The Kinetics of the Reaction of Aromatic Ketones with Nitrous Acid in Sulfuric Acid

By Yoshiro OGATA, Yoshiaki FURUYA and Masahiro ITO

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The present authors have previously reported that the rate-determining step for the nitrosation of cyclohexyl aryl ketones in sulfuric acid (SNIA process) is the enolization of the ketone.1) The present paper will describe the effect of the structure of alkyl phenyl ketones on the rate, where the alkyl groups are methyl, isopropyl and isobutyl. The rates were measured by means of ultraviolet spectrophotometry. The rate data, together with the observed reaction products, including gaseous products, were analyzed to get some information on the reaction mechanism.

Experimental

Materials.—Commercial acetophenone was purified by distillation; b. p. 195∼196.5°C. *p*-Methylacetophenone (b. p. 117.5∼118.1C/31 mmHg), *p*-chloroacetophenone2) (b. p. 126∼127.5°C/27 mmHg), propiophenone3) (b. p. 108∼109°C/23.5 mmHg) and isobutyrophenone4) (b. p. 106∼107°C/21.0 mmHg) were prepared by Friedel-Crafts reactions of the corresponding aromatics with the corresponding acid anhydrides or acyl chlorides. *m*-Nitroacetophenone5) was prepared by the nitration of acetophenone and recrystallized from ethanol; m. p. 78.8∼79.2°C.

Isonitrosoacetophenone6) was obtained by the reaction of acetophenone with methyl nitrite in ethyl ether and was recrystallized from toluene, m. p. 127∼128.5°C. Phenylglyoxal7) was prepared

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1) Y. Ogata, Y. Furuya and M. Ito, *J. Am. Chem. Soc.*, **85**, 3649 (1963).

2) "Organic Syntheses," Coll. Vol. I, 109 (1941).

3) W. T. Read, *J. Am. Chem. Soc.*, **44**, 1751 (1922).

4) C. Schmidt, *Ber.*, **22**, 3250, Anm. 2 (1891).

5) "Organic Syntheses," Coll. Vol. II, 434 (1943).

6) W. K. Slater, *J. Chem. Soc.*, **117**, 589 (1920); "Organic Syntheses," Coll. Vol. II, 363 (1943).

7) "Organic Syntheses" Coll. Vol. II, 509 (1943).

by the oxidation of acetophenone with selenium dioxide in dioxane; b. p. 94~96°C/24.8 mmHg.

The Reaction Products.—*From Acetophenone.*—A solution of 20 ml. of 2.0 M acetophenone in 98.0% sulfuric acid and a solution of 40 ml. of 1.5 M sodium nitrite in 98.0% sulfuric acid were mixed; the mixture was then kept standing at 70°C for 7 hr. The resulting solution was diluted with water and extracted with ether. The ethereal extract was treated with aqueous alkali, and the aqueous layer was then acidified with hydrochloric acid and filtered. Benzoic acid was obtained; 4.6 g. (93.0%); $\lambda_{max}=228$ mμ; m. p. and mixture m. p. 123~124.8°C.

From Propiophenone. — A mixture of propiophenone (4.0 g.) and sodium nitrite (2.8 g.) in 98% sulfuric acid was allowed to stand at 70°C for 6 hr. Benzoic acid was obtained; 3.6 g. (97%); m. p. and mixture m. p. 120.5~122°C.

From Isobutyrophenone.—A mixture of isobutyrophenone (7.2 g.) and sodium nitrite (4.2 g.) in 95% sulfuric acid was heated at 60°C for 4.5 hr. The obtained product contained benzoic acid (5.6 g. (94%); m. p. and mixture m. p. 123~124°C) and acetoxime (0.7 g. (20%); m. p. and mixture m. p. 60~61°C (lit.[8] m. p. 60°C)).

From Isonitrosoacetophenone.—Isonitrosoacetophenone (1 g.) in 98% sulfuric acid was heated for 4 hr. at 70°C, yielding benzoic acid (0.8 g. (97%); m. p. and mixture m. p. 122~123.5°C).

Ultraviolet Spectrophotometry and Chemical Analysis. — The conversion curves were prepared as has been previously described.[1] The following different extinctions were employed: acetophenone, $(E_{228}-E_{241})$ vs. $(E_{241}-E_{280})$; *p*-methylacetophenone $(E_{237}-E_{252})$ vs. $(E_{252}-E_{280})$; *p*-chloroacetophenone, $(E_{237}-E_{250})$ vs. $(E_{250}-E_{280})$; *m*-nitroacetophenone, $(E_{217}-E_{256})$ vs. $(E_{217}-E_{300})$; propiophenone, $(E_{228}-E_{240})$ vs. $(E_{240}-E_{270})$, and isobutyrophenone, $(E_{228}-E_{241})$ vs. $(E_{241}-E_{270})$.

A Typical Run for the Rate Measurements.—A solution of 5 ml. of 0.4 M acetophenone in 98.6% sulfuric acid in a stoppered flask was brought to temperature equilibrium at 70°C. Then the reaction was started by the addition of 0.5 M sodium nitrite (5 ml.) in 98.6% sulfuric acid at 70°C. Aliquots (0.5 ml. each) were taken out at appropriate time intervals, and each aliquot was diluted with methanol to a 10^{-4} M total concentration of aryl ketone plus aryl carboxylic acid. The conversion percentage was determined graphically.

Results and Discussion

Acetophenone.—The rate of the reaction of acetophenone in 98.6% sulfuric acid with an initial concentration of 0.2 M ketone and in 0.097~0.388 M nitrous acid at 70°C satisfied the second-order rate law (Table I):

$$v=k\,[\text{ketone}]\,[\text{HNO}_2]$$

Lowering the concentration of sulfuric acid resulted in an increase in the amount of by-products, including gas, and, hence, a deviation from the second-order rate law; e. g., with 86% sulfuric acid the yield of benzoic acid was poor (30%).

It has been known that isonitrosoacetophenone PhCOCH=NOH is isolable as an intermediate in the reaction of acetophenone with nitrosyl chloride in ethanolic pyridine.[9] The authors observed that isonitrosoacetophenone converted rapidly to benzoic acid in sulfuric acid at 70°C, the conversion slowing down with a decrease in the sulfuric acid concentration as measured spectrophotometrically. When the conversion was made in dilute sulfuric acid in the presence of nitrous acid, nitrous oxide was detected by gas chromatography (Table II), as reported in the reaction of isonitrosoacetophenone with nitrosyl chloride.[9] Phenyl glyoxal, which has been known as one of the other products in the reaction using nitrosyl chloride,[9] was converted to a tarry material in sulfuric acid.

TABLE I. THE RATE DATA OF NITROSATION OF ALKYL PHENYL KETONES IN 98.6% SULFURIC ACID

Ketone	Temp. °C	Initial concn. of ketone M	Initial concn. of HNO_2 M	First-order rate constant k sec^{-1}	Second-order rate constant k' *l.* mol^{-1} sec^{-1}
Acetophenone	70	0.200	0.097		2.45×10^{-4}
		0.200	0.194		2.02×10^{-4}
		0.200	0.291		2.58×10^{-4}
		0.200	0.388		2.52×10^{-4}
Propiophenone	60	0.0200	0.0198		2.40×10^{-3}
		0.0200	0.0395		2.49×10^{-3}
		0.0400	0.0198		2.28×10^{-3}
		0.0400	0.0395		2.91×10^{-3}
		0.0400	0.0792		2.54×10^{-3}
Isobutyrophenone	60	0.0100	0.0198	2.38×10^{-4}	1.49×10^{-2}
		0.0200	0.0198	1.96×10^{-4}	1.45×10^{-2}
		0.0200	0.0397	2.43×10^{-4}	0.73×10^{-2}
		0.0400	0.0198	1.97×10^{-4}	0.84×10^{-2}
		0.0200	0.0099	1.51×10^{-4}	3.68×10^{-2}

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8) "The Merck Index," Merck & Co., Rahway, New Jersey (1960), p. 9.

9) C. T. Manning and H. A. Stansbury, Jr., *J. Am. Chem. Soc.*, **81**, 3885 (1959).

Propiophenone.—The reaction in 98.6% sulfuric acid at 60°C was first-order with both ketone and nitrous acid, as in the case of acetophenone (Table I). The product contained a quantitative amount of benzoic acid. Lowering the acidity of the solution resulted in the evolution of a gas which contained nitrous oxide and carbon monoxide (Table II).

Isobutyrophenone.—The rate law was different from those of acetophenone and propiophenone in that it obeyed the following first order equation (Table I):

$$v = k\,[\text{ketone}]$$

TABLE II. GAS CHROMATOGRAPHIC ANALYSIS OF EVOLUTION GASES FROM NITOSATION MIXTURES OF ACETOPHENONE, PROPIOPHENONE AND ISONITROSOACETOPHENONE IN 86.0% SULFURIC ACID AT 70°C

Column: Activated charcoal (30～60 mesh), 3 m.
Carrier Gas: Hydrogen with a flow rate of 88 ml./min.
Temp.: 80°C

Ketone or authentic sample	Molar ratio [ketone]/[HNO_2]	Retention volume ml.	
Acetophenone	1 : 2	1500	9150
Isonitrosoacetophenone	1 : 1	1500	9150
Isonitrosoacetophenone	1 : 0	1500	—
Propiophenone	1 : 1	1500	9150
CO*	—	1500	—
N_2O**	—	—	9150

* The authentic sample was obtained by the reaction of formic acid with sulfuric acid.
** The sample was prepared by the pyrolysis of ammonium nitrate.

TABLE III. SUBSTITUENT EFFECT ON THE NITROSATION OF ACETOPHENONE

Substituent	σ	k l. mol⁻¹ sec.⁻¹
p-CH_3	−0.170	4.84×10^{-4}
H	0	2.39×10^{-4}
p-Cl	+0.227	3.83×10^{-4}
m-NO_2	+0.710	1.72×10^{-2}

Substituent Effect. — The effect of substituents (p-CH_3, p-Cl and m-NO_2) in acetophenone is shown in Table III and Fig. 1. Electron-attracting groups accelerate the reaction with Hammett's ρ value of +2.6.

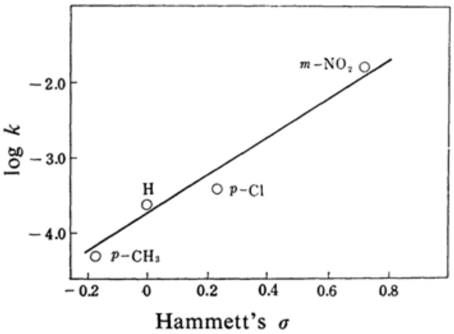
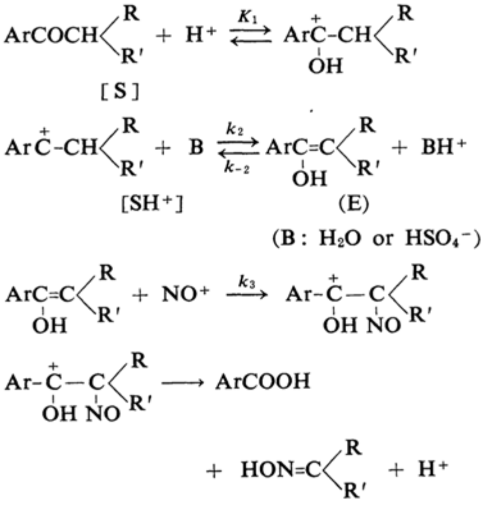


Fig. 1. Substituent effect on nitrosation of acetophenone in 98.6% sulfuric acid at 70°C.

Energies and Entropies of Activation. — The rate constants, energies and entropies of activation in 98.6% sulfuric acid at various temperatures are shown in Table IV.

Reaction Mechanism. — The above findings suggest that the rate-determining step for isobutyrophenone is the enolization of the ketone, as has been observerd in cyclohexyl phenyl



$$\underset{[\mathrm{S}]}{\mathrm{ArCOCH}{<}^{R}_{R'}} + \mathrm{H}^+ \overset{K_1}{\rightleftarrows} \mathrm{Ar}\underset{\mathrm{OH}}{\overset{+}{\mathrm{C}}}\text{-}\mathrm{CH}{<}^{R}_{R'} \tag{1}$$

$$\underset{[\mathrm{SH}^+]}{\mathrm{Ar}\overset{+}{\mathrm{C}}\text{-}\mathrm{CH}{<}^{R}_{R'}} + \mathrm{B} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \underset{(\mathrm{E})}{\mathrm{Ar}\underset{\mathrm{OH}}{\mathrm{C}}{=}\mathrm{C}{<}^{R}_{R'}} + \mathrm{BH}^+ \tag{2}$$

(B: H_2O or HSO_4^-)

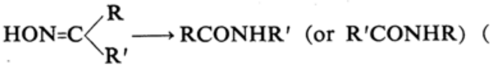
$$\mathrm{Ar}\underset{\mathrm{OH}}{\mathrm{C}}{=}\mathrm{C}{<}^{R}_{R'} + \mathrm{NO}^+ \xrightarrow{k_3} \mathrm{Ar}\text{-}\underset{\mathrm{OH}}{\overset{+}{\mathrm{C}}}-\underset{\mathrm{NO}}{\mathrm{C}}{<}^{R}_{R'} \tag{3}$$

$$\mathrm{Ar}\text{-}\underset{\mathrm{OH}}{\overset{+}{\mathrm{C}}}-\underset{\mathrm{NO}}{\mathrm{C}}{<}^{R}_{R'} \longrightarrow \mathrm{ArCOOH} + \mathrm{HON{=}C}{<}^{R}_{R'} + \mathrm{H}^+ \tag{4}$$

TABLE IV. THE RATE CONSTANTS AT VARIOUS TEMPERATURES, ENERGY OF ACTIVATION E_a AND ENTROPY OF ACTIVATION $\Delta S^{\ddagger}$ FOR THE NITROSATION OF THREE KETONES

Reaction temp. °C	Acetophenone $k\times10^4$ l. mol⁻¹ sec⁻¹	Propiophenone $k\times10^3$ l. mol⁻¹ sec⁻¹	Isobutyrophenone $k\times10^4$ sec⁻¹
50	0.18	—	0.52
60	0.63	2.52	1.62
70	2.39	5.58	3.71
80	5.16	12.7	—
E_a, kcal./mol.	24.4	20.4	21.8
$\Delta S^{\ddagger}$, e. u.	−4.3	−9.1	−10.5

ketone,[1] while the rate-determining step for acetophenone or propiophenone is an attack of nitrosonium ions.



$$HON{=}C\begin{matrix} R \\ R' \end{matrix} \longrightarrow RCONHR' \text{ (or } R'CONHR) \quad (5)$$

Defining k and K as the rate and equilibrium constants for the subscripted steps, and S and E as ketone and enol respectively, the following equations are derived by means of the stationary-state method:

$$k_2[SH^+][B] = k_{-2}[E][BH^+] + k_3[E][NO^+] \quad (6)$$

The introduction of the relation:

$$[SH^+] = K_1[H^+](a-x)/(1+K_1[H^+]) \quad (7)$$

into Eq. 6 gives Eq. 8, where $(a-x)$ is the stoichiometric concentration of ketone.

$$[E] = \frac{K_1k_2[B][H^+](a-x)}{(k_{-2}[BH^+]+k_3[NO^+])(1+K_1[H^+])} \quad (8)$$

Therefore, assuming that step 4 is very fast, the rate of the formation of benzoic acid may be expressed as:

$$v = k[NO^+][E] = \frac{K_1k_2[NO^+][B][H^+](a-x)}{(k_{-2}[BH^+]+k_3[NO^+])(1+K_1[H^+])} \quad (9)$$

The observed results imply that $k_{-2}[BH^+] \gg k_3[NO^+]$ with acetophnone and propiophenone, while $k_{-2}[BH^+] \ll k_3[NO^+]$ with isobutyrophenone and cyclohexyl aryl ketone; i. e., the rate is determined by step 2. The deprotonation of the conjugate acid of isobutyrophenone is more difficult because of the steric hindrance, electron-releasing effect of the methyl group and also the decrease in the number of α-hydrogen atoms: therefore, step 2 may be slowed down to a rate-determining step. A slight increase in the first-order rate constant with an increase in the initial concentration of nitrous acid was observed with isobutyrophenone; this may be explained by a small tendency of the rate to be rather second-order.

Electron-attracting groups in acetophenone accelerate the reaction, probably because of their favorable effect on deprotonation step 2. The substituent effect was reversed for the bromination of acetophenone in 75% aqueous acetic acid.[10] The facts may be explained by the lower acidity of the latter reaction, by which protonation step 1 is affected by substituents, while ketones in sulfuric acid are completely protonated.

A direct attack of nitrosonium ions on the α-position of ketone may lead to the second-order rate law, but this electrophilc attack is less probable because of the strong electron-withdrawal of the carbonyl group. Moreover, the rate-determining decomposition of nitrosoketone (Eq. 4) is unconceivable, since it was observed that nitrosoketone in sulfuric acid decomposes much faster than the nitrosation of the ketone. The rate of step 4 increases with an increase in the acidity of the sulfuric acid solution; hence, the amount of by-product decreases.

Summary

The rates of the reaction of acetophenone, ring-substituted acetophenones, propiophenone and isobutyrophenone with nitrous acid in 98.6% sulfuric acid have been measured by means of spectrophotometry. The rates have been expressed as $v=k[\text{ketone}][NO^+]$ with acetophenones and propiophenone, while they are $v=k[\text{ketone}]$ with isobutyrophenone. The electron-attracting groups in acetophenone accelerate the reaction with Hammett's ρ value of $+2.6$. A probable mechanism has been suggested which involves a rate-determining nitrosation of enolized ketone for acetophenone and propiophenone, and a rate-determining enolization of ketone for isbutyrophenone.

Department of Applied Chemistry
Faculty of Engineering
Nagoya University
Chikusa-ku, Nagoya

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[10] D. P. Evans, V. G. Morgan and H. B. Watson, *J. Chem. Soc.*, **1935**, 1167.