formation of the aldehyde from the alcohol then inhibits further oxidation of the toluene.

The presence of an inhibitor in addition to water was tested in the following way. A reaction was run under the usual conditions. After 1 h, approximately 9 mmol of aldehyde had been formed and the reaction solution had turned pink. At this stage, additional aliquots of 2 mmol of cobalt(II) acetate tetrahydrate and 4.8 mmol of sodium bromide were added, causing the solution to turn blue again. Further addition of 50 mmol of hydrogen peroxide over the next hour, however, yielded no additional aldehyde product.

Whatever the identity of the inhibitors, they appear to act by the decomposition of the hydrogen peroxide. No excess peroxide was detected in the reaction solutions when tested by flow injection analysis for the oxidation of iodide by peroxide.

Discussion

Jones et al.[7] appear to be the only other workers to have examined this system in detail. Our results differ from theirs in two important respects.

First, we do not find that 4-*tert*-butylbromide is an important intermediate. Their assignment of this role to the bromide is speculative and not based on any substantial evidence. There is an essential role for the bromide ion: the catalysis does not occur without it. It does not involve the 4-*tert*-butylbromide, however, for adding that to the system does not enhance product formation.

Second, we do not find that aqueous hydrogen peroxide is inferior to sodium perborate as oxidant. We have no explanation for this difference between our results and the earlier report. We do concur with their observations that the system loses its potency as the color changes from blue to pink and that further addition of cobalt and bromide is ineffectual.

In a closely related work, Gerber et al.[1] studied the dioxygen oxidation of *tert*-butyltoluene catalyzed by the similar cobalt(II) acetate−bromide system in acetic acid. There are a number of important differences between these two systems, however. The dioxygen oxidation requires higher temperatures, with their experiments conducted between 55 and 105 °C, with an optimum temperature of about 90 °C. Second, they observe further oxidation to the benzoic acid, a common feature of such autoxidation reactions. Third, the reaction is enhanced, not inhibited, by the presence of manganese acetate. Finally, they claim to observe Co(III) in the catalytic system; there is no evidence of the characteristic green cobalt(III) color in the present work. They do observe, however, that addition of water, which diminishes the concentration of tetrahedral cobalt(II), diminishes its catalytic activity. Hence, there are significant differences between the hydrogen peroxide and the dioxygen oxidation mechanisms, although they may share some common features.

We conclude the following: (a) The oxidation proceeds by a free radical mechanism, completely inhibited by TEMPO and by manganese(III) acetate. (b) Over-oxidation to benzoic acid is minimal. (c) Both cobalt(II) (or cobalt-(III)) and bromide are required, but *p-tert*-butylbenzyl bromide is not an intermediate. (d) The rate of the oxidation is slowed but not quenched by the accumulation of excess water. (e) The oxidation is inhibited by accumulation of the *p-tert*-butylbenzaldehyde product. (f) Increased yields might be obtained if the benzaldehyde product was removed as it were being produced and if less water was added with the peroxide oxidant.