

SECONDARY α -DEUTERIUM ISOTOPE EFFECTS ON BOROHYDRIDE
REDUCTIONS AND ON THE PROTONATION OF BENZALDEHYDE

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As part of a general investigation of secondary α -deuterium isotope effects on addition reactions, we have studied the reduction of benzaldehyde and benzaldehyde-d with sodium borohydride, sodium cyanoborohydride, and borane-morpholine. Since these results may be relevant to current discussions of the mechanism of borohydride reductions,¹⁻¹⁰ we report them now in preliminary form.

Pseudo-first order rates of reaction for deuterated and undeuterated aldehyde with excess reducing agent were determined by monitoring the disappearance of absorption at 246 nm. The observed second order rate constants and isotope effects are as follows:

Reagent	Solvent	$(k_{\text{H}})_{\text{obs}} \text{ M}^{-1} \text{ sec}^{-1}$	$(k_{\text{H}}/k_{\text{D}})_{\text{obs}}$
NaBH_4	i-C ₃ H ₇ OH, [NaOH] $\approx 10^{-3} \text{ M}$	5×10^{-1}	0.883 ± 0.012
NaBH_3CN	i-C ₃ H ₇ OH, "pH" = 5.3	1.1×10^{-4}	0.852 ± 0.018
NaBH_3CN	H ₂ O, pH = 5.5	1.1×10^{-4}	0.878 ± 0.005
$\text{O}(\text{C}_2\text{H}_4)_2\text{NH}\cdot\text{BH}_3$	H ₂ O, pH ≥ 5.5	4.5×10^{-3}	0.897 ± 0.010
$\text{O}(\text{C}_2\text{H}_4)_2\text{NH}\cdot\text{BH}_3$	H ₂ O, pH = 2.4	1.5×10^{-2}	0.81 ± 0.02

Second-order rate constants were calculated on the assumption that the first hydride transferred is rate determining,¹⁰ and that there are four equivalents of reducing hydride in borohydride,¹⁰ three in cyanoborohydride,¹¹ and one in morpholine-borane.⁸ The cyanoborohydride reductions, which are acid catalyzed,¹¹ were run in acetate buffers. The morpholine-borane reaction is uncatalyzed above pH = 4, and acid catalyzed at lower pH in acetate or chloroacetate buffers.^{8,9} An isotope effect of about 0.78 may be derived for the acid-catalyzed portion from measurements at pH = 2.4, where about 70% of the reaction is catalyzed. At lower pH, hydrogen evolution from decomposition of the reagent prevented accurate rate measurements.

If acid-catalysis involves rate-determining hydride transfer to protonated aldehyde, then evaluation of the isotope effect for the reduction step requires knowledge of the equilibrium isotope effect for protonation. A value $K_{\text{H}}/K_{\text{D}} = 1.06$ (for dissociation of the conjugate acid of aldehyde) was obtained from the difference in H₀ between sulfuric acid solutions which gave identical spectra for deuterated and undeuterated aldehyde in the vicinity of half-protonation. Then,

for the hydride transfer, $k_H/k_D = (K_H/K_D) [(k_H)_{\text{obs}}/(k_D)_{\text{obs}}] = 0.90$ and 0.93 for cyanoborohydride in isopropanol and water, and 0.83 for morpholine-borane.

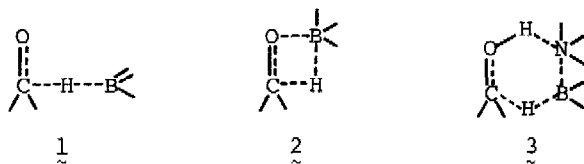
The observed isotope effects fall within the range of 10-20% per D frequently observed in reactions involving $sp^2 + sp^3$ hybridization change at carbon.¹² They are somewhat less substantial than equilibrium isotope effects recently found for addition of carbon, nitrogen, and oxygen nucleophiles to aldehyde carbonyl groups (0.78 to 0.72).^{13,14} The equilibrium isotope effect for hydride addition should be the maximum effect for complete $sp^2 + sp^3$ hybridization change. This is not directly accessible, but might be approximated using acetaldehyde \rightleftharpoons ethanol as a model. From published infrared analyses, this isotope effect might be estimated as $K_H/K_D = 0.78$.¹⁵ A superimposed inductive isotope effect similar to that for aldehyde protonation might move this to a value in the vicinity of 0.83 (for aldehyde \rightarrow alkoxide anion or protonated aldehyde \rightarrow alcohol). The observed isotope effect is thus a sizeable fraction of the probable maximum effect, suggesting that very substantial rehybridization at the carbonyl carbon has occurred by the time the transition state is reached.

Prevailing interpretations^{1-4,17} of the stereochemistry of hydride reductions of cyclohexanones seem to require an early transition state, with little rehybridization at the carbonyl carbon. Studies with morpholine-borane reductions have also been interpreted on the basis of a transition state with little hydride transfer.⁸ On the other hand, large polar substituent effects on borohydride reductions of a variety of aryl carbonyl compounds,^{6,8,16} secondary isotope effects of α -hydrogens (β -d effect),⁶ and perhaps other results^{6,18} may be best interpreted on the basis of a "late" transition state. If the secondary α -deuterium effect is largely a function of transition state hybridization, the present results are most consistent with the later transition state. They are clearly incompatible with any mechanism⁸ in which coordination at the carbonyl oxygen is *rate-determining*.

Several possibilities might be suggested to resolve the apparent contradictions about transition state structure. Most simply, the structure of the transition state may vary with the environment of the carbonyl group;^{7,9} the need to overcome resonance stabilization might result in a later transition state for aryl carbonyl compounds. Even if the transition state is similar in all cases, there appears to be no formal requirement that "progress along the reaction coordinate" must mean *parallel* change of all parameters which are modified during the rate-determining step (such as hybridization, B-H cleavage, C-H bonding). Furthermore, the magnitude of the secondary α -deuterium isotope effect may be a decidedly non-linear function of this progress,¹⁹ and may not even be simply related to the hybridization changes. We note that the isotope effect in S_N2 reactions is close to unity,¹² though the hybridization must approximate sp^2 . Apparently, congestion about the central carbon occasioned by approach of the nucleophile may compensate for the hybridization change from sp^3 to sp^2 . It is possible that attack of a nucleophile may involve substantial electronic and even

covalent interaction with the carbonyl carbon, with restriction of the bending modes of the aldehydic and α -hydrogens, before there has been much progress toward tetrahedral geometry. It may be pertinent that a theoretically calculated reaction coordinate for attack of H^- on formaldehyde pictures approach of the nucleophile from the carbon end of the carbonyl group.²⁰

A striking feature of the isotope effects we report here is their relative constancy. An uncritical application of the Hammond postulate predicts that more exothermic processes (such as reaction with a more active reductant, or hydride transfer to the *conjugate acid* of the aldehyde) should have earlier transition states, and hence, isotope effects closer to unity. However, despite sizeable differences in rates, the only marked difference in isotope effect is the *larger* effect on the acid-catalyzed morpholine-borane reduction. One interpretation of the constancy might be that all the reactions have similar hybridization at the carbonyl carbon. However, the Hammond postulate was originally stated (and should be most valid) for steps involving formation or reaction of an unstable intermediate, *via* transition states very close to it in energy and structure.²¹ Borohydride reductions are indeed exothermic and have quite low enthalpies of activation.^{1,2,8,9,22} But their strongly negative *entropies* of activation may indicate a considerable difference in structure from reactants. Furthermore, it is possible that the different reductions studied here might have reaction coordinates which differ *qualitatively*. Possibilities might include direct transfer of hydride (1) or a cyclic mechanism (2),^{2,9} perhaps with



prior complex formation. Protonation on the carbonyl oxygen should render such coordination less likely. However, another cyclic mechanism such as 3 could be imagined, or the function of the acid catalyst could be to make the borane more accessible for reaction.⁸ If the transition states compared are no longer gradations along essentially the same reaction pathway, there is no need to expect a gradation in isotope effect with variation in reagent or conditions. Then, similarity or variations in isotope effects could be quite fortuitous.

In conclusion, the substantial isotope effects found for reduction of benzaldehyde with a variety of boron hydride reagents suggest that interaction of the reagent with the carbonyl carbon is fairly well advanced in the transition state. Generalization of this result to a conclusion that all borohydride reductions have "late" transition states is quite uncertain at this stage.

References and Footnotes

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