211. Isokinetic Relationships in Alcohol Oxidation with Chromic Acid

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Summary. The activation parameters for the oxidation of 13 secondary alcohols with chromic acid have been determined. Application of a statistical treatment of *Exner* [9] shows that the reactions are isoentropic with an average entropy of activation ($\Delta S^{\neq}$) of -24.0 e.u.

The oxidation rates of secondary alcohols with chromic acid are usually rationalized in terms of release [1] or increase [2] of steric strain in going from the alcohol with an sp^3 hybridized carbon atom to the sp^2 hybridized ketone. The necessary conditions required for this argumentation are that (a) the transition state of the oxidation resembles the ketone, and (b) the activation entropies are constant so that the free energy of activation is essentially determined by the enthalpy of activation. Both conditions have been questioned recently by *Kwart* [3] who found not only a substantial difference of 7.2 *e.u.* between the activation entropies of cyclohexanol and di-*t*-butylmethanol, but also entirely different temperature dependency of the isotope effects of the two compounds.

On these grounds *Kwart* proposed two extreme transition states for the chromate ester composition, a planar cyclic symmetrical structure corresponding to a pericyclic process for normal esters and a non-planar unsymmetrical structure for highly hindered esters. His conclusions 'bring into doubt all quantitative rate comparisons and calculations based on the assumption of a commonly structured, product-like transition state for Cr(VI) oxidations of alcohols' [3].

Kwart's arguments find additional experimental support in a determination of the activation parameters of substituted cyclohexanols published by *Richer* [4]. The difference in entropies of activation between *cis* and *trans*-3,3,5-trimethylcyclohexanol was found to be 17.3 *e.u.*; between *cis* and *trans*-4-*t*-butylcyclohexanol the difference was 7.0 e.u. At 25° this gives *ca.* 5 and 2 kcal/mol respectively, while the corresponding free energies of activation differences are only 2.3 and 0.8 kcal/mol respectively. Entropy effects on groundstate energy differences of the epimeric cyclohexanols are between 0.02 and -1.16 e.u., depending upon the solvent [5]. Based on these data it seems that the importance of the entropy of activation plays an important role in oxidations and cannot be neglected. We have therefore investigated the temperature dependence of the reaction rate of a series of 13 structurally different secondary alcohols in aqueous acetic acid over a temperature range from 20° to 40°. The rate constants are given in the experimental section. Each constant represents the average of three runs with a maximum error of 5%. The activation parameters were obtained on a computer by using the formulas given by *Moore* [6]. The data are represented in Table I.

The values obtained for $\Delta S^{\neq}$ vary between -19.5 and -29.7, with the average of -24.0 e.u. If the compounds **3**, **6** and **12** which deviate by more than the standard

Table I. *Activation parameters for the oxidation of secondary alcohols with Cr (VI).* Conditions: 80% acetic acid (by volume) 0.01 N H_2SO_4

Compound	Cpd. No	$\Delta H^{\ddagger}_{25}$ [kcal]	s	$\Delta S^{\ddagger}_{25}$ [e.u.]	s	$\Delta G^{\ddagger}_{25}$ [kcal]	s	r
trans-3,3,5-trimethylcyclohexanol	**1**	10.5	0.3	–24.4	1.0	17.8	0.6	0.997
cis-3,3,5-trimethylcyclohexanol	**2**	12.1	0.4	–25.5	1.3	19.7	0.8	0.996
endo-bicyclo[3.2.1]octanol-3	**3**	10.9	0.4	–20.9	1.3	17.2	0.8	0.996
exo-bicyclo[3.2.1]octanol-3	**4**	11.8	0.2	–24.4	0.6	19.1	0.4	0.999
7-norbornanol	**5**	13.6	0.8	–24.8	2.5	21.0	1.5	0.989
2,2,4,4-tetramethylcyclobutanol	**6**	8.9	0.4	–29.7	1.2	17.8	0.7	0.994
cyclohexanol	**7**	13.1	0.2	–22.8	0.5	19.9	0.3	0.999
2-adamantanol	**8**	11.8	0.3	–23.3	0.9	18.8	0.5	0.998
2-butanol	**9**	12.2	0.1	–25.9	0.3	19.9	0.2	0.999
2-propanol	**10**	13.3	0.1	–23.2	0.3	20.2	0.2	0.999
methyl-*t*-butylmethanol	**11**	12.4	0.1	–23.8	0.5	19.5	0.3	0.999
di-*t*-butylmethanol	**12**	13.3	0.2	–19.5	0.7	19.1	0.4	0.999
1-adamantylmethylmethanol	**13**	11.6	0.3	–24.5	0.9	18.9	0.5	0.998

s: standard deviation; r: correlation coefficient for the straight lines used for the determination of rate constants.

deviation (2.4 e.u.) from the average are excluded, $\overline{\Delta S^{\ddagger}}$ becomes -24.3 ± 1.0 e.u. (Fig. 1). The latter standard deviation is close to the average standard deviation for $\Delta S^{\ddagger}$ of the individual alcohols (0.9 e.u.). At a first glance it appears that all alcohols (except **3**, **6** and **12**) have essentially the same entropy of activation. This result is clearly in contradiction to the data of *Richer* who found important variations of $\Delta S^{\ddagger}$ in his series. However, our procedure is not beyond doubt because we have removed three compounds from our series without justification. Furthermore, our hypothesis is statistically not proven.

The situation of all compounds reacting with the same $\Delta S^{\ddagger}$ (isoentropic) represents a special case of the more general isokinetic relationship of *Leffler* [7]

$$\Delta H^{\ddagger} = \beta \Delta S^{\ddagger} + h_0 \tag{1}$$

where β stands for the isokinetic temperature at which all reactions in the series proceed at the same rate. The isokinetic temperature is traditionally determined from a plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$. *Richer* concluded on the grounds of proportionality between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ that all his alcohols pass through similar transition states during oxidation [4].

Proportionally between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as determined by this method is however no criterion to prove than an isokinetic relationship holds. *Petersen* [7] and *Exner* [8] [9] have criticized the procedure because $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are determined from one and the same equation. Accordingly, their interdependence could well be accidental. *Exner* proposed a statistical treatment which allows to test unambiguously whether an isokinetic relationship in a series of reactions exists. In this procedure the sum of the standard deviations of all the points from the best straight line in an *Arrhenius* plot of ln *k* *vs.* 1/T of all the reactions in question is calculated. The isokinetic temperature is then determined by a least squares treatment in such a way that the standard deviation of the experimental points from the new straight lines, passing

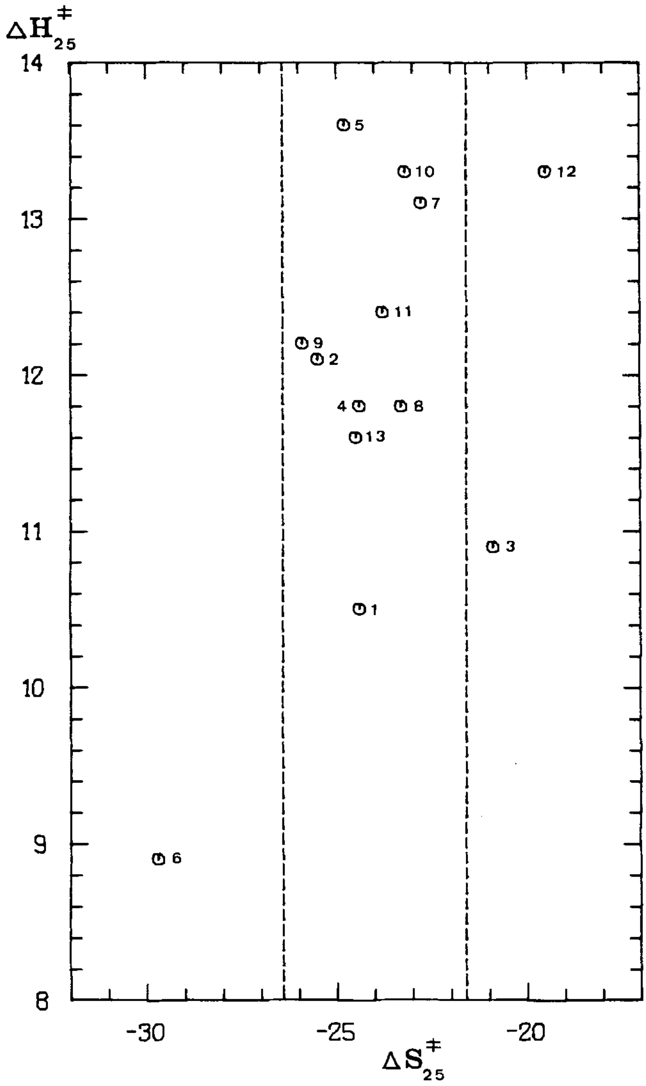

Fig. 1. *Activation entropies $\Delta S^{\ddagger}$ for oxidation of secondary alcohols with chromium (VI)*

all through one point, reaches a minimum. The hypothesis of an isokinetic relationship is accepted unconditionally if the standard deviation of the plot with the restriction of a common point for all lines is equal or lower than that in the plot without restriction.

These criteria were applied to our rate constants. A plot of ln k at 20° *vs.* ln k at 40° (Fig. 2) which is used as a preliminary test [9] reveals that *a priori* there is no reason to exclude any compounds of the series. A program for the statistical treatment of *Exner* was written and tested with the data of a sample run in [9].

The results of the calculations with our rate data and with those of *Richer* are included in Table II. Standard deviations were calculated for the isokinetic (s_0), isoentropic (s_u, $\beta = \infty$) and isoenthalpic (s_∞, $\beta = 0$) hypothesis. Table II reveals that for the total of our compounds the isoentropic condition may be accepted unconditionally because $s_{00} = s_u$. The average value for $\Delta S^{\ddagger}$ is -24.0 e.u. If we exclude compounds **6** and **12**, s_u is somewhat lower than s_{00}, which leads to the same conclusion. From the observation that $\delta = s_{00}$ we may conclude that the law of *Arrhenius* is valid [9]. The variation of s as a function of the isokinetic temperature is shown in Fig. 3, which also contains the experimental straight lines for the *Arrhenius* plot.

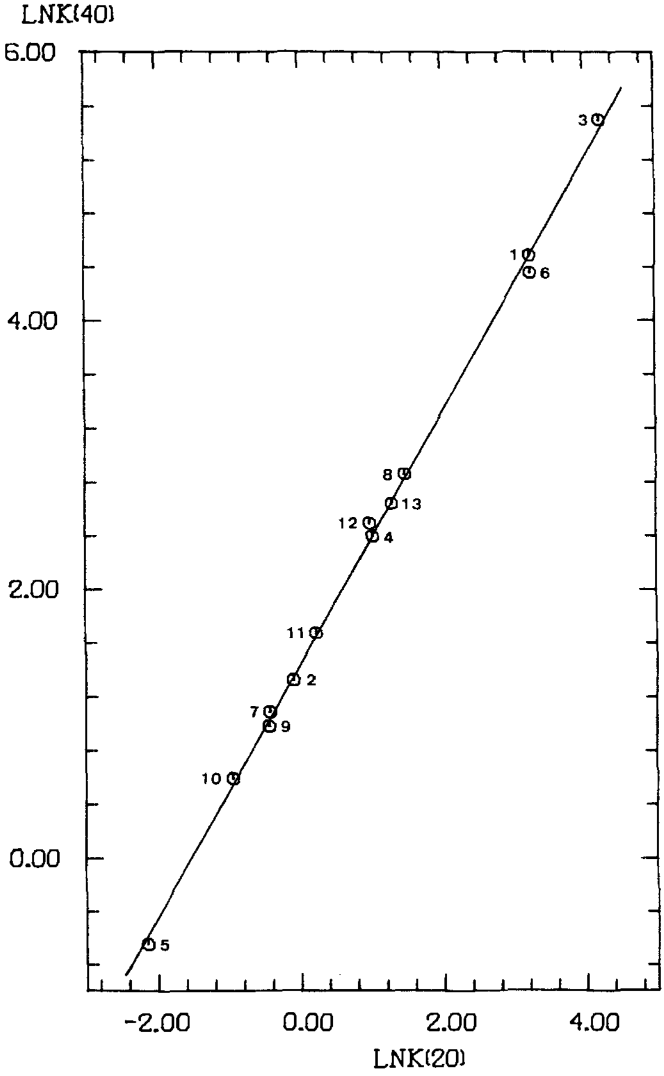

Fig. 2. *Plot of rate constants at 2 different temperatures*

Table II. *Test for isokinetic relationships in alcohol oxidation*

Ref. and tested Compounds	δ	s_{00} without restriction	s_0 iso-kinetic	s_u iso-entropic	s_∞ iso-enthalpic
This work **1–13**	0.050	0.050	0.051	0.050	0.070
This work **6** and **12** excluded	0.050	0.052	0.046	0.046	0.062
Richer [4]	0.006	0.038	0.047	0.085	0.116

δ: experimental error on ln k; s: standard deviation.

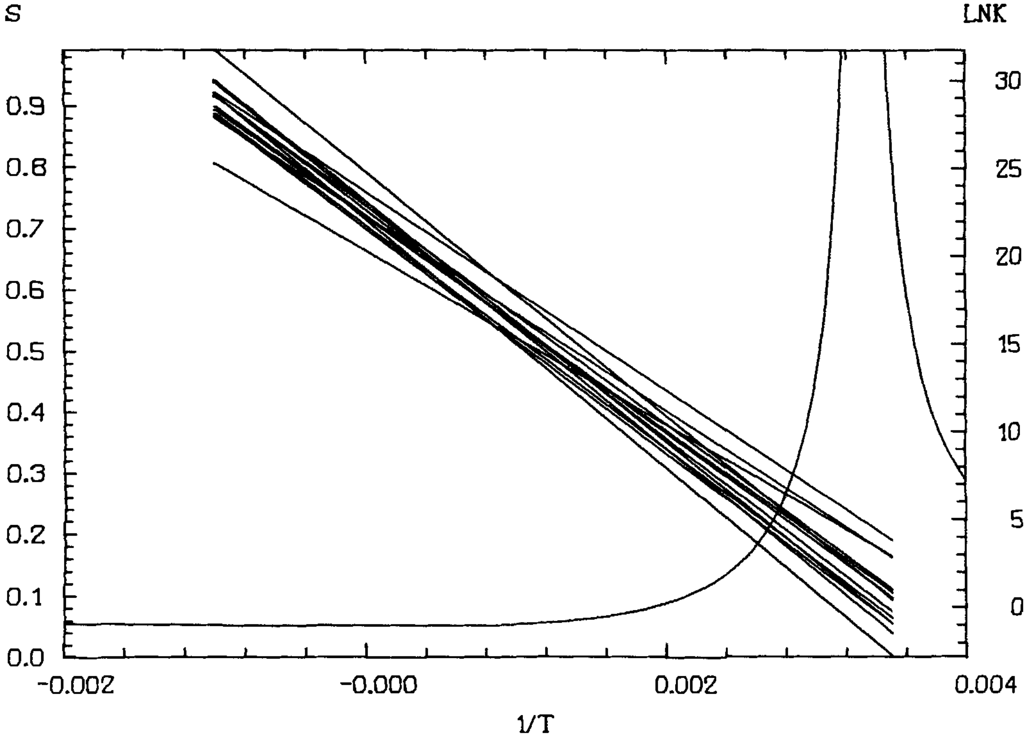

Fig. 3. *Variation of standard deviation s as a function of the isokinetic temperature.* The straight lines represent *Arrhenius* plots without restriction

Application of the same treatment for *Richer*'s data shows first that $\delta_0 \ll s_{00}$, which means that the experimental errors is substantially underestimated if the law of *Arrhenius* must hold. The isokinetic hypothesis may not be accepted unconditionally because $s_{00} < s_0$ and s_u. The number of points given is however insufficient as to allow rejection of the isokinetic hypothesis.

On the grounds of this analysis we may conclude that rate variations in chromium(VI) oxidation are due to changes in $\Delta H^{\neq}$. This situation is reflected in a plot of $\Delta H^{\neq}$ *vs.* log k (Fig. 4). The standard deviation for the plot is 0.4, which compares favorably with the average standard deviation of $\Delta H^{\neq}$ (0.3). The quantitative rate comparisons that have been questioned by *Kwart* [4] are therefore confirmed. Sterically hindered alcohols like **6** and **12** give activation entropies deviating substantially in opposite directions from the average. However, these deviations are not high enough to invalidate the isoentropic relationship, and once the isoentropic relationship is established we cannot invoke two different mechanisms. The deviations may however be explained in another way. Steric hindrance around the reacting center could give raise to a more negative $\Delta S^{\neq}$ as in the case of tetramethylcyclo-

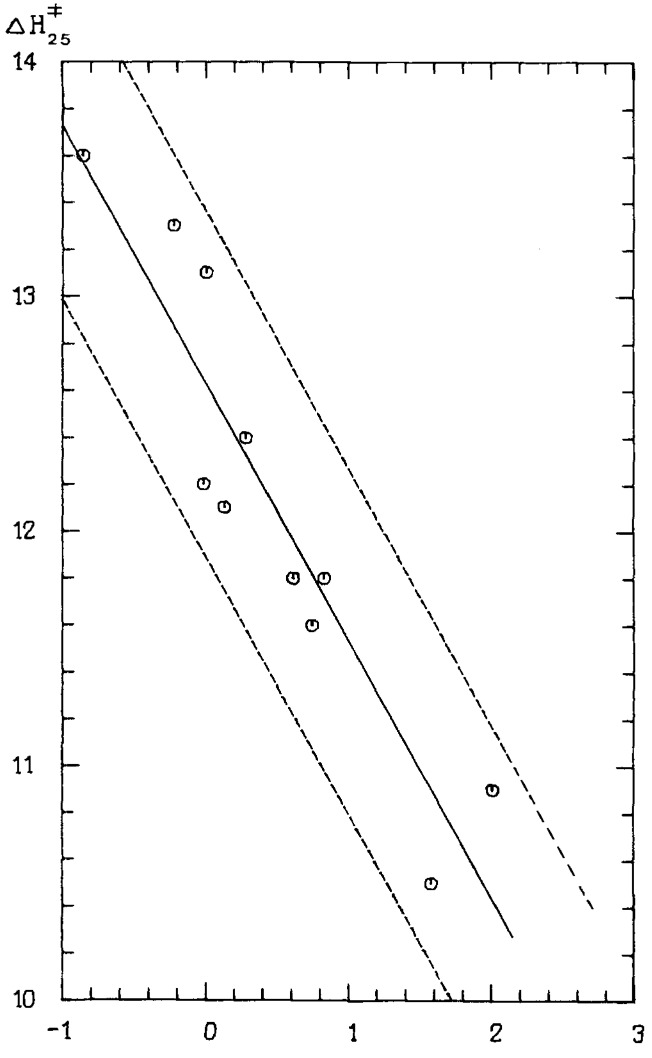

Fig. 4. *Plot of $\Delta H^{\neq}$ vs. log* k. Compounds **6** and **12** are not included in the correlation.

butanol (**6**). This effect could be counterbalanced in di-*t*-butylmethanol (**12**) by an increase in rotational freedom of the methyl groups in going from the alcohol to the less crowded ketone. In **6** the bond angle does not change during oxidation because of the cyclic structure and hence there is no change in the freedom of rotation. A change in mechanism involving participation of an additional molecule of water as proposed by *Kwart* [3] for di-*t*-butylmethanol should lead to a more negative $\Delta S^{\neq}$. The observed change goes however in the opposite direction.

Whatever the reasons for these deviations are, it appears clearly that interpretations of oxidation rates in terms of strain cannot be applied to compounds where steric crowding around the reacting center is important. On the other hand the analysis of the activation parameters shows that the majority of alcohols, and in particular those that have served as models for studying oxidation mechanisms, have the same entropy of activation and, therefore, react by the same mechanism.

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Experimental Part

Alcohols: *cis*- and *trans*-3,3,5-Trimethylcyclohexanol (**2**) and (**1**) were prepared by the reduction of the corresponding ketone (*Fluka*) with lithium aluminium hydride and separated by preparative VPC. at 130°. 3-*endo* and *exo*-Bicyclo[3.2.1]-octanol (**3**) and (**4**) were obtained according to *Jefford* [10] and *Kraus* [11] from norbornene. 7-Norbornanol (**5**) was synthetized from norbornadiene according to *Story* [12]. Reduction of 2,2,4,4-tetramethylcyclobutanone¹) and adamantanone [13] with lithium aluminium hydride gave the alcohols **6** and **8**. Di-*t*-butylmethanol (**12**) was obtained by reduction of the ketone with sodium hydride [14]. 2-(1-Adamantyl)-ethanol (**13**) was obtained as a gift from Prof. *G. H. Wahl*. The other alcohols were purchased from *Fluka* and used after purification.

The purity of the compounds was checked by VPC., and their structures confirmed by comparison of the spectra with those found in the literature.

Preparative VPC. The separations were effected on a *Perkin-Elmer* instrument, model 990 with a 3 m column of 10 mm diameter. The liquid phase was 20% FFAP on chromosorb W.

Kinetic measurements. The alcohol under investigation was weighed into a UV. cell of 1 cm path length and dissolved in 3.00 ml of 80% (by volume) acetic acid, 0.01 N in sulfuric acid. The cell was thermostated in the cell-holder of a *Techtron* 635 UV. spectrometer for 15 to 30 min. The temperature which was kept constant with a *Lauda* thermostat was measured in a reference cell by means of a thermocouple. The arrangement allowed to reproduce temperatures with en error of 0.1°. To this solution was added 0.10 ml of ammonium dichromate solution (0.03 N) using the solvent system mentioned above. The change in chromium (VI) concentration was then followed at 350 nm and recorded on *Metrohm* 478 recorder. In all runs the alcohol was used in concentrations 10–15 times higher than the initial chromium (VI) concentration.

The pseudo first-order rate constant (k_{obs} in min^{-1}) was calculated by fitting the expression

$$A = (A_0 - A_\infty)\, e^{-k_{obs} t} + A_\infty$$

to about 20 points of the recorded plots. For the calculation the subroutine LSQ of the LSK/N1 program of *Detar* [15] was used. The second-order rate constant k_2 (in M^{-1}, min^{-1}) was calculated by the expression:

$$k_2 = \frac{k_{obs}}{[ROH]}$$

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[1] We thank Prof. *C. W. Jefford* for a sample of this compound.

The activation energies and pre-exponential factors were calculated with a least squares treatment from the equation:

$$\ln k = -E_a/RT + \ln A$$

and the activation parameters from the equation given by *Moore* [6]. All calculations were performed on the CDC 3800 computer of the University of Geneva.

No correction for the reaction of the solvent with Cr (VI) was applied. The rate constants are given in Table III.

Table III. *Rate constants k_2*[a]) *for oxidation of secondary alcohols at various temperatures*

Alcohol	k_2 (20°)	k_2 (25°)	k_2 (30°)	k_2 (40°)
1	25.65	37.65	46.57	88.45
2	0.91	1.35	1.72	3.74
3	69.18	101.00	127.10	243.50 b)
4	2.78	4.10	5.47	10.96
5	0.118	0.14	0.244	0.52
6	25.90	36.30	47.55	77.58 b)
7	0.657	1.006	1.49	2.96
8	4.37	6.77	9.25	17.43
9	0.649	0.964	1.337	2.66
10	0.39	0.60	0.87	1.80
11	1.26	1.91	2.72	5.30
12	2.68	3.78	5.55	12.11
13	3.65	5.52	7.80	14.01

a) k_2 in [M^{-1}, *min*$^{-1}$]. Conditions: 80% acetic acid (by volume) 0.01 N H_2SO_4. Each constant is the average of 3 runs. Error of the average ± 5%.

b) Extrapolated from determinations at 15°. **3**: 47.69, **6**: 21.36.

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