A COMPUTER STUDY OF BOROHYDRIDE REDUCTION KINETICS AND STEREOCHEMISTRY

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Abstract—A computer simulation of the sodium borohydride reduction of an alkyl-substituted cyclohexanone in isopropanol has shown the following two apparently contradictory experimental observations to be compatible: (1) The kinetics are experimentally indistinguishable from second-order, with the first hydride transfer rate determining. (2) The *cis*:*trans* product ratio changes significantly during the course of reduction. The calculations suggest that the fourth hydride transfer is the second-slowest, with a rate constant approximately eight times that of the first.
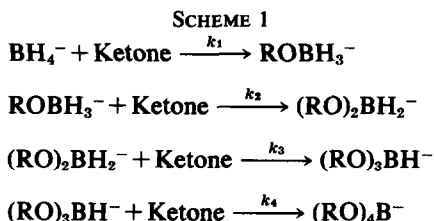
INTRODUCTION

Kinetic studies of sodium borohydride reductions of alkyl-substituted cyclohexanones have shown the reactions to be second-order within the limits of experimental detection, with the first hydride transfer being rate-determining.[1-3] Although the more highly substituted intermediate alkoxyborohydride species should be more sterically demanding than BH_4^-, no change in the ratios of epimeric alcohol products during the course of reduction would be expected if the last three hydride transfers were infinitely faster than the first. Yet significant changes in product stereochemistry have been observed during the reduction of a number of alkylcyclohexanones.[3] The present study is intended to amplify the explanation given in the previous paper:[3] that buildup of an intermediate borohydride species can lead to an observable change in product ratios and still lie outside the range of kinetic detection.

RESULTS AND DISCUSSION

A change in stereochemistry implies that the concentration of a bulky intermediate borohydride

species builds up during the reaction, and competes with BH_4^- for the remaining ketone. If the reaction is viewed as a sequence of four hydride transfers (Scheme 1),[4] one of the last three rate

SCHEME 1

$$BH_4^- + Ketone \xrightarrow{k_1} ROBH_3^-$$

$$ROBH_3^- + Ketone \xrightarrow{k_2} (RO)_2BH_2^-$$

$$(RO)_2BH_2^- + Ketone \xrightarrow{k_3} (RO)_3BH^-$$

$$(RO)_3BH^- + Ketone \xrightarrow{k_4} (RO)_4B^-$$

constants must be comparable to the first. In the following discussion, this second-slowest rate constant will be called k_s.

The fast reaction of sodium triisopropoxyborohydride with ketones[3,5] demonstrates that alkoxy substitution increases the hydride donor activity of boron. In Scheme 1, the electronic effect of successive substitution of hydride by alkoxide should tend to make the rate constants in the series progressively larger. Steric hindrance should operate in the reverse direction, particularly if the alkoxide groups are derived from a bulky ketone rather than from solvent.*

The balance of steric and electronic effects could lead to any of the following orders of rate constants: $k_4 > k_3 > k_2 > k_1$ ($k_s = k_2$), $k_4 < k_3 < k_2 > k_1$ ($k_s = k_4$), or $k_4 < k_3 > k_2 > k_1$ ($k_s = k_2$ or k_4). The progressively increasing bulk of the reducing species does not allow the order $k_4 > k_3 < k_2 > k_1$ ($k_s = k_3$); if the bulk of two alkoxide groups were sufficient to counteract the electronic effect of alkoxy substitution, then a third group would cause a further decrease in reactivity. Since, however, $k_s = k_3$ might be allowed by a different reaction scheme,† this case will also be considered.

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*The alkoxide groups in Scheme 1 could be derived from the ketone, or they could be derived from a hydroxylic solvent by a mechanism involving solvent-assisted hydride transfer.[6] In either case, alkoxide exchange with the solvent could occur in a subsequent fast step. The kinetics of the reduction of 3,3,5-trimethylcyclohexanone with sodium triisopropoxyborohydride[3] suggest that the alkoxide groups do not exchange with solvent. Other evidence suggests that alkoxy exchange with solvent does occur, at least with tetraalkoxyboronate species.[7]

†See, for example, Ref 3. A mechanism involving disproportionation of $(RO)_3BH^-$, where R = 3,3,5-trimethylcyclohexyl, was suggested to explain the kinetics of reduction of 3,3,5-trimethylcyclohexanone with sodium triisopropoxyborohydride.

To examine the effect of different choices of k_s and of the magnitude of k_s/k_1 upon product ratios and second-order rate plots, a computer program was written to simulate borohydride reductions. The program uses as input trial values of rate constants for the four hydride transfers and the product ratio (cis:trans alcohol) resulting from each step. The concentrations of all species, and cumulative product ratios, are calculated as a function of reaction time.

The reaction sequence of Scheme 1 was assumed for the calculations. In the differential equations resulting from Scheme 1, the time differential was approximated by a small time increment (0·1–0·5 sec for the calculations described below). A second-order Runge-Kutta method[8] was used to calculate the concentration of a given species from its concentration during the previous increment.

The reduction of cis-3,5-dimethylcyclohexanone was chosen for computer simulation. The observed second-order rate constant for this reaction in isopropanol at 0° with approximately stoichiometric ratios of borohydride to ketone was $1·50 \times 10^{-2}$ 1/mole-sec.[3] The trans:cis ratio of alcohol products was found to vary from 14:86 at zero percent reaction to 26·6:73·4 at one hundred percent reaction. Under the same conditions, but with a large excess of borohydride (25 moles per mole of ketone), the product ratio was 13·0:87·0. The latter result indicates that the hydride transfers prior to the second-slowest produce a total of 13% of the trans alcohol. For the purposes of the computer calculations, each of these steps was assumed to give the same amount (13%) of the trans alcohol.*

The amount given by the remaining hydride transfers was then obtained from the percentage given by the overall reaction under stoichiometric conditions (26·6%). Thus, for example, the percentages of trans alcohol from each step used as input for the case $k_s = k_3$ were: (1) 13%, (2) 13%, (3) 40·2%, (4) 40·2%. Calculations were carried out for each of the three possible choices of k_s. In each case, k_1 was set equal to $1·50 \times 10^{-2}$ 1/mole-sec. The two fast rate constants were set equal to 100 k_1, and the k_s/k_1 ratio was adjusted until the best fit to the experimental data was obtained in a plot of product ratio vs. percent reaction.

Since the experimental kinetics were indistinguishable from second-order, strict adherence to the situation $k_1 \ll k_2$, k_3, k_4 had to be assumed in

the experimental rate calculations. In order to compare these with the theoretical calculations, the theoretical and experimental data had to be treated identically. It was hoped that a decision could then be made as to whether a given deviation from second-order kinetics could have gone undetected in experimental rate plots.

To simulate experimental rate plots, eight reaction times were chosen from each set of calculated data as typical of times at which aliquots of the reaction mixture were analyzed during rate determinations.[3] These data were used to generate a rate constant assuming strict second-order kinetics. Since the experimental method measured the contribution of all borohydride species to the total hydride concentration, this assumption was made in the computer simulations; the total hydride concentration was treated as if it were all due to the BH_4^- ion. Eq. 1, in which a is the initial ketone concentration, b the initial borohydride concentration, and x the concentration of borohydride reacted at time t, is the integrated second-order rate expression for the case in which $k_1 \ll k_2$, k_3, k_4. This equation was used to generate data for a least-squares plot of kt vs. reaction time.

$$kt = \frac{1}{a-4b} \ln \frac{b(a-4x)}{a(b-x)} \qquad (1)$$

Rate constants and intercepts (kt at $t = 0$, converted to percent reaction) obtained from the least-squares plots are given in Table 1 for $k_s = k_2$, $k_s = k_3$ and $k_s = k_4$. The kinetic situations considered are those for which the calculated plots of product ratio vs. percent reaction best fit the experimental data (Fig 1).

The least-squares lines and the points to which they were fit are plotted in Fig 2. Experimental data[3] for a group of alkylcyclohexanones closely resembling cis-3,5-dimethylcyclohexanone in structure and reactivity (cyclohexanone, 3- and 4-methyl-, cis-3,5- and trans-3,4-dimethyl-, 3-t-
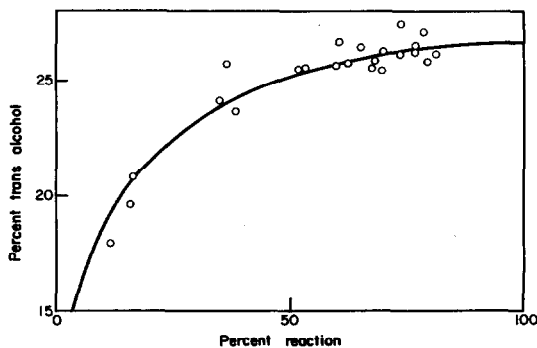

Fig 1. Calculated (line) and experimental (points) percent trans alcohol from the reduction of cis-3,5-dimethyl-cyclohexanone as a function of percent reaction; best fit for the case $k_s = k_4$.

*The stereochemistry presumably varies smoothly from the first to the last step of the reduction. Any choice of individual step product ratios would be arbitrary, however. The assumption used avoids arbitrary choices, and is valid for the purpose of the calculations if the rate constants intervening between k_1 and k_s are sufficiently large.
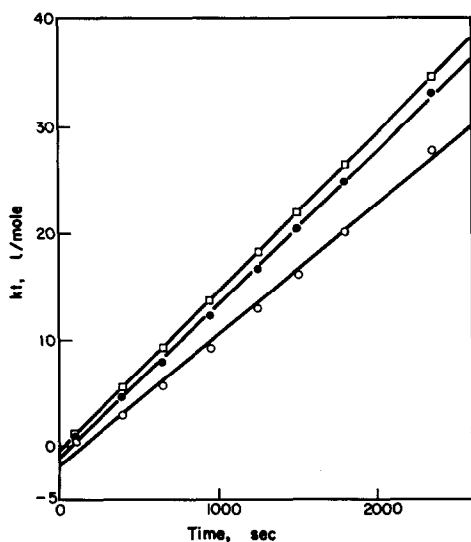
Fig 2. Calculated values of kt and least-squares lines for $k_s = k_2$ (○), $k_s = k_3$ (●) and $k_s = k_4$ (□).

butyl-, and *cis*-3,5-di-t-butylcyclohexanone) were chosen for comparison with these plots. The average RMS deviation of experimental points from the least-squares lines was found to be 0·32 l/mole. By inspection of the calculated and experimental plots, and by comparison of the RMS deviations, it was concluded that curvature of data points away from the least-squares lines would have been detected for the case $k_s = k_2$ (RMS deviation 0·62 l/mole). The curvature would not have been detected in the other two cases (RMS deviation 0·28 for $k_s = k_3$, 0·05 for $k_s = k_4$).

Experimental intercepts at $t = 0$ for the same group of cyclohexanones were within three percent of zero reaction in all cases. The calculated intercepts (Table 1) further rule out $k_s = k_2$, and also make $k_s = k_3$ very unlikely. The remaining possibility, $k_s = k_4$, fits the experimental data well. The small discrepancy between calculated and experimental intercepts (−4·6 and 1·4±1·5 percent reaction, respectively) could be caused by a systematic error in the experimental data.

Essentially identical results were obtained when

the fast rate constants were increased to 1000 k_1, or when the values used to determine the percentage of *trans* alcohol given by each hydride transfer were varied within their experimental errors (13·0%±1·0% for steps preceding the second-slowest, and 26·6%±0·4% for the overall reduction).

Buildup of an intermediate borohydride species, and its effect on the observable change in product ratios during the course of reduction, may now be examined in greater detail. Concentrations of BH_4^- and the alkoxyborohydrides calculated for the case $k_s = k_4$ are plotted in Fig 3 as a function of percent reaction (the concentration of BH_4^- has been divided by 10 to put it on scale with the other species). The concentration of the slow intermediate, trialkoxyborohydride, increases to a maximum at about 25% reaction. Since trialkoxyborohydride is responsible for almost two-thirds of the *trans* alcohol produced by the overall reaction, buildup of this intermediate leads to an easily detectable change in stereochemistry.
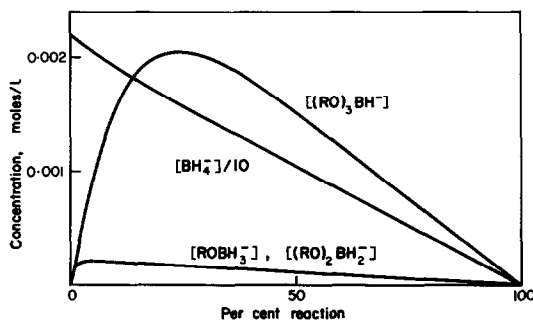

Fig 3. Concentrations of borohydride species as a function of percent reaction for the case $k_s = k_4$.

CONCLUSIONS

The calculations support the conclusion[3] that buildup of an intermediate borohydride species can lead to an observable change in product ratios during the course of a reduction and still lie outside the range of kinetic detection. They further suggest that $(RO)_3BH^-$ is the slow intermediate, with $k_4/k_1 \approx 8$.

If, as seems likely from available data,[3] the rate

Table 1. Simulated borohydride reductions of *cis*-3,5-dimethylcyclohexanone

$k_2/k_1{}^a$	k_3/k_1	k_4/k_1	Percent axial (*trans*) alcohol				k^b l/mole-sec	RMS dev,^{c} l/mole	Extrapolated % reaction at t = 0
			from BH_4^-	$ROBH_3^-$	$(RO)_2BH_2^-$	$(RO)_3BH^-$			
2	100	100	13	31·1	31·1	31·1	1·24	0·62	−22·3
100	4	100	13	13	40·2	40·2	1·44	0·28	−12·6
100	100	8	13	13	13	67·3	1·49	0·05	−4·6

$^a k_1 = 1·50 \times 10^{-2}$ l/mole-sec; ^{b}Overall rate constant by least-squares (see text); ^{c}RMS deviation of points from least-squares line.

constant for reduction of *cis*-3,5-dimethylcyclohexanone with sodium triisopropoxyborohydride is a great deal more than eight times the rate constant for reduction of the same compound with sodium borohydride, then the alkoxide groups on $(RO)_3BH^-$ must be derived from the ketone rather than the solvent (isopropanol). The case $k_8 = k_4$ should then apply to reduction in any alcohol solvent. It should be pointed out, however, that an entirely different situation may prevail in aqueous reductions. Since water is a much stronger acid than alcohols, each hydride transfer might be followed by rapid hydrolysis of the initially-formed alkoxyborohydride to a hydroxyborohydride.[9] The balance between electronic acceleration and steric hindrance would be expected to be much different for this species.

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