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Note

Enantioselective reduction of ketones in inclusion complexes with cyclomaltoheptaose in the solid state: acceleration of the reaction by ultrasound

FUMIO TODA* AND TATSUYA SHIGEMASA
Department of Industrial Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790 (Japan)

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Few enantioselective reductions of ketones in inclusion complexes with cyclomaltoheptaose (β-cyclodextrin, βCD) have been reported. Sakuraba *et al.*[1] noted that treatment of such complexes with $NaBH_4$ in aqueous NaCl at 0° gave optically active alcohols, although the optical purity was not high.

During studies of the Baeyer–Villiger reaction[2], $NaBH_4$ reduction[3], and pinacol rearrangement[4] in the solid state, we found that treatment of βCD–ketone inclusion complexes in the solid state with $NaBH_4$ resulted in enantioselective reduction, although the enantioselectivity was not high. The $(BH_3)_2$–ethylenediamine complex (**1**) also works well as a reducing reagent in the solid state and reactions are accelerated by ultrasound. The ketones studied were $RCOCH_3$ and $RCOCF_3$, where R = phenyl, 1-naphthyl, and 2-naphthyl.

When a mixture of the 1:1 βCD–ketone complex and $NaBH_4$ was kept at room temperature for 6 days, the optically active alcohol was obtained in the yields shown in Table I (entries 1, 3, 5, 6, and 8), although the optical purity was not high. The reduction was accelerated by ultrasound (entries 2 and 4), although the enantioselectivity remained low. The $(BH_3)_2$-ethylenediamine complex (**1**) can be used instead of $NaBH_4$ (entries 7 and 9).

Since it took a long time to extract the product-alcohol from the reaction mixture (see Experimental), the alcohol must remain in the cavity of the βCD so that the reduction also occurs in the cavity, thereby resulting in enantioselectivity. Reduction of the ketone in aqueous βCD with $NaBH_4$ gave the racemic alcohol. It is not clear yet how the reducing agents penetrate into the cavity of βCD. It is possible that the carbonyl group of the ketone is located at the entrance of the cavity, and this point should be clarified by the X-ray crystal structural study of βCD–ketone complexes now in progress.

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*Author for correspondence.

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TABLE I

YIELDS AND OPTICAL PURITY OF THE ALCOHOLS OBTAINED BY THE REDUCTION OF βCD–KETONE COMPLEXES IN THE SOLID STATE

Entry	*R*	*Reagent*	*Conditions*	*Reaction time (days)*	*Product [RCH(OH)CH$_3$(CF$_3$)]*		
					Yield (%)	*Optical purity (% ee)*	*Ref.*
RCOCH$_3$							
1	Phenyl	$NaBH_4$		5	77	7	6
2	Phenyl	$NaBH_4$	+Ultrasound[a]	2	100	3	
3	1-Naphthyl	$NaBH_4$		5	30	4	1
4	1-Naphthyl	$NaBH_4$	+Ultrasound	2	95	7	
5	2-Naphthyl	$NaBH_4$		5	69	3	1
RCOCF$_3$							
6	Phenyl	$NaBH_4$		5	56	11	7
7	Phenyl	**1**[b]	+Ultrasound	7	60	6	
8	1-Naphthyl	$NaBH_4$		5	50	12	1
9	1-Naphthyl	**1**	+Ultrasound	7	11	26	

[a] Ultrasonic irradiation in a cleaning bath which generates ultrasound of 23 kHz. [b] $(BH_3)_2$–ethylenediamine complex.

EXPERIMENTAL

βCD–Ketone complexes. — The complexes were prepared by a modification of the reported procedure[5]. To aqueous 15% βCD was added an equimolar amount of ketone, and the solution was warmed to 70° and then cooled to 0°. The crude 1:1 βCD–ketone complex that precipitated was collected, dried, and washed with benzene to give the pure complex in almost quantitative yield. The complexes did not have sharp melting points.

Reduction with $NaBH_4$ in the solid state. — A mixture of finely powdered βCD–ketone complex and 10 mol of $NaBH_4$ was kept at room temperature for 5 days. The mixture was then treated with dilute HCl, the alcohol was extracted by stirring with ether for 1 h, and the extract was washed with water, dried, and concentrated, to give the alcohol in the yields shown in Table I.

Reduction in the solid state with $NaBH_4$ plus ultrasound. — A mixture of finely powdered βCD–ketone complex and 10 mol of $NaBH_4$ was irradiated with ultrasound for 2 days at room temperature and then treated as above, to give the alcohol in the yields shown in Table I.

Reduction in the solid state using $(BH_3)_2$–ethylenediamine (**1**) *plus ultrasound.* — A mixture of βCD–ketone complex and 1.5 mol of **1** was irradiated with ultrasound for 7 days and then treated as above, to give the alcohol in the yields shown in Table I.

Determination of optical purity of the alcohols. — Optical purities (% ee) were determined by comparing the $[\alpha]_D$ values with those reported[1,6,7].

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