

For example, compare the isomeric acetates having in all 8 carbons ( $[R_L]_D$  40.5) and 9 carbons ( $[R_L]_D$  45).

For certain types of esters straight lines may be drawn. For example, line A results from esters of type  $(CH_3)_3CCH_2RCH_2OCOCH_3$  in which R varies regularly from ethyl (no. 14) to methyl (no. 6) to hydrogen (no. 3). Line B results from esters of type  $RCH_2OCOCH_3$  where R varies from cyclohexyl (no. 19) to cyclopentyl (no. 18) to cyclobutyl (no. 17) to cyclopropyl analog (no. 16). Line C results for esters of type  $(CH_3)_2CHCH_2RCH_2OCOCH_3$  where R varies from isopropyl (no. 13) to ethyl (no. 9) to methyl (no. 5). Ester no. 4 also falls on this line. Line D results for esters of type

$(R)_3CCH_2OCOCH_3$  where the R groups vary from triethyl (no. 15) to diethyl, methyl (no. 12) to ethyl, dimethyl (no. 10) to trimethyl (no. 7).

It is interesting to note that with the series of acetates of the branched primary alcohols a plot of their activation energies and  $\log PZ$  values (Fig. 2) gives a linear relationship for all the members except  $(C_2H_5)_3CCH_2OAc$  (no. 15) and  $(CH_3)_3CCH_2OAc$  (no. 14), which are hydrolyzed most slowly in the series and their points lie above and to the left of the isokinetic line. This is in accord with the discontinuous effect of steric hindrance as pointed out by Leffler.<sup>12</sup>

(12) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).  
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## Kinetics of the Chloromethylation of Mesitylene in Aqueous Acetic Acid

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The rate of the chloromethylation of mesitylene in acetic acid containing 10 volume % water was measured at 60° by estimating the consumed formaldehyde iodometrically and the consumed chloride ion. The rate of the disappearance of formaldehyde was found to be expressed as  $k_F[\text{mesitylene}][\text{formaldehyde}]$ , where a linear relationship with approximate unit slope (-0.96) was observed between  $\log k_F$  and the Hammett acidity function ( $H_0$ ). It was also confirmed that mesitylcarbinol and mesitylmethyl chloride are in mobile equilibrium under the experimental conditions. These results are consistent with a mechanism which involves a rate-determining attack of protonated formaldehyde on mesitylene followed by the rapid reversible formation of the chloromethyl compound.

Although many studies of chloromethylation from the synthetic standpoint have been carried out,<sup>1</sup> few data are available for the establishment of the reaction mechanism. The previous reports<sup>2</sup> on the relative rate measurements for the chloromethylation of aromatic hydrocarbons showed that the reaction appeared to involve an electrophilic attack on the aromatic nucleus. It seems to mean that the attacking species in the rate-determining step is either  $\overset{+}{C}H_2Cl$  or  $\overset{+}{C}H_2OH$ . But there is no evidence to decide which is the more probable one. The present report provides information concerning the kinetics and mechanism of the chloromethylation of mesitylene with hydrogen chloride and formaldehyde in 90 volume % aqueous acetic acid.

### Experimental

**Materials.**—Mesitylene was prepared by the cyclization of acetone<sup>3</sup> and purified by duplicate rectifications, b.p. 163–164°. 2,4,6-Trimethylbenzyl chloride (mesitylmethyl chloride) was synthesized by the condensation of mesitylene with monochloromethyl ether in glacial acetic acid,<sup>4</sup> and crystallized from ether, m.p. 37–38°. 2,4,6-Trimethylbenzyl acetate was obtained by treating the chloride with silver acetate,<sup>5</sup> b.p. 146° (24 mm.). 2,4,6-Trimethylbenzyl alcohol (mesitylcarbinol) was prepared by the saponification of the corresponding acetate,<sup>5</sup> and recrystallized from aqueous

ethanol, m.p. 88–89°. Glacial acetic acid was of the best grade available, and was used without further purification.

**Rate Measurements.**—Forty cc. of glacial acetic acid, 24 cc. of 2 *M* hydrogen chloride in acetic acid and 8 cc. of 2 *M* aqueous formaldehyde solution were mixed in a flask, and thermostated at 60°. To the mixture was added from a calibrated pipet 8 cc. of 2 *M* mesitylene in acetic acid maintained previously at the same temperature. At regular time intervals, 3-cc. aliquots were pipetted out into ca. 50 cc. of distilled water. Potassium hydroxide solution was added until the solution became alkaline, and the amount of unreacted formaldehyde was determined by iodometry.<sup>6,7</sup> Other 5-cc. aliquots were poured into ca. 50 cc. of carbon tetrachloride.<sup>8</sup> The mixture was transferred to a separatory funnel and extracted twice with ca. 50 cc. portions of distilled water. The amount of consumed chloride ion was estimated according to the Volhard method.<sup>9</sup> The rate measurement of the chloride ion consumption had to be restricted only to the early stages of the reaction in order to obtain reliable data. The discrepancy seems to depend on the use of a large excess of hydrogen chloride and its vaporization during the reaction.

**Measurements of the Acidity Function  $H_0$ .**—To obtain information on the effective acidity, the indicator ratios ( $c_B/c_{BH^+}$ ) at 412  $m\mu$  for each reaction mixture were determined spectrophotometrically using *o*-nitroaniline ( $pK_a$  -0.17)<sup>10</sup> as an indicator.<sup>11</sup> Thus the values of  $H_0$  were calculated by means of the equation<sup>12</sup> where  $c_B$  is concentra-

(6) J. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1953, p. 385.

(7) It was also ascertained that loss of formaldehyde due to the polymerization was negligible in this solvent.

(8) Since the chloromethylated compound is readily hydrolyzed, the preliminary removal of the compound by the extraction with carbon tetrachloride is necessary.

(9) J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 266.

(11) For the example, see D. S. Noyce and P. Castellfranco, *THIS JOURNAL*, **73**, 4482 (1951).

(12) Reference 10, p. 268.

(1) Cf. R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).

(2) G. Vavon, J. Bolle and J. Calin, *Bull. soc. chim. France*, [5] **6**, 1025 (1939); H. H. Szmant and J. Dudek, *THIS JOURNAL*, **71**, 3763 (1949).

(3) R. Adams and R. W. Hufferd, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 341.

(4) G. Vavon and J. Bolle, *Compt. rend.*, **204**, 1826 (1937).

(5) W. Th. Nauta and J. W. Pienske, *Rec. trav. chim.*, **55**, 1000 (1936).

tion of indicator B and  $c_{BH^+}$  is the concentration of conjugate acid of indicator

$$H_0 = \log (c_B/c_{BH^+}) + pK_a \quad (1)$$

Since acetic acid is very important as a solvent for many organic reactions, the  $H_0$  values in 90% acetic acid containing hydrogen chloride or sulfuric acid but no mesitylene were also estimated and given in Table I.

TABLE I  
ACIDITY FUNCTIONS OF 90% ACETIC ACID CONTAINING 0.20-1.00 M SULFURIC ACID OR HYDROGEN CHLORIDE AT 20°

Indicator, <i>o</i> -nitroaniline; $\epsilon_N = 5,000$ , $\lambda = 412 \mu$					
Acid	Concn., M	$H_0$	Acid	Concn., M	$H_0$
H <sub>2</sub> SO <sub>4</sub>	0.20	-0.04	HCl	0.20	0.03
	.40	-.65		.40	-.48
	.60	-1.12		.60	-.86
	.80	-1.53		.80	-1.12
	1.00	-1.89		1.00	-1.33

<sup>a</sup> In ref. 11, it has been adopted to  $\epsilon_N = 4,500$  (in water). But the authors preferred their value in the table, obtained in 90% acetic acid, as a standard to cancel the solvent effect.

**Calculations and Results.**—The second-order rate constants  $k_F$  were calculated by means of equation 3, derived by integrating equation 2.

$$v_F = dx/dt = k_F (m - x)(f - x) \quad (2)$$

If  $m = f$

$$k_F = \frac{x}{t(f - x)}$$

if  $m \neq f$

$$k_F = \frac{1}{t(f - m)} \ln \frac{m(f - x)}{f(m - x)} \quad (3)$$

Here,  $m$  and  $f$  are the initial concentrations of mesitylene and formaldehyde, respectively, and  $x$  is the concentration of consumed formaldehyde after  $t$  seconds. Since the values of  $k_F$  tend to decrease gradually as the reaction proceeds, they were calculated on the basis of the data with less than ca. 50% consumption of formaldehyde (see the last paragraph in Discussion). These  $k_F$ -values with varying molar ratios, at a constant concentration of hydrogen chloride, are listed in Table IIa; they justify rate equation 2. A slight decrease of  $k_F$ -value, when the initial concentration of mesitylene is 0.40 M, may be due to the decrease of the acidity. Furthermore, in order to ascertain that the variation in the chloride ion concentration is independent of the rate of formaldehyde consumption, the rate was also measured in sulfuric acid media in the presence or absence of chloride ion (lithium chloride). The result is shown in Table IIb. Consequently, it may be concluded that the

rate-determining attack of CH<sub>2</sub>Cl or any other species which contains chlorine atom [e.g., ClCH<sub>2</sub>OH, (ClCH<sub>2</sub>)<sub>2</sub>O] is implausible under these conditions. Finally, the effect of the acidity of the solution on the rate is given in Table IIc.

**Some Complementary Experiments.** (a) **The Equilibrium between Mesitylcarbinol (Containing its Acetate, see Below) and its Chloride.**—In the above rate measurements, it was found that the ratio of the rate of the consumption of chloride ion  $v_{Cl}$  and that of formaldehyde,  $v_F$ , approached unity with an increase of the concentration of hydrogen chloride. For example, when four equivalents of hydrogen chloride were used, 90% of the formaldehyde consumed was found to be utilized for the chloromethylation. In column a of Table III are listed percentages of chloromethyl and hydroxymethyl compounds in the reaction products calculated from the rate data. In comparison with these data, mesitylcarbinol or mesitylmethyl chloride was dissolved at 60° in 90 volume % acetic acid containing an appropriate amount of hydrogen chloride, and after ca. 5 minutes, the amount of benzyl chloride in the equilibrium state was determined by estimating the difference in the chloride ion concentration. These results with mesitylcarbinol and mesitylmethyl chloride are shown in column b and c of Table III, respectively. The data in column b agree well with those in a. A small discrepancy appearing between

TABLE II  
RATE CONSTANTS OF THE CHLOROMETHYLATION OF MESITYLCARBINOL IN 90 VOL. % ACETIC ACID AT 60.0 ± 0.5°

(a) THE EFFECT OF MOLAR RATIO				
Mesityl-ene ( <i>m</i> ), M	Initial concn. Formaldehyde ( <i>f</i> ), M	Hydrogen chloride, M	- $H_0^a$	$k \times 10^{3.5}$ l. mole <sup>-1</sup> sec. <sup>-1</sup>
0.20	0.20	0.40	0.40	0.59 ± 0.02
.20	.40	.40	.40	.56 ± .01
.40	.40	.40	.32	.51 ± .02

(b) THE EFFECT OF THE CONCENTRATION OF CHLORIDE ION				
Initial concn.; mesitylene 0.20 M, formaldehyde 0.20 M, sulfuric acid 0.60 M				
Chloride added	Concn. M	- $H_0^a$	$k \times 10^{3.5}$ l. mole <sup>-1</sup> sec. <sup>-1</sup>	
None	..	1.06	2.23 ± 0.07	
LiCl	0.15	0.98	2.17 ± .04	

(c) THE EFFECT OF THE ACIDITY					
Initial concn.; mesitylene 0.20 M, formaldehyde 0.20 M					
Concn. HCl, M	- $H_0^a$	$k \times 10^{3.5}$ l. mole <sup>-1</sup> sec. <sup>-1</sup>	Concn. HCl, M	- $H_0^a$	$k \times 10^{3.5}$ l. mole <sup>-1</sup> sec. <sup>-1</sup>
0.20	-0.10	0.17 ± 0.01	0.80	1.04	1.88 ± 0.05
.40	.40	.59 ± .02	1.00	1.26	3.21 ± .08
.60	.79	1.28 ± .04			

<sup>a</sup> Measured at 20°. <sup>b</sup> Figures following ± mean probable errors.

the values in c and those in a may be ascribed to the variation of the acidity. Therefore, it is sure that the conversion of mesitylcarbinol to the corresponding chloride is rapid and reversible.

TABLE III  
EQUILIBRIUM BETWEEN MESITYL CARBINOL (CONTAINING ITS ACETATE) AND ITS CHLORIDE AT 60° WITH VARYING ACIDITY AND WITH THREE STARTING MATERIALS  
Solvent; 90 vol. % acetic acid

Concn. of hydrogen chloride, <sup>a</sup> M	a, from mesityl-ene, %		b, from mesityl-carbinol, %		c, from mesityl-methyl chloride, %	
	Alc. + acetate	Chlo- ride	Alc. + acetate	Chlo- ride	Alc. + acetate	Chlo- ride
0.20	45	55	44	56	42	58
.40	24	76	26	74	20	80
.60	16	84	13	87	8	92

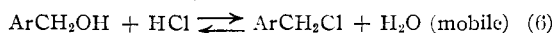
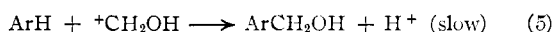
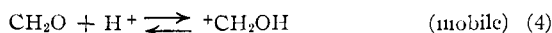
<sup>a</sup> In the case of c, 0.20 M sulfuric acid was approximately used in place of 0.20 M of hydrogen chloride to make the chlorine content in system c agree with those in systems a and b.

(b) **Side Reactions.**—Since our experiment differs from the usual synthetic chloromethylation conditions in that acetic acid was used as a solvent, the consideration of some probable side reactions seems to be necessary. (i) **The Formation of 2,4,6-Trimethylbenzyl Acetate.**—The following test was carried out in order to check this ester formation. Mesitylcarbinol (0.3004 g., 0.0020 mole) was dissolved in 90% acetic acid (10 cc.) containing 0.40 M sulfuric acid or hydrogen chloride, and heated to 60°. After ca. 5 minutes, the solution was poured into ca. 50 cc. of carbon tetrachloride, the mixture was washed into a separatory funnel with distilled water to remove acids completely, and the solvent was evaporated. The ester content in the evaporated residue was determined by saponification with an appropriate amount of alcoholic potash. When hydrogen chloride was used in the reaction solution, the concentration of chloride ion in the wash-water layer was also estimated, to determine the conversion percentage of mesitylcarbinol to chloride. For, in this case, it is apparent that the saponification value corresponds to the sum of the amounts of chloromethyl compound and acetate. In the system containing sulfuric acid, ca. 90% of the initial carbinol was found to be converted

to the acetate, while with the system containing hydrogen chloride, the conversion to chloride was *ca.* 75%, and that to ester is *ca.* 20%. Similar results were obtained in the experiment with 2,4,6-trimethylbenzyl acetate dissolved in the same solvent. These results indicate that the mobile equilibrium exists between hydroxymethylated mesitylene and its acetate, and that the amount of alcohol which remains not esterified is only below 10% under these experimental conditions. (ii) **The Acetolysis of Mesitylmethyl Chloride and the Reverse Reaction.**—Mesitylmethyl chloride (0.3373 g., 0.0020 mole) in 0.40 *M* hydrogen chloride in a solution of pure acetic acid was heated at 60° for *ca.* 5 minutes. However, no appreciable increase of the chloride ion concentration in the solution was observed. On the contrary, when 0.20 *M* trimethylbenzyl acetate in the same solution was heated, a considerable conversion (*ca.* 70%) to chloromethyl compound was recognized.

#### Discussion

On the basis of the observed experimental results, the following general mechanism<sup>13</sup> is probable.



The mechanism indicates that the rate of the consumption of formaldehyde  $v_F$  should be expressed as<sup>14</sup>

$$v_F = \frac{dx}{dt} = k_5[\text{ArH}][\text{CH}_2\text{OH}^+] = K_4 k_5 [\text{ArH}][\text{CH}_2\text{O}][\text{H}^+] = k_F (m - x)(f - x) \quad (7)$$

Therefore

$$k_F = K_4 k_5 [\text{H}^+]$$

or

$$\log k_F = -H_0 + \text{const.} \quad (8)$$

Here,  $K$  and  $k$  are the equilibrium and rate constants of the subscripted steps, respectively. Consequently, the linear relationship with unit slope between  $\log k_F$  and  $-H_0$  should be expected. The data in Table IIc fulfill this relationship as exhibited in Fig. 1. The postulated mechanism explains the effect of the substituents on the rate; *i.e.*, an electron-releasing group in an aromatic nucleus facilitates the electrophilic attack by  $\text{CH}_2\text{OH}^+$ , while with an electron-withdrawing group the reverse is true. The formation of diarylmethane and/or methylene-bridged resin as by-products is also explicable in terms of this scheme.

(13) In general, the use of acetic acid as a solvent for this reaction is seldom, hence probable equilibria with acetate ( $\text{ArCH}_2\text{OH} + \text{AcOH} \rightleftharpoons \text{ArCH}_2\text{OAc} + \text{H}_2\text{O}$ ,  $\text{ArCH}_2\text{Cl} + \text{AcOH} \rightleftharpoons \text{ArCH}_2\text{OAc} + \text{HCl}$  etc.) were eliminated to lay emphasis on the simplified general mechanism.

(14) In the same way, the rate of the consumption of chloride ion  $v_{\text{Cl}}$  may be expressed as

$$v_{\text{Cl}} = \frac{v_F}{\frac{[\text{H}_2\text{O}]}{K_6[\text{HCl}]} + 1} = \frac{K_4 k_5 [\text{ArH}][\text{CH}_2\text{O}][\text{H}^+]}{\frac{[\text{H}_2\text{O}]}{K_6[\text{HCl}]} + 1}$$

where  $K_6$  is the equilibrium constant of equation 6.

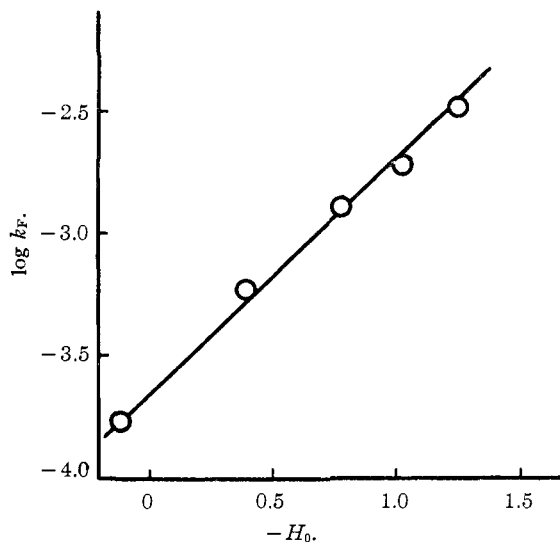
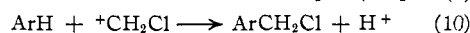
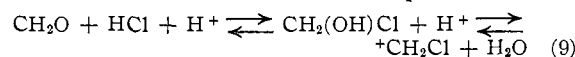


Fig. 1.—Relationship between  $\log k_F$  and  $-H_0$  (slope 0.96).

The possibility of other mechanisms will be discussed briefly. If the attack of  $\text{CH}_2\text{Cl}^+$  (step 10)<sup>15</sup> determined the rate with step 9 in mobile equilibrium,  $k_F$  would depend on the concentration of chloride ion as shown in the rate equation 11.



$$\frac{dx}{dt} = K_9 k_{10} \frac{[\text{ArH}][\text{CH}_2\text{O}][\text{HCl}][\text{H}^+]}{[\text{H}_2\text{O}]} \quad (11)$$

The attack of  $\text{ClCH}_2\text{OH}$  or  $(\text{ClCH}_2)_2\text{O}$  is found improbable by similar reasoning. Moreover, if step 9 determined the rate,  $k_F$  would be independent of the concentration of the aromatic hydrocarbon.

Finally, it is of interest to note that the rate constants  $k'_F$  calculated by equation 2' in place of equation 2 are constant over the wider range.

$$v_F = k'_F (m - px)(f - x) \quad p = 1.1-1.2 \quad (2')$$

It is apparent in the equation that the formation of diarylmethane is appreciable when  $2 > p > 1$ ; the more nucleophilic the aromatic hydrocarbon is, the larger (or closer to 2) the value of  $p$  will be; *e.g.*, in dimethylaniline,<sup>16</sup>  $p = 2$ .

**Acknowledgment.**—The authors wish to express their gratitude to Prof. R. Oda without whose aid this work would not have been possible.

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(15) In the chloromethylation with monochloromethyl ether or dichloromethyl ether in non-hydroxylic solvents, the attack of  $\text{CH}_2\text{Cl}^+$  is probable, although no kinetic evidence has yet been obtained.

(16) Y. Ogata and M. Okano, *THIS JOURNAL*, **72**, 1459 (1950).