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Reaction of Alpine-Borane with Aldehydes: Reactivity Rate Assessment by Observation of the Disappearance of the Carbonyl n - π* Peak by UV-Visible Spectroscopy

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Abstract

Due to an unexpectedly difficult reduction of indole-3-carbaldehyde and of isobutyraldehyde using the chiral reducing agent Alpine-Borane, the reactivity of several aliphatic, aromatic, and unsaturated aldehydes was investigated. This was done in order to determine whether there was a relationship between aldehyde structure and reduction rate. It was found that aliphatic aldehydes and aromatic aldehydes with no strongly electron-donating groups on the arene ring reduced faster than unsaturated aldehydes.

Introduction

As part of an ongoing project to synthesize chiral beta-deuterated amino acids, the asymmetric reduction of deuterated indole-3-carbaldehyde or an N-protected derivative thereof needed to be pursued. This proved unexpectedly difficult, yielding unchanged starting material after prolonged periods. Therefore, an investigation of the reactivity of aldehydes containing various alkyl and aryl structures with Alpine-Borane as a suitable chiral reducing agent was undertaken.

Why Use a Chiral Reducing Agent?--Sterochemistry is very important to biological molecules. Each enantiomer has very different properties when interacting with other chiral molecules. One may give a desired effect while the other gives no effect or an adverse effect. One example is thalidomide, a drug used in the 1960's to treat morning sickness in pregnant women. In this case, one isomer is an effective drug, but the other causes serious birth defects (Dhar, 1994).

Fig. 1. Reaction of a prochiral ketone to an optically active secondary alcohol.

The reduction of a prochiral ketone to an optically active secondary alcohol (Fig. 1) is one of the most common ways to produce asymmetry in a molecule. Optically active secondary alcohols are found in natural compounds, bio-

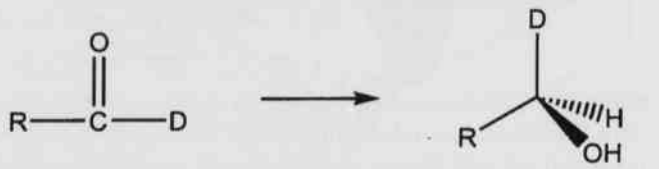

Fig. 2. Reaction of a deuterated aldehyde to an optically active primary alcohol.

compounds, liquid crystals, and are synthetic intermediates (Dhar, 1994). The reduction of a deuterated aldehyde gives an optically active primary alcohol (Fig. 2), which can then be used for mechanistic studies of chemical and biochemical processes (Midland et al., 1979).

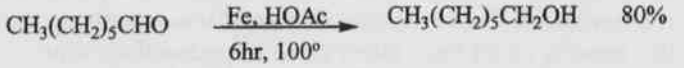

Fig. 3. Metal-Acid reduction of an aldehyde.

Early Reducing Agents.--Before the discovery of boranes as reducing agents, reduction methods often involved high temperatures, long reaction times, and low yields of the desired products. One way of reducing an aldehyde to an alcohol was a metal-acid procedure (Fig. 3; Brown and Krishnamurthy, 1979). Ketones could be reduced to alcohols by sodium in ethanol or zinc-sodium hydroxide in ethanol (Brown and Krishnamurthy, 1979). Both aldehydes and ketones could be reduced to the corresponding carbinols by the Meerwein-Ponndorf-Verley reduction (Fig. 4). Esters could by reduced to alcohols by the Bouveault-Blanc method (Fig. 5). Although the discoveries

of the Bouvealt-Blanc method and the Meerwein-Ponndorf-Verley reduction were improvements in reduction methods, better procedures were needed.

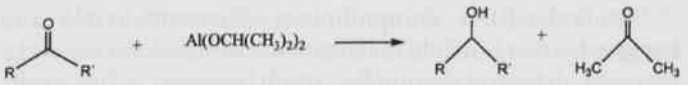

Fig. 4. Meerwein-Pondorf-Verley reduction of a ketone.

Fig. 5. Bouveault-Blanc reduction of an ester.

Discovery of Diborane as a Reducing Agent.--In 1936 H.C. Brown, then a graduate student at the University of Chicago, began to study the reaction of diborane with aldehydes and ketones in order to better understand the structure of newly synthesized borane-carbonyl. He soon discovered that aldehydes and ketones reacted quickly with diborane to form dialkoxyboranes, which gave the corresponding alcohols upon hydrolysis (Fig. 6; Brown and Krishnamurthy, 1979).

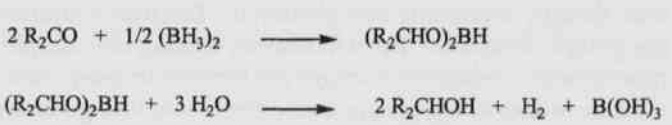

Fig. 6. Reduction of a ketone to an alcohol using diborane.

Unfortunately, diborane was in short supply at the time, so interest in the compound was marginal. During World War II, efforts to produce uranium borohydride for military testing led to new syntheses of diborane and sodium borohydride. These developments initiated new interest in borohydrides and changed procedures for the reduction of functional groups. Many more borane compounds for organic reductions have since been produced. Super-Hydride®, L- and K- Selectrides®, and LS- and KS-Selectrides™ (Figs. 7-9) are examples of alkali metal trialkylborohydrides which are capable of stereo- and regioselective reductions. Dialkylboranes and trialkylboranes have also been synthesized to achieve selective reductions (Brown and Krishnamurthy, 1979).

Dialkylboranes.--The dialkyborane 9-borabicyclo[3.3.1]nonane (9-BBN) can be synthesized by the hydroboration of 1,5-cyclooctadiene (Fig. 10; Knights and Brown, 1968). The reaction proceeds through an organoborane intermediate and leads to a 1,5 isomer, which is much more stable than the 1,4 isomer because it is composed of two fused six-membered rings, whereas the 1,4 isomer is composed of a seven-membered ring fused to a five-membered ring. (Knights and Brown, 1968).

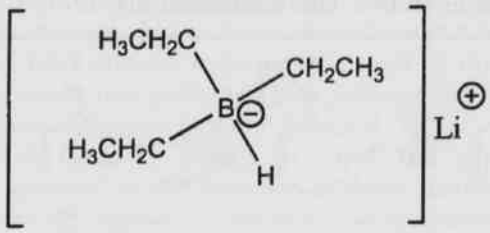

Fig. 7. Super-Hydride

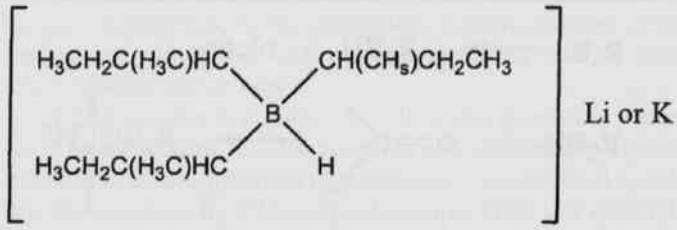

Fig. 8. L- and K-Selectrides

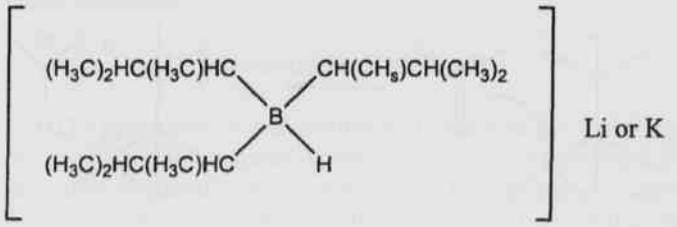

Fig. 9. LS- and KS-Selectrides

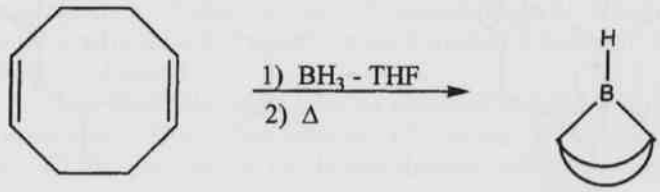

Fig. 10. Synthesis of 9-BBN.

9-BBN is superior to other dialkylboranes in that it is not sensitive to oxygen and offers a faster rate of hydrobo-

ration. The faster reaction time is due to the exposed position of the boron atom, which makes 9-BBN especially good for trapping carbanions, carbenes and similar intermediates (Knights and Brown, 1968a). 9-BBN reduces α,β-unsaturated aldehydes and ketones to allylic alcohols (Fig. 11) and is mild enough to not reduce almost all other functional groups, such as ester, amide, carboxylic acid, nitro, halogen, and nitrile. (Brown and Krishnamurthy, 1979).

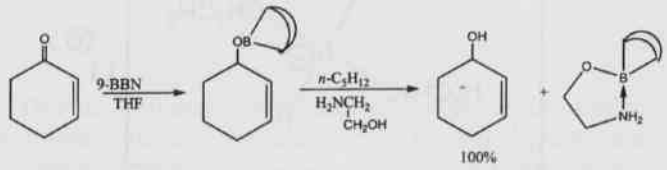

Fig. 11. Reduction of an unsaturated ketone to an allylic alcohol using 9-BBN.

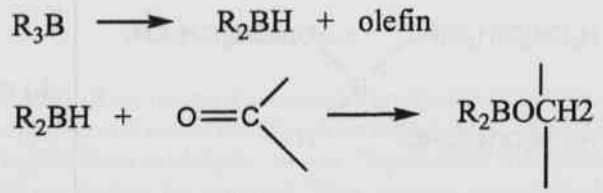

Fig. 12. Schematic of the dehydroboration - reduction process.

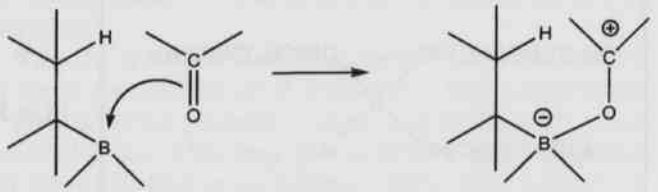

Fig. 13. Formation of the aldehyde - borane complex.

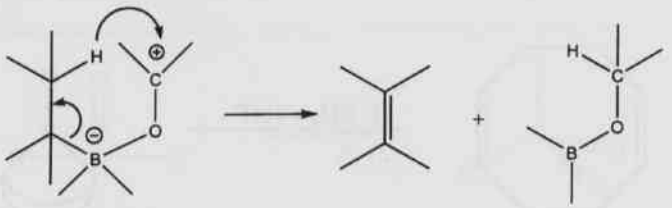

Fig. 14. Hydride delivery from the aldehyde - borane complex.

Trialkylboranes.--The addition of an alkyl group to 9-BBN expands its uses greatly. *B*-alkyl-9-BBN compounds are tolerant of many functional groups, as is 9-BBN, but *B*-alkyl-9-BBN compounds are so mild that they are capable of reducing aldehydes in the presence of ketones, which are less reactive. They are chemo- and enantioselective reducing agents whose efficiency and rate of reaction depend on the structure of the alkyl group on 9-BBN (Midland and Tramonato, 1978).

B-alkyl-9-BBN compounds reduce aldehydes and ketones by two possible mechanisms: a cyclic process and a two-step dehydroboration-reduction process. The cyclic mechanism has been shown to dominate the reduction of aldehydes, whereas the dehydroboration-reduction process takes place when hindered or unreactive ketones are reduced. The dehydroboration-reduction process begins by a slow dissociation of the trialkylborane (Fig. 12; Midland, 1989).

Evidence that the cyclic process predominates is based on second-order kinetics data, the change in rate with structural and electronic changes in the aldehyde, and the results of asymmetric reductions. (Midland and Zderic, 1982). The cyclic reduction of aldehydes involves a complex between the organoborane and the carbonyl oxygen followed by a β hydride transfer to the carbonyl carbon (Figs. 13 and 14; Midland, 1989). The yellow color when an aldehyde is added to an organoborane is due to the aldehyde-organoborane complex. Tertiary hydrogens preferentially react in presence of secondary or primary β hydrogens (Midland et al., 1979).

Mechanism and Rate of Reaction of Trialkylboranes.--Electron donating groups on benzaldehyde slow the reaction by stabilizing the positive charge on the carbonyl carbon, thereby increasing complexation. Electron-withdrawing groups destabilize the carbocation, making the complex more reactive, which encourages the hydride transfer. Since electron-withdrawing groups cause the reaction to go faster, the hydride transfer must be the rate-determining step. More evidence that the hydride transfer is the rate-determining step is the fact that hindered boranes provide faster reaction times, although they decrease complexation. This bimolecular process must also be faster than internal rotation of the complex for the hydride transfer to occur, since rotation would prevent the proper orientation for transfer (Midland and Zderic, 1982).

The rate of reduction of aldehydes by *B*-alkyl-9-BBN compounds depends on the structure of the alkyl group on 9-BBN and the structure of the aldehyde. Electron-withdrawing groups on the aldehyde increase the rate of reaction due to destabilization of the aldehyde-organoborane complex. Electron-donating groups slow down the reaction and lead to lower enantiomeric purities, possibly due to introduction of the dehydroboration-reduction side-reaction (Midland, 1989). Greater substitution at the β position of the **B**-alkyl-9-BBN compound increases the rate of reaction because it does not favor complexation, making the complex more reactive. (Midland and Zderic, 1982).

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The rate of reduction is also increased if the alkyl group of the organoborane can form a favorable syn coplanar B-C-C-H conformation. This arrangement leads to overlap of the developing pi system of the liberated olefin (Midland, 1989).

Alpine-Borane®--Alpine-Borane®, *B*-3-pinanyl-9-BBN, is one of the fastest and most efficient chiral reducing agents that can be prepared from 9-BBN. It reduces aldehydes with an enantiomeric purity that approaches enzymes (Midland et al., 1979). It can be synthesized by the hydroboration of (+)-a-pinene with 9-BBN (Fig. 15; Brown and Krishnamurthy, 1979).

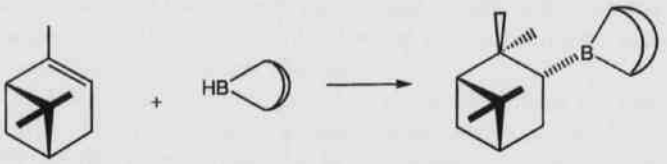

Fig. 15. Synthesis of Alpine-Borane.

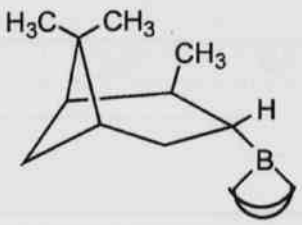

Fig. 16. Steric strain of methyl groups in Alpine-Borane.

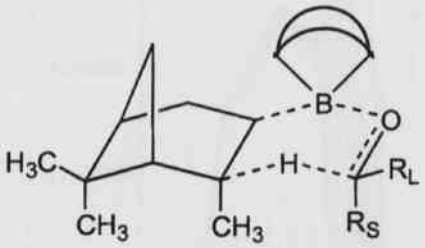

Fig. 17. Boatlike transition state of Alpine-Borane.

Several factors contribute to Alpine Borane®'s unusual reactivity. It has an ability to form a favorable coplanar B-C-C-H arrangement, which allows for favorable formation of the displaced olefin. (Midland, 1979)

Alpine-Borane® also has a buildup of steric strain which is relieved upon going to the -pinene product. This strain is caused by the *cis*-1-methyl group being forced into the gem-dimethyl groups on the four-membered ring (Fig. 16; Midland, 1979). The transition state of the reduction of an aldehyde by Alpine-Borane® resembles a boat-like cyclohexane structure (Fig. 17). Large groups are in the equatorial position, which places them as far as possible from the pinanyl group. Small groups occupy the axial position. In aldehydes, this position is occupied by a hydrogen. In ketones, an alkyl group must occupy the axial position, which leads to steric interactions with the methyl of the pinanyl group. These interactions can impede the cyclic process. In this case, Alpine-Borane® will eventually dissociate into 9-BBN and the reduction proceeds by the dehydroboration-reduction pathway. This pathway gives longer reaction times and less selectivity (Midland, 1979).

Research Goals.--In order to study the effects of aldehyde structure on the reduction of those aldehydes by Alpine-Borane®, numerous aldehydes were reduced and the reactions followed by Fourier Transform Infrared (FTIR) Spectroscopy and later, by UV-visible (UV-vis) spectroscopy. Compounds of interest included aromatic, aliphatic, para-substituted, meta-substituted, α,β-unsaturated aldehydes, and aldehydes with electron-donating and/or electron-withdrawing groups.

FTIR was the first choice to follow the reactions, where we hoped to follow the disappearance of the carbonyl peak. When this method proved unsatisfactory, we decided to follow the reactions by UV-vis spectroscopy. With this method, we were able to follow the disappearance of the carbonyl $n \rightarrow \pi^*$ transition. We were also able to obtain spectra in quick succession, which became necessary for following the faster reactions.

Materials and Methods

The reduction of one millimole of each of these aldehydes was studied: trimethylacetaldehyde (pivaldehyde, 2,2-dimethylpropanal); *p*-anisaldehyde (4-methoxybenzaldehyde); isobutyraldehyde (2-methylpropanal); butyraldehyde (butanal); citral; citronellal; benzaldehyde; *m*-anisaldehyde (3-methoxybenzaldehyde); salicaldehdye (2-hydroxybenzaldehyde); 3-nitrobenzaldehyde; 4-nitrobenzaldehyde; trans-2-hexenal; 2-ethylbutyraldehyde (2-ethylbutanal); cinnamaldehyde (3-phenylpropenal); crotonaldehyde (2-butenal, predominantly trans); trans-2-methyl-2-butenal; 3-methyl-2-butenal

Most aldehydes were used as obtained without further purification. Due to the presence of a strong -OH peak in the FTIR spectrum of the butyraldehyde used, this compound was distilled and stored over anhydrous $MgSO_4$.

Initially, 1 millimole of each compound was reacted with 1.5 millimoles of Alpine-Borane® (0.5 M in tetrahydrofuran, obtained from Aldrich Chemical Co.), and the reactions were followed by FTIR. (Fig. 18 and 19) Approximately one analysis of 32 scans was taken per hour. Using this method, little or no change was seen in spectra

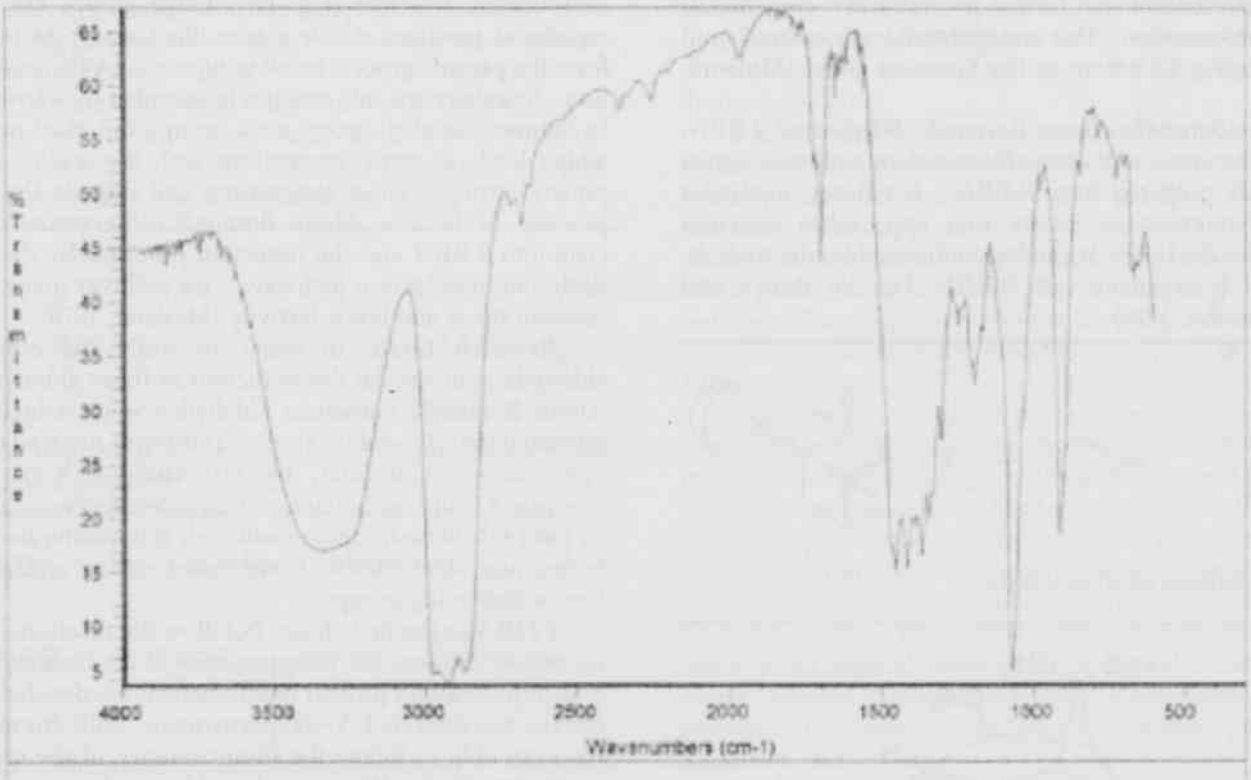

Fig. 18. FT-IR spectrum of Alpine Borane (0.5 M solution in THF).

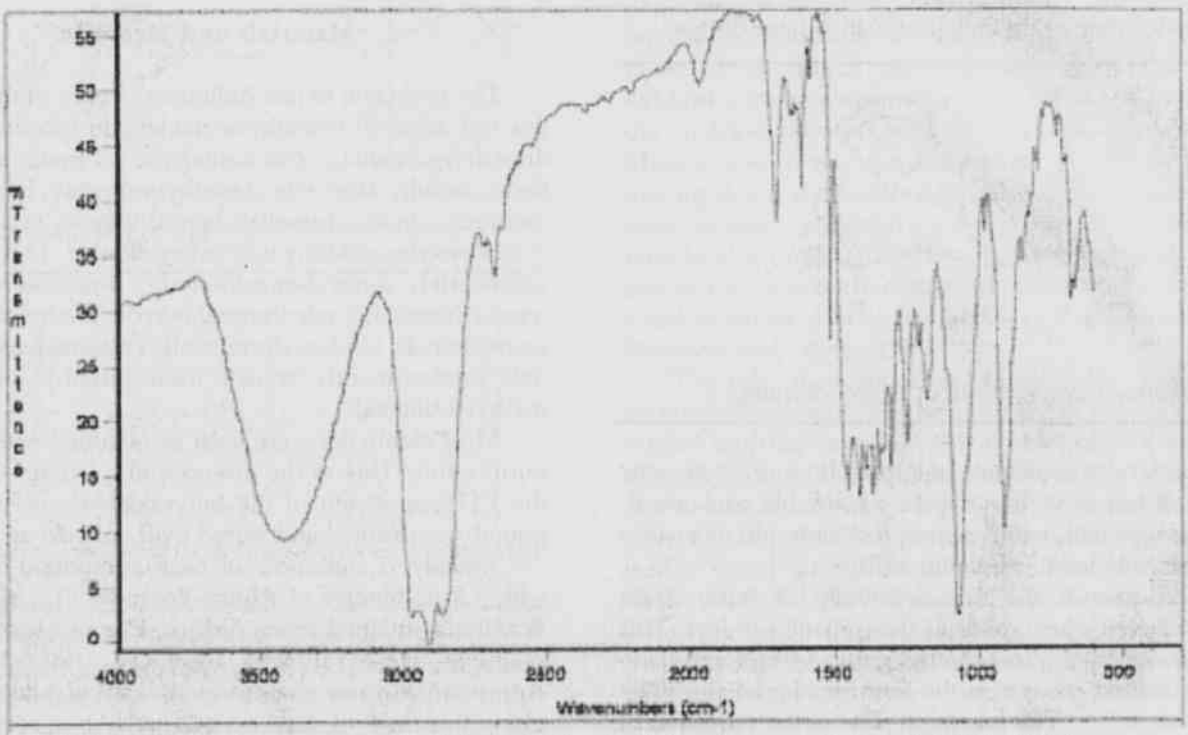

Fig. 19. FT-IR spectrum of 1 mmol p-anisaldehyde in 3 mL Alpine-Borane solution (0.5 M in THF)

over several analyses. To test the effectiveness of the Alpine-Borane® used, the reaction of benzaldehyde and Alpine-Borane was followed by thin-layer chromatography against benzaldehyde and benzyl alcohol. This test showed that the benzaldehyde had not been reduced, so a new supply of Alpine-Borane® was used thereafter. Even using the new bottle of Alpine-Borane®, no change was seen in the FTIR spectrum of benzaldehyde over several hours. Then the reduction was attempted using 3 millimoles of Alpine-Borane®, and the spectrum still showed no change. Thus, it was found that the FTIR was not an acceptable method for following these reactions for two reasons: (1) the solutions were too dilute in Alpine-Borane® to follow the disappearance of the carbonyl peak, and (2) the reduction happened so quickly that only one or two subsequent scans would have shown any change.

UV-Visible spectroscopy was chosen to follow the reactions. There were several advantages to this method over FTIR: the $n \rightarrow \pi^*$ transition in the spectrum would not be masked by the Alpine-Borane® (Figs. 21 and 22), the spectra could be taken more frequently, as often as once every seven seconds, and the spectra could easily be overlaid to show the disappearance of the $n \rightarrow \pi^*$ peak (Fig. 20).

The reactions of 1 millimole of aldehyde and 1.5 millimoles of Alpine-Borane® were run directly in the cuvette. Spectra were taken as often as the machine would allow, which was about every seven seconds. Because many of the reductions were quite rapid and essentially complete in less than one minute, this was quite helpful. The reduction times given in the next section were obtained by timing the disappearance of the $n \rightarrow \pi^*$ peak.

Results and Discussion

As expected, aliphatics were reduced very quickly. Hindered compounds, notably trimethyacetaldehyde, were reduced slightly slower than less hindered compounds.

The presence of multiple bonds did not seem to affect the reduction unless the compounds were α,β-unsaturated. In this case, resonance interactions caused the reductions to take place significantly more slowly.

Aromatics were expected to be reduced at about the same rate as alkenes or aliphatics. We found that aromaticity did not slow the reaction. Within the groups of aromatics, electron-withdrawing groups caused the reaction to proceed very quickly. Electron-donating groups slowed the reaction, but not significantly.

Tables of results for each group of compounds and discussions of individual compounds are presented. The mechanism of the reduction of isobutyraldehyde shown in Fig. 23

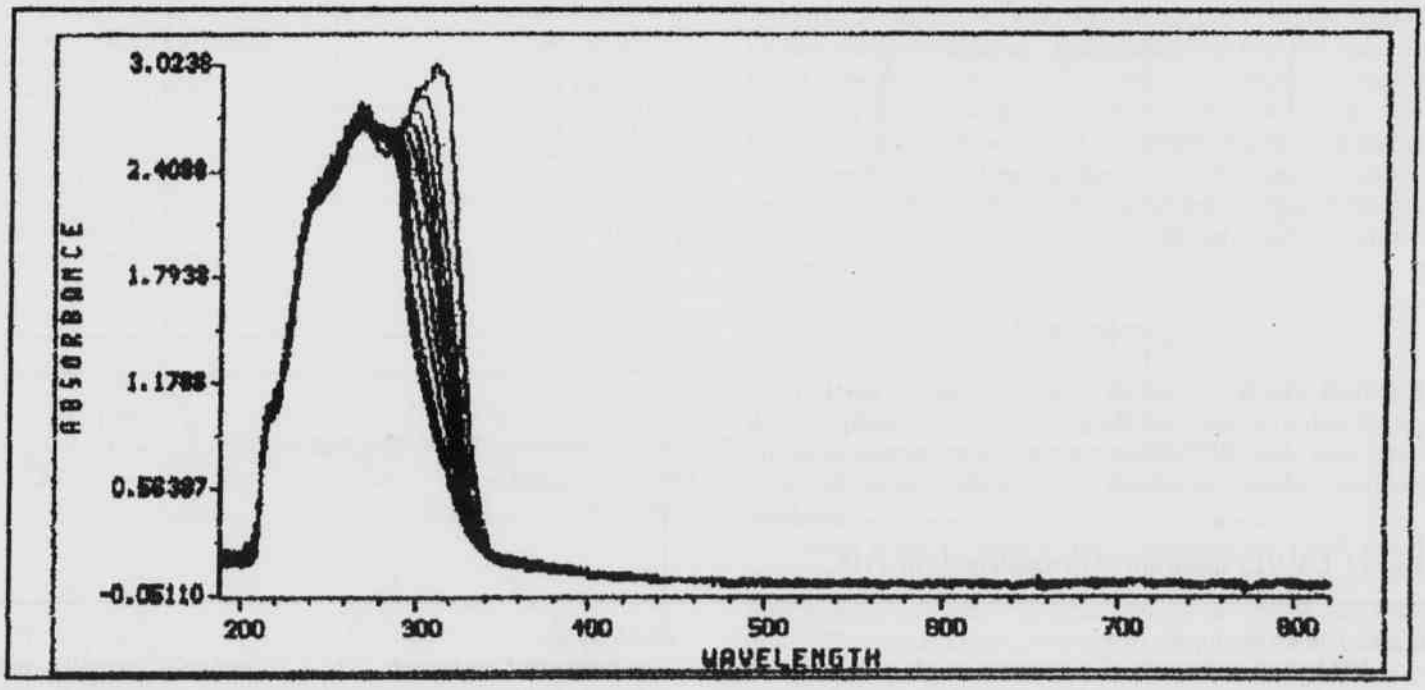

Fig. 20. Overlaid spectra of the reduction of trimethylacetaldehyde.

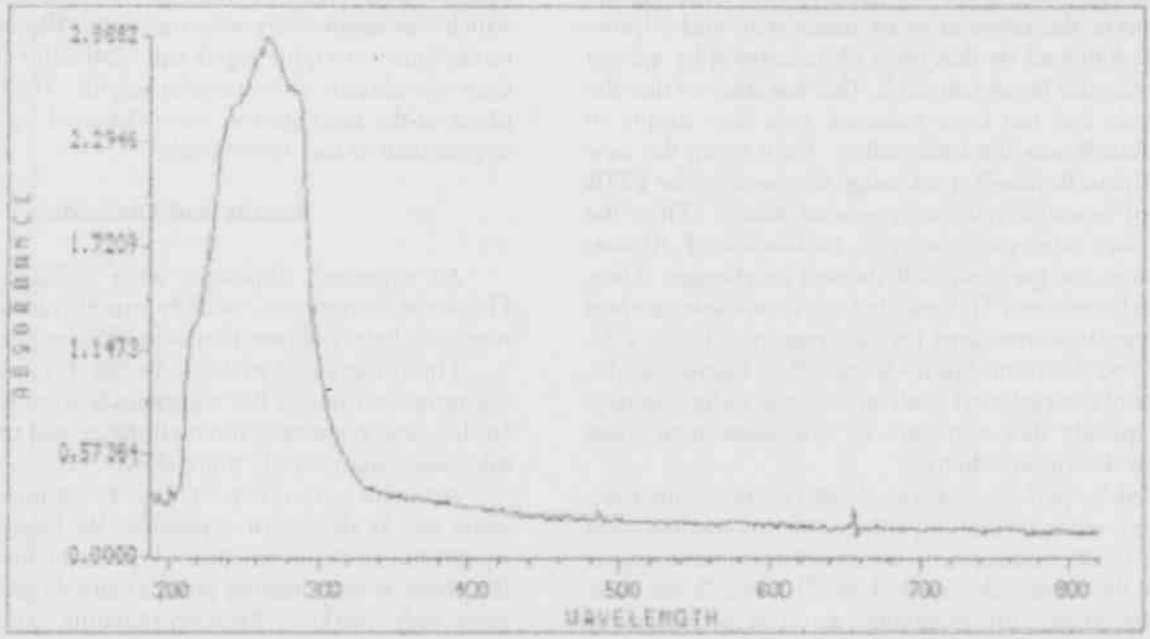

Fig. 21. UV-VIS spectrum of Alpine-Borane (0.5 M in THF)

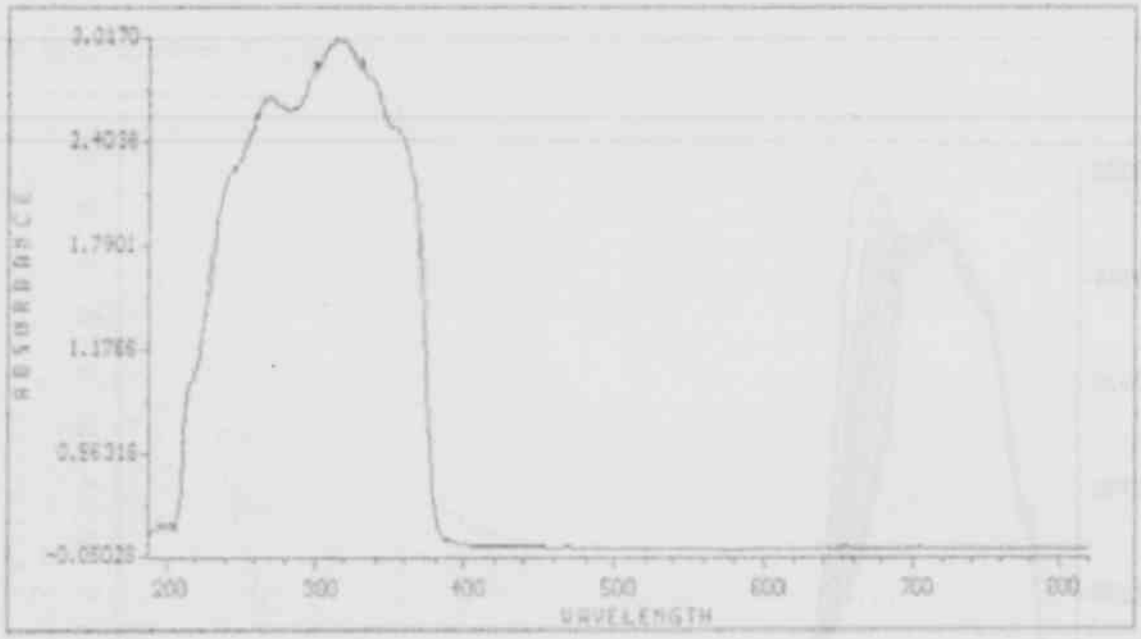

Fig. 22. UV-VIS spectrum of benzaldehyde in THF.

is given as an example.

Aliphatic Compounds.–These compounds were reduced very quickly, because minimal steric hindrances and no resonance effects were present. Significant reduction in rate occurred only when the carbon was tertiary (trimethylacetaldehyde).

Aromatic Compounds.--These compounds, overall, were reduced slightly slower than the aliphatic compounds, due to steric hindrance, and in the case of *p*-anisaldehyde, resonance effects.

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Table 1

Compound	Reaction Time
citronellal	30 seconds
butyraldehyde	1 minute
isobutyraldehyde	1 minute
2-ethylbutyraldehyde	1 minute
trimethylacetaldehyde	5 minutes

Table 2

Compound	Reaction Time
3-nitrobenzaldehyde	1 minute
4-nitrobenzaldehyde	1 minute
benzaldehyde	3 minutes
m-anisaldehyde	5 minutes
p-anisaldehyde	30 minutes

Table 3

Compound	Reaction Time
3-methyl-2-butenal	15 minutes
crotonaldehyde	20 minutes
trans-2-methyl-2-butenal	30 minutes
cinnamaldehyde	30 minutes
citral	40 minutes
trans-2-hexenal	40 minutes
salicylaldehyde	did not reduce

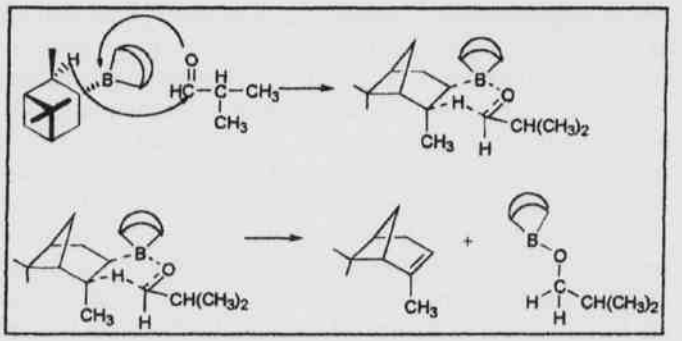

Fig. 23. Reduction of isobutyraldehyde by Alpine-Borane®.

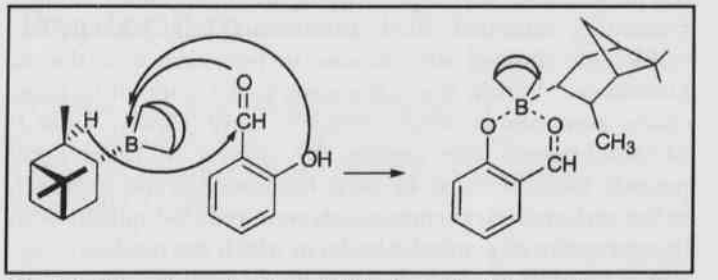

Fig. 24. Reaction of salicylaldehyde with Alpine-Borane®.

The addition of the electron-withdrawing nitro group to benzaldehyde caused 3- nitrobenzaldehyde and 4-nitrobenzaldehyde to be reduced more quickly than benzaldehyde. *p*-Anisaldehyde is reduced slowly because the methoxy group is electron- donating by resonance, stabilizing the complex. Since the hydride transfer is the rate-determining step, complex stabilization increases the reaction time for this compound. The methoxy group on *m*-anisaldehyde is in the wrong position to donate by resonance and is electron-withdrawing inductively, causing the reaction to be faster than the reduction of *p*-anisaldehyde.

α,β-***unsaturated Compounds.***--These compounds were reduced slowly because resonance decreased the double bond character of the carbonyl group. Within this group, the long-chain compounds were reduced more slowly than the shorter ones.

Trans-2-methyl-2-butenal was reduced more slowly than 3-methyl-2-butenal because the methyl group on the second carbon causes hindrance. Salicylaldehyde was not reduced by Alpine-Borane®, possibly due to a boron complex involving both oxygens of the compound (Fig. 24). Overlaid spectra show a peak moving to higher and higher wavelengths, supporting this idea. Also, the solution turned red when the Alpine-Borane® was added, instead of the yellow color that was observed with the addition of Alpine-Borane® to the other compounds.

Conclusions

Interest in the rates of reduction by Alpine-Borane® was stimulated due to the sluggish reactivity of indole-3-carboxaldehyde in tryptophan synthesis. We were also interested in future attempts to synthesize chiral primary alcohols.

Initial plans to observe the reductions by FTIR failed due to interference by Alpine-Borane® in the spectra. UV-VIS proved to be an excellent method to follow the reactions. There was no interference in the spectra which could be taken in quick succession and overlaid for easy comparison.

The three classes of compounds that were chosen for this study were aldehydes which contained saturated alkyl,

α,β-unsaturated, and aryl. Among the compounds studied containing saturated alkyl substituents, only trimethylacetaldehyde showed any increase in reduction time due to hindrance. Within the α,β-unsaturated compounds, long-chain compounds were reduced more slowly. *trans*-2-Methyl-2-butene was among the slowest of these compounds, likely because of steric hindrance in the approach to the carbonyl. Aryl compounds were reduced quickly with the exception of *p*-anisaldehyde, in which the methoxy oxygen is capable of electron donation through resonance. *m*-Anisaldehyde was reduced quickly because the methoxy group is in the wrong position to donate by resonance and is electron-withdrawing inductively. 3-nitrobenzaldehyde and 4-nitrobenzaldehyde were reduced very quickly due to the presence of the electron-withdrawing nitro group.

Each group of compounds was reduced as predicted, although we expected more variation in the reduction times among the aliphatic compounds, due to varying amounts of steric hindrance.

Literature Cited

Brown, H. C. and **S. Krishnamurthy.** 1979. Boranes for organic reductions - A forty- year odyssey. Aldrichim. Acta 12:3-11.

Dhar, R. K. 1994. Diisopinocampheylchloroborane, (DIP-Chloride™), an excellent chiral reducing reagent for the synthesis of secondary alcohols of high enantiomeric purity. Aldrichim. Acta 27: 43-51.

Knights, E. F. and **H. C. Brown.** 1968. Cyclic hydroboration of 1,5-cyclooctadiene. A simple synthesis of 9-borabicyclo[3.3.1]nonane, an unusually stable dialkylborane, J. Am. Chem Soc. 90: 5280-5281.

Knights, E. F. and **H. C. Brown.** 1968a. 9-borabicyclo[3,3,1]nonane as a convenient selective hydroborating agent. J. Am. Chem Soc. 90: 5281-5283.

Midland, M. M. and **A. Tramontano.** 1978. *B*-Alkyl-9-borabicyclo[3.3.1]nonanes as mild, chemoselective reducing agents for aldehydes. J. Org. Chem. 43: 1470-1471.

Midland, M. M.; S. Greer; A. Tramontano and **S. A. Zderic.** 1979. Chiral trialkylborane reducing agents. Preparation of 1-deuterio primary alcohols of high enantiomeric Purity. J. Am. Chem Soc. 101:2352-2355.

Midland, M. M. and **S. A. Zderic.** 1982. Kinetics of Reductions of Substituted Benzaldehydes with *B*-alkyl-9-borabicyclo[3.3.1]nonane (9-BBN). J. Am. Chem. Soc. 104:525-528.

Midland, M. M. 1989. Asymmetric reductions with organoborane reagents. Chem. Rev. 89:1553-1561.