SHORT COMMUNICATIONS

Catalysis by Cyclodextrin for *para*-Oriented Attack of Formaldehyde to Phenol

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Cyclodextrins, cyclic oligomers of 6–8 glucose units, form inclusion complexes with various guest compounds.¹ As a result, they exhibit specific catalyses in many bond cleavage reactions such as ester hydrolyses, amide hydrolyses, and decarboxylation. However, reports on selective catalyses by cyclodextrins in bond formation reactions have been rather scarce.

Previously, the authors showed that 4-hy-

droxybenzaldehyde and 4-hydroxybenzoic acid are prepared at virtually 100% selectivity by use of cyclodextrins as catalysts.^{2,3}

The present paper reports the catalytic effects of cyclodextrins in the formation of (hydroxymethyl)phenols from formaldehyde and phenol (eq 1). Cyclodextrins exhibit significant increase in selectivity and yield for the formation of (4-hydroxymethyl)phenol.

EXPERIMENTAL

Cyclodextrins were recrystallized from water. Other chemicals were purified by the usual methods.

Reactions of phenol with formaldehyde were achieved in 0.75 *N* aqueous sodium hydroxide solutions at 30°C for 1 day. The initial concentrations of phenol and formaldehyde were 0.015 M and 0.29 M, respectively. The conversion of phenol was at most 5 mol%, and the formation of phenols having two or more hydroxymethyl substituents did not occur to a

measurable extent. Product analysis was made by HPLC (JASCO C₁₈S column, 10 cm; eluent, 2:1 water–ethanol solution).

RESULTS AND DISCUSSION

Table I shows the results of the reactions between phenol and formaldehyde in 0.75 *N* aqueous sodium hydroxide solutions. In the absence of cyclodextrins, the yield of (4-hydroxymethyl)phenol is quite low. In addition, a significant amount of (2-hydroxymethyl)phenol is formed as byproduct, and the molar ratio of (4-hydroxymethyl)phenol to (2-hy-

Table I. Yield and selectivity for the formation of (4-hydroxymethyl)phenol from phenol and formaldehyde in the presence and absence of cyclodextrins^a

Additive	Concentration	Yield	
	M	mol% ^b	<i>para/ortho</i> ^c
β -Cyclodextrin	0.05	0.7	2.6
	0.1	1.2	3.5
	0.2	1.6	4.0
	0.3	2.4	4.5
	0.4	3.2	5.3
α -Cyclodextrin	0.4	2.7	2.4
D-Glucose	2.5	3.3	1.6
None	—	0.3	1.7

^a [Phenol]₀ = 0.015 M; [NaOH]₀ = 0.75 M; [HCHO]₀ = 0.29 M.

^b Yield of (4-hydroxymethyl)phenol with respect to the charged phenol for 1 day at 30°C.

^c Molar ratio of (4-hydroxymethyl)phenol to (2-hydroxymethyl)phenol.

droxymethyl)phenol is only 1.7.

The molar ratio of (4-hydroxymethyl)phenol to (2-hydroxymethyl)phenol largely increases with increasing concentration of β -cyclodextrin. At the concentration 0.4 M of β -cyclodextrin, the *para/ortho* ratio is 5.3, corresponding to 84% selectivity for (4-hydroxymethyl)phenol. The yield for (4-hydroxymethyl)phenol is also significantly increased by β -cyclodextrin. The yield (3.2 mol%) in the presence of 0.4 M of β -cyclodextrin is 10.7 times that (0.3 mol%) in its absence. Thus, β -cyclodextrin increases both the selectivity and the yield for (4-hydroxymethyl)phenol.

α -Cyclodextrin also promotes the yield of (4-hydroxymethyl)phenol. However, enhancement of the selectivity by α -cyclodextrin is minimal. Thus, the size of the cavity of cyclodextrin has overwhelming effect on the selective catalysis.

Quite importantly, D-glucoses, a non-cyclic analogue of cyclodextrins, decreases the selectivity for (4-hydroxymethyl)phenol. This definitely shows the essential role of the cyclic structure of β -cyclodextrin in the present selective catalysis.

Both the *para/ortho* ratio and the yield show saturation at large concentrations of β -cyclodextrin, indicating that the present selective catalysis proceeds *via* the formation of an inclusion complex between phenolate and β -cyclodextrin. The phenolate penetrates from the secondary hydroxyl side of the cavity with the *para*-carbon atom first.² Here, the attack by formaldehyde at the *ortho*-carbon atoms of the phenolate is suppressed by the secondary alkoxide ions of cyclodextrin. The enhancement of the reaction at the *para*-carbon atom is associated with acid catalysis by the primary hydroxyl groups of cyclodextrin in the attack of formaldehyde, accommodated in the cavity.

These arguments are definitely supported by the fact that the selective catalysis by β -cyclodextrin was observed only when the concentration of sodium hydroxide was larger than that of phenol and thus the secondary hydroxyl groups of cyclodextrin were present in their anionic forms.⁴ Under the conditions that the initial concentrations of both phenol and sodium hydroxide were 0.15 M, the selectivity in the presence of 0.1 M of β -cyclodextrin was almost identical with the value in its absence.

In conclusion, selective synthesis of (4-hydroxymethyl)phenol from phenol and formaldehyde is successfully achieved by use of β -cyclodextrin in alkaline solutions. A detailed study on the reaction mechanism is currently under way.

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REFERENCES AND NOTES

1. M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag, Berlin, 1978.
2. M. Komiyama and H. Hirai, *J. Am. Chem. Soc.*, **105**, 2018 (1983).
3. M. Komiyama and H. Hirai, *J. Am. Chem. Soc.*, **106**, 174 (1984).
4. The pK_a of the secondary hydroxyl groups are around 12: ref 1.