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Selective synthesis using cyclodextrins as catalysts 7. Preparation of 3-(hydroxymethyl)indole from indole and formaldehyde

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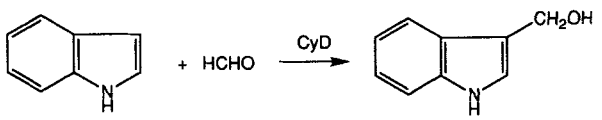
3-(Hydroxymethyl)indole (I-3) is efficiently prepared from indole and formaldehyde by use of cyclodextrins (CyDs) as catalysts in alkaline solutions at 50°C. The selectivities for I-3 in the presence of α- and γ-CyDs (150 mmol dm^{-3}) are 89 and 87%, whereas the value with β-CyD (15 mmol dm^{-3}) is 60% (the selectivity in the absence of CyDs is only 43%). The reactions proceed sequentially via 1-(hydroxymethyl)indole (I-1) and 1,3-bis(hydroxymethyl)indole (I-1,3) as the intermediates. CyDs shift the equilibrium between I-3 and I-1,3 toward I-3 by the preferential inclusion of I-3, resulting in the suppression of the formation of I-1 and I-1,3.

INTRODUCTION

Recently selective organic syntheses using cyclodextrins (CyDs) have been attracting much interest.[1 - 14] Product distribution, regiochemistry, and chirality as well as product yield were successfully modulated by CyDs. All the selective catalyses, which operate in the complexes between CyD and the reactants, have been ascribed to one (or some) of the following factors: i.e. 1) selective binding of the specific reactants by CyDs, 2) control of the mutual orientation of the reactants, 3) restriction of the molecular sizes and structures of the products and the intermediates, and 4) microsolvent effects of the cavities.

The present paper reports a novel type of selective catalysis of CyDs which takes advantage of shift of the equilibrium in the reaction mixtures toward the desired direction. By use of CyDs, 3-(hydroxymethyl)indole (**I-3**), an important chemical in industry, is selectively prepared from indole and formaldehyde (eq. 1). Formation of 1-(hydroxymethyl)indole (**I-1**) and 1,3-bis(hydroxymethyl)indole (**I-1,3**) as by-products is greatly suppressed. The catalytic mechanism is interpreted in terms of the kinetic and spectroscopic evidences.



I-3 (1)

EXPERIMENTAL

Reaction Procedures for the Hydroxymethylation of Indole

Indole and formaldehyde were stirred in aqueous solutions in the presence or the absence of CyD. Typical reaction conditions were $[\text{indole}]_0 = 7.5$, $[\text{formaldehyde}]_0 = 15$, and $[\text{CyD}]_0 = 0$–150 mmol dm^{-3} (*mM*) at 50°C and pH 12. The reaction mixtures were periodically analyzed by the reversed-phase HPLC (Merck Lichrospher 18(e) column, 10 cm, 3:1 water-acetonitrile solution; detection at 288 nm).

Characterization of Reaction Products and Intermediates

All the products and the intermediates **I-1**, **I-3**, and **I-1, 3** were separated from the reaction mixtures by use of a preparative HPLC column, and were unambiguously characterized by ^{1}H-NMR spectroscopy in DMSO-d_6. **I-1**: δ5.52 (2H, d, $\underline{CH_2}OH$); 6.39 (1H, t, $CH_2\underline{OH}$); 6.43 (1H, d, 3-CH); 7.05 – 7.55 (5H, other aromatic protons); 10.85 (1H, -NH). **I-3**: δ4.63 (2H, d, $\underline{CH_2}OH$); 4.72 (1H,

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t, $CH_2O\underline{H}$); 6.96–7.60 (5H, aromatic protons); 10.85 (1H, -NH). **I-1, 3**: δ4.63 (2H, d, 3-$\underline{CH_2}OH$); 4.81 (1H, t, 3-$CH_2O\underline{H}$); 5.46 (2H, s, 1-$\underline{CH_2}OH$); 6.35 (1H, s, 1-$CH_2O\underline{H}$); 7.02–7.60 (5H, aromatic protons).

The molar absorption coefficients of these specimens at 288 nm were used for the quantitative HPLC analysis of the reaction mixtures.

Spectroscopic Determination of the Equilibrium Constant for the Dissociation of the Complex between CyD and I-3

The equilibrium constants for the dissociation of the complexes between **I-3** and α-glucopyranosyl-β-CyD (G_1-β-CyD) or γ-CyD were determined by plotting $[\mathbf{I\text{-}3}]_0/\Delta A$ against $1/[CyD]_0$ according to the usual method.[1a] ΔA is the observed change in the absorbance at 288 nm.

For the α-CyD-**I-3** system, the plot of $[\mathbf{I\text{-}3}]_0/\Delta A$ vs. $1/[\alpha\text{-CyD}]_0$ showed a significant deviation from linearity (see the following section for detail). Thus the data were analyzed according to eq. 2, which was derived by Ricci[15] for the complex formation between indole and α-CyD, and is based on the formation of both 1:1 and 2:1 complexes.

$$[I-3]_0/\Delta A = \{K_1K_2 \cdot (1/[\alpha - CyD]_0)^2 + K_2/[\alpha - CyD]_0 + 1\} \times 1/\{\Delta\epsilon K_2/[\alpha - CyD]_0 + \Delta\epsilon'\} \quad (2)$$

Here K_1 and K_2 are the equilibrium constants for the dissociation of the 1:1 and 2:1 complexes. Δε and Δε' are the changes in the molar absorption coefficients on the formation of the 1:1 and the 2:1 complexes, respectively.

Spectroscopy

Absorption spectra were taken on a JASCO Ubest-35 spectrophotometer at 25°C. The NMR spectroscopy was carried out on a JNM-GX 400 FT NMR spectrometer.

RESULTS AND DISCUSSION

Reaction Pathway for the Hydroxymethylation of Indole

The reversed-phase HPLC on the reactions of indole and formaldehyde gave three signals in addition to the one for indole (formaldehyde is not detected at 288 nm). These three signals were definitely assigned to **I-1,3, I-3**, and **I-1** (in the order of increasing retention time) by ^{1}H-NMR spectroscopy as described in the Experimental section. No other by-products were produced.

Figure 1 (a) depicts the time-course for the reaction in the absence of CyD. In the early stage of the reaction, the N-substituted product **I-1** is rapidly formed (○). The molar fraction of **I-1** shows a steep maximum around the reaction time 1 h, and then gradually decreases. On the other hand, the fractions of **I-1,3** (◐) and of the target product **I-3** (●) monotonically and asymptotically increase with increasing reaction time. The ratio of **I-3** to **I-1,3** at 24 h is 0.75. Apparently, the first step of the reaction is hydroxymethylation of indole at the N1 atom. Then the **I-1** is hydroxymethylated at the 3 position to give **I-1,3**, which is further converted to the target compound **I-3** by the removal of the hydroxymethyl residue

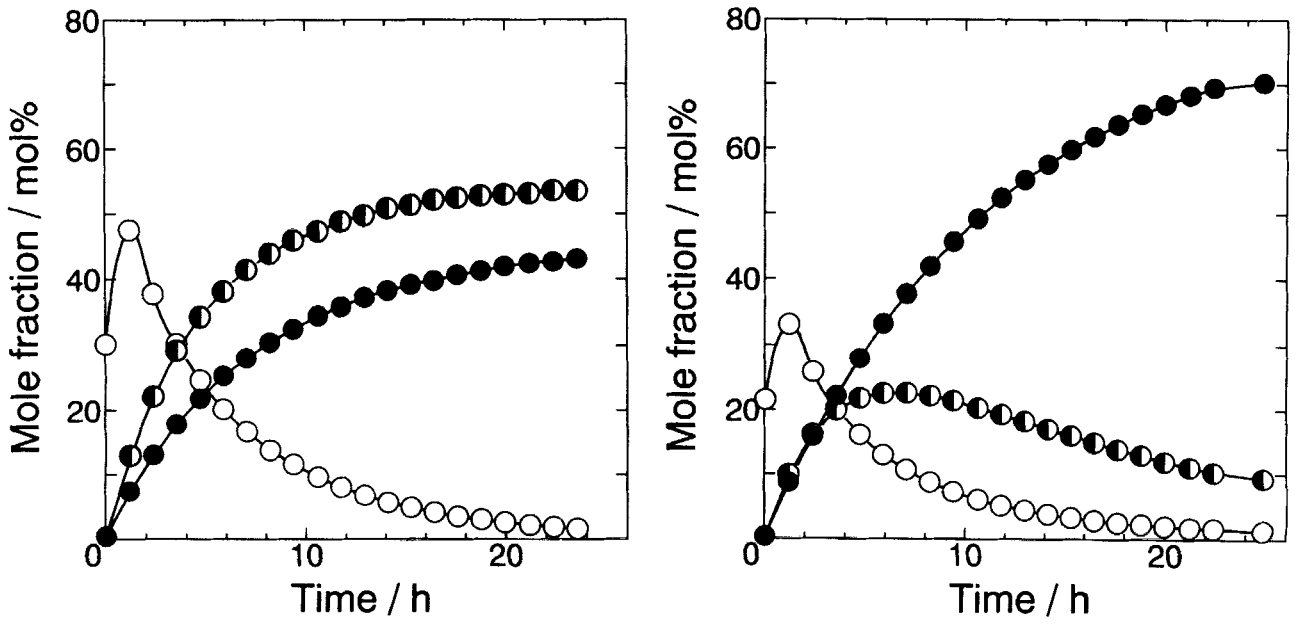

Figure 1 Time-courses for the hydroxymethylation of indole by formaldehyde (a) in the absence and (b) in the presence of α-CyD at pH 12 and 50°C: ○, I-1; ◐, I-1,3; ●, I-3; $[indole]_0$ = 7.5, $[formaldehyde]_0$ = 15, and [α-CyD] = 150 *mM*.

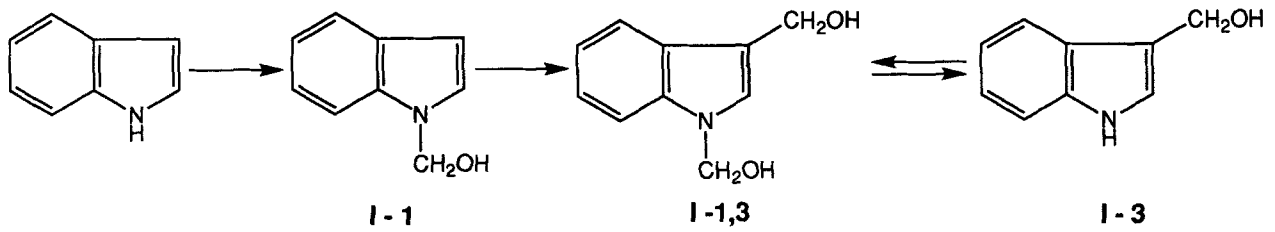

Figure 2 Reaction pathway for the formation of I-3 from indole and formaldehyde.

from the N1 atom (see Fig. 2). No induction period is perceived for the formation of either **I-1,3** or **I-3**, showing that both the step from **I-1** to **I-1,3** and the following step from **I-1,3** to **I-3** are much faster than the step from indole to **I-1**.

The asymptotical increases of the molar fractions of **I-1,3** and **I-3** in Fig. 1 (a) indicate that there exists an equilibrium between them in the reaction mixtures. This interpretation is experimentally substantiated later.

Promotion of CyDs for the Formation of I-3

CyDs efficiently promote the formation of **I-3** with respect to **I-1** and **I-1,3**. As depicted in Fig. 1 (b), **I-3** is dominantly formed in the presence of 150 *mM* of α-CyD. Formation of **I-1,3** and **I-1** is greatly suppressed. The ratio of **I-3** to **I-1,3**, attained at 24 h, is 7.8 (the selectivity for **I-3** is 89%). This is highly in contrast with the preferential formation of **I-1,3** over **I-3** in the absence of α-CyD (the **I-3/I-1,3** ratio is only 0.75 as described above: compare (b) with (a) in Fig. 1). β-CyD and γ-CyD also enhance the formation of **I-3**: the **I-3/I-1,3** ratio at 24 h in the presence of 15 *mM* of β-CyD is 1.5, whereas the value with 150 *mM* of γ-CyD is 6.7. In all the reactions, the yields of **I-3** are reasonably high (70 – 80 mole%). The sequential character of the present reaction (indole → **I-1** → **I-1,3** → **I-3**) is confirmed by the fact that the molar fractions of both **I-1** and **I-1,3** take the maxima around 0.5 h and 6 h, respectively.

The selective catalysis by CyD is more effective at higher pH. As depicted in Fig. 3, the yield for **I-3** significantly increases when the pH is increased from 10 to 12.

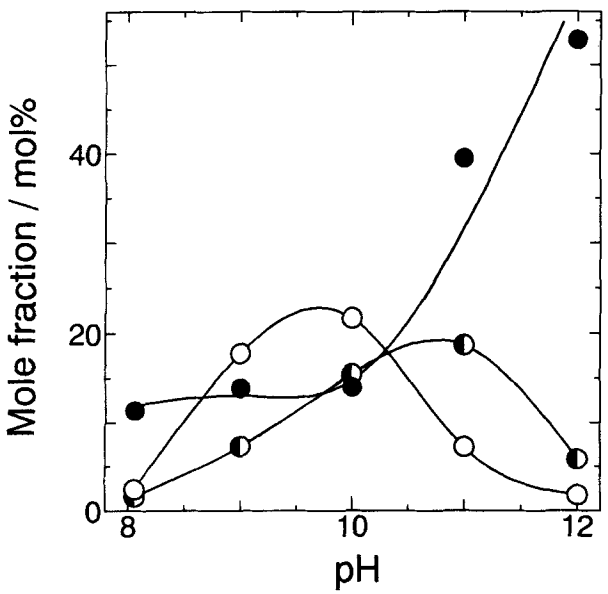

Figure 3 pH dependence of the product distribution for the hydroxymethylation of indole by formaldehyde in the presence of α-CyD (150 *mM*) at 50°C for 24 h: ○, I-1; ◐, I-1,3; ●, I-3; $[indole]_0$ = 7.5, $[formaldehyde]_0$ = 15 *mM*.

Effects of CyDs on the Equilibrium between I-1,3 and I-3

The proposed equilibrium between **I-1,3** and **I-3** has been definitely evidenced by the experiments using the authentic sample of **I-3**. When **I-3** (7.5 *mM*) was incubated with formaldehyde (7.5 *mM*) at pH 12, 50°C, the **I-3** was promptly converted to **I-1,3**, and an equilibrium mixture of **I-3** and **I-1,3** was obtained. In the absence of CyDs, the equilibrium **I-3/I-1,3** ratio was 0.63.

However, CyDs greatly shifted the equilibrium towards **I-3**. The apparent equilibrium constants between **I-1,3** and **I-3** (eq. 3) in the presence of CyDs are 40 – 120 times as large as the value in its absence (see Table 1). The equilibrium-shifting activities of CyDs are in the following order: G_1-β-CyD > γ-CyD > α-CyD. Here G_1-β-CyD having a large water-solubility was used in place of β-CyD in order to compare the result directly with those for α-CyD and γ-CyD.

Table 1 Apparent equilibrium constants between I-1,3 and I-3 in the presence and the absence of CyDs at pH 12, 50°C[a]

CyD	*[I-3]/[I-1,3] ratio in equilibrium*	*Apparent equilibrium constant (M)*
α-CyD	16	0.12
G_1-β-CyD [b]	49	0.34
γ-CyD	25	0.17
None	0.63	0.0029

a. $[I-3]_0$ = 7.5 *mM*; $[formaldehyde]_0$ = 7.5 *mM*; $[CyD]_0$ = 150 *mM*.
b. G_1-β-CyD was used in place of β-CyD due to the limited solubility of β-CyD.

Table 2 Equilibrium constants for the dissociation of the complexes between CyDs and **I-3** at pH 12 and 25°C.

CyD	*K_d (10^{-2} M)*		*Molar fraction of the complexing I-3 at $[CyD]_0$ = 15 mM*
α-CyD	K_1	0.031	0.85 (in the 1:1 complex)
	K_2	5.5	0.11 (in the 2:1 complex)
G_1-β-CyD [a]		2.2	0.41
γ-CyD		4.5	0.25

a. G_1-β-CyD was used in place of β-CyD due to the limited solubility of β-CyD.

$$\textbf{I-1,3} \rightleftharpoons \textbf{I-3} + HCHO \qquad (3)$$

Complex Formation between CyD and I-3

Absorption spectroscopy showed that both β-CyD and γ-CyD form 1:1 complexes with **I-3** at pH 12, 25°C. Plots of $[\textbf{I-3}]_0/\Delta A$ against $1/[CyD]_0$ gave fairly straight lines. The equilibrium constants K_d for the dissociation of the complexes, determined from the plots, are shown in Table 2.

However, the plot of $[\textbf{I-3}]_0/\Delta A$ vs. $1/[\alpha\text{-CyD}]_0$ showed a clear deviation from the linearity (Fig. 4). Apparently a 2:1 complex as well as 1:1 complex is formed between α-CyD and **I-3**. Thus the plot has been analyzed in terms of eq. 2 which is based on the formation of both the 1:1 and the 2:1 complexes. All the experimental points satisfactorily fit the theoretical line calculated by use of $K_1 = 3.1 \times 10^{-4}$ *M* and $K_2 = 5.5 \times 10^{-2}$ *M*. The study using a CPK molecular model has indicated that the cavity of α-CyD is too small to include **I-3** completely, and two cavities are required to accommodate **I-3** sufficiently. Formation of 2:1 complex was also reported before for the α-CyD-indole system.[15]

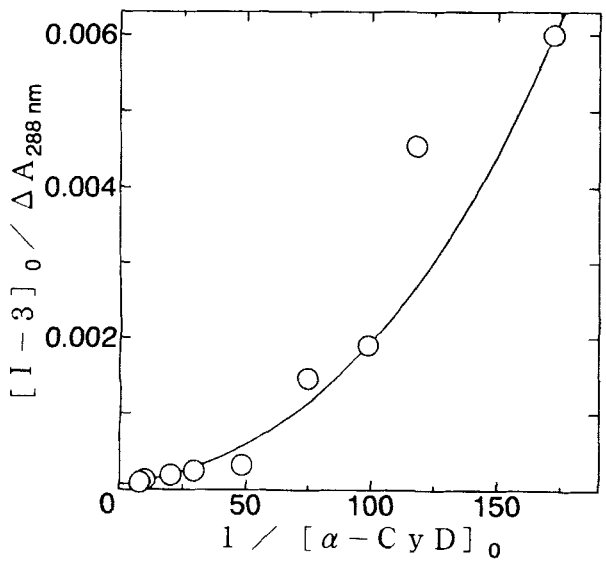

Figure 4 Plot of $[I\text{-}3]_0/\Delta A$ against $1/[\alpha\text{-CyD}]_0$ for the α-CyD-I-3 system at 25°C.

Direct spectroscopic determination of the equilibrium constants for the complexes between **I-1,3** and CyDs has not been successful, since **I-1,3**, obtained by the preparative HPLC, was rapidly converted to **I-3** during the spectroscopic measurements.

Proposed Mechanism for the CyD-Promoted Formation of I-3

The present kinetic results clearly show that the hydroxymethylation of indole by formaldehyde, either in the presence of CyDs or in their absence, proceeds via **I-1** as the intermediate (Figs. 1 and 2). The **I-1** is converted to **I-1,3** by the hydroxymethylation at the C3 position, and then to **I-3** by the removal of the N-hydroxymethyl residue. The first hydroxymethylation at the N-atom increases the electrophilicity of the C3 atom of indole so that the second hydroxymethylation can proceed smoothly.

The proposed reaction scheme is consistent with that for the 2-hydroxymethylation of pyrrole by formaldehyde.[16] There pyrrole is first hydroxymethylated at the N-atom, and then the resultant N-(hydroxymethyl)pyrrole is hydroxymethylated at the C2 atom. 2-(Hydroxymethyl)pyrrole is formed by the removal of the hydroxymethyl residue from the N-atom of the 1,2-bis (hydroxymethyl)-pyrrole.

The promotion by CyDs for the formation of **I-3**, with respect to **I-1** and **I-1,3**, is ascribed to the shift of the equilibrium between **I-1,3** and **I-3** towards **I-3** (Table 1). As schematically depicted in Fig. 5, **I-3** is included in the cavities of CyDs more favorably than **I-1,3**, since **I-1,3** is more polar due to the additional hydroxymethyl residue (the apolar cavities of CyDs favor the inclusion of more apolar guest compound).[1] Assumedly **I-3** penetrates into the cavity deeply enough for the hydroxymethyl residue to form a hydrogen bond with the alkox-

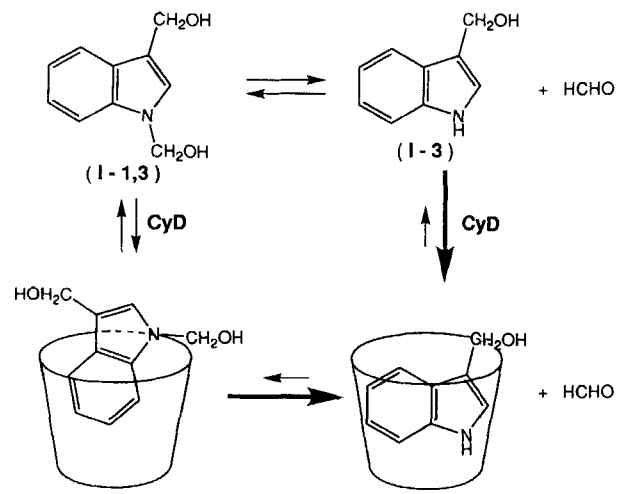

Figure 5 Proposed scheme for the CyD-promoted formation of I-3 from indole and formaldehyde.

ide ion of CyD. Thus the selective catalysis of CyD is remarkable at higher pH (Fig. 3). Note that the pK_a of the secondary hydroxyl residues of CyDs is around 12. In addition, **I-1,3** is too bulky to be efficiently accommodated in the cavities of CyDs (especially of α- and β-CyDs). The selective binding of **I-3** by CyDs results in the shift of the equilibrium towards the desired direction.

Rather hydrophilic character of the hydroxymethyl residue is supported by the fact that the CyD complexes of **I-3** are less stable than those of indole. The K_d for the G_1-β-CyD-**I-3** complex (2.2×10^{-2} *M*) is larger than the value for the β-CyD-indole complex (3.4×10^{-3} *M*).[17] Similarly, K_2 value for the 2:1 α-CyD-**I-3** complex (5.5×10^{-2} *M*) is larger than the value for the 2:1 α-CyD-indole complex (4.8×10^{-3} *M*).[14]

The time-course for the accumulation of **I-1** in the presence of α-CyD (the open circles in Fig. 1 (b)) is similar to that in its absence (the open circles in (a)). Thus the possibility that the selective formation of **I-3** by CyDs is associated with the modulation either in the step from indole to **I-1** or in the step from **I-1** to **I-1,3** is unlikely.

CONCLUSION

3-(Hydroxymethyl)indole is selectively synthesized from indole and formaldehyde by use of CyDs. The catalysis takes advantage of preferential complex formation of CyDs with the target compound over the intermediates (1-(hydroxymethyl)indole and 1,3-bis(hydroxymethyl)indole). As a result, the equilibrium between them is shifted towards the desired direction. This finding should open a new way to selective organic synthesis by CyDs.

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