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STERIC AND ELECTRONIC EFFECTS ON THE OXIDATION OF *ORTHO*-SUBSTITUTED BENZHYDROLS BY CHROMIC ACID

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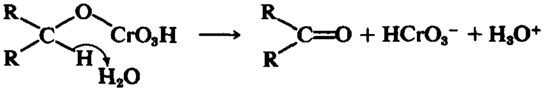
Abstract—A study has been made of the oxidation of a number of substituted benzhydrols by chromic acid in aqueous acetic acid. The reaction rate constants are linearly proportional to the K_{R^+} values of the alcohols. *ortho*-Substitution increases the rate of reaction and reduces the magnitude of the primary kinetic isotope effect. The major result of steric crowding appears to be an increase in the energy of the reactants, while the main electronic effect of substituents is to stabilize or destabilize the transition state.

Chromium (VI) has been employed extensively as an agent for the oxidation of primary and secondary alcohols; it converts primary alcohols to aldehydes or carboxylic acids and secondary alcohols to the corresponding ketones.[1] Because of its importance to synthetic organic chemistry a great deal of work has been done in an attempt to elucidate the mechanism of its reactions, and it would seem that the main characteristics have been well defined.[2,3]

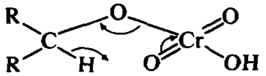
The electron transfer step has been shown to be preceded by a number of equilibria, some of which involve the formation of chromate esters as indicated below.[1,4,5]

$$\begin{gathered}
Cr_2O_7^{=} + H_2O \rightleftharpoons 2HCrO_4^- \\
HCrO_4^- + H^+ \rightleftharpoons H_2CrO_4 \\
HCrO_4^- + 2H^+ + A^- \rightleftharpoons HCrO_3A + H_2O \\
HCrO_4^- + ROH \rightleftharpoons RO{-}CrO_3^- + H_2O \\
H_2CrO_4 + ROH \rightleftharpoons ROCrO_3H + H_2O \\
H_2CrO_3A + ROH \rightleftharpoons ROCrO_2A + H_2O
\end{gathered}$$

The esters formed in these equilibria then undergo decomposition accompanied by electron transfer and C—H bond cleavage. Although it is known from the effect of deuterium substitution on the rates of reaction that this step is usually rate-determining,[4] the exact mode of decomposition has not been defined. Westheimer[4] originally suggested that the esters would decompose by transfer of a proton to a base such as water in the rate determining step (Eq 1).



However other workers have suggested that the α-hydrogen is transferred internally to a neighbouring oxygen as depicted below.[6–10] The strengths and weaknesses of these various suggestions have been thoroughly discussed elsewhere.[1,2]



The ester mechanism has been tried and tested in a variety of ways[11] but it would appear that at the present time there is little doubt as to its validity. Firm evidence for ester formation was obtained from a kinetic study of the oxidation of a sterically hindered alcohol, 3β-28-diacetoxy-6β-hydroxy-18β-12-oleanene.[12] The rate of oxidation of this alcohol was found to be unchanged by deuterium substitution in the α-position suggesting that the ester forming step had become rate determining. Furthermore, the spectroscopic observation of an intermediate ester has been reported.[13,14] In addition results which seem to indicate a steric rate retardation arising from angle strain in the developing carbonyl have been published.[15]

Both substituent and steric effects on the rate of reaction have been extensively studied and although these effects could change the magnitude of both the equilibrium constants for ester formation and the rate constant for the electron transfer step, evidence indicates that the primary effect is on the latter.[8] It appears clear that the effect of electron donating and electron withdrawing substituents is to stabilize or destabilize an electron deficient transition state; however, the reasons for steric acceleration are not as obvious and various explanations have been offered.[10,16]

Since most of the previous work on steric effects has been done using cyclic and bicyclic alcohols as reductants, we have attempted to obtain new evidence by measuring the rates of oxidation of a group of *ortho*-substituted benzhydrols.

EXPERIMENTAL

Preparation of substituted benzhydrols. The substituted benzhydrols used in this study were prepared by three standard procedures that have been previously described in the literature: (i) reduction of the corresponding ketone with LAH or deuteride,[17] (ii) reaction of an arylmagnesium halide with an aromatic aldehyde,[18] and (iii) reaction of an arylmagnesium halide with methyl formate or methyl formate-α-d.[19] The reactions have been summarized in Table 1. In every case the IR and NMR spectra were consistent with the assumed structure of the products.

Kinetic method. The rates of these reactions were studied in a solvent consisting of 69·0% acetic acid, 17·7% water and 13·3% H_2SO_4 (by weight). Because the reactions are very rapid under these conditions it was convenient to use stopped-flow techniques. The instrument employed was a Durrum Model D-110 Stopped-Flow Spectrophotometer equipped with a thermostated cell compartment. In a typical experiment solns of K_2CrO_7 ($1{\cdot}25\times10^{-4}$M) and benzhydrol ($7{\cdot}50\times10^{-3}$M) were prepared in the AcOH-water-H_2SO_4 solvent, and degassed by freezing and then slowly thawing the soln under reduced pressure (70 mm). The solns were then rapidly mixed using the instrument and plots of transmittance vs time were recorded on the oscilloscope. Then plots of ln (absorbance-final absorbance) against time were prepared and the pseudo-first order rate constants calculated. A typical plot has been reproduced in Fig. 1.

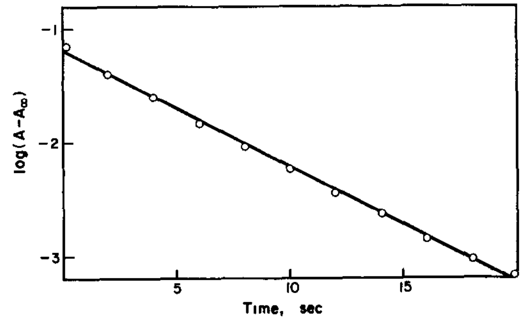


Fig. 1. Typical pseudo-first-order rate plot.

pK_{R^+} Measurements

When dissolved in conc H_2SO_4 solns diphenyl-carbinols form carbonium ions according to Eq 2.

$$R^+ + H_2O \xrightleftharpoons{K_{R^+}} ROH + H^+ \qquad [2]$$

The K_{R^+} values for these compounds may be obtained by use of the acidity function developed by Deno *et al.*[20,21] This function, originally designated by C_0, but more recently as H_R, is defined by Eq 3.

$$H_R = pK_{R^+} - \log [R^+]/[ROH] \qquad [3]$$

pK_{R^+} values had previously been measured for all but four of the alcohols required for this study, and using the H_R function it was possible to calculate these constants for the remaining benzhydrols (2-methylbenzhydrol, 2,4,4',6-tetramethylbenzhydrol, 2,2',4,4'-tetramethylbenzhydrol and 2,2',4,4',6-pentamethylbenzhydrol) by measuring the ratios of $[R^+]/[ROH]$ at different sulfuric acid concentration in the following manner.

The λ_{max} and approximate extinction coefficient were first defined for each diphenylcarbonium ion by dissolving a known quantity in 98% H_2SO_4 and recording the spectrum of the carbonium ion. Next a solution containing an appropriate concentration of the benzhydrol was prepared by dissolving a weighed amount of the alcohol in methanol. Portions of this solution (0·03 ml) were transfered to 3·0 ml volumetric flasks using a microliter syringe fitted with a Chaney adapter, the flasks were filled to the mark with H_2SO_4 solns of different concentrations and the absorbance of each soln was measured at the previously determined λ_{max}. Plots of absorbance against H_R gave typical titration curves for each of the alcohols. (Fig 2).

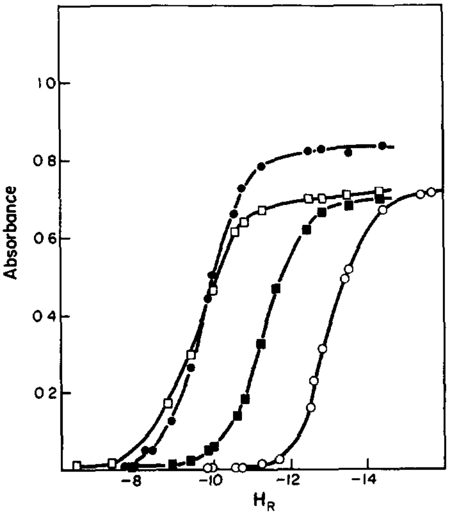


Fig. 2. Titration curves for the ionization of benzhydrols: (●) 2,2',4,4'-Tetramethylbenzhydrol, (□) 2,2',4,4'-6-Pentamethylbenzhydrol, (■) 2,4,4',6-Tetramethylbenhydrol, and (○) 2-Methylbenzhydrol.

From these titration curves values of $\log [R^+]/[ROH]$ were calculated and plotted against H_R (Fig 3). From the intercepts of these linear plots it was then possible to calculate the corresponding pK_{R^+} values. The complete results obtained from such an analysis of our results and those reported by Deno *et al*[20,21] have been summarized in Table 2.

RESULTS AND DISCUSSION

The pseudo first order rate constants obtained in this study have been summarized in Table 3. From this data it is readily apparent that substituents in the *para* positions exert the expected electronic effect and that increasing Me substitution in the *ortho* positions of benzhydrol increases the rate of oxidation. Although it is practically impossible to

Table 1. Preparation of substituted benzhydrols

Benzhydrol	Reactants	Yield (%)	Melting Point[a]
Benzhydrol	Benzophenone + $LiAlH_4$	46	67–68° (69°)[30a]
Benzhydrol-α-*d*	Benzophenone + $LiAlD_4$	53	66–67°
4-Methylbenzhydrol	4-Methylbenzophenone + $LiAlH_4$	57	54–55° (52°)[30b]
4,4′-Dimethylbenzhydrol	4,4′-Dimethylbenzophenone + $LiAlH_4$	79	72–73° (71–72°)[30c]
4-Chlorobenzhydrol	4-Chlorobenzophenone + $LiAlH_4$	73	62–63° (59–61°)[31]
4,4′-Dichlorobenzhydrol	Commercially available		94·5–95° (89–90°)[32]
2-Methylbenzhydrol	2-Methylphenyl magnesium bromide + benzaldehyde	52	93·5–94·5° (95°)[30d]
2,4,4′,6-Tetramethylbenzhydrol	4-Methylphenylmagnesium bromide + 2,4,6-trimethylbenzaldehyde	11	103–104°[b]
2,2′,4,4′,6-Pentamethylbenzhydrol	2,4-Dimethylphenylmagnesium bromide + 2,4,6-trimethylbenzaldehyde	52	106–107°[c]
2,2′,4,4′,6,6′-Hexamethylbenzhydrol	2,4,6-Trimethylphenylmagnesium bromide + 2,4,6-trimethylbenzaldehyde	70	153–154° (150·6–151·4°)[33]
2,2′-Dimethylbenzhydrol	2-Methylphenylmagnesium bromide + methyl formate	50	124–124·5° (119–119·5°)[30c]
2,2′,4,4′-Tetramethylbenzhydrol	2,4-Dimethylphenylmagnesium bromide + methyl formate	90	98–99° (101°)34[d]
2,2′,4,4′,6,6′-Hexamethylbenzhydrol-α-*d*	2,4,6-Trimethylphenylmagnesium bromide + methyl formate-α-*d*	45	151–152°

[a] Literature values in parenthesis

[b] No literature values available. Elemental analysis: Calc., C—84·95%, H—8·38%; found C—85·60%, H—8·55%

[c] No literature values available. Elemental analysis: Calc., C—84·99%, H—8·71; found C—84·70%, H—8·91%

[d] Elemental analysis: Calc., C—84·95%, H—8·33%; found C—84·53%, H—8·29%.

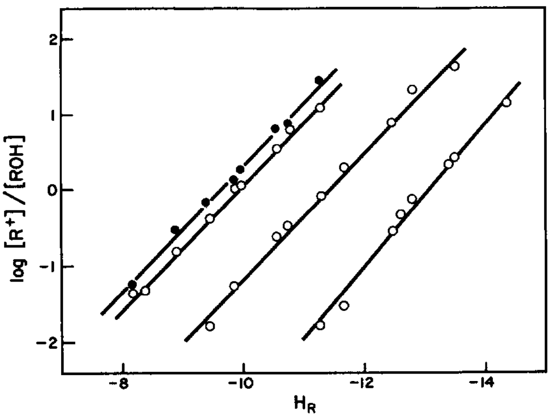


Fig. 3. Plots for pK_{R^+} determinations of 2,2′,4,4′,6-Pentamethylbenzhydrol, 2,2′,4,4′-Tetramethylbenzhydrol, 2,4,4′,6-Tetramethylbenzhydrol, and 2-Methylbenzhydrol (left to right).

Table 3. Pseudo first order rate constants for oxidation of substituted benzhydrols by Chromium(VI) in 69·0% acetic acid, 17·7% water and 13·3% H_2SO_4, [alcohol] = $3\cdot75\times10^{-3}$M, [Cr^{VI}] = $1\cdot25\times10^{-4}$M, Temp. = 40·0 ± 0·1°.

Compound	k_1(sec.$^{-1}$)[a]
4-Chlorobenzhydrol	0·0978 ± 0·0003
4,4′-Dichlorobenzhydrol	0·0855 ± 0·0011
Benzhydrol	0·102 ± 0·001
4-Methylbenzhydrol	0·172 ± 0·001
4,4′-Dimethylbenzhydrol	0·251 ± 0·002
2-Methylbenzhydrol	0·117 ± 0·001
2,2′-Dimethylbenzhydrol	0·148 ± 0·003
2,4,4′,6-Tetramethylbenzhydrol	0·255 ± 0·003
2,2′,4,4′-Tetramethylbenzhydrol	0·357 ± 0·006
2,2′,4,4′,6-Pentamethylbenzhydrol	0·539 ± 0·007
2,2′,4,4′,6,6′-Hexamethylbenzhydrol	0·794 ± 0·011
Benzhydrol-*α*-*d*	0·0258 ± 0·0002
2,2′,4,4′,6,6′-Hexamethylbenzhydrol-*α*-*d*	0·247 ± 0·002

[a] The average rate constant from four or more determinations. Error indicated as (±) is the probable deviation from the mean.

differentiate between the polar and the steric effects of *ortho* substituents it is significant to note that a good correlation exists between log k_1 and pK_{R^+} values (Fig 4). Hence although the effect is not as great, it would appear that *ortho* substituents influence the rates of oxidation in much the same way as they do the formation of carbonium ions. The low slope of the plot in Fig 4 is in accord with the suggestion previously made that the transition state of the reaction has more sp^3 than sp^2 character.[22]

It is well known that electron donating substituents increase the rate of reaction[6,23,24] presumably through stabilization of the transition state which has developed some sp^2 character. This is illustrated in Fig 5 where the rate constants for the oxidation of several substituted *α*-phenylethanols[23] have been plotted against the CO stretching frequencies of the corresponding ketones[25]. A correlation between rate and carbonyl stability is an indication that the main effect of substituents is to stabilize the developing carbonyl, although the low slope of Fig 5 suggests again that the sp^2 character of the transition state is far from fully developed.

Further information concerning the nature of the transition state comes from a consideration of the primary deuterium isotope effects. Theory predicts that the magnitude of the isotope effect is related to the symmetry of the transition state, with the largest effects being observed for the most symmetrical situation.[26] A small isotope effect would be consistent with a transition state in which the *α*—C—H bond was either extensively cleaved *or* one in which it was relatively intact, *but* not with one in which the *α*-hydrogen is in a symmetrical position with respect to the oxidant and the reductant; i.e., assuming that the hydrogen is transferred from the *α*-carbon atom to an O atom, a

Table 2. pK_{R^+} values for substituted benzhydrols

Substituents	pK_{R^+}	m[a]	n[b]	r[c]	Reference
4,4′-Dichloro	−13·97	1·08	5	0·997	Ref. #20
4-Chloro	−13·7	(No data avail.)			Ref. #21
Unsubstituted	−13·36	1·16	4	0·999	Ref. #20
Unsubstituted	−13·71	0·97	5	0·987	This work
2-Methyl	−13·05	0·98	8	0·980	This work
2,2′-Dimethyl	−12·43	0·94	5	0·998	Ref. #20
4-Methyl	−11·6	(No data avail.)			Ref. #21
2,4,4′,6-Tetramethyl	−11·37	0·84	10	0·994	This work
4,4′-Dimethyl	−10·38	0·89	4	0·999	Ref. #20
2,2′,4,4′-Tetramethyl	−9·88	0·83	9	0·997	This work
2,2′,4,4′,6-Pentamethyl	−9·65	0·80	9	0·995	This work
2,2′,4,4′,6,6′-Hexamethyl	−6·58	0·88	6	0·999	Ref. #20

[a] Slope of the plot of log [R^+]/[ROH] against —H_R
[b] Number of points
[c] Correlation coefficient

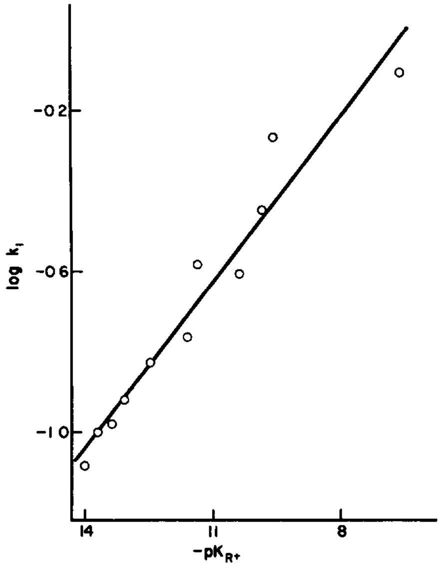


Fig. 4. Plot of log k_1 v. $-PK_{R^+}$. Slope = 0·14, Correlation coefficient = 0·97.

large isotope effect will be observed only if the partial bond between the C—H is approximately equal in strength to the partial bond between the H—O in the transition state. Conversely, a small isotope effect will be observed only if the strengths of the partial C—H and O—H bonds are very unequal in the transition state.

All available data (Table 4) indicate that the isotope effect for this reaction is smaller for alcohols containing substituents which increase the sp^2 character of the transition states, thus suggesting that the greater a symmetry introduced by these substituents is related to a more extensive cleavage of the carbon-hydrogen bond. Consequently we are drawn to the conclusion that although the α-carbon atom remains largely sp^3 in character in the transition state the C—H bond is extensively cleaved. While this may seem on the surface to be a contradiction it may simply reflect the possibility that the force constant for the O—H bond is greater than that for the C—H bond. Such a conclusion is certainly consistent with the known absorption frequencies of C—H and O—H bonds in stable compounds. Consequently it would appear that the α-carbon remains primarily sp^3 even though the C—H is extensively cleaved in the transition state.

Turning to a consideration of steric effects it has been observed in a wide variety of systems that increases in steric hindrance also increases the rate of oxidation.[27,28] However, the rate increases cannot be attributed to the same kind of transition state stabilization that electronic effects produce; there is no correlation between reaction rates and carbonyl stretching frequencies for sterically hindered alcohols.[10] For example, the rate of oxidation of *endo*-5,6-trimethylene-*endo*-2-norbornanol

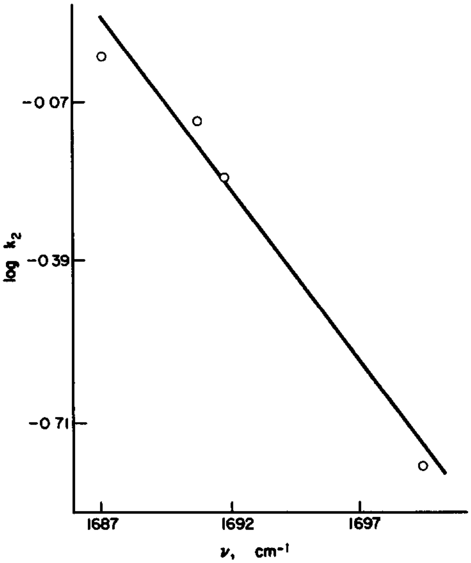


Fig. 5. Plot of log k_2 for the oxidation of substituted α-phenylethanols[23] v. $\nu_{C=O}$ for the corresponding acetophenones[5]. Slope = $6·6 \times 10^{-4}$ cm. Correlation coefficient = 0·99.

Table 4. Effect of substituents on primary deuterium isotope effects

Alcohol	Substituents	Conditions	k_H/k_D
(a) α-Phenylethanol[10]	*p*-Methoxy	30% AcOH, 0·250 H^+	3·5
	p-Chloro	30% AcOH, 0·250 M H^+	4·4
(b) Phenyltrifluoromethylcarbinol[6]	*p*-Methyl	72·2% AcOH, 3·2 M $HClO_4$	7·4
	none	72·2% AcOH, 3·2 M $HClO_4$	8·5
	m-Bromo	72·2% AcOH, 3·2 M $HClO_4$	9·8
	m-Nitro	72·2% AcOH, 3·2 M $HClO_4$	12·2
	3,5-Dinitro	72·2% AcOH, 3·2 M $HClO_4$	12·9
(c) 2-Propanol[4]	None	50·1% H_2SO_4	6·3
	1,1,1-Trifluoro	50·1% H_2SO_4	10·5

Table 5. Steric effects on the primary deuterium isotope effects

Alcohol	Substituents	Conditions	k_H/k_D
(a) *endo*-Norborneol[27]	*exo*-Benzo	70% AcOH, 0·1 M $HClO_4$	6·2[a]
	endo-Benzo	70% AcOH, 0·1 M $HClO_4$	6·1
	exo-Naphtha	70% AcOH, 0·1 M $HClO_4$	5·8
	endo-Naphtha	70% AcOH, 0·1 M $HClO_4$	3·7
(b) Benzhydrol	None	69% AcOH, 13·3% H_2SO_4	4·0
	2,2′,4,4′,6,6′-hexamethyl	69% AcOH, 13·3% H_2SO_4	3·2

[a] The authors report $k_H/k_D = 5{\cdot}85$ for this compound. However a recalculation using the rate data indicates a value of 6·2.

is 151 times greater than that of *endo*-5,6-trimethylene-*exo*-2-norbornanol despite the fact that they both give the same product.[29] Consequently in these cases the rate accelerating effects must be due to an increase in the energy of the reacting alcohols rather than to stabilization of the transition state.

It is of interest to note that the isotope effects have also been observed to decrease with increased steric hindrance for all systems that have been studied (Table 5). These observations must also be as a consequence of changes in the reactants. Increasing the steric hindrance of the alcohols would reduce the H—C—O— bond angles, increase the p-character of the α—C—H bond and decrease the force constants. This would lead to a reduction in the magnitude of the isotope effect as observed.

Hence it would appear that the increases in rate (and decreases in isotope effect) caused by electron donating substituents and steric hindrance are not attributable to identical phenomena. Electron donating substituents increase the sp^2 character of the transition state whereas steric effects destabilize the reactant alcohols.

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