Selective Synthesis of 4-Hydroxymethylphenol catalysed by Cyclodextrins having Hydroxypropyl Residues

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The selective synthesis of 4-hydroxymethylphenol from phenol and formaldehyde has been achieved using α-, β-, and γ-cyclodextrins having 2-hydroxypropyl residues.

Here we report a selective organic synthesis using modified cyclodextrins as catalysts.

Cyclodextrins (CyDs), cyclic oligomers of 6—8 glucose units, form inclusion complexes with various guest compounds.[1,2] As a result, they exhibit specific catalytic properties in various reactions.[1—5] Recently, techniques for the introduction of functional groups to CyDs were developed, providing modified CyDs for use as elegant models of enzymes.[6,7] However, reports on the use of modified CyDs as catalysts for selective organic syntheses have been scarce.

This paper reports the selective synthesis of 4-hydroxymethylphenol from formaldehyde and phenol catalysed by CyDs having hydroxypropyl residues, and demonstrates the absolute requirement for chemical modification of CyDs for effective catalysis.

α-, β-, and γ-CyDs having 2-hydroxypropyl residues (HP-CyDs: average numbers of hydroxypropyl residues per molecule, 4.8, 5.8, and 8.0, respectively) were prepared according to the literature.[8] Syntheses of hydroxymethylphenols were homogeneously achieved at 4 °C in aqueous sodium hydroxide solutions 0.75 M for 10 days under nitrogen, and the product analysis was made by h.p.l.c.

As shown in Table 1, 4-hydroxymethylphenol is selectively prepared in the presence of HP-β-CyD, with a *para*:*ortho* ratio 15.7 (selectivity 94%) at a HP-β-CyD concentration of 0.6 M (the largest one examined). Analysis of the plot of selectivity *vs.* concentration of HP-β-CyD indicates that the rate constant for the *ortho* reaction in the HP-β-CyD–phenol complex is virtually zero. The yield is 36 mol%, when the charged concentration of formaldehyde is 5.0 M. This is 16 times as large as the yield (2.2 mol%) in the absence of HP-β-CyD. HP-α-CyD and HP-γ-CyD also promote the selectivity and the yield of 4-hydroxymethylphenol. In the absence of HP-CyDs, however, a significant amount of 2-hydroxymethylphenol is formed as a byproduct, and the *para*:*ortho* ratio is only 2.1. D-Glucose, a non-cyclic analogue of CyDs, decreases the selectivity for 4-hydroxymethylphenol.

Importantly, unmodified β-CyD produces a much smaller

Table 1. Selective syntheses of 4-hydroxymethylphenol from phenol and formaldehyde catalysed by cyclodextrins having hydroxypropyl residues.[a]

Additive	Concentration/M	*para* : *ortho*[b]
HP–β-CyD	0.05	5.3
	0.3	10.1
	0.6	15.7
HP–α-CyD	0.3	4.3
HP–γ-CD	0.3	3.3
β-CyD	0.3	2.8
γ-CyD	0.3	1.9
D-Glucose	2.5	1.6
None	—	2.1

[a] $[Phenol]_0$ 0.015 M, $[NaOH]_0$ 0.75 M, $[HCHO]_0$ 0.58 M. [b] 4-Hydroxymethylphenol : 2-hydroxymethylphenol.

increase in the *para* : *ortho* ratio than HP–β-CyD. γ-CyD itself produces no increase in the ratio, in contrast with the considerable increase by HP–γ-CyD. Thus the introduction of the hydroxypropyl residues to the CyDs is essential for effective selective catalyses. The selective catalyses by HP–CyDs were observed only in strongly alkaline solutions, indicating the importance of the ionization of the secondary hydroxy groups (pK_a ~12).[1] The present finding indicates a strong possibility of designing modified CyDs for selective catalyses in various organic syntheses.

We thank the Nihon Shokuhin Kako Co. for the preparation of the modified cyclodextrins.

Received, 31st December 1987; Com. 1878

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