Configurational and Conformational Stereoselectivity in the Acid-Catalyzed Ring Opening of 1-Phenylcyclohexene Oxides

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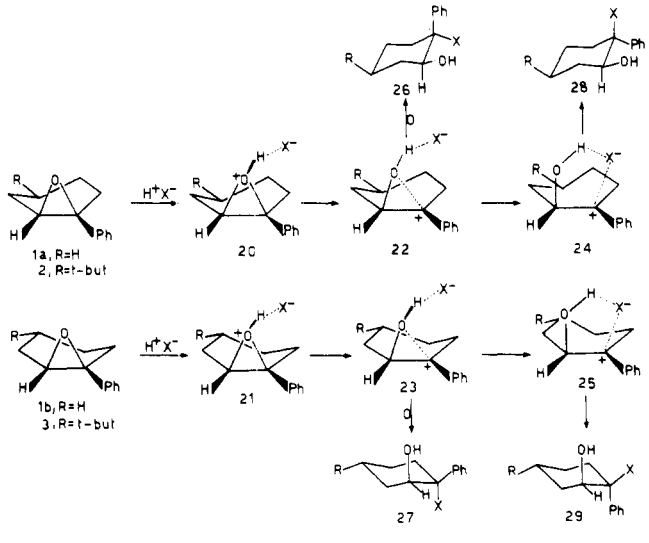
The stereoselectivities of several reactions of the conformationally mobile aryl-substituted oxiranes **1a,b** under acidic conditions were compared with those of its rigid *tert*-butyl analogues **2** and **3**. The amounts of syn adducts formed in the reactions of **2** and **3** are always higher in the case of **3**. Furthermore, the tendency toward the syn opening observed for **1** is higher than that obtained for either of the rigid epoxides. This last result can not be rationalized simply on the basis of the Winstein–Holness hypothesis that the *tert*-butyl is merely an anchor. However, the syn stereoselectivity of the reaction of **3** resembles more closely that of the nonrigid epoxide **1**, suggesting that **1** reacts preferentially through conformation **1b** corresponding to **3**. The differences in stereoselectivities observed between the reactions of **2** and **3** and the higher reactivity of **1** through conformation **1b** have been rationalized in terms of the hypothesis that one of the determining factors in these reactions is the preferential C–O bond cleavage of the protonated 1,2-epoxycyclohexane in such a way as to give an axial hydroxy group ("axial cleavage"). This observation can probably be generalized to explain the well-known Fürst–Plattner rule of the diaxial ring opening of 1,2-epoxycyclohexanes.

Recent reports strongly suggest that K-region arene oxides[1] are implicated in the carcinogenic and mutagenic activity of polycyclic arenes.[2] Aryl-substituted oxiranes can be used as models for arene oxides,[3] and a better knowledge of the mechanism of their ring opening is desirable in order to understand the chemistry and the nucleophilic reactions of K-region arene oxides.

It is well established that aryl-substituted oxiranes, such as 1-phenylcyclohexene oxide **1**, usually exhibit a high tendency toward syn addition under acidic conditions.[4] However, the stereoselectivity of the ring opening was shown to be strongly dependent on the structure of the epoxide, the nature of the substituents on the phenyl group, the solvent, the nucleophile, and the reaction conditions[4] in general. Oxirane **1** can exist in two nonequivalent half-chair conformations **1a** and **1b**[5,6] (Scheme I) of about the same energetic content, which readily undergo chair inversion. Neither examination of molecular models nor experimental evidence (NMR) reveals a strong conformational preference; however, an X-ray crystal structure of the *p*-bromo derivative of **1** indicates, at least in the solid state, conformation **1a** as the preferred one.[6] In order to get information on the importance of conformational factors, we examined reactions of **1** and of its rigid analogues **2** and **3**, in which the *tert*-butyl group constrains the 1-phenylcyclohexene oxide system into fixed half-chair conformations[7a] that are equivalent to **1a** and **1b**, respectively.

Scheme I



The first results showed[7] that also epoxides **2** and **3** exhibit a large tendency toward syn additions under acidic conditions. Furthermore, the presence of the phenyl determines the site of bond cleavage, determining the formation of products arising only from a benzylic C–O cleavage.[7]

Following the Winstein and Holness suggestion[8-11] let us assume that the *tert*-butyl group on C-4 of **2** and **3** has no influence except for its anchoring effect[10,11] and that consequently the ring opening of epoxide **1** in the conformation **1a** or **1b** is strictly equivalent to that of epoxide **2** or **3**, respectively. It would be expected that the stereoselectivity of the ring opening reactions of epoxide **1** would be similar to that either of **2** or of **3**, or intermediate between them. As previously noted,[12] however, when the reactions take place directly on a cyclohexylic carbon, as in the present case, the Winstein–Holness assumption[8-11] might be unreliable for quantitative work. On the basis of this premise, several reactions of epoxides **1**, **2**, and **3** under acidic conditions were examined. In order to make useful comparisons, it has been necessary to select reactions and reaction conditions producing the simultaneous formation of both the syn and anti adducts. Therefore, we studied the acid-catalyzed methanolysis, hydrolysis, and dichloroacetolysis of epoxides **1–3**.

Pure reference compounds were obtained in the following manner (see Scheme II). The diols **10** and **11**[13,14] and **12–15**[7a] were available from previous studies. The acid-catalyzed methanolysis of epoxides **1**, **2**, and **3** in methanol at −30 °C[15] gave mixtures in which the *trans*-hydroxy ethers **5**, **7**, and **9** were formed as the main products together with minor amounts of the corresponding cis compounds **4**, **6**, and **8**; preparative TLC of these mixtures afforded pure **5**, **7**, and **9**. When the methanolysis of the same epoxides was carried out in methylene dichloride in the presence of acid, the reactions afforded mixtures of the same hydroxy ethers in which the cis/trans ratios were markedly higher, but appreciable amounts of rearranged compounds (2-phenylcyclohexanones, 2-phenylcyclopentane-1-carboxaldehydes, and 2-phenylcyclohex-2-en-1-ols) were formed.[16] From the reaction mixtures of epoxides **1** and **3** in CH_2Cl_2, the pure *cis*-hydroxy ethers **4** and **8** were separated by TLC. When the corresponding mixture from the epoxide **2** was subjected to TLC, the hydroxy ether **6** was contaminated with the *cis*-2-phenylcyclohex-2-en-1-ol. However, oxidation of the trans diaxial hydroxy ether **9** afforded the keto ether **18**, which on reduction with borane/methyl sulfide complex gave a 4:6 mixture of **6** and **9** from which pure **6** was easily separated by TLC. Hydroxy ethers **4** and **5** and **7** and **8** were converted by oxidation, respectively,

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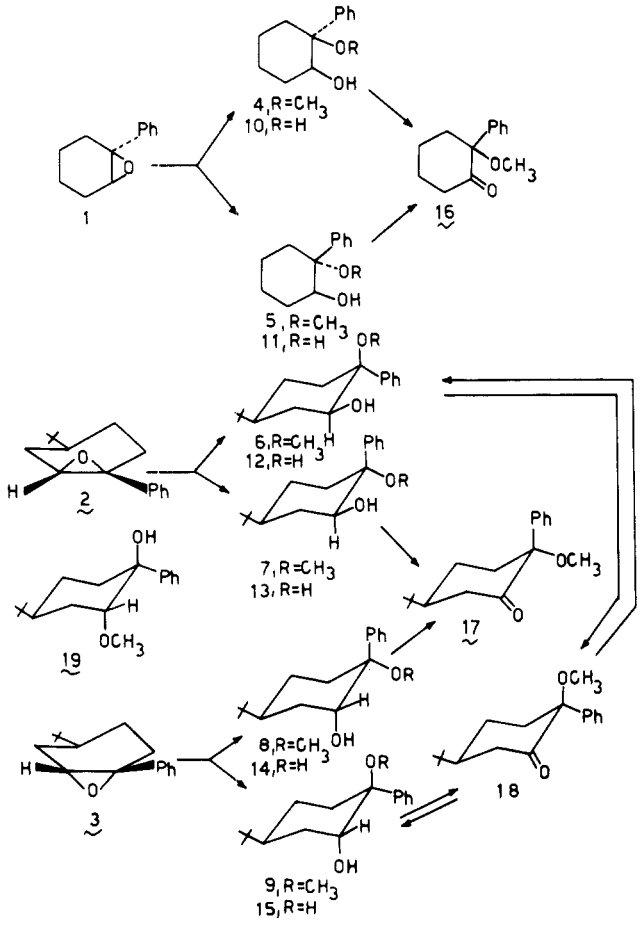
Scheme II



into the keto ethers **16** and **17**. The hydroxy ether **19** has been obtained as the only product in the reaction of epoxide **2** with sodium methoxide in methanol, according to the strong preference of oxiranes toward diaxial ring opening under basic conditions.[7a]

The oxidation of the pairs of hydroxy ethers **4** and **5**, **6** and **9**, and **7** and **8** to the same ketone proves their epimeric nature and their structure, whereas the stability of **19** to oxidation under the same conditions defines its structure. The configurations of the hydroxy ethers were deduced by NMR spectroscopy and by IR studies in the 3-μm range (see Table I). The half-bandwidths of the methinyl protons β to phenyl[4b,7,17] are consistent with the expectations for equatorial protons in **5**, **8**, **9**, and **19** and axial ones in **4**, **6**, and **7**. On the other hand, the hydroxyl-stretching bands of these compounds in dilute CCl_4 are in accordance with the presence of strong OH···O interactions in **4**, **6**, and **8** (*cis*-hydroxy ethers), a slightly weaker one in **7** (trans diequatorial hydroxy ether), and OH···π bonds in **5**, **9**, and **19** (trans diaxial hydroxy ethers).[7,16,18,19]

Table II reports the relative percentages of the syn and anti adducts formed in the acid-catalyzed methanolysis in methanol and in methylene dichloride (using two different epoxide/methanol ratios), in the acid-catalyzed hydrolysis, and in the dichloroacetolysis in cyclohexane of epoxides **1**, **2** and **3**. In the latter reactions the product compositions were determined after saponification of the monoester mixtures to the corresponding diols. Even in the acid methanolyses of **2** no trace of the hydroxy ether **19**, which could be formed by a nucleophilic nonbenzylic attack through a stereoelectronically favored diaxial ring opening,[20] could be found. Furthermore, as previously pointed out,[4,7,16] the amounts of syn adducts formed in the reactions in protic solvents are markedly lower than those obtained in nonprotic solvents.

Comparison of the stereoselectivities of the reactions of **1**, **2**, and **3** (see Table II) reveals marked and interesting differences. In particular, the amounts of syn adducts formed in the reactions of the two rigid epoxides **2** and **3** are always higher in the case of **3**. Furthermore, the tendency toward the syn opening observed for **1** is higher than that obtained for either of the rigid epoxides.

Table I. NMR and IR Data of the Hydroxy Ethers

compd	NMR δ, ppm: CHX ($W_{1/2}$, Hz)	NMR δ, ppm: CH_3O	IR: OH stretching, cm^{-1}
4	3.65 (14.0)[a]	3.14	3590[c]
5	3.73 (6.8)[a]	2.95	3602[d]
6	3.46 (<10)[a,e]	3.20	3592[c]
7	4.00 (16.5)[a]	3.02	3594[c]
8	4.44 (7.5)[a]	2.91	3574[c]
9	3.86 (6.5)[a]	3.00	3600[d]
19	3.39 (6.3)[b]	2.97	3609[d]

[a] X = OH. [b] X = OCH_3. [c] OH···O. [d] OH···π. [e] Approximate value due to the partial overlapping of the signal with that of the methoxy group.

The differences in stereoselectivity between **2** and **3** can be rationalized in terms of the hypothesis that one of the determining factors in these reactions is the preferential "axial cleavage" of the epoxidic ring[21,22] and on the basis of the mechanism suggested in order to rationalize the steric course of the ring opening of aryloxiranes under acidic conditions.[4,24] According to this mechanism (see Scheme I) the anti products (**26** or **27**) are formed by attack of a nucleophile on the backside of an intramolecular intimate ion/dipole pair **22** or **23** (originating from the protonated oxiranes **20** or **21**), whereas the syn products **28** or **29** arise by the collapse of the nucleophile separated ion/dipole pair **24** or **25**, formed by an internal rearrangement of **22** or **23** with further loosening of the dipole (OH) from the benzylic carbenium ion. In such a scheme the stereoselectivity of these reactions should be related to the competition between the conversion of the species (**22** and **23**) into the anti products (**26** and **27**) and that of the same species (**22** and **23**) into **24** and **25**, which leads to the syn products (**28** and **29**). If the intimate (**22** and **23**) and nucleophile separated ion/dipole pairs (**24** and **25**) were interconvertible in an equilibrium process, also the conversion rate of **24** and **25** into the syn products (**28** and **29**) could be of some importance in determining the stereoselectivity of these reactions. Due to the strong directive effect of the phenyl, the ring opening of **3** takes place through an "axial cleavage" of the epoxidic ring,[21,22] whereas that of the diastereoisomeric epoxide **2** must occur through an "equatorial cleavage".[21,22]

According to a statement of Hartshorn and Kirk,[22] the "axial cleavage" should follow a reaction pathway having lower energy requirements than the "equatorial" one. This is also in accordance with the principle of least nuclear motion since it can be seen from molecular models that an axial cleavage involves less change in atomic positions than an equatorial one. Consequently, the higher syn stereoselectivity of the reactions of **3** compared with that of the corresponding reactions of **2** can be attributed to a higher conversion rate of the intermediate **23** into **25**, compared with that of **22** into **24**. It is not possible to justify the differences in stereoselectivities observed between the reactions of epoxides **2** and **3** merely on the basis of the relative stability of the syn and anti adducts derived from epoxides **2** and **3** or by the well-known rule of diaxial ring opening of 1,2-epoxycyclohexanes (Fürst–Plattner rule).[20,23,25]

The higher syn stereoselectivity of the reactions of the nonrigid epoxide **1** compared with that of the corresponding reactions of both the epoxides **2** and **3** can not be rationalized simply on the basis of the hypothesis[8-11] that the *tert*-butyl is merely an anchor. The present results appear to confirm

Table II. Stereochemistry of the Ring Opening of Epoxides 1–3 under Acid Conditions at 25 °C

epoxide	solvent	acid	syn adduct, %	anti adduct, %
1	MeOH	H_2SO_4	38.0[c]	62.0[d]
2	MeOH	H_2SO_4	9.1[e]	90.9[f]
3	MeOH	H_2SO_4	21.6[g]	78.4[h]
1	MeOH/CH_2Cl_2[a]	TsOH	90.0[c]	10.0[d]
2	MeOH/CH_2Cl_2[a]	TsOH	35.8[e]	64.2[f]
3	MeOH/CH_2Cl_2[a]	TsOH	88.3[g]	11.7[h]
1	MeOH/CH_2Cl_2[b]	TsOH	82.9[c]	17.1[d]
2	MeOH/CH_2Cl_2[b]	TsOH	29.0[e]	71.0[f]
3	MeOH/CH_2Cl_2[b]	TsOH	78.9[g]	21.1[h]
1	H_2O	H_2SO_4	62.6[i]	37.4[j]
2	H_2O	H_2SO_4	40.8[k]	59.2[l]
3	H_2O	H_2SO_4	52.4[m]	47.6[n]
1	cyclohexane	$CHCl_2COOH$	94.5[i,o]	5.5[j,o]
2	cyclohexane	$CHCl_2COOH$	81.8[k,o]	18.2[l,o]
3	cyclohexane	$CHCl_2COOH$	93.5[m,o]	6.5[n,o]

[a] Molar ratio of epoxide/acid/MeOH = 1:0.1:6. [b] Molar ratio of epoxide/acid/MeOH = 1:0.1:12. [c] Hydroxy ether **4**. [d] Hydroxy ether **5**. [e] Hydroxy ether **6**. [f] Hydroxy ether **7**. [g] Hydroxy ether **8**. [h] Hydroxy ether **9**. [i] Diol **10**. [j] Diol **11**. [k] Diol **12**. [l] Diol **13**. [m] Diol **14**. [n] Diol **15**. [o] After saponification of the crude reaction mixture.

previous observations[12] that the introduction of the *tert*-butyl group introduces some distorsions in ground-state bond angles and reduces the normal flexibility of the unsubstituted cyclohexane ring in such a way as to modify its reactivity.[26]

The small energy differences observed in the present case show, however, that this influence is relatively small. Anyway the greater similarity between the behavior of epoxide **1** and that of epoxide **3** indicates that the former epoxide very probably reacts through the half-chair conformation **1b**, corresponding to **3**, rather than the alternative one **1a**, corresponding to **2**.[27]

Also the higher reactivity of the epoxide **1** through conformation **1b** can be rationalized on the basis of preferential "axial cleavage" of 1,2-epoxycyclohexanes.[21,22] The ring opening of **1** in the conformation **1b** occurs through an "axial cleavage" easier than the "equatorial" one which takes place in the ring opening in the conformation **1a**. Consequently, the epoxide **1** in conformation **1b** reacts faster than in conformation **1a**. It is interesting to note that the conformation (**1b**) through which epoxide **1** reacts preferentially is different from that (**1a**) found for the *p*-bromo derivative of **1** as the preferred one in the solid state.[6]

In conclusion, the data presented in this paper stress that the stereoselectivity of the acid-catalyzed ring opening of 1-phenylcyclohexene oxides strongly depends on configurational and conformational factors. Furthermore, contrary to the widely applied Winstein–Holness assumption,[8-11] the reactivity of the conformationally mobile epoxide **1** cannot be completely related to that of the two corresponding diastereoisomeric *tert*-butyl derivatives **2** and **3**. Finally, epoxide **1** seems to react through the conformation **1b**, which can allow an "axial cleavage" of the epoxide ring.[21,22] The present results clearly indicate that, even when the cleavage of an epoxycyclohexane goes through the intermediate formation of a carbenium ion, the C–O bond cleavage of the protonated oxirane occurs preferentially, in absence of strong directive effects (steric factors, electronic factors), in such a way as to give an axial hydroxy group. This can probably be generalized to explain the well-known Fürst–Plattner rule[20,23] on the basis of this preference for the axial cleavage of the C–O bond rather than on that of the axial approach of the nucleophile, in accordance with the fact that a considerable degree of bond breaking should exist in the transition state also for nonactivated epoxides.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra for comparison between compounds were taken on paraffin oil mulls on a Perkin-Elmer Infracord Model 137, and those for the determination of OH-stretching bands were taken with a Perkin-Elmer Model 257 double-beam grating spectrophotometer in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2-cm optical length was employed, and the concentration of the solution was 5×10^{-3} M or lower to prevent intramolecular association. NMR spectra were determined on ~10% $CDCl_3$ solutions with a JEOL C 60 HL spectrometer using Me_4Si as an internal standard. All GLC analyses were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector, using a dual column system with glass columns. **4** and **5** (columns packed with 10% ethylene glycol succinate on 80–100 mesh silanized Chromosorb W, 1.5 m × 2.5 mm): temperature of columns 120 °C, evaporator and detector 200 °C; nitrogen flow 30 mL/min; order of increasing retention times, **4** < **5**. **6** and **7** (columns packed with 3% silicon oil OV 17 on 80–100 mesh silanized Chromosorb W, 2 m × 2.5 mm): temperature of columns 170 °C, evaporator and detector 220 °C; nitrogen flow 30 mL/min; order of increasing retention times, **7** < **6**. **8** and **9** (columns packed with 10% ethylene glycol succinate on 80–100 mesh silanized Chromosorb W, 1.5 m × 2.5 mm): temperature of columns 155 °C, evaporator and detector 220 °C; nitrogen flow 30 mL/min; order of increasing retention times, **8** < **9**. **10** and **11** (columns packed with 10% ethylene glycol succinate on 80–100 mesh silanized Chromosorb W, 1.5 m × 2.5 mm): temperature of columns 160 °C, evaporator and detector 220 °C; nitrogen flow 30 mL/min; order of increasing retention times, **10** < **11**. **12** and **13**, **14**, and **15** (columns packed with 10% ethylene glycol succinate on 80–100 mesh silanized Chromosorb W, 1.5 m × 2.5 mm): temperature of columns 120 °C, evaporator and detector 220 °C; nitrogen flow 30 mL/min; order of increasing retention time, **12** < **13** and **14** < **15**. The values given in Table II were the average of at least three measurements done on at least two different runs for each reaction. Preparative TLC was performed on 2-mm layer silica gel plates (Merk F_{254}) containing a fluorescent indicator. A 75:25 mixture of petroleum ether and ether was used as the eluent, elution was repeated twice, and spots were detected under UV light (254 nm). All comparisons between compounds were made on the basis of IR and NMR spectra and GLC. Magnesium sulfate was always used as the drying agent. Evaporations were done in vacuo (rotating evaporator). Petroleum ether refers to the fraction boiling at 40–70 °C; cyclohexane and CH_2Cl_2 were refluxed over P_2O_5 and rectified.

Compounds **1**,[13] **2**,[7a] **3**,[7a] **10**,[13] **11**,[29] and **12–15**[7a] were prepared as previously described.

2-Phenyl-*cis*-2-methoxy-*r*-1-cyclohexanol (4). To **1** (0.500 g, 2.85 mmol) was added a solution of *p*-toluenesulfonic acid and methanol (molar ratio **1**/acid/methanol = 1:0.1:6) in CH_2Cl_2 (50 mL). The resulting mixture was stirred for 2 h at 25 °C and then treated with solid $NaHCO_3$ and saturated $NaHCO_3$. Evaporation of the washed (H_2O) organic solvent yielded a mixture of **4** and **5** in which **4** predominated, together with carbonylic compounds (mainly 2-phenylcyclohexanone and 1-phenylcyclopentane-1-carboxaldehyde), which was subjected to preparative TLC (a 75:25 mixture of petroleum ether and ether was used as the eluent; elution was repeated twice). Extraction of the band corresponding to the *cis*-hydroxy ether **4** (the trans isomer has a higher R_f) yielded pure **4** (0.290 g) as an oil. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.96; H, 8.79.

2-Phenyl-*trans*-2-methoxy-*r*-1-cyclohexanol (5). A solution of 1 (0.500 g) in 0.2 N H_2SO_4 in anhydrous methanol (50 mL) was stirred for 2 h at room temperature and then quenched with solid $NaHCO_3$ and saturated $NaHCO_3$, diluted with water, and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts yielded a residue (0.540 g) consisting of **4** and **5**, which was subjected to preparative TLC (a 75:25 mixture of petroleum ether and ether was used as the eluent; elution was repeated twice). Extraction of the two main bands (the one with a higher R_f contains **5**) yielded pure **4** (0.157 g) as an oil and **5** (0.206 g), mp 56–58 °C (from petroleum ether). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.81.

2-Phenyl-2-methoxycyclohexanone (16). A. A solution of **4** (0.045 g, 0.218 mmol) in acetone (3 mL) was treated with Jones reagent[30] (0.09 mL). After 15 min at room temperature, the mixture was diluted with water and extracted with ether. Evaporation of the washed (H_2O, saturated aqueous $NaHCO_3$, and H_2O) and dried ether extracts gave an oily residue of **16:** IR λ 5.80 μm (C=O); 2,4-dinitrophenylhydrazone,[31] mp 149–151 °C (from ethanol). Anal. Calcd for $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.24; N, 14.58. Found: C, 59.72; H, 5.26; N, 14.78.

B. **5** (0.045 g) was oxidized under the conditions used above to give **16** (0.039 g): 2,4-dinitrophenylhydrazone,[31] mp 149–151 °C.

***t*-5-*tert*-Butyl-2-phenyl-*t*-2-methoxy-*r*-1-cyclohexanol (9).** A solution of **3** (1.100 g, 4.78 mmol) in 0.2 N H_2SO_4 in anhydrous methanol (110 mL) was left at −30 °C for 3 h and then quenched with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$ and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts yielded a residue (1.170 g) consisting mainly of a 12:88 mixture of **8** and **9**, from which pure **9** (0.330 g) was obtained by crystallization from petroleum ether at −5 °C, mp 81–82 °C. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 78.19; H, 10.16.

***t*-5-*tert*-Butyl-2-phenyl-*c*-2-methoxy-*r*-1-cyclohexanol (8).** Treatment of **3** (0.500 g, 2.2 mmol) with a solution of *p*-toluenesulfonic acid and methanol in CH_2Cl_2 (50 mL) as described above for the preparation of **4** yielded an oil residue (0.539 g) consisting of a 96:4 mixture of **8** and **9** together with minor amounts of rearrangement products. Preparative TLC of this residue (a 75:25 mixture of petroleum ether and ether was used as the eluent; elution was repeated twice) gave pure **8** as an oil (0.380 g). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.96; H, 10.22.

***c*-5-*tert*-Butyl-2-phenyl-*t*-2-methoxy-*r*-1-cyclohexanol (7).** Reaction of **2** (1.0 g, 4.3 mmol) with 0.2 N H_2SO_4 in methanol (100 mL) as described above for the preparation of **9** yielded an oily residue mainly consisting of a mixture of **6** and **7** in an approximative ratio of 3:97, which was subjected to preparative TLC (a 75:25 mixture of petroleum ether and ether was used as the eluent; elution was repeated twice). Extraction of the band with the lower R_f gave pure **7** as an oil (0.540 g). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.85; H, 10.12.

***t*-5-*tert*-Butyl-*r*-2-methoxy-2-phenylcyclohexanone (17). A.** Oxidation of **7** (0.045 g, 0.17 mmol) with Jones reagent[30] as described above for the preparation of **16** gave **17** (0.041 g) as an oil: IR λ 5.82 μm (C=O); 2,4-dinitrophenylhydrazone,[31] mp 125–127 °C (from ethanol). Anal. Calcd for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72. Found: C, 62.93; H, 6.62; N, 12.50.

B. Compound **8** (0.045 g, 0.17 mmol) was oxidized under the same conditions, yielding pure **17** (0.038 g): 2,4-dinitrophenylhydrazone,[31] mp 125–127 °C (from ethanol).

***c*-5-*tert*-Butyl-r-2-methoxy-2-phenylcyclohexanone (18).** Oxidation of **9** (0.772 g, 2.95 mmol) under the conditions used above for the preparation of **16** gave **18** (0.680 g) as an oil: IR λ 5.82 μm (C=O); 2,4-dinitrophenylhydrazone,[31] mp 183–185 °C (from ethanol). Anal. Calcd for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72. Found: C, 62.95; H, 6.51; N, 13.03.

Reduction of 18 with Borane/Methyl Sulfide Complex. A solution of **18** (0.680 g, 2.6 mmol) in anhydrous ether (42 mL) was treated under nitrogen with borane/methyl sulfide (0.7 mL, 7.0 mmol) and then stirred for 2 h at room temperature. The resulting mixture was cooled to 0 °C, treated with anhydrous methanol (140 mL), and allowed to stand overnight. Evaporation of the methanol yielded a residue (0.637 g) consisting of a 54:46 mixture of **6** and **9**, which was subjected to preparative TLC (a 75:25 mixture of petroleum ether and ether was used as the eluent; elution was repeated twice). Extraction of the two main bands (the faster moving band contained **9**) gave **9** (0.226 g) as an oil and *c*-5-*tert*-butyl-2-phenyl-*c*-2-methoxy-*r*-1-cyclohexanol (**6**, 0.280 g), which crystallized from petroleum ether, mp 102–104 °C. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.86; H, 9.99. Found: C, 77.61; H, 10.04.

Hydroxy ether **6** was not obtained in a pure state from the reaction mixture of epoxide **2** with methanol in CH_2Cl_2 in the presence of *p*-toluenesulfonic acid. Under these reaction conditions epoxide **2** gave, in addition to the hydroxy ethers **8** and **9**, marked amounts of rearrangement products (mainly *c*-5-*tert*-butyl-2-phenylcyclohex-2-en-*r*-1-ol). When the crude reaction product was subjected to preparative TLC, hydroxy ether **6** was obtained in mixture with *c*-5-*tert*-butyl-2-phenylcyclohex-2-en-*r*-1-ol. Crystallization of this mixture from petroleum ether gave only the latter product in a pure state: mp 84.5–86 °C (lit.[32] mp 80–81.5 °C); NMR δ 6.05 (1 H, m, $W_{1/2}$ = 9.0 Hz, CH=C), 4.90 (1 H, m, $W_{1/2}$ = 15.7 Hz, CHOH), 0.95 [9 H, s, $C(CH_3)_3$]. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.67. Found: C, 83.11; H, 9.47.

***c*-4-*tert*-Butyl-1-phenyl-*t*-2-methoxy-*r*-1-cyclohexanol (19).** A solution of MeONa (1.08 g) in anhydrous methanol (10 mL) was added to **2** (0.20 g, 0.87 mmol), and the resulting mixture was refluxed for 48 h and then diluted with water and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts yielded crude **19**, which crystallized from petroleum ether at −20 °C to give pure **19**, mp 92–93 °C. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.92; H, 9.99. Found: C, 78.19; H, 10.00.

Reactions of Epoxides 1–3 in Water and Methanol in the Presence of Acid. A suspension (water) or solution (methanol) of the epoxide (0.29 mmol) in a 0.2 N solution of the acid (H_2SO_4 for the reactions in water and monohydrate *p*-toluenesulfonic acid for the reactions in methanol) in the solvent (5 mL) was stirred at 25 °C for 24 (reactions in water) and 1 h (reactions in methanol) and then quenched with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$ and throughly extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts yielded mixtures consisting (Table II) of diols (reactions in water: **10** and **11** from **1**, **12** and **13** from **2**, and **14** and **15** from **3**) and hydroxy ethers (reactions in methanol: **4** and **5** from **1**, **6** and **7** from **2**, and **8** and **9** from **3**) accompanied by small amounts of rearrangement products, which were analyzed by GLC. The solvolysis addition products were completely stable under the reaction conditions used, and rearrangement products were shown not to be derived from a further transformation of the addition products.

In the reaction of epoxide **2** in methanol no trace of the hydroxy ether **19** could be revealed.

Reactions of Epoxides 1–3 with Methanol in Methylene Dichloride in the Presence of *p*-Toluenesulfonic Acid. To the epoxide (0.29 mmol) was added a solution of monohydrate *p*-toluenesulfonic acid and anhydrous methanol, in the molar ratios (epoxide/acid/methanol) shown in Table II, in anhydrous CH_2Cl_2 (5 mL) at 25 °C. The resulting mixture was stirred for 1 h at the same temperature and then treated with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$. Evaporation of the washed (H_2O) organic solvent gave a mixture of hydroxy ethers (**4** and **5** from **1**, **6** and **7** from **2**, and **8** and **9** from **3**) accompanied by appreciable amounts of rearrangement products, which were analyzed by GLC. The solvolysis addition products of each epoxide were completely stable under the reaction condition used, and rearrangements products were shown not to be derived from a further transformation of the addition products.

In the reactions of epoxide **2** no trace of the hydroxy ether **19** could be revealed.

Reactions of Epoxides 1–3 with Dichloroacetic Acid in Cyclohexane. A solution of the epoxide (0.29 mmol) in dry cyclohexane (5 mL) at 25 °C was treated with a 1 M solution of dichloroacetic acid in the same solvent (0.32 mL) and then left at the same temperature. After 24 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and water and evaporated to dryness. The residue, consisting mainly of mixtures of monodichloroacetates, was hydrolyzed in the following way. The crude reaction products were dissolved in THF (5 mL), treated with 1 M KOH in ethanol (2 mL), and left for 5 h at room temperature. Dilution with water, extraction with ether, and evaporation of the washed (H_2O) and dried ether extracts yielded a mixture consisting of diols (**10** and **11** from **1**, **12** and **13** from **2**, and **14** and **15** from **3**), which was analyzed by GLC. Reactions of each epoxide carried out under the same conditions but stopping after a longer time of contact with the acid yielded the same product composition within experimental error.

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Registry No.—**1**, 4829-01-0; **2**, 17851-86-4; **3**, 4341-22-4; **4**, 69257-64-3; **5**, 69257-65-4; **6**, 69257-66-5; **7**, 69257-67-6; **8**, 69257-68-7; **9**, 69257-69-8; **10**, 4912-59-8; **11**, 27167-34-6; **12**, 4127-41-7; **13**, 4127-42-8; **14**, 4127-44-0; **15**, 4127-43-9; **16**, 69257-71-2; **16** 2,4-DNP, 69257-72-3; **17**, 69257-73-4; **17** 2,4-DNP, 69257-74-5; **18**, 69257-75-6; **18** 2,4-DNP, 69257-76-7; **19**, 69257-70-1; *c*-5-*tert*-butyl-2-phenylcyclohex-2-en-*r*-1-ol, 69257-77-8; methanol, 67-56-1; dichloroacetic acid, 79-43-6.

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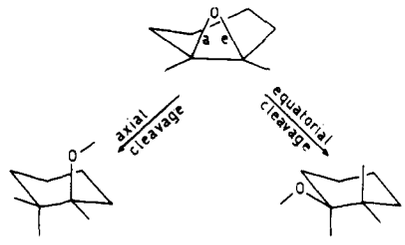

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Acid-Catalyzed Dehydration and Acetolysis of Tertiary Methyl- and *tert*-Butylcarbinols. Empirical Force Field Treatment of *tert*-Butyl/Methyl Reactivity Ratios in Solvolysis Reactions of Alcohols and *p*-Nitrobenzoates

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Rate constants have been determined for the sulfuric acid catalyzed solvolysis in anhydrous acetic acid of 28 tertiary carbinols, 23 of which contain either a methyl or a *tert*-butyl substituent at the tertiary position. The kinetic effect of replacing Me by *t*-Bu ranges from 0.03 for alkyl(1-adamantyl)-*tert*-butylcarbinols to $10^{3.3}$ for 2-alkyl-2-adamantanols. For five systems the *t*-Bu/Me values are smaller than those found in the solvolysis of the corresponding *p*-nitrobenzoates by factors ranging from $10^{1.9}$ to $10^{4.6}$, depending on the structure. Strain energy calculations by the empirical force field method (molecular mechanics) provide a coherent interpretation of reactivity data for both alcohols and *p*-nitrobenzoates, provided that the hydrocarbon model employed for the ground state takes into account the greater steric requirements of the OPNB leaving group: OPNB is modeled by Me; OH by H. In this way self-consistent reactivity/Δ(strain) correlations are obtained for both the *t*-Bu/Me ratios and substituent effects in the 2-alkyl-2-adamantyl system. Nevertheless, the fact that the individual reactivities of disparate systems are poorly correlated by strain energy calculations limits their utility as a probe for detecting anomalous behavior in the solvolysis of *exo*- and *endo*-2-norbornyl derivatives, for example. Data for the 7-norbornyl system suggest that the carbonium ion force field, used as a model of the transition state, overestimates the importance of angle strain.

The last few years have seen a considerable development in the application of empirical force field (molecular mechanics) calculations to a variety of problems concerning structure and reactivity in systems where steric factors are of much greater importance than those of polarity or conjugation.[1] In view of the relative simplicity of handling molecules containing only carbon and hydrogen atoms and of the availability of structural and thermodynamic data, the EFF method has been the most thoroughly tested and most extensively refined as regards saturated hydrocarbons. Consequently, in the treatment of species containing heteroatoms, it is common practice to make an approximation which con-

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