Kinetics of the Condensation of Urea with Acetaldehyde

YOSHIRO OGATA, ATSUSHI KAWASAKI, AND NOBUYA OKUMURA

Contribution No. 70 from the Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

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The reaction of urea and acetaldehyde in molar ratio of over 3:1 gives ethylidenediurea as a main product. The rate of reaction in aqueous solutions has been measured by means of spectrophotometric estimation of remaining acetaldehyde. The rate is expressed as $v = k[H_2NCONH_2][CH_3CHO]$. The reaction is reversible and the forward reaction is catalyzed by both general acid and general base. The Brønsted catalysis law is applicable to the general acid catalysis of the forward reaction. The reverse reaction, the decomposition of ethylidenediurea, is general acid catalyzed in acidic buffered solutions. A probable mechanism is suggested for the forward reaction involving a rate-determining reaction of urea and acetaldehyde to form ethylolurea, as is a mechanism for the reverse reaction involving a preliminary rapid decomposition of ethylidenediurea to ethylolurea.

There have been a number of kinetic studies on the condensation of formaldehyde with amides[1,2] involving urea. Most of the studies are concerned with the formation of methylolamides, and it is known that their rates are expressed as $v = k[HCHO][RCONH_2]$. However, the reaction of other aldehydes with amides have been scarcely studied. It is known that the reaction of urea with acetaldehyde gives various products with varying ratios of urea *vs.* acetaldehyde.[3] It was confirmed that the reaction of more than 3 moles of urea with 1 mole of acetaldehyde gave ethylidenediurea.

$$2NH_2CONH_2 + CH_3CHO \rightleftharpoons NH_2CONH{-}CH(CH_3){-}NHCONH_2 + H_2O \quad (1)$$

The present paper deals with the kinetic results obtained on the condensation of urea with acetaldehyde to form ethylidenediurea.

Experimental

Materials.—Commercial reagent grade acetaldehyde dried over Drierite was purified by rectification, b.p. 20.2°. Commercial reagent grade urea was purified by recrystallization from methanol, m.p. 132.5°. Ion-exchanged pure water was used as the solvent.

The Reaction Products.—Ethylidenediurea was prepared by the reaction of 1 mole of acetaldehyde and more than 3 moles of urea in an aqueous solution at room temperature. The resulting solution was evaporated under reduced pressure at 40° and, after being washed with methanol, gave crystals, m.p. 182–183° (lit.[4] m.p. 181°).

Anal. Calcd. for $C_4H_{10}N_4O_2$: mol. wt., 146. Found: mol. wt., 150 (cryoscopic method in aqueous solution).

The decomposition of the product (0.292 g.) by heating with 0.2285 *N* aqueous sulfuric acid (20 ml.) and 0.4 *N* hydroxylamine hydrochloride (10 ml.) for 2.5 hr. at 60–80° gave acetaldehyde oxime which was estimated by titration with 0.1069 *N* sodium hydroxide (60.78 ml.); *i.e.*, 2.0×10^{-3} mole of the sample gave 1.93×10^{-3} mole of acetaldehyde. The infrared spectra of this compound showed no OH peak at 3700–3500 and 1200–1000 cm.$^{-1}$.

Rate Measurements.—The concentration of acetaldehyde was measured by its absorbance at 277 mμ (absorption maximum), where urea, ethylourea, and ethylidenediurea have no appreciable absorption. The molar extinction coefficient of acetaldehyde in water was as follows: 6.67 at 12.0°; 8.02 at 24.2°; and 9.05 at 36.3°. Except in phosphate buffer (μ = 0.8) all runs were carried out at the same ionic strength (μ = 0.2) by adding sodium chloride. The hydroxide-ion catalysis was measured in a borate buffer where no appreciable catalytic effect of the buffer was observed.

A typical experiment for the rate measurements was as follows: 0.150 *M* acetaldehyde (25 ml.) in a buffered aqueous solution and 3.00 *M* urea (25 ml.) in the same buffered solution which had previously come to thermal equilibrium were mixed in a flask and immediately introduced to a glass-stoppered quartz cell thermostated at 24.2 ± 0.2° in a Hitachi spectrophotometer, type EPU-2A. The absorbance at 277 mμ was measured at known intervals of time and the concentration of acetaldehyde was calculated.

The decomposition of ethylidenediurea was carried out in a chloroacetate buffer (μ = 0.2) at 24.2°, the resulting acetaldehyde being determined spectrophotometrically.

Results and Discussion

The Order of the Reaction Rate.—Pseudo-first-order rate constants were calculated by measuring acetaldehyde in kinetic experiments, where a 10–20-fold excess of urea to acetaldehyde was used. As shown in Figure 1, the plot of the pseudo-first-order rate constant *vs.* initial concentration of urea was a straight line passing through the origin. Therefore, the rate is expressed as $v = k[H_2NCONH_2][CH_3CHO]$.

Hydronium Ion and Hydroxide Ion Catalysis.—The reaction seems to be catalyzed by H_3O^+ and OH^- ions as in the case of formaldehyde.[1d,2] A linear relationship (Figure 2) was observed between the log k and log $[H_3O^+]$ or log $[OH^-]$ at pH of 2.9–4.2 or 8.2–9.6, respectively. The plot gives two straight lines with unit slope, and log k has a minimum at pH *ca.* 6.8, which indicates both hydronium ion and hydroxide ion catalysis.

In unbuffered solutions the rate constants can be expressed as

$$k = k'[H_2O] + k''[H_3O^+] + k'''[OH^-] \qquad (2)$$

The catalytic constants, k'' and k''', can be evaluated from Figure 2.

$$k = k'[H_2O] + 1.3[H_3O^+] + 1.4[OH^-] \qquad (3)$$

A similar relationship has been reported for the condensation of urea with formaldehyde.[1d]

$$k = (5.6 \times 10^{-5}) + (1.4 \times 10^{-1}\,[H_3O^+]) + 1.7[OH^-]$$

Catalysis in Buffered Solutions.—A series of experiments were carried out in various acetate buffer concentrations with constant pH to examine the possibility of general acid and general base catalysis. The plot of second-order constant *vs.* concentration of acetate

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[1] (a) H. Kadowaki, *Osaka Kogyo Gijutsu Shikensho Hokoku*, **13**, 27 (1932); (b) G. A. Crowe and C. C. Lynch, *J. Am. Chem. Soc.*, **70**, 3795 (1948); **71**, 3731 (1949); **72**, 3622 (1950); (c) L. E. Smythe, *J. Phys. Colloid Chem.*, **51**, 369 (1949); (d) J. I. de Jong and J. de Jonge, *Rec. trav. chim.*, **71**, 643 (1952); **71**, 661 (1952); **72**, 202 (1953).

[2] J. Ugelstad and J. de Jonge, *ibid.*, **76**, 919 (1957); *Bull. soc. chim. France*, 138 (1955).

[3] (a) H. Schiff, *Ann.*, **151**, 186 (1869); (b) G. Zigeuner, E. A. Gardziella, and G. Bach, *Monatsh. Chem.*, **92**, 31 (1961).

[4] G. Klein and K. Tauböck, *Biochem. Z.*, **241**, 416 (1931). This report does not describe the preparative method of ethylidenediurea.

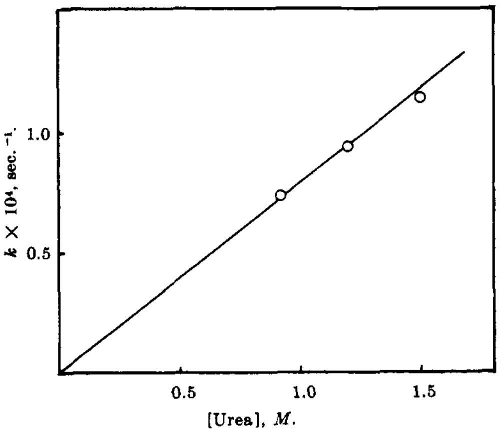

Figure 1.—Plot of the pseudo-first-order rate constant *vs.* the initial concentration of urea for the condensation of urea with acetaldehyde at 24.2°.

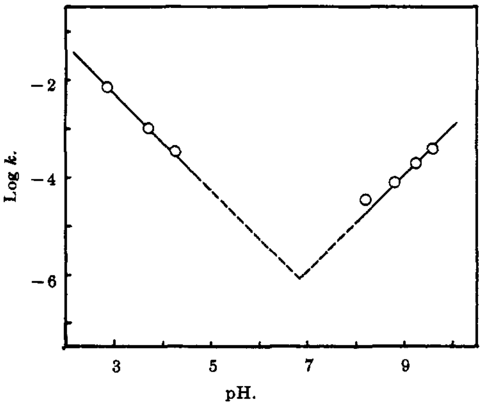

Figure 2.—The relationships between the logarithm of the second-order rate constant and pH for the condensation of urea with acetaldehyde at 24.2° and ionic strength of 0.2.

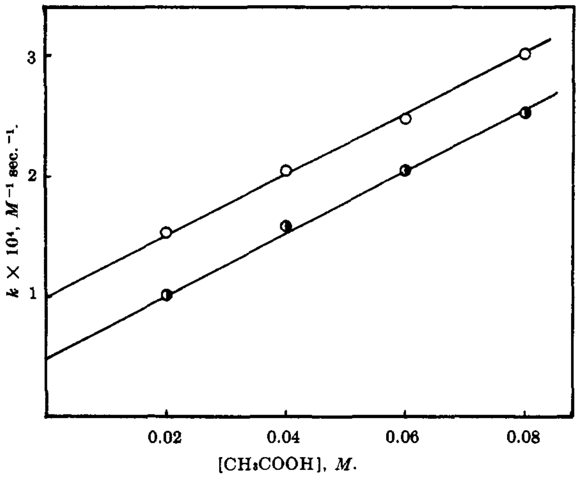

Figure 3.—The illustration of the general acid catalysis for the condensation of urea with acetaldehyde in acetate buffers at 24.2° and ionic strength of 0.2. $\gamma = [CH_3COO^-]/[CH_3COOH]$: ○, $\gamma = 0.5$; ◑, $\gamma = 1$.

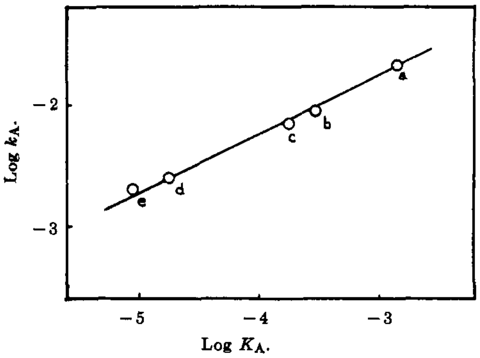

Figure 4.—Application of Brønsted catalysis law, $\log k_A = \log G_A + \alpha \log K_A$, to the condensation of urea with acetaldehyde at 24.2° and ionic strength of 0.2: a, chloroacetic acid; b, methoxyacetic acid; c, formic acid; d, acetic acid; e, pivalic acid. $\alpha = 0.46$, $G_A = 4.1 \times 10^{-1}$.

buffer shows straight parallel lines corresponding to their pH values (see Figure 3). This fact indicates that the reaction is subject to general acid catalysis with acetic acid, but not to general base catalysis with acetate ion. The slope of line gives the specific acid catalytic constant for acetic acid as 2.50×10^{-3} M^{-2} sec.$^{-1}$. Similar results were obtained with formate, chloroacetate, methoxyacetate, and pivalate buffers. The catalytic constants k_A satisfy the Brønsted catalysis law (Figure 4), where K_A is the acidity constant of the corresponding acid and G_A and α are constants.

$$\log K_A = \log G_A + \alpha \log K_A \qquad (4)$$

Figure 4 gives $\alpha = 0.46$ and $G_A = 0.41$.

On the other hand, the result with phosphate buffers shows the general acid and general base catalysis (see Figure 5). The phenomenon is explicable by the stronger basicity of monophosphate ion (secondary dissociation constant of phosphoric acid is 6.023×10^{-8} at 25°) compared with the acetate ion (the dissociation constant for acetic acid is 1.75×10^{-5}). The similar phenomenon was observed with the urea–formaldehyde reaction.[2]

The activation energy for the reaction was 9.97 kcal. mole^{-1} in water.

Equilibrium Constants.—The calculation of the overall equilibrium constant gave unsatisfactory results, which suggested an intermediary formation of ethylolurea. Therefore, the equilibrium constants were calculated using following abbreviations to represent participators.[5]

$$\underset{U}{H_2NCONH_2} + \underset{A}{CH_3CHO} \overset{K_1}{\rightleftarrows} \underset{EU}{H_2NCONHCH(CH_3)OH} \qquad (5)$$

$$\underset{EU}{H_2NCONHCH(CH_3)OH} + \underset{U}{H_2NCONH_2} \overset{K_2}{\rightleftarrows} \underset{EDU}{H_2NCONHCH(CH_3)NHCONH_2} + H_2O \qquad (6)$$

$$[A] = [A_0] - [EU] - [EDU] \qquad (7)$$

$$K_1 = \frac{[EU]}{([A_0] - [EU] - [EDU])([U_0] - [EU] - 2[EDU])} \qquad (8)$$

$$K_2 = \frac{[EDU]}{[EU]([U_0] - [EU] - 2[EDU])} \qquad (9)$$

Here, subscript 0 means the initial concentration. The introduction of the values of [EU] and [EDU] from eq. 7 and 8 into eq. 9 leads to eq. 10. The binary equation

$$K_2 = \frac{(1 - K_1[A])\{K_1[A]([A_0] - [A] - [U_0]) + ([A_0] - [A])\}}{K_1[A](2[A_0] - 2[A] - [U_0])^2} \qquad (10)$$

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[5] Similar treatment has been done in the reaction of formaldehyde and urea to form dimethylolurea: H. Sobue and K. Murakami, *Kobunshi Kagaku*, **9**, 454 (1952).

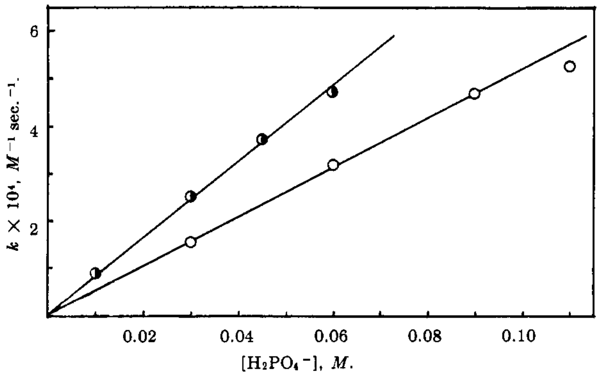

Figure 5.—The illustration of general base catalysis for the condensation of urea with acetaldehyde in phosphate buffers at 24.2° and ionic strength of 0.2. γ = [HPO_4^{-2}]/[$H_2PO_4^-$]: ○, $\gamma = 2$; ◑, $\gamma = 4$.

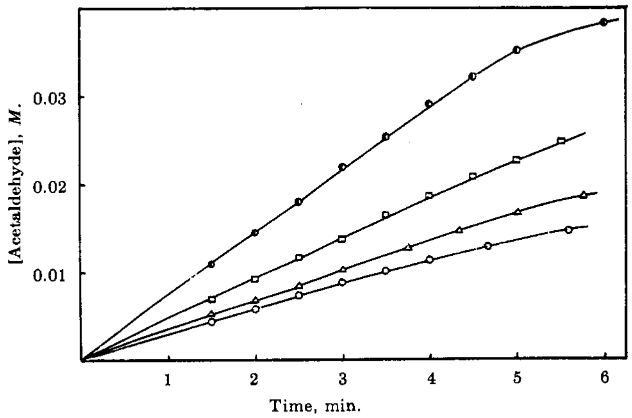

Figure 6.—The decomposition of ethylidenediurea in chloroacetate buffers (pH 3) with initial concentration of ethylidenediurea of 0.1000 M: ◐, [U_0] = 0; □, [U_0] = 0.250 M; △, [U_0] = 0.500 M; ○, [U_0] = 0.750 M.

including unknown K_1 and K_2 and measurable A_0, A, and U_0 can be solved and the calculated values are listed in Table I. The constancy of K_1 is satisfactory, while the constancy of K_2 is considerably poorer, because the value of K_2 is sensitive to the small variation in K_1. The value of K_1, 2.05 M^{-1} at 24.2°, is smaller than the corresponding value of 25.7 M^{-1} at 25° for the reaction of formaldehyde and urea[1b] and that of 22.3 M^{-1} at 25° for the reaction of formaldehyde and benzamide,[2] which means a less favorable tendency for the acetaldehyde condensation.

TABLE I

THE EQUILIBRIUM CONSTANTS FOR THE CONDENSATION OF UREA WITH ACETALDEHYDE IN WATER[a]

[A_0], M	[U_0], M	[A], M	K_1, M^{-1}	K_2, M^{-1}	$\frac{[U_0]}{[A_0]}$
0.1008	0.4506	0.0497	Standard		4.5
0.1008	0.7496	0.0332	2.02	0.803	7.0
0.1008	0.9001	0.0286	2.15	0.564	9.0
0.1008	1.2009	0.0195	1.93	0.925	12.0
0.1008	1.4990	0.0148	2.01	0.804	15.0
0.0873	1.5020	0.0142	2.10	0.540	17.1[b]
0.0605	1.2009	0.0116	2.08	0.701	19.9[c]
		Av.	2.05	0.723	

[a] At 24.2°. [b] pH 4.9. [c] pH 4.4.

The Decomposition of Ethylidenediurea in Acidic Buffered Solutions.—The decomposition of ethylidenediurea was kinetically studied in a chloroacetate buffer at pH 3.0. The following facts suggest that ethylidenediurea forms ethylolurea in a rapid equilibrium (eq. 6) and the decomposition of ethylolurea to urea and acetaldehyde is rate determining (reverse of step 5). (1) The rate of formation of acetaldehyde is of simple first order with ethylidenediurea as shown in Table II. (2) If the decomposition of ethylidenediurea (the reverse step of eq. 6) were rate determining, the rate should not be affected by the addition of urea. As shown in Figure 6, the apparent rate falls with increasing concentration of added urea, which implies the shift of equilibrium 6 to the right side by the addition of urea. (3) The decomposition of ethylidenediurea as well as the formation of ethylolurea is general acid catalyzed. In spite of this, the decomposition of methylenediurea to methylolurea which corresponds to the reverse of step 6 has been known to be not general acid catalyzed, but specific oxionium ion catalyzed.[1d] In analogy, it is probable that the reverse of step 5 is rate determining and general acid catalyzed.

TABLE II

THE DECOMPOSITION OF ETHYLIDENEDIUREA IN CHLOROACETATE BUFFER[a]

[EDU_0], M		$k_1 \times 10^3$ sec.$^{-1}$
0.1500		1.23
0.1250		1.33
0.1000		1.41
0.0750		1.37
0.0500		1.47
	Av.	1.37

[a] pH 3.0, at 24.2°, μ = 0.2. $K_1 = (2.30 \times 10^{-3})/(1.37 \times 10^{-3}) = 1.68\ M^{-1}$.

The value of K_2 (0.72 M^{-1}) in Table I implies that most of the ethylidenediurea is converted immediately to ethylolurea which decomposes slowly to urea and acetaldehyde and that the formation of ethylidenediurea needs a large excess of urea. The value of K_1 (1.68 M^{-1}) obtained from the ratio of the rate constants of the forward and the reverse reactions agrees in order with the value (2.05 M^{-1}) that was measured directly.

Reaction Mechanism.—As stated above, the formation of ethylolurea from urea and acetaldehyde is rate determining because of the observed second-order kinetics.

In a dilute aqueous solution about half of the amount of acetaldehyde is hydrated, since K_{11} [H_2O] = 1.02.[6]

$$CH_3CHO + H_2O \underset{}{\overset{K_{11}}{\rightleftarrows}} CH_3CH(OH)_2 \qquad (11)$$

Hydrated acetaldehyde is inactive as in the case of formaldehyde.[1,2]

The observed general acid catalysis may be explained by a mechanism involving a simultaneous attack of urea and acid (HA) on acetaldehyde, which is analo-

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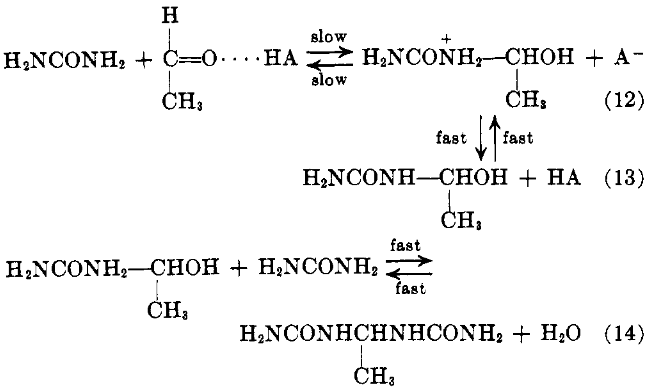
[6] The equilibrium constant was determined spectrophotometrically according to R. Bieber and G. Trümpler [*Helv. Chim. Acta*, **30**, 1860 (1947)].

gous to amide–formaldehyde[1,2] and ammonia–aldehyde[7] reactions.



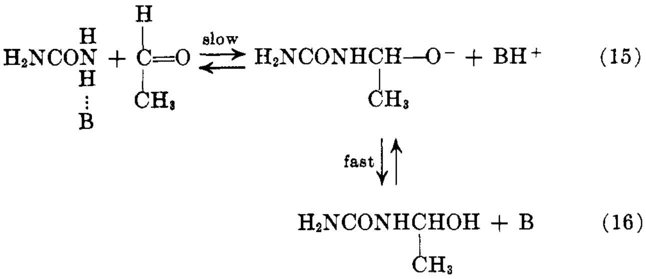
$$H_2NCONH_2 + \underset{CH_3}{\overset{H}{C}}{=}O\cdots HA \underset{slow}{\overset{slow}{\rightleftarrows}} H_2NCO\overset{+}{N}H_2{-}\underset{CH_3}{C}HOH + A^- \tag{12}$$

$$\downarrow\uparrow \text{ fast, fast}$$

$$H_2NCONH{-}\underset{CH_3}{C}HOH + HA \tag{13}$$

$$H_2NCONH_2{-}\underset{CH_3}{C}HOH + H_2NCONH_2 \underset{fast}{\overset{fast}{\rightleftarrows}} H_2NCONH\underset{CH_3}{C}HNHCONH_2 + H_2O \tag{14}$$

Similarly, the following mechanism may be suggested for the base catalysis.



$$H_2NCO\underset{\underset{B}{\vdots}}{\underset{H}{\overset{H}{N}}} + \underset{CH_3}{\overset{H}{C}}{=}O \underset{}{\overset{slow}{\rightleftarrows}} H_2NCONH\underset{CH_3}{C}H{-}O^- + BH^+ \tag{15}$$

$$\downarrow\uparrow \text{ fast}$$

$$H_2NCONH\underset{CH_3}{C}HOH + B \tag{16}$$

However, the possibility of the specific oxonium ion and the specific hydroxide ion catalysis is not ruled out on the basis of the present data.

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[7] Y. Ogata and A. Kawasaki, *Tetrahedron*, **20**, 855, 1573 (1964).

The Chemistry of Carbonyl Chloride Fluoride. I.

The Ring Opening of Cyclic Ethers with Carbonyl Chloride Fluoride

K. O. Christe and A. E. Pavlath

The Richmond Research Center, Stauffer Chemical Company, Richmond, California

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Ring opening of cyclic ethers by carbonyl chloride fluoride yielded ω-chloroalkyl fluoroformates. The reactivity of carbonyl chloride fluoride with cyclic ethers was found to decrease in the order ethylene oxide > trimethylene oxide > tetrahydrofuran > tetrahydropyran. In addition, its reaction with substituted ethylene oxides and butadiene dioxide was investigated. The ω-chloroalkyl fluoroformates, a new class of compounds, are useful for the preparation of ω-chloroalkyl fluorides or ω-fluoroalkenes. Vinyl fluoride has been prepared from ethylene oxide and carbonyl chloride fluoride in an over-all yield of about 70%. A new method for the preparation of carbonyl chloride fluoride is described. The ring opening of tetrahydrofuran with phosgene resulted in a mixture of 1,3- and 1,4-dichlorobutane. Attempts to replace the carbonyl chloride fluoride by thionyl or sulfuryl fluoride were not successful.

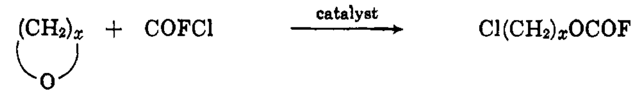
The chemistry of carbonyl chloride and carbonyl fluoride has been extensively investigated. Among many others, the reactions of carbonyl chloride with ethylene oxide and substituted ethylene oxides[1] forming ω-chloroalkyl chloroformates have been described. In the case of carbonyl fluoride and ethylene oxide[2] the unexpected $CF_3OCH_2CH_2OCOF$ has been obtained.

Ring-opening reactions of larger rings with phosgene or carbonyl fluoride have not been reported, but it is known[3] that the ring of tetrahydrofuran can be opened with hydrogen chloride, thionyl chloride, or phosphorous oxychloride, in the presence of catalysts such as zinc chloride, aluminum chloride, or aluminum oxide, yielding exclusively 1,4-dichlorobutane. In the case of carbonyl chloride fluoride, however, no other reactions with organic compounds except for ethanol and amines[4] have been described.

Since the organic fluoroformates proved in the course of our investigations to be very useful intermediates in the preparation of such compounds as fluorinated aromatics, 1,2-difluoroalkanes,[5] ω-chloroalkyl fluoride, etc., more systematic work was done in this field, part of which will be reported in this paper.

Preparation of Carbonyl Chloride Fluoride.—COFCl was first prepared from $COCl_2$ and SbF_3.[4] We found that it can be prepared more easily from $COCl_2$ and SiF_4[6] or on laboratory scale from $COCl_2$ and AsF_3. The purity of the COFCl used for the ring-opening reactions was not critical. Therefore, the crude reaction product consisting of 84 to 90% COFCl (the rest being COF_2 and $COCl_2$) could be used without further purification.

Ring Opening of Unsubstituted Cyclic Ethers with Carbonyl Chloride Fluoride.—ω-Chloroalkyl fluoroformates are formed when carbonyl chloride fluoride reacts with ethylene oxide, trimethylene oxide, tetrahydrofuran, or tetrahydropyran.



$$\underset{\smile O \smile}{(CH_2)_x} + COFCl \xrightarrow{catalyst} Cl(CH_2)_xOCOF$$

Reaction conditions, physical and spectral properties, and analytical data of the new compounds are summarized in Tables I, II, and III.

The reactivity of carbonyl chloride fluoride with cyclic ethers was found to decrease in the order ethylene oxide > trimethylene oxide > tetrahydrofuran > tetrahydropyran. This order could be expected from the

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[1] J. I. Jones, *J. Chem. Soc.*, 2735 (1957).

[2] P. E. Aldrich and W. A. Sheppard, *J. Org. Chem.*, **29**, 12 (1964).

[3] French Patent 864,758; *Chem. Abstr.*, **43**, 1433d (1949); Italian Patent 424,590; *Chem. Abstr.*, **43**, 4284*a* (1949); V. I. Lutkova, *et al.*, *Zh. Obshch. Khim.*, **25**, 2102 (1955); N. I. Shuikin, I. F. Bel'skii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 747 (1956); German (East) Patent 10,675; *Chem. Abstr.*, **52**, 16373*h* (1958).

[4] H. J. Emeléus and J. F. Wood, *J. Chem. Soc.*, 2183 (1948).

[5] K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 1644 (1965).

[6] K. O. Christe and A. E. Pavlath, *ibid.*, **29**, 3007 (1964).