Kinetics of the Oxidation of Benzhydrols to Benzophenones by Iodine in Alkaline Methanol

Yoshiro Ogata* and Kenji Nagura

Contribution No. 203 from the Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

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Oxidation of benzhydrols by iodine in alkaline methanol to give benzophenones has been kinetically studied. The rate is expressed as: $v = k_3[\mathrm{ArAr'CHOH}][\mathrm{I_2}]_a{}^2$, if $[\mathrm{I_2}]_a < [\mathrm{MeONa}]_a$, and $v = k_3[\mathrm{ArAr'CHOH}][\mathrm{MeONa}]_a{}^2$, if $[\mathrm{I_2}]_a > [\mathrm{MeONa}]_a$, where $[\ \ ]_a$ denotes the concentration of added reagents. The effect of ring substituent on the rate gives a good correlation with σ^+ but not with σ, affording a ρ^+ value of -0.677 ($r = 0.987$). The results are discussed in terms of a mechanism involving a rate-determining removal of hydride ion from the α carbon of hypoiodous benzhydroxy ester by methyl hypoiodite.

There have been a number of works on the oxidation of alcohols with halogen to carbonyl compounds.[1-4] As to the mechanism, previous workers seem to have concentrated on the following: (i) structural speculation on the transition state; (ii) the confirmation of attacking agents and the relative reactivities of various halogen-containing species.

Deno and Potter[1] suggested the similarity between the mechanism for the oxidation of alcohols with halogen and that with chromic acid involving an ester intermediate. The mechanism involving an ester-like intermediate was preferred because of the following reasons: (i) alkyl hypohalite decomposes to aldehyde or ketone and hydrogen halide;[2a] (ii) the pH–rate profile exhibits a bell-shaped curve;[1b] (iii) stereoselectivities are similar to those of the chromic acid oxidation.[3]

In contrast, Kaplan's mechanism, generally accepted for the oxidation of alcohols by bromine in acidic aqueous solutions, involves an oxidative transfer of a hydride ion (but not a proton) from α carbon.[4] Kaplan ruled out a mechanism involving alkyl hypohalites as intermediates,[4a,b] and Perlmutter suggested that molecular halogen but not hypohalous acid is an effective oxidizing agent in these reactions.[4c,d] Most other workers support the mechanism involving an attack of "molecular halogen" on α hydrogen followed by "hydride removal."[4]

However, all these previous experiments were conducted

Table I
Pseudo-First-Order Rate Constants for the Oxidation of Benzhydrols by Iodine in Alkaline Methanol at 25°

Substrate	$[\mathrm{MeONa}]_a$, M	$[\mathrm{I_2}]_a$, M	10^4k_{obsd}, sec^{-1}
$(C_6H_5)_2CHOH$	0.073	0.0909	0.217
	0.146	0.0909	0.457
	0.292	0.0909	0.680
	0.438	0.0909	0.655
	0.0364	0.136	0.202
	0.0728	0.136	0.345
	0.109	0.136	0.783
	0.146	0.136	1.83
	0.214	0.136	1.77
	0.292	0.136	1.69
	0.0182	0.182	0.232
	0.0728	0.182	0.362
	0.123	0.182	1.64
	0.182	0.182	2.80
	0.364	0.182	2.76
	0.573	0.182	2.42
	0.073	0.227	0.292
	0.109	0.227	0.732
	0.182	0.227	2.51
	0.291	0.227	3.54
	0.437	0.227	3.54
	0.728	0.227	3.37
(p-$CH_3OC_6H_4$)(C_6H_5)-CHOH	0.727	0.0455	0.996
	0.727	0.0909	3.83
	0.727	0.136	7.3
	0.727	0.182	14.0
	0.727	0.227	20.3
	0.0364	0.227	0.632
	0.0728	0.227	1.93
	0.109	0.227	4.47
	0.145	0.227	8.73
	0.200	0.227	15.9
	0.267	0.227	20.9
	0.0667	0.125	1.34
	0.133	0.125	3.10
	0.200	0.125	7.42
	0.267	0.125	6.08
	0.333	0.125	7.60
	0.0667	0.125	1.02[a]
	0.133	0.125	2.25[a]
	0.200	0.125	3.25[a]
	0.267	0.125	4.33[a]
	0.333	0.125	6.78[a]
	0.727	0.125	7.32[a]
(p-$CH_3OC_6H_4$)(p'-$CH_3C_6H_4$)CHOH	0.200	0.025	0.385
	0.200	0.040	1.75
	0.200	0.050	1.76
	0.200	0.065	3.55
	0.200	0.075	3.94
	0.200	0.090	5.81
	0.200	0.150	16.4
	0.050	0.188	1.72
	0.075	0.188	3.83
	0.100	0.188	7.23
	0.150	0.188	15.1
	0.250	0.188	24.2
	0.350	0.188	25.4
	0.400	0.188	23.6
	0.600	0.188	23.6

[a] Sodium iodide ($[\mathrm{NaI}]_a = 0.048\ M$) was added.

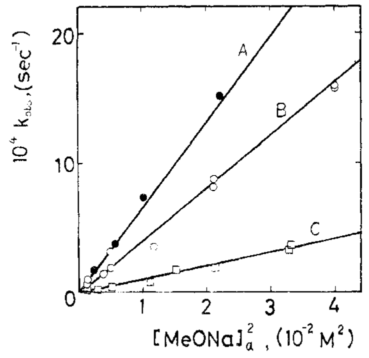


Figure 1. The plot of k_{obsd} *vs.* $[MeONa]_a^2$ for the oxidation of (A) *p*-methoxy-*p'*-methylbenzhydrol, (B) *p*-methoxybenzhydrol, and (C) benzhydrol by iodine in alkaline methanol ($[I_2]_a$ > $[MeONa]_a$) at 25°, where [ ]$_a$ denotes the concentration of added reagent. The lines in this figure correspond to those in Figure 2.

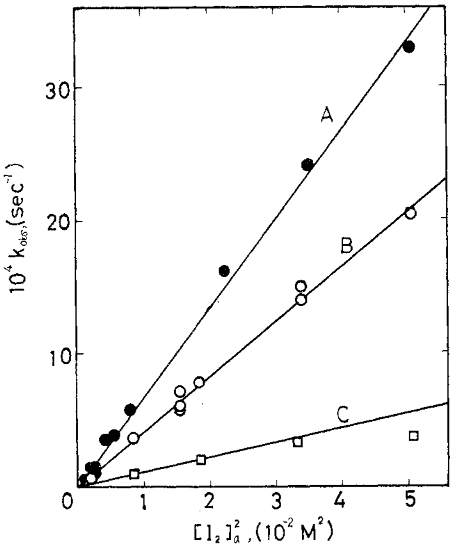


Figure 2. The plot of k_{obsd} *vs.* $[I_2]_a^2$ for the oxidation of (A) *p*-methoxy-*p'*-methylbenzhydrol, (B) *p*-methoxybenzhydrol, and (C) benzhydrol by iodine in alkaline methanol ($[I_2]_a$ < $[MeONa]_a$) at 25°, where [ ]$_a$ denotes the concentration of added reagent.

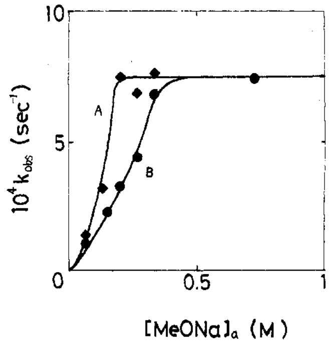


Figure 3. Plot of k_{obsd} *vs.* $[MeONa]_a$ for the oxidation of *p*-methoxybenzhydrol by iodine ($[I_2]_a$ = 0.125 *M*) in alkaline methanol at 25°: (A) $[NaI]_a$ = 0 *M*; (B) $[NaI]_a$ = 0.048 *M*.

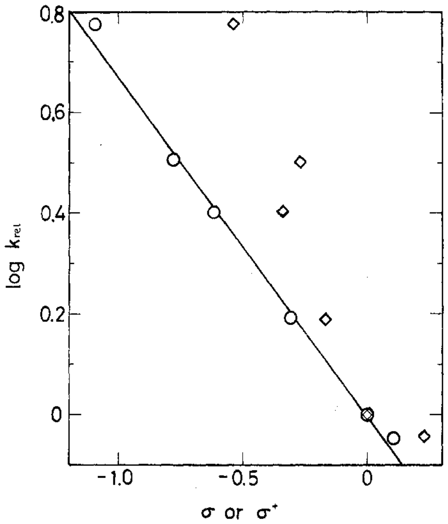


Figure 4. Hammett plot for the oxidation of benzhydrols by iodine in alkaline methanol at 25°: (O) σ^+; (◇) σ.

in acidic solutions. In basic aqueous solutions, halogen is mostly converted to inert hypohalite anion (OX^-),[5] so that the reaction is suppressed and kinetics are complicated. Hence, it is not certain whether the oxidation mechanism in acidic solutions involving the hydride removal can be applied also to that in basic solutions.

This paper reports a study on the kinetics of the oxidation of one kind of alcohol, benzhydrols, by iodine in basic conditions by following the rate by means of glc analysis of the remaining benzhydrol.

Results

Rate. The rates of the reaction of benzhydrols with a mixture of iodine and sodium methoxide in dry methanol at 25° were measured by following the decrease of benzhydrols by means of glc. Rates of iodine (45.5–227 × 10^{-3} *M*) and sodium methoxide (36.4–727 × 10^{-3} *M*) far exceed benzhydrol (4–10 × 10^{-3} *M*) so that the pseudo-first-order kinetics applied; appropriate plots were linear up to 60–80% conversion. Therefore, the decreasing amount of iodine caused by the oxidation of solvent methanol has little effect on the kinetics under these conditions.

$$v = k_{obsd}[ArAr'CHOH] \qquad (1)$$

The kinetic data are listed in Table I. Figure 1 shows the plot of k_{obsd} *vs.* the square of the concentration of added sodium methoxide ($[MeONa]_a^2$) for the reaction of some benzhydrols, where a subscript a indicates the concentration of added reagent. The rate is proportional to $[MeONa]_a^2$ and independent of the amount of added iodine ($[I_2]_a$), when $[MeONa]_a$ is smaller than $[I_2]_a$.

$$v = k_3[ArAr'CHOH][MeONa]_a^2 \qquad (2)$$

However, when $[MeONa]_a$ is larger than $[I_2]_a$, the rate is independent of $[MeONa]_a$ (Table I). Figure 2 shows the plot of the observed rate constant against $[I_2]_a^2$, where $[I_2]_a$ is smaller than $[MeONa]_a$. The rate is proportional to $[I_2]_a^2$, and the observed slope agrees with that in the plot of Figure 1.

$$v = k_3[ArAr'CHOH][I_2]_a^2 \qquad (3)$$

Figure 3 shows the effect of added iodide ion ($[NaI]_a$ = 0.048 *M*) on the rate of oxidation of *p*-methoxybenzhydrol by iodine ($[I_2]_a$ = 0.134 *M*) in methanol. The rate is suppressed by iodide ion in solutions of lower basicity but is independent of iodide ion in a solution of higher basicity.

Substituent Effect. Some ring-substituted benzhydrols were oxidized with iodine in the presence of sodium methoxide in dry methanol at 25°. The rate constant k_3 was calculated by means of eq 2 and 3, and then the relative rate, k_3(substituted)/k_3(unsubstituted), was evaluated. The relative rates are listed in Table II and plotted against Hammett's σ and Okamoto-Brown's σ^+ in Figure 4. The relative rate (k_{rel}) is correlated with σ^+ rather than σ, giving a ρ^+ value of −0.677 (r = 0.987).

Table II
Substituent Effect on the Relative Rate for the Reaction of Benzhydrols with Iodine in Alkaline Methanol at 25°

Substituent	Registry no.	k_{rel}
p-MeO,p'-Me	838-22-2	6.01
p-MeO	720-44-5	3.70
p,p'-Me$_2$	885-77-8	3.57
p-Me	1517-63-1	1.54
Unsubstituted	91-01-0	1
p-Cl	119-56-2	0.902

Table III
Effect[a] of Temperature on the Rate of the Reaction of p-Methoxybenzhydrol with Iodine in Alkaline Methanol

Temp, °C	10^2k_3, M^{-2} sec^{-1}
50.0	18.7
40.0	10.2
30.0	7.21
25.0	4.12
10.0	1.85
0.0	0.614
−14.0	0.241

[a] $\Delta H^* = 11.7$ kcal/mol, $\Delta S^* = -27.8$ eu.

Effect of Temperature. p-Methoxybenzhydrol is an appropriate substrate, since it is oxidized at a suitable rate. The rate of the oxidation of p-methoxybenzhydrol by iodine was measured in dry methanol at various temperatures. The data are listed in Table III, which gives the enthalpy and entropy of activation as 12.3 kcal/mol and −27.8 eu, respectively.

Discussion

Bell-shaped pH–rate profiles were reported in the oxidation reaction of 2-propanol[1b] and α-hydroxy acids[5a,6] with aqueous bromine. Deno[1b] and Barker[6] interpreted these phenomena by assuming hypobromous acid (HOBr) to be an effective oxidizing agent, *i.e.*, the rate increases with increasing hypobromous acid concentration at lower pH values and decreases with increasing conversion of hypobromous acid to inert hypobromite ion (OBr$^-$) at higher pH values.

However, under our conditions with alkaline methanol as solvent, hypoiodite ion (OI$^-$) cannot be formed, but iodine is converted to methyl hypoiodite (MeOI).[7]

$$I_2 + MeO^- \overset{K_4}{\rightleftharpoons} MeOI + I^- \qquad (4)$$

$$K_4 = \frac{[MeOI][I^-]}{[I_2][MeO^-]} \qquad (5)$$

Assuming that the equilibrium constant K_4 for eq 4 in methanol is similar to that in an aqueous solution, which has a value of 30–200 at 25°,[8] the concentration of methyl hypoiodite ([MeOI]) is nearly equal to the amount of added sodium methoxide ([MeONa]$_a$) in a solution of lower basicity ([MeONa]$_a$ < [I$_2$]$_a$), while [MeOI] is equal to added iodine ([I$_2$]$_a$) in a solution of higher basicity ([MeONa]$_a$ > [I$_2$]$_a$).[9]

According to Deno's mechanism,[1b] which involves the intermediary formation of hypohalite ester (2) followed by the elimination of hydrogen halide, the rate would be proportional to the concentration of methyl hypoiodite, but this was not observed.

The rate law observed by us suggests two mechanisms.

Scheme I

$$\underset{1}{ArAr'CHOH} + MeOI \underset{fast}{\overset{K_6}{\rightleftharpoons}} \underset{2}{ArAr'CHOI} + MeOH \qquad (6)$$

$$\underset{2}{ArAr'CHOI} + MeOI \underset{slow}{\overset{k_7}{\longrightarrow}} \underset{3}{ArAr'C{=}O} + MeOI + HI \qquad (7)$$

One is shown in Scheme I, which involves an attack of methyl hypoiodite on hypoiodite ester of substrate (2) formed by a mobile equilibrium of benzhydrol (1) with methyl hypoiodite. In Scheme I, with rate-determining step 7, the rate should be expressed as

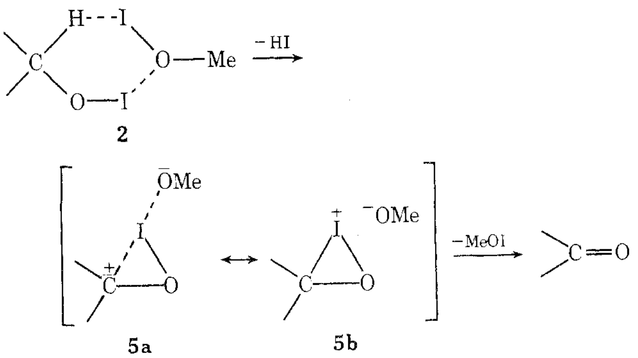
$$v = k_7K_8[1][MeOI]^2 \qquad (8)$$

Since [MeOI] is nearly equal to [MeONa]$_a$ at [MeONa]$_a$ < [I$_2$]$_a$ and is nearly equal to [I$_2$]$_a$ at [MeONa]$_a$ > [I$_2$]$_a$,[9] eq 8 leads to eq 2 and 3.

An alternative mechanism is that of Perlmutter-Hayman[4d] (see Scheme IIIA), which involves an attack of molecular iodine on α hydrogen of alkoxide anion (ArAr'CHO$^-$, 4) formed by a mobile equilibrium of 1 with methoxide ion. The observed rate law is consistent with this mechanism, *i.e.*, this mechanism leads to the rate expression $v = k[1][MeO^-][I_2] = kK_4[1][MeOI][I^-]$, which is equal to eq 8, since [I$^-$] is equal to [MeOI] in the absence of added iodide ion.[9] However, Figure 3 shows that added iodide ion suppresses the reaction. This can be explained by Scheme I but not by Perlmutter-Hayman's mechanism; that is, the concentration of methyl hypoiodite should be decreased by adding iodide ion (eq 5) so that the rate should be decreased. However, [MeO$^-$] and [I$_2$] are increased by addition of iodide ion. Hence, Scheme I is more favorable than Perlmutter-Hayman's mechanism.

Furthermore, the observed substituent effects support Scheme I. The relative rates are correlated with Okamoto-Brown's[10] σ^+ but not Hammett's σ, giving a ρ^+ value of −0.677; this fact indicates that the rate-determining step is an electrophilic attack on the α carbon of substrate or the elimination of hydride ion from α carbon and that the transition state should have a carbonium ion property.[10] The α-hydride abstraction of 2 may be accelerated by the anchimeric assistance[11] or bridging[12] by an iodine atom (Scheme II). Transition state 5 should be stabilized by an iodine atom of hypoiodite 2 by neighboring group participation.[12,13]

Scheme II

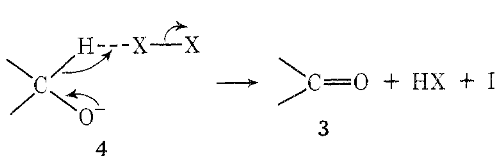


2
5a
5b

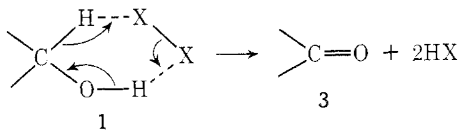
However, if anion 4 were attacked by molecular halogen, the transition state would not be carbonium ion like, and then the substituent effect would be correlated with σ but not with σ^+,[10] since the negative charge should shift to carbon simultaneously with hydride elimination (Scheme IIIA). The ρ value of −2.29 with σ (but not σ^+) has been reported for the oxidation of benzyl alcohol with bromine in aqueous acetic acid,[3h] where the mechanism involves a rate-determining removal of hydride ion from α carbon with a synchronous removal of hydroxylic proton (Scheme IIIB). Perlmutter's mechanism[4d] is based on the correlation between pK of substrate and the pH at which k_{obsd} starts increasing.[1b,4c,d] But this correlation is also explicable by our mechanism (Scheme I), *i.e.*, pK_6 should be proportional to the pK of the substrate.

Scheme III

A. Reaction of Substrate Anion (RO^-) with Molecular Halogen (X_2) (Perlmutter-Hayman's Mechanism)[4d]

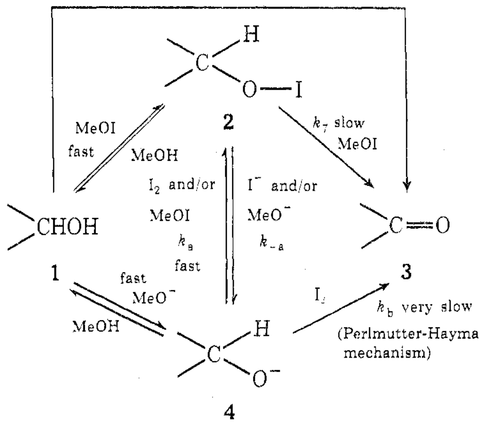


B. Reaction of Substrate (ROH) with Molecular Halogen (X_2) in Acidic Solutions[4a,f–h]



Hence Scheme I is preferable to Perlmutter-Hayman's mechanism. Benzhydroxide ion 4 should be attacked by molecular iodine and/or methyl hypoiodite on an oxygen atom rather than on an α-hydrogen atom to give hypoiodite ester **2**, *i.e.*, $k_a \gg k_b$ (Scheme IV), since the equilibria in Scheme IV are very fast.[8a] The concentration of **2** should be much higher than that of **4** at lower basicity in analogy with the case of methanol (eq 4 and 5), and the concentration of iodine [I_2] is much lower than methyl hypoiodite [MeOI] at higher basicity, so that the oxidation of **4** by molecular iodine may be much slower than that of **2** by methyl hypoiodite.

Scheme IV



$$k_a \gg k_b$$

$$k_7[\mathbf{2}][\text{MeOI}] \gg k_b[\mathbf{4}][I_2]$$

The values of ΔH^* (12.3 kcal/mol) and ΔS^* (−27.8 eu) also support our mechanism, *i.e.*, the values of ΔH^* and ΔS^* were reported to be 13.9 kcal/mol and −25.2 eu, respectively, for the Br_2 oxidation of benzyl alcohol,[4h] where a rupture of a C–H bond occurs.

Experimental Section

Materials. Unsubstituted benzhydrol is of guaranteed grade and used without further purification. *p*-Methoxy-*p′*-methyl- and *p,p′*-dimethylbenzhydrols were prepared by treatment of corresponding benzophenone with a mixture of zinc powder and sodium hydroxide in aqueous ethanol.[14] *p*-Chloro-, *p*-methyl-, and *p*-methoxybenzhydrols were prepared from the corresponding benzaldehyde by the reaction with phenylmagnesium bromide in dry ether. Prepared benzhydrols were recrystallized from *n*-hexane. The substituent of benzhydrol, melting point, and glc retention time were as follows: unsubstituted, mp 67.0–67.3° (lit.[14] 68°), 11.4 min; *p*-Cl, mp 63.0–63.2°, 17.9 min; *p*-Me, mp 53.0–54.0°, 12.4 min; *p*-MeO, mp 66.9–67.2°, 21.9 min; *p,p′*-Me_2 mp 54.5–55.2°, 19.3 min; *p*-MeO-*p′*-Me, mp 64.0–64.2°, 23.6 min. A Hitachi K-53 gas chromatograph with a flame ionization detector was used with a column packed with DEGS (13%) on Chromosorb W at temperatures increasing by 10°/min from 140 to 225° with N_2 as a carrier gas at a flow rate of 45 ml/min.

Kinetics. The reaction of benzhydrols with a mixture of iodine and sodium methoxide is irreversible. The rate of the reaction of benzhydrols ($4\text{–}10 \times 10^{-3}\ M$) in methanol with an excess of iodine ($45.5\text{–}227 \times 10^{-3}\ M$) and sodium methoxide (0.0364–0.727 M) was measured by means of glc analysis of the remaining benzhydrols. The rate could not be measured by following the iodine or hypoiodite concentration because they were unstable, changing their concentration by spontaneous decomposition or by their reaction with methanol solvent, although this change may be small. The concentration of iodine in a mixture of 0.5 M I_2 and 0.5 M MeONa in methanol decreased *ca.* 5% after 15 min, which is the longest time for kinetic runs.

A typical kinetic procedure was as follows. A mixture of appropriate amounts of methanolic sodium methoxide and benzhydrol was thermostated. The reaction was started by addition of a methanolic solution of iodine. At appropriate time intervals, aliquots were taken out and extracted with ether. The ether extract was washed with aqueous $Na_2S_2O_3$ to eliminate iodine and hypoiodite, and concentrated by evaporation of the solvent, the content of benzhydrol being measured by glc with a column packed with DEGS (13%) as stated above.

The plot of log ([ArAr′CHOH]/$[\text{ArAr'CHOH}]_0$) against time gives a straight line up to 60–80% conversion, where subscript 0 denotes initial concentration. The relative rates for all benzhydrols were calculated from k_3 values which are slopes of the lines in Figures 1 and 2.

Registry No.—Iodine, 7553-56-2.

References and Notes

(1) (a) N. C. Deno and N. H. Potter, *J. Amer. Chem. Soc.*, **89**, 3550 (1967); (b) N. C. Deno and N. H. Potter, *ibid.*, **89**, 3555 (1967).

(2) (a) F. D. Chattaway and O. G. Backberg, *J. Chem. Soc.*, **123**, 3000 (1923); (b) F. D. Chattaway and O. G. Backberg, *ibid.*, **125**, 1097 (1924).

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(4) (a) L. Kaplan, *J. Amer. Chem. Soc.*, **76**, 4645 (1954); (b) L. Kaplan, *ibid.*, **80**, 2639 (1958); (c) B. Perlmutter-Hayman and Y. Weissmann, *ibid.*, **84**, 2323 (1962); (d) B. Perlmutter-Hayman and Y. Weissmann, *ibid.*, **91**, 668 (1969); (e) C. G. Swain, R. A. Wiles, and R. F. W. Bader, *ibid.*, **83**, 1945 (1961); (f) I. R. L. Barker, W. G. Overend, and C. W. Rees, *J. Chem. Soc.*, 3263 (1964); (g) I. R. L. Barker and R. H. Dahm, *J. Chem. Soc. B*, 650 (1970); (h) P. Aukett and I. R. L. Barker, *J. Chem. Soc., Perkin Trans. 2*, 568 (1972); (i) J. G. Mason and L. G. Baird, *J. Amer. Chem. Soc.*, **94**, 6116 (1972); (j) R. M. Bater and J. S. Littler, *J. Chem. Soc. B*, 205 (1967).

(5) (a) J. M. Pink and R. Stewart, *Can. J. Chem.*, **49**, 649 (1971); (b) J. M. Pink and R. Stewart, *ibid.*, **49**, 654 (1971).

(6) P. Aukett and I. R. L. Barker, *J. Chem. Soc., Perkin Trans. 2*, 965 (1973).

(7) There may be other equilibria such as (a) $I_2 + I^- \rightleftarrows I_3^-$ (K_a), and (b) $I_2 \rightleftarrows I^- + I^+$ (K_b). However, the concentrations of reagents ([I_2] and [MeOI]) were calculated by neglecting these equilibria because of the following reasons: (i) their equilibrium constants are very small ($K_a = 1.4 \times 10^{-3}$ and $K_b = 1.9 \times 10^{-5}$ at 25° in aqueous solution); (ii) I_3^- is inert for the oxidation of alcohol.[1,4]

(8) (a) A. Skrabal, *Monatsh.*, **32**, 169 (1911); *Chem. Abstr.*, **5**, 2591 (1911); (b) Y. Chia, *U. S. Atomic Energy Comm.*, **UCRL-8311**, 87 (1958); *Chem. Abstr.*, **53**, 2914 (1958); (c) C. H. Li, *J. Amer. Chem. Soc.*, **64**, 1147 (1942).

(9) Equation 4 can be written in the form: $[\text{MeOI}]^2 - (1/K_4)\,[\text{MeOI}][I^-] - ([I_2]_a + [\text{MeONa}]_a)[\text{MeOI}] + [I_2]_a[\text{MeONa}]_a = 0$. Since [$I^-$] is equal to [MeOI] when sodium iodide is not added, $(1 - 1/K_4)[\text{MeOI}]^2 - ([I_2]_a +$

$[\mathrm{MeONa}]_a)[\mathrm{MeOI}] + [\mathrm{I_2}]_a[\mathrm{MeONa}]_a \doteq 0$. Since K_4 is considerably larger than unity, [MeOI] is equal to $[\mathrm{MeONa}]_a$ (if $[\mathrm{MeONa}]_a < [\mathrm{I_2}]_a$) or $[\mathrm{I_2}]_a$ (if $[\mathrm{MeONa}]_a > [\mathrm{I_2}]_a$).

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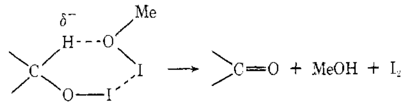
(11) (a) P. S. Fredricks and J. M. Tedder, *J. Chem. Soc.*, 3520 (1961); (b) *ibid.*, 144 (1960).

(12) (a) D. S. Ashton, J. M. Tedder, M. D. Walker, and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2,* 1346 (1973); (b) W. Thaler, *J. Amer. Chem. Soc.*, **85,** 2607 (1973).

(13) The reviewer suggested an alternative scheme in which hydride is abstracted by an oxygen atom of methyl hypoiodite.



However, since the electrophilicity of oxygen of methyl hypoiodite should be less than that of iodine, this scheme is less probable.

(14) (a) S. R. Hooley and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2,* 1053 (1973); (b) P. M. Henrichs and P. E. Peterson, *J. Amer. Chem. Soc.*, **95,** 7449 (1973).

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Solvents of Low Nucleophilicity. XV. Effects of Substituents at C-17 upon the Rates of Solvolysis of 3-Tosyloxy Steroids[1]

Paul E. Peterson* and Dhansukh M. Chevli

Department of Chemistry, St. Louis University, St. Louis, Missouri 63156, and Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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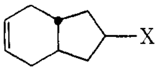
Rates of solvolysis of 3α- and 3β-tosyloxy androstanes having substituents at C-17 were determined in the solvents acetic acid, formic acid, and trifluoroacetic acid. Electronegative substituents at C-17 cause decreased solvolysis rates by factors up to sixfold. Simple electrostatic calculations show that dipole–dipole interactions are almost certainly too small and dipole–charge interactions are probably too small to account for the effects. Partial removal or delocalization of both negative poles of the dipoles *via* hydrogen bonding interactions with solvent, especially in trifluoroacetic acid, can account for the results. A larger effective dielectric constant for the interactions involving negative charges may be a contributing factor.

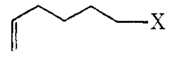
It has been generally believed that in unhindered saturated systems the effect exerted by electronegative substituents upon rates and equilibria[2] is small for substituents separated from a reaction center by several carbon atoms. However, it is now known that remote substituents may exert substantial effects particularly in various carbonium ion reactions. Typical values of k_H/k_X, the ratios of rate constants for reactions of compounds bearing the substituents H and X, respectively, are shown in Chart I for addition of trifluoroacetic acid to comparable bicyclic and acyclic alkenes.[3] The similar magnitude of effects in additions to alkenes and in tosylate solvolyses is illustrated by the data given in Chart II.[4] Based on these comparisons and on the data given in Chart III for the reaction of a 10-substituted 1-undecene, substituent effects exerted across the entire steroid polycyclic skeleton would be expected to be observable in the solvolysis of steroidal tosylates of general formula **6** (Chart III). In the present paper we report the observation of substituent effects in the acetolysis, formolysis, and trifluoroacetolysis of the steroidal tosylates, **6**. The known geometry of the steroid skeleton allows us to draw important conclusions regarding the origin and solvent dependence of the substituent effects.

Chart I



1

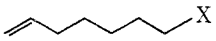
$X = CN;\ k_H/k_X = 152$



2

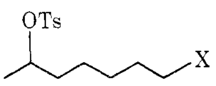
$X = CN;\ k_H/k_X = 61.8$

Chart II



3

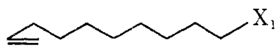
$X = Cl;\ k_H/k_X = 5.00$



4

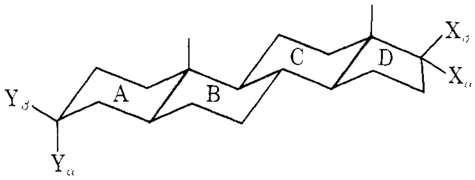
$X = Cl;\ k_H/k_X = 3.88$

Chart III



5

$X = CN,\ k_H/k_X = 2.10$



6

$Y_\beta = OTs \quad Y_\alpha = H$ or

$Y_\beta = H \quad Y_\alpha = OTs$

Description and Results. The steroidal tosylates **6**, whose structures are indicated in Table I were synthesized. Rates of solvolysis were determined, and the results are given as k_H/k_X values in Table I. Values of k_X may be calculated from data in the footnotes of Table I. The key to the preparation of the 17-cyanohydrins proved to be prior introduction of the tosylate group, followed by the reaction of the 17-ketone group with liquid hydrogen cyanide for a prolonged time. Several C-17 steroid cyanohydrins which are analogous in structure to ours are reported to be mixtures, with one isomer predominating to the extent of 85–90%.[5] In a 1946 paper,[5c] the predominant isomer was said to be the β-hydroxy compound (formerly called α). Rereading the earlier papers did not lead us to the source of this assignment, although there is a hint[5c] that optical rotations may have been used as indicators of stereochemistry. Nevertheless, subsequent workers in the steroid field have accepted the β-hydroxy configuration of the predominant isomer. This isomer, somewhat surprisingly, is said[5c] to undergo acylation (possibly because the hydroxyl is pseudoequatorial) considerably more rapidly than the α-hydroxy