Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **18:** 247–254, 1994.

Catalytic Transfer Hydrogenation of Cyclodextrin Azides and Benzylated Glucose Derivatives *

LÁSZLÓ JICSINSZKY
CYCLOLAB, Cyclodextrin Res. and Dev. Laboratory Ltd., H-1525 Budapest, P.O. Box 435, II Pusztaszeri út 59-61, Hungary

(Received: 2 February 1994; in final form: 30 June 1994)

Abstract. Debenzylation by catalytic transfer hydrogenation (CTH) of various organic compounds is a simple, fast, and safe method. Though CTH is widely used in reductions, only few data are available for the conversion of azides to amines. The number of usable transfer compounds is limited in cases of sugar derivatives, as the most common transfer materials, e.g. hydrazine hydrate or formic acid, can compete in side-reactions. The present study explores the limits of the reaction parameters and transfer compounds.

Key words: Catalytic transfer hydrogenation, reduction, aminocyclodextrin, debenzylation.

1. Introduction

The CTH method is widely used in organic preparations though it is not the favourite method. One reason for the underutilization of this method is its poor reproducibility. Though there are some general rules for choosing the appropriate reactants, the discussion of the reaction mechanism is far from complete. Heterogeneous catalytic reactions are still great challenges for both theoretical and preparative chemists.

Work with gaseous hydrogen always has some complication during the preparation of the reaction mixture, handling of catalyst and hydrogen, sampling, etc. The major difficulties can be avoided using the CTH method but the uncertainties in the implementation of a published description may lead to complete rejection of the method.

The reactions are usually carried out in methanol or aqueous methanol solutions. In absolute solvents the reductions were found to be slow and incomplete, or the scaling-up procedures could not be reproduced. It has been observed that debenzylation of larger quantities can be accelerated by adding a small amount of water to the reaction mixture. Studying the role of water during CTH, a benzylated diaza spirodecane derivative was chosen as the test molecule. Optimization experiments on the determination of the limits of the water content of methanol were also performed.

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* A part of this publication was presented at EUROCARB VII, Cracow, Poland, 22–27 Aug. 1993.
** Dedicated to Professor József Szejtli.

2. Experimental

2.1. Materials and methods

Hydrazine hydrate, ammonium formate, formic acid, methanol, sodium azide, and TLC-sheets (Art. No. 5554) were products of Merck (Darmstadt); Pd/C (10% Pd content), 1-benzyl-4-piperidone, sodium hydride, benzyl bromide, and absolute DMF were products of Janssen Chimica. Other substances were prepared in our laboratory. Melting points were determined with a Büchi OP510 apparatus, and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in D_2O on a Varian VXR-400; IR spectra were recorded in KBr on a Nicolet 205 FTIR; Densitometry: Chromtest OE-504; UV spectra were recorded in H_2O on a HP-8452A spectrometer.

2.1.1. Kinetic Experiments

The starting material (1g) was dissolved or suspended in 9 mL of absolute MeOH under nitrogen at room temperature. The reaction mixture was cooled below -20°C, 0.1 g of suspended catalyst (10% Pd/C) in 1 mL of water was added, and the reaction mixture was heated first to room temperature, when a 5 molar amount of the hydrogen donor (hydrazine hydrate, formic acid, and ammonium formate) was added, heated to reflux, and samples were obtained after 0, 1, 2.5, 5, 10, 15, 20, 25, 30, and 60 min reflux. The reaction was monitored by TLC and UV spectrophotometry; quantitative evaluation was performed by both densitometry and UV. Five parallel runs were averaged.

Pre-treatment of the catalyst: stirring in doubly distilled water at room temperature for 1, 2, 5, 10, 15, 30, and 60 min before use.

2.2.2. Preparative experiments. 8-benzyl-3-ethyl-4-methylidene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane (**1**)

1-Benzyl-4-ethynyl-4-hydroxy-piperidine was prepared from 1-benzyl-4-piperidone with acetylene and potassium *tert.*-butoxide in THF. Recrystallized from benzene. Yield: 93%; Mp.: 98–99.5°C.

1-Benzyl-4-ethynyl-4-hydroxy-piperidine (21.59, 0.1 M) was dissolved in 60 mL of 2-picoline, 29 g (0.3 M) of potassium acetate and 16 mL (14.2 g, 0.2 M) of ethyl isocyanate was added, and the mixture heated to reflux. When the reaction was complete the 2-picoline was removed, the product was dissolved in benzene, filtered through a five-fold excess (by weight) of aluminium oxide, washed with benzene, solvent was removed and the residue was recrystallized from diisopropyl ether. The obtained material was found to be identical with a sample prepared according to [8]. Yield: 27 g (95%); Mp.: 102.5–104°C.

IR (KBr): 1680–1750 cm^{-1} (broad), 1250 cm^{-1} (oxazolidinones).

6-Mono(p-toluenesulfonyl)-α (**2**), *-β-*(**3**), *and -γ-cyclodextrin* (**4**). The material was prepared by a slight modification of the procedure described in [1].

	6-Ts-αCD	6-Ts-βCD	6-Ts-γCD
Yield:	15%	43%	8%
Mp.:	> 198°C [dec.]	> 195°C [dec.]	> 196°C [dec.]

6-Monodeoxy-6-azido-α (**5**), *-β-*(**6**), *and -γ-cyclodextrin* (**7**). The 6-(*p*-toluenesulfonyl) cyclodextrin (0.05 M) was dissolved in a three-fold excess (by weight) of DMF, and 0.55 M of sodium azide was added. The reaction was heated to 100°C, and stirred for 1 h at 100°C. The almost clear solution was treated with acetone at room temperature, when a white crystalline precipitate formed. The crude product was recrystallized from 1 : 10 water–acetone mixture.

	6-N_3-αCD	6-N_3-βCD	6-N_3-γCD
Yield:	98%	99%	98%
Mp.:	> 206°C [dec.]	> 209°C [dec.]	> 202°C [dec.]

6-Monodeoxy-6-amino-α (**8**), *-β-* (**9**), *-γ-cyclodextrin* (**10**). 6-Monodeoxy-6-azido-cyclodextrin (0.005 M) was suspended in 45–60 mL of absolute MeOH under nitrogen, cooled below −20°C, 6 g of Pd/C added in 6 mL of water (suspended in 3 mL of water, and the suspending bottle was washed-in with the remaining 3 mL of water). The reaction mixture was heated to room temperature 1.3 g (0.02 M) of ammonium formate was added, and heated to reflux. After 20 min at reflux temperature, the reaction mixture was cooled to about 50°C, the catalyst was filtered off, and washed twice with 10 mL of water. Solvents were evaporated, and the crude product obtained was dissolved in 15 mL of water (pH > 9.5), acidified with concentrated HCl to pH = 1.5, clarified by charcoal (10 wt.-%) at room temperature for 30 min, filtered, washed twice with 2.5 mL of water, and 80 mL of methanol was added to obtain a crystalline product. Products were free of azide and ammonium formate (IR).

	6-NH_2-αCD·HCl	6-NH_2-βCD·HCl	6-NH_2-γCD·HCl
Yield:	97%	98%	96%
Mp.:	> 209°C [dec.]	> 215°C [dec.]	> 210°C [dec.]

To obtain the free base, 10 g of the hydrochloric salt was dissolved in 25 mL of water, 15 g of DOWEX 2X8 ion-exchanger was added and stirred for 48 h at room temperature. The ion-exchanger was filtered off, washed twice with 25 mL of water, and the solution was concentrated under reduced pressure to about half its volume, and addition of 100 mL of methanol precipitated the products.

	6-NH_2-αCD	6-NH_2-βCD	6-NH_2-γCD
Yield:	95%	96%	94%
Mp.:	> 190°C [dec.]	> 196°C [dec.]	> 195°C [dec.]

^{1}H-NMR (D_2O): **8**: 4.92d (H′1), 4.87d (H1); **9**: 4.89d (H1′), 4.83d (H1); **10**: 4.86d (H′1), 4.82d (H1).

^{13}C-NMR (D_2O): **8**: 101.80 (C1′), 101.90, 101.94, 102.02 (C1), 41.17 (C6′), 59.7, 59.73, 59.8 (C6). **9**: 101.55 (C1′), 101.70, 101.74, 101.82 (C1), 41.27 (C6′), 59.67, 59.72, 59.79 (C6). **10**: 100.93 (C1′), 101.21, 101.74, 101.38 (C1), 41.19 (C6′), 59.7, 59.75, 59.9 (C6).

1,2-O-Isopropylidene-α-D-glucofuranose (**11**). 3,5,6-Tri-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose was prepared according to known methods [2].

3,5,6-Tri-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (10 g, 0.02 M) was dissolved in 90 mL of methanol, cooled below −20°C, and 1 g of Pd/C in 10 mL of water (as described above) was added. The reaction mixture was heated to room temperature, and 9.5 g (0.15 M) of ammonium formate was added. The reaction mixture was heated to reflux, and after 5 min stirring it was cooled to room temperature. The catalyst was filtered off and washed twice with 10 mL of MeOH. The solvents were evaporated, and the product was obtained by recrystallization from water. Yield: 98%; Mp.: 161–162°C [2].

3. Results

Analysis of the literature on CTH [3,6] showed that removal of the benzyl protecting groups from various organic compounds and conversion of azides to amines [4–6] requires various reaction times, even in cases of similar structures. Both the literature we have studied and our experiments suggested the essential role of what at first-sight seems to be a secondary parameter: the water content of the reaction mixture. This parameter in some cases showed more marked effects than, e.g., the speed of stirring or solubility of the compounds.

In Figures 1, 2, and 3 the effect of water on the reaction rate and reproducibility of the experiments are demonstrated. As can be seen from these figures, the water content of the reaction mixture has the greatest effect on the reaction rate. The optimum water content is about 15 vol.-%, when we obtained the best reproducible results.

On the other hand, water can influence the activity of the catalyst. This 'toxic' effect of water also explains the slow reaction in cases when water is used as solvent. This difficulty could become an essential factor, when cyclodextrin azides need to be reduced to amine derivatives.

In Figure 4 the solubility of 6-monoazido- and 6-monoamino-cyclodextrins are demonstrated. The low solubility of the azides and their reduced form in methanol could explain the poor yield. In this unfavorable case one can conclude that stirring plays the most important role. Suprisingly, as demonstrated in Figures 5 and 6, even relatively slow stirring can result in good yields within a reasonable reaction

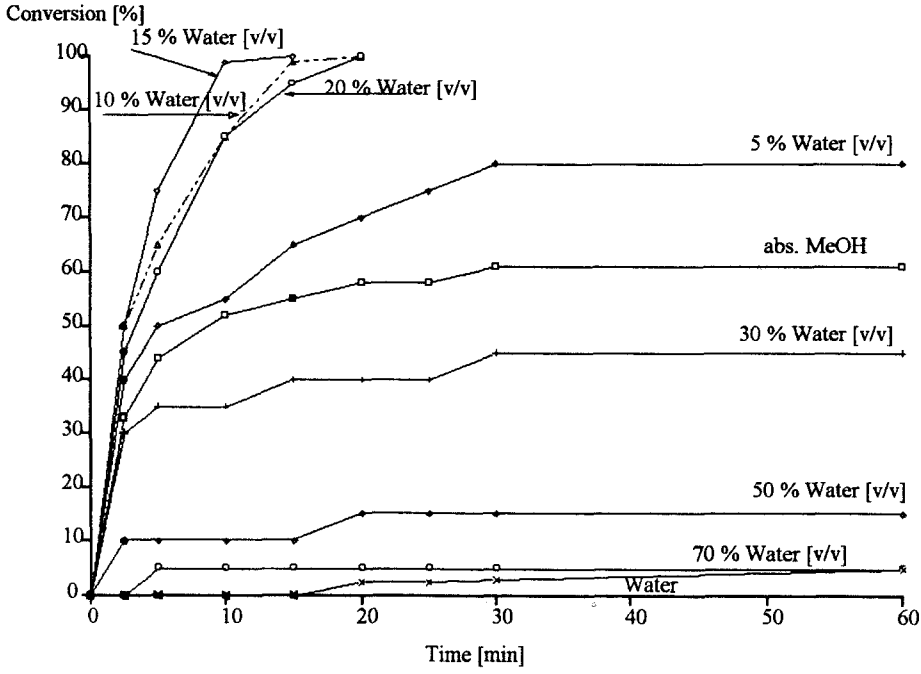

Fig. 1. Effect of water content of the reaction mixture on the benzylation of **1**.

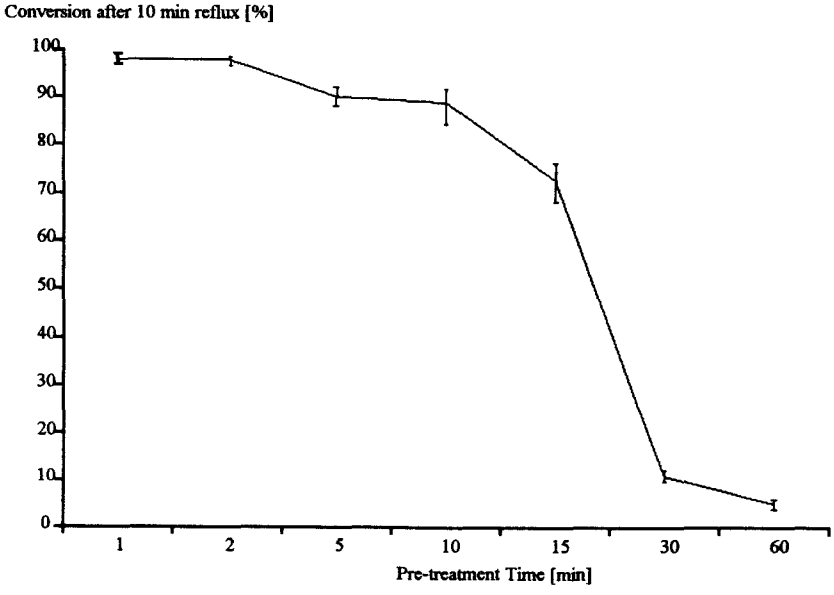

Fig. 2. Effectiveness of the catalyst on the debenzylation of **1** as a function of pre-treatment.

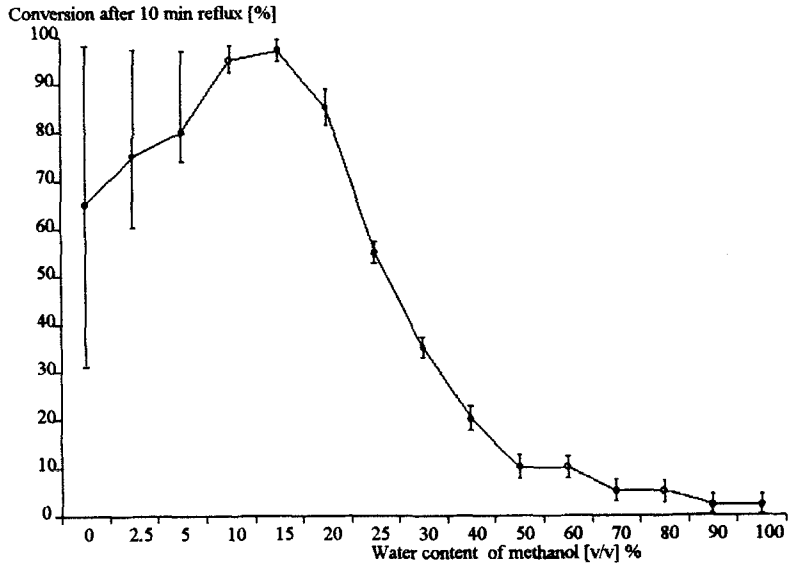

Fig. 3. Effect of the water content of methanol on the debenzylation of **1**.

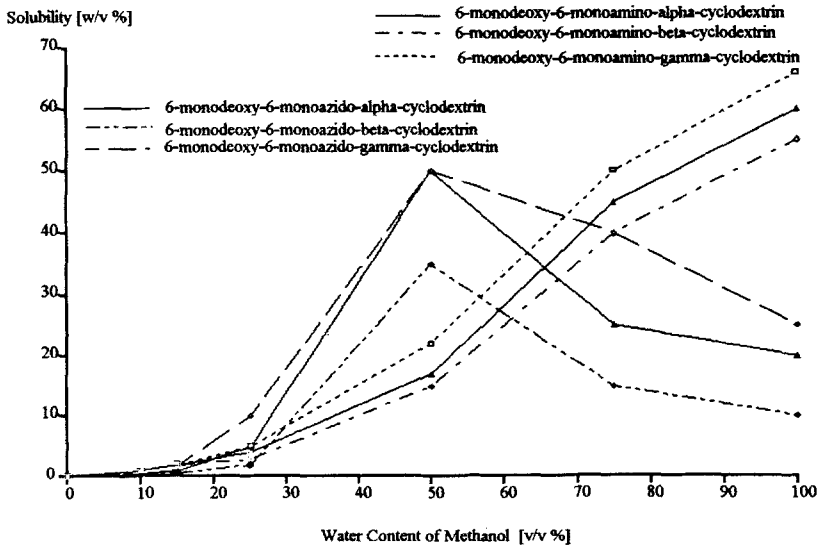

Fig. 4. Solubility of 6-monodeoxy-6-monoazido- and -6-monoamino-cyclodextrins in water–methanol systems.

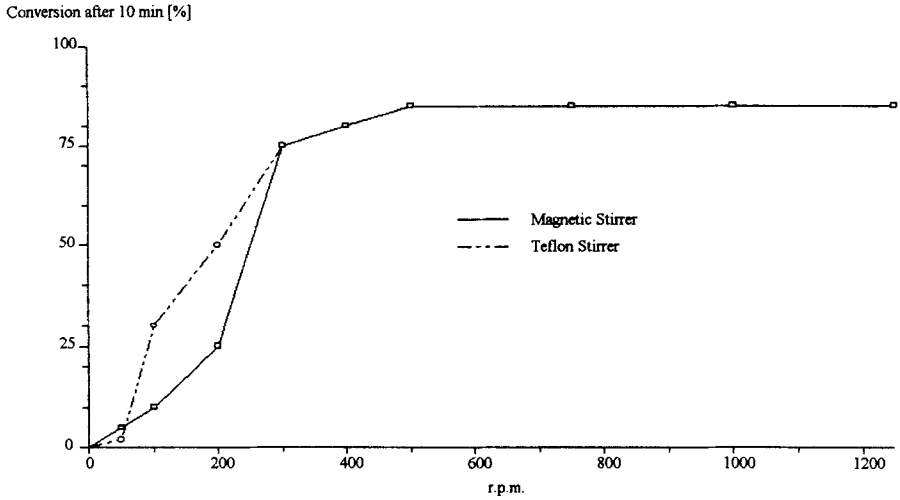

Fig. 5. Effect of stirring on the reduction of 6-monoazido-βCD.

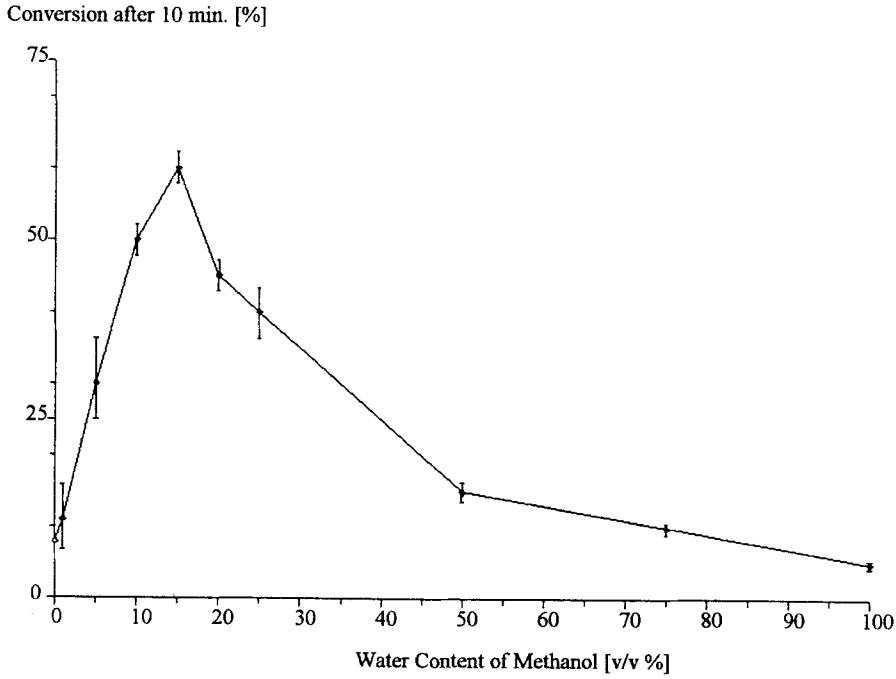

Fig. 6. Effect of water on the reduction of β-cyclodextrin azide to amine.

time. In the case of cyclodextrin derivatives it is also found that the water content has more influence than the heterogeneity of the reaction mixture.

4. Conclusions

i. Water plays an important role not only in the debenzylation of diazaspirodecanes but also in the reduction of sugar azides to amine and deprotection (e.g. debenzylation) of sugar derivatives. Increasing the amount of water results in higher yield. However, above 30–40% water, the reaction becomes slower, and the yield decreases.

ii. Apparently, water inactivates the catalyst in methanolic medium. Pretreatment of the catalyst (soaking in water) before use can deactivate the palladium catalyst.

iii. The solubility of both the starting material and the product has less influence on the reaction rate and yield, i.e. the most common parameters have less influence on the reaction. In cases of cyclodextrin azide the yield and reaction rate were high in spite of the poor solubility of both starting azide and the amine derivatives formed.

iv. Compared with hydrogenation with gaseous hydrogen the reactions are easier, faster, simpler and safer. The use of CTH to reduce cyclodextrin azides gave higher purity and better yield than both the Staudinger reaction and catalytic reduction with hydrogen. Similar results were obtained in the case of benzylated glucose derivatives, and confirmed the results obtained with a quite different organic molecule. Ammonium formate was found to be the best among the studied hydrogen transfer agents in the case of the observed glucose derivatives.

v. Exotic kinetic behavior in cases of low water content could be assumed [7].

Acknowledgement

Special thanks to M. Peredy-Kajtár (Central Research Institute for Chemistry of the Hungarian Academy of Science) for recording and evaluating the NMR spectra.

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