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Stereoselective Reduction with NADH Model BNAH through Chiral Induction in Cyclodextrins

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Stereoselective reductive debromination-cyclopropanation of 2-bromo-1-phenylethylidenemalononitrile and 2-bromo-1-β-naphthylethylidenemalononitrile by coenzyme NADH model BNAH through chiral induction in cyclodextrins is reported. The matching between substrates and cyclodextrins, the substituent effect, and the effect of cyclodextrin concentration on the optical yields have been investigated.

Coenzyme nicotinamide adenine dinucleotide (NADH) plays an important role in biological redox processes through the interconversion between a 1,4-dihydropyridine moiety and a pyridinium ion (*1*). Stereoselective reduction by NADH models has been a focus of interest. Since Ohnishi and Ohno (*2*) reported the first stereoselective reduction by a chiral 1,4-dihydropyridine derivative, numerous publications have appeared on stereospecific reduction using various NADH models (*3,8*).

Cyclodextrins are the most extensively investigated biomimetic models for enzymes. The hydrophobic character of their internal cavity enables cyclodextrins to form inclusion complexes with organic compounds (*4*) and to provide both a chiral receptor and reactive sites (*5*). For this reason, many investigators have used cyclodextrins as nanoreactors to induce regio- and enantioselectivity in a biomimetic system carried out in water (*6*).

1-Benzyl-1,4- dihydronicotinamide (BNAH) is an NADH model frequently employed in mechanistic studies. We have previously reported the reductive debromination-cyclopropanation of 2-bromo-1-phenylethylidenemalononitrile (BPM) and 2-bromo-1-β-naphthylethylidenemalononitrile (β-BNM) with BNAH to give racemic 2-phenyl-1,1-cyclopropanedicarbonitrile (PCN) (*7*) and racemic 2-β-naphthyl-1,1-cyclopropanedicarbonitrile (β-NCN)*(8),* respectively (Fig. 1). In this paper, we report on the stereoselective reduction of BPM andβ-BNM through the chiral induction of α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), γ-cyclodextrin(γ-CD), and hydroxypropyl-β-cyclodextrin (hp-β-CD) in a biomimetic system.

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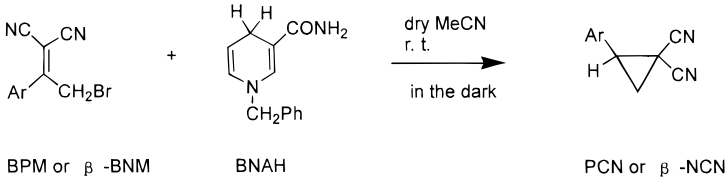

FIG. 1. The reductive debromination-cyclopropanation of BPM and β-BNM with BNAH.

MATERIALS AND METHODS

^{1}H NMR was obtained on a Bruker DMX-500 spectrometer. Mass spectrometry was carried out on a VG-ZAB-HS mass spectrometer (EI). Enantiomeric excesses (e.e.) were derived from the integral ratio of signals obtained on a Waters 600E-2487 HPLC with a Eka Chemicals AB CHI-TBB chiral column. Configuration was determined on a Shanghai Shengguang WZZ-2A auto-polarimeter.

BNAH, BPM, and β-BNM were synthesized according to the literature (*7,8*). α-CD and γ-CD were purchased from Tokyo Kasei Organic Chemicals. β-CD is a commercial product and was recrystallized from water three times. hp-β-CD was purchased from Acros Organics Co.

CD was dissolved in 1000 ml twice-distilled water. BNAH (0.4 mmol) and substrate(BPM or β-BNM) (0.1 mmol) were dissolved in 5.0 ml MeOH, respectively, and the solutions were then added to a 500-ml CD solution, respectively. The suspensions were shaken by ultrasonic vibration and deaerated by bubbling with argon. A solution of substrate was added to a solution of BNAH and the mixture was stirred for 24 h under argon at room temperature in the dark. The resulting mixture was extracted with CH_2Cl_2 (3×300 ml). The combined extracts were washed with water and dried with anhydrous Na_2SO_4. After evaporation of the solvent, the mixture was separated by column chromatography on silica with CH_3CO_2Et/petrol = 1/20 as eluent.

RESULTS AND DISCUSSION

The results of the reduction of BPM and β-BNM by BNAH with the same molar concentration of host molecule α-CD, β-CD, γ-CD, and hp-β-CD are collected in Table 1.

TABLE 1

Effect of the Matching of Host–Guest Molecules and the Effect of Substituents

Entry	A	B	C	D	E	F	G	H
Guest molecule	BPM	BPM	BPM	BPM	β-BNM	β-BNM	β-BNM	β-BNM
Host molecule	α-CD	β-CD	γ-CD	hp-β-CD	α-CD	β-CD	γ-CD	hp-β-CD
Concentration (mmol/L)	1.5279				1.5279			
Chemical yield (%)	15	10	18	14	14	12	7	16
Optical yield (% e.e.)	6.57	2.27	28.96	12.30	0.01	16.98	1.42	26.33
Configuration	*R*(+)	*S*(−)	*S*(−)	*R*(+)	*R*(+)	*R*(+)	*R*(+)	*R*(+)