

SELECTIVE SYNTHESIS OF 4-HYDROXYBENZOIC ACID USING IMMOBILIZED CYCLODEXTRIN

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ABSTRACT. β -cyclodextrin immobilized with epichlorohydrin was used for the selective syntheses of 4-hydroxybenzoic acids from phenols and carbon tetrachloride in aqueous sodium hydroxide solutions. The selectivities were 100 %, and the yields were larger than 80 mole%. The immobilized catalysts were easily separated from the reaction mixture, and were repeatedly used without measurable decrease in the catalytic activity.

1. INTRODUCTION

Cyclodextrins (CyDs) exhibit specific catalyses due to the formation of stereospecific inclusion complexes with various reagents prior to chemical transformation. However, most of the specific catalyses, previously reported on CyDs, refer to substrate specificity in bond cleavage reactions such as ester hydrolyses (1,2). Application of CyDs as selective catalysts for organic syntheses has developed only quite recently (3-13).

Previously (10,13), the authors succeeded in selective syntheses of 4-hydroxybenzoic acids from phenols and carbon tetrachloride, using β -cyclodextrin (β -CyD) as catalyst. With the use of β -CyD catalyst, a side reaction, carboxylation at the ortho-position, was largely suppressed, and 4-hydroxybenzoic acids were synthesized in selectivity larger than 95 %. In addition, various aromatic substitution and addition reactions were achieved in virtually 100 % selectivity and high yields in the presence of CyDs as catalyst (9-13). Selective catalyses involve regioselectivity, regulation of molecular sizes of intermediates and products, and/or protection of unstable products (9-13).

In this paper, it will be shown that CyDs immobilized in gels with epichlorohydrin can be successfully used for the selective syntheses of 4-hydroxybenzoic acids. Recovery of the catalysts from the reaction mixture and their reusage will be described.

2. MATERIALS AND METHODS

2.1. Preparation of Immobilized CyD Catalysts

Three types of immobilized β -CyD catalysts I, II, and III were prepared by the reaction of β -CyD with epichlorohydrin in 50 wt.-% aqueous sodium hydroxide solution at 50°C for 40 min, at the charged molar ratio 1:20, 1:10, and 1:4. After the reactions, the resulting solids were sufficiently washed with acetone and with water, and then were dried in vacuo. The molar ratios of 2-hydroxypropyl residue, derived from epichlorohydrin, to β -CyD in the immobilized catalysts I, II, and III, respectively, were 5.7, 3.3, and 1.2.

An immobilized α -CyD catalyst IV was similarly prepared from α -CyD and epichlorohydrin at the charged molar ratio 1:10.

2.2. Selective Syntheses with Immobilized CyD Catalysts

The immobilized CyD catalyst (1.5 g), phenol (1.5 g), carbon tetrachloride (3.0 ml), and metallic copper powder (0.2 g) were added to 20 ml of 20 wt.-% aqueous sodium hydroxide solution, and the reaction was carried out at 80°C for 15 h under nitrogen.

After the reaction, the mixture was centrifugated at 3000 rpm for 10 min. The liquid phase was acidified with hydrochloric acid, and was vigorously extracted with ethyl ether. The ether layer was evaporated, and was subjected to HPLC analysis (Toyo Soda Co., LS410K, MeOH-100 column, 30 cm, 25°C, eluent: 6:4 water-ethanol).

The solid obtained by centrifugation was used as the catalyst for the following selective synthesis.

3. RESULTS AND DISCUSSION

3.1. Selective Syntheses Using Virgin Immobilized CyD Catalysts

TABLE I Reactions of phenol with carbon tetrachloride in the presence and the absence of immobilized β -CyD catalysts^{a,b}

Immobilized β -CyD Catalyst	Yield (mole%)		Selectivity for 4-hydroxy- benzoic acid(%)
	4-hydroxy- benzoic acid	2-hydroxy- benzoic acid	
I	82	0	100
II	89	0	100
III	96	0	100
IV ^c	42	29	59
none	15	12	56

a. Charged amounts: phenol (1.5 g), catalyst (1.5 g), carbon tetrachloride (3 ml), and copper powder (0.2 g) in 20 ml of 20 % aqueous sodium hydroxide solution.

b. Reaction conditions: 80°C, 15 h, under nitrogen.

c. Immobilized α -CyD catalyst.

TABLE I shows the results for the reactions of phenols with carbon tetrachloride in alkaline aqueous solutions in the presence and the absence of the immobilized β -CyD catalysts. Using the immobilized catalysts I-III, 4-hydroxybenzoic acid is synthesized in 100 % selectivity and high yield (82-96 mole% with respect to the charged phenol). In their absence, however, both the selectivity (56 %) and the yield (15 mole%) are much lower. In addition, 4-hydroxy-3-methylbenzoic acid is synthesized in 100 % selectivity and 87 mole% yield by the reaction of 2-methylphenol with carbon tetrachloride under the similar conditions in the presence of the immobilized β -CyD catalyst II. Thus, the immobilized β -CyD catalysts exhibit remarkable enhancements in both the selectivity and the yield for the carboxylation of phenols at the para position with respect to the hydroxyl groups.

Quite importantly, the selectivity (100 %) exhibited by the immobilized β -CyD catalysts both for 4-hydroxybenzoic acid and for 4-hydroxy-3-methylbenzoic acid is significantly larger than the values with free β -CyD catalyst (98 % for 4-hydroxybenzoic acid and 95 % for 4-hydroxy-3-methylbenzoic acid). Formation of the ortho-carboxylated phenols is definitely inhibited in the presence of the immobilized catalysts.

In contrast, the immobilized α -CyD catalyst IV exhibits minimal selective catalysis. The selectivity (59 %) with this immobilized catalyst is almost identical with the value (56 %) in its absence, although the yield is considerably larger. The cavity of α -CyD is too small to accommodate the electrophilic species trichloromethyl cation, produced in situ from carbon tetrachloride.

3.2. Repeated Usage of Immobilized CyD Catalysts

The immobilized β -CyD catalysts I and II are insoluble in the reaction mixtures, although they show considerable swelling. Separation from the reaction mixtures are easily accomplished by centrifugation.

Fig. 1 depicts the results for the repeated usage of the immobilized catalysts I and II. The selectivity for 4-hydroxybenzoic acid remains constant at 100 %, and the yield is always larger than 80 mole%. Thus, the immobilized β -CyD catalysts are intact during the reaction and also in the recovery procedure.

The immobilized β -CyD catalyst III, which has the lowest degree of cross-linking and is soluble in the reaction mixture, is also recovered by centrifugation, after being insolubilized by acidifying the reaction mixture. The recovered catalyst is successfully reused without measurable loss in the catalytic activity.

The repeated usage of free β -CyD catalyst, which is not immobilized, is also examined. After the reaction, the reaction mixture is acidified with hydrochloric acid and β -CyD is separated by centrifugation. In the successive three repeated usage, the selectivity for 4-hydroxybenzoic acid is 100 %. In the fourth, the fifth, and the sixth runs, however, the selectivity decreases to 85, 76, and 60 %, respectively.

Easy separation of the catalysts from the products and successful repeated usage of them are certainly advantages for the immobilized β -CyD catalysts over free β -CyD catalyst from the viewpoint of practical

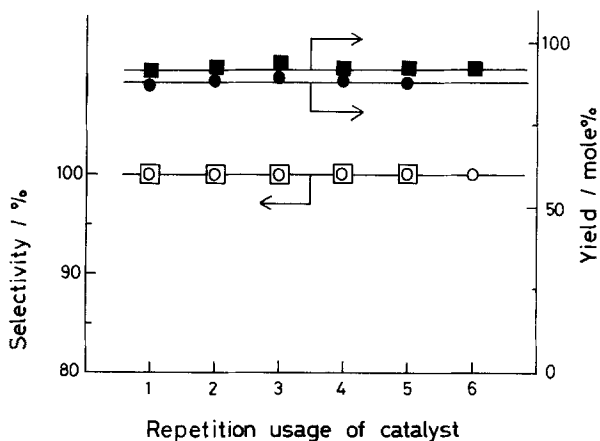


Figure 1. Selectivity and yield for the formation of 4-hydroxybenzoic acid on the repeated usage of the immobilized β -CyD catalysts in the reaction of phenol and carbon tetrachloride in 20 wt.-% aqueous sodium hydroxide solution: (\circ , \bullet) the immobilized catalyst I; (\square , \blacksquare) the immobilized catalyst II. The separation of the catalyst was carried out by centrifugation, and the recovered catalyst was charged to aqueous sodium hydroxide solution together with phenol and carbon tetrachloride in the following run.

application.

3.3. Reaction Mechanism for Selective Synthesis

The selective catalysis by the immobilized β -CyD catalysts proceed in a similar manner to that by free β -CyD catalyst (13). The β -CyD residue forms a ternary molecular complex with phenol and trichloromethyl cation, produced in situ from carbon tetrachloride with the catalysis by copper powder. As a result, the mutual conformation between phenol and trichloromethyl cation is regulated through the non-covalent interactions. The para-carbon atom of phenol is predominantly attacked by the cation, since the carbon atom is located in close proximity to the cation. 4-Hydroxybenzoic acids are selectively formed by the hydrolyses of the C-Cl bonds in the resulting intermediates.

The larger selectivity (100 %) for the immobilized β -CyD catalysts than that (95-98 %) for free β -CyD catalyst is ascribed to effective trapping of the trichloromethyl cation by the negatively charged reaction field of the immobilized catalyst, prior to the reaction between the cation and phenol. The reaction field is produced by many alkoxide ions of β -CyD residues in the immobilized catalysts: the pK_a of the secondary hydroxyl groups of CyD is around 12 (1). Thus, the less selective reaction involving free trichloromethyl cation is definitely inhibited here, and the predominance of the selective

reaction with the catalysis by the β -CyD residue is conclusive.

4. ACKNOWLEDGMENT

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