[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

Structural and Conformational Effects on the Rates of Oxidation of Secondary Alcohols by Chromic Acid[1a]

BY HAROLD KWART AND PETER S. FRANCIS[1b]

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Data on the rates of chromic acid oxidation of a variety of cyclic and acyclic cases are reported and discussed with reference to two rate-determining factors; stereoelectronic accommodation and the influence of strain relief in the transition state. The stereoelectronic effect may often account for a factor of approximately 20 in the rate. Indications are that differences in the ease of chromate ester decomposition, where steric considerations are important, can be accounted for preponderantly on the basis of steric hindrance of the ester group rather than obstruction of the approach of base to proton removal. Some estimation of the influence of a neighboring alkyl group on the oxidation rate is also discussed. A modification of the Westheimer[5] mechanism of chromic acid oxidation involving a cyclic transition state is suggested to account for these observations as well as others in the literature.

Kuivila and Becker[2] and Winstein and Holness[3] have discussed a few cases of the effects of conformation of secondary alcohols on the rates of their reaction with chromic acid. Previously[4] we have described electronic effects on the rate of oxidation of secondary alcohols under several different conditions. The purpose of this communication is to report some of the results of studies of the importance of steric and electronic factors in comparing the rates of oxidation by chromic acid of a wide range of bicyclic, alicyclic and variously substituted secondary alcohols. It is fortunate that this study and the studies of Kuivila and Becker and Winstein and Holness have all included the compound cyclohexanol. While the experimental conditions of all three studies varied in certain respects, they are believed to be similar enough to allow a fairly quantitative comparison of twelve cyclic and four acyclic cases.

Results and Discussion

The rates of chromic acid oxidation of various alochols, included in our studies and not previously reported, are shown in Table I. These are tabulated only as the second-order rate constants defined by the equation

$$-\mathrm{d[Cr^{+6}]/dt} = k_{obsd}(\mathrm{Cr^{+6}})(\mathrm{R_2CHOH}) \qquad (1)$$

which can be easily converted, for the data in 30% acetic acid, to third and fourth-order rate constants in the manner of Westheimer and co-workers[5c] by the equation

$$k_{obsd} = k_3(\mathrm{H^+}) + k_4(\mathrm{H^+})^2 \qquad (2)$$

solved simultaneously at two acid concentrations.

Application of eq. 2 to our data in 30% acetic acid solvent reveals that 60 to 75% of the total reaction rates are dependent on a first-order hydrogen ion reaction at acid concentrations of 0.25 molar. This is to be expected since the previously

TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE OXIDATION OF VARIOUS SECONDARY ALCOHOLS FOR CHROMIC ACID

	k_2, (mole/liter)$^{-1}$ min.$^{-1}$			
	30% HOAc, μ = 0.40			50% HOAc μ = 0.40,
	T = 30.2°		T = 30.1°	T = 30.2°
Alcohol	H^+ = 0.252 M	H^+ = 0.1247 M	H^+ = 0.250 M	H^+ = 0.1247 M
Isoborneol	16.6	7.09	...	...
Borneol	8.46	3.36	...	...
α-Norborneol (*endo*)	3.23	1.41	...	4.04
β-Norborneol (*exo*)	1.30	0.545	...	1.49
cis-2-Methylcyclohexanol	1.03	.427	...	1.26
trans-2-Methylcyclohexanol	0.641	.257	...	0.748
Cyclohexanol	.338	.138	...	.401
2-Propanol	.164	.069	...	.212
1-Indanol	....	...	8.77	...
α-Tetralol	....	...	5.74	...
α-(O-Tolyl)-ethanol	....	...	0.456	...

(1) (a) Presented at the 134th Meeting of the American Chemical Society, Chicago, Ill., Sept. 8, 1958. (b) Part of the data contained herein is taken from the thesis of P. S. Francis, submitted in partial fulfillment of the M.S. degree at the University of Delaware, June, 1953.

(2) H. G. Kuivila and W. J. Becker, THIS JOURNAL, **74**, 5329 (1952).

(3) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(4) H. Kwart and P. S. Francis, *ibid.*, **77**, 4907 (1955).

TABLE II

RELATIVE RATES TO CYCLOHEXANOL OF REACTION OF SECONDARY ALCOHOLS WITH CROMIC ACID IN ACIDIC MEDIA

Alcohol	In 30% HOAc, H^+ = 0.250–0.252 M, μ = 0.40 T = 30.1–30.2[a]	In 50% HOAc, H^+ = 0.1247 M, μ = 0.40, T = 30.2°[a]	In 75% HOAc, 25°, 50°[b]	In H_2O 40°, μ = 0.40 H^+ = 0.25 M[c]
Isoborneol	49.1	...	.....	..
1-Indanol	26.0	...	.....	..
Borneol	25.0	...	.....	..
α-Tetralol	17.0	...	.....	..
α-Norborneol (*endo*)	9.67	10.1	.....	..
β-Norborneol (*exo*)	3.85	3.72	.....	..
cis-2-Methylcyclohexanol	3.05	3.15	.....	..
cis-4-*t*-Butylcyclohexanol	...	...	2.40, 1.81	..
trans-2-Methylcyclohexanol	1.90	1.87	.....	..
Cyclopentanol	...	...	.....	1.39
Cyclohexanol	1.0	1.0	1.0	1.0
trans-4-*t*-Butylcyclohexanol	...	...	0.81, 0.71	..
α-(*p*-Tolyl)-ethanol	3.12	...	.....	..
α-Phenylethanol	2.35	...	.....	..
α-(*o*-Tolyl)-ethanol	1.35	...	.....	..
2-Propanol	0.49	0.53	.....	0.55

[a] This work. [b] Ref. 3. [c] Ref. 2.

(5) (a) F. Westheimer, *et al.*, *J. Chem. Phys.*, **11**, 506 (1943); (b) **17**, 61 (1949); (c) THIS JOURNAL, **73**, 65 (1951); (d) **74**, 4383 (1952); (e) **74**, 4387 (1952).

reported studies[2,5] show a maximum of 20% first-order hydrogen ion dependence in water at 0.25 molar acid concentration, and 100% first-order dependence in 86.5% acetic acid solvent.[5e]

The relative rates of reaction of these alcohols are summarized along with the relative rates reported in three other studies[2-5] in Table II. It is apparent that the relative rates do not vary significantly between 30% and 50% acetic acid. Whether the comparison can be extrapolated to media of straight aqueous and 75% acetic acid solvents may be open to question, but judging from data presently available this seems quite likely; as, for example, the similar calculated relative rates of reaction of cyclohexanol and 2-propanol in pure aqueous and 30% acetic acid solvents shown in Table II. Moreover, the rate ratio of *cis*- and *trans*-4-*t*-butylcyclohexanol is changed by less than 8 % by a 25° change in temperature in 75% acetic acid. Apparently, comparison of relative rates under extremely varied conditions can be fairly quantitative. In any case, the sixteen alcohols considered in Table II can be compared with some confidence where ultimate limitations are recognized.

There are clearly[5] two distinct steps to be considered in the over-all reaction mechanism

Esterification equilibrium step

$$RR'CHOH + HCrO_4^- + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RR'CHOCrO_3H + H_2O$$

$$K_e = k_1/k_{-1}$$

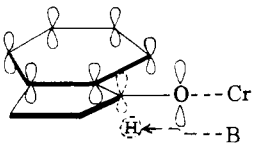
Rate-determining ester decomposition step

$$RR'CHOCrO_3H + B \xrightarrow{k_2} BH^+ + RR'C{=}O + HCrO_3^-$$

It has been suggested[2,6] that the position of the equilibrium in carboxylic esterification is largely independent of the structure of the alcohol. The analogy between carboxylic and chromic esterification is weakened, however, by the fact that, unlike the carboxylic esterification, the rate of attainment of chromate ester equilibrium, as implied in the Westheimer[5] mechanism, is not noticeably affected by the structure of the alcohol. Since this earlier work a significant variation in the position of chromate ester equilibrium as a function of polar substitution has been demonstrated.[4] Furthermore, Kläning[7] has shown significant variation in the position of chromate ester equilibrium of secondary alcohols at low acidities. Consequently, the assumption will be made here, in accord with the suggestion of Winstein and Holness, that K_e may vary with conformation and structure and the net effect on the chromic acid oxidation rate is a balancing of K_e and K_2 terms.

Evaluation of the Steroelectronic Effect as a Rate-determining Factor—Two rate-determining factors (among many) arising from structural features in the alcohol may be considered in connection with the rate of oxidation; the stereoelectronic factor and the strain relief factor. Stereoelectronic accommodation has been defined and discussed by Corey and Sneen[8] for base-catalyzed enolization, wherein the rate of reaction and, consequently, the ease of proton abstraction is significantly affected by the degree of axial interaction; *i.e.*, the extent to which delocalization of the σ-electrons in a carbon–hydrogen bond may be involved.

The operation of this factor in the course of chromic acid oxidation is best illustrated by examination of the rates of oxidation of various alcohols which have benzenoid substitution on the carbinol carbon. In the transition state for chromate ester decomposition, in which base is transferring the proton, the *p*-orbital on the carbinol carbon which is developing (dotted) as it attains a planar bond distribution is stabilized by overlapping of the aromatic ring, as shown below for the case of 1-indanol. To the extent that the aromatic ring



orbitals can attain coplanarity with the developing *p*-orbital this type of stereoelectronic accommodation will produce rate enhancement. In the case of 1-indanol the effect seems to be maximal. It is considerably reduced in the α-phenylethanols where the chromate ester complex and the methyl substituent on the carbinol carbon tend to resist attainment of coplanarity with the aromatic ring. *Ortho* substitution as in α-(*o*-tolyl)-ethanol (compared to the *p*-tolyl isomer) apparently has an added influence in preventing coplanarity and reducing stereoelectronic assistance to the rate. On the assumption that only little difference in the K_e-value has occurred with the structural change in going from 1-indanol to α-(*o*-tolyl)-ethanol, it is seen that the stereoelectronic effect in chromic acid oxidation may be able to account for almost a factor of twenty in the rate. In the case of α-tetralol the rate reduction from 1-indanol is scarcely greater than the factor distinguishing cyclohexanol and cyclopentanol. This may be interpreted as indicative of a reduction in stereoelectronic assistance arising from the greater puckering of the alicyclic ring in α-tetralol although other considerations (to be discussed later in this report) may also enter.

Evaluation of Strain Relief as a Rate-determining Factor—The possible influence of strain relief in determining the rate of chromate ester decomposition has been discussed in a few monocyclic cases by Kuivila and Becker[2] and was further emphasized in the elegant analysis of the subject by Winstein and Holness.[3] The data of Schreiber and Eschenmoser[9] on the comparative rates of chromic oxidation of the α-and β-epimers of variously substituted oxycholestane derivatives in 90.5 acetic acid medium has led these authors to presume the existence of a rate-accelerating effect arising from relief of steric strains in the chromate ester. The results we are reporting here on bicyclic cases and addi-

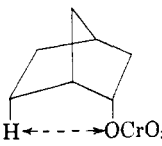
(6) N. Menschutkin, *Ann.*, **195**, 334 (1879); **197**, 193 (1879).
(7) U. Kläning, *Acta Chem. Scand.*, **2**, 1313 (1957).
(8) E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6269 (1956).
(9) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

tional alicyclic illustrations were gathered to afford a basis for studying the proposals of these workers concerning the operation of steric strain factors in the transition state of chromic oxidation.

In cyclohexyl cases, lacking data on the relative magnitudes of K_e for axial and equatorial hydroxyl groups, it is not possible to distinguish[3] whether it is the ease of steric approach of base to proton abstraction or the strain-induced instability of the chromate ester that determines the relative rates of chromate oxidation. In this connection it is interesting to examine the influence of the strain relief factor on the relative rates of oxidation of cases in the bicyclo(2.2.1)heptane system. The results in Tables I and II show that isoborneol, where the chromate ester group stands in the *exo* configuration and which is more strained due to the bridge *gem*-dimethyls, is about twice as readily oxidized as the epimeric borneol. Since the K_e term for the isoborneol is presumably smaller than for the bornecl, this result reflects a difference in the ease of ester decomposition of even more than a factor of two. This conclusion is strengthened by the results in the stripped down norbornane cases where the rate order of the *endo* and *exo* epimers is inverted, the *endo*-(α)-alcohol oxidizing almost 2.5 times as rapidly as the *exo*-(β)-alcohol. Here the *endo*-chromate ester is formed with greater difficulty and is also more unstable than the *exo* due to the strain induced by non-bonded interaction with the axial transannular hydrogen.[10] Again, the strain relieved by ester decomposition outweighs the ease of chromate ester formation in determining the relative rate of reaction of the epimers.

An additional point of significance emerges from this analysis. The rate difference between the isoborneol and the "*endo*" norborneol, a factor of five, reflects an even greater difference in k_2 since K_e of α-norborneol is clearly greater than K_e of isoborneol. This establishes that the determining factor in chromate ester decomposition is not the ease of steric approach of base to proton abstraction in the transition state. Rather the overriding importance of factors related to steric hindrance and non-bonded repulsions, possibly contributing to instability of the chromate ester, is indicated in determining the relationship of oxidation rates. If this conclusion may be extrapolated to alicyclic cases, it seems apparent that the greater rate of *cis*-vs. *trans*-4-*t*-butylcyclohexanol, is largely attributable to the greater non-bonded repulsions in the axial chromate ester rather than to the greater accessibility of the carbinol proton. It will be readily seen, too, that similar reasoning might be applied in interpreting the series norborneol >> cyclopentanol $\cong$ cyclohexanol.

The factor of ten that distinguishes the oxidation rates of *endo*-norborneol and cyclohexanol is a good indication of the massive strains and steric hindrance developed by substitution in the axial positions of a boat structure, as illustrated.



Some idea of the steric influence of an alkyl group neighboring to the seat of oxidation may be gleaned from examination of the relative rates of *cis*- and *trans*-2-methylcyclohexanol. In all conformations of both isomers, except the unlikely *trans* diaxial, the methyl group is staggered by a projected angle of only 60° from the —C—O— bond. We can thus estimate that the residual enhancement of the oxidation by a 60° staggered methyl group produces a factor of about 2.4 in the rate when making the reasonable assumptions that (1) the observed rate of oxidation for *trans*-2-methylcyclohexanol is due entirely to the equatorial conformation, and (2) the rate ratio of cyclohexanol to *pure equatorial* cyclohexanol (1.0 to 0.8)[3], determined in 75% acetic acid, is the same in 30% acetic acid. Since the rate of oxidation of α-norborneol is 9.7 times faster than cyclohexanol, we may attempt a prediction of the borneol rate by multiplying 9.7 by the 2.4 factor characteristic of the neighboring methyl group. It is perhaps fortuitous that the product, 23, is in fair agreement with the observed value of 25.

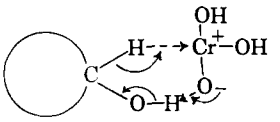
Possible Modifications of the Mechanism of Chromic Acid Oxidation of Secondary Alcohols.—It seems apparent that the Westheimer[5] mechanism must be slightly modified in the light of some of the conclusions derived from the data discussed above: (1) the abstraction of the carbinol hydrogen by the approach of an external reagent to the chromate ester in the transition state does not occur to any great extent, (2) steric acceleration of the decomposition of the chromate ester appears to be a controlling factor determining the over-all rate of oxidation, (3) stereoelectronic accommodation may contribute importantly to the ease of ester decomposition to ketone.

Roček and Krupička[11] have disputed the ester mechanism of chromate oxidation of secondary alcohols which has been employed in our article as the framework for interpretation. This work, however, has been challenged by Graham and Westheimer[12] who have also shown that the ester mechanism is most probable for the oxidation of benzaldehyde and have reiterated the consistency of this mechanism with the available data for isopropyl alcohol oxidation. The operation of a two-step mechanism for the oxidation of α-phenethyl alcohols also appears to be very probable in view of the results discussed by Kwart and Francis[4] which demonstrated that a rapid chromate ester equilibrium must be considered as a likely initial step in understanding the influence of polar substituents on the rate of reaction. Roček and Krupička have proposed a one-step transfer of hydride ion to chromate ion in concert with the development of the carbonyl double bond, which may be represented for cyclic alcohols by

(10) For a discussion of the relative stability of *endo* and *exo* isomers in norbornane and related substances see D. H. R. Barton, *J. Chem. oc.*, 1027 (1953).

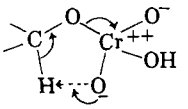
(11) J. Roček and J. Krupička, *Chemistry & Industry*, 1668 (1957), and ref. (14).

(12) G. T. E. Graham and F. H. Westheimer, THIS JOURNAL, **80**, 3030 (1958).



It is not as yet clear how this proposal[11] fits with our results since it requires the rate-determining abstraction of hydrogen by the approach of an external reagent in the transition state and it provides no sound basis for understanding the steric acceleration effects we and others[9] have observed for alicyclic and bicyclic alcohols.

A possible modification of the Westheimer mechanism, which can be reconciled with conclusions (1) and (2) above and with all the results we have considered thus far, specifies that the proton is removed in a cyclic transition state, the basic center of which resides on an electron dense oxygen on the chromate ester.[13a,b] In these circum-



stances, steric hindrance afforded by groups near the reaction center could result in rate acceleraton by restricting rotation about the C–O bond. Eliminating a number of (unstable, strained) conformations of the chromate ester the hindrance of the substituents increases the probability of attaining the five-membered cyclic transition state, pictured above, in which all the atoms involved are coplanar. Graham and Westheimer[12] have also considered an analogous cyclic transition state in the mechanism of benzaldehyde oxidation as a possible alternative to proton abstraction by water molecules acting as base.[14]

It is possible that the mere relief of steric strain in the chromate ester in going to the ketone may contribute to the rate as has been discussed for cyclohexanol and cyclopentanol derivatives[2,9,15] though this effect may not be of general importance. Furthermore, in the cyclic mechanism discussed here a good part of the diminished rate of 2-propanol (as compared to cyclohexanol and cyclopentanol oxidation) may be accounted for on the basis of reduced hindrance to rotational motion in the chromate ester.

(13) (a) Investigations currently in progress in these laboratories, bearing directly on the question of the position of this equilibrium as a function of the structure of the secondary alcohol and the acidity of the medium, do not as yet permit any specification of how extensively the alcohol has been converted to chromate ester prior to decomposition to ketonic product. (b) Similar cyclic transition states have often been suggested by R. T. Arnold and co-workers where the evidence seemed to indicate that proton transfer had *not* been effected through the direct intervention of an external base; see, for examples, R. T. Arnold, O. C. Elmer and R. M. Dodson, THIS JOURNAL, **72**, 4359 (1950), and R. T. Arnold and M. J. Danzig, *ibid.*, **79**, 892 (1957), as well as F. H. Westheimer and W. A. Jones, *ibid.*, **63**, 3283 (1941), and G. L. O'Connor and H. R. Nace, *ibid.*, **74**, 5454 (1952), **75**, 2118 (1953).

Experimental

Preparation of Alcohols.—All alcohols used were synthesized by standard techniques. Their physical constants agreed well with the literature in all cases.

Kinetic Runs.—The technique used for these runs is identical to that employed in aqueous acetic acid given by the authors in their previous publication.[4]

Acknowledgment.—We are grateful to the Hercules Powder Co. for supplying the pure samples of borneol and isoborneol.

(14) This is also consistent with the recent report of Westheimer to the 7th Reaction Mechanisms Conference, University of Chicago, Chicago, Ill., Sept. 6, 1958, indicating that the accelerating influence of added base on the rate of alcohol oxidation is sufficiently small to be a medium effect; see F. Holloway, M. Cohen and F. H. Westheimer, THIS JOURNAL, **73**, 65 (1951), as well as J. Roček and J. Krupička, *Coll. Czech. Chem. Comm.*, **23**, 2068 (1958).

(15) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954), and early articles cited therein.

NEWARK, DEL.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, STANDARD OIL CO. (INDIANA)]

Alkylation of *p*-Cresol: Effect of High Concentrations of Boron Trifluoride Catalyst

BY S. PAUL MALCHICK AND ROY B. HANNAN

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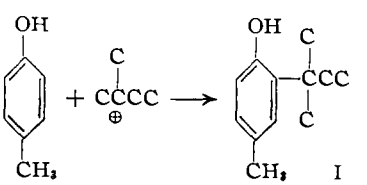
Alkylation of *p*-cresol with tertiary alkylating agents (2-methylbutene-2 or *t*-amyl chloride) in the presence of 50 mole % boron trifluoride gave less than 20% of the expected 2-*t*-alkyl-4-methylphenol. The remainder of the phenolic materials was composed of 2-*sec*-alkyl-4-methylphenols, *p*-*t*-alkylphenols and 2,2'-bismethylenediphenols. Alkylation of *p*-$C^{14}H_3C_6H_4OH$ showed that the methylene carbon atom of the 2,2'-bismethylenediphenols was originally the methyl carbon of *p*-cresol. A hydride-ion transfer as an early step in the mechanism could explain the formation of saturated hydrocarbons and the suppression of the reaction by the presence of isopentane in the alkylation.

Introduction

The alkylation of *p*-cresol in acid-catalyzed systems generally produces 2-alkyl-4-methylphenols which are used commercially as oxidation inhibitors.[1] Reaction of *p*-cresol with 2-methylbutene-2 or *t*-amyl chloride would be expected to give 2-*t*-amyl-4-methylphenol (I).

With 1–25 mole % boron trifluoride as catalyst, I is obtained in good yield. However, with concentrations of BF_3 around 50 mole %, we have observed that the alkylation products include less than 20% of I.



The effect of BF_3 concentration on the alkylation does not appear to have been studied. Moreover, in view of the good yields of desired product

(1) W. Weinrich, *Ind. Eng. Chem.*, **35**, 264 (1948); L. J. Kitchen, THIS JOURNAL, **70**, 1290 (1948).