constant, 111–112°, if there is a side chain on C^{α}. Without substitution, the angle at C^{α} increases to 115–117°. Aliphatic side chains are in equatorial or pseudo-equatorial positions whereas in the two examples with L-tyrosine, the side chain is in an axial position with the aromatic moiety folded over the diketopiperazine ring in the flag-pole conformation.[21,24]

Experimental Section

Melting points are uncorrected.

3,4-Dehydro-D,L-proline (II). This compound was prepared as described previously.[25,26] In our hands the yield never exceeded 35%: mp 239–241° dec, tlc (*sec*-butyl alcohol–acetic acid–water, 4:2:1) one spot, ninhydrin-positive. Its spectroscopic characteristics were identical with those previously reported.[26,27]

3,4-Dehydro-D,L-proline Methyl Ester Hydrochloride (III). To 20 ml of methanol, chilled at −10°, 3.0 ml of thionyl chloride was added dropwise, followed by 3.85 g (30.4 mmol) of 3,4-dehydro-D,L-proline. The clear solution was slowly warmed to 30°, and stirred at this temperature for 16 hr. From the dark brown solution the solvent was removed. After two portions of 50 ml of methanol had been added and removed *in vacuo*, the oily residue was dried *in vacuo* over KOH and finally crystallized from methanol–ether to yield 4.55 g (92%) of needles: mp 133–134° (recrystallized from chloroform–hexane); tlc (*sec*-butyl alcohol–acetic acid–water, 4:1:1) one spot, ninhydrin-positive; ir (KBr) 2700 ($^{+}NH_2$), 1740 (C=O), and 685 cm^{-1} (*cis*-vinyl protons); nmr ($CDCl_3$, δ 6.08 (mult, 2, $C_{3,4}$-H), 5.30 (mult, 1, C_2-H), 4.27 (mult, 2, C_5-H_2)) 3.87 (s, 3, OCH_3).

3,4-Dehydroproline Anhydride (IV). A solution of 3.55 g (22 mmol) of the ester hydrochloride III in the minimal amount of anhydrous methanol was made strongly alkaline with triethylamine. The triethylamine hydrochloride was completely precipitated by the addition of 60 ml of ether, and subsequent cooling at −10°. The salt was collected by filtration and washed with ether; the filtrate was concentrated to dryness, yielding 1.90 g of colorless oil which crystallized after being kept for several days in a vacuum desiccator. Unreacted starting material was removed by crystallization (benzene, or chloroform–hexane) or by ion-exchange chromatography (Dowex 40W-X8, H^{+} form). The compound is soluble in hot benzene, water, and chloroform, and insoluble in petroleum ether: yield, 1.55 g (37%) of flat plates; mp 208–210°; tlc (*sec*-butyl alcohol–acetic acid–water, 4:2:1, or 5% methanol–chloroform) one spot, ninhydrin-negative; ir (KBr) 1660 (broad, C=O) and 705 cm^{-1} (*cis*-vinyl protons); nmr ($CDCl_3$) δ 6.12 (mult, 4, vinylic protons), 5.09 (broad mult, 2, α-H), 4.30 (broad mult, 4 H, C_5-H_2); mass spectrum principal peaks at *m/e* 190 (M^{+}), 162 (M − CO), 145, 135, 123, 96, 95 (M/2), 68 (base peak), 67 (pyrroline).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.30; N, 14.64.

Supplementary Material Available. Observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-539.

(24) L. E. Webb and C. F. Lin, *J. Amer. Chem. Soc.*, **93**, 3818 (1971).
(25) A. Corbella, P. Gariboldi, and G. Jommi, *Chem. Ind. (London)*, 583 (1969).
(26) A. V. Robertson and B. Witkop, *J. Amer. Chem. Soc.*, **84**, 1697 (1962).
(27) L. F. Johnson, A. V. Robertson, W. R. J. Simpson, and B. Witkop, *Aust. J. Chem.*, **19**, 115 (1966).

The Factors Influencing Stereochemistry in the Reduction of Conformationally Mobile 2-Alkylcyclohexanones by Sodium Borohydride[1]

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Contribution from the Department of Chemistry, Carleton University, Ottawa, Canada. *Received July 19, 1973*

Abstract: Stereochemical product ratios of reduction of eight 2-substituted cyclohexanones by $NaBH_4$ in 2-propanol, and rates of reduction of eight such ketones have been measured at a variety of temperatures, thus permitting the calculation of the specific activation parameters for axial and equatorial attack by borohydride. These data permit the tackling of the question of the preferred conformation for reduction of conformationally mobile systems and also show that epimerization of the 2 substituent does not play a major role in determining stereochemical product ratio. These main conclusions and the magnitudes of the steric interactions involved in the reduction of 2-alkylcyclohexanones are summarized.

The origin of the marked stereochemical control in the reduction of cyclohexanones with metal hydride reducing agents such as sodium borohydride is a fascinating but persisting puzzle in organic chemistry. Unhindered ketones are reduced to yield a large predominance of equatorial alcohol, but this preferred mode of attack is rapidly diminished, and eventually inverted, with increasing steric hindrance around the carbonyl group. Despite a great deal of experimentation and speculation, the origin and cause of this behavior remains obscure.[2]

Our approach to this problem has been to try and obtain independent information about the transition states involved in the reduction of a variety of ketones. As a result of this work, it has become increasingly clear to us that in this regard there are different types of "hindered ketones." The majority of compounds in

(1) Support by the National Research Council of Canada is gratefully acknowledged.

(2) See, for example, (a) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); (b) D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972), and references therein.

Table I. Rate Constants for the Reduction of Ketones by $NaBH_4$ in Propan-2-ol

Ketone	Rate constant $k \times 10^4$ M^{-1} sec^{-1} at temp, °C					
	0	15	20	25	30	35
1	261 ± 5		620 ± 10	765 ± 31	924 ± 24	
2	39 ± 1.3	78.4 ± 0.7		149 ± 3	185 ± 6	224 ± 11
3	21.6 ± 0.8	47.2 ± 0.2		71.2 ± 2.8	84.4 ± 4.2	108 ± 2
4	16.9 ± 0.2	40.4 ± 0.4	45.4 ± 0.4	66.9 ± 1.5		98.0 ± 1.4
5	14.4 ± 1.0			55.7 ± 1.3	67.1 ± 1.8	74.0 ± 3.6
cis-**6**	7.38 ± 0.10		23.9 ± 0.7[a]			51.8 ± 1.0
trans-**6**	8.85 ± 0.23		27.7 ± 0.6[a]			51.7 ± 1.5
7	3.16 ± 0.06	8.55 ± 0.03		14.2 ± 0.1	19.1 ± 0.1	

[a] 21°.

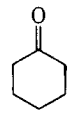
this category are so named with the implication of the presence of an axial group in a 1,3 relationship with the carbonyl group (*e.g.*, 3,3,5-trimethylcyclohexanone). Nevertheless it is known that groups substituted in the 2 position also affect stereochemical product ratio,[3,4] and thus three different types of hindrance that control stereochemistry of reduction must be recognized: (a) axial groups at C-3; (b) axial groups at C-2; and (c) equatorial groups at C-2.

Although the stereochemical outcome and the interactions involved in the case of reduction of ketones possessing a C-3 axial group have been well studied,[2] the situation with 2-substituted ketones is not nearly as clear. Two particularly awkward questions concern through which conformation a conformationally mobile 2-alkylcyclohexanone reduces, and also whether prior epimerization of the 2 substituent can further confuse the stereochemical result. Since an equatorial group at C-2 may be expected to offer some resistance to attack by borohydride no matter which side it attacks from, whereas an axial group can presumably not seriously interfere with axial attack from the opposite side of the ring, it is by no means obvious that these ketones reduce through the higher populated ground state with the substituent equatorial.

Before we could proceed further with our investigations on the nature of the transition states in the reduction of ketones with a spectrum of hindrances, a number of points regarding reduction of 2-alkylcyclohexanones needed clarification. These included the two questions posed above, the question of whether the stereochemical outcome was primarily enthalpy or entropy controlled, and the magnitudes of the interactions that an equatorial group offers to axial attack (→trans alcohol) and equatorial attack (→cis alcohol) and that an axial group offers to axial attack (→cis alcohol) and equatorial attack (→trans alcohol). This paper reports the results of our experiments aimed at providing answers to these questions.

Results

In order to approach the questions posed above, nine monocyclic cyclohexanones were selected (**1–9**).



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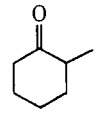

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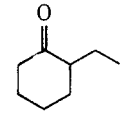

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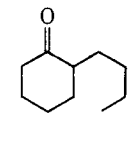

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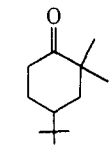

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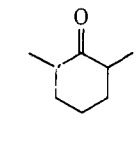

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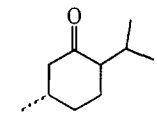

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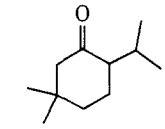

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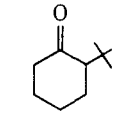

9

Ketones **4**, **7**, and **9** were prepared by oxidation of the corresponding alcohols, ketone **8** was prepared by copper catalyzed methyl Grignard addition to piperitone, and, with the exception of ketone **5**,[5] the remainder were commercially available. Overall rate constants for the reduction of ketones **1–5** were determined at various temperatures, using the spectrophotometric method previously reported.[6] These data are shown in Table I. In order to break these rate constants up into the two specific rate constants leading to cis and trans alcohols, respectively, the stereochemical product ratios were also determined (glc) at a variety of temperatures. Since the variation of product ratio with temperature is relatively small, these ratios were determined over a wider range of temperatures (0–82°) than were the kinetic measurements, and the ratios corresponding to particular temperatures were obtained graphically.[7] For cyclohexanone, it was as-

(3) B. Rickborn and M. T. Wuesthoff, *J. Amer. Chem. Soc.*, **92**, 6894 (1970).

(4) J.-C. Richer, *J. Org. Chem.*, **30**, 324 (1965).

(5) We are very grateful to Professor J.-C. Richer for a sample of 2,2-dimethyl-4-*tert*-butylcyclohexanone.

(6) D. C. Wigfield and D. J. Phelps, *J. Chem. Soc., Perkin Trans. 2*, 680 (1972).

(7) A serious experimental difficulty exists in that the rate constants refer to the rate-determining transfer of the first hydride from boron, whereas the stereochemical product ratio is a composite of the transfer of all four hydrogens. The question of whether the four steps have differing stereoselectivities has been studied by Rickborn and Wuesthoff,[3] who have, in fact, demonstrated significant changes in product ratios as reductions proceed. An error of this type in the product ratio leads to incorrect apportioning of the overall rate constant into the two specific rate constants for the transfer of the first hydride, leading to incorrect specific activation parameters. The activation entropy, however, has in any case an experimental error of up to 1.5 eu (see Table IV), and this error corresponds to an error of up to 113% in the rate constant. All cases quoted by Rickborn and Wuesthoff indicate possible maximum errors in the specific rate constants to be less than this, and in most cases a great deal less. Thus although this factor could cause rate constants to be seriously in error, the additional error in activation entropy is, even in the worst cases, tolerable. In this paper, specific rate constants are used only as a means to obtaining specific activation parameters. It would appear that the only method presently available for gaining reasonable reliability in the specific rate constants would be the curve-fitting device reported by Rickborn and Wuesthoff for extrapolation to 0% reaction. It is, however, interesting that the product ratios reported by Jones and Wise[8] for reduction by $NaBH_4$ in the presence of amines (where only the first hydride is transferred) do not differ greatly from those in the absence of amines. In

sumed that the relative modes of attack were similar to those on 4-*tert*-butylcyclohexanone and 4-methylcyclohexanone, and the "product ratios" referred to are a mean between these two compounds. Specific rate constants thus obtained are shown in Table II. Ke-

Table II. Stereochemical Product Ratios and Specific Rate Constants[a] for Reduction of Ketones by $NaBH_4$

Ketone	Temp, °C	Product ratio[b] eq:ax	k_{ax}[c] × 10^4 M^{-1} sec^{-1}	k_{eq}[c] × 10^4 M^{-1} sec^{-1}
1	0	88:12[d]	230	31
	20	86:14[d]	533	87
	25	86:14[d]	658	107
	30	86:14[d]	795	129
2	0	73:27	28.5	10.5
	15	71:29	55.7	22.7
	25	70:30	104	45
	30	70:30	130	55
	35	69:31	155	69
3	0	68:32	14.7	6.9
	15	66:34	31.2	16.0
	25	65:35	46.3	24.9
	30	65:35	54.9	29.5
	35	65:35	70.2	37.8
4	0	66:34	11.2	5.7
	15	65:35	26.3	14.1
	20	65:35	29.5	15.9
	25	65:35	43.5	23.4
	35	64:36	62.7	35.3
5	0	94.5:5.5[e]	13.6	0.8
	25	92:8[e]	51.2	4.5
	30	91:9[e]	61.1	6.0
	35	90:10[e]	66.6	7.4
cis-**6**	0	62:38	4.6	2.8
	21	62:38	14.8	9.1
	35	62:38	32.1	19.7
7	0	67:33	2.12	1.04
	15	68:32	5.81	2.74
	25	69:31	9.8	4.4
	30	70:30	13.4	5.7
8	82	40:60		
9	21	50:50		
	82	43:57		

[a] See cautionary note (ref 7). [b] Refers to disposition of hydroxyl assuming other group to be equatorial. [c] k_{ax} refers to axial attack of $NaBH_4$ on conformation assumed with other group equatorial (*i.e.*, for ketones **2**, **3**, **4**, rate constant for formation of trans alcohol). k_{eq} refers to opposite mode of attack. This designation and its relation to reality is amplified in the Discussion. [d] Mean of results on 4-*tert*-butylcyclohexanone and 4-methylcyclohexanone. [e] Estimated from the literature owing to shortage of material.[2a,4]

tones **8** and **9** proved to reduce too slowly for accurate kinetics to be measured. Their stereochemical product ratios, however, are included in Table II and are commented upon at a later stage.

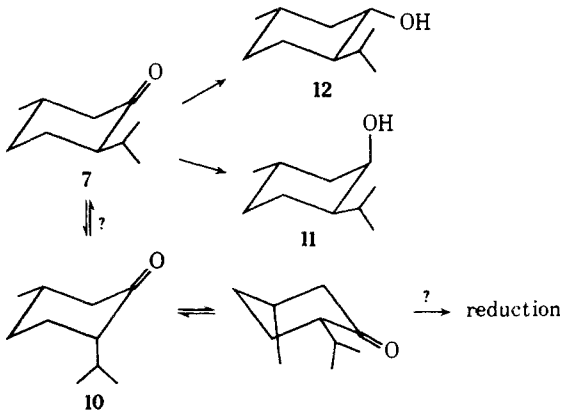

Figure 1. Possible products in the reduction of menthone.

Reduction of Menthone. Although menthone **7** has been reported to yield a 51:49 mixture of axial:equatorial alcohols with sodium borohydride in methanol,[13] there exists the possibility in the reduction of this ketone of epimerization to the isomenthone–isomenthol series, as indicated in Figure 1.

To clarify the situation, a 77.5:22.5 mixture of menthone **7** and isomenthone **10** was reduced with sodium borohydride in 2-propanol. After extensive reduction (75 hr), glc indicated the presence of three compounds a (24.7%), b (17.1%), and c (58.2%). Simultaneous injection with authentic samples confirmed the identity of compound b with isomenthone **10**, and of compound c with menthol **12**. Since peak a could either be alcohol **11** or a reduction product of isomenthone **10**, the reaction mixture was reoxidized to the menthone mixture under the nonepimerizing conditions of the Brown oxidation.[14] If compound a were alcohol **11**, the menthone:isomenthone mixture produced should be a + c:b (82.9:17.1), whereas if compound a were derived from isomenthone, the ratio would be c:a + b (58.2:41.8). The experimentally observed ratio of 84.1:15.9 shows the first possibility (*i.e.*, a ≡ **11**) to be correct, and nmr analysis of the mixture confirmed these assignments.

It appears, therefore, that under these reduction conditions, isomenthone does not undergo significant reduction,[15] and that although a small amount of epimerization takes place, reduction is considerably faster than epimerization.

In view of the small amount of epimerization, the availability of samples of menthone with only small amounts of isomenthone (3%), and the nonreduction of isomenthone, the kinetics of reduction of menthone were measured by the usual spectrophotometric

view of the very small temperature dependence of stereochemical product ratio, it would appear that the only danger of the activation enthalpies being seriously in error would be the possibility of transfer of the first hydride having a very strong temperature dependence, counteracted by the subsequent transfers having an almost equal but opposing dependence. Independent experiments on the reduction of 2-methylcyclohexanone measuring product ratios early and late in the reaction at differing temperatures, indicate that this is not the case. Furthermore, stereochemical product ratio dependence on temperature for reductions by $LiAl(O\text{-}t\text{-}Bu)_3H$,[2a,4] ($LiAl(OMe)_3H$,[2a,9] and $NaB(O\text{-}i\text{-}Pr)_3H$[2a,10-12] show in all cases small changes in the same direction as observed for reduction by $NaBH_4$.

(8) W. M. Jones and H. E. Wise, Jr., *J. Amer. Chem. Soc.*, **84**, 997 (1962).
(9) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363 (1962).
(10) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2368 (1962).
(11) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).
(12) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).
(13) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).
(14) H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem.*, **36**, 387 (1971).
(15) These results contrast with those of Hach and coworkers,[16] who reported extensive epimerization of menthone and thujone during reduction with $NaBH_4$ in 2-propanol unless at least 3% water was present in the solvent. The use of nonanhydrous solvent certainly adversely affects our kinetic plots, as it does for the methanolysis of $NaBH_4$,[17] but in our experiments use of such solvent mixtures were not necessary to avoid epimerization.
(16) V. Hach, E. C. Fryberg, and E. McDonald, *Tetrahedron Lett.*, 2629 (1971).
(17) R. E. Davis and J. A. Gottbrath, *J. Amer. Chem. Soc.*, **84**, 895 (1962).

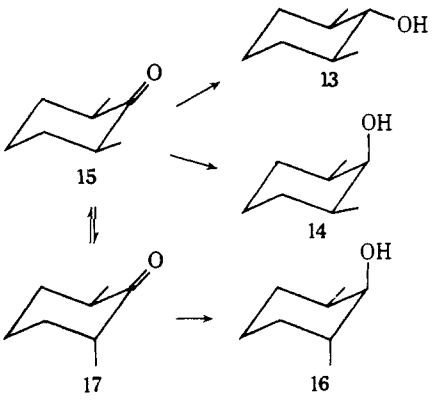

Figure 2. Possible products from reduction of 2,6-dimethylcyclohexanone.

method,[6] and subdivided into the specific rate constants for axial and equatorial attack using the product ratios of alcohols **12**:**11**. These results are summarized in Tables I and II. It is noteworthy that the stereochemical product ratios from menthone are the only ones whose trend is toward more equatorial alcohol with higher temperature.

Reduction of 2,6-dimethylcyclohexanone can give rise to three alcohols shown in Figure 2: the trans,trans alcohol **13** and the cis,cis alcohol **14** arising from *cis*-2,6-dimethylcyclohexanone **15**, and the cis,trans alcohol **16** arising from *trans*-2,6-dimethylcyclohexanone **17**. Glc analysis of reduction mixtures showed all three alcohols to be formed, although ketone **17** and alcohol **13** were not resolved.[18] After complete reduction with $NaBH_4$ in 2-propanol at 21° (70 hr), the areas of the three glc peaks were a 34.9%; b 53.4%; and c 11.6%. Identification of each alcohol was again made by use of Brown oxidation.[14] The three possibilities are shown in Table III.

Table III. Identification of Alcohols **13**, **14**, and **16**

Origin of alcohols	Cis:trans ketone ratio on oxidation
c from **17**; a, b, from **15**	88.4:11.6
b from **17**; a, c, from **15**	46.6:53.4
a from **17**; b, c, from **15**	65.1:34.9
Experimentally found	88.5:11.5

These results clearly indicate peak c (11.6%) to correspond to alcohol **16**, and the two peaks a and b to correspond to the two alcohols from *cis*-2,6-dimethylcyclohexanone **15**. It appeared likely that peak a was due to the axial alcohol **14**, and that peak b was due to the equatorial alcohol **13** on the basis that in all cases studied the axial alcohol of an axial–equatorial pair has a shorter retention time, a generally observed phenomenon on this type of separation.[19] This conclusion was consistent with examinations of the methine proton signal (adjacent to hydroxyl) areas in the nmr spectra of various reduction mixtures.

Glc analysis of product mixtures from reduction of 2,6-dimethylcyclohexanone consistently showed higher

(18) A 50-ft TCEP SCOT column gave base-line separation of all other compounds used in this study.

(19) D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc. B*, 505 (1970).

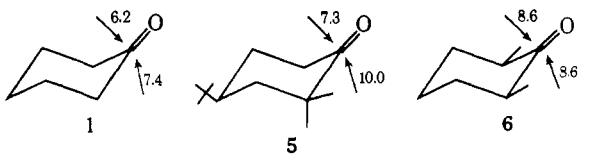

Figure 3. Enthalpies of activation to attack by sodium borohydride.

proportions of alcohol **16** than of ketone **17** in the starting mixture. Thus it appeared that epimerization of **15** to **17** was occurring, followed by reduction of **17** to alcohol **16**.

This conclusion was confirmed by following the progress of reaction by glc, and this situation (in contrast to that in the menthone reduction), coupled with the unavailability of any samples of 2,6-dimethylcyclohexanone containing greater than 92% of cis isomer, rendered the spectrophotometric method of following the reaction kinetics invalid. The kinetics were therefore measured using glc.[3] Since the reduction of trans ketone **17** is faster than that of **15**, the rate plots of formation of alcohol **16** were only valid for the first few minutes of reduction, after which time the kinetic plot deviated from linearity. The rate plots for this reduction, therefore, have fewer points and are less reliable than those for reduction of the cis ketone **15**.[20] As in the case of menthone, epimerization appears to be considerably slower than reduction. The rate constants obtained are summarized in Tables I and II.

Activation Parameters. Having obtained overall and specific rate constants at various temperatures, activation parameters were derived using standard procedures. These are summarized in Table IV.

Discussion

Inspection of the activation parameters in Table IV reveals that the effect of structural change on the ketone causes regular and systematic changes in the values of $\Delta H^{\ddagger}$, the changes in $\Delta S^{\ddagger}$ being smaller and less regular. The isokinetic plot of a number of ketones (including 2-substituted cyclohexanones) shows an isokinetic temperature of 400–500°K[21] which corresponds to predominant enthalpy control at ambient temperature.

Owing to the highly unlikely situations of ketone **5** reducing through a conformation with the *tert*-butyl group in an axial configuration, and *cis*-2,6-dimethylcyclohexanone **6** reducing through a conformation with the two methyl groups 1,3-diaxial to each other, the specific enthalpies of activation can be assigned and compared to those of cyclohexanone as shown in Figure 3.

Equatorial Attack Leading to Axial Alcohol. From attack on ketone **6**, the effect of two equatorial methyl groups is seen to be (8.6 − 7.4) = 1.2 kcal/mol. If the methyl interactions are additive, this implies *an equatorial methyl group impedes attack by 0.6 kcal/mol.*

From attack on ketone **5**, the effect of one equatorial and one axial methyl group is (10.0 − 7.4) = 2.6 kcal/mol. Since the equatorial group impedes attack by 0.6 kcal/mol, *an axial methyl group impedes attack by (2.6 − 0.6) = 2.0 kcal/mol.*

(20) Nevertheless, the overall activation parameters turn out to be very similar to those of ketone **5** (see Table IV).

(21) D. C. Wigfield and D. J. Phelps, unpublished data.

Table IV. Activation Parameters for Reduction of Ketones by Sodium Borohydride in 2-Propanol

Ketone	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}_{298}$, kcal/mol	$\Delta H^{\ddagger}_{ax}$,[a] kcal/mol	$\Delta S^{\ddagger}_{ax}$,[a] eu	$\Delta G^{\ddagger}_{ax\ 298}$,[a] kcal/mol	$\Delta H^{\ddagger}_{eq}$,[a] kcal/mol	$\Delta S^{\ddagger}_{eq}$,[a] eu	$\Delta G^{\ddagger}_{eq\ 298}$,[a] kcal/mol
1	6.4 ± 0.1	−42.1 ± 0.1	18.9	6.2 ± 0.1	−43.0 ± 0.2	19.0	7.4 ± 0.1	−42.8 ± 0.5	20.2
2	7.9 ± 0.3	−40.6 ± 1.1	20.0	7.8 ± 0.3	−41.4 ± 1.0	20.1	8.7 ± 0.3	−40.2 ± 0.9	20.7
3	6.9 ± 0.1	−45.2 ± 0.5	20.4	6.8 ± 0.1	−46.3 ± 0.5	20.6	7.5 ± 0.2	−45.2 ± 0.6	21.0
4	7.7 ± 0.3	−42.7 ± 1.1	20.4	7.8 ± 0.3	−43.4 ± 1.1	20.7	8.2 ± 0.3	−43.2 ± 1.1	21.1
5	7.5 ± 0.4	−43.8 ± 1.5	20.6	7.3 ± 0.4	−44.7 ± 1.4	20.6	10.0 ± 0.4	−40.3 ± 1.3	22.0
cis-**6**	8.6 ± 0.1	−41.1 ± 0.3	20.8	8.6 ± 0.1	−42.1 ± 0.3	21.1	8.6 ± 0.1	−43.0 ± 0.2	21.4
trans-**6**	7.8 ± 0.2	−43.6 ± 0.5	20.8						
7	9.2 ± 0.3	−40.6 ± 0.9	21.3	9.5 ± 0.3	−40.5 ± 0.9	21.6	8.7 ± 0.3	−44.6 ± 0.9	22.0

[a] See Table II, footnote *c*.

Axial Attack Leading to Equatorial Alcohol. In a similar fashion, from attack on ketone **6** the effect of two equatorial methyl groups is seen to be (8.6 − 6.2) = 2.4 kcal/mol. *Thus an equatorial methyl group impedes attack by 1.2 kcal/mol.* From attack on ketone **5**, the effect of an axial methyl group is (7.3 − 6.2 − 1.2) ≃ 0 kcal/mol. *Thus an axial methyl group does not appear to significantly impede attack*, a satisfyingly reasonable conclusion.

These interactions are summarized in Figure 4.

Thus it appears that while the natural preference of axial attack in cyclohexanone of 1.2 kcal/mol is opposed by an effect of an axial 3-methyl substituent of −2.6 kcal/mol giving a preference of equatorial attack of 1.4 kcal/mol,[21] the effect of a 2 substituent depends markedly on whether the substituent is axial or equatorial. In the presence of an equatorial substituent there is an effect slowing equatorial attack by 0.6 kcal/mol but axial attack by 1.2 kcal/mol for an overall effect of −0.6 kcal/mol opposing the natural cyclohexanone preference, and thus reducing it from 1.2 to 0.6 kcal/mol. In the presence of an axial substituent, however, there is a strong effect (2.0 kcal/mol) reinforcing the natural axial attack preference by virtue of the interaction hindering equatorial attack but leaving unchanged the energy requirement for axial attack.

The Conformation of Reduction of Mobile Systems. With these activation enthalpies from conformationally unambiguous systems at hand, coupled with the information that epimerization does not play a large role in the reduction, it becomes possible to tackle conformationally mobile systems and the question of whether a cis alcohol arises from equatorial attack on the conformation with the 2 substituent equatorial or axial attack on the conformation with the 2 substituent axial, or both, and the corresponding question for formation of a trans alcohol. The values of the activation enthalpies for these four possible reactions are shown in Table V, together with the experimentally obtained values for the reduction of the three conformationally mobile ketones **2**, **3**, and **4**.

All of the calculated values appear at first sight to be sufficiently different for experimental distinction. However, it must be noted that these values apply only to attack on conformations with the 2-alkyl group *fixed* either axial or equatorial, as the case may be. In the case of conformationally *mobile* systems, the value of $\Delta H^{\ddagger}$ for reduction through the conformation with the group axial must also include the enthalpy difference between the two conformations with the group axial or equatorial. This value is given as 1.8 kcal/mol in the case of a methyl group;[22] less for larger groups. Using the value for a methyl group, the calculated value for axial attack on the axial conformation becomes 6.2 + 1.8 = 8.0 kcal/mol, and equatorial attack on the axial conformation becomes 9.4 + 1.8 = 11.2 kcal/mol.

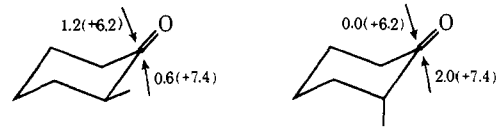

Figure 4. Enthalpy interactions of a 2-methyl group to reduction by $NaBH_4$, over and above those existing in cyclohexanone (figures in parentheses).

Table V. Enthalpies of Activation for Different Modes of Attack on Conformationally Mobile 2-Alkylcyclohexanones

Ketone	Formation of cis alcohol		Formation of trans alcohol	
2	8.7		7.8	
3	7.5		6.8	
4	8.2		7.8	
Mean	8.1		7.5	
	Eq attack on eq conformation	Axial attack on ax conformation	Axial attack on eq conformation	Eq attack on ax conformation
Calcd	8.0	6.2	7.4	9.4

Thus for the formation of the trans alcohol there would seem to be little question that this is formed *via* the equatorial conformation, the experimental mean of 7.5 being close to 7.4 and far from 11.2. The formation of the cis alcohol, however, becomes unfortunately ambiguous, both calculated modes of attack predicting 8.0 kcal/mol, in good agreement with the observed mean of 8.1 kcal/mol. These data, therefore, do not allow a decision to be made through which conformation the cis alcohol is formed, and quite possibly both conformations may contribute significantly.

Product Ratios from Other Ketones. The above discussion reveals one of the many complications in attempting to predict or rationalize product ratios from reduction of 2-alkylcyclohexanones. Such a prediction must involve a comparison of the magnitudes of the interactions involved in proceeding to the cis or trans alcohol, but in the case of the formation of the cis alcohol, there is ambiguity about which conforma-

(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 114.

tion of the ketone is involved, with 2-methylcyclohexanone possibly lying on the knife-edge and ketones lying to one side or the other, depending on other substitution patterns. Because of the 2-alkyl ketone effect[22] it would appear that ketones with larger 2-alkyl groups, for instance 2-isopropylcyclohexanone, might reduce through the axial conformation, yet it is questionable how far this argument can be pursued because of the eventual formation of the saturated alcohol with the 2-axial group. Menthone is a 2-isopropylcyclohexanone, but with an additional 5-methyl group and if the conformation is changed to that with the axial isopropyl group, then the methyl also becomes axial which will require energy as well as rather drastically affecting the rate of axial attack. Thus for menthone equatorial attack on the normal conformation is probably preferred, $\Delta H^{\ddagger}_{eq}$ not being a great deal larger than those for ketones **2**, **3**, and **4** (Table IV). As one might expect (*cf.* Figure 4), a substantially increased resistance to axial attack is observed, and the situation is reached where $\Delta H^{\ddagger}_{ax} > \Delta H^{\ddagger}_{eq}$. Owing to entropy moderation, however, the observed product ratio still reflects a preference for axial attack. A 2-*tert*-butyl group, however, as in ketone **9** brings the product ratio close to 50:50, and although the kinetics proved too slow to follow, one would expect that the enthalpies of activation would here be substantially favoring formation of the cis alcohol. Reduction of ketone **8**, again too slow to obtain rate data, provides an interesting case. Unlike menthone, conformational flip makes little energy difference so far as the methyl groups are concerned and will largely be controlled by the 2-isopropyl group. As the conformational energy of a 2-isopropyl group is *less* than that of a 2-methyl group[22] (0.4 kcal/mol), this ketone probably represents an example where the cis alcohol will be preferentially formed from the conformation with the 2 substituent axial, and the value of $\Delta H^{\ddagger}_{eq}$ can be estimated as the sum of $\Delta H^{\ddagger}_{ax}$ for 3,3,5-trimethylcyclohexanone (10.3 kcal/mol)[21] and the conformational enthalpy of the 2-isopropyl group (0.4 kcal/mol[22]) for a total of 10.7 kcal/mol. The value of $\Delta H^{\ddagger}_{ax}$ can be estimated again as the value of $\Delta H^{\ddagger}_{ax}$ for 3,3,5-trimethylcyclohexanone plus a factor of >1.2 kcal/mol (see Figure 4) (*i.e.*, >11.5 kcal/mol). Thus one would predict the cis alcohol to be favored by >0.8 kcal/mol which even after entropy moderation apparently is still reflected as a slight preference in the product ratio (see Table II).

Nature of Interactions. The interactions causing the enthalpy of activation changes we have measured and discussed are almost certainly steric in origin. However, with the question of how far along the reaction coordinate the transition state occurs still experimentally unsettled, it is not yet possible to accurately assign interactions. It is worth noting that the largest interaction (the effect of a 2-axial substituent on equatorial attack, 2.0 kcal/mol) is the interaction considered by both Richer[4] and Felkin[23] in the case where the substituent is hydrogen, as a possible cause of the "natural" preference of axial attack, assuming an early transition state. Richer considered this interaction steric; Felkin and coworkers considered it torsional. Again, on the basis of an early transition state and sp^2 carbonyl geometry, it is reasonable to expect that a 2-equatorial substituent will interfere more with axial attack than it will with equatorial attack owing to the nonsymmetrical disposition of the carbonyl group relative to the groups at the 2 position, a point first noted by Richer.[4] It is considerably less obvious how to rationalize these interactions if the transition state is late (*i.e.*, sp^3 geometry of the forming alcohol).

(23) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Cherest and H. Felkin, *ibid.*, 2205 (1968).

Conclusions

(1) The reduction of 2-alkylcyclohexanones is largely controlled by interactions that manifest themselves in the activation enthalpy, the changes in entropy of activation being smaller and the trends opposing the enthalpy changes.

(2) Epimerization does occur at the 2 position during reduction with $NaBH_4$ in 2-propanol; however, epimerization is slow in comparison to reduction and does not make a major contribution to the stereochemical product ratio.

(3) Conformationally mobile 2-alkylcyclohexanones appear to give rise to the trans alcohol through the conformation with the 2-substituent in the equatorial configuration.

(4) The data do not permit a decision to be made on the question of through which conformation the cis alcohol is formed from a 2-*n*-alkylcyclohexanone. In the case of 2-methylcyclohexanone it is likely that both conformations may be significantly involved. Other 2 substituents or groups on other positions could control whether it arises from equatorial attack on the equatorial conformation or axial attack on the axial conformation.

(5) A 2-equatorial *n*-alkyl group causes an interaction of 0.6 kcal/mol with equatorial attack and 1.2 kcal/mol with axial attack of BH_4^-. A 2-axial *n*-alkyl group causes an interaction of 2.0 kcal/mol with equatorial attack but has no effect upon axial attack. Thus each 2-equatorial group reduces the "natural" axial attack preference (1.2 kcal/mol) by 0.6 kcal/mol, while each 2-axial group reinforces it by 2.0 kcal/mol.

Experimental Section

The kinetic method has previously been described.[2b,6] Rate constants were determined at least in duplicate or until satisfactory reproducibility was obtained. Nmr spectra were obtained on a Varian T60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. All ketones except menthone (97%) and *cis*-2,6-dimethylcyclohexanone (92%) were shown to be >99% pure by glc. Attempts to improve the purity of these two ketones were not successful, the impurities being the corresponding isomers isomenthone (3%) and *trans*-2,6-dimethylcyclohexanone (8%).

Product Ratios. The ketones were reduced and worked up as previously described.[2b] Product mixtures were analyzed on a Perkin-Elmer 990 gas chromatograph using a 50 ft × 0.02 in. i.d. support-coated open tubular (S.C.O.T.) TCEP column. Carrier gas flow was 3.6–4.1 ml/min, calibrated depending on temperature of column oven; injector port 240°, manifold 240°. Table VI lists column temperature and retention times of the epimeric alcohols. Peak areas were determined electronically with an Infotronics CRS-208 integrator. Nmr analysis of the methine proton adjacent to hydroxyl gave corroborating product ratios in each case.

Glc Kinetics. The ketone (150 mg) was weighed into a 5-ml volumetric flask. The standardized hydride solution was added to the mark by pasteur pipet, half-addition being taken as zero time. The flask was inverted 13 times to ensure mixing. Aliquots of the reaction mixture were added to acid for quenching: 6 drops of reaction mixture to 2 drops of 0.1 *N* HCl; 0.2 μl of the quenched

Table VI. Glc Data for Separation of Alcohols

Ketone	Column oven temp, °C	Retention time, min Axial alcohol[a]	Equatorial alcohol
2	84	19.8	21.9
3	114	10.8	12.7
4	120	19.4	21.9
cis-**6**	108	7.6	8.8
trans-**6**	108	11.8	
7	116	13.8	18.1
8	125	11.6	16.2
9	118	13.2	15.7

[a] *I.e.*, cis to the group at the 2 position.

aliquot was then injected into the gas chromatograph. This proved a convenient amount to make the largest peak cause full-scale deflection of the chart pen and to be able to see the smallest peaks.

3,3-Dimethyl-6-isopropylcyclohexanone (8). To a stirred suspension of copper(I) iodide (20.1 g, 0.106 mol) in anhydrous ether (450 ml) under nitrogen and in an ice bath was added a 1.75 *M* solution of methyllithium (88 ml, 0.154 mol) in ether. The suspension was stirred at 0° until a tan color appeared (5 min). Piperitone (5.04 g, 0.033 mol) in anhydrous ether (125 ml) was added dropwise over 25 min. The reaction mixture was allowed to stir at 0° for 2 hr and then poured with stirring into 1 *N* HCl (1 l.). The mixture was filtered by suction to remove the inorganic precipitate and the aqueous filtrate extracted with ether (10 × 100 ml). The combined extracts were dried (brine; Na_2SO_4) and ether was removed by rotary evaporation to give a yellow liquid (5.22 g; 94%). Glc analysis showed the absence of starting ketone, but the presence of a major impurity (37%). Column chromatography (silica gel, petroleum ether) gave 3.0 g of material (90% purity) which was rechromatographed (silica gel, petroleum ether; petroleum ether–benzene (1:1)) to afford ketone in a purity of greater than 99%: δ 0.90 (6 H, d, J = 6 Hz), 0.90 (3 H, s), 1.02 (3 H, s), 1.17 (1 H, m), 1.60 (2 H, m), 1.80 (2 H, m), 2.02 (2 H, s); ν_{max} 1710 cm^{-1} (carbonyl); *m/e* 168, 153, *126*, 111, 98, 83. *Anal.* Calcd for $C_{11}H_{20}O$: C, 78.55; H, 11.86. Found: C, 78.51; H, 11.98. Simultaneous injection with a sample kindly supplied by Professor G. Stork showed identity of retention times of the two samples.

Menthone was prepared by the Brown oxidation of menthol,[14] bp 101° (12 mm) (lit.[14] 66.7° (4 mm)), $n^{20}D$ 1.4497 (lit.[14] 1.4500).

2-*n*-Butylcyclohexanone was prepared from a mixture of the corresponding alcohols by Brown oxidation,[14] bp 105–106° (15 mm) (lit.[24] 93.5° (11 mm)), $n^{20}D$ 1.4528 (lit.[24] 1.4548).

2-*tert*-Butylcyclohexanone was prepared by dichromate oxidation[25] of commercial verdol in 87% yield, bp 136–138° (20 mm) (lit.[26] 80–82° (13 mm)), $n^{20}D$ 1.4565 (lit.[26] 1.4561)).

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(24) B. B. Elsner and H. E. Strauss, *J. Chem. Soc.*, 588 (1957).
(25) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).
(26) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4243 (1962).

Aromatic Substitution. XXXIV.[1] The Differing Nature and Selectivity of the Nitration of Nitro(dinitro)benzene and -toluenes from that of Benzene and Toluene

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Abstract: The competitive and noncompetitive rates and isomer distributions of nitration of nitro(dinitro)benzene and -toluenes with nitronium salts in nitromethane and sulfuric acid solutions were determined. The reactions show high substrate selectivity indicating "late," *i.e.*, arenium ion like nature of the transition states of highest energy. This is also reflected in the increased para substitutions (related to the methyl group) in nitration of nitrotoluenes. The significant differences in the nature and selectivity of the nitronium salt nitration of benzene and toluene from those of nitro(dinitro)benzene and -toluenes are discussed in terms of the differing nature of the involved transition states.

Electrophilic nitration has been one of the most widely studied electrophilic aromatic substitution reactions and was extensively reviewed.[2–8]

The idea that the actual nitrating agent in aromatic nitration might be the nitronium ion, NO_2^+, was suggested by von Euler[9] as early as 1903 and has since then been supported by numerous authors,[10–12] most notably by Ingold.[13]

Stable nitronium salts were introduced as nitrating agents in our work[14,15] in 1956. They were found useful both in preparative nitration[16] and in the investi-

(1) Part XXXIII: G. A. Olah and P. Schilling, *Justus Liebigs Ann. Chem.*, **761**, 77 (1972).
(2) R. J. Gillespie and D. J. Millen, *Quart. Rev., Chem. Soc.*, **2**, 277 (1948).
(3) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution—Nitration and Halogenation," Academic Press, New York, N. Y., 1959.
(4) E. D. Hughes, "Theoretical Organic Chemistry Kekule Symposium," Butterworths, London, 1959, p 209.
(5) G. A. Olah and S. J. Kuhn, "Friedel-Crafts and Related Reactions," Vol. III, Part II, G. A. Olah, Ed., Wiley, New York, N. Y., 1964, Chapter 43.
(6) R. C. Miller, D. S. Noyce, and T. Vermeulen, *Ind. Eng. Chem.*, **56**, 43 (1964).
(7) J. H. Ridd in "Studies on Chemical Structures and Reactivity," J. H. Ridd, Ed., Wiley, New York, N. Y., 1966, p 133.
(8) H. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity," Cambridge University Press, New York, N. Y., 1971.
(9) H. von Euler, *Justus Liebigs Ann. Chem.*, **330**, 280 (1903).
(10) P. Walden, *Angew. Chem.*, **37**, 390 (1924).
(11) T. Ri and E. Eyring, *J. Chem. Phys.*, **8**, 433 (1940).
(12) C. C. Price, *Chem. Rev.*, **29**, 51 (1941).
(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969.
(14) G. A. Olah and S. J. Kuhn, *Chem. Ind. (London)*, 89 (1956)
(15) G. A. Olah, S. J. Kuhn, and A. Mlinko, *J. Chem. Soc.*, 4257 (1956).
(16) S. J. Kuhn and G. A. Olah, *J. Amer. Chem. Soc.*, **83**, 4564 (1961).