

CHAPTER 3

BOROHYDRIDE REDUCING AGENT DERIVED FROM ANION  
EXCHANGE RESIN : CHEMOSELECTIVE REDUCTION OF  
 $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS

CHAPTER IIIBOROHYDRIDE REDUCING AGENT DERIVED FROM ANION EXCHANGE RESIN :  
CHEMOSELECTIVE REDUCTION OF  $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS\*ABSTRACT

Borohydride exchange resin (BER) exhibits high chemoselectivity between  $\alpha,\beta$ -unsaturated aldehydes and ketones. BER reagent reduces aldehydes much faster than ketones. Chemoselectivity also observed between different types of  $\alpha,\beta$ -unsaturated ketones. Thus benzalacetone was reduced much faster than benzalacetophenone and this could be explained on the basis of steric effect.

Introduction

Selectivity provides a formidable challenge for the synthetic chemist. The ability to make a specific structural change no more, no less provides the vehicle for enhanced synthetic efficiency.

Chemoselectivity refers to functional group differentiation. In a molecule that contains more than one type of

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bond recognition of the different intrinsic reactivity of each bond type becomes the primordial concern. Thus, the differential reaction between an alkene and a carbonyl group is a relatively simple problem of chemoselectivity where as, recognition of the different reactivity of two carbonyl groups in the same molecule is a more difficult problem. Problems of chemoselectivity still represent the major obstacle in a complex organic synthesis where as many as 40 percent of the steps can involve manipulation of protecting groups clearly a major contributor to synthetic inefficiency.

Selective reduction of one carbonyl group in presence of other such groups is a frequent synthetic problem. It has been solved in various ways. A difficult, yet commonly encountered problem in organic synthesis is the clean reduction of aldehyde in the presence of keto groups. Although aldehydes are reduced faster than ketones, the absolute rates are often too fast to take advantage of the favourable difference in the relative reduction rates. Consequently in recent years various reagents have been developed for such selective reductions.

Huchins and Kandasamy have shown the unique ability of tetrabutylammonium cyanoborohydride<sup>1</sup> (TBAC) a new versatile reducing agent. In hexamethyl phosphonamide (HMPA) solvent at 25° C, TBAC is an exceptionally mild reagent which reduces only primary iodides and to a lesser extent, bromides to the corresponding hydrocarbons. Remarkably, the addition of acid

to the medium drastically alters the reducing ability of the reagent and permits the selective reduction of aldehyde to be performed fairly in the presence of most other functional groups including ketones. Competitive reduction experiments of nonaldehyde and 2-undecanone using excess of TBAC and varying acid concentration as seen, increasing the acidity rate increases and nonaldehyde completely reduces in 15 min while the ketone was essentially untouched.

In 1975 Sell used Lithium tri-*t*-butoxyhydroaluminate, sodium tetrahydroborate and lithium tetrahydroborate in stoichiometric amounts to reduce benzaldehyde in the presence of acetophenone or butanol in the presence of butanone<sup>2</sup>. Lithium tetrahydroaluminate and lithium cyanatohydroborate are found to be less selective. Similarly sodium triacetoxy borohydride was also used to reduce benzaldehyde in presence of acetophenone<sup>3</sup>.

Under usual conditions  $\text{NaBH}_4$  can not reduce aldehyde and ketone selectively. However, the recent excellent studies by Murahashi et al. and by Gribble and Ferguson have shown that boracyclononane 'ate' complex and triacetoxyborohydride can reduce aldehyde and ketone selectively. Their selectivity can be attributable to their decreased reducing capability. Y. Maki and co-workers have shown that selected thiols decreased the reducing capability of  $\text{NaBH}_4$ , and  $\text{NaBH}_4$ -thiol complex reduced aldehyde and ketone selectively<sup>4</sup>. The reduction with  $\text{NaBH}_4$ -thiol complex could be controlled by the steric factor of thiol.

H.C. Brown developed exceptionally mild, highselective new reducing agent 9 Borabicyclo (3,3,1) nonane-pyridine<sup>5</sup> (9BBN-Py) cleanly reduces the aldehyde group in the presence of keto and many other functional groups, making possible the clean, selective reduction of aldehyde groups in complex molecules. The application of this newly synthesized reagent 9 BBN-Py for the selective reduction of aldehyde in presence of ketones is summarised in Table 1.

Table 1

Relative Reactivities of Aldehydes with Respect to ketones towards 9BBN-Py. in EtOH at 25<sup>o</sup> C competition Experiment

Compound	Product	mol %
Cyclohexanone	Cyclohexanol	1.5
+		
Benzaldehyde	Benzyl alcohol	93.0
Acetophenone	1 Phenyl ethanol	2.0
+		
Benzaldehyde	Benzyl alcohol	94.0
Pentanone	3-Pentanol	2.5
+		
Octanal	1-Octanol	94.5

Diisopropyl carbanol on W-200 N-D alumina is the first reagent reported by G.H. Posner which allows reduction of an unhindered aldehyde in the presence of an unhindered cyclohexanone<sup>6</sup>. These new alcohol-alumina reagents will be useful in special cases requiring selective reduction of one carbonyl group in the presence of another or in the presence of other functional groups.

N.Y.M. Fung and co-workers reported selective reduction of aldehydes by Tributyltinhydride adsorbed on silica gel<sup>7</sup>. Tributyltinhydride is one of the more readily available and least reactive organotin hydrides. In absence of catalysts it will readily reduce strongly electrophilic species such as carbonium ions, isocyanates, isothiocyanates and carbonyl groups bearing powerful electron withdrawing functions.

Silica gel catalyzed reduction of ketones and aldehydes by tributyl tin hydride is a selective and high yield method with the advantage of mild nonbasic conditions and without the need of strong acidic workup to neutralise alkoxide salts. Reductions are performed simply and the products easily isolated in the pure state by elution off the silica gel. Most importantly, the method allows the reduction of aldehydes in the presence of ketones with a high degree of selectivity.

In 1978 Midland and Tramontato developed B-Alkyl-9-borobicyclo (3,3,1) nonanes as mild chemoselective reducing

agents for aldehydes<sup>8</sup>. The most remarkable feature of these reagents is their ability to selectivity in the reduction of aldehydes in the presence of ketones. Competition between benzaldehyde and acetophenone for single e.g. B-Siamyl-9BBN reduced in 95 % aldehyde in 2 h with no detectable reduction of ketone.

Marashashi and co-workers shown stereo; chemo and Regio-selective reduction of carbonyl groups via the Lithium-Di-n-butyl-9BBN "Ate" complex<sup>9</sup>. High chemoselectivity was realized in the reduction of benzaldehyde and acetophenone (97:3). Under these reaction conditions, methyl benzoate and benzyl cyanide were not reduced. These results indicate that this reagent should permit the chemoselective reduction of aldehyde in the presence of ketones, esters,  $\alpha$ -nitrites. It is often required to reduce specific functional groups in a stereo, chemo or regioselective manner successful approaches to such reductions have hitherto involved modification of the borohydride with sterically bulky substituents or electron - withdrawing groups. The present development therefore, provides an entirely new approach to this problems.

Use of lanthanoids for the selective ketalization and reduction of carbonyl compounds was reported by A.L. Gemal<sup>10</sup>. In most cases selective reduction of less reactive carbonyl groups in the presence of a more reactive one was done. Even if the exact nature of protective species is not yet known

this procedure should find many applications in organic synthesis.

G.C. Andrew reported ammonia-borane and t-butylamine borane are highly reactive members of the general class of amine borane reagents which exhibited chemoselective properties equal to a greater than previously reported reagents<sup>11</sup>. There has been much recent interest in the development of chemoselective reducing agents capable of distinguishing aldehyde and ketone functionality in a predictable manner. While all of these reagents are capable of reducing an aldehyde in the presence of methyl ketone, few have the ability to distinguish between aldehydes and more reactive ketones. But all these reagents have serious drawbacks such as, limited availability a high cost, need of excess of reagent, quenching of the reaction to avoid over reduction and requirement of a solid surface. We wish to report the borohydride exchange resin (BER) shows high chemiselectivity between  $\alpha,\beta$ -unsaturated alcohols in the following pages.





PRESENT WORK

During last decade or so, various reagents have been developed for such selective reductions<sup>1-11</sup>. These reagents are mostly capable of reducing aldehydes in the presence of ketones but the selective reductions between aldehydes<sup>2</sup> and between ketones<sup>9</sup> are rare. Recently we have observed that BER prepared from Amberlite IRA-400 shows selectivity in the reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds to the corresponding unsaturated alcohols (chapter II), the reduction rates being different for different carbonyl compounds. Now we wish to report regarding high chemoselectivity of BER in the reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds. The chemoselectivity was studied by competitively reducing the equimolar mixtures of  $\alpha,\beta$ -unsaturated carbonyl compounds with BER reagent. As shown in Table 1, BER reagent reduced  $\alpha,\beta$ -unsaturated aldehydes chemoselectively to corresponding alcohols in the presence of ketones (entries 1 to 5) and the rate of reduction was much faster in methanol than in ethanol (entries 1 and 5). As shown in entries 1 to 4, BER shows a very good selectivity between aldehyde and ketone with preferential reduction of aldehyde in methanol at 25° C.

The selectivity of BER is equal to or greater than that of previously reported selective reagents<sup>1-9</sup>. For example, in the selective reduction between benzaldehyde and acetophenone, 100:8 selectivity with sodium triacetoxyborohydride<sup>3</sup>;

Table 1

Chemoselective Reduction of  $\alpha,\beta$ -Unsaturated Carbonyl Compounds to Unsaturated Alcohols with Borohydride Exchange Resin at 25°C  
 [Solvent : Methanol for entries 1-4 and 6; and ethanol for entry 5]

Entry	Starting mixture	Time (hr)	% Reduction product
1	Cinnamaldehyde + Benzophenone	1.50	92.00* 5.00
2	Cinnamaldehyde + Benzalacetone	2.00	95.00 3.00
3	Cinnamaldehyde + Benzalacetophenone	2.25	93.00 2.00
4	Cinnamaldehyde + Benzalacetylacetone	2.50	90.00 3.00
5	Cinnamaldehyde + Benzophenone	3.00	91.50
6	Benzalacetone + Benzalacetophenone	5.00	85.00

\* GC trace is given in Fig. 1

100:9 with sodium borohydride in presence of thiol<sup>4</sup>, 94:2 with 9-borabicyclo (3.3.1) nonane (9BBN)-pyridine<sup>5</sup>, and 100:0 with  $\text{BH}_3\text{LiCl}$  system<sup>6</sup> have been reported. The selectivity of BER is equal to or greater than that of previously reported selective reagents<sup>3-6</sup>. A good selectivity was also observed between ketones (entry 6). Thus benzalacetone was reduced much faster than benzalacetophenone and this could be explained on the basis of steric effect.

## EXPERIMENTAL

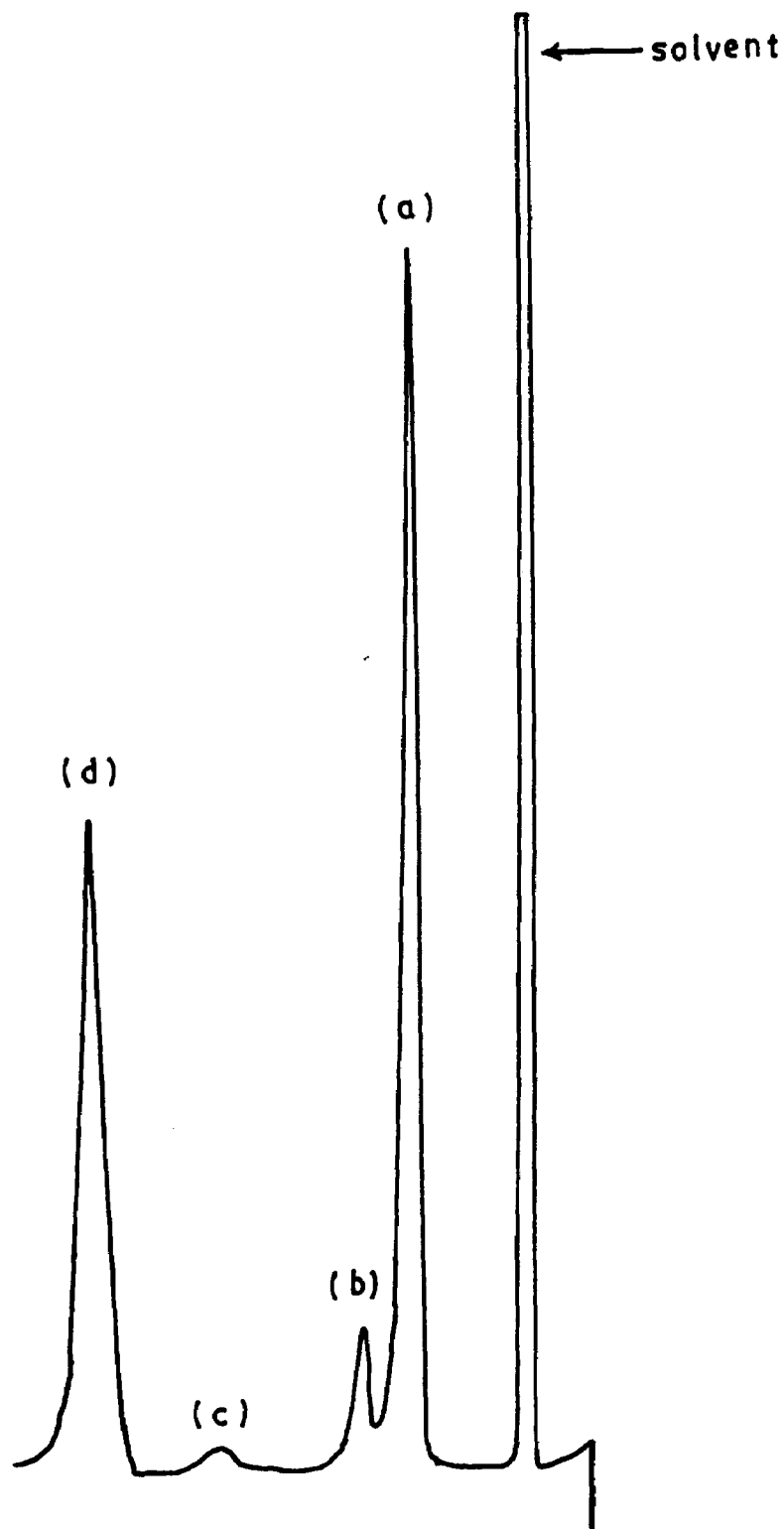
### General

Cinnamaldehyde (BDH), citral (BDH), sodium borohydride (BDH), crotonaldehyde (BDH), Benzal acetone (High Purity Chemicals Ltd.) and Benzophenone (BDH) were commercially available and distilled before use. Amberlite IRA-400 and Amberlyst A-26 resins are marketed by Rohm and Haas Ltd. The reaction solvents were reagent grade and unless indicated otherwise, were not specially dried. Benzal acetophenone, Bengal acetyl acetone and Dibenzalacetone were prepared according to the procedures given in the 'Text book of Organic Chemistry' by I.A. Vogel. IR spectra were recorded on Perkin-Elmer Infracord and PMR on 90 MHz spectrometer. Purity was checked by GLC AIMIL DUAL column gas chromatograph chromosorb-W column.

### General method for borohydride exchange resin reduction :

A mixture of  $\alpha,\beta$ -unsaturated carbonyl compounds (1 mmol each) in methanol (20 ml) was stirred with BER<sup>12</sup> (0.5 g, 2.5 mmol/gm capacity) prepared from Amberlite IRA-400 at 25° C. After the desired time (reaction monitored by TLC) the solution was filtered and the evaporation of the solvent furnished the product which was analysed by GLC using AIMIL dual column gas chromatograph model 5500 series on carbowax 40 % chromosorb-w column. The used reagent could be regenerated to its initial activity by treating with a solution of NaBH<sub>4</sub>.

Fig. 1



- (I) Column used: QF 10 % Carbowax chromosorb-w-column .  
(1/8" x 6' Stainless Steel Column) at 220°C .
- (II) Carrier flow : 30 ml/min. (0.8 Kg/cm<sup>2</sup>). Carrier gas: Nitrogen .
- (III) Detector — FID; Series x 1 .
- (IV) Instrument : CHEMITO, 3800 series gas Chromatograph .
- |                        |                    |
|------------------------|--------------------|
| (a) Cinnamyl alcohol . | (c) Benzhydrol .   |
| (b) Cinnamaldehyde .   | (d) Benzophenone . |

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