

REDUCTION OF ALDEHYDES AND KETONES WITH TETRAALKYLAMMONIUM BOROHYDRIDES

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Misinterpretations regarding the selectivity of tetraalkylammonium borohydride reductions in dichloromethane are resolved. Tetrabutylammonium borohydride offers several advantages, but both it and tetraethylammonium borohydride are highly useful synthetic reagents.

In 1976 we reported that tetrabutylammonium borohydride was a synthetically useful reagent for carrying out reductions of aldehydes and ketones in aprotic solvents such as dichloromethane or chloroform.¹ Sorrell and Pearlman have recently extended our work to the tetraethylammonium salt.² Both tetraethyl- and tetrabutylammonium borohydride are commercially available³ and offer considerable potential as reagents for synthetic organic chemistry. We report here a direct comparison of some of the physical and chemical properties of tetraethyl- and tetrabutylammonium borohydride which clarifies the relative advantages and disadvantages of the two reagents.

A definitive description of selectivity was a major thrust of our original report,¹ and we showed that there are large differences in reactivity for various classes of carbonyl compounds. Acid chlorides are most reactive, followed by aldehydes, ketones and esters in order of decreasing reactivity. High yield reductions of a keto ester, an unsaturated aldehyde and an unsaturated ketone were used to specifically demonstrate the synthetic utility of tetrabutylammonium borohydride as a selective reducing agent.

One question which remains is whether or not these reagents are useful for the selective reduction of aldehydes in the presence of ketones.² Nonanal is reduced by tetraethylammonium borohydride at a rate which is faster than that of 2-octanone by more than a factor of ten,² but this rate difference cannot be generalized to all ketones and aldehydes. Table 1 shows that substituent effects have a major influence on the relative rates of carbonyl reductions of aldehydes and ketones by borohydride ion in dichloromethane.¹ Clearly steric hindrance such as that introduced by the adjacent quaternary carbon in 2,2-dimethylpropionaldehyde can cause the carbonyl group of an aldehyde to be reduced more slowly -- at a rate comparable to that of unhindered ketones.⁴ Electronic effects of substituents also play an important role in the rate of reduction as indicated by the rate difference for octanal and benzaldehyde and by the observation² of only 53% reduction of p-anisaldehyde with tetraethylammonium borohydride after 24 hrs.

Table 1. Reduction by Tetrabutylammonium Borohydride in Dichloromethane.

Aldehyde or Ketone ^a	Relative Rate ^{b,c}
octanal	>50
benzaldehyde	11
2,2-dimethylpropionaldehyde	2
cyclohexanone	1
acetophenone	0.9
3,3-dimethyl-2-butanone	0.4

^a 1.0 M. ^b 0.25 M reducing agent. ^c Initial rates; see ref. 1.

There is little reason to believe that reductions with tetraalkylammonium borohydrides in dichloromethane should exhibit selectivities which differ markedly as a function of the cation.⁵ Even the relative reactivity of sodium borohydride toward various functional groups⁶ is comparable to that of tetrabutylammonium borohydride. We have now carried out a direct comparison of the selectivities of all three reagents, and the results are summarized in Table 2. The reduction of a 1:1 mixture of benzaldehyde and acetophenone was carried out using tetraethyl- and tetrabutylammonium borohydride in dichloromethane and sodium borohydride in 2-propanol. Each of the three reagents produced similar product ratios, which are probably the same within experimental error. Clearly there is no substantial difference in the selectivity of the two tetraalkylammonium borohydrides. The absence of any major influence on selectivity by the cation is further demonstrated by the fact that sodium borohydride in 2-propanol affords essentially the same product distribution.⁷

Table 2. Competitive Reduction of a 1:1 Mixture of Benzaldehyde and Acetophenone Using a Single Equivalent of Borohydride Ion.^{a,b}

Reducing Agent	Solvent	%C ₆ H ₅ CH ₂ OH ^c	%C ₆ H ₅ CH(OH)CH ₃ ^c
Bu ₄ N ⁺ BH ₄ ⁻	CH ₂ Cl ₂	72	28
Et ₄ N ⁺ BH ₄ ⁻	CH ₂ Cl ₂	80	20
NaBH ₄	(CH ₃) ₂ CHOH	78	22

^a Room temperature, 18-20 hrs. ^b Initial concentrations were 0.15 M borohydride, 0.6 M benzaldehyde, 0.6 M acetophenone. ^c Measured by gas chromatography.

Although the aldehyde is reduced preferentially, the product distribution is only 80:20 at best. The data in Table 2 therefore indicate that none of the three reagents should be considered generally effective for the selective reduction of aldehydes in the presence of ketones. Similar criticism can be directed against some of the other recent claims⁸⁻¹¹ for selective reduction of aldehydes in the presence of ketones (although high selectivity has been observed with certain reagents).⁹⁻¹¹

We have also directly compared tetraethyl- and tetrabutylammonium borohydride as reagents for preparative reductions of acetophenone (Table 3). The reactions were carried out with saturated solutions of reducing agent at room temperature for 16 hr. The higher yield obtained with the tetrabutylammonium salt undoubtedly reflects a rate difference corresponding to the greater solubility of this reagent.⁷ At comparable concentrations there is no reason to expect large differences in reactivity for the two reagents.

Table 3. Reduction of Acetophenone with Saturated Solutions of Tetraalkylammonium Borohydrides in Dichloromethane.^{a,b}

Reducing Agent ^c	%unreacted $C_6H_5COCH_3$	% $C_6H_5CH(OH)CH_3$
$Bu_4N^+BH_4^-$	2	98
$Et_4N^+BH_4^-$	50	50

^a Room temperature, 16 hrs. ^b Using 4 equivalents of reducing agent. ^c At 25°C the maximum solubilities in CH_2Cl_2 are: tetraethylammonium borohydride, 0.13 g/ml (0.9 M) and tetrabutylammonium borohydride, 0.31 g/ml (1.2 M).

Our results show that the value of tetraalkylammonium borohydrides as reducing agents is not in any unique selectivity relative to sodium borohydride but in their convenience because reduction can be carried out in solvents such as dichloromethane and chloroform.¹ These are superior solvents for many organic compounds, and their low boiling points and insolubility in water greatly facilitate isolation and purification of reaction products. Although commercially available,³ tetrabutylammonium borohydride can be simply and rapidly prepared from inexpensive reagents.¹² The tetrabutylammonium reagent is considerably easier to handle and purify¹² than the tetraethylammonium salt, because it is not hygroscopic and is more soluble in organic solvents. On the other hand, the greater water solubility of most tetraethylammonium salts facilitates workup of reductions with tetraethylammonium borohydride. On balance, however, we believe that the ease of handling and purification of tetrabutylammonium borohydride combine with its excellent solubility properties to make it the reagent of choice for borohydride reductions in aprotic solvents.^{1,13-15}

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3. Thiokol-Ventron Division, Alfa Catalog: #10736, tetrabutylammonium tetrahydridoborate; #14123, tetraethylammonium tetrahydridoborate.
4. In Figure 1 of our original article (ref. 1), the labels for pivalaldehyde and acetophenone were interchanged. The aldehyde does in fact react more rapidly as indicated in Table I of that paper and in Table 1 of this communication.
5. The identity of the actual reducing agent in these reactions is uncertain. For example, we previously showed that diborane is produced by a reaction between borohydride ion and dichloromethane, although it is not the sole species responsible for reduction. We have recently found that less than 3% reduction of 0.3 M acetophenone by 4 equivalents of tetrabutylammonium borohydride is observed in benzene after 36 hrs. at room temperature. This suggests that a halogenated solvent facilitates ketone reductions. Quite possibly the diborane which results from reaction with solvent catalyzes reduction by borohydride ion.
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7. At first glance the product ratios may not appear to be in accord with the expected rate ratios. However, the kinetics are not strictly second order (see ref. 1), and the nature of the reducing agent during later stages of the reduction has not been characterized. In addition the preferential reduction of aldehyde lowers its concentration, and this will lead to progressively decreasing selectivity as the reaction proceeds.
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