Regulations for the Product Distribution of the Oxidative Coupling of *p*-Cresol by Cyclodextrins

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The oxidative coupling of *p*-cresol in the aqueous solution was carried out in the presence of cyclodextrins. The production of the dimeric compound was preferentially prevented by α-cyclodextrin, while the trimerization was efficiently inhibited by γ-cyclodextrin. The different effects of these two cyclodextrins were explained by their different inclusion complex forming ability which depended on their cavity size.

When *p*-cresol (**1**) is added to the aqueous solution of $FeCl_3$, it coordinates to Fe^{3+} ion and oxidized into the radical form. Oligomers of **1** are thus produced by the coupling of the radicals. Major products of the oxidative coupling reaction were the *ortho-ortho* dimer (**2**), *ortho-para* dimer (Pummerer's ketone) (**3**), and *ortho-ortho* trimer (**4**).[1]

Cyclodextrin (CD) is a cyclic oligomer composed of α-(1,4)-linkages of six or more glucose unit members.[2,3] It has a hydrophobic cavity in which a variety of molecules can be included. In some reaction systems, production of by-products could thus be efficiently inhibited by CD.[4] The internal diameter of the cavity of the α- and γ-CD is 5.7 and 9.5 Å, respectively. Because of the large difference in the cavity size, each CD is expected to recognize the size of the guest molecules for the inclusion complex formation.

In the present study, the oxidative coupling was carried out in the presence of α- and γ-CD. The oxidation system was shown to be differently regulated by the α- and γ-CD, because of the distinct inclusion complex forming abilities which depended on their cavity size.

An aqueous solution of *p*-cresol (5.0×10^{-2} M (1 M = 1 mol dm^{-3})) was prepared, equimolar α- or γ-CD to **1** was then added to the solution, and it was stirred for 30 min at 25 °C. White precipitates were slightly produced. A prescribed amount of $FeCl_3$ was added to the solution which was then stirred for 24 h at 25 °C.

When the oxidation was carried out in the absence of CD, oil droplets were precipitated, since the oxidized products are not soluble in water unless they coordinate to an iron ion.[5] On the other hand, no oil droplet was observed in the presence of CD, while a large amount of white precipitate, i.e., the adducts of the products with CD was produced as the reaction proceeded. Neither **2** precipitated as oil droplets nor the adducts with CD was exposed to further oxidation, since the oxidizing agent, the Fe^{3+} ion, remained exclusively in the aqueous phase.

Products obtained by the oxidation[6] were determined by HPLC analyses according to our previous method.[5] As shown in Table 1, the α- and γ-CD exhibited different influences on the product distributions. The dimer production was preferentially prevented by α-CD, while the trimer production was drastically inhibited by γ-CD. In order to explain the reasons for the different influences of the α- and γ-CDs on the product distributions, changes in the contents of **1** and **2** in the aqueous phase and in the precipitates during the reaction were determined.[7]

Figure 1 showed that **1** was scarcely extracted into the oil droplet phase in the absence of CD. Most of **1** was thus involved in the aqueous oxidation system. On the other hand, nearly a half and a third of **1** were respectively precipitated as the adducts with α- and γ-CD during the reaction. Production of the dimeric compound **2** was thus efficiently controlled and most of **2** is thought to exist in the aqueous phase unless it not included by the CD.

Table 1. Influence of cyclodextrins on the product distribution of the oxidative coupling reaction

Reaction conditions		Conversion / %	Yields / %	
$[FeCl_3]$ / [**1**]	Cyclodextrin		**2**	**4**
1.0	——	32.5	12.9	14.0
	α-CD	17.1	4.3	7.8
	γ-CD	12.7	9.4	1.7
2.0	——	34.6	15.1	18.7
	α-CD	21.1	4.8	9.4
	γ-CD	19.4	14.7	2.9
5.0	——	48.0	16.2	24.8
	α-CD	25.6	5.6	14.8
	γ-CD	23.9	16.5	4.6
10.0	——	61.8	25.1	29.1
	α-CD	25.9	4.0	14.5
	γ-CD	25.9	16.3	3.6

As shown in Figure 2, when α-CD was added, **2** mostly existed in the aqueous phase during the reaction, indicating the inclusion complex of α-CD with **2** could not be readily formed. The cavity of α-CD would be too small to form a stable inclusion complex with **2**. Most of **2** produced in the reaction system was thus susceptible to be further oxidized and converted into the trimeric compound. The yield of **2** was thus remarkably decreased.

On the other hand, **2** could scarcely exist in the aqueous oxidation system in the case when γ-CD was added. The adducts of γ-CD with **2** was readily formed and precipitated. The production of the trimer compound was thus efficiently inhibited and the selectivity of the dimer production was increased.

Because of the commercial usefulness of the *ortho-ortho* direct linked *p*-cresol oligomer,[8-10] the development of the simple regulation[5,11] for the product distribution of the oxidative coupling has been required. The addition of CD is one of the simplest methods for the regulation of the oxidative coupling. After the oxidation has been carried out, CD was scarcely decomposed. Since Fe^{2+} and Fe^{3+} ions could be removed from the aqueous solution by ion-exchange separation, CD used for the reaction could be easily recycled.

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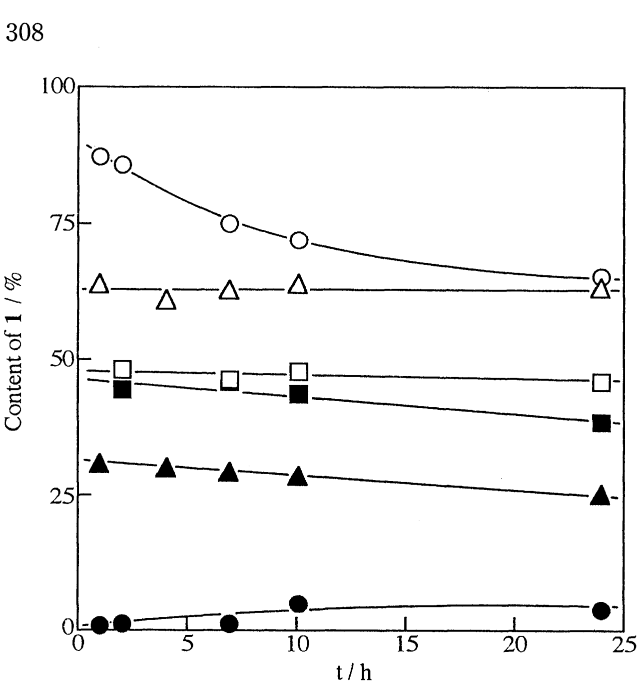

Figure 1. Distribution of the *p*-cresol (**1**) in the aqueous phase and in the precipitates or oil droplets. Concentrations of *p*-cresol and $FeCl_3$ used for the reaction were 5.0×10^{-2} M. Content of **1** existing in the aqueous phase (-○-), in the oil droplets (-●-) in the absence of CD, in the aqueous phase (-□-), in the precipitates (-■-) in the presence of α-CD, in the aqueous phase (-△-), in the precipitates (-▲-) in the presence of γ-CD.

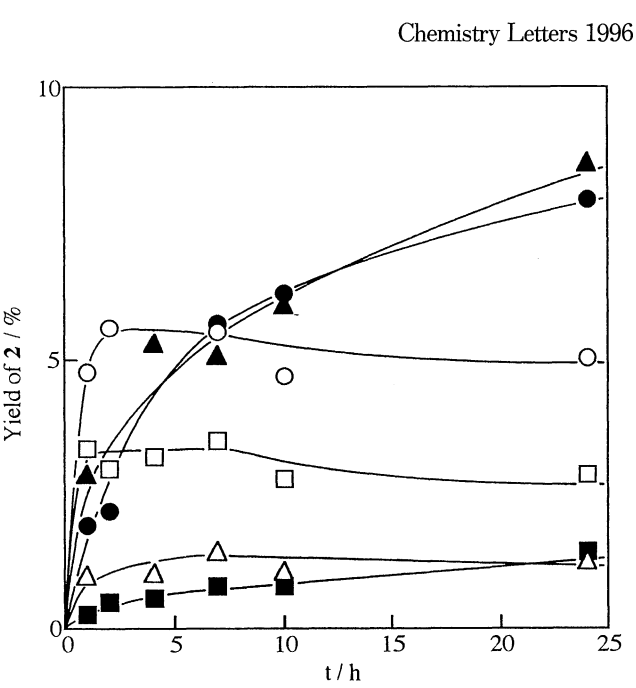

Figure 2. Distribution of the *o*-*o* dimer (**2**) in the aqueous phase and in the precipitates or oil droplets. Concentrations of *p*-cresol and $FeCl_3$ used for the reaction were 5.0×10^{-2} M. Yield of **2** existing in the aqueous phase (-○-), in the oil droplets (-●-) in the absence of CD, in the aqueous phase (-□-), in the precipitates (-■-) in the presence of α-CD, in the aqueous phase (-△-), in the precipitates (-▲-) in the presence of γ-CD.

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6 After a 24 h oxidation, diethyl ether was added to the reaction mixture. The white precipitates, adducts of the products with the CD, was then decomposed and the products were extracted by ether. The extracts were dried by sodium sulfate, and then ether was evaporated to give the products.

7 Equimolar CD and $FeCl_3$ to **1** were added to the aqueous solution of **1** (5.0×10^{-2} M). The precipitates thus produced was filtered off after a prescribed time had passed, and the filtrate was extracted using diethyl ether. On the other hand, the precipitates thus filtered off were suspended in water and extracted with ether until the adducts had completely disappeared. After removing the ether, an HPLC analysis was carried out.

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