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# REDUCTION WITH METAL HYDRIDES—XIX[1]

## COMPETITIVE REDUCTION OF ALKYLCYCLOHEXANONES: REGARDING THE CONCEPTS OF STERIC APPROACH CONTROL AND PRODUCT DEVELOPMENT CONTROL

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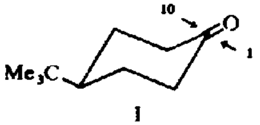
**Abstract**—Competitive rate studies have been carried out for the reduction of 4-t-butylcyclohexanone, 3,5-dimethylcyclohexanone, 3,3,5-trimethylcyclohexanone, 3,3,5,5-tetramethylcyclohexanone and 2,2-dimethyl-4-t-butylclohexanone by LAH in ether, lithium aluminium tri-t-butoxyhydride in THF, lithium aluminium trimethoxyhydride in THF and $NaBH_4$ in isopropyl alcohol and sodium triisopropoxyborohydride in isopropyl alcohol. Relative rate constants for attack of the various ketones from the axial and from the equatorial side were computed by reducing the ketones in pairs and analyzing the alcohol mixtures thus obtained. The relative rate constants support the concept of "steric approach control" but suggest that "product development control" plays at best a minor role especially in the reductions with aluminohydrides. Alternative explanations for the 10:1 ratio of equatorial to axial alcohol observed in the lithium aluminium hydride reduction of 4-t-butylcyclohexanone in ether are suggested.

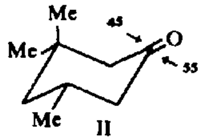
## INTRODUCTION

In 1956 Dauben, Fonken and Noyce studied the reduction of several substituted cyclohexanones of differing steric requirements with metal hydrides of differing steric bulk.[2] On the basis of their results and earlier ones reported in the literature they postulated that the steric course of such hydride reductions was governed by two factors: "product development control", i.e. a tendency to form the thermodynamically more stable substituted cyclohexanol in the case of relatively unhindered ketones and "steric approach control" for relatively unhindered ketones. "Steric approach control" leads to a reduction course in which the incoming hydride reagent approaches from the less hindered side of the plane of the carbonyl group. Later, the terminology was extended to the reaction of cyclohexanones with nucleophiles other than hydrides.

4-t-Butylcyclohexanone (I) provides a text-book example of "product development control": the more stable equatorial alcohol, trans-4-t-butylclohexanol predominates[3] in the products of lithium aluminium hydride reduction over the less stable *cis* (axial) diastereoisomer by a factor of 10 to 1. In contrast, mild "steric approach control" is seen in 3,3,5-trimethylclohexanone (II) in which the more stable[4] equatorial alcohol is now the minor product (45%); the axial alcohol, formed by approach of the hydride on the less hindered equatorial side, predominates (55%).[5]



I



II

A more clear-cut case of "steric approach control" (though less pertinent to the present investigation) is found in the 11-ketosteroids whose reduction with lithium aluminium hydride gives at least 78% (depending on the exact compound) of the less stable 11β-ol formed by approach of hydride from the less hindered 11α-side.[6]

In 1965, Brown and Deck[7] suggested that the terms "steric approach control" and "product development control" be replaced by "steric strain control" and "product stability control" in order to focus attention on the transition state of the reaction as such rather than on events which occur on the way to the transition state. Since, however, product stability control is, itself, caused by a form of steric strain (involving OH of a complex thereof) in the transition state, we feel that a further clarification of the terms is in order; we have tried to embody our understanding of their meaning—in terms of the difference between ground state and transition state energy levels—in Scheme 1.†

SCHEME 1

A: Interactions involving =O in starting ketone*
B: Interaction involving — O··· M in transition state*
C: Interaction involving ··· H in transition state*
B − A is a measure of product development control
C is a measure of steric approach control

* For the sake of clarity, only part of the interaction is shown.

We are taking "steric approach (or strain) control" to refer to the steric strain involving the incoming nucleophile in the transition state (there is no such strain in the ground state). "Product development (or stability) control" is taken to refer to the difference in strain of the oxygen (or complexed oxygen) between the transition state and the ground state (Scheme 1). (Clearly, there is some arbitrariness in dividing up the strain factors in this fashion.)

That "steric approach control", i.e. crowding of the incoming nucleophile in the transition state, is an important factor in some ketone reactions has never been questioned. However, doubts have been expressed from time to time regarding the reality of "product development control". Borohydride reduction of ketones is a very exothermic reaction ($\Delta H^\circ = -128{\cdot}2$ kcal/mol for the reduction of acetone[9]) of low activation energy ($\Delta H^\ddagger = 7{\cdot}6$ kcal/mol[10]); the activation energy of aluminohydride reductions is undoubtedly lower still, for whereas borohydride reduction has been followed kinetically,[11] to the best of our knowledge no rate studies have yet been published on the aluminohydride reduction of ketones because it is so fast. It has been pointed out[12] that for a reaction of such high exothermicity and low activation energy, the Hammond postulate[13] suggests that the transition state should resemble the starting material rather than the product and that there is therefore no obvious reason why the relative stability of the two epimeric products should be

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† We shall be concerned only with steric factors in this paper. Polar factors do come into play in ketones containing strongly polar substituents.[8]

reflected in the transition states leading to them. The argument is uncertain because the Hammond postulate on which it is based is not universally accepted and there are, in fact, some contrary indications in the case of borohydride reduction which suggest that the change from $sp^2$ to $sp^3$ hybridization has progressed extensively in the transition state. Thus,[14] cyclohexanone is reduced by borohydride 21 times as fast as cyclopentanone; the explanation[14] of this large factor on the basis of I-strain requires a substantially $sp^3$ hybridized transition state. Extensive change of hybridization toward $sp^3$ in the borohydride reduction of ketones has also been postulated on the basis of a substantial rho value (2·78) for the reduction of *p*-substituted acetophenones[15a] and on the basis of a substantial inverse isotope effect in borodeuteride reduction of ketones,[15b] although the latter result has also been interpreted[15c] in terms of a starting material like transition state. Even if the transition state for borohydride reduction is largely $sp^3$ hybridized, the same is not necessarily true for the transition state in the considerably faster aluminohydride reductions, although in one study[16] it has been tentatively concluded, on the basis of rather indirect evidence, that substantial bond breaking and making occurs in both reactions.

A second argument against "product development control" is based on the finding[3] that the more stable equatorial alcohol is formed in the $LAH_4$ reduction of I (in ether) in greater proportion (10:1) than corresponds to the equilibrium ratio (4:1 in isopropyl alcohol, 2·4:1 in the more ether-like solvent dimethoxyethane).[17] At the time it was suggested[3] that this might be due to the fact that alcohols are formed as lithium or aluminum complexes in the reduction and that the equilibrium position of these complexes might not be the same as that of the free alcohols. Subsequent work[17] has, however, thrown doubt on this saving argument, for the position of equilibrium of the aluminum alkoxide derivatives of the 4-t-butylcyclohexanols in tetrahydrofuran (*trans*:*cis* 82:18) while different from that of the free alcohols (72·5:28·5) is still appreciably less than the product ratio in THF (88·5:11·5).*

In the belief that "product development control" might not prove a satisfactory explanation of the product ratio observed in the reduction of I, alternative explanations have been devised. Most of these interpretations focus on the axial hydrogens next to the ketone group in I (at C-2 and C-6) as being the impediment to underside attack leading to the axial alcohol. Kamernitzky and Akhrem[6] ascribe the interference to dipole-dipole interactions, Richer[19] seeks it in steric interference of the approaching nucleophile with the axial hydrogens at C-2 and C-6 and Chérest and Felkin[20] ascribe the same interference to bond eclipsing factors. The geometry of the cyclohexanone is such that eclipsing with the aforementioned hydrogens in underside attack is more serious than eclipsing with the ring carbons C-2 and C-6 in topside attack.

It appeared to us that it would be difficult to establish whether "product development control" is real by investigation of the product ratio from a single ketone. Essentially only a single piece of data is obtained (the ratio) and there are two adjustable parameters (the steric approach and the product development factor) of which only the second (equilibrium ratio) is subject to independent investigation. The other parameter (steric approach factor) can always be adjusted in such a way as to make

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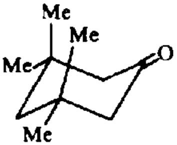
* The equilibrium of the dichloroaluminum alkoxides in ether is different, however (99·5 to 0·5).[18] It would appear that the product of $LAH_4$ reduction of a ketone should resemble $(RO)_3Al$ in the THF more than $ROAlCl_2$ in ether, but this is not certain.

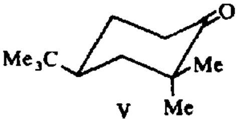
the observed product ratio conform with theory; the best that can be said is that in many cases the required steric approach factor conforms with what is otherwise known about the bulkiness of the reagent and of the substrate. The predictive power of the hypothesis is thus somewhat limited, and since, as the substrate becomes more encumbered, in general both the ease of approach of the reagent to form one diastereoisomer and the stability of the opposite diastereoisomer decrease, it is actually somewhat surprising that the predictions come out as well as they often do. (The last statement may be illustrated with compound II: introduction of the axial Me group interferes with axial attack of the hydride—to give equatorial alcohol—but it also decreases the stability of the axial alcohol. Evidently, the former factor is the more important, for the proportion of axial alcohol obtained from II is greater than that obtained from I.)

In order to overcome the handicap of having to base theory on product ratios from individual substrates alone, without a convincing comparison of the substrates *inter se*, we decided to study competitive rates of hydride reduction. Since absolute reaction rates are, at the moment, not accessible for aluminohydride reductions, relative rates were ascertained by reducing ketones pairwise with a deficient amount of hydride and studying the ratio of products gas chromatographically. For example, in the case of I and II, a deficient amount of ethereal LAH (5–20%) was added, slowly and with rapid stirring, to an equimolar mixture of I and II dissolved in ether. The products were quenched in the usual way and the ratio of the four alcohols formed from the two ketones was determined gas chromatographically. Additional ketones studied by competitive reduction are III, IV and V. Reducing agents were LAH in ether and in THF, lithium aluminum tri-t-butoxyhydride in tetrahydrofuran, lithium aluminum trimethoxyhydride in THF, sodium borohydride in isopropyl alcohol and sodium triisopropoxyborohydride in isopropyl alcohol.

III



IV



V

### RESULTS

The results of the competitive reductions are shown in Table 1. For each hydride, the relative rates of reduction are normalized to 100 for the axial attack on I to give *trans*-4-t-butylcyclohexanol. In the case of V, which is a mobile system,[21] only an overall rate could be obtained, since there is only a single product. (The overall rate is the sum of the two rates shown for V in the Table.) In order to effect an apportionment as to axial and equatorial rate, it was arbitrarily assumed that the ratio of rates of axial attack on IV as compared to II was the same as that for II as compared to I; in other words, that the second axial Me group reduced the rate of axial attack by the same factor as the first. This is probably a conservative assumption in the sense that it tends to exaggerate the rate of axial attack on IV, since steric effects generally tend to be more than additive (in terms of free energy), as they are piled on top of each other. From the point of view of the discussion, the rate of equatorial attack on IV is the more pertinent; this rate was obtained by deducting the computed axial rate from the experimental total rate. If the computed axial rate is too large, the effect will be to make the computed equatorial rate too small.

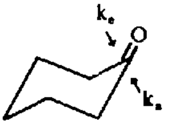
TABLE 1. COMPETITIVE RATE CONSTANTS FOR REDUCTION OF CYCLOHEXANONES WITH COMPLEX METAL HYDRIDES

| Ketone Hydride, Conditions | Rate Const[a] | I | II | III | IV[b] | V |
|---|---|---|---|---|---|---|
| LAH$_4$, | $k_e$ | 100 | 90 | 25 | (6·3) | 80 |
| ether, 0° | $k_a$ | 9·7 | 17·2 | 39 | (36) | 4·3 |
| LAH$_4$, | $k_e$ | 100 | [c] | 6·6 | [c] | 87 |
| THF, 0° | $k_a$ | 13·0 | [c] | 26 | [c] | 3·7 |
| LiAl(O-tBu)$_3$H, | $k_e$ | 100 | 59 | 0·29 | (0·0008) | 68 |
| THF, 0° | $k_a$ | 11 | 12 | 4·8 | (3·9) | 8 |
| LiAl(O-Me)$_3$H, | $k_e$ | 100 | 66 | 1·4 | (0·02) | 43 |
| THF, 0° | $k_a$ | 64 | 69 | 32 | (31) | 12 |
| NaBH$_4$, | $k_e$ | 100 | 67 | 1·7 | (0·03) | 21 |
| i-PrOH, 0° | $k_a$ | 17 | 20 | 7·4 | (6·1) | 1·2 |
| NaB(O-iPr)$_3$H, | $k_e$ | 100 | 90 | 4·3 | (0·18) | 18·4 |
| i-PrOH, 0° | $k_a$ | 44 | 51 | 21 | (11·3) | 2·4 |

[a] Average relative rate constants for several experiments; the rate constant for the formation of *trans*-4-t-butylcyclohexanol from I is arbitrarily set at 100 for each hydride. Regarding the meaning of $k_e$ and $k_a$, see (i).

[b] Only the overall rate constant ($k_e + k_a$) was determined experimentally, see text regarding apportionment.

[c] Not determined.



(i)

In order to assess the significance of the experimental findings, several controls were performed.

(1) *Reproducibility.* Because of potential mixing problems in the addition of the hydride to the mixed ketone solution, the reduction of mixtures of I and II was studied extensively at different mole ratios. The results, summarized in Table 7 (Experimental) for the LAH reductions in ether, show a variation of relative rates by a factor of not more than two in thirteen runs with a variation of the ratio of I:II from 1:1 to 1:3 and of the ratio of hydride:ketone from 0·033:1 to 0·26:1 equivalents. Even better reproducibility of the rate ratios was found with other hydrides; the number of runs for each hydride combination studied varied from two to ten. A factor of two may thus be taken as the limit of precision of our experiments and while this precision is not high, it is adequate for the purpose at hand.

(2) *Internal consistency.* If our methodology is correct, it must follow that for three different ketones combined pairwise in competitive reduction $(k_{II}/k_I)/(k_{III}/k_I) = k_{II}/k_{III}$.

Consistency checks of this type for both equatorial and axial products are summarized in Table 2 and it is seen that that deviation of the calculated from the experimental rate ratios is by no more than 25–50%; i.e. the data are consistent within the reproducibility of the individual ratios.

TABLE 2. CHECK OF RATIOS OF RATE CONSTANTS FOR INTERNAL CONSISTENCY

| Ratio | $LAH_4$, ether | | $LiAl(O\text{-}tBu)_3H$ | | $LiAl(O\text{-}Me)_3H$ | | $NaBH_4$ | |
|---|---|---|---|---|---|---|---|---|
| | *e* | *a* | *e* | *a* | *e* | *a* | *e* | *a* |
| II:I | 0·17–0·27 | 2·61–5·34 | 0·0028–0·0040 | 0·50–0·53 | 0·009–0·011 | 0·60–0·74 | 0·015–0·018 | 0·40–0·46 |
| III:I | 0·88–0·94 | 1·45–1·77 | 0·57–0·60 | 1·17–1·34 | 0·64–0·71 | 1·03–1·10 | 0·64–0·70 | 1·12–1·22 |
| II:III | 0·22–0·30 | 2·26–2·98 | 0·0042–0·0043 | 0·33–0·52 | 0·023–0·026 | 0·41–0·51 | 0·024–0·026 | 0·35–0·37 |
| II:III, calc[a] | *0·24* | *2·5* | *0·0058* | *0·41* | *0·015* | *0·63* | *0·025* | *0·37* |
| IV:II | 0·59–0·81[b] | | 0·76[b] | | 0·95–0·96[b] | | [c] | |
| IV:III | 0·46–0·54[b] | | [c] | | 0·22[b] | | [c] | |
| IV:III, calc[d] | *0·38* | | — | | *0·24* | | — | |
| IV:I | 0·50–0·58[b] | | [c] | | [c] | | 0·046–0·058[b] | |
| IV:I, calc[e] | *0·40* | | — | | — | | — | |
| IV:I, calc[f] | *0·50* | | — | | — | | — | |
| V:I | 0·77 | 0·41 | [c] | [c] | [c] | [c] | [c] | [c] |
| V:III | 0·87 | 0·22 | 1·06–1·15 | 0·58–0·59 | 0·62–0·65 | 0·19–0·20 | 0·30–0·32 | 0·050–0·069 |
| V:III, calc[g] | *0·85* | *0·25* | — | — | — | — | — | — |

[a] II:III = (II:I)/(III:I).

[b] Overall rate constants.

[c] Not determined.

[d] IV:III = (IV:II) × (II:III).

[e] IV:I = (IV:II) × (II:I).

[f] IV:I = (IV:III) × (III:I).

[g] V:III = (V:I)/(III:I).

(3) *Consistency with reported data.* In Table 5 (Experimental) the diastereoisomer ratios of the alcohols obtained from I, II, III and V are compared with corresponding ratios reported in the literature. The agreement is excellent for LAH and $NaBH_4$, somewhat less good for the alkoxyaluminohydrides, perhaps because of difficulty in exactly reproducing these reagents. It should be kept in mind that diastereomer ratios in hydride reductions are quite temperature dependent.[22]

(4) *Effect of additives.* The effect of added substances on the diastereomer ratio in the reduction of I, II, III and V is summarized in Tables 5 and 6 (Experimental). Addition of a second ketone does not affect the diastereomer ratio in reductions with LAH or alkoxyaluminohydrides. This is consistent with the previously proposed[5a] hypothesis that, during reactions with $AlH_4^-$, the $AlH_4^-$ species is constantly and rapidly regenerated by disproportionation from the intermediately formed aluminum alkoxyhydrides, so that such alkoxyaluminohydrides (if derived from secondary alcohols) play no part in the reduction process. In the case of alkoxyaluminohydride reductions it appears that there is no exchange between the alkoxy group of the hydride and that of the alcohols formed during reduction, so that once again the

reducing reagent remains invariant during the entire course of the reaction. With the borohydrides and alkoxyborohydrides, on the other hand, the product ratio is sensitive to the presence of a second ketone. This is to be expected, since alkoxyborohydrides are implicated in the latter stages of borohydride reduction[11, 23] and the alkoxy group can be exchanged with the solvent or with the reduction product of an added ketone, with resulting change in the nature of the reducing agent.

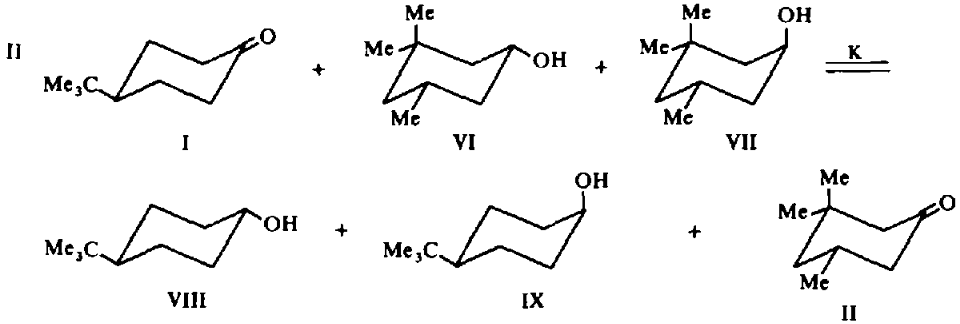
Lithium bromide or aluminum isopropoxide (Table 6) does not affect the product ratio in the LAH reduction of II and it is clear that aluminum isopropoxide effects neither reduction or equilibration under the condition of the reaction (refluxing ether).

In order to assess the importance of "product development control" in the reduction of I and II to the corresponding axial alcohols, it became desirable to establish the relative stability of these alcohols vis-à-vis the parent ketones. This can in principle be done by establishing an equilibrium[24] of the type

$$RR'C{=}O + R''R'''CHOH \rightleftharpoons RR'CHOH + R''R'''C{=}O.$$

We have recently found[25] that such equilibria can be established easily by treating an alcohol $R''R'''CHOH$ and a ketone $RR'C{=}O$ in a suitable solvent with Raney nickel long enough to reach equilibrium (as shown by the fact that the same product composition is obtained starting with $RR'CHOH$ and $R''R'''C{=}O$) but not long enough to dehydrogenate the alcohols extensively. In the present work this equilibration method was applied to the alcohols and ketones as shown in Scheme 2 and equilibrium constants were calculated both for the two axial alcohols and for the two equatorial alcohols; the pertinent data are listed in Table 3.

Scheme 2



Scheme 3

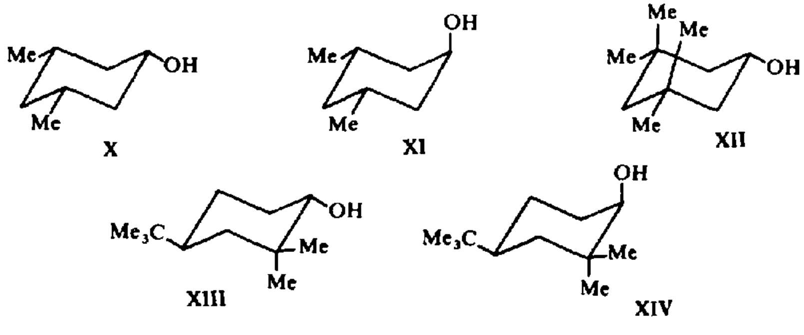


TABLE 3. EQUILIBRIUM CONSTANTS[a]

| Entry No. | Starting Mixture[b] | $K_{ax}$[c] | $\Delta G^\circ_{ax}$ kcal/mol | $K_{eq}$[d] | $\Delta G^\circ_{eq}$ kcal/mol |
|---|---|---|---|---|---|
| 1 | I + VII | 10·42 | −1·64 | 2·68 | −0·69 |
| 2 | II + IX | 0·052 | 2·07 | 0·335 | 0·77 |
| 3 | II + IX[e] | 0·066 | 1·91 | 0·363 | 0·72 |
| 4 | I + XI | 1·23 | −0·15 | 1·30 | −0·19 |
| 5 | III + IX | 0·725 | 0·22 | 0·646 | 0·30 |
| 6 | I + XII | — | — | 3·76 | −0·92 |
| 7 | IV + IX | — | — | 0·268 | 0·91 |
| 8 | V + XI | 1·03 | −0·02 | 1·23 | −0·14 |
| 9 | III + XIV | 0·835 | 0·12 | 0·801 | 0·15 |

[a] At 80°, in benzene unless otherwise indicated.

[b] Formulas VI–IX are in Scheme 2, formulas X–XIV in Scheme 3.

[c] Equilibrium constant for the two ketones and the two axial alcohols, starting mixture written on left.

[d] Equilibrium constant for the two ketones and the two equatorial alcohols, starting ketone written on left.

[e] In t-BuOH.

## DISCUSSION

As the starting point of the discussion we may take the fact that the 4-t-butylcyclohexanol equilibrium ($IX \rightleftharpoons VIII$) in ethylene glycol dimethyl ether* lies on the side of the equatorial isomer (VIII) to the extent of 2·4:1 ($\Delta G^\circ = 0{\cdot}63$ kcal/mol)[17] but that reduction of 4-t-butylcyclohexanone (I) with LAH in ether gives VIII and IX in a ratio of 10:1 ($\Delta\Delta G^{\ddagger} = 1{\cdot}4$ kcal/mol). Therefore, if product development control is real, it must be capable of inducing a substantial difference in free energy between the diastereoisomeric transition states—a difference, in fact, which is appreciably greater than the energy difference between the final products VIII and IX. Turning now to a competitive situation, it can be seen from Table 3 (entries 1–3) that equilibration of the components shown in Scheme 2 leads to a ratio of the axial alcohols IX and VII of somewhere between 10·4 and 19·2 (1/0·052), corresponding to an energy advantage of IX (vis-à-vis its ketone I) of 1·64–2·07 kcal/mol over VII (vis-à-vis its ketone II). If roughly the same relationship existed between product stability and product ratio in the competitive reduction of I and II as does in the reduction of I alone, one might expect a ratio of $k_a^{I}/k_a^{II}$ (i.e. a product ratio of IX to VII) of somewhere in excess of 15:1 and perhaps as high as 100:1 (estimated $\Delta\Delta G^{\ddagger}$ between 1·6 and 2·8 kcal/mol). This prediction in essence follows from the fact that in reduction of I to IX, oxygen is pushed against *syn*-axial hydrogen, but in the reduction of II to VII it is pushed against *syn*-axial methyl. However, as shown in Table 1, the ratio varied from a minimum of about 1:4 *in favor of* VII for aluminohydride reduction to a maximum of 2·3–2·4:1 in the cases of reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ and $NaBH_4$. (With all of these reagents, reduction of I alone produces an equatorial:axial product ratio (VIII:IX) of from 6:1 to 10:1). It seems quite clear from this finding that "product development control"—i.e. the reflection of the greater stability of the equatorial as

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* The value in diethyl ether is not known.

compared to the axial product in the corresponding transition states—can at best explain a minor part of the preference for the equatorial product.* †

An analogous situation is encountered in the competitive reduction of I and IV, Table 1). Making the earlier explained apportionment between $k_e$ and $k_a$ for IV, it is computed that equatorial attack on IV ($k_a^{IV}$) is between four times *faster* (in the case of LAH) and four times slower (in the case of NaB(O-iPr)$_3$H than equatorial attack on I ($k_a^{I}$). Yet the axial alcohol formed from I has only an H-H-OH *syn*-axial interaction where that derived from IV has two Me-OH *syn*-axial interactions which are of the order of 3·6 kcal/mol larger[26] than the interactions for I. Clearly this large energy difference is not reflected in the ratio $k_a^{I}/k_a^{IV}$. Entirely analogous observations are made (Tables 1 and 2) in competitive attack from the equatorial side (to form axial alcohols) on II and III, on II and IV and on III and IV.

In contrast to product development control, steric approach control appears to be quite real. Thus even with the most reactive reagent (LAH) the ratio of axial attack, $k_e^{I}/k_e^{II}$ is 4 and for the less reactive alkoxyaluminum hydrides and sodium borohydride the ratio varies from 23 to 345.‡ It is of interest that lithium tri-t-butoxyaluminohydride, whose internal selectivity (measured by the *cis-trans* ratio of products) is often not very different from that of LAH,§ shows the greatest selectivity between different substrates, whereas the trimethoxyhydride, whose *internal* selectivity is higher,[5a, 7] ‖ is *less* discriminating in the relative rates of axial attack on I and II.

Since, on the basis of the rather straightforward argument given above, it appears that "product development control" is not operative, the question arises as to what *does* cause the ca. 10:1 ratio of $k_e$ to $k_a$ observed in the LAH reduction of I. In order to test Richer's suggestion[19a] that the responsible factor is "steric approach control" by the axial hydrogens at C-2 and C-6, we compared the reduction of I with that of V

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* Only in reductions with LiAl(O-Me)$_3$H (where the equatorial: axial ratio of products is only 1·6:1) and with NaB(O-iPr)$_3$H (where the ratio is 2·3:1) might the product ratio be explained wholly by "product development control". These latter two cases, involving as they do rather little stereoselectivity, are not, of course, the ones in connection with which the product development control concept was originally developed.

† We do not, of course, wish to deny the possibility of product development control as a governing factor in other cases; the idea that transition states can resemble products and reflect the steric compressions in products is clearly a viable one. A case in point may be the reduction of cyclohexanones with the pyridine-n-butyllithium adduct. With this reagent, I gives 91–96% of the equatorial alcohol VIII and II, *despite its hindrance to axial attack*, gives 79% of the more stable equatorial alcohol VI: †† R. A. Abramovitch, W. C. Marsch and J. G. Saha, *Canad. J. Chem.* **43**, 2631 (1965).

‡ S. R. Landor and J. P. Regan, *J. Chem. Soc.* (C), 1159 (1967) have ascribed the formation of equatorial alcohol VI from ketone II to equatorial attack of hydride on the flexible (twist-boat) form of the ketone. Our findings do not prove or disprove this hypothesis. In the absence of a quantitative prediction of the ratio $k_a^{I}/k_a^{II}$ (or other ratios of axial attack) (which would require knowledge of the percentage of the twist form in each ketone, as well as of the rate of attack of the hydride on the twist form) a correlation with our experimental findings is not possible.

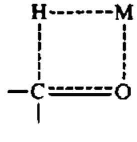
§ In the present work, LAH and LiAl(O-tBu)$_3$H give about the same product ratio from I, but in the reduction of the more sterically encumbered II, the tri-t-butoxyhydride is much more selective, in accordance with earlier findings.[5a]

‖ This statement applies to a sterically hindered ketone, such as II, where the trimethoxyhydride gives over 95% of the product of steric approach control while the t-butoxyhydride gives only 85% of that product. However, with unhindered ketones, such as I and III, the trimethoxyhydride gives nearly equal amounts of axial and equatorial alcohols. This may mean, of course, that steric approach control from the axial side becomes important with the trimethoxyhydride even in unhindered ketones.

in which the axial hydrogen at C-2 is replaced by a Me group. We expected that this would greatly enhance "steric approach control" from the underside and that therefore $k_a^V$ should be much smaller than $k_a^I$. The results (Table 1) were somewhat disappointing, however, in that the ratio $k_a^I/k_a^V$ is never in excess of 14 and for the otherwise rather sterically sensitive reduction with lithium aluminum tri-t-butoxyhydride it was as low as 1·4. This makes it unlikely that the steric encumbrance of the axial hydrogens at C-2 and C-6 plays a major role in controlling the steric course of reaction.

This leaves us with an eclipsing[20] and/or dipolar[6] factor to explain the resistance to approach of hydride from the direction of the C-2 and C-6 axial hydrogens. Although the rationalization in terms of eclipsing might appear somewhat unconventional, since eclipsing effects in an only partially formed bond might not be expected to be very important, it does explain very easily the lack of distinction between H and Me, since it is known[27] that eclipsing of Me by hydrogen (e.g. in the rotational barrier in propane) is not much different, energywise, than eclipsing of hydrogen (e.g. in the rotational barrier in ethane). In fact, an explanation of the diminuition of $k_a$ through eclipsing forces (which are not very sensitive to steric factors) accounts readily for the well known fact that, in general, $k_e > k_a$ for small reagents and molecules relatively unhindered on the axial side. On the other hand, for molecules hindered on the axial side and for more bulky reagents, $k_e$ is diminished by steric factors (*syn*-axial interactions) whereas $k_a$ (being insensitive to steric factors) is not much changed, so that, in those cases, $k_e < k_a$ ("steric approach control") as is actually observed.

The assumption of H/H eclipsing in the transition state of hydride reductions may not be as implausible as it appears at first sight. Geneste and Lamaty[15b] have postulated a transition state for hydride reduction of the type shown in Scheme 4. This transition state is compatible with the inverse isotope effect observed in borodeuteride reduction[15b] and would also account for the well-known role which *I*-strain plays in hydride reductions.[14] It implies that the hybridization of the C—O bond has changed from $sp^2$ to $sp^3$ to a substantial degree and that C—H bond formation has also proceeded appreciably in the transition state, contrary to what had been inferred from the Hammond postulate.[12] It does *not*, however, imply that the geometry of the transition state is tetrahedral: the strain involved in the 4-membered ring will probably prevent it from becoming so, which fact would account for the substantial absence of "product development control" which is experimentally observed.



Scheme 4

It cannot be excluded, however, that yet other unrecognized factors are responsible for the predominant axial attack on unhindered ketones. Thus Klein and Lichtenberg[28] following a hypotheses put forward by Schleyer[29] have recently suggested that eclipsing of the forming —O—M bond with the adjacent equatorial H-atoms is responsible for the less ready formation of the axial alcohol in unhindered cases. Such eclipsing occurs on the way from the ketone to the axial alcohol but not on the way to the equatorial alcohol, as may be readily seen in a model.

## FURTHER CONSIDERATIONS

At the outset of our investigation, there was some question as to the validity of the competitive method of rate study. We are dealing with very fast reactions and it has already been pointed out[30] that such reactions may be rate controlled by mixing and diffusion limitations. If this were to happen, the reagent entering the reaction mixture (in our case the hydride) might deplete the faster-reacting component at the point of initial contact and will then, by default, react with the slower-reacting substrate before further access of the faster-reacting component occurs. If this happens, the competitive specific rate ratio will be much less than the true ratio of rate constants. Fortunately complications of this type would be ruled out at least in the case of the reduction with lithium aluminum tri-t-butoxyhydride when, following completion of our work, Klein and Dunkelblum[1c*] were able to obtain absolute rates for this reduction for substrates I-V. The comparison of our relative rates with the ratio of their absolute rate constants is shown in Table 4 and is seen to be very satisfactory, indicating that at least with this reducing agent, difficulties due to diffusion mixing control cannot be serious.

TABLE 4. RELATIVE RATES IN REDUCTION WITH LITHIUM ALUMINIUM TRI-t-BUTOXYHYDRIDE

| Compound reduced | Lithium Aluminum Tri-t-butoxyhydride I | II | III | IV | V |
|---|---|---|---|---|---|
| $k_e/k_e^1$ abs.[a, f] | 1·00[c] | 0·007 | 0·69 | — | 0·66 |
| $k_e/k_e^1$ rel.[b, f] | 1·00[c] | 0·003 | 0·59[d] | — | 0·68 |
| $k_a/k_a^1$ abs.[a, f] | 1·00[c] | 0·58 | 0·85 | 0·40[e] | 0·54 |
| $k_a/k_a^1$ rel.[b, f] | 1·00[c] | 0·44 | 1·09 | 0·35[e] | 0·73 |

[a] As determined by Klein and Dunkelblum, Ref 1*c*.

[b] This work.

[c] Standard rate.

[d] This rate was misprinted in Ref 1*c*.

[e] Assuming $k_e = 0$, see earlier discussion.

[f] Regarding the meaning of $k_e$ and $k_a$, see Table 1. The symbols have been used here in the opposite sense from Ref 1*c*.

In the case of the considerably slower sodium borohydride reductions, our relative rates may be compared with the absolute rates determined by Brown and Muzzio.[31] Unfortunately, the systems studied are not the same and the closest comparison available is between cyclohexanone and 2,2-dimethylcyclohexanone on one hand (rate ratio, at 0°, 161/8·84 or 18·2)[31] and our ratio (Table 1) for the corresponding 4-t-butyl homologs (117/22·2 or 5·3).† The agreement here is not so satisfactory; an even more discrepant series of results is found in the steroids where the overall rate of borohydride reduction is:[32] 3-ketosteroid, 100; 6-ketosteroid 60; 11-ketosteroid 0·1 which may be compared to the ratio I, 100; II, 7·8; IV, 5·2.

Another possible complication in our study was complexing of hydride with ketone prior to reduction. If this should play a role, and if complexing were the rate-determining step, then the relative reduction rates would reflect the relative rates of

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[*] We wish to thank Professor Klein for his readiness to undertake this study after he learned of our problem.

[†] Cyclohexanone and 4-t-butylcyclohexanone react at virtually the same rate with borohydride: Ref 15*a*. Corresponding information for the 2,2-dimethyl homologs is unavailable.

TABLE 5. PRODUCT RATIOS IN REDUCTION OF KETONES WITH COMPLEX METAL HYDRIDES

| Ketone reduced | Remarks | Predominant isomer, % | |
|---|---|---|---|
| | LAH, Ether, 0° (unless otherwise indicated) | | |
| I | This work | *trans*, | 90–91 |
| | Ref 3, R.T.[a] | | 91–93 |
| | Ref 22 | | 92·5 |
| | II[b] | | 90–93 |
| | III[c] | | 90–92 |
| | IV[d] | | 91–92 |
| | V[e] | | 90 |
| II | This work | *trans*, | 58–63 |
| | This work, 34° | | 58 |
| | Ref 5*a*, R.T.[a] | | 52–55 |
| | Ref 22 | | 58 |
| | I[f] | | 58–68 |
| | III[c] | | 59–71 |
| | IV[d] | | 53–58 |
| III | This work | *cis*, | 83–84 |
| | I[f] | | 85–86 |
| | II[b] | | 84–85 |
| | IV[d] | | 82–84 |
| | V[c] | | 86 |
| V | This work | *trans*, | 94 |
| | Ref 19*a* | | 95 |
| | I[f] | | 96 |
| | III[c] | | 96 |
| | Lithium Tri-t-butoxyaluminohydride, Tetrahydrofuran, 0° (unless indicated) | | |
| I | This work | *trans*, | 90 |
| | Ref 19*a*, R.T.[a] | | 90 |
| | Ref 1*c*[g] | | 91 |
| | II[b] | | 90 |
| I | III[c] | *trans*, | 90–91 |
| II | This work | *trans*, | 96 |
| | Refs 5*a*, 19*a*, R.T.[a] | | 88 |
| | Ref 1*c*[g] | | 89 |
| | I[f] | | 94–95 |
| | III[c] | | 94–96 |
| | IV[d] | | 93–95 |
| III | This work | *cis*, | 83 |
| | Ref 1*c*[g] | | 89 |
| | II[b] | | 84 |
| | I[f] | | 81–83 |
| | V[e] | | 81–83 |
| V | This work | *trans*, | 91 |
| | Ref 19*a*, R.T. | | 100 |
| | Ref 1*c*[g] | | 92 |
| | III[c] | | 86–91 |

TABLE 5—*continued*

| Ketone reduced | Remarks | Predominant isomer, % | |
|---|---|---|---|
| **Lithium Trimethoxyaluminohydride, Tetrahydrofuran, 0° (unless indicated)** | | | |
| I | This work | *trans*, | 59 |
| | II[b] | | 62–63 |
| | III[c] | | 58–63 |
| II | This work | *trans*, | 98 |
| | Ref 5*a*, R.T.[e] | | 92 |
| | I[f] | | 98 |
| | III[c] | | 95 |
| | IV[d] | | 94–95 |
| III | This work | *cis*, | 53 |
| | II[b] | | 51 |
| | I[f] | | 51 |
| | IV[d] | | 51–53 |
| | V[e] | | 50–52 |
| V | This work | *trans*, | 84 |
| | II[b] | | 76 |
| **Sodium Borohydride, Isopropyl Alcohol, 0° (unless otherwise indicated)** | | | |
| I | This work, in MeOH/MeONa[h] | *trans*, | 84–85 |
| | This work, MeOH[i] | | 85–86 |
| | Ref 22, MeOH | | 83·5 |
| | II,[b] MeOH | | 79–82 |
| | This work, i-PrOH | | 83 |
| | Ref 22 | | 87 |
| | II[b] | | 86–87 |
| | III[c] | | 82–84 |
| | IV[d] | | 86–87 |
| II | This work, in MeOH/MeONa[h] | *trans*, | 86–87 |
| | This work, MeOH[i] | | 94 |
| | Ref 22, MeOH | | 86 |
| | Ref 23, MeOH, R.T.[e] | | 73 |
| | I,[f] MeOH | | 92–96 |
| | This work, i-PrOH | | 63–64 |
| | Ref 22 | | 62 |
| | Ref 23 | | 55–56 |
| | I[f] | | 80 |
| | III[c] | | 78 |
| III | This work, II | *cis*, | 80 |
| | I[f] | | 74–75 |
| | V[e] | | 78 |
| V | Ref 19*a*, R.T.[e] | | 92 |
| | This work, III[c] | | 94–95 |
| **Sodium Trimethoxyborohydride** | | | |
| I | This work, MeOH, 0° | *trans*, | 75–76 |
| II | This work, MeOH, 0° | *trans*, | 81 |
| | Ref 23, i-PrOH, R.T.[e] | | 65 |

Table 5—*continued*

| Ketone reduced | Remarks | Predominant isomer, % | |
|---|---|---|---|
| Sodium Triisopropoxyborohydride, Isopropyl Alcohol, 0° (unless indicated) | | | |
| I | This work | *trans*, | 75–80 |
| I | II[b] | *trans*, | 69–70 |
| | III[c] | *trans*, | 71 |
| II | This work | *trans*, | 80–83 |
| | Ref 23, diglyme, R.T.[a] | | 77 |
| | IV[d] | | 88 |
| | I[f] | | 81–83 |
| III | I[f] | *cis*, | 64 |
| | V[e] | | 66 |

[a] Room temperature.
[b] In the presence of II.
[c] In the presence of III.
[d] In the presence of IV.
[e] In the presence of V.
[f] In the presence of I.
[g] Results of J. Klein and E. Dunkelblum.
[h] Some hydrogen was evolved and a small amount of ketone was recovered.
[i] Hydrogen in excess of 3 moles per mole of borohydride was evolved and a corresponding amount of ketone was recovered.

complexing rather than the relative rates of reduction. Leaving aside the as yet unsolved question as to what importance complexing does have in these reactions, it is clear from the data in Table 4 that, at least in reductions with $LiAlH(O\text{-}t\text{-}Bu)_3$, complexing is not the rate-determining step.

A third possible complication is concerned with the various stages of hydride reductions. These are a matter of concern with $AlH_4^-$ and $BH_4^-$ though not with the trialkoxyhydrides. Arguments have previously been adduced[5a] that, during reduction with $AlH_4^-$ the intermediate alkoxyaluminohydrides disproportionate back to $AlH_4^-$ which is therefore the effective reducing agent throughout the reduction. As far as we are aware, these arguments still hold for ketones and their reduction products, secondary alcohols, although they have never been meant to apply to aldehydes and primary alcohols.[5a, 33] Unfortunately, the conditions of competitive reduction, which involve a large excess of ketone at all stages, are, if any, conducive to the formation of alkoxyaluminohydride; the small variations in product ratio upon addition of acetone and cyclohexanone (Table 6) from that previously observed when a larger amount of hydride was employed may be due to that cause.

In the case of sodium borohydride reduction, intermediate alkoxyborohydride are known to play a part[11] and the interpretation of the competitive rates is therefore not straightforward, involving, as it does, four different stages of reduction with the possibility of a large number of variations of the alkoxy groups involved. Fortunately, the simulated last stage of the reduction (reduction with sodium triisopropoxyborohydride) shows the same general features (appreciable steric approach control, substantial absence of product development control) as the overall reaction and it would therefore appear that, at least qualitatively, the earlier discussion may be applied also to all the stages of the borohydride reduction. The earlier mentioned slight discrepancy between Brown and Muzzio's absolute borohydride reaction rates[31] and our competitive rates may actually be due to the fact that their study refers only to the first stage of reduction and ours refers to all four. The data in Table 1 do, in fact, show, that the trialkoxyborohydride is less selective than borohydride itself. Attempts were made to isolate the first stage in borohydride reduction by carrying out the competitive reaction in methanol which is known[34] to destroy the second, third and fourth hydride equivalent of the $BH_4^-$ moiety after the first one has reacted.

TABLE 6. REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE (II) WITH LITHIUM ALUMINIUM HYDRIDE IN THE PRESENCE OF ADDITIVES

| Additive | % *trans* Isomer in product | No. of runs |
|---|---|---|
| None | 58–63[a] | 8 |
| $Al(O\text{-}i\text{-}Pr)_3$[b] | 60–62[c, d] | 8 |
| LiBr | 60[e] | 2 |
| Acetone | 62–63[f, g] | 3 |
| Cyclohexanone | 65–68[f, h] | 3 |

[a] Equivalent % hydride varied from 14·4 to 303%.

[b] No reduction occurs in the absence of hydride with $Al(O\text{-}i\text{-}Pr)_3$ in ether under the conditions of reaction.

[c] Equivalent % hydride varied from 29·4 to 145·0%.

[d] Moles $Al(O\text{-}i\text{-}Pr)_3$ varied from 0·5 to 2·0 per mole ketone.

[e] 0·5 or 1·0 mole.

[f] 1·0 mole ketone, 10·1–23·6% hydride.

[g] Lit[5a] 57%.

[h] Lit[5a] 58%.

Unfortunately, these attempts were not successful under the conditions of the competitive reduction which involve addition of a small amount of borohydride to a large excess of the ketones in methanol. Under these conditions, the excess ketone always competes successfully with the methanol for the second, third and fourth hydride equivalent as evidenced by the fact that less than 3 moles of hydrogen per mole of borohydride is evolved and more than one mole of ketone is reduced.

The possibility that equilibration might occur during reductions which lead to aluminum alkoxides in the presence of excess ketone[35] was considered. However, the product ratios obtained were quite different from the known equilibrium ratios, were reproducible and were invariant with time, which would seem to exclude even partial thermodynamic control.

## EXPERIMENTAL

*Alcohols and ketones.* 4-t-Butylcyclohexanone (I) was kindly supplied by the Dow Chemical Co.; it was reduced to the *trans* alcohol VIII with $LAH_4$-$AlCl_3$ under equilibrating conditions[36] and to the *cis* alcohol IX with isopropyl alcohol in the presence of chloroiridic acid and trimethyl phosphite.[37] 3,3,5-Trimethylcyclohexanone (II) and the corresponding alcohols VI and VII were prepared as described earlier,[4] as were III and its alcohols X, XI and IV and its alcohol XII.[38] 2,2-Dimethyl-4-t-butylcyclohexanone (V) and its alcohols XIII, XIV were prepared by the method of Richer and Perrault.[39] All alcohols and ketones agreed in physical constants with samples earlier prepared.

*Reductions.* The two ketones were weighed and dissolved in the desired solvent to give a soln about 0·2 M. The soln was placed in a 3-necked 250-ml round bottom flask equipped with a condenser, pressure equalized addition funnel and magnetic stirrer and was cooled to 0° by immersion in a crushed ice-water bath. A calculated amount of hydride solution (ca. 0·1 M) was slowly added from the funnel with vigorous stirring over a period of 10–15 min. Water and crushed ice were added, followed by enough 10% $H_2SO_4$ to dissolve the ppt. The aqueous layer was extracted with ether which was washed with $NaHCO_3$ aq followed by brine and dried over $Na_2SO_4$. The soln was concentrated by removing part of the ether through a 1-ft helix-packed column and the residual solution was subjected to gas chromatography.

Lithium aluminum trimethoxyhydride was prepared *in situ* by adding the calculated amount of dry MeOH to a solution of LAH in THF. The amount of $H_2$ evolved was monitored with a wet-test meter and was slightly larger than calculated. The soln was titrated with $I_2$ and $Na_2S_2O_3$, in the same way as LAH.[40] Lithium aluminum tri-t-butoxyhydride was either similarly prepared or purchased from Metal Hydrides, Inc.; material of either origin gave the same results.

$NaBH_4$ was commercial material as was LAH. LAH soln were decanted and titrated[40] prior to use. Sodium triisopropoxyborohydride was prepared as described.[41]

*Equilibrations.*[17, 25] Commercially available Raney Ni was thoroughly washed with distilled water, EtOH and benzene and was freed of traces of water and EtOH by azetropic distillation of some of the benzene. A 1 : 1 mixture of the starting alcohol and ketone was placed in the benzene (or t-BuOH, prepared by decantation) suspension of the Raney Ni and the soln was boiled at reflux. From time to time, samples were withdrawn, freed of Raney Ni and analyzed gas chromatographically. Equilibrium was deemed to be reached when several consecutive samples gave identical analyses. In all cases, equilibrium was approached from both sides (cf. Table 3).

The equilibration shown in Scheme 2 has already been discussed. In the equilibration of I and III with their respective equatorial (VIII, X) or axial (IX, XI) alcohols, the equilibrium constants should be unity; in fact they range from 1·23 to 1·55 (reciprocal of 0·646) as shown in Table 3, entries 4, 5. Similarly, the corresponding rate ratios shown in Table 1 range from 1·08 to 1·77. These deviations from unity probably reflect the lack of "conformational ideality" of our systems.[38]

In the equilibration of I and II with their respective equatorial alcohols VIII and VI, viz I + VI $\rightleftharpoons$ II + VIII (Scheme 2) one should gain the difference between an Me-H-H *syn*-axial interaction in a cyclohexane and the Me-H *syn*-axial interaction in a cyclohexanone, i.e. the "3-alkylketone effect".[42] The value of this effect appears to be about 0·4–0·5 kcal/mol[42]; a slightly larger value is found by the method used here (0·69–0·77 kcal/mol, cf. Table 3, entries 1, 2). By a similar reasoning, the gain in free energy in the equilibrium I + XII $\rightleftharpoons$ IV + VIII should be twice the amount of the 3-alkylketone effect or 0·8–1·0 kcal/mol; in this case, the experimentally found value of 0·91–0·92 kcal/mol (Table 3, entries 6, 7) is in very good agreement with prediction.

From the point of view of the kinetic investigation, the most important equilibrium is I + VII $\rightleftharpoons$ II + IX (Scheme 2). In this equilibrium the steric interactions on the left-hand side of the equation are Me-OH *syn*-axial, Me-H and OH-H; on the right-hand side one has 2 OH-H and the methyl axial interaction (2 Me-H) diminished by the 3-alkylketone effect (for II). Using 0·35 kcal/mol for OH-H in ether (one-half of the value of 0·69 kcal/mol cited earlier for axial OH in cyclohexanol), 0·85 kcal/mol for Me-H (one-half the recommended[43] value of 1·70 kcal/mol for axial Me), 2·15 kcal/mol as the value for *syn*-axial Me-OH[26] and 1·25 kcal/mol (1·70–0·45) for the residual Me axial interaction in II, the calculated free energy change for the above equilibrium is 1·25 + 0·70 − 0·85 − 0·35 − 2·15 or −1·40 kcal/mol. The observed absolute value, 1·64–2·07 kcal/mol (Table 5, entries 1, 2) is somewhat larger, but considering the uncertainties in the values used for the calculation (especially the Me-OH *syn*-axial value and the 3-alkylketone effect) and the variation in the two experimental values, the agreement is probably as good as one can hope.

The equilibria V + XI $\rightleftharpoons$ III + XIV and V + X $\rightleftharpoons$ III + XIII (Table 3, entries 8 and 9) present somewhat of a surprise. In 2,2-dimethyl-4-t-butylcyclohexanone, (V) the equatorial Me group is nearly eclipsed with the CO group and should cause no steric strain,* and the axial Me group would be expected to be subject to the normal axial Me destabilization.* In the corresponding alcohols XIII and XIV, on the other hand, one might have expected additional conformational destabilization through Me/OH *gauche* interactions: one such interaction in XIV and two in XIII. In fact, however, the equilibrium involving the axial alcohols is barely shifted away from XIV and toward XI (Scheme 3)—$\Delta G^\circ = -0{\cdot}07 \pm 0{\cdot}05$ kcal/mol—and the equilibrium involving the equatorial alcohols is not much more shifted away from XIII toward X ($\Delta G^\circ = -0{\cdot}15$ kcal/mol). However, the position of equilibrium is compatible with the finding[44,] † that

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* In propionaldehyde, the Me/C=O eclipsed conformation is actually the preferred one; the previously postulated "2-methylketone effect" seems to be ephemeral: Ref 21, pp. 20, 113.

† Dr. E. C. Gilbert in our laboratories has found essentially the same result; the earlier finding (Ref. 19a) that the equilibria are not the same must stand corrected.

the equilibrium position of the 2,2-dimethyl-4-t-butylcyclohexanols XIII and XIV and of the 4-t-butylcyclohexanols VIII and IX is virtually the same. Evidently the conformation of the molecule is such that the geminal methyl groups at C-2 have much less effect than one might have assumed.

*Gas chromatographic analysis.* The analyses have been described elsewhere.[4,5] An F & M Model 810 gas chromatograph equipped with 9½-foot 20 or 25% Carbowax 20-M on firebrick columns at 150° or 25% diglycerol on Chromosorb W columns at 90° was used with a thermal conductivity detector. Samples of pure alcohols were used to establish the response ratio.

*Results.* The results of the kinetic and equilibrium experiments are summarized in Tables 1–3, 5 and 6. Table 7 shows typical data obtained in the competitive reduction of I and II with $LAH_4$.

TABLE 7. COMPETITIVE REDUCTION OF 4-t-BUTYL-(I) AND 3,3,5-TRIMETHYLCYCLOHEXANONE (II) WITH $LAH_4$[a]

| Entry | Hydride/Ketone (%) | Products (mole %) 4-*t*-Butyl- OH-Ax (IX) | Products (mole %) 4-*t*-Butyl- OH-Eq (VIII) | Products (mole %) 3,3,5-Trimethyl- OH-Ax (VII) | Products (mole %) 3,3,5-Trimethyl- OH-Eq (VI) | IX/VIII | VII/VI | $k_{II}^{a}/k_{I}^{a}$[b] | $k_{II}^{e}/k_{I}^{e}$[b] |
|---|---|---|---|---|---|---|---|---|---|
| (II/I = 1) | | | | | | | | | |
| 1 | 3·3 | 6·7 | 63·5 | 17·4 | 12·4 | 10/90 | 58/42 | 2·61 | 0·195 |
| 2 | 5·6 | 6·3 | 59·5 | 21·7 | 12·5 | 10/90 | 64/36 | 3·41 | 0·209 |
| 3 | 5·6 | 5·4 | 59·6 | 22·3 | 12·7 | 8/92 | 64/36 | 4·12 | 0·214 |
| 4 | 9·3 | 6·3 | 60·1 | 21·0 | 12·6 | 9/91 | 62/38 | 3·34 | 0·210 |
| 5 | 13·7 | 5·8 | 57·5 | 23·1 | 13·6 | 9/91 | 63/37 | 3·99 | 0·236 |
| 6 | 16·6 | 6·6 | 57·4 | 23·0 | 13·0 | 10/90 | 64/36 | 3·49 | 0·226 |
| 7 | 20·3 | 4·8 | 54·9 | 25·7 | 14·6 | 8/92 | 64/36 | 5·34 | 0·267 |
| 8 | 20·3 | 4·5 | 58·5 | 23·9 | 13·1 | 7/93 | 65/35 | 5·31 | 0·224 |
| 9 | 26·4 | 4·5 | 61·1 | 22·7 | 11·7 | 7/93 | 66/34 | 5·03 | 0·191 |
| (II/I = 2) | | | | | | | | | |
| 10 | 11·3 | 3·6 | 40·9 | 34·7 | 20·8 | 8/92 | 63/37 | 4·71 | 0·254 |
| 11 | 17·8 | 4·3 | 45·7 | 34·0 | 16·0 | 9/91 | 68/32 | 3·86 | 0·175 |
| (II/I = 3) | | | | | | | | | |
| 12 | 12·5 | 3·3 | 41·2 | 34·5 | 21·0 | 8/92 | 62/38 | 3·44 | 0·170 |
| 13 | 20·5 | 4·2 | 41·1 | 31·6 | 23·1 | 9/91 | 58/42 | 2·56 | 0·188 |

[a] In diethyl ether at 0°.
[b] See Table 1.

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