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LIMITED ALKOXY GROUP EXCHANGE IN TETRAALKOXYBOROHYDRIDES: EVIDENCE AGAINST THE FOUR-CENTRE TRANSITION STATE IN THE BOROHYDRIDE REDUCTION OF KETONES

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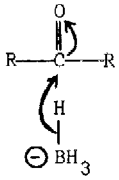
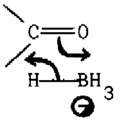
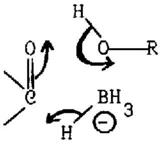
Since the discovery of sodium borohydride by Schlesinger, Brown and co-workers,[1] its use in the reduction of ketones has presented the organic chemist with a continual series of puzzles. The question of the origin of stereoselectivity in cyclohexanone reductions has so far defied rigorous solution,[2] and, even more fundamental, the actual mechanism of reduction still remains in doubt. Both the linear (A)[3] and the four-centre (B)[4] mechanistic possibilities were early recognized, to which must be added the six-centre (C) mechanism, involving a molecule of hydroxylic solvent, more recently suggested by House.[5] The linear mechanism does, of course, represent a number of different mechanisms depending on the role of solvent. It is curious and noteworthy that, in comparison with continued consideration of the four-centre mechanism,[6] the linear mechanism has been almost totally ignored.[7] We wish to present evidence indicating that the popular four-centre mechanism is of no significance in cyclohexanone reductions.



(A)



(B)



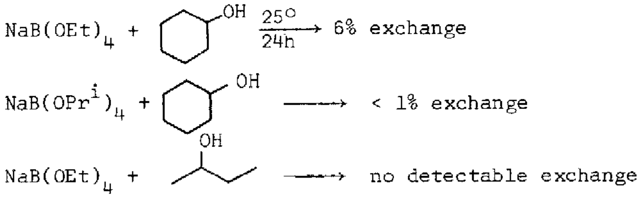
(C)

Inspection of mechanisms (A), (B), and (C) immediately reveals that these mechanisms in fact demand different products. All will give an alkoxyborohydride, and, after four steps,[3] a tetraalkoxyborohydride, but it is in the origin of the alkoxy groups where the difference lies; that origin being the newly-formed alcohol in the case of the four-centre mechanism, but the solvent in the case of the six-centre mechanism and, probably,[8] the linear mechanism also. Thus, at first sight, there would appear to be an extraordinarily simple, yet unreported, mechanistic distinction based on the analysis of the nature of the alkoxy groups in the tetraalkoxyborohydride product. This distinction, however, is clearly vitiated if there were alkoxy group exchange on boron, and, in fact, it is widely believed that this type of exchange does readily occur,[9] this belief having some experimental support.[10] Because this question was so crucial to the problem at hand, however, we have reinvestigated the type of exchange reactions shown below.

$$Na^{\oplus}{}^{\ominus}B(OR)_4 + 4R'OH \rightleftharpoons Na^{\oplus}{}^{\ominus}B(OR')_4 + 4ROH$$

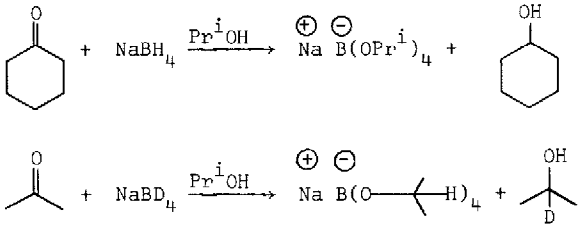
1a R=Me
1b R=Et
1c R=Pr^i

Tetraalkoxyborohydrides 1a and 1b were prepared as previously described by Brown and co-workers;[1,11] and 1c by reduction of acetone by sodium borohydride in 2-propanol. It was found that a most convenient method of rapid analysis of the tetraalkoxyborohydrides was dissolution and hydrolysis in D_2O, followed by analysis of the resulting alcohol(s) either by the pmr spectrum or by glc on a Carbowax 3000 column. Exchange reactions were performed by dissolving the tetraalkoxyborohydride in the appropriate alcohol and stirring the mixture for 24 hours at room temperature, conditions comparable to reduction conditions.[12] The tetraalkoxyborohydride was then isolated by alcohol evaporation, washed and centrifuged with dry benzene to remove traces of free alcohol, and then the alkoxy groups attached to boron analysed by nmr and glc as described above. In order to demonstrate lack of exchange by this approach, it is clearly essential to study the reaction either from both sides (e.g. $NaB(OMe)_4$ + EtOH *and* $NaB(OEt)_4$ + MeOH) or from the side which results in removal of the less volatile alcohol so as to ensure that the tetraalkoxyborohydride product is not simply an artifact of the relative boiling points of the two alcohols. Studying various possible exchanges using this method showed that, although exchange of primary alkoxy groups occurs, confirming the report of Cunningham and Pretka,[10] *little or no exchange of secondary alkoxy* groups by secondary alcohols occurred. Some specific examples are shown below.



$NaB(OPr^n)_4$ + *t*-amyl alcohol → no detectable exchange

This crucial lack of alkoxy exchange clearly removes objection to, and renders valid, the mechanistic distinction based on product analysis mentioned above. Investigation of the nature of the tetraalkoxyborohydrides formed in ketone reductions showed, as the following two reactions exemplify, that the alkoxy group attached to boron is consistently that of the alcohol solvent and not that of the newly-formed alcohol.[13]



As this result, taken in combination with the lack of alkoxy exchange on boron, is clearly inconsistent with the four-centre mechanism of reduction (B), which demands the newly formed alcohol to be attached to boron, it must be concluded that this mechanism is of no significance in the borohydride reduction of ketones.[14] Further work aimed at defining the role of solvent and distinguishing mechanisms (A) and (C) is in progress.

Acknowledgement

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References and Notes

1. H. I. Schlesinger, H. C. Brown, H. R. Hoekstra, and L. R. Rapp, J. Amer. Chem. Soc., 75, 199 (1953).
2. *See for example D. C. Wigfield and D. J. Phelps, Can. J. Chem., 50, 388 (1972).*
3. H. C. Brown, O. H. Wheeler, and K. Ichikawa, Tetrahedron 1, 214 (1957).
4. D. R. Vail and D.M.S. Wheeler, J. Org. Chem., 27, 3803 (1962).
5. H. O. House. Modern Synthetic Reactions. W. A. Benjamin, Inc., 2nd Ed., 1972. p. 52.
6. *See for example Reference 2; E. L. Eliel and Y. Senda, Tetrahedron 26, 2411 (1970);* J. B. Hendrickson, D. J. Cram, and G. S. Hammond. Organic Chemistry. McGraw-Hill Book Company. 3rd Ed., 1970. pp. 458-459; O. R. Vail and D.M.S. Wheeler, J. Org. Chem., 27, 3803 (1962); P. Geneste and G. Lamaty, C. R. Acad. Sci., Series C, 266, 1387 (1968); A. F. Cockerill and D. M. Rackham, J. Chem. Soc. Perkin II, 2076 (1972); B. Caro and G. Jouen, Tetrahedron Letters 2061, 3539 (1974).
7. See, however, P. Geneste and G. Lamaty, Bull. Soc. Chim. Fr., 669 (1968); who explicitly recognized the question.
8. In the case of mechanism (A), the product will depend on the exact role of the solvent.
9. See for example B. Rickborn and M. T. Wuesthoff, J. Amer. Chem. Soc., 92, 6894 (1970) and references therein.
10. G. L. Cunningham and F. Pretka. Canadian Patent 631, 509 (1961).
11. H. C. Brown and E. J. Mead, J. Amer. Chem. Soc., 78, 3614 (1956).
12. We are also currently making studies of exchange under more vigorous conditions.
13. An amusing corollary of this result is that the routine hydrolysis following a borohydride reduction may be entirely unnecessary.
14. Strictly speaking, this conclusion applies only to the last step of the four[3] sequential hydride transfers. The unlikely possibility of the first three transfers resulting in solvent attached to boron being due to rapid alkoxy exchange followed by a specific process with no exchange is not experimentally ruled out by these experiments. The fast rate of reduction of $NaBH(OPr^{i})_3$ compared to disproportionation[15], however, makes this possibility very improbable.
15. H. C. Brown, E. J. Mead, and C. J. Shoaf, J. Amer. Chem. Soc., 78, 3616 (1956).