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β-Cyclodextrin-Epichlorohydrin Copolymers as Efficient Catalysts in Phase-Transfer-Catalyzed Nucleophilic Substitution Reactions[1)]†

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Copolymers of β-cyclodextrin (β-CD) with epichlorohydrin showed much higher phase-transfer catalytic activity than β-CD in liquid-liquid two-phase nucleophilic displacement reactions. The enhanced efficiency of the polymer catalysts was attributed to the cooperative effect of more than one β-CD group in polymers in bringing a substrate from an organic phase to an aqueous phase.

Phase-transfer-catalyzed nucleophilic substitution reactions in liquid-liquid two-phase systems are usually carried out by using catalysts such as crown ethers and tetraalkylammonium halides which bring nucleophiles from an aqueous phase to an organic phase.[2)] Several reports have appeared recently on "inverse" or "counter" phase-transfer reactions in which organic molecules were brought into an aqueous phase from an organic phase.[1,3)] Although the use of phase-transfer agents such as β-cyclodextrin (cycloheptaamylose, β-CD) is very attractive in inverse phase-transfer reaction systems because of the wide applicability, β-CD showed low catalytic efficiency for nucleophilic substitution reactions in such a system.[1,3a)] We report here that copolymers (1) of β-CD with epichlorohydrin (EP) and methylated copolymers (2) showed much higher catalytic activities than β-CD for these reactions.

The copolymers 1a-d in Table 1 were prepared according to the reported method.[4)] The molar ratio between EP and β-CD in feed was varied from 3 to 10. Methylated copolymers 2a and 2b were prepared from 1b according to the procedure reported.[5)] The catalytic activities of β-CD, 1, and 2 were studied in reaction (1) in liquid-liquid two-phase systems. An organic phase of 10 mmol of a substrate and 15 ml of an aqueous phase containing a nucleophile at a concentration of 4.0 mol dm^{-3} with a catalyst were stirred mechanically at 1200 rpm at 90 °C. While the copolymers 1a-c were soluble in the aqueous phase, 1d was insoluble in the two-phase system, probably due to the high cross-linking density. Pseudo-first-order rate constants were obtained by following the reaction by HPLC and GC. Yields of 65-90% were obtained in reactions between octyl bromide and sodium azide, sodium thiocyanate, sodium iodide, and sodium cyanide in 5 h in the presence of 0.5 mmol of β-CD. When the reaction of octyl bromide with aqueous sodium iodide was repeated three times in the presence of 1.0 mmol of β-CD, by replacing the organic phase with fresh substrate and adding iodide ion after each reaction cycle, yields of

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†This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

Table 1. Rate constants of phase-transfer-catalyzed reactions between alkyl bromide and aqueous sodium iodide at 90 °C

No.	Catalyst: EP/β-CD ratio in feed	Catalyst: Amount/ mmol (mg)	Pseudo-first-order rate constant, $k^{a)} \times 10^6$ /s^{-1} — Substrate: $n\text{-}C_8H_{17}Br$	$n\text{-}C_{12}H_{25}Br$	$n\text{-}C_{18}H_{37}Br$
β-CD	-	0.2 (227)	33.5	0.56	0.09
1a	$3(3\times10^4)^{b)}$	$0.2^{c)}$ (246)	$56.4^{d)}$	4.25	2.34
1b	$5(1.5\times10^4)^{b)}$	$0.2^{c)}$ (245)	63.5	4.96	2.69
1c	$7(3.5\times10^4)^{b)}$	$0.2^{c)}$ (243)	$80.8^{d)}$	8.28	6.03
1d	10	$0.2^{c)}$ (276)	$49.2^{d)}$	-	-
$2a^{e,f)}$	5	$0.1^{c)}$ (142)	59.6	$28.3^{g)}$	7.21
$2b^{e,h)}$	5	$0.06^{c)}$ (100)	13.4	-	-
TBAI	-	0.1	98.1	30.0	15.9
None	-	-	4.9	0.35	0.18
$Ethanol^{i)}$	-	-	$9.2^{j)}$	$9.7^{j)}$	$11.2^{j)}$

a) $k_{observed}-k_{uncatalyzed}$. b) Molecular weight measured by a membrane osmometer using N,N-dimethylacetamide as a solvent. c) Based on the β-CD content of copolymers calculated from carbon analysis, assuming the structure $\{\beta\text{-CD}\}_m\{CH_2CH(OH)CH_2\}_n$.[4,6] d) Interpolated. e) Prepared from a different batch of 1b that was used in rate measurement. f) Degree of methylation: 22%.[5] g) Amount of 2a: 0.12 mmol. h) Degree of methylation: 92%.[5] i) Homogeneous reaction at 60 °C. [RBr]=[NaI]= 0.167 mol dm^{-3}. j) Second-order rate constant, $k \times 10^4$ dm^3 mol^{-1} s^{-1}.

$RBr + NaX \longrightarrow RX + NaBr$ (1) R: $n\text{-}C_8H_{17}$, $n\text{-}C_{12}H_{25}$, $n\text{-}C_{18}H_{37}$; X: I, Cl, CN, N_3, SCN

86-90% were observed in all cases.

Either amylose or a homopolymer of EP, prepared similarly as 1 without β-CD, did not show significant catalytic activities. The reactivity order of nucleophiles, $N_3^- > I^- > SCN^- > CN^- \gg Cl^-$,[7] was similar to that in homogeneous reactions in methanol, and different from that in two-phase reactions with conventional phase-transfer catalysts.[8] A β-CD catalyzed two-phase reaction of octyl bromide with aqueous sodium hydroxide gave a mixture of 1-octanol (22%) and 1-octene (78%) with no dioctyl ether produced.[9] These facts indicate that the two-phase reaction in the presence of β-CD proceeded via an inclusion complex of β-CD which brings a substrate molecule from the organic phase to the aqueous phase.

As shown in Table 1, β-CD was less efficient than tetrabutylammonium iodide (TBAI), one of the efficient phase-transfer catalysts, by a factor of 6 for octyl bromide and by a factor of 300 for octadecyl bromide. The large difference in reactivity between the two alkyl bromides in the present two-phase system, in spite of their similar reactivities in ethanol, suggests that the reaction rate was strongly affected by the partition of a substrate between the two phases. Harada et al. also reported that the catalytic efficiency of cyclodextrins decreased sharply with the increase in size of the substrate in the oxidation of olefins.[3e]

The reaction was much faster when catalyzed by 1. The copolymer catalysts 1 were 1.5-2.5 times as effective as β-CD for octyl bromide, and 25-60 times as effective as β-CD for octadecyl bromide. The difference in the rate increase brought about by the polymer catalysts, depending on the size of the substrate,

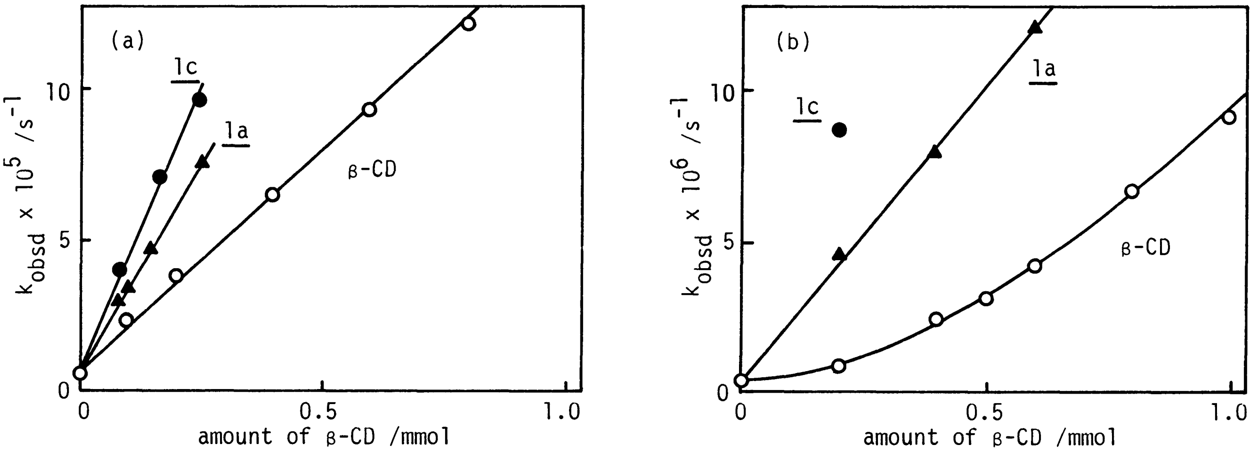

Fig. 1. The dependence of pseudo-first-order rate constants of the reaction between an alkyl bromide and aqueous sodium iodide on the amount of β-CD units. Substrate: (a) octyl bromide, (b) dodecyl bromide. The curve for β-CD in (b) was drawn based on the Eq. $k_{obsd} = 9.02\times10^{-6}[\beta\text{-CD}]^{1.7} + 0.35\times10^{-6}$.

can be explained by the number of β-CD units in the inclusion complex. In the present phase-transfer reactions, rate constants, $k_{catalyzed}$, were linearly dependent on the concentration of β-CD with octyl bromide as a substrate, while 1.7th-order dependency was observed with dodecyl bromide as a substrate, as shown in Fig. 1. The dependency was higher than second order with octadecyl bromide as a substrate.10) The results indicate the contribution of a complex between a large substrate and more than one β-CD molecule to the phase-transfer reaction. It has been reported that alkyl compounds formed coaxially bound complexes with cyclodextrins. Schlenk and Sand showed that the molar ratio between β-CD and a carboxylic acid in a crystalline complex varies from 0.6 to 2.7, depending on the size of the acid from C_6 to C_{18}.11) Large aromatic compounds also form complexes with two cyclodextrin rings.12)

Participation of multiple β-CD units seems to be essential, if large hydrophobic molecules are to be brought into the aqueous phase. However, the formation of a termolecular complex between two β-CD molecules and a substrate is not feasible at low β-CD concentrations. Complex formation of a substrate with more than one β-CD unit can be achieved more easily, if β-CD-containing polymers are used.12) The polymers are expected to hold β-CD rings close to each other. In the case of 1, in contrast to β-CD, the reaction rates were linearly dependent on the concentration of the catalyst regardless of the size of the substrate. This indicates that a polymer catalyst can provide binding sites for large substrates which presumably consist of two or more β-CD rings working cooperatively.

As shown in Table 1, a further increase in catalytic activity was observed with 2a. The catalyst 2a was about 150 times as effective as β-CD for octadecyl bromide. Methylation of cyclodextrin increases the affinity toward large substrates.13) The catalyst 2b showed much lower efficiency, because it was insoluble in the aqueous phase. In the present system, the catalyst or more importantly the catalyst-substrate complex must be water-soluble to effect the phase-transfer reactions.

Polymer-supported phase-transfer catalysts have been attracting considerable attentions, because they offer easy separation of catalysts from the products. However, they did not show higher catalytic activity than low molecular weight catalysts with few exceptions.[14)] In the present case, the polymer catalysts showed much higher efficiency than β-CD, due to the cooperative effect of more than one β-CD group in the polymer catalysts. The results suggest the practical utility of cyclodextrin-containing polymers as catalysts in inverse phase-transfer reactions. Further study is in progress on phase-transfer catalysts based on cyclodextrins.

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