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Specific Catalysis by α-Cyclodextrin on the Dichlorocarbene Attack at Phenolate

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A selective attack of dichlorocarbene at the para-position of phenolate has been achieved by using α-cyclodextrin and the reaction mechanism has been studied by the ^{13}C-NMR and ^{1}H-NMR spectroscopy. The attack of the carbene at the para-position of phenolate (82%) is dominant over the attack at the ortho-position (18%) in the presence of 0.15 mol dm^{-3} of α-cyclodextrin, which is in contrast with the predominance of the ortho-attack (59%) over the para-attack (41%) in the absence of α-cyclodextrin.

Specificity is one of the important characteristics of the cyclodextrin catalyses.[1] This specificity has been attributed to the complex formation of the substrate with cyclodextrin prior to the chemical transformation. However, detailed analysis on the origin of the specificity has been scant, mainly because of poor information on the structures of the inclusion complexes of cyclodextrin in solution.

In previous papers, the time-averaged conformations of the inclusion complexes were determined by use of the ^{1}H-NMR[2,3] and ^{13}C-NMR[4] spectroscopy. Furthermore, a much larger magnitude of the catalysis of α-cyclodextrin in the cleavage of *m*-nitrophenyl acetate than that in the cleavage of *p*-nitrophenyl acetate was satisfactorily interpreted in terms of the structures of the inclusion complexes of the substrates and α-cyclodextrin.[5]

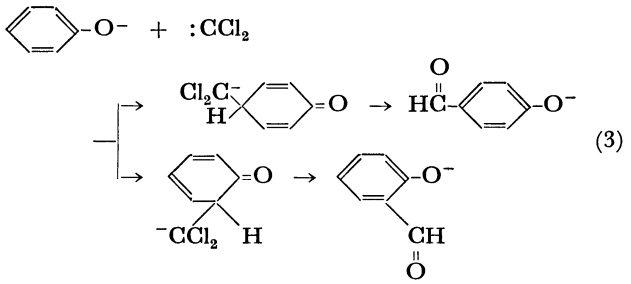
In the present paper, the α-cyclodextrin-catalyzed para-selective attack of dichlorocarbene at phenolate is shown. Furthermore, the origin of the selectivity is clarified by using the time-averaged structure of the α-cyclodextrin-phenolate complex, determined by the ^{13}C-NMR and ^{1}H-NMR spectroscopy.

Experimental

Determination of the Para-Ortho Selectivity in the Dichlorocarbene Attack at Phonolate. Dichlorocarbene, prepared *in situ* from chloroform and sodium hydroxide, was allowed to react with phenolate as shown in Eqs. 1—3 (Reimer-Tiemann reaction).[6] The reactions were carried out in 0.2 mol dm^{-3} NaOH solution at 30 °C, and the initial concentrations of phenolate, chloroform, and α-cyclodextrin, respectively, were in the regions of 5×10^{-3}—2×10^{-2}, 1×10^{-2}—4×10^{-2}, and 0—1.5×10^{-1} mol dm^{-3}. The rate and the selectivity in the attack at phenolate were determined by the absorption spectroscopy on the hydrolysis products, hydroxybenzaldehydes, of the adducts of dichlorocarbene with phenolate.[7] The concentrations of *p*- and *o*-hydroxybenzaldehydes were determined by using the absorptions at 330 and 378 nm, respectively.

$$CHCl_3 + OH^- \rightleftharpoons CCl_3^- + H_2O \quad (1)$$

$$CCl_3^- \longrightarrow :CCl_2 + Cl^- \quad (2)$$



(3)

Determination of the Time-averaged Position of Phenolate in the Cavity of α-Cyclodextrin. The time-averaged position of phenolate was determined by use of the position of each of the carbon atoms of phenolate in the cavity of α-cyclodextrin, estimated by the ^{13}C-NMR spectrsocopy. The depths of the penetration of the carbon atoms of phenolate were estimated from the observed ^{13}C-NMR chemical shift changes by using the relationship between the depth of the penetration and the ^{13}C-NMR chemical shift changes reported in the previous paper.[5] As shown previously,[5] the change of the ^{13}C-NMR chemical shift of the aromatic carbon atom of the guest compound on the complex formation with α-cyclodextrin is governed by the depth of the penetration of the carbon atom in the cavity, irrespective of the substituents of the benzene moieties of the guest compounds.

The ^{13}C-NMR spectrometry was run in 0.2 mol dm^{-3} NaOD solution on a JEOL PFT-100 spectrometer operating at 25.03 MHz, connected with JEOL EC-100 computer. The ^{13}C-NMR chemical shifts were determined by use of sodium formate as the internal standard. The ^{1}H-NMR spectra were taken on a JEOL PS-100 spectrometer in 0.2 mol dm^{-3} NaOD solution. The signal of HOD was used as the internal reference.

TABLE 1. THE PARA : ORTHO SELECTIVITY IN THE DICHLOROCARBENE ATTACK AT PHENOLATE IN THE PRESENCE OF α-CYCLODEXTRIN[a,b]

[α-Cyclodextrin]$_0$ / 10^{-1} mol dm^{-3}	Conversion of phenolate / %	Products	
		Para : Ortho molar ratio	Para selectivity/%
0	12	0.71	41
0.071	9.7	0.77	44
0.15	8.1	0.85	46
0.25	6.0	0.99	50
0.35	4.3	1.11	53
0.60	2.3	1.71	63
1.0	1.5	3.55	78
1.5	0.95	4.65	82

a) In 0.2 mol dm^{-3} NaOH solution; [phenolate]$_0=10^{-2}$ and [chloroform]$_0=3\times10^{-2}$ mol dm^{-3}; the reaction time is two days. b) The subscript 0 refers to the initial concentration.

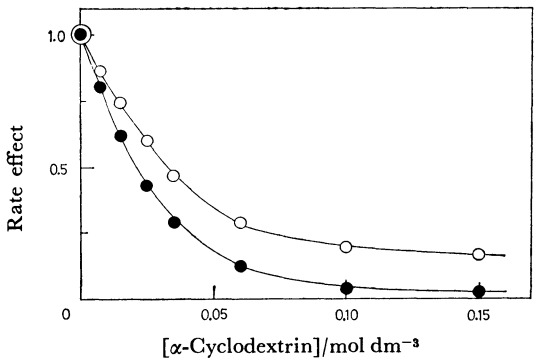


Fig. 1. Effects of α-cyclodextrin on the rates of the para-attack (○) and the ortho-attack (●) of dichlorocarbene at phenolate; the rates of the para-attack and the ortho-attack in the absence of α-cyclodextrin are taken as unity.

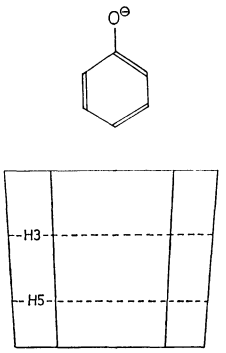


Fig. 2. Time-averaged conformation of the α-cyclodextrin–phenolate complex; ---H3--- and ---H5--- show the planes comprised of the corresponding six atoms of α-cyclodextrin.

Results

Effect of α-Cyclodextrin on the Orientation of the Dichlorocarbene Attack at Phenolate. Table 1 shows the dependence of the para-ortho ratio in the dichlorocarbene attack at phenolate on the concentration of α-cyclodextrin. In the absence of α-cyclodextrin, the attack at the ortho-carbon atom (59%) was dominant over the attack at the para-carbon atom (41%). However, α-cyclodextrin changed the specificity of this reaction from the ortho-selectivity to the para-selectivity. The ratio of the para-attack to the ortho-attack increased with the increase of the concentration of α-cyclodextrin. At the concentration of 0.15 mol dm^{-3}, the ratio was 4.65, which corresponded to 82% para-selectivity.

The variations of the initial concentrations of phenolate and chloroform in the regions of 5×10^{-3}—2×10^{-2} and 1×10^{-2}—4×10^{-2} mol dm^{-3}, respectively, showed little effect on the para-ortho ratio at a fixed initial concentration of α-cyclodextrin.

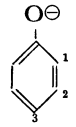
The para-selectivity in the presence of α-cyclodextrin came from the larger magnitude of the suppression of the ortho-attack by α-cyclodextrin than that of the para-attack as shown in Fig. 1. For example, 0.15 mol dm^{-3} of α-cyclodextrin decreased the rate of the ortho-attack and that of the para-attack, respectively, by 41 and 6.3 fold with respect to the rates in the absence of α-cyclodextrin, which resulted in the para-ortho ratio of 4.65. The ratio in the absence of α-cyclodextrin was 0.71.

No reaction product between α-cyclodextrin and dichlorocarbene was detected in the present reactions. Thus, the reaction mixture with the initial concentrations of phenolate, chloroform, and α-cyclodextrin, respectively, of 10^{-2}, 4×10^{-2}, and 5×10^{-2} mol dm^{-3} was acidified with hydrochloric acid after 2 d at 30 °C, and was then vigorously extracted with chloroform. The ^{1}H-NMR and IR spectroscopy on the white powder, obtained after the evaporation of the aqueous layer, showed that all α-cyclodextrin remained intact during the reaction.

Time-averaged Position of Phenolate in the Cavity of α-Cyclodextrin. Figure 2 depicts the time-averaged position of phenolate in the cavity of α-cyclodextrin determined by the ^{13}C-NMR spectroscopy. The depths of the penetration of the carbon atoms of phenolate in the cavity, determined from the changes of the ^{13}C-NMR chemical shifts on the complex formation (see Experimental Section) and listed in Table 2, were used here. The agreements between the observed changes of the ^{13}C-NMR chemical shifts and the calculated ones are fair as shown in Table 2.

Table 2. Observed and calculated values of the ^{13}C-NMR chemical shift changes of phenolate on the complex formation with α-cyclodextrin, and the depths of the penetration of the carbon atoms in the cavity

Carbon atoms[a]	^{13}C-NMR chemical shift change/ppm[b]		Depth of the penetration/Å[c]
	Obsd	Calcd	
1	+0.33	—[d]	−3.7
2	+0.54	+0.55	−2.3
3	+0.12	+0.07	−1.6

a) The numbering system is as follows; 

b) The positive sign shows the increase of the shielding. c) The depth from the plane comprised of the six H-3 atoms (see Fig. 2) of α-cyclodextrin. The negative sign refers to the region in the side of the secondary hydroxyl groups. d) The position of the carbon atom was so far away from the region examined previously (Ref. 4) that the calculation was not made.

In the time-averaged conformation of Fig. 2, phenolate penetrates in the cavity with the hydrogen atom on the para-carbon atom as a head from the secondary hydroxyl side of α-cyclodextrin.

The validity of this conformation of the complex was further supported by the ^{1}H-NMR spectroscopy. In this conformation, the anisotropic shielding effects of the aromatic ring of phenolate on the H-3 and H-5 atoms of α-cyclodextrin (see Fig. 2), estimated by using the table of Johnson and Bovey[8] as described previously,[2] are −0.07 and −0.07 ppm, respectively.

Table 3. Effect of chloroform on the ^{13}C-NMR chemical shift changes due to the complex formation of α-cyclodextrin with phenolate

System[a]	Changes of ^{13}C-NMR chemical shifts of phenolate/ppm[b]		
	C-1	C-2	C-3
α-Cyclodextrin(10^{-1}) -phenolate(3×10^{-2})	+0.28	+0.43	+0.10
α-Cyclodextrin(10^{-1}) -phenolate(3×10^{-2}) -chloroform(3×10^{-2})	+0.02	+0.02	0.00

a) The numbers in parentheses are the concentrations in mol dm^{-3} unit in 0.2 mol dm^{-3} NaOD solution. b) The numbering system of the carbon atoms is shown in the footnote a) of Table 2. The positive sign shows the increase of the shielding.

Here the negative sign refers to the decrease of the shielding. These values show fair agreements with the corresponding observed changes of the ^{1}H-chemical shifts (−0.07 and −0.08 ppm, respectively, for the H-3 and H-5 atoms).

Effect of Chloroform on the Complex Formation between α-Cyclodextrin and Phenolate. The changes of the ^{13}C-NMR chemical shifts of phenolate on the complex formation with α-cyclodextrin were highly suppressed by the addition of chloroform (Table 3). The changes of the chemical shifts of all the carbon atoms of phenolate were virtually none in the presence of 3×10^{-2} mol dm^{-3} of chloroform. This result indicates that the complex formation between chloroform and α-cyclodextrin takes place competitively with that between phenolate and α-cyclodextrin. Almost all of phenolate are free from the complex formation with α-cyclodextrin in the reaction mixtures used in the present study.

Discussion

The reaction between dichlorocarbene and phenolate in the presence of α-cyclodextrin proceeds as the one between the carbene complexed with α-cyclodextrin and free phenolate. The complex formation of chloroform with α-cyclodextrin almost completely inhibits the complex formation of phenolate with α-cyclodextrin in the reaction mixture as shown in Table 3. Chloroform, complexed with α-cyclodextrin, is converted to dichlorocarbene according to Eqs. 1 and 2. Alternative pathway of the formation of the complex between α-cyclodextrin and the carbene, where the carbene is formed in solution followed by complexation with α-cyclodextrin, is unlikely, since the carbene in solution is so unstable that its life-time is short.

Figure 3 schematically depicts the mechanism of the para-selectivity of the catalysis by α-cyclodextrin in the dichlorocarbene attack at phenolate. Toward the carbene, formed inside the cavity of α-cyclodextrin, phenolate can approach in two ways such as A and B, which should predominantly result in the para-attack and the ortho-attack, respectively, because of a sterical reason. The para-selectivity observed in

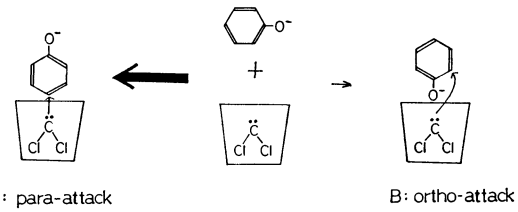


Fig. 3. Proposed mechanism of the α-cyclodextrin-catalyzed selective para attack of dichlorocarbene at phenolate.

the present study is attributable to the predominant occurrence of the approach of the phenolate in the type A, which is due to the fact that the penetration of the hydrogen atom on the para-carbon atom of the phenolate in the cavity as a head is more favorable than the penetration of the phenoxide oxygen atom as a head. The approach in the type A should be easier than that in the type B, since the penetration of the apolar aromatic moiety of phenolate in the apolar cavity of α-cyclodextrin is more stable than the penetration of the polar phenoxide oxygen atom in the apolar cavity.

The above argument is definitely supported by the time-averaged conformation of the α-cyclodextrin–phenolate inclusion complex shown in Fig. 2. Penetration of phenolate in the cavity with the side of the para-carbon as a head in the complex strongly indicates the predominant formation of the transition state involving the penetration of the para-carbon of phenolate in the cavity (type A).

The mechanism involving the dichlorocarbene formed inside the cavity is consistent with the suppression of the rates of the reactions between phenolate and dichlorocarbene by α-cyclodextrin (Fig. 1). Since the carbene is formed *via* anion of chloroform as shown in Eq. 1, the negative charges of the secondary hydroxyl groups electrostatically prevent the formation of the carbene. The secondary hydroxyl groups of α-cyclodextrin exist mostly in the anionic forms in the reaction mixture, since their pK_a is around 12.[1] Steric hindrance by α-cyclodextrin should also reduce the reactivity of the carbene. The suppression of the reaction by α-cyclodextrin also indicates that the formation of dichlorocarbene by the reaction of chloroform with the alkoxide ion of α-cyclodextrin (in place of hydroxide ion in Eq. 1) is less important.

The para-selectivity in the present reaction is consistent with those in the β-cyclodextrin-catalyzed Reimer-Tiemann reaction of phenolate[9] and the α-cyclodextrin-catalyzed chlorination of anisole.[10]

In conclusion, a selective attack of dichlorocarbene at the para-position of phenolate was achieved by using α-cyclodextrin. α-Cyclodextrin regulated the orientation of phenolate with respect to the carbene on the mutual access, resulting in the specific catalysis.

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