Kinetics, Stereochemistry, and Mechanism of the Sodium Borohydride Reduction of Alkyl-Substituted Cyclohexanones[1]

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Abstract: The previously used method for determining the kinetics of sodium borohydride reduction of cyclohexanones was shown to be inadequate, giving rise to small errors leading to measurably low rate constants. A silver nitrate–ethylenediamine potentiometric method gave correct values as shown by correspondence with the rate constants determined directly by vpc analysis. Changes in stereochemistry during the course of reduction were observed with some substituted cyclohexanones, implying a significant buildup of an intermediate borohydride species. Second-order rate constants (in isopropyl alcohol at 0°) were determined for the following cyclohexanones (all 10^{-2} M^{-1} sec^{-1}): unsubstituted, 2.35; 2-methyl, 0.42; 3-methyl, 1.79; 4-methyl, 2.94; 2,2-dimethyl, 0.103; 3,3-dimethyl, 0.0532; 4,4-dimethyl, 3.52; *cis*-3,4-dimethyl, 0.646; *trans*-3,4-dimethyl, 1.97; *cis*-3,5-dimethyl, 1.50; *trans*-3,5-dimethyl, 0.0577; 2,5,5-trimethyl, 0.00717; 3,3,5-trimethyl, 0.047; 3,3,5,5-tetramethyl, 0.0034; 3-*tert*-butyl, 1.42; *cis*-3,5-di-*tert*-butyl, 0.897; *trans*-3,5-di-*tert*-butyl, 0.0221. The following spiranocyclohexanones were similarly examined: spiro[5.5]undecan-3-one, 2.36; spiro[4.5]decan-8-one, 3.01; spiro[3.5]nonan-7-one, 3.01; spiro[2.5]octan-6-one, 3.44; 4-methylenecyclohexanone, 11.6. The rate constants and stereochemical results are discussed in terms of steric, electronic, and conformational effects.

Since the work of Garrett and Lyttle in 1953,[4] in which the reaction of a ketone with sodium borohydride was shown to occur at a measurable rate, a number of kinetic studies of this reaction have been carried out. While all four hydrides are utilizable in this reduction, a simple second-order kinetic expression is obeyed, demonstrating that, at least to a first approximation, the initial hydride transfer from BH_4^- is the slowest and hence rate determining. The most extensive work in this area has been carried out by Brown and his coworkers,[5–11] who have clarified many of the mechanistic aspects of the reaction, including electronic, steric, and angle strain effects. These authors have recommended a method of purification of sodium borohydride,[5] and the use of isopropyl alcohol solvent for kinetic studies. The reaction was shown to be quite solvent dependent, occurring most rapidly in polar (water and methanol) and least rapidly in nonpolar (diglyme) solvents.[5] Isopropyl alcohol is advantageous for reasons of solubility of reactants and moderate rates for most ketones at ordinary temperatures. Other kinetic studies, dealing with steroidal ketones,[12] aryl ketones,[13–15] substituted cyclohexanones,[16] and aliphatic ketones[17] have been reported.

The present study was undertaken to examine the steric, electronic, and conformational effects of methyl substitution at the three ring positions of cyclohexanone.

Results and Discussion

The Analytical Method. Rate constants for the borohydride reduction of carbonyl compounds have previously been determined either spectrophotometrically (aryl ketones) or titrimetrically using an iodate procedure introduced by Lyttle, Jensen, and Struck,[18] and modified by Brown and coworkers.[6] While several authors[6,12,16] have reported satisfactory results using the titrimetric method, others have noted problems with this procedure.[19] The intrinsic error of the method is rather large, as it involves a considerable excess of iodate, and consequent determination of a small differences between large numbers. More important, though, are the possibilities for (a) hydrolysis of borohydride and related species, (b) fast reaction with ketone during analysis,[19] and (c) reaction of alkoxyborohydride intermediates *via* a process of undetermined stoichiometry. Brown and Boyd[20] have in fact demonstrated that the reaction of iodate with borohydride in basic solution is very slow, and hence oxidation of the borohydride is accomplished only after acidification of the iodate–iodide solution (presumably by iodine). The relatively fast reduction of ketones in aqueous media can thus become a major source of error, particularly with reactive carbonyl compounds. Brown[6] has pointed out this difficulty in connection with the reduction of benzaldehyde, which in a typical second-order rate plot shows a nonzero intercept at zero time corresponding to about 7% reaction.[21]

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(1) Support by the National Science Foundation (GP 9383) is gratefully acknowledged.

(2) Alfred P. Sloan Fellow, 1967–1969; to whom correspondence should be addressed.

(3) NDEA Title IV Fellow, 1964–1967.

(4) E. R. Garrett and D. A. Lyttle, *J. Amer. Chem. Soc.*, 75, 6051 (1953).

(5) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *ibid.*, 77, 6209 (1955).

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(18) D. A. Lyttle, E. H. Jensen, and W. A. Struck, *Anal. Chem.*, 24, 1843 (1952).

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In more recent work using the same analytical procedure, Sun and Neidig[22] found a significant intercept also for the reduction of phenyl cyclopropyl ketone. These authors suggested the possibility of some side reaction utilizing borohydride. An alternate explanation could involve any of the possibilities noted here.

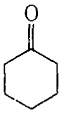
Our attempts to apply the modified potassium iodate procedure[6] for the kinetic analysis of cyclohexanone gave erratic rate constants with distinct, positive intercepts at zero time. A wide variety of oxidants and conditions were explored[23] in an effort to develop a

$$2HIO_4 + 3BH_4^- + H_2O \xrightarrow{16e^-} 2I^- + 3H_2BO_3^- + 4H_2 + 2H^+$$

more useful titrimetric procedure; with few exceptions,[23] however, added ketone substantially affected the analytical results.

At this point we learned that the silver nitrate–ethylenediamine method of Brown and Boyd[20] had been refined for use as a potentiometric technique.[24] This procedure was modified slightly (Experimental Section) for kinetic application, and shown to give good results with the cyclic ketones studied here. The method gives total hydride equivalence, not just BH_4^-. Nearly all compounds examined gave reproducible, straight-line, second-order kinetic plots with zero time intercepts equal to zero within experimental error.[25]

The rate constants for the reduction of ketones **1–22** obtained by this method are shown in Table I. For these kinetic determinations, initial sodium borohydride concentrations ranged from about 0.004 to 0.034 *M*, depending on the reactivity of the substrate ketone. Initial ketone concentrations ranged from 0.020 to 0.135 *M*; the molar ratio of borohydride to ketone was generally held within 20% of the stoichiometric ratio (1:4). While the less reactive ketones gave rate constants unaffected by the ratio of reactants, a small but apparently real correlation was noted for the more reactive ketones ($k \geq 10^{-2}$ l./mol sec). Excess ketone (15% mol %) typically gave values about 3–4% lower than k at the stoichiometric ratio, with excess borohydride showing the opposite effect. This behavior will be discussed further in the section dealing with the stereochemistry of reduction.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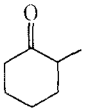
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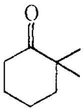
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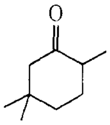
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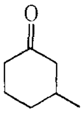
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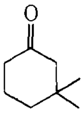
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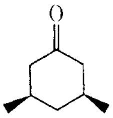
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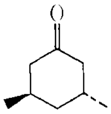
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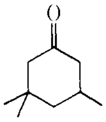
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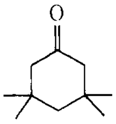
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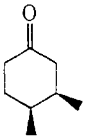
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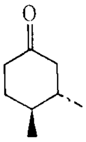
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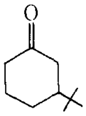
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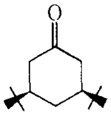
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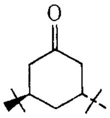
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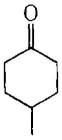
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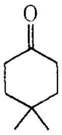
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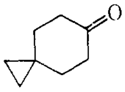
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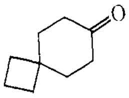
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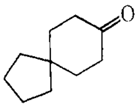
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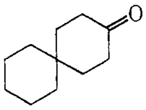
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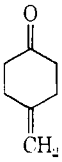

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Table I. Rate Constants (AgED$^+$ Method) for Reduction by Sodium Borohydride in Isopropyl Alcohol at 0°

Compd	10^2k, l./mol sec	k_{rel}
1	2.35 ± 0.09^a	100
2	0.421 ± 0.006^a	18
3	0.103 ± 0.001^b	4.4
4	0.00717 ± 0.00001^b	0.30
5	1.79 ± 0.03^b	76
6	0.0532 ± 0.0007^a	2.3
7	1.50 ± 0.03^a	64
8	0.0577 ± 0.0002^b	2.5
9	0.0470 ± 0.0009^a	2.0
10	0.0034 ± 0.0003^a	0.14
11	0.646 ± 0.005^a	27
12	1.97 ± 0.02^a	84
13	1.42 ± 0.03^a	60
14	0.897 ± 0.006^a	38
15	0.0221 ± 0.0004^b	0.94
16	2.94 ± 0.04^b	125
17	3.52 ± 0.06^a	150
18	3.44 ± 0.10^a	146
19	3.01 ± 0.05^a	128
20	3.01 ± 0.10^a	128
21	2.36 ± 0.09^a	100
22	11.6 ± 0.6^a	494

[a] Average deviation from the average of three determinations. [b] From two determinations.

The rate constants shown in Table I, for the few cases where comparison data are available, are significantly higher than the literature values. Using the neutral iodate analytical procedure, both Brown and Ichikawa[7] and Kwart and Takeshita[16] found $k = 1.61 \pm 0.01 \times 10^{-2}$ l./mol sec for the reduction of cyclohexanone under the same reaction conditions used here. The latter authors[16] also reported a value of 1.90×10^{-2} for 4-methylcyclohexanone. When these constants are compared to the present data for **1** and **16** (Table I), it is seen that the AgED$^+$ method gives values which are 50 ± 5% higher than those reported earlier. Although there was reason to believe that the iodate method might give erroneous results, it was felt that this discrepancy would be further clarified by a third independent method of rate constant determination. The procedure used was following the loss of ketone by vapor phase chro-

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(21) Calculated from the data given in ref 6; note that Figures 2 and 3 in this reference have been interchanged.

(22) S. F. Sun and P. R. Neidig, *J. Org. Chem.*, 34, 1854 (1969).

(23) The following gave unsatisfactory analytical results: potassium periodate, lithium iodate in IPA (isopropyl alcohol), potassium bromate, tetramethylammonium iodate in IPA, periodate acid (in water or IPA), iodic acid, sodium hypoiodite, iodine in IPA, ferric chloride in IPA or water, hydrogen peroxide, silver nitrate in IPA, silver acetate, salicylate, or lactate (insufficient solubility in IPA), silver fluoride or silver perchlorate in IPA. Of these reagents, only periodic acid gave reproducible results and values which were unaffected by the presence of ketone; however, the reproducibility was somewhat dependent on the ratio of periodic acid to borohydride, thus negating the usefulness of this reagent for kinetic analysis. The reaction of periodic acid with borohydride approximates the stoichiometry

(24) We are indebted to Dr. Charles (Chips) Brown for suggesting this procedure and furnishing details of its application.

(25) The reaction of AgED$^+$ with borohydride occurs very rapidly and cleanly, and is unaffected by added 4-methylcyclohexanone. The stoichiometry of the reaction is

$$BH_4^- + 8AgED^+ + 10OH^- \longrightarrow BO_3^{3-} + 8Ag^0 + 7H_2O$$

The stoichiometric relationship holds over a wide range of reactant ratios, and as little as 10% excess AgED$^+$ was used satisfactorily in the present work.

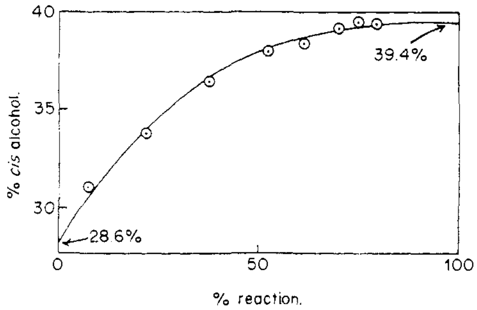

Figure 1. Stereochemical dependence on per cent reaction for 2-methylcyclohexanone.

matography (vpc); values obtained by this method are shown in Table II.

Table II. Comparison of Rate Constants (10^2k mol^{-1} sec^{-1}) Obtained by Vpc and AgED$^+$ Methods

Ketone	k (vpc)	k (AgED$^+$)
2	0.399 ± 0.006[a]	0.421
4	0.00721 ± 0.00006[b]	0.00717
5	2.17 ± 0.19[b]	1.79
7	1.61 ± 0.13[c]	1.50
9	0.0455 ± 0.0004[c]	0.0470
11	0.82 ± 0.10[b]	0.646
12	2.43 ± 0.10[b]	1.97
13	1.48 ± 0.03[d]	1.42
14	0.84 ± 0.02[d]	0.897
16	3.19 ± 0.04[b]	2.94

[a] Average deviation from the mean of five determinations. [b] Two determinations. [c] Four determinations. [d] Three determinations.

The vpc method is inherently subject to greater error[26] than a titrimetric procedure, and consequently the agreement between the rate constants from the AgED$^+$ and vpc methods can only be described as excellent. In the few cases where the values differ beyond the average deviations, the vpc rate constants are higher, *i.e.*, in the wrong direction to fortify the values obtained by the iodate procedure. The data clearly indicate that the AgED$^+$ method is yielding the correct absolute rate constant for sodium borohydride reduction of ketones in isopropyl alcohol.

Observation of an Intermediate. In the course of vpc rate determinations, an interesting and unexpected observation was made. The ketones used in each case give rise to two isomeric alcohols, and the ratio of these products *changed during the course of reduction.*

Careful control experiments were undertaken, subjecting several product mixtures to the analytical and extraction procedures used to prepare the vpc samples. This treatment did not affect the alcohol ratios, ruling out the possibility that the changing ratios might be an artifact of the conditions used.

Equation 1 was chosen as a mathematical expression adaptable to the vpc data, and readily fit to the different data sets by a computerized least-squares analysis.

$$\%\ \text{alcohol A} = A_{100} - B(\%\ \text{reaction} - 100)^3 \quad (1)$$

The equation of best fit to the data was used to obtain extrapolated product ratios at 0 and 100% reaction.[27] An example with experimental values and calculated curve for 2-methylcyclohexanone (**2**) is shown as Figure 1.

The extrapolated values for the various systems examined are given in Table III. All but two of the ten ketones examined show significant variation in product ratio with extent of reduction. The two exceptions are 2,5,5-trimethylcyclohexanone (**4**) and 3,3,5-trimethylcyclohexanone (**9**). These ketones differ from the others listed in Table III in one other regard; the rate constants for reduction are significantly lower for **4** and **9**. Viewed in terms of the more stable chair conformations (*i.e.*, with axial alkyl group and 1,3-diaxial interactions minimized), the axial alcohol product increases with extent of reaction for all ketones listed in Table III. This trend would be anticipated if a bulkier reducing agent were developing during the course of reduction, and competing with sodium borohydride for remaining ketone. The results were obtained, as noted earlier, using approximately the stoichiometric ratio of ketone to borohydride (4:1), conditions which could conceivably cover a wide range in ratio of borohydride to intermediate alkoxyborohydride over the course of negligible to complete reduction.

Table III. Product Distributions as a Function of Per Cent Reaction; $NaBH_4$ Reduction of Alkylcyclohexanones in IPA

Ketone	% alcohol product	
	0% reaction[a]	100% reaction[a]
2	25.1 ± 2.5	39.9 ± 1.0 cis
4	29.0 ± 0.7	29.4 ± 0.8 trans
5	12.6 ± 1.2	23.8 ± 0.1 trans
7	14.3 ± 2.3	26.6 ± 0.4 trans
9	58.1 ± 1.8	61.7 ± 0.9 trans
11	13.1 ± 0.5	18.4 ± 0.2 trans
12	11.9 ± 0.9	22.9 ± 0.6 trans, cis[b]
13	17.4 ± 0.5	23.9 ± 0.2 trans
14	18.7 ± 2.2	29.9 ± 0.7 trans
16	11.2 ± 0.4	23.9 ± 0.3 cis

[a] Average deviations obtained from the number of runs indicated in the footnotes of Table II. [b] This stereochemical designation refers to the geometry of the 3- and 4- methyl group, respectively, relative to the hydroxyl group.

In order to test further the hypothesis of an intermediate, the stereochemistry of reduction of three ketones by excess sodium borohydride was examined. These data are presented in Table IV. Again the

Table IV. Effect of Borohydride:Ketone Ratio on Stereochemistry of Reduction

Ketone	[$NaBH_4$]/[ketone]	% alcohol
2	0.25	39.9 cis
	2.63	30.8
7	0.25	26.6 trans
	2.77	17.6
	24.3	13.0
9	0.25	61.7 trans
	1.28	60.6
	2.84	59.1
	25.3	54.9

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(26) Relatively large error limits are involved in area measurements at both high and low per cent ketone conversion.

(27) In eq 1, % alcohol A refers to the per cent of one of the alcohols, arbitrarily chosen; A_{100} is the per cent A at 100% reaction, and B is a curve-fitting constant.

more reactive ketones **2** and **7** exhibit greater sensitivity to excess borohydride concentration, in agreement with the data given in Table III and the previously noted small but real correlation between reagent concentrations and rate constants for the more readily reduced systems.

Having established that some intermediate borohydride reduction species has a finite lifetime under these reaction conditions, attempts were made to examine the nature of this intermediate. Viewing the reduction as a sequential four-step reaction (eq 2–5, K = ketone) and considering the enhanced hydride donor activity associated with alkoxy substitution on boron, one might expect the presumed initially formed alkoxyborohydride (k_2) to resemble most closely in reactivity borohydride itself, with subsequent reduction steps (eq 4 and 5) being even faster. Consequently, we first attempted to prepare an alkoxyborohydride of the type involved in eq 3, using sodium isopropoxide and either borane–tetrahydrofuranate (in THF) or diborane.

$$K + BH_4^- \xrightarrow{k_1} BH_3(OR)^- \qquad (2)$$

$$K + BH_3(OR)^- \xrightarrow{k_2} BH_2(OR)_2^- \qquad (3)$$

$$K + BH_2(OR)_2^- \xrightarrow{k_3} BH(OR)_3^- \qquad (4)$$

$$K + BH(OR)_3^- \xrightarrow{k_4} B(OR)_4^- \qquad (5)$$

Treatment of sodium isopropoxide with excess borane in THF gave a white precipitate which proved to be sodium borohydride, formed nearly quantitatively according to eq 6. Since borane might have acted to

$$3NaO\text{-}i\text{-}Pr + 4BH_3 \longrightarrow B(O\text{-}i\text{-}Pr)_3 + 3NaBH_4 \qquad (6)$$

catalyze the disproportionation of any sodium isopropoxyborohydride formed, this experiment was repeated using just 1 mol of borane/mol of alkoxide. Although the residue from vacuum removal of the volatiles from this reaction had the appropriate weight for the desired product, the proton nmr spectrum of the THF solution showed the presence of appreciable sodium borohydride; apparently disproportionation according to eq 7 had occurred.

$$4NaBH_3(O\text{-}i\text{-}Pr) \longrightarrow 3NaBH_4 + NaB(O\text{-}i\text{-}Pr)_4 \qquad (7)$$

Finally, the reaction of solid sodium isopropoxide with gaseous diborane was examined. Heat was evolved. Vacuum removal of the volatile material gave a residue of sodium borohydride. Hence, even in the absence of solvent, disproportionation according to eq 6 occurs readily.[28]

We next turned our attention to the presumed final intermediate in the reduction sequence (eq 5), the trialkoxyborohydride species. Attempted synthesis of tricyclohexyl borate by the general method of Brown, Mead, and Shoaf[30] failed, giving an undistillable viscous liquid. Jones and Wise[29] have reported similar difficulties in the preparation of the 4-*tert*-butylcyclohexyl analog. Consequently, it was decided to work with the known sodium triisopropoxyborohydride.[31] Brown[31] has reported that this material reacts very rapidly with acetone in the solvents isopropyl alcohol, THF, and diglyme. It was felt that by using a very unreactive ketone it might be possible to follow a reduction kinetically, and 3,3,5-trimethylcyclohexanone (**9**) was chosen for this purpose. Having first established that $AgED^+$ yields correct[32] analytical values for triisopropoxyborohydride alone and in the presence of the reactive ketone 4-methylcyclohexanone, three kinetic determinations were made at 0° in IPA. Again rather unexpected results were obtained. In two runs, a small excess of ketone **9** was used; the second-order rate plots indicated that by the time the first point was examined (within 2 min), half of the available hydride had been used. Subsequent reaction occurred at an easily determinable rate to give the constants shown in Table V. Several interesting aspects of this reaction are evident from these data. The large *y* intercept (extent of reaction at time zero) is not due to (a) reaction of $BH(O\text{-}i\text{-}Pr)_3^-$ with solvent, as shown by the correspondence of $AgED^+$ and vpc rate constants, or (b) fast reaction during the quenching step, since the $BH(O\text{-}i\text{-}Pr)_3^-$ analysis was unaffected by the presence (in the quenching solution) of the much more reactive ketone **16**. It must therefore be caused by an initial very fast reaction followed by a measurably slower second-order reaction. The observation that, with excess ketone, 50% of the available hydride is consumed in the fast step appears to be significant. A possible mechanistic explanation is shown in eq 8–12.

Table V. The Reaction of 9 with Sodium Triisopropoxyborohydride in IPA at 0°

[**9**]/ $[BH(O\text{-}i\text{-}Pr)_3^-]$	10^2k, l./mol sec AgED$^+$	10^2k, l./mol sec Vpc	% reaction at $t = 0$ AgED$^+$	% reaction at $t = 0$ Vpc
1.46	2.45	3.04	50	44
1.32	2.41	2.43	49	53
0.63	~4.8	~3.9	67	70

$$2BH(O\text{-}i\text{-}Pr)_3^- \rightleftharpoons BH_2(O\text{-}i\text{-}Pr)_2^- + B(O\text{-}i\text{-}Pr)_4^- \qquad (8)$$

$$BH_2(O\text{-}i\text{-}Pr)_2^- + K \xrightarrow{k_1} BH(O\text{-}i\text{-}Pr)_2(OR)^- \qquad (9)$$

$$2BH(O\text{-}i\text{-}Pr)_2(OR)^- \rightleftharpoons BH_2(OR)_2^- + B(O\text{-}i\text{-}Pr)_4^- \qquad (10)$$

$$BH_2(OR)_2^- + K \xrightarrow{k_2} BH(OR)_3^- \qquad (11)$$

$$2BH(OR)_3^- \rightleftharpoons BH_2(OR)_2^- + B(OR)_4^- \qquad (12)$$

According to this scheme rapid disproportionation steps (eq 8, 10, 12) connect the rapid initial reduction (eq 9) and the subsequent slower reaction of eq 11. Al-

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(28) This facile disproportionation is analogous to the reported reaction of sodium methoxide with diborane [H. I. Schlesinger, H. C. Brown, H. R. Hoekstra, and L. R. Rapp, *J. Amer. Chem. Soc.*, 75, 199 (1953)]. This observation does not, of course, rule out the alkoxyborohydride as a reactive intermediate in the reduction sequence. Jones and Wise[29] have also attempted to examine the reaction of an alkoxyborohydride by treating a mixture of sodium 4-*tert*-butylcyclohexyl oxide and the corresponding ketone with diborane in diglyme solvent. This approach is subject to considerable uncertainty (even for stereochemical studies in diglyme) and was obviated in the present work by the fast reaction of diborane with isopropyl alcohol.

(29) W. M. Jones and H. E. Wise, Jr., *J. Amer. Chem. Soc.*, 84, 997 (1962).

(30) H. C. Brown, E. J. Mead, and C. J. Shoaf, *ibid.*, 78, 3613 (1956).

(31) H. C. Brown, E. J. Mead, and C. J. Shoaf, *ibid.*, 78, 3616 (1956).

(32) Analysis of active hydride under kinetic conditions was complicated somewhat by the concurrent reaction of triisopropoxyborohydride with IPA, for which an approximate first-order rate constant at 0° of 1.5×10^{-5} sec^{-1} was obtained. The values from the $AgED^+$ method using freshly mixed solutions at 0° were in reasonable agreement with those obtained by hydrogen evolution, and were unaffected by ketone in the quenching solution. In contrast, the iodate procedure gave very low hydride values which were greatly affected by the presence of ketone.

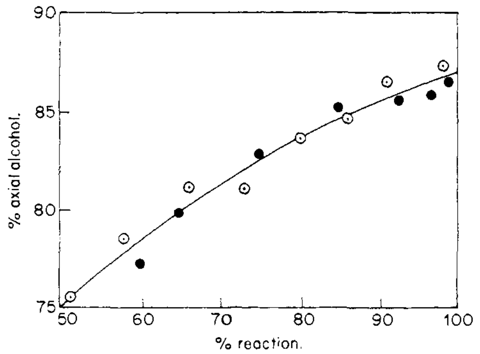

Figure 2. Reduction of 9 with $NaBH(O\text{-}i\text{-}Pr)_3$.

though other explanations are possible, this scheme can accommodate the experimental observations.[33] These observations require that, at least on the time scale required for reduction, there is no facile exchange of alkoxide groups on boron with the IPA solvent.[34] Since our data suggest that substituting a bulky (but still secondary) alkoxide for isopropoxide leads to a hydride donor of considerably diminished reactivity, it is clear that the relative rates of the "fast" steps in borohydride reductions (*i.e.*, eq 3–5) cannot be safely generalized; a balance between electronic and bulk effects of the alkoxide groups could lend to the situation in which the next to slowest step might correspond to eq 3 for one ketone and eq 4 or 5 for another.

The third run listed in Table V represents an attempt, through the use of insufficient ketone, to observe ongoing reduction before the initial, reactive alkoxyborohydride species was consumed. Some curvature in the rate plot was observed, reflected in the higher approximate rate constant reported in the table. The greater extent of reaction (loss of ketone) at extrapolated $t = 0$ is also in agreement with the suggested mechanism.

The proposed mechanism also has certain stereochemical consequences, in particular that the bulkier, less reactive borohydride species should be more stereoselective in its reaction. The vpc rate determinations (Table V) allowed the simultaneous observation of this phenomenon, as shown for the first two runs (with excess ketone) in Figure 2. If initial reduction were governed only by the very reactive species, and the latter half of the reduction controlled by a single bulkier alkoxyborohydride, a strictly linear behavior would be expected in Figure 2. Although there is some apparent curvature, the nearly linear behavior suggests that the reactive species first formed by disproportionation of triisopropoxyborohydride gives about 75% of the axial alcohol product; to account for the final total product distribution (86–87% axial), the bulkier reagent must be giving axial alcohol in a highly (nearly 100%) stereoselective manner.

Some time ago Haubenstock and Eliel[36a] reported that the molar ratios of sodium borohydride to 3,3,5-trimethylcyclohexanone had no effect on the stereochemical course of the reduction: a twofold excess of hydride gave the same amount (55 ± 1%) of axial alcohol as the stoichiometric ratio of reactants. They therefore concluded that the subsequent steps in reduction must be a great deal faster than the initial hydride transfer, a conclusion augmented by the earlier kinetic studies. As we have seen, though, this particular ketone **9** is one which happens to be *relatively* insensitive to the borohydride–substrate concentration ratio, as shown by the negligible change in stereochemical outcome through the course of a reduction under approximately equivalent concentration conditions (Table III) and the small change detected when a 100-fold excess of borohydride was used (Table IV). Since our data with triisopropoxyborohydride clearly show that some bulkier hydride donor exhibits considerably higher selectivity (approaching 100%) than borohydride itself, we also must conclude that, for this ketone, the subsequent reduction steps must be sufficiently faster than the initial hydride transfer that no (or a negligible amount of) intermediate alkoxyborohydride species is developed with this system. It should again be noted that this behavior is associated with ketones having the smallest rate constants, which could imply simply that the rate of the first hydride transfer for these compounds is diminished relatively more than the rates for subsequent steps, when compared to the faster ketones. Comparison of the rate constant for borohydride reduction of **9** (Table I) and the constant for the presumed final (and possibly next-slowest) hydride transfer for this ketone (Table V) shows that the latter is faster by a factor of ~50. A factor of this magnitude between the slowest and second-slowest hydride transfer steps would preclude the stereochemical observation of intermediate buildup under our kinetic conditions.

The stereochemistry of reduction by triisopropoxyborohydride of two relatively unhindered ketones, *cis*-

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[33] A presumably simpler explanation might avoid the initial disproportionation, *i.e.*

$$BH(O\text{-}i\text{-}Pr)_3^- + K \xrightarrow{k_1} B(O\text{-}i\text{-}Pr)_3(OR)^-$$

$$B(O\text{-}i\text{-}Pr)_3(OR)^- + BH(O\text{-}i\text{-}Pr)_3^- \rightleftharpoons BH(O\text{-}i\text{-}Pr)_2(OR)^- + B(O\text{-}i\text{-}Pr)_4^-$$

$$BH(O\text{-}i\text{-}Pr)_2(OR)^- + K \xrightarrow{k_2} B(O\text{-}i\text{-}Pr)_2(OR)_2^-$$

This scheme, however, implies that the tetraalkoxy borate ion is a stable entity, whereas it is highly probable that rapid (and perhaps extensive) dissociation occurs. As such, the bulkier alkoxy group would be rapidly lost from the reaction sequence (replaced by isopropoxide from solvent), making a simplified mechanistic scheme such as this untenable. It is for this reason that we propose a dihydroboron species as the active reducing agent. Although sodium triisopropoxyborohydride is reported not to disproportionate (as in eq 8) appreciably in THF solvent, it is conceivable that a quite different situation prevails in IPA. Trimethoxyborohydride is known[30] to disproportionate in this manner.

$$B(O\text{-}i\text{-}Pr)_3(OR)^- \rightleftharpoons B(O\text{-}i\text{-}Pr)_4 + OR^-$$

[34] In a recent study of the borohydride reduction α,β-unsaturated aldehydes and ketone, an effort was made to examine this question.[35] β-Alkoxy alcohols are formed in this reaction; in IPA solvent, the alkoxy group is invariably derived from solvent. Added triisopropyl borate diminishes but does not totally prevent formation of these products. These data demonstrate (a) that the tetraisopropoxy borate anion disproportionates as discussed in ref 32; and (b) this disproportionation leads to rapid equilibration of reduction product B–OR species with solvent alcohol. Thus it appears necessary to call on highly specific disproportionation steps (as in eq 8–12) to explain the present observations.

[35] M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).

[36] (a) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2368 (1962). (b) The stereochemical dependence on borohydride to ketone ratio also puts into question some observations on the temperature dependence of this reduction process [P. T. Lansbury and R. E. MacLeay, *J. Org. Chem.*, **28**, 1940 (1963)]. Even if this ratio were maintained constant, the unknown temperature dependence of the reaction of any intermediate alkoxyborohydride species would make interpretation of temperature effects tenuous.

3,5-dimethylcyclohexanone (**7**) and 4-methylcyclohexanone (**16**), was also examined. The data are shown in Table VI. The second run with **7** was stopped short of completion as a check on possible, but unexpected, product equilibration. The greater amount of axial product in the longer time experiment excludes equilibration, and supports the observation made with ketone **9**, *i.e.*, that reduction with this reagent involves (at least) two hydride donor species of differing selectivity. The proportions of "axial" products are much higher than observed through the course of kinetic runs using borohydride (Table III), as required by the proposed mechanism. Assuming a very fast initial consumption of half the available hydride (and ketone), an appropriate rate constant from the incomplete run with **7** can be calculated. This value, 22×10^{-2} l./mol sec, is approximately 15 times faster than the rate constant for sodium borohydride. Although a crude value, this ratio is smaller than that found in reductions of **9** with the two reagents, and is in agreement with the suggestion that stereochemical observation of an intermediate alkoxyborohydride species is more probable with the more reactive ketones.

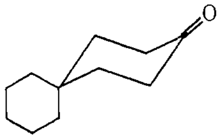
Table VI. Reductions with Triisopropoxyborohydride in IPA at 0°

Ketone	$[\mathrm{K}]/[\mathrm{BH(OR)_3^-}]$	Time, min	% reaction	% alcohol
7	1.2	320	100	46.7 trans
7	1.2	12	94	43.2
16	1.1	30	100	40.0 cis

Having taken some pains to demonstrate that a finite concentration of intermediate alkoxyborohydride species is developed during the course of sodium borohydride reduction of ketones, it becomes important to distinguish between stereochemical and kinetic observation of the intermediate. Thus, at first glance, it might seem that good straight-line second-order plots, as obtained and used for the rate constants in Table I, are inconsistent with the buildup of an intermediate. However, if the alkoxyborohydride intermediate has very different steric requirements leading to stereoselectivity in reduction which differs greatly from that observed with borohydride itself, any amount of intermediate, small but greater than steady state, can lead to stereochemical observation and still lie outside the range of kinetic detection. The good second-order plots suggest that, at least to a first approximation, this is the case with the systems examined in the present work. A consequence is that the rate constants, as reported in Table I, do represent, probably within a few per cent error at most, the true values for the initial hydride transfer from borohydride. Confidence limits of ±5% were set on individual rate constant determinations, and, as shown in Table I, the experimental values were quite reproducible.

Alkyl Substituent Effects. Alkyl substitution can affect the rate of borohydride reduction of cyclohexanone in a variety of ways which can be classified as primarily inductive, steric, or conformational in nature. Kwart and Takeshita[16] have shown that electronegative groups in the 4 position of this ketone exert a rate-enhancing effect in reduction, and a linear free energy relationship is observed using inductive substituent constants. However, 4-alkyl substitution also caused small but real rate enhancement, an observation borne out by the present work. Kwart chose to invoke a novel inverse inductive effect for the alkyl group (both methyl and *tert*-butyl), citing kinetic data for the addition of an arylsulfenyl halide to substituted cyclohexenes[37] to support this thesis. It has subsequently been shown, however, that similar rate effects in epoxidation[38] and methylenation[39] of 4-alkylcyclohexenes are due to conformational rather than inductive features of the alkyl substituent.

Examination of the data in Table I shows that, for many of the examples studied, alkyl substituent effects are to a first approximation energetically additive. For example, a relative rate factor for 4,4-dimethylcyclohexanone of 1.56 (cyclohexanone = 1.00) is calculated by squaring the factor for 4-methylcyclohexanone; the observed relative rate is 1.50. One might expect behavior of this kind for a conformationally independent electronic effect, while a simple conformational rationale is not evident. However, convincing evidence against a controlling inductive effect from 4-alkyl substituents is provided by the spiro[5.5] ketone **21**. This interesting molecule has constrained tetrahedral geometry at the spiro carbon; any effort to relieve nonbonded interactions in one ring by altering bond angles at this position causes a comparable increased interaction in the other cyclohexane ring. Thus **21** is, of all the compounds studied, the best geometrical model for cyclohexanone itself; at the same time it furnishes an undistorted 4,4-dialkylcyclohexanone for examination of inductive effects isolated from conformational complications. A negligible inductive effect predicts no difference in rate for reduction of cyclohexanone and **21**, in precise agreement with experimental observation. The rate enhancement of 4,4-dimethylcyclohexanone must therefore be associated with some kind of conformational distortion. A reasonable suggestion might be the operation of a Thorpe–Ingold effect,[40] *i.e.*, interaction between the methyl groups causing a decrease in the C_3–C_4–C_5 bond angle. Models suggest that this would have the effect of flattening the carbonyl end of the ring, effectively destabilizing the reduction transition state. Very recently, Lambert and coworkers[41] have determined the crystal structure of 4,4-diphenylcyclohexanone. Although the C_4 external angle (phenyl-C_4-phenyl) is normal (110.5°), the internal angle (C_3-C_4-C_5) is depressed to 105.9°, and the carbonyl portion of the ring is flattened relative to cyclohexane, these effects being attributed by the authors to the geometrical requirements of the car-



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[37] H. Kwart and L. J. Miller, *J. Amer. Chem. Soc.*, **83**, 4552 (1961).

[38] B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

[39] B. Rickborn and J. H. Chan, *ibid.*, **32**, 3576 (1967).

[40] (a) R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915); (b) C. K. Ingold, *ibid.*, 305 (1921); (c) S. Searles, E. F. Lutz, and M. Tamres, *J. Amer. Chem. Soc.*, 82, 2932 (1960); (d) P. von R. Schleyer, *ibid.*, **83**, 1368 (1961).

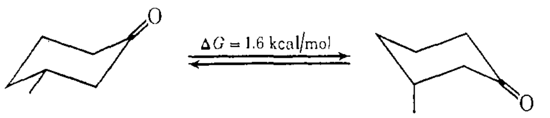
[41] J. B. Lambert, R. E. Carhart, and P. W. R. Corfield, *ibid.*, **91**, 3567 (1969).

bonyl group (*i.e.*, as opposed to operation of Thorpe–Ingold forces). Assuming that the crystalline unstrained geometry of 4,4-diphenylcyclohexanone would hold as well for 4,4-dimethylcyclohexanone in solution, it appears that some as yet unexplained distortion causes the observed rate increase of the latter relative to cyclohexanone.

Although Thorpe–Ingold distortion does not appear to be important in the reduction of **17**, the spiro ketones **18**–**22** were prepared to test the effect of extreme variation of the external C_4 angle, with the view that decreased angle should lead to an increase in rate of reduction. The rate constants do increase as anticipated, although the increments are rather small considering the large exocyclic bond angle changes. While the data may be taken as support for the operation of the Thorpe–Ingold effect, other explanations are possible. As an extreme case of exocyclic–C_4 bond angle compression, 4-methylenecyclohexanone (**22**) also fits the Thorpe–Ingold pattern with a substantial rate increase. However, a significant part of this acceleration may be ascribed to the inductive effect of the carbon–carbon double bond.[42] Also, the relative importance of the flexible (twist–boat) conformation is unknown for this system (see further discussion below).

Substitution of a methyl into the 2 position of cyclohexanone is expected on the basis of inductive, steric, and/or torsional[44] effects to lead to a decrease in the rate of reduction, and this is observed (Table I, compound **2**). It is less obvious that substitution of a second methyl group at the same position (**3**) would cause a very similar factor in rate decrease. Since the first methyl substituent exists preferentially in the equatorial conformation[45] the second substituent might have been expected to exert a more pronounced role on the rate of reduction. Even so, the overall 20-fold rate decrease (**3** relative to **1**) is substantially greater than the rate factor (1.4) found for similar systems (4-*tert*-butyl) in the reduction by lithium tri-*tert*-butoxyaluminohydride,[46] and suggests that whatever factors are involved, sodium borohydride reduction represents a more sensitive probe than the use of the complex aluminum reagent.

Referring again to Table I, the series of 3-methylcyclohexanones presents some interesting features. It should first be noted that an equational methyl group exerts a small rate-retarding effect on the reduction. This is best seen in the rate constant for *cis*-3,5-dimethylcyclohexanone (**7**); this material, at least to a good first approximation, can be viewed as conformationally pure, with the methyl groups strongly preferring the diequatorial form. Assuming that each methyl group contributes equally to the rate decrease, a rate constant for equatorial 3-methylcyclohexanone of 1.88×10^{-2} mol^{-1} sec^{-1} is calculated. Similarly, using data from **7** and **9**, an imaginary k of 0.074×10^{-2} is found for axial 3-methylcyclohexanone. These relative rate factors (0.80 for equatorial 3-methyl, 0.0315 for axial 3-methyl) can then be used to calculate expected relative rates for other members of this series. Thus the $k_{\rm rel}$ value for 3,3- and *trans*-3,5-dimethylcyclohexanone is calculated to be 2.52, compared to the experimental values of 2.3 (**6**) and 2.5 (**8**). Reasonably good agreement is also obtained in other comparisons, *e.g.*, with compounds **4** and **10**. The calculated rate constants for the equatorial and axial 3-methylcyclohexanone can also be used in conjunction with the measured value for **5** (1.79×10^{-2}) to calculate[47] the free-energy difference between the conformers of this ketone (eq 13). This value is of interest in connection with the "3-alkyl ketone effect,"[48] for which various determinations, all involving equilibration studies of dialkylcyclohexanones,[49] have led to estimates of ΔG (eq 13) on the order of 1.4 kcal/mol. Thus, depending on the reference *A* value chosen for the methyl group in cyclohexane (1.8–1.9 kcal/mol), the 3-alkyl ketone effect determined by equilibration would be 0.4–0.5 kcal/mol. We may also apply the kinetic approach to evaluate the conformational equilibrium for **11** (eq 14), since this also should directly reflect the 3-methyl ketone effect. As indicated, this calculation leads to a value of 0.55 kcal/mol; although in good agreement with direct equilibration results,[49] this value may be in error because of some unknown kinetic effect of vicinal dimethyl substitution.[50] Perhaps most significant is the fact that these two independent methods (equilibration and kinetics) involve quite different assumptions but lead to comparable values for the 3-alkyl ketone effect.



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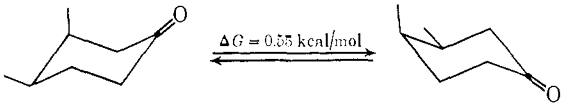

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Like the 3-methyl substituent, the 3-*tert*-butyl group exerts a rate-diminishing effect on borohydride reduction. The greater magnitude of this effect is in keeping with the proposal that the rate reflects a ring distortion that is magnified by the bulkier *tert*-butyl group.[51] It is of interest that the second equatorial *tert*-butyl group in **14** diminishes the rate by the same factor as the first such group (**13**), a good illustration of the energetic additivity of nonvicinal substituent effects.

In a study of the rates and stereochemistry of lithium tri-*tert*-butoxyaluminum hydride reduction of substituted cyclohexanones,[46] Klein, Dunkelblum, Eliel, and Senda have noted that axial 3-methyl substitution

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[42] A $\sigma_{\rm I}$ value of +0.2 was estimated using the procedure of Taft, *et al.*;[43] given a ρ value of +2.3,[16] it appears that almost half of the increased rate of **22** relative to **1** could be due to this inductive effect.

[43] R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, 85, 709 (1963).

[44] M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

[45] See, for example, B. Rickborn, *J. Amer. Chem. Soc.*, 84, 2414 (1962).

[46] J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).

[47] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955).

[48] W. Klyne, *Experientia*, 12, 119 (1956).

[49] For an excellent description of this problem and references to earlier work, see N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, 88, 2999 (1966).

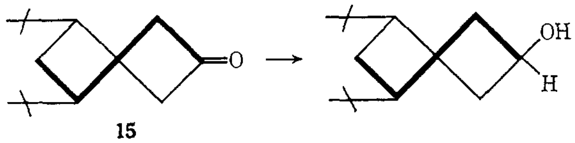
[50] Such an effect apparently operates in the reduction of *trans*-3,4-dimethylcyclohexanone (**12**), where the rate constant is significantly smaller than anticipated on the basis of simple conformational considerations.

[51] Kwart and Takeshita[16] have already shown that 4-*tert*-butylcyclohexanone is reduced faster than 4-methylcyclohexanone. Again we suggest a ring distortion effect by both substituents which parallels the bulk of the group.

has only a slight effect (if any) on hydride attack from the equational side of the carbonyl group, while axial attack is greatly inhibited. Since it might prove tempting to extend these observation to other ketone reactions, it is worth noting here that this does not hold true for borohydride reductions. The data in Table III for 0% reaction may be taken as the stereochemical results of the first hydride transfer from the borohydride ion.[52] Inspection of these data in conjunction with the rate constants for **1**, **7**, **8**, **9**, and **10** shows clearly that no amount of variation in stereochemical outcome can account for the overall rate factor of nearly 10^3 seen in this series. We suggest again that borohydride reduction represents a more sensitive probe of ketone structure than the trialkoxyaluminum hydride reagent.

The twist or flexible conformation of cyclohexanone may be important in either the ground state or transition state for borohydride reduction. Allinger and his coworkers have calculated, on the basis of equilibration of 3,5-di-*tert*-butylcyclohexanone,[49,53] that the boat conformation of cyclohexanone is destabilized relative to the chair by 3.3 kcal/mol (ΔG). Although this value is lower than that for cyclohexane (4.9 kcal/mol), it is sufficiently high that boat conformations will not, in the absence of specific substituent effects, contribute significantly to the ground-state ketone population. Allinger[47] has estimated that the twist conformer may contribute 4% (25°) to the equilibrium population of *trans*-3,5-dimethylcyclohexanone. On the other hand, 3,3,5,5-tetramethylcyclohexanone (**10**), in which the large diaxial methyl–methyl interaction[54] might lead one to expect a substantial contribution from the boat form, apparently strongly favors the chair conformation.[53,55] Lambert[56] has suggested on the basis of nmr data that the boat form may be important in 4,4-dimethylcyclohexanone, although his later work[37] on X-ray analysis of 4,4-diphenylcyclohexanone shows that this is not the case for the latter compound in the solid state. Landor and Regan[57] have argued that the twist transition state may be important in the lithium dialkoxyaluminum hydride reduction of 3,3,5-trimethylcyclohexanone. If we view the alcohol as a good model for the borohydride reduction transition state, the nmr data of Chiurdoglu[58] and Stolow[59] and coworkers are of considerable interest. The products of **1**, **17**, **18**, and **21** are shown to be conformationally very similar. In apparent contradiction to the implication that the alcohol product of **18** is a normal chair conformer, Bhacca, Wolff, and Ho[60] have concluded that ring A in a 3-spirocyclopropyl steroid prefers the twist conformation.

Of the systems examined in the present work, only *trans*-3,5-di-*tert*-butylcyclohexanone **15** clearly prefers[49] the twist conformation, and as such will serve as our model for this ground state. The product alcohol from **15** should also strongly prefer the twist conformation, and consequently we can with confidence assign the twist conformation to the transition state for this reaction (eq 15). The analysis of the expected rate of reduction of **15** is as follows: the ground-state sp^2 boat is energetically unfavorable by 3.3 kcal/mol; if the transition state resembles a fully developed sp^3 boat, it would be energetically unfavorable (relative to a chair system) by 4.9 kcal/mol. The difference between these figures, $4.9 - 3.3 = 1.6$ kcal/mol, represents the net increase in activation energy ($\Delta\Delta G^{\ddagger}$) expected for reduction of **15** relative to, *e.g.*, **14**. The experimentally determined difference is 2.0 kcal/mol, in close enough agreement to suggest that this picture is at least qualitativity correct.



(15)

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Of the remaining ketones examined in this work, compound **22** is considered the most likely to exist in a twist conformation, using as an analog 1,4-cyclohexanedione.[49] As in the dione, though, it is difficult to assign relative absolute energy levels, *i.e.*, whether higher or lower than chair cyclohexanone. If the latter is assumed, and a boat transition state is viewed as unfavorable (since the product alcohol should prefer the chair conformation)[61] one would expect a diminished rate for **22**. The opposite result is observed. As noted earlier, the enhanced rate of **22** may be satisfactorily accounted for by assuming a somewhat distorted (Thorpe–Ingold effect) chair.[42]

One final point should be made in regard to the question of twist ground and transition states. The rate constants calculated for the highly hindered 3,3,5,5-tetramethylcyclohexanone (**10**) by squaring the relative rates for **6** and **8** differ only by factors of 2 and 3 from the observed value. The ground states of **6** and **8** should not involve appreciable quantities of nonchair conformers, and one may therefore argue on kinetic grounds that **10** must also strongly prefer the chair conformation, in agreement with Allinger's suggestion.[53] It does not appear possible to rule out the twist transition state for compounds **4**, **6**, **8**, **9**, and **10**, although the magnitude of the activation energy increase is not sufficient to accommodate a fully developed sp^3 twist conformation. For this reason, we prefer the alternate argument that the rates are diminished largely by steric interactions associated with the axial 3-methyl substituent(s).

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(52) This is not strictly true for **4** and **9** because the very small changes observed through the course of these reductions did not allow accurate extrapolation. However, our results with triisopropoxyborohydride show that the bulkier reagent leads to increased equatorial attack, so the 0% reaction figures for **4** and **9** in Table III represent maximum figures.

(53) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).

(54) N. L. Allinger, and M. A. Miller, *ibid.*, 83, 2145 (1961).

(55) (a) P. Laszlo and A. Speert, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. 139; (b) recently M. Balasubramanian and A. D'Souza [*Tetrahedron*, **25**, 2973 (1969)] have suggested on the basis of dipole moment calculations and measurements that 3-*p*-bromophenyl-3,5,5-trimethylcyclohexanone exists in the twist form. It appears, however, that minor deformations in the assumed perfect chair conformation would lead to the opposite conclusion.

(56) (a) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967); (b) see also J. E. Nordlander, J. M. Blank, and S. P. Jindal, *Tetrahedron Lett.*, 3477 (1969).

(57) S. R. Landor and J. P. Regan, *J. Chem. Soc. C*, 1159 (1967).

(58) G. Ransbotyn, R. Ottinger, J. Reisse, and G. Chiurdoglu, *Tetrahedron Lett.*, 2535 (1968).

(59) R. D. Stolow and T. Groom, *ibid.*, 5781 (1968).

(60) N. S. Bhacca, M. E. Wolff, and W. Ho, *ibid.*, 5427 (1968).

(61) Methylenecyclohexane exhibits no appreciable amount of nonchair conformer by nmr: (a) J. T. Gerig, *J. Amer. Chem. Soc.*, **90**, 1065 (1968); (b) F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968).

Experimental Section

Kinetic Method. A special rate apparatus was constructed for adding the reactants, stirring the reacting solution, and rapidly transferring precisely measured aliquots to the quenching reagent.[62] The entire apparatus was immersed in a well-stirred ice bath during a rate determination. A known volume of stock sodium borohydride solution (all work was done in IPA solvent) was measured into the reaction flask from a storage buret, and magnetic stirring at 0° was started. The ketone solution, consisting of a weighed sample in a known volume of IPA, was contained in a flask equipped with a small silicone rubber stopper which could be blown out by applying 2–3 psi of nitrogen pressure, releasing the contents into the reaction flask within about 0.2 sec. At appropriate time intervals samples of the reaction mixture were transferred, by nitrogen pressure, into a calibrated measuring bulb which was also immersed in the ice bath. The measured aliquots were then rapidly (within about 2 sec) forced into a stirred solution of the quenching reagent.

Initial borohydride concentrations ranged from 0.004 to 0.034 *M*, and initial ketone concentrations from 0.020 to 0.135 *M*. Most kinetic determinations were made with approximately equivalent concentrations of reagents, with the reactivity of the system determining the actual amounts used. The volume of the initial reaction mixtures was normally adjusted to approximately 85 ml; eight aliquots (8.124 ml each) were normally taken, at times chosen so that the last aliquot fell at about 85% reaction.

A computer program was written to calculate the rate constants and related information. The computation included a modified least-squares treatment, with instructions to note and reject points which deviated from the least-squares line by more than twice the root-mean-square deviation of all values.

The quenching solution was prepared by treating solutions of 0.13 *M* aqueous silver nitrate (adjusted in volume to contain at least a 10 mol % excess of silver ion over the amount needed to react with the borohydride) with about 1 ml of ethylenediamine for each 20 ml of solution. The resulting silver ethylenediamine ($AgED^+$) nitrate solutions, stored in the dark, were stable for at least 1 hr. Just prior to the addition of borohydride solution, approximately 3 ml of 6 *N* NaOH was added for each 20 ml of $AgED^-$ solution.

The kinetic aliquots were then forced into the $AgED^+$ solution, and the resultant black (silver metal) mixtures stirred for an additional 15–30 sec prior to rapid titration with 0.036 *M* KI. This was accomplished by the potentiometric method using a silver–0.1 *M* KCl/calomel electrode pair. The end points were not particularly sharp, but could be accurately determined by constructing a plot of KI volume *vs.* potential. Such a plot was constructed for at least one titration in each kinetic determination and used to obtain accurate iodide volume for the remaining titrations. The titrations were performed rapidly to avoid decomposition of the basic $AgED^+$ solutions; the stability of these solutions could be enhanced by additional ethylenediamine, but only at the expense of end point sharpness.

Vpc Kinetics and Stereochemical Determinations. Titrated aliquots were stored in the dark until ready for extraction. Each aliquot was rinsed into a separating funnel with 15 ml of 6 *N* sulfuric acid, followed by about 20 ml of water and 15 ml of ether. A second extraction involved 7–8 ml of ether. In each extraction, the greenish gray precipitate of AgI was taken with the ether. The combined ether extracts were shaken with a few milliliters of saturated salt solution and allowed to settle. A small amount of the supernatant liquid was drawn off with a pipet, filtered through glass wool, and analyzed directly by vpc, without prior evaporation of the solvent.

Controls on this procedure were run with a number of the systems examined. As an example, a known mixture of 2-methylcyclohexanone (46.1%) and 2-methylcyclohexanol, 53.9% (38.1% cis, 61.9% trans), when carried through the titration and extraction procedure, analyzed as 44.8% ketone and 55.2% alcohol, the latter in a cis-trans ratio of 37.8:62.2. Other ketone–alcohol systems gave similarly satisfactory controls. A variety of vpc columns and conditions was used to effect separation of these ternary mixtures.[62] The individual product(s) of each ketone (mostly known alcohols) were isolated and spectrally characterized.

Sodium Borohydride Solutions. Commercial sodium borohydride was purified by the method of Brown, *et al.*[5] Reagent grade IPA was dried by 24-hr reflux with calcium hydride, followed by fractional distillation. Analysis with Karl Fischer reagent indicated less than 0.001% water. Stock solutions of sodium borohydride in IPA (*ca.* 0.05 *M*) were analyzed by the basic iodate method, the $AgED^+$ procedure, and by measurement of the hydrogen evolved on acidification; all three methods gave identical values (±1%).

Sodium Triisopropoxyborohydride. This material was prepared using the method of Brown, Mead, and Shoaf.[31] Hydrogen evolution on treatment with dilute acid indicated a purity of 79.4%. A sample was dissolved in IPA at 0° and analyzed by the iodate, periodic acid, and $AgED^+$ procedures; the iodate method gave very low active hydride titers. Periodic acid gave somewhat better results, but the values were depressed by added 4-methylcyclohexanone in the quenching solution. As with sodium borohydride itself, only the $AgED^+$ procedure gave accurate, reproducible results which were unaffected by added ketone.

Reaction of 9 with Sodium Triisopropoxyborohydride. The following procedure is typical of runs made with this complex hydride, except that determination of the rate of reaction of this material with solvent was omitted in later runs.

A finely powdered sample, 0.816 g (3.055 mmol) of sodium triisopropoxyborohydride was weighed into the rate apparatus under dry nitrogen. IPA, 74.7 g, which had been precooled to 0° was then added. Prolonged stirring (*ca.* 4 hr) at 0° was required to effect complete solution. Three aliquots were then taken at times (after addition of the IPA) of 285, 340, and 370 min, titrated by the $AgED^+$ method, and the data used to determine the approximate first-order rate constant (1.5×10^{-5} sec^{-1}) for reaction of the hydride with IPA solvent.

To the remaining solution was added a precooled mixture of 0.310 g of 9 in 10.1 ml of IPA. By using the known volumes of solution and the rate of decomposition of the hydride, the initial concentration of hydride was calculated to be 0.020 *M*, while the ketone was 0.028 *M*. Eight aliquots were then examined at times ranging from 2 to 254 min, and analyzed first by the $AgED^+$ procedure, then by vpc. The rate constants were calculated from the simple 1:1 stoichiometry second-order rate expression.

Reductions with Excess Borohydride. These reactions were carried out in the same manner as the kinetic runs, at 0°. The initial borohydride concentration was maintained constant at 0.0508 *M*, while the ketone (*e.g.*, **7**) was varied from 0.0184 to 0.0021 *M*. Control experiments were carried out to assure the accuracy of the vpc product determinations.

Ketones. Referring to Table I, compounds **1**, **2**, **5**, **10**, and **16** were obtained from commercial sources and purified by distillation from a Teflon spinning band column. The synthesis of spiro[2.5]octan-6-one has been described elsewhere.[63] All materials used for kinetics exhibited the expected ir and nmr spectra and were >99.8% pure by vpc analysis, except as otherwise noted.

2,2-Dimethylcyclohexanone (3). Methylation of **2** by the procedure of Vanderwerf and Lemmerman[64] gave crude **3** in 87% yield. Vpc analysis indicated that this material contained *ca.* 21% *cis*-2,6-dimethylcyclohexanone and 3% 2,2,6-trimethylcyclohexanone. The mixture was converted to a semicarbazone, which after four recrystallizations from aqueous ethanol, had mp 184.1–184.9°. This derivative was hydrolyzed in aqueous acid to give (quantitative from the semicarbazone, 17% from **2**) pure **3**, bp 85° (32 mm).[65]

3,3-Dimethylcyclohexanone (6). Catalytic reduction of dimedone, following the procedure of Doering and Beringer,[66] gave crude 3,3-dimethylcyclohexanol. Jones oxidation gave, on careful distillation, pure **6**, bp 80.5° (30 mm).[67]

4,4-Dimethylcyclohexanone (17). The procedure of Eliel and Lukach[68] gave 4,4-dimethyl-2-cyclohexenone, bp 47–48° (3 mm), in 33% yield. Catalytic reduction[69] gave **17**, 77%, bp 77.5–78° (23 mm), mp 43–44°.

***cis*-3,4-Dimethylcyclohexanone (11).** *cis*-4,5-Dimethylcyclohexene was prepared as described earlier.[38] Hydroboration was ac-

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[62] Details of construction of this apparatus, and of vpc columns and conditions used in this work will be forwarded on request.

[63] M. T. Wuesthoff and B. Rickborn, *J. Org. Chem.*, **33**, 1311 (1968).

[64] C. A. Vanderwerf and L. W. Lemmerman, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 44.

[65] F. E. King, T. J. King, and J. G. Topliss, *J. Chem. Soc.*, 919 (1957).

[66] W. v. E. Doering and F. M. Beringer, *J. Amer. Chem. Soc.*, **71**, 2225 (1949).

[67] O. H. Wheeler and J. Z. Zabicky, *Can. J. Chem.*, 36, 656 (1958).

[68] E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

[69] F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, 28, 1347 (1963).

complished by adding 360 ml of 1 *M* borane in THF over a period of 2 hr to a solution of 0.34 mol of the olefin in 150 ml of THF. After the usual basic peroxide cleavage and extraction, evaporation of the pentane solvent gave 42 g (0.33 mol, 97%) of a mixture of *cis,cis*- and *trans,trans*-3,4-dimethylcyclohexanols. Jones oxidation of 40.5 g gave 26 g of pure spinning band distilled **11**, bp 95.5° (35 mm); semicarbazone, mp 170–171°.[70]

Vpc analysis[62] established that the major product from hydroboration of *cis*-4,5-dimethylcyclohexene (presumably the trans,trans alcohol[72]) was identical with the minor product from borohydride reduction of **11**.

***trans*-3,4-Dimethylcyclohexanone (12).** Hydroboration of *trans*-4,5-dimethylcyclohexene[38] gave a mixture (46% "axial," 54% "equatorial-OH" by vpc) of alcohols in excellent yield. Jones oxidation of 32.8 g gave, after distillation, 23 g (71%) of pure **12**; semicarbazone,[70] mp 172–173°.

***cis*-3,5-Dimethylcyclohexanone (7).** Commercial 3,5-dimethylphenol was purified by distillation (bp 80–85°, 3 mm) and then catalytically hydrogenated; 97 g of the phenol in 150 g of acetic acid with 3 g of 5% Rh on aluminum was reduced at 100°, 20–50 psig. The crude product was subjected to Jones oxidation. The ketone was converted to the semicarbazone, which had mp 194.8–195.1° after two recrystallizations from aqueous ethanol; 59.7 g of purified derivative was obtained. Hydrolysis and distillation gave **7**, bp 90.5–91° (49 mm),[73] contaminated with 2.5% of the trans isomer **8**. Because of the large difference in rate of reduction (with **8** reacting much slower), this material was used directly in the kinetic determinations, using the corrected concentration for **7**.

***trans*-3,5-Dimethylcyclohexanone (8).** Treatment of 5-methyl-2-cyclohexenone[74] with methylmagnesium iodide in the presence of cuprous chloride, as described by Allinger and Riew,[75] gave a mixture of products containing mostly **8**. This mixture was partially separated by alumina (basic I) chromatography using pentane-ether solvent, with the desired material (*ca.* 90% pure) being eluted with 40% ether in pentane. Spinning band distillation gave **8**, bp 94.5° (44 mm); 2,4-DNP derivative,[75] mp 109–109.5°. Vpc analysis indicated contamination by 2.4% of the cis isomer **7**. This material was used directly in the kinetics experiments, where the faster reacting **7** led to a positive *y* intercept (*ca.* 4% reaction), but did not appreciably alter the slope (rate constant).

2,5,5-Trimethylcyclohexanone (4). Dimedone was converted to 2,5,5-trimethyl-1,3-cyclohexanedione by the method of Stetter.[76] This material was hydrogenated and then oxidized (overnight, 0°) with excess Jones reagent. Spinning band distillation gave a cut, bp 94–95° (41 mm), 97% pure, which on redistillation gave **4** in high purity; semicarbazone,[77] mp 175–175.5°.

The product alcohols from borohydride reduction of **4** were identified as follows. Ketone **17** was converted to 1,4,4-trimethylcyclohexanol by treatment with methylmagnesium iodide, and the alcohol was then dehydrated to give 1,4,4-trimethylcyclohexene. Hydroboration followed by oxidative cleavage gave a sample of *trans*-2,5,5-trimethylcyclohexanol.

3,3,5-Trimethylcyclohexanone (9). Commercial 3,3,5-trimethylcyclohexanol was Jones oxidized to the ketone which was purified by spinning band distillation, bp 97.5–97.7° (41 mm).[78]

3-*tert*-Butylcyclohexanone (13). Commercial 3-*tert*-butylphenol was hydrogenated in acetic acid solution on a high-pressure apparatus using rhodium on alumina catalyst. Jones oxidation of the resultant mixture gave **13**, purified by spinning band distillation, bp 80.5° (4.5 mm).[79]

***cis*-3,5-Di-*tert*-butylcyclohexanone (14).** The high-pressure hydrogenation (Rh on alumina) of commercial 3,5-di-*tert*-butylphenol gave crude material which was recrystallized once from aqueous methanol, mp 95–105°. Jones oxidation of 23.7 g of this material gave 23.8 g of solid ketone; recrystallization from 90 ml of pentane at −20° gave an initial crop of 6.4 g, white needles, mp 42.7–43.1°, 99.6% pure by vpc.[80]

***trans*-3,5-Di-*tert*-butylcyclohexanone (15).** A solution of lithium diethylamide was prepared by careful addition of 1.3 l. of 1.6 *M* butyllithium (in hexane) to an ice-cold solution of 132 g of diethylamine in 1.3 l. of ether. With stirring, a solution of 200 g (1.3 mol) of mixed *cis*- and *trans*-4-*tert*-butylcyclohexene oxide[81] in 200 ml of ether was added over a period of 2 hr. The resultant solution was refluxed for 29 hr, after which water (cautiously at first) was added. The organic solution was washed with 10% HCl, and bicarbonate solution, and then dried. The residue from solvent evaporation was then distilled through a Vigreux column giving a forerun of nearly pure *cis*-4-*tert*-butylcyclohexene oxide (plus some ketone), then a fraction (74.7 g), bp 92–96° (5 mm), estimated by vpc to contain *ca.* 80% *trans*-5-*tert*-butyl-2-cyclohexenol.[82] Jones oxidation of this crude material gave 73.3 g of pale yellow liquid; spinning band distillation gave 30 g of material, bp 91.5° (5 mm), which by vpc contained 86% 5-*tert*-butyl-2-cyclohexenone[79] and 14% impurity, probably 4-*tert*-butyl-2-cyclohexenone.

A solution of 28.1 g of this enone mixture in 150 ml of ether was added dropwise to a mixture of 70 ml of 2.7 *M* *tert*-butylmagnesium chloride (in ether), 100 ml of ether, and *ca.* 20 mg of cuprous chloride.[75] After addition was completed, the solution was stirred an additional 12 hr, then decomposed with 5% HCl. The ethereal solution, after the usual washing and drying, was rotary evaporated to give a pale yellow semisolid residue weighing 36.4 g. Vpc analysis indicated that the residue contained, among other products, starting material and **15** and **14** in a ratio of about 60:40. Initial separation was effected by alumina chromatography, with a mixture of **14** and **15** being eluted with 20% ether in pentane. Three recrystallizations of 16 g of this mixture from pentane at −20° gave 4.0 g of fine white needles, mp 78.6–79.0°, which by vpc was shown to be >99% pure **15**.[80]

Spiro[3.5]nonan-7-one (19). The procedure of Cason and Rapoport[83] was used to prepare diethyl cyclobutane-1,1-dicarboxylate in 68% yield. A solution of 150 g of the diester was added to LAH (40 g) in THF, and the mixture stirred for 15 hr. After the usual work-up (with salt saturated solutions), rotary evaporation gave 76 g (88%) of fairly pure 1,1-di(hydroxymethyl)cyclobutane.[84] Treating 50 g of the diol with methanesulfonyl chloride in pyridine led to, after work-up, 99 g (85%) of the dimesylate as a tan solid. A solution of 66 g of this derivative and 65 g of KCN in 250 ml of DMF was heated on a steam bath for 6 hr. After work-up, 26.2 g (81% crude yield) of 1,1-di(cyanomethyl)cyclobutane was obtained. Basic hydrolysis gave 30.7 g (91%) of impure cyclobutane-1,1-diacetic acid, mp 111–121°. A small sample once recrystallized from chloroform-hexane had mp 135.5–137° (lit.[85] mp 140°).

This diacid was next reduced using 20 g of LAH to give 19.5 g (76% crude yield) of 1,1-di(2-hydroxyethyl)cyclobutane, which was converted to the dimesylate, 30.5 g of light brown liquid. This in turn was used to form 1,1-di(2-cyanoethyl)cyclobutane as described above; 15.5 g (94%) of a dark brown liquid was obtained. This crude product was hydrolyzed to give 16.8 g (87%) of a brown oil which slowly solidified. This crude cyclobutane-1,1-di-2-propionic acid was treated directly with 2 g of barium hydroxide and the mixture heated with a flame. The volatile effluent was spinning band distilled to give 2.5 g of the desired ketone **19**. The nmr and ir spectra of this material were in excellent agreement with the assigned structure: ir 920 (w), 1135, 1235, 1320, 1340, 1430, 1450, 1720 (vs) cm^{-1}; nmr (neat) (external TMS) 1.5–2.2 (m), 1.8 (s) ppm. Vpc indicated the presence of about 5% volatile impurities. It was established that these impurities did not react with borohydride, and consequently it was possible to use this distilled product, with correct concentration, directly in the kinetic runs.

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(70) The semicarbazone[71] of the product of hydrogenation of 3,4-dimethyl-2-cyclohexenone has mp 172.5–173°; it is not clear which geometric isomer is involved.

(71) H. E. Baumgarten and R. L. Eifert, *J. Org. Chem.*, **18**, 1177 (1953).

(72) The axial methyl group is known to inhibit cis attack in hydroboration: *cf.* (a) D. J. Pasto and F. M. Klein, *ibid.*, **33**, 1468 (1968); (b) J. Klein, E. Dunkelblum, and D. Avrahami, *ibid.*, **32**, 935 (1967).

(73) N. L. Allinger, *J. Amer. Chem. Soc.*, 81, 232 (1959).

(74) J. P. Blanchard and H. L. Goering, *ibid.*, 73, 5863 (1951).

(75) N. L. Allinger and C. K. Riew, *Tetrahedron Lett.*, 1269 (1966).

(76) H. Stetter in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, pp 59, 93.

(77) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, 37, 1870 (1959).

(78) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, 26, 3504 (1961).

(79) C. Djerassi, E. J. Warawa, R. E. Wolff, and E. J. Eisenbraun, *ibid.*, **25**, 917 (1960).

(80) M. Hanack and K. Heinz, *Justus Liebigs Ann. Chem.*, 682, 75 (1965).

(81) B. Rickborn and J. Quartucci, *J. Org. Chem.*, 29, 2476 (1964).

(82) (a) B. Rickborn and R. P. Thummel, *ibid.*, 34, 3583 (1969); (b) R. P. Thummel and B. Rickborn, *J. Amer. Chem. Soc.*, **92**, 2064 (1970).

(83) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1962, p 406.

(84) The authors wish to thank Mr. Frank Setaro for carrying out this preparation.

(85) H. Najer, R. Guidicelli, and J. Sette, *Bull. Soc. Chim. Fr.*, 2572 (1964).

Although the overall yield of **19** is rather low from this multistep procedure, other approaches failed to give any of the desired product (or intermediates).[86]

Spiro[4.5]decan-8-one (20). The procedure of Baird and Winstein[87] was modified slightly to accommodate a preparative scale reaction. In several experiments, attempted distillation of the spiro[4.5]deca-6,9-dien-8-one lead to the dienone–phenol rearrangement product. Consequently, it proved simpler to reduce the dienone directly without purification. The isolated product, **20**, had bp 90° (4 mm),[87] and showed no impurities by vpc.

Spiro[5.5]undecan-3-one (21). The procedure of Burnell and Taylor[88] was used to form cyclohexane-1,1-di-2-propionic acid, which was cyclized to **21** using the KF method described by Helmkamp and Johnson.[89] The product had bp 128° (11 mm), and was 98.3% pure by vpc; 2,4-dinitrophenylhydrazone, mp 127–128° (lit.[88] mp 121°).

4-Methylenecyclohexanone (22). The monobenzoate of 1,4-cyclohexanediol was prepared as described earlier.[90] Oxidation gave 4-benzoyloxycyclohexanone,[90] mp 62–63°. Hydrolysis gave 4-hydroxycyclohexanone,[90] bp 90–92° (0.8 mm).

Triphenylmethylenephosphorane was generated from 170 g (0.42 mol) of phosphonium iodide in *tert*-butyl alcohol with potassium *tert*-butoxide, following the procedure of Schlosser and Christmann.[91] The 4-hydroxycyclohexanone, 47.9 g (0.42 mol), was added to the refluxing ylide solution, and the resulting mixture stirred overnight at *ca.* 45°. The pale orange solution was taken up in 3 l. of ice-water and extracted five times with ether. The combined organic solution was then washed with water, saturated salt solution, and dried with sodium sulfate. The ether was evaporated, and about 300 ml of *tert*-butyl alcohol then removed by distillation at 150 mm. At this point 200 ml of triethyleneglycol was added to maintain the triphenylphosphine oxide in solution, and the residue distilled giving 40.1 g (0.36 mol, 85%) of 4-methylenecyclohexanol as a colorless oil, bp 58.5° (1.8 mm).

Jones oxidation of 38.1 g (0.34 mol) of this material gave 33.5 g of a pale yellow oil, which on spinning band distillation gave 27.2 g (0.25 mol, 73%) of very pure **22**: bp 70° (21 mm); ir 900 (s), 1140, 1230, 1305, 1325 (w), 1350 (w), 1430 (w), 1445, 1655, 1730 (vs), C–H str. 3070 cm^{-1}; nmr 2.44 (m, 8 H), 4.92 (s, 2 H).

Anal. Calcd for $C_7H_{10}O$: C, 76.3; H, 9.2. Found: C, 76.0; H, 9.2.

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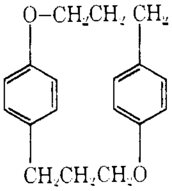
(86) For example, treatment of 1,1-di(mesyloxymethyl)cyclobutane with diethyl sodiomalonate gave as the only isolable product 53% diethyl spiro[3.3]heptane-2,2-dicarboxylate. Attempted intramolecular cyclization of the tosylate of 4-(3-hydroxypropyl)-3-cyclohexenone (as in the preparation of 20) gave no detectable spiro[3.5]non-5-en-7-one, but instead the major product appeared to be the dioxa[4.4]paracyclophane,



Attempted condensation of cyclobutanecarboxaldehyde with methyl vinyl ketone, following the procedure in the preparation of **17** gave very low yields, if any, of the spiro enone. If view of the difficulty experienced in preparing and handling this aldehyde, this line was abandoned.

(87) R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, 84, 788 (1962).

(88) R. H. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3486 (1954).

(89) G. K. Helmkamp and H. W. Johnson, Jr., "Selected Experiments in Organic Chemistry," W. H. Freeman, San Francisco, Calif., 1964, p 77.

(90) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

(91) M. Schlosser and K. F. Christmann, *Angew. Chem.*, 76, 683 (1964).

Mechanisms of Elimination Reactions. XVI. Stereochemistry of Elimination from 2- and 3-Hexyltrimethylammonium Ions. An Explanation of the Syn–Anti Dichotomy[1]

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Abstract: Stereospecifically deuterated 3-hexyl-*4-d*-, 3-hexyl-*2-d*-, and 2-hexyl-*3-d*-trimethylammonium iodides were prepared and subjected to elimination reactions under a variety of conditions. The product proportions, deuterium contents of products, and assumed isotope effects were combined to calculate the amount of syn elimination expected in the absence of the deuterium label. Syn elimination is important only in the production of *trans*-olefin, and increases with increasing strength of the attacking base. Under any given set of conditions, the importance of the syn → trans route increases in the order 2-hexyl → 2-ene < 3-hexyl → 2-ene < 3-hexyl → 3-ene. These results are shown to be consistent with a steric theory of syn elimination in which the key assumption is that the bulky trimethylammonio group forces the γ and β′ groups on the alkyl chain into conformations where they hinder approach of base to the anti β-hydrogen, thereby raising the energy of the anti → trans above that of the syn → trans route. The range of applicability of the theory is discussed.

Until a few years ago, it was generally believed that bimolecular elimination reactions showed a strong preference for trans–anti departure of the leaving group and the β-hydrogen.[3–6] Exceptions to this rule were attributed to special circumstances such as strong activation at the β-carbon[7–12] or a rigid ring

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