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Catalytic transfer hydrogenation of sugar derivatives

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Abstract

Cyclodextrin azides were successfully converted to the corresponding amino derivatives. When sugar derivatives are transformed, the appropriate transfer agents are limited in number because the most common transfer compounds, e.g. hydrazine hydrate or formic acid, can compete in side reactions. This work aimed to study and standardize the reaction conditions for the preparation of cyclodextrin azides. For hydrazine hydrate, formic acid, and ammonium formate, 10–25% water content in the reaction mixture was found to be optimum both for azide–amine conversion and removal of the benzyl group. The extreme flammability of the reaction mixture can be avoided by using water for the suspension of the catalyst. The use of the different hydrogen donors to promote the catalytic transfer hydrogenation of 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was also investigated. Transformation of the furanose form into the pyranose form of glucose can be achieved in one step using formic acid as hydrogen donor, while using hydrazine hydrate the furanose form could be retained. The reaction time did not surpass 20 min even the in case of the less soluble 6-monoazido-β-cyclodextrin.

Keywords: Catalytic transfer hydrogenation; Sugar derivatives; Amino derivatives; Cyclodextrin; Reduction

1. Introduction

Working with gaseous hydrogen (preparation of the reaction mixture, handling of catalyst and hydrogen, sampling, etc.) is generally an uncomfortable operation. The major difficulties can be avoided using the catalytic transfer hydrogenation method.

Debenzylation by catalytic transfer hydrogenation of various organic compounds is a simple, fast, and safe method. However it is widely used in organic preparations; only some data are available for its use to convert azides to amines, probably due to the poor reproducibility of some reported results. The reaction mechanism is far from being completely understood (Braude & Linstead, 1954). Heterogeneous catalytic reactions are still a great challenge for both theoretical and preparative chemists.

Usually, these reactions are carried out in methanol or aqueous methanol solutions. In abs. solvents the reductions were found to be slow and incomplete; or the scaling-up procedures could not be reproduced. Optimization experiments for determination of the limits of the water content of the reaction mixture were also performed. While in our former study both the starting material and the product had limited solubility under the applied reaction conditions (Jicsinszky, 1994), in the present case no solubility problems were found. Our previous studies were extended for methylated β-cyclodextrin azide, and the present method was also demonstrated to promote debenzylation of a glucose derivative. (Preparation of amino cyclodextrins via azido derivatives is shown in Scheme 1 and debenzylation of the protected D-glucose derivatives is shown in Scheme 2.)

2. Materials and methods

Hydrazine hydrate, cyclohexene, tetraline, formic acid, methanol, sodium azide, *p*-toluenesulfonyl chloride, glucose, and methyl glucopyranoside, were products of Merck (Darmstadt); Pd/C (10 % Pd content) and abs. DMF were products of Janssen Chimica, and sodium hydride, iodomethane and charcoal were products of Fluka; these chemicals were used without further purification, except *p*-toluenesulfonyl chloride. Other substances were prepared in our laboratory.

Strongly basic ion-exchanger is from Fluka (Dowex MWA-1, 35-75 mesh, Art. No.: 44440)

Silicagel 60 used for column chromatography was purchased from Merck (0.063–0.200 mm, Art. No.: 1.07734.)

Thin layer chromatography (TLC) was performed on

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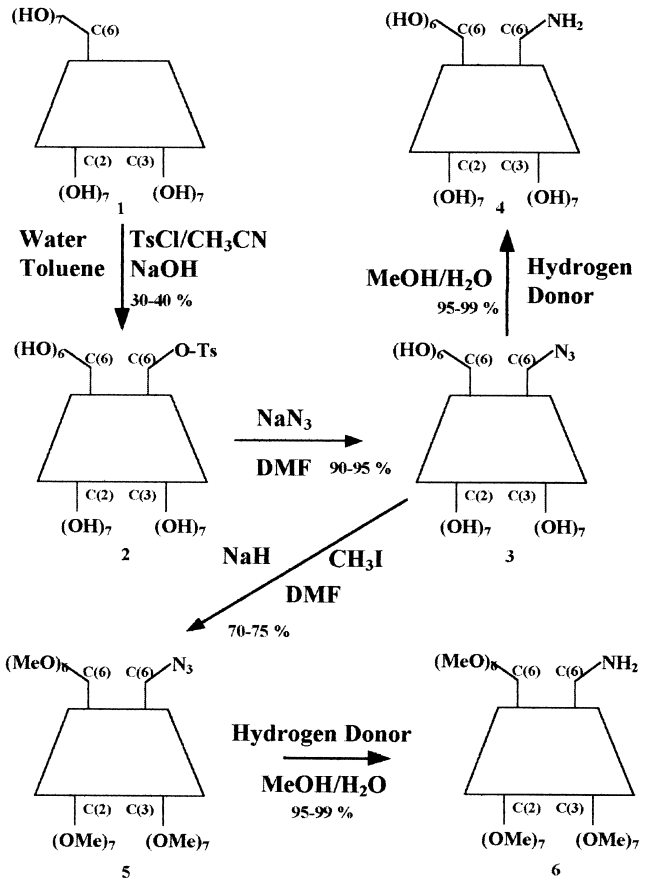
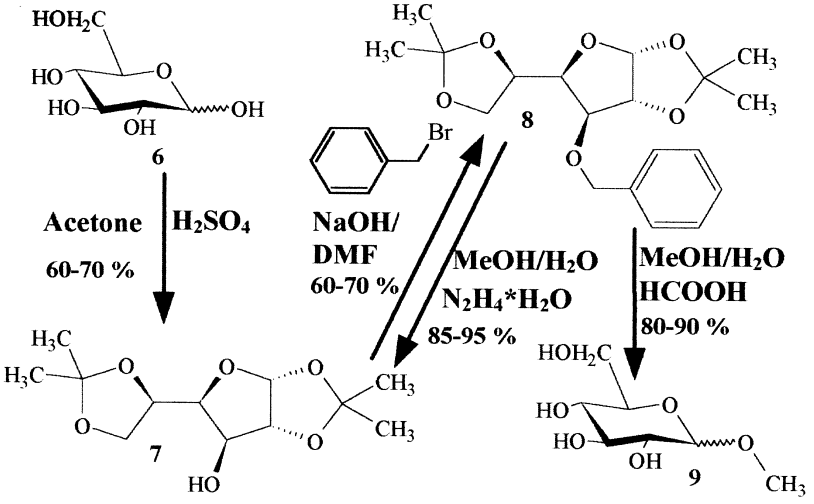


Scheme 1.

aluminum sheets coated with silicagel 60 F254 (Merck, Art. No.: 1.05554.).

TLC-plates were developed in a saturated chamber, with 10 cm running distance.

Solvent I: 10:7 (v/v) 1,4-dioxane–cc. NH_3/H_2O
Solvent II: acetone
Solvent III: 2:1 benzene–acetone
Solvent IV: 4:1:1 acetonitrile–MeOH–cc. NH_3/H_2O



Scheme 2.

Melting points were determined on a Büchi OP510, and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in D_2O on Varian VXR-400; IR spectra were recorded in KBr on Nicolet 205 FTIR; Densitometry: Chromtest OE-504; UV spectra were recorded in H_2O on a HP-8452A spectrometer. Optical rotations were measured on a Carl-Zeiss apparatus at sodium D line (589 nm), 0.1 m length in 1% aq. solutions, at 25°C.

2.1. Kinetic experiments

The starting material (1 g) was dissolved or suspended in abs. MeOH (9 cm^3) under nitrogen at room temperature The reaction mixture was cooled to −25°C, then the suspended catalyst (0.1 g, 10% Pd/C) in water (1 cm^3) was added, and the reaction mixture was heated to room temperature. Then 4 molar-fold excess of the hydrogen donor (hydrazine hydrate, formic acid, ammonium formate, cyclohexene, and decaline) was added, and the mixture heated to reflux. The samples were obtained after 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 made by both densitometry and UV. Five parallel runs were averaged.

Pre-treatment of the catalyst was accomplished by stirring it in twice-distilled water at room temperature for 1, 2, 5, 10, 15, 30, and 60 min before use.

2.2. Purification of p-toluenesulfonyl chloride

Commercially available *p*-toluenesulfonyl chloride is dissolved in dry methylene chloride. The insoluble *p*-toluenesulfonic acid is filtered off and the removal of solvent resulted in pure *p*-toluenesulfonyl chloride.

2.3. 6-Mono(p-toluenesulfonyl)-β-cyclodextrin (**2**) (modified method of Petter & Salek, 1990)

β-Cyclodextrin (11.35 g, 0.01 mol) was dissolved in hot water (110 cm^3) and toluene (2 cm^3) was added under vigorous stirring, and allowed to cool to room temperature. The formed βCD/toluene complex crystallized, was filtered off and used in wet form.

The previously obtained βCD/toluene complex was dissolved in water (250 cm^3) containing sodium hydroxide (0.6 g, 0.015 mol) at room temperature, and cooled to 15°C. *p*-Toluenesulfonyl chloride (2.4 g, 0.0125 mol) in acetonitrile (12 cm^3) is added during 45–60 min. The cooling bath was removed, allowing to warm up to room temperature and the mixture was stirred for additional 2 h at room temperature. The cloudy reaction mixture was kept at 4–6°C overnight, neutralized (pH 6–6.5) with hydrochloric acid, and kept in refrigerator for 1 day.

The obtained solid was filtered off, and washed with water. The crude product was dried at room temperature in the presence of phosphorous pentoxide in vacuo (5.6 g, ~40%, contained ~10% unsubstituted βCD. The crude product was dissolved in boiling 50% EtOH (150 cm^3), and EtOH was removed by distillation under reduced pressure, the obtained solid is filtered off at 40°C, and washed with water. The recrystallization was repeated twice and the unsubstituted βCD content falls below 1.5%. Yield: 4.4 g, 34%, white crystals, m.p.: 172–173°C (dec.). R_f: 0.42–0.45 (Solvent I).

2.4. 6-Monodeoxy-6-monoazido-β-cyclodextrin (**3**)

Compound **2** (65.3 g, 0.05 mol) was dissolved in abs. DMF (325 cm^3), and sodium azide (3.9 g, 0.06 mol) was added. The reaction mixture was heated to 105–110°C, and stirred for 1 h at this temperature. The almost clear solution was treated with acetone at room temperature, and a white crystalline precipitate was formed. The crude product was recrystallized from 1:10 water–acetone mixture. Yield: 57.4 g, 99%, white crystals, m.p.: 243–244°C (dec.). R_f: 0.39–0.41 (Solvent I).

2.5. 6-Monodeoxy-6-monoamino-β-cyclodextrin (**4**)

Compound **3** (5.9 g, 0.005 mol) was suspended in abs. MeOH (54 cm^3) under nitrogen, and cooled to −25°C, Pd/C (0.6 g) in water (6 cm^3) was added (suspended in water (3 cm^3), and the bottle was washed-in with the remaining water (3 cm^3)). The reaction mixture was heated to room temperature, hydrazine hydrate (1.3 g, 0.025 mol) was added, and further heated to reflux. After 20 min stirring at reflux temperature, the reaction mixture was cooled to about 50°C, the catalyst was filtered off, and washed twice with water (10 cm^3). After evaporation of the solvents, the crude product (5.4 g) obtained was dissolved in water (15 cm^3), pH > 9.5, acidified with conc. HCl to pH = 2.5, clarified by charcoal (10 wt%) at room temperature for 30 min, filtered, washed twice with water (2.5 cm^3), and methanol (80 cm^3) was added to get a crystalline product. The product was free of azide and of hydrazine, as detected by IR. Yield: 5.3 g (HCl salt), almost white crystals, 90%, m.p.: 222–224°C (dec.). R_f: 0.26–0.29 (Solvent I).

2.6. Heptakis(2,3-di-O-methyl)-hexakis(6-O-methyl)-6-monodeoxy-6-monoazido-β-cyclodextrin (**5**)

Compound **4** (5.9 g, 0.005 mol) was dissolved in abs. DMF (60 cm^3), and sodium hydride (9.6 g, 0.40 mol, 80% susp. in palm oil) was added. After cooling to room temperature, iodomethane (5.0 g, 0.35 mol) was added. The reaction mixture was stirred for 1 h at room temperature, then MeOH (20 cm^3) was added to decompose the excess of NaH. Solvents were removed by evaporation under reduced pressure. The crude product was chromatographed on a 25-fold silicagel column using chloroform. The product was free of hydroxyl groups as confirmed by IR. Yield: 5.2 g, 71%, white crystals, m.p.: 105–108°C. R_f: 0.57–0.60 (Solvent II).

2.7. Heptakis(2,3-di-O-methyl)-hexakis(6-O-methyl)-6-monodeoxy-6-monoamino-β-cyclodextrin (**6**)

Compound **5** (7.3 g, 0.005 mol) was dissolved in abs. MeOH (65 cm^3) under nitrogen, and cooled to 25°C. Pd/C (0.7 g) added in water (7 cm^3; suspended in 4 cm^3, and washed-in with the remaining water (3 cm^3)). The reaction mixture was heated to room temperature, hydrazine hydrate (1.3 g, 0.025 mol) was added, and the mixture was further heated to reflux. After 10 min stirring under reflux, the reaction mixture was cooled to room temperature. The catalyst was filtered off and washed three times with methanol (7 cm^3). Solvents were evaporated, and the crude product (6.9 g) was dissolved in water (35 cm^3), pH $>$ 9.5, acidified with conc. HCl to pH = 4.0, clarified by charcoal (10 wt%) at room temperature for 30 min, filtered, washed twice with water (5 cm^3), freeze dried. The product was free of azide and hydrazine as confirmed by IR. Yield: 7.0 g (HCl salt), almost white solid, 95%, m.p.: 158–161°C (dec.). R_f: 0.22–0.25 (Solvent II).

2.8. 1:2,5:6-Diisopropylidene α-D-glucofuranose (**7**) (modified method of Whistler, Wolfrom & BeMiller, 1963)

2.8.1. Method A

Dried glucose (18.0 g, 0.1 mol) was suspended in dried acetone (360 cm^3), cooled to −5°C and cc. sulfuric acid (15 g, 0.15 mol) is added dropwise at 0–5°C. The reaction mixture was allowed to warm up to room temperature and stirred for additional 3 hrs. The orange colored solution was neutralized with NaOH (15 g) in water (20 cm^3), sodium sulfate was filtered off and acetone was removed in vacuo. The crude product was recrystallized three times from water. Yield: 16.9 g, 65%, white crystals, m.p.: 105–108°C. R_f: 0.47–0.50 (Solvent III).

2.8.2. Method B

Compound **8** (8.8 g, 0.025 mol) was dissolved in abs. MeOH (80 cm^3) under nitrogen, cooled to 25°C, Pd/C (0.9 g) added in water (9 cm^3; suspended in 6 cm^3, and washed-in with the remaining water (3 cm^3)). The reaction mixture was heated to room temperature, hydrazine hydrate (1.3 g, 0.025 mol) was added, and the reaction mixture was heated to reflux. After 10 min stirring under reflux, the reaction mixture was cooled to room temperature. The catalyst was filtered off and washed three times with methanol (9 cm^3). The crude product was recrystallized from water. Yield: 5.9 g, 90%, white crystals, m.p.: 107–109°C. R_f: 0.47–0.50 (Solvent III).

2.9. 3-O-Benzyl-1:2,5:6-di-O-isopropylidene α-D-glucofuranose (**8**)

Compound **7** (13.0 g, 0.05 mol) was dissolved in abs. DMF (65 cm^3), and sodium hydroxide (10 g, 0.25 mol) was added, cooled to room temperature, and benzyl bromide (34 g, 0.2 mol) was added. The reaction mixture was stirred for 1 h at room temperature, then 1 h at 40°C, and neutralized with 0.1 N HCl. Solvents were removed by evaporation under reduced pressure. The crude product was chromatographed on a 25-fold silicagel column using *n*-hexanechloroform mixtures. The purified product was free of hydroxyl groups as confirmed by IR. Yield: 12.6 g, 72%, dense colorless oil. R_f: 0.54–0.57 (Solvent III).

2.10. α,β-D-Methyl glucopyranoside (**9**)

2.10.1. Method A

Compound **8** (8.8 g, 0.025 mol) was dissolved in abs. MeOH (80 cm^3) under nitrogen, cooled to 25°C, Pd/C (0.9 g) added in water (9 cm^3; suspended in 6 cm^3, and washed-in with the remaining water (3 cm^3)). The reaction mixture was heated to room temperature, formic acid (3.8 cm^3, 4.6 g, 0.1 mol) was added, and the reaction mixture was heated to reflux. After 10 min stirring under reflux, the reaction mixture was cooled to room temperature. The catalyst was filtered off and washed three times with methanol (9 cm^3). Yield: 4.6 g, 92%, white solid. The crude product is obtained by evaporation of solvents, and it was identical to the sample prepared by H_2SO_4/MeOH from β-cyclodextrin. Although exact anomeric composition was not determined, a dominant α-anomer was detected. R_f: 0.29–0.31 (Solvent IV). $[\alpha]_D^{25} = 108 \pm 2.5°$.

2.10.2. Method B

β-Cyclodextrin (1.1 g, 0.001 mol) was suspended in abs. MeOH (20 cm^3), cc. sulfuric acid (1 cm^3) was added. The reaction mixture was heated under reflux until TLC showed completion of methanolysis (5 h). The reaction mixture was cooled to room temperature and neutralized by ion-exchanger. The crude product is obtained by filtration, decolorizing with charcoal and evaporation of solvents. Yield: 1.2 g, 85%, white solid, which was identical with an authentic sample. Exact anomeric composition was not determined, a dominant α-anomer was detected. R_f: 0.29–0.31 (Solvent IV). $[\alpha]_D^{25} = 108 \pm 2.5°$.

3. Results and discussion

Analysis of the literature on catalytic transfer hydrogenation (Bieg & Szeja, 1985) showed that removal of the benzyl protecting groups from various organic compounds and conversion of azides to amines (Gartisier, Sleva & Delmoch, 1983; Malik, Preston, Archibald, Cohen & Baum, 1989; Ram & Ehrenkampfer, 1988; Scriven & Turnbull, 1988) require various reaction times even when similar structures are involved. Both the studied literature and our experiments suggested the essential role of 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 (Jicsinszky, 1994).

Usually the reductions require a well-determined sequence of operations. In the case of the catalytic transfer

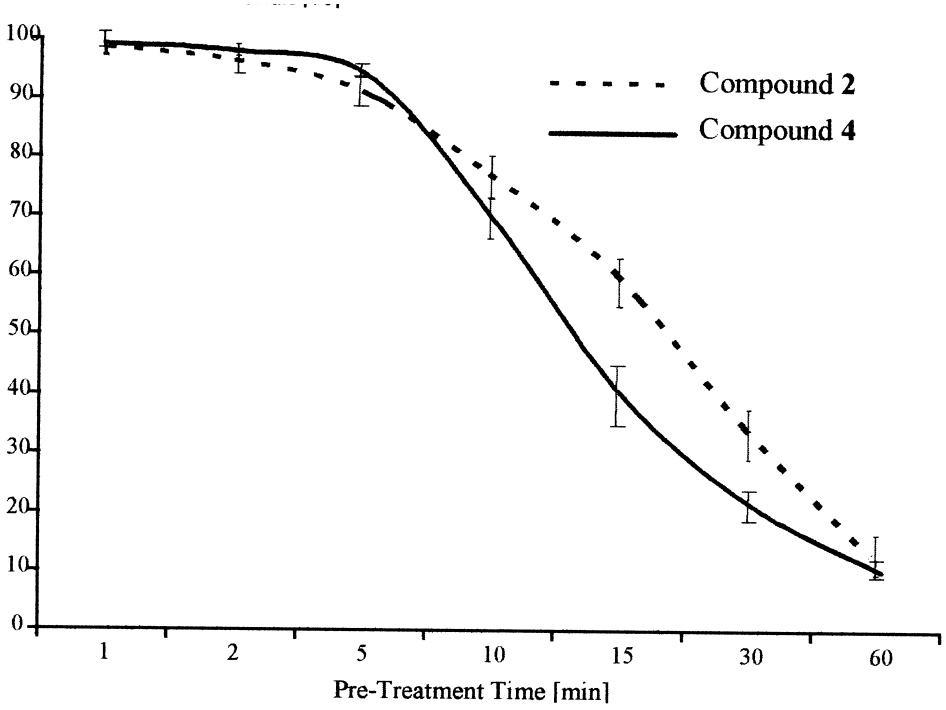


Fig. 1. Conversion of azides (**2**, **4**) to amines (**3**, **5**) after 10 min as a function of pre-treatment, using hydrazine hydrate as the hydrogen donor.

hydrogenation, due to the very short reaction time the work with the reactants may determine the success of the reaction, as demonstrated in Fig. 1. The catalyst poisoning effect of water is a surprising and rarely documented feature of the used Pd/C catalyst. In order to study the influence of the pre-treatment time, the catalyst was soaked in water before use. As can be concluded from Fig. 1 the catalyst must be added to the reaction mixture as fast as possible to reach its maximum efficiency. However, it had been found that in abs. methanol the reproducibility of reductions were out of tolerance. In order to investigate the role of water content of the reaction mixture, a systematic study was performed by addition of defined amounts of water to the reaction mixture. As it can be shown in Fig. 2, increasing the amount of water

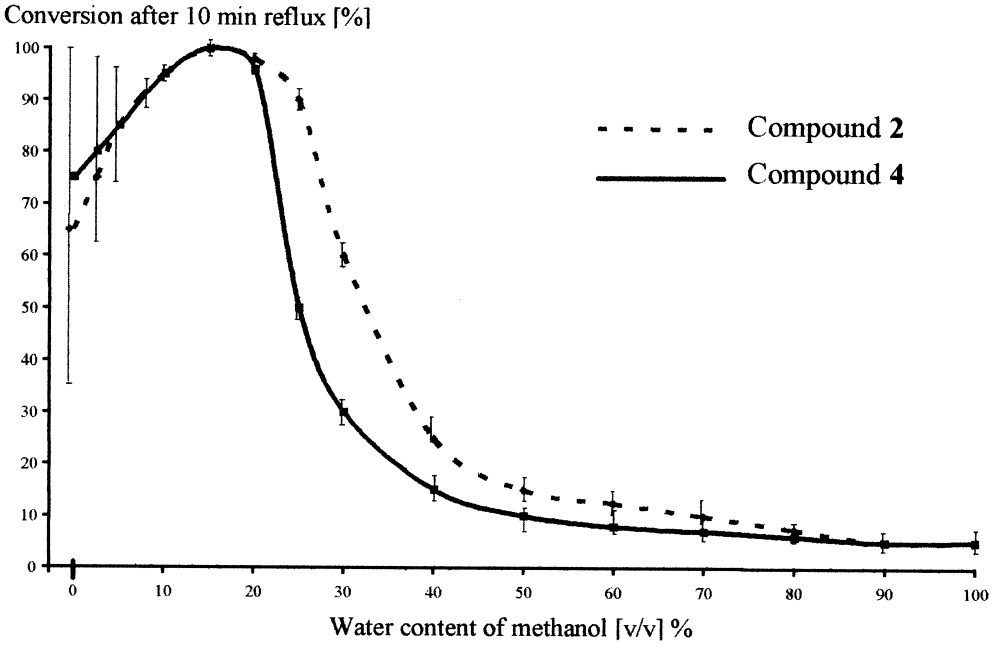


Fig. 2. Effect of the water content of methanol on the reduction of **2** and **4**, using hydrazine hydrate and ammonium formate as hydrogen donors.

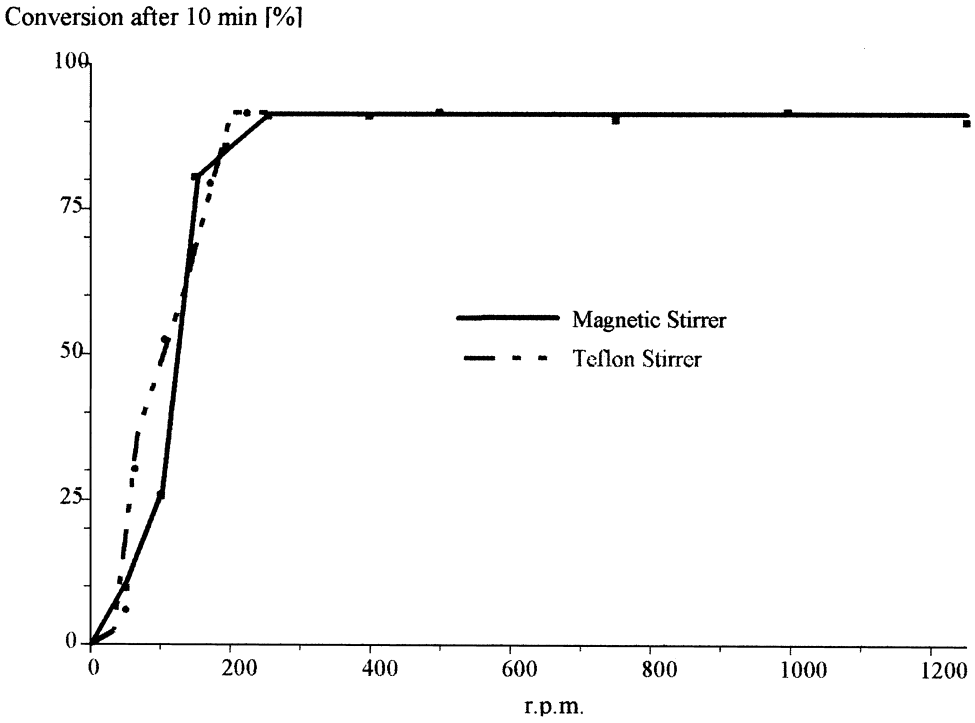


Fig. 3. Effect of stirring on the reduction of 6-monodeoxy-6-monoazido-βCD at 15% water content of MeOH, using hydrazine hydrate as hydrogen donor.

dramatically reduces the error of reproducibility, and the best results can be obtained in a wide range (10–25%) of water content. Then, the poisoning effect compensates the acceleration, which results in lower conversion and less reproducibility.

The non-methylated β-cyclodextrin azide has low solubility at low water-contents of methanol. Due to the poor solubility of both catalyst and substrate, the speed of stirring should be an important factor. Surprisingly, this factor had the least influence on the conversion, as demonstrated in

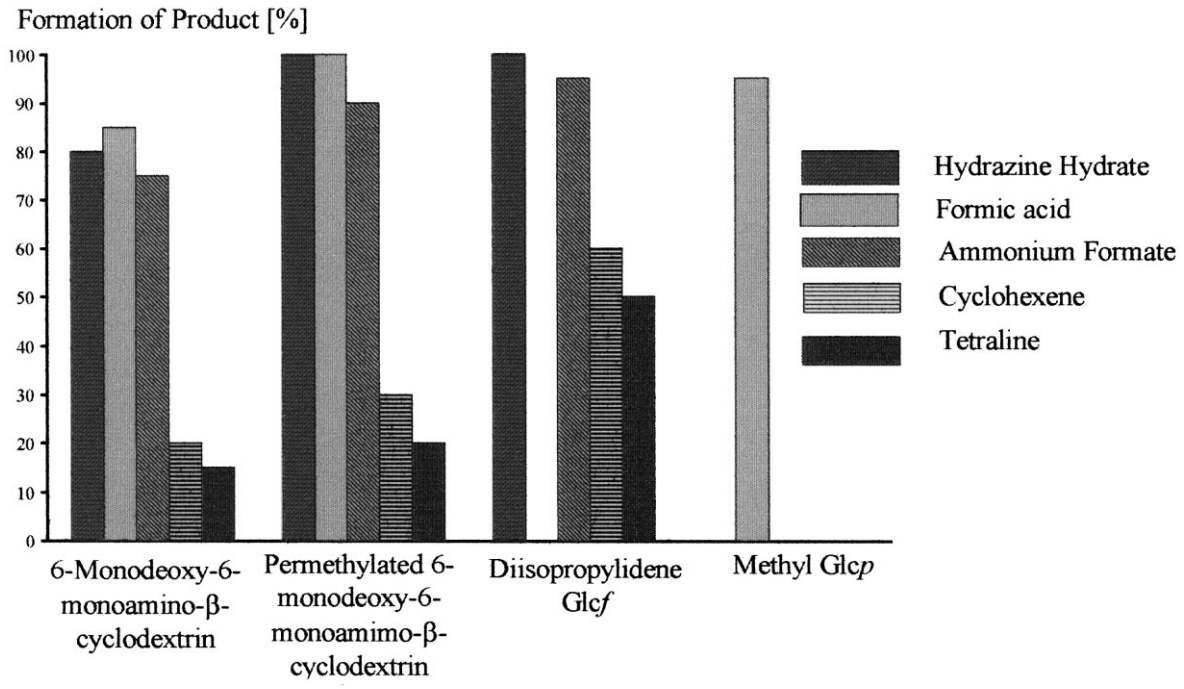


Fig. 4. Effectivity of hydrogen donors in the conversion of **2** to **3**, **4** to **5**, and **7** to **6** and **8** near the optimal conditions, after 15 min reaction time.

Fig. 3. It was also found that in well-soluble compounds even the spontaneous reflux may be enough to reach the complete conversion without significant extension of reaction time. The experimental difficulty caused by the spontaneous turbulency of boiling was avoided by application of 5°C lower temperature than the boiling point.

From the synthetic point of view, the catalytic transfer hydrogenation of acid-labile derivatives is particularly interesting. In this case the appropriate choice of the hydrogen donor can direct the synthesis. This is demonstrated with compound **9**. When retaining the furanose conformation of the glucose unit is aimed neutral or basic hydrogen donors must be applied. However, using an acidic hydrogen donor, such as formic acid, transformation of the furanose form to the pyranose one can be carried out in one step. This is important when protection and manipulation require one conformation but the target molecule has the other one. Unfortunately, in most cases the furanose/pyranose transformation is not as simple as in the studied case. The effect of acids on both the starting material and its hydrogenated form must be investigated.

Among the studied hydrogen transfer reagents hydrazine hydrate and formic acid and its salt have been found to be the best donors, as can be concluded from Fig. 4. The use of formic acid is particularly important, because this compound is effective in both its acidic and neutral (as salt) forms.

4. Conclusions

Water plays an important role in catalytic transfer hydrogenation reactions. Increasing the amount of water results in higher yield, until the optimal water content, 10–30%, is reached. However, above 30–40% of water, the reaction becomes slower, and the yield decreases.

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

When cyclodextrin azides were the starting materials the yield and reaction rate were high despite the poor solubility of both starting "unsubstituted azide" and formed "unsubstituted amine" derivatives. The permethylated β-cyclodextrin azide could be reduced within several minutes. The small reaction time differences observed for these azides could be assigned to the different solubilities, which have no substantial influence on the reaction rate and yield, i.e. the most common parameters have less influence on the reaction.

Catalytic transfer hydrogenation is an easier, faster, simpler, and safer method when compared to the hydrogenation with gaseous hydrogen. The use of catalytic transfer hydrogenation to reduce cyclodextrin azides gave higher purity and better yield than both the Staudinger reaction and the catalytic reduction with hydrogen. Also good results were obtained for debenzylation of **9**. Hydrazine hydrate was found to be the best transfer agent among the studied ones for the derivatives studied. An additional advantage of the hydrazine hydrate is its easy separation from the product.

General optimal reaction condition can be given as follows:

- 80–90% aqueous methanol as solvent;
- hydrazine hydrate as hydrogen donor;
- fastest possible assembly of reactants.

In special cases the reaction product can be controlled by the use of hydrogen donor.

Acknowledgements

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