

## Conformational Analysis. IX.<sup>1a</sup> Equilibrations with Raney Nickel. The Conformational Energy of the Hydroxyl Group as a Function of Solvent

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The catalytic epimerization of the 4-*t*-butylcyclohexanols, 3,5-dimethylcyclohexanols, and 3,3,5-trimethylcyclohexanols with Raney nickel has been studied as a function of solvent. Equilibration data for the first two alcohols lead to a conformational free energy of hydroxyl (energy difference between axial and equatorial OH) of  $0.90 \pm 0.05$  kcal./mole in hydroxylic solvents (isopropyl or *t*-butyl alcohol) in complete agreement with the value previously found by aluminum alkoxide equilibration. In aprotic solvents (cyclohexane, benzene, toluene, tetrahydrofuran, 1,2-dimethoxyethane) the corresponding value is smaller (0.6–0.7 kcal./mole) in accordance with theoretical prediction. The equilibrium constant for aluminum alkoxides in tetrahydrofuran is similar to that for the free alcohols in isopropyl alcohol. Equilibration of the epimeric 3,3,5-trimethylcyclohexanols confirms the value of 2.4 kcal./mole previously established for the CH<sub>3</sub>–OH syn-axial interaction. Epimerization (attended by dehydrogenation) of 3,5-dimethylcyclohexanol equilibrates all three diastereoisomeric alcohols and the two diastereoisomeric ketones and allows calculation of a conformational energy value of 1.96 kcal./mole for methyl and of a “3-alkylketone effect” of about 0.5 kcal./mole.

Conformational equilibria of the type shown in Figure 1 have been the subject of intensive study in the past 10 years.<sup>2–4</sup> Of the various methods employed to determine them (kinetic,<sup>5</sup> equilibrium, and spectroscopic, especially n.m.r.<sup>6</sup>) the equilibrium method is the most straightforward. In this method the conformational equilibrium shown in Figure 1 (which is so rapidly established as not to lend itself to direct chemical study) is replaced by a configurational equilibrium in a “biased”<sup>5</sup> system of the type shown in Figure 2. Provided this equilibrium can be established chemically and assuming<sup>7</sup> that the equilibrium constant is the same

as that in Figure 1, this constant ( $K_X$ ) can then be evaluated in the 4-*t*-butyl system by classical methods, such as g.l.p.c. analysis, and the conformational free energy is calculated as  $-\Delta G^\circ_X = RT \ln K_X$ .

The conformational free energies of some 40 atoms or groups have been listed.<sup>2–4</sup> In most instances, values for one and the same group obtained by different (often quite different) methods are reasonably constant, say within  $\pm 0.2$  kcal. mole. A disturbing exception from this generally satisfactory state of affairs is found in the case of the hydroxyl group where experimental conformational free energies range from a low of 0.29 to a high of 1.25 kcal./mole. Table I contains a summary of the about 30 values found in the literature, along with conditions of temperature and solvent, method used, and citation. This paper is concerned with resolving the chaotic situation implied in Table I.

The first five determinations of  $-\Delta G^\circ_{OH}$  comprise a kinetic value in aqueous acetic acid<sup>8</sup> of 0.8 kcal./mole, an equilibrium value of 0.96 kcal./mole in isopropyl alcohol,<sup>9</sup> a kinetic value of 0.55 kcal./mole in pyridine,<sup>10</sup> an equilibrium value of 0.9 kcal./mole in water,<sup>11</sup> and a spectroscopic value of 0.4 kcal./mole in carbon disulfide.<sup>12</sup> On the basis of this information it was suggested in 1960<sup>5</sup> that the conformational equilibrium of hydroxyl was a function of solvent, being in the vicinity of 0.4–0.6 kcal./mole in an aprotic solvent and about 0.8–1.0 kcal./mole in a hydrogen-donating solvent. This suggestion seemed intuitively reasonable, since an equatorial hydroxyl should be more exposed to hydrogen bonding by solvent than an axial one and hydrogen bonding should thus confer additional stability on the equatorial conformation.

This explanation of the range of  $-\Delta G^\circ_{OH}$  subsequently was disputed<sup>13–17</sup> on the following grounds.

(7) Regarding this assumption, cf. ref. 4 and forthcoming paper by E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J.-C. Richer.

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(16) G. Chiurdoglu and W. Masschelein, *ibid.*, **70**, 767 (1961).

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(1) (a) Presented at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965. For part VIII see E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961); (b) the Radiation Laboratory is operated under contract with the Atomic Energy Commission. This is AEC Document No. COO-38-427.

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, “Conformational Analysis,” Interscience Publishers, Inc., New York, N. Y., 1965.

(3) M. Hanack, “Conformation Theory,” Academic Press Inc., New York, N. Y., 1964.

(4) E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965).

(5) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

(6) H. Feltkamp and N. L. Franklin, *Angew. Chem.*, **77**, 798 (1965).

Table I

Entry no.	$-\Delta G^{\circ}_{OH}$	Method	Temp., °C.	Solvent	Ref.
1	0.29-0.37	Infrared	?	CH <sub>2</sub> Cl <sub>2</sub> , CHCl <sub>3</sub> , CCl <sub>4</sub> , CS <sub>2</sub> , Br(CH <sub>2</sub> ) <sub>2</sub> Br, (CH <sub>3</sub> ) <sub>2</sub> CO, xylene, toluene, C <sub>6</sub> H <sub>6</sub> , <i>n</i> -hexane	<i>a</i>
2	0.31-0.41	Infrared	?	Pure liquid	<i>b</i>
3	0.33	Thermochem.	25	H <sub>2</sub> O (pH 5.5)	<i>c</i>
4	0.33-0.35	Infrared	Reflux	CHCl <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , CS <sub>2</sub> , CCl <sub>4</sub> , (CH <sub>3</sub> ) <sub>2</sub> CO	<i>d</i>
5	0.33-0.37	Infrared	?	Xylene, toluene, C <sub>6</sub> H <sub>6</sub> , <i>n</i> -hexane	<i>a</i>
6	0.36-0.41	Infrared	?	Pure liquid, CH <sub>2</sub> Cl <sub>2</sub> , CHCl <sub>3</sub> , CCl <sub>4</sub> , Br(CH <sub>2</sub> ) <sub>2</sub> Br, CS <sub>2</sub> , (CH <sub>3</sub> ) <sub>2</sub> CO	<i>a</i>
7	0.376	Infrared	-30 to +50(?)	Pure liquid	<i>e</i>
8	0.4	Infrared	20	CS <sub>2</sub>	<i>f</i>
9	0.41	Equilib.	110-170	C <sub>6</sub> H <sub>12</sub>	<i>g</i>
10	0.43 ± 0.17	N.m.r.	20	CCl <sub>4</sub>	<i>h</i>
11	0.47 ± 0.04	Equilib.	110-170	C <sub>6</sub> H <sub>12</sub>	<i>g</i>
12	0.52 ± 0.04	Equilib.	90	Abs. EtOH	<i>g</i>
13	0.52-0.56	Kinetic	25	C <sub>6</sub> H <sub>5</sub> N	<i>i</i>
14	0.6	N.m.r.	Reflux	Ca. 10% CCl <sub>4</sub>	<i>j</i>
15	0.65	N.m.r.	26	CS <sub>2</sub>	<i>k</i>
16	0.64-0.66	Raman	30-68	Pure liquid	<i>l</i>
17	0.73 ± 0.02	N.m.r.	30	CCl <sub>4</sub>	<i>m</i>
18	0.75	N.m.r.	40	CCl <sub>4</sub>	<i>n</i>
19	0.8	N.m.r.	40	C <sub>6</sub> H <sub>5</sub> N, CH <sub>3</sub> SOCH <sub>3</sub>	<i>n</i>
20	0.8	Kinetic	40	75% HOAc	<i>o</i>
21	0.825	N.m.r.	36	CCl <sub>4</sub>	<i>p</i>
22	0.835	N.m.r.	36	C <sub>6</sub> H <sub>5</sub> N	<i>p</i>
23	0.840	N.m.r.	36	Isooctane	<i>p</i>
24	0.88 ± 0.02	N.m.r.	30	2-D-2-PrOH	<i>m</i>
25	0.9	Equilib.	22	H <sub>2</sub> O	<i>q</i>
26	0.96	Equilib.	89	<i>i</i> -PrOH	<i>r</i>
27	0.975	N.m.r.	36	C <sub>6</sub> H <sub>5</sub> Br	<i>p</i>
28	0.98-1.12	Equilib.	Reflux	C <sub>6</sub> H <sub>6</sub> , toluene, xylene	<i>g</i>
29	1.0	Equilib.	89	<i>i</i> -PrOH	<i>g</i>
30	1.0	N.m.r.	28	CCl <sub>4</sub>	<i>s</i>
31	1.05	N.m.r.	36	<i>t</i> -BuOH	<i>p</i>
32	1.07	N.m.r.	?	10% CCl <sub>4</sub>	<i>t</i>
33	1.25	N.m.r.	28	D <sub>2</sub> O	<i>s</i>

<sup>a</sup> Reference 14. <sup>b</sup> Reference 13. <sup>c</sup> M. A. Kabayama and D. Patterson, *Can. J. Chem.*, **36**, 563 (1958); M. A. Kabayama, D. Patterson, and L. Piche, *ibid.*, **36**, 557 (1958). <sup>d</sup> Reference 15. <sup>e</sup> W. Masschelein, *J. Mol. Spectry.*, **10**, 161 (1963). <sup>f</sup> Reference 12. <sup>g</sup> Reference 16. <sup>h</sup> H. Booth, *Tetrahedron*, **20**, 2211 (1964). <sup>i</sup> Reference 10, 20. <sup>j</sup> Reference 21. <sup>k</sup> W. C. Neikam and B. P. Dailey, *J. Chem. Phys.*, **38**, 445 (1963). <sup>l</sup> P. Neelakantan, *Proc. Indian Acad. Sci.*, **A57**, 94 (1963). <sup>m</sup> Reference 19. <sup>n</sup> R. J. Ouellette, *J. Am. Chem. Soc.*, **86**, 4378 (1964). <sup>o</sup> Reference 8. <sup>p</sup> Reference 28. <sup>q</sup> Reference 11. <sup>r</sup> Reference 9. <sup>s</sup> F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962). <sup>t</sup> E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).

(1) Infrared determination, even in a hydrogen donor solvent such as chloroform, gave consistent values in the lower range.<sup>12-15</sup> (2) Equilibration by means of Raney nickel<sup>18</sup> gave virtually the same low value (in the vicinity of 0.5 kcal./mole) in both cyclohexane and ethanol.<sup>16</sup> (3) Suspicion was thrown on the often-used aluminum isopropoxide-isopropyl alcohol-acetone (Meerwein-Ponndorf-Verley-Oppenauer or MPVO) method of equilibration by the contention

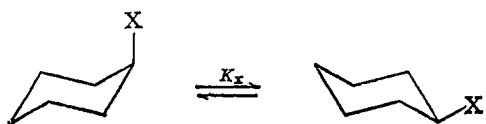


Figure 1.

that in this method the material equilibrated might not all be present as the free alcohols ROH (*cis* or

sodium isopropoxide-fluorenone in isopropyl alcohol at 180° gave a mixture containing 71.2% *trans* isomer (from *trans*) or 72.3% *trans* isomer (from *cis*) corresponding to  $-\Delta G^{\circ} = 0.83-0.87$  kcal./mole.

(18) Method of G. Darzens and M. Meyer, *Compt. rend.*, **273**, 1712 (1953), first applied to cyclohexanol epimerization by E. G. Peppiatt and R. J. Wicker, *J. Chem. Soc.*, 3122 (1955).

*trans*) but that some of it might be present as alkoxides, ROAl(*i*-PrO)<sub>2</sub>, for which the equilibrium constant might be quite different from that for the free alcohols

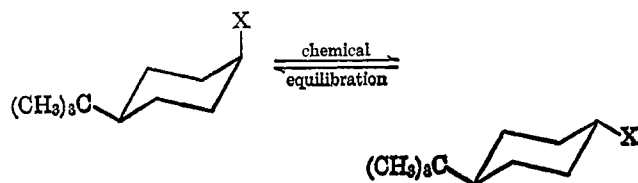


Figure 2.

(probably more in favor of the equatorial complex). This contention was backed up by some experiments on the equilibration of potassium alcoholates derived from *cis*- and *trans*-4-*t*-butylcyclohexanol<sup>17</sup>; in this case position of equilibrium did, indeed, vary with the amount of metal used, from a high of 93% to a low of 75% of *trans* isomer. However, no experiments involving aluminum alkoxides were presented.

It appeared to us that either one should be able to demonstrate dependence of the aluminum-alkoxide induced equilibrium on the concentration of aluminum

alkoxide, or else the equilibrium induced by Raney nickel should be equivalent to that induced by alkoxide at comparable temperatures in the same solvents. The investigations detailed below indicate that the second alternative is the correct one.

The results of a number of Raney nickel catalyzed equilibrations of 4-*t*-butylcyclohexanol as found in the present investigation are summarized in Table II.

**Table II.** Raney Nickel Catalyzed Equilibrations of 4-*t*-Butylcyclohexanol

Entry no.	Solvent	Temp., °C.	<i>trans</i> isomer at equil., %	$-\Delta G^\circ$ , kcal./mole
1	Cyclohexane	80	70.0	0.60 ± 0.03
2	Cyclohexane	150	70.2	0.72
3	Benzene	80	72.5	0.69 ± 0.03
4	Toluene	110	70.5	0.67 ± 0.04
5	1,2-Dimethoxyethane	80	71.0	0.63 ± 0.03
6	Tetrahydrofuran	56	72.5	0.69
7	<i>t</i> -Butyl alcohol	82	77.5	0.88 ± 0.03
8	<i>t</i> -Butyl alcohol	150	74.0	0.88
9	Isopropyl alcohol	82	79.0	0.94 ± 0.03
10	Isopropyl alcohol <sup>a</sup>	82	78.6 <sup>a</sup>	0.93 ± 0.03
11	<i>t</i> -Butyl alcohol-benzene 1:0.25	75	77.4	0.86
12	1:1	75	76.8	0.83
13	1:1.5	75	76.3	0.81
14	1:4	75	75.2	0.77
15	1:6	75	74.0	0.73

<sup>a</sup> Meerwein-Ponndorf-Oppenauer equilibration with aluminum isopropoxide catalyst. Previous values: 79 ± 2% (ref. 9); 77.4-81.1% (ref. 16), and 79.5 ± 0.5% (ref. 24).

Comparison of entries 9 and 10 immediately indicates that there is no difference between Raney nickel and aluminum isopropoxide catalyzed epimerization; moreover, entries 7-10 suggest a value of 0.88-0.94 (recorded as 0.90 ± 0.05) kcal./mole for the conformational energy of hydroxyl in the hydrogen-donor solvents isopropyl and *t*-butyl alcohol. In contrast, significantly lower values for  $-\Delta G^\circ_{\text{OH}}$  are found in the aprotic solvents cyclohexane, benzene, toluene, 1,2-dimethoxyethane, and tetrahydrofuran (entries 1-6 in Table II); values range from 0.60 to 0.72 and are recorded as 0.6-0.7 kcal./mole, disregarding the small and marginally significant differences between individual solvents in this group. It might be noted that the value of 0.90 ± 0.05 kcal./mole in hydrogen-donor solvents is in fair agreement with the value of 0.8 kcal./mole obtained in aqueous acetic acid by a kinetic method,<sup>8</sup> the value of 0.88 ± 0.02 kcal./mole in isopropyl alcohol-2-*d* by n.m.r.<sup>19</sup> and the equilibrium value of 0.9 kcal./mole in water.<sup>11</sup> Similarly, the range of 0.6-0.7 kcal./mole in aprotic solvents agrees reasonably with the kinetic value of 0.52 kcal./mole<sup>10</sup> (recently slightly revised upward to<sup>20</sup> 0.56 kcal./mole) and n.m.r. values of 0.6 kcal./mole<sup>21</sup> and 0.73 ± 0.02 kcal./mole<sup>19</sup> in carbon tetrachloride.

One may compare the above experimental values with values calculated on the basis that the only difference between axial and equatorial hydroxyl is in the entropy of mixing of the various accessible rotational

conformations of the OH group and that the axial group is constrained to two staggered rotational conformations (the third one, with the hydrogen pointing toward the ring, being excluded<sup>21a</sup>) whereas the equatorial group has three rotational conformations (all staggered). With that (probably oversimplified) premise, the calculated entropy difference between equatorial and axial unbonded OH is  $R \ln 3 - R \ln 2$  or 0.81 cal./deg. mole and the resulting free-energy difference at 353°K. is 0.29 kcal./mole. For hydrogen-bonded OH, assuming that in the axial case only bonding from the outside of the ring is possible, the corresponding entropy difference will be  $R \ln 6 - R \ln 2$  or 2.20 cal./deg. mole, for whereas the axial hydroxyl will still have only two (mirror-image) populated conformations, the equatorial hydroxyl will now have six (three pairs of mirror images), as may be readily seen in Dreiding models. The calculated free-energy difference is thus 0.78 kcal./mole at 353°K. The calculated values do not agree exactly with the experimental, in part no doubt because enthalpy differences (e.g., due to steric repulsion of axial oxygen) have been disregarded. However, they do show the proper trend and order of magnitude and, if one were to assume a  $\Delta H$  of 0.25 kcal./mole in favor of the equatorial isomer, the calculated  $\Delta G$  values would then become 0.54 kcal./mole for unbonded and 1.03 kcal./mole for bonded OH, both within about 0.1 kcal. of the observed values (although, unfortunately, deviating from these values in opposite directions). To say the least, the calculation suggests that the observed difference between bonded and unbonded hydroxyl is of the right order of magnitude and that the observed conformational energies for both appear to be reasonable.

The question now arises as to why previous values in the literature (Table I) are so discrepant, and, in particular, why the previous criticism<sup>13-17</sup> of our earlier contention<sup>5</sup> that some of the observed spread is due to hydrogen bonding (a contention which now turns out to be correct) is invalid. Examination of the data in Table I reveals that virtually all the very low values for  $-\Delta G^\circ_{\text{OH}}$  (seven of the first eight entries<sup>22</sup>) were derived from infrared measurements. These measurements involve the relative intensity of equatorial and axial C-O stretching bands in cyclohexanol, either as a function of temperature or in relation to the intensity of analogous bands in rigid models (4-*t*-butylcyclohexanols).<sup>23</sup> It has already been pointed out elsewhere,<sup>24</sup> however, that the C-O stretching bands in cyclohexanol are not well defined and that the bands used in infrared measurements may have contributions from skeletal vibrations which probably render the results from intensity measurements spurious.

The previously reported<sup>16</sup> equilibration data with Raney nickel (entries 9 and 12 in Table I) are appreciably lower than the values found in the present investigation. In the present work, equilibrium was ap-

(21a) NOTE ADDED IN PROOF. Cf. H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, **85**, 3046 (1963).

(22) The remaining entry refers to a determination in a relatively complex system (sugar); the value obtained may not apply to a simple cyclohexanol.

(23) For details of these methods, cf. ref. 2, pp. 142-149.

(24) A. H. Lewin, Ph.D. Dissertation, University of California at Los Angeles, 1963; W. Hüchel and Y. Riad, *Ann.*, **637**, 33 (1960); see also E. L. Eliel, C. C. Price, R. J. Convery, and T. J. Prosser, *Spectrochim. Acta*, **10**, 423 (1958).

(19) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

(20) F. J. Biros, Ph.D. Dissertation, University of Notre Dame, 1964.

(21) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

**Table III.** Reduction of Alkylcyclohexanones with Raney Nickel in Methanol, Ethanol, and 2-Propanol

Cyclohexanone	Axial isomer formed, %	Solvent	Results of catalytic hydrogenation (from lit.)
4- <i>t</i> -Butyl	78 ( <i>cis</i> )	EtOH	78 <sup>a</sup>
	78 ( <i>cis</i> )	MeOH	
3-Methyl	64 ( <i>trans</i> )	EtOH	73, <sup>b</sup> 70, <sup>a</sup> 66, <sup>c</sup> 62 <sup>d</sup>
4-Methyl	63 ( <i>cis</i> )	EtOH	80, <sup>b</sup> 53 <sup>a</sup>
	58 ( <i>cis</i> )	<i>i</i> -PrOH	
2-Methyl	60 ( <i>cis</i> )	EtOH	93 <sup>c</sup>
3,3,5-Trimethyl	96.5 ( <i>trans</i> )	EtOH	83 <sup>b</sup>

<sup>a</sup> Reference 10. <sup>b</sup> R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).  
<sup>c</sup> W. Hüchel, M. Maier, E. Jordan, and W. Seeger, *Ann.*, 616, 46 (1958). <sup>d</sup> W. Hüchel and J. Kurz, *Chem. Ber.*, 91, 1290 (1958).

**Table IV.** Equilibration of 4-*t*-Butylcyclohexanol (B) and Its Aluminum Alkoxide<sup>a</sup>

Entry no.	Solvent	Volume, ml.	Temp., °C.	Wt. of B, g.	Wt. of Al(O- <i>i</i> -Pr) <sub>3</sub>	<i>trans</i> isomer found, %
1	2-Propanol	80-100	82	1.0	2.5	78.6, 78.8
2	2-Propanol	100	82	1.0	20	79.0
3	2-Propanol plus Benzene	(20) (60)	Reflux	1.0	4.0	77.6, 77.9
4	Tetrahydrofuran	75	66	1.2	3.0	78.6, 78.6
5	Tetrahydrofuran	100 <sup>b</sup>	66	1.5	5.0	81.7, 82.0
6	Benzene	80 <sup>b</sup>	80	1.5	5.0	80.3, 80.6
7	Toluene	80 <sup>c</sup>	110	1.0	3.0	78.3, 79.4

<sup>a</sup> Equilibrium reached from both sides in all cases. <sup>b</sup> After prior azeotropic distillation with benzene. <sup>c</sup> After prior azeotropic distillation with toluene.

proached from both sides, analysis was effected by gas-liquid partition chromatography (g.l.p.c.) on several different instruments using pure *cis*- and *trans*-4-*t*-butylcyclohexanol to check response ratios, and the data were found to be highly reproducible (composition within a 1% range in numerous runs) so that the possibility of error is quite remote. The most likely difficulty with the earlier work<sup>16</sup> lies in the analysis, effected by infrared spectroscopy. This is probably less accurate than gas chromatography, especially since Raney nickel equilibrated samples of epimeric alcohols generally contain the corresponding ketone as a third component (often in quite large amount). Ketone would tend to cause more difficulty in infrared than in gas chromatographic analysis (where a stationary phase, Carbowax 20M, was used which resolved both alcohols and the ketone satisfactorily).

A much less likely possibility is that equilibrium was not, in fact, reached in the earlier work. In this connection it is of interest that, in our hands, equilibrations in methanol, ethanol, or isopropyl alcohol proceeded quite sluggishly. In fact, treatment of ketone with Raney nickel in these solvents permitted isolation of alcohol mixtures rich in the (less stable) axial isomer (Table III), no doubt the product of a kinetically controlled hydrogen transfer from the solvent to the alkylcyclohexanone *via* the Raney nickel surface. Equilibration in isopropyl alcohol (Table II, entries 9 and 10) could be effected only with a large excess of Raney nickel. However, since equilibrium was approached from both sides in the earlier work,<sup>16</sup> lack of thermodynamic control was probably not the problem encountered. Our results with Raney nickel under

hydrogen pressure at 150° (conditions similar to those used earlier<sup>16</sup>) led to equilibrium compositions (Table II, entries 2, 8; also Table VI, entry 2) quite different from those reported<sup>16</sup> and in good agreement, as far as  $\Delta G^\circ$  is concerned, with those established at lower temperatures.

It should be mentioned here that the equilibrium composition of the *trans*-2-decalols over Raney nickel in cyclohexane at 180° corresponding to 68% of the equatorial or  $\alpha$  isomer,<sup>25</sup> while superficially resembling Chiurdoglu's result<sup>16</sup> with 4-*t*-butylcyclohexanol (66% *trans* isomer at 110° in cyclohexane) in fact, because of the difference in temperature, supports the results reported in the present work, the  $-\Delta G^\circ$  value calculated from the decalol result being 0.68 kcal./mole.

We must now discuss the possibility raised<sup>17</sup> that aluminum alkoxide catalyzed equilibrations reflect

not the equilibrium of the free alcohols but, at least in part, that of the derived aluminum alkoxides. *A priori*, this contention might receive some credence from the finding<sup>26</sup> that the equilibrium of epimeric ROAlCl<sub>2</sub> complexes in ether is far different and much more on the side of the equatorial alcohol than the equilibrium of the corresponding free alcohols ROH. To dispel this particular objection, one must show either that the position of equilibrium in isopropyl alcohol is independent of the ratio of added Al(O-*i*-Pr)<sub>3</sub> catalyst to ROH to be epimerized or else that the position of equilibrium for (RO)<sub>3</sub>Al is not greatly different from that for ROH. The former point was, in fact, demonstrated by showing (Table IV, entries 1 and 2) that increasing aluminum isopropoxide concentration eightfold does not affect the position of equilibrium. That the equilibrium for the complex is close to that for the free alcohol in isopropyl alcohol was also shown by mixing 4-*t*-butylcyclohexanol with excess aluminum isopropoxide in benzene or toluene, removing the isopropyl alcohol formed by azeotropic distillation, and then carrying out equilibration of the complex. The results are shown in Table IV (entries 3-7) and should be compared with the normal MPVO equilibration in isopropyl alcohol (entries 1, 2).

It is clear that the epimerization of the aluminum 4-*t*-butylcyclohexyl oxide in tetrahydrofuran, benzene, or toluene leads to nearly the same position of equilibrium as the epimerization of 4-*t*-butylcyclohexanol in the presence of aluminum alkoxide in isopropyl al-

(25) W. Hüchel and D. Rücker, *Ann.*, 666, 30 (1963).

(26) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, 82, 1367 (1960); E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, 30, 3809 (1965).

cohol, although the equilibrium in tetrahydrofuran, benzene, or toluene is appreciably shifted toward the *trans* side in comparison to the equilibrium of the free alcohols in the same solvents (Table II). The data can be interpreted in only one of two ways: either (a) the equilibrium position found and recorded in Table IV ( $80 \pm 2\%$  *trans*) represents, in all cases, exclusively the equilibrium of the alkoxide,  $(RO)_3Al$ , where  $R = 4-t$ -butylcyclohexyl, or (b) the equilibrium position of the alkoxide in benzene, toluene, and tetrahydrofuran is virtually the same as that of the (mainly) free alcohol in isopropyl alcohol. We consider the former alternative (a) most unlikely (since it requires *all* the *4-t*-butylcyclohexanol to exist as aluminum alkoxide in the presence of a large excess of isopropyl alcohol) and are therefore forced to the latter (b) which, in turn, implies that even *if* the equilibration in isopropyl alcohol involves the alkoxide to a small extent, the position of equilibrium would not be greatly affected thereby. This is, of course, in accord with the data of Table IV, entries 1 and 2.

It is surprising that the position of the  $(RO)_3Al$  equilibrium in tetrahydrofuran (82:18) is so different from that<sup>26</sup> of the  $ROAlCl_2$  complex in ether which corresponds to 99.5% *trans* isomer. Possibly the difference arises from a much higher degree of solvation of  $ROAlCl_2$  as compared to  $(RO)_3Al$ , solvation being responsible for the larger bulk of  $OAlCl_2$  (which therefore shuns the axial position).

Since hydrogen bonding to the oxygen of the hydroxyl group increases its conformational energy, one must inquire whether the value of 0.6–0.7 kcal./mole measured in aprotic solvents is not already affected by intermolecular hydrogen bonding between solute molecules. The solutions studied were initially 2% or *ca.* 0.13 *M*; by the time equilibrium was reached the concentration of alcohol was no doubt appreciably less because of conversion of some of the material to ketone.<sup>27</sup> Nevertheless, intermolecular hydrogen bonding even in 0.1 *M* solution of alcohols is appreciable and the possibility exists that the  $-\Delta G^\circ$  values in aprotic solvents (Table II, entries 1–5) are already affected by such bonding and that the true value for *free* hydroxyl would be lower. Certainly, however, association is far from complete; the addition of *t*-butyl alcohol to a solution of *t*-butylcyclohexanol in benzene (Table II, entries 10–14) leads to a notable increase in  $-\Delta G^\circ$ , presumably by enhancing hydrogen bonding. The fact that  $-G^\circ_{OH}$  is the same in hydrogen-acceptor solvents (dimethoxyethane, THF) as in nonacceptors (benzene, cyclohexane) also speaks against any residual effect of association, since the oxygenated solvents should supplant the cyclohexanol molecules as hydrogen acceptors.

Among the higher  $-\Delta G^\circ$  values for hydroxyl listed in Table I, there are several values determined by n.m.r. spectroscopy in aprotic solvents. These data as well as n.m.r. values in protic solvents are summarized in Table V. The values are derived from carbinol proton positions unless otherwise indicated.

(27) Hydrogen bonding to the ketone is unimportant since it would involve the cyclohexanol only as a hydrogen donor, not as an acceptor. The existing data (*e.g.*,  $-\Delta G^\circ_{OH}$  in pyridine) suggest that in hydrogen-acceptor solvents (if not, at the same time, also hydrogen donors)  $\Delta G^\circ_{OH}$  is the same as in other aprotic solvents.

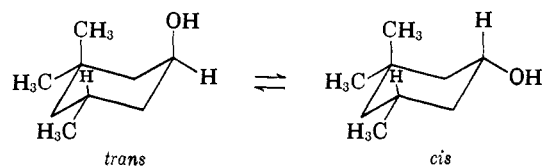


Figure 3.

It has been suggested<sup>28</sup> that the n.m.r. values support the idea of a solvent effect on  $-\Delta G^\circ_{OH}$ ; however, when all the data are considered, the picture seems erratic. In our own laboratories we have been unable so far to demonstrate a solvent effect by n.m.r. measurements,<sup>29</sup> possibly because at the concentrations normally used for n.m.r. measurement extensive intermolecular hydrogen bonding occurs. This point certainly merits further study.

Table V. Conformational Free Energies for Hydroxyl by N.m.r.

Solvent	$-\Delta G^\circ$ , kcal./ mole	Ref.
$CCl_4$	$0.43 \pm 0.17$	a
$CCl_4$	0.6	b
$CS_2$	0.65	c
$CCl_4$	0.73	d
$CCl_4$	0.75	c
$C_6H_5N$ , MeSOMe	0.8	e
$CCl_4$	0.82	f
$C_6H_5N$	0.83	f
Isooctane	0.84	f
$CH_3CDOHCH_3$	0.88	d
$C_6H_5Br$	0.97	f
$CCl_4$	1.0	g
<i>t</i> -BuOH	1.05	f
$CCl_4$	1.07	h
$H_2O$	1.25	g

<sup>a</sup> H. Booth, *Tetrahedron*, **20**, 2211 (1964). Value from coupling constants. <sup>b</sup> Reference 21. <sup>c</sup> W. C. Neikam and B. P. Dailey, *J. Chem. Phys.*, **38**, 445 (1963). <sup>d</sup> Reference 19. <sup>e</sup> R. J. Ouellette, *J. Am. Chem. Soc.*, **86**, 4378 (1964). Value from OH proton position. <sup>f</sup> Reference 28. <sup>g</sup> F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962). Value from coupling constants. <sup>h</sup> E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962). The value was derived from an indirect argument which may not be valid.

Among the equilibrations over which controversy has arisen were those of the 3,3,5-trimethylcyclohexanols. Aluminum isopropoxide leads to an equilibrium composition of 94% *cis* (Figure 3,  $-\Delta G^\circ = 1.96$  kcal./mole) from which, since  $\Delta G = 2Me/H - Me/H - OH/H - Me/OH$  (where the symbol X/Y stands for a *syn*-axial X–Y interaction), it follows that the Me/OH methyl-hydroxyl *syn*-axial interaction is 2.4 kcal./mole.<sup>30</sup> (Values taken for Me/H are 0.85 kcal./mole, for OH/H 0.45 kcal./mole—in both cases one-half of  $-\Delta G^\circ$  for the axial group.) When the above value for Me/OH was checked by Raney nickel catalyzed equilibration in cyclohexane at 125°, a much lower value of 1.4 kcal./mole was claimed, equilibrium (Figure 3) corresponding to 71.8–73.3% *cis*.<sup>31</sup>

(28) J. Reisse, J. C. Celotti, D. Zimmermann, and G. Chiurdoglu, *Tetrahedron Letters*, 2145 (1964).

(29) T. H. Williams, unpublished results.

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

(31) G. Chiurdoglu and W. Masschelein, *Bull. soc. chim. Belges*, **70**, 782 (1961).

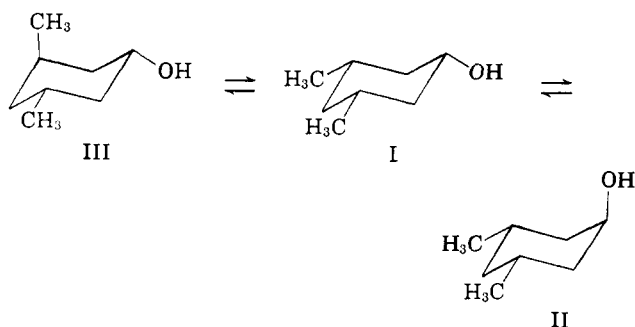


Figure 4.

In our hands, however, the equilibrium in Figure 3 in isopropyl alcohol at 82° established over Raney nickel corresponds to 95% *cis* isomer, in very good agreement with the earlier result with aluminum isopropoxide.<sup>30</sup> Findings in other solvents are summarized in Table VI. The values in cyclohexane at 80 and 150° are quite different from those reported<sup>31</sup> at 125 (*vide supra*) and 140° (69–70.8% *cis*).

Table VI. Equilibria of the 3,3,5-Trimethylcyclohexanols and 3,5-Dimethylcyclohexanols Established by Means of Raney Nickel

Solvent	Temp., °C.	—Stable isomer found, %—	
		3,3,5-Tri-methylcyclohexanol	3,5-Di-methylcyclohexanol
Cyclohexane	80	90	71
	150	88	...
Benzene	80	93	73.5
<i>t</i> -BuOH	82	94	77.5
<i>i</i> -PrOH	82	95	78
<i>i</i> -PrOH <sup>a</sup>	82	94.5	78

<sup>a</sup> MPVO method. Previous data: for 3,3,5-trimethylcyclohexanol 94 ± 0.5% (ref. 30); for 3,5-dimethylcyclohexanol, 77.6–78.6% (F. Biros, unpublished).

From the data in Table VI, the value of the methyl-hydroxyl *syn*-axial interaction is confirmed as 2.4–2.5 kcal./mole in protic solvents. In cyclohexane, the value is 1.94 kcal./mole and in benzene 2.21 kcal./mole; these values bracket that of 2.15 kcal./mole in pyridine found by the kinetic method.<sup>10</sup>

Table VI also lists data for the 3,5-dimethylcyclohexanols. Since, when the methyl groups are *cis* to each other the two resulting epimers are essentially conformationally homogeneous (Figure 4 (I, II); the methyl groups in the alternative conformation would have to be *syn*-axial which leads to a destabilization of about 5.5 kcal./mole<sup>32</sup>), the equilibrium (I/II) of the two diastereoisomers epimeric about the hydroxyl group should directly reflect  $\Delta G^\circ_{OH}$  and should therefore correspond to the equilibrium of *trans*- and *cis*-4-*t*-butylcyclohexanol in corresponding solvents. Comparison of Table VI with Table II (entries 1, 3, 7, 9, 10) shows that the agreement is, indeed, satisfactory and that the *cis*-3,5-dimethylcyclohexanols are appropriately conformationally biased systems, similar to the 4-*t*-butylcyclohexanols.

Raney nickel catalyzed epimerization of the 3,5-dimethylcyclohexanols in benzene, cyclohexane, and *t*-butyl alcohol yielded an unexpected bonus in that not only the two methyl-*cis* (*meso*) isomers but also the

(32) N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

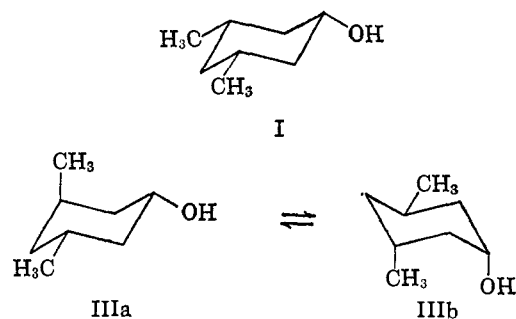


Figure 5.

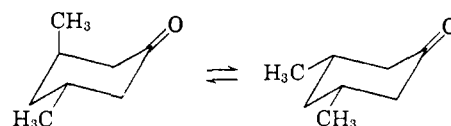


Figure 6.

methyl-*trans* (*dl*) isomer (III) were equilibrated after some time (Figure 4). Equilibration also occurred of the ketones (*cis*- and *trans*-3,5-dimethylcyclohexanone) formed concomitantly by dehydrogenation. The ratio of *cis*, *trans*- to *cis*, *cis*-3,5-dimethylcyclohexanol (III/I) (average of 27 measurements) was 11.5:88.5 and that of the corresponding ketones was 22:78 (± 2%). From the alcohol data, considering that the *cis*, *trans* isomer exists to the extent of about 5% in the form IIIb (Figure 5) it follows that  $K = I/(IIIa + IIIb) = I/1.05 IIIa$ . To obtain the conformational free energy of methyl, one needs the ratio I/IIIa which is thus equal to 1.05*K* and since, experimentally  $K = 88.5/11.5 = 7.7$ ,  $1.05K = 8.08$  whence  $-\Delta G = 1.47$  kcal./mole. To convert this to  $-\Delta G^\circ_{Me}$  one must further take into account that the *cis*, *trans* isomer is a *dl* pair and therefore favored by an entropy of mixing of  $R \ln 2$  (another way of seeing this is to note that epimerization of either methyl group in I will give III, so that III is favored by a probability factor of two); after correcting for this one finds that  $-\Delta G^\circ_{Me} = 1.96$  kcal./mole. This is somewhat higher than the currently accepted liquid phase value of 1.7 kcal./mole<sup>2</sup> and closer to the gas phase value of 1.9 kcal./mole but within satisfactory range of either.

From the ketone equilibrium (Figure 6) one calculates  $-\Delta G^\circ = 0.90$  kcal./mole and, again correcting for the entropy of mixing of  $R \ln 2$  of the *dl*-*trans* isomer, one obtains 1.39 kcal./mole as the difference between equatorial and axial methyl in a 3-methylcyclohexanone. This value is in very good agreement with that (1.36 kcal./mole) obtained<sup>33</sup> by a completely analogous (but less clean) equilibration over palladium at 220° and supports a 3-alkyl ketone effect of about 0.5 kcal./mole,<sup>34</sup> this being the difference between  $-\Delta G^\circ_{Me}$  in a methylcyclohexane and a 3-methylcyclohexanone in which one of the *syn*-axial Me/H interactions is missing.

In summary, then, the following conclusions have been reached from this work. (1) The long-established Meerwein-Ponndorf-Verley-Oppenauer (MPVO) method is entirely valid for establishing equilibrium between epimeric alcohols.

(33) N. L. Allinger and L. A. Freiberg, *ibid.*, **84**, 2201 (1962).

(34) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 777 (1964).

**Table VII.** Equilibrations Starting with Ketones or Phenols in Isopropyl Alcohol at 82°

Starting material	Stable alcohol at equilibrium (%)
4- <i>t</i> -Butylcyclohexanone	<i>trans</i> -4- <i>t</i> -Butylcyclohexanol (79.5)
4- <i>t</i> -Butylphenol	<i>trans</i> -4- <i>t</i> -Butylcyclohexanol (79.5)
4- <i>t</i> -Butylcyclohexanol <sup>a</sup>	<i>trans</i> -4- <i>t</i> -Butylcyclohexanol (79.0)
3,5-Dimethylcyclohexanone	<i>cis,cis</i> -3,5-Dimethylcyclohexanol (78.7)
3,5-Dimethylphenol	<i>cis,cis</i> -3,5-Dimethylcyclohexanol (78.4)
3,5-Dimethylcyclohexanol <sup>a</sup>	<i>cis,cis</i> -3,5-Dimethylcyclohexanol (77.8)
3,3,5-Trimethylcyclohexanone	<i>cis</i> -3,3,5-Trimethylcyclohexanol (94.7)
3,3,5-Trimethylcyclohexanone <sup>b</sup>	<i>cis</i> -3,3,5-Trimethylcyclohexanol (87.5)
3,3,5-Trimethylcyclohexanol <sup>a</sup>	<i>cis</i> -3,3,5-Trimethylcyclohexanol (94.8)

<sup>a</sup> Data from Table II, included for comparison. <sup>b</sup> In cyclohexane at 150°.

(2) The conformational energy of the hydroxyl group is solvent dependent as expected, being 0.6–0.7 kcal./mole in aprotic solvents such as cyclohexane and 0.90 ± 0.05 kcal./mole in hydrogen-donor solvents, such as *t*-butyl alcohol.

(3) The equilibrium position of epimeric alcohols in isopropyl alcohol is similar to that of the corresponding aluminum alkoxides in hydrocarbon or ether solvents.

(4) Raney nickel is a convenient reagent for the equilibration of epimeric alcohols. Its advantages over aluminum alkoxide are that it can be used in a wide variety of solvents and that equilibrium is usually established more rapidly. The catalyst is removed easily prior to analysis (by filtration; no further work-up is necessary) and, if one works in isopropyl alcohol as solvent, one may use not only alcohols but ketones or even phenols (Table VII) as starting materials for equilibration experiments.<sup>35</sup> The only disadvantage of Raney nickel is that when used in nonreducing solvents it dehydrogenates the alcohols to be epimerized to ketones and the experiment must be terminated before this dehydrogenation has gone too far.

(5) In reducing solvents (such as isopropyl alcohol) Raney nickel, through its adsorbed hydrogen, reduces ketones to predominantly axial alcohols. However, on prolonged contact, and especially at higher temperatures, reduction is followed by equilibration and the more stable equatorial alcohols are produced. This, undoubtedly, is what happens also in catalytic reductions of ketones using Raney nickel catalyst.

### Experimental Section

*trans*-4-*t*-Butylcyclohexanol,<sup>26</sup> m.p. 80.5–81°, phthalate, m.p. 146–147° (lit.<sup>9</sup> m.p. 81–82° and 146–147°), and *cis*-4-*t*-butylcyclohexanol,<sup>9</sup> m.p. 81–82°, *p*-nitrobenzoate, m.p. 131–133° (lit.<sup>9</sup> m.p. 82.5–83.5° and 133–134°) were prepared as previously described. Both isomers appeared homogenous on a 10-ft. Carbowax 20M column by g.l.p.c. analysis. *cis*-, m.p. 34–35°, and *trans*-3,3,5-trimethylcyclohexanol, m.p. 53–55° (lit.<sup>30</sup> m.p. 36–38° and 58.5°), were available from a previous investigation,<sup>20</sup> as were *cis,cis*-3,5-dimethylcyclohexanol, b.p. 80° (12 mm.), *n*<sup>20</sup><sub>D</sub> 1.4548 (lit.<sup>36</sup> b.p. 83° (17 mm.), *n*<sup>20</sup><sub>D</sub> 1.4550); *trans,trans*-3,5-dimethylcyclohexanol, b.p. 79° (17 mm.), m.p. 40–41° (lit.<sup>37</sup> b.p. 79–80° (17 mm.), m.p. 39–40°);

(35) If analysis is to be carried out gas chromatographically, it is not necessary to isolate or prepare the alcohols at all, except possibly as gas chromatographic standards. However, it appears that the response ratio of epimeric alcohols is usually quite close to unity (see Experimental Section).

(36) A. Skita and W. Faust, *Ber.*, **72B**, 1127 (1939).

and *cis,trans*-3,5-dimethylcyclohexanol, b.p. 82–83° (17 mm.), *n*<sup>20</sup><sub>D</sub> 1.4605 (lit.<sup>37</sup> b.p. 89–90° (17 mm.)).

**Gas-Liquid Chromatographic Analysis.** Analyses carried out with a Wilkens Aerograph Model A-90-P instrument with thermal conductivity detector or with an Autoprep Model A-700 instrument similarly equipped as well as with an F & M Model 60 instrument equipped with a flame-ionization detector were generally in good agreement. Columns used were diglycerol (25% on Chromosorb W 60–80 or on firebrick), 10-ft. column, at 90–120° or Carbowax 20M (20% on Chromosorb W 60–80, with or without 5% KOH), 10-ft. column at 130–160°. Peak areas were measured by a compensating polar planimeter. All analyses were reproducible to at least ±1%, usually ±0.5% and under optimum conditions ±0.3%. In critical cases, equilibrium mixtures from different solvents were analyzed consecutively in order to minimize calibration errors. Flame ionization and thermal conductivity detectors gave the same relative areas in all cases where analyses were duplicated on two instruments. The range of ten analyses of a 4-*t*-butylcyclohexanol mixture was ±0.5%, as was that for five analyses of a 3,5-dimethylcyclohexanol mixture. Response ratios for *cis*- and *trans*-4-*t*-butylcyclohexanol were about 1.01:1. Mixtures containing, respectively, 51.4, 66.5, and 79.0% *trans* isomer gave area percentages of 50.9, 66.1, and 78.4%.

**Raney Nickel Equilibrations.** The Raney nickel was either prepared from the alloy<sup>37</sup> or purchased from Raney Catalyst Co., Chattanooga, Tenn. In all cases the catalyst was washed thoroughly with water until the washings were neutral and then with absolute ethanol. For reactions in ethanol the catalyst was used as such; for reactions in methanol and isopropyl alcohol it was rinsed with the appropriate solvent. For equilibrations in nonhydroxylic solvents it was rinsed with benzene, residual ethanol removed by azeotropic distillation with part of the benzene, and the catalyst was stored under benzene. It was then rinsed with other solvents just before use as appropriate.

For equilibrations in benzene, cyclohexane, toluene, tetrahydrofuran, 1,2-dimethoxyethane, or *t*-butyl alcohol, 0.8–1.2 g. of the alkylcyclohexanol and 0.3–0.5 g. of the corresponding ketone were dissolved in 50–80 ml. of the solvent in a 100-ml. flask. Raney nickel (2.0–5.0 g.) was added and the suspension (containing, also, a boiling stick) was boiled gently using a calcium chloride protected reflux condenser. Aliquots of

(37) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

5–10 ml. were withdrawn with a pipet every 12–24 hr., filtered, concentrated as necessary and analyzed by g.l.p.c. Equilibration was usually complete after 12–24 hr.

Since ketone is formed by dehydrogenation of alcohol, it was found later that it could be omitted from the mixture. Also the equilibration may be started with pure ketone.

Equilibrations under hydrogen pressure at elevated temperatures were performed in a 183-ml. or 300-ml. rocking steel bomb at hydrogen pressures of 50–500 p.s.i. and temperatures of  $150 \pm 5^\circ$ . The reaction was terminated by stopping the shaker and, in some cases, by cooling the bomb in ice water.

For equilibrations in isopropyl alcohol, 4.0 g. of the alkylcyclohexanone, alkylcyclohexanol, or phenol were dissolved in 100 ml. of the dry alcohol (previously distilled from aluminum isopropoxide) in a three-necked flask. Twenty grams of Raney nickel were added and the mixture was boiled at reflux with mechanical stirring to avoid bumping and promote good contact with the catalyst. Samples of 5–7 ml. were withdrawn after 1, 24, 36, 48, 60, and 80 hr., filtered, concentrated carefully, and analyzed. Equilibrium is reached in approximately 1 day; thus, in a typical run involving 4-*t*-butylphenol, the percentage of *trans* alcohol at the end of the time indicated was 66.0% (1 hr.), 75.8% (4 hr.), 77.2% (6.5 hr.), 77.8% (22 hr.), 78.5% (29 hr.), and 78.5% (49 hr.).

For the reductions carried out under kinetic control (Table III), 4 g. of the ketone was refluxed with 4 g. of Raney nickel in 50 ml. of solvent. In a typical run with 4-*t*-butylcyclohexanone in ethanol, the percentage of *cis*-4-*t*-butylcyclohexanol at the end of the time indicated was 79% (8 hr.), 78% (21 hr.), 76.5% (50 hr.), and 77% (86 hr.).

Average results of Raney nickel equilibrations of alcohols are tabulated in Tables II and VI; of ketones and phenols in Table VII. The following composition data will give an indication of the approach to equilibrium from the two sides in typical runs; the system, solvent, and total number of runs for that system and solvent are also indicated. 4-*t*-Butylcyclohexanol (*trans* as percentage of *cis* + *trans*) had the following composition data: in cyclohexane (four runs), from *cis*, 70.0%, from *trans*, 70.0%; in benzene (eight runs), from *cis*, 72.5%, from *trans*, 72.4%; in *t*-butyl alcohol (seven runs), from *cis*, 77.8%, from *trans*, 77.0%; in isopropyl alcohol, from ketone, 79.5%, from phenol, 79.5%; from alcohols (five runs), 79.0%. 3,5-Dimethylcyclohexanol had the following composition data: (*cis,cis* as percentage of *cis,cis* + *trans,trans*) in cyclohexane (two runs) from *trans,trans*, 70.9%, from *cis,cis*, 71.1%; in benzene (eight runs), from

*trans,trans*, 73.4%, from *cis,cis*, 73.1%; in *t*-butyl alcohol (four runs) from *trans,trans*, 77.4%, from *cis,cis*, 77.5%; from ketone, 77.4%; in isopropyl alcohol, from ketone, 78.7%, from phenol, 78.4%, from alcohol, 77.7%; and (*cis,trans* as percentage of *cis,trans* + *cis,cis*) in cyclohexane, 11.8, 11.2%; in benzene, 11.2, 12.4%; in *t*-butyl alcohol, 11.5, 11.2%. 3,3,5-Trimethylcyclohexanol had the following composition data: (*cis* as percentage of *cis* + *trans*) in cyclohexane (two runs) from *cis*, 89.5%, from *trans*, 89.9%; in benzene (ten runs) from *cis*, 92.4%, from *trans*, 93.7%; in *t*-butyl alcohol (two runs) from *cis*, 94.0%, from *trans*, 94.2%; in isopropyl alcohol, from ketone, 94.7%, from *cis*, 94.9%. In all cases reaction was continued until three consecutive samples agreed in composition, usually within better than 0.5%.

In high-temperature equilibrations (data included in Tables II and VI) equilibrium was approached from both sides also. Typical results (at  $150^\circ$ ) are: 4-*t*-butylcyclohexanol, in cyclohexane, 70.0 and 70.3% *trans* (bomb quenched in ice water); in *t*-butyl alcohol, 73.9 and 74.1% *trans* (bomb quenched in ice water); 3,3,5-trimethylcyclohexanol, in cyclohexane, 88.0%, 87.9% *cis* (from *trans*), 87.3% *cis* (from *cis*), 87.5% *cis* (from ketone), 88.2% *cis* (from *cis*, bomb quenched in ice water).

**Aluminum Isopropoxide Equilibrations.** These equilibrations were carried out as described previously<sup>9</sup> using isopropyl alcohol distilled over aluminum isopropoxide and aluminum isopropoxide purified by dissolution in benzene, filtration, and distillation at reduced pressure. The alcohol (0.5–1.5 g.) was boiled in 50–100 ml. of isopropyl alcohol and 1 ml. of acetone containing 0.5–1.5 g. of aluminum isopropoxide for 1 week at reflux (system protected by drying tube). The solution was quenched into 150 ml. of 30% aqueous sulfuric acid and ice and extracted three times with 200-ml. portions of ether, and the ether was washed with aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate, and concentrated. The residue was analyzed by gas-liquid partition chromatography.

For equilibrations of complexes, the desired alkylcyclohexanol was boiled in benzene or toluene (dried over  $\text{LiAlH}_4$ ) with aluminum isopropoxide for 4 hr. and the isopropyl alcohol-solvent azeotrope was then distilled off over 2–3 hr., more solvent being added as necessary. Acetone (1 ml.) was then added and the mixture was refluxed for 1 week (5.5 days in the case of toluene). Quenching was as described above. The results are tabulated in Table IV. Each entry except the second is the average of two runs (one from *cis*, one from *trans* starting material) the results of which are shown in the last column.