

Solid AMP, m.p. 22–23°, was obtained by cooling the product of the oxidation of acetaldehyde in ethyl acetate solution (as described above) to –78°, and then washing the crystals with cold ether. The solid AMP from the two preparations was mixed as ether slurries and dried under vacuum at –10°. The m.p. of this mixture was 22–23°.

**Preparation of Peracetic Acid from AMP at Various Temperatures.**—Several experiments were performed on AMP solutions of 30 to 40% concentration in ethyl acetate freed of excess acetaldehyde as described above. These solutions were fed at the rate of 100 to 125 ml./hr. through a jacketed glass coil which was heated by a liquid under reflux in the jacket. The temperature in each run was fixed by the choice of the liquid used for heating purposes. The coil was fabricated from 8-mm. o.d. glass tubing and had an internal volume of 48 ml. The pressure in the system was controlled at 200 mm. After going through the coil, the peroxide mixture, in most cases largely in the vapor phase, was led to an up-draft Friedrich condenser, which served as a dephlegmator. Free acetaldehyde, along with some solvent, went past the dephlegmator and was collected in a cold trap. The condensate from the dephlegmator, collected in an ice-cooled flask, consisted of peracetic acid, AMP, ethyl acetate and by-product acetic acid. By passing this condensate through the coil a second time the amount of unconverted AMP could be reduced and the peracetic acid content increased. The table summarizes the results of a series of these runs.

Temp. of heating liquid, °C.	Pressure, mm.	Total peroxide recovered, %		Yield of peracetic acid, %	
		After 1st pass	After 2nd pass	After 1st pass	After 2nd pass
50	200	82	74	21	44
150	200	69	66	34	55
172	200	64	61	46	54
255	200	14	9	3	6

**Determination of Peracetic Acid.**—A 1–2-g. sample of peracetic acid solution is introduced into an erlenmeyer flask containing a mixture of 60 ml. of acetic acid and 5 ml. of saturated aq. potassium iodide solution. The peroxide oxidizes iodide ion to free iodine. The flask is swirled briefly to mix the solutions and complete the reaction. The

contents are immediately titrated with 0.1 *N* aq. sodium thiosulfate solution to a colorless end-point.

**Determination of AMP.**—A sample of a solution of AMP is analyzed exactly as that described for peracetic acid except that 60 ml. of 50% aq. sulfuric acid is substituted for 60 ml. of acetic acid.

**Determination of Solutions Containing AMP and Peracetic Acid.**—A sample of the solution is analyzed for total peroxide using the procedure outlined above for the determination of AMP. A second sample of 1–2 g. is added to a flask containing 50 ml. of water. The flask is stoppered, heated to 50° for 30 minutes, and cooled to room temperature. Then 50 ml. of acetic acid and 5 ml. of saturated aq. potassium iodide are added, and the flask is swirled and titrated with 0.1 *N* aq. sodium thiosulfate solution. The second analysis gives the amount of free peracetic acid, and the difference between the two analyses gives the AMP.

**Determination of Acetic Acid in Solutions of Peracetic Acid or AMP.**—The solution is first analyzed for peracetic acid or AMP as described above. Another sample (1–2 ml.) is introduced into an erlenmeyer flask containing 50 ml. of water. Pure acetaldehyde (15 ml.) is added to the flask and, after mixing, is allowed to stand for 10–15 minutes. All of the peroxide is converted to acetic acid. The flask contents are titrated with 0.5 *N* aq. sodium hydroxide solution using phenolphthalein indicator. The acetic acid present in the original solution is then equal to the total acetic acid, as determined by the second sample, minus the acetic acid which came from the decomposition of peroxide which was determined in the first sample.

**Determination of Unreacted Acetaldehyde in AMP Solutions.**—A sample (5 g.) of AMP solution is added to 50 ml. of distilled water in a flask. To this solution is added 10 ml. of an approximately 25% solution of peracetic acid. A blank is also prepared where exactly the same amount of peracetic acid solution is added to 50 ml. of water. Both solutions are stoppered and heated to 50° for 30 minutes. Then, after cooling, to each is added 50 ml. of acetic acid and 5 ml. of saturated aq. sodium iodide. Each solution is then titrated with 0.1 *N* sodium thiosulfate. The difference in titrations is used to calculate the unreacted acetaldehyde as

$$\% \text{ acetaldehyde} = \frac{\text{Diff. in Na}_2\text{S}_2\text{O}_4(\text{ml.}) \times N_{\text{Na}_2\text{S}_2\text{O}_4} \times 4.4}{\text{wt. sample} \times 2}$$

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## Conformational Analysis. II. Esterification Rates of Cyclohexanols<sup>1</sup>

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Rates of esterification of cyclohexanol, *cis*- and *trans*-4-*t*-butylcyclohexanol, *cis*- and *trans*-4-, *cis*- and *trans*-3- and *trans*-2-methylcyclohexanol, *cis*- and *trans*-4-phenylcyclohexanol, 3,3-dimethylcyclohexanol, 4,4-dimethylcyclohexanol and the acyclic analogs butanol-2 and benzylmethylcarbinol with acetic anhydride and, in some cases, propionic anhydride and isobutyric anhydride in excess pyridine as the solvent have been determined. From those data, the conformational equilibrium constant for hydroxyl (concentration of cyclohexanol with equatorial hydroxyl over that with axial hydroxyl) is calculated to be about 2.4 corresponding to a free energy difference of 0.5 kcal./mole and the interaction energy of 1,3-diaxial methyl and hydroxyl is estimated at 2.15 kcal./mole. The consistency of the data is examined.

The importance of conformation on reactivity in cyclohexane systems was first pointed out in 1950 by D. H. R. Barton<sup>2</sup> in a paper which has been of incalculable benefit to subsequent workers during the last seven years. Among other things, Barton<sup>2</sup>

pointed out that an equatorial substituent in cyclohexane is less hindered and therefore, in general, more reactive than an axial substituent.<sup>3</sup> His examples come largely from rigid systems, such as substituted decalins, steroids or terpenes in which the axial or equatorial nature of a substituent can be ascertained unequivocally. It was subsequently

(1) Paper I in this series: E. L. Eliel and C. Pillar, *THIS JOURNAL*, **77**, 3600 (1955). The present paper is taken from the Ph.D. thesis of Carl A. Lukach and was presented in part before the Organic Division at the Meeting of the American Chemical Society at Atlantic City, N. J., September 19, 1956.

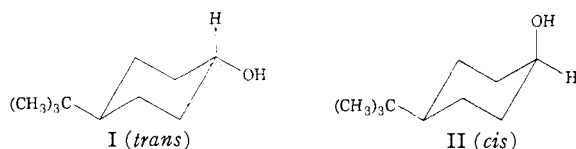
(2) D. H. R. Barton, *Experientia*, **6**, 316 (1950); see also D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953), and *Experientia Supplementum II*, 121 (1956); D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(3) For background information and explanation of terminology see: (a) W. Klyne, "Progress in Stereochemistry. I," Butterworths, London, England, 1954, Chapter 2. (b) W. G. Dauben and K. S. Pitzer in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 1. (c) H. D. Orloff, *Chem. Revs.*, **54**, 347 (1954).

suggested by one of us<sup>4</sup> that in a *mobile* mono- or poly-substituted cyclohexane system, such as that shown in Fig. 1, where the two possible chair conformations are readily interconvertible,<sup>5</sup> both conformations and their relative rate of reaction must be taken into account in ascertaining reactivity.

While the present work—designed to put the earlier speculations<sup>4</sup> on a more quantitative basis—was under way, Winstein and Holness<sup>6</sup> derived a very useful relationship between the specific reaction rate  $k$  for any reaction of a molecule (such as that in Fig. 1) which may exist in two conformations, the mole fractions  $N_a$  and  $N_e$  of the two conformations E and A at equilibrium and the respective individual rate constants  $k_a$  and  $k_e$ , this relation being  $k = N_a \cdot k_a + N_e \cdot k_e$ . We have independently derived an equivalent relationship  $k = (k_e K + k_a)/(K + 1)$  where  $K$  is the equilibrium constant between the conformations E and A. From this may be obtained the expression  $K = (k_a - k)/(k - k_e)$  (i) expressing the equilibrium constant  $K$  in terms of specific rates  $k_a$ ,  $k_e$ , and  $k$ .

Winstein and Holness<sup>6</sup> have used equation (i) (or an equivalent relationship) to determine conformational equilibrium constants for several substituents in cyclohexane, including the hydroxyl group for which they report a free energy difference  $\Delta F^0$  ( $= -RT \ln K$ ) of  $-0.8$  kcal./mole at  $40^\circ$ ,<sup>7</sup> obtained from oxidation rates with chromic acid in 75% acetic acid. Here  $k$  in equation (i) is the rate constant for oxidation of cyclohexanol. For  $k_e$  and  $k_a$  the rate constants for oxidation of the *trans*- (I) and *cis*- (II) *t*-butylcyclohexanols were used since it was shown, on theoretical grounds, that the *t*-butyl group will occupy exclusively the equatorial position so that the two stereoisomers are entirely in forms I and II. To justify the use of  $k_e$



and  $k_a$  so obtained for the parent compound cyclohexanol in equation (i) entails the further assumption that the *t*-butyl group exerts no direct polar or steric effect across the ring. The absence of appreciable polar effects of alkyl groups across the ring is suggested by the finding that in several reactions, *cis*-3- and *trans*-4-*t*-butyl substituted compounds,<sup>6</sup> *trans*-3- and *cis*-4-*t*-butyl substituted compounds<sup>6</sup> and (see below) *trans*-3- and *cis*-4-methyl substituted compounds react at nearly the same rate implying little if any difference in polar effect of 3- and 4-substituents. More decisive evidence for the absence of disturbing polar effects comes from  $pK$  measurements of cyclohexanecarboxylic acid and its *cis*-3 and *trans*-4-methyl homologs—the three com-

(4) E. L. Eliel, *Experientia*, **9**, 91 (1953); see also W. G. Dauben, R. C. Tweit and L. C. Mannerskantz, *THIS JOURNAL*, **76**, 4420 (1954).

(5) C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946), has made an approximate calculation of the energy barrier between the chair forms as 9–10 kcal./mole. Since the two conformational isomers have never been isolated, it is almost certain that the barrier is indeed small compared to the activation energy of ordinary chemical reactions.

(6) S. Winstein and N. J. Holness, *THIS JOURNAL*, **77**, 5562 (1955).

(7) This is the tabulated value in ref. 6. Experimental values are  $-1.17$  kcal./mole at  $25^\circ$  and  $-0.66$  kcal./mole at  $50^\circ$ .

pounds are of identical acid strength within the limits of experimental error<sup>8</sup>—and from the fact that the acetylation rates of cyclohexanol (Table I, entry 1 below) and 4,4-dimethylcyclohexanol (Table I, entry 8) are identical within the limits of experimental error. The latter observation also suggests the absence of direct steric effects of substituents at  $C_4$ , an assumption which would also appear reasonable from models.<sup>9</sup>

The present investigation is concerned with a determination of the conformational equilibrium constant of the hydroxyl group by means of equation (i) using the reaction of cyclohexanols with an acid anhydride (acetic, propionic or isobutyric) in a large excess (15- to 20-fold) of pyridine. This reaction follows second-order kinetics (first order in acetic anhydride and first order in the cyclohexanol) as evidenced by the constancy of the second-order constants within individual runs and the near-constancy of rate constants determined at different concentrations of acetic anhydride, alcohol and pyridine (provided the pyridine remains in large excess) (see Experimental). Typical rate constants at  $25^\circ$  for cyclohexanol, the 4-*t*-butylcyclohexanols and a number of methylcyclohexanols are summarized in Table I; this table also lists the equilibrium constants  $K$ , calculated from the rate constants by means of equation (i) and the corresponding free energy differences.

TABLE I

SECOND-ORDER RATE CONSTANTS (L. MOLE<sup>-1</sup> SEC.<sup>-1</sup>  $\times 10^6$ ) FOR THE REACTION OF CYCLOHEXANOLS WITH ACETIC ANHYDRIDE IN PYRIDINE AT  $25^\circ$ ; ALSO EQUILIBRIUM CONSTANTS AND FREE ENERGY DIFFERENCES<sup>a</sup>

Entry	Alcohol	$k \times 10^6$	$K$	$\Delta F^0$ , kcal./mole
1	Cyclohexanol	8.37	2.40	-0.52
2	<i>trans</i> -4- <i>t</i> -Butylcyclohexanol	10.65	$\infty^b$	....
3	<i>cis</i> -4- <i>t</i> -Butylcyclohexanol <sup>c</sup>	2.89	0 <sup>b</sup>	....
4	<i>trans</i> -4-Methylcyclohexanol	9.66	6.84	-1.14
5	<i>cis</i> -4-Methylcyclohexanol	3.76	0.126	1.22
6	<i>cis</i> -3-Methylcyclohexanol	10.71	$\infty$	....
7	<i>trans</i> -3-Methylcyclohexanol	3.94	0.156	1.11
8	4,4-Dimethylcyclohexanol	8.43	2.50	-0.55
9	3,3-Dimethylcyclohexanol	9.88	9.08 <sup>c</sup>	-1.32 <sup>c</sup>
			12.8 <sup>d</sup>	-1.53 <sup>d</sup>

<sup>a</sup> Data obtained at equimolar concentration of alcohol and anhydride; see Experimental. <sup>b</sup> Assumed. <sup>c</sup> Assuming  $k_a = 2.89 \times 10^{-6}$ . <sup>d</sup> Assuming  $k_a = 0$ ; see text.

The  $\Delta F^0$  values in Table I require comment. It must be realized that these values no more than indicate orders of magnitude, since  $K$  in equation (i) is obtained as a quotient of two differences, one of which is usually small and therefore affected by a large relative error.

Focusing attention on entries 1–3, the value of  $-0.5$  kcal./mole seems reasonable for the difference in free energy between equatorial and axial hydroxyl. Other values reported for this difference

(8) J. F. J. Dippy, S. R. C. Hughes and J. W. Laxton, *J. Chem. Soc.*, 4102 (1954). After this paper was submitted, H. Boaz (private communication) showed that the  $pK_a$ 's of cyclohexanecarboxylic and *trans*-4-*t*-butylcyclohexanecarboxylic acids are also very nearly identical.

(9) R. Cornubert, *Bull. soc. chim. France*, 996 (1956), suggests that the *t*-butyl group at  $C_4$  may crowd the axial hydrogens at  $C_3$  and  $C_5$ . Although this might lead to a "buttressing effect" which might, in turn, affect reactivity at  $C_1$ , no evidence for this has been noted in our work.

are the already mentioned value<sup>6</sup> of  $-0.8$  kcal./mole at  $40^\circ$  (from chromic acid oxidation studies in 75% acetic acid),  $-0.9$  kcal./mole (from an ingenious argument based on formation of complex borates from cyclitols in aqueous solution)<sup>10</sup> and  $-0.96$  kcal./mole at  $89^\circ$  (from direct equilibrium studies in isopropyl alcohol).<sup>11</sup> (Because of the difference in solvents and temperature, complete agreement of the  $\Delta F^0$  values should perhaps not be expected.)

Entries 4 and 5 provide a check on the consistency of the data. The energy required for moving a methyl group from an equatorial to an axial position may be taken as  $-1.8$  kcal./mole.<sup>12</sup> Since the corresponding energy for hydroxyl is  $-0.5$  kcal./mole (*vide supra*), the calculated free energy difference for *cis*-4-methylcyclohexanol with equatorial hydroxyl and its conformational isomer with axial hydroxyl is  $1.8 - 0.5$  or  $1.3$  kcal./mole, since the energy gained by moving the hydroxyl group to the equatorial position is more than made up by the energy lost in moving methyl to an axial position (*cf.* Fig. 1). The calculated value of  $1.3$  kcal./mole

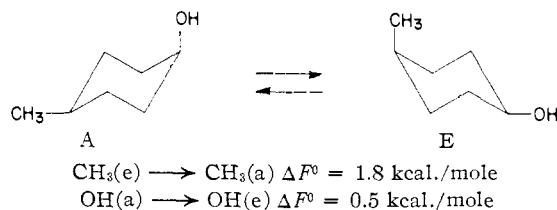


Fig. 1.

is in good agreement with the observed  $1.22$  kcal./mole. For *trans*-4-methylcyclohexanol the agreement is not so good: the calculated value for moving methyl and hydroxyl from axial to equatorial positions (Fig. 2) is  $-0.5 - 1.8$  or  $-2.3$  kcal./mole

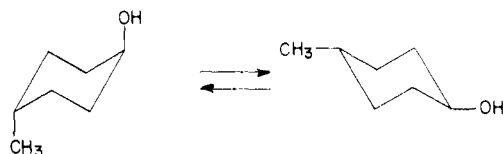


Fig. 2.

as compared to an experimental value of only  $-1.14$  kcal./mole. The discrepancy may possibly be due to the presence of slow-reacting impurities in the *trans*-4-methylcyclohexanol sample.

Next, consider entries 6 and 7. In *cis*-3-methylcyclohexanol (entry 6), the hydroxyl function must be almost entirely equatorial, since otherwise an interaction between axial hydroxyl and axial methyl

(10) S. J. Angyal and D. J. McHugh, *Chemistry & Industry*, 1147 (1956).

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

(12) C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, **69**, 2488 (1947). Others have used values as low as  $-1.6$  kcal./mole for this parameter, which is actually a potential energy value. However, the corresponding enthalpy difference—F. D. Rossini, "Selected Values of Properties of Hydrocarbons," U. S. Govt. Printing Office, Washington, D. C., 1947—and free energy difference—A. K. Roebuck and B. L. Evering, *THIS JOURNAL*, **75**, 1631 (1953); G. Chiurdoglu, J. Versluys-Evrard and J. Decot, *Bull. soc. chim. Belg.*, **66**, 192 (1957)—do not differ substantially from it. That the equating of enthalpy differences with free energy differences common in this type of work is not always safe has been pointed out by N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).

on the same side of the chair (Fig. 3, A, R = H) would arise. This would make the diaxial form of



Fig. 3.

*cis*-3-methylcyclohexanol considerably less favorable even than the diaxial form of *trans*-4-methylcyclohexanol. In fact, the acetylation rate of *cis*-3-methylcyclohexanol is the same as that of *trans*-4-*t*-butylcyclohexanol (entry 2) confirming the consistency of the assumption that the hydroxyl group is entirely equatorial in both compounds. *trans*-3-Methylcyclohexanol (entry 7) has one axial and one equatorial group, just as *cis*-4-methylcyclohexanol (entry 5) and therefore, unless there were a polar effect due to the more proximate 3-methyl group, the two isomers should be acetylated at the same rate. This is very nearly true; it is doubtful whether the difference between the two rates (3.76 and 3.94) is significant.

Entry 8 provides a check on the assumption, already discussed, that an alkyl group at  $C_4$  exerts no direct influence on reaction at  $C_1$ .

Entry 9 leads to an estimate of the order of magnitude of the interaction of an axial hydroxyl at  $C_1$  with an axial methyl group at  $C_3$  (Fig. 3, A, R =  $\text{CH}_3$ ). Unfortunately some uncertainty is introduced, because the values of  $k_a$  (equation i) to be used for 3,3-dimethylcyclohexanol is not obvious. If one uses  $k_a = 2.89 \times 10^{-5}$  (entry 3), one obtains the first values for  $K$  and  $\Delta F^0$  listed in Table I, entry 9. Actually, however, because of the increased steric interference of the axial methyl group in the acetylation of the axial isomer of 3,3-dimethylcyclohexanol (Fig. 3, A, R =  $\text{CH}_3$ ),  $k_a$  is likely to be considerably smaller than  $2.89 \times 10^{-5}$ ; in fact it might be a better approximation to put  $k_a = 0$ —an assumption which leads to the second values for  $K$  and  $\Delta F^0$  in Table I, entry 9.<sup>13</sup> On this basis the difference in free energy between the conformational isomers is  $1.5$  kcal./mole.

On the basis of this value, the OH(1a)- $\text{CH}_3$ (3a) interaction may be calculated as follows: In Fig. 3 (A, R =  $\text{CH}_3$ ) one has the following three 1a-3a interactions:  $\text{CH}_3\text{-H}$ ,  $\text{OH-H}$  and  $\text{OH-CH}_3$ . Using  $0.9$  kcal./mole for  $\text{CH}_3\text{-H}$ ,<sup>12</sup>  $1/2 \times 0.5$  or  $0.25$  kcal./mole for  $\text{OH-H}$  (*vide supra*) and  $X$  kcal./mole for  $\text{OH-CH}_3$ , the total interaction energy will be  $1.15 + X$ . In the equatorial isomer (Fig. 3, E, R =  $\text{CH}_3$ ), the total interaction energy due to the axial methyl group will be  $1.8$  kcal./mole. Since the difference between A and E (Fig. 3, R =  $\text{CH}_3$ ) is found to be  $1.5$  kcal./mole, one has  $1.15 + X - 1.8 = 1.5$  or  $X = 2.15$  kcal./mole. This is a reasonable value, in view of the fact that the corresponding value for  $\text{CH}_3$ (1a)- $\text{CH}_3$ (3a) is estimated<sup>12</sup> as at least  $3.6$  kcal./mole (total interaction  $5.4$  kcal./mole minus  $1.8$  kcal./mole for two  $\text{CH}_3\text{-H}$  interac-

(13) A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949), have shown that 2-acetoxycyclohexane, in which the 2-acetoxy and 10-methyl groups are 1-3 diaxial, is saponified considerably slower than other acetoxycyclohexanes containing equatorial or simple axial acetoxy groups.

tions) and that the corresponding value for OH-(1a)-OH(3a) is 1.9 kcal./mole.<sup>10,14</sup>

On the basis of the above, the energy level of the diaxial isomer of *cis*-3-methylcyclohexanol (Fig. 3, R = H) should be 1.5 + 1.8 or 3.3 kcal./mole in excess of that of the diequatorial isomer. This corresponds to a *K* of *ca.* 230 and leads to the prediction, borne out experimentally, that the specific acetylation rate for *cis*-3-methylcyclohexanol should be identical to *k<sub>e</sub>*, within the limits of experimental error.

One difficulty in applying equation (i) to the calculation of conformational equilibrium constants in this work lay in the small spread between the extreme rates *k<sub>e</sub>* and *k<sub>a</sub>*. In the hope of obtaining a larger spread of data, we turned to a study of propionylation and isobutyrylation of cyclohexanols with propionic and isobutyric anhydride. Unfortunately, as indicated in Table II, the spread between *k<sub>e</sub>* and *k<sub>a</sub>* is smaller for the more bulky anhydrides than for acetic anhydride. The reason for this is not yet well understood.

TABLE II

SECOND-ORDER RATE CONSTANTS (L. MOLE<sup>-1</sup> SEC.<sup>-1</sup> × 10<sup>6</sup>) FOR THE REACTION OF CYCLOHEXANOLS WITH PROPIONIC AND ISOBUTYRIC ANHYDRIDE IN PYRIDINE<sup>a</sup>; ALSO EQUILIBRIUM CONSTANTS AND FREE ENERGY DIFFERENCES

Alcohol	<i>k</i> × 10 <sup>6</sup>	<i>K</i>	<i>F</i> <sup>0</sup> , kcal./mole
Cyclohexanol	4.43 (5.70)	2.35 (2.42)	-0.50 (-0.53)
<i>trans</i> -4- <i>t</i> -Butylcyclohexanol	5.39 (7.16)	∞ <sup>b</sup>	...
<i>cis</i> -4- <i>t</i> -Butylcyclohexanol	2.18 (2.18)	0 <sup>b</sup>	...
<i>trans</i> -4-Methylcyclohexanol	5.15	12.4	-1.51
<i>cis</i> -4-Methylcyclohexanol	2.73	0.21	0.93

<sup>a</sup> Values in parentheses refer to the propionic anhydride, others to isobutyric anhydride. <sup>b</sup> Assumed.

The *K* and  $\Delta F^0$  values for cyclohexanol in Table II are in excellent agreement with those in Table I. The values for the *cis*- and *trans*-4-methyl homologs are not in such good agreement, but it must be remembered that because of the very small spread between *k* and *k<sub>e</sub>* (or *k<sub>a</sub>*) for these compounds, especially for the data in Table II, a small variation in the experimental rate constants will produce a very large variation in the calculated equilibrium constants.

Some other acetylation rates measured in the course of this work are summarized in Table III. The data for the phenylcyclohexanols (entries 10, 11) were obtained in the hope of establishing conformational equilibrium constants for these compounds. This hope was frustrated when it was found that *trans*-4-phenylcyclohexanol (entry 10) is acetylated *faster* than the (all-equatorial) *trans*-4-*t*-butylcyclohexanol (Table I, entry 2; *k* = 10.65 × 10<sup>-5</sup>). Isobutyrylation of *trans*-4-phenylcyclohexanol (*k* = 6.17 × 10<sup>-5</sup> l. mole<sup>-1</sup> sec.<sup>-1</sup>) was also

(14) (a) One might wonder about the closeness of the OH-OH and OH-CH<sub>3</sub> values, in view of the considerably larger size of CH<sub>3</sub>. However, the OH-OH interaction is increased by dipolar repulsion which is probably only partly compensated by hydrogen bonding. (b) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956), have advanced an interesting argument to show that the interactions involved in 1-3 diaxial methyl and hydroxyl are less severe than those involved in a single axial isopropyl group.

TABLE III

MISCELLANEOUS SECOND-ORDER RATE CONSTANTS (L. MOLE<sup>-1</sup> SEC.<sup>-1</sup> × 10<sup>6</sup>) FOR THE REACTION OF CYCLOHEXANOLS WITH ACETIC ANHYDRIDE IN PYRIDINE AT 25°

Entry	Alcohol	<i>k</i> × 10 <sup>6</sup>
10	<i>cis</i> -4-Phenylcyclohexanol	3.91
11	<i>trans</i> -4-Phenylcyclohexanol	11.6
12	Butanol-2	8.66
13	1-Phenyl-2-propanol	16.8
14	<i>trans</i> -2-Methylcyclohexanol	11.3

found to be faster than isobutyrylation of *trans*-4-*t*-butylcyclohexanol (*k* = 5.39 × 10<sup>-5</sup> l. mole<sup>-1</sup> sec.<sup>-1</sup>). Comparison of the acetylation rate of 1-phenyl-2-propanol, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CHOHCH<sub>3</sub> (entry 13), with butanol-2, CH<sub>3</sub>CH<sub>2</sub>CHOHCH<sub>3</sub> (entry 12), suggests that the acceleration is due to a polar effect of the phenyl substituent. Under these circumstances, equation (i) cannot be applied, since *k<sub>e</sub>* and *k<sub>a</sub>* will be different for the phenylcyclohexanols than for the *t*-butylcyclohexanols. Since a phenyl group is electron withdrawing whereas a methyl group is electron donating, it is rather surprising that *trans*-2-methylcyclohexanol (entry 14) also has a specific acetylation rate in excess of *k<sub>e</sub>*. Further experiments on 2-alkylcyclohexanols will be required to elucidate the nature of the accelerative effect in this case.

The methods chosen for preparation of the alkylcyclohexanols used in this study (see Experimental) were arrived at after considerable trial and error and, in some cases, constitute improvements over published procedures. In particular, improved methods were devised for the synthesis of 4,4-dimethylcyclohexanol<sup>15,16</sup> and the equatorial-axial (*cis*-2 and -4; *trans*-3) methylcyclohexanols. The latter were obtained by catalytic reduction of the corresponding ketones with platinum in acetic acid containing hydrochloric acid.<sup>17</sup> Contrary to indications made recently,<sup>18</sup> this method gave alcohols (after saponification of the alcohol-acetate mixture obtained in the reduction) sufficiently rich in the desired stereoisomer to allow ready purification through a crystalline derivative.

### Experimental<sup>19</sup>

**Equatorial-Axial Isomers of Methylcyclohexanol.**<sup>17</sup>—The appropriate methylcyclohexanone (obtained by dichromate oxidation of the corresponding commercial methylcyclohexanol or else purchased as such) was reduced catalytically at a hydrogen pressure of 55–60 p.s.i., using 1.0 g. of platinum oxide for 22.4 g. (0.20 mole) of ketone dissolved in 100 ml. of glacial acetic acid containing 7.6 g. of gaseous hydrogen chloride. The calculated amount of hydrogen was taken up in about ten minutes. The catalyst was filtered and the combined filtrates from several reductions were poured into water and ice extracted three times with petroleum ether (b.p. 40–60°). The extracts were washed three times with saturated sodium bicarbonate solution, dried over sodium sulfate and magnesium sulfate and concentrated. Saponification of esters was accomplished by boiling for 10 hr. with aqueous methanolic potassium hydroxide. [For the above

(15) W. Franke and J. Bueren, German Patent 833,645 (1952); *C. A.*, **47**, 2205a (1953).

(16) R. F. Miller and R. Adams, *THIS JOURNAL*, **58**, 787 (1936).

(17) P. Auziani and R. Cornubert, *Bull. soc. chim. France*, [5] **12**, 359 (1945); M. Claudon, *ibid.*, **17**, 627 (1950).

(18) G. Stork and W. N. White, *THIS JOURNAL*, **78**, 4617 (1956).

(19) All melting and boiling points uncorrected. Microanalyses by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra recorded by Mr. Rolland Ro on a Baird double-beam instrument.

amounts, 15 g. (0.27 mole) of potassium hydroxide, 30 ml. of water and 120 ml. of methanol were employed.] Methanol (100 ml.) was fractionally distilled from the saponification mixture and the product was then extracted with four portions of petroleum ether which were combined, dried over sodium sulfate and magnesium sulfate and concentrated. The crude alcohol was then distilled at reduced pressure (10–25 mm.); typical yields were 59–69%.

**cis-2-Methylcyclohexanol.**—Crude material obtained as described above was converted to the acid phthalate with phthalic anhydride in pyridine. The yield of phthalate, m.p. 102–104° (lit.<sup>20</sup> 102–104°) after four recrystallizations from hexane was 40%. Saponification of the phthalate gave *cis*-2-methylcyclohexanol, b.p. 65° (16 mm.), in 48% yield. The material had prominent bands in the infrared at 9.83, 10.23 and 10.60  $\mu$  and did not show any diagnostic bands corresponding to the *trans* isomer (*vide infra*).

**trans-3-Methylcyclohexanol.**—The crude material was converted to the *p*-nitrobenzoate by treatment with the acid chloride in pyridine. After two recrystallizations from methanol the derivative (50% yield) melted at 61.5–62.5° (lit.<sup>21</sup> 60–61°). Saponification with aqueous methanolic sodium hydroxide gave the pure alcohol, b.p. 80–81° (50 mm.), in 70% yield. The material showed prominent absorption bands in the infrared at 8.78, 10.05 and 10.60  $\mu$  and was free of the diagnostic bands of the *cis* isomer (*vide infra*).

**cis-4-Methylcyclohexanol** was purified *via* the *p*-nitrobenzoate, m.p. 95–96° (lit.<sup>20</sup> 96°), obtained in 39% yield after two recrystallizations from petroleum ether (b.p. 40–60°). Saponification gave the alcohol, b.p. 70° (12 mm.), in 71% yield. This material showed prominent infrared bands at 8.75, 9.30, 9.66, 10.14 and 10.81  $\mu$  and was free of the diagnostic bands of the *trans* isomer (*vide infra*).

**trans-2-Methylcyclohexanol.**—Commercial 2-methylcyclohexanol was equilibrated by means of aluminum isopropoxide.<sup>22</sup> The recovered material (88% yield, b.p. 90–91° (49 mm.)) was converted to the 3,5-dinitrobenzoate by treatment with freshly prepared dinitrobenzoyl chloride and pyridine. The derivative, m.p. 117–118.5° (lit.<sup>20</sup> 117°), resulted in 60% yield after recrystallization from octane followed by two recrystallizations from methanol. Saponification yielded *trans*-2-methylcyclohexanol, b.p. 72° (20 mm.) (lit.<sup>23</sup> b.p. 60.7–61° (10.5 mm.)), in 55% yield. The material had prominent infrared absorption bands at 9.39, 9.50 and 9.63  $\mu$  and was free of the diagnostic bands of the *cis* isomer (*vide supra*).

**cis-3-Methylcyclohexanol.**—The crude alcohol, obtained by lithium aluminum hydride reduction of the ketone<sup>24</sup> (92% yield), was converted to the acid phthalate, m.p. 90–92° (lit.<sup>23</sup> 90–92°) after one recrystallization from hexane, in 61% yield. Saponification yielded the pure alcohol, b.p. 72° (11 mm.), in 91% yield. The material had prominent infrared bands at 9.08, 9.55 and 9.78  $\mu$  and was free of the diagnostic bands of the *trans* isomer (*vide supra*).

**trans-4-Methylcyclohexanol.**—The crude alcohol, prepared in 76% yield by lithium aluminum hydride reduction of the corresponding ketone,<sup>24</sup> was converted to the 3,5-dinitrobenzoate, m.p. 143.5–144.2° (lit.<sup>20</sup> 142°) after three recrystallizations from ethyl acetate–pentane, in 51% yield. Saponification gave the pure alcohol, b.p. 75° (14 mm.), in 70% yield. It had prominent infrared bands at 9.16, 9.52 and 9.91  $\mu$  and was free of the diagnostic bands of the *cis* isomer (*vide supra*).

**4,4-Dimethylcyclohexanol** was prepared by a modification of a patented method.<sup>15</sup> A mixture of 70 g. (1 mole) of freshly distilled methyl vinyl ketone and 72 g. (1 mole) of freshly distilled isobutyraldehyde was dissolved in 100 ml. of water and sufficient methanol to ensure homogeneity. The solution was added slowly to a well-stirred solution of 3.7 g. of potassium hydroxide in 20 ml. of methanol whose temperature was raised slowly to 75–80° by external heating. At the end of the addition the mixture was cooled and ex-

tracted seven times with 100-ml. portions of ether which were combined, washed three times with water, dried over sodium sulfate and concentrated. Distillation yielded 30.7 g. (25%) of a fraction boiling at 60–74° (3 mm.) considered crude 4,4-dimethyl-2-cyclohexenone. This material was hydrogenated in 100 ml. of acetic acid over 0.5 g. of platinum oxide at room temperature and *ca.* 60 p.s.i. until two equivalents of hydrogen were taken up. The solution was then filtered, poured into water and extracted with five 100-ml. portions of ether which, in turn, were washed with water, aqueous sodium bicarbonate and again water, dried over sodium sulfate and concentrated to yield 19.3 g. (63%) of crude 4,4-dimethylcyclohexanol which was purified *via* the phthalate, m.p. 92.5–94° (67% yield).

*Anal.* Calcd. for C<sub>16</sub>H<sub>20</sub>O<sub>4</sub>: C, 69.54; H, 7.29. Found: C, 69.64; H, 7.21.

Saponification of the phthalate gave pure 4,4-dimethylcyclohexanol, b.p. 83.5–83.8° (15 mm.), in 77% yield. This material was identical in infrared spectrum with the compound obtained from *p*-cresol by a Reimer–Tiemann reaction with chloroform followed by hydrogenation.<sup>16</sup>

**3,3-Dimethylcyclohexanol**<sup>25</sup> was prepared by hydrogenation of 5,5-dimethyl-1,3-cyclohexadiene (dimegone) and purified *via* the *p*-nitrobenzoate, m.p. 82–83° (lit.<sup>25</sup> 83–83.5°). Saponification of the latter (69% yield) gave the pure alcohol, b.p. 84.8° (16 mm.), *n*<sub>D</sub><sup>20</sup> 1.4561 (lit.<sup>25</sup> 74–76° (8 mm.)).

**Other Substrates.**—Cyclohexanol was purified either by fractionation through a 60-cm. helix-packed column or through its 3,5-dinitrobenzoate. *Anal.* Hydroxyl, calcd. 16.81; found<sup>26</sup> 16.79.

*cis*- and *trans*-4-*t*-butylcyclohexanol and *cis*- and *trans*-4-phenylcyclohexanol were prepared as described in the accompanying paper.<sup>11</sup>

Butanol-2 was redistilled through a Vigreux column.

1-Phenyl-2-propanol was obtained by sodium borohydride reduction of the corresponding ketone (88% yield), b.p. 101–101.5° (14 mm.), *n*<sub>D</sub><sup>20</sup> 1.5208, free of carbonyl impurity according to infrared spectrum.

Acetic anhydride was distilled through a 60-cm. helix-packed column, b.p. 139.9° (760 mm.), for the center cut which was used in the kinetic study. The material contained some acetic acid; it was assayed as described.<sup>27</sup>

Propionic anhydride was similarly purified and assayed; b.p. 167° (745 mm.). Isobutyric anhydride was prepared from the acid, acid chloride and pyridine,<sup>28</sup> the acid chloride, in turn, being prepared from the acid and benzoyl chloride.<sup>28</sup> It boiled at 92° (34 mm.) and was assayed as the other anhydrides.

Pyridine was distilled over potassium hydroxide pellets through a large column taking precautions to exclude moisture. Butanol-1 was distilled through a Vigreux column, b.p. 117°.

**Kinetic Measurements.**<sup>29</sup> **General Procedure.**—Acetic anhydride (weighed) was dissolved in pyridine in a 100-ml. volumetric flask and placed in a thermostat at 25.0 ± 0.05°. A solution of the appropriate alcohol (weighed) in 5 ml. of pyridine was similarly adjusted in temperature. To start the reaction, 25 ml. of the acetic anhydride solution was pipetted into the alcohol solution. Two-milliliter aliquots of this solution were withdrawn from time to time by means of a pipet, quenched in 50 ml. of cold distilled water and titrated with tenth-normal standard base using phenolphthalein as an indicator, after the addition of 10 ml. of *n*-butyl alcohol which served to dissolve the ester formed and prevent its hydrolysis during titration. A blank titration on 2 ml. of pyridine, 50 ml. of water and 10 ml. of *n*-butyl alcohol was deducted from the sample titers.

The reaction is R–OH + Ac<sub>2</sub>O → R–OAc + AcOH, and since it was established in preliminary experiments that, in

(20) L. M. Jackmann, A. K. Macheth and J. A. Mills, *J. Chem. Soc.*, 1717 (1949).

(21) S. Siegel, *THIS JOURNAL*, **75**, 1317 (1953).

(22) W. G. Dauben, G. J. Fonken and D. S. Noyce, *ibid.*, **78**, 2579 (1956). We are indebted to Professor W. G. Dauben for disclosing this method to us in advance of publication.

(23) R. Arnold, G. Smith and R. Dodson, *J. Org. Chem.*, **15**, 1258 (1950).

(24) D. S. Noyce and D. B. Denney, *THIS JOURNAL*, **72**, 5743 (1950).

(25) W. v. E. Doering and F. M. Beringer, *ibid.*, **71**, 2221 (1949).

(26) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 9–12.

(27) G. S. Shaw, *Can. Chem. and Proc. Ind.*, **25**, 197 (1941).

(28) H. C. Brown, *THIS JOURNAL*, **60**, 1325 (1938); C. F. H. Allen, C. J. Kibler, D. M. McLachlin and C. V. Wilson, *Org. Syntheses*, **26**, 1 (1946).

(29) Further details of the procedure as well as tables of data may be found in the Ph.D. thesis of Carl Lukach, University of Notre Dame, Notre Dame, Indiana, 1957, available on inter-library loan.

the presence of pyridine, excess anhydride is almost instantaneously hydrolyzed to acetic acid in the quenching process, the titer falls in the course of the reaction as half of the acetyl groups of the anhydride are converted to ester (which was shown not to be hydrolyzed under the conditions of the titration).

In the early runs, difficulties were encountered in that rate constants calculated over the course of the reaction drifted and the infinity titer indicated that the reaction proceeded only to about 95% completion. The difficulty appeared to be due to hydrolysis of some of the acetic anhydride at the very beginning of the reaction, probably due, mainly, to traces of water in the pyridine. To obviate this difficulty the acetic anhydride-pyridine solution was prepared as indicated above, a 25-ml. aliquot was pipetted into 5 ml. of pyridine and the resulting solution was assayed for acetic anhydride.<sup>27</sup> The same amount of acetic anhydride was then considered to be present in the kinetic run carried out as described above and the amount of alcohol weighed out was selected accordingly. With this method there was no drift in the kinetic runs and the infinity titer, in cases where it was checked, indicated that the reaction had gone to 99+% completion.

Table IV shows a typical kinetic run with cyclohexanol. Other runs were followed up to 40-60% completion. Table V is a summary of most of the rate constants determined in this work. It may be seen that the reproducibility of the data at equal concentration of alcohol and anhydride is excellent but that there is a slight discrepancy with data obtained at other ratios and reagents. A change of the pyridine-acetic anhydride ratio from 15:1 to 20:1 had little effect on the rate constants.

TABLE IV

## TYPICAL KINETIC RUN IN THE REACTION OF ACETIC ANHYDRIDE AND CYCLOHEXANOL IN PYRIDINE AT 25°

Concentration alcohol = concentration anhydride = 0.02062 mole; normality base = 0.1223 N;  $a = 1.2835 \times 10^{-3}$  mole/l.

Time, sec.	Base, ml.	$\Delta$ Base, ml.	$x \times 10^3$	$(a-x) \times 10^3$	$k \times 10^5$	Reaction, %
0	21.67	0	....	....	..	
2992	20.24	1.43	0.1749	1.1086	(8.22)	13.6
4745	19.52	2.15	.2630	1.0205	8.46	20.6
19333	16.31	5.36	.6555	0.6279	8.41	46.6
21061	16.11	5.56	.6800	.6035	8.34	53.1
23546	15.82	5.85	.7155	.5680	8.34	55.8
26582	15.51	6.16	.7534	.5301	8.33	58.8
28673	15.32	6.35	.7766	.5068	8.33	60.6
$8.37 \pm 0.04$						

TABLE V

SUMMARY OF EXPERIMENTAL RATE CONSTANTS<sup>30</sup>

Alcohol	Mole	Anhydride	Mole	$k \times 10^5$ , l. mole <sup>-1</sup> sec. <sup>-1</sup>
Cyclohexanol	0.020620	Acetic	0.020620	8.37*
	.020620	Acetic	.020620	8.37*
	.014245	Acetic	.028226	8.67 <sup>c</sup>
	.041984	Acetic	.021203	8.66 <sup>c</sup>
	.02120	Acetic	.02120	8.67 <sup>d</sup>
	.023732 <sup>a</sup>	Acetic	.023732	8.26 <sup>d</sup>
	.023732 <sup>b</sup>	Acetic	.023732	8.40 <sup>d</sup>
	.021306	Propionic	.021306	5.70*
	.021306	Propionic	.021306	5.70*
	.0175988	Isobutyric	.017599	4.43*
.017599	Isobutyric	.017599	4.43*	
<i>trans</i> -4- Butyl- cyclo- hexanol	0.012381	Acetic	0.012381	10.7*
	.012699	Acetic	.012699	10.6*
	.01439	Acetic	.01439	11.1 <sup>d,c</sup>
	.01439	Acetic	.01439	12.2 <sup>d,c</sup>
	.01512	Acetic	.01536	10.4 <sup>d,c</sup>
	.01277	Acetic	.02528	11.1 <sup>d,c</sup>
	.01276	Acetic	.02528	10.8 <sup>d,c</sup>
	.015957	Propionic	.015957	7.16*
<i>cis</i> -4- <i>t</i> -Butyl- cyclo- hexanol	.015957	Propionic	.015957	7.15*
	.012538	Isobutyric	.012538	5.39*
	.012538	Isobutyric	.012538	5.39*
	0.012585	Acetic	0.012585	2.89*
	.012585	Acetic	.012585	2.90*
	.01481	Acetic	.01481	2.81 <sup>d,c</sup>
	.01481	Acetic	.01481	2.81 <sup>d,c</sup>
	.015117	Acetic	.01536	2.96 <sup>d</sup>
	.01279	Acetic	.02587	2.94 <sup>d,c</sup>
	.01274	Acetic	.02587	2.92 <sup>d,c</sup>
	.014811	Propionic	.014811	2.18*
	.014811	Propionic	.014811	2.18*
	.012640	Isobutyric	.012640	2.18*
	.012640	Isobutyric	.012640	2.17*
	<i>trans</i> -4- Methyl- cyclo- hexanol	0.017564	Acetic	0.017564
.017564		Acetic	.017564	9.65*
.01760		Acetic	.01760	9.67 <sup>c</sup>
.01760		Acetic	.01760	9.67 <sup>c</sup>
.017608		Acetic	.017890	9.84 <sup>d</sup>
.01329		Acetic	.02726	9.10 <sup>c</sup>
.01331		Acetic	.02726	9.00 <sup>c</sup>
.017466		Isobutyric	.017466	5.16*
.017466		Isobutyric	.017466	5.14*
<i>cis</i> -4-Methyl- cyclo- hexanol		0.017379	Acetic	0.017379
	.017379	Acetic	.017379	3.76*
	.01843	Acetic	.01843	3.91 <sup>c</sup>
	.01743	Acetic	.01843	3.95 <sup>c</sup>
	.017608	Acetic	.017890	3.73 <sup>d</sup>
	.01335	Acetic	.02761	3.66 <sup>c</sup>
	.01356	Acetic	.02761	3.69 <sup>c</sup>
	.017316	Isobutyric	.017316	2.73*
	.017316	Isobutyric	.017316	2.73*
	<i>cis</i> -3-Methyl- cyclo- hexanol	.017685	Acetic	.017685
.017685		Acetic	.017685	10.7*
<i>trans</i> -3- Methyl- cyclohexanol	.017722	Acetic	.017722	3.93*
	.017722	Acetic	.017722	3.94*
<i>trans</i> -2- Methyl- cyclohexanol	.018044	Acetic	.018044	11.3*
	.018044	Acetic	.018044	11.3*
<i>cis</i> -4-Phenyl- cyclo- hexanol	.014388	Acetic	.014388	3.91*
	.014388	Acetic	.014388	3.91*
<i>trans</i> -4- Phenyl- cyclo- hexanol	.014256	Acetic	.014256	11.6*
	.014256	Acetic	.014256	11.6*
	.014128	Isobutyric	.014128	6.17*
3,3-Dimeth- ylcyclo- hexanol	.010935	Acetic	.010935	9.88*
	.010935	Acetic	.010935	9.87*
4,4-Dimeth- ylcyclo- hexanol	.014653	Acetic	.014653	8.43*
	.014653	Acetic	.014653	8.43*
Butanol-2	.017122	Acetic	.017122	8.66*
	.017122	Acetic	.017122	8.65*
1-Phenyl-2- propanol	.017234	Acetic	.017234	16.8*
	.017234	Acetic	.017234	16.8*

<sup>a</sup> Fifteen mole excess of pyridine. <sup>b</sup> Twenty mole excess of pyridine. <sup>c</sup> Acetic anhydride-pyridine mixture added to undiluted alcohol. <sup>d</sup> There is a slight uncertainty about the acetic anhydride assay in these runs.

(30) In some of the early runs the change in acetic anhydride assay upon the addition of pyridine was not taken into account. The best runs are starred in Table V and summarized in Tables I, II and III.

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Ro and the preparation of 4,4-dimethylcyclohexanol was undertaken by Mr. John D. Ryan. We thank Professor David Y. Curtin, University of Illinois, for helpful advice.  
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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

### Conformational Analysis. III. Epimerization Equilibria of Alkylcyclohexanols<sup>1</sup>

BY ERNEST L. ELIEL AND ROLLAND S. RO<sup>2</sup>

RECEIVED FEBRUARY 16, 1957

The *cis*- and *trans*-4-*t*-butylcyclohexanols have been equilibrated by means of aluminum isopropoxide in isopropyl alcohol. The equilibrium, determined by infrared and gas chromatographic analysis, corresponds to 79% *trans* and 21% *cis* isomer involving a free energy difference of  $-0.96$  kcal./mole, in good agreement with values determined by other methods. Equilibria for the 2-, 3- and 4-methylcyclohexanols and 4-phenylcyclohexanols have been similarly determined and are compared with values in the literature.

In the accompanying paper<sup>1</sup> the equilibrium between the *conformational* isomer of cyclohexanol with an axial hydroxyl group and the isomer with an equatorial hydroxyl group has been determined by a kinetic method. The equilibrium constant was found to be 2.4 corresponding to a free energy difference of  $-0.5$  kcal./mole. A more direct way of approaching this equilibrium is through the *cis*- and *trans*-4-*t*-butylcyclohexanols which, though they are stable *configurational* isomers, may be equilibrated by means of aluminum isopropoxide.<sup>3</sup> Since the *t*-butylcyclohexanols are conformationally homogeneous,<sup>4</sup> the equilibrium between the configurational isomers is as represented in Fig. 1 and thus corresponds to the conformational equilibrium between axial and equatorial hydroxyl. The equilibrium concentration of the two isomers (Fig. 1) was determined both by infrared analysis and

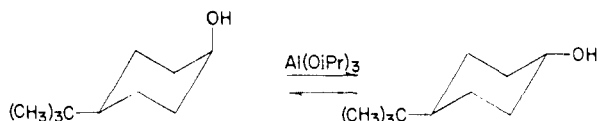


Fig. 1.

by vapor phase chromatography and corresponds to  $79 \pm 2\%$  *trans* and  $21 \pm 2\%$  *cis* isomer, giving an equilibrium constant of 3.76 and a free energy difference of  $-0.96$  kcal./mole. This value, which refers to isopropyl alcohol at  $89^\circ$  as a solvent,<sup>5</sup> is in good agreement with earlier values of  $-0.8$  (at  $40^\circ$  in 75% acetic acid)<sup>4</sup> and  $-0.9$  (in water)<sup>6</sup> and in fair agreement with that of  $-0.5$  (at  $25^\circ$  in pyridine) reported in the accompanying paper.<sup>1</sup>

(1) Paper II, E. L. Eliel and C. A. Lukach, *THIS JOURNAL*, **79**, 5980 (1957).

(2) Texas Co. Fellow, 1954-1956. From the Ph.D. Thesis of Rolland S. Ro.

(3) W. G. Dauben, G. J. Fonken and D. S. Noyce, *THIS JOURNAL*, **78**, 2579 (1956). Professor Dauben kindly made this work available to us in advance of publication, and we wish to acknowledge correspondence with him regarding the equilibria in question both prior and subsequent to publication of his paper.

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

(5) Since a large excess of isopropyl alcohol was present in the equilibration, it may be assumed that most of the *t*-butylcyclohexanol was present as such rather than as an aluminum salt.

(6) S. J. Angyal and D. J. McHugh, *Chemistry & Industry*, 1147 (1956).

It is of some interest to compare the above equilibrium (Fig. 1) with one between alkylcyclohexanols which are not conformationally homogeneous and where both conformational isomers of the two epimers must be considered, such as the 4-methylcyclohexanols (Fig. 2). In this case, the epimeriza-

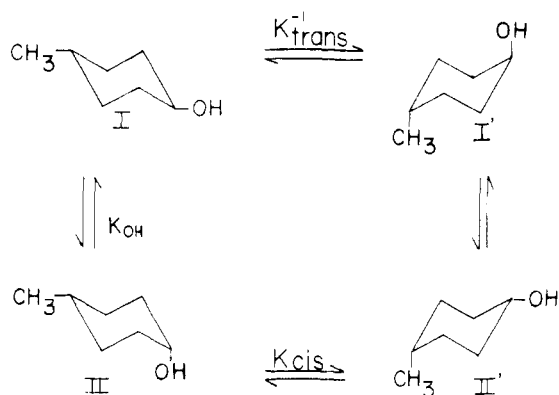


Fig. 2.

tion equilibrium constant  $K_{epi} = (I + I')/(II + II')$ , since this constant is based on stoichiometric concentrations. This expression may be transformed as

$$K_{epi} = \frac{I}{II} \times \frac{1 + I'/I}{1 + II'/II} = K_{OH} \frac{1 + K_{trans}^{-1}}{1 + K_{cis}} \quad (i)$$

Since  $K_{trans}^{-1} < K_{cis}$  it follows that  $K_{epi} < K_{OH}$ . The data in Table I, obtained by infrared and gas chromatographic analyses, bear out this prediction.

TABLE I  
EPIMERIZATION EQUILIBRIA AT  $89^\circ$   
Stable isomer.<sup>a</sup> ( $K_{epi}$ ), %

Compound	By gas chromatography	
	By infrared	
4- <i>t</i> -Butylcyclohexanol	77-81 (3.35-4.30)	79 (3.76)
4-Methylcyclohexanol	69-71 (2.23-2.44)	68.5 (2.18)
3-Methylcyclohexanol	77-79 (3.35-3.76)	77 (3.35)
2-Methylcyclohexanol	High	>94 <sup>b</sup>
4-Phenylcyclohexanol	70 ± 5	...

<sup>a</sup> *trans*-4-, *cis*-3- and *trans*-2-isomer. <sup>b</sup> Tentative result; it is possible that equilibrium was not reached.