

Two Phase Reduction of Carbonyl Compounds with Sodium Borohydride

Jin Soon Chong* and Nung Min Yoon**

*Department of Chemistry, Chon-Nam University, Kwang-Ju, Korea.

**Department of Chemistry, Sogang University, Seoul, Korea.

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Abstract Possibility of two phase reduction of carbonyl compounds to the corresponding alcohols was studied. Thus the 0.5 M ether solutions of the representative carbonyl compounds were treated with alkaline stabilized sodium borohydride aqueous solution at room temperature. Butyraldehyde was reduced rapidly within one hr., whereas other aldehydes tested; heptaldehyde, benzaldehyde, and 1-naphthaldehyde were reduced in 6-12 hr. 2-Heptanone was reduced much slowly; 87% in 48 hr., however, acetophenone was reduced moderately; 92% in 12 hr. and cycloalkanones were reduced rapidly (cyclohexanone in 0.5 hr., and cyclopentanone in 3-6 hr.).

Introduction

Unlike a strong reducing agent, lithium aluminum hydride, sodium borohydride is a mild reducing agent, and has been used extensively for the various kinds of selective reduction.^{1,2}

However, sodium borohydride is insoluble in ether and tetrahydrofuran, more common solvents for organic compounds, whereas lithium aluminum hydride is readily soluble in these solvents. Therefore it is customary to use such solvents as methanol, ethanol, isopropyl alcohol, pyridine, alkaline water, and diglyme for the reduction with sodium borohydride. Although diglyme dissolves the hydride moderately, its reducing ability was found to be significantly changed.³

On the other hand, Brown and Garg reported a convenient two phase reduction for the oxi-

dation of secondary alcohols to ketones.⁴

Therefore we studied the possibility of the two phase reduction of carbonyl compounds in ether with alkaline stabilized aqueous sodium borohydride solution, in order to overcome the possible difficulties due to the solvent for the sodium borohydride reduction.

Experimental

Materials. All the carbonyl compounds and the glpc standards used were checked for their purity by their refractive index. The commercial sodium borohydride (Ventron) was used without further purification. Analysis by hydrogen evolution measurement on hydrolysis showed 98% purity.

General procedure for two phase reduction

The two phase reduction of heptaldehyde is described as a representative of the procedure. In a 100 ml. flask, fitted with an inlet tube, a magnetic stirrer and a reflux condenser through which a gas meter is connected, there was placed a 15 ml. of 0.25 M sodium borohydride solution in 0.25 M NaOH aqueous solution (3.75 mmoles NaBH_4 , that is 15 mmoles hydride). A 20 ml. of 0.5 M heptaldehyde solution in ether, which is also 0.5 M in mesitylene added as an internal standard for the glpc analysis was added at a time while the solution was moderately stirred. After 1hr., 2ml. of the ether layer was taken out and analyzed for heptaldehyde and heptyl alcohol using Carbowax 20M column, with F&M 720. Analysis showed 52% yield of heptyl alcohol and 45.2% of heptaldehyde remained. These estimation was made by area measurements, and the retention time of heptaldehyde and heptyl alcohol were 2.4min. and 7.1min., using 6 feet of 1/4 inch Carbowax 20M column, at 140 °C. with flow rate of 57 ml./min. The 2 ml. aliquots were also taken out at 3, 6 and 12 hr., and the glpc analysis showed 88, 97, and 100% yields of heptyl alcohol respectively.

In the case of 1-naphthaldehyde, the reaction could not be followed by glpc analysis, therefore the 2 ml. aliquots of the ether layer were added to 2,4-dinitrophenylhydrazine solution. There was no precipitate of 2,4-dinitrophenylhydrazone after 6 hr., indicating the completion of the reduction. The absence of aldehyde was also checked by I.R.

Tests for the distribution of hydride and alcohol in two phases. The 4 ml. of the ether layer was hydrolyzed with 2 N sulfuric acid solution, in order to find out any hydride in ether layer. There was no hydrogen evolution observed, showing no active hy-

dride present in ether layer. And the whole aqueous layer was hydrolyzed after the reaction, extracted with ether, and glpc analysis showed no heptyl alcohol in this aqueous layer.

Two phase reduction of 1-naphthaldehyde on a preparative scale. In a 300 ml.

round bottom flask, fitted with a magnetic stirrer, and an inlet tube, there was placed a 0.72 g. of sodium borohydride (18.75 mmoles) dissolved in 75 ml. of 0.25 M NaOH solution. A 7.81 g. of 1-naphthaldehyde (50 mmoles) dissolved in 100 ml. of ether was added at a time while the solution was moderately stirred. After 6 hr. at room temperature, the ether layer was separated without prior hydrolysis and dried over anhydrous magnesium sulfate, and the ether was evaporated away by distillation. The residue was dried completely under reduced pressure, and there was obtained a 7.5 g. of crude 1-naphthyl-methanol (95%). This was dissolved in 20 ml. of a mixture of ether and ethanol (1:1 v/v) and left in the open air. On the gradual evaporation of the solvent, 7.27 g. of a needle crystal of 1-naphthyl-methanol (92% yield), m. p. 59.5°C (lit⁵, 60°C) was obtained.

Results and Discussion

First, we tested the possibility of the two phase reduction with heptaldehyde, and followed the reaction with the formation of heptanol by glpc. The results are summerized in Table 1. As shown in entry 1, when 10 mmoles of the aldehyde in 20 ml. of ether was treated with 2.5 mmoles (10 mmoles of hydrides) of sodium borohydride in 20ml. of 0.1 M sodium hydroxide solution, the reaction slowed down considerably after 3 hr., and there was practically no hydride left after 12 hr. Apparently

the 0.1 M NaOH solution is not stable enough for our purposes. Therefore we added 2.5 mmoles of the hydride in 10 ml. of 0.25 M NaOH (entry 2). The solution became more stable and the rate of reaction also increased, however, the observed result, 91% yield in 12 hr. was felt inadequate for practical purposes. The more faster reaction was realized by adding 15 mmoles of "hydride" (50% excess) in 15 ml. of 0.25 M NaOH solution (entry 3.). Thus it was proved that the aldehyde in its 0.5 M concentration in ether could be reduced in 6-12 hr. at room temperature, using only 50% excess of the hydride.

Table 1. Two Phase Reduction of Heptaldehyde at Room Temperature.

Entry	Heptaldehyde Mmole	NaBH ₄ Mmole	Reduction, % hr.			
			1.0	3.0	6.0	12.0
1.	10 ^b	2.5(dissolved in 20 ml. of 0.10M NaOH)	27	62	67	71
2.	10 ^b	2.5(dissolved in 10 ml. of 0.25M NaOH)	33	65	81	91
3.	10 ^b	3.75(dissolved in 15 ml. of 0.25M NaOH)	52	88	97	100

- a. % of reduction estimated by analysis of methyl-alcohol.
 b. 20 ml. of 0.5 M solution.

The reaction time is a little longer, but the 50% excess is a good economy when compared to the large excess commonly used in hydroxylic solvents. Therefore we applied this method to the four aldehydes and four ketones. The results are summarized in table 2. Butyraldehyde was reduced rapidly within one hr., whereas the other aldehyde tested, heptaldehyde, benzaldehyde, and 1-naphthaldehyde were all completed in 6-12 hr., Apparently the water solubility of butyraldehyde is responsible to the fast reaction. On the other hand, the reduction rates of ketones were varied widely. Thus the representative aliphatic ketone, 2-heptanone was reduced

very slowly; 87.7% in 48 hr., but acetophenone was faster about four times than 2-heptanone 92% in 12hr. Cyclic ketones were reduced much faster than 2-heptanone or acetophenone. Thus cyclopentanone was reduced in 3-6 hr. and cyclohexanone was rapidly reduced within 1 hr.

Table 2. Two Phase Reduction of Representative Carbonyl Compounds in Ether with Aqueous Sodium Borohydride at Room Temperature.

Compound ^a	Reduction, % hr.				
	1.0	3.0	6.0	12.0	48.0
Butyraldehyde	100				
Heptaldehyde	52	88	97	100	
Benzaldehyde	78	95	98	100(89) ^c	
1-Naphthaldehyde			100 ^b (92) ^c		
2-Heptanone	9	18	20		87.7
Acetophenone	32	52	68	92	
Cyclopentanone	88	92	100		
Cyclohexanone	100(90) ^c				

- a. 10 mmoles of each carbonyl compound(20 ml. of 0.5 M ether solution) was reduced with 3.75 mmoles of sodium borohydride which was dissolved in 15 ml. of 0.25 M sodium hydroxide solution.
 b. % of reduction estimated by glpc analysis of the corresponding alcohols.
 c. % of yield, estimated by the isolation of the product.
 d. The completion of the reaction was checked by the absence of 2,4-dinitrophenylhydrazone

The rates of reduction of these ketones are parallel to those in isopropyl alcohol previously studied.^{6,7} Another points of interest are, whether the product alcohols distribute in ether and aqueous layer, either free or alkylborate forms, and are there any active hydride in ether layer. We confirmed that there is practically no alcohol in water layer and no hydride in ether layer. We believe this makes the two phase reduction more attractable, because the products can be isolated simply by taking out the ether layer and distillation.

Conclusion

Aldehydes and ketones can be reduced conveniently by the two phase reduction. We are going to study further the reducibility of other functional groups and the stereochemistry of ketone reduction to establish the two phase reduction as a means of selective reductions.

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