

249. Conformational Analysis and Chromic Acid Oxidation. Oxidation Rates and Equilibrium Constants of Epimeric Alcohols

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Summary. The linear free energy relationship of *Sicher* for relative reactivity towards chromic acid oxidation ($\Delta\Delta G_{Ox}^\ddagger$) as a function of thermodynamic stability (ΔG_{eq}^0) has been reexamined with 23 pairs of epimeric alcohols. The plot of $\Delta\Delta G_{Ox}^\ddagger$ vs. ΔG_{eq}^0 has a slope of 0.8, a correlation coefficient of 0.97 and a standard deviation of 0.23 kcal/mol on $\Delta\Delta G_{Ox}^\ddagger$. The limitations of the relationship and the exceptions are discussed.

Some time ago *Sicher* [1] suggested that the ratio of the rates of oxidation of an epimeric pair of alcohols with chromic acid could be regarded as an approximate value for the free energy difference ΔG of these alcohols through the relationship¹⁾

$$\Delta G = RT \ln \frac{k_a}{k_e} \quad (1)$$

This equation turned out to be of fundamental importance for the understanding of the steric effects operating in the alcohol oxidation. The relationship was verified later by *Wilcox* [2], *Eliel* [3] and *Richer* [4] and it provided the grounds for various hypotheses concerning the geometry of the transition state of the reaction [1] [2].

Recently we found a relationship between oxidation rates and the strain difference between alcohols and the corresponding ketones, as evaluated by means of molecular mechanics [5]. It allows to rationalize oxidation rates within a factor of *ca.* 2 in the average. However, some compounds correlate badly, and the exceptions can only in part be explained by deviations of the entropies of activation from the normal value [6]. From this viewpoint the correlation of *Sicher* is of particular interest. It correlates two experimental quantities, so that no assumptions concerning the reaction mechanism have to be made. Furthermore, it only considers the strain difference between epimeric alcohols, leading to one and the same ketone. The strain of the transition states needs *not* to be known, so that the more difficult part of the problem is eliminated. One might therefore expect that the success (or failure) of the *Sicher* correlation should provide a reasonable estimation of the minimal uncertainties one would encounter in any other rationalization of oxidation rates such as the one we used ourselves.

Unfortunately, the general validity of *Sicher's* relationship is questionable. It is based on 10 pairs of epimeric alcohols, 8 of which are cyclohexanols. The k_a/k_e -ratios of 9 of the epimeric pairs are in the range of 1.7 to 6.6, with a single value at 33.6, and the rate constants are spread out over a range of only 65. Therefore it appeared

¹⁾ a and e refer to the more (a) and less (e) strained alcohol.

Table 1. Rate Constants for Oxidation and Equilibrium Constants of Epimeric Alcohols

Alcohol	No.	$k_{\text{rel}}^{\text{a}}$	$k_{\text{a}}/k_{\text{e}}^{\text{b}}$	$\Delta\Delta G_{\text{Ox}}^{\ddagger \text{c}}$	$K_{\text{eq}}(^{\circ}\text{C})^{\text{d}}$	$\Delta G_{\text{eq}}^{\text{e}}$	Ref.	
							Ox.	K_{eq}
<i>trans</i> -2-methylcyclohexanol	1a	1.05						
			4.0	0.82	4.56 (80)	1.06	[3]	[3]
<i>cis</i> -2-methylcyclohexanol	1b	4.19						
<i>cis</i> -3-methylcyclohexanol	2a	0.86						
			3.91	0.81	3.54 (80)	0.89	[3]	[3]
<i>trans</i> -3-methylcyclohexanol	2b	3.35						
<i>trans</i> -4-methylcyclohexanol	3a	0.76						
			2.89	0.63	3.00 (80)	0.77	[3]	[3]
<i>cis</i> -4-methylcyclohexanol	3b	2.20						
<i>cis-cis</i> -3,5-dimethylcyclohexanol	4a	0.89						
			5.58	1.02	3.55 (80)	0.89	[4]	[7]
<i>trans-trans</i> -3,5-dimethylcyclohexanol	4b	4.95						
<i>cis</i> -3,3,5-trimethylcyclohexanol	5a	1.34						
			27.9	1.97	17.20 (80)	2.00	[3]	[8]
<i>trans</i> -3,3,5-trimethylcyclohexanol	5b	37.43						
<i>cis</i> -3- <i>t</i> -butylcyclohexanol	6a	0.90						
			6.09	1.07	5.25 (80)	1.16	[3]	[3]
<i>trans</i> -3- <i>t</i> -butylcyclohexanol	6b	5.47						
<i>trans</i> -4- <i>t</i> -butylcyclohexanol	7a	0.73						
			3.2	0.69	3.76 (80)	0.93	[3]	[3]
<i>cis</i> -4- <i>t</i> -butylcyclohexanol	7b	2.34						
2,2-dimethyl-4- <i>t</i> -butyl- <i>trans</i> -cyclohexanol	8a	3.15						
			1.66	0.30	1.50 (80)	0.28	[4]	[9]
2,2-dimethyl-4- <i>t</i> -butyl- <i>cis</i> -cyclohexanol	8b	5.24						
2- <i>exo</i> -norbornanol	9a	1.53						
2- <i>endo</i> -norbornanol	9b	9.89	6.46	1.11	4.00 (100)	1.06	[10]	[2]
borneol	10a	25.0						
isoborneol	10b	49.1	1.96	0.40	2.45 (100)	0.66	[11]	[2]
2,4,4- <i>cis</i> -trimethylcyclopentanol	11a	5.25						
			3.75	0.78	3.05 (150)	0.94	[5]	†)
2,4,4- <i>trans</i> -trimethylcyclopentanol	11b	1.40						
<i>endo</i> -bicyclo[3.2.1]-octanol-2	12a	2.00						
			4.57	0.90	4.43 (150)	1.25	[5]	†) §)
<i>exo</i> -bicyclo[3.2.1]-octanol-2	12b	9.14						
<i>endo</i> -bicyclo[3.2.1]-octanol-3	13a	100.4						
			24.8	1.90	29.3 (100)	2.50	[5]	[12]
<i>exo</i> -bicyclo[3.2.1]-octanol-3	13b	4.08						

Table 1 (continued)

Alcohol	No.	$k_{rel}^a)$	$k_a/k_e^b)$	$\Delta\Delta G_{Ox}^\ddagger)^c)$	$K_{eq} (^{\circ}C)^d)$	$\Delta G_{eq}^0)^e)$	Ref.	
							Ox.	K_{eq}
<i>endo</i> -bicyclo[3.2.1]- octanol-8	14a	12.60					[5]	f)
<i>exo</i> -bicyclo[3.2.1]- octanol-8	14b	0.25	50.72	2.33	8.62 (160)	1.85		
<i>endo</i> -bicyclo[3.3.1]- nonanol-2	15a	7.78					f)	[13]
<i>exo</i> -bicyclo[3.3.1]- nonanol-2	15b	8.07	1.04	0.02	2.25 (94)	0.56		[14]
<i>endo</i> -bicyclo[3.3.1]- nonanol-3	16a	32.67					f)	[14]
<i>exo</i> -bicyclo[3.3.1]- nonanol-3	16b	7.10	4.60	0.90	31.25 (94)	2.51		
α -nopinol	17a	1.79						
β -nopinol	17b	11.80	15.20	1.61	19.00 (80)	2.07	[5]	f)
α -isonopinol	18a	26.90						
β -isonopinol	18b	30.00	1.10	0.06	1.50 (80)	0.28	[5]	f)
isoverbanol	19a	15.70						
neoisoverbanol	19b	67.60	4.30	0.86	1.66 (160)	0.44	f)	f)
<i>endo</i> -5,6-trimethylene-2- <i>exo</i> -norbornanol	20a	2.40						
<i>endo</i> -5,6-trimethylene-2- <i>endo</i> -norbornanol	20b	514.0	214.2	3.18	> 99 (150)	> 3.9 (4.16) ^{f)}	[5]	f)
<i>endo</i> -2,3-trimethylene-8- <i>endo</i> -norbornanol	21a	47.1						
<i>endo</i> -2,3-trimethylene-8- <i>exo</i> -norbornanol	21b	1.86	25.21	1.91	22.25 (160)	2.67	[10]	f)
3 α -cholestanol	22a	0.7						
3 β -cholestanol	22b	2.1	3.0	0.65	5.25 (80)	1.16	[15]	[3]
2- <i>endo</i> -dinorbornanol	23a	2037						
2- <i>exo</i> -dinorbornanol	23b	8.62	236.3	3.22	> 99 (160)	> 3.9 (4.21)	[16] ^{f)}	f)
2- <i>trans</i> - <i>t</i> -butyl- cyclohexanol	24a	9.76						
2- <i>cis</i> - <i>t</i> -butyl- cyclohexanol	24b	46.0	4.7	0.92	–	(1.20) ^{f)}	[3]	h)

a) Rate constants in 80% acetic acid, 0.01 N H₂SO₄ at 25° relative to cyclohexanol. Conditions for values in the literature vary slightly.

b) a and e refer to the more (a) and less (e) strained alcohol.

c) $\Delta\Delta G_{Ox}^\ddagger = RT \ln k_a/k_e$ (kcal/mol).

d) K_{eq} determined in 2-propanol with aluminiumisopropoxide; $K_{eq} = [\text{epimer e}]/[\text{epimer a}]$.

e) $\Delta G_{eq}^0 = RT \ln K_{eq}$, assuming $\Delta S_{eq}^0 = 0$; (kcal/mol).

f) This work.

g) Literature value is $K = 17.18$ (88°) [17].

h) Equilibrium not attained [3].

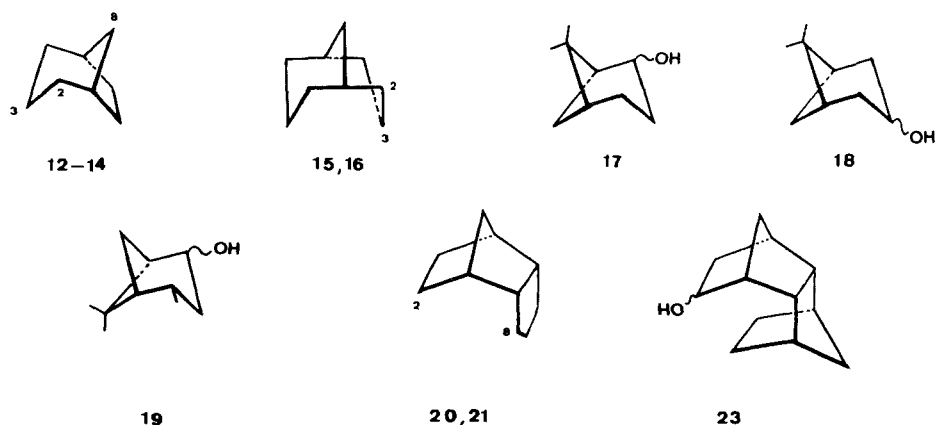
i) Values in parentheses are calculated by means of eq. (1).

desirable to test the applicability of *Sicher's* relationship with other alcohols of more structural variation, larger k_a/k_e -ratios and over a wider rate range. We have therefore investigated rate and equilibrium constants of a series of secondary alcohols of various structures. The rate constants in the whole series of 23 compounds vary now by a factor of 8000, and the k_a/k_e -ratios from 1.1 to 236. The study includes literature data for the methylcyclohexanols **3–5**, *t*-butylcyclohexanols **6–8**, 2-norbornanol (**9**) and borneol (**10**) [1–4]. The new compounds are 2,4,4-trimethylcyclopentanol (**11**), the bicyclo[3.2.1]octanols **12–14**, bicyclo[3.3.1]nonanols **15** and **16**, nopinol (**17**) and isonopinol (**18**), isoverbanol (**19**), the *endo*-5,6-trimethylenenorbornanols **20** and **21**, 3-cholestanol (**22**) and 2-dinorbornanol (**23**) (*endo*-tetracyclo[4.4.0.1^{2,5}.1^{7,10}]dodecanol-3). Table 1 contains the corresponding rate and equilibrium constants, which are also represented in Fig. 1.

As some equilibrium constants are determined at different temperatures, we are forced to make the approximation that the ΔG^0 -values are independent of temperature. This is not entirely justified since *Elie* [19] has shown that the equilibration entropies in protic solvents are of the order of -0.5 to -1.15 cal/grad · mol. Most of the constants in Table 1 were determined between 80 and 100°, with only few exceptional cases at 150 or 160°. For the latter an uncertainty of *ca.* 0.1 kcal/mol is introduced by this procedure.

For the alcohols **20** and **23** it was impossible to obtain an accurate value for the equilibrium constants, the equilibrium lying so much on the side of the more stable epimer that only a lower limit could be set on ΔG_{eq}^0 (< 3.9 kcal/mol). This estimation is corroborated by the strain in the corresponding methyl hydrocarbons, as determined by force-field calculations [5] [18]. The strain difference between the methyl analogues of **20a** and **20b** is 5.11, and it is 5.23 between **23a** and **23b**. We have

Scheme



noted in other cases that the use of the methyl model for the alcohol in the calculations leads to an overestimation of the strain difference between the epimeric alcohols [18]. The true values can be expected to be between 4 and 5 kcal/mol.

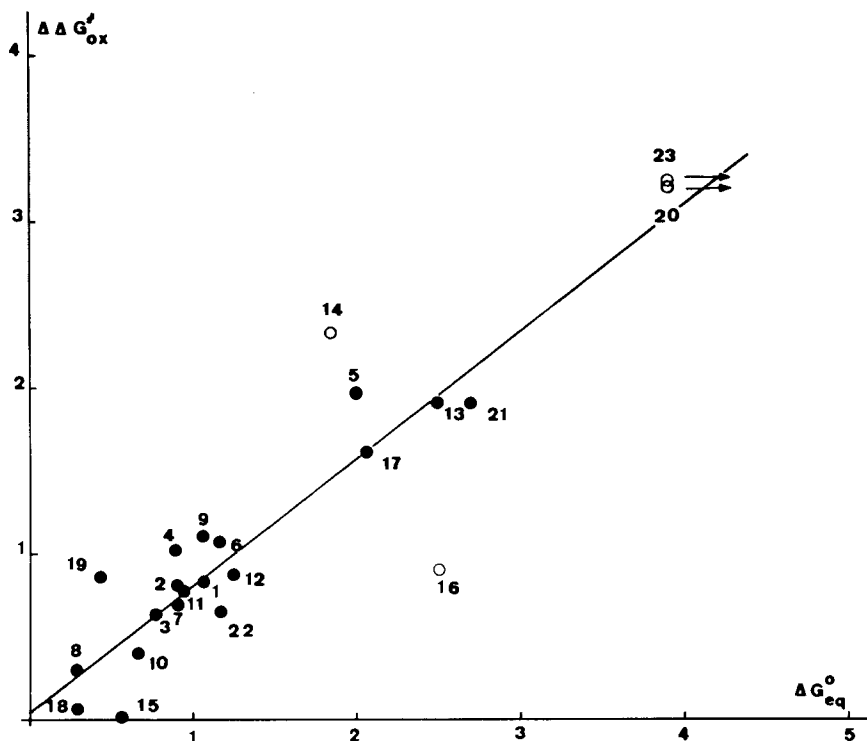


Fig. 1. Reactivity ($\Delta\Delta G_{\text{Ox}}^{\ddagger}$) and stability (ΔG_{eq}^0) of epimeric alcohols (Data from Table 1)

Inspection of Fig. 1 shows that two alcohols **14** and **16** fall out of the correlation (see below). For the remaining compounds the slope of the regression line is 0.80, the intercept 0.016, the standard deviation on $\Delta\Delta G_{\text{Ox}}^{\ddagger}$ 0.23 and the correlation coefficient 0.97. If the compounds **20** and **23** are also eliminated, because the equilibrium constants could not be determined precisely, the slope changes slightly to 0.76, while the correlation coefficient drops to 0.92. Although this latter value is poor, the correlation is statistically still significant. In all cases studied we find the more strained epimer to react at a faster rate in the oxidation than the less strained one, as predicted by the equation of *Sicher*. In a quantitative sense agreement is however much less convincing, in particular when the exceptions **14** and **16** are considered. A good part of the scatter in the points is due to experimental error. The rate constants have an error of 5% which leads to an uncertainty of *ca.* 0.06 kcal/mol in $\Delta\Delta G_{\text{Ox}}^{\ddagger}$. For ΔG_{eq}^0 the errors quoted for the literature-values [19] are in the order of 5%, which is also the error in our measurements. It may be somewhat higher in those cases where the equilibrium is strongly displaced towards one of the epimers. For the compounds measured at 150 and 160° there is an additional uncertainty of 0.1 kcal/mol mentioned above, so that the total error for the ΔG_{eq}^0 -values varies between *ca.* 0.1 and 0.25 kcal/mol. Although this is considerable it does not account for all of the scatter. We can only speculate about additional causes. One reason may be that the rate constants

taken from the literature were determined under different conditions. It is known that solvent composition and temperature have a certain influence on the k_a/k_e -ratios. Another reason could come from small changes in the transition state structure, for example variations in solvation. These could in principle be detected in the entropies of activation; however, in our measurements [6] the error in the activation entropies (± 1 cal/grad \cdot mol) is much too big as to allow any such conclusions.

According to the *Hammond* postulate [20] the more reactive alcohols should have 'earlier' transition states than the less reactive ones. This should lead to a systematic distortion of the *Sicher* plot. Compounds with high ΔG_{eq}^0 -values would show lower k_a/k_e -ratios than predicted from the equation. No such effect is seen in the plot. Within our limits of detection it appears therefore that the transition state should not change its position on the reaction coordinate.

The mechanism of the chromic acid oxidation of alcohols consists in the rate-determining break-down of an intermediate chromate ester, formed in a rapid pre-equilibrium step [23]. The deuterium isotope effect should be expected to be sensitive to variations in the structure of the transition state of the oxidation. Although the isotope effects reported for various alcohols do indeed vary considerably from 3.7 [21] to 8.9 [22], no relationship between rates and isotope effects can be established. However, the isotope effect may vanish completely when sterically hindered alcohols are oxidized [23], so that esterification becomes rate-determining [24]. *Baker & Mason* [21] suggested that the low isotope effect of 3.7 for 5,6-*endo*-naphtho-2-*endo*-norbornanol might be due to the fact that both, ester formation *and* decomposition, are partially rate-determining. As such partial change in the rate-determining step could lead to scatter in the *Sicher* plot, we have determined the isotope effect for one of the most hindered alcohols in our series, namely the *endo* epimer of *endo*-5,6-trimethylene-2-norbornanol (**20**). The value of 5.8 obtained in 40% acetic acid is in the normal range. It is expected that for the less hindered alcohols a change of the rate-determining step is even less likely.

The slope of 0.8 ± 0.15 of our correlation line is in good agreement with the values of 0.9 [2] and 1.0 [3, 4] reported in the literature. We may thus conclude that the transition states for oxidation of epimeric alcohols are to *ca.* 80% energetically equivalent. This is illustrated by the energy diagram for the oxidation of *exo*- and *endo*-bicyclo[3.2.1]octanol-3 (**13**) shown in Fig. 2. The ΔG^\ddagger -values given refer to experimental data from ref. [6]. For this alcohol pair agreement between the experimental and the calculated energy difference between the two transition states is excellent; it is considerably less so for the alcohols deviating strongly from the straight line in Fig. 1.

The *Sicher* correlation breaks down for the alcohols **14** and **16**. In the case of **14** we had observed earlier that the *endo* isomer **14a** deviates by almost two standard deviations from the regression line in the plot of $\log k$ vs. Δ strain (ketone-alcohol) [5]. Since the equilibrium constant, determined at 160°, was in reasonable agreement with the value obtained by force-field calculations [18], it appeared that the rate of the *endo* isomer **14a** was responsible for the deviation in the *Sicher* plot. Therefore synthesis of **14a** was repeated and the rate constant redetermined; however, the value obtained was identical with the previous one. At the present time we can offer

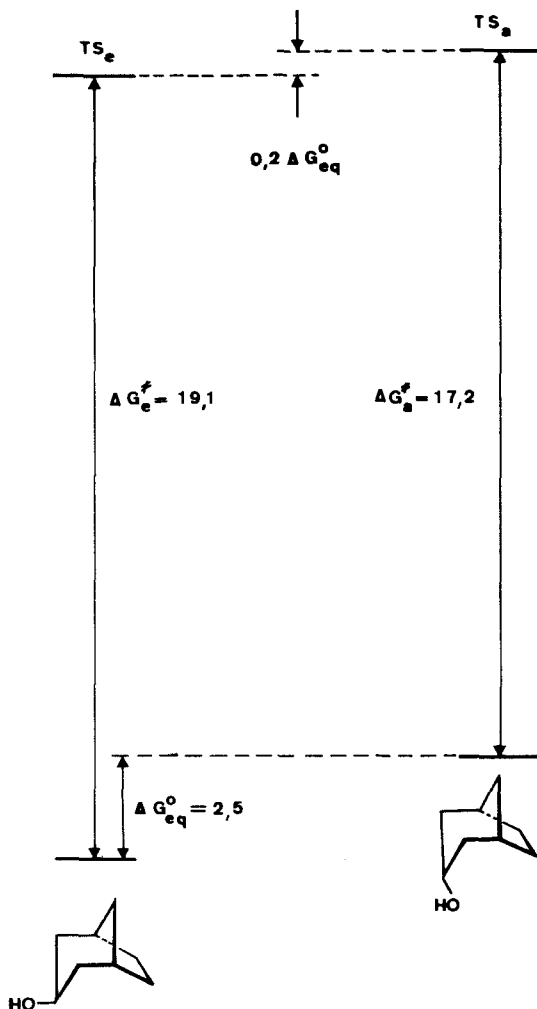


Fig. 2. Energy diagram for the oxidation of exo and endo-bicyclo[3.2.1]-octanol-3 (**13a** and **13b**). The free energies of activation are experimental values quoted from ref. [6]

no explanation for the behaviour of the pair **14**, which will need further investigation. For the pair **16**, the 3-bicyclo[3.3.1]nonanols, deviation from the plot is even worse. In this case an explanation may be found if the conformations of the alcohols are considered. In the *endo* alcohol **16a** the cyclohexane ring carrying the hydroxyl group is in a boat conformation, with the 3-substituent occupying an equatorial position [14]. The *exo* isomer **16b** has both cyclohexane rings in the chair conformation with the 3-substituent equatorial [14]. Force-field calculations for the corresponding ketone show a local minimum for the chair-boat conformation ($\Delta H_0 = -56.20$ kcal/mol) and a chair-chair conformation with considerably lower energy

($\Delta H_0 = -60.75$ kcal/mol [18]). It is conceivable that oxidation of **16a** leads first to a ketone in the high-energy conformation. In this case the transition state would be different from that of **16b**, and the *Sicher* correlation need not hold.

In summary, the following conclusions may be drawn from this investigation. The *Sicher* correlation is generally applicable to epimeric alcohols of different structures within the limitations indicated (standard deviation 0.23 kcal/mol on $\Delta\Delta G_{Ox}^\ddagger$) although there are exceptions. Therefore, it appears that all alcohols studied have very similar transition states. The scatter found in the correlation will most likely also appear in other structure-reactivity correlations for alcohol oxidation. The slope of the regression line of the *Sicher* plot of 0.8 suggest that the transition states for oxidation of epimeric alcohols are energetically almost equivalent; however, the correlation allows no conclusions concerning the structure of the transition state.

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Experimental Part

Alcohols. The alcohols were synthesized according to procedures given in the literature (Table 2). The identity was confirmed by NMR. and mass spectra. When necessary, final purification was achieved by preparative VPC. (column FFAP).

Table 2. *Synthesis of alcohols*

Alcohol	No	Method/reference
2,4,4-trimethylcyclopentanol	11	ketone [25], LAH reduction
bicyclo[3.2.1]octanol-2	12	ketone (<i>Fluka</i>), LAH reduction
bicyclo[3.2.1]octanol-3	13	[26]
bicyclo[3.2.1]octanol-8	14	[27]
bicyclo[3.3.1]nonanol-2	15	[28]
bicyclo[3.3.1]nonanol-3	16	[28]
nopinol	17	[29]
isonopinol	18	[29]
isoverbanol	19	[30]
<i>endo</i> -5,6-trimethylene-2-norbornanol	20	[31]
<i>endo</i> -2,3-trimethylene-8-norbornanol	21	[32] singlet oxygen reaction with dicyclopentadiene followed by catalytic hydrogenation
2-dinorbornanol	23	[16]

Kinetic measurements. The runs were measured in 80% (by volume) acetic acid, 0.01N in sulfuric acid at 25.0°. The details of the procedure are given in [7]. Only the pure alcohol epimers were used without any detectable contamination by the isomeric compounds, except for compound **15b**, where the reactivity was obtained from a mixture of **15a** and **15b**.

Equilibrations. The equilibrations were carried out at the temperatures indicated in Table 1 for one to two weeks according to the procedure described by Wilcox [10]. For the alcohols **14** the time was four weeks until equilibration was achieved. The mixtures were analyzed by VPC. (column FFAP) and the composition determined by electronic integration. For compounds **20** and **23** separation was not possible. A lower limit could be determined for the equilibrium constant by NMR.

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