

SHORT COMMUNICATIONS

Immobilized β -Cyclodextrin Catalyst for Selective Synthesis of 4-Hydroxybenzaldehyde*

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Application of cyclodextrins, cyclic oligomers of 6—8 glucose molecules, to selective organic syntheses has developed especially in the last several years.¹⁻¹⁰ However, use of immobilized cyclodextrin as a catalyst for selective syntheses is rather few, and only two reactions, chlorination of anisole¹¹ and carboxylation of phenol,¹² have been successfully achieved using the immobilized cyclodextrin.

In previous papers,^{6,8,9} the authors showed that with the use of β -cyclodextrin as catalyst, 4-hydroxybenzaldehyde was synthesized in virtually 100% selectivity by the reaction of phenol and chloroform in aqueous alkaline solution. Formation of 2-hydroxybenzaldehyde, which prevailed in the absence of β -cyclodextrin, was almost perfectly inhibited in its presence. 4-Hydroxybenzaldehyde is a valuable intermediate in industry for the syntheses of drugs, insecticides, and dyes.

In this paper, selective synthesis of 4-hydroxybenzaldehyde with the use of the β -cyclodextrin immobilized with epichlorohydrin is described. Recovery of the immobilized cyclodextrin catalyst from the reaction mixtures and its repeated use are shown.

EXPERIMENTAL

The immobilized β -cyclodextrin catalyst was prepared as follows, with a modification of the method in the literature.¹³ β -Cyclodextrin (50.0 g) and sodium tetrahydroborate (0.050 g) were dissolved in 80 ml of 50 wt% aqueous sodium hydroxide solution. To this mixture, epichlorohydrin (68.0 ml) was dropwise added at 50°C. After 40 min, the resulting solid was thoroughly washed with acetone and water, and dried in vacuo at 60°C for 12 h. The immobilized β -cyclodextrin catalyst was obtained in the form of beads of diameter 1—3 mm. The immobilized catalyst was composed of β -cyclodextrin and 2-hydroxypropyl residues, derived from epichlorohydrin, in a molar ratio 1.0:5.7, as determined by elemental analysis. Obsd: C, 48.40%; H, 7.13%. Calcd: C, 48.42%; H, 7.03%.

For the selective synthesis, the immobilized β -cyclodextrin catalyst (4.50 g) and phenol (0.30 g) were charged to 30 ml of 20 wt% aqueous sodium hydroxide solution, and chloroform (3.0 ml) was added dropwise at 60°C to the mixture which was vigorously stirred with a magnetic stirrer.

After the reaction for 8 h, the mixture was

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Table I. Selective synthesis of 4-hydroxybenzaldehyde using the immobilized β -cyclodextrin catalyst

Immobilized β -cyclodextrin catalyst	Number of repeated usage	Yield/mol% ^a		Selectivity for 4-hydroxy- benzaldehyde
		4-Hydroxy- benzaldehyde	2-Hydroxy- benzaldehyde	
Presence	1	59	0.4	99
	2 ^b	66	0.3	100
	3 ^b	65	0.4	99
Absence	—	18	35	34

^a Yield with respect to the charged phenol.

^b Catalysis by the immobilized β -cyclodextrin catalyst separated by centrifugation after the preceding run of selective synthesis.

subjected to centrifugation. 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 GLPC.

The solid obtained on centrifugation was used in the following selective synthesis. There, the reaction procedure was exactly identical with that described above, except for the use of the recovered catalyst in place of virgin one.

RESULTS AND DISCUSSION

As shown in Table I, the immobilized β -cyclodextrin catalyst exhibits virtually 100% selectivity for 4-hydroxybenzaldehyde in the reaction of phenol and chloroform in alkaline aqueous solution. Formation of 2-hydroxybenzaldehyde, which is dominant in the absence of the immobilized catalyst, is largely suppressed. The yield of 4-hydroxybenzaldehyde in the presence of the immobilized β -cyclodextrin catalyst is much larger than the value in its absence. Thus, selective synthesis of 4-hydroxybenzaldehyde is successfully carried out with the use of the immobilized catalyst.

The yield (59 mol%) of 4-hydroxybenzaldehyde for the immobilized β -cyclodextrin catalyst is almost identical with the value (66 mol%) for the reaction using free β -cyclodextrin as catalyst.

The immobilized β -cyclodextrin catalyst was

easily separated from the reaction mixture by centrifugation. With repeated usage of the recovered catalyst, high selectivity and high yield were also attained (Table I). Higher yields in the second and the third usages than the value in the first usage are associated with the fact that a small amount of 4-hydroxybenzaldehyde remains in the catalyst separated from the reaction mixture by centrifugation.

The immobilized catalyst was also recovered from the reaction mixture by filtration. The recovered catalyst exhibited both high selectivity and high yield in the following reaction.

The selective synthesis with the immobilized β -cyclodextrin catalyst probably proceeds in a similar manner to that with the free β -cyclodextrin catalyst.⁹ The selective synthesis proceeds via formation of a ternary molecular complex composed of a β -cyclodextrin residue in the immobilized catalyst, chloroform, and phenol (in its anionic form). Here, chloroform is located inside the cavity of the β -cyclodextrin residue, and phenol sits shallowly at the top of the cavity, as clearly shown by ¹H NMR spectroscopy⁹ on aqueous alkaline solutions containing free β -cyclodextrin, phenol, and chloroform. Importantly, phenol penetrates into the cavity from the side involving the *para*-carbon atom. Penetration of this apolar side in the apolar cavity is energetically more favorable than the penetration of the polar

side involving the phenoxide oxygen atom in the cavity. As the result, dichlorocarbene, prepared *in situ* from chloroform by the reaction with hydroxide ion, selectively attacks the *para*-carbon atom of phenol located near by. Thus, selective catalysis by the β -cyclodextrin residue in the immobilized catalyst is attributable to regulation of the mutual conformation between phenol and dichlorocarbene through noncovalent interaction with each of them.

In conclusion, selective synthesis of 4-hydroxybenzaldehyde from phenol and chloroform is successfully carried out by use of the immobilized β -cyclodextrin catalyst, prepared from β -cyclodextrin and epichlorohydrin. The immobilized catalyst is effectively recovered from the reaction mixture, and is repeatedly used without a measurable decrease in catalytic activity. The present findings can extend the scope of the practical application of cyclodextrins as catalysts for selective syntheses.

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