Transition State Analysis:[1] Evidence against Product Development Control in the Sodium Borohydride Reduction of Ketones

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Summary The kinetic isotope effects in the reduction of ketones of varying degrees of steric hindrance by $NaBH_4$ and $NaBD_4$ are small, inverse, and essentially independent of the amount of steric hindrance, a result in direct conflict with the steric-approach-control–product-development-control explanation of the axial : equatorial alcohol product ratios observed.

THE fact that reduction of cyclic ketones by complex metal hydrides gives stereochemical product ratios markedly dependent on the degree of steric hindrance around the carbonyl group has long been of interest.[2] In general it is found that sterically hindered ketones give predominantly axial alcohols whereas non-hindered ketones give the equatorial product. A number of explanations for this phenomenon has been suggested. The original explanation of Dauben *et al.*[2] involved the concepts of steric approach control and product development control, implying an early transition state for hindered ketones and a later transition state for unhindered ketones. The alternative explanations require an early transition state in all cases with the direction of hydride attack controlled either by steric strain[3] or torsional strain.[4] In recent years all three explanations have been invoked to explain various product ratios,[5-10] and, although there has occasionally been a tendency to discount product development control,[5,6] it has recently been considered a factor in the reductions of ketones[8] and orthoesters.[10] However, most conclusions have been based on product ratios, a parameter that does not reliably give information on the nature of the transition state involved.

Owing to the fundamental difference in the types of explanation, it seemed unlikely that all could be valid and we decided to attempt to establish unambiguously whether the position of the transition state along the reaction coordinate varied with the degree of steric hindrance around the ketone being reduced. For this reason, we have measured the kinetics of reduction of various ketones by sodium borohydride and sodium borodeuteride and determined the deuterium kinetic isotope effects, the magnitude of this effect being a direct measure of the extent of bond breaking in the transition state. The graded series of ketones range from cholestan-3-one, giving 99% equatorial product to 3,3,5-trimethylcyclohexanone, giving a predominance of axial alcohol.† The results (see Table) are, to our knowledge, the first direct evidence concerning the nature of the transition state in this type of reaction.

Isotope effects and product ratios in the reduction of cyclic ketones

Ketone	$k_H{}^a \times 10^4$ ($l\ mol^{-1}\ s^{-1}$)	$k_D{}^a \times 10^4$ ($l\ mol^{-1}\ s^{-1}$)	k_H/k_D	Axial : equatorial product ratio
Cyclohexanone	765	1290	0·59	—
Cholestan-3-one	314	528	0·59	1 : 99
3-Methylcyclohexanone	604	936	0·65	25 : 75
2-Methylcyclohexanone	146	195	0·75	31 : 69
3,3,5-Trimethylcyclohexanone	21·8	31·5	0·67	55 : 45
3,3,5,5-Tetramethylcyclohexanone	1·92	2·72	0·71	—

[a] The rates were determined spectrophotometrically at 25° by the disappearance of the n—π^* ketone band. The second-order rate constants were invariant over a range of concentrations and compraed favourably with values reported for acetone, cyclohexanone. acetophenone, and 2-methylcyclohexanone by Brown *et al.* using the titrimetric method.[11,12]

Three important points emerge from an analysis of the values obtained. Firstly, the isotope effects are inverse. This, although unusual, was not unexpected since hydrolysis of sodium borohydride is known to give rise to an inverse effect,[13] presumably due to the primary isotope effect of the hydrogens being transferred being outweighed by an opposing secondary effect of the other three hydrogens on boron.‡ Secondly, and most importantly, the k_H/k_D values are almost constant and show no systematic trend despite considerable product ratio changes. This strongly suggests that the extent of boron–hydrogen bond-breaking in the transition state is similar in all cases,§ in direct contradiction to the steric-approach-control–product-development-control suggestion.[2] Thirdly, although the magnitude of the primary isotope effect is masked by the secondary inverse effect, the fact that inversion does occur suggests that the primary effect must be quite small, which is consistent with an early transition state for all the ketones as required by the steric and torsional strain explanations.[3,4]

Although the evidence appears to show that product development control is not operating in this particular case, we emphasize that the concept[2] is useful, and may be relevant to a number of other organic reactions.[1,14,15] However, in the borohydride reduction of ketones, it appears that product ratios should be rationalized in terms

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† The series is further extended to 3,3,5,5-tetramethylcyclohexanone, which is considerably more hindered than 3,3,5-trimethylcyclohexanone but for which no product ratio can be determined. Unfortunately, 11-keto-steroids, which give almost exclusively axial products,[2] react too slowly for accurate determination of isotope effects.

‡ The rate-determining step in the reduction is transfer of the first hydrogen.[11] Thus the isotope effect reflects the summed effect of all four boron hydrogens on this step.

§ It is possible that the constant k_H/k_D value could arise from a constant balance of primary and secondary effects.

of steric or torsional strain and not in terms of transition states that occur at various different points along the reaction co-ordinate.

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