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THE SELECTIVE REDUCTION OF ALDEHYDES USING POLYETHYLENE GLYCOL-SODIUM BOROHYDRIDE DERIVATIVES AS PHASE TRANSFER REAGENTS

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ABSTRACT: A phase transfer reagent derived from PEG-sodium borohydride was developed which controlled both the activity and the amount of the reagent in the organic phase. Using this reagent under solid-liquid phase transfer conditions, it was found that aldehydes could be selectively reduced in the presence of ketones without concurrent reduction of the ketone group. The reactions were conducted at room temperature and were generally complete within two hours.

In this report, a ***phase transfer reagent*** prepared from readily available and inexpensive starting materials will be described. Traditionally, phase transfer reactions have been conducted using an inorganic reagent with a phase transfer *catalyst* such as a crown ether, polyether, or onium salt.[1] However, unlike these more traditional approaches, the phase transfer moiety was attached to the borohydride reagent to facilitate the transfer of the insoluble reagent into the

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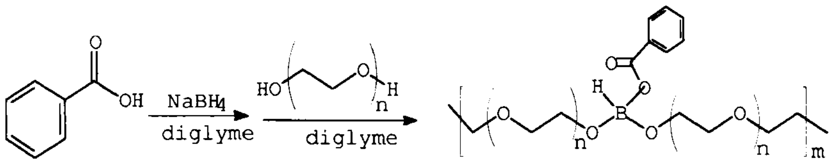
organic layer. Using this approach, the amount of the reducing agent present in the same phase as the substrate was controlled by the phase transfer process. In previous studies, it was shown that the amount of active hydride present in the organic phase was 2-5% using similar species.[2] Additionally, the activity of the borohydride moiety was altered by treating the sodium borohydride with benzoic acid.

It has been shown that the activity and selectivity of sodium borohydride can be affected by the introduction of a variety of side groups. For instance, attaching polyethylene glycol to sodium borohydride results in a reducing agent that has an activity that is intermediate between sodium borohydride and lithium aluminum hydride.[3] Furthermore, attaching chiral side groups to the sodium borohydride results in increased stereoselectivity when prochiral ketones were used. Presumably, a decrease in the activity of the reducing agent accompanies this increased stereoselectivity.[4,5]

During this study, it was found that decreasing the activity of the of the reagent and using phase transfer to control the amount of the reagent in solution resulted in an increase in the chemoselectivity of the process. The new borohydride reagent was prepared by allowing a solution of sodium borohydride in 2-methoxyethyl ether to react with benzoic acid dissolved in 2-methoxyethyl ether. The progress of the reaction was monitored by the evolution of hydrogen. After this reaction had run to completion, a solution of polyethylene glycol in 2-methoxyethyl ether was added to the mixture. Again, the progress of the reaction was monitored by hydrogen evolution. At the end of the reaction period a waxy,

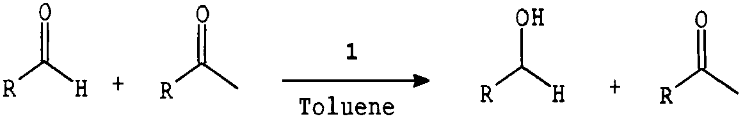


1

Scheme 1

white solid, **1**, was obtained, see Scheme 1. Even though the material did not undergo rapid degradation under ambient atmosphere, it was stored under nitrogen to prevent the possibility partial hydrolysis. Analysis of the active hydride showed that normal loadings were between 1.1-1.4 meq of hydride/g of solid. Additional ^1H nmr and ir analysis indicated the presence of the aromatic group, the polyethylene glycol chains, and B-H bonds.[6] The loadings were reported in the manner commonly used for polymers because the nmr spectrum and physical properties of the reagent were consistent with those of a polymer.[7] For this reason, it was thought the reagent was actually a condensation type polymer containing borohydride links throughout the network.

As a means of evaluating the chemoselectivity of **1**, equimolar amounts of the aldehyde and corresponding methyl ketone dissolved in toluene were added to a suspension of **1** in toluene, see Scheme 2. This approach placed the aldehyde



Scheme 2

and the ketone were in direct competition with each other. As an additional observation, the suspended reagent appeared somewhat swollen, much like a gel polymer. In all cases, the aldehyde was selectively reduced. Each run consisted of four side-by-side reactions from which the average of the pseudo-first-order rate constants was used as the rate constant for that run. Additionally, the standard deviation among the rate constants was taken to be the uncertainty in the rate constant.

After reviewing the data in Table 1, it was apparent that the phase transfer reagent was sensitive to the steric environment near the carbonyl group, in which only the more active substrates underwent productive reactions under the mild conditions of the reactions. Relatively unhindered aldehydes such as butanal, hexanal, and heptanal gave gas chromatographic yields in the 90% range. The activities gave no clear indication that increasing the chain length of the carbon group had any effect on the reduction. However, increasing the steric hindrance near the carbonyl group by introducing bulkier groups (e.g. isopropyl or phenyl) resulted in a noticeable decrease in both yield of the product and the rate constant of the reaction. This sensitivity to the steric environment was further attenuated by having carbon groups on both sides of the carbonyl group. When ketones were used as substrates the reaction was completely suppressed. There were two major reasons for this chemoselectivity: the bulky benzoyloxy group in the vicinity of the hydride unit and the relatively nonpolar solvent of the reaction. While the benzoyloxy group increased the possibility of steric repulsion with other carbon groups, the solvent interacted with the polymer chain of the reagent as a *theta*

Table 1: Competitive Aldehyde and Ketone Reductions[a]

Substrate	% Yield	Rate $10^5k(s^{-1})^b$
Butanal	90	9.45 ± 0.65[c]
2-Pentanone	Trace[d]	0
Hexanal	92	8.75 ± 0.75
2-Heptanone	0	0
Heptanal	90	8.40 ± 0.50
2-Octanone	0	0
Benzaldehyde	83	6.50 ± 0.90
Acetophenone	0	0
2-Methylpropanal	85	7.20 ± 0.50
Benzophenone	0	0

a. The yields listed are based on gc analysis of the product mixture after two hours. The reaction conditions are provided in the Experimental section.
b. Pseudo-first-order rate constant with respect to carbonyl disappearance. The samples for the rate studies were taken during the first two hours of the reaction and did not include the 24 hour sample at the end of the reaction.
c. The uncertainties are the standard deviations of four side-by-side reactions.
d. A small gc signal that corresponded to 2-pentanol appeared in two of the four runs. In both cases, the amount of product was less than 1% after 24 hours.

solvent. This resulted in the carbon chains contracting and the reactive site being less available for reaction.[8] This led to the selectivity normally associated with gel polymers; namely, the mass transfer of the substrates and products from the bulk solvent to the polymer matrix.[9]

Once it was established the reductions were taking place in high gc yields, the reactions were scaled up to a 10 mmol scale and the products were isolated and

Table 2: Isolated Yields of Aldehyde Reductions[e,f]

Substrate	Product	Compound No.	Purified Yield (%)
2-Methylpropanal	2-Methylpropanol	**2**	66
Hexanal	1-Hexanol	**3**	78
Heptanal	1-Heptanol	**4**	78
Benzaldehyde	Benzyl alcohol	**5**	62
2-Octanone	No reaction	**N/A**	0

e. The data concerning the product identification may be found in reference 12.

f. The reaction time was two hours at 21-23 °C.

purified. The data in Table 2 indicate that reasonable yields of purified products could be prepared using **1** as a phase transfer reagent.

EXPERIMENTAL

General: The starting materials and solvents were purchased from Aldrich Chemical Company and used without further purification. The 2-methoxyethyl ether was the 99.5% anhydrous grade. Infrared spectra were obtained from a Perkin-Elmer 1420 grating spectrometer. ^1H nmr were obtained from a Varian Associates EM 360A Nuclear Magnetic Resonance Spectrometer and the chemical shifts are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. The boiling points reported were uncorrected. The gas chromatographic analysis was conducted using a Varian model 3400 gas chromatograph equipped with a 6 ft Carbowax column (10%), TCD detector, and variable temperature capabilities.

General Experimental Procedure for Preparation of PEG-Bound Sodium Benzoyloxyborohydride, 1: In a typical reaction a three-necked round-bottomed flask equipped with a small stirrer bar, rubber septum, and a nitrogen inlet tube was charged with 5.0 mL (2.5 mmol) of 0.5 M sodium borohydride in anhydrous 2-methoxyethyl ether. This was followed by slow addition of 0.30 g (2.5 mmol) of benzoic acid dissolved in 3 mL of 2-methoxyethyl ether via syringe. This addition normally requires about 20 min. Once the addition was complete, the mixture was gently stirred until the evolution of hydrogen subsided.[10] At this point 0.50 g of polyethylene glycol (400 MW) dissolved in 3 mL of 2-methoxyethyl ether was added over a 5 min period to the milky suspension. The resulting mixture was allowed to stir at room temperature (21-23°C) for 1 h. At the conclusion of the hydrogen evolution, 20-30 mL of anhydrous diethyl ether was added to the mixture and excess solvent was carefully removed via cannula. The solid was washed at least three times in this fashion. The remaining ether was removed by maintaining a gentle flow of nitrogen over the solid for 2 h.[11]

General Procedure for Phase Transfer Reduction: A round-bottomed flask equipped with a side-arm, stirrer bar and septa was charged with ca. 2.0 meq of hydride and 15 mL of toluene. A mixture of 1.5 mmol of aldehyde, 1.5 mmol of ketone, and 0.5 mmol of a hydrocarbon reference was dissolved in 4.0 mL of toluene was added rapidly to the suspended reagent. During the course of the reaction, 0.5 mL aliquots were taken and subjected to gc analysis. The reaction temperature was 21-23°C throughout all reactions. Additionally, since it has been shown that the disappearance of the substrate in similar phase transfer reactions exhibits first-order kinetics, the rate constants were determined using a linear-least-squares regression program.

For synthetic scale reactions, this procedure was carried out on a 10 mmol scale. The products were isolated by washing the mixture with water to remove borohydride by-products, and the organic layer was dried over $MgSO_4$. The product was isolated by fractional distillation.[12]

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References and Notes

1. Starks, C.M., Liotta, C.L. and Halpern, M. "Phase Transfer Catalysis," Chapman and Hall, New York, **1994**, pp. 1-25.
2. (a) Blanton, J.R. and Kruzska, S.J. *Microchemical Journal* **1993**, *47*, 120.; (b) Blanton, J.R. *Reactive and Functional Polymers* **1996**, manuscript in press.
3. (a) Santaniello, E., Ferraboschi, P., Fiecchi, A., Grisenti, P. and Manzocchi, A. *Gazzetta Chimica Italiana* **1987**, *117*, 701; (b) Santaniello, E., Ferraboschi, P., Fiecchi, A., Grisenti, P. and Manzocchi, *J. Org. Chem.* **1987**, *52*, 671; (c) Santaniello, E., Fiecchi, A., Manzocchi, A. and Ferraboschi, A. *J. Org. Chem* **1983**, *48*, 3074.
4. Bianchi, G., Achilli, F. and Gamba,A. *J. Chem. Soc. Perkin Trans.* **1988**, 417.

5. (a) Adjidjonou, K. and Caze, C. *Eur. Polym. J.* **1994**, *30*, 395; (b) Adjidjonou, K. and Caze, C. *Eur. Polym. J.* **1995**, *31*, 749.

6. When **1** was dissolved in water, it underwent a slow hydrolysis.

7. This was a possiblity that was put forth by Santaniello in reference 3c using stoichiometric data. However, the work was not pursued using spectroscopic data.

8. This phenomenon is probably the reason **1** was less reactive toward ketones than the acyloxyborohydrides reported in the literature.

9. Polymer supported: Tomoi, M. and Ford, W.T. "Polymeric Phase Transfer Catalysts Using Functional Polymers," Sherrington, D.C. and Hodge, P, eds., Wiley and Sons, New York, **1988**, pp170-190.

10. It was noted that vigorous stirring led to a gelatinous material that behaved as a poor reducing agent. Analysis of this material was not conclusive except the amount of active hydride was substantially lower.

11. The amount of active hydride was determined using a modification of the technique reported by Morton International for the analysis of borohydrides: "Sodium Borohydride Digest, third ed.,"Morton International, Andover, MA, 1995, pp 48-52. The meq of hydride determined in this manner were divided by the weight of the sample to yield a loading in meq of hydride/g of reagent. All samples gave loadings between 1.1 and 1.4 meq of hydride/g of reagent.

12. [Compd. No.: ir (paraffin oil), cm^{-1}; ^1H nmr (solvent), δ ppm] Compd. **1**: ir, 3300, 2800, 2250, 1620, 1050; nmr (D_2O) 8.1-7.5 (m, Ar-H), 3.7

(strong s, PEG chain), 3.4 (s, CH_2O-BH-), 1.7, 0.45, -0.9, -2.2(4 singlets, B-H). Compd. **2**: bp (°C), 106-108; ir, 3500, 1050; nmr, 3.2 (t, CH_2-O), 2.1 (broad s, OH), 1.5 (heptet, C-H), 1.0 (d, CH_3-). Compd. **3**: bp (°C), 153-156; ir, 3500, 1050; nmr, 3.6 (broad triplet, CH_2-O), 2.0-1.0 (mutiple signals), 1.0 (triplet, CH_3-). Compd. **4**: bp (°C), 171-174; ir, 3500, 1050; nmr, 3.5 (broad triplet, CH_2-O), 2.0-1.0 (mutiple signals), 1.0 (triplet, CH_3-). Compd. **5**: bp (°C), 203-205; ir, 3500, 3100, 1500, 1450, 1050; nmr, 7.3 (s, Ar-H), 4.6 (s, CH_2-O), 2.1 (s, -OH).

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