The Stereochemistry of Autoxidation of Methylcyclohexanes

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(Received August 30, 1974)

Autoxidation of 1, *c*-3, *c*-5- or 1, *c*-3, *t*-5-trimethylcyclohexane with oxygen in the presence of azobisisobutyronitrile at 60 °C and subsequent reduction with lithium aluminium hydride gave 1, *t*-3, *t*-5- and 1, *c*-3, *c*-5-trimethyl-*r*-1-cyclohexanol in the same ratio of 1/0.85. Such an almost random attack of oxygen on both sides of intermediate methylcyclohexyl radicals was also observed in autoxidation of 1,2-dimethyl-, 1,4-dimethyl-, and 1,1,3,5-tetramethylcyclohexanes. Approximate relative reactivities of tertiary hydrogens in various steric environments in methylcyclohexanes towards abstraction were determined. Steric effects on the attack of oxygen and the abstraction of hydrogen are discussed.

Although the autoxidation of hydrocarbons with formation of hydroperoxides has been extensively studied, the stereochemical features of the reaction seem to deserve more detailed investigation. The present paper deals with the relative reactivity of tertiary hydrogens in various steric environments in methylcyclohexanes towards abstraction and the stereochemistry of the reaction of oxygen with intermediate methylcyclohexyl radicals.

Results and Discussion

Methylcyclohexanes were autoxidized with oxygen in the presence of azobisisobutyronitrile at 60 °C and the stereoisomeric hydroperoxides formed were reduced with lithium aluminium hydride. Since this reagent is expected to reduce stereospecifically the hydroperoxides to the corresponding alcohols,[1] the alcohol compositions reflect the hydroperoxide compositions of the oxidates. The reduced oxidates were analysed by gas-liquid partition chromatography (glpc).

1,3,5-Trimethylcyclohexanes. 1,*c*-3,*c*-5-Trimethylcyclohexane (**1**) gave two products 1,*t*-3,*t*-5- and 1, *c*-3,*c*-5-trimethyl-*r*-1-cyclohexanol (**5** and **6**), while the 1,*c*-3,*t*-5-isomer (**2**) afforded, besides these alcohols, a third one (**7**). Samples of alcohols **5** and **6** were collected and separated by glpc. The analytical and spectral data show that both of them are monohydric tertiary alcohols, which must have been derived from intermediate radical **3** (Fig. 1).

The configurations of alcohols **5** and **6** are assigned on the basis of the IR data. It has been reported that, in a considerable number of secondary and tertiary cyclohexanols, an axial hydroxyl group has a free O–H stretching absorption in the IR spectrum at a higher frequency than that of its equatorial epimer.[2] For example, *c*-4-*t*-butyl-1-methyl- (with an axial hydroxyl) and *t*-4-*t*-butyl-1-methyl-*r*-1-cyclohexanol (with an equatorial hydroxyl) absorb at 3616—7 and 3611—2 cm^{-1}, respectively.[2c,d] According to this correlation, it is concluded that alcohol **5** has an axial hydroxyl group and alcohol **6** an equatorial one, since alcohols **5** and **6** absorb at 3617 and 3611 cm^{-1}, respectively. The assignments are further supported by NMR measurements of the proton resonance due to a hydroxyl group (see Experimental Part).

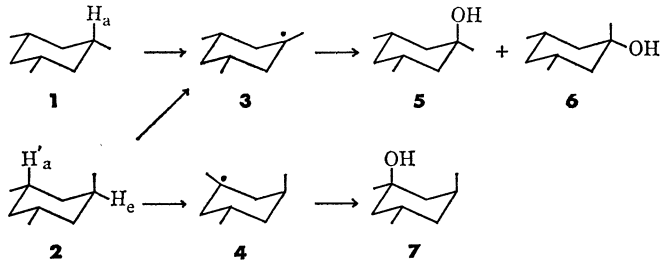

Fig. 1. Autoxidation of 1,3,5-trimethylcyclohexanes.

Isolation of alcohol **7** was not successful. Unquestionably it was derived from intermediate radical **4** generated by abstraction of H_a' in structure **2**, and two forms resulting from axial and equatorial attack of oxygen on radical **4** are of identical configuration and conformationally interconvertible. No other products were detected, indicating that the reaction took place only at tertiary hydrogen atoms.

As shown in Table 1, stereoisomeric 1,3,5-trimethylcyclohexanes **1** and **2** give epimeric alcohols **5** and **6** in the same ratio (1/0.85). Apparently, trimethylcyclohexane **1** or **2**, on abstraction of H_a or H_e, gives radical **3** as a common intermediate. Oxygen attacks this radical from the axial side a little more readily than from the equatorial side. In view of conformational energy, the intermediate peroxy radical corresponding to alcohol **5** should be favoured, at equilibrium, over that corresponding to alcohol **6** by a factor of about 4;[3] consequently, the observed ratio of 1/0.85 indicates an almost random attack of oxygen on both sides of radical **3**. The planar structure of cyclohexyl radicals at the radical centre[5] suggests that oxygen will attack radical **3** with equal probability on both sides of the ring, but the slight preference for axial attack of oxygen may be accounted for by the steric hindrance by the axial hydrogen atoms at positions 2 and 6 to oxygen approaching from the equatorial side. Such steric hindrance has also been suggested to explain the stereochemistry of several reactions including reduction of various cyclohexanones with metal hydrides.[6] It may also be possible that the torsional bond-bond interactions in the transition state suggested by Jensen and coworkers[7] may be a controlling factor in causing this preference.

The relative amounts in which trimethylcyclohexa-

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Table 1. Autoxidation of 1,3,5-trimethylcyclohexanes[a]

	Trimethylcyclohexane mmol	Azobisisobutyronitrile mmol	Hydroperoxide mmol	Alcohols[b] (mmol) 5	6	7	Total
1	9.16	0.038	0.43	0.205 (1	0.174 : 0.85	0 : 0)	0.38
1	9.16	0.036	0.46	0.228 (1	0.191 : 0.84	0 : 0)	0.42
2	9.37	0.037	0.55	0.193 (1	0.165 : 0.85	0.059 : 0.31)	0.42
2	9.31	0.037	0.50	0.184 (1	0.158 : 0.86	0.059 : 0.32)	0.40

a) At 60.2 °C for 48 hr. b) After reduction with lithium aluminium hydride.

Table 2. Autoxidation of 1,4- and 1,2-dimethylcyclohexanes

	Dimethylcyclohexane mmol	Azobisisobutyronitrile mmol	Temp. °C	Reaction time hr	Hydroperoxide mmol	Mole ratio of alcohols[a] **11** : **12** or **16** : **17**
1,4-[b]	10.4	0.036	60.2	48	0.38	1 : 0.71
	10.4	0.038	100.3	5	0.46	1 : 0.75
	10.4	0.037	110.5	4	0.70	1 : 0.76
13	7.0	0.026	60.5	24	0.18	1 : 1.28
13	7.1	0.024	60.2	48	0.30	1 : 1.13
14	6.9	0.024	60.2	48	0.055	1 : 1.16
14[c]			60.2	48		1 : 1.19

a) After reduction with lithium aluminium hydride. b) A mixture of **8** and **9** (75/25). c) Competitive autoxidation with trimethylcyclohexane **1**.

nols **5**, **6**, and **7** are formed reflect approximately the relative reactivities of H_e, H_a, and H_a' towards abstraction. In the accepted scheme of autoxidation[8] involving propagation and termination steps subsequent to initiation:

$$R\cdot + O_2 \rightarrow ROO\cdot \quad \text{(addition)}$$

$$RH + ROO\cdot \rightarrow ROOH + R\cdot \quad \text{(abstraction)}$$

$$2ROO\cdot \rightarrow \text{Inert product} \quad \text{(termination)}$$

the rate constants for abstraction and termination are assumed to be independent of minor difference in structure between the isomeric methylcyclohexylperoxy radicals, and the usual steady-state approximation gives, for the autoxidation of trimethylcyclohexane **1**, the following equation:

$$d([\mathbf{5}^*]+[\mathbf{6}^*])/dt = k_a[H_a](r_i/k_t)^{1/2} \quad (1)$$

where the numerals with an asterisk denote the hydroperoxides corresponding to the alcohols shown in Fig. 1, r_i is the rate of initiation, k_t the rate constant of termination, and k_a that of abstraction of hydrogen atom H_a. Similarly, in the autoxidation of trimethylcyclohexane **2**, we obtain

$$d([\mathbf{5}^*]+[\mathbf{6}^*]+[\mathbf{7}^*])/dt = (k_e[H_e]+k_a'[H_a'])(r_i/k_t)^{1/2} \quad (2)$$

and

$$(d[\mathbf{7}^*]/dt)/\{d([\mathbf{5}^*]+[\mathbf{6}^*])/dt\} = k_a'[H_a']/k_e[H_e] \quad (3)$$

where k_e and k_a' are the rate constants of abstraction of hydrogen atoms H_e and H_a', respectively. Since the autoxidations of hydrocarbons **1** and **2** were carried out under almost the same conditions, we have

$$\frac{d([\mathbf{5}^*]+[\mathbf{6}^*] \text{ from } \mathbf{1})/dt}{d([\mathbf{5}^*]+[\mathbf{6}^*]+[\mathbf{7}^*] \text{ from } \mathbf{2})/dt} = \frac{k_a[H_a]}{k_e[H_e]+k_a'[H_a']} \quad (4)$$

By substituting for the rates of formation of hydroperoxides in Eqs. 3 and 4 the amounts of the corresponding alcohols obtained given in Table 1, since the extent of autoxidation was very limited, the relative rates of hydrogen abstraction are calculated to be $k_e/k_a=2.6$ and $k_a'/k_a=0.22$. Thus, H_e is more reactive than H_a, since it is a less hindered equatorial hydrogen; moreover, the steric strain between the axial methyl group and hydrogens at positions 3 and 5 will be relieved in the transition state of hydrogen abstraction. In contrast, H_a' is less reactive because of the steric hindrance by the axial methyl group at position 3.

1,4- and 1,2-Dimethylcyclohexanes. 1,4- and 1,2-Dimethylcyclohexanes gave corresponding stereoisomeric 1,4-dimethyl- (**11** and **12**) and 1,2-dimethylcyclohexanols (**16** and **17**) (Figs. 2 and 3). These were identified by comparing their glpc retention times with those of authentic samples. The observed ratios **11**/**12** and **16**/**17** are shown in Table 2.

Döring *et al.*[9] reported that *cis*- or *trans*-1,4-dimethylcyclohexane, on autoxidation at 95—110 °C and subsequent reduction with triphenylphosphine or sodium sulphite, afforded alcohols **11** and **12** in a ratio of 1/0.24, which is considerably different from our result (1/0.74), while the ratio of axial to equatorial attack of oxygen on 4-*t*-butyl-1-methylcyclohexyl radical was 1/0.83, in agreement with our data on 1,3,5-trimethylcyclohexanes. The value of 1/0.74 for **11**/**12** is close to that for **5**/**6** from radical **3**, and this is what is

expected, because 1,4-dimethylcyclohexyl radicals are in a rapid conformational equilibrium before reacting with oxygen (**10e** and **10a** in Fig. 2), conformer **10e** predominating over conformer **10a** approximately to the same extent that prevails in the case of methylcyclohexane. The rapid equilibration is supported by Ogawa and Fessenden's conclusion[5b] that the change of linewidth in the ESR spectrum of cyclohexyl radical with temperature (−85—0 °C) corresponds to an activation energy for the ring inversion of 4.9 kcal/mol, which corresponds to a rate of *ca.* 10^9 s^{-1} at 60 °C. Thus, the rate of the inversion will be faster than that of the reaction with oxygen.[10]

With 1,2-dimethylcyclohexanes, the formation of alcohol **17** is slightly favoured over that of alcohol **16**. Conformer **15a** might play a role because of eclipsing of the two methyl groups in conformer **15e** (Fig. 3).

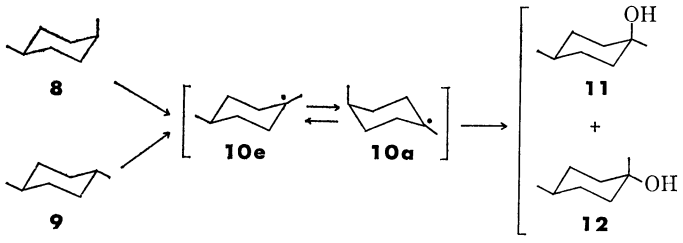


Fig. 2. Autoxidation of 1,4-dimethylcyclohexanes.

The relative reactivity of the axial tertiary hydrogen in *trans*-1,2-dimethylcyclohexane (**14**) towards abstraction was determined by competitive oxidation with trimethylcyclohexane **1**, using the same kind of equation as Eq. 3. The results are shown in Tables 4 and 5. The axial hydrogen in dimethylcyclohexane **14** is less reactive than H_a in trimethylcyclohexane **1**. This retardation is probably due to the steric hindrance by the equatorial methyl group at position 2 to approach of peroxy radicals and/or a crowded transition state with the incipient eclipsing of the two methyl groups.

1,1,3,5-Tetramethylcyclohexanes. Glpc analysis of the reduced oxidate from *cis*- (**18**) or *trans*-1,1,3,5-tetramethylcyclohexane (**19**) revealed two main product peaks. Apparently, these are due to stereoisomeric alcohols **21** and **22** derived from intermediate radical **20** (Fig. 4); the shorter retention time agrees with that of an authentic sample of 1,3,3,*t*-5-tetramethyl-*r*-1-cyclohexanol (**21**) prepared from 3,3,5-trimethylcyclohexanone and methylmagnesium iodide.[13] Although there should be a considerable energy difference (*ca.* 2.0 kcal/mol[14]) between the products from axial and equatorial attack of oxygen on radical **20**, an almost random attack of oxygen was observed also in this case (Table 3). The ratio of axial to equatorial oxygen attack on radical **20** (1/0.96) is slightly smaller than that of oxygen attack on radical **3** (1/0.85), apparently

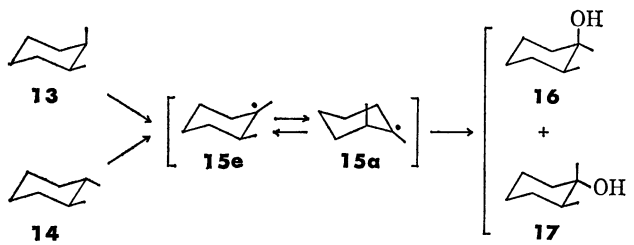


Fig. 3. Autoxidation of 1,2-dimethylcyclohexanes.

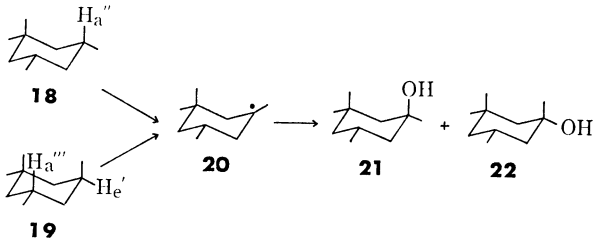


Fig. 4. Autoxidation of 1,1,3,5-tetramethylcyclohexanes.

Table 3. Autoxidation of 1,1,3,5-tetramethylcyclohexanes

Tetramethylcyclohexane mmol		Azobisisobutyronitrile mmol	Temp. °C	Reaction time hr	Hydroperoxide mmol	Mole ratio of alcohols[a] 21 : 22
18	5.57	0.024	59.8	48	0.030	1 : 1.0
18[b]			60.0	48		1 : 1.0
19	5.68	0.024	59.8	24	0.70	1 : 0.91
19[b]			60.0	24		1 : 0.91

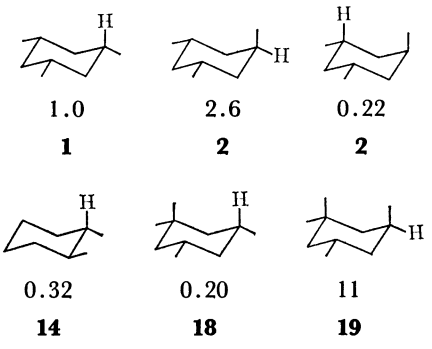
a) After reduction with lithium aluminium hydride. b) Competitive autoxidation with trimethylcyclohexane **1**.

Table 4. Competitive autoxidation[a]

Methylcyclohexane mmol		Azobisisobutyronitrile mmol	Reaction time hr	Hydroperoxide mmol	Mole ratio of alcohols[b] **16 : 17 : 5 : 6** or **21 : 22 : 5 : 6**
14	5.54	0.037	48	0.095	0.80 : 0.95 : 1 : 0.81
1	1.22				
18	5.58	0.061	48	0.10	0.44 : 0.44 : 1 : 0.83
1	1.53				
19	1.44	0.030	24	0.30	0.82 : 0.75 : 1 : 0.79
1	6.11				

a) At 60.0 °C. b) After reduction with lithium aluminium hydride.

Table 5. Relative rates of hydrogen abstraction from methylcyclohexanes



1.0	2.6	0.22
1	**2**	**2**
0.32	0.20	11
14	**18**	**19**

because of the steric effect of the axial methyl group at position 3 in radical **20**.

The relative rate of hydrogen abstraction from tetramethylcyclohexane **18** or **19** was determined by competitive autoxidation with 1,3,5-trimethylcyclohexane **1**. The results are shown in Tables 4 and 5. The relative reactivity of H_a'' in hydrocarbon **18** (0.20) agrees reasonably with that of H_a' in trimethylcyclohexane **2** (0.22). It is noteworthy that equatorial hydrogen H_e' in hydrocarbon **19** is much more reactive (relative reactivity, 11).[16] This large value is certainly due to steric acceleration caused by relief of the 1,3-diaxial strain between the two methyl groups at positions 1 and 3 in the transition state for hydrogen abstraction.

Experimental

All melting points and boiling points are uncorrected. Analytical glpc measurements were carried out with a Perkin-Elmer model 154D instrument. Preparative scale glpc was carried out with a Yanagimoto preparative gas chromatograph and an F & M Prep Master 775. NMR data were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a Nihon-Bunko DS-402G or a Perkin-Elmer 112G spectrometer.

1,3,5-Trimethylcyclohexanes. Mesitylene was hydrogenated in acetic acid over platinum oxide at 30—45 °C with an initial pressure of 50 atm of hydrogen to yield a mixture of 1,*c*-3,*c*-5- (**1**) and 1,*c*-3,*t*-5-trimethylcyclohexane (**2**) in a ratio of 83/17. This mixture was separated into each isomer by preparative glpc on a Silicone DC-550 column at 100 °C. Reinjection of the collected materials showed that the *cis* isomer was free of impurities and that the *trans* isomer contained 1.6% of **1**. The IR and NMR spectra were identical with those published.[17,18]

1,2- and 1,4-Dimethylcyclohexanes. Hydrogenation of *o*-xylene by the same procedure as above afforded a mixture of *cis*- (**13**) and *trans*-1,2-dimethylcyclohexane (**14**) in a ratio of 88/12. Dehydration of 1,2-dimethylcyclohexanol, prepared from methylmagnesium iodide and 2-methylcyclohexanone, followed by hydrogenation in methanol with hydrogen at 1 atm on 5% palladium-on-charcoal at room temperature gave a 22/78 mixture of *cis*- and *trans*-1,2-dimethylcyclohexane. From these mixtures each isomer was obtained by preparative glpc using a Silicone DC-550 column at 95 °C: *cis* isomer **13**, n_D^{20} 1.4349 (lit,[19] n_D^{20} 1.43596); *trans* isomer **14**, n_D^{20} 1.4259 (lit,[19] n_D^{20} 1.42695). Reinjection of the collected materials showed that the *cis* isomer contained 1.9% of **14** and that the *trans* isomer was free of impurities.

1,4-Dimethylcyclohexanes were prepared from *p*-xylene in the same manner as with 1,3,5-trimethylcyclohexanes, the *cis*/*trans* ratio being 75/25. This mixture was used without separating it into the isomeric components.

1,1,3,5-Tetramethylcyclohexanes. A procedure similar to that of Allinger and Miller[20] was used. Isophorone was hydrogenated in methanol over palladium-on-charcoal to yield 3,3,5-trimethylcyclohexanone, which was then converted with methylmagnesium iodide into 1,3,3,*t*-5-tetramethyl-*r*-1-cyclohexanol (**21**), mp 80.5—81.5 °C (lit,[13] 80—81.5 °C). Dehydration of this alcohol with formic acid followed by hydrogenation in acetic acid with hydrogen at 1 atm on platinum oxide at room temperature yielded a mixture of *cis*- (**18**) and *trans*-1,1,3,5-tetramethylcyclohexane (**19**) in a ratio of 1.34/1. The components were separated by preparative scale glpc using an SE-30 column at 128 °C: the *cis* isomer, bp 153—153.5 °C (lit,144.5—145 °C,[20] 152.4—152.5 °C[21]), n_D^{20} 1.4300 (lit, n_D^{25} 1.4288,[20] n_D^{20} 1.4319[21]); the *trans* isomer, bp 157.5—158 °C (lit, 148.5—149 °C,[20] 156.4—156.5 °C[21]), n_D^{20} 1.4357 (lit, n_D^{25} 1.4342,[20] n_D^{20} 1.4370[21]). Each of the collected materials showed no impurities on reinjection.

General Procedure of Autoxidation Experiments. Samples (1.0—1.5 ml) of methylcyclohexanes were autoxidized with oxygen at 1 atm in the presence of azobisisobutyronitrile (4—6 mg) in a small glass vessel attached to a gas burette. The reaction temperature was controlled by immersing the vessel in a constant temperature oil bath. The samples were stirred by means of a glass-encased magnetic stirring bar. At a conversion of less than 10% the reaction was stopped, and a portion (0.20—0.50 ml) of the oxidate was withdrawn to determine the hydroperoxide content by the iodometric method of Wagner *et al.*[22]

The rest of the oxidate was transferred into a dropping funnel, using 10 ml of anhydrous ether to rinse the reaction vessel, and was added to a suspension of 0.5 g of lithium aluminium hydride in 10 ml of anhydrous ether with stirring. The mixture was heated under reflux for 2 hr and then allowed to stand overnight at room temperature. Excess of lithium aluminium hydride was destroyed with dilute sulphuric acid, and the aqueous phase extracted with three 10 ml portions of ether. The combined ether solutions were washed with 5% sodium hydrogencarbonate solution and dried over anhydrous sodium sulphate, and then the ether was removed. The resulting solution was analysed for alcohols by glpc.

Product Identification. *1,3,5-Trimethylcyclohexanols*: 1,3,5-Trimethylcyclohexanols **5** and **6** were isolated by preparative glpc using a Carbowax column at 130 °C from reduced oxidate of a mixture of 1,3,5-trimethylcyclohexanes **1** and **2**.

1,t-3,t-5-Trimethyl-r-1-cyclohexanol (5): n_D^{20} 1.4498 (Found: C, 75.95; H, 12.71%. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76%); ν_{max} (0.022 M in CCl_4) 3617 cm^{-1} (OH); δ (0.71 M in CCl_4) 0.85 (d, J 6 Hz, 6H, 3-CH_3 and 5-CH_3), 1.14 (s, 3H, 1-CH_3), 0.2—1.9 (complex, ring protons), 2.32 (s, 1H, OH).[23] The signal of OH proton was shifted to δ 1.02 upon dilution to 0.158 M.

1,c-3,c-5-Trimethyl-r-1-cyclohexanol (6): mp 41.5—42.5 °C (Found: C, 76.26; H, 12.86%. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76%); ν_{max} (0.022 M in CCl_4) 3611 cm^{-1} (OH); δ (0.71 M in CCl_4) 0.91 (d, J 5 Hz, 6H, 3-CH_3 and 5-CH_3), 1.15 (s, 3H, 1-CH_3), 0.3—1.8 (complex, ring protons), 2.90 (s, 1H, OH).[23] The signal of OH proton was shifted to δ 1.38 upon dilution to 0.158 M.

1,4- and 1,2-Dimethylcyclohexanols: The products from 1,4- and 1,2-dimethylcyclohexanes were identified by comparison of their glpc retention times with those of authentic samples

of 1,*c*-4- (**11**) and 1,*t*-4-dimethyl-*r*-1-cyclohexanol (**12**) and those of the components of a mixture of 1,*c*-2- (**16**) and 1,*t*-2-dimethyl-*r*-1-cyclohexanol (**17**). Authentic samples of alcohols **11** and **12** were obtained by reaction of 4-methylcyclohexanone with methylmagnesium iodide, followed by separation of the resulting *cis* and *trans* mixture (**11**/**12**=1/1) by glpc using a Carbowax column at 140 °C: alcohol **11**, mp 66—68 °C (lit,[24] 72.5 °C); alcohol **12**, mp 23—24 °C (lit,[24] 24 °C). A sample of a **16** and **17** mixture was prepared from 2-methylcyclohexanone and methylmagnesium iodide, the **16**/**17** ratio being 3.8/1 in fairly good agreement with the reported value (3/1).[25]

1,3,3,5-Tetramethylcyclohexanols: The preparation of 1,3,3-*t*-5-tetramethyl-*r*-1-cyclohexanol (**21**) has been described above. Glpc analysis of the reduced oxidate from 1,1,3,5-tetramethylcyclohexane **18** or **19** revealed two main product peaks corresponding to alcohol **21** and the epimeric alcohol **22**, the shorter retention time agreeing with that of a sample of alcohol **21**.

Product Analysis. The reduced oxidate from 1,3,5-trimethylcyclohexane **1** or **2** was examined by glpc on a Carbowax column 4 m long at 165 °C; the order of elution was alcohols **5**, **7**, and **6**. Quantitative analysis for alcohol **5** or **6** was carried out using anisole as an internal standard. Since the mole ratio was found to be approximately equal to the peak area ratio with stereoisomers **5** and **6** [mol **5**/mol **6**=0.974× (area **5**/area **6**)], the amount of alcohol **7**, whose authentic specimen was not available, was estimated on the assumption that the mole ratio of **7**/**5** equals the peak area ratio. Stereoisomeric 1,2- or 1,4-dimethylcyclohexanols were analysed using a Carbowax column 2 m long at 150 °C; the order of elution was alcohols **16** and **17** or alcohols **11** and **12**. Analysis of the alcohols from competitive autoxidation of 1,2-dimethylcyclohexane **14** with trimethylcyclohexane **1** was carried out on a Carbowax column (2 m) and a Ucon Oil LB-550-X column (2 m) connected in series at 160 °C; alcohols were eluted in the order **16**, **5**, **17**, and **6**. The products from autoxidation of tetramethylcyclohexane **18** or **19** and competitive autoxidation with trimethylcyclohexane **1** were analysed with the above-mentioned series of columns at 170 °C; the elution of alcohols took place in the order **5**, **21**, **6**, and **22**.

It is apparent that in each pair of the epimeric alcohols examined the one, which has an hydroxyl group predominantly in the axial position, has a shorter retention time than the other, when chromatographed on polyethylene glycol (Carbowax) or polypropylene glycol (Ucon Oil). This observation is in accord with the results by Komer *et al.*,[26] who studied the retention times of the epimeric 2-, 3-, and 4-alkylcyclohexanols using glycerol or erythritol as a stationary phase.

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3) Assuming that the energy difference between **5** and **6** is the difference in conformational energy between methyl (1.7 kcal/mol[4]) and an oxygen function (*ca.* 0.7 kcal/mol[4]), *i.e.*, *ca.* 1.0 kcal/mol.

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