Acknowledgment. This work was supported, in part, by National Science Foundation Grant G-7371, and by Grant 266-A from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

Conformational Analysis. XII.[1] Acetylation Rates of Substituted Cyclohexanols. The Kinetic Method of Conformational Analysis

Ernest L. Eliel and Francis J. Biros[2]

Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received February 16, 1966*

Abstract: The three diastereoisomeric 3,5-dimethylcyclohexanols, the two diastereoisomers of 3-methyl-5-isopropylcyclohexanol and of 3,5-di-*t*-butylcyclohexanol in which the alkyl groups are *cis*, and *cis*-3-methyl-*cis*-5-*t*-butylcyclohexanol have been prepared and their structure and stereochemistry have been established. Acetylation rates of the above compounds as well as of *cis*- and *trans*-2-methyl-, -2-ethyl-, -2-isopropyl-, and -2-*t*-butylcyclohexanol, -3-isopropyl- and -3-*t*-butylcyclohexanol, -4-*t*-butylcyclohexanol, *cis*-3-methylcyclohexanol, *trans*-4-methylcyclohexanol, 3,3-dimethylcyclohexanol, *cis*- and *trans*-3,3,5-trimethylcyclohexanol, cyclohexanol, menthol, *cis,cis*-2-methyl-4-*t*-butylcyclohexanol, and 3,3,5,5-tetramethylcyclohexanol have been measured and compared to previously determined acetylation rates of substituted cyclohexanols. The basis of the kinetic method of conformational analysis is discussed. The chemical shift of the carbinol protons in the above alcohols is examined in the light of a previously established correlation.

One of the aims of conformational analysis[3] is to establish the position of equilibria of the type shown in Figure 1.[4] Among the numerous methods devised to this end[3,4] is the kinetic method.[5,6] In this method, a chemical reaction of the system shown in Figure 1 is considered as involving discrete reactions of the equatorial and axial conformational isomers; it then follows[3-7] that $k = (k_eK + k_a)/(K + 1) = N_ek_e + N_ak_a$ where k is the empirical rate constant for the chemical reaction under study, k_e and k_a are the corresponding rate constants for the pure equatorial and pure axial conformations, respectively, K is the equilibrium constant for the equilibrium shown in Figure 1, and N_e and N_a are the mole fractions of the two conformational isomers existing at equilibrium ($N_e/N_a = K$, $N_e + N_a = 1$). The above equation may be transformed into

$$K = (k_a - k)/(k - k_e)$$

and, in this form, may serve to evaluate the desired equilibrium constant K, provided one can obtain values for k_a and k_e as well as k. It has been suggested[5] that k_a and k_e may be taken as the specific reaction rates (for the reaction under study) of *cis*- and *trans*-4-*t*-butyl-substituted compounds, shown in Figure 2. The conditions for the validity of this suggestion (which has served as the basis of a number of experimental determinations of conformational equilibrium constants) have been stated quite explicitly[3,4,7] and are the following. (1) The 4-*t*-butylcyclohexyl compounds (Figure 2) must exist virtually exclusively in the conformation with equatorial *t*-butyl. (2) The *t*-butyl group must not exercise a polar effect on the reaction. (3) The *t*-butyl group must not exercise a steric effect on the reaction. (4) The *t*-butyl group must not distort either the ground state or transition state of the reaction in such a way as to affect the activation energy.

Of these assumptions, the first one is normally quite safe, for the conformational preference of the *t*-butyl group for the equatorial position amounts to at least 4.4 kcal/mole[8,9] and since corresponding preferences for various X groups (Figure 2) which have been explored by the kinetic method usually do not exceed 1.7 kcal/mole, it may be estimated that at or near room temperature, at least 99% of the *cis* isomer and virtually all the *trans* isomer are in the conformations shown in Figure 2. The second assumption has been subjected to some scrutiny mainly through an examination of pK values of various conformationally homogeneous (or nearly homogeneous) cyclohexanecarboxylic acids.[10-14]

(1) Paper XI: E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J.-C. Richer, *J. Am. Chem. Soc.*, **88**, 3327 (1966).
(2) From the Ph.D. Dissertation of Francis J. Biros, University of Notre Dame, 1964.
(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965.
(4) E. L. Eliel, *Angew. Chem., Intern. Ed. Engl.*, **5**, 761 (1965).
(5) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).
(6) E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957).
(7) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).
(8) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).
(9) *Cf.* E. L. Eliel and T. J. Brett, *ibid.*, **87**, 5039 (1965), for details of the argument leading to this figure.
(10) J. F. J. Dippy, S. R. C. Hughes, and J. W. Laxton, *J. Chem. Soc.*, 4102 (1954).
(11) R. D. Stolow, *J. Am. Chem. Soc.*, **81**, 5806 (1959).
(12) M. Tichý, J. Jonàš, and J. Sicher, *Collection Czech. Chem. Commun.*, 24, 3434 (1959).
(13) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Koninkl. Ned. Akad. Wetenschap Proc., Ser. B*, **64**, 161 (1961).
(14) P. F. Sommer, C. Pascual, V. P. Arya, and W. Simon, *Helv. Chim. Acta*, **46**, 1734 (1963).

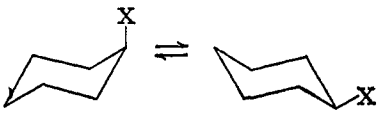

Figure 1.

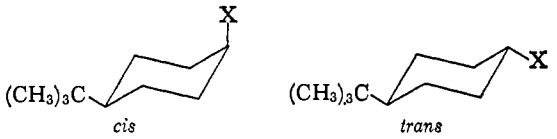

Figure 2.

The most detailed of these determinations,[13] reproduced in excerpt in Table I suggests that there is at least no polar effect of substituents in the 4 position. The conformationally homogeneous *trans*-4-alkylcyclohexanecarboxylic acids all have essentially the same pK and the pK values for the *cis* acids and the unsubstituted acid are consistent with the accepted conformational free-energy values for the alkyl and carboxyl groups. There are variations in the 3 series, but is is not clear whether they are due to polar effects, deformation effects,[1] or both.

Table I. pK Values of Alkylcyclohexanecarboxylic Acids in 50% Ethanol at 25°

Alkylcyclohexanecarboxylic acid	pK Found Eq	pK Found Axial	pK Calcd[a] Eq	pK Calcd[a] Axial
Unsubstituted	6.30		6.31	
4-*t*-Butyl	6.28	6.78	[6.28][b]	[6.78][b]
4-Isopropyl	6.26	6.66	6.28	6.59
4-Ethyl	6.28	6.57	6.28	6.54
4-Methyl	6.26	6.53	6.28	6.52
3-*t*-Butyl	6.42	6.95	[6.42][c]	[6.95][c]
3-Isopropyl	6.41	...	6.42	6.75
3-Methyl	6.31	...	6.42	6.67
3,5-Dimethyl	6.35	...	6.42	6.95
3,5-Di-*t*-butyl	6.56	...	6.42	6.95
2-Methyl	6.24	6.52	...	...
2-Ethyl	6.38	6.67	...	...
2-Isopropyl	6.47	7.16	...	...
2-*t*-Butyl	6.65	7.45	...	...

[a] Using the equation[11] $K_{acid} = (K_eK + K_a)/(K + 1)$ where K_{acid} is the acidity constant of the acid in question, K_e is the acidity constant of the equatorial (*trans*-4- or *cis*-3-*t*-butyl-substituted) acid, and K_a is the acidity constant of the axial (*cis*-4- or *trans*-3-*t*-butyl-substituted) acid. K is the conformational equilibrium constant and is calculated assuming additivity of conformational free energies,[4] $\Delta G°$, and the following $-\Delta G°$ values:[9] Me, 1.65; Et, 1.75; *i*-Pr, 2.00; COOH, 1.35 (unpublished result of M. C. Reese). [b] Standards for 4 series. [c] Standards for 3 and 3,5 series.

The absence of a direct steric effect of a 4-*t*-butyl group is difficult to demonstrate experimentally, but, although such an effect has been postulated to exist,[15] it appears unlikely from model considerations and no clear-cut evidence for such an effect has ever come forth. This leaves the distortion effect as the most likely course of failure of the kinetic method of conformational analysis. Since it is known and has been pointed out in the literature[16] that the kinetic method does, on occasion, fail, it seemed advisable to try to get more experimental information about the distortion effect (and possibly also polar and steric effects, which might not be cleanly separable from distortion effects). Our approach was to study, in the main, differently substituted but conformationally homogeneous systems. If distortion (and other) effects make the reactivity of *cis*- and *trans*-4-*t*-butyl-substituted cyclohexyl-X compounds differ from that of unsubstituted cyclohexyl-X in its axial and equatorial conformation, it is then also to be expected that differently substituted but otherwise conformationally homogeneous and analogous cyclohexyl-X derivatives will differ in reactivity from each other.

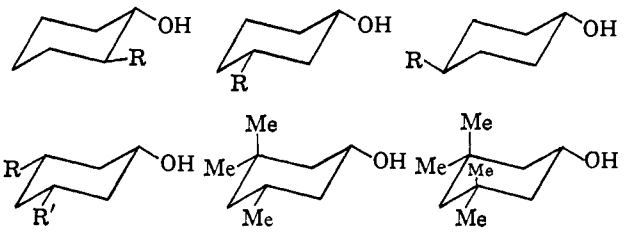

Figure 3. Equatorial alcohols.

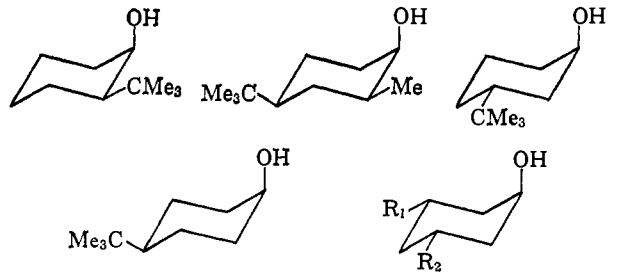

Figure 4. Axial alcohols.

The system chosen for study was the cyclohexanol system, since a wide variety of substituted cyclohexanols in diastereoisomerically pure form are relatively easy to synthesize, and because a convenient kinetic method for assaying the system—acetylation with acetic anhydride in pyridine at room temperature—was already at hand.[6] The conformationally homogeneous compounds used—2-, 3-, and 4-*t*-butylcyclohexanols, other *trans*-2-, *cis*-3-, and *trans*-4-alkyl-substituted cyclohexanols, *trans,trans*- and *cis,cis*-3,5-dialkylcyclohexanols, and a few others—are depicted in Figures 3 (equatorial alcohols) and 4 (axial alcohols). A few other alkylcyclohexanols, *e.g.*, *cis*-2-, *trans*-3-, and *cis*-4-alkylcyclohexanols, were included in the study for completeness even though they are not conformationally homogeneous; *trans*-3,3,5-trimethylcyclohexanol, *cis,trans*-3,5-dimethylcyclohexanol, and 3,3-dimethylcyclohexanol were included to assess the effect of a *syn*-axial methyl–hydroxyl interaction.

Experimental Section

Alkylcyclohexanols. In general, epimeric alkylcyclohexanol mixtures rich in the equatorial isomer were prepared by mixed hydride equilibration[17] of epimeric mixtures available commercially or prepared by catalytic reduction of phenols. Chromic acid oxidation of the alcohol mixtures to ketones followed by catalytic reduction over platinum (from platinum oxide) in acetic acid–hydrochloric acid[8] or fractional distillation of crude alcohols[18]

(15) R. Cornubert, *Bull. Soc. Chim. France*, 996 (1956).
(16) *E.g.*, W. Hückel and M. Hanack, *Ann.*, **616**, 18 (1958); H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **86**, 1161 (1964).
(17) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, 30, 3809 (1965).
(18) E. L. Eliel and R. G. Haber, *ibid.*, **23**, 2041 (1958).

through a 5-ft Podbielniak column yielded mixtures rich in the axial alcohols. In most cases, the alcohols were purified through crystalline derivatives, although in a few instances fractional distillation or crystallization of the alcohols themselves gave pure specimens as demonstrated by gas chromatography.

cis-2-Methylcyclohexanol had bp 64° (15 mm), n^{20}D 1.4640; hydrogen phthalate had mp 102–104° (lit.[6,18] bp 65° (16 mm), $n^{18.2}$D 1.4648; phthalate, mp 102–104°). *trans*-2-Methylcyclohexanol had bp 65–66° (10 mm), n^{20}D 1.4611; 3,5-dinitrobenzoate had mp 119–120° (lit.[6,18] bp 72° (20 mm), $n^{19.7}$D 1.4613; 3,5-dinitrobenzoate, mp 117–118.5°). *cis*-3-Methylcyclohexanol had bp 72–73° (12 mm), n^{20}D 1.4575 (lit.[6,18] bp 72° (11 mm), n^{20}D 1.4550). 3,3-Dimethylcyclohexanol had bp 74–75° (9 mm), n^{20}D 1.4559; *p*-nitrobenzoate had mp 82–83° (lit.[6] bp 84.8° (16 mm), n^{20}D 1.4561; *p*-nitrobenzoate mp 82–83°). *cis*-4-*t*-Butylcyclohexanol had mp 82–83°; *p*-nitrobenzoate had mp 132–133° (lit.[19] mp 82.5–83.5°; *p*-nitrobenzoate, mp 133–134°). *trans*-4-*t*-Butylcyclohexanol had mp 80–81° (lit.[19] mp 81–82°). *cis*-3,3,5-Trimethylcyclohexanol had mp 34–35°; acid phthalate had mp 127–128.5° (lit.[20] mp 36–38°; phthalate, mp 127.5–129°). *trans*-3,3,5-Trimethylcyclohexanol had mp 53–55° (lit.[20] mp 58.5°). All these compounds were prepared as described before.[6,17,19,20] *trans*-4-Methylcyclohexanol was purchased from Columbia Organic Chemicals Co. and redistilled, bp 73–74° (12 mm), n^{20}D 1.4569 (lit.[6,18] bp 75° (14 mm), n^{21}D 1.4531); material so obtained was homogeneous (glpc). Menthol was recrystallized from hexane, mp 41–42° (lit. mp 42.5°), and was gas chromatographically homogeneous. Cyclohexanol was distilled through a 48-cm helix-packed column, bp 160° (745 mm) (lit. bp 161.5°).

cis-2-*t*-Butylcyclohexanol was kindly contributed by the Dow Chemical Co.,[21] mp 55–56° (lit.[22] mp 56.8–57.7°), and was gas chromatographically homogeneous; *trans*-2-*t*-butylcyclohexanol, similarly contributed,[21] melted at 83.5–84.5° (lit.[22] mp 84.4–85.0°), and was also homogeneous, according to glpc.

cis- and *trans*-3-*t*-Butylcyclohexanols had been prepared in the course of another investigation[23] by catalytic reduction of 3-*t*-butylphenol followed by fractional distillation. The slightly impure *cis* isomer was purified through the acid phthalate, mp 135–136° (lit.[5] mp 136.0–136.8°). Saponification yielded gas chromatographically homogeneous *cis*-3-*t*-butylcyclohexanol, bp 108–109° (14 mm), mp 39.5–40.5° (lit.[5] mp 40–41°). *trans*-3-Butylcyclohexanol was furnished by West[23] as the acid phthalate, mp 154–155° (lit.[5] mp 154.5–155.5°), which, upon saponification, yielded the gas chromatographically pure alcohol, bp 88° (6 mm), mp 47–48° (lit.[5] bp 85° (5 mm), mp 44–45°).

cis-2-Ethylcyclohexanol was obtained by fractional distillation through a 5-ft Podbielniak column of a commercial 2-ethylcyclohexanol sample (K & K Laboratories) containing, according to the gas chromatogram, cyclohexanol, *cis*- and *trans*-2-ethylcyclohexanol, and an unknown impurity. After a forerun of cyclohexanol, *cis*-2-ethylcyclohexanol, bp 74° (17 mm), n^{20}D 1.4659 (lit.[24] bp 71–73° (15 mm)), gas chromatographically homogeneous, was collected. Its infrared spectrum showed absence of ketone and *trans* isomer; prominent peaks were found at 2.99, 3.45, 6.87–6.97, 8.37, 10.11, and 10.36 μ.

***trans*-2-Ethylcyclohexanol.** "Mixed hydride"[25] was prepared by slowly adding 100 ml of anhydrous ether to 20.8 g (0.156 mole) of aluminum chloride kept at 0° in a 500-ml, three-necked, round-bottom flask equipped with a magnetic stirrer, calcium chloride protected reflux condenser, and pressure-equalized addition funnel. When solution was complete, 32.3 ml of a 1.29 *M* solution (0.039 mole) of lithium aluminum hydride ($LiAlH_4$) was added slowly with stirring which was continued for 0.5 hr. The solution was allowed to warm to room temperature and 20 g (0.156 mole) of *cis*-2-ethylcyclohexanol in 100 ml of anhydrous ether was added slowly with stirring. The solution was boiled for 1 hr and then 2.79 g of acetone was added. Boiling was continued for 1 hr, then the solution was cooled and quenched with water, followed by 10% sulfuric acid in the usual way. The ether layer was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated to give 18.8 g (*ca.* 95%) of crude product which, according to gas chromatographic analysis, contained the *cis*- and *trans*-2-ethylcyclohexanols in a 2.6:97.4 ratio, in addition to some 2-ethylcyclohexanone.

The crude product was converted to the 3,5-dinitrobenzoate by the method of Brewster and Ciotti[26] using 3,5-dinitrobenzoic acid and *p*-toluenesulfonyl chloride. After three recrystallizations from methanol, the ester was recovered in 41% yield, mp 103–104° (lit.[24] mp 104–105°).

Hydrolysis of the ester by means of aqueous methanolic potassium hydroxide[6] yielded *trans*-2-ethylcyclohexanol in 87% yield, bp 68° (2 mm), n^{20}D 1.4663 (lit.[24] bp 81–83° (15 mm)).

The infrared spectrum showed a trace of ketone and possibly a trace of the *cis* isomer. Prominent peaks were found at 2.95, 3.02, 3.45, 6.94, 9.5–9.6, 10.40, 11.07, and 11.8–11.9 μ.

***cis*-2-Isopropylcyclohexanol.** Commercial 2-isopropylcyclohexanol (K & K Laboratories) was fractionated[27] on a 40 × 1 cm spinning-band column. The early fractions, bp 86–92° (14 mm), contained 94.3% *cis* isomer, according to glpc analysis. These fractions crystallized partially on standing. Three recrystallizations from hexane returned gas chromatographically pure *cis*-2-isopropylcyclohexanol, 43% recovery, mp 51–52° (lit.[28] mp 50.2–50.5°).

***trans*-2-Isopropylcyclohexanol** was prepared as described for *trans*-2-ethylcyclohexanol above, starting with a *cis*-rich mixture of epimers. The crude product contained, in addition to 2-isopropylcyclohexanone, the *trans* and *cis* alcohols in a 96.9:3.1 ratio. From this mixture, gas chromatographically pure *trans*-2-isopropylcyclohexanol was obtained by repeated recrystallization from hexane in 46% recovery, mp 63–64°; 3,5-dinitrobenzoate, mp 133–134° (lit.[28] mp 64.4°; 3,5-dinitrobenzoate, mp 134–134.5°).

***cis*- and *trans*-3-Isopropylcyclohexanol.** A solution of 45.6 g (0.33 mole) of *m*-isopropylphenol in 100 ml of 95% ethanol was hydrogenated in a Parr shaker in the presence of 10 g of 5% rhodium on alumina at room temperature and 34 psi. The theoretical amount of hydrogen was taken up in 3.1 hr. The solution was filtered and concentrated, and the residue was taken up in ether. The ether solution was washed with 100-ml portions of 10% aqueous sodium hydroxide followed by brine, dried over magnesium sulfate, concentrated, and distilled to give 40.9 g (87%) of mixed 3-isopropylcyclohexanols, bp 92–100° (12 mm), shown, by gas chromatographic analysis, to contain 62.9% *trans* and 37.1% *cis* isomer. This material was fractionally distilled through a 5-ft Podbielniak column using 100 ml of diethylene glycol (bp 244.5°) as a chaser. The composition of the distillate was monitored gas chromatographically on a 10-ft Carbowax 20M column at 170°, He flow rate 94 ml/min. The early fractions boiled at 102.5° (17 mm) (recovery 23.2 g), n^{20}D 1.4662 (lit.[29] bp 101° (15 mm), n^{20}D 1.4659 for the *trans* isomer) and were gas chromatographically homogeneous; prominent infrared peaks were found at 2.92, 3.45, 6.90, 7.36, 7.46, 8.8–8.9, 10.3, and 11.31 μ (in $CHCl_3$). Following an intermediate fraction (8.2 g) there was then collected 9.7 g, bp 109.4° (17 mm), n^{20}D 1.4649, of *cis* isomer (lit.[29] bp 106° (15 mm), n^{20}D 1.4651) which was also gas chromatographically pure; prominent infrared peaks were found at 2.95, 3.45, 6.90, 7.35, 9.6–9.8, 10.21, and 10.61 μ ($CHCl_3$).

***cis,cis*-3,5-Dimethylcyclohexanol.** The hydrogenation of 100 g (0.82 mole) of 3,5-dimethylphenol in the presence of 10 g of Raney nickel and 0.1 g of sodium hydroxide in a steel bomb at 1600 psi hydrogen led to the uptake of the theoretical amount of hydrogen in 3.8 hr. The contents of the bomb was dissolved in 500 ml of ether and filtered, and the filtrate was washed with three 200-ml portions of 10% sodium hydroxide, followed by brine, then dried over magnesium sulfate and concentrated. Distillation afforded 92.3 g (88%) of 3,5-dimethylcyclohexanol, bp 81° (13 mm), containing, according to gas chromatographic analysis, 65.1% *cis,cis*, 28.4% *trans,trans*, and 6.5% *cis,trans* isomer.

Equilibration with mixed hydride[17] (*vide supra*) of 15 g of the above material[30] (using 15.9 g of $AlCl_3$, 175 ml of ether, 35.7 ml of

(19) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).
(20) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).
(21) We are indebted to Dr. Walter Trapp for the samples of *cis*- and *trans*-2-butylcyclohexanol. These compounds are available by careful fractional distillation of the commercially available acetate mixture (Dow) followed by saponification.
(22) H. L. Goering, R. L. Reeves, and H. H. Espy, *J. Am. Chem. Soc.*, **78**, 4926 (1956).
(23) J. West, Ph.D. Dissertation, University of Notre Dame, 1965.
(24) C. Kucera, *Dissertation Abstr.*, **16**, 2307 (1956).
(25) E. L. Eliel, *Record Chem. Progr.*, **22**, 129 (1961). See also ref 17.
(26) J. H. Brewster and C. J. Ciotti, *J. Am. Chem. Soc.*, 77, 6214 (1955).
(27) The authors thank Sr. Lucetta Barnard, C. S. C., for carrying out this fractionation.
(28) W. Hückel and R. Neidlein, *Chem. Ber.*, **91**, 1391 (1958).
(29) W. Hückel and K. Thiele, *ibid.*, **94**, 96 (1961).
(30) Alternatively, commercial material (see below) may be submitted to equilibration.

0.84 *M* $LiAlH_4$, and 2.97 g of acetone) gave 14.5 g (96%) of 96.7% pure *cis,cis*-3,5-dimethylcyclohexanol, bp 83–84° (12 mm). This material was converted to the 3,5-dinitrobenzoate by means of 3,5-dinitrobenzoyl chloride in pyridine, yield 47%, mp 80–81° (lit.[31] mp 77–78°). Saponification gave gas chromatographically pure *cis,cis*-3,5-dimethylcyclohexanol, bp 80° (12 mm), $n^{20}D$ 1.4548 (lit.[31] bp 83° (17 mm), $n^{20}D$ 1.4550) in 45% yield. Prominent infrared bands were found at 3.0, 3.45, 6.80, 7.22, 7.30, 8.95, 9.6–9.9, 10.29, 10.58, 11.01, and 11.71 μ.

***trans,trans*-3,5-Dimethylcyclohexanol.** Two hundred grams of commercial 3,5-dimethylcyclohexanol (Aldrich Chemical Co.) was subjected to fractional distillation on a 5-ft Podbielniak column. The first three fractions, bp 77–79° (17 mm), were shown by gas chromatographic analysis to be pure *trans,trans* material and amounted to 29.4 g. They crystallized on standing, mp 40–41° (lit.[31] bp 79–80 (17 mm), mp 39–40°). The hydrogen phthalate melted at 105–106° (lit.[31,32] mp 106°).

***cis,trans*-3,5-Dimethylcyclohexanol.** 3,5-Dimethylcyclohex-2-en-1-one, bp 87° (9 mm), $n^{20}D$ 1.4822 (lit. bp 86–89° (9 mm),[33] $n^{20}D$ 1.4828[34]), was prepared from acetaldehyde and ethyl acetoacetate in 51% yield[34] and was hydrogenated using 4.0 g of rhodium on alumina for 25 g of ketone in 100 ml of 30% aqueous ethanol at 50 psi. Hydrogen absorption ceased after about 6 hr being only 75% complete. The catalyst was filtered and the combined filtrate from six batches was concentrated and extracted with six 50-ml portions of ethyl ether. The ether extract was washed with water and brine, dried over magnesium sulfate, and concentrated to give a residue of 131.6 g (85% yield). This material, according to its gas chromatogram, consisted of a mixture of *cis*- and *trans*-3,5-dimethylcyclohexanone (56.4% *cis*, 43.6% *trans* by later assignment) and *trans,trans*-, *cis,cis*-, and *cis,trans*-3,5-dimethylcyclohexanols (54.7, 31.3, and 14.0% of alcohol fraction).

The crude material was subjected to distillation on a 5-ft Podbielniak column. The initial fractions were pure *cis*-3,5-dimethylcyclohexanone followed by increasing amounts of *trans* isomer; a total of 7.6 g of the latter varying in purity from 94.9 to 98.0% (by glpc) was collected between 80.0 and 81.8° (23 mm), $n^{20}D$ 1.4475 for 98% pure material[35] (lit.[36] $n^{25}D$ 1.4465).

The ketone (7.5 g) in 50 ml of ether was reduced to alcohol (6.91 g, 91%, bp 79–81° (15 mm)) by means of lithium aluminum hydride (1.9 g in 50 ml of ether) in the usual way. The crude alcohol was converted to the 3-nitrophthalate by means of 3-nitrophthalic anhydride in pyridine. The ester, after three recrystallizations from ethyl acetate–petroleum ether (bp 30–60°), weighed 11.1 g (64%) and melted at 153–154°.

Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96. Found: C, 59.44; H, 5.91.

Saponification of the 3-nitrophthalate gave *cis,trans*-3,5-dimethylcyclohexanol, bp 58° (2 mm), $n^{20}D$ 1.4608 (lit.[31] bp 89–90° (17 mm)), in 84% yield. The material was gas chromatographically homogeneous and its infrared and nmr spectra were compatible with the assigned structure (strong bands found at 3.02, 3.49, 6.90, 7.30, 9.08, 9.70, and 9.93 μ in the infrared, two methyl doublets at −53.4, −56.1, −59.4, and −64.0 cps, and a carbinol multiplet centered on −221 cps—at 60 Mcps measured from tetramethylsilane—in the nmr).

The same material, bp 82–83° (17 mm), $n^{20}D$ 1.4605, was also synthesized in 3% over-all yield from methallylsuccinic anhydride[37] *via* 3-keto-5-methylcyclohex-4-enecarboxylic acid,[38] *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone,[38] *trans*-5-methyl-*cis*-3-hydroxymethylenecyclohexanol, the corresponding tosyloxymethylene compound and its tetrahydropyranyl derivative, and, finally, reduction with lithium aluminum hydride.[39] This did not appear to be a feasible method of synthesis in quantity, however.

***cis*-3-Methyl-5-isopropylcyclohexanone.** 3-Methyl-5-isopropylcyclohex-2-en-1-one was prepared from isobutyraldehyde and ethyl acetoacetate in 50% yield in similar fashion as the 5-methyl homolog,[34] bp 120–122° (13 mm), $n^{20}D$ 1.4865 (lit.[33,34] bp 120–122° (15 mm), $n^{20}D$ 1.4867). The enone (40 g) dissolved in 100 ml of ethanol was hydrogenated in the presence of 2.5 g of palladium on charcoal at a pressure of 42 psi. Hydrogen absorption ceased after 2 hr. The solution was filtered, concentrated, and distilled to give 30.2 g (74%) of *cis*-3-methyl-5-isopropylcyclohexanone, bp 80° (4 mm), $n^{20}D$ 1.4499, characterized as the 2,4-dinitrophenylhydrazone (recrystallized from aqueous ethanol), mp 143–144°.

Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.64. Found: C, 57.53; H, 6.70.

As shown below, the ketone was mainly the *cis* isomer.

3-Methyl-5-isopropylcyclohexanols. In a typical experiment, 30 g (0.19 mole) of *cis*-3-methyl-5-isopropylcyclohexanone (*vide supra*) in 125 ml of glacial acetic acid was hydrogenated in the presence of 2.0 g of platinum oxide at an initial pressure of 42 psi. The theoretical amount of hydrogen was taken up in 2 hr. The solution was filtered and poured into 500 ml of 25% aqueous sodium hydroxide which was then extracted with six 100-ml portions of ether. The combined ether extracts were washed with brine, dried over magnesium sulfate, and concentrated to give 27.8 g (92%) of crude product which, according to gas chromatographic analysis, contained essentially two components in a 34.5:65.5 ratio. (A small shoulder on one of the peaks suggested the presence of at least one other isomer in very minor amounts.)

***trans,trans* Isomer.** The above mixture (27 g) was chromatographed on 2 lb of neutral alumina using benzene as a solvent and eluent. Fractions 7–11 contained 1.38 g of ketone and were discarded. Fractions 12–32 were empty. Fractions 33–90 produced 7.08 g of *trans,trans* alcohol which was redistilled to give 6.48 g of *trans*-3-methyl-*trans*-5-isopropylcyclohexanol, bp 80° (2.5 mm), $n^{20}D$ 1.4627. The material was gas chromatographically homogeneous. The infrared spectrum (strong bands at 3.02, 3.45, 6.90, 7.28, 7.37, 8.76, 9.95, and 10.55 μ) and nmr spectrum were compatible with the assigned structure. The 3,5-dinitrobenzoate, recrystallized from methanol, melted at 115–116°.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33. Found: C, 58.20; H, 6.20.

***cis,cis* Isomer.** Another batch of the above crude alcohol (17.0 g) was equilibrated by means of mixed hydride (from 14.67 g of $AlCl_3$ and 25.9 ml of 0.93 *M* $LiAlH_4$ solution) and acetone (2.97 g) to give 15.6 g (92%) of material containing 97.6% *cis,cis* alcohol. This alcohol was converted to the 3,5-dinitrobenzoate by means of 3,5-dinitrobenzoic acid and *p*-toluenesulfonyl chloride[26] in 48% yield (after three recrystallizations from methanol), mp 105–106°.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33. Found: C, 58.35; H, 6.61.

Saponification of the ester yielded *cis*-3-methyl-*cis*-5-isopropylcyclohexanol, bp 87° (3 mm), $n^{20}D$ 1.4634, in 65% yield. The material was gas chromatographically homogeneous and its infrared spectrum (prominent peaks at 3.02, 3.41, 6.89, 7.35, 9.59, and 9.75 μ) and nmr spectrum were compatible with the assigned structure.

3-Methyl-5-*t*-butylphenol. This material was commercially availabe (from Aldrich Chemical Co.) but has not been described in the literature. After sublimation it melted at 40–41° and its infrared spectrum was compatible with the assigned structure.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.43; H, 9.94.

This phenol was different in infrared spectrum and melting point from 2-methyl-6-*t*-butylphenol (commercial sample, bp 109° (4 mm), $n^{20}D$ 1.5240), 2-methyl-4-*t*-butylphenol (commercial sample, bp 96° (4 mm), $n^{20}D$ 1.5207), and 2-*t*-butyl-4-methylphenol (prepared by *t*-butylation of *p*-cresol with *t*-butyl alcohol,[40] mp 39–40° (lit.[40] mp 44°)). For further structure proof, 3-methyl-5-*t*-butylphenol was reduced to *m*-*t*-butyltoluene. To 6.35 g (0.0387 mole) of the phenol in 20 ml of carbon tetrachloride was added 5.52 g (0.04 mole) of diethyl phosphite, followed by 4.04 g (0.04 mole) of triethylamine, added dropwise. The solution was permitted to stand overnight and water added to dissolve amine salts. The organic layer was separated and washed successively with two 100-ml portions of 10% hydrochloric acid, two 100-ml portions of 10% aqueous sodium hydroxide, and brine. After drying over potassium carbonate and concentration, the residue weighed 6.25 g (0.022 mole). It was dissolved in 150 ml of liquid ammonia and 1.01 g

(31) A. Skita and W. Faust, *Ber.*, **72B**, 1129 (1939).
(32) J. v. Braun and E. Anton, *ibid.*, **60**, 2438 (1927).
(33) E. C. Horning, M. Denekas, and R. Field, *J. Org. Chem.*, **9**, 547 (1944).
(34) E. C. Hornig, M. Denekas, and R. Field, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 317.
(35) For an improved synthesis of the *trans* ketone, see N. L. Allinger and C. K. Riew, *Tetrahedron Letters*, 1269 (1966).
(36) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 232 (1959).
(37) D. D. Phillips and A. W. Johnson, *ibid.*, **77**, 5977 (1955).
(38) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 1732 (1961).
(39) *Cf.* H. L. Goering and C. Serres, *J. Am. Chem. Soc.*, **74**, 5908 (1952).
(40) A. Chichibabin, *Compt. Rend.*, **198**, 1239 (1934).

(0.044 g-atom) of sodium metal in small pieces was added at such a rate as to avoid excessive frothing. Upon completion of the addition, 2.02 g (0.022 mole) of absolute ethanol was added to the blue solution and the ammonia was allowed to evaporate. The residue was taken up in ether, washed with 10% sodium hydroxide solution, dried over magnesium sulfate, concentrated, and carefully distilled to give 2.65 g (45%) of *m*-*t*-butyltoluene, bp 50° (10 mm), n^{20}D 1.4947, identical in infrared spectrum with an authentic sample, bp 50° (10 mm), n^{20}D 1.4947.

***cis*-3-Methyl-*cis*-5-*t*-butylcyclohexanol.** A solution of 24 g (0.14 mole) of 3-methyl-5-*t*-butylphenol in 100 ml of 95% ethanol was hydrogenated at 150° and 2520 psi in the presence of 4 g of Raney nickel in a steel bomb. The theoretical amount of hydrogen was taken up in 4.75 hr. The product was worked up in the usual way (*vide supra*) to give 22.3 g (93%) of 3-methyl-5-*t*-butylcyclohexanols, bp 116–125° (12 mm). Gas chromatographic analysis indicated that all four expected diastereoisomers were present, to the extent of 22.2, 4.2, 64.8, and 8.8%.

The crude mixture was equilibrated with mixed hydride (from 17.34 g of $AlCl_3$ and 34.4 ml of 0.93 *M* ethereal $LiAlH_4$) in 75 ml of ether as described (*vide supra*) using 2.96 g of acetone. The recovered material, 20.8 g (92%), boiled at 125–129° (15 mm) and consisted of two isomers in 91.3:8.7 ratio.

The material so obtained was converted[26] to the 3,5-dinitrobenzoate, mp 107–108° after three recrystallizations from methanol (41% yield).

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.63. Found: C, 59.27; H, 6.99.

Saponification of the ester yielded *cis*-3-methyl-*cis*-5-*t*-butylcyclohexanol in 86% yield, bp 94° (3 mm), n^{20}D 1.4668. The material was gas chromatographically homogeneous and its infrared spectrum (prominent peaks at 3.02, 3.41, 6.91, 7.39, 9.25, and 9.72 μ) and nmr spectrum were compatible with the assigned structure.

3,5-Di-*t*-butylcyclohexanol. A solution of 22 g (0.106 mole) of 3,5-di-*t*-butylphenol (Aldrich Chemical Co., mp 91–92° (lit.[41] mp 93–95°)) in 100 ml of glacial acetic acid was hydrogenated in the presence of 1.0 g of platinum black at a pressure of 50 psi in a Parr shaker. The theoretical amount of hydrogen was absorbed in 12 hr. After the usual work-up there was obtained 18.12 g (80%) of 3,5-di-*t*-butylcyclohexanol consisting, according to gas chromatographic analysis, of 42.3% of *trans,trans*, 52.9% of *cis,cis*, and 4.8% of *cis,trans* isomers. This composition is somewhat different from that (58:40:2) reported elsewhere.[42]

***trans,trans* Isomer.** This isomer was separated from the above mixture by column chromatography on alumina. In a typical chromatogram, 9.7 g of alcohol mixture on 500 g of neutral alumina using benzene containing 5% ethyl acetate as a solvent and eluent yielded 3.98 g of pure *trans,trans* isomer in fractions 10–20. Recrystallization from hexane afforded 2.56 g, mp 101–102° (lit.[42] mp 100.8–101.7°), of gas chromatographically pure material whose infrared spectrum (prominent peaks at 2.76, 2.95, 3.45, 6.85, 7.21, 7.35, 8.98, 9.81, and 10.02 μ) and nmr spectrum were compatible with the assigned structure.

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.18; H, 13.37.

***cis,cis* Isomer.** The crude mixed hydrogenation product (20 g) was equilibrated in 100 ml of ether by means of mixed hydride prepared from 12.53 g of $AlCl_3$ and 25.2 ml of 0.93 *M* ethereal $LiAlH_4$ using 2.97 g of acetone (*vide supra*). There was recovered 18.8 g (94%) of material containing 93.1% *cis,cis* alcohol. This material was converted[26] to the 3,5-dinitrobenzoate which, after recrystallization from methanol, melted at 183.5–184.5° (lit.[42] mp 185.0–186.0°), yield 15.6 g (44%).

Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44. Found: C, 62.06; H, 7.42.

Saponification of the ester yielded *cis,cis*-3,5-di-*t*-butylcyclohexanol, mp 115–116° (lit.[42] mp 115.9–116.5°), in 71% yield. The material was gas chromatographically homogeneous and its infrared spectrum (prominent peaks at 2.79, 2.95, 3.50, 6.90, 7.23, 7.39, 9.11, 9.60, 9.88, and 10.0 μ) and nmr spectrum were compatible with the assigned structure.

3,3,5,5-Tetramethylcyclohexanone.[43,44] A solution of 198.8 g (1.4 moles) of methyl iodide in 200 ml of anhydrous ether was added in the usual way to 34 g (1.4 g-atoms) of mg turnings to prepare the Grignard reagent which was filtered through glass wool under nitrogen pressure into an ice-cooled, dry, 2-l. flask equipped with thermometer, condenser, addition funnel, and stirrer. Freshly prepared dry cuprous chloride (1.4 g) was added to the solution with stirring followed by 115 g (0.8 mole) of isophorone in 200 ml of anhydrous ether. The addition required 2 hr and the temperature was kept below 8°. The solution was then boiled for 2 hr, allowed to stand overnight, and decomposed by the addition of ice followed by 200 ml of concentrated hydrochloric acid and 200 ml of saturated aqueous ammonium chloride. The layers were separated and concentrated aqueous ammonia (50 ml) was added to the aqueous layer to effect solution of all salts. The aqueous layer was then extracted with two 200-ml portions of ether. The combined ether solutions were washed with water and brine, dried over magnesium sulfate, and concentrated; distillation of the residue yielded 32 g (26%) of 3,3,5,5-tetramethylcyclohexanone, bp 56–60° (7 mm), n^{20}D 1.4528 (lit.[43] bp 59–61° (5.5 mm), n^{20}D 1.4520).

3,3,5,5-Tetramethylcyclohexanol. Twenty grams of the above ketone in 100 ml of ether was reduced with 3 g of lithium aluminum hydride in 150 ml of ether in the usual way. The product was sublimed to give 15.8 g (77%) of 3,3,5,5-tetramethylcyclohexanol, homogeneous by gas chromatography, mp 84–85° (lit.[44] mp 86°).

***cis*-2-Methyl-*cis*-4-*t*-butylcyclohexanol.** This material was prepared by Mr. James Dorsey by catalytic hydrogenation of 2-methyl-4-*t*-butylphenol over rhodium on alumina at room temperature and 60 psi in a Parr shaker. The crude material (containing some unreduced phenol) was chromatographed on 20 times its weight of alumina using benzene–hexane and eluting, consecutively, with benzene–hexane (1:1), benzene, ether–benzene (1:4), ether–benzene (1:1), and ether. From 15 g of crude alcohol was thus isolated 3.88 g of *cis*-2-methyl-*cis*-4-*t*-butylcyclohexanol, mp 81–82°, undepressed by admixture of an authentic sample kindly supplied by Dr. Jiri Sicher (lit.[45] mp 78–79°). The material was eluted with benzene–ether (1:1) and ether.

Kinetic Measurements. Pyridine (Eastman) was fractionally distilled over barium oxide through a 48-cm helix-packed column. The fraction boiling at 114.8° was collected in a moisture-protected receiver and stored in the dark over potassium hydroxide pellets. Acetic anhydride (Eastman) was distilled through a 48-cm helix-packed column the center fraction, bp 139.8°, being collected. Distilled material was distributed over a number of glass ampoules in 10-ml portions and sealed under dry nitrogen. Prior to each kinetic run, an ampoule was opened and the anhydride was assayed[46] for acetic anhydride and acetic acid content. Approximately 10 g of the anhydride was weighed accurately and made up to 100 ml with pyridine in a volumetric flask at 25.00°. Twenty-five milliliters of this solution was pipetted into exactly 5 ml of dry pyridine and the resulting solution was assayed as follows. Three 2-ml aliquots were quenched in 50 ml of water each and titrated with standardized *ca.* 0.1 *N* sodium hydroxide using phenolphthalein as indicator. Let *A* be the average amount of base consumed. Then an additional three 2-ml aliquots were added to 5-ml portions of dry, redistilled aniline, allowed to stand for 0.5 hr, diluted with 40 ml of water, and also titrated, the average amount of base consumed being *B*. Then the percentage of acetic anhydride is

$$\frac{10{,}290(A - B)N}{W}$$

and the percentage of acetic acid is

$$\frac{6005(2B - A)N}{W}$$

where *N* is the normality of the sodium hydroxide and *W* is the weight of acetic anhydride reagent in the 2-ml aliquot ($^1/_{60}$ of the original weight taken).

The acetic anhydride in pyridine solution remaining in the thermostat was used for the kinetic run, as described previously[6] except that carbon tetrachloride (Spectrograde) was added during the titration instead of *n*-butyl alcohol (to dissolve the acetate ester formed).

(41) J. Elder and R. Mariella, *Can. J. Chem.*, **41**, 1653 (1963).
(42) M. Hanack and K.-W. Heinz, *Ann.*, **682**, 75 (1965).
(43) M. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).
(44) G. Chiurdoglu and A. Moquestrau, *Bull. Soc. Chim. Belges*, **63**, 357 (1954).
(45) F. Šipoš, J. Krupicka, M. Tichý, and J. Sicher, *Collection Czech. Chem. Commun.*, **27**, 2079 (1962).
(46) G. S. Shaw, *Can. Chem. Proc. Ind.*, **25**, 197 (1941).

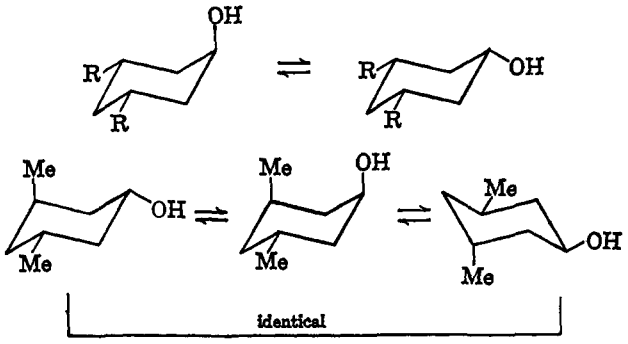

Figure 5.

Discussion

Structure, Configuration, and Purity of Substrates. The monoalkylcyclohexanols and 3,3,5-trimethylcyclohexanols used in this investigation are known compounds and their origin and physical properties left little doubt as to their structure. Moreover, in almost all cases, configurational assignment is supported by the fact that the less stable (equatorial–axial) isomer was converted into the more stable (equatorial–equatorial) one either by equilibration with mixed hydride (see the Experimental Section) or with aluminum isopropoxide or Raney nickel.[1,47] The 3,5-dimethylcyclohexanols are also known compounds and their structure is supported by the method of synthesis in the present investigation. The previously assigned configurations are supported by the fact that in the present study the *trans,trans* isomer (axial hydroxyl) was epimerized to the *cis,cis;* this leaves the *cis,trans* configuration for the third stereoisomer (which cannot, of course, be so epimerized; *cf.* Figure 5). The configurations of *cis,cis*- and *trans,trans*-3,5-di-*t*-butylcyclohexanol follow analogously; the third (*cis,trans*) isomer was not isolated in the present investigation but has been described elsewhere;[42] interestingly (but not unexpectedly) it exists in the flexible rather than the chair conformation. The constitution of these compounds follows from their synthesis from 3,5-di-*t*-butylphenol whose structure has recently been established.[41] The constitution of the 3-methyl-5-isopropylcyclohexanols follows from their synthesis from 3-methyl-5-isopropylcyclohex-2-en-1-one of known structure. The configurational assignment is somewhat more complex in this case because there are four diastereoisomeric *dl* pairs. If one tentatively assumes that the 3-methyl-5-isopropylcyclohexanone obtained by catalytic hydrogenation of the corresponding cyclohexenone is the *cis* isomer, the alcohols formed by further reduction would be the *cis,cis* and the *trans,trans* (Figure 6). This hypothesis is corroborated by the finding that equilibration of the mixture with mixed hydride gives very largely (97.6%) a single isomer, presumably the all-equatorial *cis,cis*. If one were dealing with the *cis,trans* series, epimerization of the alcohol could only lead from the *cis,trans* to the *trans,cis* and, as shown in Figure 6, equilibrium for the corresponding complexes should *not* lie way over on one side, since they would differ only by an axial methyl group (conformational energy[9] 1.75 kcal/mole) in one and an axial isopropyl group (conformational energy[9] 2.00 kcal/mole) in which case

(47) E. L. Eliel and S. Schroeter, *J. Am. Chem. Soc.*, 87, 5031 (1965).

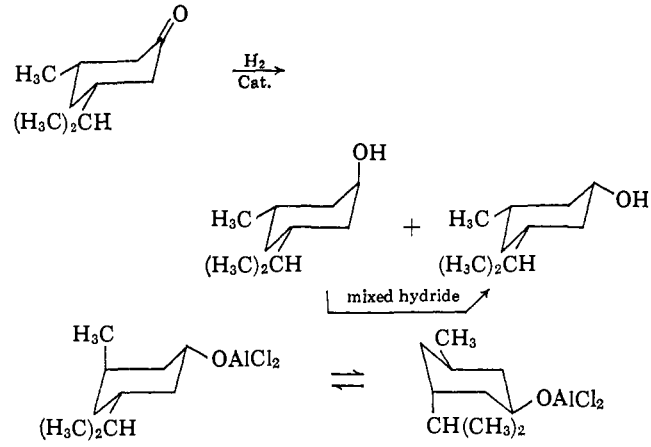

Figure 6.

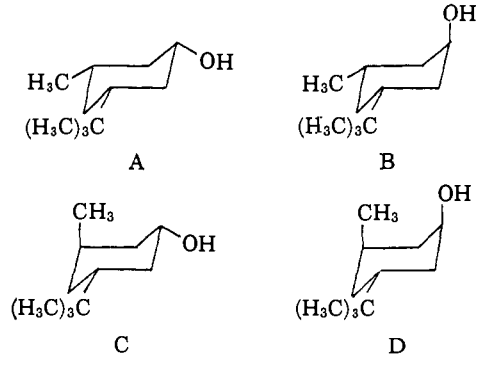

Figure 7.

equilibrium would correspond to about a 60:40 composition of stereoisomers. The configurational assignment made in the Experimental Section and based on the above argument is further supported by the nmr spectra of the alcohols (see below) which indicate that one alcohol is essentially equatorial (wide C*H*OH signal at −210 cps) and the other largely axial (narrow carbinol signal at −243 cps). In the *cis,trans* series (Figure 6) it is clear that *both* alcohols should be largely equatorial and should therefore have widely split (axial) carbinol protons at about the same (high-field) position.

The configurational situation in the 3-methyl-5-*t*-butyl series is not so clear-cut. Hydrogenation of 3-methyl-5-*t*-butylphenol gave all four stereoisomeric 3-methyl-5-*t*-butylcyclohexanols (denoted in the sequel as A, B, C, and D) in a ratio of 64.8:22.2:8.8:4.2. A is epimeric with B about the hydroxyl as is C with D, as proven by the fact that epimerization of the mixture with mixed hydride gave two isomers only, A (91.3%) and C (8.7%). Clearly, epimerization has converted B to A and D to C.[48] There is, however, no immediate way of telling whether the A/B or the C/D series is the one in which the alkyl groups are *cis* with respect to each other, for, in this case, because of the overriding conformational bias of the *t*-butyl group (which will always tend to be equatorial), *each* series now has one isomer with equatorial hydroxyl (A and C) and one with axial hydroxyl (B and D) (*cf.* Figure 7). It is tempting to hypothesize

(48) The calculated percentages after epimerization are 87.0:13.0. The actual figures make it appear that *both* B and D have been converted to A, but this appears theoretically inconceivable. We rather believe that a fractional loss during work-up following epimerization or an unusual accumulation of measuring errors in the gas chromatography accounts for the discrepancy.

that in this case, also, the predominantly formed isomers (A and B) in the catalytic hydrogenation process are the isomers in which the alkyl groups are *cis* and this will be corroborated in the next section by an nmr argument somewhat more sophisticated than that based on carbinol proton line width.

At the onset of this investigation, there was some question as to the constitution of the 3-methyl-5-*t*-butylcyclohexanols also, for although their precursor—3-methyl-5-*t*-butylphenol—was commercially available, its structure had never been demonstrated in the literature. This point was settled by reducing the phenol to *m*-*t*-butyltoluene (proving that the methyl and *t*-butyl groups are *meta* to each other) on one hand and by demonstrating, on the other, that the phenol was different from all the other methyl-*t*-butylphenols (the 2,4, 4,2, and 2,6 isomers) in which the two alkyl groups are *meta* to each other.

The purity of all the compounds used for kinetic studies was established by gas chromatography.

Nmr Spectra. The nmr spectra of a number of the compounds used in the present investigation had been previously recorded and the chemical shifts of the corresponding carbinol (C*H*OH) protons have been reported.[49,50] It was found, empirically, that there is an additive effect of various alkyl substituents on the chemical shift of an equatorial as well as an axial cyclohexanol. The chemical shift of the carbinol proton in any polyalkylcyclohexanol can therefore be predicted with a reasonable degree of accuracy (quite often ± 2cps) by adding to the basic shifts[51] of an equatorial cyclohexanol ($-\nu$ = 206 cps) and of an axial cyclohexanol ($-\nu$ = 242 cps) the parameters indicated in Tables II and III. (All shifts refer to tetramethylsilane as standard and are to be measured in carbon tetrachloride at 60 Mc/sec.) The shifts for *cis*- and *trans*-3-isopropylcyclohexanol (208 and 242 cps) and *cis*-3-methyl-*cis*-5-isopropylcyclohexanol and its *trans,trans* isomer (210 and 243 cps) determined in the course of the present investigation were, in fact, previously[50] used to assign parameters for 3-isopropyl groups as indicated in Tables II and III.

It is now of interest to see how well the found and predicted carbinol shifts for 3,5-dimethyl- and 3,5-di-*t*-butylcyclohexanol agree and also to try to assign the configuration of the 3-methyl-5-*t*-butylcyclohexanol prepared in the present work. Appropriate comparisons are made in Table IV.

Table II. Shift Parameters for Equatorial Cyclohexanols[a] (cps)

2-Me (eq) −28	3-Me (eq) 1.5	4-*i*-Pr (eq) 3[c]
2-Et (eq) −21	3-*i*-Pr (eq) 2[b]	4-*t*-Bu (eq) −3
2-*i*-Pr (eq) −11	3-*t*-Bu (eq) 0	2-Me (ax) 11.5
2-*t*-Bu (eq) −2	4-Me (eq) −3	3-Me (ax) 10.5
		3-*i*-Pr (ax) ~11[b]

[a] From ref 49 unless otherwise indicated. Shift parameters are to be added to a basic value of $-\nu$ = 206 cps to obtain the predicted $-\nu$ (at 60 Mc/sec from TMS in 10% carbon tetrachloride solution) for the appropriate alkylcyclohexanol (equatorial OH). [b] Ref 50. [c] Calculated from data of J. I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961).

Table III. Shift Parameters for Axial Cyclohexanols[a] (cps)

2-Me (eq) −17	3-Me (eq) −0.5	4-*t*-Bu (eq) −5
2-*i*-Pr (eq) −6[b]	3-*i*-Pr (eq) 1.5[c]	2-Me (ax) −24
2-*t*-Bu (eq) 7	3-*t*-Bu (eq) 2	3-Me (ax) 5

[a] From ref 49 unless otherwise indicated. Shift parameters are to be added to a basic value of $-\nu$ = 242 cps to obtain the predicted $-\nu$ (at 60 Mc/sec from TMS in 10% carbon tetrachloride solution) for the appropriate alkylcyclohexanol (axial OH). [b] Based on a shift of 240 cps for *cis*-2-isopropylcyclohexanol[49] now known—R. D. Stolow, *J. Am. Chem. Soc.*, **86**, 2170 (1964)—to exist virtually completely in the conformation with equatorial isopropyl and axial hydroxyl. [c] Ref 50.

Table IV. Comparison of Calculated and Experimental Carbinol Proton Shifts[a] in 3,5-Dialkylcyclohexanols

Entry	3,5-Dialkylcyclohexanol	$-\nu$ Calcd	$-\nu$ Found
1	*cis,cis*-3,5-Dimethyl	209	209[b]
2	*trans,trans*-3,5-Dimethyl	241	241[b]
3	*cis,trans*-3,5-Dimethyl	218[c]	221
4	*cis,cis*-3,5-Di-*t*-butyl	206	203
5	*trans,trans*-3,5-Di-*t*-butyl	246	246
6	*cis*-3-Methyl-*cis*-5-isopropyl	209.5[d]	210
7	*trans*-3-Methyl-*trans*-5-isopropyl	(243)[e]	243[e]
8	3-Methyl-5-*t*-butyl	207.5[f]	208
		216.5[g]	

[a] In cps measured from TMS in 10% carbon tetrachloride at 60 Mc/sec. [b] Ref 49. [c] In the OH-equatorial conformation. The calculated value for the OH-axial conformation is 246.5 cps and if this conformation exists to the extent of 5%, the calculated value is 219.5. [d] Using *cis*-3-isopropyl parameter calculated from *cis*-3-isopropylcyclohexanol. [e] Agreement with experimental values is not significant, since experimental value was used to calculate *trans*-3-isopropyl parameter. [f] For isomer A, Figure 7. [g] For isomer C, Figure 7.

It is clear that in all cases where independent assignment of both configuration and calculated carbinol shift is possible (entries 1–6) the agreement between calculated and observed shift is very good. It also turns out that the carbinol proton shift in 3-methyl-5-*t*-butylcyclohexanol is in excellent agreement with the assignment of the *cis,cis* configuration to this compound and in very poor agreement with the only other possible *trans,cis* assignment. (The equilibration experiments discussed earlier rule out the *trans,trans* and *cis,trans* configurations.) We therefore assign the *cis*-3-methyl-*cis*-5-*t*-butylcyclohexanol structure to this compound, a structure which is also intuitively compatible with the finding that this isomer is the major product of catalytic hydrogenation of 3-methyl-5-*t*-butylphenol.

Additional, though more tenuous, corroboration of the above configurations comes from an inspection of the spin–spin coupling constants of the methyl group with the ring proton in the methyl-substituted cyclohexanols. It has been suggested[52] that this splitting is close to zero in cyclohexanes with equatorial methyl and in excess of 5 cps in cyclohexanes with axial methyl groups. Data collected in the present investigation (Table V) unfortunately are not so clear-cut: although splitting for equatorial methyl is often less than 5 cps (though far from zero), in some cases it is as large as 6.5 cps. On the other hand, the splitting for axial

(49) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).

(50) S. H. Schroeter and E. L. Eliel, *J. Org. Chem.*, 30, 1 (1965).

(51) These "basic shift" parameters are themselves empirical values. The parameters were chosen in ref 49 so as to give an optimum over-all fit with experimental data there reported but have since been found to give good predictions for other compounds as well (*e.g.*, ref 50).

(52) J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960).

methyl groups is, indeed, in excess of 6 cps for all compounds examined and the fact that the 3-methyl-5-*t*-butylcyclohexanol studied has a splitting of only 4.3 cps therefore provides additional evidence for the equatorial position of the methyl group in this compound (isomer A rather than C in Figure 7).

Table V. Nuclear Magnetic Resonance Methyl Absorption Splittings for Some Substituted Cyclohexanols

Cyclohexanol	Doublet, cps[a]	Conformation of methyl group	J ($CHCH_3$), cps
Isomenthol	45.8, 52.8	a	7.0
cis-3,3,5-Trimethyl	48.9, 55.1	e	6.2
Neoisomenthol	51.3, 57.0	a	6.5
trans,trans-3,5-Dimethyl	46.4, 52.9	e	6.5
trans-2-Methyl-*cis*-4-*t*-butyl	51.8, 58.3	a	6.5
cis,cis-2,6-Dimethyl	55.0, 59.5	e	4.5
trans-3,3,5-Trimethyl	48.4, 54.5	e	6.1
cis,cis-3,5-Dimethyl	52.7, 57.0	e	4.3
trans-2-Methyl-*trans*-4-*t*-butyl	55.6, 60.0	e	4.4
cis-2-Methyl-*trans*-4-*t*-butyl	51.9, 58.0	a	6.1
trans-2-Methyl	56.7, 61.1	e	4.4
cis-3-Methyl	52.0, 56.9	e	4.9
trans-4-Methyl	50.9, 54.9	e	4.3
cis,trans-3,5-Dimethyl	53.4, 56.1	e	6.0
	59.4, 64.0	a	7.9
cis,cis-3-Methyl-5-*t*-butyl	54.1, 58.4	e	4.3
cis,cis-3-Methyl-5-isopropyl	53.4, 58.0	e	4.6

[a] At 60 Mc/sec downfield from tetramethylsilane in 10% carbon tetrachloride solution. Spectra recorded by Dr. T. H. Williams.[49]

Kinetic Data. The acetylation rates for all the alkylcyclohexanols investigated in the present investigation are listed in Tables VI, VII, and VIII: equatorial alcohols in the 3,4, and 3,5 series in Table VI, axial alcohols in the same series in Table VII, and 2-alkylcyclohexanols in Table VIII. It is immediately obvious that conformationally analogous compounds may differ in rate by as much as 24% (compare entries 2 and 5 in Table VI) in the equatorial series and as much as 42% (compare entries 15 and 17 in Table VII) in the axial series, even when the substituents are in the relatively remote 3, 4, and 5 position. When substituents are placed in the 2 position (Table VIII), much larger rate factors (*e.g.*, entries 27 and 28) may appear, depending on the size of the 2-alkyl groups.

Table VI. Acetylation Rates of Equatorial Alcohols with Substituents in the 3, 4, and 5 Positions[a]

Entry	Cyclohexanol	$k \times 10^5$ l./mole sec
1	*trans*-4-*t*-Butyl	10.8
2	*cis*-3-*t*-Butyl	10.5
3	*cis*-3-Methyl	10.85
4	*cis*-3-Isopropyl	10.85
5	*cis,cis*-3,5-Dimethyl	13.1
6	*cis,cis*-3,5-Di-*t*-butyl	11.3
7	*cis*-3-Methyl-*cis*-5-isopropyl	12.4
8	*cis*-3-Methyl-*cis*-5-*t*-butyl	11.5
9	*cis*-3,3,5-Trimethylcyclohexyl	12.2
10	3,3,5,5-Tetramethylcyclohexyl	11.0
11	*trans*-4-Methyl[b]	9.84
12	Cyclohexanol[b]	8.60
13	3,3-Dimethyl[b]	9.92
14	*cis*-3-*trans*-5-Dimethyl[b]	9.95

[a] At 25.00° in pyridine. Data are average of two or more kinetic runs. In all cases, equal concentrations of alcohol and acetic anhydride were used. [b] Conformationally heterogeneous system; see text.

Table VII. Acetylation Rates of Axial Alcohols with Substituentsin the 3, 4, and 5 Positions[a]

Entry	Cyclohexanol	$k \times 10^5$ l./mole sec
15	*cis*-4-*t*-Butyl	2.92
16	*trans*-3-*t*-Butyl	3.38
17	*trans,trans*-3,5-Di-*t*-butyl	4.14
18	*trans,trans*-3,5-Dimethyl	3.37
19	*trans*-3-Methyl-*trans*-5-isopropyl	3.42
20	*trans*-3-Isopropyl[b]	3.88
21	*trans*-3,3,5-Trimethylcyclohexyl[c]	2.45

[a] See footnote *a*, Table VI. [b] Conformationally heterogeneous; see text. [c] Special case because of methyl–hydroxyl *syn*-axial interaction; see text.

Table VIII. Acetylation Rates of 2-Substituted Alcohols[a]

Entry	Cyclohexanol	$k \times 10^5$ l./mole sec
1	*trans*-4-*t*-Butyl	10.8[b]
22	*trans*-2-*t*-Butyl	5.47
23	*trans*-2-Methyl	11.5
24	*trans*-2-Ethyl	11.45
25	*trans*-2-Isopropyl	11.8
26	Menthol	12.9
15	*cis*-4-*t*-Butyl	2.92[b]
27	*cis*-2-*t*-Butyl	0.31
28	*cis*-2-Methyl-*cis*-4-*t*-butyl	1.74
29	*cis*-2-Methyl[c]	2.55
30	*cis*-2-Ethyl[c]	1.80
31	*cis*-2-Isopropyl[c]	0.83

[a] See footnote *a*, Table VI. [b] Data included for comparison. [c] Conformationally heterogeneous, see text.

We shall deal with the 2-alkylcyclohexanol data (Table VIII) first, since they are easier to rationalize. The fact that 2-alkylcyclohexanols react sometimes faster (compare entry 23 with 1) and other times slower (compare 22 with 1 or 27 with 15) than the corresponding conformationally homogeneous *cis*- or *trans*-4-*t*-butylcyclohexanol immediately suggests that two opposing factors must be at work in the 2 series. The accelerative factor is operative mainly in the *trans* (equatorial) series where all but 2-*t*-butylcyclohexanol (entry 22) react faster than the equatorial standard (compare entries 23–26 with 1). The retarding factor is operative in the *cis* series (compare entries 27–31 with 15). In both cases the 2-*t*-butyl compounds (entries 22 and 27) react significantly slower than all the other 2-alkyl compounds of like conformation. This suggests quite reasonably that the retarding factor is steric, a suggestion which is also in accord with the lower rates in the *cis*-2-alkylcyclohexanol series, since it has already been pointed out in the accompanying paper[1] that, because of the natural flattening of the cyclohexane ring,[53] *cis*-1,2 substituents are closer to

(53) M. Davis and O. Hassel, *Acta Chem. Scand.*, 17, 1181 (1963).

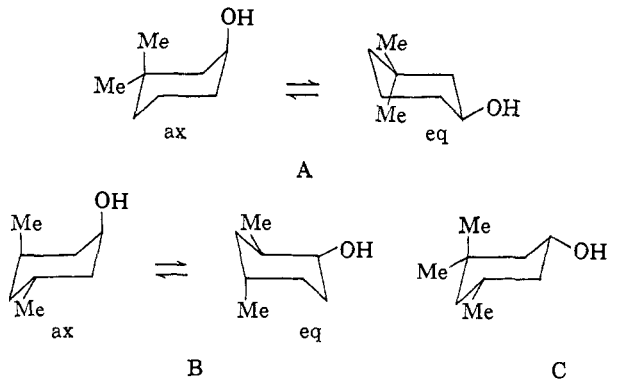

Figure 8.

each other than *trans*-1,2 substituents.[54] The counterplaying accelerative effect is probably polar in nature and due to the electron-donating effect of the alkyl groups.[55] Such an effect has already been seen in the pK_a values of the 2-alkylcyclohexanecarboxylic acids (Table I) which are weaker than their 3 and 4 isomers.[13] The data in the *trans* series, 23–25 (where the compounds are essentially conformationally homogeneous, *i.e.*, diequatorial), indicate that the inductive effect of the various alkyl groups (methyl, ethyl, isopropyl) is nearly the same and the increase in the *cis* series from isopropyl (entry 31) to ethyl (entry 30) to methyl (entry 29) should probably be ascribed to the increased contribution of the minor OH-equatorial conformation as the alkyl group becomes smaller. Comparison of entry 28 (conformationally homogeneous, axial OH) with 27 indicates, however, that this is not the entire story and that there is an inherent increase in rate from *cis*-2-*t*-butyl to *cis*-2-methyl, presumably due to the smaller size of methyl compared to *t*-butyl. That the conformationally slightly hetereogeneous *cis*-2-isopropylcyclohexanol (entry 31) reacts only about half as fast as the homogeneous *cis*-2-methyl-*cis*-4-*t*-butyl compound (entry 28) despite the presence of some of the fast-reacting[5,6] OH-equatorial conformation in the former definitely indicates that some of the steric hindrance factor persists in the *cis*-2-isopropyl compound, and the fact that even the conformationally heterogeneous *cis*-2-methylcyclohexanol (entry 29) reacts slower than *cis*-4-*t*-butylcyclohexanol (entry 15) suggests a marked persisting steric effect even with *cis*-2-methyl. This is in contrast to *trans*-2-methyl (entry 23) where the retarding effect is either not present or completely swamped by the counteracting inductive effect. (One might logically assume that the inductive effect is the *same* in the *cis*-2-alkyl and *trans*-2-alkyl series for the same alkyl group and that the difference is due to the lesser steric effect in the latter.)

Unfortunately, no such straightforward interpretation presents itself in the 3,4, and 3,5 series and, in fact, despite considerable searching we have not yet been able to come up with a complete explanation of the data in these series. It has been argued elsewhere[1] that an axial substituent can bend outward (away from the *syn*-axial hydrogens) less easily in a *trans*-3- than in a *cis*-4-substituted compound. If this is so, the hydroxyl group should be more encumbered and presumably slower reacting in the *trans*-3 series. The data in Table VII suggest, however, that the contrary is the case: *cis*-4-*t*-butylcyclohexanol (entry 15) is acetylated more slowly than any of the axial alcohols in the 3 and 3,5 series (entries 16–19). A polar acceleration is a possible, but not very attractive explanation for the trend in the axial series.[56]

trans-3-Isopropylcyclohexanol reacts at about the right rate for a compound 93% axial and 7% equatorial ($k = N_e k_e + N_a k_a$ (ref 5) and $k_e = 10.5$ (entry 2), $k_a = 3.38$ (entry 16)) which is compatible with an energy difference of 1.6 kcal/mole between the two conformations, in agreement with values of 0.7 and 2.3 kcal/mole for the conformational energies of hydroxyl[47] and isopropyl,[9] respectively.

The picture in the equatorial series (entries 1–10) is even more puzzling. A rate-accelerating inductive effect does not seem to operate in this series, for such an effect should be cumulative for alkyl groups in the 3 and 5 positions. Comparison of entry 1 (Table VI) with 2 and 3 on one hand and 5 and 6 on the other indicates, however, that the effect is not additive. The only explanation which occurs to us is that flattening of the cyclohexane ring[53,54] occurs to different extents in differently substituted cyclohexanols. The resulting subtle differences in shape of these alkylcyclohexanols might then, in turn, affect the reactivity of the alcohol function. An explanation of this type is certainly quite vague at the present stage of knowledge; to make it more meaningful would require detailed physical studies (*e.g.*, by X-ray or electron diffraction) of the exact shape of a number of variously substituted cyclohexane derivatives.

The rate for cyclohexanol corresponds to a conformational equilibrium constant[6] of $K = (k_a - k)/(k - k_e) = (2.92 - 8.60)/(8.60 - 10.8) = 2.58$, corresponding to $\Delta G°_{OH} = -0.56$ kcal/mole, in fair agreement with other values (0.6–0.7 kcal/mole[47]) in aprotic solvents.

In previous work[6] we had calculated the value of the OH–CH_3 *syn*-axial interaction from the acetylation rate of 3,3-dimethylcyclohexanol (Figure 8A), but there was some uncertainty as to what value to take for k_a in this case. Since the acetylation rate of *trans*-3,3,5-trimethylcyclohexanol (Figure 8C) is now available, it seems best to use this rate for k_a in this instance. The value to be taken for k_e is also uncertain, but we have continued to use the value for *cis*-3-methylcyclohexanol. Then using for k either the acetylation rate of 3,3- or of *cis*,*trans*-3,5-dimethylcyclohexanol (Figure 8B), one may calculate the conformational equilibrium constant $K = (k_a - k)/(k - k_e) = (2.45 - 9.93)/(9.93 - 0.85) = 8.13$, giving $\Delta G°$ 1.24 kcal/mole. Assuming a *syn*-axial Me–H interaction of 0.85 kcal/mole and OH–H of 0.3 kcal/mole, this leads[6] to a *syn*-axial Me–OH interaction energy of 1.8 kcal/mole, unfortunately lower than the earlier estimated value[6] of 2.15 kcal/mole which agrees better with the thermodynamic value of 2.4 kcal/mole.[20,47] A similarly poor agreement is obtained in the conformational analysis of *trans*-4-methylcyclohexanol which should exist to the extent of 98.3% in the conformation with equatorial hydroxyl and whose acetylation rate should therefore be experimentally indistinguishable from that of the

(54) *Cf.* R. A. Wohl, *Chimia*, **18**, 219 (1964).

(55) There is some question on the inductive effect of alkyl groups: see H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, **83**, 4552 (1961); R. C. Fort and P. von R. Schleyer, *ibid.*, **86**, 4194 (1964).

(56) H. R. Nace and R. H. Nealey, *ibid.*, **88**, 65 (1966).

conformationally homogeneous *cis*-3-methyl and *trans*-4-*t*-butyl compounds; in fact, however, its rate is palpably lower (Table VI, entries 11, 1, and 3).

The Kinetic Method of Conformational Analysis. The lack of constancy of the reaction rates in a series of conformationally analogous 3-, 4- and 3,5-substituted compounds, such as 1–10 (Table VI) or 15–19 (Table VII), raises, of course, serious questions regarding the kinetic method of conformational analysis. In this method it is necessary to assume that k_a and k_e for cyclohexyl-X are the same as those for a conformationally homogeneous alkylcyclohexyl-X which serves as a conformational model. The present work shows that the choice of an appropriate model is insecure; others[57] have experienced similar difficulties. For example, it has already been shown that, using acetylation data for cyclohexanol and its *cis*- and *trans*-4-*t*-butyl homologs, one obtains a reasonable value (0.56 kcal/mole) for the conformational energy of hydroxyl. However, were one to choose *cis,cis*- and *trans,trans*-3,5-dimethylcyclohexanol as conformationally homogeneous models (and such a choice would appear entirely reasonable), the conformational equilibrium constant of hydroxyl would be calculated to be $K = (3.37 - 8.60)/(8.60 - 13.1) = 1.16$, whence $\Delta G°_{OH} = 0.1$ kcal/mole, a manifestly erroneous value which disagrees with everything else in the literature. Looking at it in another way, the lack of constancy of "k_e" and "k_a" in conformationally rigid models makes it impossible to assert which of the various values, if any, apply to the monosubstituted, conformationally heterogeneous system.

In view of these severe problems, it is quite surprising that the kinetic method has given as good results as it has: several conformational energy values determined by the kinetic method are in very good agreement with values obtained by other, theoretically more firmly based methods.[3,4] The agreement is excellent for hydroxyl, carbethoxyl, and tosyl[58] and only slightly less good for amino and bromine;[59] on the other hand, clear-cut failures have occurred for carboxyl and acetate.[59] It must be concluded either that whatever success the kinetic method has had is entirely accidental or (and we are more inclined to this second view) that, perhaps fortuitously, the *cis*- and *trans*-4-*t*-butyl compounds originally used as conformational models in virtually all the studies so far completed do serve the purpose and give useful results, whereas other conceivable conformational models do not. If this is so, it would mean that the 4-*t*-butyl compounds are more free of polar and steric difficulties and simulate whatever distortions occur in the ground and transition states of the monosubstituted compounds better than do other conformationally homogeneous compounds. In any case, it would be well to view the kinetic method with reserve and to use it only when other methods are not readily available.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research under Grant 266-A.

(57) J. Sicher, personal communication; J. Krupička, J. Sicher, J. Závada, and M. Tichý to be submitted; V. J. Shiner and J. Jewett, *J. Am. Chem. Soc.*, **87**, 1382, 1383 (1965); W. H. Saunders and K. T. Finley, *ibid.*, **87**, 1384 (1965); see also ref 16 and 23. These investigations deal with more limited series of compounds than those studied in the present work.

(58) Two out of three determinations in the case of tosyl. The third one[5] is in major disagreement.

(59) See ref 3, pp 436–444.

Chemistry of Cyclopropanols. IV. The Solvolysis of Cyclopropyl Tosylates[1,2]

C. H. DePuy,[3] L. G. Schnack, and J. W. Hausser

Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa. *Received February 19, 1966*

Abstract: The rates of acetolysis of a series of 1- and 2-arylcyclopropyl tosylates have been determined. Solvolysis proceeds with *simultaneous* ring opening, leading directly to arylallyl cations. This transformation is postulated to be highly stereospecific, with substituents *trans* to the leaving group rotating *outward* and those *cis* to the leaving group rotating *inward*. This hypothesis is used to explain a number of cases of previously anomalous reactivities among halonorcaranes.

Although it has been known for many years that cyclopropyl compounds undergo nucleophilic substitution reactions only with the greatest reluctance,[4] there are few quantitative data available with which to draw detailed conclusions about the mechanism by which, if suitably forced, reactions do occur. In fact, the only pertinent study is that of Roberts and Chambers[5] who showed that the acetolysis of cyclopropyl tosylate leads, at 170°, to allyl acetate at a rate 2×10^{-5} times that of cyclohexyl tosylate. Recent synthetic methods developed in our laboratories for a

(1) Support of this research by a grant from the National Science Foundation is gratefully acknowledged.

(2) A preliminary account of a portion of this work has been reported: C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *J. Am. Chem. Soc.*, **87**, 4006 (1965).

(3) Address correspondence to Department of Chemistry, University of Colorado, Boulder, Colo. 80302.

(4) G. Gustavson, *J. Pract. Chem.*, [2] **43**, 396 (1891).

(5) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).