Selective Syntheses using Cyclodextrins as Catalysts Part 5.[1] *para*-Selective Hydroxymethylation of Phenol by Formaldehyde using Hydroxypropyl Cyclodextrins

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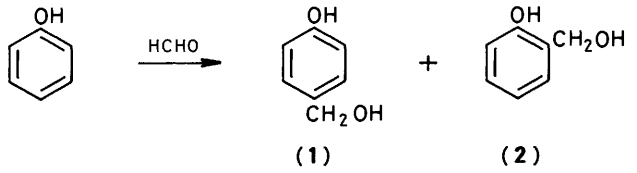
4-(Hydroxymethyl)phenol (**1**) has been selectively synthesized from phenol and formaldehyde by use of hydroxypropyl cyclodextrins (HP-CyDs) as catalysts. In the presence of 0.6 mol dm^{-3} (M) of HP-β-CyD (degree of substitution 5.8) at 4 °C, the rate constant (k_1) for the formation of (**1**) is 16 times as large as that (k_2) for the formation of 2-(hydroxymethyl)phenol (**2**) as by-product. In its absence, however, the k_1/k_2 ratio is only 2.1. Significantly, the selectivity-enhancing effects of the HP-CyDs are much larger than those of CyDs without the chemical modification: the k_1/k_2 ratios in the presence of 0.3M of α-, β-, and γ-CyDs are only 2.5, 2.9, and 1.9. Kinetic analyses indicate that the hydroxypropyl residues increase the selectivity by the interaction with the formaldehyde accommodated in the cavity of the HP-CyD.

Recently much attention has been given to selective organic syntheses using cyclodextrins (CyDs), cyclic oligomers of 6—8 glucose units,[2,3] as catalysts. The selective syntheses of 4-chloroanisole,[4] a vitamin K analogue,[5] 4-hydroxybenzaldehyde,[6] and 4-hydroxybenzoic acid[7] have been reported.

Furthermore, refined techniques for the regioselective introduction of functional groups into CyDs have been developed, particularly by Breslow and Tabushi.[8,9] The modified CyDs were used as elegant models of enzymes. However, reports on the use of the modified CyDs as catalysts for selective organic syntheses have been relatively scarce.

In a preliminary communication,[10] the present author showed that the selective synthesis of 4-(hydroxymethyl)phenol (**1**) from phenol and formaldehyde (see Scheme) is achieved by CyDs having 2-hydroxypropyl residues (HP-CyDs).



(**1**) (**2**)

Scheme.

This paper reports the results of detailed analyses of the HP-CyD-catalyzed selective syntheses of (**1**). Definitive requirements of the hydroxy groups in the 2-hydroxypropyl residues introduced for effective catalysis are outlined. A mechanism for selective synthesis is proposed.

Results

Selective Synthesis of (**1**) *Catalysed by HP-CyDs.*—Table 1 shows the selectivity [the ratio of the rate constant (k_1) for the formation of (**1**) to that (k_2) for the formation of 2-(hydroxymethyl)phenol (**2**)] in the presence and in the absence of the HP-CyDs. In their absence, a considerable amount of (**2**) is formed as by-product, and the k_1/k_2 ratios are only 2.1 at 4 °C and 1.7 at 30 °C.

The ratio asymptotically increases with an increase in the concentration of the HP-CyDs. The largest value is 15.7, which is attained at 4 °C by 0.6M of the HP-β-CyD (DS: the average number of the 2-hydroxypropyl residues per one CyD molecule, 5.8). This corresponds to a selectivity of 94% for (**1**) around the conversion 10 mol% of phenol. For all the HP-CyDs the selectivity increases with an increase in the DS value.

Table 1. The k_1/k_2 ratios for the reactions of phenol and formaldehyde in the presence and the absence of HP-CyDs[a,b]

Additive	DS	k_1/k_2[c] at 4 °C	k_1/k_2[c] at 30 °C
HP-β-CyD	5.8	10.1 15.7[d]	6.5 (2.4)
	4.3	8.6	
	3.6	8.1	
HP-γ-CyD	8.0	3.3	4.1 (1.7)
	5.9	3.2	
	4.0	2.8	
HP-α-CyD	4.8	4.3	2.7 (1.5)
2-Hydroxyisobutyl-β-CyD	3.5	5.2	
β-CyD		2.8	4.4
γ-CyD		1.9	1.4
α-CyD		2.5	2.3
Pentakis-6-*O*-methyl-β-CyD	5.0	2.8	3.1
None		2.1	1.7 (1.2)

[a] Abbreviations. HP-CyD, hydroxypropyl CyD; DS, the average number of the substituents per one CyD molecule. [b] Reaction conditions: $[Phenol]_0 = 0.015$, $[NaOH]_0 = 0.75$, and $[HCHO]_0 = 0.58$M; the concentration of the additive is 0.3M unless otherwise noted. [c] The numbers in parentheses show the results for the reactions under the identical conditions except that $[NaOH]_0 = 0.015$M. [d] [HP-β-CyD] = 0.6M.

In addition to the increase of the selectivity, the HP-CyDs accelerate the formation of (**1**). The yield of (**1**) (27 mol%) in the presence of 0.3M of the HP-β-CyD (DS 5.8) is more than 5-fold larger than the value (5.1 mol%) in its absence (the reaction conditions: $[HCHO]_0 = 0.58$M at 30 °C for 5 days). The yield is further increased by an increase in the concentration of formaldehyde.

Quite importantly, the selectivity-enhancing effects of the HP-CyDs are much larger than those of CyDs without the hydroxypropyl residues. In the presence of 0.3M of the HP-β-CyDs (DS 5.8, 4.3, and 3.6) at 4 °C, the k_1/k_2 ratios are 4.8, 4.1, and 3.9 times as large as the value in their absence. However, intact β-CyD increases the ratio only by 40%. α- and γ-CyDs without the chemical modification shows only marginal effects on the k_1/k_2 ratio. Thus, the effects of the hydroxypropyl residues are remarkable.

Table 2. Comparison of the catalytic parameters of the HP-β-CyD (DS 5.8) and β-CyD

Temp. (°C)	Catalyst	K_d[a] (10^{-1}M)	$\frac{k_1(\text{complex})}{k_1(\text{free})}$	$\frac{k_2(\text{complex})}{k_2(\text{free})}$
4	HP-β-CyD	3.1 (2.8)[b]	12	1.3
	β-CyD	6.8	8.7	4.8
30	HP-β-CyD	3.6 (3.3)[b]	18	2.3
	β-CyD[c]	8.3	23	5.0

[a] The kinetically determined equilibrium constants for the dissociation of the complex involved in the reactions. [b] The K_2 values of the HP-β-CyD-formaldehyde complex evaluated by the competitive inhibition method. [c] Data from ref. 1.

The selective syntheses by the HP-CyDs were also successfully achieved, when larger concentrations of phenol were used. The k_1/k_2 ratio was 10.5 under the conditions that $[\text{phenol}]_0$ = 0.3, $[\text{HP-β-CyD}]_0$ = 0.6, and $[\text{HCHO}]_0$ = 0.58M at 4 °C.

2-Hydroxyisobutyl-β-CyD (DS 3.5) showed larger selectivity-enhancing effect than intact β-CyD (Table 1). However, the effect of pentakis-6-*O*-methyl-β-CyD is virtually identical with that of β-CyD at 4 °C and is smaller at 30 °C. Thus, the hydroxy groups in the 2-hydroxypropyl and the 2-hydroxyisobutyl residues, covalently introduced to the CyDs, are essential for the effective catalysis.

Heptakis-2,6-dimethyl-β-CyD, heptakis-2,3,6-trimethyl-β-CyD, and hexakis-2,6-dimethyl-α-CyD showed no measurable effects either on the selectivity or on the yield. The secondary hydroxy groups of CyDs are also required for the catalysis.

When the charged molar ratio of sodium hydroxide to phenol was 1.0, in place of the ratio 50 hitherto employed, the selectivity-enhancing effects of the HP-CyDs were much smaller, as shown in the parentheses in Table 1. At a molar ratio 5.0, however, the selectivities were almost identical with the values at a ratio of 50. Thus, the molar ratio of sodium hydroxide to phenol must be larger than 1.0 for effective catalysis by the HP-CyDs.

Kinetics of the HP-β-CyD-Catalysed Selective Synthesis of (**1**).—Table 2 lists the equilibrium constants for the dissociation of the complexes (K_d) for the selective syntheses by the HP-β-CyD (DS 5.8), determined from the dependence of k_{obs} [the total rate constant for the formation of (**1**) and (**2**)] on the $[\text{HP-β-CyD}]_0$, together with the values for the reactions by β-CyD. All the values are constant irrespective of the concentration of formaldehyde.

The kinetically determined K_d values (0.31M at 4 °C and 0.36M at 30 °C) for the HP-β-CyD complex involved in the HP-β-CyD-catalyzed selective syntheses are almost identical with the equilibrium constants (K_2: 0.28M at 4 °C and 0.33M at 30 °C) for the dissociation of the complex between the HP-β-CyD and formaldehyde. The K_2 values have been independently determined in 0.75M aqueous sodium hydroxide by the competitive inhibition with formaldehyde of the complex formation between the HP-β-CyD and 4-nitrophenolate. The equilibrium constants (K_1: 0.021M at 4 °C and 0.032M at 30 °C) for the dissociation of the HP-β-CyD-phenolate complex are considerably smaller than the K_d values. This result shows that it is the HP-β-CyD–formaldehyde complex that participates in the present selective syntheses.

The K_d values for the HP-β-CyD are *ca.* 2 times smaller that those for β-CyD. The guest binding ability of the β-CyD residue is promoted by the introduction of the hydroxypropyl groups.

The partial rate constants for the selective syntheses were determined by use of equation (2), where k_1 and R_2 are the

$$[k_2(\text{free}) - k_1(\text{free})/R]/F = -k_2(\text{complex}) + k_1(\text{complex})/R \quad (2)$$

partial rate constants for the formations (**1**) and (**2**) respectively. The terms 'complex' and 'free' refer to the formaldehyde in the 'complexed' and the 'free' states; R is the ratio k_1/k_2 of the observed rate constants for the formation of (**1**) and (**2**); F is the equilibrium ratio of the 'complexed' formaldehyde to 'free' formaldehyde, and has been estimated by use of the K_d value. Equation (**2**) was first used by Breslow for the α-CyD-catalysed *para*-selective chlorination of anisole.[11]

The plots of the data according to equation (2) gave straight lines, and the values of k_1(complex) and k_2(complex) were evaluated from the intercepts and the slopes.

For the HP-β-CyD-catalysed reaction at 4 °C, the k_1(complex)/k_1(free) ratio is 12, whereas the k_2(complex)/k_2(free) ratio is only 1.3 (Table 2). Thus, the ratio of k_1(complex) to k_2(complex) is 19 (the maximal selectivity 95%). In the β-CyD-catalysed reaction, however, the formation of both (**1**) and (**2**) is largely accelerated by complex formation, resulting in a smaller selectivity (79%). The same result has been obtained also for the reactions at 30 °C.

The sum (2.5×10^{-4} h^{-1}) of k_1(complex) and k_2(complex) for the HP-β-CyD-catalysed reaction at 4 °C is almost identical with the maximal rate constant $k_{max.}$(2.8×10^{-4} h^{-1}), determined independently from the k_{obsd} *vs.* $[\text{HP-β-CyD}]_0$ plot. This confirms the validity of the present kinetic analyses.

Discussion

Kinetic Analysis.—The significant increase in the selectivity with an increase in the concentration of the HP-β-CyD (DS 5.8), even in the region where the concentration is much larger than the dissociation constant (K_1) of the HP-β-CyD-phenolate complex and thus most of the charged phenolate is complexed with the HP-β-CyD (Table 1), shows that the formation of this complex is not sufficient for the selective synthesis. Rather, the selective catalysis further requires formation of a complex between the HP-β-CyD and formaldehyde. The selective syntheses involve the reactions between the HP-β-CyD-formaldehyde complex and phenolate.

This argument is definitely supported by the fact that the kinetically determined K_d values are almost identical with the dissociation constants K_2 values of the HP-β-CyD–formaldehyde complex (Table 2).

The essential role of the HP-CyD–formaldehyde complex for the selective syntheses is further confirmed by the gradual increase of the k_1/k_2 ratio with a decrease in the charged concentration of formaldehyde. The ratios are 10.1, 12.1, and 13.5 at the concentrations of formaldehyde 0.58, 0.29, and 0.15M, when the concentrations of the HP-β-CyD and phenolate are kept constant (0.30 and 0.015M at 4 °C). The molar fraction of the complexed formaldehyde increases in this order.

The possibility that the selective syntheses proceed by the reaction between the HP-CyD–phenolate complex and free formaldehyde is ruled out, since 0.02M of the HP-β-CyD shows only marginal effects on the selectivity and the yield at 4 °C. Here, about half of the charged phenolate is complexed with the HP-β-CyD (K_1 = 0.021M).

Enhancement of the Catalytic Activity of CyD by the Introduction of Hydroxypropyl Residues.—The proposed mechanism for the present selective syntheses is schematically depicted in the Figure. Phenolate approaches the formaldehyde, accommodated in the cavity of HP-CyD, from the side involving the *para*-carbon atom, since the cavity favours this apolar side of

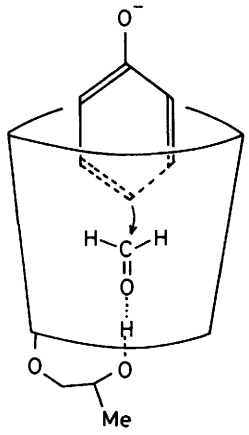


Figure.

the phenolate more than the polar side involving the phenoxide oxygen atom.[6,7,12] As a result, the attack by the formadehyde takes place preferentially at the *para*-carbon atom of the phenolate. Reactions at the *ortho*-carbon atoms are sterically inhibited.

The above argument has been definitely supported by the ^{13}C n.m.r. spectroscopy. The resonance of the *ortho*-carbon atoms of phenol shifted toward higher magnetic field by 0.2 p.p.m., and those for the *meta*- and the *para*-carbon atoms shifted toward lower magnetic field by 0.3 and 1.0 p.p.m., when the HP-β-CyD (DS 5.8: 0.1M) was added to an 0.75M NaOD solution of phenol. This shows the penetration of the phenol into the cavity with the *para*-carbon atom first, since the larger magnitude of the downfield shift refers to the deeper penetration.[13]

The hydroxypropyl groups, situated on the primary hydroxy side of the cavity, form hydrogen bonds with the formaldehyde and enhance its inclusion. A CPK molecular model study has shown that the hydroxypropyl residues possess quite appropriate positions for the hydrogen bonding. In fact, the HP-β-CyD shows *ca.* 2-fold smaller K_d values than the values for intact β-CyD (Table 2). The selectivities for the HP-CyD-catalysed reactions are larger, since the contribution of the selective reaction involving the complexed formaldehyde is more significant.

Furthermore, the hydrogen bonds strictly regulate the position of the formaldehyde in the cavity and make the *para*-reaction still more dominant. In the catalysis by β-CyD without the chemical modification, however, the included formaldehyde has greater mobility, which allows the *ortho*-reaction to proceed to some extent. The ratio (19) of the partial rate constants, k_1(complex)/k_2(complex), for the catalysis by the HP-β-CyD is considerably larger than the value (3.8) for β-CyD. The enhanced catalytic activity of the 2-hydroxyisobutyl-β-CyD is also ascribed to the same effects as described above.

The proposed hydrogen bonds are strongly supported by the fact that pentakis-6-*O*-methyl-β-CyD, which has a similar structure as the HP-β-CyDs and the 2-hydroxyisobutyl-β-CyD, but has no hydroxy groups available for the effective hydrogen bonding with the formaldehyde, shows virtually the same catalytic activity as β-CyD itself.

The attack at the *ortho*-positions of phenolate by formaldehyde, which is free from the complex formation with the HP-CyD, is effectively suppressed, since almost all of the phenolate is complexed with the HP-CyD in the reaction mixtures. In the complex the *ortho*-carbon atoms of the phenolate are located near the secondary alkoxide ions of the HP-CyD, and the negatively-charged transition state for the reaction[14] is destabilized by the electrostatic repulsion from the alkoxide ions. Thus, selective catalysis is observed only when the charged molar ratio of sodium hydroxide to phenol is larger than 1.0 (Table 1) and the media are sufficiently alkaline to dissociate the secondary hydroxy groups (pK_a *ca.* 12).[2] The importance of the secondary hydroxy groups is also shown by the absence of catalytic activity for heptakis-2,6-dimethyl-β-CyD and hexakis-2,6-dimethyl-α-CyD.

The proposed mechanism for the selective syntheses is consistent with those for the selective syntheses of 4-hydroxybenzaldehyde[6] from phenol and chloroform, and of 4-hydroxybenzoic acid[7] from phenol and carbon tetrachloride, catalysed by CyD without chemical modification. In these cases the mutual orientation of phenol and chloroform or carbon tetrachloride is regulated by the interactions with CyD in such ways that the reactions occur selectively at the *para*-position of phenol. In the present selective syntheses, the complex formation between intact CyDs and formaldehyde is less efficient owing to the smaller hydrophobicity of formaldehyde compared with that of chloroform and carbon tetrachloride. Thus, for the enhancement of the complex formation, the introduction of the hydroxypropyl residues into CyDs is a necessity.

The present results as well as the recent developments of the techniques for the chemical modification of CyDs[8,9] suggest possibilities for the molecular design of modified CyDs as catalysts for particular organic syntheses.

Experimental

Materials.—HP-CyDs were prepared by the reactions of CyDs and propylene oxide in alkaline solutions according to the literature.[15] The DS values were determined by ^1H n.m.r. spectroscopy. Most hydroxymethylation occurred (83—96% according to the ^{13}C n.m.r. spectroscopy) at the primary hydroxy groups of CyDs. The HP-CyDs have narrow and symmetrical distributions with respect to the degree of substitution.[15] 2-Hydroxyisobutyl-β-CyD (DS 3.5)[16] and pentakis-6-*O*-methyl-β-CyD[17] were prepared by literature methods.

Selective Syntheses of (**1**).—The reactions of phenol with formaldehyde were carried out in 0.75M aqueous sodium hydroxide under nitrogen unless otherwise noted. The charged concentrations of phenol, formaldehyde, and HP-CyD were 0.015—0.30, 0.15—0.58, and 0.0—0.6M. The reaction mixtures were periodically analysed by h.p.l.c. (JASCO $C_{18}S$ column, 10 cm; eluant, 2:1 water–ethanol solution acidified with acetic acid). The formation of phenols having two or more hydroxymethyl substituents did not take place to a measurable extent.

Kinetic Analysis.—All the reactions satisfactorily followed first-order kinetics. The values of $k_{max.}$ and K_d were evaluated by applying the least-squares method to the plots of the k_{obs} *vs.* $[HP\text{-}CyD]_0$. Here, the charged concentration of formaldehyde was kept constant.

Spectroscopy.—Absorption spectra were taken on a JASCO Ubest-50 spectrophotometer with a variable temperature attachment. The equilibrium constants (K_1) for the dissociation of the complex between HP-CyD and phenolate were determined by a literature method.[18] ^1H and ^{13}C N.m.r. spectroscopy was made on a Bruker AM-500 spectrometer.

Acknowledgements

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