

## Oxidation of Aldehydes to Carboxylic Acids with Hydrogen Peroxide and PTSA Catalyzed by $\beta$ -Cyclodextrin

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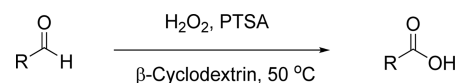
**Key Words** : Aldehydes, Carboxylic acids, Cyclodextrin, Peroxide, Oxidation

Carboxylic acids are widespread in nature and have broad applications in organic chemistry, pharmaceutical industry, material science, and bioorganic chemistry. Regarding their great significance in organic synthesis, numerous protocols for their preparations have been developed.<sup>1</sup> Traditionally, conversion of aldehydes to the corresponding carboxylic acids has been accomplished by assistance of transition metal based strong oxidants such as Jones reagent,<sup>2</sup> oxone, potassium permanganate,<sup>3</sup> [Ni(acac)<sub>2</sub>],<sup>4</sup> Pd/C,<sup>5</sup> and bismuth(III) nitrate pentahydrate.<sup>6</sup> Other metal-free oxidants were also reported which include oxone,<sup>7</sup> CO<sub>2</sub>/coenzyme thiamine pyrophosphate,<sup>8</sup> and O<sub>2</sub>/porphyrin sensitizers.<sup>9</sup> Among other oxidants, hydrogen peroxide received great attention for the oxidation of aldehydes owing to its environmentally benign property to produce water as by product together with its cost effective advantage. For examples, hydrogen peroxide has been successfully mediated aldehyde oxidation oxidations in combination with a variety metallic reagents such as NaOCl,<sup>10</sup> Na<sub>2</sub>WO<sub>4</sub>,<sup>11</sup> SeO<sub>2</sub>,<sup>12</sup> [CH<sub>3</sub>(*n*-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>N]HSO<sub>4</sub>,<sup>13</sup> RuCl<sub>3</sub>,<sup>14</sup> methyltrioxorhenium,<sup>15</sup> KOH,<sup>16</sup> *N*-methylpyrrolidin-2-one hydrotribromide,<sup>17</sup> AgNO<sub>3</sub>,<sup>18</sup> biomimetic flavin,<sup>19</sup> and Amberlyst 15/acetic acid.<sup>20</sup> However, above mentioned methods have one or more limitations which include the use of halide containing metal reagents, strong oxidizer, sophisticated phase transfer catalyst, severe basic conditions, and toxic organic solvents. Thus it is desirable to develop more general hydrogen peroxide promoted oxidation conditions for aldehydes in more facile and mild reaction system with ease of manipulation.  $\beta$ -Cyclodextrin has been successfully utilized as a supramolecular catalyst for the various organic transformations with high selectivity. For instances,  $\beta$ -cyclodextrin catalyzed oxidation of alcohols to the corresponding aldehydes or ketones were achieved using NBS in aqueous methanol/acetone mixed solvent<sup>21</sup> or *o*-iodoxybenzoic acid in aqueous acetone.<sup>22</sup>

As part of a program aimed at the development of environmentally friendly oxidation protocols, we thus focused our attention on the development of new method for the oxidation of aldehydes to the corresponding carboxylic acids in the absence of any expensive and hazardous reagents such as transition metal catalysts, halide reagents and toxic organic solvents.

Herein, we report  $\beta$ -cyclodextrin catalyzed oxidation of aldehydes to the corresponding carboxylic acids using hydro-

gen peroxide and *p*-toluenesulfonic acid (PTSA). Initially we attempted the oxidation reaction of benzaldehyde with 30% aqueous hydrogen peroxide (5.0 equiv.) and PTSA (1.0 equiv.) at 50 °C. It turned out the progress of oxidation reaction of benzaldehyde was very sluggish at the attempted conditions to give desired benzoic acid only 19% yield after 24 h. Yield was not improved after prolonged reaction times (48 h). Absence of PTSA at the present reaction conditions also gave unchanged starting materials. Considering that  $\beta$ -cyclodextrin may facilitate the organic reactions in water, we turned to modified procedure to add  $\beta$ -cyclodextrin (0.1 equiv.) to reagent combination of aqueous hydrogen peroxide and PTSA to promote oxidation of benzaldehyde. In our delight, the oxidation of benzaldehyde proceeded smoothly to give benzoic acid in significantly higher yield of 98% after 15 h at 50 °C. For optimization studies, the oxidation of benzaldehyde to benzoic acid was tested in the presence of various acids which include PTSA, methanesulfonic acid, sulfuric acid, nitric acid, hydrochloric acid, and acetic acid. Among these acids tested, the best result was obtained with PTSA in terms of reaction times and yields. To the best of



our knowledge, there is no literature report on the oxidation of benzaldehyds using  $\beta$ -cyclodextrin in combination of hydrogen peroxide and PTSA under our reaction conditions. We subsequently found that a range of aromatic and aliphatic aldehyde substrates could be converted into corresponding carboxylic acids in high yields under the present reaction

**Table 1.** Effect of the different acids for oxidizing benzaldehyde to benzoic acid<sup>a</sup>

Entry	Acid	Yield (%) <sup>b</sup>
1	PTSA	98
2	Methanesulfonic acid	63
3	Sulfuric acid	36
4	Nitric acid	56
5	Hydrochloric acid	19
6	Acetic acid	54

<sup>a</sup>Reaction conditions: 1.0 mmol benzaldehyde, 5.0 mmol of H<sub>2</sub>O<sub>2</sub>, 1.0 mmol of acid, 0.1 mmol  $\beta$ -CD, 50 °C. <sup>b</sup>Isolated yield.

**Table 2.**  $\beta$ -Cyclodextrin catalyzed oxidation of aldehydes with  $H_2O_2$ /PTSA

Entry	Aldehyde	Acid	Yield (%) <sup>a</sup>
1	PhCHO	PhCOOH	98
2	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> COOH	85
3	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> COOH	88
4	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> COOH	78
5	4-BrC <sub>6</sub> H <sub>4</sub> CHO	4-BrC <sub>6</sub> H <sub>4</sub> COOH	91
6	4-ClC <sub>6</sub> H <sub>4</sub> CHO	4-ClC <sub>6</sub> H <sub>4</sub> COOH	80
7	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	91
8	4-FC <sub>6</sub> H <sub>4</sub> CHO	4-FC <sub>6</sub> H <sub>4</sub> COOH	92
9	2-Naphtaldehyde	2-Naphtoic acid	80
10	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CHO	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> COOH	84
11	C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> )CHO	C <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> )COOH	83
12	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> CHO	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>2</sub> COOH	77
13	PhCH=CHCHO	PhCH=CHCOOH	82
14	C <sub>3</sub> H <sub>9</sub> CHO	C <sub>3</sub> H <sub>9</sub> COOH	80
15	C <sub>6</sub> H <sub>11</sub> CHO	C <sub>6</sub> H <sub>11</sub> COOH	70
16	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CH <sub>2</sub> CHO	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CH <sub>2</sub> COOH	72

<sup>a</sup>Isolated yield.

protocol and the results are summarized in Table 2. As shown in the Table 2, aromatic aldehydes with electron donating and electron withdrawing substituents in aromatic rings provided equally high yields of the corresponding carboxylic acids. In addition, acid sensitive methoxy groups on the aromatic rings or double bond in *trans*-cinnamaldehyde were not affected at the present reaction conditions (entries 3-4, 13). Previously similar hydrogen peroxide mediated methods in acidic conditions failed to give satisfactory yields of such acid sensitive substituents containing aldehydes.<sup>20</sup> Relatively inactive aliphatic aldehydes were also oxidized to the corresponding carboxylic acids in high yields (entries 12, 14-16). Role of  $\beta$ -cyclodextrin can be presumed to coordinate the carbonyl oxygen of aldehydes and oxygen of sulfonyl moiety of peroxy *p*-toluenesulfonic acid with hydrogen of hydroxyl group of  $\beta$ -cyclodextrin to assist the formation of inclusion complex. Presumably oxidation reactions proceeded by the reaction of aldehydes with peroxy *p*-toluenesulfonic acid, preformed *via* treatment of PTSA with hydrogen peroxide, to give peroxy hemi-acetal intermediates which readily rearranged to give carboxylic acids. Analogous mechanistic pathway was recently proposed for the oxidation of aldehydes with resin supported sulfonic acid and hydrogen peroxide.<sup>24</sup>

In summary, we have developed a new procedure for the oxidation of aromatic and aliphatic aldehydes to the corresponding acids using aqueous hydrogen peroxide with PTSA in the presence of  $\beta$ -cyclodextrin catalyst. Mildness of reaction conditions, high selectivity, experimental easiness, and environmentally friendly nature should make present method synthetically attractive.

### Experimental

All aldehydes,  $\beta$ -cyclodextrin, PTSA, and 30% hydrogen peroxide were obtained from commercial source (Aldrich)

and used as received. The courses of all reactions were monitored by TLC using silica gel plates. Standard <sup>1</sup>H-NMR spectra were recorded in CDCl<sub>3</sub> by the Varian Gemini 2000 (300 MHz) spectrometer with tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded with a Micro-mass Autospec spectrometer. All products were known and identified by comparison of their <sup>1</sup>H-NMR spectra with those of reported literature data.

**General Procedure.** To a solution of 30% hydrogen peroxide (5.0 mmol) was added aldehyde (1.0 mmol), PTSA (1.0 mmol) and  $\beta$ -cyclodextrin (0.1 mmol). The reaction mixture was stirred for 15 h at 50 °C. After cooling to room temperature, the reaction mixture was dissolved in the solution of 10% aqueous sodium bicarbonate, extracted into diethyl ether (2 × 25 mL), and washed with water. The aqueous layer was acidified to pH 3 with 2 M hydrochloric acid. The product was extracted with dichloromethane (2 × 25 mL) and dried over magnesium sulfate. Evaporation of organic layer under reduced pressure gave the desired carboxylic acid.

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