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Carbohydrate Polymers 47 (2002) 373–376

Carbohydrate Polymers

www.elsevier.com/locate/carbpol

Improved solubility of β-cyclodextrin inclusion complexes by using liquid ammonia as a solvent and the possibility of asymmetric reduction

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Received 14 September 2000; revised 5 February 2001; accepted 16 February 2001

Abstract

Dramatic improvement in the poor solubility of β-cyclodextrin (β-CD) and its inclusion complexes in water was achieved by using liquid ammonia (liq. NH_3) instead of water as the solvent. Asymmetric $NaBH_4$ reduction of the carbonyl groups of the inclusion complexes in liq. NH_3 was examined in a homogeneous condition to give the corresponding alcohols with moderate chirality. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Cyclodextrins; Liquid ammonia; Asymmetric reduction; Inclusion complexes

Cyclodextrins (CDs) are well-known cyclic oligosaccharides composed of several glucose residues linked with *O*-α-D-glucopyranosyl-(1 → 4)-bonds, and they provide a hydrophobic cavity as a functional chiral binding site for hydrophobic guest molecules with the appropriate size for the cavity in aqueous solution (Bender & Komiyama, 1978). Therefore, synthetic approaches to prepare artificial enzymes by means of CDs employed as active sites have been widely investigated (Wenz, 1994; Breslow, 1995). Although β-CD is the most readily available among the CDs and provides an appropriately sized cavity, it shows remarkably poor solubility in water in contrast with other CDs (French, Levine, Pazur & Norberg, 1949). In addition, the inclusion complexes of β-CD with a guest compound are also known to show less solubility in aqueous media. Hitherto, an asymmetric reduction of β-CD inclusion compounds having the carbonyl group employing sodium borohydride ($NaBH_4$) in aqueous suspension has been reported by several groups (Fornasier, Reniero, Scrimin & Tonellato, 1985; Kawajiri & Motohashi, 1989; Sakuraba, Inomata & Tanaka, 1984). Despite the fact that similar conditions were used for the reduction of acetylferrocene, however, the resultant alcohol showed the opposite optical rotations (Fornasier, et al., 1985; Kawajiri & Motohashi, 1989). Since the reaction conditions were heterogeneous due to the low solubility of the β-CD inclusion complex in water, it seems that the asymmetric reduction of the carbonyl group of acetylferrocene did not proceed smoothly and that the yield of the product was therefore poor. In order to enhance the solubility of the inclusion complexes, we have explored possible alternative solvents as completely solvating agents of β-CD inclusion complexes, and we found that liquid ammonia (liq. NH_3) is a promising solvent. In this paper, we describe the asymmetric reduction of carbonyl compounds included by β-CD in the presence of $NaBH_4$ in liq. NH_3.

One:one stoichiometric inclusion complexes of acetophenone **1** and acetylferrocene **2** with β-CD, respectively, were prepared in water by the usual method, as shown in Fig. 1. A keto acid, 3-(*p*-toluoyl)propionic acid (Burcker, 1988), which is a highly hydrophilic compound, showed high solubility in water even in the presence of the same molar amount of β-CD. Hence, a colorless aqueous solution was evaporated to dryness in order to prepare the inclusion complex **3**. The formation of inclusion complexes was confirmed by examination of ^1H NMR spectra of the inclusion complexes. The high magnetic field shifts of H-3 and H-5, respectively, in the β-CD moiety of an inclusion complex from the original chemical shifts of β-CD itself indicated that the guest compound existed near H-3 and H-5 in the hydrophobic cavity of the β-CD moiety. Since the preparation of the inclusion complexes was accomplished, the effectiveness of liq. NH_3 as a solvent to dissolve those inclusion complexes was examined. It was found that the inclusion complexes were quickly dissolved in liq. NH_3, even when the inclusion complex **2** was added to a stirred solution of liq. NH_3. Liq. NH_3 proved to be an effective solvent, showing remarkably

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PII: S0144-8617(01)00189-8

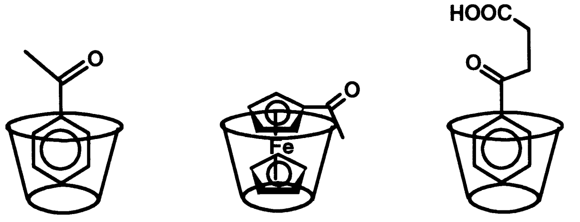


Fig. 1. Structures of guest compounds included by β-cyclodextrin.

improved solubility in comparison with that of water. Thus, liq. NH_3 was used as a solvent for asymmetric reduction of the guest compounds included by β-CD.

$NaBH_4$ reduction of a carbonyl compound in order to obtain the corresponding alcohol is generally carried out in an aqueous or alcoholic condition. In the course of our study, $NaBH_4$ reduction of acetophenone without β-CD in liq. NH_3 was initially attempted, and the reduction proceeded successfully to afford the corresponding alcohol as a racemate. Therefore, we next attempted the reduction of an acetophenone-β-CD complex **1** by means of $NaBH_4$ in liq. NH_3. The reaction was homogeneous and proceeded smoothly to give the corresponding alcohol **4** having $[\alpha]_D^{25} = -0.19°$ (~0% ee) in 66% chemical yield, as shown in Fig. 2. On the other hand, 1-ferrocenylethanol **5** (Gokel, Marquarding & Ugi, 1972) having $[\alpha]_D^{25} = -3.68°$ (12% ee) was isolated from the reaction mixture of the acetylferrocene-β-CD complex **3** with $NaBH_4$ in liq. NH_3 in 74% chemical yield. These results suggest that in the reaction with **1**, the hydride simultaneously attacks the carbonyl carbon from both sides without any influence from the hydrogen bond caused by β-CD, as shown in Fig. 3(A), while in the reaction with **2**, an influence of β-CD through the hydrogen bond between the hydroxy group of the β-CD and the carbonyl oxygen atom of the acetylferrocene was observed (Fig. 3(B)). Consequently, the hydride could attack the carbocation from the opposite side to β-CD to provide an alcohol with an (*R*)-(−) configuration as the sole product. This finding is consistent with the fact that the acetylferrocene molecule is accommodated in the cavity of β-CD by axial orientation (Harada & Takahashi, 1984), and therefore the reduction of the acetylferrocene showed stereochemical results. In addition, the stereoselectivity of the reduction of the acetylferrocene supports the result obtained by Kawajiri and Matsuhashi using aqueous media (Kawajiri & Motohashi, 1989).

As the $NaBH_4$ reduction of carbonyl compounds included by β-CD in liq. NH_3 was successful, we turned our attention toward the reduction of a keto acid, such as 3-(*p*-toluoyl)-propionic acid, in which the carboxylic group is highly hydrophilic. In our previous study, reduction of an α-keto acid, phenyl pyruvic acid, was attempted using the same strategy as that employed for **1** and **2**. Although the reaction proceeded smoothly, isolation of the product from the reaction mixture was unsuccessful due to the high solubility of the alcohol in water. For that reason, a γ-keto acid as the precursor of γ-hydroxy acid, which can be converted into its lactone with less hydrophilicity by a H^+-mediated lactonization, was selected for the application of $NaBH_4$ reduction in liq. NH_3. Thus, the $NaBH_4$ reduction in liq. NH_3 of **3** followed by the lactonization in the presence of HCl gave lactone **6** as the enantiomeric mixture quantitatively in Scheme 1. To determine the enantiomeric excess of the product by optical resolution, further manipulation by using (*S*)-(−)-1-phenylethylamine to **6** was attempted. The amidation gave a diastereomeric mixture **7**, and the enantiomeric excess of the resultant diastereomer was estimated to be 2.6% ee as judged by the area ratio in the HPLC profile as shown in Fig. 4. Therefore, despite the fact that the $NaBH_4$ reduction of 3-(*p*-toluoyl)propionic acid included by β-CD proceeded smoothly in liq. NH_3, the resulting lactone **6**, however, had very limited chirality. Since this stereochemistry was close to that of **1**, we speculate that a hydride attack occurred at the carbocation from both sides.

In conclusion, the use of liq. NH_3 instead of water as a solvent to create a homogeneous solution of β-CD inclusion complexes was found to be efficient and useful. Asymmetric reduction of the carbonyl group of the guest compounds included by β-CD in liq. NH_3 in the presence of $NaBH_4$ proceeded homogeneously to provide the corresponding alcohols with limited chirality.

1. Experimental

1.1. Materials and methods

Unless otherwise stated, all commercially available solvents and reagents were used without further purification. Melting points were measured with a Laboratory Devices MELTEMP II apparatus and were uncorrected. The optical rotations were determined with a JASCO DIP-1000 digital polarimeter. The IR spectra were obtained using a JASCO FT/IR-300E spectrophotometer. The ^1H NMR spectra were recorded at 400 MHz with a Bruker AM-400 spectrometer or at 200 MHz with a Varian Gemini-2000 spectrometer in chloroform-*d* or deuterium oxide. Tetramethylsilane (TMS) or methanol (3.3 ppm) were used as internal standards. Ring-proton assignments in NMR were made on the basis of the

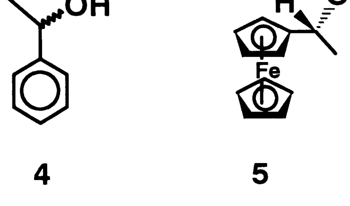


Fig. 2. Structures of isolated alcohols produced by $NaBH_4$ reduction in liq. NH_3.

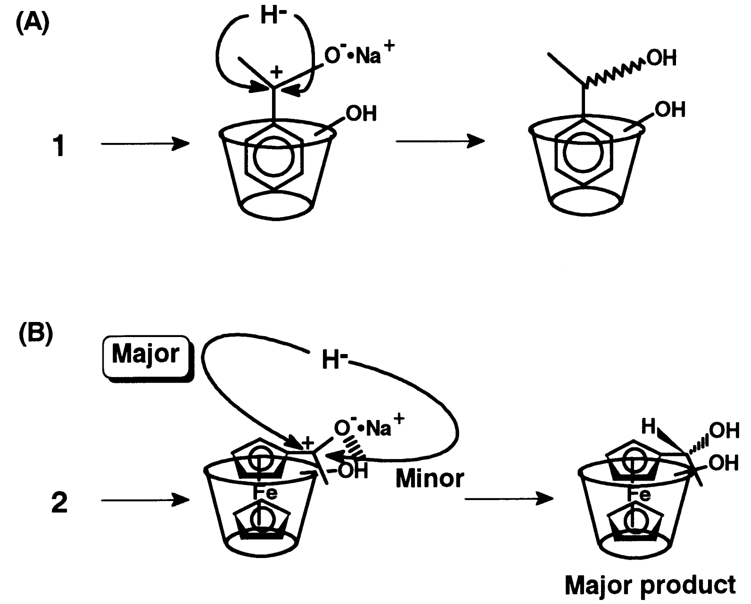


Fig. 3. Proposed mechanism for asymmetric reduction of the carbonyl compound included by β-CD.

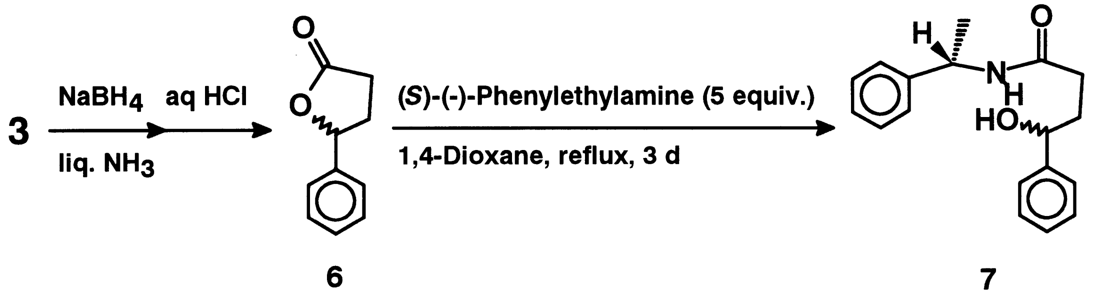
results of first-order analysis of the spectra, and the assignments were supported by the results of homonuclear decoupling experiments. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel $60F_{254}$ (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany). For detection of the intermediates, TLC sheets were sprayed with: (a) a solution of 85:10:5 (v/v/v) methanol-*p*-anisaldehyde-concentrated sulfuric acid and heated for a few minutes (for carbohydrate) or (b) an ethanolic solution of 7% phosphomolybdic acid and heated similarly. Column chromatography was performed on silica gel (Silica Gel 60; 63–200 μm, E. Merck). All extractions were concentrated below 45°C under diminished pressure. HPLC was performed using a Finepak SIL column (0.46 mm × 250 mm, JASCO) at ambient temperature. The column was equilibrated with hexane–ethyl acetate (6:4, v/v) and run at a flow rate of 1.0 ml/min. For the detection of the sample on HPLC, UV 254 nm was used.

1.2. Preparation of inclusion complexes of β-CD with guest molecules

β-CD–acetophenone complex (**1**). To a stirred solution of β-CD (10.15 g, 7.5 mmol) in water (550 ml) was added dropwise acetophenone (901 mg, 7.5 mmol) at rt. After 7 h, the reaction mixture was cooled to 4°C and left for 22 h. Resulting crystals were collected by filtration, washed with diethyl ether, and dried in vacuo to give white powdery **1** (5.84 g, 62%): IR (KBr) 3368 ($\nu_{O\text{-}H}$), 1686 ($\nu_{C=O}$) cm^{-1}.

β-CD–acetylferrocene complex (**2**). To a solution of β-CD (5.00 g, 4.4 mmol) in water (275 ml) was added a solution of acetylferrocene (1.00 g, 4.4 mmol) in diethyl ether (20 ml) at rt with stirring. The resulting mixture was stirred for 6 h at rt and then left for 2 h at 4°C. The orange-colored crystals were filtered off, washed with diethyl ether, and dried in vacuo to afford **2** (5.09 g, 85%): IR (KBr) 3349 (ν_{O-H}), 1673 ($\nu_{C=O}$) cm^{-1}.

β-CD–3-(p-toluoyl)propionic acid complex (**3**). 3-(*p*-Toluoyl)propionic acid (Burcker, 1988) (1.19 g,



Scheme 1.

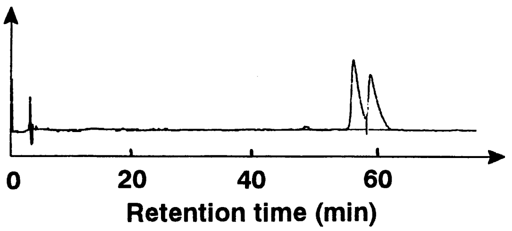


Fig. 4. HPLC profile of **7** as a diastereomeric mixture. **7** was injected into an optical resolution column. Elution conditions are described in the Section 1.

6.16 mmol) was added to a solution of β-CD (7.00 g, 6.16 mmol) in water (1540 ml) with stirring. The solution was further stirred for 18 h at rt, and the resulting mixture was evaporated in vacuo to give **3** (7.36 g, 90%) as white powder: IR (KBr) 3370 ($\nu_{\text{O-H}}$), 1684 ($\nu_{\text{C=O}}$) cm^{-1}, ^{1}H NMR δ (400 MHz, D_2O) 2.44 (s, 3H, Ph-C*H*$_3$), 2.76 (t, 2H, $J = 6.5$ Hz, CH_2), 3.36 (m, 2H, CH_2), 3.59 (t, 7H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.65 (dd, 7H, $J_{1,2} = 3.6$ Hz and $J_{2,3} = 10.0$ Hz, H-2), 3.74 (dt, 7H, H-5), 3.86–3.92 (m, 21H, H-3 and H-6), 5.07 (d, 7H, H-1), 7.41 (d, 2H, $J = 7.9$ Hz, Ph-*H*), 7.93 (d, 2H, $J = 8.2$ Hz, Ph-*H*).

Reduction of acetophenone included by β-CD (**1**). Inclusion complex **1** (3.00 g, 2.39 mmol) was added three-portionwise to liq. NH_3 at ca. −40°C, giving a clear solution. To this solution was added $NaBH_4$ (226 mg, 5.98 mmol), and the solution was stirred for 2 days at ca. −40°C. After evaporation of NH_3, water (30 ml) was added to the resulting mixture, and the solution was then cooled to 0°C. To the cooled solution was added 1 M aq. HCl [6 mL, (1 M = 1 mol dm^{-3})] and then $CHCl_3$ (400 ml), and the mixture was stirred for 18 h. The mixture was filtered, and the insoluble mass was further extracted using chloroform (100 ml and 200 ml) with stirring. The filtrate and extracts were combined, partitioned, dried over anhydrous sodium sulfate, and concentrated to provide **4** as a colorless syrup: $[\alpha]_D^{25} = +0.19°$ (*c* 1.39, $CHCl_3$), IR (neat) 3365 ($\nu_{\text{O-H}}$), 3085, 3061, 3029 ($\nu_{\text{C-H}}$) cm^{-1}.

Reduction of acetylferrocene included by β-CD (**2**). $NaBH_4$ (315 mg, 8.33 mmol) was added to a solution of 2 (0.50 g, 2.20 mmol) in liq. NH_3 (250 ml) at ca. −40°C, and the solution was stirred for 2 days at the same temperature. After removing NH_3, the residue was diluted with water (50 ml), 1 M aq. HCl (8 ml), and $CHCl_3$ (400 ml). The mixture was stirred for 23 h at rt. The mixture was filtered and the filtrate was partitioned. The insoluble mass was further extracted with chloroform (twice) overnight with continuos stirring, then filtered. Both of the $CHCl_3$ solutions were combined, evaporated, and dried in vacuo to give orange-colored **5** (375 mg, 74%): mp 61–68°C; $[\alpha]_D^{27} = -3.68°$ (*c* 2.47, $CHCl_3$), IR (KBr) 3213 ($\nu_{\text{O-H}}$), 3087 ($\nu_{\text{C-H}}$) cm^{-1}.

Reduction of 3-(*p-toluoyl)propionic acid included by β-CD* (**3**). A solution of **3** (3.00 g, 2.26 mmol) and $NaBH_4$ (210 mg, 5.65 mmol) in liq. NH_3 (250 ml) was stirred for 2 days at ca. −40°C. Liq. NH_3 was evaporated, and the residue was treated with 6 M aq. HCl (40 ml) and $CHCl_3$ (400 ml) with stirring for 20 h at rt. The resulting mixture was filtered, and the filtrate was partitioned. The organic layer was washed with water and concentrated to afford **6** as white crystals: mp 70–71°C, $[\alpha]_D^{28} = +1.23°$ (*c* 1.99, $CHCl_3$), IR (KBr) 3040 ($\nu_{\text{O-H}}$), 1766 ($\nu_{\text{C=O}}$) cm^{-1}, ^{1}H NMR δ (200 MHz, $CDCl_3$) 2.21 (m, 2H, CH_2), 2.36 (s, 3H, Ph-C*H$_3$*), 2.65 (m, 2H, CH_2), 5.48 (m, 1H, CH), 7.17–7.24 (m, 4H, 4Ph-*H*).

(S)-1-*Phenylethylamidation of* **6**. A mixture of **6** (100 mg, 0.57 mmol) and (S)-(−)-1-phenylethylamine (345 mg, 2.85 mmol) in 1,4-dioxane (1.0 ml) was stirred at 100°C for 68 h. After evaporation, the residue was diluted with $CHCl_3$. The $CHCl_3$ solution was successively washed with 5% aq. sulfuric acid, saturated sodium hydrogen bicarbonate, and water, then dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel with toluene–ethyl acetate (2:1, v/v) as the eluent to give amide **7** as light-yellow crystals: mp 96–98°C, $[\alpha]_D^{22} = -70°$ (*c* 2.29, $CHCl_3$), IR (KBr) 3558 ($\nu_{\text{O-H}}$), 3306 ($\nu_{\text{N-H}}$), 3064, 3030 ($\nu_{\text{C=H}}$), 1646 ($\nu_{\text{C=O}}$), 1543 ($\delta_{\text{N-H}}$) cm^{-1}, ^{1}H NMR δ (400 MHz, $CDCl_3$) 1.43 (d, 3H, $J = 6.9$ Hz, PhCHC*H$_3$*),1.99 (m, 2H, CH_2), 2.27 (m, 2H, CH_2), 2.32 (s, 3H, Ph-C*H$_3$*), 3.79 (br d, 1H, $J = 10.7$ Hz, OH), 4.65 (m, 1H, CH_2C*H*), 5.07 (m, 1H, MeC*H*), 6.18 (br s, 1H, NH), 7.10–7.33 (m, 9H, 9Ph-*H*).

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