The product gave negative tests for halogen and a positive test for olefinic unsaturation with tetranitromethane. Its infrared spectrum showed a band at $6.1\ \mu$ and the absence of bands at 5.8–$6.0\ \mu$.

Analysis of Products.—Preliminary qualitative analysis of all products was made by comparison of infrared spectra with spectra of authentic samples. When the physical constants and the spectrum of the product indicated a pure compound had been obtained, a characteristic derivative generally was prepared and compared with an authentic sample. Authentic samples of the carbinols listed as products in Tables I and II were commercial materials except: 3,3-dimethyl-2-butanol by the LAH reduction[38] of pinacolone[39]; 1-chloro-2-propanol by the LAH reduction[40] of chloroacetone,[41] 3-phenoxy-1-propanol by the reaction of sodium phenoxide with trimethylene chlorohydrin,[42] 1-phenoxy-2-propanol by LAH reduction of 1-phenoxy-2-propanone, 2,4,4-trimethylpentanol-3 by the reaction of isobutyraldehyde and *t*-butylmagnesium chloride,[43] and cyclopentylcarbinol by the LAH reduction of cyclopentanecarboxyaldehyde.[44] Samples of 2,4,4-trimethylpentanol-1, 2,4,4-trimethylpentanol-2 and 2,2,3,3-tetramethylbutanol-1 were not readily available and these products were characterized through suitable derivatives.

When a mixture was obtained, the product was analyzed quantitatively by mass spectrometry[45] or by vapor phase chromatography. The vapor phase chromatographic analysis was carried out on a Wilkens Aerograph instrument in conjunction with a Brown Electronik recorder. Helium was used as the carrier gas maintained at 8 p.s.i. at flow rates of 60–100 ml. per minute. Components were identified by comparison of their retention times with the retention times of authentic samples. When necessary components were collected and identified by infrared spectroscopy. Areas under the peaks were measured with a planimeter and the mole ratio of components calculated from area ratios. Authentic mixtures were analyzed in all cases to verify the assumption that peak areas were proportional to mole ratios. Table III gives the epoxide reduced and the substrate and temperature used for an efficient separation of the products obtained as shown in Tables I and II.

TABLE III

CONDITIONS FOR VAPOR PHASE CHROMATOGRAPHIC ANALYSES

Products from	Substrate	T, °C.
Tetramethylethylene oxide	Ucon-polar	88–89
Epichlorohydrin	Tide detergent	100–105
α-Methylstyrene oxide	Tide detergent	17
α-Diisobutylene oxide	Ucon-polar	129
β-Diisobutylene oxide	Ucon-polar	129
Cyclohexene oxide	Ucon-polar	139

Acknowledgment.—This work is a contribution from the Radiation Project of the University of Notre Dame, supported, in part, under Atomic Energy Commission contract AT(11-1)-38 and Navy loan equipment contract Nonr-06900. We are indebted to Professor V. J. Traynelis and Dr. Zoltan Welvart for helpful suggestions. The vapor phase chromatographic equipment for this investigation was acquired under National Science Foundation Grant G-4058.

NOTRE DAME, IND.

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[38] *Cf.* A. A. Bothner-By, THIS JOURNAL, **73**, 846 (1951).

[39] G. A. Hill and E. W. Flosdorf, ref. 25, p. 462.

[40] C. A. Stewart and C. A. VanderWerf, THIS JOURNAL, **76**, 1259 (1954).

[41] E. R. Buchanan and H. Sargent, *ibid.*, **67**, 400 (1945).

[42] S. G. Powell, *ibid.*, **45**, 2708 (1923).

[43] F. C. Whitmore and A. L. Houk, *ibid.*, **54**, 3714 (1932).

[44] A generous sample was supplied by Professor George F. Hennion, University of Notre Dame.

[45] *Cf.* E. L. Eliel, T. J. Prosser and G. W. Young, *J. Chem. Ed.*, **34**, 72 (1957), and literature there cited.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Reduction with Metal Hydrides. VIII. Reductions of Ketones and Epimerization of Alcohols with Lithium Aluminum Hydride–Aluminum Chloride[1,2]

BY ERNEST L. ELIEL AND MARK N. RERICK

RECEIVED JULY 28, 1959

Whereas lithium aluminum hydride (LAH) reduced 4-*t*-butylcyclohexanone to a mixture of 90% *trans*-4-*t*-butylcyclohexanol (I) and 10% *cis*-4-*t*-butylcyclohexanol (II), LAH–AlCl$_3$ (1:4 ratio) yields 80% *trans*- and 20% *cis*-alcohol under kinetically controlled conditions. Addition of excess ketone or acetone at the end of the reaction leads to thermodynamic control of the reaction products with conversion of the alcohol mixture to one containing over 99% of the *trans* isomer in less than fifteen minutes. The fast reaction and overwhelming preponderance of the *trans* isomer is ascribed to the nature of the species equilibrated which are bulky aluminum complexes, not readily accommodated in the axial position of the cyclohexane ring. The equilibration procedure has been utilized to determine the conformational equilibrium values for methyl and phenyl groups. The conformational free energy differences (*A*-values) are 1.5 ± 0.1 kcal./mole for methyl and *ca.* 2.6 kcal./mole for phenyl.

There have been several recent papers[3] indicating that the reducing action of LAH–AlCl$_3$ combinations differs from that of LAH alone. For example, in our own laboratories we have observed that epoxides may be reduced in a different way by LAH–AlCl$_3$ than by LAH alone[2,4] and that acetals, unaffected by LAH, are reduced to ethers by the "mixed reagent."[5] Wheeler and Mateos[6] have reported that cholestanone, reduced to a mixture of 88% 3-β-hydroxycholestane (equatorial OH) and 12% 3-α-hydroxycholestane (axial OH) by LAH, gives exclusively the beta (equatorial) isomer with the mixed reagent. The need for substantial quantities of *trans*-4-*t*-butylcyclohexanol (I, equatorial hydroxyl) in other work prompted us to try to apply this reduction to the commercially available 4-*t*-butylcyclohexanone.

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[1] Presented in part at the San Francisco National Meeting, Am. Chem. Soc., April 14, 1958.

[2] Paper VII, E. L. Eliel and M. N. Rerick, THIS JOURNAL, **82**, 1362 (1960).

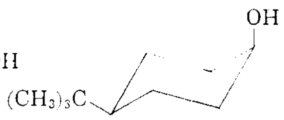
[3] For a summary, see M. N. Rerick, "Selective Reductions of Organic Compounds with Complex Metal Hydrides," Metal Hydrides, Inc., Beverly, Mass., 1959.

[4] E. L. Eliel and D. W. Delmonte, THIS JOURNAL, **80**, 1744 (1958).

[5] E. L. Eliel and M. N. Rerick, *J. Org. Chem.*, **23**, 1088 (1958). See also E. L. Eliel and V. G. Badding, THIS JOURNAL, **81**, 6087 (1959).

[6] O. H. Wheeler and J. L. Mateos, *Chemistry & Industry*, 395 (1957); *Can. J. Chem.*, **36**, 1431 (1958).

I



II

Somewhat to our surprise, the reduction of 4-*t*-butylcyclohexanone with the mixed reagent gave *less trans*-4-*t*-butylcyclohexanol (I) than reduction with LAH alone. The same was true of 4-methylcyclohexanone and 4-phenylcyclohexanone. The pertinent results are summarized in Table I. Interestingly enough, the changed proportion of the products is observed not only with a 1:3 or 1:4 ratio of LAH to $AlCl_3$ (entries 2, 1, reagent presumably $AlHCl_2$) but also with a 1:1 ratio (entry 3, reagent presumably AlH_2Cl). On the other hand, with a 3:1 ratio of LAH to $AlCl_3$ (entry 4, presumed reagent AlH_3) the proportion of *cis*- and *trans*-products is the same as with LAH alone (entry 5).

TABLE I

REDUCTION OF 4-ALKYLCYCLOHEXANONES WITH $LiAlH_4$–$AlCl_3$

Run	Cyclohexanone	LAH,[a] mole	$AlCl_3$,[a] moles	Yield, %	*trans*,[b] %
1	4-*t*-Butyl-	0.275	1.0	95	78–82
2	4-*t*-Butyl-	.275	0.75	96	79–83
3	4-*t*-Butyl-	.275	.25	88	79
4	4-*t*-Butyl-	.275	.083	95	88–89
5	4-*t*-Butyl-	.275	.0	99	88–90[c]
6	4-Methyl-	.278	.0	76	79–81[d]
7	4-Methyl-	.275	1.1	92	76–77
8	4-Phenyl-	.50	0.0	89	90–91
9	4-Phenyl-	.312	1.25	99	85–86

[a] Normalized to one mole ketone; most runs were carried out on one-tenth this scale. [b] Analyses by infrared and/or vapor phase chromatography; the range indicates the reproducibility of the analyses. [c] Ref. 7 reports 91–93%; the present figure probably is more accurate. [d] Ref. 7.

The rationale of product composition in the reduction of ketones to a mixture of epimeric alcohols by metal hydrides has been discussed elsewhere.[8] It is of interest that "product development control," *i.e.*, formation of the more stable product (in the present case the *trans* isomer) is more marked with LAH alone than with the LAH–$AlCl_3$ reagent. This may be because the "mixed reagent" is more bulky and therefore somewhat more prone than LAH alone to approach from the less hindered (equatorial) side to give the (less stable) *cis* isomer. In this respect, the "mixed reagent" appears to resemble sodium borohydride which previously has been shown[8] to be subject to "steric approach control" to a greater extent than LAH. The greater bulkiness of reagents such as $AlHCl_2$ and AlH_2Cl as compared with AlH_4^- may be in part due to the size of the chlorine atoms and in part to the fact that tricovalent aluminum is strongly coördinated with solvent ether molecules.

If one assumes that the *t*-butyl group in 4-*t*-butylcyclohexanone and the corresponding alcohols is entirely in the equatorial position,[9] then the result of the reduction of this ketone with LAH or AlH_3 (entry 4) means that equatorial and axial alcohols are produced in a 8.9:1.1 ratio whereas LAH–$AlCl_3$ (entries 1–3) produces these alcohols in a 8:2 ratio. In 4-methylcyclohexanone, based on the experiments to be discussed below, it appears that 92% of the molecules have equatorial methyl substituents and 8% have axial methyl substituents.[10] The former (e-CH_3 ketone) should give rise to 92 × 0.89 or 82% e-CH_3-e-OH (*i.e.*, *trans*) alcohol and 92 × 0.11 or 10% e-CH_3-a-OH (*i.e.*, *cis*) alcohol. The latter (a-CH_3 ketone) should give rise to 8 × 0.89 or 7% a-CH_3-e-OH (*i.e.*, *cis*) alcohol and 8 × 0.11 or 1% a-CH_3-a-OH (*i.e.*, *trans*) alcohol. Thus the predicted percentage *trans*-4-methylcyclohexanol formed is 82 + 1 or 83% and the predicted percentage *cis*-4-methylcyclohexanol is 10 + 7 or 17%. These percentages would appear to agree, within the limit of combined experimental error, with the experimental finding of 79–81% *trans* (Table I, entry 6). Similar considerations, applied to the reduction of 4-methylcyclohexanone with mixed hydride, lead to a prediction of 75% *trans*- and 25% *cis*-4-methylcyclohexanol product in good agreement with the experimental 76–77% *trans* (entry 7). For 4-phenylcyclohexanone, assuming the phenyl group to be axial in 98.5% of the molecules (see below) the agreement is not as good: 87.5% *trans*-4-phenylcyclohexanol predicted *vs.* 90–91% found (entry 8) in the straight hydride reduction and 79.5% *trans* predicted *vs.* 85–86% found (entry 9) in the mixed hydride reduction. This may mean that either the fundamental steric assumptions are particularly poor for the phenyl group or, perhaps more likely, that the phenyl group introduces a disturbing polar influence.[11]

The experiments so far discussed failed in their original purpose to produce pure I. However, in one reduction of 4-*t*-butylcyclohexanone with LAH–$AlCl_3$ we did obtain nearly pure I. When this matter was investigated in detail, it was found that, fortuitously, an excess of 4-*t*-butylcyclohexanone was present in this particular run. Deliberate use of an excess of ketone (Table II, run 10) produced almost isomerically pure I. Essentially the same result was obtained (Table II, runs 1 and 2) by adding acetone at the end of the reduction and allowing the mixture to boil for 15 minutes. It was evident that this led to a change in product composition to nearly pure *trans* isomer *after reduction was complete;* aliquots of the reduction product removed *prior to* the addition of acetone showed the usual 80–20 composition. (Compare runs 1 and 2 in Table I with the corresponding runs in Table II; these refer to the same reaction, part of which was worked up prior

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(7) E. L. Eliel and R. S. Ro, THIS JOURNAL, **79**, 5992 (1957).

(8) W. G. Dauben, G. J. Fonken and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(9) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(10) It is assumed here that the change from tetrahedral geometry at carbon 1 in methylcyclohexane to trigonal geometry at carbon 4 in 4-methylcyclohexanone does not affect the conformational equilibrium of the methyl group. Recent work by R. A. Benkeser and E. W. Bennett, THIS JOURNAL, **80**, 5414 (1958), casts some doubt on the correctness of this assumption. Further work undoubtedly is required to indicate how good (or bad) this assumption is and the calculations here are presented because they have a bearing on this point.

(11) Difficulties due to polar effects of phenyl have been encountered previously: E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957).

TABLE II

EPIMERIZATIONS AND ATTEMPTED EPIMERIZATIONS OF 4-ALKYLCYCLOHEXANOLS WITH $LiAlH_4$–$AlCl_3$

Run	Starting material	LAH,[a] mole	$AlCl_3$,[a] moles	Ketone added[b]	Yield,[c] %	*trans*,[d] %
10	4-*t*-Butylcyclohexanone	0.229	0.834	No	94	99–100[e]
1[f]	4-*t*-Butylcyclohexanone	.275	1.0	Yes, A	95	98–99[e]
2[f]	4-*t*-Butylcyclohexanone	.275	0.75	Yes, A	96	92–95[e]
3[f]	4-*t*-Butylcyclohexanone	.275	.25	Yes, A	88	78–81[e]
4[f]	4-*t*-Butylcyclohexanone	.275	.083	Yes, A	95	88–90[e]
11	4-*t*-Butylcyclohexanone	.275	.0	Yes, A	93	89–91[e]
12[g]	4-*t*-Butylcyclohexanone	.344	1.25	No	99	95–96
13	4-*t*-Butylcyclohexanone	.275	1.0	No[h]	93	82–83
14	4-*t*-Butylcyclohexanol[i]	.275	1.0	Yes, A	96	96–97[e]
15	4-*t*-Butylcyclohexanol[i]	.0	1.0	Yes, B	91	81–82[e]
16	*trans*-4-*t*-Butylcyclohexanol	.275	1.0	No	91	98–99
17	4-Methylcyclohexanol[j]	.275	1.1	Yes, M	92	91.0[e]
18	*trans*-4-Methylcyclohexanol	.275	1.0	Yes, M	87	92.5–93.2[e]
19	4-Phenylcyclohexanol[k]	.312	1.25	Yes, P	87	97.7–98.1[e]
20	*trans*-4-Phenylcyclohexanol	.312	1.25	Yes, P	80	99.1–99.2[e]

[a] Normalized to one mole of starting material; most runs were carried out on one-tenth this scale. [b] Ketone (A = acetone, B = 4-*t*-butylcyclohexanone, M = 4-methylcyclohexanone, P = 4-phenylcyclohexanone) added at the end of the completion of the reaction of starting material and the reagent; see Experimental. [c] Trace amounts of ketone in the product are not taken into account in the calculation of the yield. [d] Out of total alcohol produced, disregarding any ketone; analyses by infrared and/or vapor phase chromatography. The range indicates the reproducibility of the analyses. [e] Parent ketone also present. [f] Split run; an aliquot of the reaction mixture was worked up before addition of ketone to give the products shown in Table I. Excess ketone was added to the remainder and worked up to give the products shown herein. [g] Inverse addition of the mixed hydride solution to ketone. [h] Methyl acetate used in place of acetone. [i] Mixture of 81% *trans* and 19% *cis*. [j] Mixture of 77% *trans* and 23% *cis*. [k] Mixture of 79% *trans* and 21% *cis*.

to the addition of acetone and the remainder following the addition of acetone and 10–15 min. boiling.) It also was noted that when acetone was added at the end of the reduction, 4-*t*-butylcyclohexanone (which had been completely consumed in the reduction) was regenerated.

As a result of these experiments, it became clear that the complex formed from 4-*t*-butylcyclohexanone upon reduction with LAH–$AlCl_3$ undergoes a rapid equilibration of the Meerwein–Ponndorf–Oppenauer type[12] in the presence of excess ketone (4-*t*-butylcyclohexanone or acetone). The position of the equilibrium is almost entirely on the side of the *trans* complex. The equilibrating complex may be generated starting with a mixture of 4-*t*-butylcyclohexanols (rather than the ketone), as shown in Table II, run 14. Not unexpectedly, *inverse* addition of the mixed hydride solution to the ketone (run 12) results in a product close to the equilibrium mixture, since under these conditions ketone is present in excess throughout the reduction and equilibration may occur concomitant with reduction. That a true equilibration rather than destruction of the *cis* isomer is involved follows from run 14, Table II, in which a 4-*t*-butylcyclohexanol mixture containing 20% *cis* isomer gave nearly pure *trans* isomer in 96% yield. Even more convincing in this respect is the evidence embodied in runs 17 and 18 where equilibrium (corresponding to *ca.* 92% *trans*-4-methylcyclohexanol complex) was reached from both sides.

Several aspects of the equilibration are of interest. One concerns the conditions of the equilibration. It is necessary, as in other equilibrations of the Meerwein–Ponndorf–Oppenauer type,[13] to have ketone present. Excess alkylcyclohexanone or added acetone seemed equally effective in the equilibration of the 4-*t*-butylcyclohexanol complexes, but equilibration of 4-phenylcyclohexanol and 4-methylcyclohexanol complexes proceeded readily only in the presence of an excess of the corresponding ketone. In these cases attempted equilibration with acetone did not proceed to completion and led to discoloration of the reaction mixture, possibly due to the formation of condensation products. Addition of methyl acetate instead of ketone at the end of the reaction (run 13) fails to produce equilibration. The ratio of aluminum chloride to lithium aluminum hydride in the "mixed reagent" is of crucial importance. No equilibration occurs, even in the presence of added acetone, with $AlCl_4$:LAH ratios of 1:1 and 1:3 (Table II, runs 3 and 4) nor is equilibration by acetone effected in the absence of aluminum chloride altogether (Table II, run 11). A 3:1 ratio of chloride to hydride does produce equilibration (Table II, run 2), but a 4:1 ratio is even more effective (Table II, run 10) and is recommended for all practical purposes. The reagent present at a 3:1 ratio of chloride to hydride is probably[14] $AlHCl_2$

$$LiAlH_4 + 3AlCl_3 \longrightarrow LiCl + 4AlHCl_2$$

and the equilibrating species may thus be $ROAlCl_2$. The fourth mole of aluminum chloride may merely ensure that this material is really present in adequate stoichiometric amount, or it may actually perform a function of its own in the equilibration. No isomerization was produced by aluminum chloride in the absence of lithium aluminum hydride (Table II, run 15).

The time and temperature conditions for the equilibration are quite remarkable. In the case of 4-*t*-butylcyclohexanol, equilibration is substan-

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[12] *Cf.* A. L. Wilds in R. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. 2, 1944, Chap. 5; and C. Djerassi, *ibid.*, Vol. 6, 1951, Chap. 5.

[13] *Cf.* W. v. E. Doering and T. C. Aschner, THIS JOURNAL, **71**, 838 (1949); also refs. 7 and 8.

[14] E. Wiberg and M. Schmidt, *Z. Naturforsch.*, **6b**, 460 (1951).

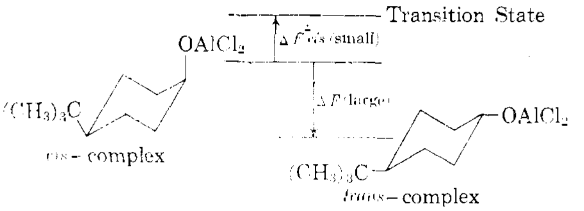

Fig. 1.—Equilibration of 4-*t*-butylcyclohexanol complexes.

tially complete after 15 min. boiling in ethereal solution (35°). With 4-phenyl- and 4-methylcyclohexanol, the reaction time was extended to about 7–14 hours. Even so, the conditions compare favorable with other recipes[7,8,13] which call for prolonged boiling (*ca.* 100 hours) in isopropyl alcohol solutions or heating to elevated temperatures in sealed tubes.[15]

Equally striking is the position of the equilibria shown in Table II. It is known[7] that the equilibrium mixture of the 4-*t*-butylcyclohexanols contains 79% of the *trans* isomer,[16] that of the 4-methylcyclohexanols 70% of the *trans* isomer and that of the 4-phenylcyclohexanols 79% of the *trans* isomer.[17] The equilibrium compositions obtained in the present investigation correspond to much higher *trans* content, namely, 99–100% for 4-*t*-butylcyclohexanol, 91–93% for 4-methylcyclohexanol and 98–99% for 4-phenylcyclohexanol. A plausible explanation is that ordinary equilibrations of the Meerwein–Ponndorf–Oppenauer type are carried out in isopropyl or *t*-butyl alcohol as a solvent and therefore the species equilibrated are the *free* alcohols[18]; whereas in the present work the species equilibrated are aluminum complexes of the alcohols, possibly of the type ROAlCl$_2$. The bulk of the alkoxide group (possibly further swelled by solvation) ensures that this group will have a strong tendency to occupy the equatorial position.[19]

Our data show that the *cis*-4-*t*-butylcyclohexyl–OAlCl$_2$ $\rightleftarrows$ *trans*-4-*t*-butylcyclohexyl–OAlCl$_2$ equilibrium is almost completely shifted to the right.

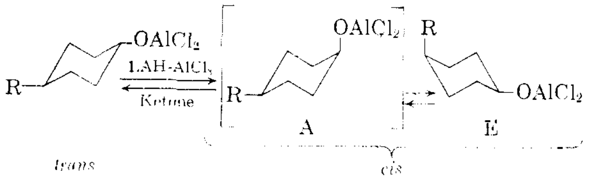

Fig. 2.—Equilibration of alkylcyclohexanol complexes.

In agreement with this is the observation that *cis*-4-*t*-butylcyclohexanol is equilibrated much more rapidly than the other two *cis*-4-alkylcyclohexanols with which we worked. Steric crowding of the –OAlCl$_2$ group in the axial position evidently makes the axial isomer quite unstable and, at the same time, produces a strong steric acceleration to isomerization. The energetic situation is depicted in Fig. 1.

The situation with the other alkylcyclohexanol complexes is more complicated because their alkyl substituents (unlike the 4-*t*-butyl group[9]) are not constrained to the equatorial position. The conformational situation is depicted in Fig. 2. The *trans* isomer is nearly exclusively in the equatorial–equatorial conformation. Upon equilibration, the –OAlCl$_2$ group is to some extent forced into the axial position, but the resulting A-form of the *cis* isomer (R–group equatorial, –OAlCl$_2$ axial) may undergo a facile ring inversion into the E-form of the *cis* isomer (R– group axial, –OAlCl$_2$ equatorial). The fact that in the case of 4-*t*-butylcyclohexanol the equilibrium of the complexes is over 99% on the side of the *trans* isomer means that the free energy required to place the –OAlCl$_2$ group in the axial position is over 3 kcal./mole. Therefore, for any moderate-sized R– group, the A form of the *cis* isomer makes only a very minor contribution and may, for all practical purposes, be neglected. Thus, thermodynamically speaking, the species in equilibrium are the (e,e) *trans* form and the E-form of the *cis* isomer. These, however, differ only in the fact that one has an equatorial R– group and the other an axial R– group, and the energetic difference between them should be equal to the energetic difference between equatorial and axial R. For the methyl group, the equilibrium corresponds to about 92 ± 1% *trans*; hence the equilibrium constant is (92 ± 1)/(8 ± 1) or 11.5 ± 1.5 and the free energy difference ΔF between equatorial and axial methyl at 35° is RT ln (11.5 ± 1.5) or 1.5 ± 0.1 kcal./mole.[19a] This value is in good agreement with a value previously derived from thermodynamic properties.[20,21] Similar calculation for phe-

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[15] An increase in rate in Meerwein–Ponndorf reduction by AlCl(O-*i*-Pr)$_2$ as compared to Al(O-*i*-Pr)$_3$ has been observed previously by G. Gal, G. Tokar and I. Simonyi, *Acta Chem. Acad. Sci. Hung.*, **7**, 421 (1955), and G. Gal and E. Krasznai, *ibid.*, **15**, 211 (1958); **16**, 369 (1958).

[16] We consider the agreement of this percentage with that of the amount of *trans* isomer in the kinetically controlled reduction product of 4-*t*-butylcyclohexanone with mixed hydride (Table I, entries 1–3) purely fortuitous. At first we thought that the product of runs 1–3, Table I, had been equilibrated, but an attempt to convert pure *trans*-alcohol I to an 80-20 mixture of I and II (Table II, run 16) failed completely.

[17] The figure for 4-phenylcyclohexanol was obtained by gas chromatographic analysis of an equilibrium mixture obtained in the course of another investigation (ref. 7) and supersedes the previous value (ref. 7) of "70 ± 5%" based on a very crude infrared analysis. (The 4-phenylcyclohexanols do not have intense distinctive infrared bands suitable for analysis.)

[18] Sodium or aluminum salts of the alcohols to be equilibrated will be present in only very small concentration, since they are in equilibrium with the free alcohols and the sodium (or aluminum) salts of isopropyl or *t*-butyl alcohol.

[19] The situation here resembles that in the isomerization of the xylenes in hydrogen fluoride solution by boron trifluoride. The elegant investigations by D. A. McCaulay and A. P. Lien, THIS JOURNAL, **74**, 6246 (1952), have shown that at low BF$_3$ to xylene ratio, an equilibrium mixture corresponding to the thermodynamic stability of the three xylenes is obtained; but at a 1:1 BF$_3$ to xylene ratio the equilibrium mixture corresponds to nearly pure *m*-xylene because this isomer forms by far the most stable HF–BF$_3$ complex.

[19a] ADDED IN PROOF (1/7/60).—Mr. T. Brett in our laboratory has found that the equilibrium of the 3-methylcyclohexanol complexes corresponds to 95.5% of *cis* (e,e) isomer, or a ΔF of 1.8 kcal/mole. The difference between the values for the 3- and 4-series probably is significant and will be discussed elsewhere.

[20] C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947). Professor Donald S. Noyce, University of California, Berkeley, has kindly informed us that he has obtained a very similar value for the methyl equilibrium by an entirely independent method.

[21] J. E. Kilpatrick, H. G. Werner, C. W. Beckett, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **39**, 523 (1947), report free energy differences between epimeric dimethylcyclohexanes (1,2; 1,3 and 1,4) of 1.49–1.61 kcal./mole, in good agreement with the value reported here. It is not clear, however, whether values found for the dimethylcyclohexane free energy differences should be expected to be the same for the free energy difference between equatorial and axial

nyl leads to an equilibrium constant of 98.5/1.5 or 65.7 and a free energy difference between equatorial and axial phenyl of *ca.* 2.6 kcal./mole. This would place phenyl in order of size somewhere between ethyl and isopropyl,[9] the smaller size of phenyl as compared to isopropyl presumably being due to the fact that an axial phenyl ring can turn its flat side toward the interfering axial hydrogens in the 3- and 5-position, whereas in the case of isopropyl, at the least the methine hydrogen atom must point in the direction of the axial ring hydrogens.

Whereas the ΔF value for methyl probably is reasonably accurate, the same cannot be claimed for phenyl, not only because it is experimentally very difficult to measure equilibria in the 99:1 range with any accuracy, but also since the phenyl group, because of its previously mentioned polar influence, may introduce disturbing factors into the theoretical considerations. However, as shown in Table III, the conclusion that phenyl is considerably larger than methyl (approaching, in size, *t*-butyl) is well supported by several different data.

TABLE III

PERCENTAGE OF *trans*-4-ALKYLCYCLOHEXANOL FORMED IN VARIOUS REACTIONS AND EQUILIBRATIONS

	4-*t*-Butyl	4-Phenyl	4-Methyl
Equilibrations of free alcohols	79	79	70
Equilibration of complexes	>99	98	92
Reduction with $LiAlH_4$	89	90	80
Reduction with $LiAlH_4$–$AlCl_3$	80	86	77

The method here outlined obviously lends itself to the indirect determination of conformational free energy differences by an equilibrium method for groups which, unlike hydroxyl[7] and carbethoxy,[22] cannot themselves be epimerized by chemical means. Further extensions of this method are under study in our laboratories.

The reduction of 4-*t*-butycyclohexanone (commercially available) with LAH–$AlCl_3$ followed by equilibration of the complex is by far the most convenient method of synthesizing *trans*-4-*t*-butylcyclohexanol and is described in detail in the Experimental. The only contaminant is some 4-*t*-butylcyclohexanone which can be removed readily by crystallization.

Experimental

Melting points and boiling points are uncorrected. Elementary analysis by Midwest Microlab, Indianapolis, Ind.

Ketones.—Commercial samples of 4-*t*-butylcyclohexanone and 4-methylcyclohexanone were purified before use: 4-*t*-butylcyclohexanone, m.p. 49.5–51.0° (from petroleum ether, b.p. 35–60°) (lit.[23] m.p. 49–50°); 4-methylcyclohexanone, b.p. 68–69° (25 mm.), $n^{20}D$ 1.4454 (lit.[24] b.p. 168°, 1.4448). 4-Phenylcyclohexanone was prepared according to the method of Ungnade,[25] m.p. 77–78° after one recrystallization from petroleum ether, b.p. 35–60° (lit.[25] m.p. 77–78°). Gas chromatography (*vide infra*) of the 4-alkylcyclohexanones showed them to be free of contaminating alcohols. Acetone was distilled from potassium permanganate, dried over anhydrous potassium carbonate and distilled from fresh carbonate.

General Reduction Procedures.—Reductions were carried out in a 500-ml. flask equipped with a Hershberg stirrer, reflux condenser and dropping funnel. The latter two were protected with calcium chloride drying tubes. Anhydrous aluminum chloride, sublimed reagent, was weighed out in a dry-box. Dissolutions of aluminum chloride in anhydrous ether and preparations of mixed hydrides were accomplished at ice-bath temperature. Additions of ketone to the mixed hydrides were carried out at room temperature. Reaction mixtures were hydrolyzed with water and dilute sulfuric acid. Last traces of solvent were removed from liquid samples by passing a gentle stream of dry nitrogen over the surface and from solid samples by applying 30-mm. vacuum in a desiccator. A few typical procedures are described in detail below.

Reduction of 4-*t*-Butylcyclohexanone. (a) **In the Presence of Excess Mixed Hydride.**—To a solution of 13.34 g. (0.1 mole) of anhydrous aluminum chloride in 100 ml. of anhydrous ether was added 23.3 ml. (0.0275 mole) of 1.18 *M* ethereal lithium aluminum hydride. After stirring the homogeneous solution for 0.5 hour, a solution of 15.4 g. (0.1 mole) of 4-*t*-butylcyclohexanone in 100 ml. of anhydrous ether was added dropwise over a period of one hour. The mixture was boiled for 2 hours, excess hydride destroyed with 20 ml. of water, and the precipitate formed dissolved in 45 ml. of 10% sulfuric acid. Extraction, drying over potassium carbonate and concentration gave 14.7 g. (94% yield) of 4-*t*-butylcyclohexanol. Infrared analysis (*vide infra*) showed the material to contain 81–82% *trans* and 18–19% *cis* isomer and ketone to be absent.

(b) **In the Presence of Excess 4-*t*-Butylcyclohexanone** (Table II, Run 10).—The mixed hydride was prepared as in (a) from 13.34 g. (0.1 mole) of aluminum chloride and 23.3 ml. (0.0275 mole) of 1.18 *M* ethereal lithium aluminum hydride. A solution of 18.4 g. (0.12 mole) of 4-*t*-butylcyclohexanone in 100 ml. of anhydrous ether was added over a period of 1 hour and the mixture refluxed for 2 hours. Addition of 17 ml. of water gave a precipitate which was dissolved in 50 ml. of 10% sulfuric acid. Extraction, drying over potassium carbonate and concentration gave 17.5 g. (94% yield) of crude product. Infrared analysis indicated the ratio of products to be 99–100% *trans* and 0–1% *cis*-4-*t*-butylcyclohexanol. In addition the sample contained an estimated 1–3% 4-*t*-butylcyclohexanone. A small sample was treated with Girard T reagent and analyzed by gas chromatography (*vide infra*). No *cis*-4-*t*-butylcyclohexanol could be detected. A sample of the ketone-contaminated product was recrystallized twice from petroleum ether, b.p. 35–60°, and sublimed to give pure *trans*-4-*t*-butylcyclohexanol, m.p. 82.5–83° (lit.[7] m.p. 81–82°).

(c) **In the Presence of Acetone—Split Run** (Tables I and II, Run 1).—The mixed hydride was prepared as in (a) from 13.34 g. (0.1 mole) of aluminum chloride and 23.3 ml. (0.0275 mole) of 1.18 *M* ethereal lithium aluminum hydride. A solution of 15.4 g. (0.1 mole) of 4-*t*-butylcyclohexanone in 100 ml. of ether was added and the mixture boiled two hours. A 5-ml. aliquot of the reaction mixture was removed and added to water and dilute sulfuric acid. Extraction, drying and concentration gave 0.15 g. of 4-*t*-butylcyclohexanol containing 81–83% *trans* and 17–19% *cis* isomers, with no ketone (infrared). To the bulk of the cloudy white reaction mixture was added 2.9 g. (0.05 mole) of acetone. After stirring 10 minutes, the clear yellow[26] mixture was hydrolyzed with 25 ml. of water and 50 ml. of 10% sulfuric acid. Extraction, drying and concentration gave 14.65 g. of crude product (95% over-all yield). Infrared and gas chromatographic analyses showed this material to contain *trans*- and *cis*-4-*t*-butylcyclohexanol in a 98-99 to 1-2 ratio, in addition to 3–5% 4-*t*-butylcyclohexanone. The ketone was further characterized by its 2,4-dinitrophenylhydrazone, m.p. 151.5–153.0°. The melting point was not depressed by admixture of an authentic sample of 4-*t*-butylcyclohexanone 2,4-dinitrophenylhydrazone, m.p. 152–153°. An analytical sample of the latter melted 151.5–152.5°.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.65; H, 6.84; N, 16.86.

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methylcyclohexane, in as much as the former differences are affected by contributions to the entropy of symmetry numbers and entropies of mixing; *cf.* ref. 20.

(22) E. L. Eliel and R. V. Acharya, unpublished.

(23) L. Schmerling, THIS JOURNAL, **69**, 1121 (1947).

(24) H. E. Ungnade and A. D. McLaren, *J. Org. Chem.*, **10**, 29 (1945).

(25) H. E. Ungnade, *ibid.*, **13**, 361 (1948).

(26) It was noted that in reductions of 4-*t*-butylcyclohexanone in which equilibration occurred the solutions became yellow after excess ketone was added. The color disappeared completely upon hydrolysis.

Runs 2, 3, 4, Tables I and II, were carried out in a similar manner except that the amount of aluminum chloride was varied. An identical experiment was performed (Table II, run 13) in which methyl acetate was used in place of acetone. The composition of the 4-*t*-butylcyclohexanol was 82–83% *trans*, 17–18% *cis*, both before and after the excess methyl acetate was added. It was noted in the preparation of mixed hydrides that copious precipitates were formed when the ratio chloride to hydride was 3:1, 1:1 and 1:3, whereas when the ratio was 4:1 an essentially homogeneous solution resulted. Such a reagent may be used conveniently in an inverse addition as described below.

(d) **Inverse Addition** (Table II, Run 12).—The mixed hydride was prepared in the usual manner from 13.34 g. (0.1 mole) of aluminum chloride and 23.3 ml. (0.0275 mole) of 1.18 *M* ethereal lithium aluminum hydride. The hydride containing a small amount of granular precipitate was transferred to a dropping funnel of another apparatus using dry nitrogen pressure. The mixed hydride was added dropwise to a solution of 12.3 g. (0.08 mole) of 4-*t*-butylcyclohexanone in 100 ml. of anhydrous ether over a period of one hour. The mixture was boiled two hours, hydrolyzed with water, extracted and dried. Concentration gave 12.45 g. (99% yield) of 4-*t*-butylcyclohexanol containing 95–96% *trans* and 4-5% *cis* isomers. Ketone was absent (infrared and gas chromatography).

Equilibrations of 4-Alkylcyclohexanols. (a) **4-*t*-Butylcyclohexanol** (Table II, Run 14).—To mixed hydride, prepared from 3.99 g. (0.03 mole) of aluminum chloride and 7 ml. (0.00825 mole) of 1.18 *M* ethereal lithium aluminum hydride, was added a solution of 4.68 g. (0.03 mole) of 4-*t*-butylcyclohexanol (82–83% *trans*) in 30 ml. of anhydrous ether. After boiling two hours, 0.87 g. (0.015 mole) of acetone was added and stirred 10 minutes. The yellow solution was hydrolyzed with 10 ml. of water and 35 ml. of 10% sulfuric acid. Extraction, drying and concentration gave 4.49 g. (96% yield) of crude product. Infrared and gas chromatographic analysis indicated the material to contain 96–97% *trans* and 3-4% *cis* 4-*t*-butylcyclohexanol. In addition, the sample contained *ca.* 1% 4-*t*-butylcyclohexanone, identified as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 151–153°.

(b) **4-Methylcyclohexanol** (Table II, Run 17).—The mixed hydride was prepared from 22.0 g. (0.165 mole) of aluminum chloride and 38 ml. (0.041 mole) of 1.1 *M* ethereal lithium aluminum hydride. A solution of 16.8 g. (0.15 mole) of 4-methylcyclohexanone in 100 ml. of anhydrous ether was added and the mixture refluxed two hours. A 25-ml. aliquot was removed and hydrolyzed with water and 10% sulfuric acid. Isolation of the product in the usual manner gave an oil which contained 77% *trans*- and 23% *cis*-4-methylcyclohexanol by gas chromatography (*vide infra*). A solution of 3.36 g. of 4-methylcyclohexanone in 50 ml. of anhydrous ether was added and aliquots removed at 15-minute intervals and worked up in the usual manner. The bulk of the solution was worked up after 90 minutes. Analysis of the latter sample showed it to contain *trans*- and *cis*-4-methylcyclohexanol in an 88:12 ratio in addition to 13% 4-methylcyclohexanone. This sample was again allowed to react with mixed hydride in the presence of ketone. Analysis of samples removed after 285 and 360 minutes gave identical analyses of 91% *trans*- and 9% *cis*-4-methylcyclohexanol containing 18% 4-methylcyclohexanone (92% over-all return). Attempts to bring about a similar equilibration with acetone were unsuccessful and gave highly colored viscous liquids.

(c) ***trans*-4-Methylcyclohexanol** (Table II, Run 18).—Pure *trans*-4-methylcyclohexanol[27] was equilibrated as in the previous experiment, *i.e.*, by a double equilibration procedure, over a total period of 810 minutes. Analysis of the final two aliquots removed indicated the material contained 92.5–93.2% *trans*- and 6.8-7.5% *cis*-4-methylcyclohexanol in the presence of 26% 4-methylcyclohexanone (87% over-all return).

(d) **4-Phenylcyclohexanol** (Table II, Run 19).—The mixed hydride was prepared from 4.37 g. (0.0328 mole) of aluminum chloride and 7.8 ml. (0.0082 mole) of 1.05 *M* ethereal lithium aluminum hydride. A solution of 4.6 g. (0.0262 mole) of 4-phenylcyclohexanol (79% *trans*) in 100 ml. of anhydrous ether was added. After completion of the addition, 1.2 g. (0.0068 mole) of 4-phenylcyclohexanone in 35 ml. of ether was added. Aliquots were removed and worked up as usual and analyzed by gas chromatography (*vide infra*) (87% over-all return). The final sample (490 minutes reaction time) was allowed to react with Girard T reagent and the ketone-free product isolated in the usual way. Gas chromatographic analysis indicated the sample contained 97.7–98.1% *trans*- and 1.9–2.3% *cis*-4-phenylcyclohexanol.

(e) ***trans*-4-Phenylcyclohexanol** (Table II, Run 20).—Pure *trans*-4-phenylcyclohexanol[7] was equilibrated over a period of 450 minutes as in (d) above. Analysis by gas chromatography (after removal of ketone with Girard T reagent) of samples removed after 140 and 450 minutes gave identical analyses, *i.e.*, 99.1–99.2% *trans*- and 0.8–0.9% *cis*-4-phenylcyclohexanol (80% over-all return).

(f) **4-t-Butylcyclohexanol with Aluminum Chloride** (Table II, Run 15).—An attempt to equilibrate a sample containing 81–82% *trans*- and 18–19% *cis*-4-*t*-butylcyclohexanol in the presence of the parent ketone with ethereal aluminum chloride was unsuccessful.

Analyses of Products.—Infrared spectra were recorded on a Baird model 4–55 instrument. Quantitative infrared analysis of mixtures of *cis*- and *trans*-4-*t*-butylcyclohexanols was made by a comparison of the ratio of the intensities of the bands (at 10.20 μ for *trans*/9.90 μ for *cis* and at 10.20 μ for *trans*/10.51 μ for *cis*) with intensities of bands in calibration spectra. Gas chromatographic analysis was carried out as previously described.[2] Analyses of mixtures of *cis*- and *trans*-4-methylcyclohexanols in the presence of the parent ketone were carried out on a glycerol column.[28] A Tide detergent column was used for the analysis of *cis* and *trans* isomers of 4-*t*-butylcyclohexanol[5] and 4-phenylcyclohexanol. Analysis of mixtures of the former containing less than 4% *cis* isomer and mixtures of the latter containing less than 10% *cis* isomer were found to be more accurate after previous removal of any contaminating ketone if it were present.

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[27] Prepared according to the method of E. L. Eliel and C. A. Lukach, THIS JOURNAL, **79**, 5986 (1957).

[28] R. Komers, K. Kochloefl and V. Bazant, *Chemistry & Industry*, 1465 (1958).