The chlorination of propiophenone; determination of pK_a value and of the course of the reaction

J. PETER GUTHRIE[1] AND JOHN COSSAR

Department of Chemistry, University of Western Ontario, London, Ont., Canada N6A 5B7

Received December 11, 1989[2]

J. PETER GUTHRIE and JOHN COSSAR. Can. J. Chem. **68**, 2060 (1990).

Chlorination of propiophenone in alkaline aqueous solution leads to formation of α-hydroxypropiophenone as the first detectable intermediate; this undergoes slower oxidation to aromatic acids without any accumulation of further intermediates. From the rates of the initial chlorination we have been able to determine the pK_a value as 17.56 ± 0.51.

Key words: propiophenone, chlorination, hydrolysis, rearrangement, pK_a.

J. PETER GUTHRIE et JOHN COSSAR. Can. J. Chem. **68**, 2060 (1990).

La chloration de la propiophénone en solution aqueuse alcaline conduit à la formation de l'α-hydroxypropiophénone en tant que premier intermédiaire décelable; ce composé s'oxyde lentement en acides aromatiques sans accumulation subséquente d'intermédiaires. La mesure des vitesses de chloration initiale nous a permis de déterminer un pK_a de 17,56 ± 0,51.

Mots clés : propiophénone, chloration, hydrolyse, transposition, pK_a.

[Traduit par la revue]

Introduction

We have developed a method for determining pK_a values of simple ketones by analysis of the kinetics of chlorination in alkaline solution (1, 2). This method has been applied to a series of ring-substituted acetophenones (3). We now wish to report its application to propiophenone. Propiophenone is known to undergo halogenation followed by cleavage to benzoic acid (4). This was believed to involve formation of α,α-dihalopropiophenone, followed by hydrolysis and oxidative cleavage (5). We now find that, at least under the conditions we use for kinetics, the actual reaction course is different, and that propiophenone undergoes one rapid chlorination, followed by rapid hydrolysis that competes with the second chlorination, and then slow further oxidation of the α-hydroxypropiophenone. Furthermore, the oxidation products include not just benzoic acid but mandelic acid, atrolactic acid, and phenylglyceric acid (6).

Results

In Table 1 are the results of our kinetics studies of propiophenone. This reaction at first appeared deceptively simple because the absorbance–time curves could be fitted to an integrated rate law, eq. [1], with a single exponential followed by a linear decrease in absorbance; see Fig. 1. We have not identified the process responsible for the slow decrease in absorbance at long times. If this were followed to completion we assume that it would become nonlinear, and probably exponential, but the time required would be inordinately long. For the length of time that we did follow the reaction, the slow final phase was satisfactorily linear, as shown by the behavior of the residuals plot. However closer examination of the data

$$[1] \quad \text{Absorbance} = a_1 + a_2 \exp(-a_3 t) + a_4 t$$

showed that there were consistent deviations of calculated from experimental absorbance values in the sense to be expected if there were a faster process with a small amplitude. The data gave a better fit to an integrated rate law with two exponential terms, eq. [2]; see Fig. 2. In Fig. 2 the quantity labeled log $(A - A_\infty)$ is corrected by subtracting subsequent terms in the rate law.

$$[2] \quad \text{Absorbance} = a_1 + a_2 \exp(-a_3 t) + a_4 \exp(-a_5 t) + a_6 t$$

Thus in terms of eq. [1] we plot log (Absorbance $- a_1 - a_4 t$), and in terms of eq. [2] we plot log (Absorbance $- a_1 - a_6 t$) or log (Absorbance $- a_1 - a_4 \exp(-a_5 t) - a_6 t$). The key indication that eq. [1] is inadequate and eq. [2] is satisfactory comes from examination of the residuals plots, of $A_{obs} - A_{calc}$, in Fig. 2. In Fig. 2a there is a clear pattern of deviations, first negative, then positive, then negative again, which are large relative to the noise level in the residuals plot; by contrast, in Fig. 2b the residuals curve shows no deviations from the zero line that are consistently greater than the noise level. Now that microcomputers provide convenient access to computational power and graphics display, use of residuals plots should be seen as an essential part of data analysis, to confirm that the fitting process truly accounts for all systematic variations in the data, leaving only random noise.

The observation of an integrated rate law with two exponentials implies the accumulation of an intermediate. Product isolation experiments at a time when most of the propiophenone had reacted but much of the intermediate had not been consumed gave a mixture, which was shown by nmr analysis and chromatographic isolation to have 2-hydroxy-1-phenyl-1-propanone, HPP,[3] as the major component and the only neutral material present besides residual propiophenone. HPP was identified by comparison with an authentic sample, and with spectroscopic data from the literature. The nmr spectrum of the isolated material showed no sign of 1-hydroxy-1-phenyl-2-propanone, HPA. When the reaction was followed by hplc analysis of samples quenched at suitable times it was found that propiophenone disappeared rapidly, with HPP as the only detectable neutral product. However, these experiments were done with ketone in excess, so that hypochlorite was totally consumed. There was a subsequent reaction of the HPP, which represents base-catalyzed isomerization to HPA.

The presence of HPP implies rapid hydrolysis of 2-chloro-1-phenyl-1-propanone, CPP. To confirm this we prepared a sample of CPP and demonstrated that it undergoes rapid hydroxide-catalyzed hydrolysis: see Table 2. The second-order rate

[1]Author to whom correspondence may be addressed.

[2]Revision received July 13, 1990.

[3]Abbreviations used: Prop, propiophenone; HPP, 2-hydroxy-1-phenyl-1-propanone; HPA, 1-hydroxy-1-phenyl-2-propanone; CPP, 2-chloro-1-phenyl-1-propanone.

TABLE 1. Kinetics of chlorination of propiophenone[a]

[Ketone] (10^4 M)	[OCl^-] (10^4 M)	[OH^-] (M)	a_1	a_2	a_3 (10^4 s^{-1})	a_4	a_5 (10^4 s^{-1})	a_6 (10^6 A s^{-1})	l	n	f
0.647	37.1	0.0489	1.181	0.029	9.89 (0.64)	0.143	2.13 (0.029)	−0.43 (0.009)	1	5.5	0.71
0.301	19.3	0.0490	1.250	−0.013	7.48 (2.46)	0.170	2.00 (0.028)	−0.46 (0.007)	2	5.4	0.86
0.155	9.39	0.0490	1.499	−0.053	5.57 (0.54)	0.264	1.51 (0.027)	−0.65 (0.007)	5	5.7	0.99
0.0752	4.54	0.0490	1.456	−0.054	4.76 (0.48)	0.252	1.062 (0.019)	−0.69 (0.005)	10	5.5	1.06
0.0744	4.58	0.0999	1.475	−0.050	7.40 (0.75)	0.244	1.64 (0.024)	−0.56 (0.006)	10	5.4	1.06
0.151	9.71	0.0997	1.571	−0.067	8.49 (1.32)	0.270	2.67 (0.076)	−0.60 (0.011)	5	5.6	0.99
0.289	19.6	0.0994	1.278	−0.015	13.55 (4.21)	0.162	3.27 (0.032)	−0.32 (0.005)	2	5.2	0.91
0.647	39.8	0.0986	1.292	0.020	3940. (19750)	0.148	4.16 (0.0002)	−0.30 (0.00)	1	5.4	0.95
0.642	39.3	0.196	1.277	0.010	18.74 (6.31)	0.141	7.18 (0.125)	−0.82 (0.022)	1	4.7	0.63
0.287	19.7	0.196	1.296	−0.026	23.27 (4.11)	0.160	6.45 (0.115)	−0.93 (0.022)	2	4.6	0.95
0.151	9.56	0.196	1.549	−0.055	18.86 (2.05)	0.252	4.52 (0.073)	−1.44 (0.017)	5	5.4	1.05
0.0742	4.83	0.196	1.579	−0.036	12.93 (4.96)	0.216	2.76 (0.048)	−1.25 (0.018)	10	4.9	1.03
0.0745	4.73	0.426	1.580	−0.071	24.05 (1.68)	0.224	7.35 (0.091)	−0.93 (0.023)	10	3.8	1.31
0.151	10.0	0.430	1.669	−0.066	39.54 (3.70)	0.223	10.88 (0.19)	−1.23 (0.050)	5	3.9	1.14
0.290	19.1	0.430	1.269	−0.051	40.87 (4.81)	0.171	15.28 (0.45)	−0.69 (0.048)	2	3.9	0.98
0.652	38.8	0.431	1.279	−0.002	7.11 (119.)	0.140	15.91 (0.40)	−0.82 (0.073)	1	4.0	
20.8	1.47	0.0196	0.0139	−1.791	6.949 (0.384) 0.491 (0.027)[d]	1.762	0.9082 (0.333)	[c]			
10.4	1.18	0.0196	0.0167	−3.214	3.993 (0.162) 0.453 (0.018)[d]	3.183	0.949 (0.0245)	[c]			
10.5	1.19	0.0099	0.1125	−2.163	2.903 (0.181) 0.329 (0.021)[d]	2.046	0.621 (0.0503)	[c]			
10.2	1.15	0.0384	0.0014	−4.956	6.089 (0.213) 0.687 (0.024)[d]	4.935	1.817 (0.0703)	[c]			

[a]In aqueous solution at 25°C, ionic strength 1.0 (KCl). Followed by absorbance measurements at 292 nm unless otherwise stated. Absorbance–time data were fitted to $y = a_1 + a_2 \exp(-a_3 t) + a_4 \exp(-a_5 t) + a_6 t$. n is the stoichiometry, calculated from eq. [3]. f is the fraction of CPP that undergoes hydrolysis to HPP, calculated from eq. [4].
[b]Not included in the least-squares fit to eq. [4] (Table 3).
[c]Followed by hplc. Peak integration – time data were fitted to $y = a_1 + a_2 \exp(-a_3 t) + a_4 \exp(-a_5 t)$.
[d]k_{II}[OCl], calculated from κ_ψ*[OCl]/[ketone], for comparison with uv kinetics.

constant for this hydrolysis is 1.45 ± 0.06 M^{-1} s^{-1}. This is similar to the rate constant observed for monochloroacetone, i.e., 1.19 M^{-1} s^{-1} (2). Clearly, hydrolysis of CPP is fast relative to subsequent reactions of hydroxypropiophenone. The actual chlorination is normally slower than enolate formation (7, 8), so that the overall kinetics are first order in [OCl^-] except at very high [OCl^-]. The rate constant for enolate formation is 0.026 M^{-1} s^{-1} (see below), which is almost 100 times slower than that for hydrolysis, and the overall chlorination reaction will be slower still at the hypochlorite concentrations used for kinetics.

Following the kinetics of propiophenone chlorination by uv spectroscopy at the absorbance maximum for hypochlorite was not completely satisfactory because the initial rapid reaction was accompanied by only a small change in absorbance, which changed from an increase to a decrease with changing reagent concentrations. Under conditions where the absorbance change was very small, the rate of the initial reaction could not be determined reliably at the λ_{max} of the hypochlorite. The initial reaction could be followed by hplc, where we could cleanly follow disappearance of propiophenone or appearance of HPP, the only observable intermediate under the conditions employed. However, it was only feasible to use this technique with low concentrations of hypochlorite and ketone in excess, in order to have amounts of products that could be accurately measured. If the hypochlorite concentrations were high, then the rates became too fast for sampling. These data are also found in Table 1.

The minimum mechanism for these kinetics is shown in Scheme 1. For the overall reaction described by Scheme 1 we can derive an equation for the absorbance as a function of time. We start with the differential equations, [3], where k_{13} is the steady-state rate constant for conversion of propiophenone into CPP, n is the number of moles of hypochlorite consumed per mole of propiophenone, and f is the fraction of CPP that is hydrolyzed to HPP rather than undergoing a second chlorination.

$$\begin{aligned} &d[\text{Prop}]/dt = -k_{13}[\text{Prop}] \\ [3]\quad &d[\text{HPP}]/dt = k_{13} f[\text{Prop}] - k_{45}[\text{HPP}] \\ &d[OCl^-]/dt = -k_{13}[\text{Prop}](1 + (1-f)(n-1)) \\ &\qquad\qquad - k_{45}[\text{HPP}](n-1) \end{aligned}$$

Integration, and substitution into the equation for the total absorbance, Absorbance = $\epsilon_{\text{Prop}}[\text{Prop}]l + \epsilon_{\text{HPP}}[\text{HPP}]l + \epsilon_{\text{OCl}}[\text{OCl}]l$, leads to eq. [4]:

$$\begin{aligned} [4]\quad &\text{Absorbance} = \epsilon_{\text{OCl}}\{[\text{OCl}]_0 - n[\text{Prop}]_0\}l \\ &+ [\text{Prop}]_0 l\{\epsilon_{\text{Prop}} - \epsilon_{\text{HPP}} k_{13} f/(k_{13} - k_{45}) \\ &\quad + \epsilon_{\text{OCl}}(n - k_{13} f(n-1)/(k_{13} - k_{45}))\} \exp(-k_{13} t) \\ &+ [\text{Prop}]_0 l\{\epsilon_{\text{HPP}} k_{13} f/(k_{13} - k_{45}) \\ &\qquad + \epsilon_{\text{OCl}} k_{13} f(n-1)/(k_{13} - k_{45})\} \exp(-k_{45} t) \\ &= \text{Absorbance}_0 + \alpha \exp(-k_{13} t) + \beta \exp(-k_{45} t) \end{aligned}$$

from which we can derive expressions for n and f:

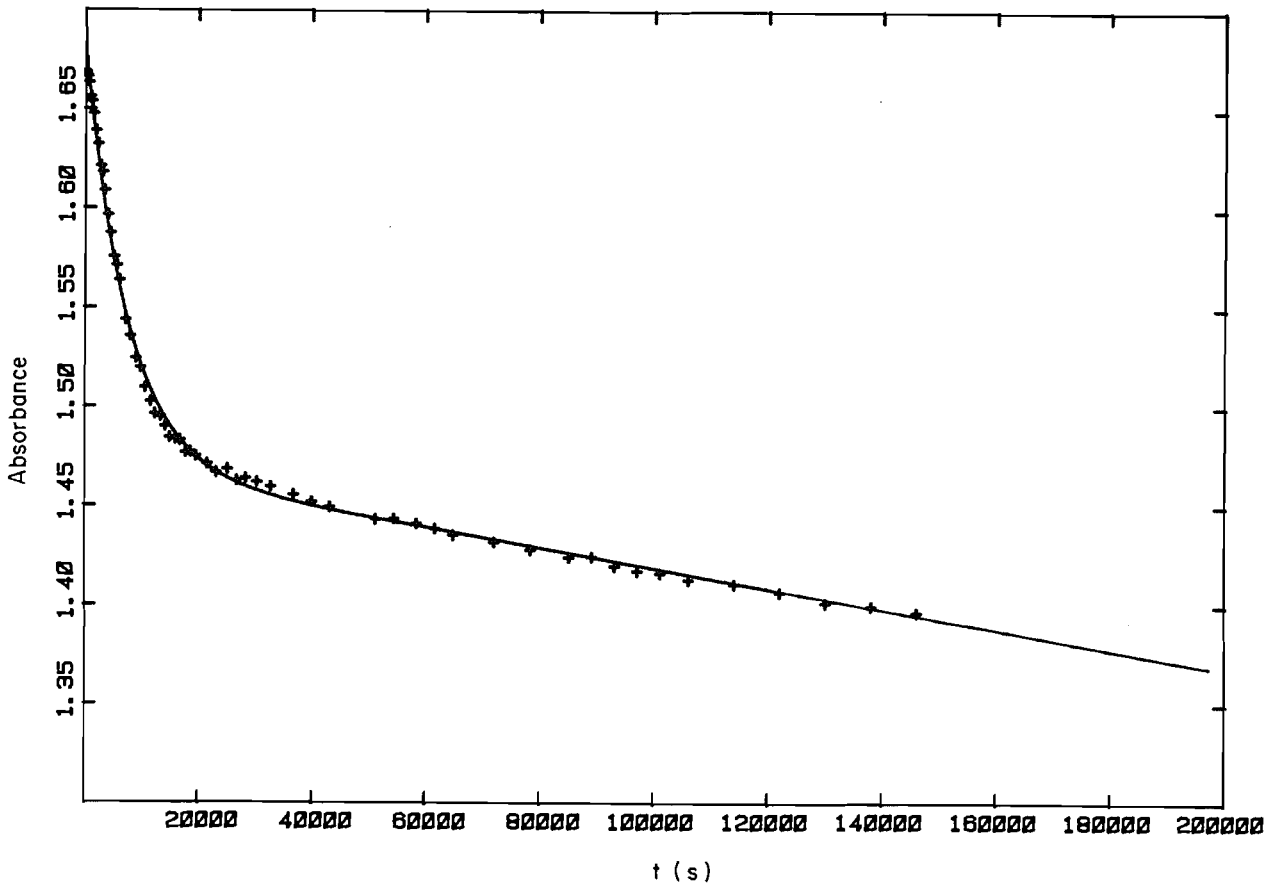


FIG. 1. Chlorination of propiophenone; absorbance–time curve for the reaction of 7.44×10^{-6} M propiophenone with 4.58×10^{-4} M hypochlorite in 0.0999 M hydroxide at ionic strength 1.0. The data were fitted by least squares to $A = a_1 + a_2 \exp(-a_3 t) + a_4 t$.

[5] $$n = \{(a + b)/([\text{Prop}]_0 l) - \epsilon_{\text{Prop}}\}/\epsilon_{\text{OCl}}$$

[6] $$f = b(k_{13} - k_{45})/(k_{13}[\text{Prop}]_0 l(\epsilon_{\text{HPP}} + (n - 1)\epsilon_{\text{OCl}}))$$

Values for n and f are included in Table 1.

For substituted acetophenones we found that the first chlorination step was rate determining under the usual conditions for chlorination kinetics (3), and the observed rates followed the rate law given in eq. [7]:

[7] $$v = k_{\text{obs}}[\text{Ketone}]$$
$$k_{\text{obs}} = \{k_{\text{II}}^0 + k_{\text{II}}^-[\text{OH}^-]\}[\text{OCl}^-]$$

If the same rate law applied for k_{13} of propiophenone, then in terms of Scheme 1, $k_{\text{II}}^0 = k_{12}k_{23}^0K_w/k_{21}K_a^{\text{HOCl}}$, and $k_{\text{II}}^- = k_{12}k_{23}^-/k_{21}$. For the initial phase of the kinetics, where the rate of chlorination of propiophenone is being followed, it was found that the pseudo-first-order rate constants for a set of experiments at fixed hydroxide concentration were not linearly dependent upon hypochlorite concentration, but showed a tendency to level off at high $[\text{OCl}^-]$. Thus for propiophenone enolate, halogenation and reprotonation are competitive. For this situation we may derive the following expression for the rate law:

[8] $$k_{\text{obs}} = k_{13} = \frac{k_{12}(k_{23}^0K_w/K_a^{\text{HOCl}} + k_{23}^-[\text{OH}^-])[\text{OCl}^-]}{k_{21} + (k_{23}^0K_w/([\text{OH}^-]K_a^{\text{HOCl}}) + k_{23}^-)[\text{OCl}^-]}$$

This may be transformed into a form convenient for fitting to the data:

[9] $$k_{\text{obs}} = k_{13} = (a_1 + a_2[\text{OH}^-])/(1/[\text{OCl}^-] + a_1/a_3[\text{OH}^-] + a_2/a_3)$$

where $a_1 = k_{\text{II}}^0$, $a_2 = k_{\text{II}}^-$, and $a_3 = k_{12}$. The data from Table 1 were fitted to eq. [7]. A few runs, where the uncertainties in the rate constants for the initial phase were very large, were not included in these calculations. To include the hplc data, we calculated initial "pseudo-first-order rate constants" $= k_{\text{obs}}[\text{OCl}^-]_0/[\text{Prop}]_0$; these experiments were actually done with ketone in excess. We can use the observed pseudo-first-order rate constants, defined by $v = k_{\text{obs}}[\text{OCl}]$, because the major reaction path is conversion of propiophenone to hydroxypropiophenone, which consumes only one OCl^-. In general one must remember that the observed rate constant includes the stoichiometry number for ketone in excess conditions, but not for hypochlorite in excess conditions (1). The above discussion assumes that $[\text{OCl}^-]$ is essentially constant throughout a particular kinetics experiment. Examination of the concentrations and stoichiometries in Table 1 shows that in each case, for reactions with OCl^- in excess, less than 10% of the OCl^- was consumed. We also fitted the second-order rate constants for the hplc experiments to eq. [7]. For the determination of the pK_a it was more satisfactory to use the directly measured rate constants at low $[\text{OCl}^-]$ for low $[\text{OH}^-]$ (these are data from hplc experiments) and extrapolated values at high $[\text{OH}^-]$ (these are data from uv kinetics) to give the final fit to eq. [7]. The required extrapolation was carried out by fitting data at constant $[\text{OH}^-]$ to eq. [10], and calculating the apparent second-order rate constant from the parameters so obtained.

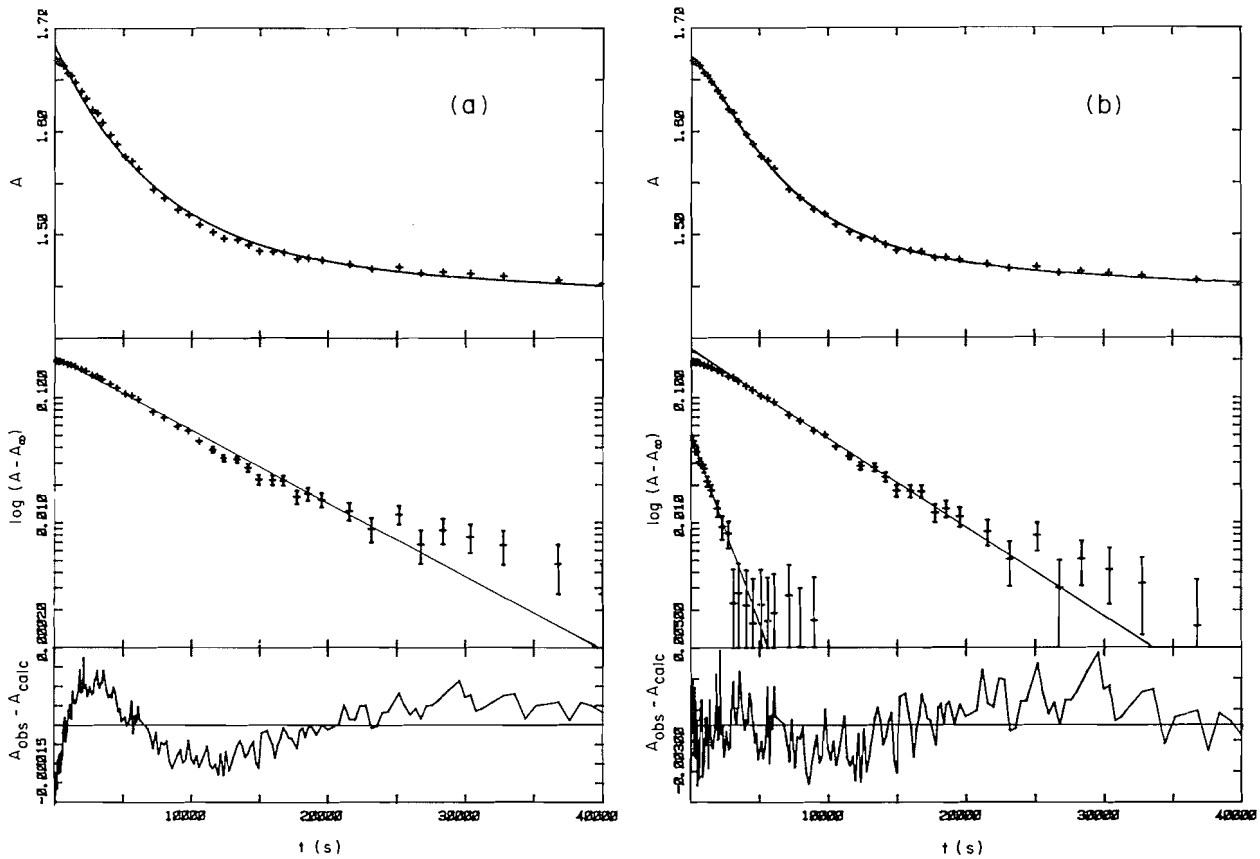
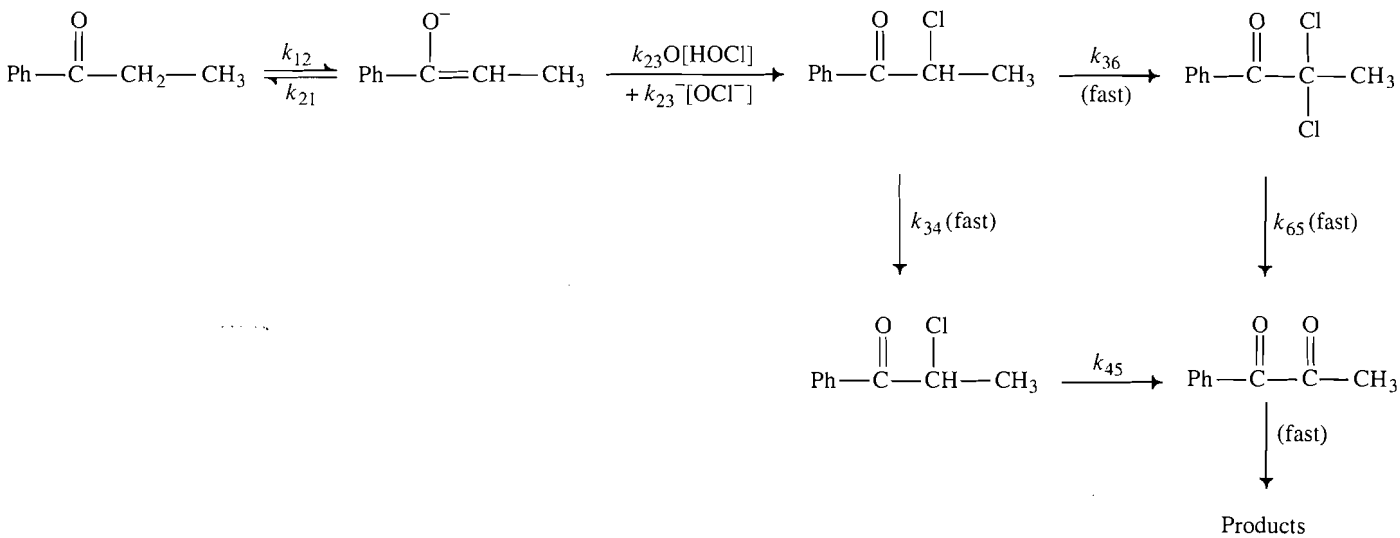


FIG. 2. Chlorination of propiophenone; absorbance–time curve for the reaction of 7.44×10^{-6} M propiophenone with 4.58×10^{-4} M hypochlorite in 0.0999 M hydroxide at ionic strength 1.0. Only data for the first 40 000 s of reaction are shown. These figures show the corresponding semilog and residuals plots as well. (a) The data were fitted to $A = a_1 + a_2 \exp(-a_3 t) + a_4 t$. (b) The data were fitted by least squares to $A = a_1 + a_2 \exp(-a_3 t) + a_4 \exp(-a_5 t) + a_6 t$. The semilog plots show $\log(A - A_0)$ corrected for subsequent terms in the rate law as described in the text.



SCHEME 1

[10] $k_{obs} = b_1/(1 + b_2/[OCl^-])$

In terms of the parameters of eq. [4], $b_1 = a_3[OH^-]$, and $b_2 = a_3/(a_1 + a_3[OH^-])$. Then $b_1/b_2 = a_1 + a_2[OH^-]$. The fit to eq. [7] was largely determined by the data from hplc kinetics, but the precision of the derived parameters was improved when the extrapolated values were included. The parameters from the two sets of calculations are in good agreement. The parameters determined by least squares, and the pK_a value based on a_1, are found in Table 3. Figure 3b shows the experimental points and the surface fitted to them using eq. [7].

The kinetics of the second phase of propiophenone chlorination (Table 1) showed a clear dependence on hydroxide concentration, and seemed to depend on hypochlorite concentration as

TABLE 2. Kinetics of further reactions of α-chloro and α-hydroxy-ketones[a]

(a) Hydrolysis of α-chloropropiophenone[b]

[Ketone] (10^4 M)	$[OH^-]_{in}$ (10^4 M)	$[OH^-]_{fin}$ (10^4 M)	a_1	a_2	a_3 (10^3 s^{-1})	$a_3/[OH^-]$ (M^{-1} s^{-1})
0.0872	4.6	3.3	1.013	−0.154	0.629 (0.003)	1.37
0.0872	16.3	15.8	1.005	−0.148	2.32 (0.007)	1.43
0.0872	30.9	30.1	1.024	−0.146	4.46 (0.030)	1.44
0.143	69.2	68.3	1.652	−0.220	10.2 (0.078)	1.48
0.140	115.7	112.4	0.810[c]	−0.096	17.8 (0.12)	1.54
0.109	190.	189.	0.630[c]	−0.068	27.3 (0.24)	1.44
					avg.	1.45 (0.06)

(b) Reaction of α-hydroxypropiophenone with hypochlorite[d]

[Ketone] (10^4 M)	$[OCl^-]$ (10^4 M)	$[OH^-]$ (M)	a_1	a_2	a_3 (10^3 s^{-1})	$a_3/[OH^-]$ (M^{-1} s^{-1})	n
1.7	34.1	0.416	1.043[e]	0.289	1.60 (0.006)	0.00385	2.4
1.68	35.3	0.423	0.004[f]	2.046	1.31 (0.089)	0.0031	
0.227	4.65	0.437	1.435	0.392	1.48 (0.012)	0.0034	2.5
0.227	4.67	0.101	1.380	0.454	0.446 (0.0016)	0.00442	3.2
0.237	4.69	0.0500	1.328	0.523	0.205 (0.0008)	0.00411	3.8
1.72	35.1	0.0479	1.004	0.389	0.207 (0.0007)	0.00432	4.0
					avg.	0.00387 (0.00052)	

[a]All in aqueous solution at 25°C. Data are fitted by least squares to: Absorbance = $a_1 + a_2 \exp(-a_3 t) + a_4 t$. $k_{II} = a_3/[OH^-]$.
[b]Reactions carried out in 10-cm cells unless otherwise noted, and followed by measuring absorbance at 246 nm.
[c]5-cm cells were used.
[d]Reactions were carried out in 10-cm cells and followed by measuring absorbance at 292 nm, unless otherwise noted. n is the stoichiometry, calculated from $n = (a_2/l[HPP]_0 - \epsilon_{HPP})/\epsilon_{OCl}$.
[e]1-cm cells were used.
[f]Followed by hplc.

TABLE 3. Least-squares parameters and derived pK_a values for ketones[a]

(a) Results of least-squares fitting of kinetics of chlorination

Reaction	Equation	a_1	a_2	a_3
First phase (all data)	[7]	0.152 (0.038)	13.5 (1.65)	0.0259 (0.0042)
First phase[b]	[5]	0.140 (0.034)	11.85 (1.52)	
First phase[c]	[5]	0.150 (0.037)	11.4 (1.64)	
Second phase (HPP data)	[11]	0.00387 (0.00052)		

(b) pK_a values derived from kinetics

Compound	k_{II}^0	k_{II}^-	pK_a[d]	log k_2^-
PhCOEt	0.140 ± 0.034	11.9 ± 1.5	17.59 ± 0.51	4.67 ± 0.51

[a]All in aqueous solution at 25°C.
[b]Data at all $[OH^-]$, including values extrapolated to low $[OCl^-]$.
[c]Data at low $[OH^-]$ and low $[OCl^-]$ only.
[d]Calculated using log $k_{23}^0 = 9.23$ (1) and $pK_a^{HOCl} = 7.53$ (25).

well. However, kinetics starting with HPP (Table 2) clearly show no dependence on hypochlorite concentration. These kinetics, based on simple single exponential behavior, give inherently more reliable rate constants. The best description of the kinetics appears to be eq. [11], with $k_{OH} = 3.87 \times 10^{-3}$ M^{-1} s^{-1}. Figure 3b shows the experimental points and the surface so calculated.

$$[11] \quad k_{obs} = k_{OH}[OH^-]$$

For propiophenone the stoichiometry of the halogenation was calculated using eq. [3]; these values are given in Table 1. The total consumption of halogenating agent over the course of a reaction was greater than 3 hypochlorites per propiophenone, and appeared to approach a limit of 6. A value as high as 6 is intelligible in terms of the reactions shown in Scheme 2. The numbers in square brackets under the final products in Scheme 2 represent the number of equivalents of hypochlorite consumed to form that product.

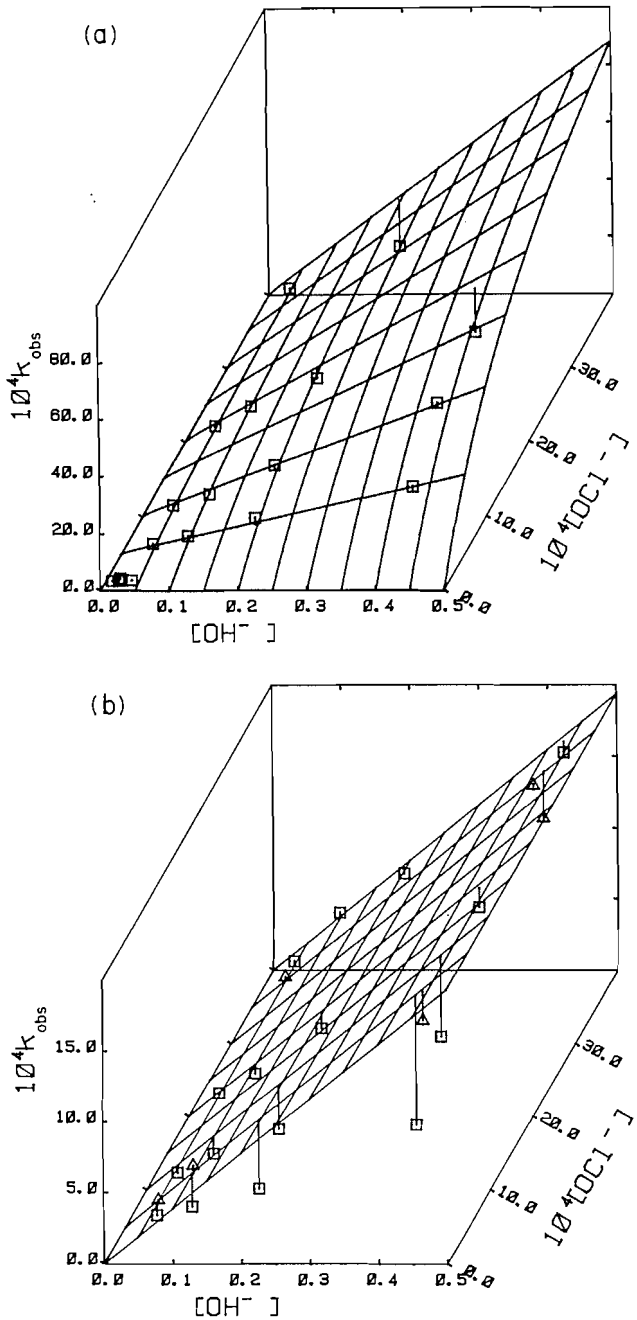


FIG. 3. Chlorination of propiophenone. (a) Initial phase; k_{obs} as a function of $[OCl^-]$ and $[OH^-]$. The surface is calculated using eq. [7], with parameters determined by least-squares fitting. (b) Second phase; k_{obs} as a function of $[OCl^-]$ and $[OH^-]$. The surface is calculated using eq. [9], with an average second-order rate constant from Table 2.

The stoichiometry number shows little dependence on $[OCl^-]$ at fixed $[OH^-]$, but shows a definite decline as $[OH^-]$ increases. The data do not really define a curve, but the high $[OH^-]$ limit might be 3. Figure 5 shows the average stoichiometry numbers for each $[OH^-]$ as a function of $[OH^-]$, with a line fitted to the data on the assumption that the limiting values are $n = 6$ and $n = 3$, eq. [12]. These limiting values are plausible in terms

$$[12] \quad n = 3 + 3/(1 + 4.08[OH^-])$$

of predominant formation of phenylglycerate at high $[OH^-]$ (6) and of benzoate at low $[OH^-]$. Production of benzoate suggests a crucial partitioning either at 3-chloro-1-phenyl-1,2-propanedione or 3-hydroxy-1-phenyl-1,2-propanedione, with high $[OH^-]$ favoring hydrolysis of the chloro compound and (or) rearrangement of the hydroxy compound, and low $[OH^-]$ favoring chlorination. Scheme 2 is complex, and much remains to be determined. At that, this scheme may be too simple, because a reasonable mechanism can be written involving rearrangement of chloroketones rather than hydroxyketones; this would give the same products. Evidence in hand suggests that benzoate, mandelate, atrolactate, and 2-phenylglycerate are all products of the reaction; further investigations of the later stages of the chlorination of propiophenone are underway, and will be reported in due course.[4]

The fraction of CPP that undergoes hydrolysis to HPP can be calculated using eq. [4], and the values are given in Table 1. The precision of these values is not high, but there is a trend for f to increase at low $[OCl^-]$ and decrease at high $[OCl^-]$, and there is no apparent relationship to $[OH^-]$. This suggests that the rate law for the second chlorination leading to 2,2-dichloro-1-phenyl-2-propanone is $v = k_{36}[OH^-][OCl^-][CPP]$. If so, then

$$[13] \quad 1/f = 1 + k_{36}[OCl^-]/k_{34}$$

A very approximate value of $k_{36} = 120\ M^{-2}\ s^{-1}$ can be extracted from the data, but this is only an order of magnitude estimate at this time.

If we use the measured extinction coefficients, k_{13} values calculated from eq. [9], k_{45} values calculated from eq. [11], n values calculated from eq. [12], and f values calculated from eq. [13], we can approximately reproduce the observed values of the preexponential factors α and β. In particular, we reproduce the alternation in sign of α with changing concentrations of hypochlorite. Since α and β are frequently small differences in large numbers, considerable uncertainty is to be expected in the calculated values.

The hplc kinetics also showed double exponential behavior, with initial formation of HPP being followed by conversion of most of it into another, very similar, compound. This second product was shown to be 1-hydroxy-1-phenyl-2-propanone, HPA. The hplc kinetics were carried out with ketone in excess, so the second phase of the reaction represents a process not involving hypochlorite, and occurring after the hypochlorite had been consumed. The wavelength used for hplc analysis was chosen for efficient detection of HPP, and was not efficient for HPA, so the precision of the analytical data for HPA formation in these experiments was low. The rate constants for disappearance of HPP in the hplc kinetics, expressed as second-order rate constants $k_{obs}/[OH^-]$, are similar to the analogous second-order rate constants calculated for the second phase of the uv kinetics starting with propiophenone, and to the second-order rate constants calculated from uv kinetics starting with HPP. This demonstrates that the rate-determining step for both chlorination and isomerization is the same, namely proton abstraction by OH^-.

That the equilibrium constant for isomerization favored HPA, rather than HPP with the carbonyl conjugated with the benzene ring, surprised us but has been confirmed in other work to be reported later.[4]

We have prepared 2-hydroxy-1-phenyl-1-propanone and studied its kinetics of chlorination. The observed rates match the rates of the second phase of propiophenone chlorination, although less precisely than one would wish: see the Discussion.

The initial product of chlorination of 1-phenyl-2-hydroxy-1-propanone is expected to be 2-chloro-1-phenyl-2-hydroxy-1-propanone. This would be expected to have an extremely

[4] J. P. Guthrie and J. Cossar, work in progress.

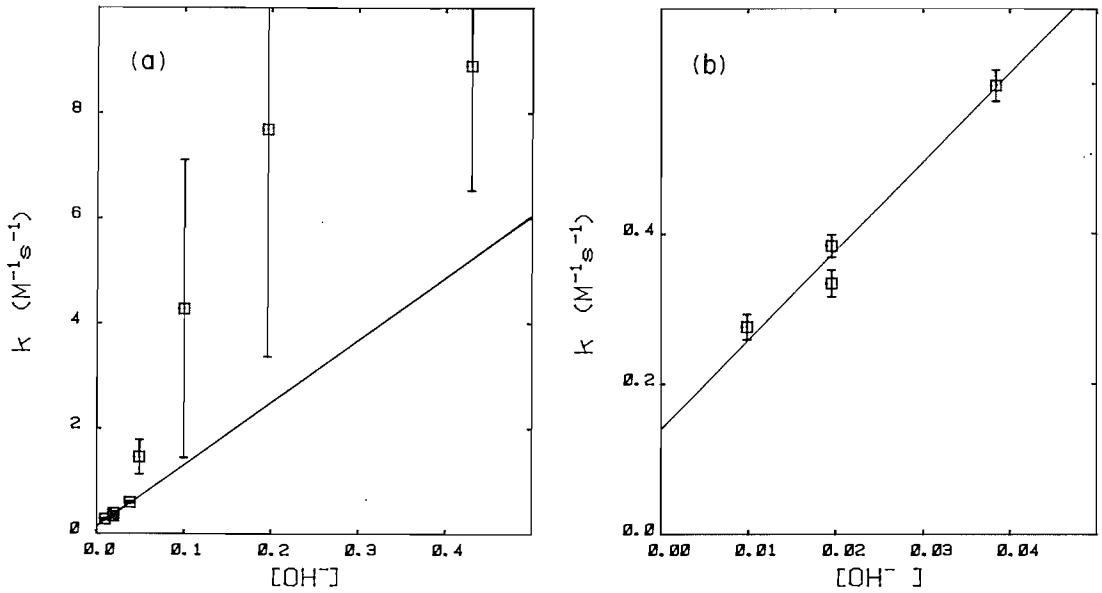


FIG. 4. Chlorination of propiophenone; k_2 at low concentrations of [OCl^-] as a function of [OH^-]. The line is calculated using parameters determined by least-squares fitting. (a) All data, including extrapolated values from experiments at high [OH^-]. (b) Only data from experiments at low [OH^-], followed by hplc.

short lifetime before losing chloride ion to give 1-phenyl-1,2-propanedione.

Discussion

For propiophenone, the kinetics of chlorination were not simple first order. The absorbance–time curves could only be described by using two exponential terms. This contrasts with the behavior seen for acetone or acetophenone where the first chlorination step is clearly rate limiting under similar conditions. This complexity arises because of slower reaction of the hydroxyketone formed by hydrolysis of the monochlorinated starting material. The shift in behavior from acetophenone to propiophenone was unexpected.

The second chlorination of propiophenone does not appear to compete with hydrolysis at very low hypochlorite concentrations, as in the kinetics followed by hplc, but can compete at the highest hypochlorite concentrations used for uv kinetics, as shown by the f values deduced from the integrated rate law. It is surprising that the halogenation rate constant is as slow as it seems to be, because the corresponding rate constant for propiophenone is ca. $4 \times 10^4\ M^{-1}\ s^{-1}$. Introducing a chlorine has caused a dramatic decrease in the rate of chlorination. This is likely to be partially a steric effect because the rate constant for the reaction of isobutyrophenone enolate with hypochlorite is ca. $1 \times 10^4\ M^{-1}\ s^{-1}$. Since methyl and chloro are roughly the same size, there could be a steric explanation for a 4-fold decrease in rate constant, but this leaves a 90-fold additional decrease to be explained for CPP. The equilibrium constant for the second halogenation step is likely to be less favorable than for the first (1), and thus, with a smaller thermodynamic driving force, the rate constant is less.

The rate constants for the reaction of hypochlorite with α-hydroxypropiophenone should match, whether they are measured starting with α-hydroxypropiophenone or with propiophenone. Although the observed rate constants are close, there are differences amounting to a factor of two at low [OCl^-]. We have established that hydrolysis of chloropropiophenone is rapid with respect to the observed reaction. It is likely that there is a partitioning of α-chloropropiophenone between

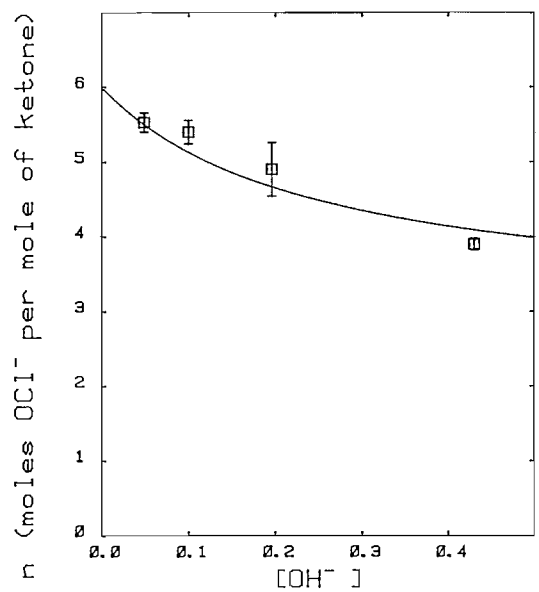
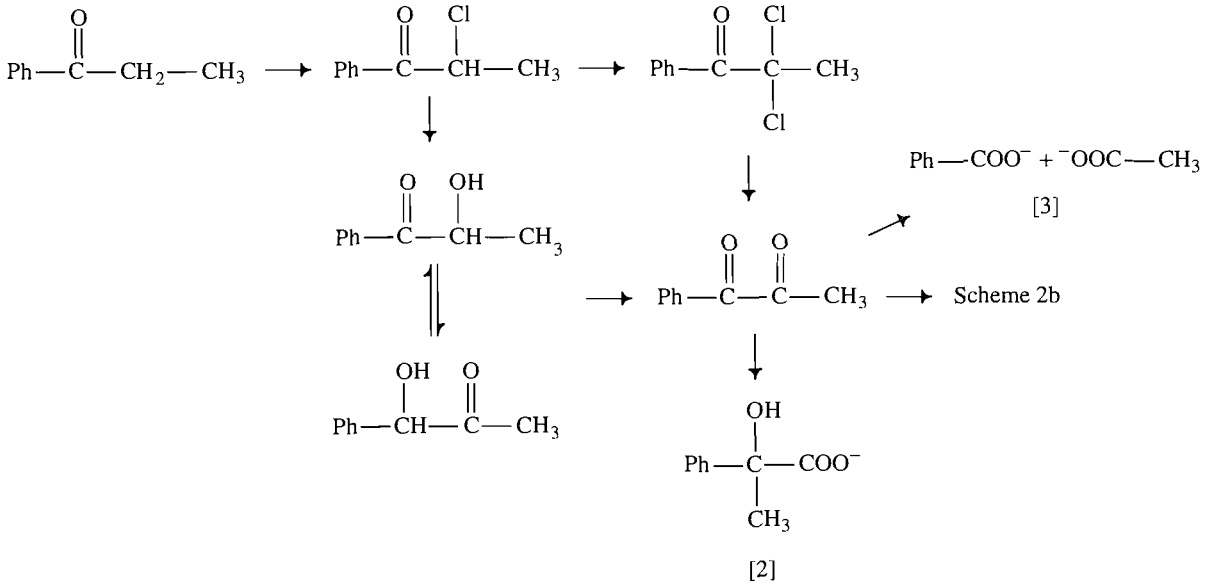


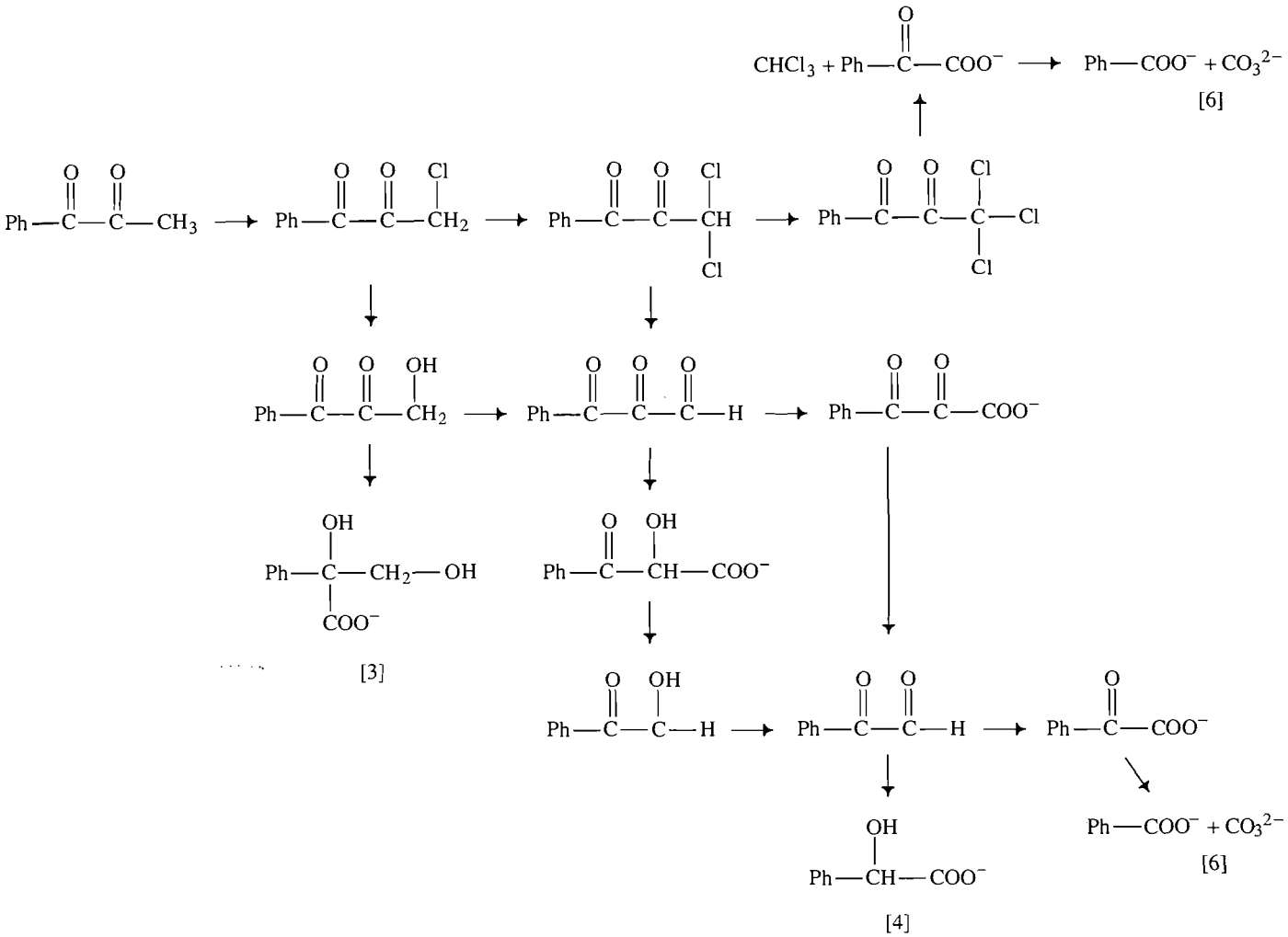
FIG. 5. Chlorination of propiophenone: overall stoichiometry, n, (moles of OCl^- per mole of propiophenone) as a function of [OH^-]. Values for different [OCl^-] and the same [OH^-] were very similar and have been averaged. The line is calculated assuming limiting values of $n = 3$ and $n = 6$ for $n = 3 + 3/(1 + 4.08[OH^-])$.

chlorination and hydrolysis, but it is very probable, by analogy with simpler ketones (2), that hydrolysis of the α,α-dichloropropiophenone is also rapid, and we know[5] that 1-phenyl-1,2-propanedione reacts rapidly. Thus the only intermediate that might reasonably be expected to accumulate is α-hydroxypropiophenone, and hplc experiments have confirmed that this is the only detectable intermediate for the conditions used. Nonetheless, the direct kinetics of α-hydroxypropiophenone chlorination give rate constants that are independent of [OCl^-], while the second phase of the kinetics of propiophenone chlori-

[5] J. P. Guthrie and J. Cossar, unpublished observations.



SCHEME 2a



SCHEME 2b

nation gave rate constants that seemed to show a dependence of $[OCl^-]$ at low $[OCl^-]$ although the rates become independent of $[OCl^-]$ at high $[OCl^-]$, and these limiting values matched those found in experiments starting with HPP.

This discrepancy is disturbing, but we suspect that it arises from the complexity of the reaction being followed when one starts with propiophenone. The rate constants for the two phases of the reaction that can be detected differ by factors of 2.6–4.7, which means that only the last small part of the absorbance change is solely determined by the hydroxypropiophenone

reaction, and the parameters determined by the least-squares procedure are highly correlated. Thus we conclude that the uv kinetics starting with propiophenone are of little use in quantitative determination of the kinetics of either the initial or the later reactions, although they are useful in qualitatively defining the process.

For propiophenone, the hydroxyketone accumulated as an intermediate and was the only detectable intermediate in the reaction. The initial reaction is expected to be chlorination to give α-chloropropiophenone; we have shown that hydroxide-catalyzed hydrolysis of the chloroketone is rapid. This hydrolysis would be expected to be slow by the classical S_N2 mechanism, because it takes place at a secondary center (9). It would be expected to be slow by the classical S_N1 solvolysis mechanism because reaction occurs next to a carbonyl group. Although S_N1 reactions at tertiary centers next to a carbonyl are known, they occur at rates similar to those at the analogous secondary centers with the acyl function replaced by hydrogen (10). In any case the reaction rate is first order in hydroxide, so that it cannot be solvolysis. A plausible mechanism is addition of hydroxide, followed by intramolecular nucleophilic displacement.

The alkaline hydrolysis of α-chloropropiophenone has been observed before (11), but under the conditions used (50% aqueous ethanol) the solvolysis was slower, and isomerization of α-hydroxypropiophenone to 1-phenyl-1-hydroxy-2-propanone occurred at very similar rates. Our findings are different in that we observed no isomerization, but the reaction is faster in pure water, and consequently can be carried out at a lower temperature (25°C rather than 60°C).

The rates of deprotonation for Me-CO-CH_3, 0.173 M^{-1} s^{-1} (12), Me-CO-CH_2-Me, 0.038 M^{-1} s^{-1} (13, 14), and Me-CO-$CHMe_2$, 0.0026 M^{-1} s^{-1} (13, 14), or Ph-CO-CH_3, 0.244 M^{-1} s^{-1} (15), Ph-CO-CH_2-Me, 0.0259 M^{-1} s^{-1} (this work), and Ph-CO-$CHMe_2$, 0.00243 M^{-1} s^{-1} (16), 0.0031 M^{-1} s^{-1} (17) show a similar progressive decrease with increasing level of substitution. The relative rates are 1:0.22:0.015 and 1:0.11:0.010 respectively. Propiophenone, pK_a 17.56, is more acidic than acetophenone, pK_a 18.24 (18), 18.4 (3), and isobutyrophenone, pK_a 18.18 (17), 18.26 (16), is very similar to acetophenone. The difference between propiophenone and acetophenone is barely outside experimental error. If it is real, it suggests that there are opposing effects of methyl substitution upon ketone acidity. This seems plausible enough, because methyl groups would stabilize the C=C of the enol or enolate, but would also introduce a destabilizing *cis* interaction with either the O^- or phenyl. There could be interference with solvation of the O^-, and there might be an electronic effect whereby electron release by methyl is acid weakening. With this many effects it is easier to rationalize than to predict. Bordwell *et al.* found pK_a values, in dimethyl sulfoxide as solvent, of 24.7, 24.4, and 26.3 for acetophenone, propiophenone, and isobutyrophenone, respectively (19).

We have been able to determine a pK_a value for propiophenone by analysis of the kinetics of chlorination. The chlorination reactions followed paths that were unexpected because of the remarkably rapid alkaline hydrolysis of the initial chloroketone product. The behavior of propiophenone was further complicated because of unexpectedly slow chlorination of HPP, the first observable intermediate in the reaction. Chlorination of even such a simple substrate as propiophenone is clearly a very complicated reaction, and further investigation will be needed to unravel all of the complexities.

Experimental

Materials

Sodium hydroxide and potassium chloride were reagent grade, used without further purification. Sodium hypochlorite solutions were prepared by bubbling chlorine into aqueous sodium hydroxide; the hypochlorite concentration of the resulting solution was determined either by the absorbance at 292 nm, using $\epsilon_{292} = 352$, or by titration (2). The sodium hydroxide concentration of kinetics solutions was determined by titration (2). All extinction coefficients, ϵ, are in units of M^{-1} cm^{-1}.

Propiophenone, Aldrich "99%", was purified by distillation; bp 107–109°C (20 Torr; 1 Torr = 133.3 Pa); mp 17–18.5°C (lit. (20) mp 18.6°C); uv spectrum in water: λ_{max} 244 (ϵ_{max} 12 000); $\epsilon_{292} = 800$.

2-Chloro-1-phenyl-1-propanone

Propiophenone (13.4 g, 0.1 mol), in diethyl ether (300 mL), was placed in a round-bottomed flask fitted with a reflux condenser and cooled in a Dry Ice – acetone bath while chlorine gas (5.7 g, 0.08 mol) was bubbled in. Cooling was continued with an ice–water bath while HCl gas was fed in slowly for 15 min until the reaction started and the mixture began to reflux. The reaction was nearly complete after 10 min, as judged by the disappearance of color. After 20 min further standing with cooling by the ice–water bath, the solution was washed into a separatory funnel using petroleum ether (bp 60–80°C) (200 mL) and washed once with water (250 mL), once with 1 M $KHCO_3$ (250 mL), and once with 1 M KCl (250 mL). The organic layer was dried with Na_2SO_4 and evaporated to yield a yellow liquid (15.5 g). ^1H nuclear magnetic resonance indicated that the product was 40% propiophenone and 60% monochloropropiophenone. Fractional distillation gave pure material in the final fraction: bp 130–131°C (20 Torr) (lit. (21) bp 126.5–127°C (18 Torr)); uv (in 1 M KCl): λ_{max} 252 nm (ϵ_{max} 11 000 ± 300), $\epsilon_{246} = 10\,000$, $\epsilon_{292} = 1600$; ^1H nmr (200 MHz, $CDCl_3$) δ: 1.74 (3H, d, J = 7 Hz, CH_3-), 5.26 (1H, q, J = 7 Hz, CH_3-CHCl-), 7.42–7.46 (3H, m) and 7.96–8.06 (2H, m, C_6H_5-CO).

2-Hydroxy-1-phenyl-1-propanone

2-Chloro-1-phenyl-1-propanone (1.5 g, 8.9 mmol) was dissolved in methanol (60 mL) and added to 1000 mL of 0.011 M NaOH and stirred vigorously for 10 min at room temperature (23°C). The base was then neutralized with 4 M H_3PO_4 (3 mL) to approximately pH 7. The neutral solution was extracted with $CHCl_3$ (200 mL, 100 mL, 100 mL) and evaporated to yield 1.3 g of a viscous liquid. Thin-layer chromatography (tlc) showed about 80% conversion to the ketol. The mixture was chromatographed on a column of silica (40 g) and eluted with 10% EtOAc in petroleum ether. The second uv-active component eluted was almost pure ketol (1.056 g). This was crystallized from Et_2O at −80°C, filtered in the cold, washed with cold pentane, and dried in vacuum at 0°C, to give 0.784 g (5.22 mmol, 59%) of the ketol, mp 18–19°C; uv (in 1 M aqueous KCl, average of 3 experiments): λ_{max} 246.5 (ϵ_{max} 11 400 ± 100), ϵ_{292} 850; ^1H nmr (200 MHz, $CDCl_3$, TMS) δ: 1.46 (3H, d, J = 7 Hz, CH_3-CH(OH)-), 3.82 (1H, d, J = 6 Hz, HO-), 5.17 (1H, quintet, J = 7 Hz, CH_3-CH(OH)-), 7.45–7.68 (3H, m, aromatic H, *m* and *p*), 7.91–7.97 (2H, m, aromatic H, *o*), 2.09 (0.04 H, s, CH_3- of 1-hydroxy-1-phenyl-2-propanone).

1-Hydroxy-1-phenyl-2-propanone

1-Phenyl-1,2-propanedione-2-oxime (Aldrich, 99%) (2.0 g, 12 mmol) was dissolved in ethanol (15 mL) and added to a solution of KBH_4 (1.0 g, 20 mmol) in 75% ethanol/25% water (20 mL). The solution was heated to 50°C for 3 min; an initially formed yellow color disappeared by this time. The solution was stirred at room temperature for 2 h, and then concentrated to 10 mL, added to 1 M aqueous Na_2CO_3 (30 mL) and extracted with ether (3 × 50 mL). The extracts were dried (Na_2SO_4) and evaporated, yielding 2.1 g of a white solid. Crystallization from 50% ethanol – water (40 mL) gave 1.0 g pure 1-hydroxy-1-phenyl-2-propanone oxime, mp 112–113°C (lit. (22) mp 112°C). A second crop from 35% ethanol gave 0.4 g, mp 111–112°C; ^1H nmr (60 MHz, in 1:1 CD_3OD:$CDCl_3$) δ: 1.9 (3H, s), 4.3 (2H, br), 5.3 (1H, s), 7.3–7.4 (5H, m). 1-Hydroxy-1-phenyl-2-propanone oxime (0.8 g, 4.8 mmol) was dissolved in 90% levulinic acid/10% water (15 mL) and let stand at

room temperature for 16 h. The solution was added to pH 7 phosphate buffer, 0.5 M in phosphate (250 mL), and extracted with $CHCl_3$ (3 × 120 mL). The extracts were dried (Na_2SO_4) and evaporated, yielding 0.9 g of oily liquid containing about 10–20% levulinic acid. Chromatography on silica (50 g), eluting with a gradient of 0–20% EtOAc in petroleum ether, gave 445 mg of material that was 80–90% pure by ^1H nmr analysis. This material was given a bulb-to-bulb distillation (50–70°C at 0.1 Torr) and then crystallized at low temperature with 2:1 ether/pentane as solvent. In this way 260 g of material, mp 9.5–11°C, was obtained (lit. (23) bp 66°C at 0.2 Torr); uv (1 M KCl) λ_{max} 258 nm (ϵ_{max} 410), ϵ_{292} 235; ^1H nmr analysis showed less than 3% of HPP; ^1H nmr (200 MHz, $CDCl_3$) δ: 2.01 (3H, s, CH_3-CO), 4.58 (1H, d, J = 4 Hz, OH), 5.06 (1H, d, J = 3 Hz, CH), 7.27–7.33 (5H, m, C_6H_5).

Methods

Thin-layer chromatography was carried out using Analtech 250-μm Silica Gel GF plates or Macherey–Nagel Polygram SIL G/UV precoated plastic sheets (0.25 mm). Column chromatography was carried out using Terochem silica gel, no. 1918.

The hplc analyses were carried out using C18 reverse phase columns (Waters Radial Pak), with mixtures of aqueous buffers and methanol as eluting solvent, and uv detection.

Least-squares calculations were carried out using FORTRAN programs written for the purpose; nonlinear least squares and the Marquardt algorithm (24) were used for other than straight line correlations.

Kinetics procedures

All reactions were studied in aqueous solution at 25°C and ionic strength 1.0 M (KCl) using apparatus and procedures previously described (2). Reactions were initiated by injecting (Hamilton syringe) a known amount of a stock solution of the ketone into thermally equilibrated hydroxide/hypochlorite solution in a quartz uv cell.

Hydrolysis of chloropropiophenone

A stock solution of α-chloropropiophenone in methanol was kept in a refrigerator between uses; the uv spectrum did not change, indicating that there was no deterioration. Freshly prepared hydroxide solutions, ionic strength 1 M with KCl, were titrated immediately before use and immediately after the runs, with 0.05 M HCl standardized against tris base. Kinetics were initiated by injecting a suitable amount of stock solution of α-chloropropiophenone into hydroxide solution previously thermostatted in 5- or 10-cm quartz cells; reaction was followed at 246 nm. The kinetics showed a rapid increase in absorbance followed by a slower (300 times slower) decrease in absorbance. The second phase is attributed to equilibration with 1-hydroxy-1-phenyl-2-propanone; further discussion of this behavior will be deferred to a subsequent paper.[4] Data for 20 half-lives of the initial reaction were fitted to a single exponential plus linear tail form of the integrated rate law, leading to the rate constants shown in Table 2.

Chlorination of propiophenone and hydroxypropiophenone

Reactions monitored by uv absorbance were carried out as described above. Reactions monitored by hplc were carried out in a thermostatted flask and samples were taken and injected at suitable intervals using an autosampler. In some cases 1.0-mL samples were taken manually and quenched ($NaHSO_3$ and H_3PO_4) for later analysis. The peaks for HPP and HPA were assigned by comparison with those for authentic samples prepared as described above.

Product studies

Propiophenone (103 mg, 0.766 mmol) was added to 2 L of a solution 0.040 M in NaOH and 0.0050 M in NaOCl. After 40 min (4 half-lives for the first phase of reaction and less than 1 half-life for the second phase) 1 M $NaHSO_3$ solution (10 mL) was added to stop the reaction. Extraction of the alkaline solution with diethyl ether (3 × 300 mL), drying, and evaporation gave 45.8 mg; tlc and nmr analysis showed that the major component was 2-hydroxy-1-phenyl-1-propanone with some propiophenone present. Acidification of the aqueous solution using concentrated HCl (9 mL), followed by extraction with diethyl ether (3 × 300 mL), drying, and evaporation gave 64 mg; tlc identified benzoic acid as a major component, although two other spots were seen. The crude material extracted from the alkaline product solution was purified by column chromatography on silica gel using 1:1 $CCl_4/CHCl_3$ as eluant with a linear gradient from 0 to 5% ethanol. Kugelrohr distillation at 70°C, 0.2 Torr; uv (in 1 M aqueous KCl): λ_{max} 246 nm (ϵ_{max} 10 000); ^1H nmr (200 MHz, $CDCl_3$, TMS) δ: 1.46 (3H, d, J = 7 Hz, CH_3-), 3.80 (1H, br, OH), 5.13 (1H, quartet, J = 7 Hz, CH(OH)), 7.38–7.62 (3H, m, aromatic), 7.82–7.92 (2H, m, aromatic). Exact Mass calcd. for $C_9H_{10}O$: 150.06792; found: 150.06807.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

1. J. P. Guthrie, J. Cossar, and A. Klym. J. Am. Chem. Soc. **106**, 1351 (1984).
2. J. P. Guthrie and J. Cossar. Can. J. Chem. **64**, 1250 (1986).
3. J. P. Guthrie, J. Cossar, and A. Klym. Can. J. Chem. **65**, 2154 (1987).
4. M. W. Farrar and R. Levine. J. Am. Chem. Soc. **71**, 1496 (1949).
5. R. Levine and J. R. Stephens. J. Am. Chem. Soc. **72**, 1642 (1950).
6. J. P. Guthrie and J. Cossar. Can. J. Chem. Submitted for publication.
7. P. D. Bartlett. J. Am. Chem. Soc. **56**, 967 (1934).
8. P. D. Bartlett and J. R. Vincent. J. Am. Chem. Soc. **57**, 1596 (1935).
9. A. Streitwieser, Jr. Solvolytic displacement reactions. McGraw–Hill, New York. 1962. p. 16.
10. X. Creary. J. Am. Chem. Soc. **106**, 5568 (1984).
11. G. Richard. C. R. Hebd. Seances Acad. Sci. **214**, 673 (1942).
12. R. P. Bell and H. C. Longuet-Higgins. J. Chem. Soc. 636 (1946).
13. A. Kankaanpera, L. Oinonen, and P. Salomaa. Acta Chem. Scand. **A31**, 551 (1977).
14. J. P. Guthrie. Can. J. Chem. **57**, 1177 (1979).
15. J. R. Jones, R. E. Marks, and S. C. Subba Rao. Trans. Faraday Soc. **62**, 111 (1966).
16. P. Pruszynski, Y. Chiang, A. J. Kresge, N. P. Schepp, and P. A. Walsh. J. Phys. Chem. **90**, 3760 (1986).
17. J. P. Guthrie and J. Cossar. Can. J. Chem. **68**, 397 (1990).
18. Y. Chiang, A. J. Kresge, and J. Wirz. J. Am. Chem. Soc. **106**, 6392 (1984).
19. F. G. Bordwell, J. E. Bartmess, and J. E. Hautala. J. Org. Chem. **43**, 3095 (1978).
20. R. C. Weast (*Editor*). Handbook of chemistry and physics. 48th ed. Chemical Rubber Co., Cleveland, OH. 1967.
21. E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters. J. Org. Chem. **28**, 630 (1963).
22. P. Rabe. Chem. Ber. **45**, 2163 (1912).
23. J. W. Lynn and J. English. J. Am. Chem. Soc. **73**, 4284 (1951).
24. P. R. Bevington. Data reduction and error analysis for the physical sciences. McGraw–Hill, New York. 1969.
25. W. P. Jencks and J. Regenstein. *In* Handbook of biochemistry. 1st ed. *Edited by* H. A. Sober. Chemical Rubber Co., Cleveland, OH. 1968.