Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07. Found: C, 72.96; H, 4.15; N, 7.27, 7.45.

3-(4'-Fluoro-4-biphenylyl)cyclohex-2-en-1-one. Prepared from 4-fluoro-4'-iodobiphenyl (16.0 g) by the method used for 3-(*p*-fluorophenyl)cyclohex-2-en-1-one, the ketone was obtained as an amorphous, yellow powder which resisted purification. It was characterized as the azine which separated from xylene as a bright lemon-yellow powder, mp 270.5–271°.

Anal. Calcd for $C_{36}H_{30}F_2N_2$: C, 81.79; H, 5.72; F, 7.19; N, 5.30. Found: C, 81.56; H, 5.88; F, 7.31; N, 5.55.

3-Amino-4''-fluoroterphenyl. The above azine (0.55 g) was boiled under reflux with 10% palladized charcoal (0.30 g) in triglyme (35 ml) for 42 hr, then filtered and poured into water. The precipitate was collected and sublimed under vacuum. The sublimate of 3-amino-4''-fluoroterphenyl (0.23 g, 42%) after crystallization from ethanol had mp 194–195°.

Anal. Calcd for $C_{18}H_{14}FN$: C, 82.11; H, 5.36; F, 7.22; N, 5.32; mol wt, 263. Found: C, 81.69; H, 5.18; F, 7.35; N, 5.48; mol wt (mass spectrum), 263.

3-Cyano-4''-fluoroterphenyl. Dehydration of *m*-iodobenzamide (24.7 g) with thionyl chloride[29] gave *m*-iodobenzonitrile (18.4 g, 80%) as a colorless oil, bp 77° (0.3 mm), which solidified on standing, mp 39.5–41° (lit.[30] mp 41°). A mixture of *m*-iodobenzonitrile (10 g), 4-fluoro-4'-iodobiphenyl (18 g), and copper powder (30 g, Metals Desintegrating Corp., Elizabeth, N. J.) was heated for 23 hr at 200–215°. The product was extracted with xylene in a Soxhlet and the extract cooled to 0° and filtered to remove 4,4'''-difluoroquaterphenyl (3.5 g), mp and mmp 316.5–317°. The filtrate was concentrated and chromatographed on alumina, using gradient elution with benzene–ligroin (Skelly B). 3-Cyano-4''-fluoroterphenyl was eluted first; after crystallization from ethanol and sublimation it formed colorless plates (3.3 g, 28%), mp 110.5–111.5°.

Anal. Calcd for $C_{19}H_{12}FN$: C, 83.50; H, 4.43; N, 5.13; mol wt, 273. Found: C, 83.30; H, 4.34; N, 5.17; mol wt (mass spectrum), 273.

Further elution gave 3,3'-dicyanobiphenyl which after repeated recrystallization from ethanol followed by sublimation was obtained as a colorless powder (1.0 g, 11.2%), mp 205–205.5°.

Anal. Calcd for $C_{14}H_8N$: C, 82.33; H, 3.95; N, 13.72; mol wt, 204. Found: C, 82.50; H, 4.04; N, 13.67; mol wt (mass spectrum), 204.

Methyl 4''-Fluorobiphenyl-3-carboxylate. A mixture of methyl *m*-iodobenzoate (10 g), 4-fluoro-4'-iodobiphenyl (17.1 g), and copper powder (30 g) was heated for 23 hr at 190–200°. The product was worked up in the same way as the analogous nitrile, using benzene–pentane for the gradient elution. Methyl 4''-fluorobiphenyl-3-carboxylate (4.9 g, 44%) crystallized from ethanol in colorless needles, mp 138.5–140°.

Anal. Calcd for $C_{19}H_{15}FO_2$: C, 78.42; H, 4.94; F, 6.20; mol wt, 306. Found: C, 78.24; H, 4.75; F, 6.26; mol wt (mass spectrum), 306.

4,4'''-Difluoroquaterphenyl (2.0 g) was the only isolable byproduct.

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(29) J. A. Krynitsky and H. W. Carhart, "Organic Syntheses," Coll. Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1963, p 436.

(30) P. Griess, *Ber.*, 2, 369 (1869).

Conformational Analysis. XI. Configurational Equilibria and Chromic Acid Oxidation Rates of Alkylcyclohexanols. Deformation Effects[1]

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Abstract: Results of Raney nickel and aluminum alkoxide catalyzed epimerizations of various alkylcyclohexanols are compared. The two methods agree in solvent isopropyl alcohol. In benzene the equilibria are somewhat displaced toward the axial alcohols. The *cis–trans* equilibria of 3- and 4-methyl-, ethyl-, and isopropylcyclohexanols are consistent with those of the (conformationally homogeneous) 3- and 4-*t*-butylcyclohexanols making the assumption that in each separate series the conformational energies of alkyl and hydroxyl are additive. The configurational equilibrium positions are different in the 2-, 3- and 4-alkylcyclohexanol series. The results in the 2 series are explained assuming that the cyclohexane ring is flattened, which leads to a greater *gauche* interaction of *cis* (e,a) substituents as compared to *trans* (e,e). In the case of 2-ethyl- and 2-isopropylcyclohexanol, there is also involved a steric interaction of certain rotational conformations of the alkyl substituent with the equatorial hydroxyl group of the *trans* isomer. Results in the 3 series are tentatively explained by eclipsing of the alkyl group at C_3 with hydrogen at C_2 when the hydroxyl group at C_1 is axial. Only hydrogen–hydrogen eclipsing is involved in the 4 series. This interpretation is supported by a study of the chromic acid oxidation rates of the various alkylcyclohexanols.

In a previous publication[3] we have compared the results of Raney nickel catalyzed equilibration of the epimeric 4-*t*-butylcyclohexanols, 3,5-dimethylcyclohexanols, and 3,3,5-trimethylcyclohexanols with previously available data on *cis–trans* equilibria established with aluminum isopropoxide. It was concluded[3] that, when the solvent is the same (isopropyl alcohol), the equilibrium mixtures produced by the two reagents are the same, as they should be, and the the equilibrium is solvent dependent, being more on the side of the alcohol with equatorial hydroxyl in hydrogen-donating solvents than in aprotic solvents.

In the present work we have extended the Raney nickel and aluminum alkoxide catalyzed *cis–trans* equilibrations to other conformationally homogeneous 3-alkyl- and 3,5-dialkyl-substituted cyclohexanols as well as to some conformationally heterogeneous 2-, 3-, and 4-alkylcyclohexanols. The results are sum-

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(1) Paper X: E. L. Eliel and T. J. Brett, *J. Am. Chem. Soc.*, 87, 5039 (1965).

(2) The Radiation Laboratory is operated under contract with the Atomic Energy Commission. This is AEC Document No. COO-38-436.

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

Table I. Epimerization Equilibrium Constants for Various Conformationally Homogeneous Alkylcyclohexanols

Cyclohexanol	Solvent	Catalyst	Stable isomn, %^{a}	K_{epi}	$-\Delta G°$, kcal/mole
3-*t*-Butyl	Benzene	Raney Ni	76	3.17	0.81
	t-BuOH	Raney Ni	83.5	5.06	1.14
	i-PrOH	Raney Ni	84.0	5.25	1.16
	i-PrOH	Al(O-*i*-Pr)$_3$	84.7	5.53	1.20
4-*t*-Butyl^{b}	*i*-PrOH	Raney Ni	79.0	3.76	0.94
cis-3,5-Dimethyl^{b}	*i*-PrOH	Raney Ni	78.0	3.55	0.89
cis-3-Methyl-5-isopropyl	*i*-PrOH	Al(O-*i*-Pr)$_3$	83.1	4.92	1.12
cis-3-Methyl-5-*t*-butyl	*i*-PrOH	Al(O-*i*-Pr)$_3$	83.7	5.14	1.15
cis-3,5-di-*t*-Butyl	*i*-PrOH	Al(O-*i*-Pr)$_3$	81.6	4.43	1.04
4-Phenyl^{c}	*i*-PrOH	Al(O-*i*-Pr)$_3$	79	3.76	0.93
trans-2-Decalol^{d}	*i*-PrOH	Al(O-*i*-Pr)$_3$	79	3.76	0.93
3-Cholestanol^{e}	*i*-PrOH	Al(O-*i*-Pr)$_3$	84	5.25	1.16

^{a} Per cent stable isomer (equatorial alcohol) at equilibrium at the boiling point of the solvent (*ca.* 80°). Data are ±1% or better. ^{b} Data from ref 3, included for comparison. ^{c} E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960). ^{d}W. Hückel and D. Rücker, *Ann.*, **666**, 30 (1963). ^{e} H. R. Nace and G. L. O'Connor, *J. Am. Chem. Soc.*, **73**, 5824 (1951).

Table II. Epimerization Equilibria of Various Conformationally Heterogeneous Alkylcyclohexanols

Cyclohexanol	Solvent	Catalyst	Stable isomn, %^{a}	K_{epi}	$-\Delta G°$, kcal/mole
2-Methyl	Benzene	Raney Ni	77.0	3.35	0.85
	t-BuOH	Raney Ni	81.0	4.26	1.02
	i-PrOH	Raney Ni	82.0	4.56	1.06
	i-PrOH	Al(O-*i*-Pr)$_3$	83–85^{b,c}	4.88–5.67	1.11–1.22
2-Ethyl	*i*-PrOH	Raney Ni	77.0	3.35	0.85
	i-PrOH	Al(O-*i*-Pr)$_3$	76.8	3.31	0.84
2-Isopropyl	Benzene	Raney Ni	74.0	2.85	0.73
	C_6H_{12}^{d}	Raney Ni	67.5	2.08	0.61
	t-BuOH	Raney Ni	78.5	3.65	0.91
	t-BuOH^{d}	Raney Ni	74.0	2.85	0.88
	i-PrOH	Raney Ni	80.0	4.00	0.97
	i-PrOH	Al(O-*i*-Pr)$_3$	69 ± 6^{e}		
3-Methyl	Benzene	Raney Ni	72.6	2.65	0.68
	t-BuOH	Raney Ni	75.5	3.08	0.79
	i-PrOH	Raney Ni	78.0	3.55	0.89
	i-PrOH	Al(O-*i*-Pr)$_3$	77–79^{b,f}	3.35–3.76	0.85–0.93
3-Ethyl	*i*-PrOH	Raney Ni	78.0	3.55	0.89
3-Isopropyl	*i*-PrOH	Raney Ni	81.0	4.26	1.02
	i-PrOH	Al(O-*i*-Pr)$_3$	80.5^{g}	4.13	0.99
4-Methyl	Benzene	Raney Ni	70.0	2.33	0.59
	t-BuOH	Raney Ni	74.0	2.85	0.73
	i-PrOH	Raney Ni	75.0	3.00	0.77
	i-PrOH	Al(O-*i*-Pr)$_3$	75.0^{h}	3.00	0.77
4-Ethyl	*i*-PrOH	Raney Ni	74.3	2.89	0.75
	i-PrOH	Al(O-*i*-Pr)$_3$	74.5^{i}	2.92	0.75
4-Isopropyl	*i*-PrOH	Raney Ni	77.0	3.35	0.85
	i-PrOH	Al(O-*i*-Pr)$_3$	76.5^{j}	3.26	0.83

^{a} Per cent stable isomer (equatorial alcohol) at equilibrium at the boiling point of the solvent (*ca.* 80°). Precision is better than ±1%. ^{b} Data of W. G. Dauben and R. E. Bozak, *J. Org. Chem.*, **24**, 1596 (1959). ^{c} Data of W. Hückel and A. Hubele, *Ann.*, **613**, 27 (1958). ^{d} At 150°. ^{e} Ref 13. It is unlikely that equilibrium was reached. ^{f} Data from ref 7. ^{g} W. Hückel and K. Thiele, *Chem. Ber.*, **94**, 96 (1961), report 80%. ^{h} Data from this investigation; earlier reports [M. G. Combe and H. B. Henbest, *Tetrahedron Letters*, 1365 (1961); W. G. Dauben and R. E. Bozak, *J. Org. Chem.*, **24**, 1596 (1959); ref 7; and A. H. Lewin, Ph.D. Dissertation, University of California at Los Angeles, 1962] range from 69 to 73%. ^{i} This work; A. H. Lewin (preceding reference) reports 71%. ^{j} A. H. Lewin, footnote *h*.

marized in Table I for the conformationally homogeneous cyclohexanols and in Table II for the conformationally heterogeneous systems. Some data from the literature are included for comparison. Also compared in Tables I and II are epimerization equilibria established in different solvents as well as *cis–trans* equilibrium positions in isopropyl alcohol established by means of Raney nickel on one hand and by means of aluminum isopropoxide on the other.

Experimental Section

Alkylcyclohexanol mixtures were obtained by recrystallizing or redistilling appropriately substituted phenols (commercially available) and hydrogenating in methanolic solution over Raney nickel at 200 psi and 150–200° or in ethanolic solution over rhodium on alumina at 60 psi and room temperature. Mixtures rich in equatorial isomers were obtained by "mixed hydride" equilibration[4] of hydrogenation products, or by "mixed hydride" reduction–equilibration of appropriate alkylcyclohexanones, prepared, in turn, by chromic acid oxidation of the alcohol mixtures. Mixtures rich in axial alcohols were obtained by fractional distillation of the crude alcohols[5] or by catalytic reduction of the ketones over platinum (from platinum oxide) in acetic acid–hydrochloric acid. Individual procedures for all the compounds used in this investigation are recorded elsewhere.[1,4–11] The physical constants of a number of

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(4) *Cf.* E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).

(5) *Cf.* E. L. Eliel and R. G. Haber, *ibid.*, **23**, 2041 (1958).

(6) E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957).

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

(8) J.-C. Richer and E. L. Eliel, *J. Org. Chem.*, **26**, 972 (1961).

(9) E. L. Eliel and F. J. Biros, *J. Am. Chem. Soc.*, **88**, 3334 (1966).

(10) J.-C. Richer and G. Perrault, *Can. J. Chem.*, **43**, 18 (1965).

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

compounds prepared in the epimerically pure state agreed with those in the literature: 3-*t*-butylcyclohexanol, *cis*, acid phthalate, mp 135–136° (lit.[12] mp 135–136°), *trans*, acid phthalate, mp 154.5–155° (lit.[12] mp 154–155°); 2-isopropylcyclohexanol, *cis*, mp 51° (lit.[13] mp 50–51°), *trans*, mp 64–64.5° (lit.[14] 63–64.4°); 2-ethylcyclohexanol, *trans*, 3,5-dinitrobenzoate, mp 104–105° (lit.[14] mp 103–105°); 2-methylcyclohexanol, *trans*, 3,5-dinitrobenzoate, mp 117–118° (lit.[6] mp 117–118.5°); 4-ethylcyclohexanol, *trans*, 3,5-dinitrobenzoate, mp 133–135° (lit.[1] mp 132.5–133.5°); 4-methylcyclohexanol, *trans*, 3,5-dinitrobenzoate, mp 144.5–146.5° (lit.[6] mp 143.5–144°); 3-methylcyclohexanol, *cis*, acid phthalate, mp 90–92° (lit.[6] mp 90–92°).

The Raney nickel catalyzed and aluminum isopropoxide catalyzed equilibrations were carried out as previously described.[3] Analyses were effected gas chromatographically using Carbowax 20M,[3] glycerol[15] (for the methylcyclohexanols), or diglycerol on firebrick (or on Chromosorb W 60–80) columns.[16] Response ratios were determined for 2-isopropylcyclohexanol and 3-*t*-butylcyclohexanol on a Wilkens A-90-P gas chromatograph with a thermal conductivity detector maintained at 300°. Synthetic mixtures containing 49.6, 72.6, and 29.1% (by weight) of *trans*-2-isopropylcyclohexanol (rest *cis*) gave 49.5, 72.3, and 28.9% area of *trans* peak (expressed as percentage of *trans* + *cis*). Similarly, synthetic mixtures containing 84.7, 64.0, 52.4, and 29.5% of *cis*-3-*t*-butylcyclohexanol (rest *trans*) gave analyses of 84.7, 64.2, 53.0, and 30.0% *cis* from the measured area ratios. Since the discrepancy between weight and area ratio is within the limit of experimental error here as in the previous cases tested,[3] it was assumed that in all cases of alkylcyclohexanol analysis, weight ratios of epimers may be equated to peak area ratios. This assumption is supported by the finding that, in a number of cases, analysis of the same mixture with thermal conductivity detection and with flame ionization detection (using an F & M Model 609 instrument) gave results concordant within the ±1% assumed limit of accuracy of the analysis.

The following are the experimentally determined product compositions in terms of the percentage of the more stable isomer (symbols: s, equilibrium approached from side of more stable alcohol, l, from side of less stable alcohol, k, from ketone, p, from phenol[3]) using Raney nickel (at reflux temperature, unless otherwise stated). 2-Methylcyclohexanol: (in C_6H_6) (s) 76.8 ± 0.2, (l) 76.8 ± 0.2; (in C_6H_{12} at 150°) (s) 72.5 ± 1.5, (l) 71.0 ± 1.5, (k) 73.7 ± 0.6; (in *t*-BuOH) (s) 81.1 ± 0.3, (l) 80.5 ± 0.4; (in *i*-PrOH) (s) 82.0 ± 0.3, (k) 81.7 ± 0.3. 2-Ethylcyclohexanol: (in *i*-PrOH) (s) 76.0 ± 1.0, (l) 77.1 ± 0.3. 2-Isopropylcyclohexanol: (in C_6H_6) (l) 74.0 ± 0.1; (in C_6H_{12} at 150°) (s) 67.3 ± 0.3; (l) 68.0 ± 0.5; (in *t*-BuOH) (l) 79.7 ± 0.9; (in *t*-BuOH at 150°) (s) 73.9 ± 0.2, (l) 73.8 ± 0.3; (in *i*-PrOH) (s) 79.7 ± 0.4, (l) 80.5 ± 0.5. 3-Methylcyclohexanol: (in C_6H_6) (s) 72.0 ± 1.1, (l) 72.0 ± 0.3; (in *t*-BuOH) (l) 75.5 ± 0.3; (in *i*-PrOH) (s) 78.4 ± 0.3, (k) 78.1 ± 0.1, (p) 77.9 ± 0.2. 3-Ethylcyclohexanol: (in *i*-PrOH) (p) 78.0 ± 0.5. 3-Isopropylcyclohexanol: (in *i*-PrOH) (l) 81.0 ± 0.1. 3-*t*-Butylcyclohexanol: (in C_6H_6) (l) 75.6 ± 1.1 (some 4-*t*-butylcyclohexanol was present); (in *t*-BuOH) (l) 83.5 ± 0.5; (in *i*-PrOH) (s) 83.5 ± 0.6, (l) 83.8 ± 0.5, (p) 84.0 ± 0.2. 4-Methylcyclohexanol: (in C_6H_6) (s) 70.8 ± 0.3, (l) 69.6 ± 0.5; (in *t*-BuOH) (l) 74.2 ± 0.4; (in *i*-PrOH) (s) 75.0 ± 0.4, (k) 74.7 ± 0.4, (p) 74.7 ± 0.1; (in 1,2-dimethoxyethane) (s) 71.6 ± 0.2. 4-Ethylcyclohexanol: (in *i*-PrOH) (s) 75.1 ± 0.3, (l) 74.5 ± 0.4. 4-Isopropylcyclohexanol: (in *i*-PrOH) (s) 76.8 ± 0.5. Norborneol: (in *i*-PrOH) (s) 82.0 ± 0.2, (k) 82.8 ± 0.4; (in C_6H_6) (s) 80.6 ± 0.6, (l) 79.6 ± 0.6, (k) 80.5 ± 0.5.

The following data, similarly recorded, refer to aluminum isopropoxide catalyzed equilibrations (in isopropyl alcohol at reflux temperature). 2-Ethylcyclohexanol: (s) 77.0, (l) 76.6. 3-Isopropylcyclohexanol: (s) 80.0 (l) 81.0. 3-*t*-Butylcyclohexanol: (s) 84.1, (l) 85.4. 4-Methylcyclohexanol: (s) 74.9, (k) 75.2. 4-Ethylcyclohexanol: (s) 74.5. 3-Methyl-5-isopropylcyclohexanol: (s) 83.7, (l) 82.5. 3-Methyl-5-*t*-butylcyclohexanol: (s) 83.7. 3,5-di-*t*-Butylcyclohexanol: (s) 81.2, (l) 82.1.

The chromic acid oxidation rates reported in Table V were determined spectrophotometrically, measuring disappearance of absorption of CrO_3 at 350 mμ as described elsewhere.[15,17] The solvent was 75% aqueous acetic acid, temperature 25.0°.

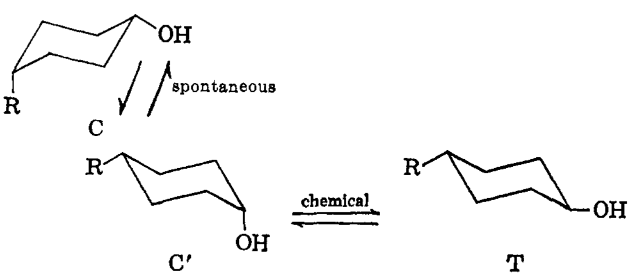

Figure 1.

Discussion

In the first instance, the data in Tables I and II confirm the previously reached conclusion[3] that the configurational isomer with equatorial hydroxyl is favored to a greater extent in protic solvents (isopropyl alcohol, *t*-butyl alcohol) than in an aprotic solvent (benzene), presumably due to the effects of hydrogen bonding. Also, once again the data in both tables show good agreement between *cis–trans* equilibria established in isopropyl alcohol by means of aluminum isopropoxide and by means of Raney nickel. The only apparent exceptions in this regard are 2-isopropylcyclohexanol and 4-ethyl- and 4-methylcyclohexanol. In the case of 2-isopropylcyclohexanol, equilibration with aluminum isopropoxide[13] is extremely slow and equilibrium was probably not reached; in contrast, equilibration with Raney nickel is rapid and leads to the same mixture starting with *cis*-rich or *trans*-rich starting alcohol. In the case of 4-ethylcyclohexanol, repetition of the aluminum isopropoxide catalyzed equilibration led to a revision of the earlier determined equilibrium constant; the new constant agrees with that obtained with Raney nickel. In the case of 4-methylcyclohexanol, the four previous determinations of the equilibrium constant (using aluminum isopropoxide) span an unusually wide range; here again, redetermination brought the constant in line with that obtained through use of Raney nickel as a catalyst.

Additivity of Conformational Energies. One of the standing problems in conformational analysis is whether conformational energies are additive,[18,19] *e.g.*, whether the position of conformational equilibrium between C and C′ in Figure 1 can be assessed by subtracting the conformational energy of hydroxyl from that of alkyl. The present work throws some light on this question.

In a previous paper[1] it was shown that for a configurational (*cis–trans*) equilibrium in a disubstituted cyclohexane

$$1/K_{\mathrm{epi}} = 1/K_{\mathrm{OH}} + 1/K_{\mathrm{R}} \qquad (1)$$

Here it is shown that K_{epi} represents the experimental epimerization equilibrium constant ([*trans*]/[*cis*]), K_{OH} and K_{R} are the conformational equilibrium constants for hydroxyl and alkyl, respectively, and the reasonable

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[12] S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).

[13] W. Hückel and R. Neidlein, *Chem. Ber.*, **91**, 1391 (1958).

[14] C. Kucera, *Dissertation Abstr.*, **16**, 2307 (1956).

[15] J.-C. Richer and C. Gilardeau, *Can. J. Chem.*, 43, 538 (1965).

[16] R. Komers and K. Kochloefl, *Collection Czech. Chem. Commun.*, **28**, 46 (1963).

[17] Preliminary publication: J.-C. Richer, L. A. Pilato, and E. L. Eliel, *Chem. Ind.* (London), 2007 (1961).

[18] For discussions of this point, see: (a) E. L. Eliel, *J. Chem. Educ.*, 37, 126 (1960); (b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 236.

[19] See also E. L. Eliel, *Angew Chem.*, 77, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, 4, 761 (1965).

assumption is made that the *trans*-4 isomer exists exclusively in the diequatorial conformation T, the diaxial conformation contributing negligibly. (A similar situation should pertain in the 3-alkylcyclohexanol series, except that in that series the diequatorial isomer is the *cis* and the equatorial–axial is the *trans*.)

Implicit in the derivation of eq 1 is the assumption that $[T]/[C] = K_R$ and $[T]/[C'] = K_{OH}$ or, in other words, that the conformational equilibrium constants for alkyl and hydroxyl in the system in Figure 1 are the same as for an isolated alkylcyclohexane and isolated cyclohexanol. Clearly this carries the further implication that the conformational energies in Figure 1 are additive, for, if $[T]/[C] = K_R$ and $[T]/[C'] = K_{OH}$ it follows that

$$[C']/[C] = K_R/K_{OH}$$

hence

$$-RT \ln ([C']/[C]) = -RT \ln K_R + RT \ln K_{OH}$$

or

$$\Delta G°_{(C \rightleftharpoons C')} = \Delta G°_R - \Delta G°_{OH}$$

which is an explicit statement of the additivity principle for the system considered.

Thus, if it can be shown that eq 1 holds, the additivity of conformational free energies is demonstrated. Data concerning this point are summarized in Table III. For reasons to be explained below, different values for K_R and K_{OH} must be used in the 3 and 4 series (the 2 series is not considered, since appropriate data for K_{OH} are lacking and since additivity of conformational energies in this series is not to be expected). The values of K_R are taken from the previous paper,[1] the value for $K_{OH}{}^4$ (4 series) is taken[3] as 2.64 in boiling benzene and 3.76 in boiling isopropyl alcohol, and the value for $K_{OH}{}^3$ (3 series) is derived from the experimental results for 3-*t*-butylcyclohexanol (Table I and II) as 3.17 in benzene and 5.25 in isopropyl alcohol. Comparison of K_{epi} values calculated on this basis with experimental data in Table III indicates that the two sets in the 4 series agree well within the limits of combined experimental error. Thus the conformational energies in this series are clearly additive.[20] In the 3 series, for reasons to be discussed below, the agreement is slightly less good.

Table III. Calculated and Experimental Values for K_{epi} and Percentage Composition

Compound	Solvent	K_{epi} (% stable isomer)	
		Calcd	Found
4-Methylcyclohexanol	Benzene	2.19 (68.7)	2.33 (70)
	i-PrOH	2.91 (74.4)	3.00 (75)
4-Ethylcyclohexanol	*i*-PrOH	3.02 (75.1)	3.00 (75)
4-Isopropylcyclohexanol	*i*-PrOH	3.23 (76.4)	3.35 (77)
3-Methylcyclohexanol	Benzene	2.68 (72.8)	2.65 (72.6)
	i-PrOH	4.04 (80.1)	3.54 (78)
3-Ethylcyclohexanol	*i*-PrOH	4.20 (80.8)	3.54 (78)
3-Isopropylcyclohexanol	*i*-PrOH	4.68 (82.4)	4.26 (81)

Comparison of 2, 3, and 4 Series. In Table IV are compared the epimerization equilibria of corresponding alkylcyclohexanols with the alkyl group in the 2, 3, and 4 position. In all cases, the equilibrium constant for the 4-alkylcyclohexanol is smaller than the corresponding one in the 3 and 2 series. In the case of the methylcyclohexanols, the 2 isomer has the highest epimerization equilibrium constant, but with the other alkylcyclohexanols, the 3 isomer has the highest amount of diequatorial epimer at equilibrium. We shall now try to account for these findings.

Table IV. Epimerization Equilibria of Corresponding Alkylcyclohexanols in Isopropyl Alcohol

Alkylcyclohexanol	K_{epi}		
	2 Series	3 Series	4 Series
Methylcyclohexanol	4.56	3.54	3.00
Ethylcyclohexanol	3.35	3.54	3.00
Isopropylcyclohexanol	4.00	4.26	3.35
t-Butylcyclohexanol	(4.71)[a]	5.25	3.76

[a] Value calculated from ratio of chromic acid oxidation rates, *vide infra*.

In trying to predict the positions of epimeric equilibrium in 4-methylcyclohexanol and 2-methylcyclohexanol one might assume, as a first approximation, that the differences in group interaction energies between *cis* and *trans* isomers are the same. In both cases, the *cis* isomer exists in two conformations, one (predominant) with axial hydroxyl, the other with axial methyl. The *trans* isomer in its greatly predominant conformation has only equatorial groups in both cases. The *cis* isomer of 2-methylcyclohexanol has an additional methyl–hydroxyl *gauche* interaction, but as long as one assumes that the molecules exist as perfect chairs, exactly the same interaction occurs in the diequatorial *trans*-2 isomer, so that in the difference between *cis* and *trans* it will cancel out. To be sure, the methyl–hydroxyl *gauche* interaction is absent in the diaxial conformation of *trans*-2-methylcyclohexanol, but since less than 3% of the molecules are in this conformation (at 80°), this does not make a palpable difference in the calculation.

Thus one would predict that, in the first approximation, the difference in free energy between *cis* and *trans* isomers should be the same for 2- and 4-methylcyclohexanol. In fact, however, there is a difference of 0.29 kcal/mole between $\Delta G°$ in the 4 series (0.77 kcal/mole) and the 2 series (1.06 kcal/mole). The origin of this difference is not hard to understand. It is now known[21] that bond angles in cyclohexane are not exactly tetrahedral but that (similarly as in propane) they are expanded to 111.5°. This leads to a flattening of the chair accompanied, in turn, by a change in torsional angles[22] in such a fashion that equatorial–equatorial bonds diverge (torsional angle *ca.* 65°) and equatorial axial bonds converge (torsional angle *ca.* 55°).[23] As a result, there will be substantially greater compression between equatorial and axial groups than between equatorial and equatorial groups which, in turn, results in an additional energetic disadvantage for the *cis*-1,2 (e,a) isomer *vis-à-vis* the *trans* (e,e) isomer as compared to the situation in the 1,4 series. The magnitude of

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[20] Hopefully this may be true in other cases as well, but it is obviously not safe to generalize from four pieces of data.

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

[22] *Cf.* R. A. Wohl, *Chimia*, **18**, 219 (1964).

[23] These are the angles in cyclohexane itself. It is possible that in a 1,2-disubstituted cyclohexane, as a result of the mutual compression of the groups, the torsional angles are increased somewhat for both isomers. This point remains to be explored by physical methods.

this effect is difficult to assess *a priori*, but its experimentally determined magnitude of 0.3 kcal/mole is within the range of 0.25 (for Me_e–OH_e *vs.* Me_e–OH_a) to 0.45 (for Me_e–OH_e *vs.* Me_a–OH_e) kcal/mole defined by a detailed study of 2-methyl-4-*t*-butylcyclohexanol equilibria by Sicher and co-workers.[24]

Corresponding "1,2-effects"[22,25] are probably responsible for the difference in equilibrium position with "mixed hydride" between the 2-methylcyclohexanol complexes[26] (*ca.* 98% *trans*) and the 4-methylcyclohexanol complexes[1] (92.3% *trans*), for the greater degree of intramolecular hydrogen bonding in *cis*-1,2-cyclohexanediol compared to the *trans* isomer,[27] and for the short fall of the experimental entropy difference of 0.72 cal/deg mole[28] between *cis*- and *trans*-1,2-dimethylcyclohexane below the calculated 1.27 cal/deg mole.[29]

We see, then, that in a second approximation the difference in equilibrium position between the 2- and 4-methylcyclohexanol epimers is explained through a greater *gauche* Me–OH interaction in the *cis*-2 isomer as compared to the *trans*-2. If this were the whole story, a similar difference (0.29 kcal/mole) should appear in the ethylcyclohexanols, isopropylcyclohexanols, and *t*-butylcyclohexanols. In fact, however, the difference is *smaller* for the higher homologs, amounting to only 0.08 kcal/mole for the ethyl compound, 0.12 for the isopropyl, and an estimated 0.16 for the *t*-butyl. Therefore yet another factor must come into play for these compounds and, in fact, must *oppose* the 1,2-effect. When one calculates the difference in free energy between *cis*- and *trans*-2-alkylcyclohexanols from first principles using the following parameters:[30] Me–OH 1,3-*syn*-axial interaction, 2.4 kcal/mole; Me–H *syn*-axial interaction, 0.9 kcal/mole; OH–H *syn*-axial interaction, 0.45 kcal/mole; OH–Me *gauche* interaction (e,e), 0.45 kcal/mole, (e,a), 0.80 kcal/mole;[31] one obtains calculated *cis–trans* differences at 80° between epimeric 2-alkylcyclohexanols (in kcal/mole) as follows: 2-methyl, 1.09 kcal/mole; 2-ethyl, 0.99 kcal/mole; 2-isopropyl, 0.83 kcal/mole; *t*-butyl, 1.25 kcal/mole. The experimental values are: 2-methyl, 1.06 kcal/mole; 2-ethyl, 0.85 kcal/mole; 2-isopropyl, 0.97 kcal/mole; 2-*t*-butyl (estimated), 1.09 kcal/mole. Although the agreement is by no means perfect, especially with regard to ethyl *vs.* isopropyl, the calculated values anticipate the experimental trend Me > Et, *i*-Pr < *t*-Bu. In qualitative terms, the nonmonotonous trend is produced by the tendency of the (unsymmetrical) ethyl and isopropyl groups, when equatorial, to predominate in the conformation in which the single terminal methyl group (in the case of ethyl) or both terminal methyl groups (in the case of isopropyl) point sideways rather than upward, since the upward conformation entails an extra Me–H *syn*-axial interaction. Now in this preferred rotational conformation of the equatorial alkyl group an axial hydroxyl group (*cis* isomer) can be accommodated without difficulty, but accommodation of an equatorial hydroxyl group (in the *trans* isomer) causes a severe *syn*-axial Me–OH interaction in both otherwise preferred conformations of the isopropyl compound and in one of the two otherwise preferred conformations of the ethyl compound (Figure 2). These conformations thus become unfavorable with resultant bias *against* the *trans* (e,e) isomer and diminution of the equilibrium constant [*trans*]/[*cis*]. These considerations[32] do not apply to the spherically symmetrical methyl and *t*-butyl groups; therefore the equilibria of the 2-methyl- and 2-*t*-butylcyclohexanols are further shifted to the *trans* side than those for the 2-ethyl and 2-isopropyl homologs. The 2-*t*-butyl case differs from the 2-methyl case in that *both* configurational isomers are conformationally homogeneous with resulting increase in $-\Delta\Delta G°$; unfortunately the experimental data are not reliable enough to support the calculation in this case.

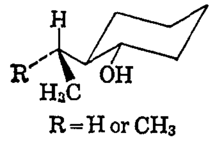

Figure 2.

Whereas the explanation for the difference in epimerization equilibrium position between 1,2- and 1,4-disubstituted compounds is thus fairly straightforward, the difference between the 1,4 and 1,3 series[33] is harder to account for. Nevertheless, this difference is quite real, amounting, in terms of free energy, to 0.12 kcal/mole for methyl, 0.14 kcal/mole for ethyl, 0.17 kcal/mole for isopropyl, and 0.23 kcal/mole for *t*-butyl (in isopropyl alcohol as solvent; the corresponding value for *t*-butyl in benzene is 0.13 kcal/mole); it thus increases with the size of the alkyl group. A corresponding difference is found in the equilibration of alkylcyclohexanol complexes with mixed hydride[1] (equilibration of alkyl groups) where it amounts to 0.19 kcal/mole for methyl and ethyl and 0.40 kcal/mole for isopropyl. The same phenomenon is found in the oxidation rates of corresponding 3- and 4-alkylcyclohexanols (see below). (It is interesting to note that the difference in

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[24] (a) J. Sicher, personal communication; (b) F. Šipoš, J. Krupička, M.Tichy, and J. Sicher, *Collection Czech. Chem. Commun.*, 27, 2079 (1962).

[25] *Cf.* also 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, p 77. The authors consider only deformation induced by compression of the 1,2-placed groups, not the inherent deformation of the flattened cyclohexane ring. However, this does not change the argument greatly.

[26] J.-C. Richer, unpublished observations, using the method described in ref 1 and 4.

[27] L. P. Kuhn, *J. Am. Chem. Soc.*, 74, 2492 (1952).

[28] H. M. Huffman, S. S. Todd, and G. D. Oliver, *ibid.*, 71, 584 (1949).

[29] C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, 69, 2488 (1947). The difference is ascribed to "cogwheeling" of the methyl groups in the *cis* (but not the *trans*) isomer, an explanation which is cogent only if the methyl groups are closer together in the *cis* compound.

[30] *Cf.* ref 25, pp 23–26, for the nature of such calculations, and pp 44 and 52 for the magnitude of some of the parameters used. Details of the calculations have been deposited as Document No. 8916 with the ADI Auxiliary Publications Project Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting $1.25 for photoprints, or $1.25 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

[31] The e,e value is that recommended by Sicher[24] and the e,a value is the average of values of 0.7 kcal/mole for OH_a–Me_e and 0.9 kcal/mole for OH_e–Me_a recommended by the same author. If one took the actual values for the latter two parameters rather than an average, the result would be to diminish slightly the calculated *cis–trans* differences and thus to improve the agreement with experimental results. The calculated trend in the series Me–Et–*i*-Pr–*t*-Bu would not be greatly affected by this change.

[32] Earlier adduced by R. D. Stolow, *J. Am. Chem. Soc.*, 86, 2170 (1964).

[33] The equilibria in the 3,5-dialkylcyclohexanol series generally fit in with those in the 3-alkylcyclohexanol series except for the 3,5-dimethylcyclohexanol case[3] which, disturbingly, agrees with the 4 series rather than the 3 series.

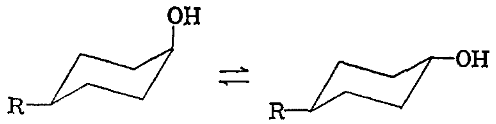

Figure 3.

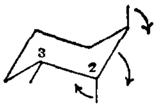

Figure 4.

free energies between epimeric 4-*t*-butylcyclohexanols, amounting to 0.93 kcal/mole in isopropyl alcohol and 0.68 kcal/mole in benzene, is "normal," *i.e.*, it corresponds to the accepted range of conformational energies of the hydroxyl group, suggesting that the equilibrium depicted in Figure 3 is the same whether R = H or R = *t*-Bu. In contrast, the epimerization free energy in the 3-*t*-butylcyclohexanol series, 0.81 kcal/mole in benzene, 1.16 kcal/mole in isopropyl alcohol, must be considered "excessive"). Clearly these differences cannot be explained in terms of the inherent deformation of the cyclohexane ring from the perfect chair shape, for this deformation affects 3-substituted, 4-substituted, and unsubstituted cyclohexanes equally.

We would like to put forth the following tentative hypothesis to account for the observed results. An axial substituent in a cyclohexane, through its natural tendency to bend away from the interfering *syn*-axial hydrogens at positions 3 and 5,[34] *increases* the flattening of the cyclohexane ring but in uneven fashion; the flattening is more severe in the region of C$_1$, C$_2$, and C$_6$ than at C$_{3-5}$, giving the molecule a somewhat cyclohexanone-like shape. Model considerations indicate that this additional deformation of the ring leads to eclipsing of the substituents at C$_3$ with those at C$_2$; in particular, an equatorial substituent at C$_3$ will be eclipsed with an axial substituent at C$_2$ and *vice versa.* In contrast, substituents at C$_4$ are not greatly affected by the additional deformation and remain staggered (except for the effect of the flattening of the ring as a whole which is present in any cyclohexane) with respect to substituents at C$_3$. Thus the outward bending of the axial substituent at C$_1$ encounters no particular difficulty in an unsubstituted cyclohexane or in a 4-substituted cyclohexane but does lead to an unfavorable C$_2$–C$_3$ eclipsing when there is a substituent at C$_3$ (Figure 4). This phenomenon may be expected to increase the free energy of an axial substituent at C$_1$ when there is an additional substituent at C$_3$, either by forcing the substituent at C$_3$ into an unfavorable eclipsed position or by interfering with the bending away of the axial substituent at C$_1$ from the *syn*-axial hydrogens. It might be noted that in the comparison of $\Delta G°$ for epimerizations in 1,3- and 1,4-disubstituted compounds, the above interpretation ascribes the origin of the difference to the energy level of the equatorial–axial rather than the equatorial–equatorial position isomers. This point cannot be checked through the equilibrium data themselves (since compounds of the 3 series were not equilibrated with compounds of the 4 series), but it can be elucidated by the oxidation data recorded below. In fact, it turns out that axial-(*trans*) 3-methylcyclohexanol is oxidized 1.53 times as fast as the axial (*cis*) 4 isomer; the corresponding factor for the *t*-butylcyclohexanols is 2.33. The corresponding factors for the equatorial–equatorial analogs are 1.12 in the methyl series and 1.24 in the *t*-butyl series. The data suggest that the major cause for increase in oxidation rate in the 3 series (as compared with the 4 series) is some form of steric strain in the axially substituted (*cis*) 3-alkylcyclohexanols.

It must be stressed that our hypothesis at this stage is still quite tentative and that further experiments are required to support or refute it. There is one at first sight objectionable feature in the hypothesis in that it ascribes the observed differences between the 3 and 4 series essentially to a difference in H–H *vs.* alkyl–H eclipsing. It is known, however,[35] that bond eclipsing energies are not primarily steric in origin and are not greatly dependent on the nature of the substituents on the bonds. There *is*, nevertheless, a small difference in eclipsing energy, amounting to about 0.3–0.5 kcal/mole,[35] between the barriers in ethane (H–H) and propane (Me–H) and this difference may be sufficient to account, in the manner indicated above, for the small differences in free energies of epimerization recorded in this paper. In fact, assuming a sinusoidal potential barrier[35] and a difference in barrier height of 0.4 kcal/mole between H–H and H–Me, one computes a torsional angle of 30° for an observed difference of 0.2 kcal/mole between *cis*-4-methylcyclohexanol (H–H eclipsing) and *trans*-3-methylcyclohexanol (Me–H eclipsing). The order of magnitude of this angle (between equatorial C$_3$ and axial C$_2$ bonds) is not unreasonable, considering that in cyclohexane itself the angle is 55° and that the parameters chosen for the estimate are very approximative at best.

Since the eclipsing energy varies slightly from one alkyl group to another, it is not surprising that a perfect correlation of calculated and experimental epimerization equilibrium constants shown in Table III is not achieved in the 3-alkylcyclohexanol series.

Chromic Acid Oxidation Rates. Oxidation rates of a number of simple alkylcyclohexanols have been measured in our laboratories[15,17] and are included in this paper for comparison with epimerization data, as explained below. The data (in 75% acetic acid, by volume, at 25.0°) are summarized in Table V.

Before discussing the bearing of these data on the epimerization studies, it should be mentioned that they are in good agreement with analogous data previously obtained in the steroid series[36] and, in particular, that they are entirely consistent with the now well-documented theory that chromic acid oxidation rate increases as ground-state compression of the starting alcohol becomes more severe.[37] Thus the 2-alkylcyclohexanols, because of the additional alkyl–hydroxyl *gauche* interaction, react faster than corresponding 3 or 4 isomers (compare compounds **2** with **5** and **6**,

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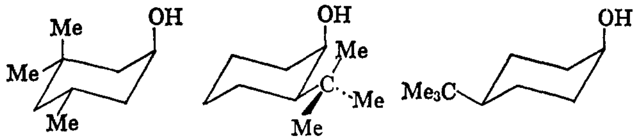
[34] *Cf.* O. Hassel and E. Wang Lund, *Acta Cryst.*, **2**, 309 (1949); V. A. Atkinson and O. Hassel, *Acta Chem. Scand.*, **13**, 1737 (1959).

[35] *Cf.* ref 25, pp 7–9.

[36] J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

[37] For a recent discussion and disposition of earlier objections, *cf.* J. Roček, F. H. Westheimer, A. Eschenmoser, L. Moldoványi, and J. Schreiber, *ibid.*, **45**, 2554 (1962); *cf.* also ref 25, pp 81–84.



9 12 16

Figure 5.

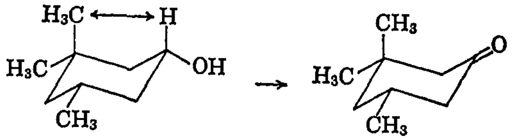


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Figure 6.

Table V. Chromic Acid Oxidation Rates (l. mole^{-1} sec^{-1} in 75% Acetic Acid at 25°)

	Compound	Av rate	Rel rate[a]
1	Cyclohexanol	5.53	1.38
2	*trans*-2-Methylcyclohexanol	5.8	1.44
3	*cis*-2-Methylcyclohexanol	23.2	5.78
4	*trans*-3-Methylcyclohexanol	18.51	4.60
5	*cis*-3-Methylcyclohexanol	4.74	1.18
6	*trans*-4-Methylcyclohexanol	4.21	1.05
7	*cis*-4-Methylcyclohexanol	12.15	3.00
8	4,4-Dimethylcyclohexanol	7.00	1.74
9	*trans*-3,3,5-Trimethylcyclohexanol	252.5	62.7
10	*cis*-3,3,5-Trimethylcyclohexanol	7.52	1.87
11	*trans*-2-*t*-Butylcyclohexanol	54.0	13.4
12	*cis*-2-*t*-Butylcyclohexanol	254.5	63.2
13	*trans*-3-*t*-Butylcyclohexanol	30.25	7.52
14	*cis*-3-*t*-Butylcyclohexanol	4.97	1.24
15	*trans*-4-*t*-Butylcyclohexanol	4.02	1.00
16	*cis*-4-*t*-Butylcyclohexanol	13.0	3.23

[a] 4-*t*-Butylcyclohexanol = 1.00.

3 with **4** and **7**, **11** with **14** and **15**, and **12** with **13** and **16**). Axial alcohols almost always react faster than equatorial:[38] compare **3** with **2**, **4** with **5**, **7** with **6**, **9** with **10**, **12** with **11**, **13** with **14**, and **16** with **15**. Additional compression by *syn*-axial groups produces marked increases in rate due to strain relief in the transition state: compare **9** and **12** with **16** or **11** with **15** (Figure 5). A minor amount of strain relief is also observed in **10** which reacts faster than **5** presumably due to relief of methyl–hydrogen eclipsing ("3-alkylketone effect"[39]) as seen in Figure 6. The faster rate of oxidation of 4,4-dimethylcyclohexanol as compared to cyclohexanol (**8** *vs.* **1**) has been explained elsewhere[17,39] in terms of a "4-alkylketone effect."

The bearing of the difference in oxidation rates between the position isomers *trans*-3- and *cis*-4-*t*-butylcyclohexanol on the interpretation of the equilibrium compositions in the 3 and 4 series has already been discussed. A slightly different comparison is made in Table VI where ratios of oxidation rates of *epimers* are juxtaposed with equilibrium constants. It has already been pointed out by other investigators[24b,40] as well as by one of us[16] that there exists a linear free-energy relationship between relative stability of alcohols and their chromic acid oxidation rates. In fact the slope of the correlation line is close to unity,[16] so that, as indicated in Table VI, the magnitude of k_a/k_e is almost the same as that of K_{epi} corrected to the same temperature. In terms of energetics, this means[40a] that the transition states for oxidation of epimers are closely similar in energy so that the difference in ground states determines the difference in activation energy (Figure 7). Thus, at least in a first approximation, the ratio of oxidation rates may be substituted for the epimerization equilibrium constant in cases where the latter is not available; in the present study this has been done in the case of 2-*t*-butylcyclohexanol (Table IV).

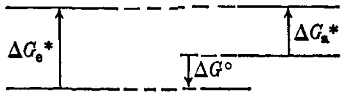

Figure 7.

Table VI. Comparison of Ratios of Oxidation Rates with Equilibrium Constants

Alkylcyclohexanol	k_a/k_e[a]	K_{epi}[b]	K_{epi} (corr)[c]
2-Methylcyclohexanol	4.00	4.56	6.0
3-Methylcyclohexanol	3.91	3.54	4.6
4-Methylcyclohexanol	2.89	3.00	3.7
2-*t*-Butylcyclohexanol	4.71	*d*	...
3-*t*-Butylcyclohexanol	6.09	5.25	7.1
4-*t*-Butylcyclohexanol	3.23	3.76	4.8
3,3,5-Trimethylcyclohexanol	33.6	17.2[e]	29.3
3,5-Dimethylcyclohexanol	5.58[f]	3.55[g]	4.48
2,2-Dimethyl-4-*t*-butylcyclohexanol	1.67[f]	1.50[h]	1.61

[a] Ratio of chromic acid oxidation rates of axial and equatorial epimers. [b] Equilibrium constant of epimers in isopropyl alcohol at 80°. [c] Equilibrium constants corrected to 25°, assuming constancy of $\Delta G°$ (*i.e.*, $\Delta S° = 0$). [d] Not available, equilibration not achieved with either aluminum isopropoxide or Raney nickel. [e] Ref 11. [f] Ref 16. [g] Ref 3. [h] Ref 10.

Equilibrium of Norborneols. It has been pointed out in this paper and the previous one[3] that the alkylcyclohexanol equilibria are solvent dependent. In contrast, Wilcox, *et al.*,[40] have found nearly the same position of equilibrium for the norborneols with aluminum isopropoxide in isopropyl alcohol and with sodium–fluorenone in toluene and have concluded that the position of equilibrium is nearly solvent independent. We have therefore studied the equilibration of the norborneols with Raney nickel and find 82.4% *exo* isomer at equilibrium in boiling isopropyl alcohol ($\Delta G° = 1.08$ kcal/mole, in good agreement with the value of 1.04 kcal/mole computed from the equilibration studies with aluminum alkoxide at 100–110°[40]) and 80 ± 1% ($\Delta G° = 0.97$ kcal/mole) in benzene. The effect of solvent, in this case, is indeed less than in the case of the alkylcyclohexanols, possibly because the possibilities of hydrogen bonding to the solvent are sterically limited in *both exo-* and *endo*-norborneol.[41]

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(38) For an interesting exception and its logical explanation, *cf.* ref 37.

(39) *Cf.* ref 25, pp 113–115.

(40) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

(41) R. J. Ouellette, G. E. Booth, and K. Lipstok, *J. Am. Chem. Soc.*, **87**, 3436 (1965), have presented evidence that intermolecular (*i.e.*, associative) hydrogen bonding in carbon tetrachloride is more important for *exo*-norborneol than for the *endo* isomer. This difference may, however, have its origin in the different hydrogen-*donor* qualities of the epimers, in which case it would not conflict with our present suggestion that the epimers are nearly equivalent hydrogen *acceptors* (toward donor isopropyl alcohol).

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

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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]

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