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SHORT COMMUNICATIONS

# Immobilized β-Cyclodextrin Catalyst for Selective Synthesis of 4-Hydroxybenzoic Acid

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Cyclodextrins, cyclic oligomers of glucose molecules,[1,2] were used in the selective syntheses of some chemicals.[3-13] The selective catalyses involve regioselectivity, regulation of molecular size of intermediates and products, and/or protection of unstable products.

Previously,[10,13] selective synthesis of 4-hydroxybenzoic acid from phenol and carbon tetrachloride was carried out using β-cyclodextrin as catalyst. Formation of 2-hydroxybenzoic acid was largely inhibited by β-cyclodextrin, resulting in 99% selectivity for 4-hydroxybenzoic acid.

This paper reports that the β-cyclodextrin immobilized by epichlorohydrin is a still better catalyst for the selective synthesis of 4-hydroxybenzoic acid. A selectivity as high as 100% is achieved with this immobilized catalyst. Furthermore, separation of the catalyst from the reaction mixture and reusage of the recovered catalyst are described.

## EXPERIMENTAL

An immobilized β-cyclodextrin catalyst was prepared by the reaction of 50.0 g (44.1 mmol) of β-cyclodextrin and 34.5 ml (441 mmol) of epichlorohydrin at 50°C for 40 min in 80 ml of 50 wt% aqueous sodium hydroxide solution containing 50 mg (1.3 mmol) of sodium tetrahydroborate. The resulting solid was sufficiently washed with acetone and with water, and then was dried *in vacuo* at 60°C for 12 h. The catalyst was obtained in a form of beads of diameter 1—3 mm. The molar ratio of β-cyclodextrin and 2-hydroxypropenyl residue, derived from epichlorohydrin, was 1.0 : 3.3, as determined by elemental analysis. Obsd: C, 47.00%; H, 6.60%. Calcd: C, 46.80%; H, 6.72%.

In the selective synthesis of 4-hydroxybenzoic acid, phenol (1.5 g, 15.9 mmol), copper metallic powder (0.2 g, 3.1 mmol), and the immobilized β-cyclodextrin catalyst (1.5 g, 1.1 milliequivalent of β-cyclodextrin residue) were charged to 20 ml of 20 wt% aqueous sodium hydroxide solution. Then carbon tetrachloride (3.0 ml, 31.1 mmol) was added. The reaction was carried out at 80°C for 15 h under nitrogen with vigorous stirring.

After the reaction, the reaction mixture was centrifugated at 3000 rpm for 10 min. The liquid layer was sufficiently extracted with diethyl ether after being acidified with hydrochloric acid, and the ether layer was evaporated. The product analysis was made with the use of HPLC (Toyo Soda Co., LS410K, MeOH-100 column, 30 cm, 25°C, eluent: 6 : 4 water–ethanol).

The solid obtained by centrifugation was further used as the catalyst in the following run.

## RESULTS AND DISCUSSION

As shown in Table I, 4-hydroxybenzoic acid is synthesized at 100% selectivity and in 89 mol% yield in the presence of the immobilized β-cyclodextrin catalyst. In its absence, however, the selectivity is 56% and the yield is only 15 mol%.

The immobilized catalyst was easily recovered from the reaction mixture by centrifugation, as a solid containing copper powder. In the following runs, where only phenol and carbon tetrachloride were additionally charged to the recovered solid in 20 wt% aqueous sodium hydroxide solution, the selectivity for 4-hydroxybenzoic acid was 100% and the yield was satisfactorily high, as also shown in Table I. Furthermore, 100% selectivity and yields larger than 90 mol% were attained in the following three runs. Thus, no decrease in the catalytic activity was detected up to six (the maximum number examined) repeated usage of the catalyst.

The repeated use of free β-cyclodextrin, which was not immobilized, was also examined. After the reaction under identical conditions for the reaction with the immobilized catalyst, the reaction mixture was acidified with hydrochloric acid, followed by centrifugation. The recovered β-cyclodextrin was used for the following runs. In the successive three runs, the selectivity for 4-hydroxybenzoic acid was 100%. In the fourth, the fifth, and the sixth runs, however, the selectivity decreased to 85%, 76%, and 60%, respectively. The decrease in the selectivity with increasing number of repeated runs is attributable to loss of β-cyclodextrin during the recovery of the catalyst after each of runs.

The selective synthesis using the immobilized β-cyclodextrin catalyst probably proceeds in a similar manner as shown for the selective synthesis using free β-cyclodextrin.[13] β-Cyclodextrin regulates the mutual conformation between phenol and trichloromethyl cation, produced in situ from carbon tetrachloride with the catalysis of copper powder, through non-covalent interactions with each of them. The para-carbon atom of phenol is selectively attacked by the cation, since it is located near the cation due to the regulation.

Quite a high selectivity exhibited by the immobilized β-cyclodextrin catalyst is associated with the negatively charged reaction field produced by alkoxide ions of the β-cyclodextrin residues. The p$K_a$ of the secondary hydroxyl groups of β-cyclodextrin is

**Table I.** Selective synthesis of 4-hydroxybenzoic acid using the immobilized β-cyclodextrin catalyst

| Immobilized β-cyclodextrin catalyst | Number of repeated usage | Carboxylation yield mol% *para*[a] | Carboxylation yield mol% *ortho*[b] | Selectivity[c] |
|---|---|---|---|---|
| Presence | 1 | 89 | 0 | 100 |
| | 2[d] | 91 | 0 | 100 |
| | 3[d] | 93 | 0 | 100 |
| Absence | — | 15 | 12 | 56 |

[a] Yield for 4-hydroxybenzoic acid with respect to the charged phenol.

[b] Yield for 2-hydroxybenzoic acid with respect to the charged phenol.

[c] Selectivity for 4-hydroxybenzoic acid.

[d] Catalysis by the immobilized catalyst, recovered by centrifugation from the reaction mixture.

around 12.[1] This reaction field effectively traps trichloromethyl cations, and thus the selective reactions involving the catalysis of the β-cyclodextrin residues is still more predominant to the nonselective reactions without the catalysis of the β-cyclodextrin residues.

In summary, selective synthesis of 4-hydroxybenzoic acid is successfully achieved using the β-cyclodextrin immobilized by epichlorohydrin. The catalyst is easily recovered from the reaction mixture and can be repeatedly used without apparent decrease in the activity.

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