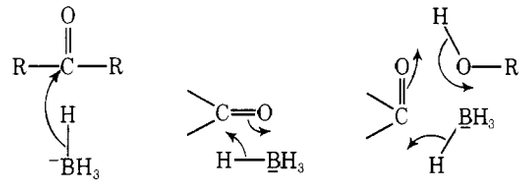
The Kinetic Role of Hydroxylic Solvent in the Reduction of Ketones by Sodium Borohydride. New Proposals for Mechanism, Transition State Geometry, and a Comment on the Origin of Stereoselectivity

Summary: The kinetic order with respect to 2-propanol in the reduction of cyclohexanone by sodium borohydride is found to be 1.5, and an acyclic mechanism is proposed; in consequence of this mechanism a purely steric rationalization of stereoselectivity is suggested, in which the axial hydrogen at C-4 plays a crucial role.

Sir: In a recent communication,[1] we have shown that the four-center transition state mechanism (B) is of no significance in the nonphotochemical borohydride reduction of ketones in 2-propanol. In order to make distinction between the two other most probable mechanisms[2]—the six-membered cyclic (C) and the linear acyclic (A)—knowledge of the kinetic



A B C

role of hydroxylic solvent was clearly of crucial importance. Although it has been known since 1961 that hydroxylic solvent is required in these reductions,[3] such a kinetic study has not yet been reported. No measurable reduction of cyclohexanone occurs in pure, dry diglyme,[3,4] and, therefore, we have measured the pseudo-second-order rate constants of reduction[5] as a function of 2-propanol concentration in the range 0.2 M and higher. The results, shown graphically in Figure 1, clearly show the surprising result that, in this concentration range,[6] the order with respect to 2-propanol is neither first nor second, but ½. Thus the overall process for sodium borohydride reduction of cyclohexanone in 2-propanol is rate = k[ketone][BH_4^-][Pr-*i*-OH]$^{3/2}$ with an overall kinetic order of 7/2 and a rate constant of $k = 9.7 \times 10^{-4}$ l.$^{5/2}$ mol$^{-5/2}$ s^{-1} at 25 °C.

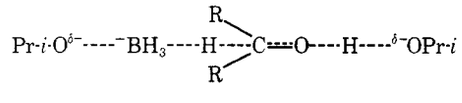
This order with respect to solvent is clearly inconsistent with the six-center mechanism (C) incorporating one molecule of solvent, and places severe constraints on other possible mechanisms. We wish to put forward what appears to be the simplest interpretation of this phenomenon, the consequences of which, in combination with other recent data, leads to a new and extremely simple explanation of the stereoselectivity of cyclohexanone reductions.

The half order is suggestive of pre-dissociation,

$$\text{Pr-}i\text{-OH} + \text{S (or S}^-) \overset{K}{\rightleftharpoons} \text{Pr-}i\text{-O}^- + {}^+\text{SH (or SH)} \quad (1)$$

where S could represent solvent or one of several species that could be present in the complex reaction mixture arising from reduction with, or alcoholysis of, sodium borohydride.[7] If the rate-determining reduction step is an acyclic push-pull mechanism as shown in Scheme I

Scheme I. Proposed Transition State for Borohydride Reduction of Ketones



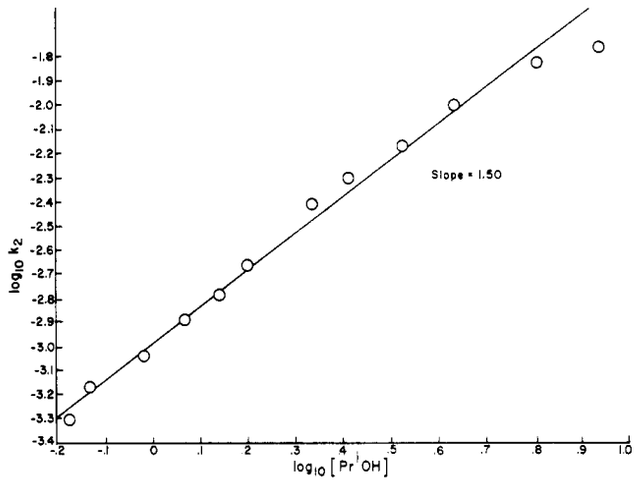


Figure 1. Reduction of cyclohexanone with sodium borohydride. Logarithm of the pseudo-second-order rate constant as a function of the logarithm of 2-propanol concentration.

involving isopropoxide and 2-propanol,[8] the rate expression must be that shown in eq 2.

$$\text{rate} = k[\text{ketone}][BH_4^-][\text{Pr-}i\text{-OH}][\text{Pr-}i\text{-O}^-] \quad (2)$$

If the isopropoxide is derived by the equilibrium of eq 1, and if [Pr-*i*-O$^-$] = [SH], it follows that

$$[\text{Pr-}i\text{-O}^-] = K^{1/2}[\text{Pr-}i\text{-OH}]^{1/2} \quad (3)$$

where [S] is disregarded as constant. Substituting (3) into (2) one obtains

$$\text{rate} = kK^{1/2}[\text{ketone}][BH_4^-][\text{Pr-}i\text{-OH}]^{3/2} \quad (4)$$

which is of the form experimentally observed.[13] Although a number of objections may be raised against this simple treatment, the mechanism is consistent with experimental observations, including the recent demonstration[1] that the free alcohol is the product and the alkoxy group attached to boron is derived from solvent, and, at present, there do not seem to be grounds for the proposal of a more involved kinetic scheme. It is of considerable interest that the mechanism proposed is, with the exception of the solvent participation, the linear mechanism (A) suggested by Brown and co-workers in the original mechanistic work on borohydride reductions,[15] and, in addition, this group has not only proposed a similar mechanism involving one 2-propanol molecule,[16] but has also concluded, from a solvent study, that one requirement for the reaction is the ability of the solvent to ionize.[3]

It is noteworthy that the presently proposed mechanism assigns no role to the metal cation. This is not an oversight. Although studies have indicated that, in some related reductions, the cation does play an important role,[3,17,18] there is, as far as we are aware, no evidence for a role for Na^+ in *$NaBH_4$ reductions in 2-propanol.* Indeed there is evidence to the contrary: Brown and co-workers have demonstrated a negligible rate increase in such reductions upon addition of NaI,[3] in contrast, for example, to the results of Li^+ addition, and Pierre and Handel have demonstrated the ineffectiveness of crown ethers in preventing $NaBH_4$ reductions in methanol.[17]

Finally, we note that the idea of the long acyclic transition state apparently generates a new rationalization of stereo-

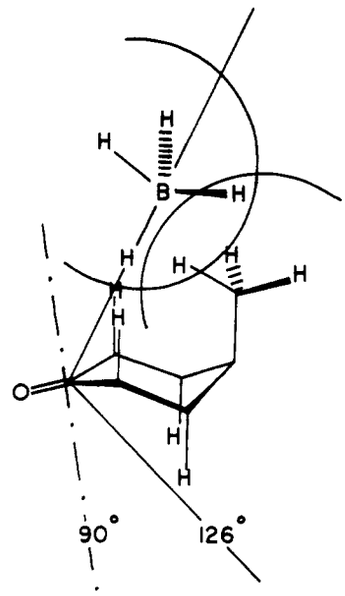


Figure 2. Attack on cyclohexanone at 126°, illustrating the effect of an axial group at C-4.

selectivity in these cyclohexanone reductions. If this attack occurs at 126° to the carbonyl group,[19] rather than at 90°, it is evident from molecular models that steric interactions with the axial hydrogen or other group at C-4 may become severe. We attempt to illustrate this point in Figure 2; what is not evident from this diagram is that the groups attached to C-4 are the only ones in the same plane as the carbonyl group. Molecular models indicate that in fact an attacking group at 126° approaches as closely to the axial group at C-4 as it does to the other axial groups, all of which are already known to markedly affect stereoselectivity. We propose that the intrinsic preference for "axial" attack may simply be the balance between the interference of two (axial 3, 5) vs. three (axial 2, 6, *and 4*) hydrogens, and that this stereoselection is modified in a predictable manner[20] by larger groups at these crucial positions. An axial methyl group at C-4 does in fact have a pronounced effect,[20] which is not accounted for by other rationalizations.

Acknowledgment. We thank the National Research Council of Canada for financial support.

References and Notes

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(2) For more detailed discussion of these mechanisms, see ref 1.
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(5) The details of the kinetic procedure have previously been published: D. C. Wigfield and D. J. Phelps, *J. Chem. Soc., Perkin Trans. 2*, 680 (1972); D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972).
(6) The original range considered was 0.2 M to 2.0 M, above which concentration, flattening of the plot may be expected. As it turns out such flattening in this reaction is not apparent until the solvent concentration reaches ~6.5 M. We wish to acknowledge some most helpful and informative discussions with Professor C. H. Langford on the question of appropriate solvent concentrations.
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(8) It is interesting that a somewhat similar step involving hydroxide ion and water has been proposed in the mechanism of homogeneous hydrogenation of ketones by rhodium catalysts.[9] We are grateful to Professor B. R. James for bringing this to our attention. It is also noteworthy that the four- and six-center mechanisms for reaction of ketones with aluminum alkyls have recently been discarded.[10] The unusual feature of nucleophilic attack on an apparently negatively charged site is not without precedent;[11] LCAO-SCF calculations, however, indicate the boron of BH_4^- to be nearly neutral, with all of the negative charge spread on the hydrogens.[12]
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(13) The possibility exists that the apparent order of 1.5 could arise from the fortuitous mixing of true first- and second-order processes. The benzidene rearrangement, for example, shows an apparent order of 1.6 for this reason.[14] In the present reaction, however, a plot of $k/$[Pr-*i*-OH] vs. [Pr-*i*-OH] showed marked curvature, inconsistent with the mixture of processes.
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A Total Synthesis of *C*-Nucleoside Analogue of Virazole

Summary: A synthesis of 5-carboxamido-3-(β-D-ribofuranosyl)-1,2,4-triazole has been developed by treating β-D-ribofuranosyl-1-carboximidic acid methyl ester with oxamido hydrazide followed by dehydrative ring closure of the open chain product by heating at 135 °C.

Sir: Several approaches[1-10] have recently been developed for synthesis of nucleosides possessing the unusual *C*-ribosyl linkage (*C*-nucleosides). In the area of *C*-triazole nucleosides, the recently reported method[9] lends itself only to the synthesis of 1,2,3-triazole *C*-nucleosides. A synthesis of DL-5-(1-β-ribofuranosyl)-3-amino-1,2,4-triazole has also been achieved[3] by a reaction of DL-2,5-anhydro-3,4-*O*-isopropylidene allonic acid lactone with aminoguanidine and subsequent removal of the isopropylidene blocking, but the approach seems to have limited application as far as the variation of C-5 substituents on the triazole nucleus is concerned. We describe here a high yield procedure for the synthesis of *C*-nucleosides of 1,2,4-triazole derivatives which has potential for wider application in the synthesis of such nucleosides. The utility of our method has been demonstrated by a total synthesis of 5-carboxamido-3-(β-D-ribofuranosyl)-1,2,4-triazole (**4**) which is a *C*-nucleoside analogue of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide.[11]

Reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[12] (**1**) with catalytic amounts of $NaOCH_3$ in CH_3OH at room temperature for 1 h led to the formation of the deblocked imidic ester **2** (mp 142–143 °C) in 60–85% yield: NMR (Me_2SO-d_6) δ 3.59 (s, 3, OCH_3), 3.50–3.90 (m, 5, 2′-, 3′-, 4′-C—H and 5′-CH_2), 4.06 (d, 1, 1′-C—H, $J_{1'-2'}$ = 2 Hz), 4.93 (br s, 3, 2′-, 3′-, 5′-OH), 8.25 (s, 1, C=NH). The imidic ester **2** is susceptible to a facile nucleophilic displacement reaction with a variety of nucleophiles. For instance with ammonia or hydrazine, it formed the corresponding amidine and amidrazone ribosyl derivatives respectively. For the synthesis of open-chain precursors **3** of 1,2,4-triazole nucleosides, the imidic ester **2** was treated with the appropriate carboxylic acid hydrazides. Compound **3** (R′ = $CONH_2$) was thus synthesized in almost quantitative yield by reacting stoichiometric amounts of **2** and oxamido hydrazide in dimethyl sulfoxide at room temperature for 18 h. The structure of **3** (R′ = $CONH_2$) was established by ^1H NMR (Me_2SO-d_6): δ 3.6 (m, 2, 2′- and 3′-C—H), 3.8 (m, 1, 4′-C—H), 3.95 (m, 2, 5′-C—H_2),